

Supplementary data

Synthesis and evaluation of new Designed Multiple Ligands directed towards both peroxisome proliferator-activated receptor- γ and angiotensin II type 1 receptor

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1. Chemical protocols for the synthesis of strategy B and C molecules

4'-{4-[4-(2,4-Dioxo-thiazolidin-5-ylmethyl)phenoxy]methyl}imidazol-1-ylmethyl}biphenyl-2-carboxylic acid dipotassium salt (32)

In a Parr flask was introduced Pd/C (75 mg, 10% Pd), then a solution of compound **30** (72 mg, 0.13 mmol) in dioxane (8 mL) was added. The suspension was shaken in the presence of H₂ (70 psi) for 4 days at room temperature, filtered on celite[®], and the solvent was removed under vacuum. The residue was dissolved in CH₂Cl₂ (5 mL), then trifluoroacetic acid (1 mL) was added. The mixture was stirred 1.5 h at room temperature. The solvent was evaporated and the residue was dissolved in EtOAc (30 mL). The solution was washed with water (3 × 15 mL), dried (MgSO₄) and the solvent was removed under vacuum to give a residue which was purified by column chromatography (eluent: CH₂Cl₂/MeOH, 96/4) to give a yellow solid. The latter was dissolved in EtOAc (15 mL) and the organic phase was extracted with a 16 mM aqueous KOH solution (4 × 5 mL). The aqueous phases were gathered and evaporated. The residue was purified by reversed-phase column chromatography (eluent: H₂O /MeOH, 70/30) to give after freeze-drying 27 mg (0.05 mmol, 38% yield) of white solid. M.p. 218-222 °C. IR (KBr) ν (cm⁻¹): 3435, 2924, 1560, 1508, 1388, 1227. ¹H NMR (250 MHz, D₂O): δ 3.02 (dd, A part of an ABX system, *J* = 8.5, 14.2 Hz, 1H, PhCH₂), 3.28 (dd, B part of an ABX system, *J* = 4.2, 14.2 Hz, 1H, PhCH₂), 4.56 (dd, X part of an ABX system, *J* = 4.2, 8.5 Hz, 1H, CH), 5.00 (s, 2H, CH₂O), 5.24 (s, 2H, CH₂N), 6.95 (d, *J* = 8.6 Hz, 2H, H_{arom}), 7.15-7.32 (m, 4H, H_{arom}), 7.34-7.57 (m, 7H, 6×H_{arom} + H_{imidazole}), 7.84 (s, 1H, H_{imidazole}). ¹³C NMR (62.9 MHz, D₂O): δ 37.6 (CH₂), 50.5 (CH₂N), 59.0 (CH), 64.2 (CH₂O), 115.9 (CH_{arom}), 120.4, 127.1, 127.7, 127.8 (CH_{arom}), 128.9 (CH_{arom} + C_{arom}), 129.9, 130.8 (CH_{arom}), 131.3, 135.9, 136.7, 137.8, 138.8, 139.6, 141.3, 156.6, 179.0 (C=O), 190.4 (C=O), 195.0 (C=O). ESI-MS (pos. mode): *m/z* = 514.14 ([M-2K+3H]⁺). Anal. Calcd for C₂₈H₂₁K₂N₃O₅S (589.74): C, 57.02; H, 3.59; N, 7.13. Found: C, 56.81; H, 3.48; N, 6.91.

4'-{2-Butyl-4-[4-(2,4-dioxo-thiazolidin-5-ylmethyl)-phenoxy]methyl}-imidazol-1-ylmethyl}-biphenyl-2-carboxylic acid dipotassium salt (33)

In a Parr flask was introduced Pd/C (73 mg, 10% Pd), then a solution of compound **31** (73 mg, 0.12 mmol) in dioxane (8 mL) was added. The suspension was shaken in the presence of H₂ (70 psi) for 4 days at room temperature, filtered on celite[®], and the solvent was removed under vacuum. The residue was dissolved in CH₂Cl₂ (3 mL), then trifluoroacetic acid (1.5 mL) was added. The mixture was stirred 1.5 h at room temperature. The solvent was evaporated and the residue was dissolved in EtOAc (30 mL). The solution was washed with water (3 × 15 mL), dried (MgSO₄) and the solvent was removed under vacuum to give a residue which was dissolved in EtOAc (10 mL) and the organic phase was extracted with a 11 mM aqueous KOH solution (4 × 5 mL). The aqueous phases were gathered and evaporated. The residue was purified by reversed-phase column chromatography (eluent: H₂O /MeOH, 70/30) to give after freeze-drying 22 mg (0.03 mmol, 28% yield) of white solid. M.p. 208-212 °C. IR (KBr) ν (cm⁻¹): 3419, 2957, 2924, 1567, 1508, 1386, 1219. ¹H NMR (250 MHz, D₂O): δ 0.85 (t, *J* = 7.3 Hz, 3H, CH₃), 1.20-1.36 (m, 2H, CH₂), 1.51-1.63 (m, 2H, CH₂), 2.71 (t, *J* = 7.3 Hz, 2H, CH₂), 3.05 (dd, A part of an ABX system, *J* = 8.3, 14.3 Hz, 1H, PhCH₂), 3.33

(dd, B part of an ABX system, $J = 3.9, 14.3$ Hz, 1H, PhCH₂), 4.57 (dd, X part of an ABX system, $J = 3.9, 8.3$ Hz, 1H, CH), 5.05 (s, 2H, CH₂O), 5.24 (s, 2H, CH₂N), 7.00 (d, $J = 8.3$ Hz, 2H, H_{arom}), 7.14-7.17 (m, 3H, 2×H_{arom} + H_{imidazole}), 7.25 (d, $J = 8.3$ Hz, 2H, H_{arom}), 7.38-7.53 (m, 6H, H_{arom}). ¹³C NMR (62.9 MHz, D₂O): δ 13.0 (CH₃), 21.6 (CH₂), 25.6 (CH₂), 29.4 (CH₂), 37.4 (CH₂), 48.9 (CH₂N), 58.7 (CH), 64.0 (CH₂O), 116.1 (CH_{arom}), 120.9, 126.8 (CH_{arom} + C_{arom}), 127.4, 128.6 (CH_{arom}), 128.7, 129.7, 130.5 (CH_{arom}), 131.1, 134.0, 135.8, 137.6, 139.4, 140.7, 150.6, 156.3, 178.7 (C=O), 194.6 (C=O), 204.9 (C=O). ESI-MS (neg. mode): $m/z = 568.19$ ([M-2K+H]⁻). Anal. Calcd for C₃₂H₂₉K₂N₃O₅S (645.85): C, 59.51; H, 4.53; N, 6.51. Found: C, 59.25; H, 4.38; N, 6.72.

2-Butyl-1H-imidazole-4-carbaldehyde (**34**)

To a solution of (2-Butyl-1H-imidazol-4-yl)methanol (1.00 g, 6.48 mmol) in water (6 mL) was added activated MnO₂ (5.30 g, 61.04 mmol). The suspension was irradiated in a microwave oven for 35 minutes at 300 W. The solvent was removed under vacuum to give a residue which was purified by column chromatography (eluent: CH₂Cl₂/MeOH, 90:10) to give 610 mg (4.01 mmol, 62% yield) of yellow solid. M.p. 118-119 °C. ¹H NMR (250 MHz, DMSO-*d*₆): δ 0.87 (t, $J = 7.3$ Hz, 3H, CH₃), 1.22-1.36 (m, 2H, CH₂), 1.58-1.70 (m, 2H, CH₂), 2.61-2.68 (m, 2H, CH₂), 7.94-7.96 (br s, 1H, H_{imidazole}), 9.62 (s, 1H, CHO), 12.72 (br s, 1H, NH).

3-(2-Butyl-1H-imidazol-4-yl)propionic acid ethyl ester (**35**)

To an ice-cooled solution of (EtO)₂POCH₂CO₂Et (6.63 g, 29.56 mmol) in anhydrous DMF (20 mL) under argon was added 60% NaH (1.14 g, 28.38 mmol) and the mixture was stirred for 30 minutes. A solution of compound **34** (1.80 g, 11.82 mmol) in anhydrous THF (16 mL) was added and the suspension was stirred for 1 h at 0°C and 1 h at room temperature. The mixture was acidified with a 5% aqueous citric acid solution and EtOAc (100 mL) was added. The organic phase was washed with water (5 × 50 mL), dried (MgSO₄) and the solvent was removed under vacuum. The residue was dissolved in EtOH (150 mL) and 10% Pd/C (1.00 g) was added. The suspension was stirred in the presence of H₂ for 48 h at room temperature, filtered on celite[®], and the solvent was removed under vacuum. The residue was purified by column chromatography (eluent: CH₂Cl₂/EtOAc, 40/60, then CH₂Cl₂/MeOH, 97/3) to give 2.09 g (9.32 mmol, 79% yield) of white solid. M.p. 56-57 °C. IR (film) ν (cm⁻¹): 2958, 2928, 2872, 1736, 1448, 1373, 1182. ¹H NMR (250 MHz, DMSO-*d*₆): δ 0.87 (t, $J = 7.3$ Hz, 3H, CH₃), 1.13-1.35 (m, 5H, 2×CH₂ + CH₃), 1.57 (m, 2H, CH₂), 2.50-2.73 (m, 6H, 3×CH₂), 4.04 (q, $J = 7.2$ Hz, 2H, CO₂CH₂), 6.54 (br s, 1H, H_{imidazole}), 11.35 (br s, 1H, NH). ¹³C NMR (62.9 MHz, DMSO-*d*₆): δ 13.6 (CH₃), 14.0 (CH₃), 21.7 (CH₂), 27.6 (CH₂), 30.2 (CH₂), 33.5 (CH₂C=O), 59.6 (OCH₂), 113.8 (C_{imidazole}), 147.1 (CH_{imidazole}), 172.4 (C=O). ESI-MS (pos. mode): $m/z = 225.16$ ([M+H]⁺). Anal. Calcd for C₁₂H₂₀N₂O₂ (224.30): C, 64.26; H, 8.99; N, 12.49. Found: C, 64.01; H, 9.12; N, 12.54.

3-(2-Butyl-1H-imidazol-4-yl)-propan-1-ol (36)

To an ice-cooled suspension of LiAlH₄ (1.31 g, 34.64 mmol) in anhydrous THF (50 mL) under argon was added a solution of compound 35 (1.94 g, 8.66 mmol) in anhydrous THF (30 mL). The suspension was stirred for 1 h at room temperature and an aqueous saturated K₂CO₃ solution (10 mL) and EtOAc (100 mL) were added. The organic phase was washed with water (3 × 50 mL), dried (MgSO₄) and the solvent was removed under vacuum. The residue was purified by column chromatography (eluent: CH₂Cl₂/MeOH, 85/15) to give 960 mg (5.27 mmol, 61% yield) of colorless liquid. IR (film) ν (cm⁻¹): 3161, 2930, 1451, 1055. ¹H NMR (250 MHz, DMSO-*d*₆): δ 0.87 (t, *J* = 7.3 Hz, 3H, CH₃), 1.28 (m, 2H, CH₂), 1.51-1.72 (m, 4H, 2×CH₂), 2.41-2.54 (m, 4H, 2×CH₂), 3.31 (br s, 1H, OH), 3.41 (t, *J* = 6.4 Hz, 2H, CH₂OH), 6.51 (s, 1H, H_{imidazole}), 11.19 (br s, 1H, NH). ¹³C NMR (62.9 MHz, DMSO-*d*₆): δ 13.7 (CH₃), 21.8 (CH₂), 23.2 (CH₂), 27.7 (CH₂), 30.3(CH₂), 32.3 (CH₂), 60.4 (CH₂OH), 115.6 (C_{imidazole}), 135.3 (C_{imidazole}), 146.9 (CH_{imidazole}). ESI-MS (pos. mode): *m/z* = 183.15 ([M+H]⁺). Anal. Calcd for C₁₀H₁₈N₂O (182.26): C, 65.90; H, 9.95; N, 15.37. Found: C, 65.70; H, 9.72; N, 15.54.

4'-[2-Butyl-4-(3-hydroxypropyl)imidazol-1-ylmethyl]biphenyl-2-carboxylic acid tert-butyl ester (37) and 4'-[2-Butyl-5-(3-hydroxypropyl)imidazol-1-ylmethyl]biphenyl-2-carboxylic acid tert-butyl ester (38)

To a solution of **36** (660 mg, 3.62 mmol) in anhydrous DMF (4 mL) under argon were added *tert*-butyl-4'-(bromomethyl)biphenyl-2-carboxylate (628 mg, 1.81 mmol) and K₂CO₃ (500 mg, 3.62 mmol) and the mixture was stirred at 80 °C for 18 h. To the solution was added EtOAc (30 mL) and the organic phase was washed with water (4 × 10 mL), dried (MgSO₄) and the solvent was removed under vacuum. The residue was purified by column chromatography (eluent: CH₂Cl₂/MeOH, 98/2) to give 650 mg (1.45 mmol, 80% yield) of compound **37** (colorless liquid) and 45 mg (0.10 mmol, 6% yield) of compound **38** (colorless liquid).

Compound **37**. IR (film) ν (cm⁻¹): 3369, 2932, 2872, 1706, 1367, 1303, 1129. ¹H NMR (400 MHz, DMSO-*d*₆): δ 0.85 (t, *J* = 7.3 Hz, 3H, CH₃), 1.18 (s, 9H, *t*-Bu), 1.31 (m, 2H, CH₂), 1.55 (m, 2H, CH₂), 1.67 (m, 2H, CH₂), 2.43 (m, 2H, CH₂), 2.54 (m, 2H, CH₂), 3.43 (t, *J* = 6.4 Hz, 2H, CH₂OH), 4.56 (br s, 1H, OH), 5.12 (s, 2H, CH₂N), 6.78 (s, 1H, H_{imidazole}), 7.17 (d, *J* = 8.2 Hz, 2H, H_{arom}), 7.26 (d, *J* = 8.2 Hz, 2H, H_{arom}), 7.34 (dd, *J* = 1.4, 7.6 Hz, 1H, H_{arom}), 7.45 (dt, *J* = 1.4, 7.6 Hz, 1H, H_{arom}), 7.56 (dt, *J* = 1.4, 7.6 Hz, 1H, H_{arom}), 7.67 (dd, *J* = 1.4, 7.6 Hz, 1H, H_{arom}). ¹³C NMR (100.6 MHz, DMSO-*d*₆): δ 13.7 (CH₃), 21.9 (CH₂), 24.7 (CH₂), 25.8 (CH₂), 27.2 (*t*-Bu), 29.7 (CH₂), 32.3 (CH₂), 47.9 (CH₂N), 60.6 (CH₂OH), 80.8, 115.6, 126.6 (CH_{arom}), 127.4, 128.6 (CH_{arom}), 129.1, 130.3, 130.9, 132.6, 136.9, 139.6, 140.2, 140.7, 146.7, 167.3 (C=O). ESI-MS (pos. mode): *m/z* = 449.28 ([M+H]⁺). Anal. Calcd for C₂₈H₃₆N₂O₃ (448.60): C, 74.97; H, 8.09; N, 6.24. Found: C, 74.90; H, 8.46; N, 6.23.

Compound **38**. IR (film) ν (cm⁻¹): 3369, 2930, 2871, 1706, 1368, 1303, 1172, 1129, 755. ¹H NMR (400 MHz, DMSO-*d*₆): δ 0.83 (t, *J* = 7.3 Hz, 3H, CH₃), 1.18 (s, 9H, *t*-Bu), 1.29 (m, 2H, CH₂), 1.56 (m, 2H, CH₂), 1.67 (m, 2H, CH₂), 2.43-2.54 (m, 4H, 2×CH₂), 3.42 (m, 2H, CH₂OH), 4.47 (br s, 1H, OH), 5.19 (s, 2H, CH₂N), 6.65 (s, 1H, H_{imidazole}), 6.95 (d, *J* = 8.2 Hz, 2H, H_{arom}), 7.25 (d, *J* = 8.2 Hz, 2H, H_{arom}), 7.34 (dd, *J* = 0.9, 7.6 Hz, 1H, H_{arom}), 7.45 (dt, *J* = 1.4, 7.6 Hz, 1H, H_{arom}), 7.56 (dt, *J* = 1.4, 7.6 Hz, 1H, H_{arom}), 7.66 (dd, *J* = 1.4, 7.6 Hz, 1H,

H_{arom}). ^{13}C NMR (100.6 MHz, $\text{DMSO-}d_6$): δ 13.7 (CH_3), 20.4 (CH_2), 21.8 (CH_2), 26.0 (CH_2), 27.2 (*t*-Bu), 29.4 (CH_2), 31.1 (CH_2), 45.3 (CH_2N), 60.0 (CH_2OH), 80.8, 123.2, 125.3 (CH_{arom}), 127.4, 128.7 (CH_{arom}), 129.1, 130.3, 130.9, 131.4, 132.7, 136.6, 140.0, 140.6, 147.4, 167.4 ($\text{C}=\text{O}$). ESI-MS (pos. mode): $m/z = 449.28$ ($[\text{M}+\text{H}]^+$). Anal. Calcd for $\text{C}_{28}\text{H}_{36}\text{N}_2\text{O}_3$ (448.60): C, 74.97; H, 8.09; N, 6.24. Found: C, 74.75; H, 8.23; N, 6.18.

4'-(2-Butyl-4-{3-[4-(2,4-dioxo-thiazolidin-5-ylmethyl)phenoxy]propyl}imidazol-1-ylmethyl)biphenyl-2-carboxylic acid dipotassium salt (39)

To a solution of compound **37** (210 mg, 0.47 mmol) in anhydrous THF (2 mL) under argon were added triphenylphosphine (160 mg, 0.61 mmol) and 5-(4-hydroxybenzyl)-3-tritylthiazolidine-2,4-dione (242 mg, 0.52 mmol). The solution was cooled to 15°C, and a solution of DEAD (96 μL , 0.61 mmol) in anhydrous THF (2 mL) was added dropwise. The mixture was stirred for 3 h at room temperature and the solvent was evaporated. The residue was purified by column chromatography (eluent: $\text{CH}_2\text{Cl}_2/\text{EtOAc}$, 80/20) to give 262 mg of residue. The latter was dissolved in CH_2Cl_2 (3 mL) and trifluoroacetic acid (3 mL) was added. The solution was stirred for 1 h at room temperature and was concentrated at reduced pressure. The residue was dissolved in EtOAc (10 mL) and the organic phase was extracted with a 0.47 M aqueous KOH solution (4×2 mL). The aqueous phases were gathered and evaporated. The residue was purified by reversed-phase column chromatography (eluent: $\text{H}_2\text{O}/\text{MeOH}$, 30/70) to give after freeze-drying 84 mg (0.12 mmol, 26% yield) of white solid. M.p. 170-171 °C. IR (KBr) ν (cm^{-1}): 3434, 2928, 1560, 1510, 1388, 1223. ^1H NMR (250 MHz, D_2O): δ 0.80 (t, $J = 7.3$ Hz, 3H, CH_3), 1.23 (m, 2H, CH_2), 1.50 (m, 2H, CH_2), 1.95 (m, 2H, CH_2), 2.55-2.64 (m, 4H, $2 \times \text{CH}_2$), 2.75 (dd, A part of an ABX system, $J = 9.6, 14.0$ Hz, 1H, PhCH_2), 3.22 (dd, B part of an ABX system, $J = 3.2, 14.0$ Hz, 1H, PhCH_2), 3.86 (m, 2H, CH_2O), 4.31 (dd, X part of an ABX system, $J = 3.2, 9.6$ Hz, 1H, CH), 4.98 (s, 2H, CH_2N), 6.53 (s, 1H, $\text{H}_{\text{imidazole}}$), 6.73 (d, $J = 8.2$ Hz, 2H, H_{arom}), 7.03-7.06 (m, 4H, H_{arom}), 7.19-7.51 (m, 6H, H_{arom}). ^{13}C NMR (62.9 MHz, D_2O): δ 13.1 (CH_3), 21.7 (CH_2), 23.1 (CH_2), 25.5 (CH_2), 27.6 (CH_2), 29.7 (CH_2), 37.7 (CH_2), 48.7 (CH_2N), 59.1 (CH), 67.3 (CH_2O), 114.6 (CH_{arom}), 117.1, 126.9 (CH_{arom}), 127.0, 127.4, 128.7 (CH_{arom}), 129.7, 130.3 (CH_{arom}), 130.9, 135.8, 137.6, 138.1, 139.4, 140.7, 149.3, 157.1, 178.5 ($\text{C}=\text{O}$), 189.8 ($\text{C}=\text{O}$), 194.4 ($\text{C}=\text{O}$). ESI-MS (neg. mode): $m/z = 596.22$ ($[\text{M}-2\text{K}+\text{H}]^-$). Anal. Calcd for $\text{C}_{34}\text{H}_{33}\text{K}_2\text{N}_3\text{O}_5$, 1.5 KOH (758.06): C, 53.87; H, 4.59; N, 5.54. Found: C, 53.93; H, 4.90; N, 5.41.

4'-{4-[4-(2,4-Dioxo-thiazolidin-5-ylmethyl)phenoxy]methyl}-[1,2,3]triazol-1-ylmethyl}biphenyl-2-carboxylic acid tert-butyl ester (42)

In a Parr flask was introduced Pd/C (200 mg, 10% Pd), then a solution of compound **40** (382 mg, 0.67 mmol) in dioxane (30 mL) was added. The suspension was shaken in the presence of H_2 (70 psi) for 4 days at room temperature, filtered on celite[®], and the solvent was removed under vacuum. The residue was purified by column chromatography (eluent: $\text{CH}_2\text{Cl}_2/\text{EtOAc}$, 80/20) to give 347 mg (0.61 mmol, 91% yield) of yellow solid. M.p. 82-85 °C. IR (film) ν (cm^{-1}): 3436, 1694, 1511, 1304. ^1H NMR (250 MHz, CDCl_3): δ 1.23 (s, 9H, *t*-Bu), 3.12 (dd, A part of an ABX system, $J = 9.2, 14.1$ Hz, 1H, PhCH_2), 3.43 (dd, B part of an ABX system, $J = 4.0, 14.1$ Hz, 1H, PhCH_2), 4.50 (dd, X part of an ABX system, $J = 4.0, 9.2$ Hz, 1H, CH), 5.19 (s, 2H, CH_2O), 5.59 (s, 2H, CH_2N), 6.93 (d, $J = 8.5$ Hz, 2H, H_{arom}), 7.15 (d,

$J = 8.5$ Hz, 2H, H_{arom}), 7.30-7.53 (m, 7H, H_{arom}), 7.58 (s, 1H, H_{triazole}), 7.80 (dd, $J = 1.4$, 7.5 Hz, 1H, H_{arom}), 7.92 (br s, 1H, NH). ^{13}C NMR (62.9 MHz, CDCl_3): δ 27.8 (*t*-Bu), 37.9 (CH_2), 53.7 (CH), 54.2 (CH_2N), 62.2 (CH_2O), 81.6, 115.2 (CH_{arom}), 122.7, 127.6, 127.9 (CH_{arom}), 128.4, 129.5 (CH_{arom}), 130.0, 130.5, 130.6 (CH_{arom}), 131.0, 132.9, 133.4, 141.3, 142.8, 144.7, 157.9, 167.8 (C=O), 170.3 (C=O), 174.1 (C=O). ESI-MS (pos. mode): $m/z = 515.14$ ($[\text{M}-t\text{Bu}+2\text{H}]^+$), (571.20 ($[\text{M}+\text{H}]^+$), 593.19 ($[\text{M}+\text{Na}]^+$). Anal. Calcd for $\text{C}_{31}\text{H}_{30}\text{N}_4\text{O}_5\text{S}$ (570.66): C, 65.25; H, 5.30; N, 9.82. Found: C, 65.38; H, 5.26; N, 9.55.

4'-(4-{2-[4-(2,4-Dioxo-thiazolidin-5-ylmethyl)phenoxy]ethyl}-[1,2,3]triazol-1-ylmethyl)-biphenyl-2-carboxylic acid tert-butyl ester (43)

In a Parr flask was introduced Pd/C (500 mg, 10% Pd), then a solution of compound **41** (1.00 g, 1.72 mmol) in dioxane (40 mL) was added. The suspension was shaken in the presence of H_2 (70 psi) for 2 days at room temperature, filtered on celite[®], and the solvent was removed under vacuum. The residue was purified by column chromatography (eluent: $\text{CH}_2\text{Cl}_2/\text{AcOEt}$, 60/40) to give 1.00 g (1.72 mmol, 100% yield) of yellow solid. M.p. 84-86 °C. IR (film) ν (cm^{-1}): 3448, 2976, 1700, 1511, 1304, 1246. ^1H NMR (250 MHz, CDCl_3): δ 1.22 (s, 9H, *t*-Bu), 3.10 (dd, A part of an ABX system, $J = 9.2$, 14.2 Hz, 1H, PhCH_2), 3.20 (t, $J = 6.5$ Hz, 2H, CH_2), 3.42 (dd, B part of an ABX system, $J = 4.0$, 14.2 Hz, 1H, PhCH_2), 4.22 (t, $J = 6.5$ Hz, 2H, CH_2O), 4.48 (dd, X part of an ABX system, $J = 4.0$, 9.2 Hz, 1H, CH), 5.56 (s, 2H, CH_2N), 6.82 (d, $J = 8.6$ Hz, 2H, H_{arom}), 7.12 (d, $J = 8.6$ Hz, 2H, H_{arom}), 7.30 (s, 4 H, H_{arom}), 7.33-7.51 (m, 4 H, H_{arom}), 7.79 (dd, $J = 1.0$, 7.6 Hz, 1H, H_{arom}). ^{13}C NMR (62.9 MHz, CDCl_3): δ 26.3 (CH_2), 27.8 (*t*-Bu), 37.9 (CH_2), 53.7 (CH), 54.1 (CH_2N), 67.0 (CH_2O), 81.5, 115.0 (CH_{arom}), 122.0, 127.6, 127.8 (CH_{arom}), 128.1, 129.5 (CH_{arom}), 130.0, 130.6 ($\text{CH}_{\text{arom}} + \text{C}_{\text{arom}}$), 131.0, 132.9, 133.7, 141.3, 142.6, 145.2, 158.3, 167.9 (C=O), 170.2 (C=O), 174.0 (C=O). ESI-MS (pos. mode): $m/z = 529.17$ ($[\text{M}-t\text{Bu}+2\text{H}]^+$), 584.21 ($[\text{M}+\text{H}]^+$), 607.22 ($[\text{M}+\text{Na}]^+$), 623.31 ($[\text{M}+\text{K}]^+$). Anal. Calcd for $\text{C}_{32}\text{H}_{32}\text{N}_4\text{O}_5\text{S}$ (584.68): C, 65.73; H, 5.52; N, 9.58. Found: C, 65.96; H, 5.59; N, 9.41.

4'-(4-[4-(2,4-Dioxo-thiazolidin-5-ylmethyl)phoxymethyl]-[1,2,3]triazol-1-ylmethyl)-biphenyl-2-carboxylic acid dipotassium salt (44)

To a solution of compound **42** (408 mg, 0.71 mmol) in CH_2Cl_2 (10 mL) was added trifluoroacetic acid (5 mL). The solution was stirred at room temperature for 1.5 h and the solvent was evaporated. The residue was dissolved in EtOAc (30 mL) and the organic phase was washed with water (3×15 mL), and then extracted with a 40 mM aqueous KOH solution (4×5 mL). The aqueous phases were gathered and evaporated. The residue was purified by reversed-phase column chromatography (eluent: $\text{H}_2\text{O}/\text{MeOH}$, 60/40) to give after freeze-drying 329 mg (0.56 mmol, 78% yield) of white solid. M.p. 216-219 °C. IR (KBr) ν (cm^{-1}): 3411, 1560, 1508, 1387, 1219. ^1H NMR (250 MHz, D_2O): δ 3.02 (dd, A part of an ABX system, $J = 8.3$, 14.2 Hz, 1H, PhCH_2), 3.27 (dd, B part of an ABX system, $J = 4.2$, 14.2 Hz, 1H, PhCH_2), 4.54 (dd, X part of an ABX system, $J = 4.2$, 8.3 Hz, 1H, CH), 5.19 (s, 2H, CH_2O), 5.64 (s, 2H, CH_2N), 6.93 (d, $J = 8.4$ Hz, 2H, H_{arom}), 7.20 (d, $J = 8.4$ Hz, 2H, H_{arom}), 7.30-7.52 (m, 8H, H_{arom}), 7.99 (s, 1H, H_{triazole}). ^{13}C NMR (62.9 MHz, D_2O): δ 37.3 (CH_2), 53.6 (CH_2N), 61.4 (CH_2O), 115.5 (CH_{arom}), 125.1, 126.9, 127.5, 128.0 (CH_{arom}), 128.7, 128.8 (CH_{arom}), 129.7, 130.6 (CH_{arom}), 131.4, 133.7, 137.5, 139.4, 141.5, 143.6, 156.0, 178.6 (C=O),

190.0 (C=O), 194.6 (C=O). ESI-MS (neg. mode): $m/z = 513.13$ ($[M-2K+H]^-$), 535.12 ($[M-2K+Na]^-$). Anal. Calcd for $C_{27}H_{20}K_2N_4O_5S$ (590.73): C, 54.90; H, 3.41; N, 9.48. Found: C, 54.96; H, 3.12; N, 9.41.

4'-(4-{2-[4-(2,4-Dioxo-thiazolidin-5-ylmethyl)phenoxy]ethyl}-[1,2,3]triazol-1-ylmethyl)-biphenyl-2-carboxylic acid dipotassium salt (45)

The same protocol as for the synthesis of compound **44** was applied to compound **43** (772 mg, 1.32 mmol) with the same volumes of CH_2Cl_2 , trifluoroacetic acid, and EtOAc. The organic phase was extracted with a 1.01 M aqueous KOH solution (4×2 mL). The aqueous phases were gathered and evaporated. The residue was purified by reversed-phase column chromatography (eluent: $H_2O/MeOH$, 60/40) to give after freeze-drying 671 mg (1.11 mmol, 84% yield) of white solid. M.p. 221-223 °C. IR (KBr) ν (cm^{-1}): 3422, 2924, 1560, 1511, 1387, 1222. 1H NMR (250 MHz, D_2O): δ 2.93 (dd, A part of an ABX system, $J = 8.8, 14.1$ Hz, 1H, $PhCH_2$), 3.10 (t, $J = 5.8$ Hz, 2H, CH_2), 3.23 (dd, B part of an ABX system, $J = 3.8, 14.1$ Hz, 1H, $PhCH_2$), 4.23 (t, $J = 5.8$ Hz, 2H, CH_2O), 4.48 (dd, X part of an ABX system, $J = 3.8, 8.8$ Hz, 1H, CH), 5.58 (s, 2H, CH_2N), 6.75 (d, $J = 8.3$ Hz, 2H, H_{arom}), 7.10 (d, $J = 8.3$ Hz, 2H, H_{arom}), 7.32 (m, 3H, H_{arom}), 7.40-7.53 (m, 5H, H_{arom}), 7.76 (s, 1H, $H_{triazole}$). ^{13}C NMR (62.9 MHz, D_2O): δ 25.1 (CH_2), 37.5 (CH_2), 53.5 (CH_2N), 58.9 (CH), 67.0 (CH_2O), 114.8 (CH_{arom}), 123.8, 126.9, 127.5, 128.1 (CH_{arom}), 128.7, 128.8 (CH_{arom}), 129.7, 130.4 (CH_{arom}), 130.9, 133.8, 137.5, 139.4, 141.5, 145.2, 156.7, 178.6 (C=O), 189.9 (C=O), 194.5 (C=O). ESI-MS (neg. mode): $m/z = 527.14$ ($[M-2K+H]^-$), 549.12 ($[M-2K+Na]^-$). Anal. Calcd for $C_{28}H_{22}K_2N_4O_5S$, KOH, H_2O (678.88): C, 49.54; H, 3.71; N, 8.25. Found: C, 49.74; H, 3.69; N, 8.12.

4'-(5-Butyl-4-formyl-[1,2,3]triazol-1-ylmethyl)biphenyl-2-carboxylic acid tert-butyl ester (46) and 4'-(4-Butyl-5-formyl-[1,2,3]triazol-1-ylmethyl)biphenyl-2-carboxylic acid tert-butyl ester (47)

To a solution of *tert*-butyl-4'-(azidomethyl)biphenyl-2-carboxylate (158 mg, 0.51 mmol) in a 4/1 mixture of CH_3CN and water was added hept-2-ynal (39 mg, 0.35 mmol). The reaction mixture was irradiated in a sealed tube for 30 minutes at 250 W and 200 psi. The solvent was evaporated, hept-2-ynal (39 mg, 0.35 mmol) was added again, and the mixture was irradiated. After 5 irradiations, the solvent was evaporated and the residue was purified by column chromatography (eluent: CH_2Cl_2) to give 40 mg (0.09 mmol, 19% yield) of compound **46** as a colorless liquid and 7 mg (0.02 mmol, 3% yield) of compound **47** as a colorless liquid. Compound **46**. IR (film) ν (cm^{-1}): 3445, 1685, 1636. 1H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, $J = 7.2$ Hz, 3H, CH_3), 1.25 (s, 9H, *t*-Bu), 1.34 (m, 2H, CH_2), 1.45 (m, 2H, CH_2), 2.92 (m, 2H, CH_2), 5.60 (s, 2H, CH_2N), 7.26 (m, 3H, H_{arom}), 7.33 (m, 2H, H_{arom}), 7.41 (dt, $J = 1.5, 7.6$ Hz, 1H, H_{arom}), 7.49 (dt, $J = 1.5, 7.6$ Hz, 1H, H_{arom}), 7.80 (dd, $J = 1.5, 7.6$ Hz, 1H, H_{arom}), 10.21 (s, 1H, CHO). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 13.7 (CH_3), 22.6 (CH_2), 23.1 (CH_2), 27.7 (*t*-Bu), 30.3 (CH_2), 51.6 (CH_2N), 81.5, 127.1 (CH_{arom}), 127.6, 129.5 (CH_{arom}), 129.9, 130.5, 130.9, 132.9, 133.0, 141.1, 141.6, 142.7, 144.2, 167.7 (C=O), 186.2 (CHO). ESI-MS (pos. mode): $m/z = 420.23$ ($[M+H]^+$). Anal. Calcd for $C_{25}H_{29}N_3O_3$ (419.52): C, 71.57; H, 6.97; N, 10.02. Found: C, 71.48; H, 6.78; N, 10.23.

Compound **47**. IR (film) ν (cm^{-1}): 3436, 1689, 1638, 1303, 1129. ^1H NMR (400 MHz, CDCl_3): δ 0.94 (t, $J = 7.3$ Hz, 3H, CH_3), 1.17 (s, 9H, *t*-Bu), 1.41 (m, 2H, CH_2), 1.76 (m, 2H, CH_2), 2.94 (m, 2H, CH_2), 5.89 (s, 2H, CH_2N), 7.27 (m, 3H, H_{arom}), 7.37 (m, 3H, H_{arom}), 7.47 (dt, $J = 1.5, 7.6$ Hz, 1H, H_{arom}), 7.78 (dd, $J = 1.5, 7.6$ Hz, 1H, H_{arom}), 9.95 (s, 1H, CHO). ^{13}C NMR (100.6 MHz, CDCl_3): δ 13.9 (CH_3), 22.5 (CH_2), 24.9 (CH_2), 27.8 (*t*-Bu), 32.2 (CH_2), 53.8 (CH_2N), 81.4, 127.5, 128.0 (CH_{arom}), 129.2 (CH_{arom}), 129.9, 130.5, 130.9, 133.0, 133.6, 141. ; 142.5, 155.8, 167.9 (C=O), 178.4 (CHO). ESI-MS (pos. mode): $m/z = 420.23$ ($[\text{M}+\text{H}]^+$).

4'-(5-Butyl-4-hydroxymethyl-[1,2,3]triazol-1-ylmethyl)biphenyl-2-carboxylic acid tert-butyl ester (48)

To a solution compound **46** (115 mg, 0.27 mmol) in EtOH under argon at 0 °C was added NaBH_4 (31 mg, 0.81 mmol). The reaction mixture was stirred 15 minutes at the same temperature and water (10 mL) was added and the mixture was stirred 2 minutes at 0 °C. The mixture was extracted by EtOAc (3 \times 5 mL), and the organic phase was washed by water (3 \times 5 mL), dried (MgSO_4), and the solvent was evaporated. The residue was purified by column chromatography (eluent: $\text{CH}_2\text{Cl}_2/\text{EtOAc}$, 75/25) to give 116 mg (0.27 mmol, 100% yield) of yellow liquid. IR (film) ν (cm^{-1}): 3355, 2958, 2928, 1706, 1303, 1129. ^1H NMR (250 MHz, CDCl_3): δ 0.88 (t, $J = 7.3$ Hz, 3H, CH_3), 1.26-1.52 (m, 13H, $2\times\text{CH}_2 + t\text{-Bu}$), 2.60-2.90 (m, 3H, $\text{CH}_2 + \text{OH}$), 4.74 (s, 2H, CH_2OH), 5.55 (s, 2H, CH_2N), 7.19-7.32 (m, 5H, H_{arom}), 7.44 (m, 2H, H_{arom}), 7.78 (dd, $J = 1.4, 7.6$ Hz, 1H, H_{arom}). ^{13}C NMR (62.9 MHz, CDCl_3): δ 13.8 (CH_3), 22.6 ($2\times\text{CH}_2$), 27.8 (*t*-Bu), 31.1 (CH_2), 52.0 (CH_2N), 56.3 (CH_2OH), 81.5, 127.0 (CH_{arom}), 127.6, 129.4 (CH_{arom}), 129.9, 130.6, 130.9, 133.0, 133.8, 135.2, 141.3, 142.4, 144.7, 167.8 (C=O). ESI-MS (pos. mode): $m/z = 422.24$ ($[\text{M}+\text{H}]^+$). Anal. Calcd for $\text{C}_{25}\text{H}_{31}\text{N}_3\text{O}_3$ (421.53): C, 71.23; H, 7.41; N, 9.97. Found: C, 71.02; H, 7.54; N, 10.12.

4'-{5-Butyl-4-[4-(2,4-dioxo-3-tritylthiazolidin-5-ylmethyl)phenoxyethyl]-[1,2,3]triazol-1-ylmethyl}biphenyl-2-carboxylic acid tert-butyl ester (49)

To a solution of compound **48** (104 mg, 0.25 mmol) in anhydrous THF (2 mL) under argon were added triphenylphosphine (85 mg, 0.32 mmol) and 5-(4-hydroxybenzyl)-3-tritylthiazolidine-2,4-dione (125 mg, 0.27 mmol). A solution of DEAD (50 μL , 0.32 mmol) in anhydrous THF (1 mL) was then added dropwise and the mixture was stirred at room temperature for 3 h. The solvent was evaporated and the residue was purified by column chromatography (eluent: cyclohexane/EtOAc, 90/10) to give 110 mg (0.13 mmol, 51% yield) of white solid. M.p. 87-89 °C. IR (film) ν (cm^{-1}): 3056, 3028, 2957, 2937, 2872, 1756, 1690, 1610, 1600, 1584, 1510, 1492, 1477, 1449, 1367, 1300, 1244, 1178, 1131, 1090, 1036, 1005, 910, 732. ^1H NMR (250 MHz, CDCl_3): δ 0.84 (t, $J = 7.3$ Hz, 3H, CH_3), 1.26-1.51 (m, 13H, $2\times\text{CH}_2 + t\text{-Bu}$), 2.65 (m, 2H, CH_2), 3.05 (dd, A part of an ABX system, $J = 9.0, 14.2$ Hz, 1H, PhCH_2), 3.43 (dd, B part of an ABX system, $J = 3.8, 14.2$ Hz, 1H, PhCH_2), 4.36 (dd, X part of an ABX system, $J = 3.8, 9.0$ Hz, 1H, CH), 5.15 (s, 2H, CH_2O), 5.54 (s, 2H, CH_2N), 6.94 (d, $J = 8.5$ Hz, 2H, H_{arom}), 7.11-7.51 (m, 24H, H_{arom}), 7.80 (br d, 1H, $J = 7.8$ Hz, H_{arom}). ^{13}C NMR (62.9 MHz, CDCl_3): δ 13.8 (CH_3), 22.6 (CH_2), 22.7 (CH_2), 27.8 (*t*-Bu), 30.9 (CH_2), 37.9 (CH_2), 50.7 (CH_2N), 51.9 (CH), 62.0 (CH_2O), 81.5, 115.2 (CH_{arom}), 126.9 (CH_{arom}), 127.0 (CH_{arom}), 127.4, 127.5 (CH_{arom}), 128.5, 128.7 (CH_{arom}), 129.4 (CH_{arom}), 129.9, 130.6, 130.7

(CH_{arom}), 130.9, 133.0, 133.9, 136.7, 141.1, 141.3, 141.7, 142.3, 158.1, 167.8 (C=O), 169.7 (C=O), 173.3 (C=O). ESI-MS (pos. mode): $m/z = 869.37$ ([M+H]⁺). Anal. Calcd for C₅₄H₅₂N₄O₅S (869.08): C, 74.63; H, 6.03; N, 6.45. Found: C, 74.64; H, 6.09; N, 6.35.

4'-{5-Butyl-4-[4-(2,4-dioxo-thiazolidin-5-ylmethyl)phenoxy]methyl}-[1,2,3]triazol-1-ylmethyl}biphenyl-2-carboxylic acid (50)

To a solution of compound **49** (80 mg, 0.09 mmol) in CH₂Cl₂ (5 mL) was added trifluoroacetic acid (5 mL) and the reaction mixture was stirred at room temperature for 30 minutes. The solvent was evaporated and the residue was purified by column chromatography (eluent: CH₂Cl₂/MeOH, 90/10) to give 44 mg (0.08 mmol, 83% yield) of white solid. M.p. 127-129 °C. IR (KBr) ν (cm⁻¹): 3440, 2957, 2924, 1692, 1511, 1234. ¹H NMR (250 MHz, DMSO-*d*₆): δ 0.76 (t, $J = 7.1$ Hz, 3H, CH₃), 1.14-1.37 (m, 4H, 2×CH₂), 2.71 (m, 2H, CH₂), 3.03 (dd, A part of an ABX system, $J = 9.4, 14.2$ Hz, 1H, PhCH₂), 3.32 (dd, B part of an ABX system, $J = 4.0, 14.2$ Hz, 1H, PhCH₂), 4.82 (dd, X part of an ABX system, $J = 4.0, 9.4$ Hz, 1H, CH), 5.08 (s, 2H, CH₂O), 5.63 (s, 2H, CH₂N), 6.98 (d, $J = 8.4$ Hz, 2H, H_{arom}), 7.20 (m, 4H, H_{arom}), 7.34 (m, 3H, H_{arom}), 7.44 (br t, $J = 7.6$ Hz, 1H, H_{arom}), 7.55 (br t, $J = 1.4, 7.6$ Hz, 1H, H_{arom}), 7.72 (br d, $J = 7.6$ Hz, 1H, H_{arom}), 11.88-12.71 (s, 2H, NH + CO₂H). ¹³C NMR (62.9 MHz, DMSO-*d*₆): δ 13.5 (CH₃), 21.7 (CH₂), 30.4 (CH₂), 36.5 (CH₂), 50.5 (CH₂N), 53.4 (CH), 61.0 (CH₂O), 114.6 (CH_{arom}), 127.0 (CH_{arom}), 127.3, 128.7 (CH_{arom}), 129.1, 129.3, 130.3 (CH_{arom}), 130.4, 130.7, 134.7, 136.7, 140.2, 140.3, 140.6, 157.2, 167.6 (C=O), 172.3 (C=O), 176.7 (C=O). ESI-MS (neg. mode): $m/z = 569.18$ ([M-H]⁻), 591.17 ([M-2H+Na]⁻). Anal. Calcd for C₃₁H₃₀N₄O₅S (570.66): C, 65.25; H, 5.30; N, 9.82. Found: C, 65.18; H, 5.09; N, 10.05.

Synthesis of compounds 51 and 52 was already reported[37]

(±) 4'-{2-[4-(2,4-Dioxo-thiazolidin-5-ylmethyl)phenoxy]methyl}-2,5,7,8-tetramethylchroman-6-ylloxymethyl}biphenyl-2-carboxylic acid tert-butyl ester (53)

In a Parr flask was introduced Pd/C (382 mg, 10% Pd), then a solution of compound **51** (362 mg, 0.51 mmol) in dioxane (40 mL) was added. The suspension was shaken in the presence of H₂ (55 psi) for 24 h at room temperature, filtered on celite[®], and the solvent was removed under vacuum. The residue was purified by column chromatography (eluent: cyclohexane/EtOAc, 75/25) to give 296 mg (0.42 mmol, 82% yield) of white low melting point solid. IR (film) ν (cm⁻¹): 3445, 3197, 2927, 1755, 1704, 1513, 1456, 1368, 1303, 1248, 1163, 1128, 1087, 1046. ¹H NMR (250 MHz, CDCl₃): δ 1.30 (s, 9 H, *t*-Bu), 1.44 (s, 3 H, CH₃), 1.93 (m, 1 H, chromane 3-*H_aH_b*), 2.11 (m, 4 H, chromane 3-*H_aH_b* + CH₃), 2.20 (s, 3 H, CH₃), 2.25 (s, 3 H, CH₃), 2.65 (br t, $J = 6.8$ Hz, 2 H, chromane 4-H₂), 3.11 (dd, A part of an ABX system, $J = 9.4, 14.1$ Hz, 1 H, CH₂), 3.46 (dd, B part of an ABX system, $J = 3.8, 14.1$ Hz, 1 H, CH₂), 3.90, 4.00 (AB system, $J = 9.2$ Hz, 2 H, OCH₂), 4.51 (dd, X part of an ABX system, $J = 3.8, 9.4$ Hz, 1 H, CH), 4.75 (s, 2 H, OCH₂), 6.89 (d, $J = 8.6$ Hz, 2 H, H_{arom}), 7.14 (d, $J = 8.6$ Hz, 2 H, H_{arom}), 7.29-7.58 (m, 7 H, H_{arom}), 7.80 (d, $J = 10.1$ Hz, 1 H, H_{arom}), 8.28 (br s, 1 H, NH). ¹³C NMR (62.9 MHz, CDCl₃): δ 12.0 (CH₃), 12.2 (CH₃), 13.1 (CH₃), 20.4 (CH₂), 23.0 (CH₃), 27.8 (*t*-Bu), 28.7 (CH₂), 37.9 (CH₂), 53.6 (CH), 72.9, 74.5, 74.7, 81.5, 115.2, 117.7, 123.2, 126.3, 127.3, 127.4, 128.0, 128.4, 128.9, 129.8, 130.4, 130.7, 130.8,

133.1, 137.0, 141.6, 142.0, 147.6, 148.8, 158.8, 168.2 (C=O), 170.1 (C=O), 173.9 (C=O). ESI-MS (pos. mode): $m/z = 730.28$ ($[M+Na]^+$). Anal. Calcd for $C_{42}H_{45}NO_7S$ (707.87): C, 71.26; H, 6.41; N, 1.98. Found: C, 71.15; H, 6.53; N, 2.03.

(±) 4'-{2-[4-(2,4-Dioxothiazolidin-5-ylmethyl)phenoxy]methyl}-2,5,7,8-tetramethylchroman-6-yloxymethyl}biphenyl-2-carboxylic acid (**54**)

A few peaks are doubled in 1H and ^{13}C NMR, due to the presence of diastereomers

To a solution of compound **53** (221 mg, 0.31 mmol) in CH_3CN (10 mL) was added a 3 M aqueous HCl solution (4 mL) and the mixture was heated to reflux for 45 minutes. The solvents were evaporated and the residue was dissolved with EtOAc (30 mL). The organic phase was washed with water (2×15 mL), and then extracted with a 5% aqueous $NaHCO_3$ solution (10×10 mL). The aqueous phase was brought acidic with 3 M HCl and extracted with EtOAc (3×15 mL). The gathered organic phases were washed with brine (3×10 mL), dried ($MgSO_4$), and concentrated under vacuum to give a residue which was dissolved in a 1:1 mixture of CH_3CN and water (20 mL). The solution was submitted to freeze-drying to give 86 mg (0.13 mmol, 42% yield) of white powder. M.p. 70-72 °C. IR (film) ν (cm^{-1}): 3202, 3057, 2925, 1755, 1698, 1513, 1455, 1247, 1086, 1043, 737. 1H NMR (250 MHz, $CDCl_3$): δ 1.43 (s, CH_3), 1.91 (m, 1 H, chromane 3- H_aH_b), 2.05-2.12 (m, 1 H, chromane 3- H_aH_b), 2.07 (s, 1.5 H, CH_3), 2.09 (s, 1.5 H, CH_3), 2.17 (s, 3 H, CH_3), 2.21 (s, 1.5 H, CH_3), 2.22 (s, 1.5 H, CH_3), 2.63 (br t, $J = 6.5$ Hz, 2 H, chromane 4- H_2), 3.11 (dd, A part of an ABX system, $J = 9.3, 14.2$ Hz, 1 H, CH_2), 3.44 (dd, B part of an ABX system, $J = 3.9, 14.2$ Hz, 1 H, CH_2), 3.90, 3.99 (AB system, $J = 9.2$ Hz, 2 H, OCH_2), 4.50 (dd, C part of an ABX system, $J = 3.9, 9.3$ Hz, 1 H, CH), 4.74 (s, 2 H, OCH_2), 6.88 (d, $J = 8.0$ Hz, 2 H, H_{arom}), 7.13 (d, $J = 8.0$ Hz, 2 H, H_{arom}), 7.30-7.63 (m, 7 H, H_{arom}), 7.96 (d, $J = 7.5$ Hz, 1 H, H_{arom}), 8.5 (br s, 1 H, NH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 12.0 (CH_3), 12.2 (CH_3), 13.1 (CH_3), 20.4 (CH_2), 22.9 (CH_3), 23.0 (CH_3), 28.7 (CH_2), 37.8 (2 peaks, CH_2), 53.8 (CH), 72.9 (OCH_2), 74.5 (OC_{quat}), 74.7 (OCH_2), 115.2, 117.7, 123.2, 126.3, 127.4, 127.7, 127.8, 127.9, 128.4, 128.5, 128.8, 129.5, 130.5, 130.8, 131.4, 132.2, 137.1, 140.8, 143.2, 147.6, 148.7, 158.8, 170.6, 172.1, 174.3, 174.4. ESI-MS (neg. mode): $m/z = 650.18$ ($[M-H]^-$). Anal. Calcd for $C_{38}H_{37}NO_7S, \frac{1}{4} H_2O$ (656.27): C, 69.55; H, 5.76; N, 2.13. Found: C, 69.66; H, 5.63; N, 2.48.

(±) 4'-(2-{4-[2-*tert*-Butoxycarbonyl-2-(2-methoxycarbonylphenylamino)ethyl]phenoxy}methyl)-2,5,7,8-tetramethylchroman-6-yloxymethyl}biphenyl-2-carboxylic acid *tert*-butyl ester (**56**)

Preparation of the triflate intermediate: to an ice-cooled solution of anhydrous pyridine (931 μ L, 11.51 mmol) in dry CH_2Cl_2 (15 mL) under argon was added dropwise trifluoromethane sulfonic anhydride (468 μ L, 2.78 mmol). A solution of compound **55** (964 mg, 1.92 mmol) in dry CH_2Cl_2 (15 mL) was added and the mixture was stirred at the same temperature for 30 minutes. The solvent was evaporated and the residue was dissolved in EtOAc (100 mL). The organic phase was washed with a 5% aqueous $NaHCO_3$ solution (2×40 mL), water (2×40 mL), dried ($MgSO_4$), and the solvent was removed under vacuum to give a liquid yellow residue.

Condensation with compound 23: to a solution of the above triflate in DMF (10 mL) under argon were added K_2CO_3 (2.03 g, 3.84 mmol) and a solution of compound **23** (712 mg, 1.92

mmol) in DMF (10 mL). The reaction mixture was stirred under argon for 3 days at room temperature, then EtOAc (150 mL) was added and the organic phase was washed with water (5 × 40 mL), dried (MgSO₄), and the solvent was removed under vacuum. The residue was purified by column chromatography (eluent: cyclohexane/EtOAc, 85/15) to give 650 mg (0.76 mmol, 40% yield) of yellow low melting point solid. IR (film) ν (cm⁻¹): 3342, 2977, 2931, 1728, 1704, 1693, 1608, 1582, 1512, 1458, 1392, 1368, 1303, 1247, 1162, 1127, 752. ¹H NMR (250 MHz, CDCl₃): δ 1.30 (s, 9H, *t*-Bu), 1.38 (s, 9H, *t*-Bu), 1.44 (s, 3H, CH₃), 1.93 (m, 1H, chromane 3-*H_aH_b*), 2.12 (s, 3H, CH₃), 2.16 (m, 1H, chromane 3-*H_aH_b*), 2.02 (s, 3H, CH₃), 2.25 (s, 3H, CH₃), 2.65 (br t, *J* = 6.7 Hz, 2H, chromane 4-*H₂*), 3.10 (m, 2H, CH₂), 3.87 (s, 3H, OCH₃), 3.96 (m, 2H, OCH₂), 4.23 (m, 1H, CH), 4.76 (s, 2H, OCH₂Ph), 6.60 (d, *J* = 7.8 Hz, 2H, H_{arom}), 6.85 (d, *J* = 8.6 Hz, 2H, H_{arom}), 7.17 (d, *J* = 8.6 Hz, 2H, H_{arom}), 7.23-7.58 (m, 8H, H_{arom}), 7.80 (dd, *J* = 7.7, 1.4 Hz, 1H, H_{arom}), 7.91 (dd, *J* = 8.1, 1.7 Hz, 1H, H_{arom}), 8.18 (d, *J* = 7.3 Hz, 1H, NH). ¹³C NMR (62.9 MHz, CDCl₃): δ 12.0 (CH₃), 12.2 (CH₃), 13.0 (CH₃), 20.4 (CH₂), 23.1 (CH₃), 27.6 (*t*-Bu), 27.9 (*t*-Bu), 28.7 (CH₂), 38.0 (CH₂), 51.7 (CH), 58.3 (OCH₃), 72.8, 74.5, 74.7, 81.5, 81.8, 111.2, 111.8 (CH_{arom}), 114.8 (CH_{arom}), 115.5 (CH_{arom}), 117.8, 123.2, 126.2, 127.3 (CH_{arom}), 127.4 (CH_{arom}), 128.3, 128.9 (CH_{arom}), 129.2, 129.8 (CH_{arom}), 130.6 (CH_{arom}), 130.7 (CH_{arom}), 1303.8 (CH_{arom}), 131.9 (CH_{arom}), 133.1, 134.5 (CH_{arom}), 137.0, 141.5, 142.0, 147.6, 148.8, 149.9, 158.3, 168.1 (C=O), 168.8 (C=O), 171.8 (C=O). ESI-MS (pos. mode): *m/z* = 878.42 ([M+Na]⁺), 856.44 ([M+H]⁺), 744.32 ([M-2*t*Bu+3H]). Anal. Calcd for C₅₃H₆₁NO₉ (856.05): C, 74.36; H, 7.18; N, 1.64. Found: C, 74.25; H, 7.36; N, 1.39.

(±) 4'-(2-{4-[2-Carboxy-2-(2-methoxycarbonyl-phenylamino)ethyl]phenoxyethyl}-2,5,7,8-tetramethylchroman-6-yloxymethyl)biphenyl-2-carboxylic acid (**57**) and (±) 2-{1-Carboxy-2-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)phenyl]ethylamino}benzoic acid methyl ester (**58**)

To a solution of compound **56** (296 mg, 0.35 mmol) in CH₂Cl₂ (10 mL) was added trifluoroacetic acid (10 mL) and the solution was stirred at room temperature for 1.5 h. The mixture was concentrated under reduced pressure and the residue was dissolved in EtOAc (40 mL). The organic phase was washed with water (3 × 20 mL), and was further extracted with a 5% aqueous NaHCO₃ solution (3 × 10 mL). The organic phase was washed with water (3 × 20 mL), dried (MgSO₄), and concentrated under vacuum to give extract A. The basic aqueous phases were gathered and brought to acidic pH by addition of 10% aqueous HCl solution. The latter suspension was extracted with EtOAc (3 × 20 mL). The organic phases were gathered, washed with water (3 × 20 mL), dried (MgSO₄), and concentrated under vacuum to give extract B. Extract A was purified by column chromatography (eluent: CH₂Cl₂/MeOH, 95/5). The obtained residue was dissolved in a mixture of CH₃CN (7 mL) and water (3 mL) to give after freeze-drying 50 mg (0.09 mmol, 26% yield) of compound **58** as an off-white solid. Extract B was purified by reversed-phase column chromatography (eluent: H₂O /MeOH, 95/5 to 0/100). The fractions were concentrated under vacuum. The residue was dissolved in a mixture of CH₃CN (7 mL) and water (3 mL) to give after freeze-drying 59 mg (0.08 mmol, 23% yield) of compound **57** as a light yellow solid.

Compound **57**. Low-melting point solid. IR (KBr) ν (cm⁻¹): 3435, 2928, 2851, 1705, 1684, 1508, 1248. ¹H NMR (250 MHz, DMSO-*d*₆): δ 1.32 (s, 3H, CH₃), 1.84 (m, 1 H, chromane 3-

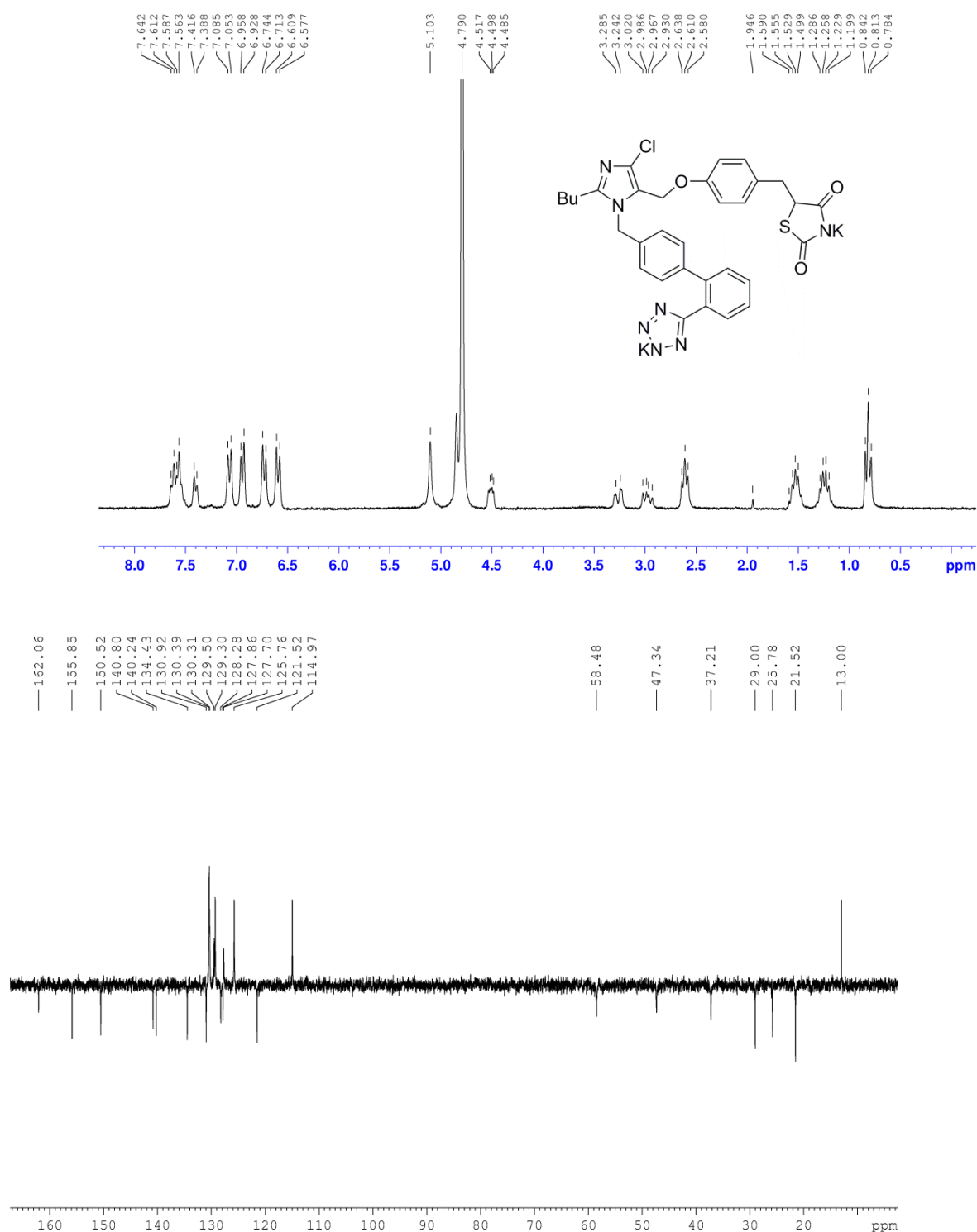
H_aH_b), 1.99 (m, 4H, CH_3 + chromane 3- H_aH_b), 2.14 (br s, 6H, CH_3), 2.62 (m, 2H, chromane 4- H_2), 2.98 (dd, A part of an ABX system, $J = 14.0, 6.6$ Hz, 1H, CH_2), 3.12 (dd, B part of an ABX system, $J = 14.0, 4.8$ Hz, 1H, CH_2), 3.78 (s, 3H, OCH_3), 3.95 (m, 2H, OCH_2), 4.40 (m, 1H, CH), 4.66 (s, 2H, OCH_2), 6.61 (t, $J = 7.5$ Hz, 1H, H_{arom}), 6.71 (d, $J = 8.7$ Hz, 1H, H_{arom}), 6.88 (d, $J = 8.4$ Hz, 2H, H_{arom}), 7.11 (d, $J = 8.4$ Hz, 2H, H_{arom}), 7.31-7.64 (m, 8H, H_{arom}), 7.74 (br d, $J = 7.4$ Hz, 1H, H_{arom}), 7.80 (dd, $J = 8.0, 1.5$ Hz, 1H, H_{arom}), 7.96 (d, $J = 7.8$ Hz, 1H, NH). ^{13}C NMR (62.9 MHz, $\text{DMSO-}d_6$): δ 11.8 (CH_3), 12.6 (CH_3), 19.6 (CH_2), 21.8 (CH_3), 27.9 (CH_2), 36.6 (CH_2), 51.6 (CH), 56.3 (OCH_3), 72.5, 73.9, 74.2, 109.7, 111.9 (CH_{arom}), 114.5 (CH_{arom}), 115.1 (CH_{arom}), 117.5, 122.0, 125.7, 127.3 (CH_{arom}), 127.4, 127.6 (CH_{arom}), 128.4 (CH_{arom}), 128.9, 129.1 (CH_{arom}), 130.2 (CH_{arom}), 130.5 (CH_{arom}), 130.8 (CH_{arom}), 131.2 (CH_{arom}), 132.5, 134.8 (CH_{arom}), 136.5, 140.4, 140.6, 147.0, 148.0, 149.3, 157.6, 167.9 (C=O), 169.6 (C=O), 173.3 (C=O). ESI-MS (neg. mode): $m/z = 764.44$ ($[\text{M}-2\text{H}+\text{Na}]^-$), 742.54 ($[\text{M}-\text{H}]^-$). Anal. Calcd for $\text{C}_{45}\text{H}_{45}\text{NO}_9$ (743.84): C, 72.66; H, 6.10; N, 1.88. Found: C, 72.34; H, 6.35; N, 1.97.

Compound **58**. Low-melting point solid. IR (KBr) ν (cm^{-1}): 3447, 2924, 2857, 1670, 1608, 1512, 1250. ^1H NMR (250 MHz, CDCl_3): δ 1.29 (s, 3H, CH_3), 1.77 (m, 2H, chromane 3- H_aH_b), 1.98 (m, 2H, chromane 3- H_aH_b), 2.05 (s, 6H, 2 x CH_3), 2.11 (s, 3H, CH_3), 2.56 (m, 2H, chromane 4- H_2), 2.85 (m, 1H, CH_2), 3.12 (m, 1H, CH_2), 3.59 (s, 3H, OCH_3), 3.70 (m, 2H, OCH_2), 4.10 (s, 1H, CH), 6.33 (m, 2H, H_{arom}), 6.58 (d, $J = 7.3$ Hz, 2H, H_{arom}), 6.96 (m, 3H, H_{arom}), 7.68 (d, $J = 7.5$ Hz, 1H, H_{arom}), 7.99 (s, 1H, NH). ^{13}C NMR (62.9 MHz, CDCl_3): δ 11.4 (CH_3), 12.0 (CH_3), 12.3 (CH_3), 20.4 (CH_2), 22.8 (CH_3), 28.8 (CH_2), 51.6 (CH), 38.0 (CH_2), 68.2 (OCH_3), 72.7, 74.2, 110.1, 112.3 (CH_{arom}), 114.5 (CH_{arom}), 114.9 (CH_{arom}), 117.5, 118.8, 121.5, 122.7, 130.4, 130.7 (CH_{arom}), 131.7 (CH_{arom}), 134.8 (CH_{arom}), 145.0, 145.3, 150.3, 157.8, 169.4 (C=O). ESI-MS (pos. mode): $m/z = 556.27$ ($[\text{M}+\text{Na}]^+$). Anal. Calcd for $\text{C}_{31}\text{H}_{35}\text{NO}_7$ (533.61): C, 69.78; H, 6.61; N, 2.62. Found: C, 69.65; H, 6.72; N, 2.58.

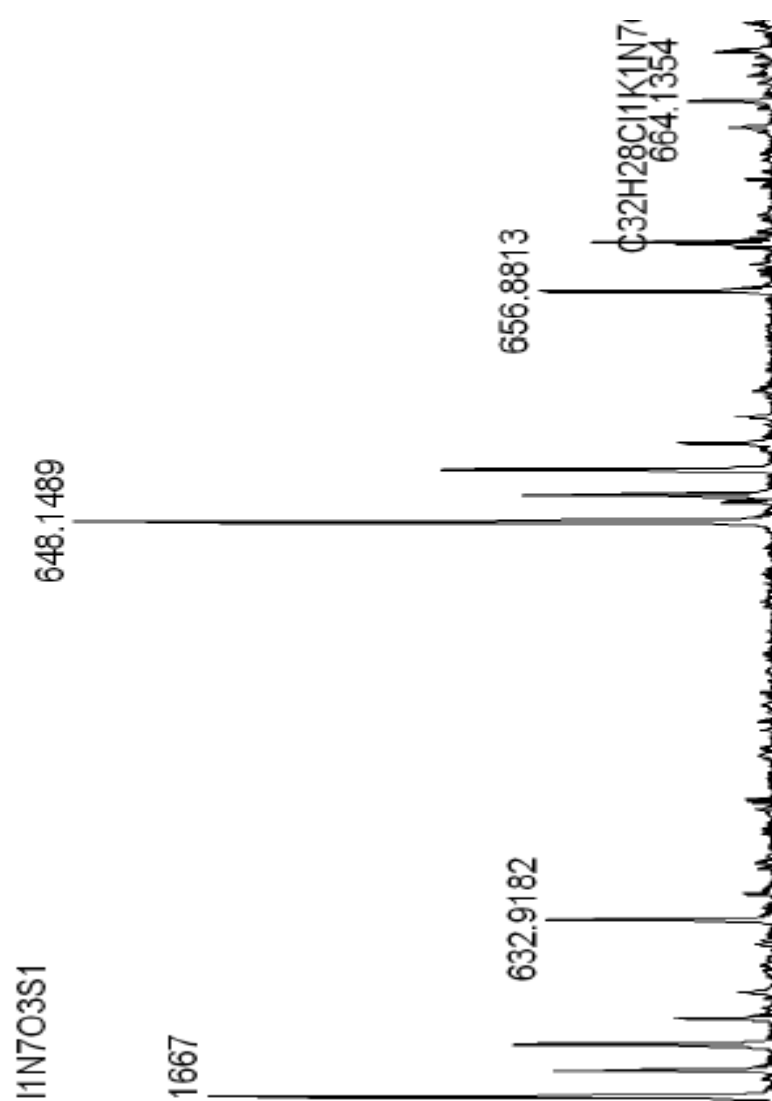
2. ^1H and ^{13}C NMR spectra and mass spectra of tested compounds

As mentioned in the experimental part, NMR spectra were recorded at 303K on a Bruker DPX250 (250 MHz for ^1H and 62.9 MHz for ^{13}C) spectrometer. Mass spectra were recorded on a micrOTOFq (Bruker) ESI/QqTOF spectrometer except those of compounds **51**, **52**, **54**, **57**, and **58**, recorded on a VG-Platform Micromass-Waters (ESI+/quad) spectrometer.

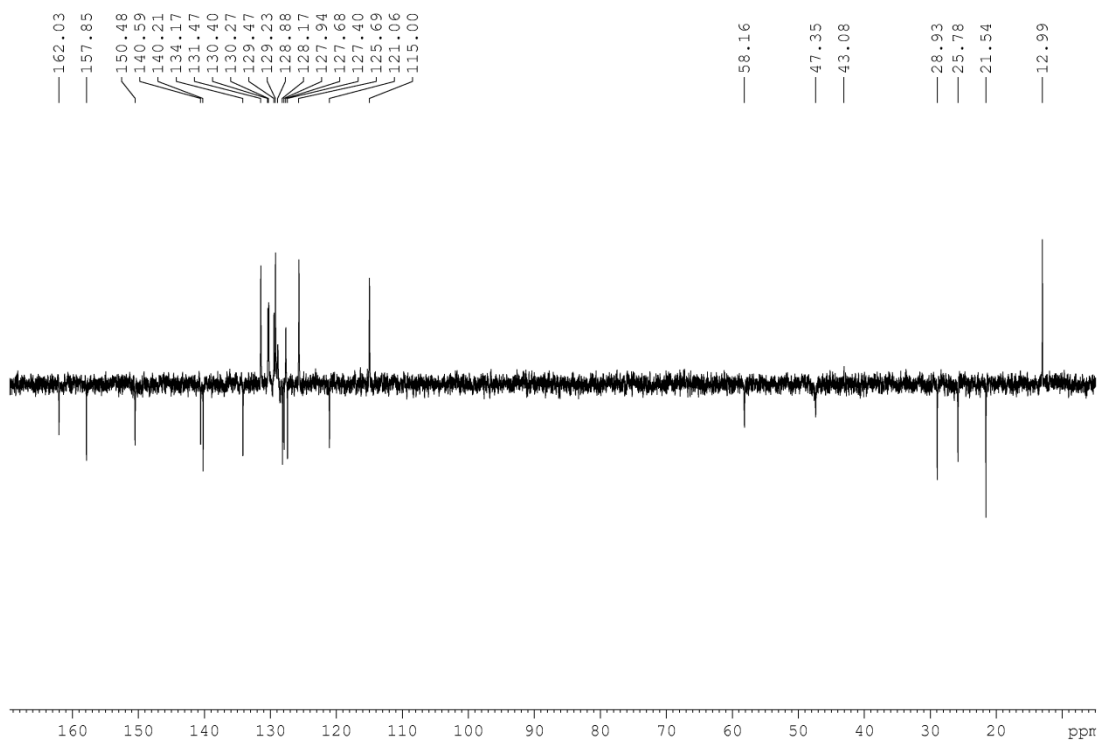
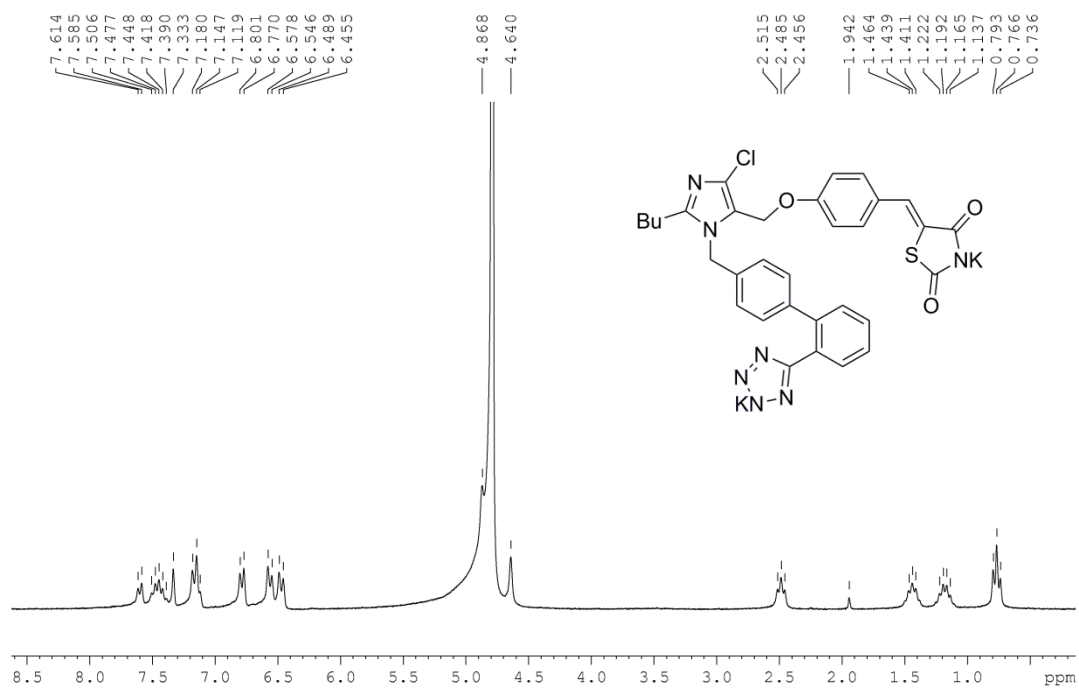
2.1. Compound **5** (D_2O)



C32H28Cl1N7Na1O3S1



2.2. Compound 7 (D₂O)

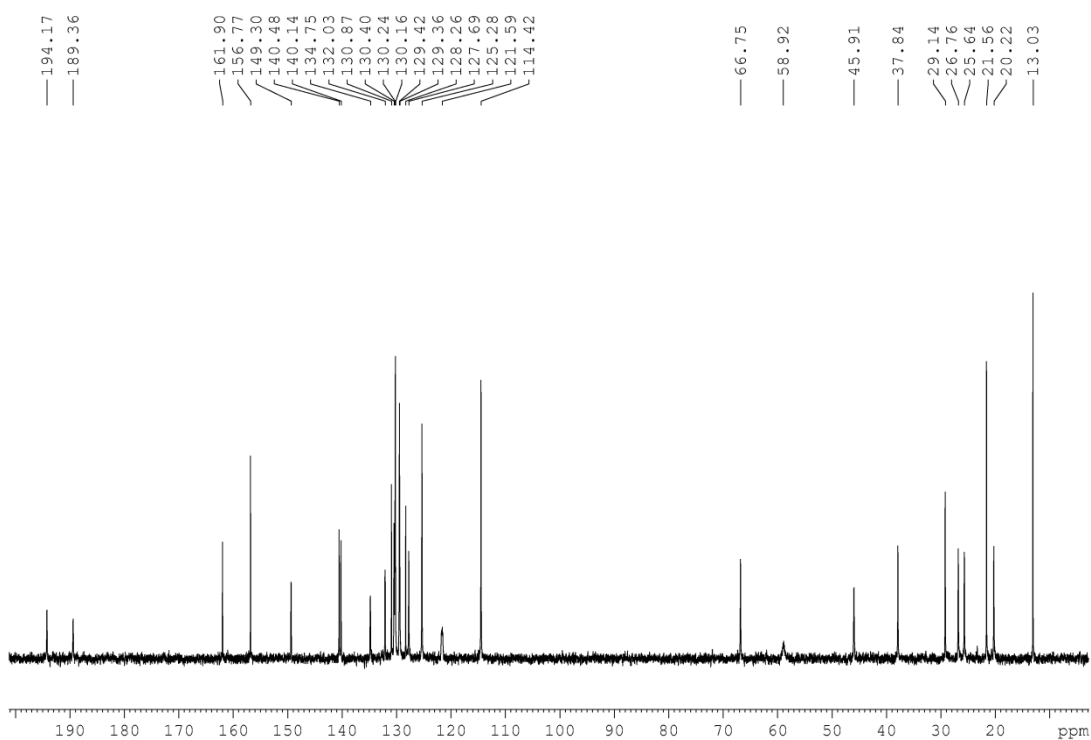
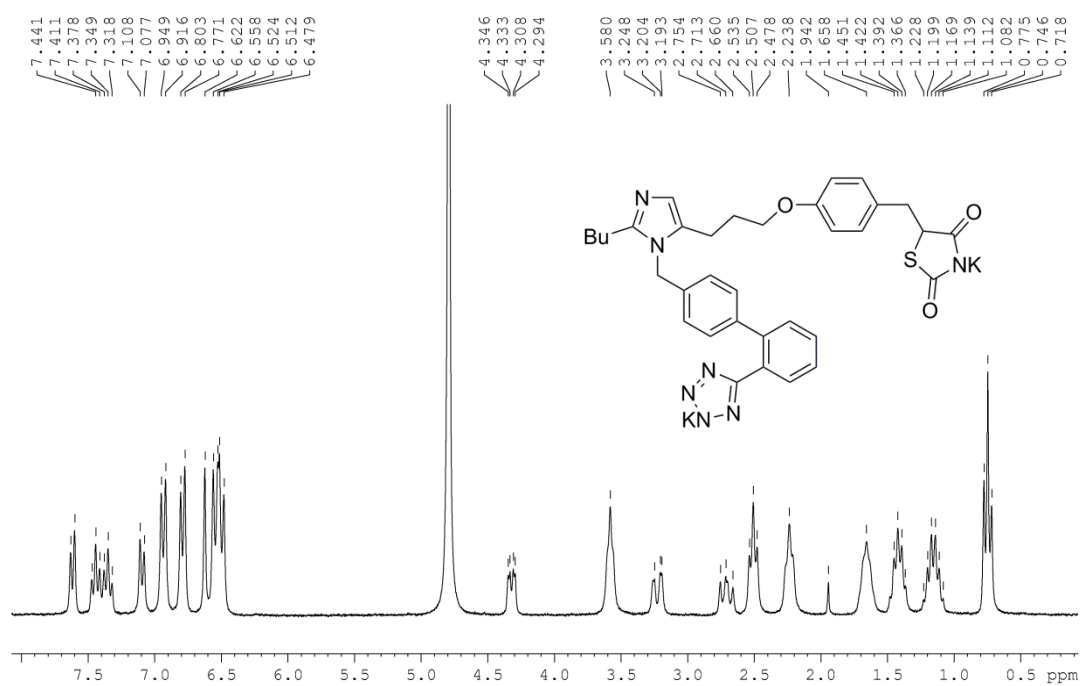


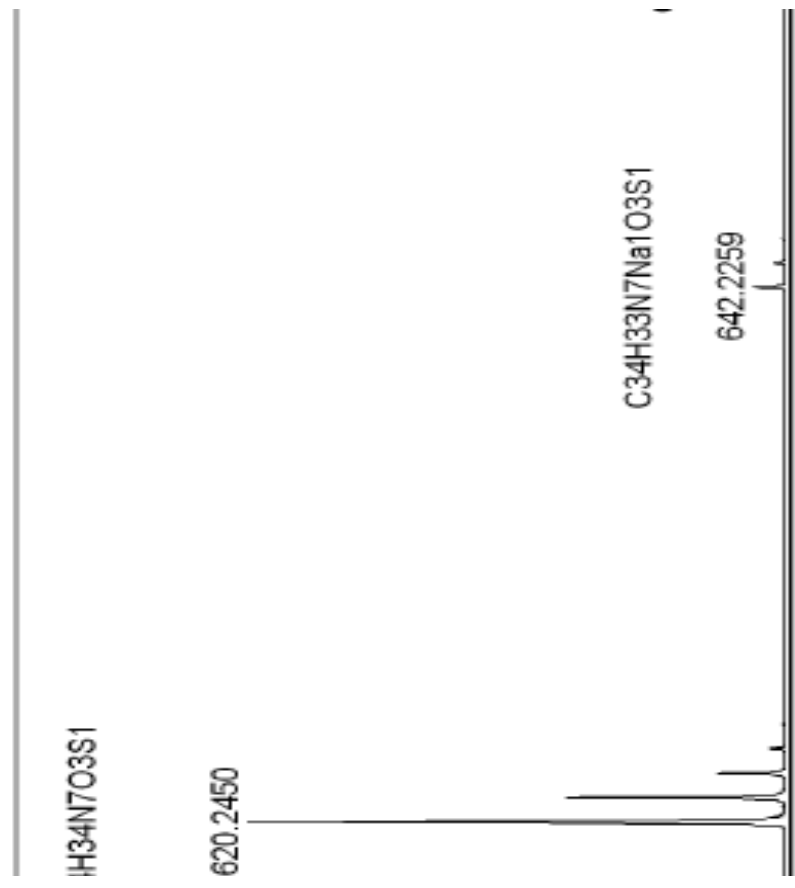
C32H27Cl1N7O3S1

624.1587

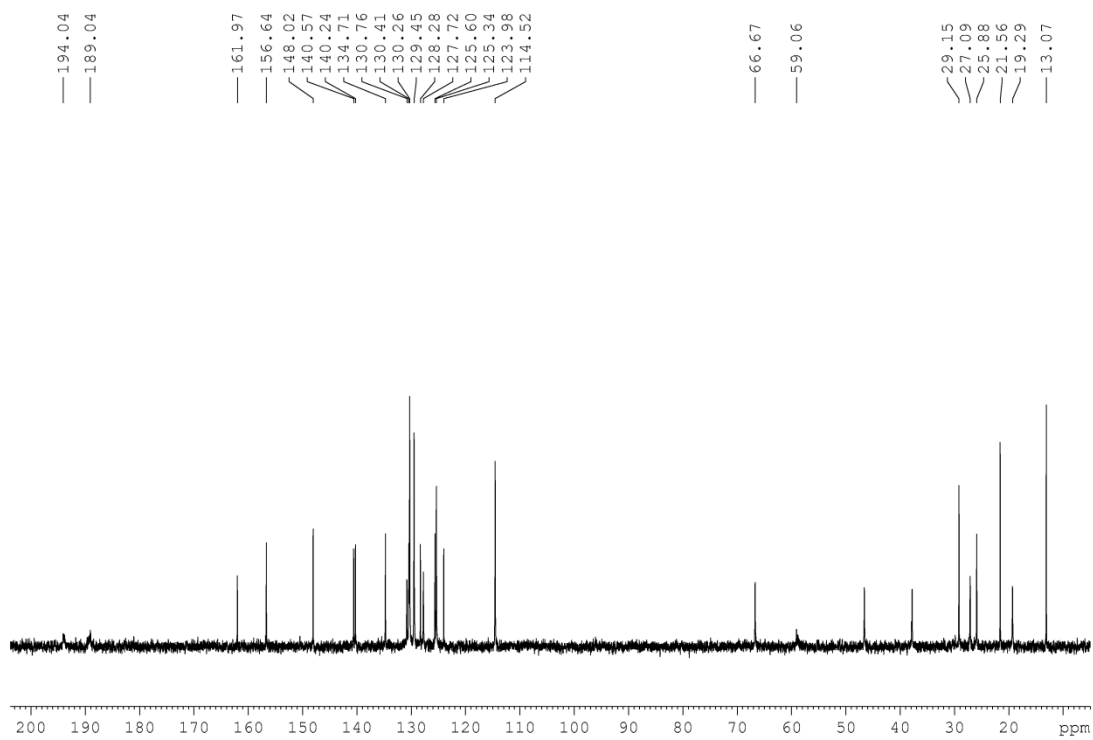
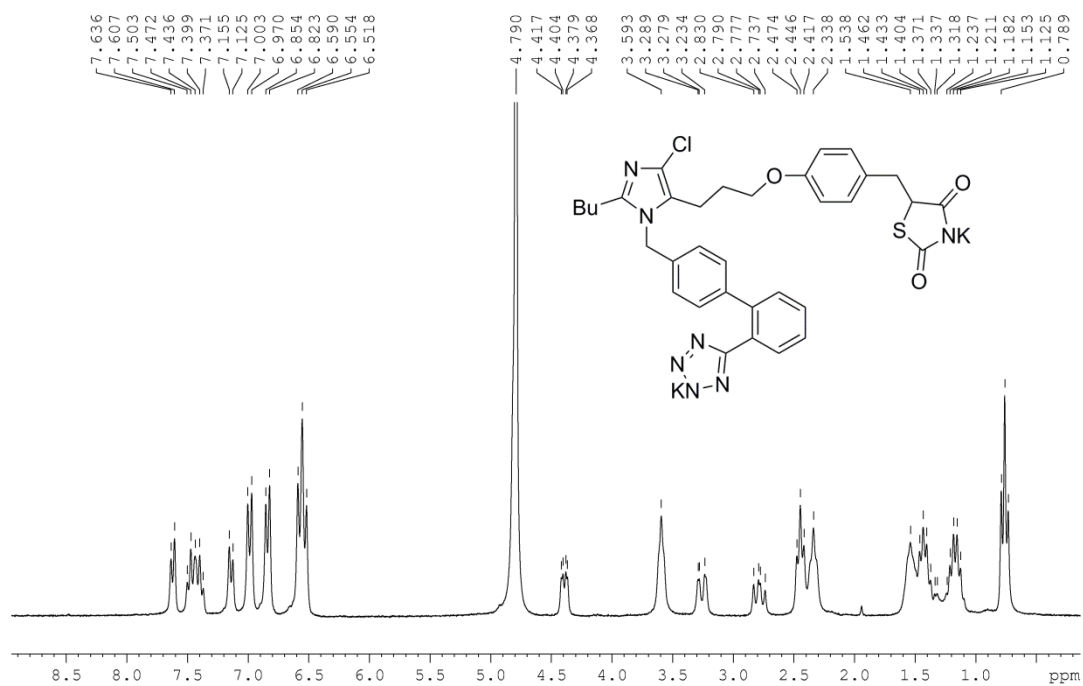
C32H26Cl1N7Na1C
646.1404

2.3. Compound **16** (D₂O)

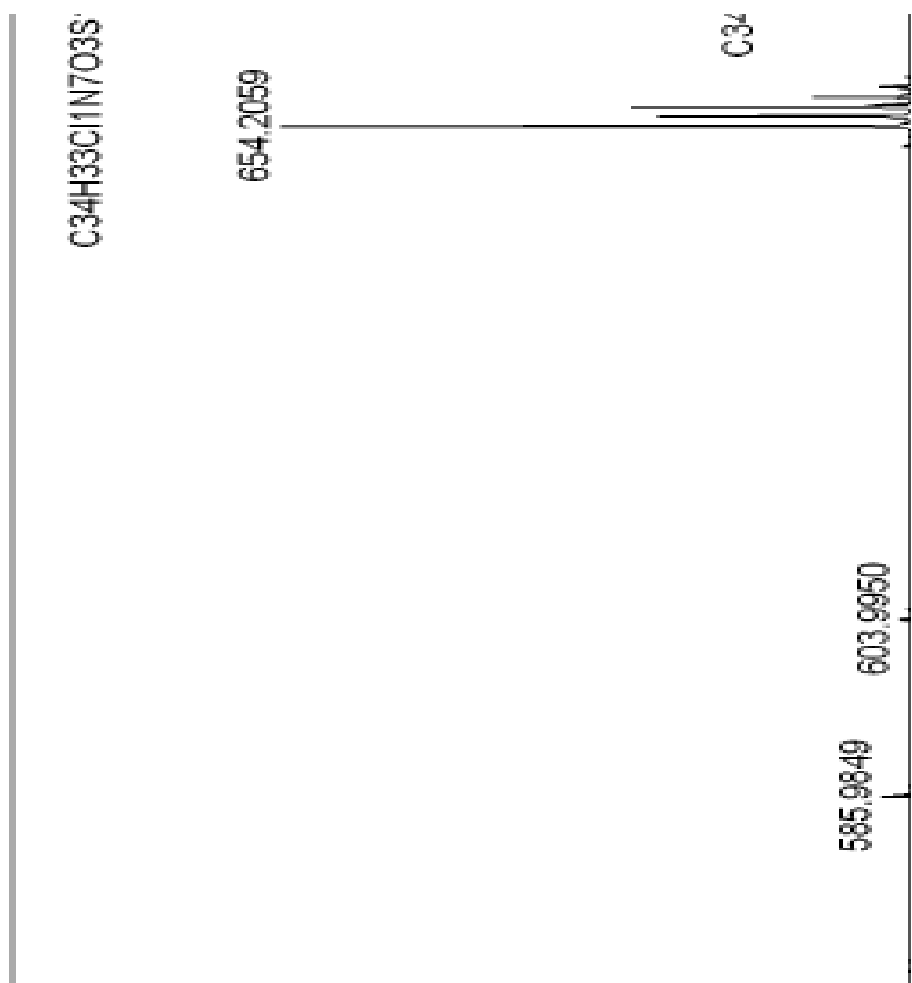


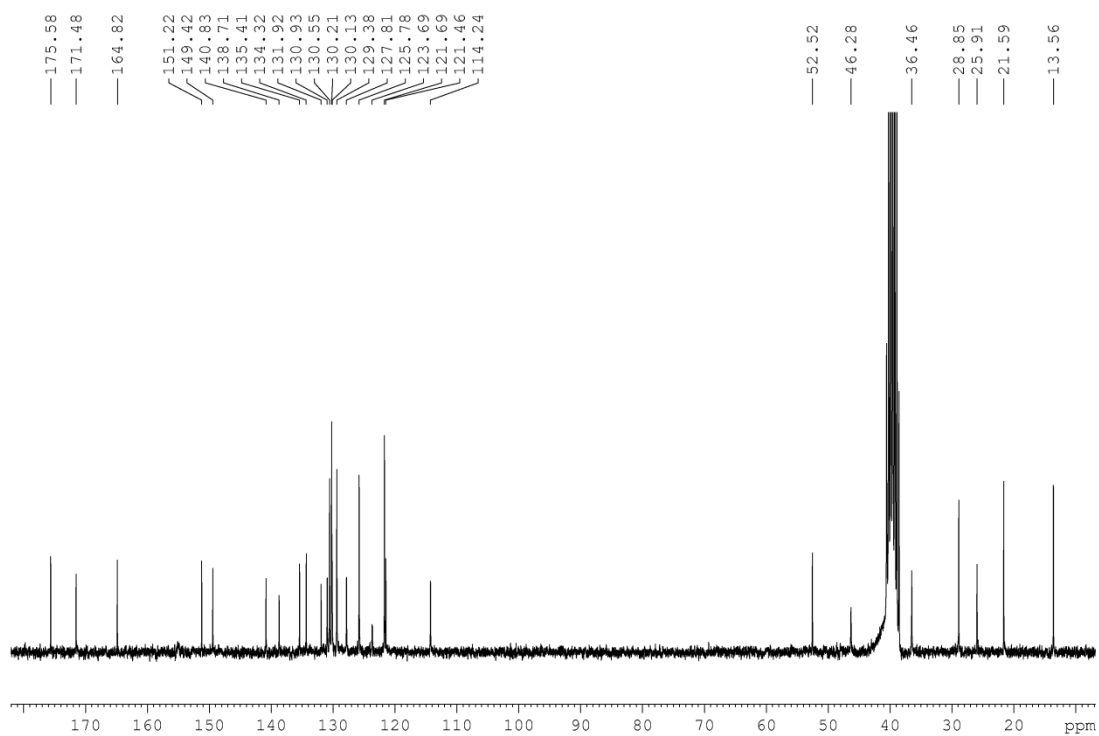
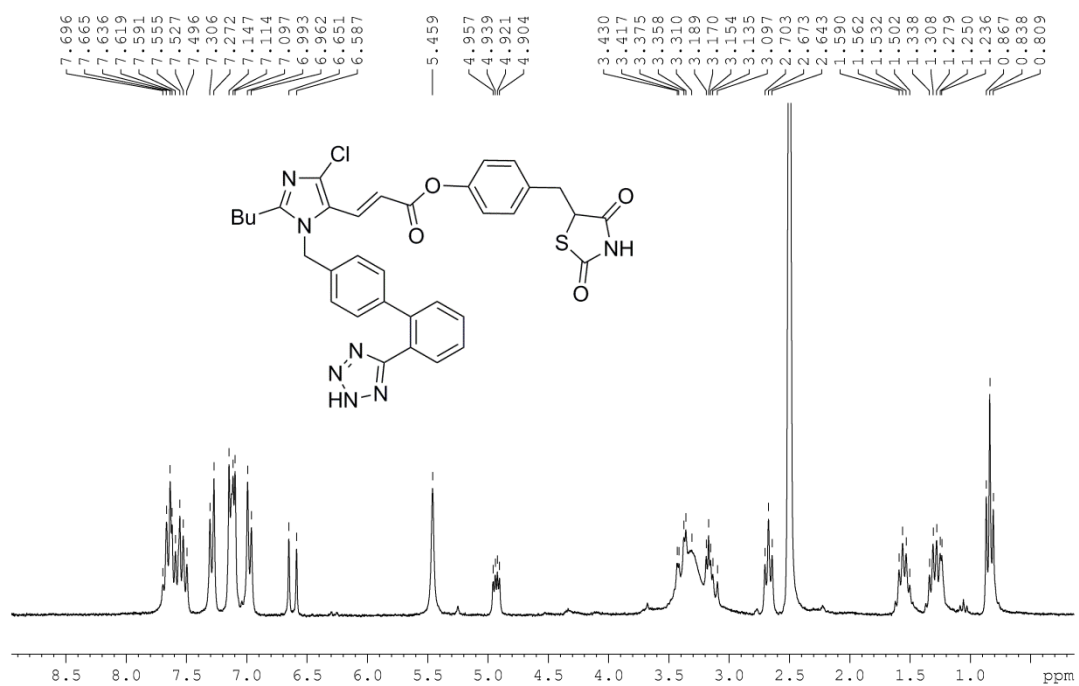


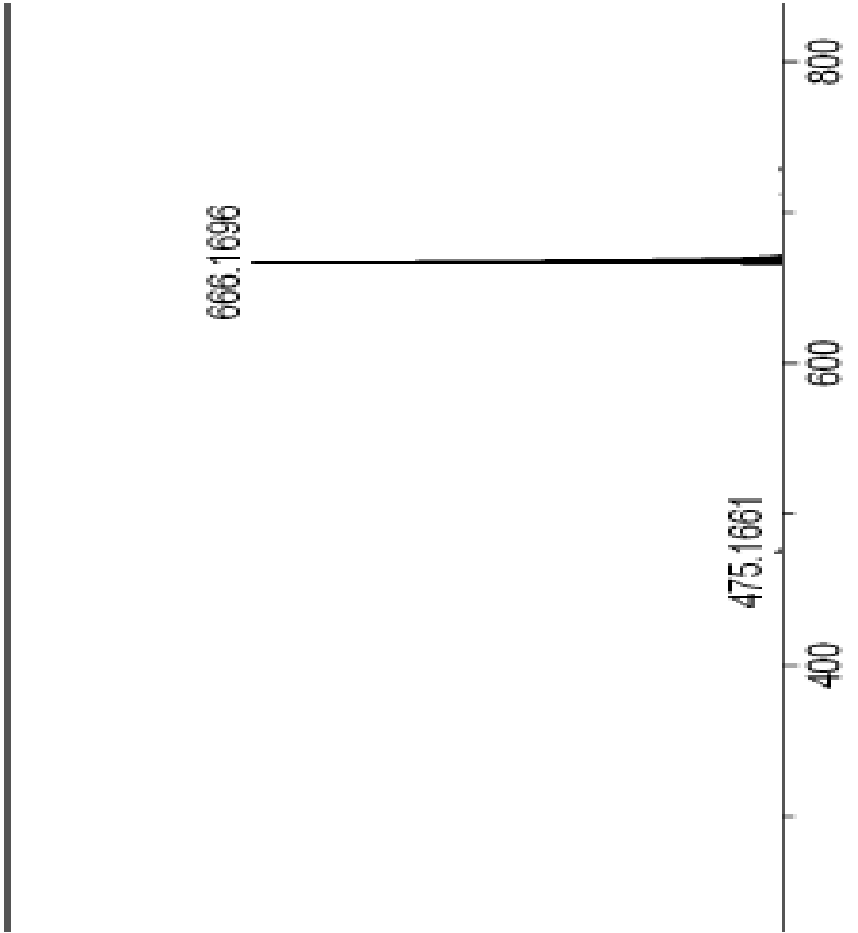
2.4. Compound **18** (D₂O)



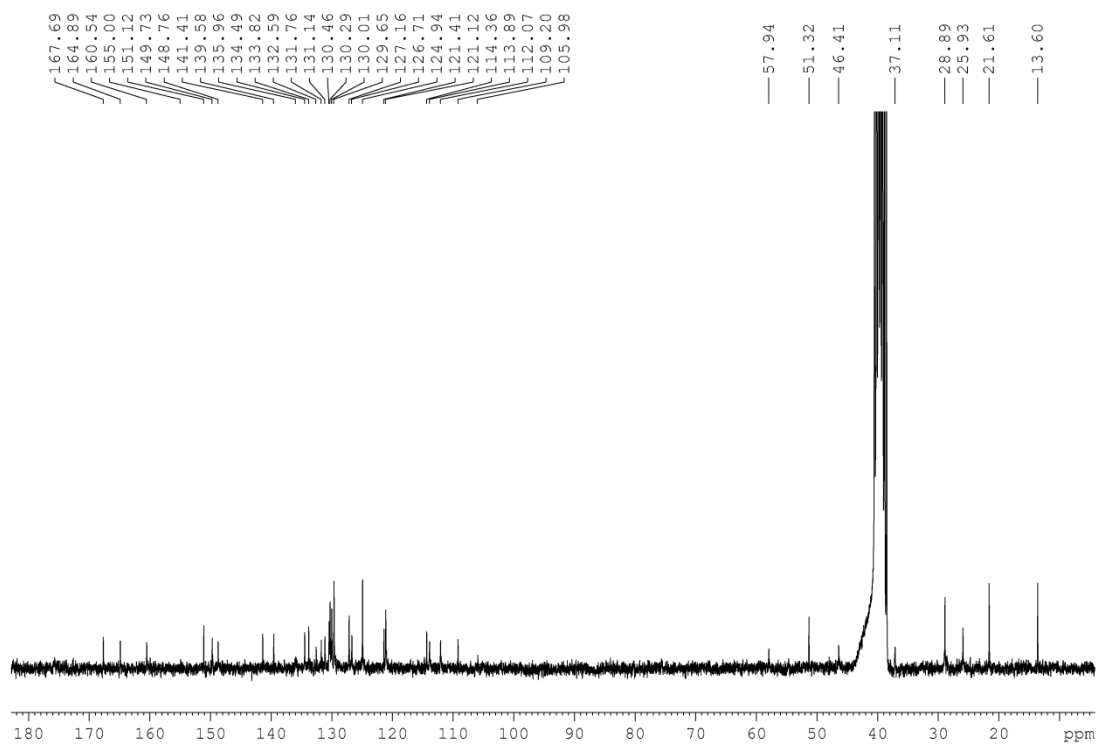
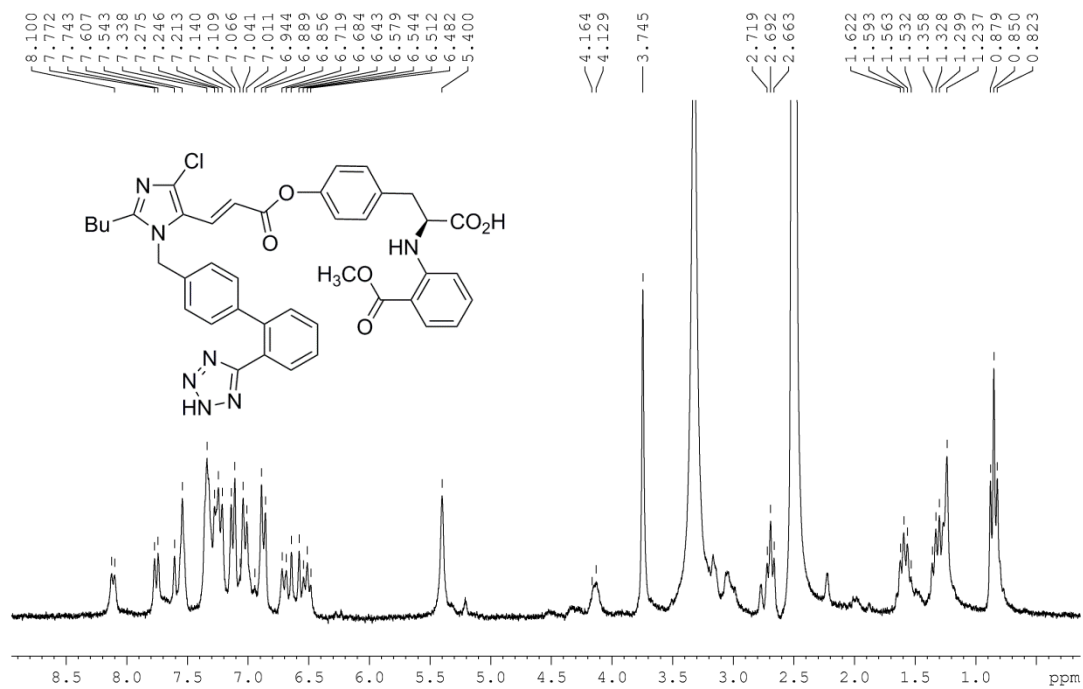
2.5. Compound **22** (DMSO-*d*₆)







2.6. Compound **25** (DMSO-*d*₆)



C41H37Cl1N7O6

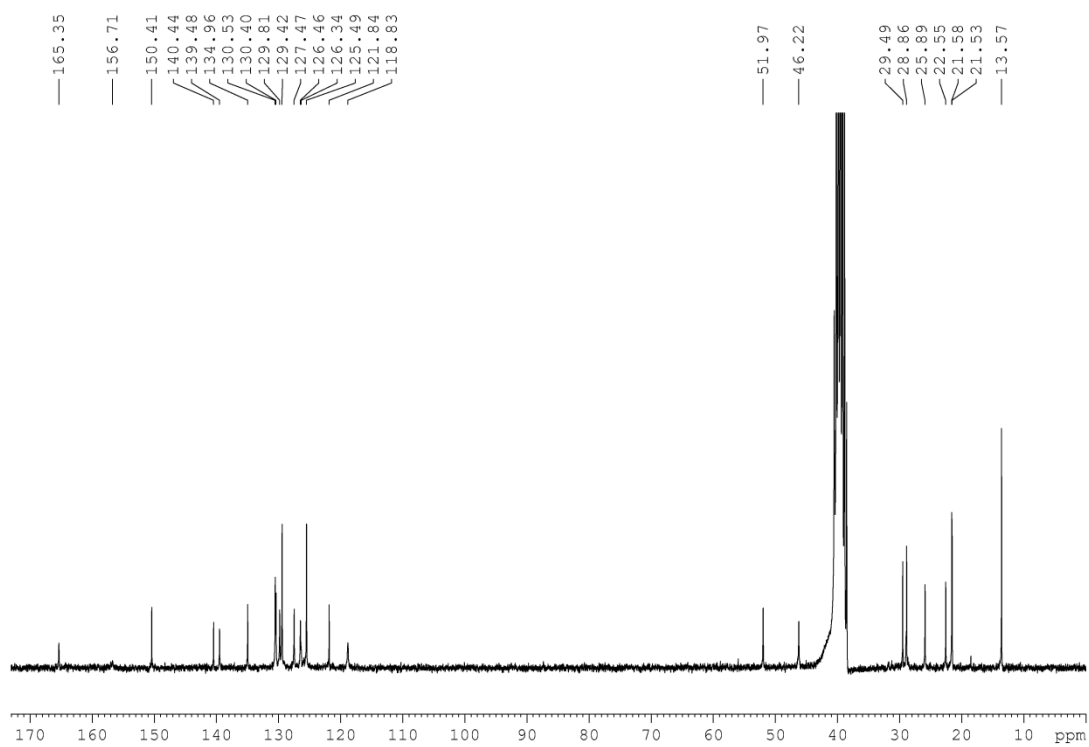
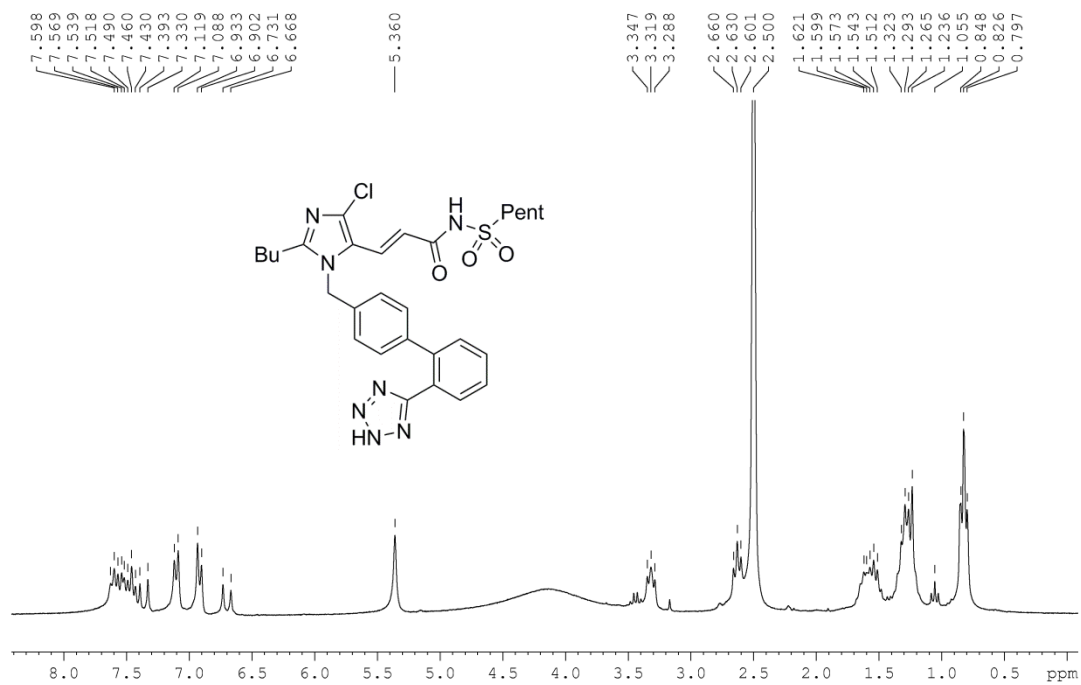
758.2518

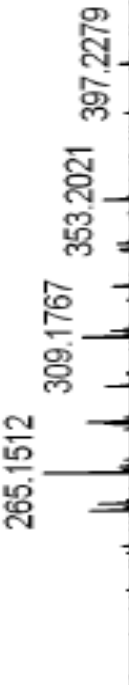
x5

772.2466

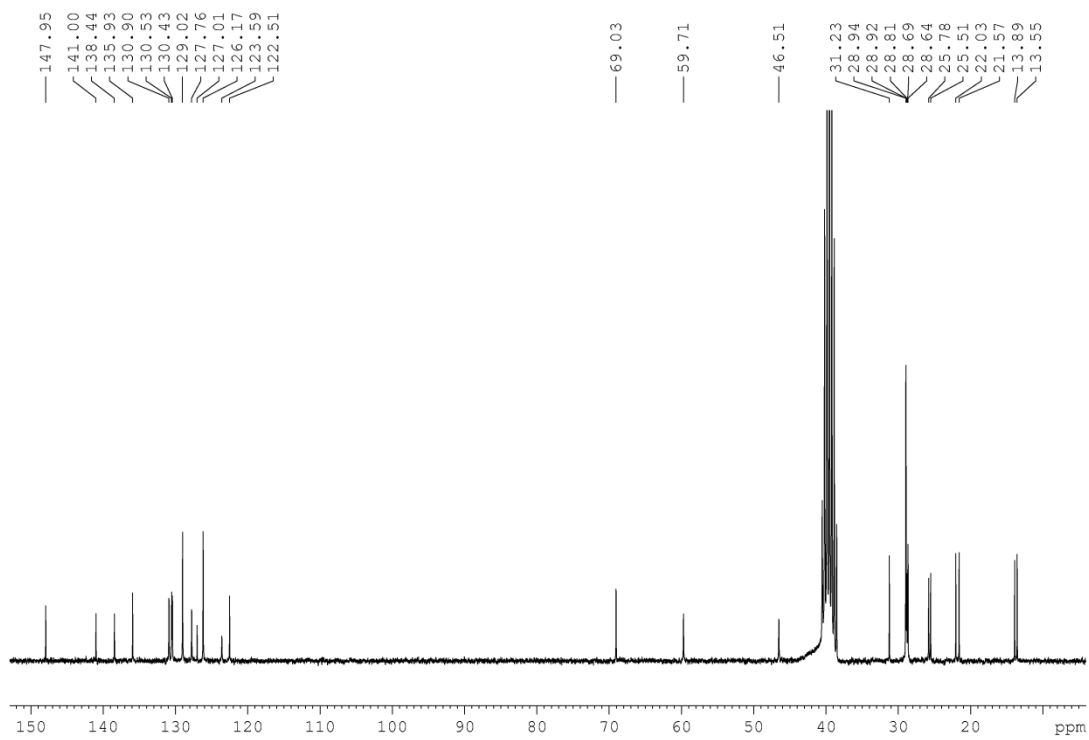
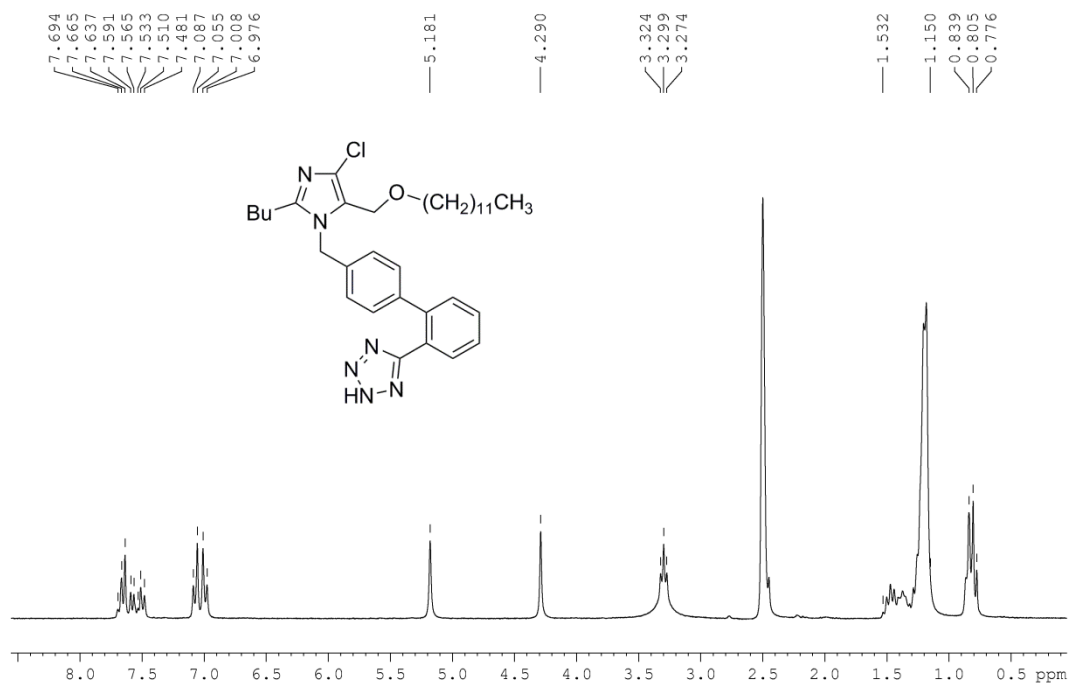
750 755 760 765 770 775

2.7. Compound **27** (DMSO-*d*₆)



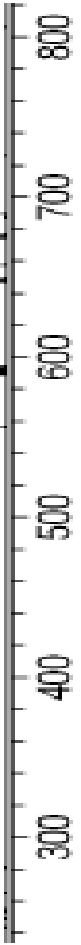


2.8. Compound **29** (DMSO-*d*₆)

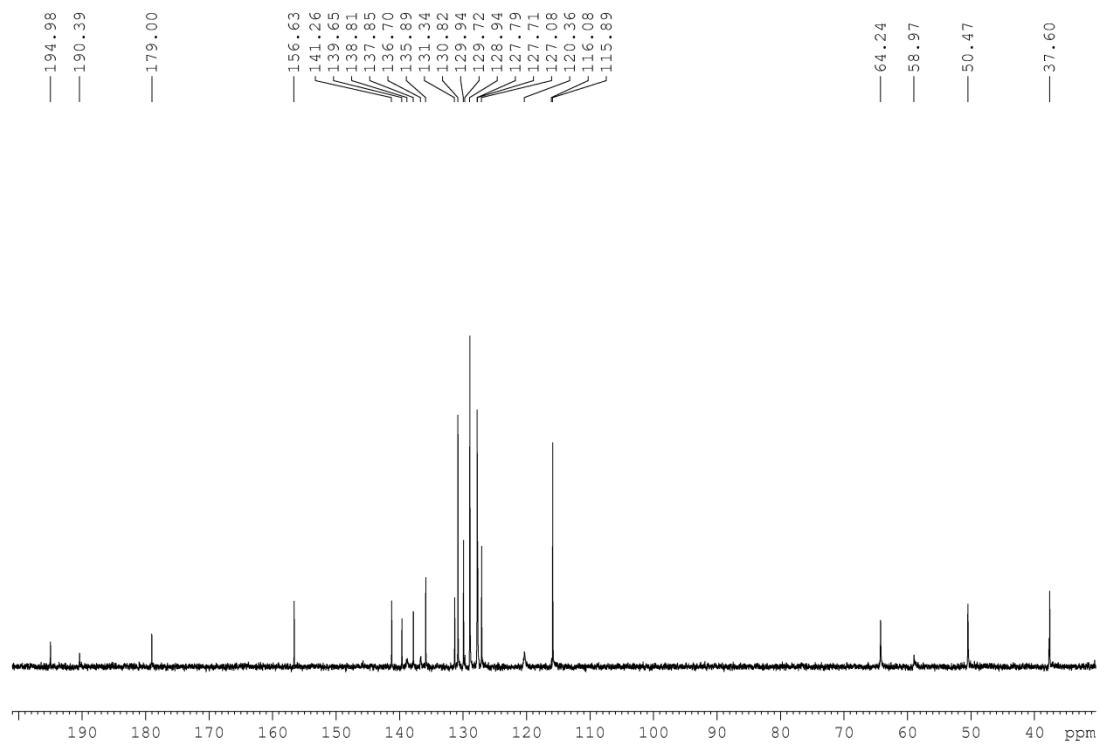
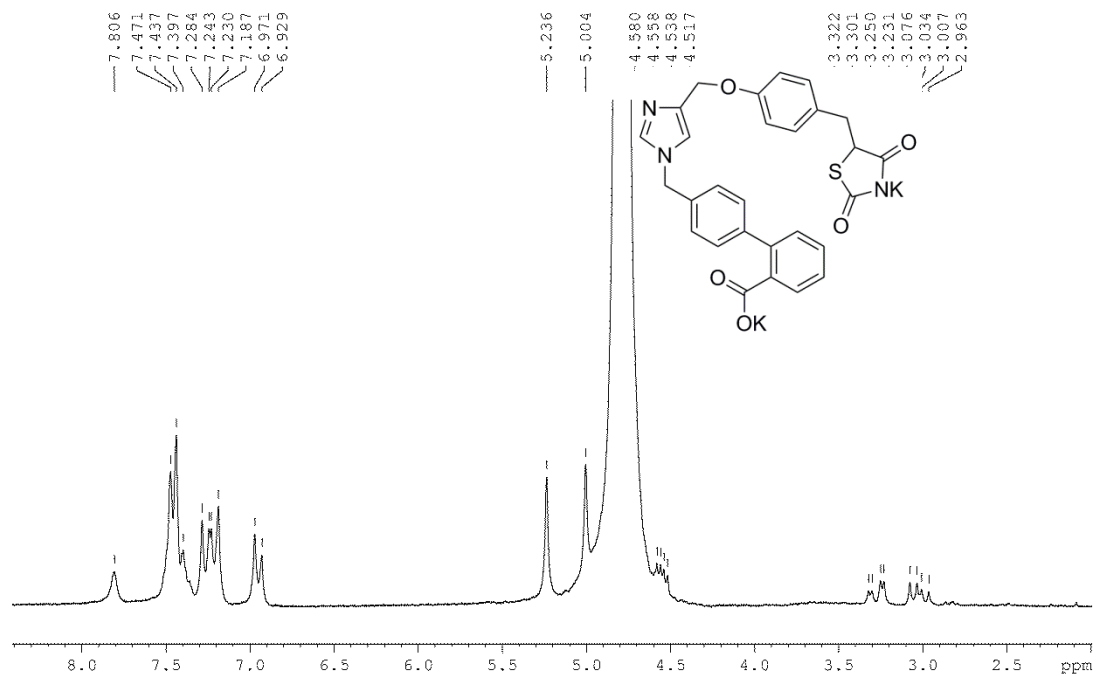


589.3445

674.3219



2.9. Compound **32** (D₂O)



C32H27Cl1N7O3S1

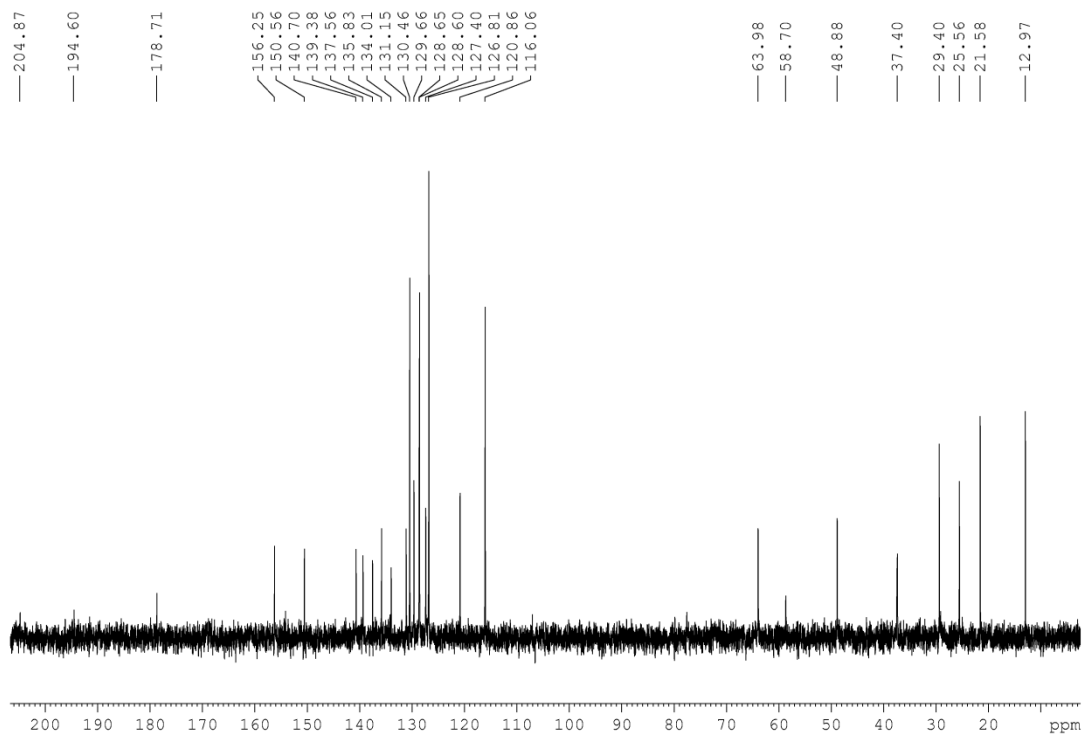
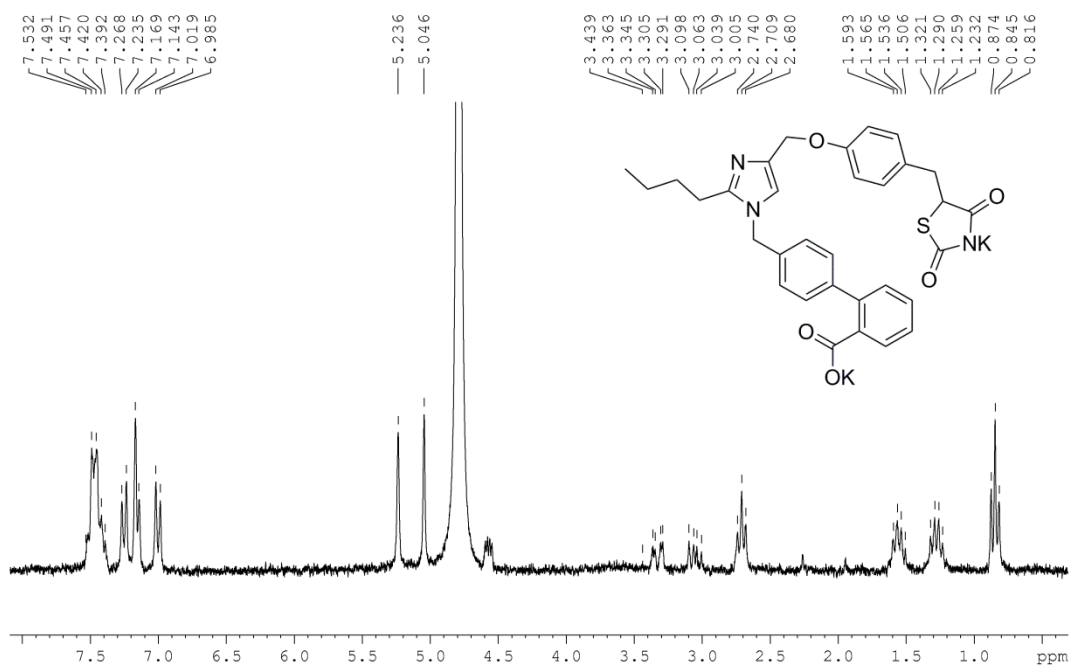
624.1587



C32H26Cl1N7Na1O3S1
646.1404



2.10. Compound **33** (D₂O)



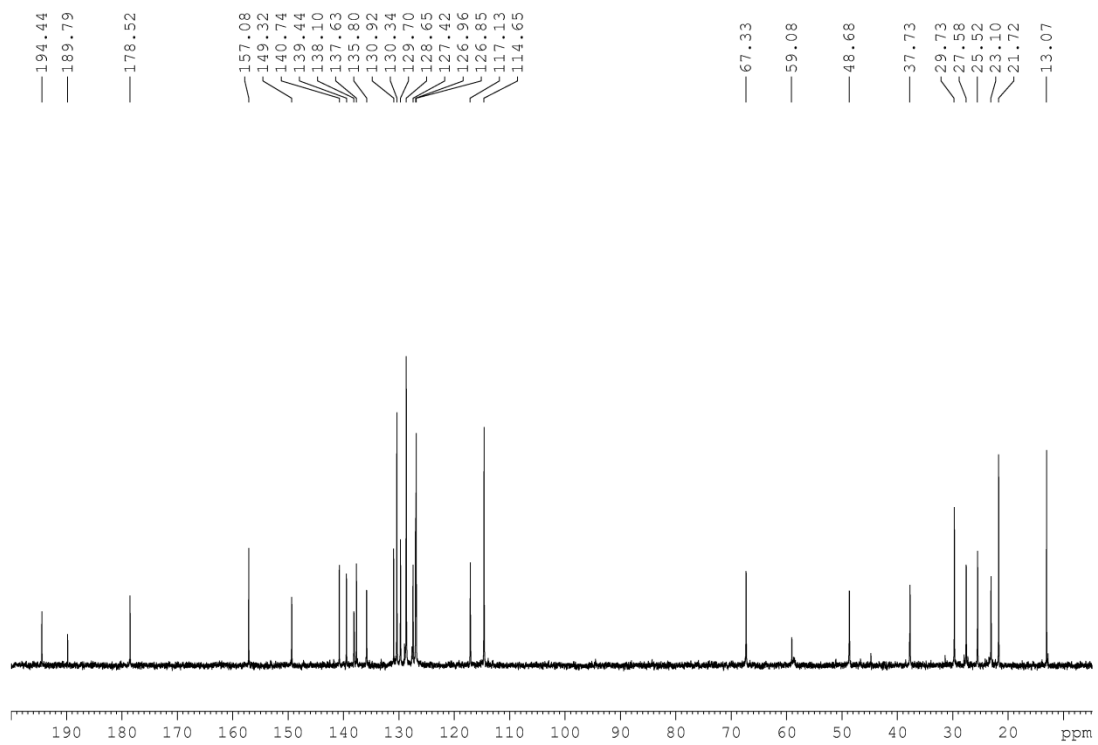
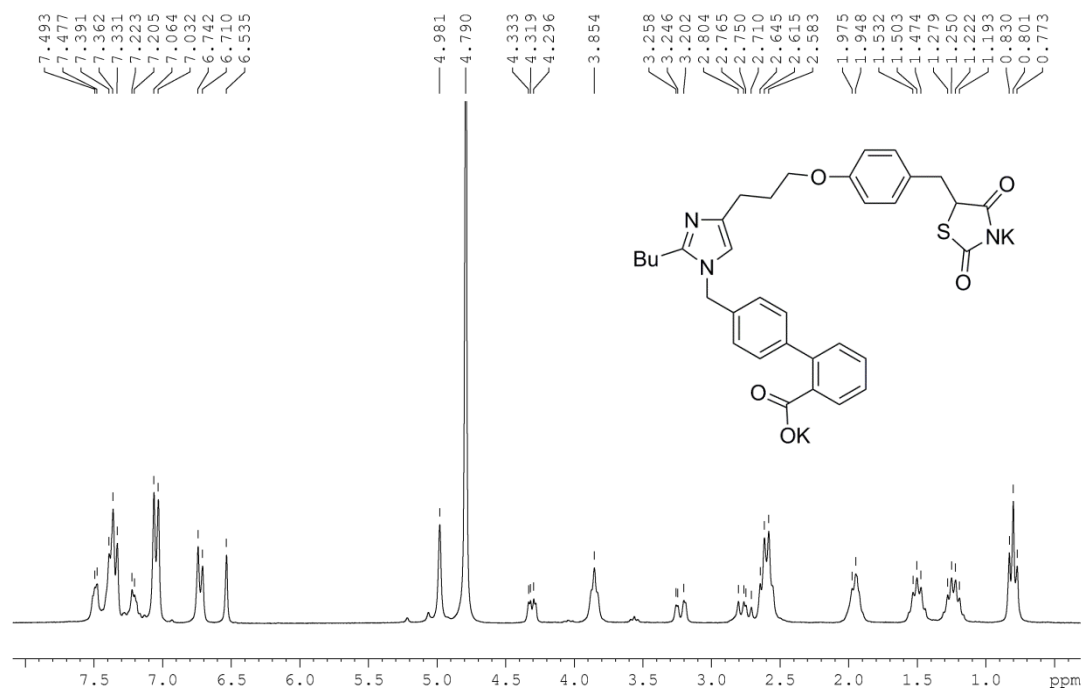
C32H30N3O5S1

568.1908

C32H29N3Na1O5S1
590.1740

C32H28N3K1O5S1
606.1690

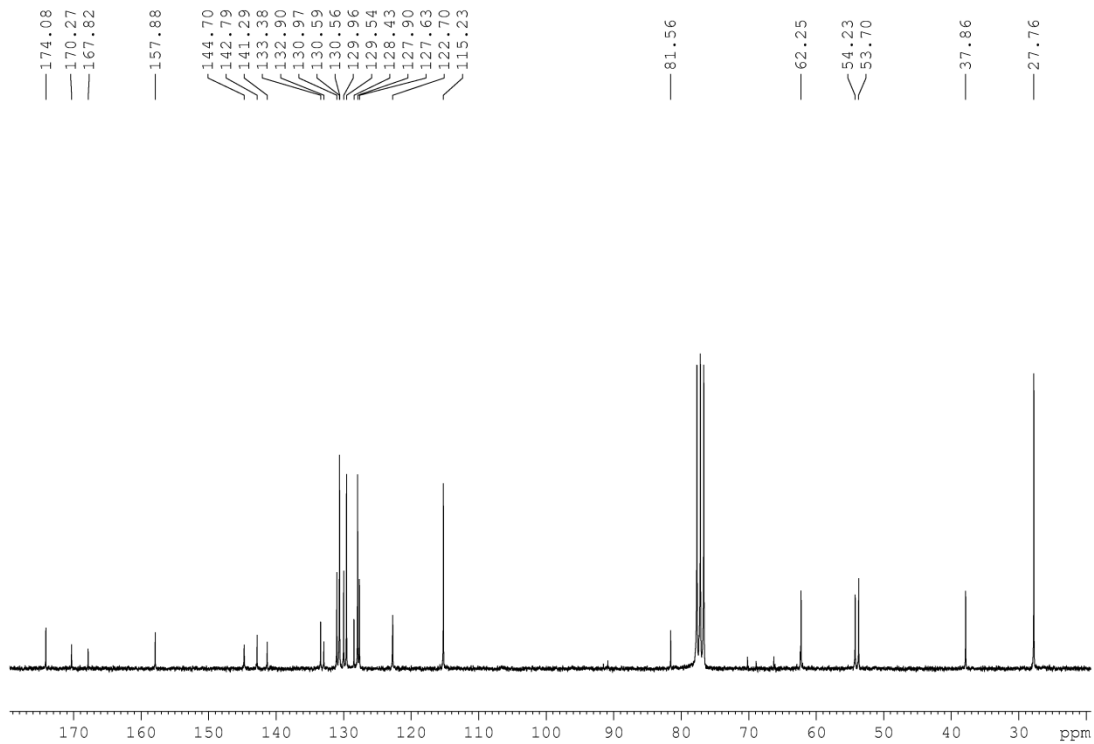
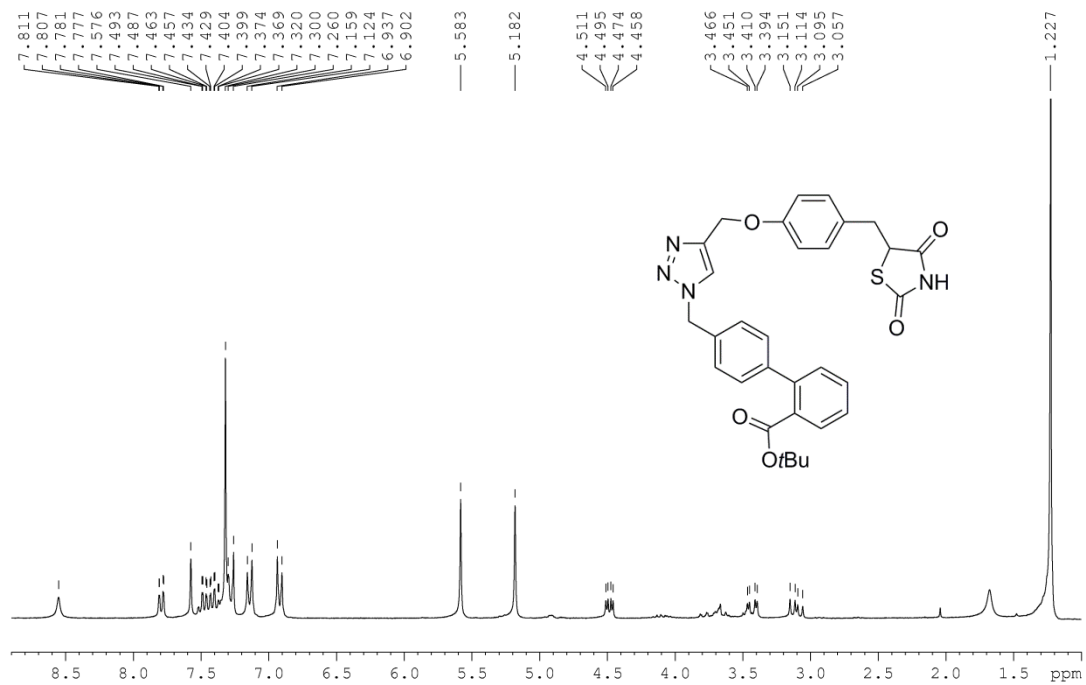
2.11. Compound **39** (D₂O)

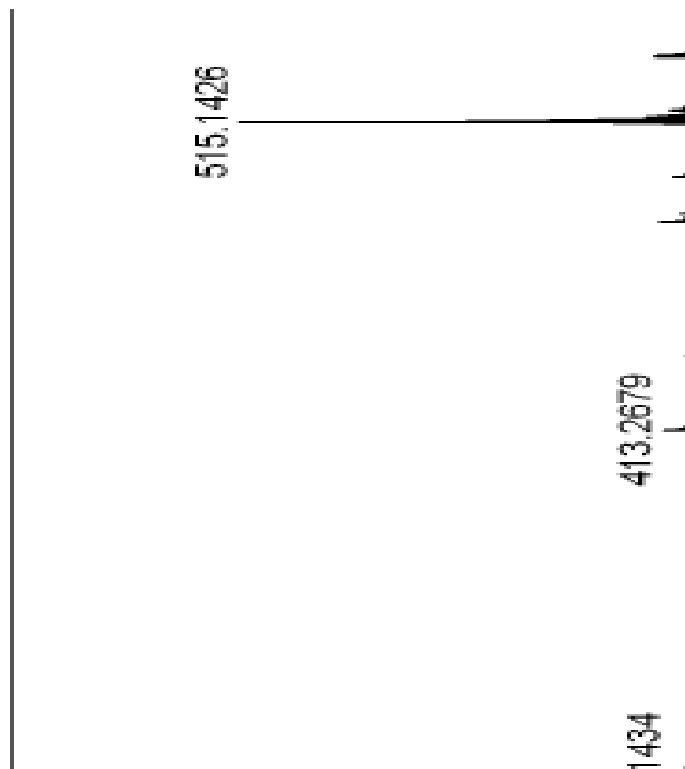


C34H33N3N_a105S1
618.2059

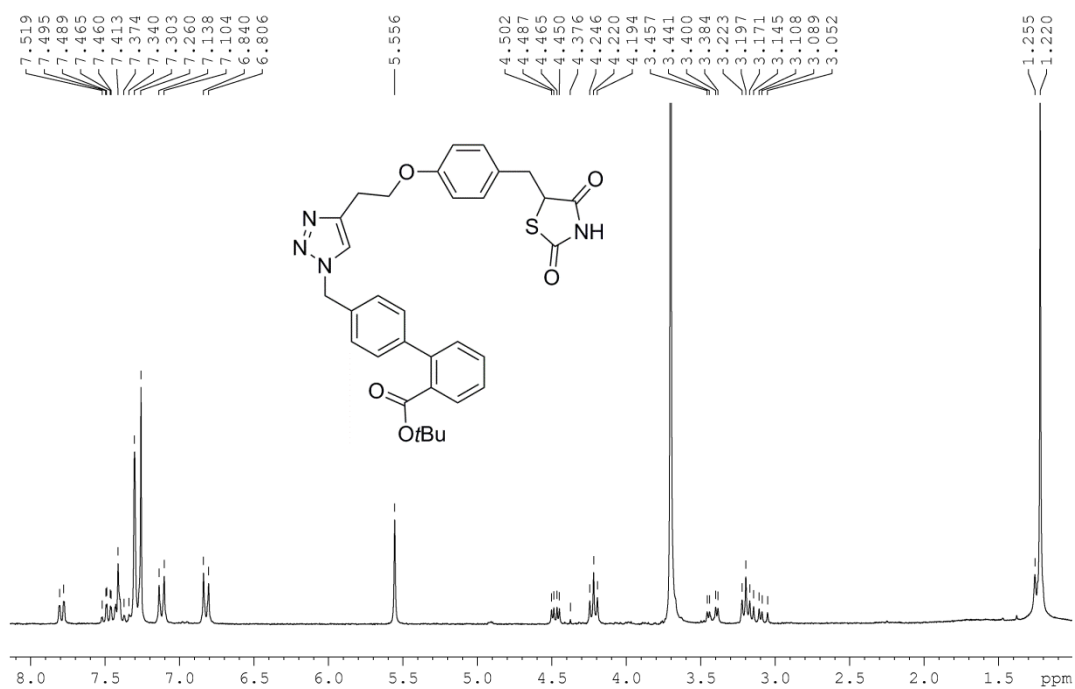
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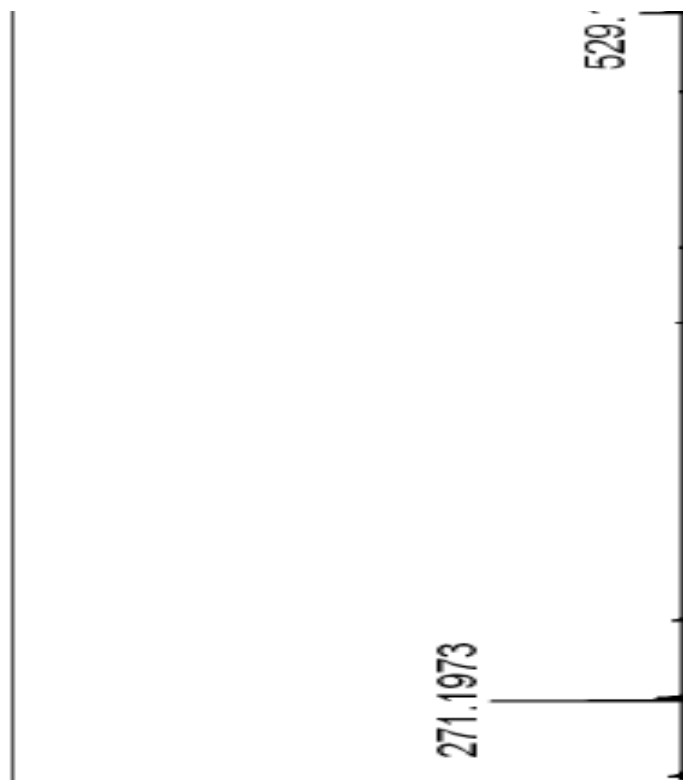
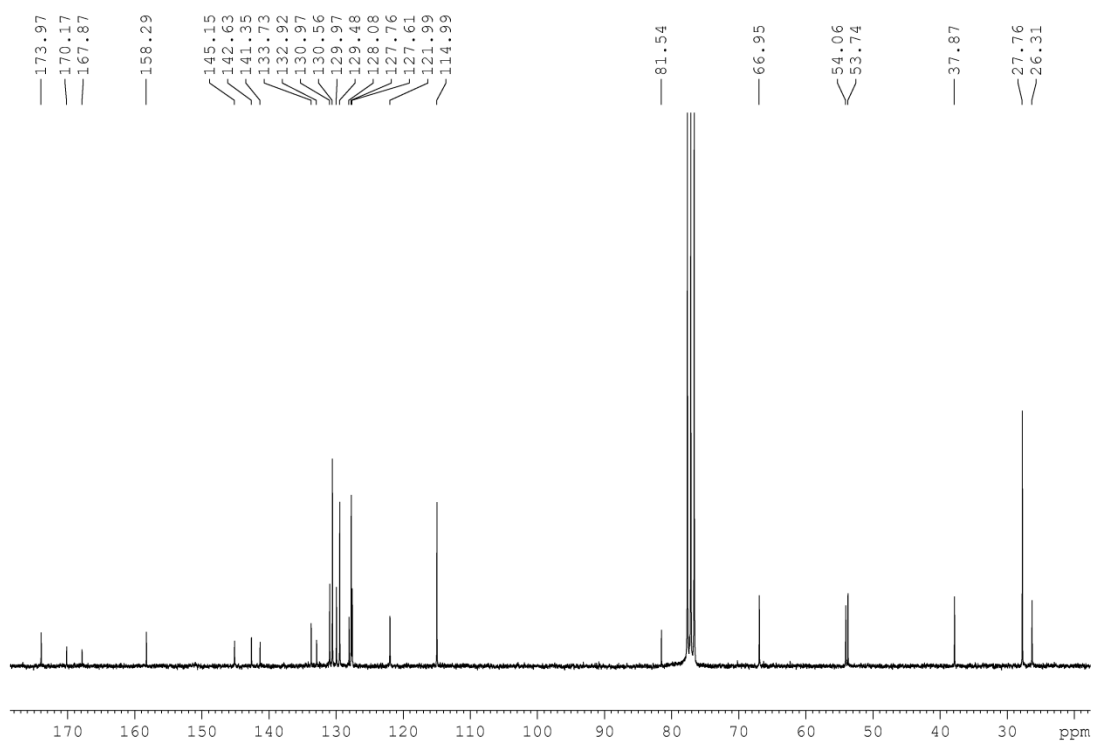
2.12. Compound **42** (CDCl₃)



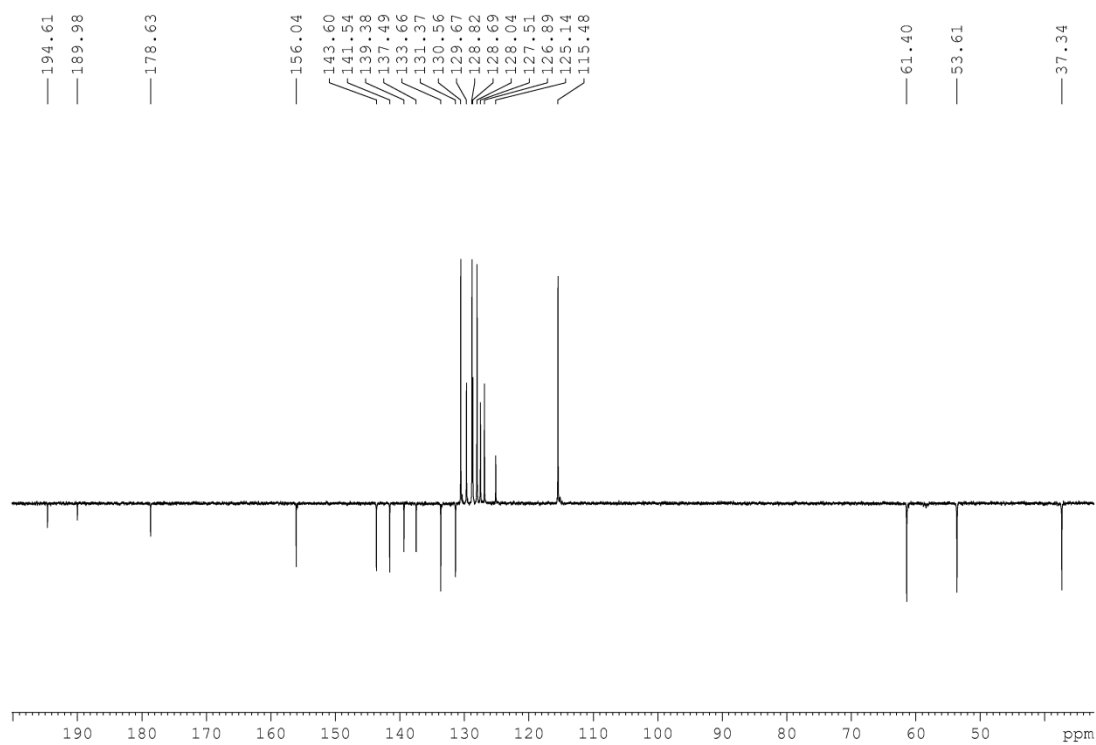
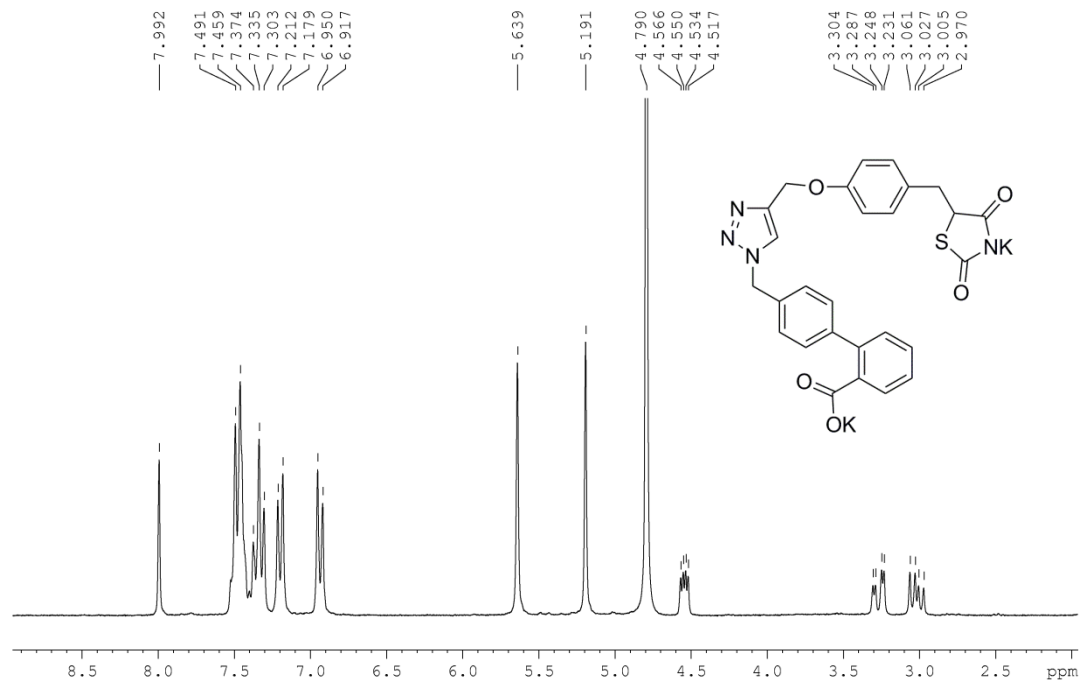


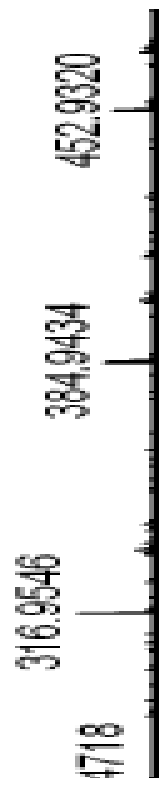
2.13. Compound **43** (CDCl₃)



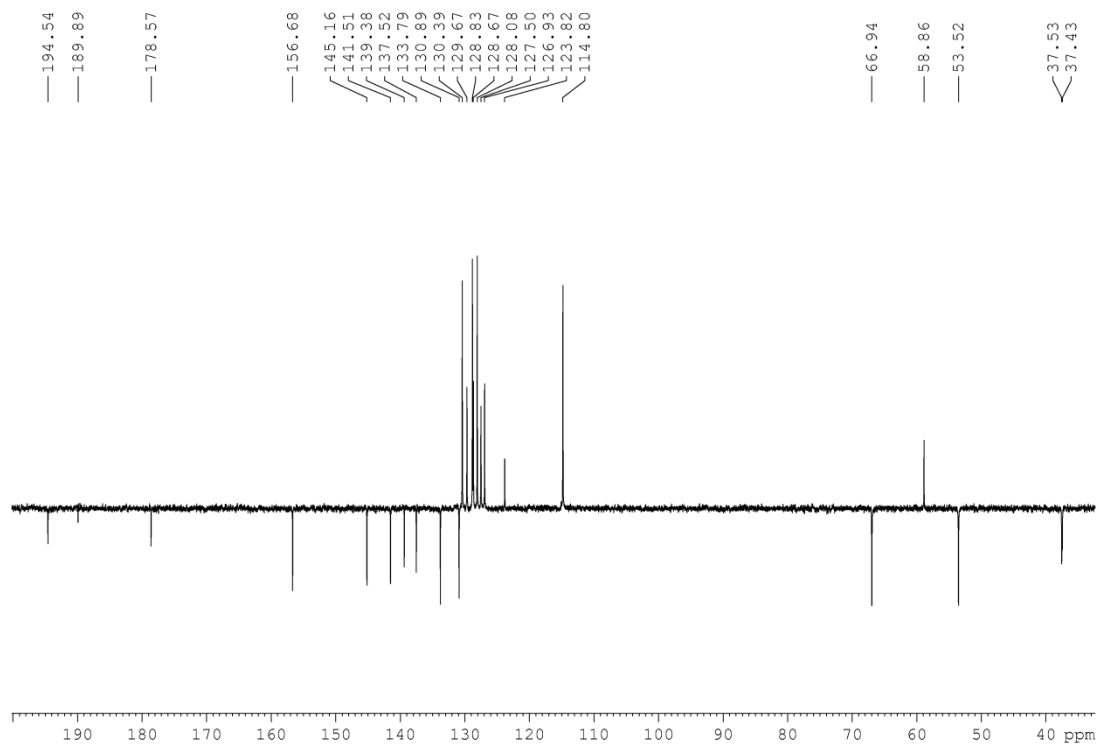
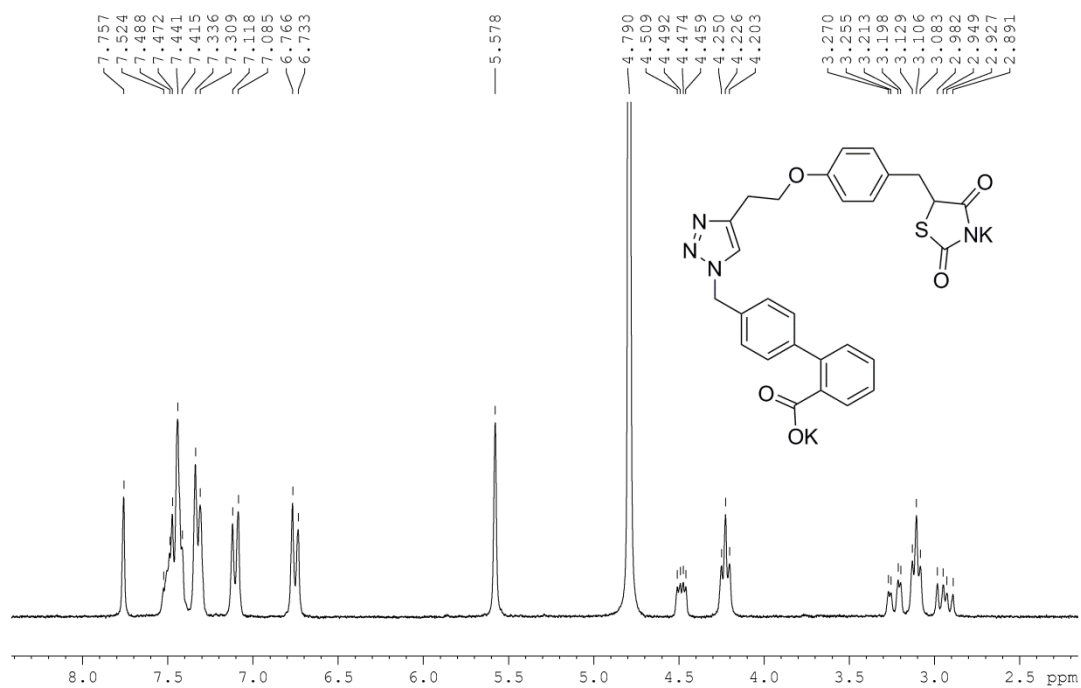


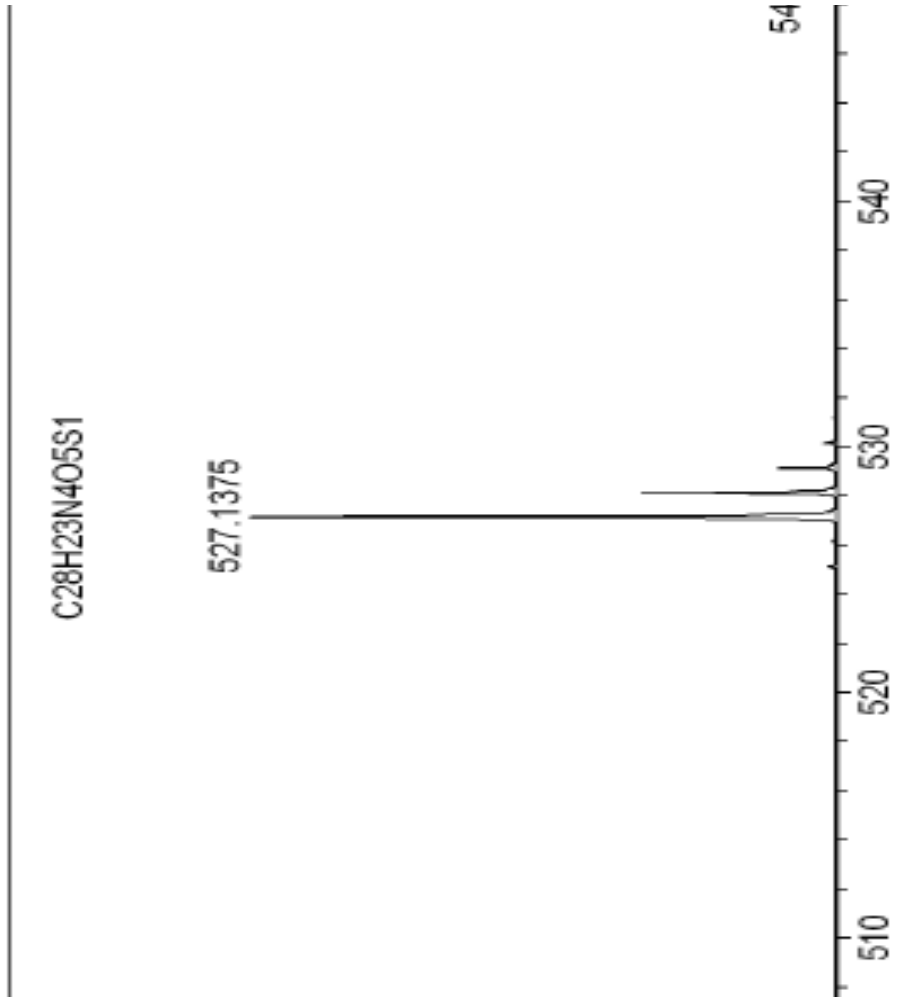
2.14. Compound **44** (D₂O)



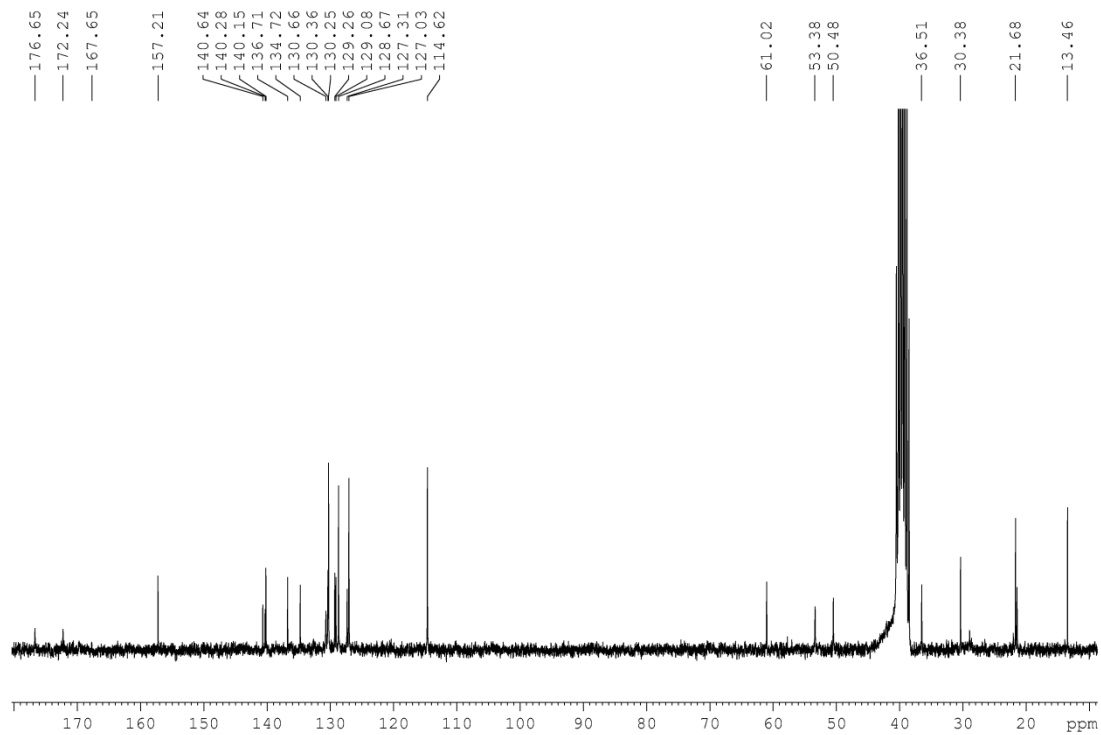
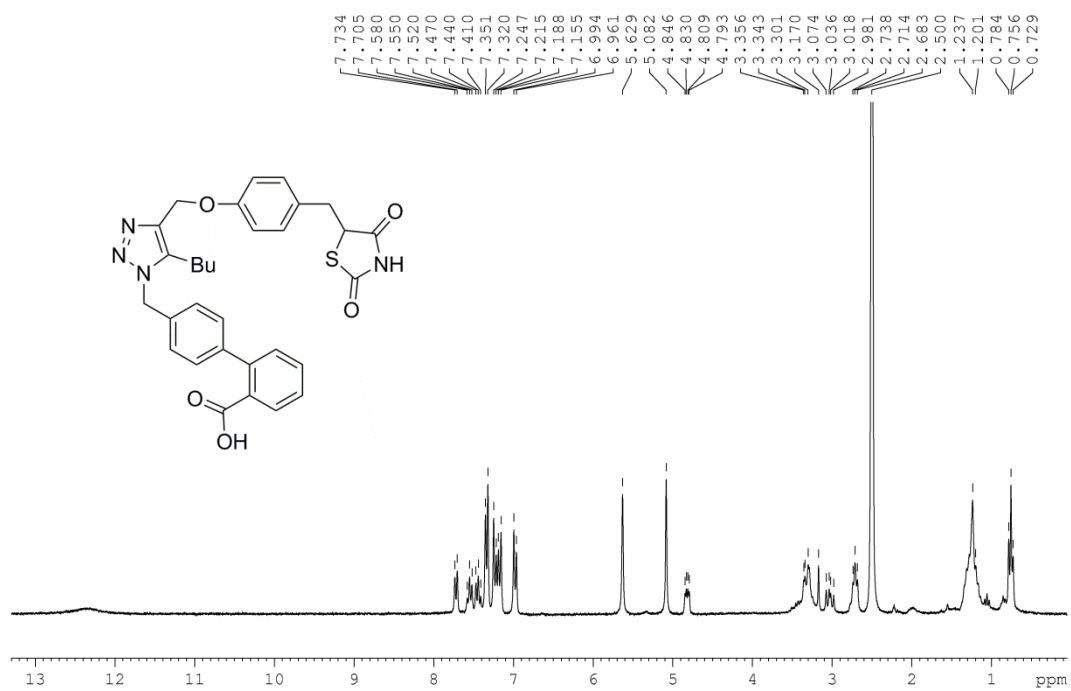


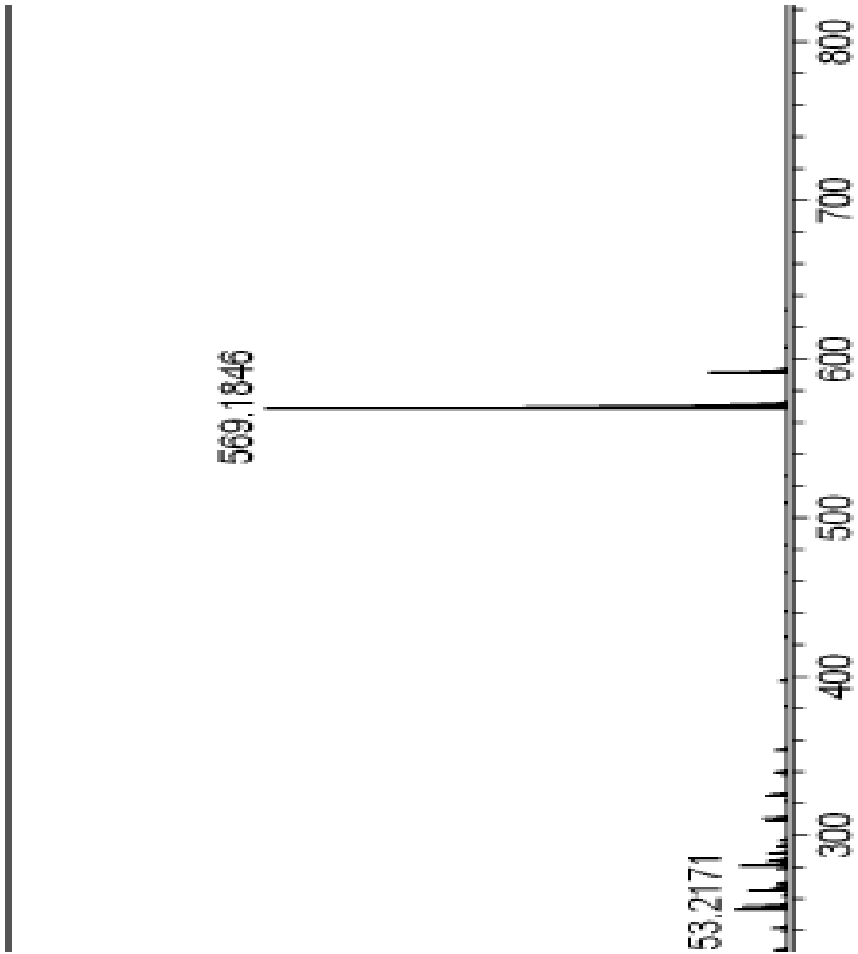
2.15. Compound **45** (D₂O)



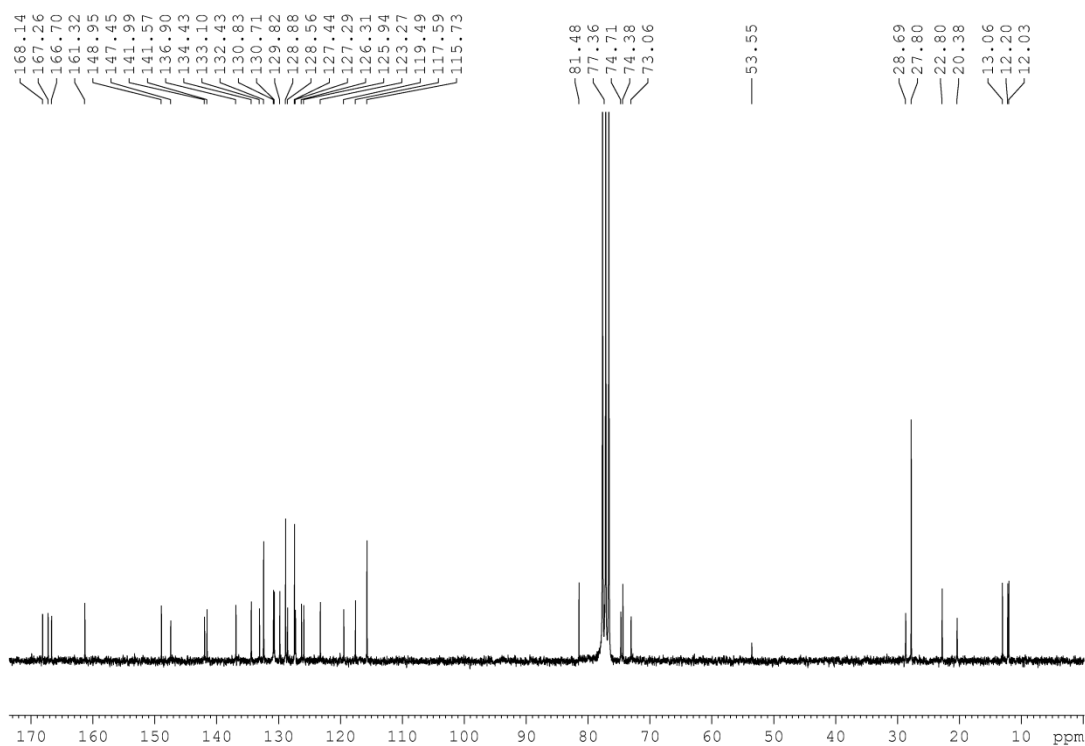
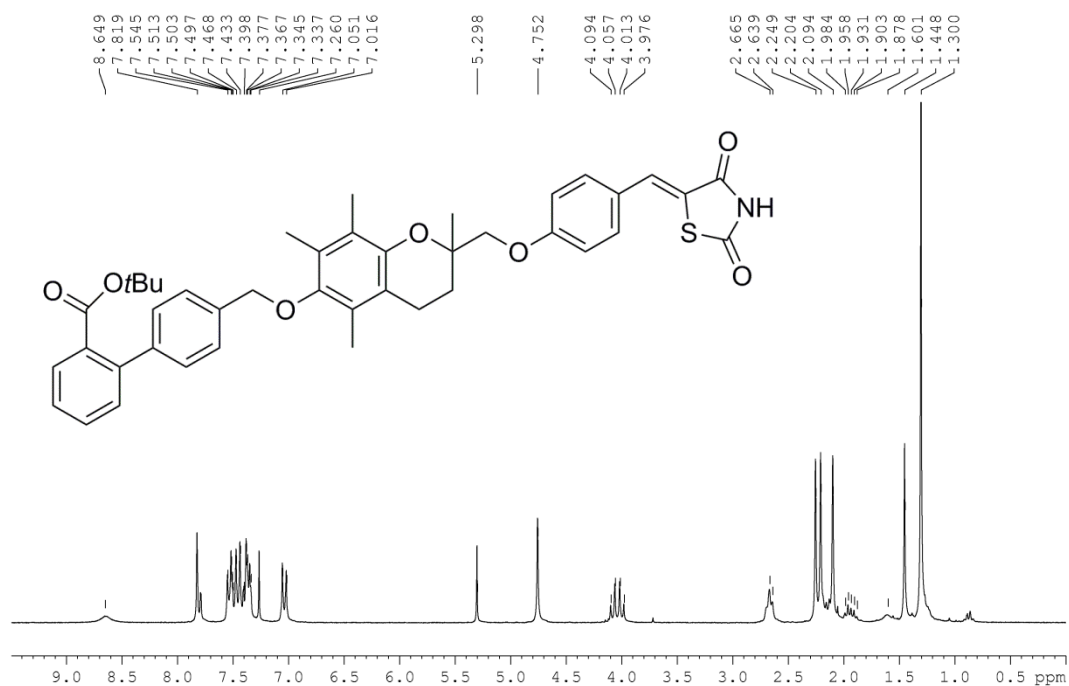


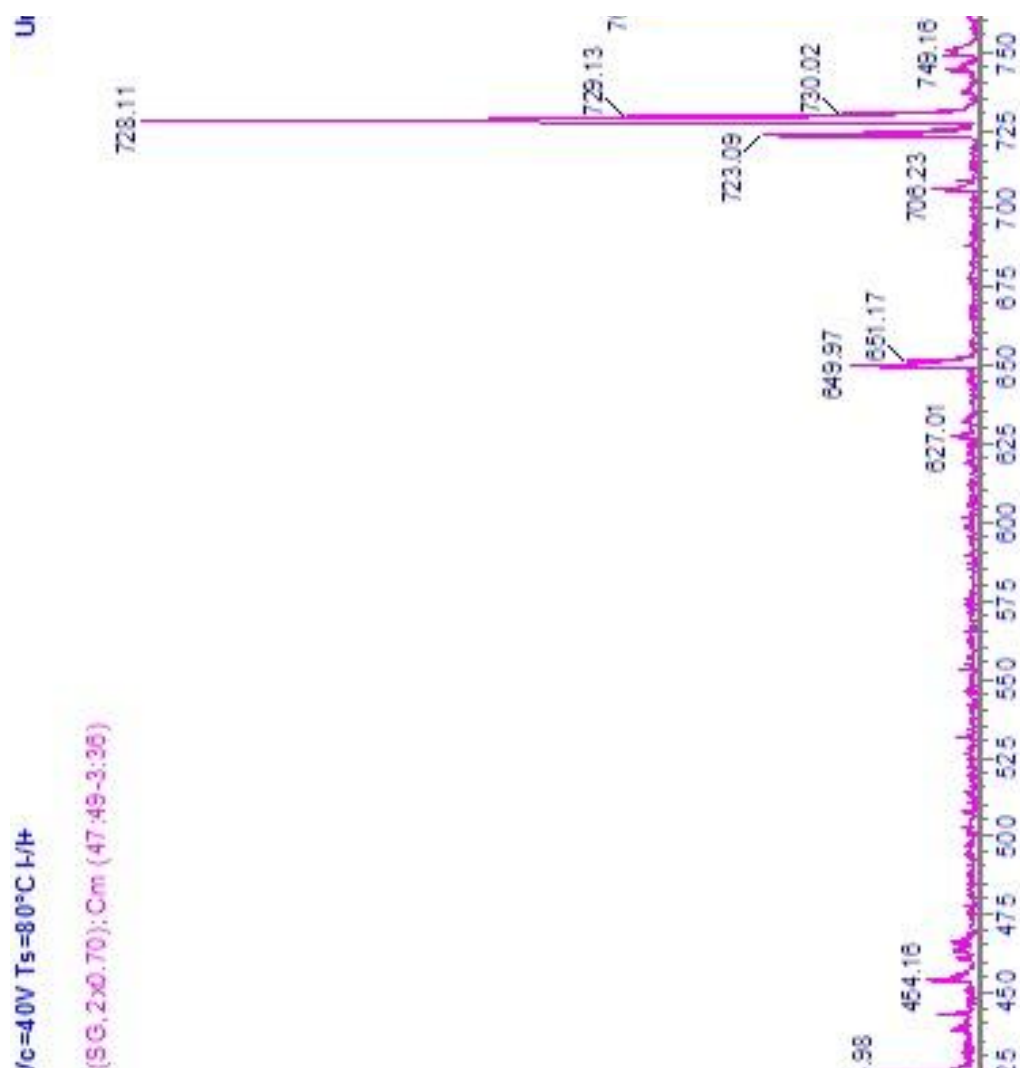
2.16. Compound **50** (DMSO-*d*₆)



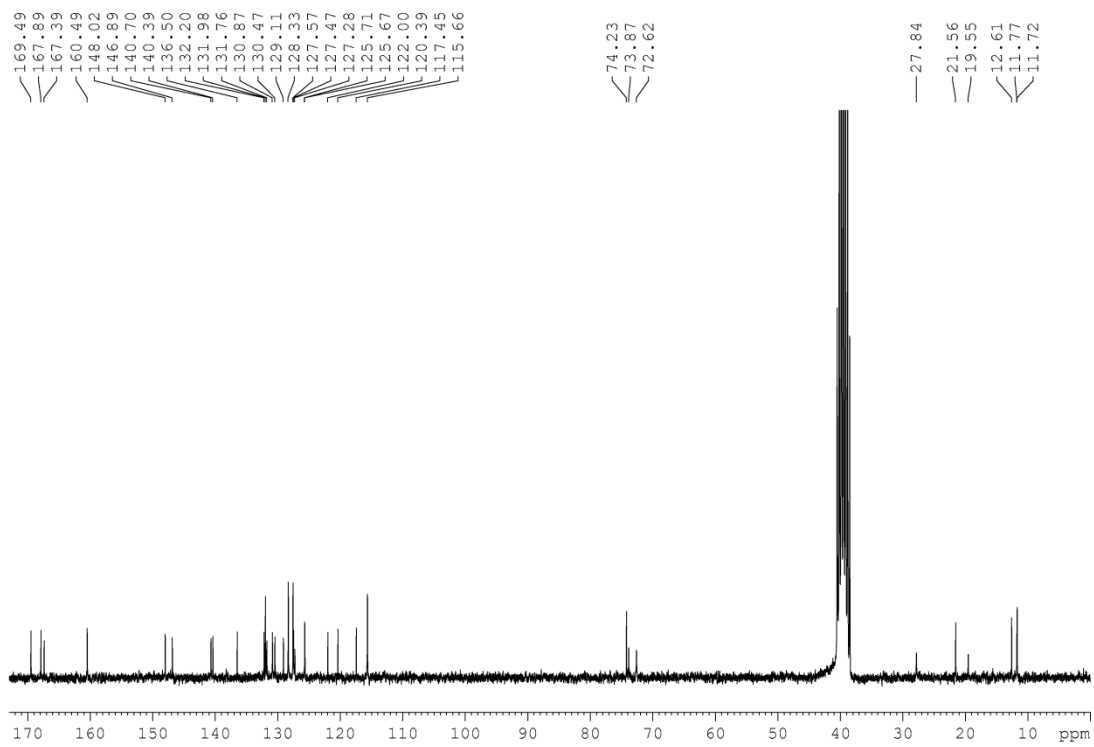
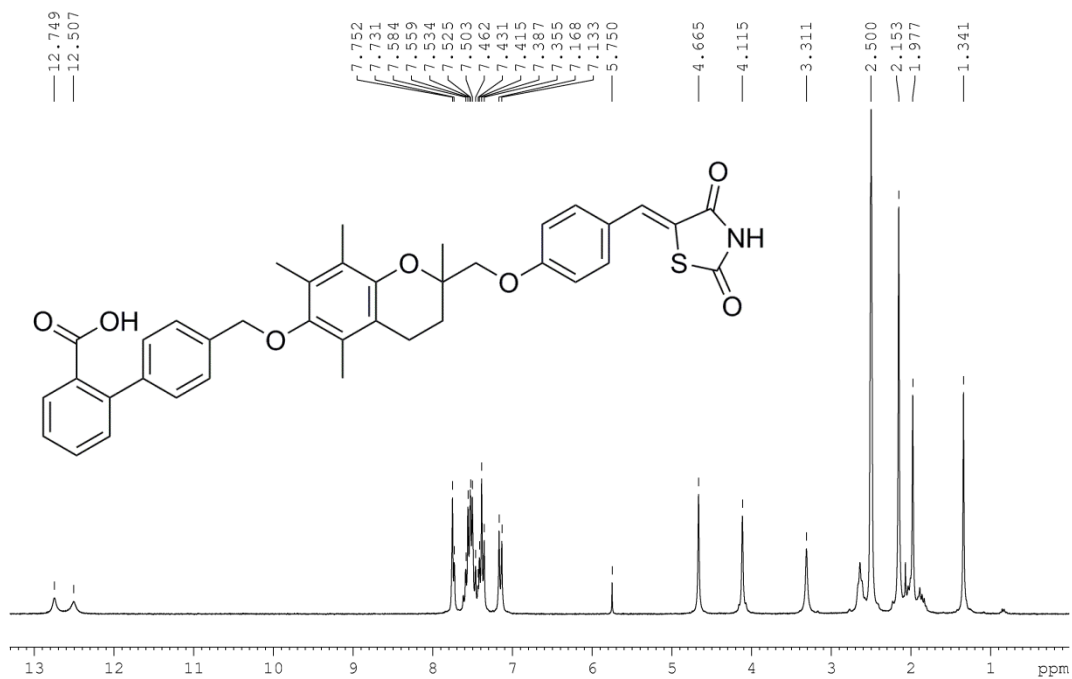


2.17. Compound **51** (CDCl₃)

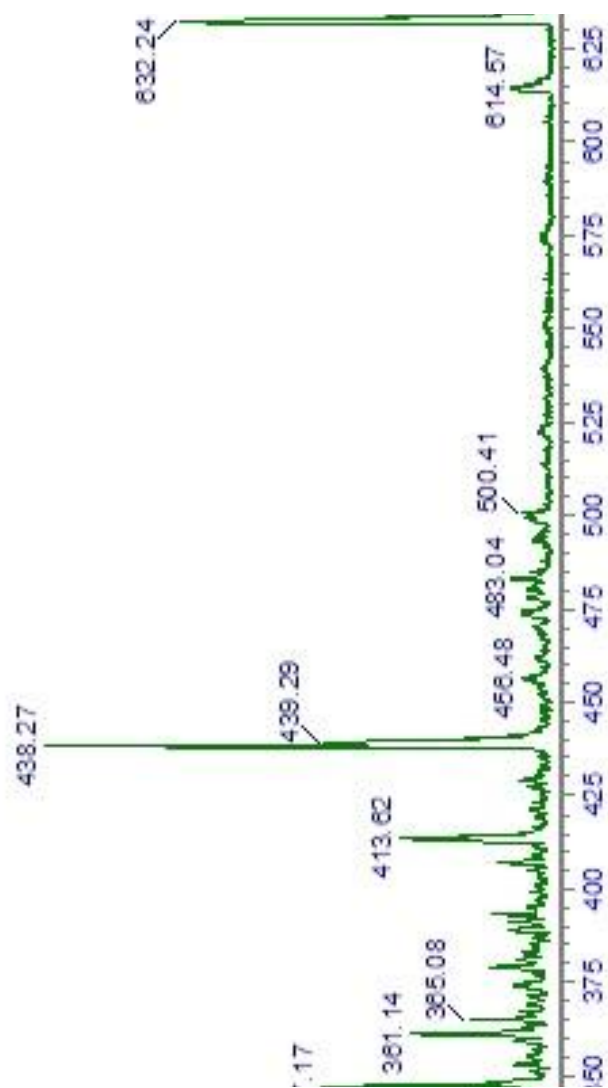




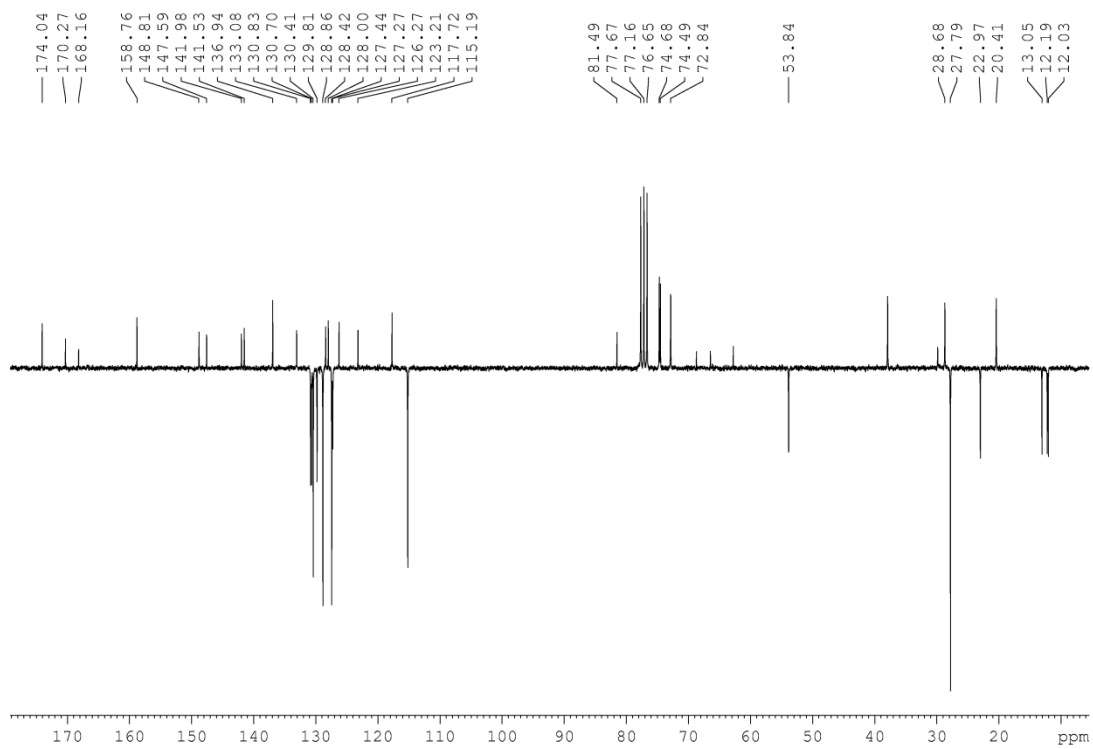
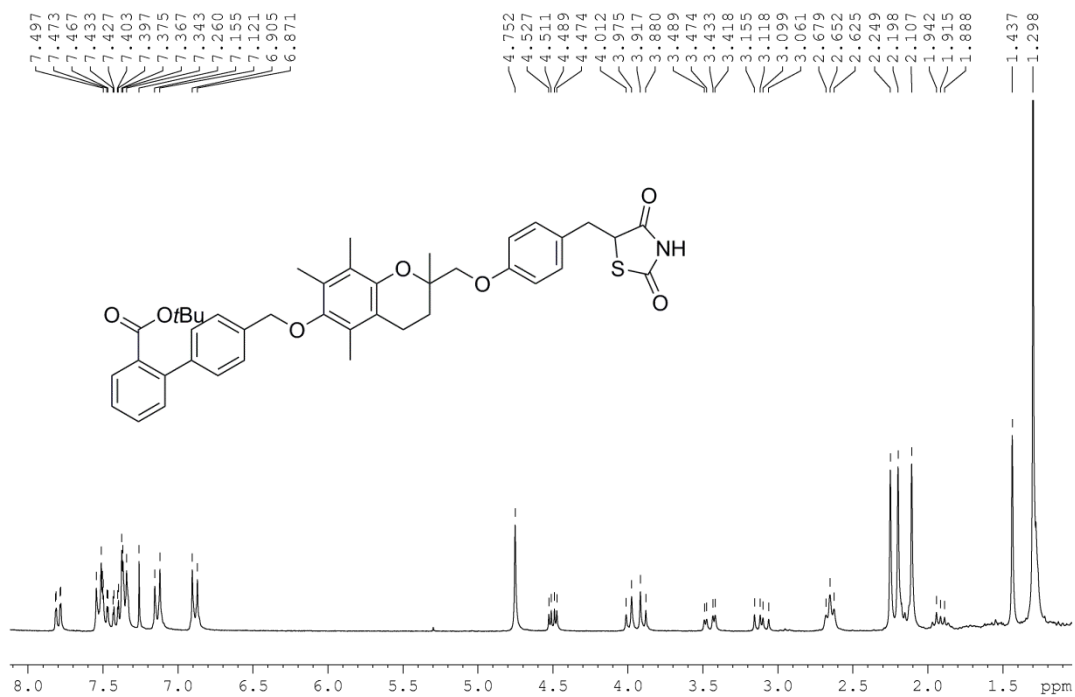
2.18. Compound **52** (DMSO- d_6)

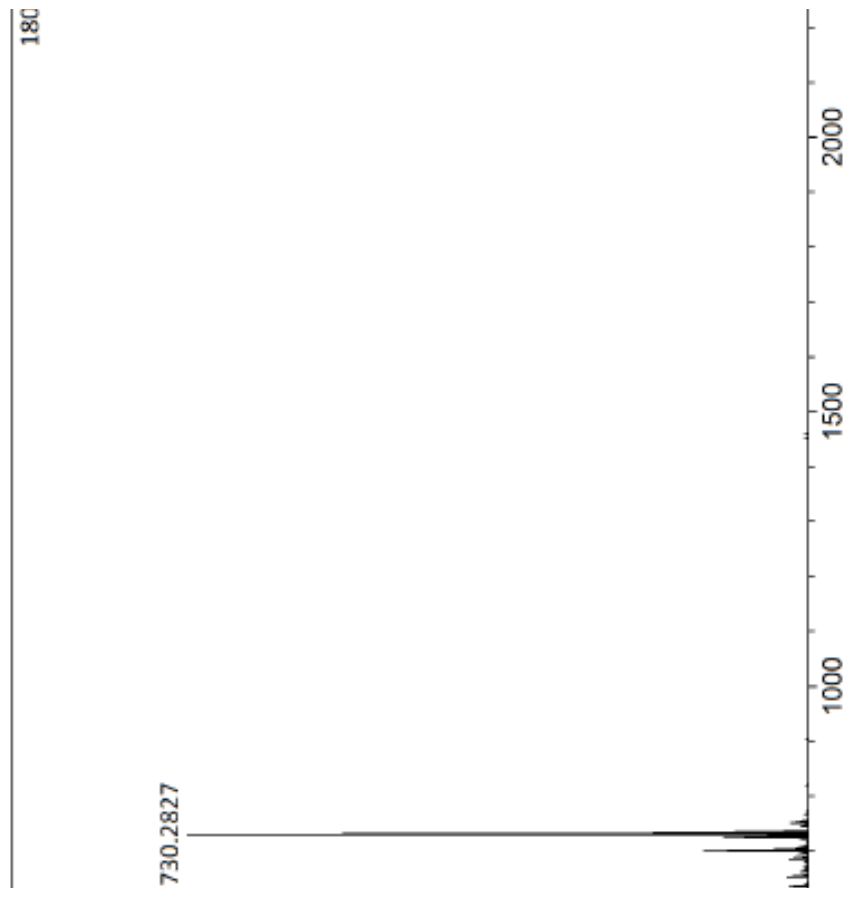


OH Vc=40V Ts=80°C
m (130:193)

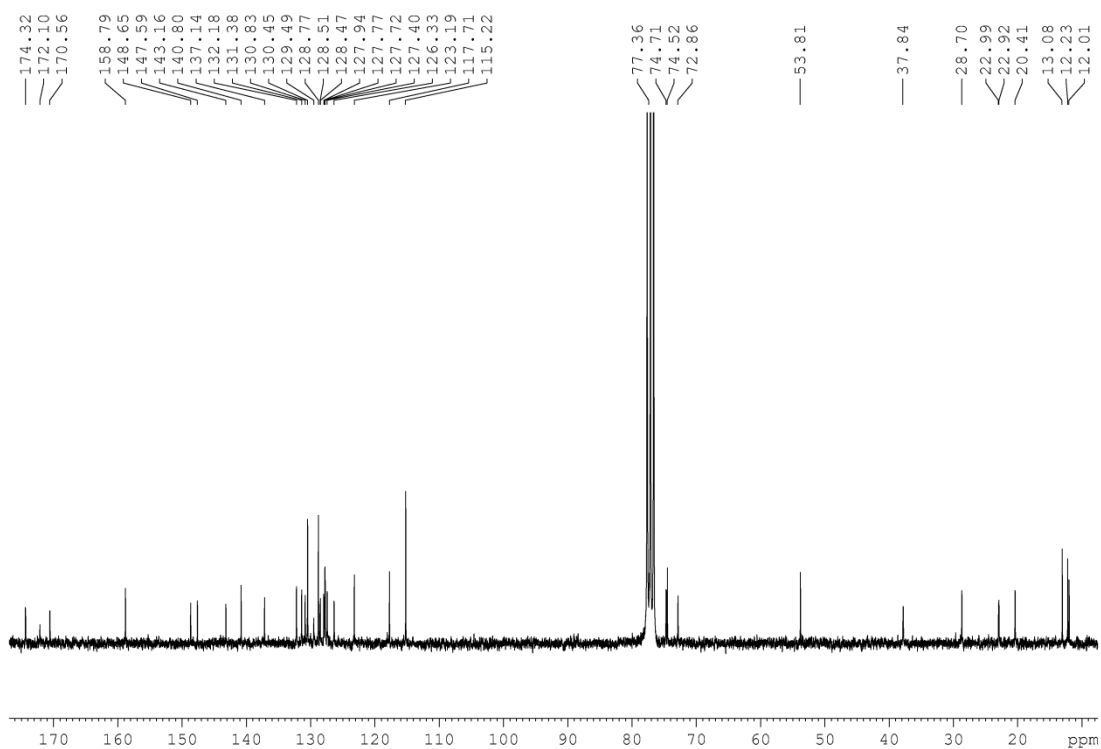
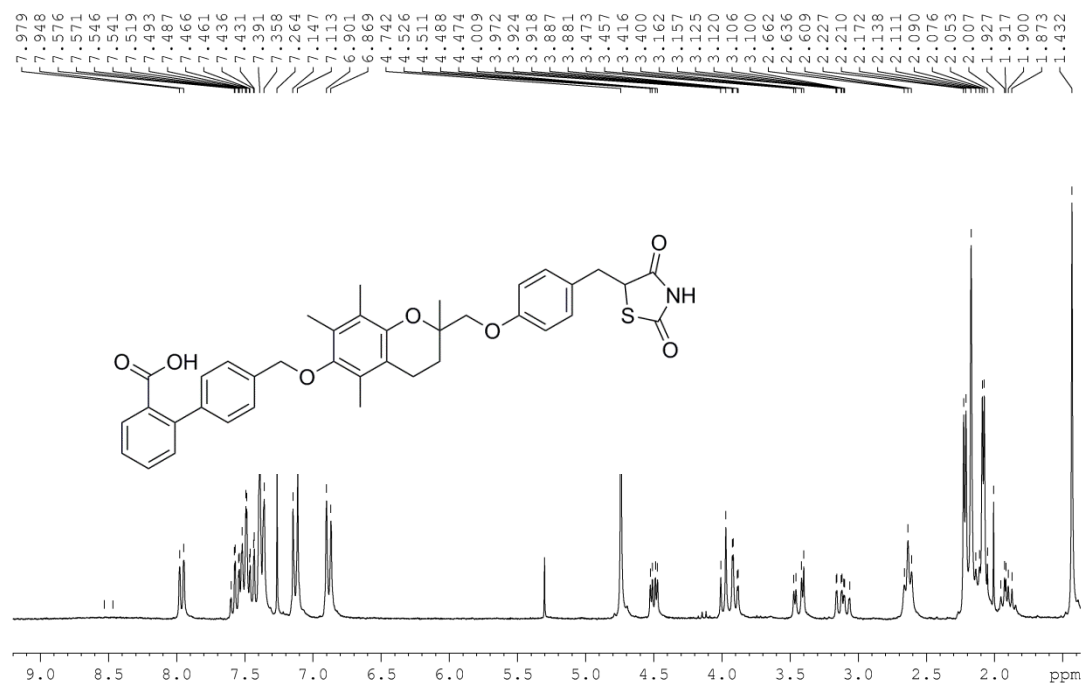


2.19. Compound **53** (CDCl₃)



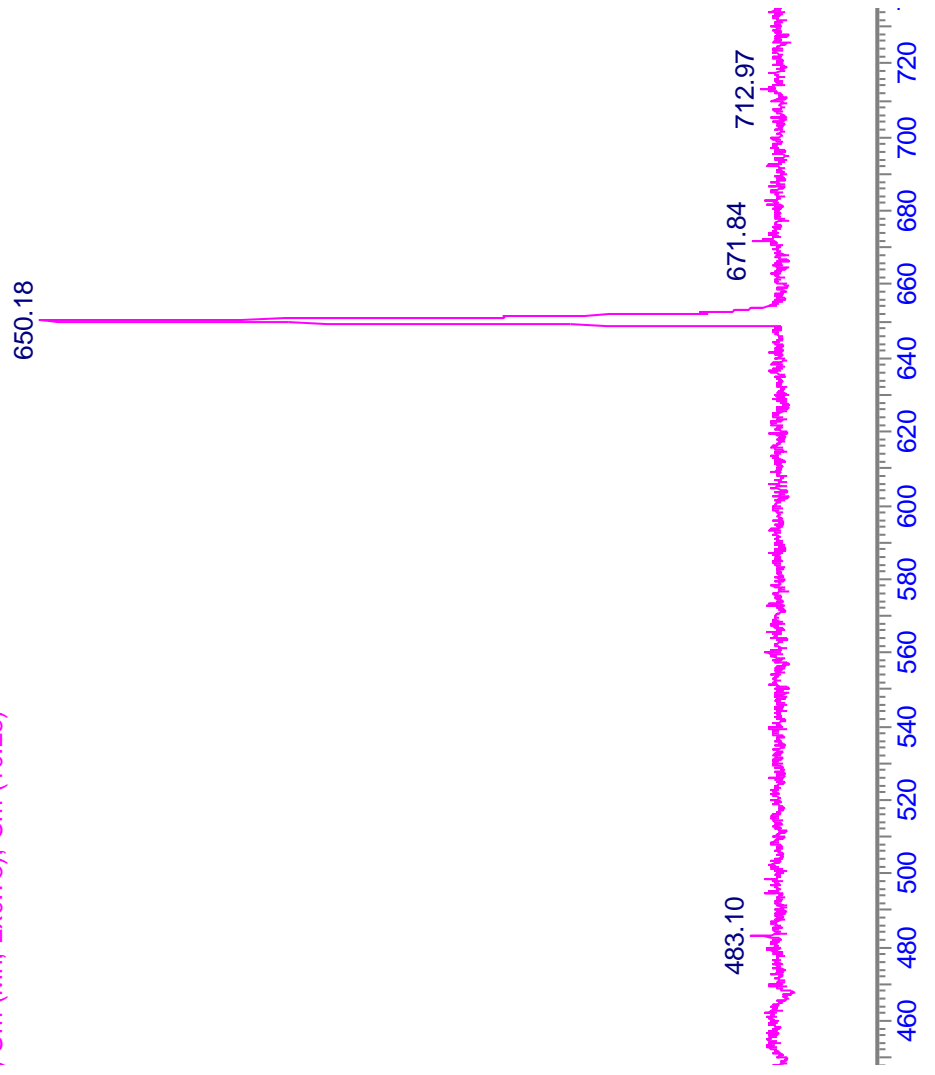


Compound **54** (CDCl₃)

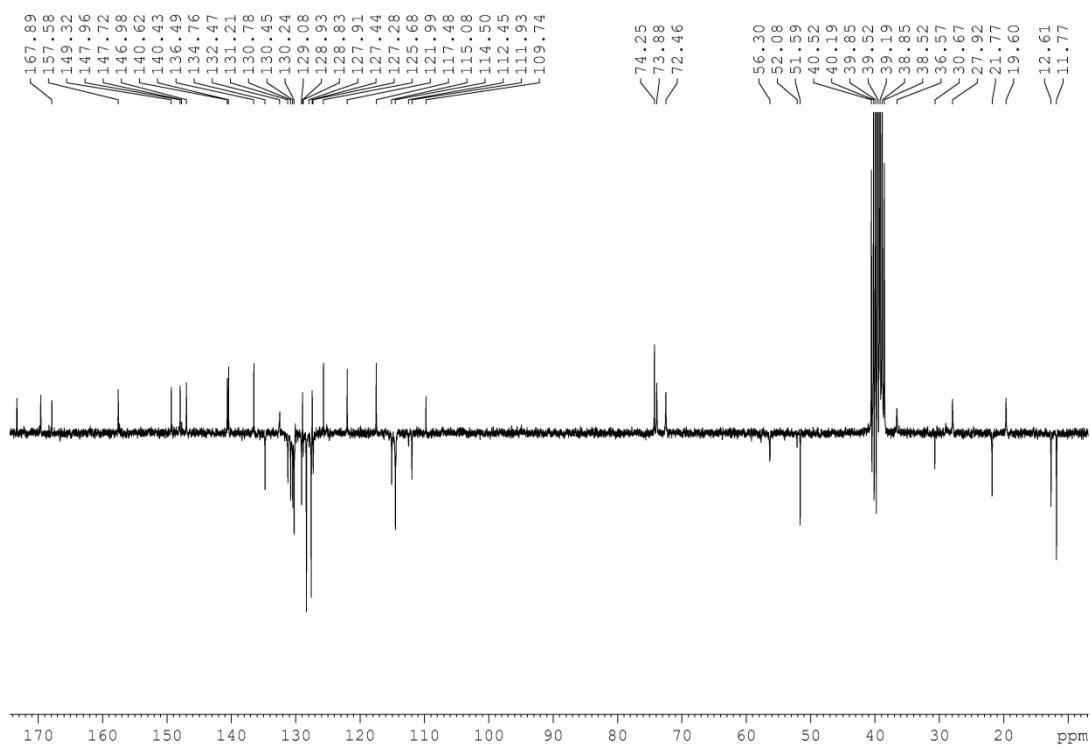
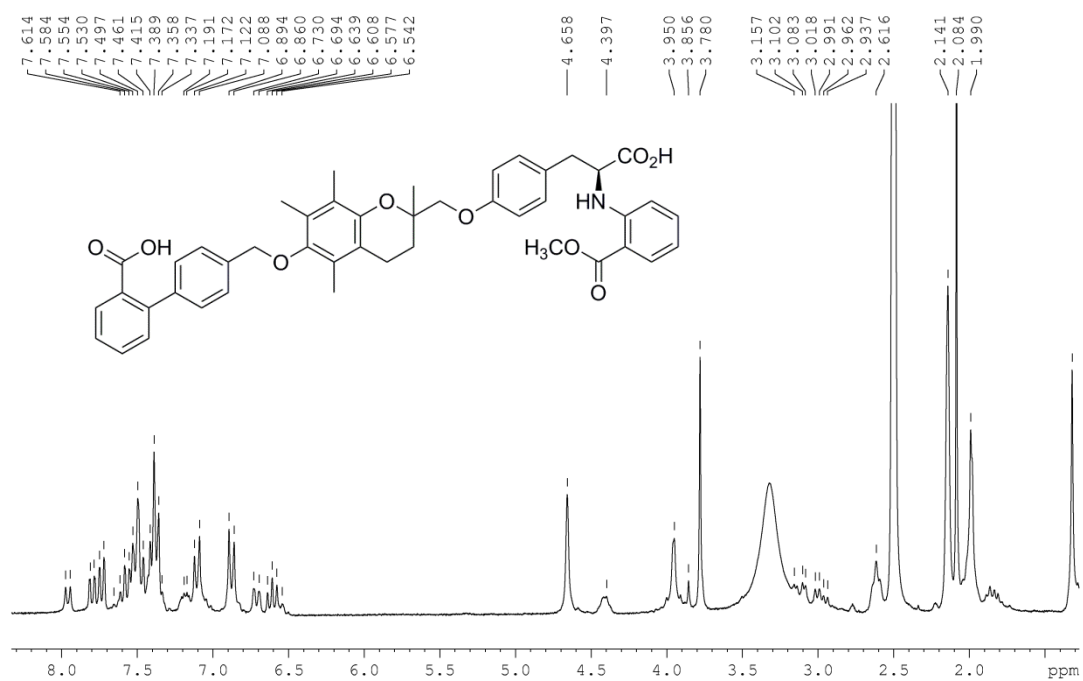


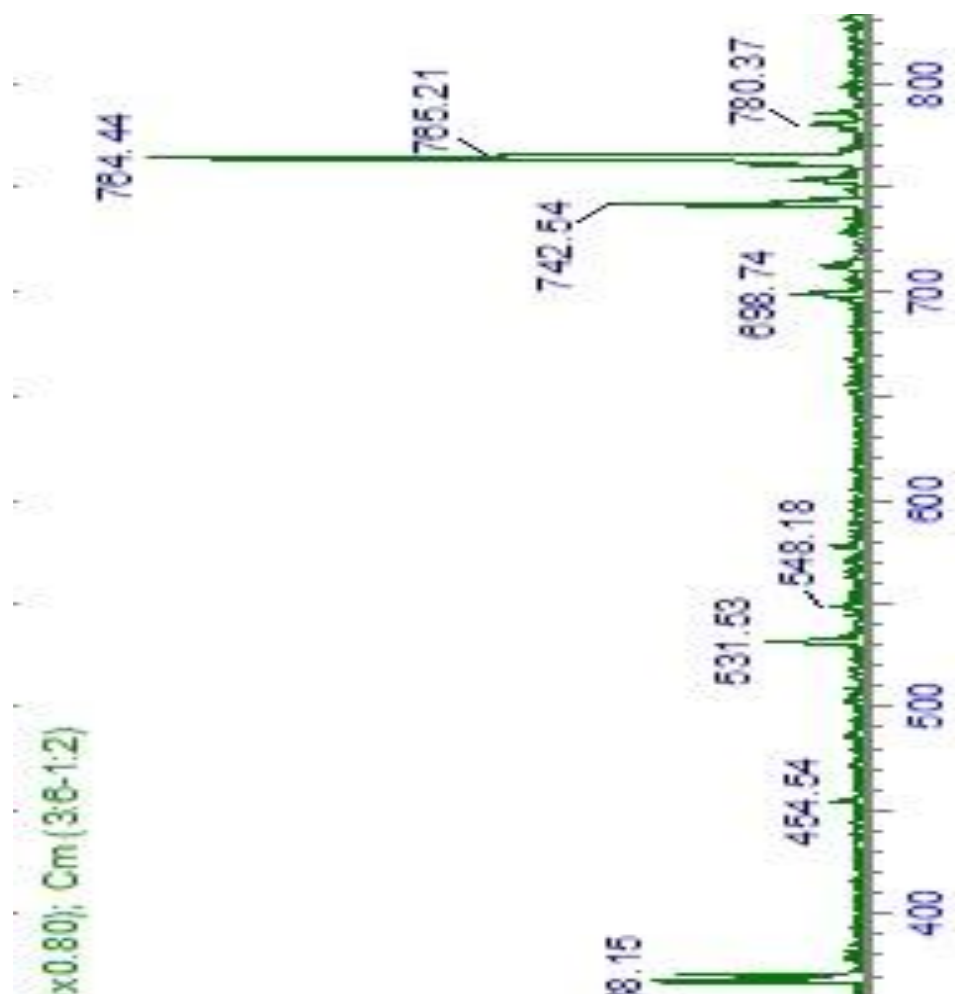
:=40V Ts=80°C

) Sm (Mn, 2x0.75); Cm (10:25)



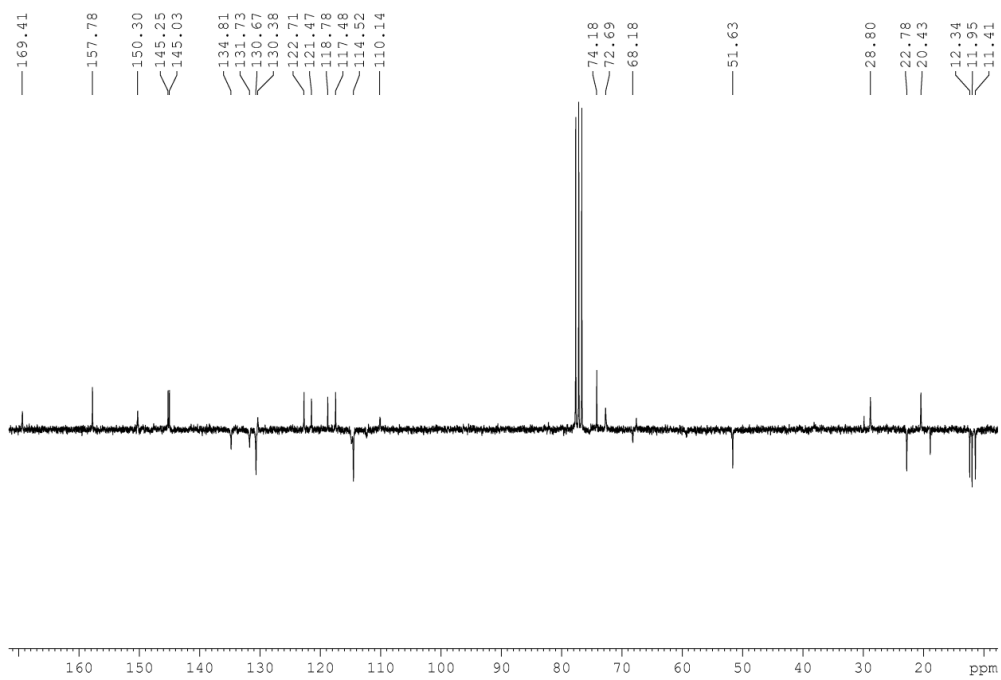
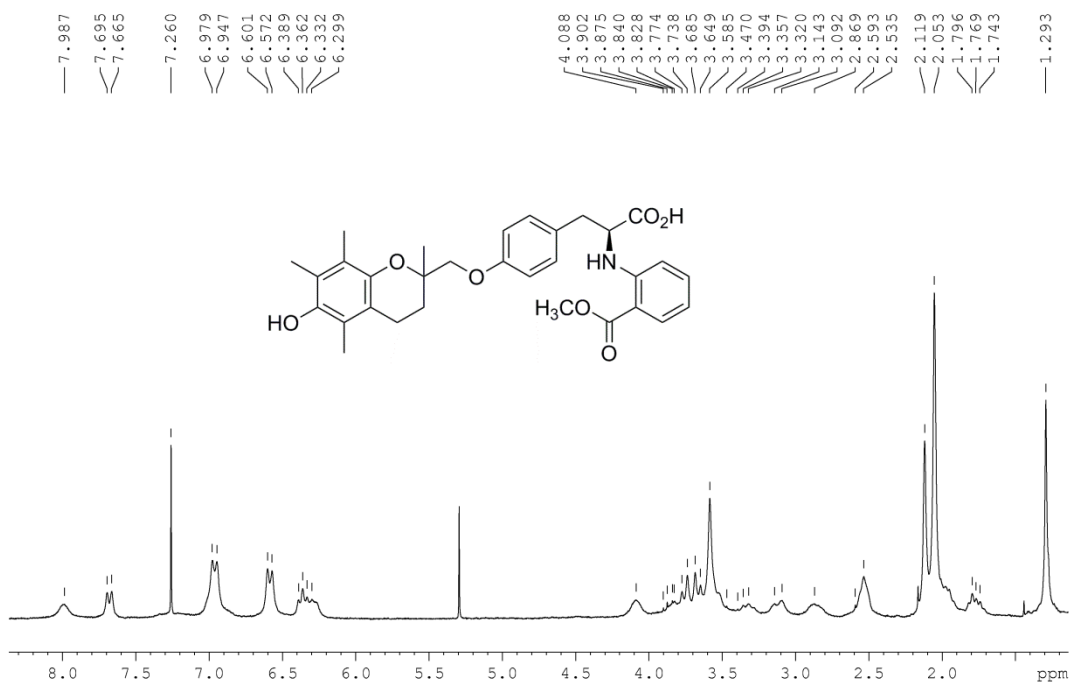
2.20. Compound **57** (DMSO-*d*₆)



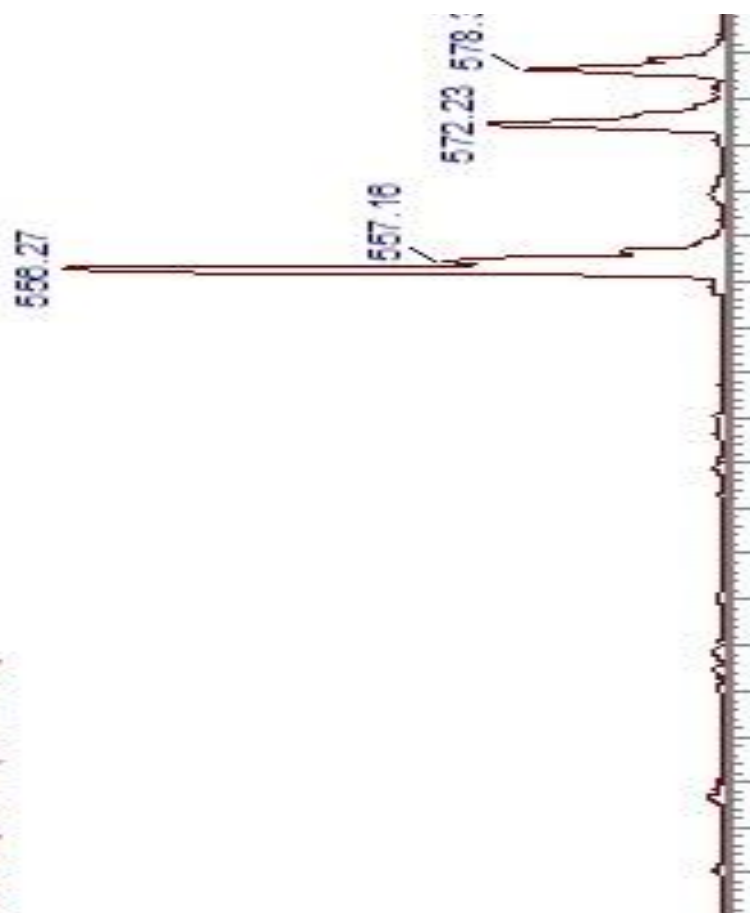


Compound **58** (CDCl_3)

^1H spectrum recorded at 313K in order to get a better resolution



$I_c=40V$ $T_s=80^\circ C$ ES+
1x0.80; Cm (7:11-1:8)



3. Screening test for the AT₁ antagonist properties of the molecules

In order to rapidly screen amongst our molecules the ones blocking the activation of the AT₁ receptor, we developed a test based on the intracellular calcium release induced by Angiotensin II in vascular smooth muscle cells (see § 6.2.2. Evaluation of AT₁ blocking). We validated this protocol by assessing the inhibition of calcium release induced by losartan.

As shown in Figure S1., in cells exposed to Angiotensin II (10^{-9} M), a dramatic increase in fluorescence was observed (+1000%) compared to unexposed control cells. Preincubation (20 min) of cells with 10 μ M of losartan before adding Angiotensin II resulted in a 78% reduction in the fluorescence measured. This test thus enabled us to rapidly discriminate the molecules blocking the AT₁ receptor.

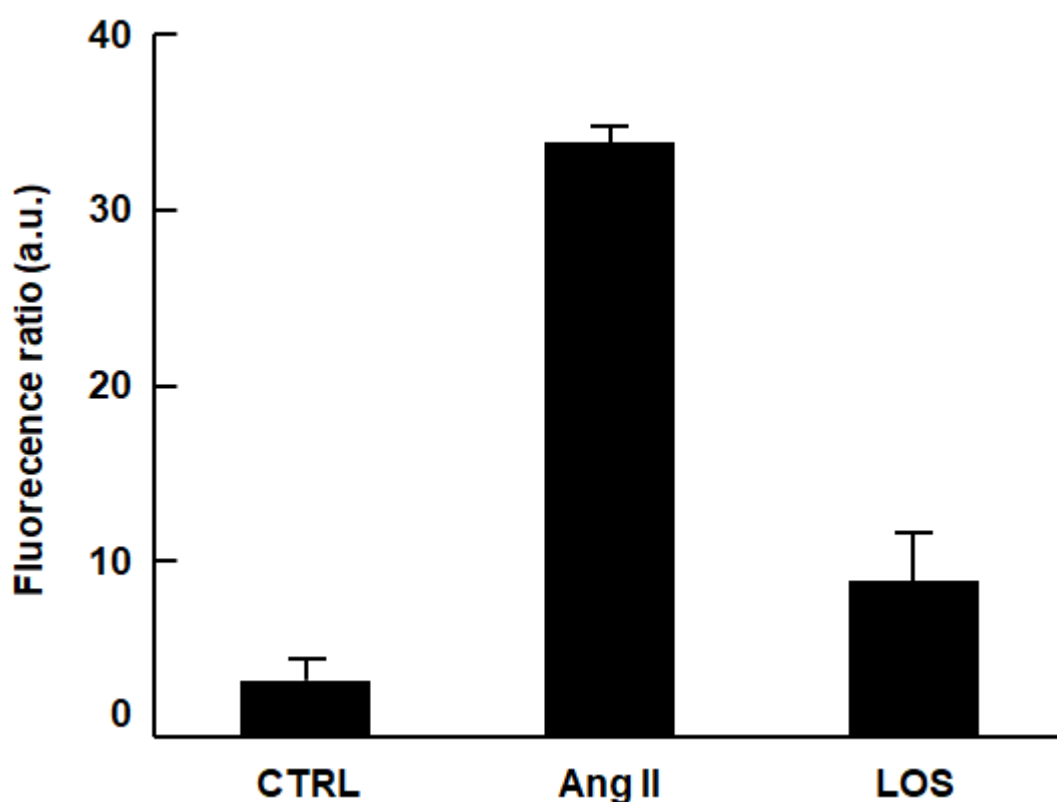


Fig. S1. Fluorescence level (arbitrary unit) measured in rat aortic smooth muscle cells in basal conditions (CTRL), after Angiotensin II stimulation (Ang II, 10^{-9} M) or after incubation with losartan (10 μ M, 20 min) prior to AngII stimulation (LOS). Calcium release was detected in the presence of a fura-2 am molecular probe (see experimental part). Values correspond to a fluorescence ratio and are the mean of 4 independent assays.

4. Molecular docking

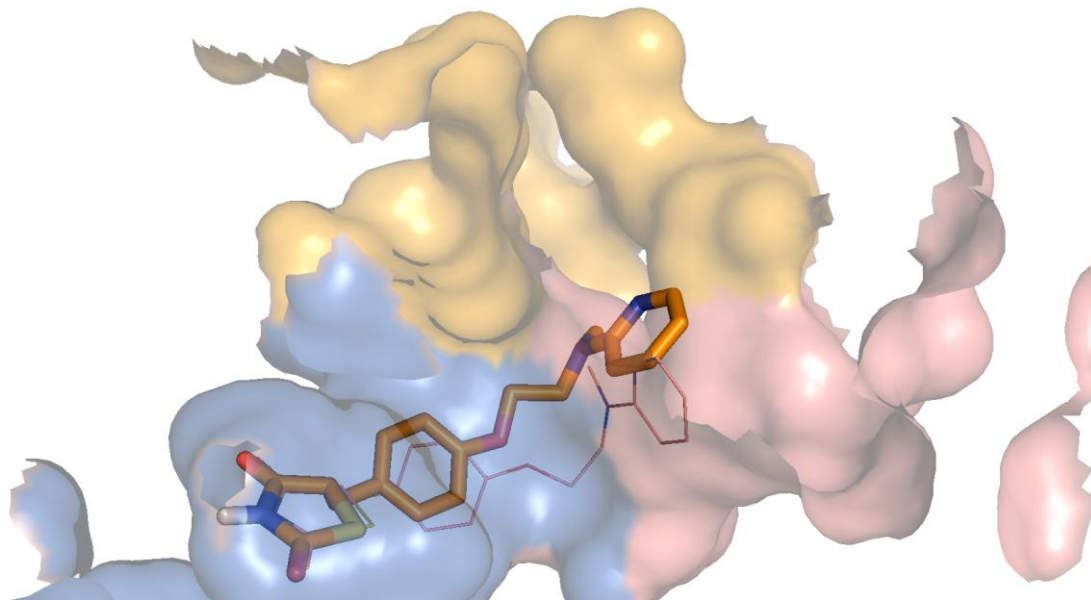


Fig. S2. Lowest binding free energy pose for rosiglitazone obtained with the AutoDock software. PPAR- γ structure is extracted from PDB code 2PRG. *Molecule in sticks*: rosiglitazone; *molecule in lines*: co-crystallized rosiglitazone; *blue, salmon and yellow surfaces*: Arm I, Arm II and Entrance regions, respectively.

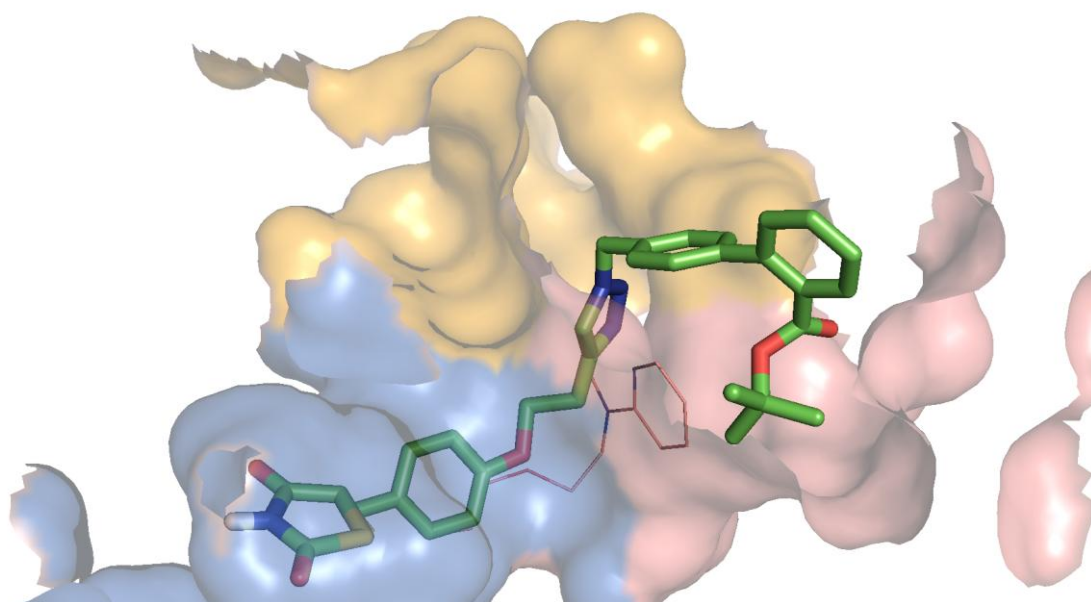


Fig. S3. Lowest binding free energy pose for compound **43** obtained with the AutoDock software. PPAR- γ structure is extracted from PDB code 2PRG. *Molecule in sticks*: compound **43**; *molecule in lines*: co-crystallized rosiglitazone; *blue, salmon and yellow surfaces*: Arm I, Arm II and Entrance regions, respectively.

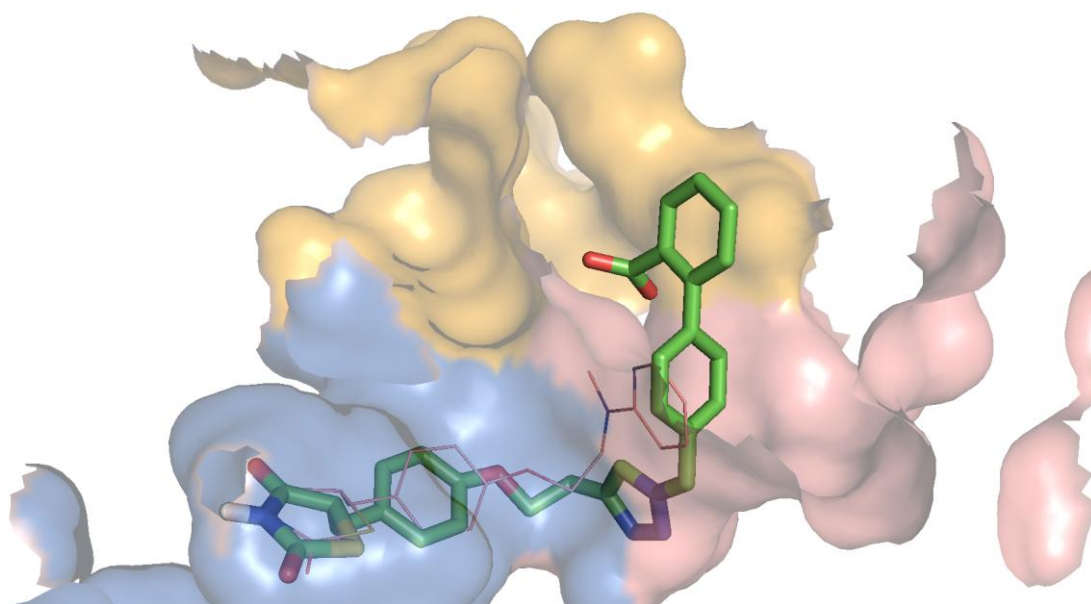


Fig. S4. Lowest binding free energy pose for compound **45** obtained with the AutoDock software. PPAR- γ structure is extracted from PDB code 2PRG. *Molecule in sticks: compound 45; molecule in lines: co-crystallized rosiglitazone; blue, salmon and yellow surfaces: Arm I, Arm II and Entrance regions, respectively.*

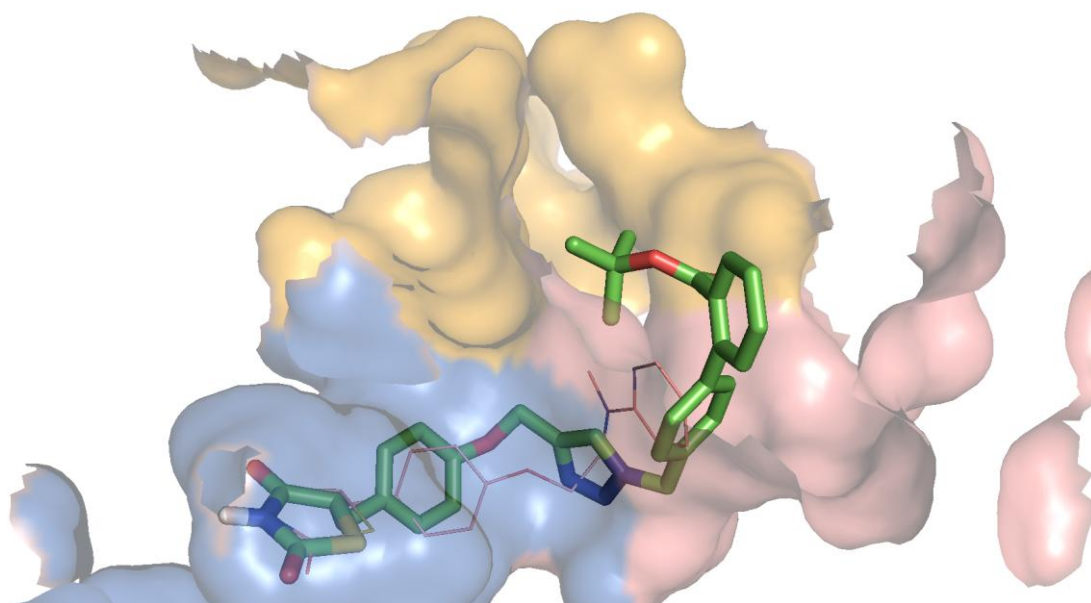


Fig. S5. Lowest binding free energy pose for compound **42** obtained with the AutoDock software. PPAR- γ structure is extracted from PDB code 2PRG. *Molecule in sticks: compound 42; molecule in lines: co-crystallized rosiglitazone; blue, salmon and yellow surfaces: Arm I, Arm II and Entrance regions, respectively.*

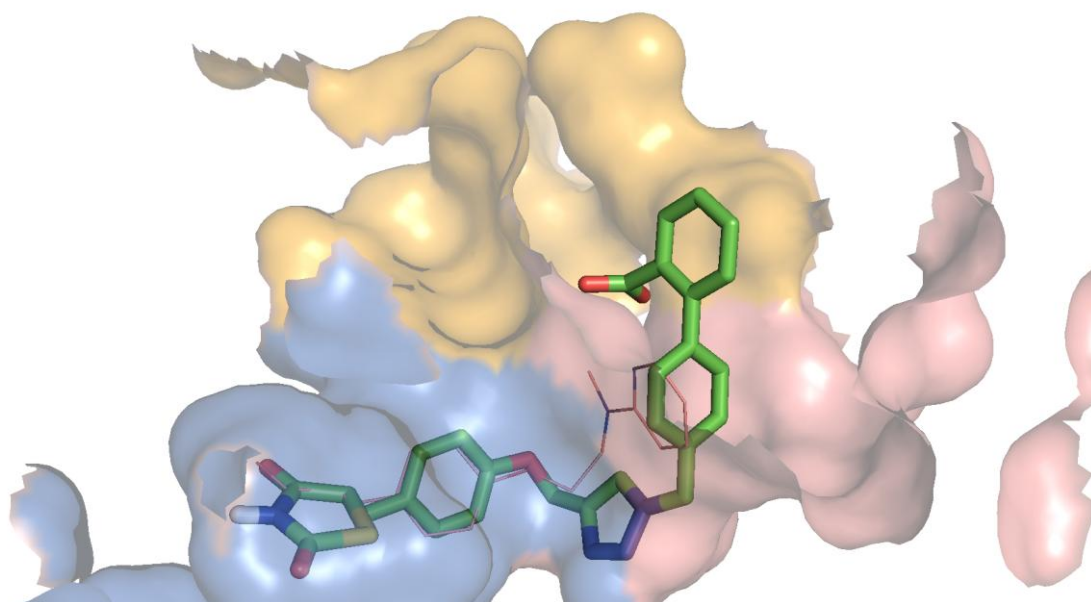


Fig. S6. Lowest binding free energy pose for compound **44** obtained with the AutoDock software. PPAR- γ structure is extracted from PDB code 2PRG. *Molecule in sticks: compound 44; molecule in lines: co-crystallized rosiglitazone; blue, salmon and yellow surfaces: Arm I, Arm II and Entrance regions, respectively.*

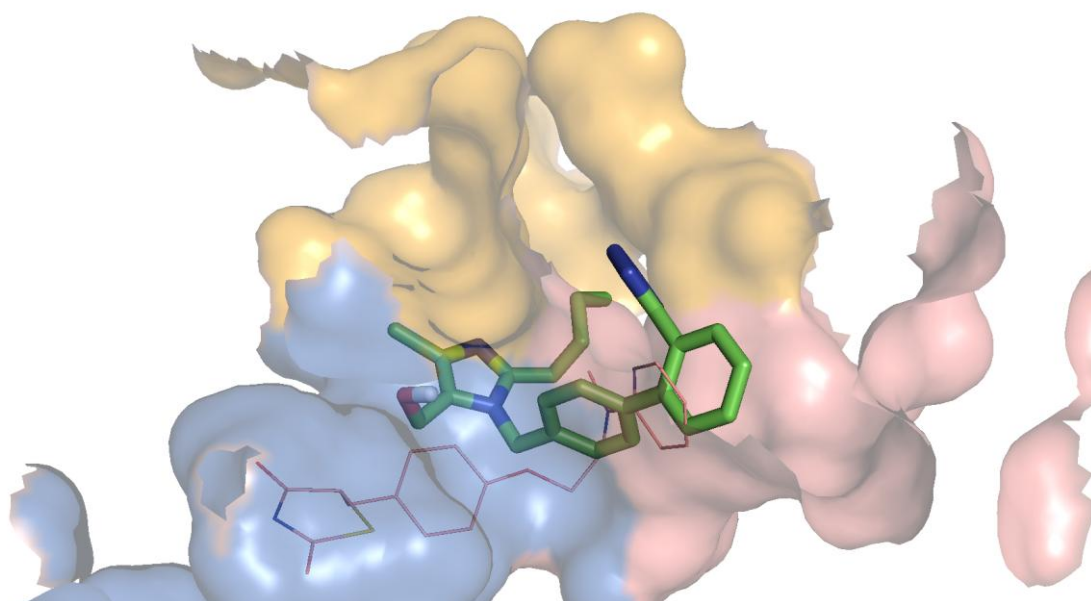


Fig. S7. Lowest binding free energy pose for losartan obtained with the AutoDock software. PPAR- γ structure is extracted from PDB code 2PRG. *Molecule in sticks: losartan; molecule in lines: co-crystallized rosiglitazone; blue, salmon and yellow surfaces: Arm I, Arm II and Entrance regions, respectively.*

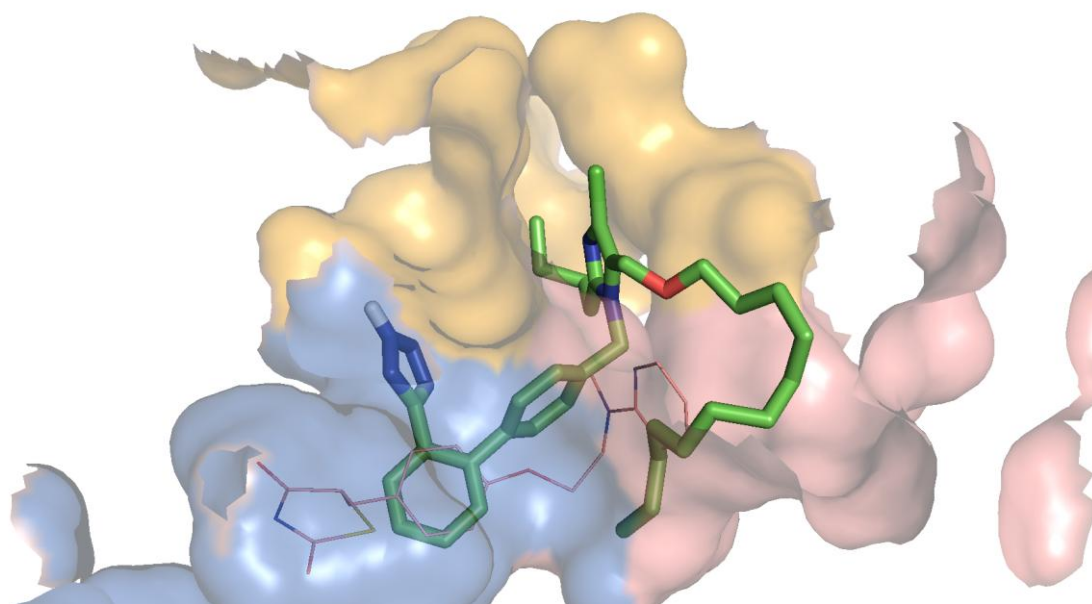


Fig. S8. Lowest binding free energy pose for compound **29** obtained with the AutoDock software. PPAR- γ structure is extracted from PDB code 2PRG. *Molecule in sticks: compound 29; molecule in lines: co-crystallized rosiglitazone; blue, salmon and yellow surfaces: Arm I, Arm II and Entrance regions, respectively.*

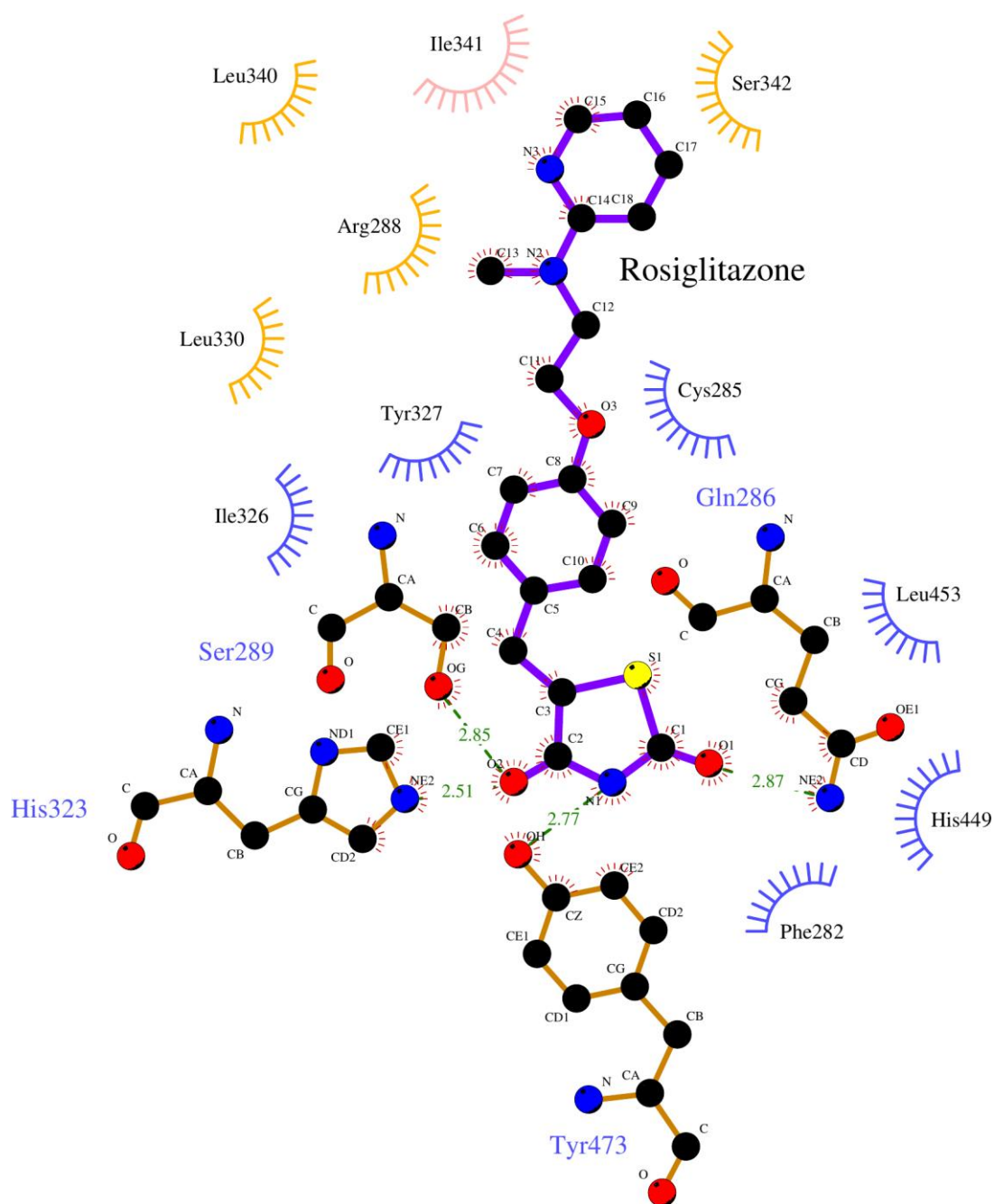


Fig. S9. LigPlot+ representation of the hydrophobic contacts and the hydrogen bonds between rosiglitazone and PPAR- γ structure extracted from PDB code 2PRG. Residues belonging to Arm I, Arm II and Entrance regions are depicted in blue, salmon and yellow, respectively.

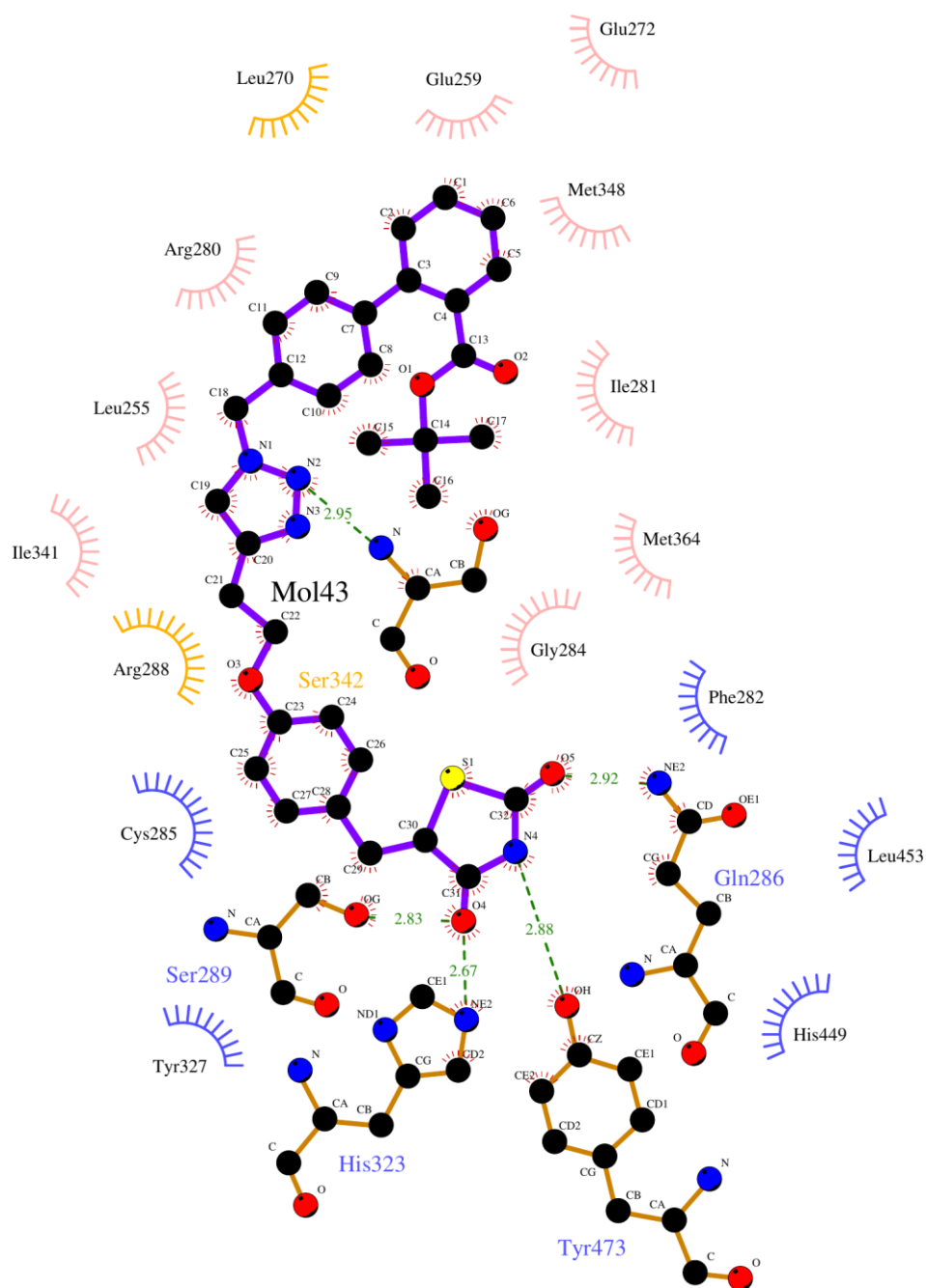


Fig. S10. LigPlot+ representation of the hydrophobic contacts and the hydrogen bonds between compound **43** and PPAR- γ structure extracted from PDB code 2PRG. Residues belonging to Arm I, Arm II and Entrance regions are depicted in blue, salmon and yellow, respectively.

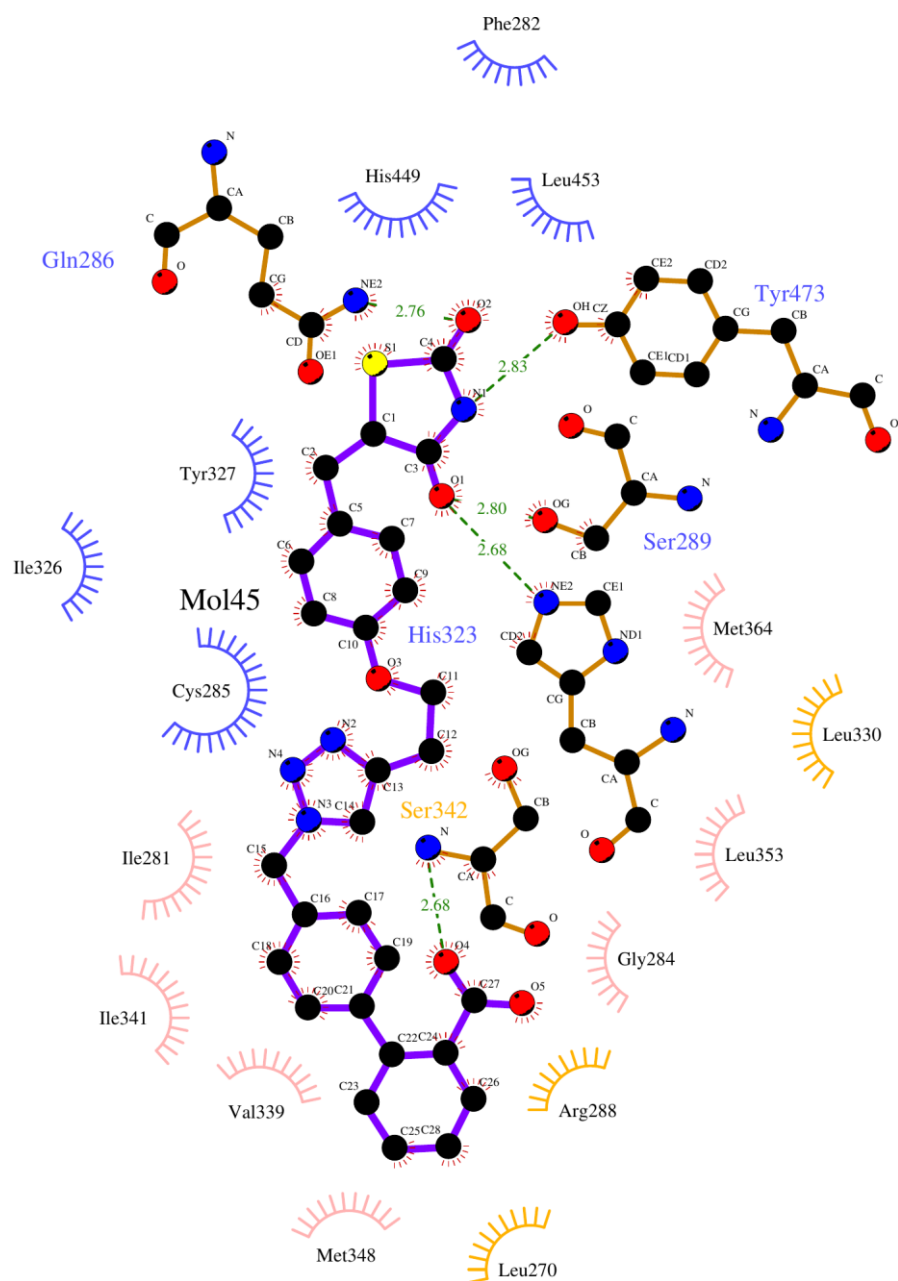


Fig. S11. LigPlot+ representation of the hydrophobic contacts and the hydrogen bonds between compound **45** and PPAR- γ structure extracted from PDB code 2PRG. Residues belonging to Arm I, Arm II and Entrance regions are depicted in blue, salmon and yellow, respectively.

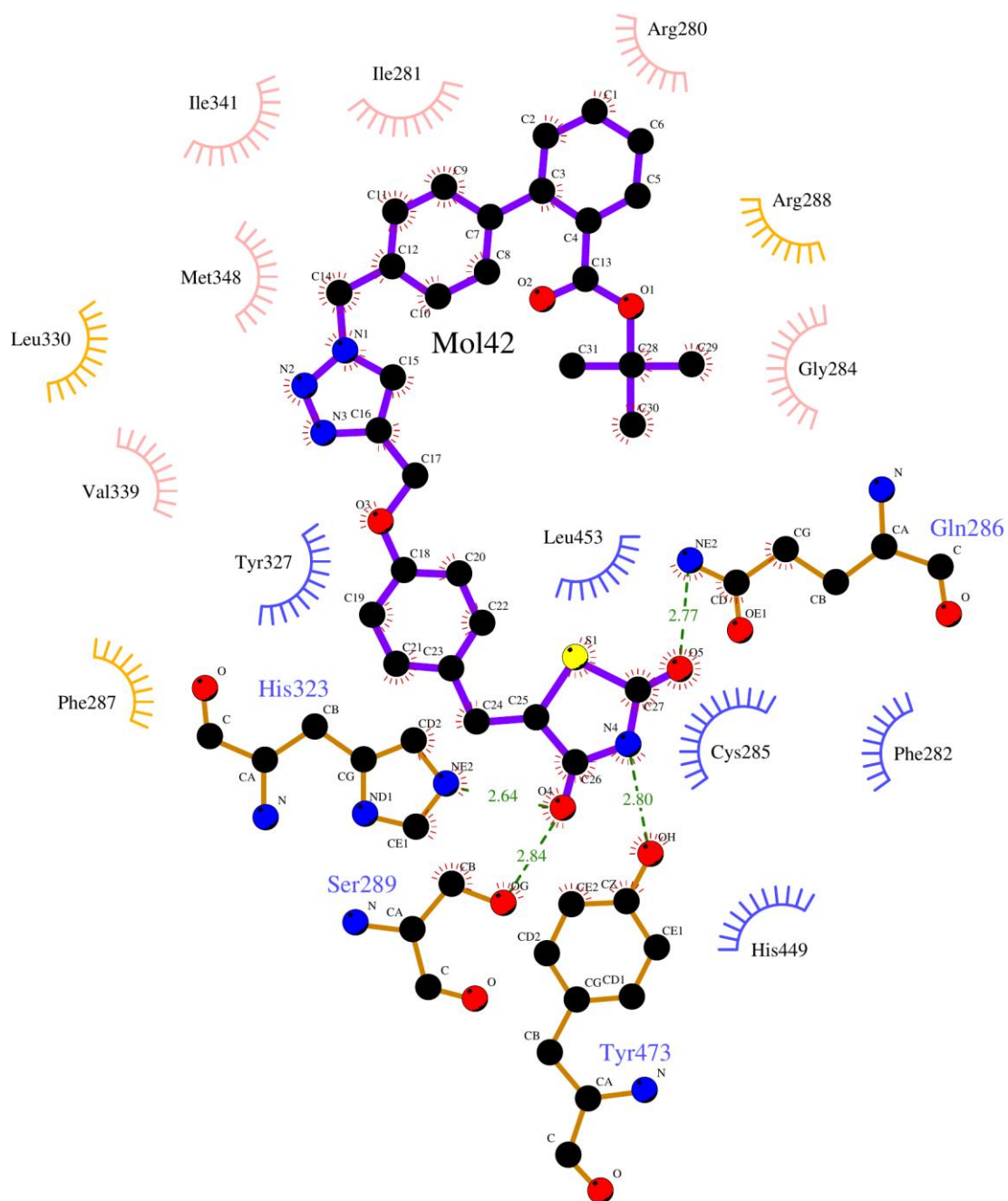


Fig. S12. LigPlot+ representation of the hydrophobic contacts and the hydrogen bonds between compound **42** and PPAR- γ structure extracted from PDB code 2PRG. Residues belonging to Arm I, Arm II and Entrance regions are depicted in blue, salmon and yellow, respectively.

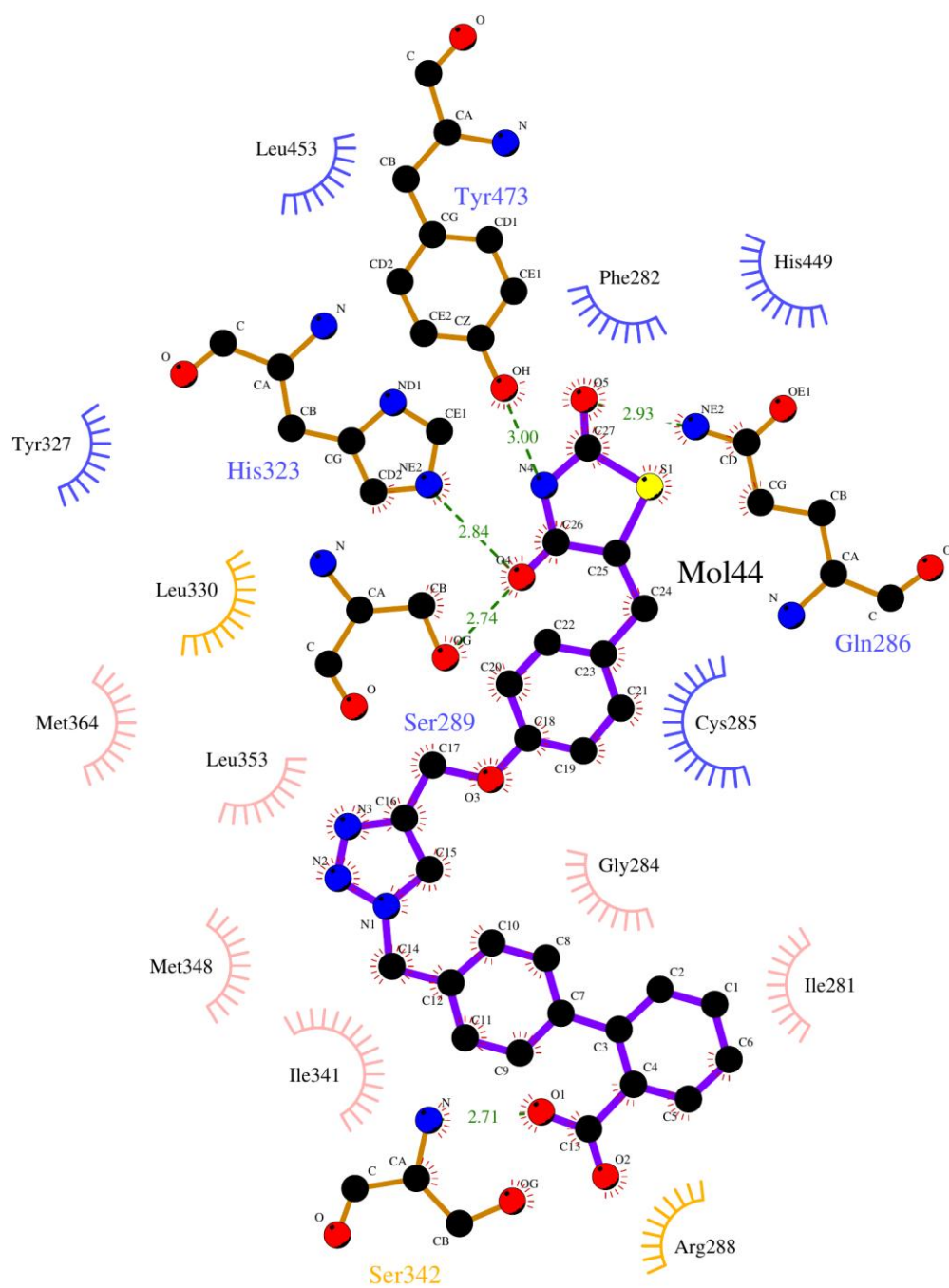


Fig. S13. LigPlot+ representation of the hydrophobic contacts and the hydrogen bonds between compound **44** and PPAR- γ structure extracted from PDB code 2PRG. Residues belonging to Arm I, Arm II and Entrance regions are depicted in blue, salmon and yellow, respectively.

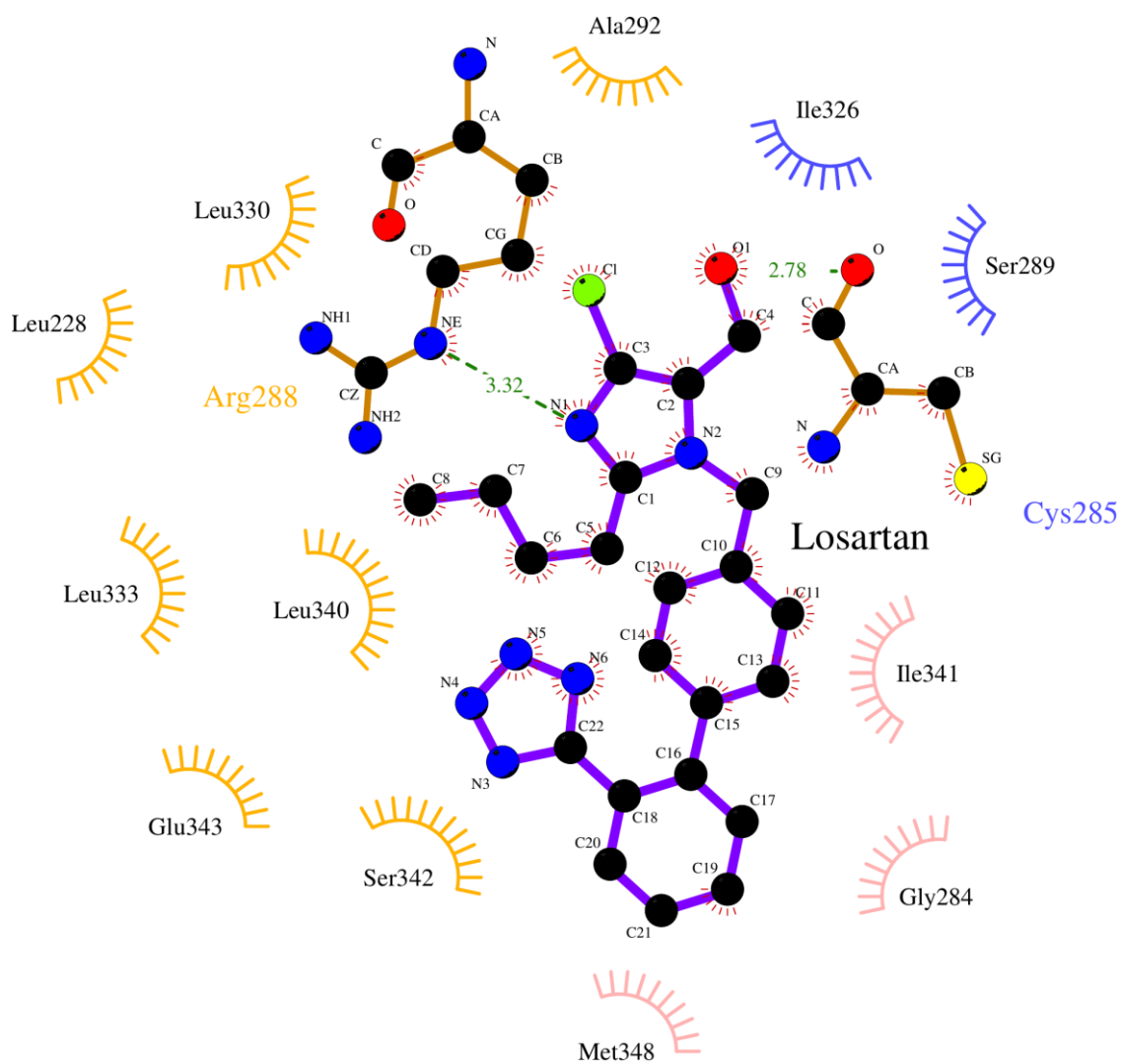


Fig. S14. LigPlot+ representation of the hydrophobic contacts and the hydrogen bonds between losartan and PPAR- γ structure extracted from PDB code 2PRG. Residues belonging to Arm I, Arm II and Entrance regions are depicted in blue, salmon and yellow, respectively.

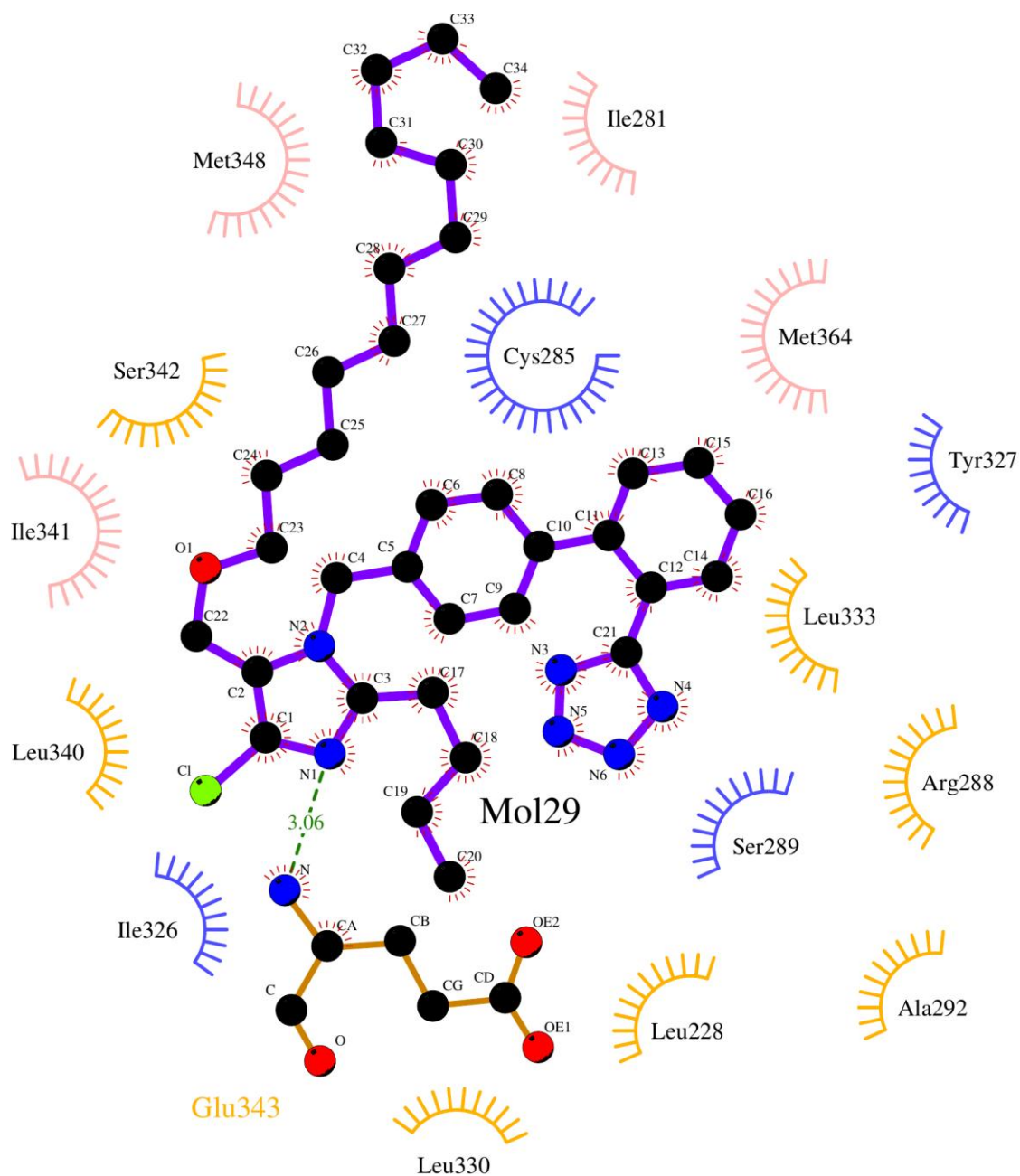


Fig. S15. LigPlot+ representation of the hydrophobic contacts and the hydrogen bonds between compound **29** and PPAR- γ structure extracted from PDB code 2PRG. Residues belonging to Arm I, Arm II and Entrance regions are depicted in blue, salmon and yellow, respectively.

Table S1: Comparison of all interactions between ligands and PPAR γ found by the LigPlot+ software. “Contact” refers to ligand-protein hydrophobic interactions while “H-bond” refers to hydrogen bonds between the ligand and PPAR γ .

Contact	Rosiglitazone	Mol54	Mol43	Mol45	Mol42	Mol44	Losartan	Mol29
<i>Arm I</i>								
Phe282	Contact	Contact	Contact	Contact	Contact	Contact	-	-
Cys285	Contact	Contact	Contact	Contact	Contact	Contact	H-Bond	Contact
Gln286	H-Bond	H-Bond	H-Bond	H-Bond	H-Bond	H-Bond	-	-
Ser289	H-Bond	H-Bond	H-Bond	H-Bond	H-Bond	H-Bond	Contact	Contact
His323	H-Bond	H-Bond	H-Bond	H-Bond	H-Bond	H-Bond	-	-
Ile326	Contact	-	-	Contact	-	-	Contact	Contact
Tyr327	Contact	Contact	Contact	Contact	Contact	Contact	-	Contact
His449	Contact	Contact	Contact	Contact	Contact	Contact	-	-
Leu453	Contact	Contact	Contact	Contact	Contact	Contact	-	-
Leu469	-	Contact	-	-	-	-	-	-
Tyr473	H-Bond	H-Bond	H-Bond	H-Bond	H-Bond	H-Bond	-	-
<i>Arm II</i>								
Leu255	-	-	Contact	-	-	-	-	-
Glu259	-	-	Contact	-	-	-	-	-
Glu272	-	-	Contact	-	-	-	-	-
Arg280	-	-	Contact	-	Contact	-	-	-
Ile281	-	-	Contact	Contact	Contact	Contact	-	Contact
Gly284	-	-	Contact	Contact	Contact	Contact	Contact	-
Val339	-	Contact	-	Contact	Contact	-	-	-
Ile341	Contact	Contact	Contact	Contact	Contact	Contact	Contact	Contact
Met348	-	-	Contact	Contact	Contact	Contact	Contact	Contact
Leu353	-	-	-	Contact	-	Contact	-	-
Met364	-	Contact	Contact	Contact	-	Contact	-	Contact
<i>Entrance</i>								
Leu228	-	-	-	-	-	-	Contact	Contact
Thr268	-	H-Bond	-	-	-	-	-	-
Leu270	-	Contact	Contact	Contact	-	-	-	-
Phe287	-	-	-	-	Contact	-	-	-
Arg288	Contact	Contact	Contact	Contact	Contact	Contact	H-Bond	Contact
Glu291	-	Contact	-	-	-	-	-	-
Ala292	-	-	-	-	-	-	Contact	Contact
Leu330	Contact	Contact	-	Contact	Contact	Contact	Contact	Contact
Leu333	-	Contact	-	-	-	-	Contact	Contact
Leu340	Contact	Contact	-	-	-	-	Contact	Contact
Ser342	Contact	H-Bond	H-Bond	H-Bond	-	H-Bond	Contact	Contact
Glu343	-	Contact	-	-	-	-	Contact	H-Bond