Supplementary Information for:

Rational design and structure-activity relationship studies of quercetin-amino acid hybrids targeting the anti-apoptotic protein Bcl-xL

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Contents

1. Synthetic procedure for the quercetin – amino acid analogues

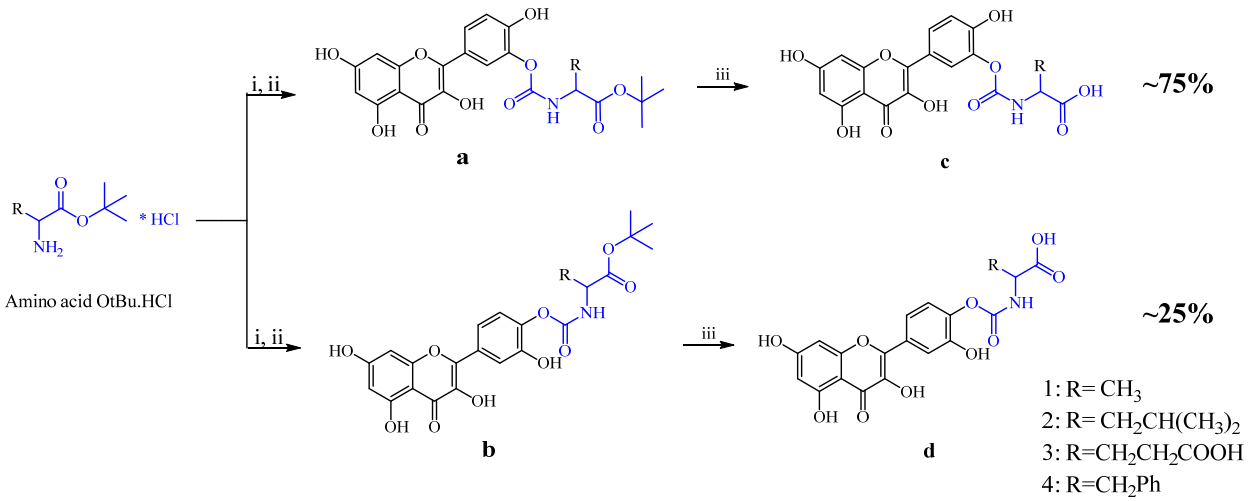
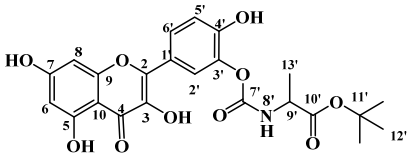


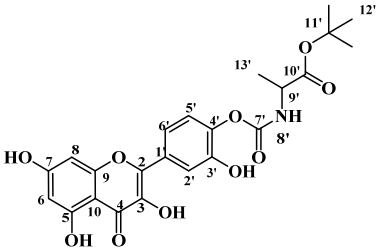
Figure S1: General synthetic scheme of Quercetin-amino acids. i) BNPC, DIPEA, THF, rt, 12h; ii) Quercetin, rt, 12h; iii) TFA/CH_2Cl_2 (1/10, v/v), 0 ^{0}C to rt, 4h.

2. NMR and MS Characterization of the four quercetin – amino acid analogues

2.1 NMR and MS characterization of 3'-O-CO-(Ala-OtBu)-Quercetin (1a) and 4'-O-CO-(Ala-OtBu)-Quercetin (1b) (76%).



1a



1b

^{1}H-NMR characterization of 1a (500 MHz, DMSO-d_6, 25°C): δ = 12.47 (s, 1 H, 5-OH), 10.84 (s, 1 H, 7-OH), 10.40 (s, 1 H, 4'-OH), 9.58 (s,1 H, 3-OH), 8.13 (d, J = 7.3 Hz, 1 H, 8'-NH), 7.94 (dd, J = 8.7 Hz, 2.2 Hz, 1 H, 6'-H), 7.88 (d, J = 2.2 Hz, 1 H, 2'-H), 7.09 (d, J = 8.6 Hz, 1 H, 5'-H), 6.48 (d, J = 2.0 Hz, 1 H, 8-H), 6.23 (d, J = 2.0 Hz, 1 H, 6-H), 4.05- 3.99 (m, 1 H, 9′-H), 1.46 (s, 9 H, 12′-H), 1.35 (d, J = 7.2, 3 H, 13'-H) ppm;

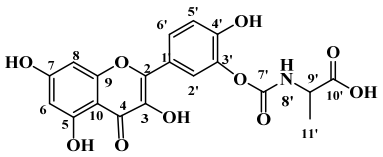
^{13}C-NMR (500 MHz, DMSO-d_6, 25°C): δ = 177.04 (C4), 172.64 (C10'), 164.87 (C7), 161.51 (C5), 157.04 (C9), 154.54 (C7'), 152.5 (C4'), 146.64 (C2), 126.62 (C6′), 123.79 (C2′), 122.50 (C1'), 117.33 (C5′), 103.86 (C10), 98.91 (C6), 94.22 (C8), 81.34(C11'), 50.97 (C9'), 28.40 (C12'), 17.74 (C13') ppm;

^{1}H-NMR characterization of 1b (500 MHz, DMSO-d_6, 25°C): δ = 12.41 (s, 1 H, 5-OH), 10.89 (s, 1 H, 7-OH), 10.00 (s, 1 H, 3'-OH), 9.69 (s, 1 H, 3-OH), 8.12 (d, J = 7.3 Hz, 1 H, 8'-NH), 7.81 (d, J = 2.0 Hz, 1 H, 2'-H), 7.61 (dd, J = 8.6, 2.0 Hz, 1 H, 6'-H), 7.18 (d, J = 8.6Hz, 1 H, 5'-H), 6.45 (d, J = 2.0 Hz, 1 H, 8-H), 6.24 (d, J = 2.0 Hz, 1 H, 6-H), 4.05- 3.99 (m, 1 H, 9′-H), 1.46 (s, 9 H, 12′-H), 1.35 (d, J = 7.2 Hz, 3 H, 13'-H) ppm;

^{13}C-NMR (500 MHz, DMSO-d_6, 25°C): δ = 177.02 (C4), 172.64 (C10'), 164.86 (C7), 161.65 (C5), 157.00 (C9), 154.50 (C7'), 150.31 (C3'), 146.32 (C2), 140.77 (C4'), 137.75 (C3), 129.4 (C1'), 124.20 (C5′), 119.24 (C6'), 116.55 (C2′), 103.98 (C10), 98.97 (C6), 94.07 (C8), 81.34 (C11'), 50.97 (C9'), 28.40 (C12'),17.74 (C13') ppm;

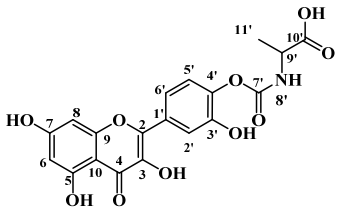
Mass characterization of 1a and 1b regioisomers: MS (ESI) m/z: $[M-H]^-$ for $C_{23}H_{23}NO_{10}$: calcd: 473.13, found: 472.1.

2.2 NMR and MS characterization Synthesis of 3'-O-CO-Ala-Quercetin (1c) and 4'-O-CO-Ala-Quercetin (1d) (94%).



1c

74.1%



1d

25.9%

^{1}H-NMR characterization 1c (500 MHz, DMSO-d_6, 25^{o}C): δ = 12.66 (bs, 1 H, 11'-OH), 12.47 (s, 1 H, 5OH), 10.85 (s, 1 H, 7–OH), 10.39 (s, 1 H, 4'-OH), 9.56 (s, 1 H, 3-OH), 8.10 (d, J = 7.4 Hz, 1 H, 8'-NH), 7.93 (dd, J = 8.6 Hz, 2.2 Hz, 1 H, 6'-H), 7.90 (d, J = 2.2 Hz, 1 H, 2'-H), 7.09 (d, J = 8.6Hz, 1 H, 5'-H), 6.50 (d, J = 2.0 Hz, 1 H, 8-H), 6.23 (d, J = 2.0 Hz, 1 H, 6-H), 4.12- 4.09 (m, 1 H, 9′-H), 1.39- 1.37 (m, 3 H, 11′-H) ppm;

^{13}C-NMR (500 MHz, DMSO-d_6, 25^{o}C): δ = 176.5 (C4), 174.7 (C10'), 164.83 (C7), 161.6 (C5), 157.04 (C9), 154.46 (C7'), 152.63 (C4'), 146.57 (C2), 139.4 (C3'), 126.45 (C6′), 123.73 (C2′), 122.77 (C3), 122.66 (C1′), 117.19 (C5′), 103.95 (C10), 103.91 (C8), 99.05 (C6), 50.33 (C9'), 18.13 (C11') ppm.

^{1}H-NMR characterization 1d (500 MHz, DMSO-d_6, 25^{o}C): δ = 12.66 (bs, 1 H, 11'-OH), 12.41 (s, 1 H, 5OH), 10.87 (s, 1 H, 7–OH), 9.99 (s, 1H, 3'-OH), 9.68 (s, 1H, 3-OH), 8.09 (d, J = 7.4 Hz, 1 H, 8'-NH), 7.81 (d, J= 2.1 Hz, 1 H, 2'-H), 7.61 (dd, J = 8.6 Hz, 2.2 Hz, 1 H, 6'-H), 7.19 (d, J = 8.6Hz, 1 H, 5'-H), 6.45 (d, J = 2.0 Hz, 1 H, 8-H), 6.24 (d, J = 2.0 Hz, 1 H, 6-H), 4.12- 4.06 (m, 1 H, 9′-H), 1.39- 1.37 (m, 3 H, 11′-H) ppm;

^{13}C-NMR (500 MHz, DMSO-d_6, 25^{o}C): δ = 176.5 (C4), 174.7 (C10'), 164.83 (C7), 161.7 (C5), 156.92 (C9), 154.46 (C7'), 150.22 (C3'), 146.39 (C2), 140.97 (C4'), 129.29 (C1′), 124.10 (C5′), 122.77 (C3), 119.23 (C6′), 116.54 (C2′), 104.06 (C10), 99.12 (C6), 94.02 (C8), 50.1 (C9'), 18.13 (C11') ppm.

Mass characterization of 1c and 1d regioisomers: **Mass:** MS (ESI) m/z: $[M+H]^+$ for $C_{19}H_{15}NO_{10}$: calcd: 417.07; found: 417.9, 438.0 $[M+Na]^+$

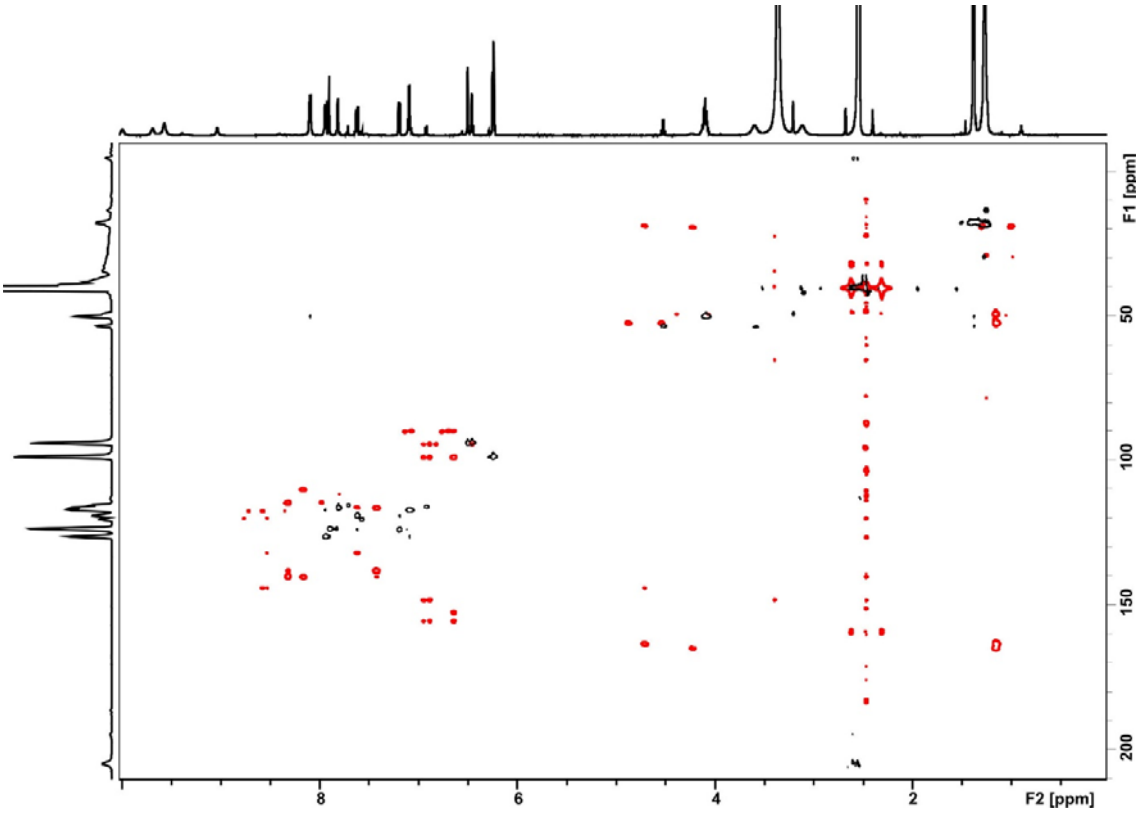
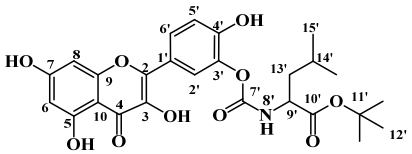
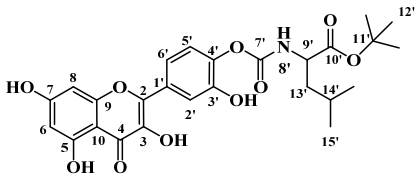


Figure S2. ^{1}H-^{13}C HSQC (colored in black) and ^{1}H-^{13}C HMBC (colored in red) spectra of 1c and 1d.

2.3 NMR and MS characterization Synthesis of 3'-O-CO-(Leu-OtBu)-Quercetin (2a) and 4'-O-CO-(Leu-OtBu)-Quercetin (2b) (75%):



2a



2b

^{1}H-NMR characterization 2a (500 MHz, DMSO-d_6, 25^{o}C): δ = 12.47 (s, 1 H, 5-OH), 10.83 (s, 1H, 7-OH), 10.40 (s, 1 H, 4'-OH), 9.57 (s, 1 H, 3-OH), 8.09 (d, J = 7.8 Hz, 1 H, 8'-NH), 7.94 (dd, J = 8.6 Hz, 2.2 Hz, 1 H, 6'-H), 7.88 (d, J = 2.2 Hz, 1 H, 2'-H), 7.08 (d, J = 8.6Hz, 1 H, 5'-H), 6.48 (d, J = 2.0 Hz, 1 H, 8-H), 6.23 (d, J = 2.0 Hz, 1 H, 6-H), 4.01- 3.96 (m, 1 H, 9′-H), 1.82-1.74 (m, 1 H, 14'-H), 1.67-1.60 (m, 1 H, 13'a-H), 1.56-1.52 (m, 1 H, 13′b-H), 1.46 (s, 9 H, 12'H), 0.93 (d, J = 6.5, 6 H, 15'H) ppm;

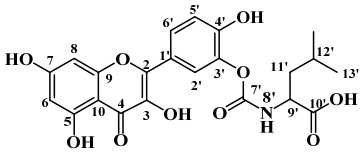
^{13}C-NMR (500 MHz, DMSO-d_6, 25^{o}C): δ = 176.7 (C4), 172.5 (C10'), 164.75 (C7), 161.62 (C5), 156.95 (C9), 154.80 (C7'), 152.63 (C4'), 146.58 (C2), 139.90 (C3'), 132.45 (C3), 126.63 (C6'), 123.63 (C2′), 122.62 (C1'), 117.26 (C5′), 103.86 (C10), 99.09 (C6), 94.21 (C8), 81.49 (C11'), 53.89 (C9'), 40.47 (C13'), 28.50 (C12'), 24.96 (C14'), 22.09 (C15') ppm.

^{1}H-NMR characterization 2b (500 MHz, DMSO-d_6, 25^{o}C): δ = 12.41 (s, 1 H, 5-OH), 10.89 (s, 1 H, 7-OH), 10.00 (s, 1 H, 3'-OH), 9.68 (s, 1 H, 3-OH), 8.10 (d, J = 7.8 Hz, 1 H, 8'-NH), 7.81 (d, J = 2.2 Hz, 1 H, 2'-H), 7.61 (dd, J = 8.6Hz, 2.2 Hz, 1 H, 6'-H), 7.18 (d, J = 8.6Hz, 1 H, 5'-H), 6.45 (d, J = 2.0 Hz, 1 H, 8-H), 6.24 (d, J = 2.0 Hz, 1 H, 6-H), 4.01- 3.96 (m, 1 H, 9′-H), 1.82-1.74 (m, 1 H, 14'-H), 1.67-1.60 (m, 1 H, 13'a-H), 1.56-1.52 (m, 1 H, 13′b-H), 1.46 (s, 9 H, 12'H), 0.93 (d, J = 6.5, 6 H, 15'H) ppm;

^{13}C-NMR (500 MHz, DMSO-d_6, 25^{o}C): δ = 172.50 (C10'), 164.93 (C7), 161.73 (C5), 154.80 (C7'), 157.09 (C9), 150.31 (C3'), 146.20 (C2), 141.00 (C4'), 122.62 (C1'), 119.34 (C6′), 117.26 (C5′), 116.56 (C2'), 103.90 (C10), 99.19 (C6), 94.06 (C8), 81.49 (C11'), 53.89 (C9'), 40.47 (C13'), 28.50 (C12'), 24.96 (C14'), 22.09 (C15') ppm.

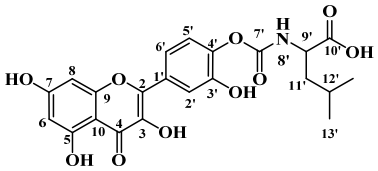
Mass characterization of 2a and 2b regioisomers: **Mass:** MS (ESI) m/z: $[M-H]^-$ for $C_{26}H_{29}NO_{10}$: calcd: 515.18; found: 514.2.

2.4 NMR and MS characterization Synthesis of 3'-O-CO-Leu-Quercetin (2c) and 4'-O-CO-Leu-Quercetin (2d) (90%):



2c

73.5%



2d

26.5%

^{1}H-NMR characterization 2c (500 MHz, DMSO-d_6, 25^{o}C): δ = 12.67 (bs, 1 H, 10'-OH), 12.47 (s, 1 H, 5OH), 10.83 (s, 1H, 7-OH), 10.39 (s, 1 H, 4'-OH), 9.57 (s, 1 H, 3-OH), 8.07 (d, J = 8.1 Hz, 1 H, 8'-NH), 7.94 (dd, J = 8.6 Hz, 2.0 Hz, 1 H, 6'-H), 7.89 (d, J = 2.0 Hz, 1 H, 2'-H), 7.08 (d, J = 8.6Hz, 1 H, 5'-H), 6.49 (d, J = 1.8 Hz, 1 H, 8-H), 6.23 (d, J = 1.8 Hz, 1 H, 6-H), 4.08-4.03 (m, 1 H, 9′-H), 1.82-1.76 (m, 1 H, 12'-H), 1.69-1.62 (m, 1 H, 11'a-H), 1.60-1.54 (m, 1 H, 11′b-H), 0.94 (d, J= 6.5Hz, 6 H, 13'-H) ppm;

^{13}C-NMR (500 MHz, DMSO-d_6, 25^{o}C): δ = 176.76 (C4), 174.77 (C10'), 164.82 (C7), 161.58 (C5), 157.95 (C9), 152.55 (C4'), 146.69 (C2), 139.7 (C3'), 136.77 (C3), 126.54 (C6'), 123.63 (C2′), 117.22 (C5′), 103.91 (C10), 99.09 (C6), 94.27 (C8), 53.08 (C9'), 40.57 (C11'), 24.95 (C12'), 22.00 (C13') ppm.

^{1}H-NMR characterization 2d (500 MHz, DMSO-d_6, 25^{o}C): δ = 12.67 (bs, 1 H, 10'-OH), 12.41 (s, 1 H, 5OH), 10.89 (s, 1 H, 7-OH), 9.96 (s, 1 H, 3'-OH), 9.68 (s, 1 H, 3-OH), 8.07 (d, J = 8.1 Hz, 1 H, 8'-NH), 7.80 (d, J = 2.0 Hz, 1 H, 2'-H), 7.62 (dd, J = 8.6Hz, 2.0 Hz, 1 H, 6'-H), 7.18 (d, J = 8.6 Hz, 1 H, 5'-H), 6.45 (d, J = 1.8 Hz, 1 H, 8-H), 6.24 (d, J = 1.8 Hz, 1 H, 6-H), 4.08-4.03 (m, 1 H, 9′-H), 1.82-1.76 (m, 1 H, 12'-H), 1.69-1.62 (m, 1 H, 11'a-H), 1.60-1.54 (m, 1 H, 11′b-H), 0.94 (d, J = 6.5, 6 H, 13'H) ppm;

^{13}C-NMR (500 MHz, DMSO-d_6, 25^{o}C): δ = 177.01 (C4), 174.77 (C10'), 165.09 (C7), 161.64 (C5), 157.15 (C9), 150.20 (C3'), 146.40 (C2), 141.00 (C4'), 137.76 (C3), 124.08 (C5'), 119.35 (C6′), 116.51 (C2′), 103.95 (C10), 99.24 (C6), 94.02 (C8), 53.08 (C9'), 40.57 (C11'), 24.95 (C12'), 22.00 (C13') ppm.

Mass characterization of 2c and 2d regioisomers: **Mass:** MS (ESI) m/z: $[M+H]^{+}$ for $C_{22}H_{21}NO_{10}$: calcd: 459.12; found: 459.4.

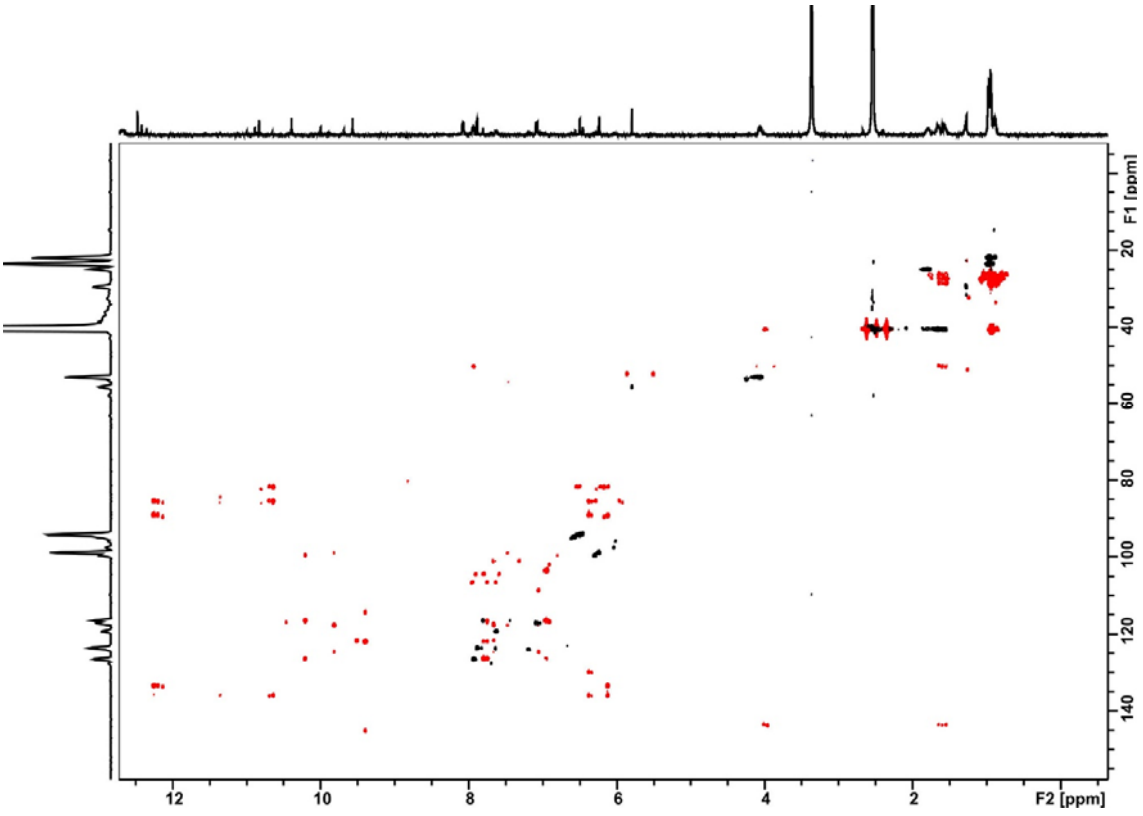
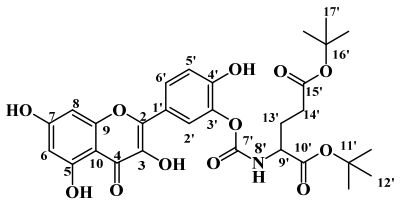
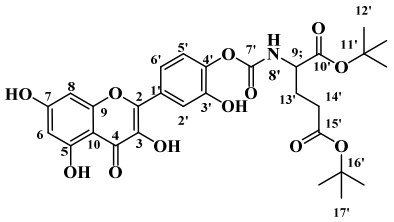


Figure S3. ^{1}H-^{13}C HSQC (colored in black) and ^{1}H-^{13}C HMBC (colored in red) spectra of 2c and 2d.

2.5 NMR and MS characterization Synthesis of 3'-O-CO-(Glu-OtBu)-Quercetin (3a) and 4'-O-CO-(Glu-OtBu)-Quercetin (3b) (71%):



3a



3b

^{1}H-NMR characterization 3a (500 MHz, DMSO-d_6, 25^{o}C): δ = 12.47 (s, 1 H, 5-OH), 10.84 (s, 1 H, 7-OH), 10.36 (s, 1 H, 4’-OH), 9.55 (s, 1 H, 3-OH), 8.11 (d, J = 7.5 Hz, 1 H, 8’-NH), 7.95 (dd, J = 8.6 Hz, 2.2 Hz, 1 H, 6’-H), 7.8 (d, J = 2.2 Hz, 1 H, 2’-H), 7.09 (d, J = 8.6Hz, 1 H, 5’-H), 6.48 (d, J = 2.0 Hz, 1 H, 8-H), 6.23 (d, J = 2.0 Hz, 1 H, 6-H), 4.04- 3.99 (m, 1 H, 9′-H), 2.00 (m, 2 H, 14’-H), 1.87 (m, 2 H, 13’-H), 1.47 (s, 9 H, 17′-H), 1.45 (s, 9 H, 12’-H) ppm;

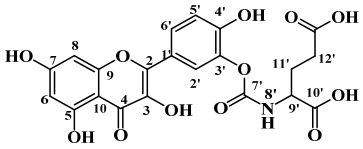
^{13}C-NMR (500 MHz, DMSO-d_6, 25^{o}C): δ = 176.81 (C4), 172.31 (C15’), 172.31 (C10’), 164.80 (C7), 161.60 (C5), 157.00 (C9), 154.75 (C7’), 152.44 (C4’), 146.59 (C2), 139.59 (C3’), 126.72 (C6′), 123.73 (C2′), 122.63 (C1’), 117.30 (C5′), 103.92 (C10), 98.96 (C6), 94.25 (C8), 81.7 (C11’), 80.72 (C16’), 54.62 (C9’), 28.48 (C17’), 28.48 (C12’), 27.00 (C14’), 27.00 (C13’) ppm.

^{1}H-NMR characterization 3b (500 MHz, DMSO-d_6, 25^{o}C): δ = 12.41 (s, 1 H, 5-OH), 10.88 (s, 1 H, 7-OH), 9.97 (s, 1 H, 3’-OH), 9.68 (s, 1 H, 3-OH), 8.11 (d, J = 7.5 Hz, 1 H, 8’-NH), 7.81 (d, J = 2.2 Hz, 1 H, 2’-H), 7.62 (dd, J = 8.6, 2.2 Hz, 1 H, 6’-H), 7.18 (d, J = 8.6Hz, 1 H, 5’-H), 6.45 (d, J = 2.0 Hz, 1 H, 8-H), 6.24 (d, J = 2.0 Hz, 1 H, 6-H), 4.04- 3.99 (m, 1 H, 9′-H), 2.00 (m, 2 H, 14’-H), 1.87 (m, 2 H, 13’-H), 1.47 (s, 9 H, 17′-H), 1.45 (s, 9 H, 12’-H) ppm;

^{13}C-NMR (500 MHz, DMSO-d_6, 25^{o}C): δ = 177.03 (C4), 172.31 (C10’), 172.30 (C15’), 164.80 (C7), 161.60 (C5), 157.00 (C9), 154.75 (C7’), 150.21 (C3’), 146.36 (C2), 140.86 (C4’), 129.55 (C1′), 124.15 (C5′), 119.33 (C6’), 116.61 (C2′), 103.92 (C10), 98.96 (C6), 94.14 (C8), 81.70 (C11’), 80.72 (C16’), 54.62 (C9’), 28.48 (C17’), 28.48 (C12’), 27.05 (C14’), 27.05 (C13’) ppm.

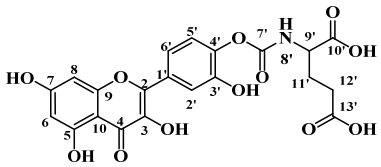
Mass characterization of 3a and 3b regioisomers: **Mass:** MS (ESI) m/z: $[M-H]^-$ for $C_{29}H_{33}NO_{12}$: calcd: 587.20; found: 586.3.

2.6 NMR and MS characterization Synthesis 3'-O-CO-Glu-Quercetin (3c) and 4'-O-CO-Glu-Quercetin (3d) (86%):



3c

76.1%



3d

23.4%

^{1}H-NMR characterization 3c (500 MHz, DMSO-d_6, 25^{o}C): δ = 12.85 (bs), 12.47 (s, 1 H, 5-OH), 10.84 (s, 1 H, 7-OH), 10.36 (s, 1 H, 4'-OH), 9.55 (s, 1 H, 3-OH), 8.14 (d, J = 8.2 Hz, 1 H, 8'-NH), 7.92 (dd, J = 8.6 Hz, 2.2 Hz, 1 H, 6'-H), 7.79 (d, J = 2.2 Hz, 1 H, 2'-H), 7.06 (d, J = 8.6Hz, 1 H, 5'-H), 6.48 (d, J = 2.0 Hz, 1 H, 8-H), 6.23 (d, J = 2.0 Hz, 1 H, 6-H), 4.27 - 4.22 (m, 1 H, 9´H), 3.16 - 3.11 (m, 2 H, 12'-H), 3.01 - 3.29 (m, 2 H, 11'-H) ppm;

^{13}C-NMR (500 MHz, DMSO-d_6, 25^{o}C): δ = 177.01 (C4), 173.77 (C13'), 173.44 (C10'), 164.81 (C7), 161.67 (C5), 156.88 (C9), 154.99 (C7'), 152.26 (C4'), 146.70 (C2), 139.42 (C3'), 126.7 (C6´), 123.83 (C1´), 123.73 (C2'), 117.31 (C5´), 103.99 (C10), 98.98 (C6), 94.25 (C8), 56.46 (C9'), 37.36 (C11'), 37.36 (C12') ppm.

^{1}H-NMR characterization 3d (500 MHz, DMSO-d_6, 25^{o}C): δ = 12.85 (bs), 12.41 (s, 1 H, 5-OH), 10.88 (s, 1 H, 7-OH), 9.97 (s, 1 H, 3'-OH), 9.68 (s, 1 H, 3-OH), 8.15 (d, J = 8.2 Hz, 1 H, 8'-NH), 7.78 (dd, J = 2.2 Hz, 1 H, 2'-H), 7.58 (d, J = 8.6, 2.2 Hz, 1 H, 6'-H), 7.07 (d, J = 8.4Hz, 1 H, 5'H), 6.44 (d, J = 2.0 Hz, 1 H, 8-H), 6.23 (d, J = 2.0 Hz, 1 H, 6-H), 4.27 - 4.22 (m, 1 H, 9´-H), 3.16 - 3.11 (m, 2 H, 12'-H), 3.01 - 3.29 (m, 2 H, 11'-H) ppm;

^{13}C-NMR (500 MHz, DMSO-d_6, 25^{o}C): δ = 177.01 (C4), 173.77 (C13'), 173.44 (C10'), 165.07 (C7), 161.67 (C5), 157.23 (C9), 154.99 (C7'), 150.28 (C3'), 146.50 (C2), 140.89 (C4'), 129.47 (C1´), 124.01 (C5´), 119.30 (C6'), 116.54 (C2´), 104.03 (C10), 98.98 (C6), 94.25 (C8), 56.46 (C9'), 37.36 (C11'), 37.36 (C12') ppm.

Mass characterization of 3c and 3d regioisomers: **Mass:** MS (ESI) m/z: $[M-H]^-$ for $C_{21}H_{17}NO_{12}$: calcd: 475.08; found: 474.0.

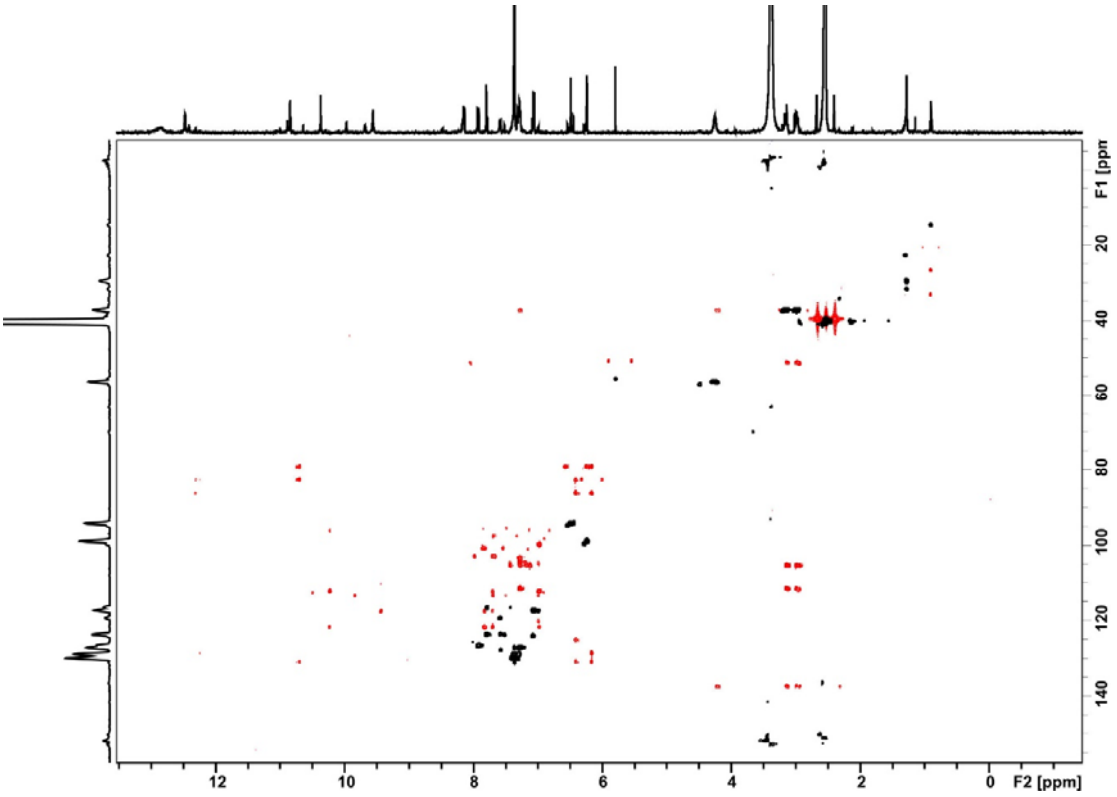
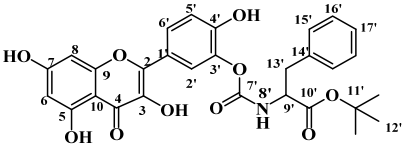
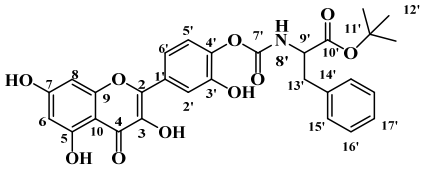


Figure S4. ^{1}H-^{13}C HSQC (colored in black) and ^{1}H-^{13}C HMBC (colored in red) spectra of 3c and 3d.

2.7 NMR and MS characterization 4'-O-CO-(Phe-OtBu)-Quercetin (4a) and 4'-O-CO-(Phe-OtBu)-Quercetin (4b) (67%):



4a



4b

^{1}H-NMR characterization 4a (500 MHz, DMSO-d_6, 25^{o}C): δ = 12.47 (s, 1 H, 5-OH), 10.84 (s, 1H, 7-OH), 10.39 (s, 1 H, 4'-OH), 9.57 (s, 1 H, 3-OH), 8.20 (d, J = 7.7 Hz, 1 H, 8'-NH), 7.93 (dd, J = 8.7 Hz, 2.2 Hz, 1 H, 6'-H), 7.82 (d, J = 2.2 Hz, 1 H, 2'-H), 7.36-7.34 (m, 4 H, 15' and 16'-H), 7.30-7.26 (m, 1 H, 17'-H), 7.08 (d, J = 8.7Hz, 1 H, 5'-H), 6.48 (d, J = 2.0 Hz, 1 H, 8-H), 6.23 (d, J = 2.0 Hz, 1 H, 6-H), 4.22- 4.17 (m, 1 H, 9′-H), 3.08-2.98 (m, 2 H, 13'-H), 1.39 (s, 9 H, 12'-H) ppm;

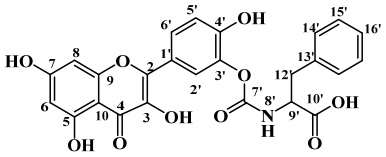
^{13}C-NMR (500 MHz, DMSO-d_6, 25^{o}C): δ = 176.81 (C4), 171.42 (C10'), 164.76 (C7), 161.63 (C5), 156.98 (C9), 154.59 (C7'), 152.45 (C4'), 146.56 (C2), 139.54 (C3'), 138.2 (C14'), 136.89 (C3), 130.03 (C15'), 129.05 (C16'), 127.32 (C17'), 126.69 (C6'), 123.69 (C2′), 122.45 (C1'), 117.25 (C5′), 103.91 (C10), 98.98 (C6), 94.25 (C8), 81.66 (C11'), 57.08 (C9'), 37.56 (C13'), 28.43 (C12') ppm.

^{1}H-NMR characterization 4b (500 MHz, DMSO-d_6, 25^{o}C): δ = 12.41 (s, 1 H, 5-OH), 10.88 (s, 1 H, 7-OH), 9.99 (s, 1 H, 3'-OH), 9.68 (s, 1 H, 3-OH), 8.21 (d, J = 7.8 Hz, 1 H, 8'-NH), 7.80 (d, J = 2.1 Hz, 1 H, 2'-H), 7.59 (dd, J = 8.6 Hz, 2.1 Hz, 1 H, 6'-H), 7.36-7.34 (m, 4 H, 15' and 16'-H), 7.30-7.26 (m, 1 H, 17'-H), 7.10 (d, J = 8.6Hz, 1 H, 5'-H), 6.44 (d, J = 2.0 Hz, 1 H, 8-H), 6.24 (d, J = 2.0 Hz, 1 H, 6-H), 4.22- 4.17 (m, 1 H, 9′-H), 3.08-2.98 (m, 2 H, 13'-H), 1.39 (s, 9 H, 12'-H) ppm;

^{13}C-NMR (500 MHz, DMSO-d_6, 25^{o}C): δ = 177.07 (C4), 171.46 (C10'), 164.95 (C7), 161.74 (C5), 157.04 (C9), 154.59 (C7'), 150.27 (C3'), 146.27 (C2), 140.87 (C4'), 138.20 (C14'), 130.03 (C15'), 129.05 (C16'), 127.32 (C17'), 124.05 (C5'), 122.45 (C1'), 119.32 (C6′), 116.59 (C2′), 104.02 (C10), 98.98 (C6), 94.14 (C8), 81.66 (C11'), 57.08 (C9'), 37.56 (C13'), 28.43 (C12') ppm.

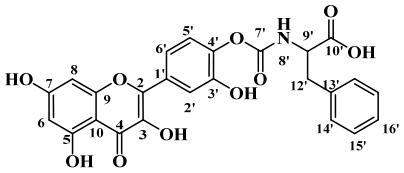
Mass characterization of 4a and 4b regioisomers: **Mass:** MS (ESI) m/z: $[M-H]^-$ for $C_{29}H_{27}NO_{10}$: calcd: 549.16; found: 548.2.

2.8 NMR and MS characterization of 3'-O-CO-Phe-Quercetin (4c) and 4'-O-CO-Phe-Quercetin (4d) (90%):



4c

74.8%



4d

25.2%

^{1}H-NMR characterization 4c (500 MHz, DMSO-d_6, 25^{o}C): δ = 12.88 (bs, 1H, 11'-OH), 12.47 (s, 1 H, 5OH), 10.85 (s, 1H, 7-OH), 10.37 (s, 1 H, 4'-OH), 9.55 (s, 1 H, 3-OH), 8.14 (d, J = 8 Hz, 1 H, 8'-NH), 7.92 (dd, J = 8.7 Hz, 2.2 Hz, 1 H, 6'-H), 7.79 (d, J = 2.2 Hz, 1 H, 2'-H), 7.36-7.35 (m, 4 H, 14' and 15'-H), 7.31-7.26 (m, 1 H, 16'-H), 7.06 (d, J = 8.6Hz, 1 H, 5'-H), 6.48 (d, J = 2.0 Hz, 1 H, 8-H), 6.23 (d, J = 2.0 Hz, 1 H, 6-H), 4.27- 4.22 (m, 1 H, 9′-H), 3.14 (dd, J = 14.0 Hz, 4.4Hz, 1 H, 12a'-H), 2.99 (dd, J = 9.6Hz, 4.2Hz, 1 H, 12b'-H) ppm;

^{13}C-NMR (500 MHz, DMSO-d_6, 25^{o}C): δ = 174.04 (C10'), 165.03 (C7), 161.77 (C5), 157.07 (C9), 152.45 (C4'), 146.74 (C2), 139.57 (C3'), 138.64 (C13'), 130.02 (C14'), 129.01 (C15'), 127.3 (C16'), 126.70 (C6'), 123.83 (C2′), 122.63 (C1'), 117.40 (C5′), 104.00 (C10), 99.10 (C6), 94.34 (C8), 56.54 (C9'), 37.39 (C12') ppm.

^{1}H-NMR characterization 4d (500 MHz, DMSO-d_6, 25^{o}C): δ = 12.88 (bs, 1 H, 11'-OH), 12.40 (s, 1 H, 5OH), 10.89 (s, 1 H, 7-OH), 9.97 (s, 1 H, 3'-OH), 9.67 (s, 1 H, 3-OH), 8.15 (d, J = 7.8 Hz, 1 H, 8'-NH), 7.78 (d, J = 2. Hz, 1 H, 2'-H), 7.58 (dd, J = 8.6 Hz, 2.1 Hz, 1 H, 6'-H), 7.36-7.35 (m, 4 H, 14' and 15'-H), 7.32-7.26 (m, 1 H, 16'-H), 7.07 (d, J = 8.6Hz, 1 H, 5'-H), 6.44 (d, J = 2.2 Hz, 1 H, 8-H), 6.23 (d, J = 2.2 Hz, 1 H, 6-H), 4.27- 4.22 (m, 1 H, 9′-H), 3.14 (dd, J = 14.0 Hz, 4.4Hz, 1 H, 12a'-H), 2.99 (dd, J = 9.6Hz, 4.2Hz, 1 H, 12b'-H) ppm;
^{13}C-NMR (500 MHz, DMSO-d_6, 25^{o}C): δ = 174.04 (C10'), 165.09 (C7), 161.50 (C5), 157.26 (C9), 150.15 (C3'), 146.74 (C2), 140.84 (C4'), 138.64 (C13'), 130.02 (C14'), 129.64 (C1'), 129.01 (C15'), 127.30 (C16'), 124.16 (C5'), 119.50 (C6′), 116.66 (C2′), 104.00 (C10), 99.10 (C6), 94.23 (C8), 56.54 (C9'), 37.39 (C12') ppm.

Mass characterization of 4c and 4d regioisomers: **Mass:** MS (ESI) m/z: $[M+H]^+$ for $C_{25}H_{19}NO_{10}$: calcd, 493.10; found: 516.0 $[M+Na]^+$.

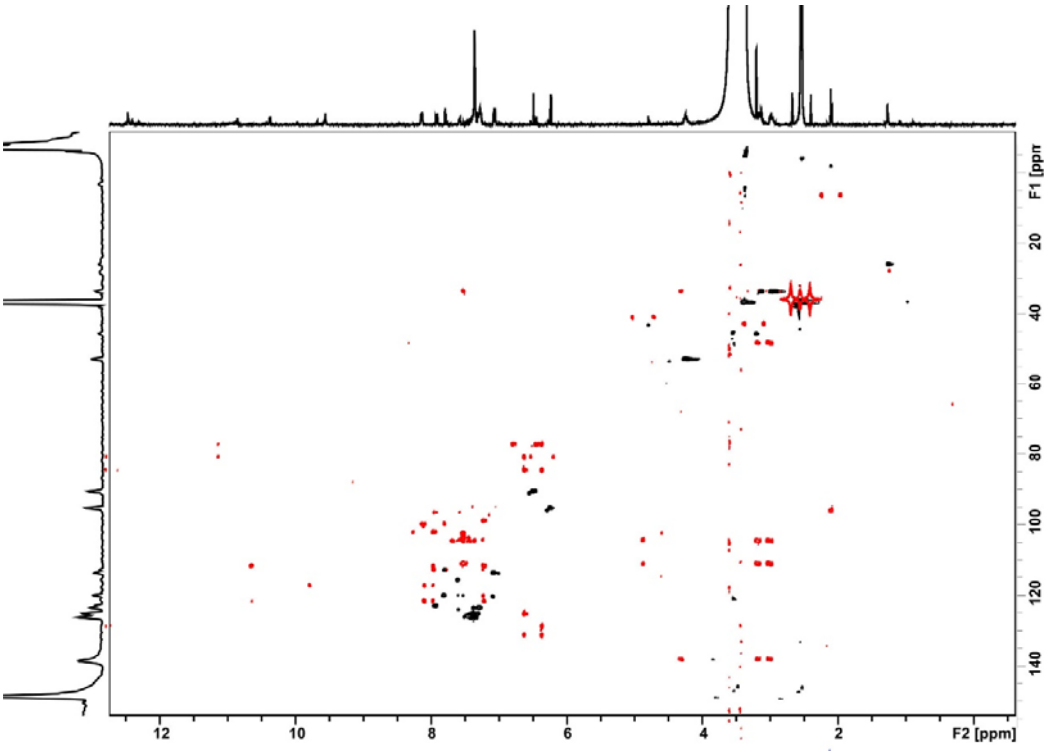


Figure S5. ^{1}H-^{13}C HSQC (colored in black) and ^{1}H-^{13}C HMBC (colored in red) spectra of 4c and 4d.

3. Mass and IR spectra of the four synthesized hybrids

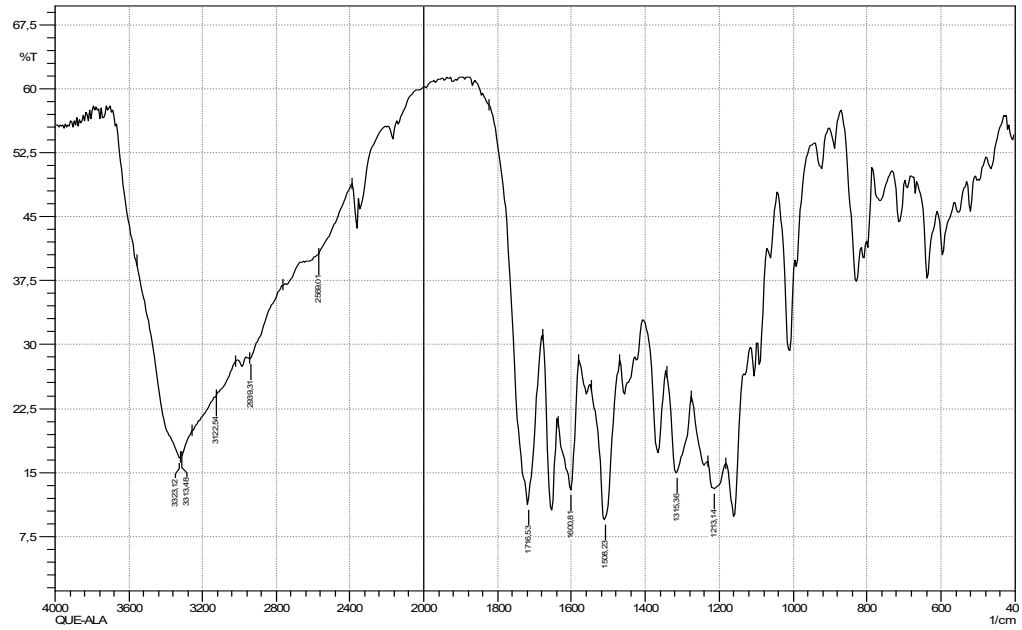


Figure S6. IR spectrum of Quercetin-Alanine.

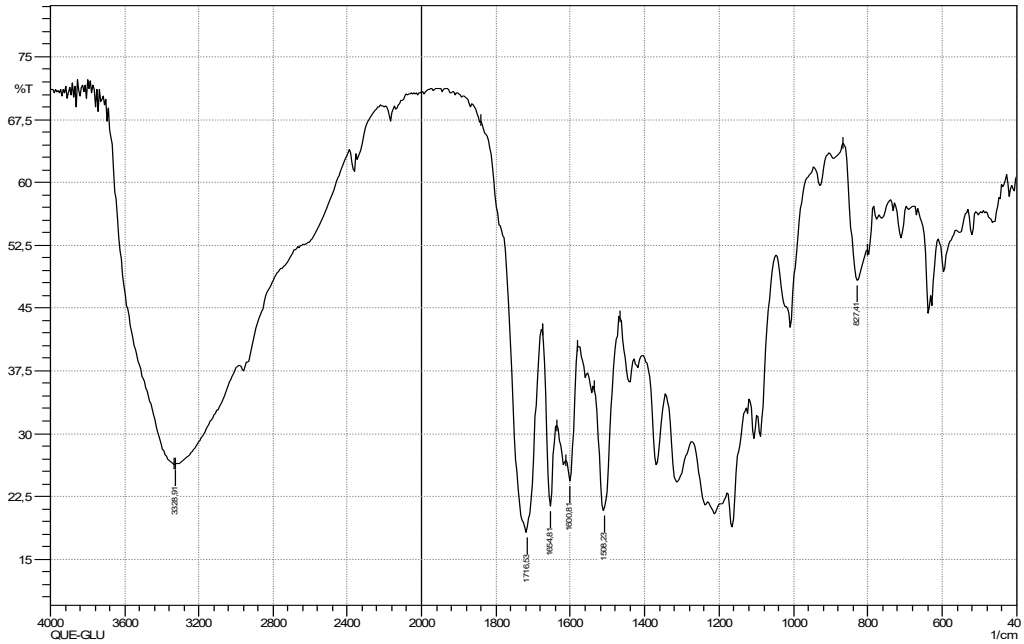


Figure S7. IR spectrum of Quercetin-Glutamic acid.

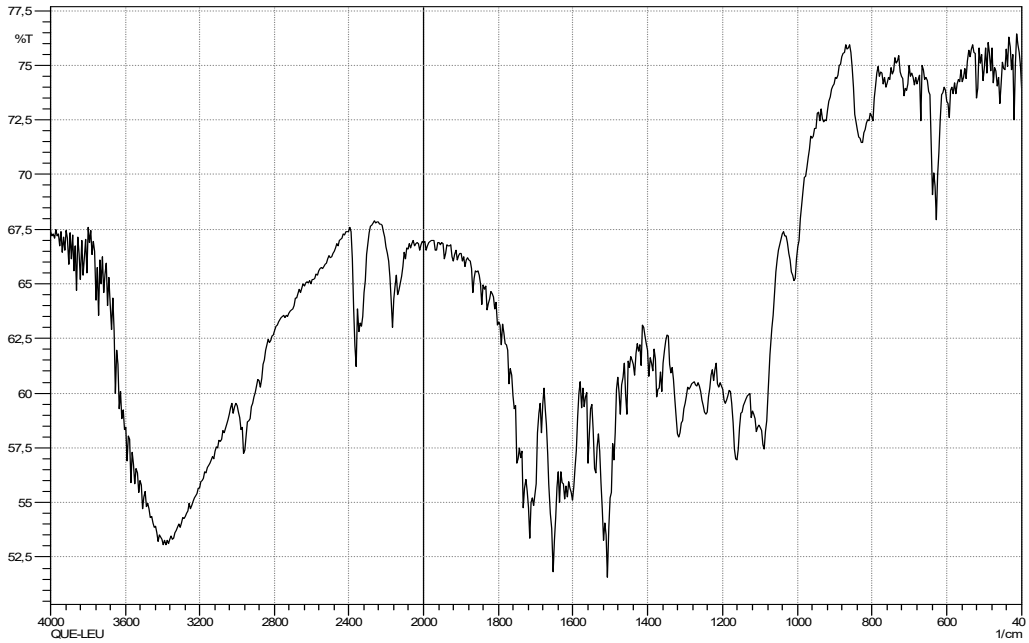


Figure S8. IR spectrum of Quercetin-Leucine.

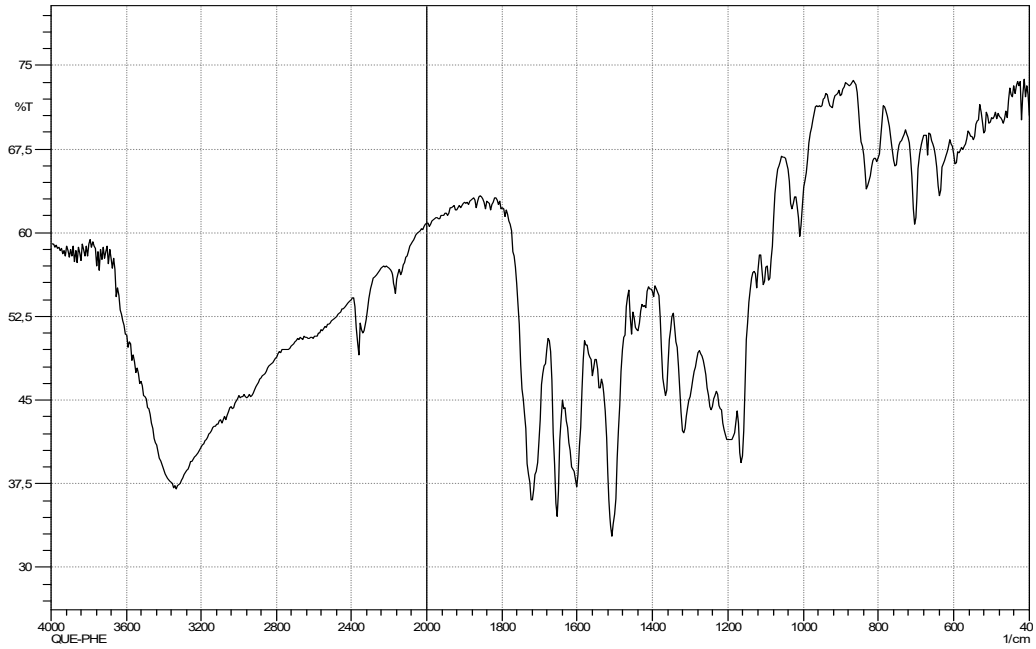


Figure S9. IR spectrum of Quercetin-Phenylalanine.

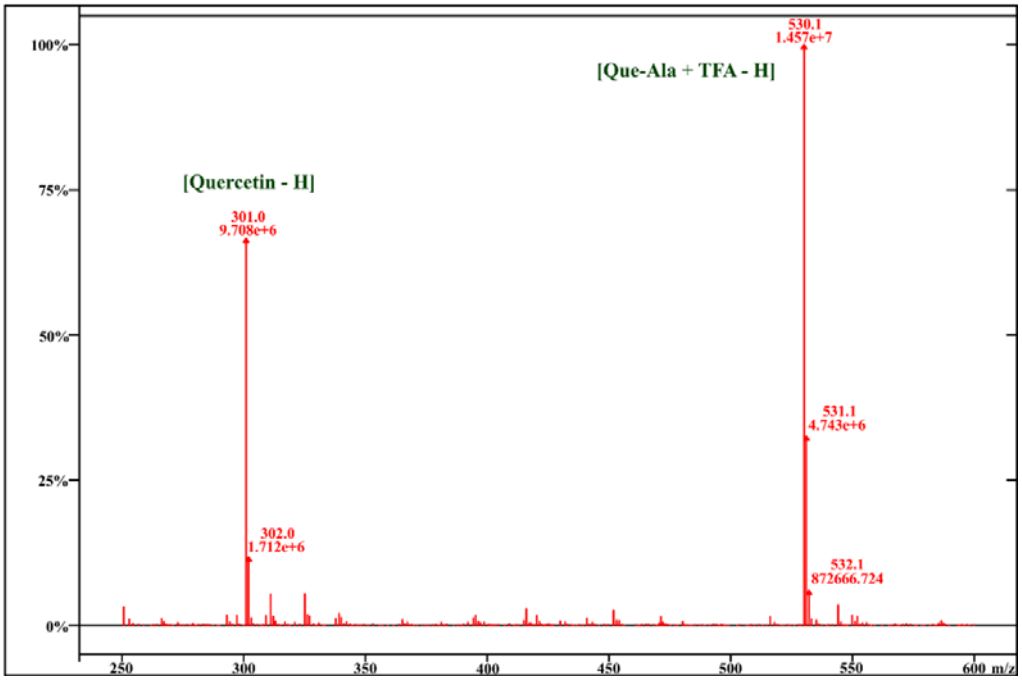


Figure S10. ESI Mass spectrum of Quercetin-Alanine in negative ion mode.

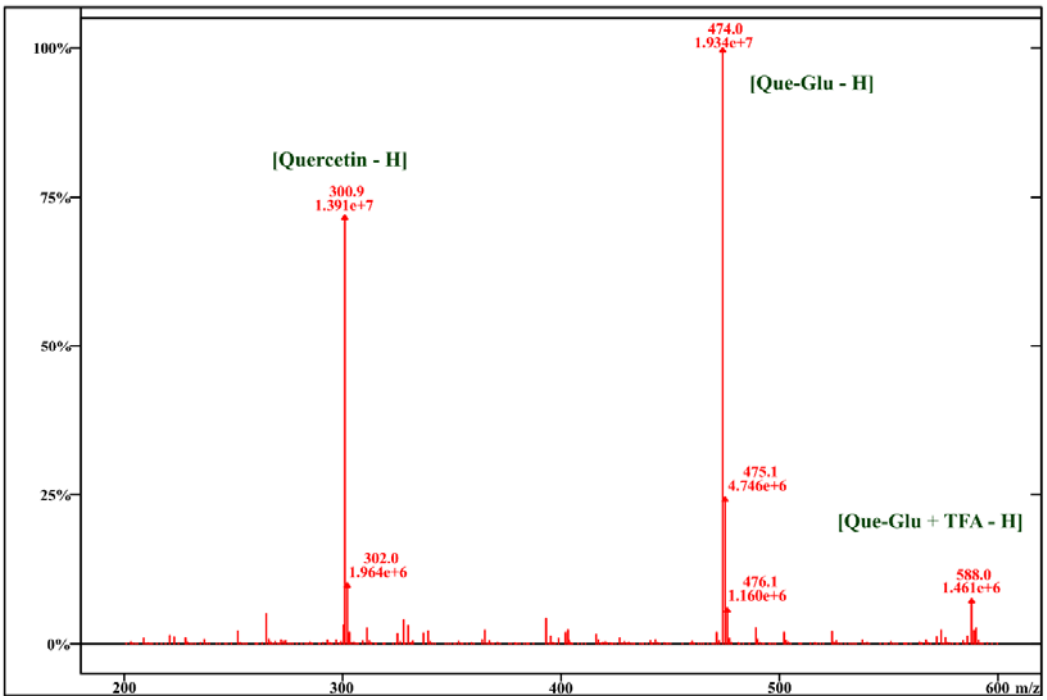


Figure S11. ESI Mass spectrum of Quercetin-Glutamic acid in negative ion mode.

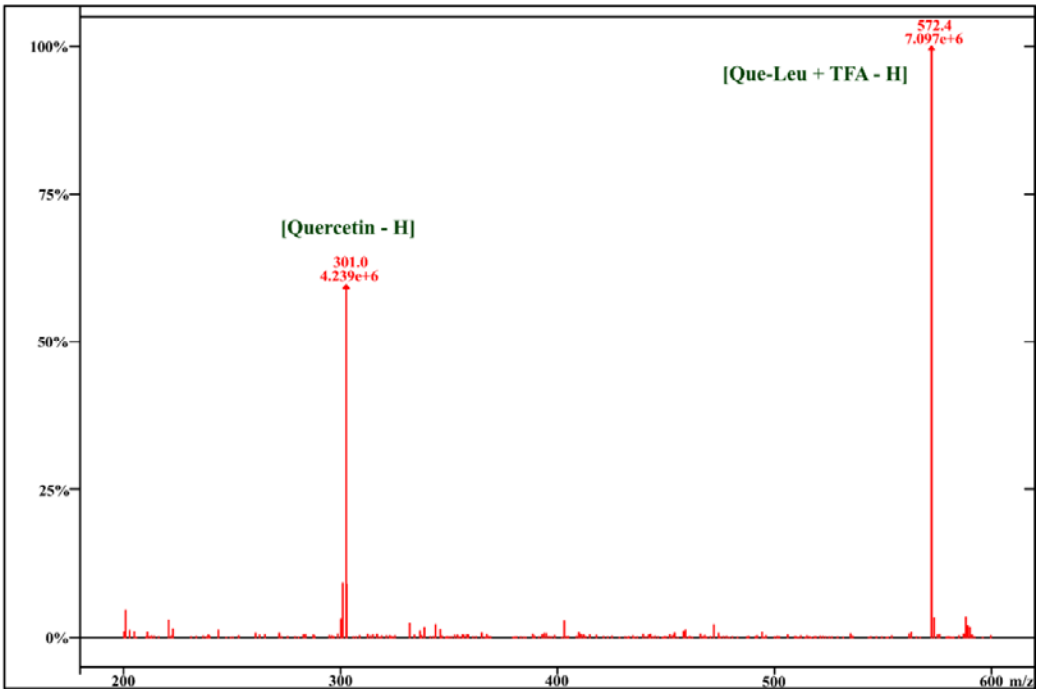


Figure S12. ESI Mass spectrum of Quercetin-Leucine in negative ion mode.

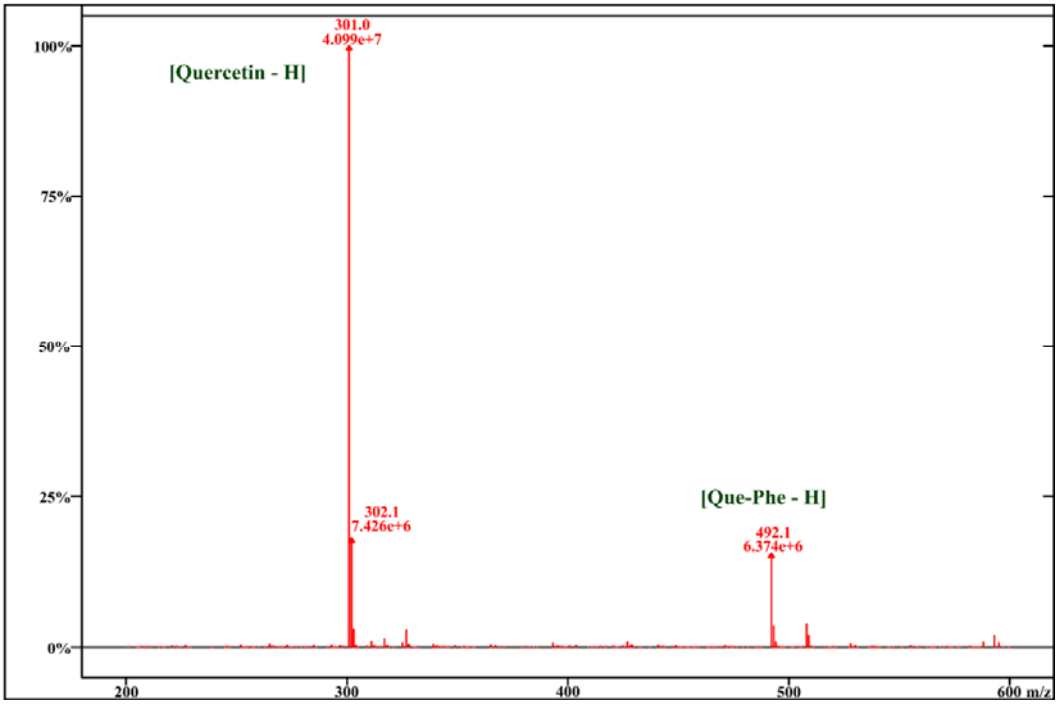


Figure S13. ESI Mass spectrum of Quercetin-Phenylalanine in negative ion mode.

4. 2D and 3D representation of the binding poses of the quercetin analogues.

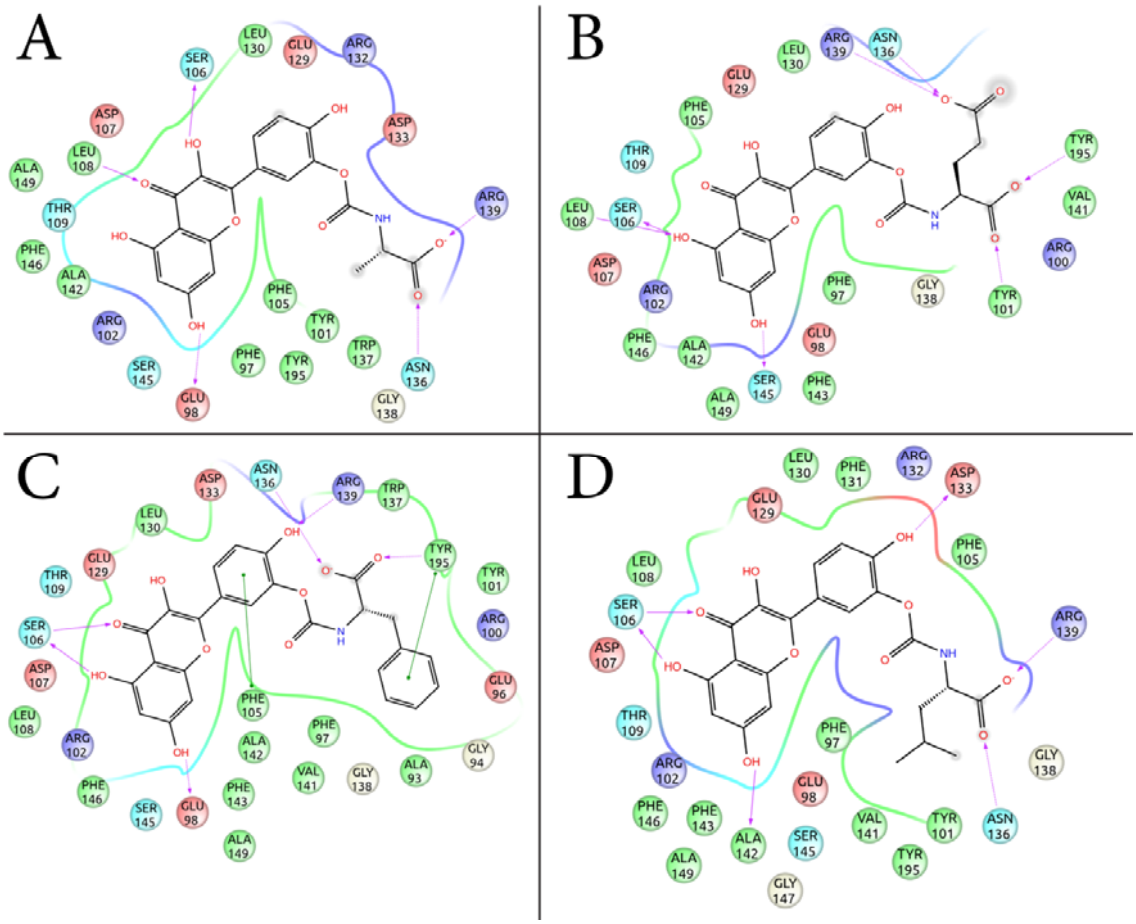


Figure S14. 2D representation of the binding poses of the quercetin analogues: A) Que-Ala3; B) Que-Glu3; C) Que-Phe3 and D) Que-Leu3 in the crystal structure of Bcl-xLwith PDB ID 3ZLR.

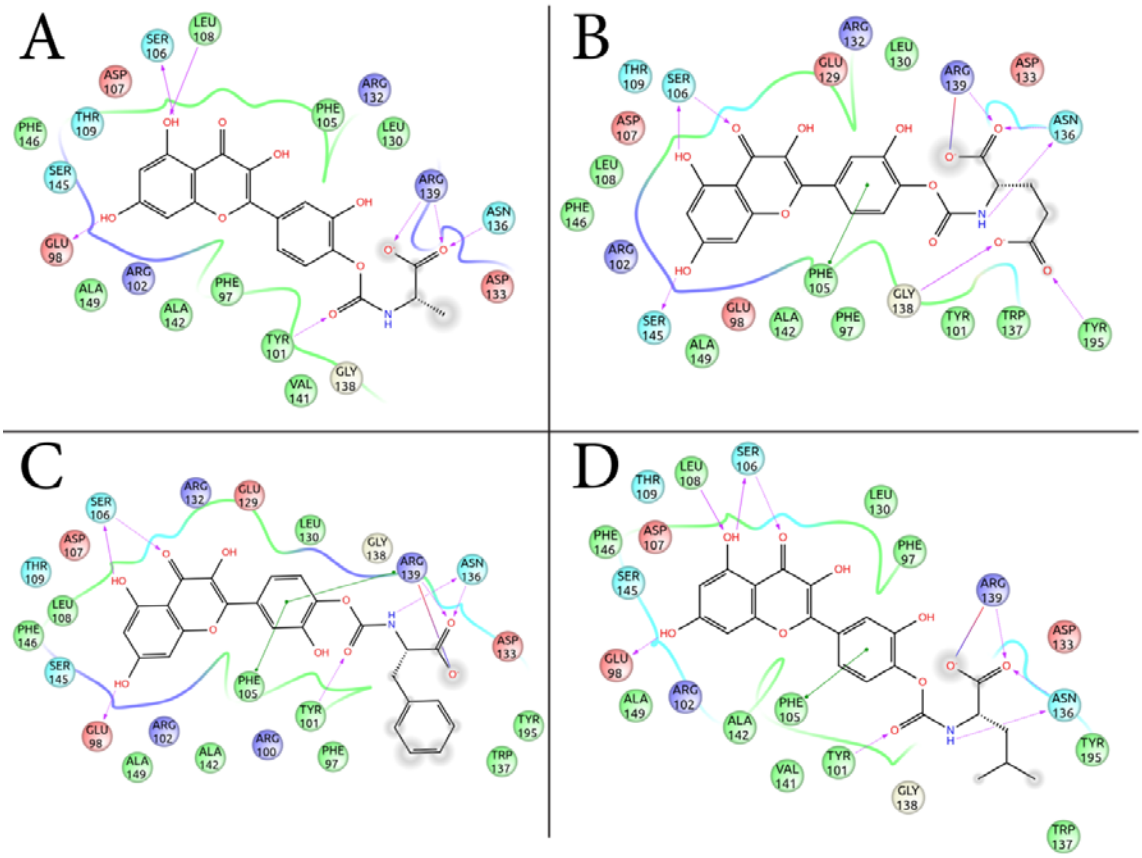


Figure S15. 2D representation of the binding poses of the quercetin analogues: A) Que-Ala4; B) Que-Glu4; C) Que-Phe4 and D) Que-Leu4 in the crystal structure of Bcl-xLwith PDB ID 3ZLR.

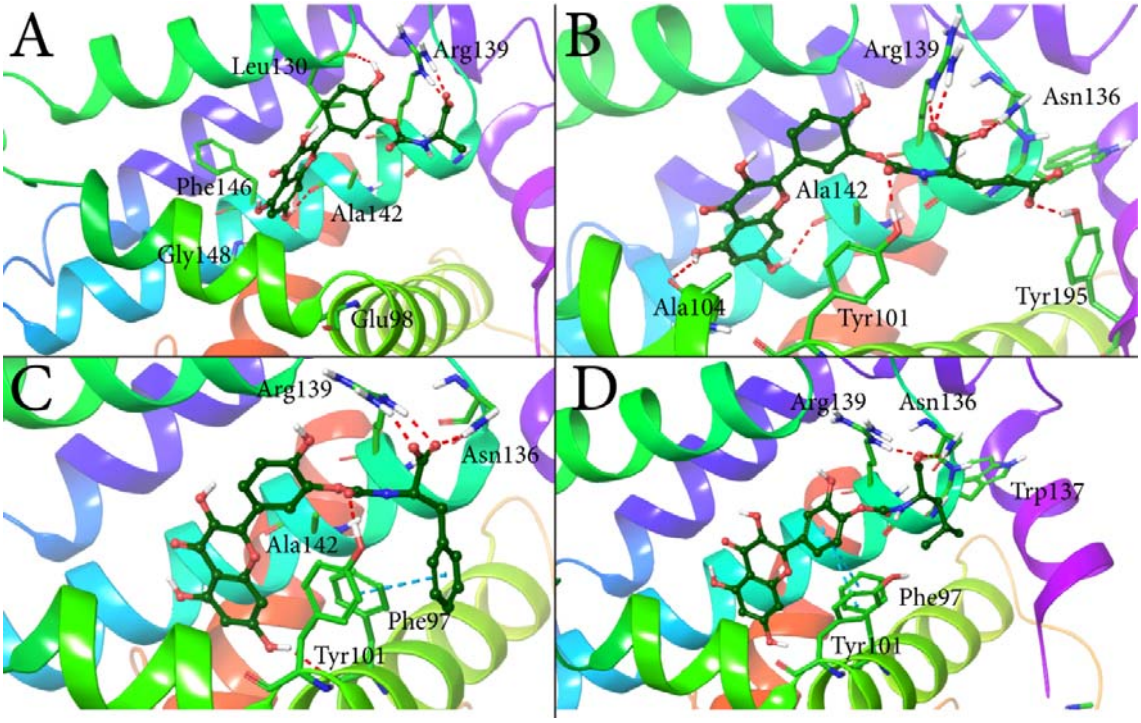


Figure S16. 3D representation of the binding poses of the quercetin analogues: A) Que-Ala3; B) Que-Glu3; C) Que-Phe3 and D) Que-Leu3 in the crystal structure of Bcl-xLwith PDB ID 2YXJ.

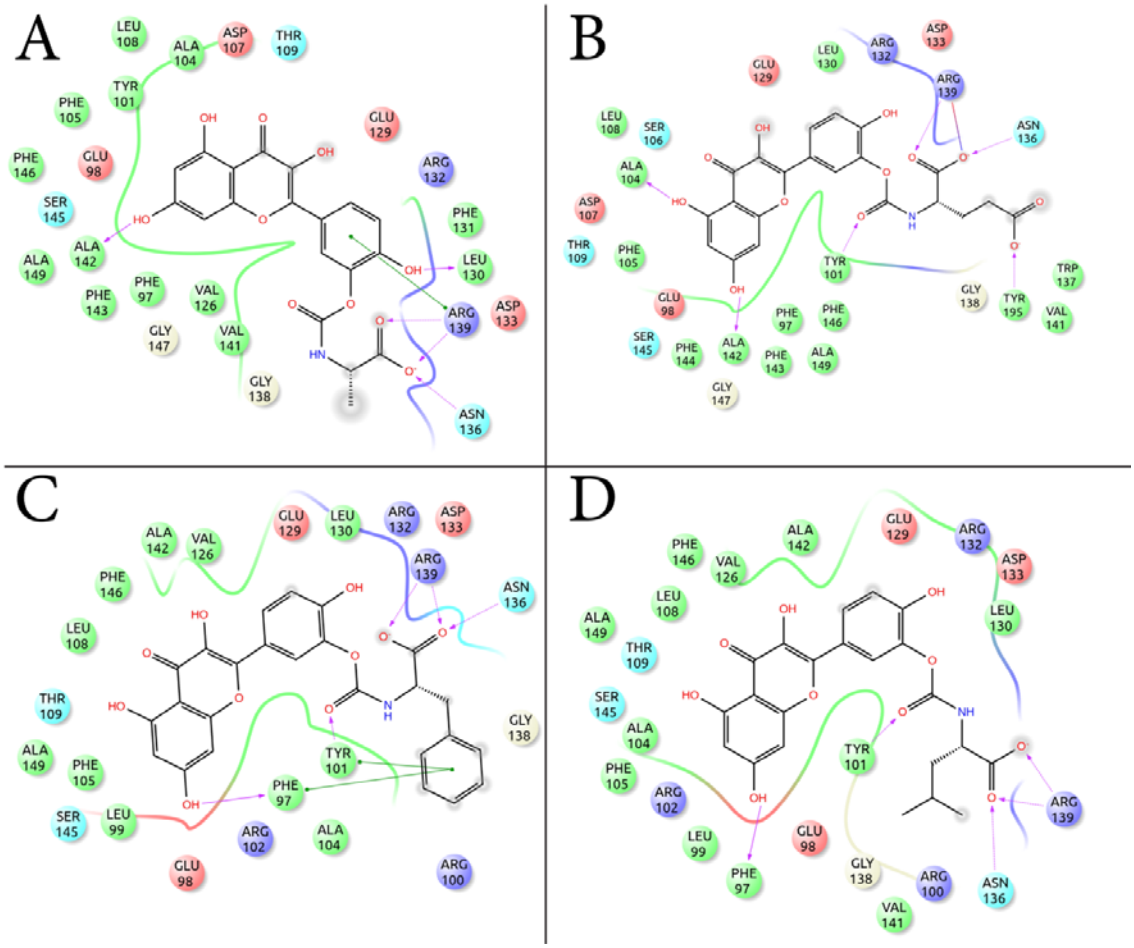


Figure S17. 2D representation of the binding poses of the quercetin analogues: A) Que-Ala3; B) Que-Glu3; C) Que-Phe3 and D) Que-Leu3 in the crystal structure of Bcl-xLwith PDB ID 2YXJ.

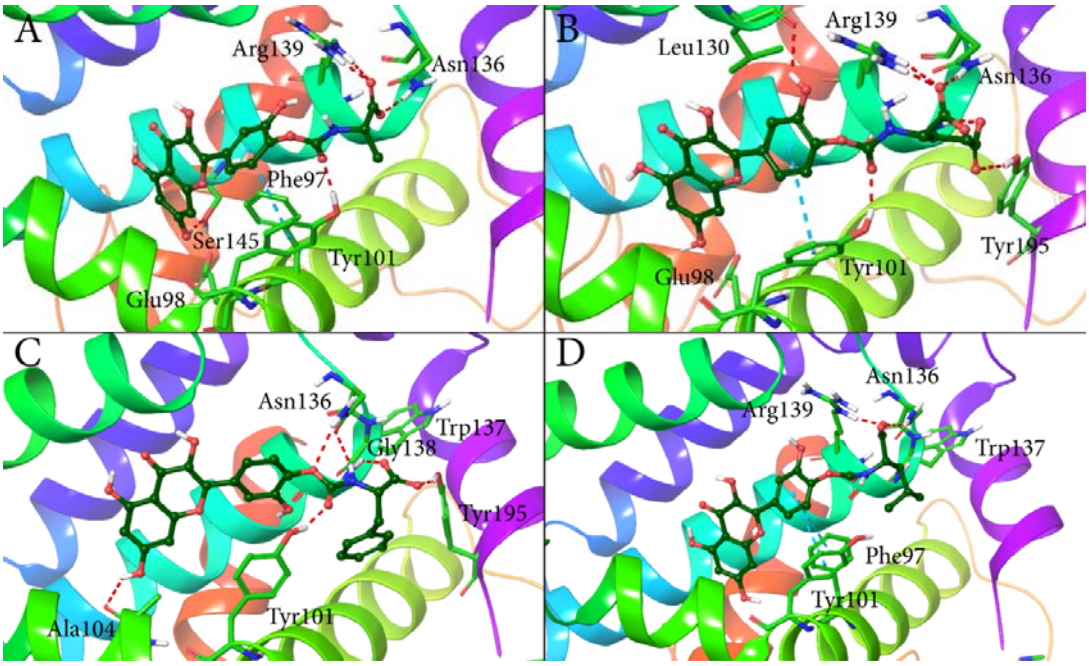


Figure S18. 3D representation of the binding poses of the quercetin analogues: A) Que-Ala4; B) Que-Glu4; C) Que-Phe4 and D) Que-Leu4 in the crystal structure of Bcl-xLwith PDB ID 2YXJ.

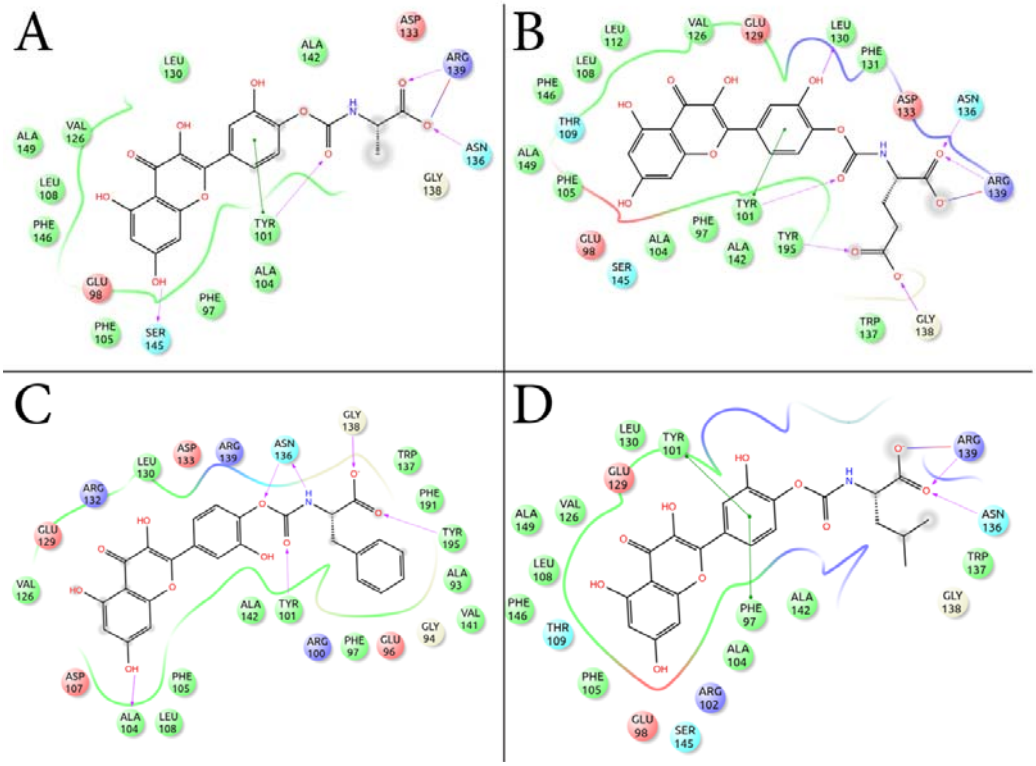


Figure S19. 2D representation of the binding poses of the quercetin analogues: A) Que-Ala4; B) Que-Glu4; C) Que-Phe4 and D) Que-Leu4 in the crystal structure of Bcl-xLwith PDB ID 2YXJ.

5. Fluorescence spectroscopic study and K_d determination of Bcl-xL and quercetin-amino acid analogues.

5.1 Fluorescence spectroscopic study of the Bcl-xL and Que-Ala interaction and K_d determination.

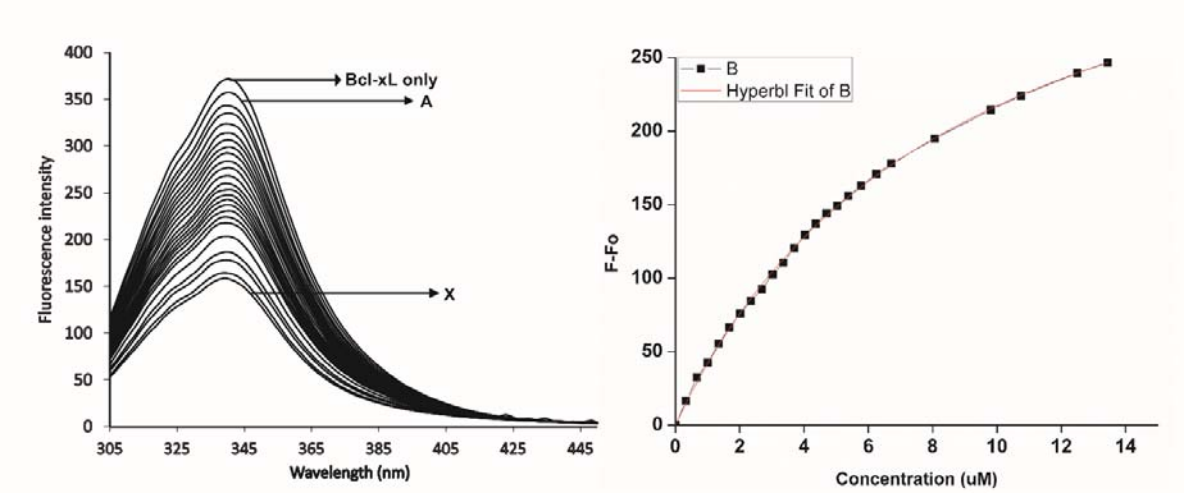


Figure S20. Fluorescence spectroscopic study of the Bcl-xL and Que-Ala interaction (right) and K_d determination (left). The concentration of Bcl-xLwas 2 uM. A-X curves represent titrations with incremental concentrations of Que-Ala (0.33, 0.67, 1.00, 1.34, 1.68, 2.01, 2.35, 2.68, 3.02, 3.36, 3.69, 4.03, 4.36, 4.70, 5.04, 5.37, 5.77, 6.24, 6.72, 8.06. 9.81, 10.75, 12.49 and 13.44 uM, respectively). K_d = 8.7 ± 0.2 uM.

5.2 Fluorescence spectroscopic study of the Bcl-xL and Que-Leu interaction and K_d determination.

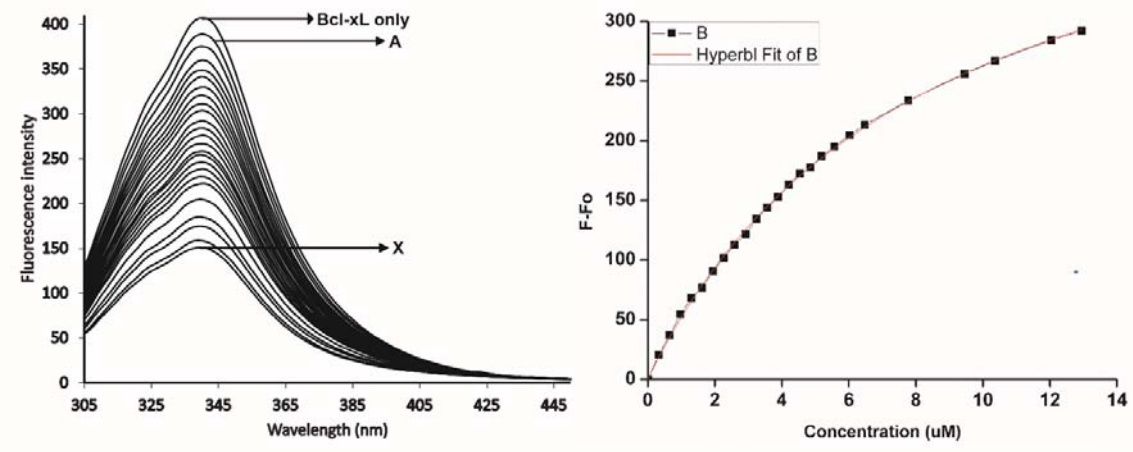


Figure S21. Fluorescence spectroscopic study of the Bcl-xL and quercetin-leucine interaction (right) and K_d determination (left). The concentration of Bcl-xLwas 2 uM. A-X curves represent titrations with incremental concentrations of quercetin-leucine (0.32, 0.64, 0.97, 1.29, 1.61, 1.94, 2.26, 2.59, 2.91, 3.23, 3.56, 3.88, 4.20, 4.53, 4.85, 5.18, 5.56, 6.02, 6.47, 7.77, 9.45, 10.36, 12.04 and 12.95 uM, respectively). K_d = 8.2 ± 0.1 uM.

5.3 Fluorescence spectroscopic study of the Bcl-xL and Que-Phe interaction and K_d determination.

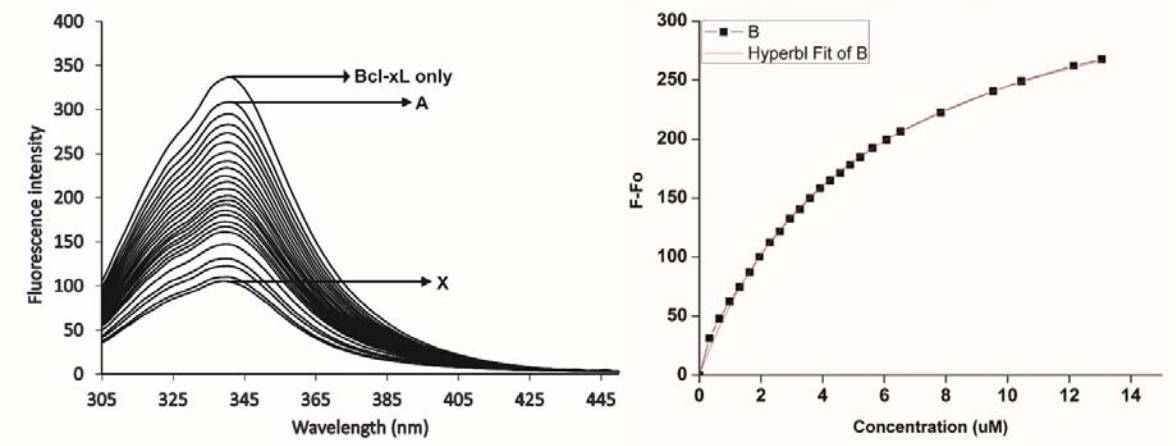


Figure S22. Fluorescence spectroscopic study of the Bcl-xL and quercetin-phenylalanine interaction (right) and K_d determination (left). The concentration of Bcl-xLwas 2 uM. A-X curves represent titrations with incremental concentrations of quercetin-phenylalanine (0.32,

0.65, 0.97, 1.30, 1.63, 1.95, 2.28, 2.61, 2.93, 3.26, 3.59, 3.91, 4.24, 4.56, 4.89, 5.22, 5.61, 6.07, 6.52, 7.83, 9.53, 10.44, 12.14 and 13.05 uM, respectively). K_d = 5.3 ± 0.2 uM

5.4 Fluorescence spectroscopic study of the Bcl-xL and Que-Glu interaction and K_d determination.

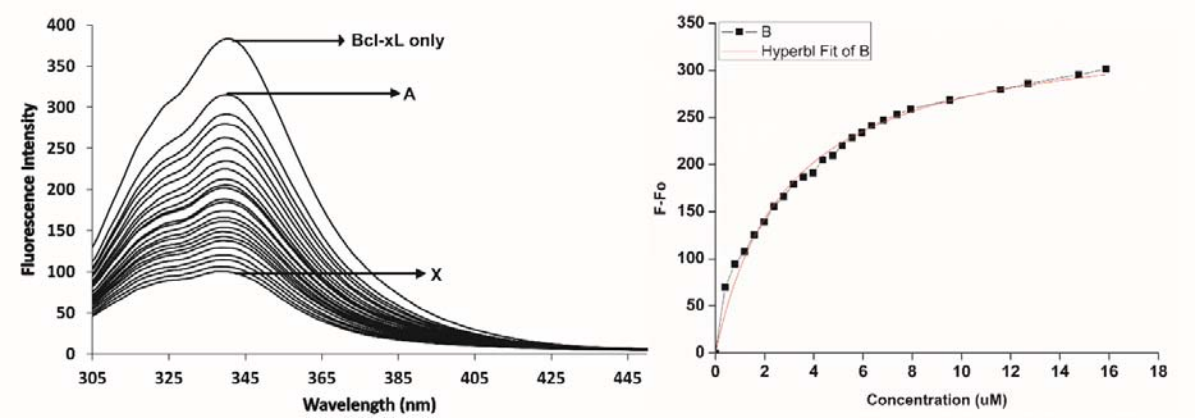


Figure S23. Fluorescence spectroscopic study of the Bcl-xL and Que-Glu interaction (right) and K_d determination (left). The concentration of Bcl-xLwas 2 uM. A-X curves represent titrations with incremental concentrations of Que-Glu (0.39, 0.79, 1.19, 1.58, 1.98, 2.38, 2.77, 3.17, 3.57, 3.96, 4.36, 4.76, 5.15, 5.55, 5.95, 6.35, 6.82, 7.38, 7.93, 9.52, 11.58, 12.70, 14.76 and 15.87 uM, respectively). K_d = 2.8 ± 0.1 uM.

6. Mapping the Bcl-xL-quercetin binding interface by 2D $^{1}H-^{15}N$ HSQC NMR.

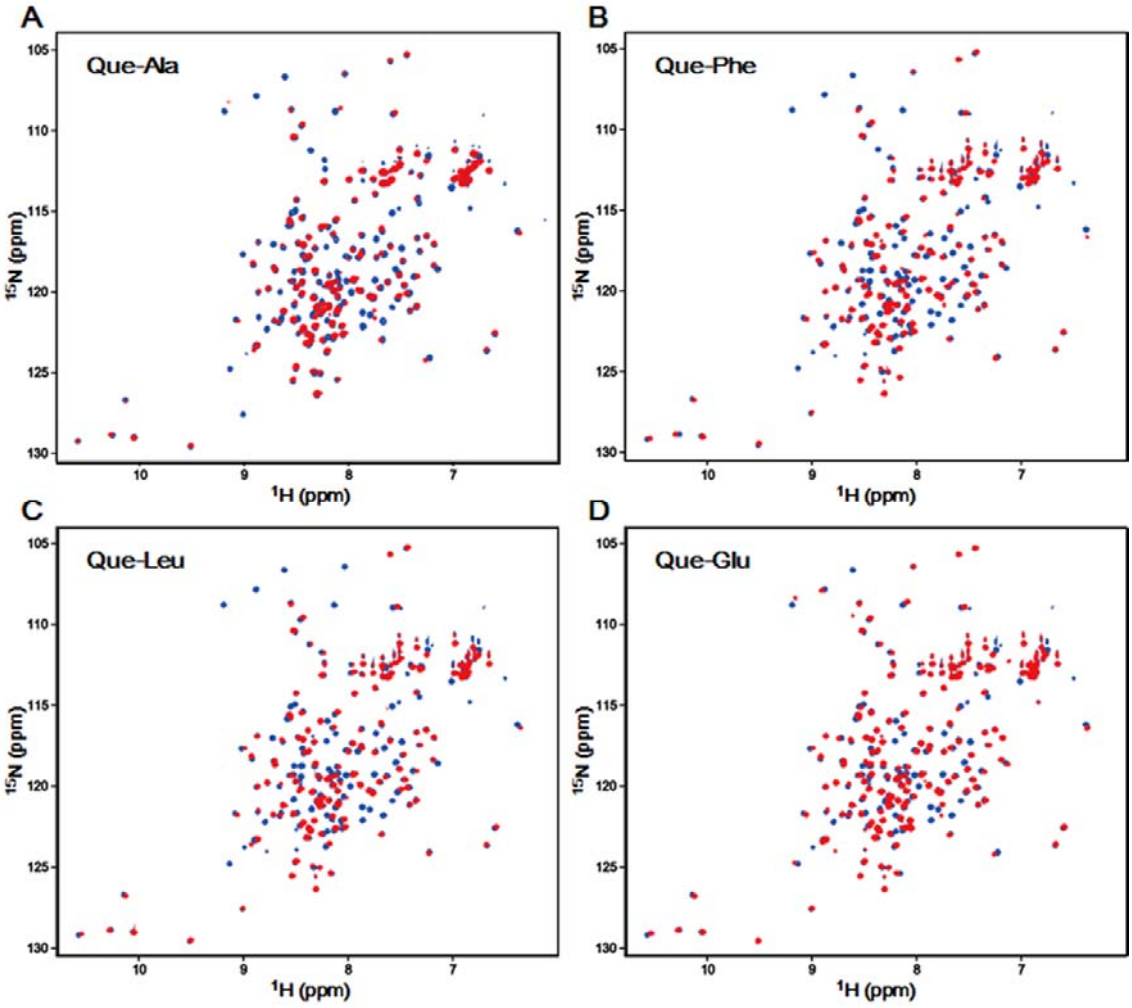


Figure S24. Mapping the Bcl-xL-quercetin binding interface by NMR. 2D $^{1}H-^{15}N$ HSQC full spectra of ^{15}N-labeled Bcl-xLprotein without (blue crosspeaks) and with the addition of quercetin analogues (red crosspeaks) (molar ratio 1:4).

7. Weighted ΔCS values for Quercetin-amino acid analogues.

Table S1: Weighted ΔCS values. The residues showing ΔCS > 0.1 ppm are colored in red, whereas ΔCS > 0.05 ppm are colored in blue.
* '0' indicates the disappearance of crosspeak upon ligand binding.
** 'N/A' indicates that the NMR assignment in free Bcl-xL is not available.
*** Not assigned due to peak overlap

Residue	ΔCS for QUE_ALA	ΔCS for QUE_E	ΔCS for QUE_PHE	ΔCS for QUE_LEU	
M1	0.021858637	0.015498387	0.023349518	0.018766992	
S2	0.00614817	0.01888915	0.021730163	0.011575837	
Q3	0.025573424	0.0085557	0.01479189	0.080087452	
S4	0.031003226	0.003	0.01118034	0.004898979	
N5	0.020736441	0.031260198	0.036894444	0.029495762	
R6	0.003286335	0.0085557	0.010246951	0.009011104	
E7	0.026717036	0.012441865	0.015779734	0.007224957	
L8	0.01077961	0.021232051	0.01744133	0.014703741	
V9	0.008173127	0.008590693	0.029003448	0.021913466	
V10	0.035239183	0.018138357	0.03822303	0.025063918	
D11					Not assigned due to peak overlap
F12	0.021042814	0.013630847	0.030561414	0.02051341	
L13	0.011009087	0.009	0.005899152	0.017005881	
S14	0.012688578	0.021466253	0.0400025	0.015336232	
Y15	0.026551836	0.00678233	0.024449949	0.01020784	
K16	0.021042814	0.013630847	0.030561414	0.02051341	
L17	0.043391243	0.003	0.037600532	0.019641792	
S18					N / A
Q19	0.023340951	0.025314028	0.020099751	0.019230185	
K20	0.007668116	0.004024922	0.025043961	0.012876335	
G21	0.021936271	0.004024922	0.004582576	0.004024922	
Y22	0.014240786	0.016334014	0.020596116	0.006	
S23	0.005761944	0.038920432	0.00969536	0.014	
W24	0.037759767	0.02041568	0.029577018	0.022117866	
S25	0.065770814	0.04526809	0.068606122	0.02774527	
Q26	0.013747727	0.008354639	0.011567195	0.00626099	
F27	0.014064139	0.021730163	0.031205769	0.009011104	
S28	0.02167487	0.024754798	0.039207142	0.02163793	
D29	0.025573424	0.0085557	0.01479189	0.008294577	
V30	0.029583779	0.007348469	0.006	0.00501996	
E31	0.02417023	0.016155494	0.025317978	0.019462785	
E32	0.023702321	0.020223748	0.027889066	0.022895414	
N33	0.022561028	0.01356466	0.018330303	0.012680694	
R34	0.015684387	0.006340347	0.004494441	0.003741657	
T35	0.031767908	0.032003125	0.021042814	0.020596116	
E36	0.027298352	0.020571825	0.020223748	0.020668817	
A37	0.025043961	0.009165151	0.010639549	0.009797959	
P38					Proline

E39	0.013069047	0.017469974	0.01047855	0.010334409	
G40	0.021559221	0.009	0.009391486	0.00811172	
T41	0.010733126	0.016099689	0.020302709	0.019057807	
E42	0.022040871	0.025694357	0.020104726	0.022842942	
S43	0.023047776	0.054444467	0.051718469	0.050890078	
E44	0.013483323	0.024203306	0.025195238	0.022720035	
A85	0.008049845	0.011567195	0.007861298	0.00501996	
V86	0.002408319	0.01200833	0.00244949	0.00742967	
K87	0.026687076	0.00614817	0.026404545	0.020302709	
Q88	0.019462785	0.015336232	0.036772272	0.038907583	
A89	0.027495454	0.027799281	0.038512336	0.038026307	
L90	0.08411183	0.067536657	0	0	
R91	0.032003125	0.049570152	0.162810319	0.101863634	
E92	0.039620702	0.033178306	0.046	0.018782971	
A93	0.12856827	0.052257057	0.020104726	0.022842942	
G94	0.252571178	0.189020634	0	0	
D95	Not assigned due to peak overlap	0	0	0	
E96					N / A
F97	Not assigned due to peak overlap	Not assigned due to peak overlap	0	0	
E98	0.115537007	0	0	0	
L99	0.049680982	0	0	0	
R100	0	0.042341469	0	0.049032642	
Y101	0.037094474	0	0	0	
R102	0.019626513	0.014703741	0.022004545	0.011009087	
R103	0.019390719	0.00676757	0.017285832	0.014064139	
A104	0.096932967	0	0	0	
F105	0.005761944	0.038920432	0.00969536	0.014	
S106	0	0	0	0	
D107	0.030727838	0	0	0	
L108	0	0	0	0	
T109	0.021559221	0.009	0.009391486	0.00811172	
S110	0.248851763	0.117888931	0	0	
Q111	0.171956971	0.103100921	0	0	
L112	0	0	0	0	
H113	0.016149303	0.009011104	0.015931102	0.004	
I114	0	0.012441865	0	0	
T115					N / A
P116					Proline
G117					N / A
T118	0	0	0	0	
A119					N / A
Y120	0.036276714	0.039227541	0.0085557	0.032707797	
Q121	0	0.038835551	0	0	
S122	0	0.042647391	0	0	

F123				N / A
E124	0.063183859	0.055450879	0.061540231	0.062194855
Q125	0.097196708	0.061743016	0.078452533	0.065259482
V126	0.053555579	0.022667157	0.04215685	0
V127	0	0	0	0
N128	0.054459159	0.075546012	0.064070274	0.079869894
E129	0.034842503	0.033612498	0.037971042	0.03047622
L130	0	0	0	0
F131	0	0	0.104690974	0
R132	0.076571535	0.055219562	0.039952472	0.013190906
D133	0.069657735	0.036894444	0.023430749	0
G134	0.046175751	0.030740852	0.03726929	0.048641546
V135	0.070378974	0.072609917	0.052438535	0.055894544
N136	0.060636623	0.089800891	0.211425637	0.094877816
W137	Not assigned due to peak overlap	0.125963487	0	0
G138	0	0.098737024	0	0
R139	0.07783187	0	0	0
I140	0.136285729	0.140576669	0	0
V141	0.064529063	0.060506198	0	0.03555559
A142	0.118367225	0	0	0
F143	0.074021618	0.033154185	0	0.066904409
F144	0.018708287	0.021789906	0	0.038340579
S145	0	0.089465077	0	0
F146	0.053933292	0.042227953	0	0
G147	0.020493902	0.021113976	0.035344024	0.018579559
G148	0.054591208	0.032499231	0	0.053710334
A149	0.037971042	0.015620499	0.089368898	0.039306488
L150	0.018444511	0.01200833	0.018809572	0.021019039
C151	0.014696938	0.0083666	0.036348315	0.024592682
V152	0.066616815	0.042647391	0.062025801	0.043453423
E153	0.016149303	0.009011104	0.015931102	0.004
S154	0.022275547	0.009602083	0.01485934	0.007602631
V155	0.007	0.024149534	0.018574176	0.023430749
D156	0.013630847	0	0	0
K157	0.060894992	0.044375669	0.074711445	0.051070539
E158	0.02433516	0.022289011	0.029031018	0.017023513
M159	0.019869575	0.024919872	0.031368774	0.028003571
Q160	0.011036304	0.007758866	0.013535139	0.010733126
V161	0.02041568	0.003577709	0.015159156	0.001
L162	0.014449913	0.013718601	0.014064139	0.01505988
V163	0.019626513	0.014703741	0.022004545	0.011009087
S164	0.034187717	0.018809572	0.011874342	0.015
R165	0.03902307	0.032707797	0.013747727	0.018335757
I166	0.032252132	0.022645088	0.032523837	0.02433516
A167	0.023345235	0.022275547	0.015931102	0.017697457
A168	0.018138357	0.01003992	0.00409878	0.007224957

W169	0.041099878	0.019209373	0.02488373	0.018487834	
M170	0.034744784	0.025957658	0.038285768	0.026627054	
A171	0.038026307	0.072174788	0.04844791	0.050281209	
T172	0.074021618	0.057504782	0.067714105	0.054781384	
Y173	0	0	0	0.112321859	
L174	0.028217016	0.014310835	0.010733126	0.00303315	
N175	0.05485253	0.053682399	0.043758428	0.039713977	
D176	0.005761944	0.038920432	0.00969536	0.014	
H177	0.038486361	0.019256168	0.01505988	0.01523811	
L178	0.02167487	0.0085557	0.011567195	0.012837445	
E179	0.029516097	0.063771467	0.031131977	0.050217527	
P180					Proline
W181	0.017023513	0.010440307	0.023276598	0.00438178	
I182	0.004669047	0.029223278	0.025938389	0.026866336	
Q183	0.007348469	0.018143869	0.048309419	0.022578751	
E184	0.012561847	0.025254703	0.072119346	0.037280021	
N185	0.031767908	0.01077961	0.053732672	0.029668165	
G186	0.019230185	0.007348469	0.036334557	0.019626513	
G187	0.016431677	0.01479189	0.054990908	0.03354102	
W188	0.026187783	0.02905512	0.02041568	0.025694357	
D189	0.053233448	0.05711217	0.096354554	0.080126151	
T190	0.024935918	0.041782772	0.022275547	0.034939948	
F191	0.03822303	0.032863353	0.035386438	0.043692105	
V192	0.036044417	0.057628118	0.107525811	0	
E193	0.05691397	0.048787293	0.056760902	0.091165783	
L194	0.032074912	0.023004347	0	0	
Y195	0.039194387	0	0	0	
G196	0.102079381	0.092267004	0	0	
N197	0.04531887	0.051915316	0	0	
N198	0.02433516	0.063283489	0	0.052026916	
A199	0.03555559	0.041349728	0.088032948	0.084651048	
A200	0.032261432	0.016099689	0.039809547	0.062737549	
A201	0.019778777	0.01300769	0.051544156	0.055138009	
E202	0.047667599	0.072008333	0.076499673	0.068042634	
S203	0.035159636	0.042482938	0.071111181	0.065940883	
R204	0.028368997	0.017285832	0.067363195	0.060474788	
K205	0.061788348	0.04587156	0	0.092456476	
G206	0.042341469	0.025976913	0.057690554	0.056	
Q207	0.020302709	0.018444511	0.012680694	0.009859006	
E208	0.020044949	0.020302709	0.023155993	0.028639134	
R209	0.038026307	0.072174788	0.04844791	0.050281209	
L210	0.047812132	0.125927757	0.097143193	0.102196869	
E211	0.029342802	0.070998592	0.052438535	0.055894544	

Table S2: Per residue decomposition of the MM-GBSA scores in kcal/mol (contribution higher than -0.5 kcal/mol and lower than 1 kcal/mol are shown in blue, contributions between -1 and -2 kcal/mol are shown in yellow, contributions higher than -2 kcal/mol are shown in red).

Residue	ΔH Que_Ala	ΔH Que_Ala4	ΔH Que_Glu	ΔH Que_Glu4	ΔH Que_Phe	ΔH Que_Phe4	ΔH Que_Leu	ΔH Que_Leu4
R GLY -4	-0.004196201	-0.004568858	-0.00875506	-0.009068233	-0.006108973	-0.005954261	0.002796394	0.005467383
R PRO -3	-0.000369158	-0.000181955	-0.0002027	-9.15E-05	-0.000947513	-0.000180955	0.000187977	0.00035866
R LEU -2	0.000563609	0.000188703	0.00012072	-1.12E-05	-0.000274431	-0.000246438	0.000239343	0.000992502
R GLY -1	0.000476631	-2.70E-05	-0.00023369	0.000220195	3.35E-05	-2.52E-05	0.00243989	0.001307423
R SER 0	0.00048163	0.001426893	0.000809798	0.000709573	0.000298925	0.001269183	0.00207998	0.004505374
R MET 1	0.000130717	0.000259435	0.000262434	0.000430142	-0.0001987	3.85E-05	-0.00065609	-0.001567494
R SER 2	-2.72E-05	0.000128718	-0.00017521	0.000170957	-3.52E-05	-0.00012122	0.001417146	0.001738815
R GLN 3	0.000111222	0.001861785	-8.77E-05	0.000111972	-0.000124969	0.001247438	0.000823544	0.004571357
R SER 4	0.001473632	0.001182454	0.001268433	0.001374156	-0.000172207	0.001872282	0.001210447	0.003347163
R ASN 5	0.000459635	0.000276931	0.000803299	0.000859785	-0.000164459	0.000536616	0.000196951	0.006949263
R ARG 6	-0.003590352	-0.007781055	-0.00991102	-0.007536866	-0.007578105	-0.004255436	-0.01226543	-0.002653087
R GLU 7	0.007733817	0.017089978	0.026275431	0.017980005	0.003586603	0.018510372	0.008099475	0.008616596
R LEU 8	0.000338915	6.87E-05	0.000369408	0.000933767	0.000106223	2.52E-05	-0.00027493	0.000980505
R VAL 9	-7.42E-05	8.00E-06	4.02E-05	0.000228693	0.00023844	-2.10E-05	7.72E-05	0.000341415
R VAL 10	0.00016171	0.000545114	6.20E-05	0.000669083	0.000188453	0.000305924	0.000206198	0.000331417
R ASP 11	0.015344164	0.014186953	0.029824044	0.027781805	0.004300925	0.011742564	0.005647588	0.017586853
R PHE 12	0.000464134	-0.000181955	-0.00014496	6.82E-05	0.00012072	-0.000157211	0.000305174	-1.92E-05
R LEU 13	0.000163459	-0.000191952	-0.00020845	0.000156711	0.000311672	-0.000109223	0.000383654	-0.000224944
R SER 14	0.000566608	-0.000149713	-0.00046463	0.00031992	0.000295676	-0.000257936	4.42E-05	0.000245189
R TYR 15	0.000906773	0.000356161	0.000486128	0.00075956	6.17E-05	0.000218695	7.60E-05	-0.000489378
R LYS 16	-0.006619595	-0.003231442	-0.00789178	-0.007698325	-0.008099725	-0.00291802	-0.00874406	-0.005094476
R LEU 17	4.85E-05	-0.000214946	-0.00042964	-0.000250937	0.000350162	-0.000180705	0.000611097	-0.0001997
R SER 18	0.00035841	-1.10E-05	-8.02E-05	0.000406148	7.42E-05	1.05E-05	-0.00031792	-0.000425894
R GLN 19	0.000589103	-6.22E-05	-0.00031292	0.00028093	0.000392152	0.00016196	0.000539115	-0.000431392
R LYS 20	-0.005245439	-0.002477381	-0.00596901	-0.006153712	-0.009992752	-0.00387828	-0.00756686	-0.003133717
R GLY 21	-0.000258935	1.62E-05	0.00031967	0.000557111	0.000808798	0.000213447	4.02E-05	-0.000180455
R TYR 22	-4.37E-05	-0.000134716	-0.00064659	-0.000712822	0.000980255	-0.00027818	0.000363159	-0.000149213
R SER 23	-2.60E-05	-0.000252687	-0.00133517	-0.001362909	0.001135216	-1.15E-05	0.000442139	0.000104474
R TRP 24	-4.85E-05	-0.000341165	-0.001001	-0.000912522	0.000193452	-0.00012147	0.000148213	-0.000312922
R SER 25	0.000170707	-9.50E-05	0.000580605	0.000415146	0.000508373	-0.000251937	0.000164709	0.000105474
R GLN 26	0.001463134	0.000871032	0.001387653	0.001809548	0.002505624	0.00103849	0.002131467	0.001642089
R MET 83	0.001468383	0.002035741	0.003547863	0.003338915	0.001924019	0.001716321	0.002205949	0.000947263
R ALA 84	0.001057236	0.001157961	0.002504374	0.002215696	0.001995251	0.00075881	0.001791052	0.001633842
R ALA 85	0.001962759	0.001705574	0.002906023	0.002352162	0.00336191	0.000855036	0.002565359	0.001845789
R VAL 86	0.0033999	0.00227968	0.005764559	0.003317171	0.004060485	0.003270182	0.00203874	0.003342664
R LYS 87	-0.004861285	-0.004726568	-0.02177256	-0.013809798	-0.003888028	0.001625594	-0.00395726	-0.00383854
R GLN 88	0.003068233	0.003196951	0.005457886	0.005029743	0.005264934	0.002626343	0.004298675	0.004537366
R ALA 89	0.004781555	0.002352912	0.007995251	0.004497876	0.001151962	0.002537116	0.001583854	0.00148088
R LEU 90	0.006770557	-0.014419645	0.005507373	-0.012272932	-0.008028743	-0.003495626	-0.01808573	-0.006510872
R ARG 91	-0.002846538	0.004019245	-0.01356161	-0.004372157	0.001743108	-0.00123819	-0.00077281	0.016466513
R GLU 92	0.031293177	0.025910772	0.067948013	0.04524194	0.035467383	0.029232942	0.025301675	0.025220195
R ALA 93	0.004301675	-0.017090477	-0.00054036	-0.013744564	-0.052887662	-0.006023342	-0.02294987	-0.003697326
R GLY 94	0.01004199	0.045690577	0.038142928	0.058352596	0.017948968	0.018102474	0.050016496	0.011151968

R ASP 95	0.05244164	0.099296176	0.113279539	0.12259985	0.071313422	0.052628593	0.072405399	0.051615846
R GLU 96	0.075715821	0.016924269	0.369866823	0.064941765	0.072219335	0.052229479	0.042260551	0.04976031
R PHE 97	-0.765581976	-1.51239704	-1.63702448	-1.500655087	-1.743136022	-0.807388354	-1.49272324	-1.285558883
R GLU 98	0.107420145	-0.227822577	0.102447498	-0.472374522	0.097911369	0.240059652	0.277368266	0.166554052
R LEU 99	0.024184454	0.019376906	-0.01692477	0.032298925	0.003385654	0.003654586	0.013146213	0.005615846
R ARG 100	-0.094892619	-0.048629093	-6.88096242	-0.040545324	-0.069394499	-0.09374567	-0.04839416	-0.012227989
R TYR 101	-1.20583977	-0.563781707	-4.87013592	-0.824769222	-0.648974157	-0.673903244	-0.46576947	-0.700766459
R ARG 102	-2.608783923	-3.251807815	-1.82399122	-3.704338451	-1.971443345	-0.2138168	-2.37538371	-2.090751087
R ARG 103	-6.961083644	-0.128741958	0.004424906	-0.128041229	-0.038496496	-0.004228238	-0.02620145	-0.069645664
R ALA 104	-0.861316334	-0.467285194	0.00180155	-0.067814667	-0.116108023	-0.625269416	-0.11687225	-0.131505071
R PHE 105	-0.458549052	-2.19497821	-1.49270315	-2.038377043	-3.881646011	-3.993481474	-3.77626845	-2.725629699
R SER 106	-0.21837508	-0.56550371	-0.30458088	-0.401352577	-0.319650209	-1.554455637	-0.3663222	-0.086762459
R ASP 107	-0.594586063	-0.51740232	-0.42690656	-0.703408191	-0.518995965	-0.817301385	-0.5286634	-1.156848295
R LEU 108	-2.635863141	-3.026740773	-2.74963642	-2.516701754	-2.734780463	-2.838764218	-2.73321653	-2.731241073
R THR 109	-0.160763205	-0.297590484	-0.48591342	-0.657298553	-0.500627053	-0.898675202	-0.30825475	-0.333848583
R SER 110	0.032551112	0.005983754	0.013502374	0.008309423	0.019585854	0.011000101	0.017379405	0.023461885
R GLN 111	0.050803497	0.029581355	0.032441173	0.026978005	0.039866034	0.027377156	0.044858512	-0.003229443
R LEU 112	-0.005130217	-0.014664334	-0.00255911	-0.011308423	-0.005512122	-0.00384054	-0.00963609	-0.289632195
R HIE 113	0.011925019	0.012193702	0.006077731	0.008066733	0.006143964	0.01088153	0.009502624	0.009779055
R ILE 114	-7.40E-05	-0.005231942	-0.00275056	-0.00307898	-0.002567358	4.25E-05	-0.00060085	-0.000550862
R THR 115	0.002631092	0.003071232	0.002323669	0.00299925	0.002242689	0.002780305	0.002508373	0.002445639
R PRO 116	-0.000368908	-0.000243689	-1.82E-05	3.55E-05	-0.000181705	-0.000419145	-0.0001897	-0.000310672
R GLY 117	0.00128143	0.00143989	0.001116721	0.001006248	0.001155711	0.001084979	0.001306673	0.00084154
R THR 118	0.00251962	0.002576106	0.00288028	0.002127718	0.003247188	0.001941765	0.002875781	0.00235841
R ALA 119	0.002033992	0.002550862	0.00284179	0.003143464	0.002422394	0.002139465	0.001973257	0.001784304
R TYR 120	0.001997501	0.002709323	0.003452387	0.003846288	0.002652087	0.002263184	0.002526868	0.003453137
R GLN 121	0.006237941	0.006256686	0.006395651	0.006354661	0.005930017	0.005351912	0.006157211	0.004348163
R SER 122	0.006973257	0.00795926	0.009277931	0.008896026	0.009452887	0.0076001	0.008779055	0.00648013
R PHE 123	-0.019064234	-0.017153212	-0.01776531	-0.01215821	-0.024347913	-0.015077731	-0.02097851	-0.009418895
R GLU 124	0.027275931	0.031995751	0.043677581	0.052986753	0.025068733	0.031047238	0.026890027	0.036282929
R GLN 125	0.025014246	0.017808298	0.022787303	0.020567858	0.024044239	0.020377906	0.02540115	0.016355411
R VAL 126	-0.045629343	-0.09143914	-0.06025394	-0.050322419	-0.062234635	-0.040206948	-0.07696701	-0.017613597
R VAL 127	-0.084627593	-0.050412897	-0.07121595	-0.041379155	-0.09056161	-0.050228193	-0.09168783	-0.039566858
R ASN 128	-0.012295676	0.027125969	0.015137466	0.0110005	-0.011244689	0.007694076	-0.01104074	0.007477131
R GLU 129	-0.124467784	0.016951571	-0.02541038	0.114173134	-0.350957877	0.081810799	-0.20583171	0.062580956
R LEU 130	-2.262032605	-1.235181995	-2.22185767	-1.06924255	-2.550340409	-1.347438883	-2.49493241	-1.206532355
R PHE 131	-0.093054986	0.053713322	-0.04547563	0.022448638	-0.080486097	-0.044325919	-0.05472972	0.029646838
R ARG 132	-0.137378057	-1.663305455	-0.17209155	-1.12753364	-0.211806996	-0.024251697	-0.08515814	-0.039914621
R ASP 133	0.305640826	0.519955396	0.651481686	0.51835193	0.41010436	0.474258938	0.433172764	0.368852862
R GLY 134	0.003884185	-0.013952012	0.020286941	0.016624828	0.003381432	-0.035802192	0.00343739	-0.02625789
R VAL 135	-0.019146463	0.007954761	-0.03476081	0.002871282	0.009945264	-0.035905731	-0.00154161	-0.041830409
R ASN 136	-2.547162684	-0.113661389	-3.26204997	-0.617817554	-1.149330922	-2.68340413	-2.01274441	-2.578851678
R TRP 137	-0.079232692	-0.045141715	-0.11821495	-0.051308801	-0.199620162	-0.085937755	-0.09919091	-0.071129376
R GLY 138	-0.253487478	-0.100519702	-0.6758947	-0.196574011	-0.861170724	-0.306100782	-0.41622306	-0.344025439
R ARG 139	-6.53374757	-5.835365149	-9.86321479	-7.402474466	-4.52176815	-6.217256505	-7.21671762	-7.70137065
R ILE 140	-0.074660335	-0.067491627	-0.09098725	-0.069245189	-0.149301175	-0.100016246	-0.09456086	-0.076214696
R VAL 141	-0.091541615	-0.288591602	-0.2967856	-0.297845539	-0.621745791	-0.362890827	-0.24166232	-0.309040036
R ALA 142	-0.752026923	-1.155619077	-1.131429	-1.146744835	-1.288971536	-1.649421787	-0.72119023	-1.45294541

R PHE 143	-0.103550362	-0.105651087	-0.22479955	-0.115051237	-0.195922519	-0.15767456	-0.19548363	-0.144308289
R PHE 144	-0.06632042	-0.136567358	-0.18757886	-0.159229193	-0.184660335	-0.131693577	-0.19447263	-0.141299925
R SER 145	-0.487156134	-2.388101738	-1.40884616	-1.79095133	-1.423593618	-1.465436217	-0.87324692	-1.509139869
R PHE 146	-1.095176076	-2.232325299	-2.28723035	-2.095820585	-1.957643057	-1.739044187	-1.96163728	-1.523370792
R GLY 147	0.035613847	0.015913522	0.014468133	0.020536616	0.015148463	0.02723919	0.026492877	0.016265934
R GLY 148	-0.024300425	-0.160228193	-0.06044364	-0.193695595	-0.062755311	-0.107786553	-0.05491002	-0.085819545
R ALA 149	-0.245603138	-0.589987217	-0.57678405	-0.732988367	-0.544442718	-0.63709022	-0.38125424	-0.529335839
R LEU 150	-0.047229443	-0.132860513	-0.06725269	-0.091717921	-0.068650587	-0.068083229	-0.0645516	-0.026866283
R CYS 151	0.006504624	0.014132717	0.007290177	0.010781805	0.009421645	0.0103994	0.011073982	0.003565609
R VAL 152	-0.003944014	-0.025745564	-0.01652962	-0.039005999	-0.012897276	-0.014747063	-0.0089985	-0.017657586
R GLU 153	0.031116471	0.049974006	0.072190952	0.058826293	0.056907023	0.039663834	0.040896026	0.032793052
R SER 154	0.002928268	0.007149463	0.003953762	0.006381155	0.004452387	0.005004999	0.004188453	0.004815296
R VAL 155	0.000797301	0.002202199	0.000866783	0.001410897	0.001210947	0.001738065	0.001545864	0.002322419
R ASP 156	0.016550362	0.029713822	0.036428143	0.034589603	0.025704574	0.019933767	0.022283679	0.017748313
R LYS 157	0.001075731	-0.002202449	-0.01124594	-0.01287853	-0.000463384	0.00080055	-0.00223919	-0.000342664
R GLU 158	0.005378155	0.009663584	0.013406898	0.012872782	0.00844139	0.006331917	0.00724094	0.007053237
R MET 159	0.001071482	0.001500125	0.00163959	0.001538865	0.001097226	0.001552112	0.001098725	0.001528368
R GLN 160	0.001816796	0.003033992	0.002976256	0.003060235	0.002706823	0.002325669	0.002353412	0.002012497
R VAL 161	0.001170957	0.001769808	0.002097976	0.001749063	0.00167933	0.001836041	0.001597851	0.001536366
R LEU 162	0.000883029	0.000846288	0.001550612	0.000964509	0.001317921	0.001067733	0.000775306	0.001427893
R VAL 163	0.00231842	0.002930767	0.004190202	0.003816546	0.003463634	0.003325419	0.003008248	0.003090977
R SER 164	0.001505624	0.002230192	0.002597101	0.001987753	0.002543114	0.002049488	0.002286678	0.001708073
R ARG 165	-0.00152162	-0.003058235	-0.00794051	-0.008350162	-0.001249438	-0.001055486	-0.00152562	-0.001896526
R ILE 166	-0.00104074	-0.004889528	-0.00105299	-0.005033742	-0.001741815	-0.002629093	-0.00217071	-0.001767308
R ALA 167	0.00128193	0.001411647	0.002579355	0.002146213	0.001045989	0.001185454	0.001266433	0.00112122
R ALA 168	0.000823044	0.000778555	0.001312172	0.001322919	0.001083229	0.000788803	0.001058985	0.001043739
R TRP 169	0.000567108	0.000301175	0.002644339	0.000869533	0.002585354	0.000947763	0.001966508	0.002299675
R MET 170	-0.001907523	-0.001971507	-0.00611922	-0.001103224	-0.006893777	-0.004726318	-0.00257361	-0.003132467
R ALA 171	0.000485129	0.000264934	0.000391152	-2.75E-06	-0.000583854	0.000171957	-8.95E-05	5.75E-06
R THR 172	0.002949013	0.002669833	0.002877531	0.002368658	0.005233942	0.002770807	0.004823544	0.003191452
R TYR 173	-0.003896276	0.000343664	-0.00019845	0.00420045	-0.003965509	0.003053987	-0.00234491	0.006024994
R LEU 174	-0.00028068	0.000506623	-0.00108773	0.000371907	-0.001087228	0.000289678	-0.00077331	0.000331167
R ASN 175	0.002962259	0.000923519	0.003370657	0.00183904	0.003824794	0.003313672	0.003162209	0.002127968
R ASP 176	0.023664584	0.024751312	0.037236441	0.033108723	0.023947513	0.02436166	0.025808548	0.025820545
R HIE 177	0.015348913	0.012128968	0.015307923	0.013574856	0.017677831	0.015175706	0.017830542	0.014178455
R LEU 178	-0.003477881	-0.003589353	-0.00475381	-0.00303999	-0.00387828	-0.00372032	-0.00418695	-0.004382654
R GLU 179	0.023296426	0.018509373	0.044950012	0.029837041	0.023596101	0.023425394	0.021669083	0.024174706
R PRO 180	0.000104474	-0.000301675	0.000248938	-0.00019895	-1.30E-05	0.000581855	0.000171707	0.00052087
R TRP 181	-0.006860035	-0.002712072	-0.00602049	-0.002827543	-0.009263434	-0.008420895	-0.01076856	-0.007587853
R ILE 182	-0.002602349	-0.001229193	-0.00254736	-0.001396651	-0.002710322	-0.001947513	-0.00229218	-0.00223844
R GLN 183	0.001389403	0.000173457	0.001890777	-0.000268183	0.001655086	0.001407898	0.0016006	0.00156061
R GLU 184	0.027677581	0.021668333	0.039837541	0.034757311	0.024093977	0.030366658	0.028220445	0.031844539
R ASN 185	0.009070482	0.005082729	0.010789553	0.006327168	0.011897776	0.011036491	0.010073232	0.011310172
R GLY 186	0.000576356	-1.95E-05	0.000652837	-0.000688578	0.000887278	0.000813547	0.000476881	0.000755311
R GLY 187	0.004058485	0.002669833	0.005433642	0.001384654	0.00463959	0.004541865	0.004220945	0.004220945
R TRP 188	-0.000364909	0.001013997	-0.00149288	0.000695076	-0.000268683	-2.90E-05	0.003542864	-0.000362409
R ASP 189	0.016252437	0.013094976	0.033776056	0.017769308	0.013803549	0.016224694	0.017487878	0.016131967
R THR 190	0.004435641	0.003650337	0.005418395	7.82E-05	0.005587353	0.004818545	0.005698825	0.008347663

R PHE 191	-0.00595901	-0.001914771	-0.00989628	0.001704324	-0.015135536	-0.004630092	-0.00845714	-0.002025994
R VAL 192	-0.000288178	0.001124219	0.003531867	0.000917021	0.001730317	0.00035841	0.002388153	0.000221195
R GLU 193	0.020122219	0.019027493	0.055771057	0.019176456	0.028145214	0.01995951	0.038169958	0.014263184
R LEU 194	0.001262434	0.004448138	0.016387873	0.002445639	-0.005784997	-0.000438584	0.025531587	0.001345914
R TYR 195	0.014190596	0.021901189	-0.01366382	0.006898025	0.040371295	0.025903177	-0.0995663	0.013935717
R GLY 196	0.00272132	0.003768808	0.007211601	0.004027493	0.000826793	0.00235941	0.017494376	0.000786553
R ASN 197	0.016993002	0.03651862	0.012755906	0.02563984	0.036651087	0.016156211	0.056514025	0.012941515
L MOL 1	-14.26272859	-9.241710289	-10.4480786	-6.246816036	-10.24299003	-10.26826564	-9.36459659	-9.450279576

8. LogP values and retention times

Table S3. Retention times in HPLC of the parent compound Quercetin and the four hybrids.

Compound Name	**Retention Time in HPLC**
Que	13.5 min
Que-Ala	14 min
Que-Glu	12.9 min
Que-Leu	18.3 min
Que-Phe	18.6 min