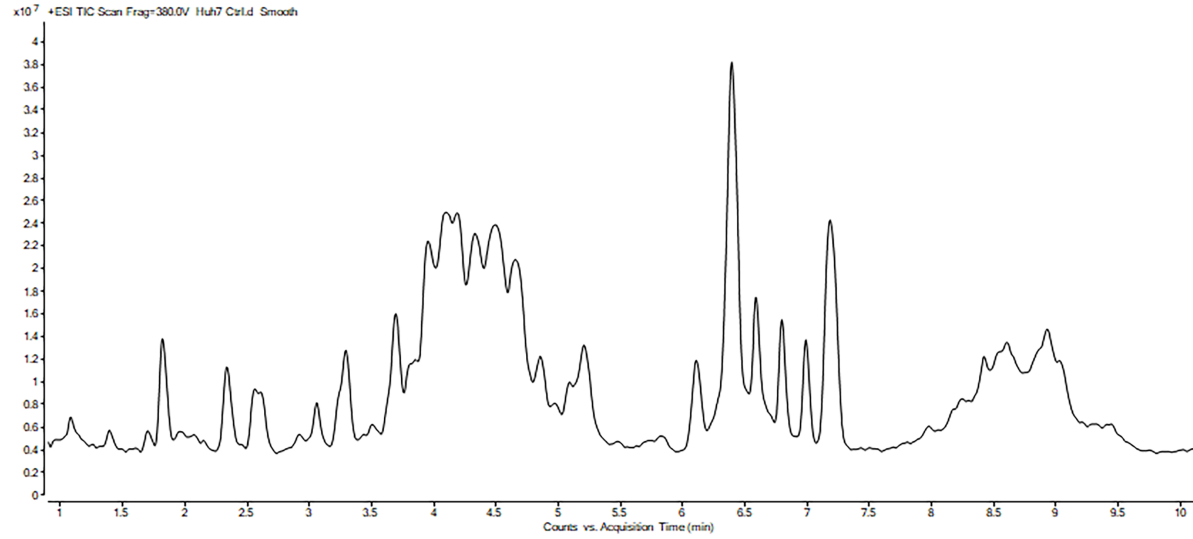
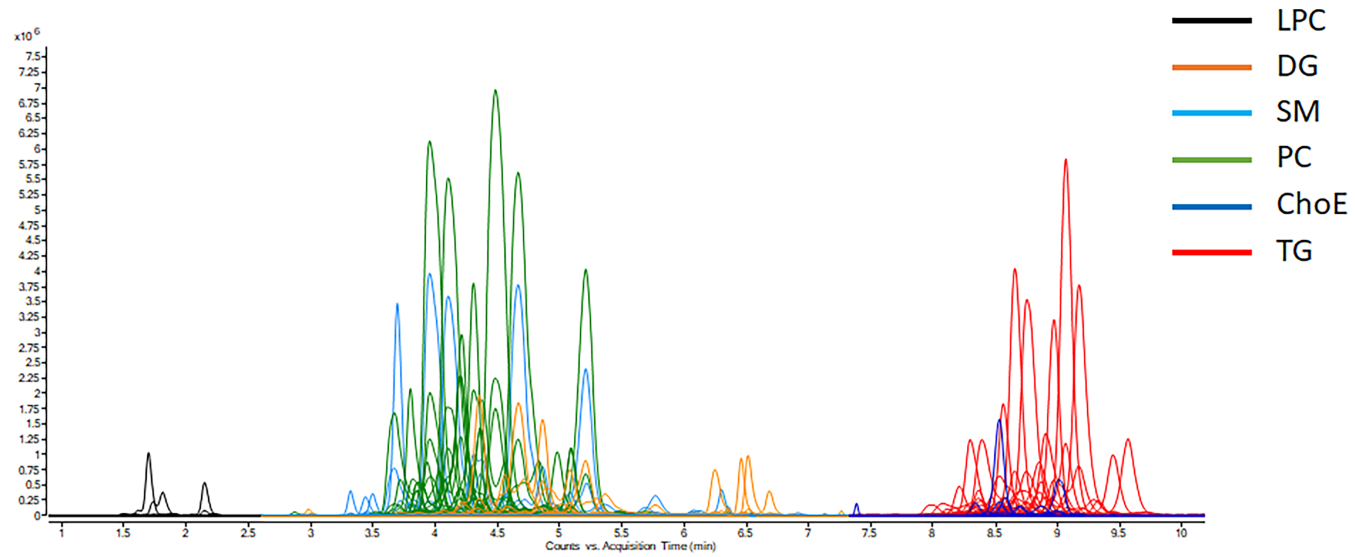
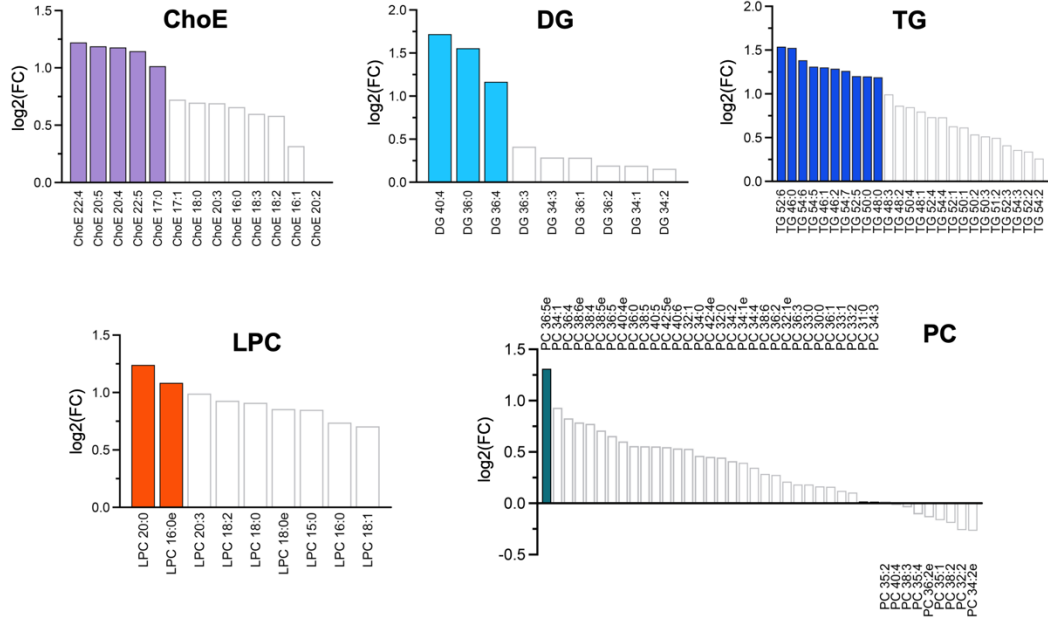
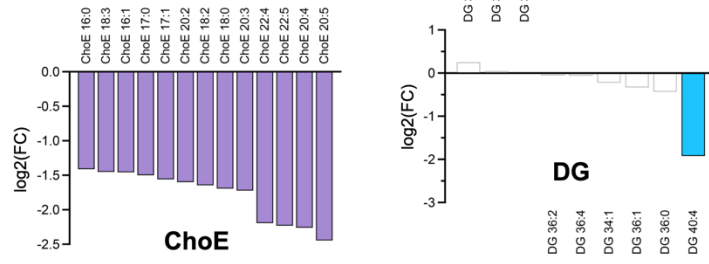
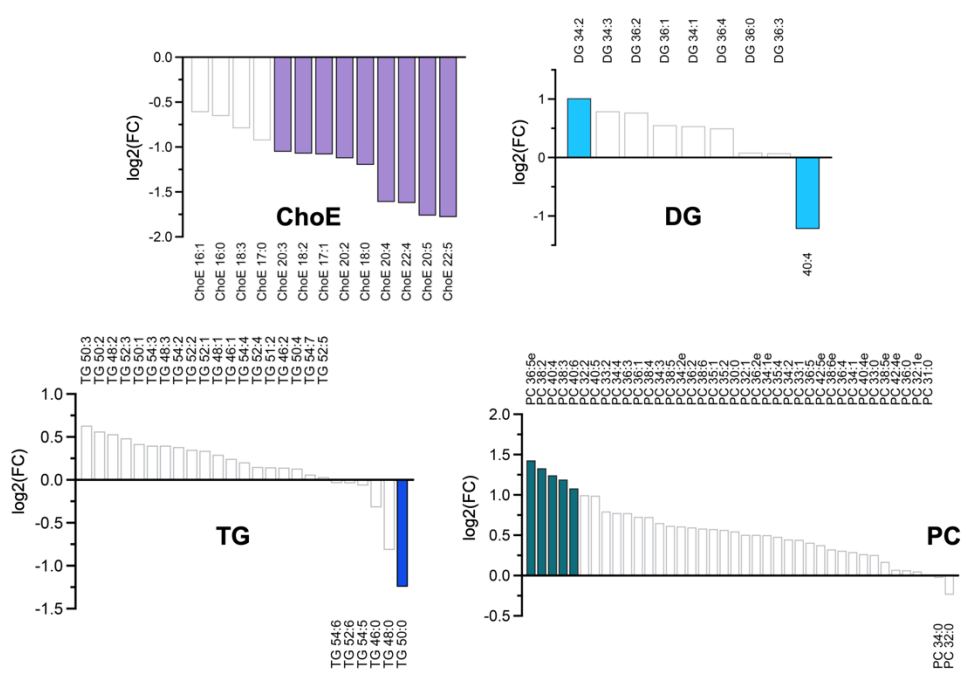


**Silibinin suppresses the hyperlipidemic effects of the  
ALK-tyrosine kinase inhibitor lorlatinib in hepatic cells**

**SUPPLEMENTARY INFORMATION**  
(Figures S1 and S2, Tables S1 to S7)

**A****B**

**Figure S1. Representative chromatograms of lipidomic analyses in Huh-7 cells.** **A.** Total Ion Chromatogram (TIC) of lipidomic analysis using UHPLC-ESI-QTOF-MS/MS in untreated Huh-7 cells. **B.** Overlapped Extracted Ion Chromatograms (EIC) of different lipid species. ChoE: cholesteryl esters; DG: diglycerides; LCP: lysophosphatidylcholines; PC: phosphatidylcholines; SM: sphingomyelins; TG: triglycerides.

**A****B****C**

**Figure S2. Silibinin impedes lorlatinib-induced hypertriglyceridemia and hypercholesteremia traits in human hepatic cells.** Fold-change (treatment/untreated control) of lipid species (expressed as median) in Huh-7 hepatocytes treated with 1  $\mu\text{mol/L}$  lorlatinib (A), 100  $\mu\text{mol/L}$  silibinin (B), and lorlatinib *plus* silibinin (C) for 48 h. Colored bars indicate statistically-significant ( $p < 0.05$ ) fold-changes. ChoE: cholesteryl esters; DG: diglycerides; TG: triglycerides; LPC: lysophosphatidylcholines; PC: phosphatidylcholines.

**Table S1. Relative concentration ( $\mu\text{mol}/\text{mg}$  protein) of diglycerides (DG) in Huh-7 cells cultured (24 h) in the absence/presence of silibinin (SBN) and/or lorlatinib**

|                | Untreated |                 | SBN (100 $\mu\text{mol}/\text{L}$ ) |                 | lorlatinib (1 $\mu\text{mol}/\text{L}$ ) |                 | lorlatinib + SBN |                 |
|----------------|-----------|-----------------|-------------------------------------|-----------------|--|-----------------|------------------|-----------------|
|                | Median    | (Q1–Q3)         | Median                              | (Q1–Q3)         | Median                                   | (Q1–Q3)         | Median           | (Q1–Q3)         |
| <b>DG 34:1</b> | 15.107    | (12.395–16.562) | 12.375                              | (10.746–14.38)  | 16.654                                   | (15.513–17.831) | 21.171           | (18.457–23.958) |
| <b>DG 34:2</b> | 16.979    | (13.604–19.155) | 19.08                               | (18.167–21.445) | 17.722                                   | (16.953–20.108) | 32.692           | (30.842–36.391) |
| <b>DG 34:3</b> | 2.076     | (1.724–2.430)   | 2.071                               | (1.983–2.351)   | 2.474                                    | (2.244–2.845)   | 3.492            | (3.319–3.964)   |
| <b>DG 36:0</b> | 0.774     | (0.742–0.801)   | 0.566                               | (0.548–0.601)   | 2.250                                    | (2.172–2.375)   | 0.804            | (0.786–0.865)   |
| <b>DG 36:1</b> | 8.068     | (6.428–8.305)   | 5.747                               | (5.473–6.556)   | 8.885                                    | (8.455–9.963)   | 10.95            | (10.013–12.085) |
| <b>DG 36:2</b> | 19.235    | (15.459–20.836) | 17.291                              | (16.302–19.224) | 20.022                                   | (19.455–22.991) | 30.847           | (29.449–33.641) |
| <b>DG 36:3</b> | 1.540     | (1.489–1.978)   | 1.684                               | (1.576–1.866)   | 2.186                                    | (1.864–2.675)   | 1.682            | (1.442–2.223)   |
| <b>DG 36:4</b> | 1.920     | (1.734–1.994)   | 1.754                               | (1.680–1.934)   | 4.172                                    | (3.809–4.624)   | 2.688            | (2.437–2.825)   |
| <b>DG 40:4</b> | 2.844     | (2.629–2.985)   | 0.721                               | (0.676–0.819)   | 9.158                                    | (8.900–9.689)   | 1.209            | (1.113–1.299)   |

**Table S2. Relative concentration ( $\mu\text{mol}/\text{mg}$  protein) of triglycerides (TG) in Huh-7 cells cultured (24 h) in the absence/presence of silibinin (SBN) and/or lorlatinib**

|                | Untreated |                 | SBN (100 $\mu\text{mol}/\text{L}$ ) |                 | lorlatinib (1 $\mu\text{mol}/\text{L}$ ) |                 | lorlatinib + SBN |                 |
|----------------|-----------|-----------------|-------------------------------------|-----------------|--|-----------------|------------------|-----------------|
|                | Median    | (Q1–Q3)         | Median                              | (Q1–Q3)         | Median                                   | (Q1–Q3)         | Median           | (Q1–Q3)         |
| <b>TG 46:0</b> | 0.626     | (0.531–0.630)   | 0.522                               | (0.501–0.538)   | 1.549                                    | (1.455–2.016)   | 0.462            | (0.435–0.522)   |
| <b>TG 46:1</b> | 1.028     | (0.890–1.077)   | 1.001                               | (0.959–1.059)   | 2.111                                    | (1.967–3.099)   | 1.152            | (1.021–1.356)   |
| <b>TG 46:2</b> | 0.468     | (0.418–0.513)   | 0.491                               | (0.480–0.521)   | 1.025                                    | (0.951–1.382)   | 0.504            | (0.447–0.593)   |
| <b>TG 48:0</b> | 1.097     | (1.060–1.188)   | 1.056                               | (0.882–1.112)   | 2.372                                    | (2.147–3.040)   | 0.589            | (0.431–0.886)   |
| <b>TG 48:1</b> | 3.172     | (3.117–3.605)   | 3.468                               | (3.404–3.762)   | 5.318                                    | (5.041–6.738)   | 4.132            | (3.646–4.440)   |
| <b>TG 48:2</b> | 2.674     | (2.574–2.848)   | 3.070                               | (2.971–3.286)   | 4.451                                    | (4.275–5.807)   | 3.880            | (3.292–4.554)   |
| <b>TG 48:3</b> | 0.629     | (0.615–0.665)   | 0.647                               | (0.633–0.706)   | 1.146                                    | (1.080–1.524)   | 0.809            | (0.729–0.985)   |
| <b>TG 50:0</b> | 0.536     | (0.504–0.557)   | 0.439                               | (0.360–0.484)   | 1.142                                    | (1.089–1.393)   | 0.191            | (0.139–0.342)   |
| <b>TG 50:1</b> | 6.317     | (5.626–6.914)   | 6.316                               | (5.877–6.549)   | 9.399                                    | (8.740–10.609)  | 8.418            | (8.130–8.613)   |
| <b>TG 50:2</b> | 8.537     | (7.504–9.159)   | 9.143                               | (8.771–9.523)   | 11.302                                   | (11.039–13.647) | 12.471           | (12.143–12.484) |
| <b>TG 50:3</b> | 3.380     | (2.933–3.543)   | 3.680                               | (3.457–3.945)   | 4.462                                    | (4.089–5.345)   | 5.041            | (4.317–5.828)   |
| <b>TG 50:4</b> | 0.580     | (0.552–0.603)   | 0.499                               | (0.468–0.529)   | 1.054                                    | (0.880–1.195)   | 0.621            | (0.529–0.751)   |
| <b>TG 51:2</b> | 2.259     | (2.081–2.528)   | 1.903                               | (1.899–2.137)   | 2.969                                    | (2.862–3.759)   | 2.621            | (2.317–2.683)   |
| <b>TG 52:1</b> | 2.267     | (2.003–2.420)   | 2.158                               | (1.870–2.248)   | 3.455                                    | (2.862–4.004)   | 2.785            | (2.723–2.920)   |
| <b>TG 52:2</b> | 12.662    | (10.864–13.699) | 11.698                              | (10.929–11.869) | 16.188                                   | (13.647–17.389) | 15.768           | (15.151–16.392) |
| <b>TG 52:3</b> | 8.818     | (7.839–9.243)   | 9.529                               | (8.596–9.700)   | 12.354                                   | (10.026–12.385) | 12.122           | (11.482–12.493) |
| <b>TG 52:4</b> | 2.087     | (1.957–2.377)   | 1.894                               | (1.796–1.957)   | 3.787                                    | (3.100–3.948)   | 2.399            | (2.257–2.507)   |
| <b>TG 52:5</b> | 0.533     | (0.521–0.553)   | 0.398                               | (0.387–0.418)   | 1.312                                    | (1.062–1.370)   | 0.543            | (0.471–0.633)   |
| <b>TG 52:6</b> | 0.246     | (0.220–0.268)   | 0.183                               | (0.167–0.185)   | 0.708                                    | (0.595–0.825)   | 0.232            | (0.199–0.282)   |
| <b>TG 54:2</b> | 2.935     | (2.514–3.326)   | 2.821                               | (2.359–2.944)   | 3.515                                    | (3.239–3.759)   | 3.807            | (3.545–4.069)   |
| <b>TG 54:3</b> | 9.029     | (6.792–9.845)   | 7.594                               | (7.456–8.066)   | 11.096                                   | (9.734–11.86)   | 11.245           | (10.702–11.544) |
| <b>TG 54:4</b> | 3.980     | (3.492–4.291)   | 3.347                               | (3.084–3.473)   | 6.556                                    | (5.885–7.076)   | 4.621            | (4.101–4.792)   |
| <b>TG 54:5</b> | 1.686     | (1.642–1.724)   | 1.234                               | (1.186–1.258)   | 4.411                                    | (3.406–4.830)   | 1.609            | (1.593–1.627)   |

|                |       |               |       |               |       |               |       |               |
|----------------|-------|---------------|-------|---------------|-------|---------------|-------|---------------|
| <b>TG 54:6</b> | 0.997 | (0.960–1.142) | 0.735 | (0.683–0.746) | 2.731 | (2.242–3.179) | 1.000 | (0.960–1.076) |
| <b>TG 54:7</b> | 0.931 | (0.915–1.021) | 0.693 | (0.654–0.718) | 2.095 | (2.035–2.682) | 0.982 | (0.920–1.106) |

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**Table S3. Relative concentration ( $\mu\text{mol}/\text{mg}$  protein) of phosphatidylcholines (PC) in Huh-7 cells cultured (24 h) in the absence/presence of silibinin (SBN) and/or lorlatinib**

|                 | Untreated |                 | SBN (100 $\mu\text{mol}/\text{L}$ ) |                 | lorlatinib (1 $\mu\text{mol}/\text{L}$ ) |                  | lorlatinib + SBN |                 |
|-----------------|-----------|-----------------|-------------------------------------|-----------------|--|------------------|------------------|-----------------|
|                 | Median    | (Q1–Q3)         | Median                              | (Q1–Q3)         | Median                                   | (Q1–Q3)          | Median           | (Q1–Q3)         |
| <b>PC 30:0</b>  | 6.405     | (5.118–6.937)   | 5.379                               | (5.174–6.243)   | 6.654                                    | (6.326–7.452)    | 9.079            | (7.901–9.773)   |
| <b>PC 31:0</b>  | 3.415     | (2.727–3.774)   | 2.265                               | (2.157–2.574)   | 3.243                                    | (3.017–3.670)    | 3.322            | (3.059–3.496)   |
| <b>PC 32:0</b>  | 15.784    | (13.155–16.908) | 9.342                               | (9.223–10.114)  | 20.672                                   | (18.773–22.556)  | 12.665           | (12.273–13.717) |
| <b>PC 32:1</b>  | 41.601    | (34.358–45.369) | 42.745                              | (41.334–46.236) | 56.675                                   | (54.510–62.270)  | 56.336           | (54.025–60.809) |
| <b>PC 32:1e</b> | 0.631     | (0.549–0.745)   | 0.423                               | (0.381–0.652)   | 0.780                                    | (0.662–0.811)    | 0.623            | (0.438–0.941)   |
| <b>PC 32:2</b>  | 10.379    | (7.446–11.559)  | 12.917                              | (11.945–14.888) | 7.800                                    | (7.438–8.849)    | 19.704           | (17.130–21.125) |
| <b>PC 33:0</b>  | 2.818     | (2.327–3.265)   | 2.350                               | (2.268–2.621)   | 3.109                                    | (2.967–3.427)    | 3.364            | (3.092–3.573)   |
| <b>PC 33:1</b>  | 12.16     | (9.664–13.345)  | 11.141                              | (10.634–12.379) | 12.338                                   | (11.522–13.927)  | 15.984           | (14.539–16.894) |
| <b>PC 33:2</b>  | 1.115     | (0.854–1.266)   | 1.079                               | (1.007–1.384)   | 1.113                                    | (1.064–1.257)    | 1.862            | (1.634–2.076)   |
| <b>PC 34:0</b>  | 4.608     | (3.847–4.698)   | 2.771                               | (2.547–3.203)   | 5.917                                    | (5.429–6.549)    | 4.239            | (3.973–4.558)   |
| <b>PC 34:1</b>  | 51.720    | (43.818–55.688) | 44.476                              | (43.811–48.347) | 93.696                                   | (91.390–100.415) | 61.235           | (57.209–65.474) |
| <b>PC 34:1e</b> | 0.700     | (0.520–0.787)   | 0.604                               | (0.568–0.715)   | 0.856                                    | (0.799–0.950)    | 0.935            | (0.851–1.028)   |
| <b>PC 34:2</b>  | 38.098    | (31.369–41.923) | 37.539                              | (36.238–40.854) | 49.219                                   | (44.698–53.364)  | 50.38            | (47.057–53.648) |
| <b>PC 34:2e</b> | 0.874     | (0.713–0.998)   | 0.672                               | (0.640–0.907)   | 0.709                                    | (0.675–0.755)    | 1.408            | (1.019–1.506)   |
| <b>PC 34:3</b>  | 5.841     | (4.462–6.531)   | 5.903                               | (5.612–6.805)   | 5.578                                    | (5.118–6.157)    | 8.815            | (7.869–9.525)   |
| <b>PC 34:4</b>  | 0.771     | (0.614–0.836)   | 0.831                               | (0.780–0.967)   | 0.930                                    | (0.844–1.024)    | 1.286            | (1.120–1.367)   |
| <b>PC 35:1</b>  | 7.539     | (5.623–8.474)   | 6.545                               | (6.327–7.730)   | 6.392                                    | (5.728–7.026)    | 10.867           | (9.444–11.642)  |
| <b>PC 35:2</b>  | 6.528     | (5.154–7.323)   | 6.508                               | (6.177–7.348)   | 6.219                                    | (5.750–6.996)    | 9.368            | (8.563–10.009)  |
| <b>PC 35:4</b>  | 1.991     | (1.639–2.367)   | 2.145                               | (2.036–2.373)   | 1.817                                    | (1.637–2.103)    | 2.919            | (2.289–3.166)   |
| <b>PC 36:0</b>  | 0.144     | (0.136–0.154)   | 0.086                               | (0.085–0.107)   | 0.209                                    | (0.187–0.240)    | 0.156            | (0.126–0.172)   |
| <b>PC 36:1</b>  | 23.236    | (18.201–25.375) | 23.301                              | (22.443–26.714) | 24.222                                   | (22.536–27.057)  | 36.729           | (32.578–40.415) |
| <b>PC 36:2</b>  | 40.944    | (32.394–45.118) | 39.690                              | (39.461–44.726) | 46.840                                   | (44.353–50.893)  | 59.556           | (54.484–63.853) |
| <b>PC 36:2e</b> | 0.114     | (0.083–0.131)   | 0.100                               | (0.095–0.106)   | 0.101                                    | (0.090–0.106)    | 0.154            | (0.127–0.180)   |

|                 |        |                 |        |                 |        |                 |        |                 |
|-----------------|--------|-----------------|--------|-----------------|--------|-----------------|--------|-----------------|
| <b>PC 36:3</b>  | 19.137 | (15.120–21.227) | 21.699 | (21.136–25.041) | 20.945 | (18.943–22.717) | 31.596 | (28.917–33.683) |
| <b>PC 36:4</b>  | 14.654 | (13.650–15.620) | 13.768 | (12.888–14.909) | 26.422 | (22.340–29.315) | 18.568 | (16.184–19.618) |
| <b>PC 36:5</b>  | 4.383  | (4.014–4.479)   | 4.055  | (3.684–4.522)   | 6.790  | (6.113–7.305)   | 5.650  | (5.331–6.025)   |
| <b>PC 36:5e</b> | 0.304  | (0.265–0.553)   | 0.838  | (0.531–0.900)   | 0.749  | (0.597–1.436)   | 1.189  | (0.509–1.437)   |
| <b>PC 38:2</b>  | 2.035  | (1.630–2.307)   | 3.083  | (2.704–3.763)   | 1.747  | (1.526–1.942)   | 4.971  | (4.247–5.735)   |
| <b>PC 38:3</b>  | 3.083  | (2.572–3.732)   | 4.548  | (4.312–5.591)   | 2.875  | (2.711–3.493)   | 7.412  | (6.261–7.813)   |
| <b>PC 38:4</b>  | 6.837  | (6.203–7.052)   | 7.055  | (6.730–8.292)   | 12.355 | (8.634–13.664)  | 10.930 | (10.219–11.943) |
| <b>PC 38:5</b>  | 9.205  | (6.367–9.755)   | 7.047  | (6.709–8.775)   | 12.838 | (10.587–13.421) | 12.874 | (11.692–13.573) |
| <b>PC 38:5e</b> | 0.124  | (0.112–0.130)   | 0.125  | (0.048–0.126)   | 0.193  | (0.176–0.225)   | 0.132  | (0.099–0.179)   |
| <b>PC 38:6</b>  | 7.724  | (6.355–8.296)   | 7.943  | (7.652–8.893)   | 9.312  | (7.567–10.337)  | 11.184 | (9.903–12.163)  |
| <b>PC 38:6e</b> | 0.222  | (0.200–0.258)   | 0.201  | (0.128–0.223)   | 0.353  | (0.316–0.487)   | 0.299  | (0.221–0.33)    |
| <b>PC 40:4</b>  | 0.312  | (0.232–0.360)   | 0.457  | (0.425–0.558)   | 0.298  | (0.264–0.327)   | 0.701  | (0.608–0.813)   |
| <b>PC 40:4e</b> | 0.064  | (0.054–0.068)   | 0.050  | (0.045–0.056)   | 0.087  | (0.085–0.105)   | 0.076  | (0.058–0.089)   |
| <b>PC 40:5</b>  | 1.333  | (1.178–1.438)   | 1.568  | (1.550–1.921)   | 1.883  | (1.759–2.114)   | 2.582  | (2.315–2.926)   |
| <b>PC 40:6</b>  | 2.004  | (1.843–2.221)   | 2.507  | (2.286–3.134)   | 2.981  | (2.661–3.179)   | 4.222  | (3.863–4.769)   |
| <b>PC 42:4e</b> | 0.042  | (0.036–0.046)   | 0.034  | (0.031–0.040)   | 0.056  | (0.05–0.063)    | 0.043  | (0.04–0.046)    |
| <b>PC 42:5e</b> | 0.084  | (0.067–0.104)   | 0.085  | (0.079–0.098)   | 0.118  | (0.114–0.139)   | 0.117  | (0.09–0.126)    |

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**Table S4. Relative concentration ( $\mu\text{mol}/\text{mg}$  protein) of lysophosphatidylcholines (LPC) in Huh-7 cells cultured (24 h) in the absence/presence of silibinin (SBN) and/or lorlatinib**

|                  | Untreated |               | SBN (100 $\mu\text{mol}/\text{L}$ ) |               | lorlatinib (1 $\mu\text{mol}/\text{L}$ ) |               | lorlatinib + SBN |               |
|------------------|-----------|---------------|-------------------------------------|---------------|--|---------------|------------------|---------------|
|                  | Median    | (Q1–Q3)       | Median                              | (Q1–Q3)       | Median                                   | (Q1–Q3)       | Median           | (Q1–Q3)       |
| <b>LPC 15:0</b>  | 0.052     | (0.041–0.067) | 0.045                               | (0.037–0.062) | 0.094                                    | (0.082–0.112) | 0.056            | (0.047–0.083) |
| <b>LPC 16:0</b>  | 2.004     | (1.575–2.348) | 2.095                               | (1.794–2.953) | 3.165                                    | (2.917–3.708) | 2.901            | (2.366–3.731) |
| <b>LPC 16: e</b> | 0.012     | (0.009–0.014) | 0.007                               | (0.006–0.009) | 0.023                                    | (0.022–0.027) | 0.009            | (0.008–0.011) |
| <b>LPC 18:0</b>  | 1.105     | (0.885–1.223) | 1.353                               | (1.132–1.761) | 1.911                                    | (1.805–2.236) | 1.862            | (1.555–2.259) |
| <b>LPC 18:0e</b> | 0.008     | (0.007–0.008) | 0.006                               | (0.005–0.007) | 0.014                                    | (0.012–0.015) | 0.007            | (0.006–0.009) |
| <b>LPC 18:1</b>  | 1.065     | (0.731–1.434) | 0.842                               | (0.721–1.339) | 1.630                                    | (1.184–2.396) | 1.163            | (0.973–1.883) |
| <b>LPC 18:2</b>  | 0.106     | (0.063–0.143) | 0.068                               | (0.060–0.123) | 0.188                                    | (0.118–0.282) | 0.096            | (0.079–0.179) |
| <b>LPC 20:0</b>  | 0.022     | (0.021–0.023) | 0.029                               | (0.024–0.03)  | 0.047                                    | (0.046–0.059) | 0.039            | (0.031–0.041) |
| <b>LPC 20:3</b>  | 0.058     | (0.028–0.075) | 0.030                               | (0.024–0.06)  | 0.080                                    | (0.049–0.173) | 0.044            | (0.036–0.096) |

**Table S5. Relative concentration ( $\mu\text{mol}/\text{mg}$  protein) of phosphatidylethanolamines (PE) in Huh-7 cells cultured (24 h) in the absence/presence of silibinin (SBN) and/or lorlatinib**

|                 | Untreated |               | SBN (100 $\mu\text{mol}/\text{L}$ ) |                 | lorlatinib (1 $\mu\text{mol}/\text{L}$ ) |                 | lorlatinib + SBN |                  |
|-----------------|-----------|---------------|-------------------------------------|-----------------|--|-----------------|------------------|------------------|
|                 | Median    | (Q1–Q3)       | Median                              | (Q1–Q3)         | Median                                   | (Q1–Q3)         | Median           | (Q1–Q3)          |
| <b>PE 32:0</b>  | 0.121     | (0.108–0.141) | 0.115                               | (0.086–0.125)   | 0.231                                    | (0.201–0.271)   | 0.137            | (0.129–0.178)    |
| <b>PE 36:4</b>  | 12.901    | (8.92–13.929) | 14.38                               | (13.745–16.186) | 15.311                                   | (14.832–17.361) | 18.76            | (17.928–19.9375) |
| <b>PE 36:5e</b> | 0.714     | (0.665–0.779) | 0.673                               | (0.569–0.733)   | 1.339                                    | (0.925–1.395)   | 1.026            | (0.954–1.0558)   |
| <b>PE 38:5e</b> | 0.381     | (0.322–0.393) | 0.321                               | (0.302–0.386)   | 0.649                                    | (0.592–0.743)   | 0.491            | (0.461–0.514)    |

**Table S6. Relative concentration ( $\mu\text{mol}/\text{mg}$  protein) of sphingomyelins (SM) in Huh-7 cells cultured (24 h) in the absence/presence of silibinin (SBN) and/or lorlatinib**

|                | Untreated |                 | SBN (100 $\mu\text{mol}/\text{L}$ ) |                 | lorlatinib (1 $\mu\text{mol}/\text{L}$ ) |                 | lorlatinib + SBN |                 |
|----------------|-----------|-----------------|-------------------------------------|-----------------|--|-----------------|------------------|-----------------|
|                | Median    | (Q1–Q3)         | Median                              | (Q1–Q3)         | Median                                   | (Q1–Q3)         | Median           | (Q1–Q3)         |
| <b>SM 32:0</b> | 0.296     | (0.240–0.334)   | 0.408                               | (0.392–0.450)   | 0.350                                    | (0.343–0.395)   | 0.539            | (0.508–0.569)   |
| <b>SM 32:1</b> | 1.361     | (1.167–1.538)   | 1.232                               | (1.186–1.395)   | 2.087                                    | (1.758–2.338)   | 1.810            | (1.645–2.113)   |
| <b>SM 32:2</b> | 0.021     | (0.016–0.022)   | 0.016                               | (0.013–0.017)   | 0.032                                    | (0.024–0.032)   | 0.020            | (0.019–0.022)   |
| <b>SM 33:1</b> | 1.395     | (1.174–1.549)   | 1.184                               | (1.119–1.307)   | 1.877                                    | (1.798–2.085)   | 1.618            | (1.505–1.748)   |
| <b>SM 34:1</b> | 16.065    | (13.679–17.477) | 13.074                              | (12.542–13.614) | 22.397                                   | (20.913–24.645) | 16.438           | (15.900–17.524) |
| <b>SM 34:2</b> | 1.406     | (1.185–1.494)   | 1.186                               | (1.157–1.323)   | 1.973                                    | (1.880–2.189)   | 1.677            | (1.572–1.773)   |
| <b>SM 35:0</b> | 1.800     | (1.363–1.958)   | 1.888                               | (1.764–2.167)   | 1.702                                    | (1.617–1.855)   | 2.674            | (2.416–2.881)   |
| <b>SM 35:1</b> | 0.611     | (0.513–0.678)   | 0.369                               | (0.355–0.400)   | 0.803                                    | (0.742–0.888)   | 0.486            | (0.462–0.517)   |
| <b>SM 36:0</b> | 0.177     | (0.156–0.186)   | 0.128                               | (0.126–0.132)   | 0.297                                    | (0.284–0.335)   | 0.143            | (0.132–0.150)   |
| <b>SM 36:1</b> | 0.938     | (0.873–0.997)   | 0.555                               | (0.532–0.561)   | 1.764                                    | (1.596–1.956)   | 0.614            | (0.601–0.643)   |
| <b>SM 36:2</b> | 0.491     | (0.420–0.530)   | 0.390                               | (0.375–0.427)   | 0.702                                    | (0.633–0.757)   | 0.530            | (0.503–0.558)   |
| <b>SM 38:1</b> | 0.421     | (0.371–0.466)   | 0.310                               | (0.303–0.345)   | 0.595                                    | (0.574–0.639)   | 0.412            | (0.379–0.444)   |
| <b>SM 38:2</b> | 0.081     | (0.075–0.085)   | 0.054                               | (0.049–0.054)   | 0.151                                    | (0.145–0.171)   | 0.055            | (0.054–0.058)   |
| <b>SM 39:1</b> | 0.142     | (0.121–0.153)   | 0.107                               | (0.104–0.121)   | 0.210                                    | (0.198–0.234)   | 0.136            | (0.123–0.146)   |
| <b>SM 40:0</b> | 0.177     | (0.126–0.205)   | 0.206                               | (0.203–0.232)   | 0.286                                    | (0.274–0.326)   | 0.269            | (0.231–0.289)   |
| <b>SM 40:1</b> | 1.146     | (0.937–1.220)   | 0.875                               | (0.795–0.943)   | 1.575                                    | (1.498–1.852)   | 1.169            | (1.022–1.248)   |
| <b>SM 40:2</b> | 0.678     | (0.568–0.720)   | 0.520                               | (0.500–0.558)   | 0.891                                    | (0.785–0.983)   | 0.670            | (0.628–0.726)   |
| <b>SM 41:1</b> | 0.487     | (0.395–0.522)   | 0.392                               | (0.351–0.423)   | 0.637                                    | (0.579–0.762)   | 0.554            | (0.527–0.598)   |
| <b>SM 41:2</b> | 0.034     | (0.031–0.044)   | 0.031                               | (0.026–0.032)   | 0.065                                    | (0.054–0.078)   | 0.041            | (0.036–0.046)   |
| <b>SM 42:1</b> | 1.434     | (1.288–1.745)   | 1.615                               | (1.513–1.713)   | 2.064                                    | (1.676–2.242)   | 1.855            | (1.698–1.918)   |
| <b>SM 42:2</b> | 2.493     | (2.035–2.733)   | 2.190                               | (2.075–2.375)   | 3.149                                    | (2.980–3.542)   | 2.946            | (2.616–3.172)   |

|                |       |               |       |               |       |               |       |               |
|----------------|-------|---------------|-------|---------------|-------|---------------|-------|---------------|
| <b>SM 42:3</b> | 0.630 | (0.524–0.655) | 0.411 | (0.395–0.413) | 0.805 | (0.789–0.950) | 0.420 | (0.388–0.486) |
| <b>SM 43:1</b> | 0.104 | (0.087–0.130) | 0.089 | (0.087–0.105) | 0.128 | (0.119–0.146) | 0.091 | (0.089–0.097) |
| <b>SM 43:2</b> | 0.301 | (0.241–0.337) | 0.232 | (0.224–0.255) | 0.358 | (0.339–0.401) | 0.309 | (0.287–0.329) |

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**Table S7. Relative concentration ( $\mu\text{mol}/\text{mg}$  protein) of cholesterol esters (ChoE) in Huh-7 cells cultured (24 h) in the absence/presence of silibinin (SBN) and/or lorlatinib**

|                  | Untreated |                 | SBN (100 $\mu\text{mol}/\text{L}$ ) |                 | lorlatinib (1 $\mu\text{mol}/\text{L}$ ) |                   | Lorlatinib + SBN |                 |
|------------------|-----------|-----------------|-------------------------------------|-----------------|--|-------------------|------------------|-----------------|
|                  | Median    | (Q1–Q3)         | Median                              | (Q1–Q3)         | Median                                   | (Q1–Q3)           | Median           | (Q1– Q3)        |
| <b>ChoE 16:0</b> | 8.017     | (6.695–8.384)   | 2.937                               | (2.566–3.137)   | 11.335                                   | (11.192–13.242)   | 4.902            | (4.288–5.361)   |
| <b>ChoE 16:1</b> | 18.886    | (16.302–26.857) | 7.298                               | (6.573–8.925)   | 25.820                                   | (23.602–28.986)   | 13.832           | (12.687–14.819) |
| <b>ChoE 17:0</b> | 1.080     | (0.970–1.130)   | 0.371                               | (0.367–0.382)   | 2.170                                    | (2.030–2.215)     | 0.568            | (0.493–0.607)   |
| <b>ChoE 17:1</b> | 3.697     | (3.306–3.962)   | 1.214                               | (1.130–1.355)   | 5.670                                    | (5.415–6.781)     | 1.771            | (1.545–1.854)   |
| <b>ChoE 18:0</b> | 2.500     | (2.398–2.926)   | 0.835                               | (0.752–0.865)   | 4.365                                    | (3.681–4.782)     | 1.107            | (1.064–1.269)   |
| <b>ChoE 18:2</b> | 23.460    | (20.805–25.330) | 7.393                               | (7.038–7.777)   | 33.284                                   | (30.618–39.288)   | 11.057           | (10.731–11.237) |
| <b>ChoE 18:3</b> | 9.300     | (8.319–9.577)   | 3.182                               | (3.139–3.520)   | 12.818                                   | (12.373–15.356)   | 5.188            | (4.825–5.634)   |
| <b>ChoE 20:2</b> | 6.224     | (5.056–7.357)   | 2.088                               | (1.884–2.195)   | 6.459                                    | (5.193–7.023)     | 2.892            | (2.36–3.299)    |
| <b>ChoE 20:3</b> | 29.276    | (22.698–30.894) | 7.915                               | (7.695–9.037)   | 42.167                                   | (41.084–48.000)   | 13.402           | (12.338–13.755) |
| <b>ChoE 20:4</b> | 51.820    | (46.507–56.194) | 10.818                              | (10.014–11.434) | 107.967                                  | (104.761–132.255) | 16.964           | (16.229–17.320) |
| <b>ChoE 20:5</b> | 32.124    | (29.012–37.344) | 5.857                               | (5.696–6.506)   | 68.788                                   | (65.756–87.599)   | 9.858            | (9.128–10.151)  |
| <b>ChoE 22:4</b> | 12.329    | (11.526–12.776) | 2.650                               | (2.547–2.793)   | 27.538                                   | (24.473–32.807)   | 4.093            | (3.542–4.234)   |
| <b>ChoE 22:5</b> | 27.912    | (26.452–30.841) | 5.862                               | (5.682–6.574)   | 59.058                                   | (55.8–72.323)     | 9.102            | (6.283–9.537)   |