# Supporting information

# Nutrient-Based Chemical Library as a Source of Energy Metabolism Modulators

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## Supplementary Chemistry Notes

**General part**

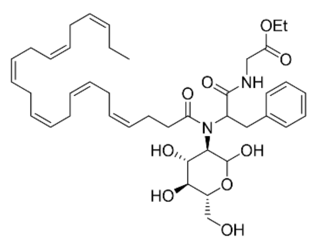
Unless otherwise noted all solvents and chemicals for chemical synthesis were purchased used without further purification. Some synthetic compounds were purified using a flash column system Shoko Scientific Purif‐α2. Preparative layer chromatography was carried out with glass PLC plates, pre-coated with silica gel 60 F254 (Merck). Low‐resolution mass spectra were obtained using a Shimadzu LCMS‐2010EV in ESI mode. LC-MS conditions were as follows: Shimadzu Shim‐pack XR‐ODS column (2.2 µm, 3.0× 50 mm); solvent gradient, A, 0.1% trifluoroacetic acid (TFA) in H2O; B, acetonitrile with gradient (0–3.5 min: B, 10–100%; 3.5–5 min: B, 100%; 5–5.5 min: B 10% at 40 °C); flow rate, 0.7 mL/min; detector, 220 nm. High‐resolution mass spectra (HRMS) were obtained using a JEOL MStation JMS‐700 in FAB mode or Bruker SolariX in ESI mode. 1H‐NMR spectra were collected by Bruker Avance III 800US Plus NMR or Bruker Avance III 600US Plus NMR. Chemical shifts were reported in δ(ppm) relative to tetramethylsilane.

**Experimental procedures**

Typical procedure for library compound synthesis

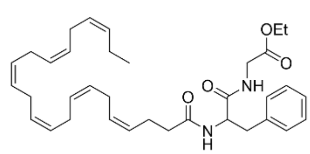
To a solution of an amine (0.14 mmol), a carboxylic acid (0.14 mmol) and an aldehyde (0.14 mmol) in EtOH (0.5 mL) and sat. $NaHCO_3$ aq. (0.1 mL) was added isocyanoethylacetate (0.14 mmol) and stirred for 2 h. The reaction mixture was charged on a PTLC plate and separated with $CHCl_3$-MeOH.

Modified synthesis of molecule **1**



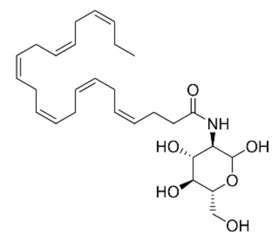
To a solution of D-(+)-glucosamine hydrochloride (150 mg), DHA (245 µL), phenylacetoaldehyde (82 µL) and LiOH・$H_2O$ (30 mg) in water (5 mL) and EtOH (0.5 mL) was added ethyl isocyanoacetate (77 µL). After stirring for 2 h, the reaction mixture was charged on a silica gel column and eluted with $CHCl_3$/MeOH (100:0 ~ 80:20) to give molecule **1** (25.8 mg, 5.1% yield, dr = 1:1). $^1$H-NMR (600 MHz, $CDCl_3$) δ: 7.39 - 7.26 (5H, m), 6.71 - 6.46 (1H, m), 5.63 - 5.29 (12H, m), 4.74 - 4.67 (1H, m), 4.23 - 4.13 (2H, m), 4.05 – 3.98 (1H, m), 3.97 - 3.96 (1H, m), 3.90 - 3.88 (2H, m), 3.80 - 3.72 (2H, m), 3.62 - 3.59 (1H, m), 3.47 - 3.39 (1H, m), 2.86 -2.80 (10H, m), 2.53 - 2.30 (4H, m), 2.07 (2H, quintet of doublet, $J$ = 1.2, 0.6 Hz), 1.26 (3H, dt, $J$ = 22.8, 7.2 Hz), 0.97 (3H, t, $J$ = 7.2 Hz). $^{13}$C-NMR (150MHz, $CDCl_3$) δ: 176.20, 174.38, 173.32, 172.71, 170.29, 170.27, 137.89, 137.44, 132.06, 129.48, 129.20, 129.18, 129.14, 129.02, 128.95,128.59, 128.53, 128.31, 128.30, 128.27, 128.26, 128.24, 128.23, 128.21, 128.16, 128.11, 127.90, 127.89, 127.48, 127.39, 127.03, 93.97, 93.10, 75.37, 71.82, 71.68, 71.26, 71.12, 68.71, 65.18, 62.71, 62.49, 62.18, 62.03, 61.77, 61.66, 58.39, 42.06, 41.78, 35.56, 35.20, 34.14, 34.10, 25.68, 25.67, 25.66, 25.64, 25.63, 25.54, 22.68, 22.58, 20.57, 14.29, 14.11, 14.10. HRMS (FAB, m/z, $[M+Na]^+$) calculated For $C_{41}H_{58}N_2O_9Na$: 745.4040 found 745.4043.

Synthesis of Molecule **3**



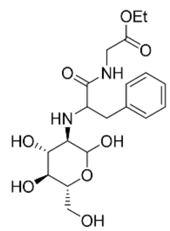
To a solution of DHA (35 µL), DL-Phenylalanylglycine ethyl ester **2** (30 mg) and HATU (42 mg) in DMF (1 mL) was added DIEA (80 µL). After stirring for 1 h, the reaction mixture was quenched with water (5 mL) and extracted by EtOAc (2 mL×3). The organic layer was washed with sat. NaCl aq., dried over $Na_2SO_3$ and concentrated *in vacuo* to give a crude product. The crude product was purified by flash silica gel column chromatography with n-hexane/EtOAc (95:5 ~ 80:20) to give **3** (36.4 mg, 61% yield). $^1$H-NMR (600 MHz, DMSO-d6) δ: 8.46 - 8.38 (1H, m), 8.09 (1H, d, $J$ = 8.4 Hz), 7.18 - 7.17 (5H, m), 5.36 - 5.17 (12H, m), 4.58 - 4.48 (1H, m), 4.09 (2H, q, $J$ = 7.2 Hz), 3.88 - 3.78 (2H, m), 3.03 (2H, dd, J = 13.8, 4.2), 2.85 - 2.68 (10H, m), 2.52 - 2.00 (6H, m), 1.19 (3H, t, $J$ = 7.2 Hz), 0.91 (3H, t, $J$ = 7.8 Hz). $^{13}$C-NMR (150MHz, DMSO-d6) δ: 171.84, 171.29, 169.56, 137.88, 131.44, 129.03, 128.99, 128.00, 127.96, 127.91, 127.87, 127.82, 127.79, 127.78, 127.76, 127.73, 127.62, 127.58, 126.03, 60.31, 53.43, 40.63, 37.49, 34.89, 25.10, 25.09, 25.08, 25.00, 25.00, 22.85, 19.92, 14.00, 13.94. HRMS (ESI, m/z, $[M+Na]^+$) calculated For $C_{35}H_{48}N_2O_4Na$: 583.35063 found 583.35008.

Synthesis of Molecule **4**[1]



To a solution of DHA (98 µL), D-glucosamine hydrochloride (60 mg) and DIEA (53 µL) in EtOH (2 mL) was added DMT-MM (93 mg) and stirred for 3 h. The reaction mixture was charged on a PTLC plate and separated with $CHCl_3$ / MeOH (80:20) to give molecule **4** (9.8 mg, 7.2% yield). $^1$H-NMR (600 MHz, DMSO-d6) δ: 7.57 (1H, d, *J* = 8.4 Hz), 6.43 - 6.38 (1H, m), 5.56 - 5.25 (12H, m), 4.82 - 4.77 (1H, m), 4.58 (1H, d, *J* = 5.4 Hz), 4.53 (1H, t, *J* = 5.4 Hz), 4.43 (1H, t, *J* = 4.8 Hz), 3.75- 3.66 (1H, m), 3.64 - 3.55 (3H, m), 3.52 - 3.44 (2H, m), 2.85 - 2.77 (10H, m), 2.22 - 2.28 (2H, m), 2.12 - 2.19 (2H, m), 1.99 -2.06 (2H, m), 0.92 (3H, t, *J* = 7.8 Hz). $^{13}$C-NMR (150MHz, DMSO-d6) δ: 161.78, 131.45, 129.04, 129.00, 128.06, 128.02, 127.81, 127.79, 127.77, 127.75, 127.67, 127.60, 126.84, 90.49, 71.04, 70.34, 69.67, 64.28, 61.02, 31.17, 25.11, 25.10, 25.05, 25.01, 24.37, 22.95, 21.97, 14.02. HRMS (ESI, m/z, $[M+Na]^+$) calculated For $C_{28}H_{43}NO_6Na$: 512.29826 found 512.29839.

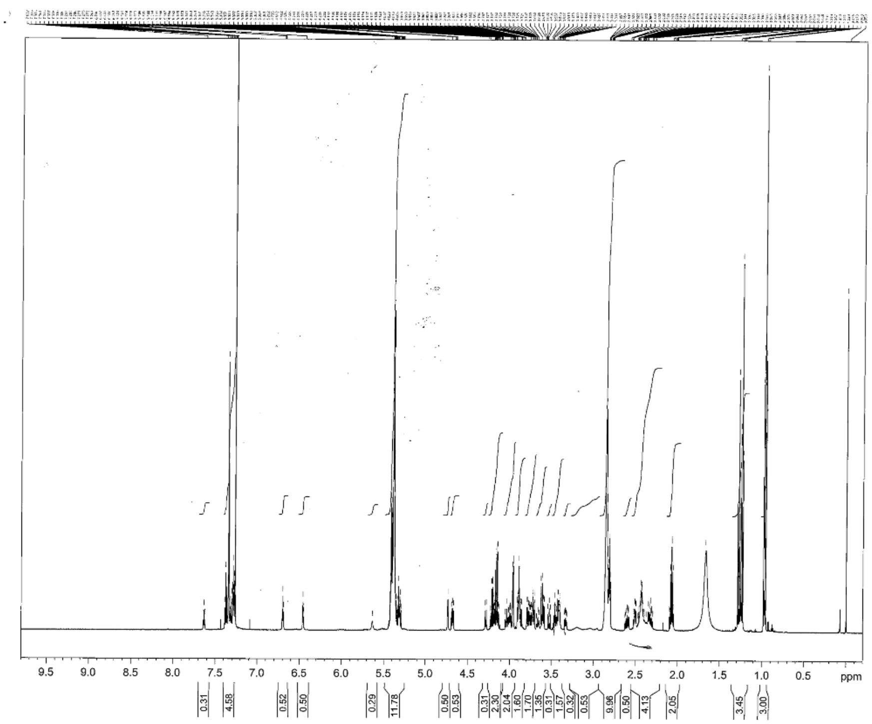
Synthesis of Molecule **5**[2]



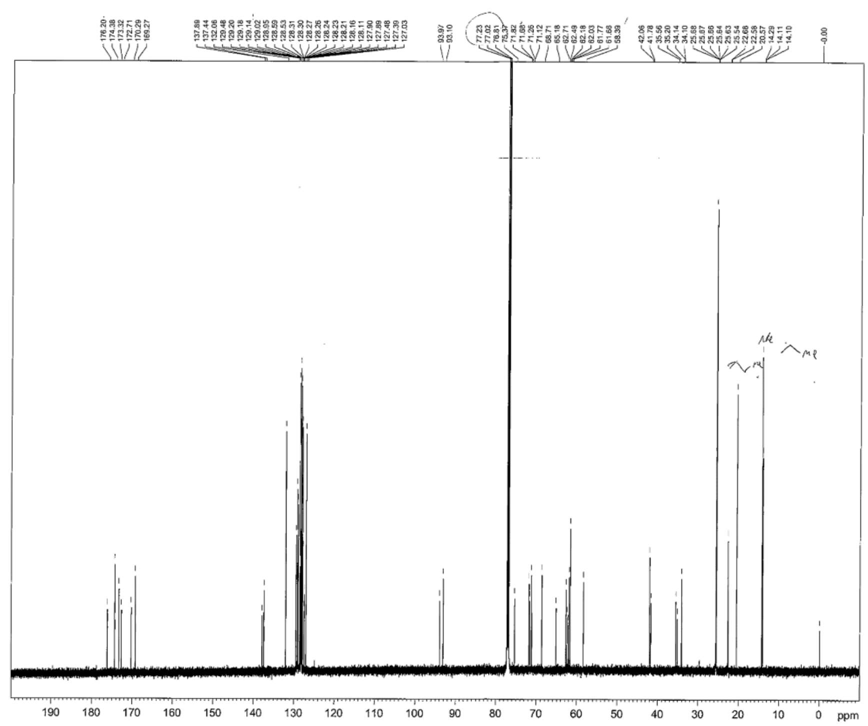
To a solution of D-glucosamine hydrochloride (107 mg), boric acid (31 mg), phenylacetoaldehyde (66µL) and LiOH・$H_2O$ (21 mg) in water (2 mL) was added ethyl isocyanoacetate (40µL). After stirring for 2h, the reaction mixture was charged on PTLC plate and separated with $CHCl_3$/MeOH (80:20) to give molecule **5** (10.5 mg, 5.3% yield, dr = 1:1). $^1$H-NMR (600 MHz, DMSO-d6) δ: 8.76 - 8.24, (1H, m), 7.33 - 7.16 (5H, m), 6.67 -6.09 (1H, m), 4.97 - 4.91 (2H, m), 4.89 - 4.74 (1H, m), 4.51 - 4.30 (1H, m), 4.09 (2H, q, *J* = 7.2 Hz), 3.88 - 3.77 (2H, m), 3.75 -3.48 (1H, m),3.48 - 3.20 (6H, m, $H_2O$ peak overwrapped) 3.09 - 2.98 (2H, m), 2.98 - 2.71 (1H, m), 1.21 - 1.18 (3H, m). $^{13}$C-NMR (200MHz, DMSO-d6) δ: 174.39, 174.04, 169.86, 169.58, 137.82, 137.67, 129.32, 129.07, 129.04, 128.91, 128.20, 127.93, 91.33, 89.64, 76.70, 75.96, 73.57, 72.11, 71.92, 71.72, 70.63, 69.67, 69.47, 63.08, 61.07, 60.99, 60.41, 60.31, 40.63, 40.57, 33.55, 33.07,13.95, 13.84. HRMS (ESI, m/z, $[M+Na]^+$) calculated For $C_{19}H_{28}N_2O_8Na$: 435.17379 found 435.17390.

**Structural characterization**

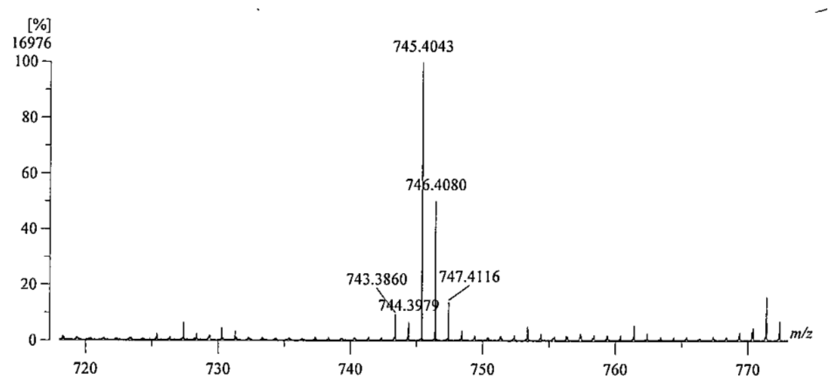
$^{1}H$ (600 MHz) NMR spectrum of molecule **1** in $CDCl_3$



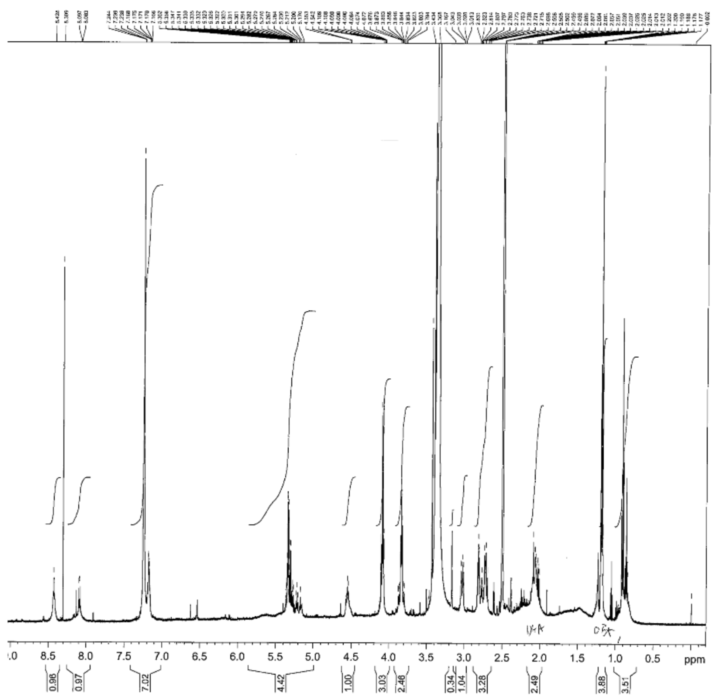
$^{13}C$ (150 MHz) NMR spectrum of molecule **1** in $CDCl_3$



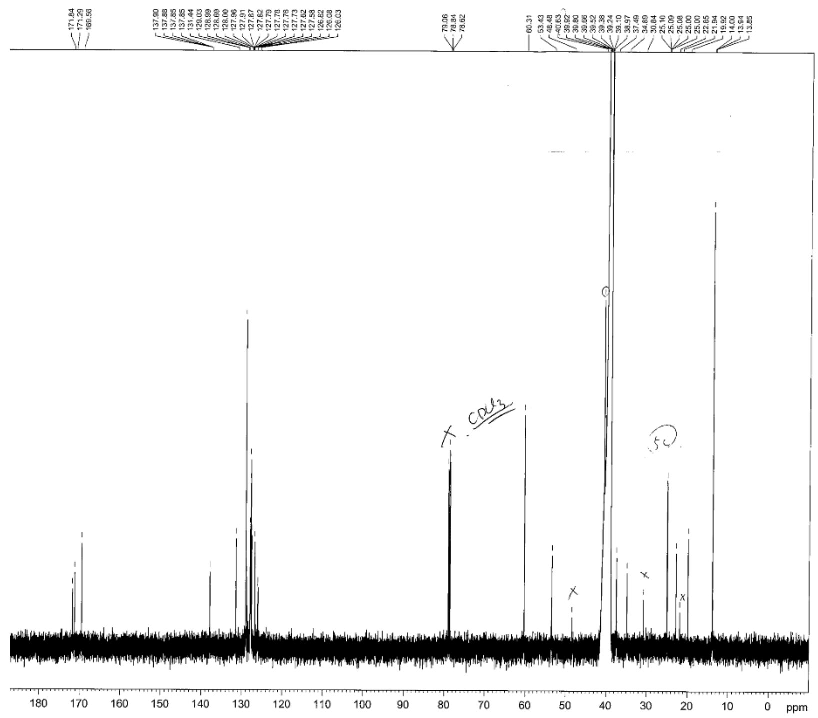
HRMS spectrum of molecule **1**



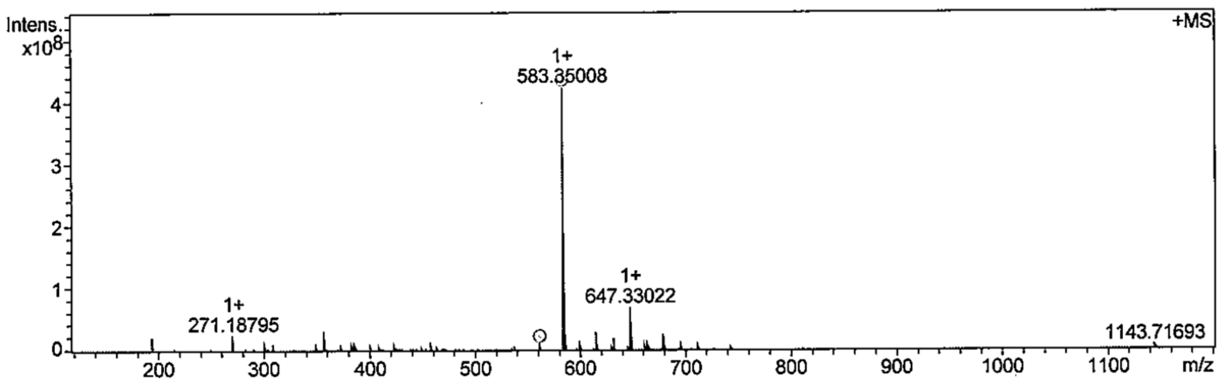

[1]H (600 MHz) NMR spectrum of molecule **3** in DMSO-d6



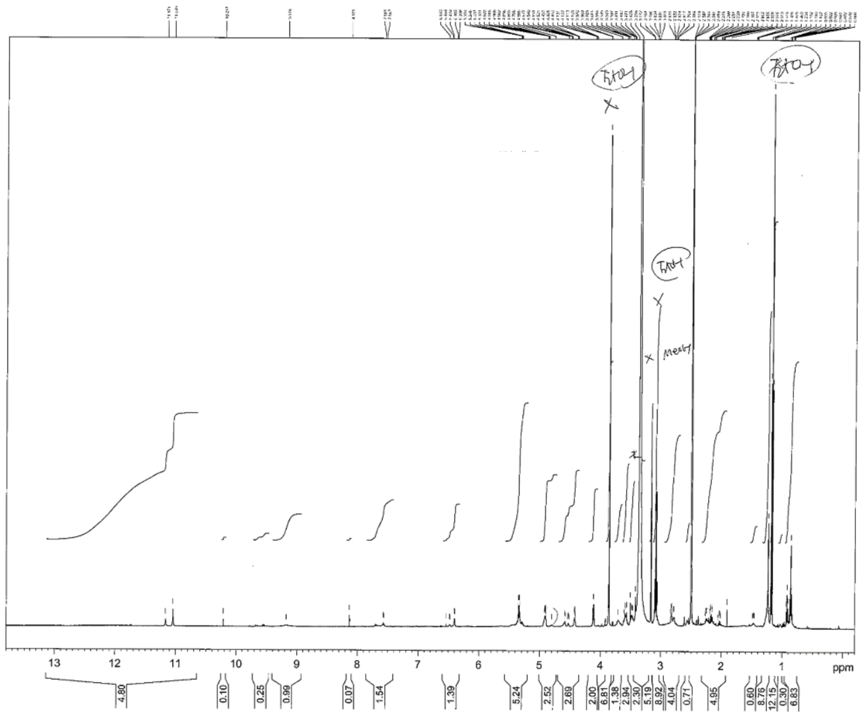
$^{13}C$ (150 MHz) NMR spectrum of molecule **3** in DMSO-d6



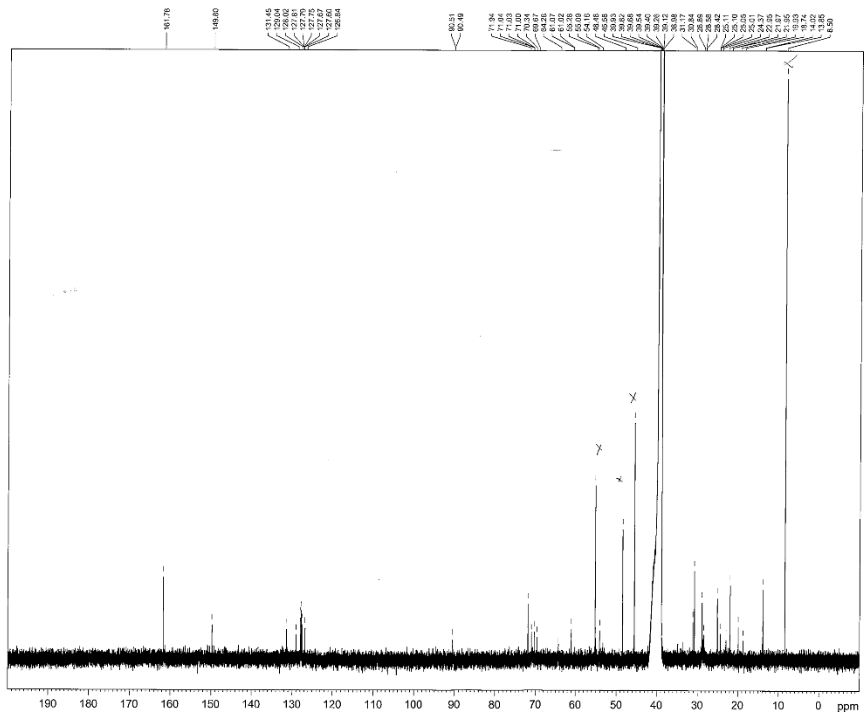

HRMS spectrum of molecule **3**



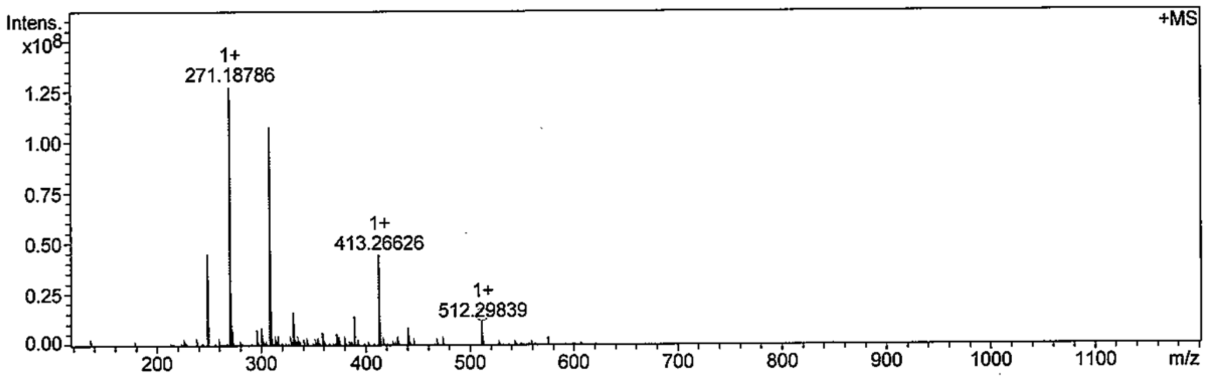
$^{1}$H (600 MHz) NMR spectrum of molecule **4** in DMSO-d6



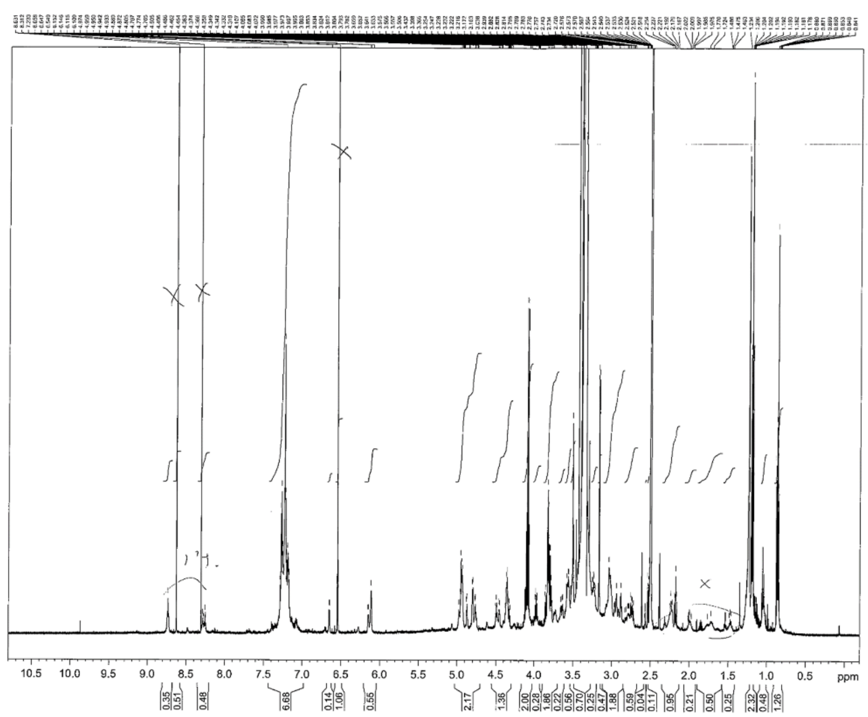
$^{13}$C (150 MHz) NMR spectrum of molecule **4** in DMSO-d6



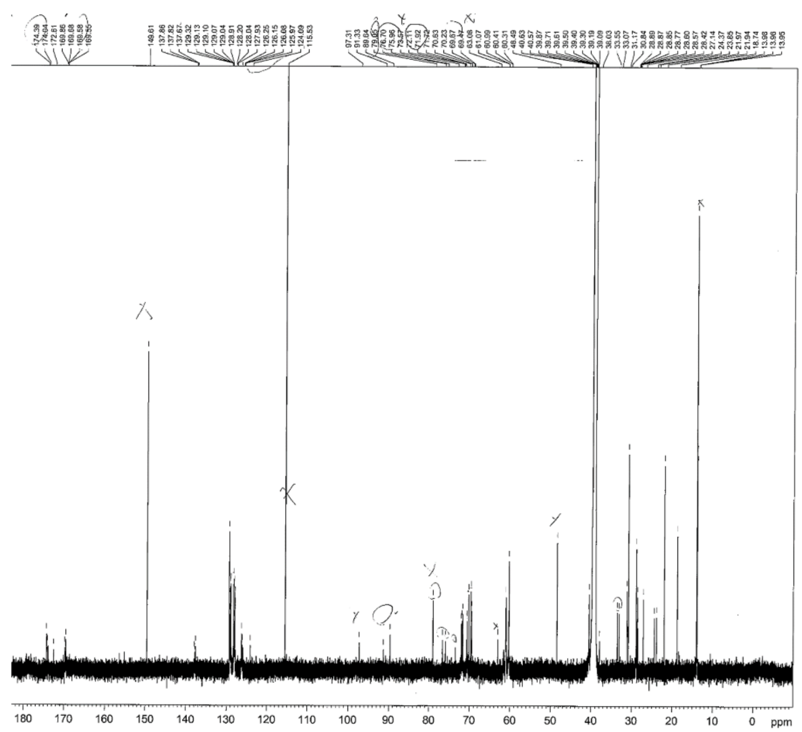
HRMS spectrum of molecule **4**



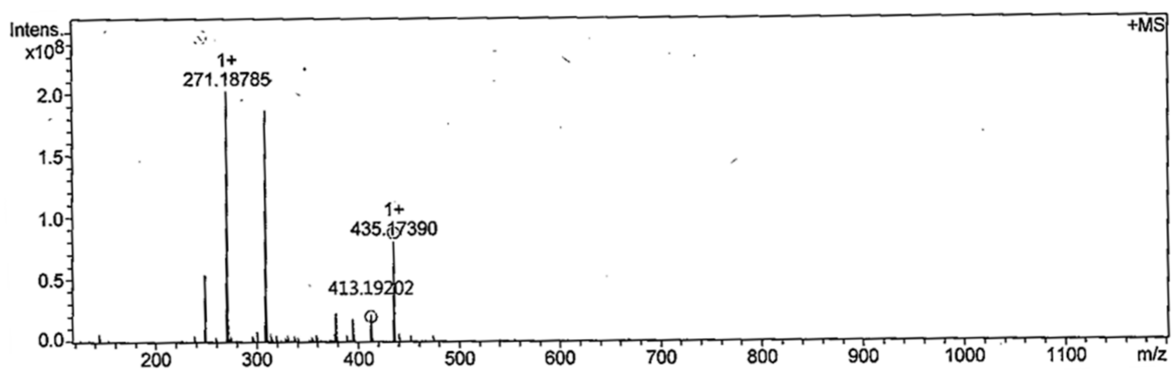

[1]H (600 MHz) NMR spectrum of molecule **5** in DMSO-d6



$^{13}C$ (200 MHz) NMR spectrum of molecule **5** in DMSO-d6




HRMS spectrum of molecule **5**



## Supplementary Biology Notes

### Antibodies

Anti SREBP-2 (IgG-7D4)[3] were obtained from Division of Metabolic Medicine, Research Center for Advanced Science and Technology, The University of Tokyo. Anti β-actin (IgG-Ac-40) was obtained from Abcam. Anti AMPK-α(IgG-C20) was from Santa Cruz Biotechnology Inc. Anti phospho-AMPKα(Thr172) (IgG-40H9) was from Cell Signaling Technology.

### Cell Culture

CHO-K1 cells were maintained in a medium A (1:1 mixture of Ham's F-12 medium and DMEM, supplemented with 100 units/mL penicillin, 100 mg/mL streptomycin sulfate, and 5% [v/v] fetal bovine serum) at 37℃in a humidified 5% CO2 incubator. Hepa 1-6 cells were maintained in a medium B (DMEM, supplemented with 100 units/mL penicillin, 100 mg/mL streptomycin sulfate, and 10% [v/v] fetal bovine serum) at 37℃in a humidified 5% CO2 incubator. Caco-2 cells were maintained in a medium C (DMEM, supplemented with 100 units/mL penicillin, 100 mg/mL streptomycin sulfate, 1% non-essential amino acids, and 10% [v/v] fetal bovine serum) at 37℃in a humidified 5% CO2 incubator.

### Luciferase Reporter Assay

SREBP Reporter Assay

On day 0, CHO-K1 cells were added to 96-well plates at $1.0\times10^4$ cells per well in medium A. On day 1, the cells were co-transfected with an SRE-1-driven luciferase reporter plasmid (pSRE-Luc) and a β-gal reporter plasmid with a constitutively active actin promoter (pAc-β-gal) at a 20/1 ratio, using FuGENE HD Transfection Reagent (Promega), as instructed in the manufacturer's protocol. After 12-hr incubation, the cells were washed with PBS and then incubated in medium D (1:1 mixture of Ham's F-12 medium and DMEM, supplemented with 100 units/mL penicillin, 100 mg/mL streptomycin sulfate, 5% [v/v] lipid-depleted serum, 50 μM compactin, and 50 μM lithium mevalonate) containing the specific test compounds. Stock solutions of each compound in DMSO were prepared and added to medium A to give a 1000-fold (v/v) dilution (0.1% DMSO). After 24 h of incubation, the cells in each well were lysed by freeze-thaw with Reporter Lysis Buffer (Promega), and aliquots were used for measuring luciferase and β-gal activities. Luciferase activity was measured using the Steady-Glo Luciferase Assay System (Promega), and β-gal activity was measured using the β-Galactosidase Enzyme Assay System (Promega). Luciferase activity was normalized to β-gal activity.

LXR Reporter Assay

On day 0, CHO-K1 cells were added to 96-well plates at $1.0\times10^4$ cells per well in medium A. On day 1, the cells were co-transfected with an LXR-driven luciferase reporter plasmid (pLXR-Luc) and a β-gal reporter plasmid with a constitutively active actin promoter (pAc-β-gal) at a 20/1 ratio, using FuGENE HD Transfection Reagent (Promega), as instructed in the manufacturer's protocol. After 12-hr incubation, the cells were washed with PBS and then treated with medium A containing the specific test compounds. Stock solutions of each compound in DMSO were prepared and added to medium A to give a 1000-fold (v/v) dilution (0.1% [v/v] DMSO). After 24 h incubation, luciferase and β-gal activities were measured in a same manner as described above.

### Western blot analysis

At the end of incubation, the cells were washed three times with cold PBS, and lysed with buffer A (50 mM Tris-HCl [pH 7.5], 150 mM NaCl, 1% [v/v] Nonidet P-40, 0.5% [w/v] sodium deoxycholate, 8 M urea, and protease inhibitor cocktail (Nacalai Tesque)). The cell lysates were passed 20 times through a 25G needle and centrifuged at 7,000×g at 4℃for 10 min. The supernatants were transferred to new tubes. The resulting lysate was mixed with 0.20 volume of 6×SDS sample buffer (Nacalai Tesque) and incubated at room temperature for 1 h. The samples were separated on a 4-15% Tris-HCl precast SDS PAGE gel (BIO-RAD) and blotted using specific antibodies. The specific bands were visualized using enhanced chemiluminescence (ECL Prime Western Blotting Detection Reagent, GE Healthcare) on an ImageQuant LAS 500 (GE Healthcare).

### Glucose uptake assay

Glucose uptake was determined using Glucose Uptake Cell-Based Assay Kit (Cayman Chemical). On day 0, Caco-2 cells were added to 96-well plates at $1.0\times10^4$ cells per well in medium C. The medium was changed every 1-2 days, and the culture was carried out for 21 days. Then the cells were starved in medium E (glucose-free DMEM, supplemented with 100 units/mL penicillin, 100 mg/mL streptomycin sulfate) for 60 min. The cells were washed with PBS and then incubated for 3 h in medium E containing the specific test compounds (1000 fold dilution, 0.1% DMSO) and 2-NBDG (200 μM). After three-time extensive wash with cold Cell-Based Assay Buffer (Cayman Chemical), fluorescent intensity was measured by a microplate reader (MTP-880) with the 490-nm excitation and 530-nm emission. Glucose uptake was quantified relative to DMSO control in %.

The selectivity of molecule **1** to GLUTs was evaluated in GLUT-overexpressing HEK293 cells. HEK293 cells were transiently transfected with an expression vector of each of GLUT1-4 (*SLC2A1-4*) and then treated with varied concentrations of molecule **1**. Uptake of fluorescently-labeled glucose analog 2-NBDG was measured as described above.

### Mice glucose tolerant test

Prior to the test, male ICR mice were fasted for 24 h. Molecules **1** or **3** were orally administrated simultaneously or prior to oral administration of glucose. (i) Co-administration: D-glucose 12.5 mg with or without molecules **1** or **3** (6.25 μmol) in distilled water (250 μL) were orally administrated into the mice. (ii) Pretreatment: molecules **1** or **3** (6.25 μmol) in distilled water (250 μL) were orally administrated 10 min before administration of D-glucose (12.5mg) in distilled water (250 μL). At 5, 15, 30, 60, 90 and 120 min after the D-glucose administration, blood was obtained from a tail (5 μL) and assessed for glucose levels using a blood glucose self-monitoring kit (Eidia). Changes in continuous variables between the two examples were assessed using paired t-test.

**Hexokinase inhibition assay**

Effects of **1** (10 μM), molecules **3-5** (10 μM) and 3-bromopyruvic acid (positive control, 40 mM) on human hexokinase was measured using a Hexokinase Assay kit (BioVision) according to the manufacture's protocol. Briefly, glucose was converted to glucose-6-phosphate by hexokinase, and the glucose-6-phosphate is oxidized by glucose-6-phosphate dehydrogenase to form NADH, which reduces a colorless probe to a colored product with strong absorbance at 450 nm.

## Supplementary Figures

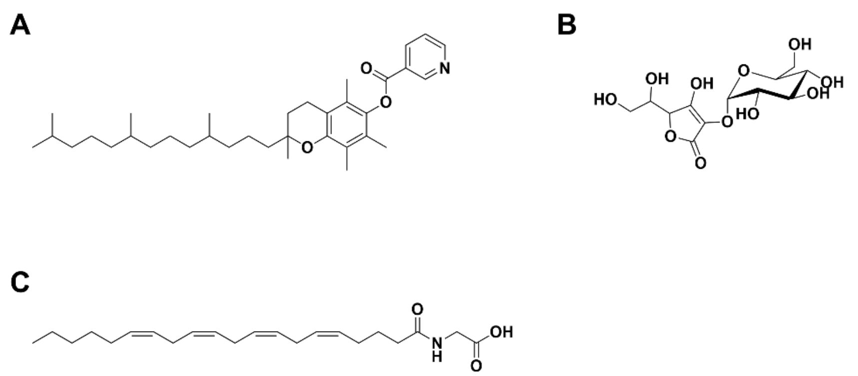



Figure S1. Examples of nutrient conjugates. (A) Tocopherol nicotinate. (B) AA-2G. (C) NA-Gly.

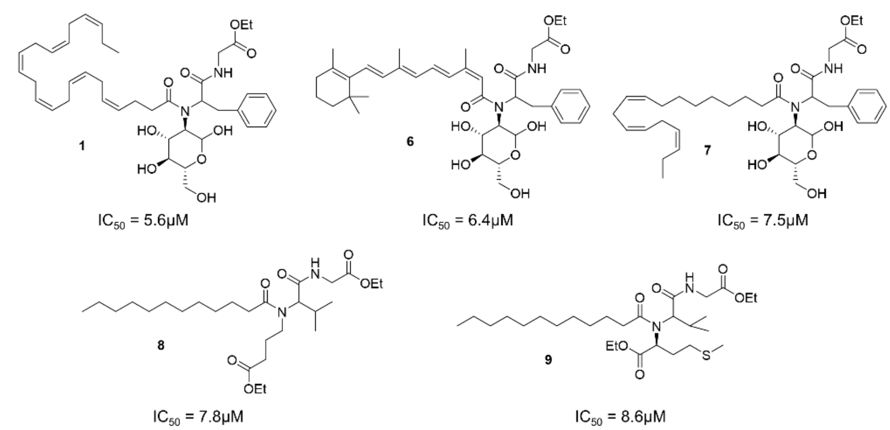



Figure S2. Chemical structures of 5 screening hits and their $IC_{50}$ values.

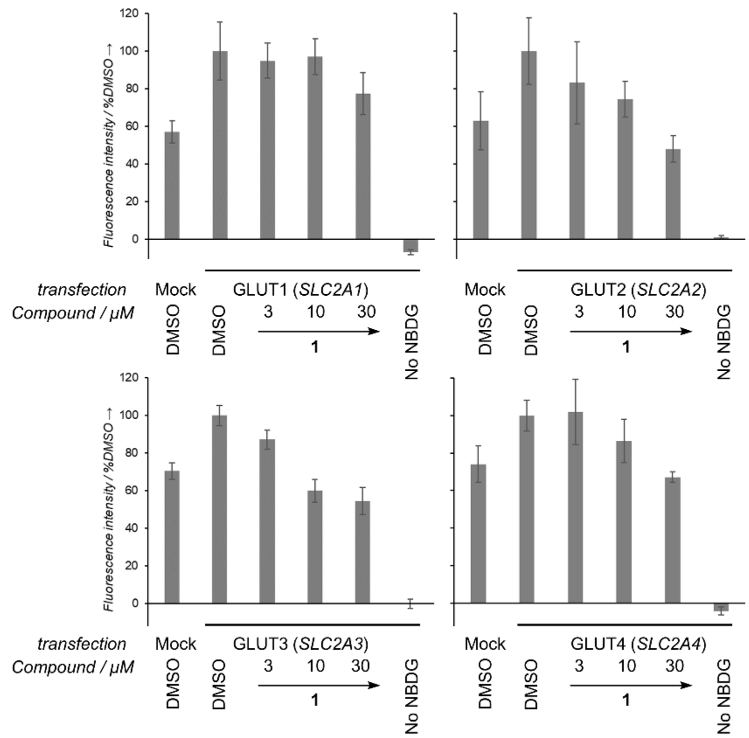



Figure S3. The ability of molecule **1** to block the glucose uptake in GLUT-overexpressing HEK293 cells. HEK293 cells were transiently transfected with an expression vector of each of GLUT1-4 (*SLC2A1-4*) and then treated with varied concentrations of molecule **1**. Uptake of fluorescently-labeled glucose analog 2-NBDG was measured. After extensive wash, fluorescence of the cells was measured with a fluorescence plate reader (excitation: 490 nm; emission: 530 nm).

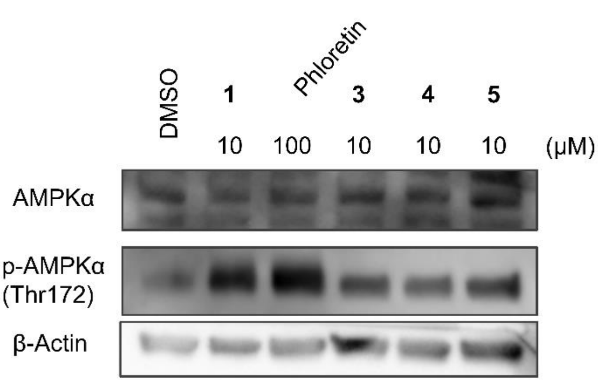



Figure S4. AMPK activation by molecule 1. Hepa 1-6 cells were treated with molecule **1** (10 μM), phloretin (100 μM), or molecules **3-5** (10 μM), and the cell lysates were analyzed by western blots with an antibody specific for phosphor-Thr172 AMPK. It is evident that molecule **1** activates AMPK phosphorylation just as phloretin while molecules 3-5 have no detectable effects.

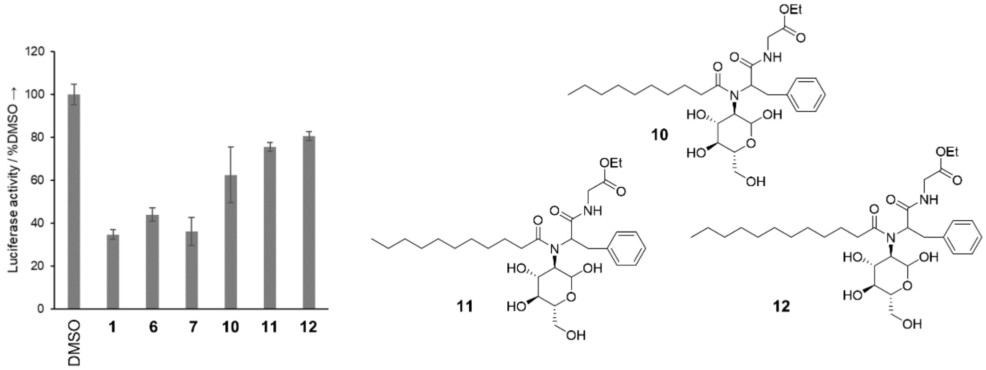



Figure S5. SREBP inhibitory activities of molecule **1**, **6**, **7** and molecules **10-12**. Luciferase activities were measured at a concentration of 10 μM after 24-h incubation.

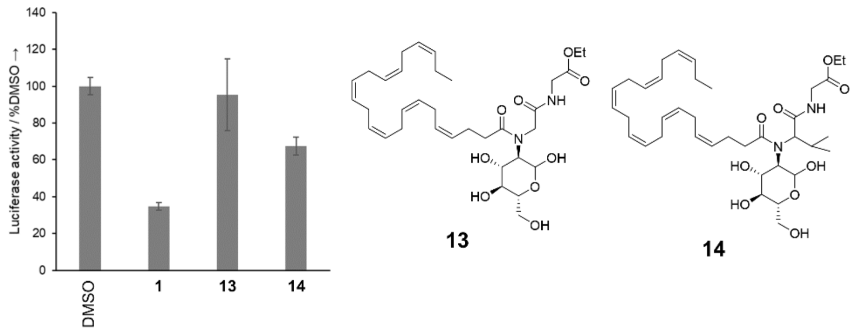



Figure S6. SREBP inhibitory activities of molecule **1** and molecules **13-14**. Luciferase activities were measured at a concentration of 10 μM after 24-h incubation.

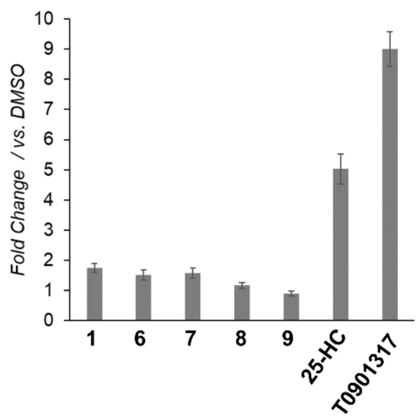



Figure S7. LXR reporter gene assay in CHO-K1 cells. CHO-K1 cells were co-transfected with an LXR-driven luciferase reporter plasmid (pLXR-Luc) and a β-gal reporter plasmid with a constitutively active actin promoter (pAc-β-gal). The cells were then treated with 5 μM of molucle **1** , molucles **6-9**, 25-HC, or T0901317 (LXR agonist)[4]. After 24-h incubation, luciferase and β-gal activities were measured.

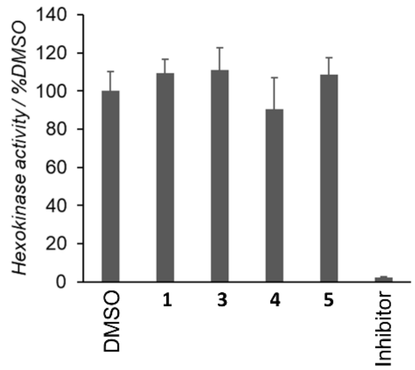
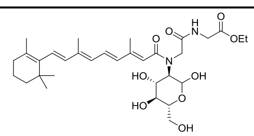
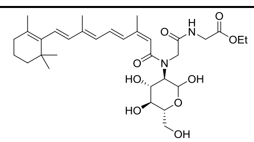
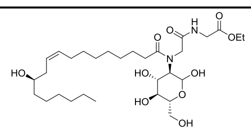
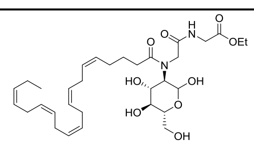
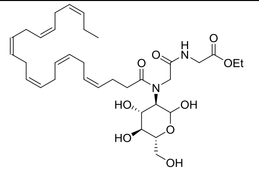
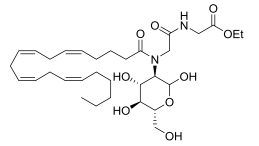
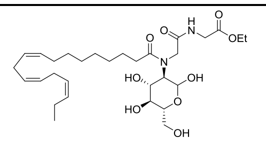
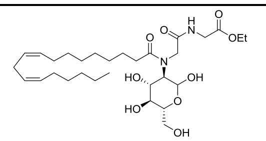
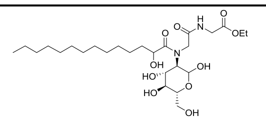
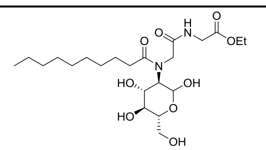
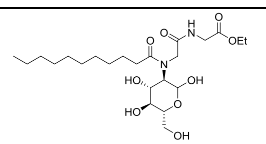
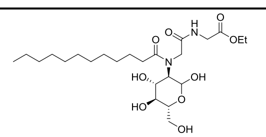
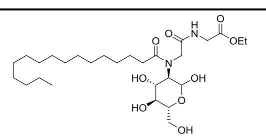
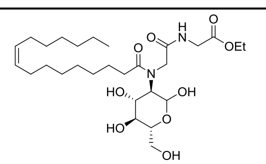


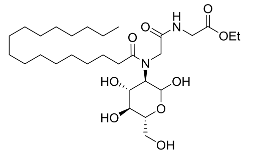
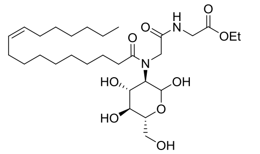
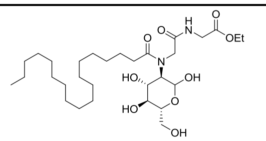
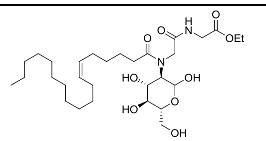
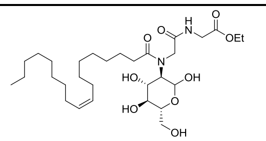
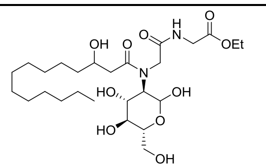
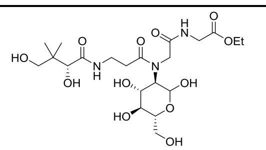
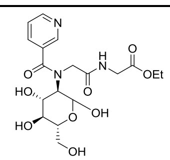
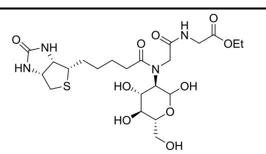
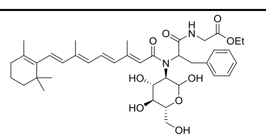

Figure S8. Effects on human hexokinase. Hexokinase activity was measured in the presence of of **1** (10 μM), molecules **3-5** (10 μ) or a known inhibitor (3-bromopyruvic acid, 40 mM) using a Hexokinase Assay kit (BioVision). Glucose was converted to glucose-6-phosphate by hexokinase, and the glucose-6-phosphate is oxidized by glucose-6-phosphate dehydrogenase to form NADH, which reduces a colorless probe to a colored product with strong absorbance at 450 nm.

## Supplementary Table

**Table S1. Structures, chemical yield , LC-MS data, and SREBP inhibitory activity of library compounds.**

| No. | Structure | M.W. | yield (%) | LC-MS RT (min.) | LC-MS m/z | LC-MS Purity (area%) | SREBP Inhibition @10 μM (% ) (Primary Screening) |
|---|---|---|---|---|---|---|---|
| **15** |  | 604.74 | 12.8 | 4.21 | 605 $[M+H]^+$ | 96.8 | 19.6 |
| **16** |  | 604.74 | 15.9 | 4.20 | 605 $[M+H]^+$ | 81.5 | 6.3 |
| **17** |  | 602.77 | 5.3 | 3.57 | 603 $[M+H]^+$ | 97.6 | 21.5 |
| **18** |  | 606.76 | 12.8 | 3.75 | 607 $[M+H]^+$ | 95.5 | -80.2 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **13** |  | 632.80 | 15.0 | 4.45 | 633 [M+H]$^+$ | 91.9 | 4.7 |
| **19** |  | 608.77 | 23.6 | 4.51 | 609 [M+H]$^+$ | 95.8 | -124.0 |
| **20** |  | 582.74 | 16.4 | 4.17 | 583 [M+H]$^+$ | 95.6 | 26.6 |
| **21** |  | 584.75 | 16.5 | 3.65 | 585 [M+H]$^+$ | 97.4 | 9.2 |
| **22** |  | 548.67 | 10.9 | 3.08 | 549 [M+H]$^+$ | 92.1 | 16.0 |
| **23** |  | 476.57 | 20.1 | 2.46 | 477 [M+H]$^+$ | 87.0 | -43.7 |
| **24** |  | 490.59 | 18.3 | 2.67 | 491 [M+H]$^+$ | 94.2 | 9.1 |
| **25** |  | 504.62 | 14.6 | 2.91 | 505 [M+H]$^+$ | 99.3 | -6.4 |
| **26** |  | 560.73 | 3.1 | 3.98 | 561 [M+H]$^+$ | 99.1 | 38.0 |
| **27** |  | 558.71 | 13.7 | 4.19 | 559 [M+H]$^+$ | 94.6 | 45.6 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **28** |  | 574.76 | 13.3 | 4.23 | 597 [M+Na]+ | 93.3 | 40.6 |
| **29** |  | 572.74 | 12.5 | 3.73 | 573 [M+H]+ | 87.5 | 51.7 |
| **30** |  | 588.78 | 12.7 | 4.54 | 589 [M+H]+ | 93.4 | 37.3 |
| **31** |  | 586.77 | 20.0 | 4.14 | 587 [M+H]+ | 96.7 | 41.5 |
| **32** |  | 586.77 | 12.2 | 4.01 | 587 [M+H]+ | 95.8 | 41.9 |
| **33** |  | 548.67 | 11.7 | 3.62 | 549 [M+H]+ | 94.0 | 21.7 |
| **34** |  | 523.54 | 6.5 | 1.23 | 524 [M+H]+ | 94.2 | 6.4 |
| **35** |  | 427.41 | 6.2 | 0.63 | 428 [M+H]+ | 99.3 | -1.9 |
| **36** |  | 548.61 | 2.9 | 1.14 | 549 [M+H]+ | 88.9 | 1.6 |
| **37** |  | 694.87 | 2.8 | 4.62 | 695 [M+H]+ | 95.8 | 65.6 |

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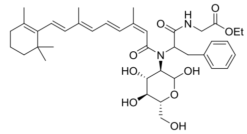
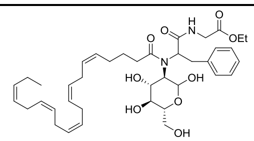
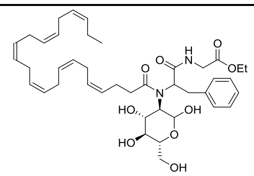
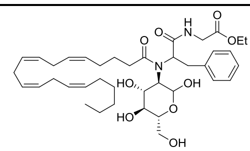
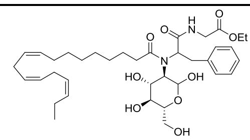
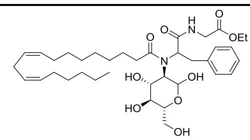
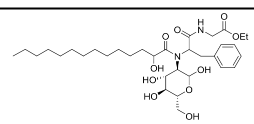
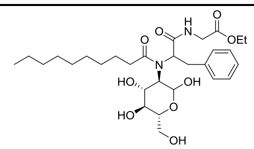
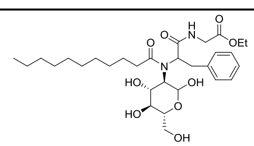
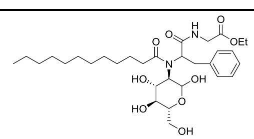
|---|---|---|---|---|---|---|---|
| **6** |  | 694.87 | 3.3 | 4.59 | 695 [M+H]$^+$ | 70.1 | 89.5 |
| **38** |  | 696.88 | 2.9 | 3.89 | 697 [M+H]$^+$ | 89.9 | 79.9 |
| **1** |  | 722.92 | 5.1 | 4.04 | 745 [M+Na]$^+$ | 96.8 | 90.8 |
| **39** |  | 698.90 | 2.7 | 4.83 | 699 [M+H]$^+$ | 97.2 | 77.3 |
| **7** |  | 672.86 | 3.3 | 4.59 | 673 [M+H]$^+$ | 97.2 | 90.2 |
| **40** |  | 674.88 | 2.9 | 4.05 | 675 [M+H]$^+$ | 84.6 | 81.6 |
| **41** |  | 638.80 | 4.6 | 3.57 | 639 [M+H]$^+$ | 84.7 | 82.4 |
| **10** |  | 566.69 | 2.9 | 2.94 | 567 [M+H]$^+$ | 72.0 | 62.4 |
| **11** |  | 580.72 | 2.7 | 3.16 | 581 [M+H]$^+$ | 93.7 | 75.5 |
| **12** |  | 594.75 | 2.8 | 3.38 | 595 [M+H]$^+$ | 91.7 | 36.6 |

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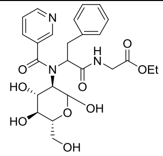
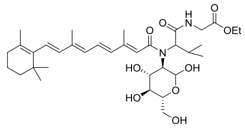
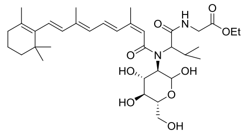
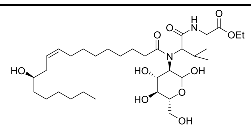
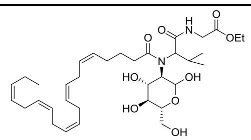
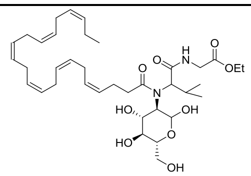
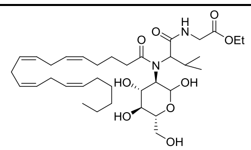
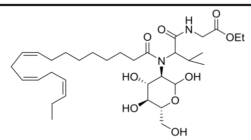
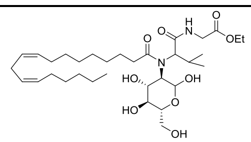
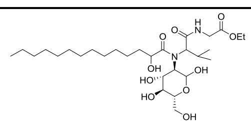
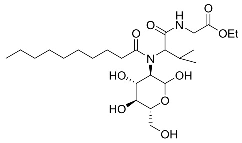
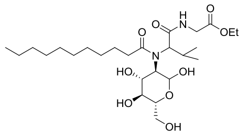
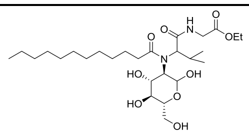
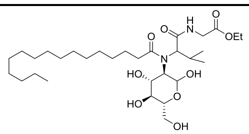
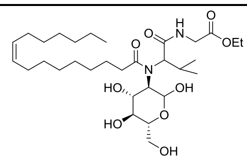
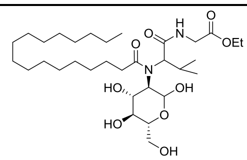
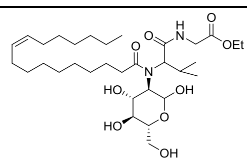
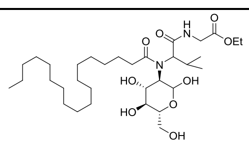
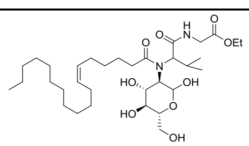
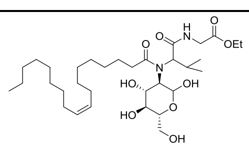
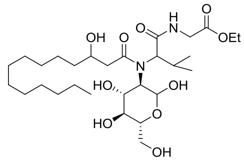
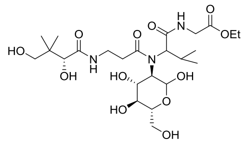
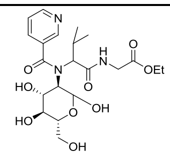
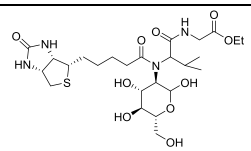
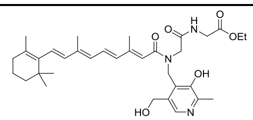
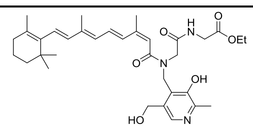
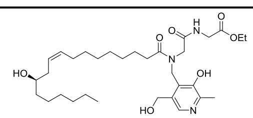
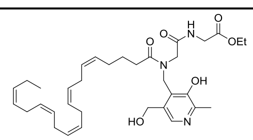
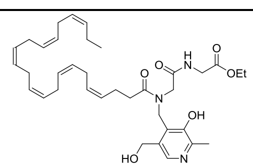
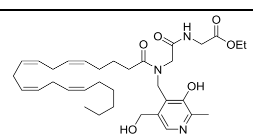
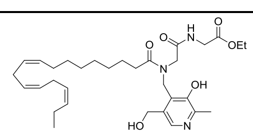
|---|---|---|---|---|---|---|---|
| **42** |  | 517.54 | 5.0 | 1.33 | 518 [M+H]+ | 87.8 | 18.1 |
| **43** |  | 646.82 | 9.9 | 3.73 | 647 [M+H]+ | 85.8 | 33.8 |
| **44** |  | 646.82 | 11.9 | 3.71 | 647 [M+H]+ | 97.2 | 51.3 |
| **45** |  | 644.85 | 3.7 | 3.50 | 645 [M+H]+ | 77.6 | 44.6 |
| **46** |  | 648.84 | 2.9 | 3.70 | 649 [M+H]+ | 75.9 | 66.3 |
| **47** |  | 674.88 | 3.0 | 3.89 | 675 [M+H]+ | 66.9 | 67.3 |
| **48** |  | 650.85 | 16.5 | 3.97 | 651 [M+H]+ | 91.2 | 36.6 |
| **49** |  | 624.82 | 2.9 | 3.72 | 625 [M+H]+ | 93.6 | 43.7 |
| **50** |  | 626.83 | 3.1 | 4.09 | 649 [M+Na]+ | 69.0 | 45.1 |
| **51** |  | 590.76 | 2.9 | 3.42 | 591 [M+H]+ | 92.7 | 30.5 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **52** |  | 518.65 | 3.3 | 2.85 | 519 [M+H]$^+$ | 96.9 | 26.9 |
| **53** |  | 532.68 | 8.4 | 3.06 | 533 [M+H]$^+$ | 96.3 | 24.5 |
| **54** |  | 546.70 | 7.7 | 3.28 | 547 [M+H]$^+$ | 86.7 | 17.8 |
| **55** |  | 602.81 | 10.4 | 4.19 | 603 [M+H]$^+$ | 99.1 | 26.0 |
| **56** |  | 600.79 | 4.8 | 3.84 | 601 [M+H]$^+$ | 92.9 | 52.7 |
| **57** |  | 616.84 | 2.8 | 4.43 | 617 [M+H]$^+$ | 95.6 | 33.5 |
| **58** |  | 614.82 | 7.4 | 4.03 | 615 [M+H]$^+$ | 96.0 | 50.3 |
| **59** |  | 630.86 | 5.4 | 4.75 | 653 [M+Na]$^+$ | 96.2 | 27.8 |
| **60** |  | 628.85 | 3.5 | 4.25 | 651 [M+Na]$^+$ | 83.0 | 37.1 |
| **61** |  | 628.85 | 6.5 | 4.27 | 629 [M+H]$^+$ | 84.3 | 8.5 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **62** |  | 590.76 | 3.1 | 3.31 | 613 [M+Na]+ | 85.5 | 21.7 |
| **63** |  | 565.62 | 5.9 | 1.34 | 588 [M+Na]+ | 99.6 | 14.6 |
| **64** |  | 469.49 | 13.7 | 1.18 | 470 [M+H]+ | 91.1 | 11.3 |
| **65** |  | 590.69 | 8.2 | 1.52 | 613 [M+Na]+ | 98.5 | 9.1 |
| **66** |  | 593.77 | 2.9 | 3.16 | 594 [M+H]+ | 96.3 | 38.2 |
| **67** |  | 593.77 | 5.2 | 3.08 | 594 [M+H]+ | 98.4 | 49.5 |
| **68** |  | 591.79 | 3.3 | 2.75 | 592 [M+H]+ | 99.0 | -3.1 |
| **69** |  | 595.78 | 4.8 | 3.07 | 596 [M+H]+ | 99.2 | 39.9 |
| **70** |  | 621.82 | 12.2 | 3.21 | 622 [M+H]+ | 99.0 | -2.7 |
| **71** |  | 597.80 | 8.6 | 3.25 | 598 [M+H]+ | 99.5 | 30.0 |
| **72** |  | 571.76 | 11.2 | 3.09 | 572 [M+H]+ | 98.9 | -16.0 |

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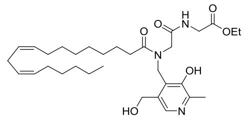
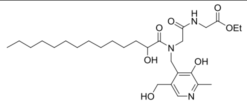
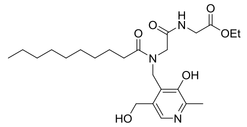
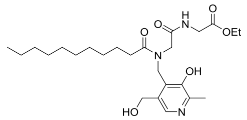
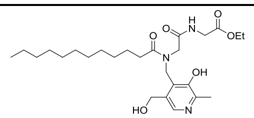
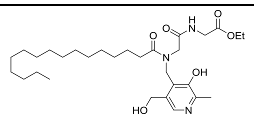
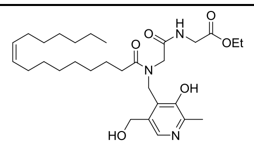
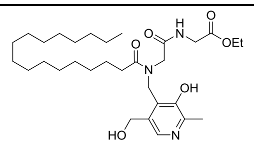
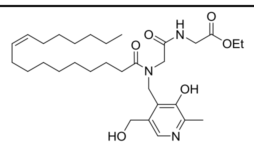
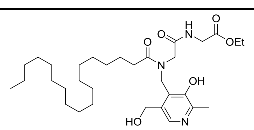
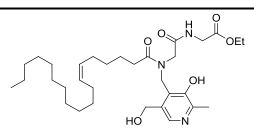
|---|---|---|---|---|---|---|---|
| **73** |  | 573.78 | 11.7 | 3.26 | 574 [M+H]+ | 94.8 | 64.3 |
| **74** |  | 537.70 | 7.0 | 2.82 | 538 [M+H]+ | 96.5 | 8.5 |
| **75** |  | 465.59 | 12.7 | 2.44 | 466 [M+H]+ | 99.0 | 34.8 |
| **76** |  | 479.62 | 12.1 | 2.60 | 480 [M+H]+ | 96.6 | -1.1 |
| **77** |  | 493.65 | 10.9 | 2.78 | 494 [M+H]+ | 98.5 | 26.8 |
| **78** |  | 549.75 | 11.0 | 3.46 | 550 [M+H]+ | 96.9 | -26.5 |
| **79** |  | 547.74 | 9.3 | 3.11 | 548 [M+H]+ | 99.1 | 51.1 |
| **80** |  | 563.78 | 3.3 | 4.73 | 564 [M+H]+ | 87.3 | -5.0 |
| **81** |  | 561.76 | 10.3 | 3.26 | 562 [M+H]+ | 94.7 | 42.2 |
| **82** |  | 577.81 | 5.1 | 3.69 | 578 [M+H]+ | 87.5 | 12.3 |
| **83** |  | 575.79 | 7.4 | 3.44 | 576 [M+H]+ | 98.7 | 56.1 |

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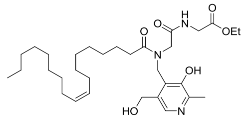
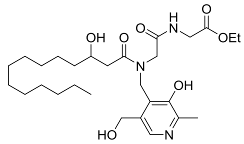
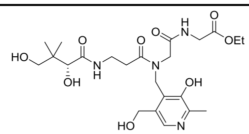
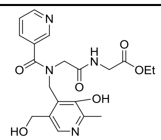
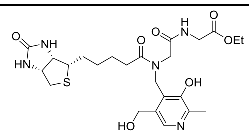
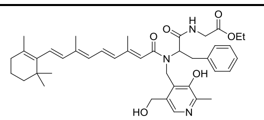
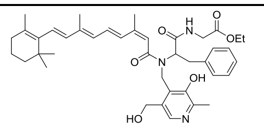
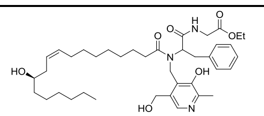
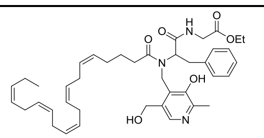
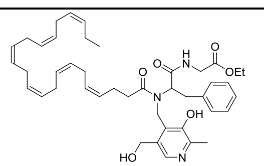
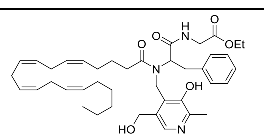
|---|---|---|---|---|---|---|---|
| **84** |  | 575.79 | 7.9 | 3.40 | 576 $[M+H]^+$ | 87.4 | 65.3 |
| **85** |  | 537.70 | 4.9 | 2.73 | 538 $[M+H]^+$ | 92.3 | -1.8 |
| **86** |  | 512.56 | 8.4 | 1.03 | 513 $[M+H]^+$ | 96.2 | 9.0 |
| **87** |  | 416.43 | 3.6 | 0.85 | 417 $[M+H]^+$ | 96.4 | 5.1 |
| **88** |  | 537.63 | 6.4 | 1.24 | 538 $[M+H]^+$ | 90.6 | 12.7 |
| **89** |  | 683.89 | 3.4 | 3.38 | 684 $[M+H]^+$ | 98.0 | 70.9 |
| **90** |  | 683.89 | 6.1 | 3.25 | 684 $[M+H]^+$ | 91.9 | 66.4 |
| **91** |  | 681.92 | 4.0 | 2.92 | 682 $[M+H]^+$ | 87.9 | 77.4 |
| **92** |  | 685.91 | 6.1 | 3.22 | 686 $[M+H]^+$ | 96.0 | -58.1 |
| **93** |  | 711.94 | 5.2 | 3.36 | 712 $[M+H]^+$ | 99.0 | -36.2 |
| **94** |  | 687.92 | 5.9 | 3.39 | 688 $[M+H]^+$ | 98.5 | -15.7 |

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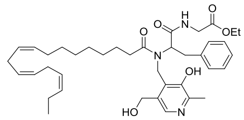
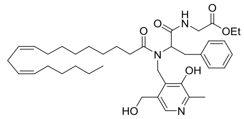
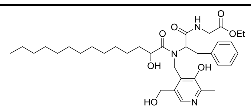
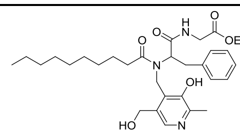
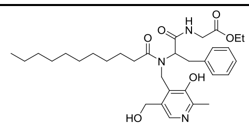
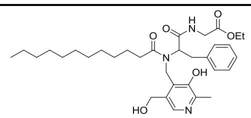
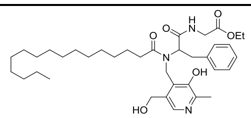
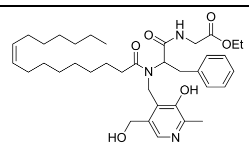
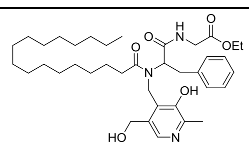
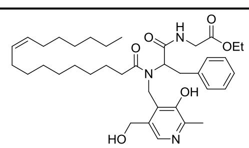
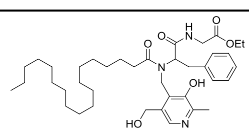
|---|---|---|---|---|---|---|---|
| **95** |  | 661.88 | 5.2 | 3.25 | 662 $[M+H]^+$ | 99.1 | 64.4 |
| **96** |  | 663.90 | 6.6 | 3.44 | 664 $[M+H]^+$ | 86.9 | 63.9 |
| **97** |  | 627.82 | 3.6 | 3.10 | 628 $[M+H]^+$ | 93.9 | 50.9 |
| **98** |  | 555.72 | 8.2 | 2.70 | 556 $[M+H]^+$ | 92.3 | 40.7 |
| **99** |  | 569.74 | 5.5 | 2.84 | 570 $[M+H]^+$ | 85.0 | 25.6 |
| **100** |  | 583.77 | 8.0 | 2.97 | 584 $[M+H]^+$ | 88.2 | 50.8 |
| **101** |  | 639.88 | 6.5 | 3.56 | 640 $[M+H]^+$ | 78.9 | 10.7 |
| **102** |  | 637.86 | 4.3 | 4.52 | 638 $[M+H]^+$ | 92.4 | 67.4 |
| **103** |  | 653.91 | 3.6 | 4.91 | 654 $[M+H]^+$ | 92.1 | 36.1 |
| **104** |  | 651.89 | 4.4 | 4.64 | 652 $[M+H]^+$ | 91.4 | 84.4 |
| **105** |  | 667.93 | 2.9 | 5.10 | 668 $[M+H]^+$ | 75.7 | 8.4 |

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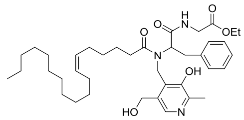
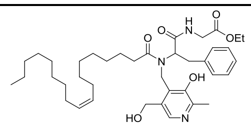
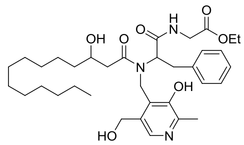
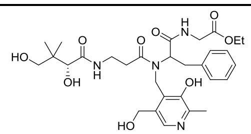
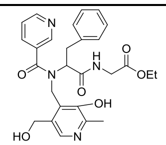
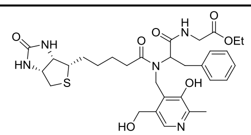
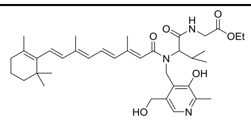
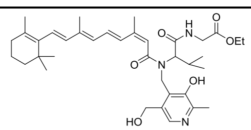
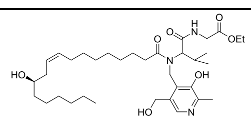
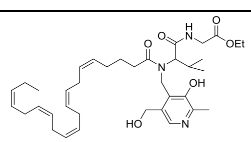
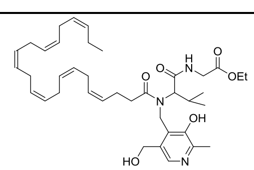
|---|---|---|---|---|---|---|---|
| **106** |  | 665.92 | 3.4 | 4.84 | 666 [M+H]+ | 99.6 | 81.8 |
| **107** |  | 665.92 | 3.6 | 4.79 | 666 [M+H]+ | 87.6 | 69.2 |
| **108** |  | 627.82 | 4.9 | 4.22 | 628 [M+H]+ | 76.6 | 52.9 |
| **109** |  | 602.69 | 2.8 | 1.43 | 638 [M+H]+ | 94.0 | -34.1 |
| **110** |  | 506.56 | 11.0 | 1.35 | 507 [M+H]+ | 99.6 | -3.6 |
| **111** |  | 627.76 | 3.3 | 1.59 | 628 [M+H]+ | 85.5 | -14.5 |
| **112** |  | 635.85 | 7.2 | 3.28 | 636 [M+H]+ | 86.1 | 56.6 |
| **113** |  | 635.85 | 8.0 | 3.10 | 636 [M+H]+ | 95.3 | 73.7 |
| **114** |  | 633.87 | 3.6 | 2.82 | 634 [M+H]+ | 97.9 | 75.2 |
| **115** |  | 637.86 | 7.5 | 3.13 | 638 [M+H]+ | 97.2 | 0.3 |
| **116** |  | 663.90 | 4.0 | 3.27 | 664 [M+H]+ | 97.4 | 13.6 |

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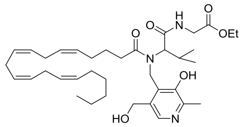
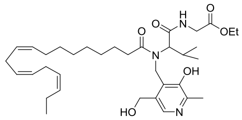
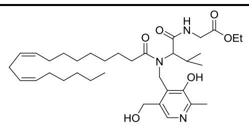
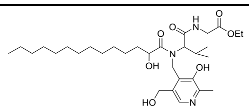
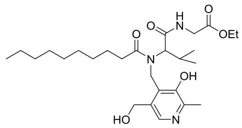
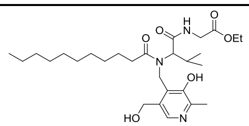
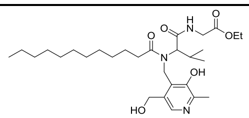
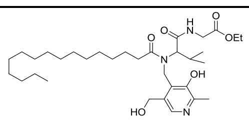
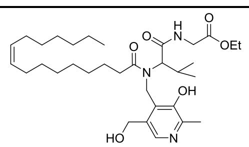
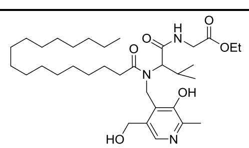
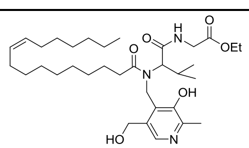
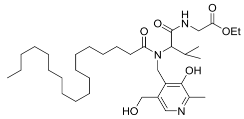
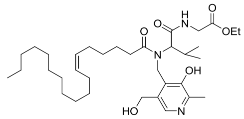
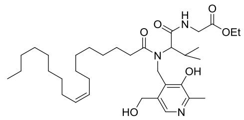
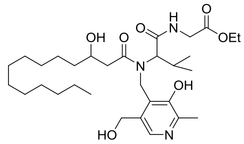
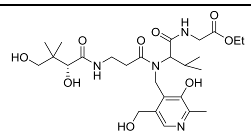
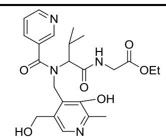
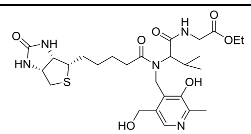
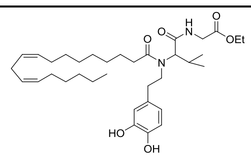
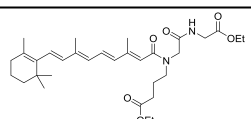
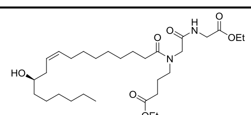
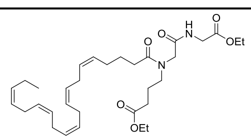
|---|---|---|---|---|---|---|---|
| **117** |  | 639.88 | 3.7 | 3.30 | 640 [M+H]$^+$ | 98.7 | 23.8 |
| **118** |  | 613.84 | 6.4 | 3.15 | 614 [M+H]$^+$ | 99.7 | 42.2 |
| **119** |  | 615.86 | 8.0 | 3.29 | 616 [M+H]$^+$ | 99.5 | 79.9 |
| **120** |  | 579.78 | 5.3 | 3.04 | 580 [M+H]$^+$ | 93.0 | 78.2 |
| **121** |  | 507.67 | 7.6 | 3.08 | 508 [M+H]$^+$ | 98.0 | 33.3 |
| **122** |  | 521.70 | 8.1 | 3.59 | 522 [M+H]$^+$ | 98.1 | 47.1 |
| **123** |  | 535.73 | 7.9 | 2.87 | 536 [M+H]$^+$ | 99.9 | 60.7 |
| **124** |  | 591.83 | 4.0 | 3.46 | 592 [M+H]$^+$ | 99.9 | 81.3 |
| **125** |  | 589.82 | 5.2 | 3.23 | 590 [M+H]$^+$ | 97.9 | 79.1 |
| **126** |  | 605.86 | 5.1 | 3.60 | 606 [M+H]$^+$ | 98.9 | 78.4 |
| **127** |  | 603.85 | 5.4 | 3.37 | 604 [M+H]$^+$ | 99.2 | 77.0 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **128** |  | 619.89 | 7.0 | 3.75 | 620 [M+H]+ | 97.7 | 78.0 |
| **129** |  | 617.87 | 7.1 | 3.54 | 618 [M+H]+ | 99.0 | 82.9 |
| **130** |  | 617.87 | 6.1 | 3.51 | 618 [M+H]+ | 87.8 | 81.7 |
| **131** |  | 579.78 | 10.2 | 2.94 | 580 [M+H]+ | 96.4 | 83.4 |
| **132** |  | 554.64 | 13.4 | 1.30 | 555 [M+H]+ | 99.2 | 50.9 |
| **133** |  | 458.52 | 10.3 | 1.21 | 459 [M+H]+ | 98.0 | 28.7 |
| **134** |  | 579.71 | 3.0 | 1.47 | 580 [M+H]+ | 88.2 | 22.4 |
| **135** |  | 600.84 | 5.1 | 4.27 | 601 [M+H]+ | 94.4 | 20.7 |
| **136** |  | 556.74 | 83.0 | 4.11 | 557 [M+H]+ | 97.8 | 71.0 |
| **137** |  | 554.77 | 9.9 | 3.53 | 555 [M+H]+ | 94.6 | 52.4 |
| **138** |  | 558.76 | 12.0 | 3.96 | 559 [M+H]+ | 91.1 | -57.4 |

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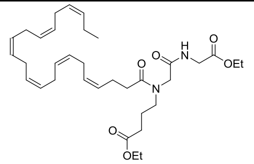
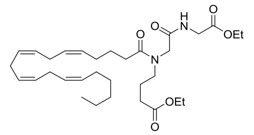
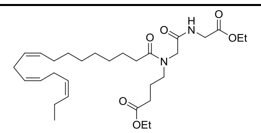
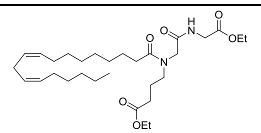
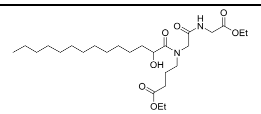
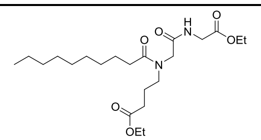
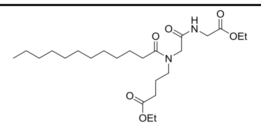
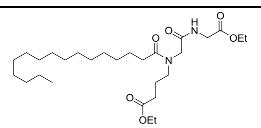
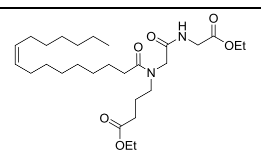
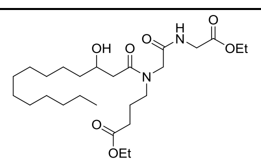
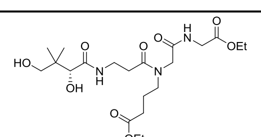
|---|---|---|---|---|---|---|---|
| **139** |  | 584.80 | 5.1 | 4.11 | 585 [M+H]+ | 82.4 | 16.0 |
| **140** |  | 560.78 | 4.6 | 4.20 | 561 [M+H]+ | 95.8 | -7.2 |
| **141** |  | 534.74 | 4.1 | 4.00 | 535 [M+H]+ | 84.0 | 72.7 |
| **142** |  | 536.75 | 10.2 | 4.20 | 537 [M+H]+ | 94.6 | 41.4 |
| **143** |  | 500.68 | 3.0 | 3.85 | 501 [M+H]+ | 96.8 | 15.0 |
| **144** |  | 428.57 | 9.5 | 3.24 | 429 [M+H]+ | 99.2 | 30.1 |
| **145** |  | 456.62 | 4.2 | 3.68 | 457 [M+H]+ | 99.1 | -2.1 |
| **146** |  | 512.73 | 7.0 | 4.51 | 513 [M+H]+ | 96.8 | 26.3 |
| **147** |  | 510.72 | 16.2 | 4.12 | 511 [M+H]+ | 99.8 | 24.2 |
| **148** |  | 500.68 | 7.3 | 3.70 | 501 [M+H]+ | 99.8 | 32.4 |
| **149** |  | 475.54 | 3.9 | 1.54 | 476 [M+H]+ | 94.8 | 24.5 |

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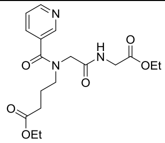
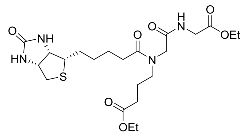
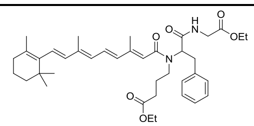
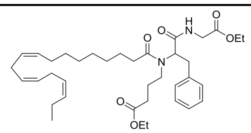
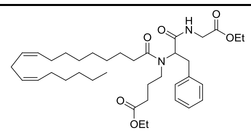
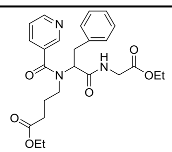
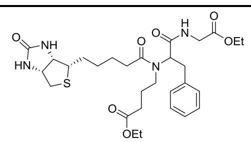
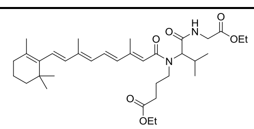
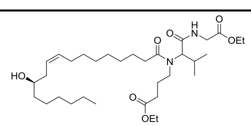
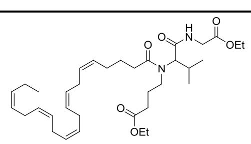
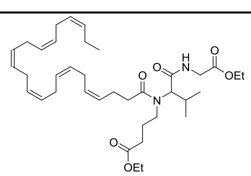
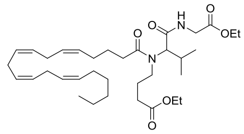
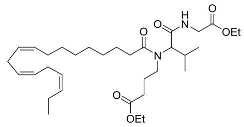
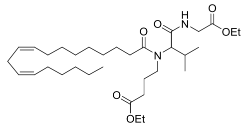
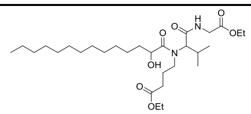
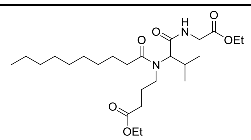
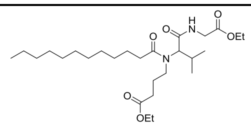
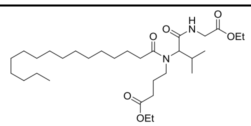
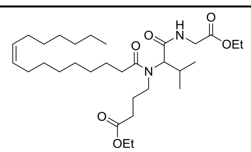
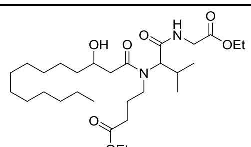
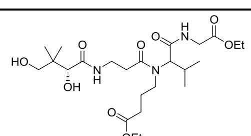
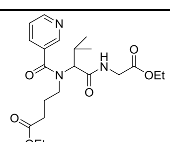
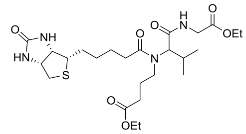
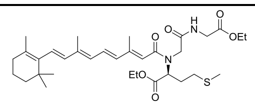
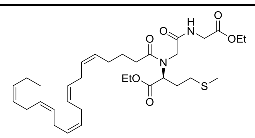
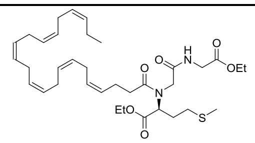
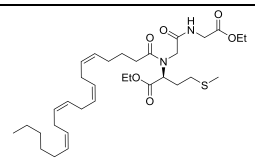
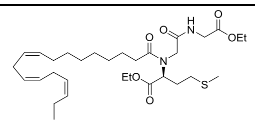
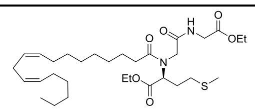
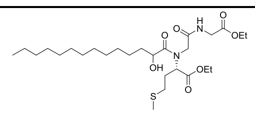
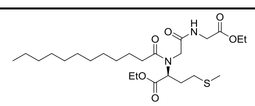
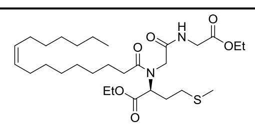
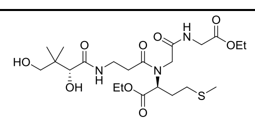
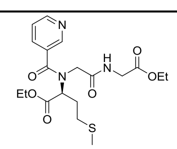
|---|---|---|---|---|---|---|---|
| **150** |  | 379.41 | 17.5 | 1.31 | 378 [M+H]⁺ | 95.3 | 32.1 |
| **151** |  | 500.61 | 7.1 | 1.73 | 501 [M+H]⁺ | 98.2 | 13.0 |
| **152** |  | 646.87 | 4.1 | 4.56 | 647 [M+H]⁺ | 92.6 | 83.5 |
| **153** |  | 624.86 | 2.9 | 4.89 | 625 [M+H]⁺ | 78.7 | 60.9 |
| **154** |  | 626.88 | 3.0 | 4.48 | 627 [M+H]⁺ | 90.6 | 81.8 |
| **155** |  | 469.54 | 4.6 | 2.00 | 470 [M+H]⁺ | 98.3 | 43.3 |
| **156** |  | 590.74 | 2.7 | 2.35 | 591 [M+H]⁺ | 92.3 | 57.0 |
| **157** |  | 598.83 | 3.0 | 4.50 | 599 [M+H]⁺ | 99.4 | 74.0 |
| **158** |  | 596.85 | 3.2 | 3.99 | 597 [M+H]⁺ | 77.8 | 69.5 |
| **159** |  | 600.84 | 5.1 | 4.37 | 601 [M+H]⁺ | 93.5 | 48.4 |
| **160** |  | 626.88 | 5.6 | 4.55 | 627 [M+H]⁺ | 90.1 | 42.1 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **161** |  | 602.86 | 6.0 | 4.72 | 603 [M+H]+ | 77.5 | 48.0 |
| **162** |  | 576.82 | 3.6 | 4.44 | 577 [M+H]+ | 94.4 | 60.5 |
| **163** |  | 578.84 | 13.2 | 4.77 | 579 [M+H]+ | 94.3 | 41.4 |
| **164** |  | 542.76 | 13.4 | 4.25 | 543 [M+H]+ | 94.3 | cell death |
| **165** |  | 470.65 | 12.0 | 3.79 | 471 [M+H]+ | 98.8 | cell death |
| **8** |  | 498.71 | 15.2 | 4.14 | 499 [M+H]+ | 99.0 | 95.1 |
| **166** |  | 554.81 | 9.0 | 5.29 | 555 [M+H]+ | 99.0 | cell death |
| **167** |  | 552.80 | 16.2 | 4.64 | 553 [M+H]+ | 95.8 | cell death |
| **168** |  | 542.76 | 3.2 | 4.12 | 543 [M+H]+ | 87.9 | cell death |
| **169** |  | 517.62 | 2.8 | 2.00 | 518 [M+H]+ | 83.4 | 57.9 |
| **170** |  | 421.49 | 17.8 | 1.84 | 422 [M+H]+ | 98.8 | 56.4 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **171** |  | 542.69 | 2.9 | 2.19 | 543 [M+H]+ | 86.2 | 44.3 |
| **172** |  | 602.83 | 5.0 | 4.35 | 603 [M+H]+ | 87.8 | 41.9 |
| **173** |  | 604.85 | 3.0 | 4.09 | 605 [M+H]+ | 75.5 | 46.2 |
| **174** |  | 630.89 | 2.9 | 4.23 | 631 [M+H]+ | 79.0 | 21.3 |
| **175** |  | 606.86 | 3.6 | 4.47 | 607 [M+H]+ | 94.5 | 64.9 |
| **176** |  | 580.83 | 4.3 | 4.23 | 581 [M+H]+ | 84.7 | 4.1 |
| **177** |  | 582.84 | 2.7 | 4.55 | 582 [M+H]+ | 80.4 | 61.0 |
| **178** |  | 546.76 | 3.8 | 4.06 | 547 [M+H]+ | 91.2 | 14.8 |
| **179** |  | 502.71 | 3.0 | 4.00 | 503 [M+H]+ | 76.6 | 14.3 |
| **180** |  | 556.80 | 4.6 | 4.42 | 557 [M+H]+ | 98.5 | 45.5 |
| **181** |  | 521.63 | 6.6 | 1.89 | 522 [M+H]+ | 83.9 | 22.6 |
| **182** |  | 425.50 | 3.7 | 1.72 | 426 [M+H]+ | 94.4 | 3.0 |

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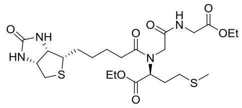
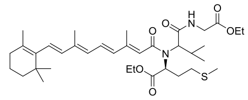
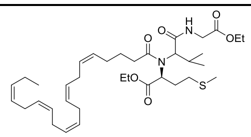
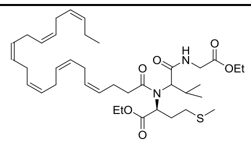
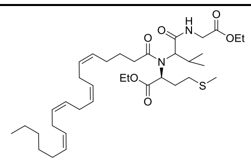
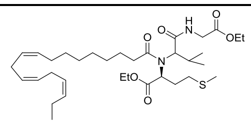
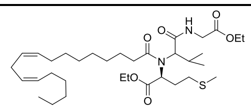
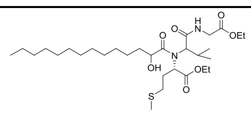
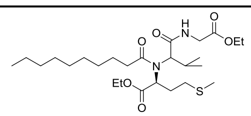
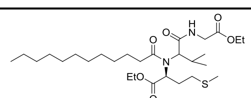
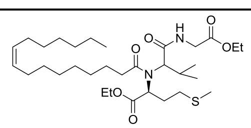
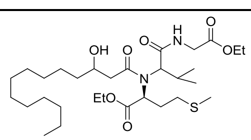
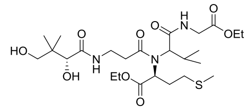
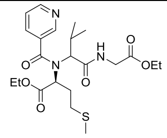
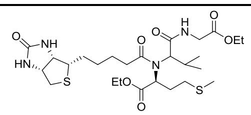
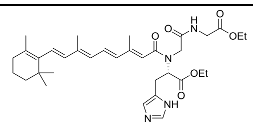
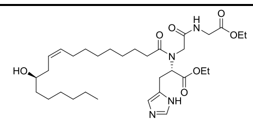
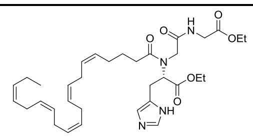
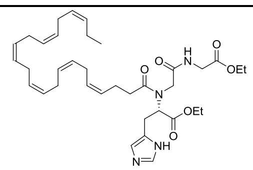
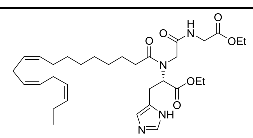
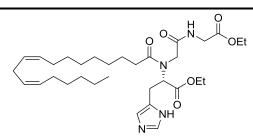
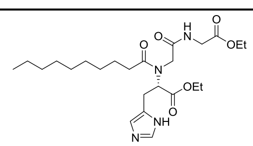
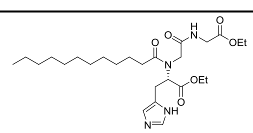
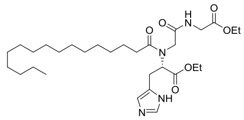
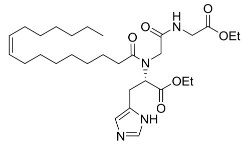
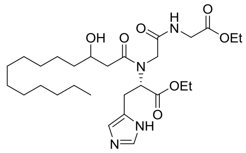
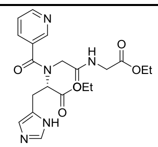
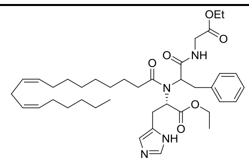
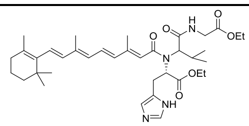
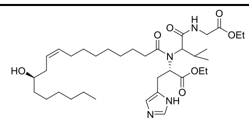
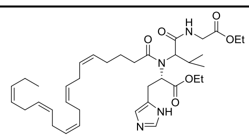
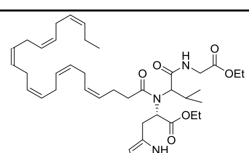
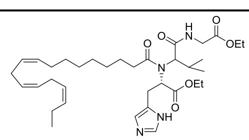
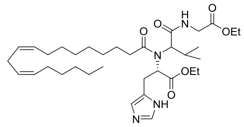
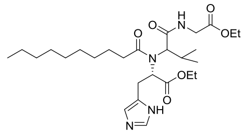
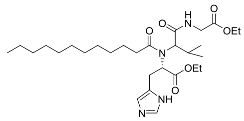
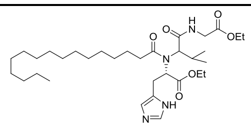
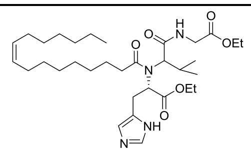
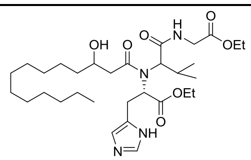
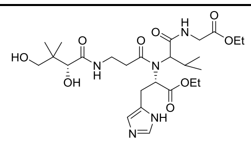
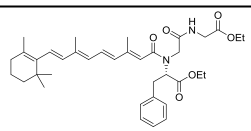
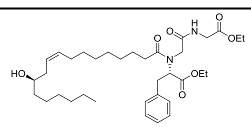
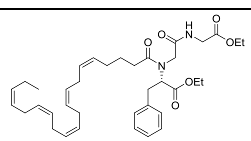
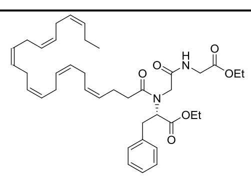
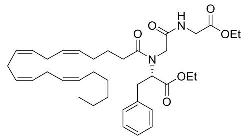
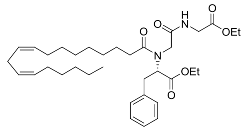
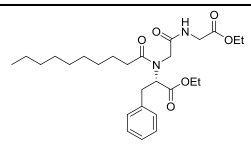
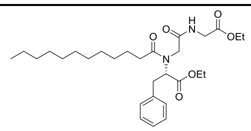
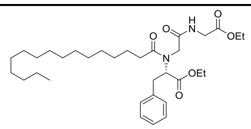
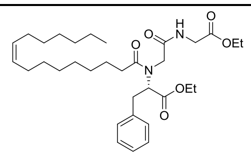
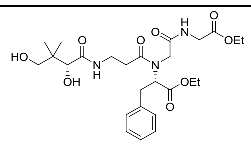
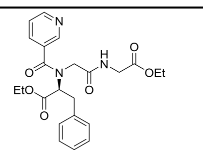
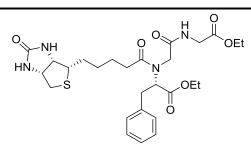
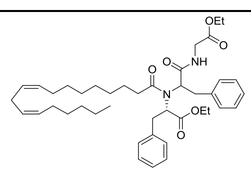
|---|---|---|---|---|---|---|---|
| **183** |  | 546.70 | 6.5 | 2.07 | 547 $[M+H]^+$ | 98.0 | 15.4 |
| **184** |  | 644.91 | 3.1 | 4.73 | 645 $[M+H]^+$ | 78.9 | 57.3 |
| **185** |  | 646.93 | 3.3 | 4.57 | 647 $[M+H]^+$ | 94.2 | 45.7 |
| **186** |  | 672.97 | 3.2 | 4.78 | 673 $[M+H]^+$ | 84.2 | 32.9 |
| **187** |  | 648.94 | 4.1 | 4.94 | 649 $[M+H]^+$ | 88.1 | 46.7 |
| **188** |  | 622.91 | 3.6 | 4.63 | 623 $[M+H]^+$ | 86.6 | 51.4 |
| **189** |  | 624.92 | 4.8 | 4.91 | 625 $[M+H]^+$ | 86.5 | 59.7 |
| **190** |  | 588.85 | 3.8 | 4.53 | 589 $[M+H]^+$ | 88.3 | 46.6 |
| **191** |  | 516.74 | 3.7 | 3.97 | 517 $[M+H]^+$ | 93.8 | 66.0 |
| **9** |  | 544.79 | 5.5 | 4.29 | 545 $[M+H]^+$ | 99.0 | 74.3 |
| **192** |  | 598.88 | 3.1 | 4.91 | 599 $[M+H]^+$ | 95.5 | 51.1 |
| **193** |  | 588.85 | 3.5 | 4.34 | 589 $[M+H]^+$ | 89.6 | 67.2 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **194** |  | 563.71 | 8.9 | 2.34 | 564 [M+H]$^+$ | 97.2 | -17.6 |
| **195** |  | 467.58 | 4.7 | 2.24 | 468 [M+H]$^+$ | 93.5 | -9.8 |
| **196** |  | 588.78 | 7.9 | 2.48 | 589 [M+H]$^+$ | 96.9 | -12.9 |
| **197** |  | 608.78 | 5.6 | 3.07 | 609 [M+H]$^+$ | 81.9 | 18.5 |
| **198** |  | 606.81 | 5.3 | 2.74 | 607 [M+H]$^+$ | 87.7 | 23.2 |
| **199** |  | 610.80 | 8.3 | 3.02 | 611 [M+H]$^+$ | 80.6 | -7.5 |
| **200** |  | 636.83 | 7.2 | 3.18 | 637 [M+H]$^+$ | 72.2 | 21.6 |
| **201** |  | 586.77 | 12.4 | 2.99 | 587 [M+H]$^+$ | 87.5 | 16.3 |
| **202** |  | 588.79 | 9.9 | 3.16 | 589 [M+H]$^+$ | 92.3 | 25.5 |
| **203** |  | 480.61 | 13.1 | 2.40 | 481 [M+H]$^+$ | 83.6 | -11.9 |
| **204** |  | 508.66 | 10.3 | 2.68 | 509 [M+H]$^+$ | 86.6 | 33.7 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **205** |  | 564.77 | 6.1 | 3.31 | 565 [M+H]+ | 89.1 | 25.8 |
| **206** |  | 562.75 | 2.7 | 2.56 | 563 [M+H]+ | 87.1 | 25.8 |
| **207** |  | 552.71 | 3.0 | 2.57 | 553 [M+H]+ | 84.3 | 0.4 |
| **208** |  | 431.45 | 9.1 | 1.12 | 432 [M+H]+ | 98.2 | 10.4 |
| **209** |  | 678.92 | 4.3 | 3.48 | 679 [M+H]+ | 73.7 | 24.0 |
| **210** |  | 650.86 | 3.1 | 3.24 | 651 [M+H]+ | 96.8 | 45.4 |
| **211** |  | 648.89 | 4.5 | 2.90 | 649 [M+H]+ | 98.2 | 59.3 |
| **212** |  | 652.88 | 7.5 | 3.05 | 653 [M+H]+ | 98.0 | 4.8 |
| **213** |  | 678.92 | 5.2 | 3.24 | 679 [M+H]+ | 96.3 | 4.2 |
| **214** |  | 628.86 | 5.0 | 3.09 | 629 [M+H]+ | 97.1 | 9.3 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **215** |  | 630.87 | 6.9 | 3.42 | 631 [M+H]+ | 85.3 | 53.4 |
| **216** |  | 522.69 | 9.4 | 3.30 | 523 [M+H]+ | 99.8 | 6.8 |
| **217** |  | 550.74 | 13.6 | 3.34 | 551 [M+H]+ | 92.4 | 58.1 |
| **218** |  | 606.85 | 3.2 | 3.42 | 607 [M+H]+ | 98.6 | 55.3 |
| **219** |  | 604.83 | 5.8 | 3.30 | 605 [M+H]+ | 97.9 | 70.0 |
| **220** |  | 594.79 | 3.7 | 3.39 | 595 [M+H]+ | 94.5 | 9.1 |
| **221** |  | 569.66 | 9.2 | 1.50 | 570 [M+H]+ | 98.2 | -13.5 |
| **222** |  | 618.82 | 3.2 | 4.50 | 619 [M+H]+ | 88.5 | 62.2 |
| **223** |  | 616.84 | 4.7 | 3.99 | 617 [M+H]+ | 77.2 | 7.9 |
| **224** |  | 620.83 | 2.9 | 3.95 | 621 [M+H]+ | 91.4 | 46.4 |
| **225** |  | 646.87 | 4.1 | 4.57 | 647 [M+H]+ | 86.8 | 22.0 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **226** |  | 622.85 | 3.4 | 4.69 | 623 [M+H]$^+$ | 85.2 | 65.4 |
| **227** |  | 598.83 | 3.2 | 4.79 | 599 [M+H]$^+$ | 96.0 | 27.9 |
| **228** |  | 490.64 | 2.8 | 3.84 | 491 [M+H]$^+$ | 95.4 | 56.1 |
| **229** |  | 518.70 | 2.9 | 4.17 | 519 [M+H]$^+$ | 97.4 | 47.8 |
| **230** |  | 574.80 | 3.2 | 5.29 | 575 [M+H]$^+$ | 99.8 | 63.3 |
| **231** |  | 572.79 | 2.7 | 4.64 | 573 [M+H]$^+$ | 87.4 | 33.1 |
| **232** |  | 537.61 | 3.7 | 2.10 | 538 [M+H]$^+$ | 87.5 | 0.0 |
| **233** |  | 441.48 | 5.8 | 2.00 | 442 [M+H]$^+$ | 96.4 | -6.6 |
| **234** |  | 562.68 | 3.2 | 2.26 | 563 [M+H]$^+$ | 93.9 | 5.9 |
| **235** |  | 688.95 | 5.2 | 5.48 | 689 [M+H]$^+$ | 87.1 | 22.5 |

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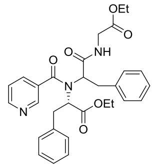
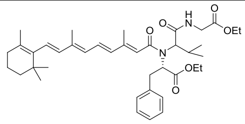
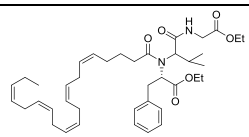
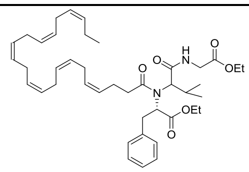
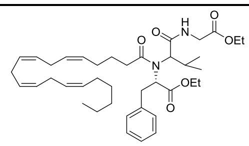
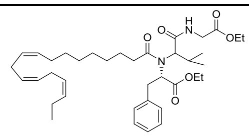
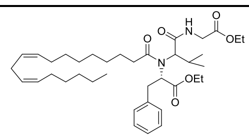
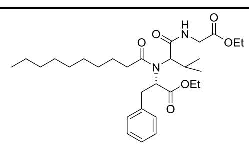
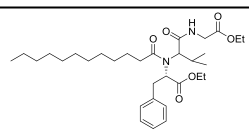
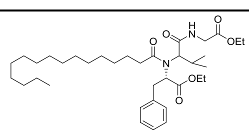
|---|---|---|---|---|---|---|---|
| **236** |  | 531.61 | 4.0 | 2.70 | 532 [M+H]+ | 89.9 | 8.1 |
| **237** |  | 660.90 | 3.9 | 4.90 | 661 [M+H]+ | 91.5 | 70.9 |
| **238** |  | 662.91 | 3.3 | 4.71 | 663 [M+H]+ | 88.1 | 25.4 |
| **239** |  | 688.95 | 4.6 | 4.95 | 711 [M+Na]+ | 96.7 | 38.7 |
| **240** |  | 664.93 | 4.0 | 5.14 | 687 [M+Na]+ | 94.8 | 33.6 |
| **241** |  | 638.89 | 4.5 | 4.77 | 661 [M+Na]+ | 89.1 | 15.3 |
| **242** |  | 640.91 | 4.8 | 5.18 | 641 [M+H]+ | 87.1 | 7.3 |
| **243** |  | 532.72 | 2.9 | 4.29 | 555 [M+Na]+ | 86.4 | -25.9 |
| **244** |  | 560.78 | 3.3 | 4.72 | 583 [M+Na]+ | 98.5 | 67.5 |
| **245** |  | 616.88 | 2.9 | 3.57 | 617 [M+H]+ | 94.2 | -7.6 |

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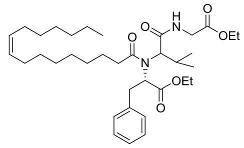
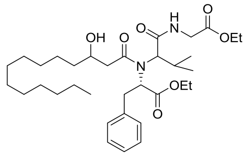
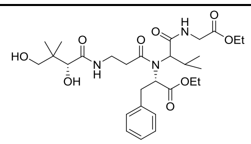
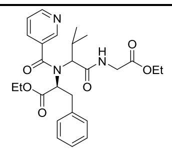
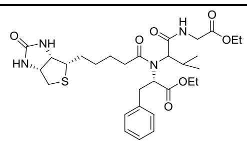
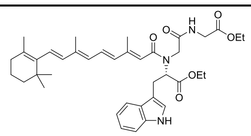
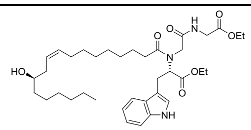
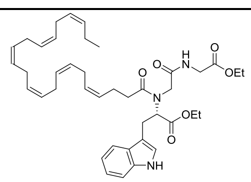
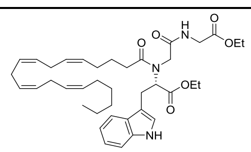
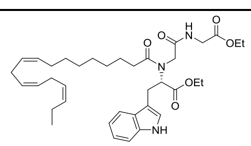
|---|---|---|---|---|---|---|---|
| **246** |  | 614.87 | 3.4 | 5.08 | 637 [M+Na]+ | 92.2 | 16.4 |
| **247** |  | 604.83 | 2.8 | 4.49 | 627 [M+Na]+ | 89.9 | 67.9 |
| **248** |  | 579.69 | 3.7 | 2.80 | 580 [M+H]+ | 87.2 | 3.0 |
| **249** |  | 483.57 | 2.7 | 2.44 | 484 [M+H]+ | 96.3 | 29.7 |
| **250** |  | 604.76 | 4.8 | 2.66 | 627 [M+Na]+ | 91.8 | 18.4 |
| **251** |  | 657.85 | 15.7 | 4.23 | 658 [M+H]+ | 90.7 | 45.9 |
| **252** |  | 655.88 | 3.2 | 3.85 | 656 [M+H]+ | 84.0 | 54.7 |
| **253** |  | 685.91 | 6.9 | 4.34 | 686 [M+H]+ | 98.5 | 21.8 |
| **254** |  | 661.88 | 4.7 | 4.42 | 662 [M+H]+ | 97.1 | 32.5 |
| **255** |  | 635.85 | 19.0 | 4.21 | 636 [M+H]+ | 88.2 | 29.4 |

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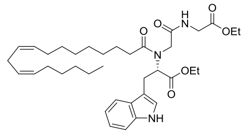
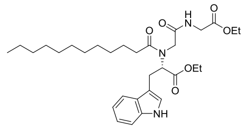
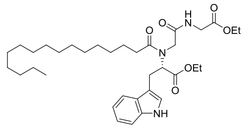
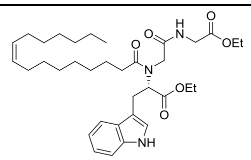
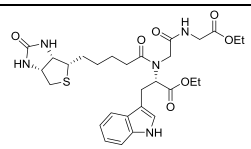
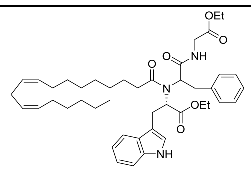
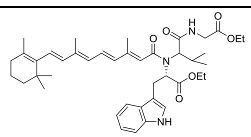
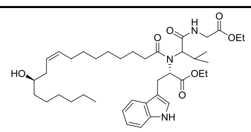
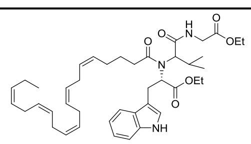
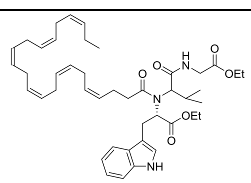
|---|---|---|---|---|---|---|---|
| **256** |  | 637.86 | 3.8 | 4.51 | 638 $[M+H]^+$ | 91.9 | 43.2 |
| **257** |  | 557.73 | 4.1 | 4.00 | 558 $[M+H]^+$ | 91.4 | 12.8 |
| **258** |  | 613.84 | 3.5 | 4.88 | 614 $[M+H]^+$ | 85.1 | 24.6 |
| **259** |  | 611.82 | 3.3 | 4.42 | 612 $[M+H]^+$ | 96.0 | 53.0 |
| **260** |  | 601.72 | 4.9 | 2.24 | 602 $[M+H]^+$ | 84.2 | 22.3 |
| **261** |  | 727.99 | 4.9 | 5.00 | 728 $[M+H]^+$ | 79.9 | 17.8 |
| **262** |  | 699.93 | 5.2 | 4.41 | 700 $[M+H]^+$ | 90.9 | 53.8 |
| **263** |  | 697.96 | 8.7 | 4.15 | 698 $[M+H]^+$ | 81.4 | 2.9 |
| **264** |  | 701.95 | 3.1 | 4.25 | 702 $[M+H]^+$ | 98.9 | 45.1 |
| **265** |  | 727.99 | 2.7 | 4.51 | 750 $[M+Na]^+$ | 99.6 | 21.7 |

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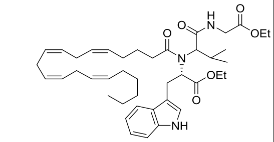
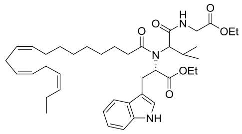
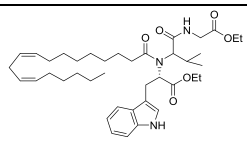
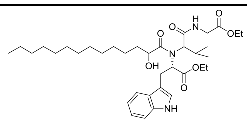
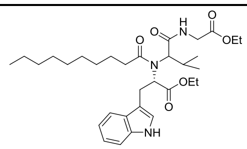
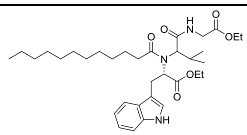
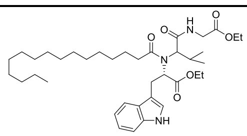
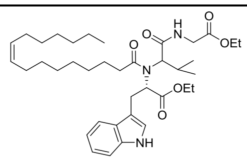
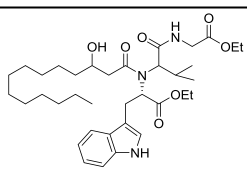
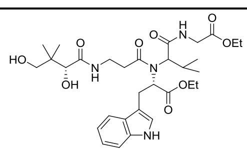
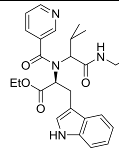
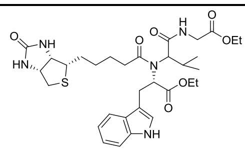
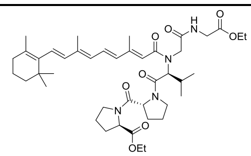
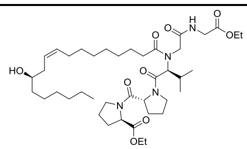
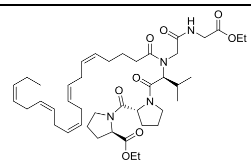
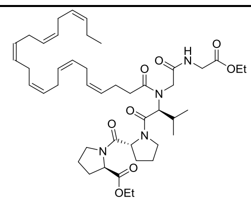
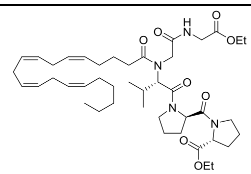
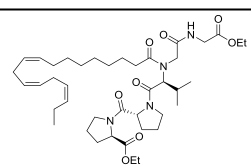
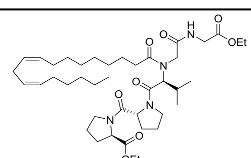
|---|---|---|---|---|---|---|---|
| **266** |  | 703.97 | 2.9 | 4.62 | 704 $[M+H]^+$ | 88.3 | 37.7 |
| **267** |  | 677.93 | 20.8 | 4.60 | 700 $[M+Na]^+$ | 96.8 | 17.7 |
| **268** |  | 679.94 | 3.2 | 4.73 | 702 $[M+Na]^+$ | 94.9 | 29.2 |
| **269** |  | 643.87 | 2.9 | 4.37 | 644 $[M+H]^+$ | 92.4 | 33.4 |
| **270** |  | 571.76 | 6.9 | 4.01 | 572 $[M+H]^+$ | 92.8 | 68.2 |
| **271** |  | 599.81 | 5.7 | 4.34 | 600 $[M+H]^+$ | 96.3 | 40.8 |
| **272** |  | 655.92 | 9.8 | 5.10 | 678 $[M+Na]^+$ | 95.1 | 41.5 |
| **273** |  | 653.91 | 4.9 | 4.61 | 676 $[M+Na]^+$ | 98.8 | 32.4 |
| **274** |  | 643.87 | 2.9 | 4.26 | 644 $[M+H]^+$ | 89.6 | 60.1 |
| **275** |  | 618.73 | 2.8 | 2.38 | 641 $[M+Na]^+$ | 83.6 | 6.3 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **276** |  | 522.60 | 4.1 | 2.88 | 523 [M+H]+ | 96.8 | 41.2 |
| **277** |  | 643.80 | 3.6 | 2.52 | 523 [M+H]+ | 93.3 | 2.9 |
| **278** |  | 765.01 | 4.9 | 4.17 | 788 [M+Na]+ | 96.6 | 75.6 |
| **279** |  | 763.03 | 3.4 | 3.92 | 787 [M+Na]+ | 94.7 | 59.0 |
| **280** |  | 767.02 | 4.9 | 4.35 | 768 [M+H]+ | 99.2 | 52.4 |
| **281** |  | 793.06 | 8.1 | 4.56 | 816 [M+Na]+ | 97.4 | 18.2 |
| **282** |  | 769.04 | 5.4 | 4.69 | 770 [M+H]+ | 98.2 | 34.6 |
| **283** |  | 743.00 | 2.8 | 4.42 | 765 [M+Na]+ | 99.2 | cell death |
| **284** |  | 745.02 | 5.9 | 4.75 | 746 [M+H]+ | 97.2 | 65.0 |

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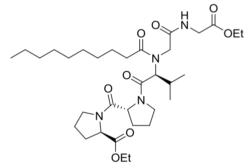
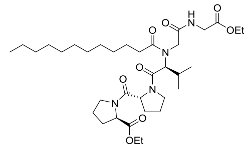
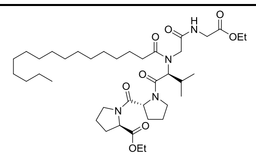
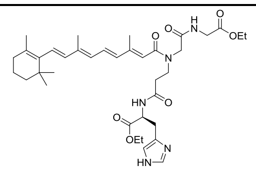
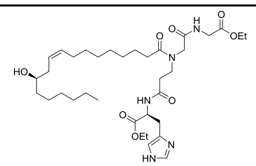
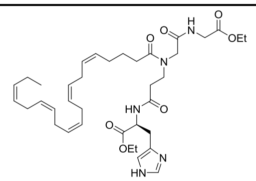
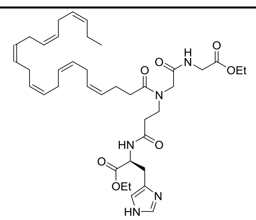
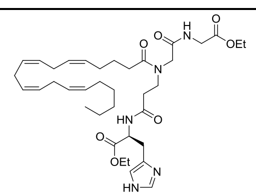
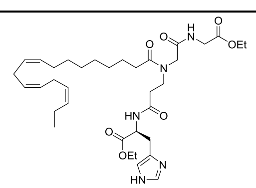
|---|---|---|---|---|---|---|---|
| **285** |  | 636.83 | 13.1 | 3.71 | 637 [M+H]$^+$ | 97.7 | 26.4 |
| **286** |  | 664.89 | 8.3 | 4.11 | 665 [M+H]$^+$ | 99.6 | 75.6 |
| **287** |  | 720.99 | 4.8 | 5.30 | 721 [M+H]$^+$ | 97.8 | cell death |
| **288** |  | 679.86 | 7.8 | 2.90 | 680 [M+H]$^+$ | 90.3 | 46.4 |
| **289** |  | 677.88 | 3.6 | 2.58 | 678 [M+H]$^+$ | 97.1 | 24.4 |
| **290** |  | 681.88 | 4.5 | 2.91 | 682 [M+H]$^+$ | 99.6 | 9.2 |
| **291** |  | 707.91 | 2.9 | 3.06 | 708 [M+H]$^+$ | 99.7 | -0.2 |
| **292** |  | 683.89 | 3.0 | 3.06 | 684 [M+H]$^+$ | 96.4 | -4.6 |
| **293** |  | 657.85 | 8.4 | 3.29 | 658 [M+H]$^+$ | 98.8 | -7.2 |

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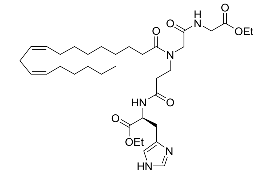
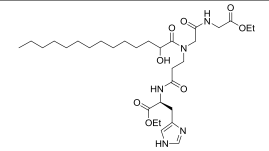
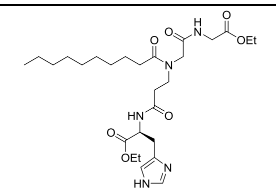
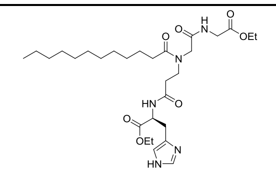
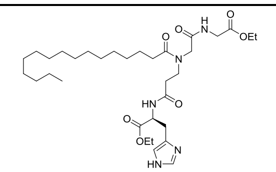
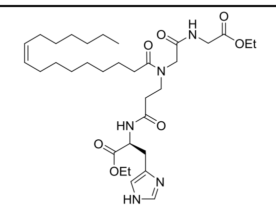
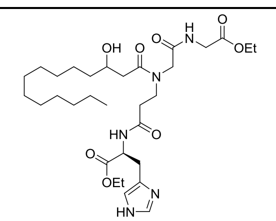
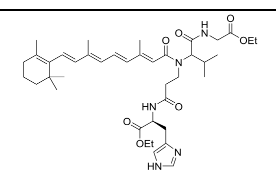
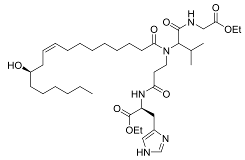
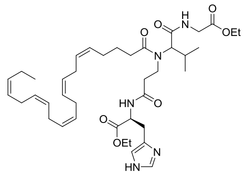
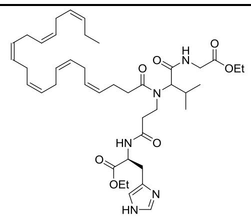
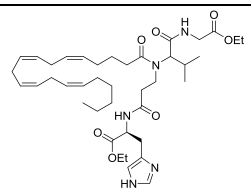
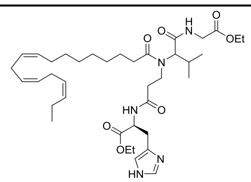
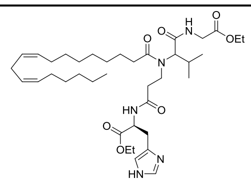
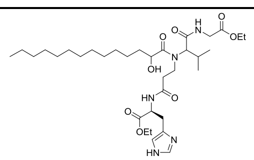
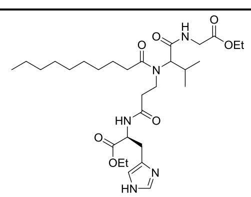
|---|---|---|---|---|---|---|---|
| **294** |  | 659.87 | 8.3 | 3.02 | 660 [M+H]$^+$ | 95.5 | 16.6 |
| **295** |  | 623.79 | 5.6 | 2.72 | 624 [M+H]$^+$ | 94.9 | 25.6 |
| **296** |  | 551.69 | 7.8 | 2.23 | 552 [M+H]$^+$ | 99.1 | 18.7 |
| **297** |  | 579.74 | 10.3 | 2.53 | 580 [M+H]$^+$ | 95.6 | -1.3 |
| **298** |  | 635.85 | 3.7 | 3.13 | 636 [M+H]$^+$ | 98.0 | 35.5 |
| **299** |  | 633.83 | 6.0 | 2.91 | 634 [M+H]$^+$ | 96.8 | 7.5 |
| **300** |  | 623.79 | 2.9 | 2.61 | 624 [M+H]$^+$ | 92.2 | 35.7 |
| **301** |  | 721.94 | 3.7 | 3.18 | 722 [M+H]$^+$ | 96.1 | 9.4 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **302** |  | 719.97 | 5.6 | 2.79 | 720 [M+H]$^+$ | 95.4 | 21.8 |
| **303** |  | 723.96 | 3.0 | 3.10 | 724 [M+H]$^+$ | 98.9 | 3.9 |
| **304** |  | 749.99 | 3.1 | 3.28 | 750 [M+H]$^+$ | 81.6 | 7.6 |
| **305** |  | 725.97 | 2.7 | 3.29 | 726 [M+H]$^+$ | 90.7 | 6.3 |
| **306** |  | 699.93 | 3.7 | 3.11 | 700 [M+H]$^+$ | 98.5 | 16.6 |
| **307** |  | 701.95 | 4.0 | 3.25 | 702 [M+H]$^+$ | 96.0 | 42.2 |
| **308** |  | 665.87 | 4.0 | 3.02 | 666 [M+H]$^+$ | 83.0 | 23.0 |
| **309** |  | 593.77 | 4.1 | 2.51 | 594 [M+H]$^+$ | 98.5 | -9.1 |

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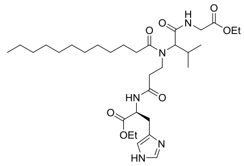
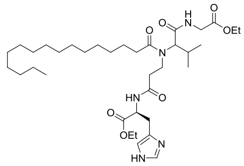
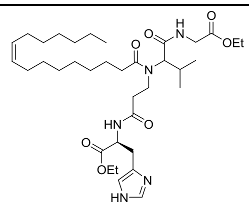
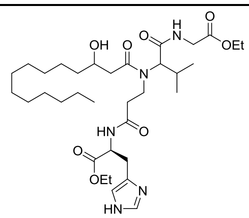
|---|---|---|---|---|---|---|---|
| **310** |  | 621.82 | 3.3 | 2.83 | 622 [M+H]$^+$ | 94.0 | 15.9 |
| **311** |  | 677.93 | 3.0 | 3.39 | 678 [M+H]$^+$ | 99.3 | 32.4 |
| **312** |  | 675.91 | 3.1 | 3.18 | 676 [M+H]$^+$ | 98.0 | 68.0 |
| **313** |  | 665.87 | 3.6 | 2.88 | 666 [M+H]$^+$ | 88.1 | 21.8 |

# References


(1) Kunishima, M.; Kawachi, C.; Morita, J.; Terao, K.; Iwasaki, F.; Tani, S. 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methyl-morpholinium chloride: an efficient condensing agent leading to the formation of amides and esters. *Tetrahedron* **1999**, 55, 13159.

(2) Kumar, A,; Saxena, D.; Gupta, M. K. Boric acid catalyzed Ugi three-component reaction in aqueous media. *RSC Adv*. **2013**, *3*, 4610.

(3) Yang, J.; Brown, M. S.; Ho, Y. K.; Goldstein, J. L. Three Different Rearrangements in a Single Intron Truncate Sterol Regulatory Element Binding Protein-2 and Produce Sterol-resistantPhenotype in Three Cell Lines. ROLE OF INTRONS IN PROTEIN EVOLUTION. *J. Biol. Chem.* **1995**, *270*, 12152.

(4) Schultz, J. R.; Tu, H.; Luk, A.; Repa, J. J.; Medina, J. C.; Li, L.; Schwendner, S.; Wang, S.; Thoolen, M.; Mangelsdorf, D. J.; Lustig, K. D.; Shan, B. Role of LXRs in control of lipogenesis. *Genes Dev*. **2000**, *14*, 2831.