Analysis of Low Molecular Weight Substances and Related Processes Influencing Cellular Cholesterol Efflux

Dmitry Y. Litvinov1 · Eugeny V. Savushkin1 · Alexander D. Dergunov1

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Abstract
Cholesterol efflux is the key process protecting the vascular system from the development of atherosclerotic lesions. Various extracellular and intracellular events affect the ability of the cell to efflux excess cholesterol. To explore the possible pathways and processes that promote or inhibit cholesterol efflux, we applied a combined cheminformatic and bioinformatic approach. We performed a comprehensive analysis of published data on the various substances influencing cholesterol efflux and found 153 low molecular weight substances that are included in the Chemical Entities of Biological Interest (ChEBI) database. Pathway enrichment was performed for substances identified within the Reactome database, and 45 substances were selected in 93 significant pathways. The most common pathways included the energy-dependent processes related to active cholesterol transport from the cell, lipoprotein metabolism and lipid transport, and signaling pathways. The activators and inhibitors of cholesterol efflux were non-uniformly distributed among the different pathways: the substances influencing ‘biological oxidations’ activate cholesterol efflux and the substances influencing ‘Signaling by GPCR and PTK6’ inhibit efflux. This analysis may be used in the search and design of efflux effectors for therapies targeting structural and functional high-density lipoprotein deficiency.

Key Points
We performed a comprehensive analysis of the various substances influencing cholesterol efflux, with pathway enrichment using the Reactome database.
The activators and inhibitors of cholesterol efflux are non-uniformly distributed among different pathways.
The substances influencing biological oxidation activate cholesterol efflux, and the substances influencing signaling by G protein-coupled receptors (GPCR) and non-receptor tyrosine kinase (PTK6) inhibit efflux.

1 Review Cholesterol Transport

High-density lipoprotein (HDL) heterogeneity influences its atheroprotective effect via reverse cholesterol transport from macrophage to the liver [1]. Cholesterol efflux from a macrophage to the extracellular cholesterol acceptor is the first, and rate-limiting, step of reverse cholesterol transport [2, 3]. Four mechanisms of cholesterol efflux, namely aqueous diffusion, facilitated diffusion mediated by the scavenger receptor class B member 1 (SR-B1) receptor, and active unidirectional efflux mediated by the ATP binding cassette subfamily A member 1 (ABCA1) and the ATP binding cassette subfamily G member 1 (ABCG1) transporters are known [4]. ATP hydrolysis with concomitant conformational transition is required for cholesterol efflux by ABCA1 and ABCG1 transporters. The SR-B1 mediates cholesterol efflux by facilitated diffusion via hydrophobic tunnel within the molecule. Various HDL fractions and lipid-free apolipoprotein A1 (apoA-1) are able to accept cell-derived cholesterol with a different efficiency [2]. Cholesterol transport between intracellular compartments proceeds by both energy-dependent and energy-independent processes [5]. The energy-dependent vesicular traffic partly contributes to cholesterol flux between endoplasmic reticulum, plasma membrane (PM) and endocytic vesicles. The membrane contact sites and lipid transfer proteins are involved in non-vesicular lipid traffic [6–11]. Importantly, the PM cholesterol is the cholesterol that participates in the efflux to the extracellular acceptors [12].
Cholesterol efflux from the macrophage is clinically significant for two reasons. First, there is a significant relationship between the cholesterol efflux capacity (CEC) of apolipoprotein B (apoB)-depleted plasma and the manifestations of various cardiovascular events. The predictive significance of CEC for cardiovascular risk is stronger than for HDL cholesterol level [13–16]. The second reason is the positive effect of efflux stimulation on the regression of atherosclerotic plaques [15, 17, 18].

The molecular events in cellular cholesterol efflux, along with the contribution of various pathways, have been extensively studied; however, there is no systematic evaluation of the influence of various low molecular weight substances on cholesterol efflux as a process directed by both donor and acceptor participants. A combined cheminformatic and bioinformatic approach has been applied in the present review to classify and compare the known efflux effectors. Our work may be applicable in the targeted therapy of structural and functional HDL deficiency.

### 2 Effectors of Cholesterol Efflux

The PubMed database was initially searched using the term ‘cholesterol efflux’, and papers involving the use of low molecular weight substances were selected. This analysis of published data on the influence of low molecular weight substances on cholesterol efflux with various donors and acceptors revealed 191 substances with activating and inhibiting effects (Table 1). These substances were grouped into the following classes by means of small-molecule high-throughput screening (Fig. 1): (1) inhibitors and activators of SR-B1 receptors or ABC transporters, including sulfonylureas (inhibitors of ATP-sensitive K+ channels); (2) cyclic nucleotides, nucleotide triphosphates, ligands of nucleotide-dependent protein kinases; (3) nuclear receptor ligands and their precursors; (4) cytokines and their receptors; (5) hormones, hormone receptor ligands (excluding ligands of nuclear receptors), hormone metabolism and growth factors; (6) lipid metabolism—intracellular and extracellular; (7) fatty acids and lipid membrane-disturbing agents; (8) protein kinase B, mammalian target of rapamycin, phosphati
dylinositol-phospholipase C; (9) ceramide signaling; (10) mitogen-activated protein kinase and non-receptor tyrosine kinase signaling; (11) ion channels and Ca2+ regulation; (12) protein synthesis and degradation; (13) structural and trafficking proteins and their ligands; (14) DNA-dependent processes; (15) other factors; (16) vitamins, coenzymes and metabolites; and (17) extracts, components of plants, and other natural sources. Overall, 153 substances were present in the Chemical Entities of Biological Interest (ChEBI) database [220].

The subsequent Reactome database search [221] identified 67 substances, and 9 substances were excluded due to dual activating and inhibiting properties. Pathway enrichment was then performed for the remaining 58 substances using the standard Reactome tools with a ‘small molecules’ key. The significant (p < 0.05) 93 pathways were selected, including 45 from 58 substances. The number of significant pathways was reduced to 31 by the replacement of pathways of very low level with higher-level (parent) pathways (Table 2). These pathways included the Neuronal System (R-HSA-112316); transcriptional regulation of white adipocyte differentiation (R-HSA-381340); the citric acid (TCA) cycle and respiratory electron transport (R-HSA-1428517); integration of energy metabolism (R-HSA-163685); metabolism of vitamins and cofactors (R-HSA-196854); biological oxidations (R-HSA-211859); fatty acid metabolism (R-HSA-8978868); regulation of lipid metabolism by peroxisome proliferator-activated receptor-α (PPARα; R-HSA-400206); metabolism of steroids (R-HSA-8957322); metabolism of amino acids and derivatives (R-HSA-71291); cell junction organization (R-HSA-446728); signaling by nerve growth factor (R-HSA-166520); signaling by Wnt (R-HSA-195721); visual phototransduction (R-HSA-2187338); signaling by GPCR (R-HSA-372790); signaling by retinoic acid (R-HSA-5362517); death receptor signaling (R-HSA-73887); signaling by PTK6 (R-HSA-8848021); disorders of transmembrane transporters (R-HSA-5619115); diseases of signal transduction (R-HSA-5663202); metabolic disorders of biological oxidation enzymes (R-HSA-5579029); diseases of carbohydrate metabolism (R-HSA-5663084); immune system (R-HSA-168256); plasma lipoprotein assembly, remodeling, and clearance (R-HSA-174824); transport of bile salts and organic acids, metal ions, and amine compounds (R-HSA-425366); transport of vitamins, nucleosides, and related molecules (R-HSA-425397); metabolism of proteins (R-HSA-392499); circadian clock (R-HSA-400253); vesicle-mediated transport (R-HSA-5653656); RNA polymerase II transcription (R-HSA-73857); and digestion and absorption (R-HSA-8963743). Importantly, the energy-dependent processes (R-HSA-1428517, R-HSA-163685, R-HSA-211859, R-HSA-5619115, R-HSA-5579029), lipoprotein metabolism and lipid transport (R-HSA-400206, R-HSA-8957322, R-HSA-174824, R-HSA-5653656) and signaling pathways (R-HSA-166520, R-HSA-195721, R-HSA-372790, R-HSA-5619115, R-HSA-73887, R-HSA-8848021, R-HSA-5663202) are included (Table 2).
| Substance used for cell treatment | Description of the substance | Cells<sup>a</sup> | Acceptor of cholesterol | References |
|----------------------------------|-------------------------------|-----------------|------------------------|------------|
| **Inhibitors and activators of SR-B1 receptor or ABC transporters including sulfonylureas (inhibitors of ATP-sensitive K⁺ channels)** | | | | |
| **Stimulation** | | | | |
| Diphenoquinone | Supposedly an oxidized metabolite of probucol; inhibits calpain-mediated degradation of ABCA1 | THP-1, HEK293 expressing ABCA1 | ApoA-I | [19] |
| Glyburide<sup>b</sup> (glibenclamide) | A sulfonylurea antidiabetic drug; inhibitor of ATP-sensitive K⁺ channels | RAW 264.7 | HDL | [20] |
| IMB2026791 | An xanthone compound that enhances binding of apoA-I to ABCA1 | CHO, CHO expressing ABCA1, THP-1 cells | ApoA-I, HDL (CHO expressing ABCA1, THP-1 cells) | [21] |
| Spiroquinone | Supposedly an oxidized metabolite of probucol; inhibits calpain-mediated degradation of ABCA1 | THP-1, HEK293 expressing ABCA1 | ApoA-I | [19] |
| **Inhibition** | | | | |
| BLT-1 - BLT-5 | Inhibitors of SR-B1; increases binding affinity of SR-B1 for HDL | IdLA-7 cells stably transfected to express SR-B1 | HDL | [22] |
| BLT-1, BLT-4 | Inhibitors of SR-B1; increases binding affinity of SR-B1 for HDL | RAW 264.7, 3T3 L-1-derived adipocytes | ApoA-I | [23, 24] |
| Compound 1 (methyl 3α-acetoxy-7α,12α-di[(phenylaminocarbonyl)amino]-5β-cholan-24-oate) | A novel inhibitor of ABCA1 | RAW 264.7 | ApoA-I, taurocholate, peptide 18A (i.e. 2F) | [25] |
| Compound 2 (N-[2-((4-nitrophenylaminocarbonyl)amino)ethyl]-N,N-di[2-((4-methylphenylsulfonyl)amino)ethyl]lamine) | A novel inhibitor of ABCA1 | RAW 264.7 | ApoA-I | [25] |
| Glyburide<sup>b</sup> (glibenclamide) | A sulfonylurea antidiabetic drug; a general inhibitor of ABC transporters, including ABCA1 | J774, RAW 264.7, THP-1, fibroblasts, SMC, HEK293 expressing ABCA1, 3T3 L-1-derived adipocytes | ApoA-I | [20, 23, 26, 27] |
| Wheat germ agglutinin | A lectin; inhibits generation of microparticle by ABCA1 | RAW 264.7 | No acceptor | [25] |
| Probucol | An inhibitor of ABCA1-mediated lipid efflux, lipid-lowering drug, an antioxidant, stimulates cellular lipids synthesis | J774, MPM Astrocytes | ApoA-I, ApoA-II (MPM), ApoE (MPM) | [29–31] |
| | | THP-1, WI-38 human fibroblast cells, MAC-T | ApoA-I | [19, 33, 34] |
Table 1 (continued)

| Substance used for cell treatment | Description of the substance | Cellsa | Acceptor of cholesterol | References |
|----------------------------------|------------------------------|--------|-------------------------|------------|
| PSC833                           | Inhibits ABCA1; a non-immunosuppressive cyclosporine not inhibiting calcineurin; an inhibitor of ABCB1 and ABCB4 | ABCA1-expressing BHK cells, THP-1 | ApoA-I | [35] |

**Cyclic nucleotides, nucleotide triphosphates, ligands of nucleotide-dependent protein kinases**

**Stimulation**

| Substance | Description | Cells | Acceptor of cholesterol | References |
|-----------|-------------|-------|-------------------------|------------|
| 8-Br-cAMP | cAMP analog | RAW 264.7, J774, astrocytes | ApoA-I, ApoE2, ApoE3, ApoE4, HDL | [36] |
| A-769662 | Activator of AMPK | THP-1 | ApoA-I | [38] |
| ATP (up to 0.1–1 μM; inhibition over 1–10 μM) | Nucleoside triphosphate | RAW 264.7, ABCA1-expressing BHK cells | ApoA-I | [39] |
| ATP, 1 mM | Nucleoside triphosphate | Primary mouse type II pneumocytes | No acceptor | [40] |
| AICAR (5-aminomidazole-4-carboxamide ribonucleoside) | An activator of AMPK | J774 | HDL | [41] |
| cAMP analog | | MPM, J774, L-cell | ApoA-I, HDL3 (J774) | [28–30] |
| CPT-cAMP (8-(4-chlorophenylthio)cAMP) | PKA-anchoring inhibitor | ABCA1-expressing BHK cells, RAW 264.7 | No acceptor; also ApoA-I in a separate experiment | [42] |

**Inhibition**

| Substance | Description | Cells | Acceptor of cholesterol | References |
|-----------|-------------|-------|-------------------------|------------|
| Apyrase | ATP hydrolysis to AMP | RAW 264.7 and ABCA1-expressing BHK cells | ApoA-I | [39] |
| MDL-12330A | An inhibitor of adenylyl cyclase | RAW 264.7 | ApoA-I | [43] |
| PKI | A PKA inhibitor | ABCA1-expressing BHK cells | ApoA-I | [44] |
| Oligomycin | An inhibitor of ATP synthase; inhibits mitochondrial respiration | THP-1 | ApoA-I | [45] |
| Sodium orthovanadate | A specific inhibitor of P-type ATPases and protein phosphotyrosine phosphatases | Fibroblasts, SMC | ApoA-I | [26] |

**Nuclear receptor ligands and their precursors**

**Stimulation**

| Substance | Description | Cells | Acceptor of cholesterol | References |
|-----------|-------------|-------|-------------------------|------------|
| 9-cis-retinoic acid | A retinoid that activates RXRs and RARs | Astrocytes | ApoA-I, HDL | [46] |
| 13-cis-retinoic acid | A retinoid that is neither an RAR nor an RXR agonist | Astrocytes | ApoA-I, HDL | [46] |
| 13-hydroxy linoleic acid | Natural PPAR agonist | RAW 264.7 | ApoA-I | [47] |
| 22(R)-hydroxycholesterol | An oxysterol, natural LXR activator | hPBMC, mBMDM, RAW 264.7, THP-1 | ApoA-I, HDL (THP-1) | [48–51] |
| 22(R)-hydroxycholesterol with 9-cis-retinoic acid | LXR/RXR agonist | J774, MPM, astrocytes, primary mouse type II pneumocytes | ApoA-I, HDL (astrocytes, CaCo-2), no acceptor (CaCo-2) | [32, 40, 52–54] |
| 24(S),25-epoxycholesterol | An oxysterol, natural LXR activator | mBMDM, hPBMC | ApoA-I | [48] |
| Substance used for cell treatment                  | Description of the substance                                                                 | Cells<sup>a</sup>                          | Acceptor of cholesterol | References  |
|--------------------------------------------------|-----------------------------------------------------------------------------------------------|--------------------------------------------|-------------------------|-------------|
| **9-cis-β-carotene**                              | A precursor for 9-cis-retinoic acid that stimulates cholesterol efflux                        | RAW 264.7, MPM                            | HDL                     | [55]        |
| Acetyl-podocarpic dimer                           | LXR agonist                                                                                   | hPBMC, THP-1, primary human fibroblasts    | ApoA-I                  | [51]        |
| All-trans β-carotene                              | Vitamin A precursor                                                                          | RAW 264.7                                  | HDL                     | [55]        |
| All-trans retinoic acid (tretinoin)              | A retinoid that activates RARs                                                                | Astrocytes                                 | ApoA-I, HDL             | [46]        |
| Baicalin                                          | PPARγ agonist                                                                                 | THP-1                                      | HDL2, HDL3              | [56]        |
| Bezafibrate                                      | A lipid-lowering fibrate drug, an agonist of PPARα                                            | THP-1                                      | apoB-depleted plasma    | [57]        |
| E17110                                           | A novel benzofuran-2-carboxylate derivative with potential LXRβ agonist activity               | RAW 264.7                                  | ApoA-I, HDL             | [58]        |
| Ethyl 2,4,6-trihydroxybenzoate                   | An LXR agonist isolated from Celtis biondii                                                   | THP-1                                      | HDL                     | [59]        |
| Fenofibric acid                                  | A fibrate; used for the treatment of dyslipidemia, a PPARα agonist                            | hPBMC                                      | HDL                     | [60]        |
| GW1929                                           | PPARγ agonist                                                                                 | THP-1                                      | HDL3, ApoA-I            | [61]        |
| GW3965                                           | LXR agonist                                                                                   | MPM, RAW 264.7, THP-1, Huh7.5 (hepatoma cells), 3T3 L-1-derived adipocytes, blastic plasmacytoid dendritic cell neoplasm cell line CAL-1 (a myeloid leukemia cell line) | ApoA-I, HDL2 (THP-1, CAL-1), HDL3 (THP-1) | [23, 62–66] |
| GW4064                                           | FXR agonist                                                                                   | THP-1                                      | No acceptor             | [67]        |
| Isosylibin A                                     | A partial PPARγ agonist                                                                       | THP-1                                      | ApoA-I                  | [68]        |
| K-877                                            | Selective PPARβ modulator                                                                     | hPBMC                                      | HDL                     | [60]        |
| Methoprene                                       | Synthetic selective RXR agonist                                                               | Astrocytes                                 | ApoA-I, HDL             | [46]        |
| N-Acylthiadiazoline compound 2                   | LXRβ agonist                                                                                 | MPM                                        | ApoA-I                  | [64]        |
| (racemate or R enantiomer)                      | Pioglitazone<sup>b</sup>                                                                       | THP-1, RAW 264.7                           | ApoA-I, HDL, HDL2 (THP-1), HDL3 (THP-1), human plasma (THP-1) | [68–71] |
| Rosiglitazone                                    | Synthetic PPAR agonist                                                                        | hPBMC, MPM, THP-1                          | ApoA-I, HDL (THP-1), HDL2 (THP-1), HDL3 (THP-1) | [62, 72–74] |
|                                                 |                                                                                               | RAW 264.7                                  | HDL                     | [75]        |
| Substance used for cell treatment | Description of the substance | Cells<sup>a</sup> | Acceptor of cholesterol | References |
|----------------------------------|-----------------------------|----------------|------------------------|------------|
| TO-1317 (TO-901317)              | LXR agonist                 | J774, MPM, RAW 264.7, THP-1, CaCo-2, MAC-T (ApoA-I) | ApoA-I, HDL, HDL3 (MPM), no acceptor (THP-1), taurocholate-phosphatidylcholine micelles (CaCo-2) | [34, 54, 59, 76–81] |
|                                  | Blastic plasmacytoid dendritic cell neoplasm cell line CAL-1 (a myeloid leukemia cell line) |               |                        | [66] |
| Telmisartan                      | Angiotensin II receptor antagonist; also activates PPAR<sub>γ</sub> | HepG2, human foreskin fibroblasts | ApoA-I | [82, 83] |
| Tributyltin chloride             | An organotin compound; an RXR activator | RAW 264.7 | ApoA-I | [76] |
| Wy14643                          | PPAR<sub>α</sub> activator | hPBMC | ApoA-I | [72] |
| Inhibition                       | PPAR<sub>γ</sub> ligand | MPM | ApoA-I | [84] |
| 15d-PGJ2 (15-Deoxy-delta(12,14)-prostaglandin J(2)) | PPAR<sub>δ</sub> and, to a lesser extent, PPAR<sub>α</sub> agonist | MPM | ApoA-I | [84] |
| Pioglitazone<sup>b</sup>          | PPAR agonist | MPM | ApoA-I | [84] |
| Troglitazone                     | PPAR<sub>γ</sub> and, to a lesser extent, PPAR<sub>α</sub> agonist | MPM | ApoA-I | [84] |
| TTNPB (4-[(E)-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-1-propenyl]benzoic acid) | Synthetic selective RAR agonist | Astrocytes | ApoA-I, HDL | [46] |

**Cytokines and their receptors**

**Stimulation**

| Substance used for cell treatment | Description of the substance | Cells<sup>a</sup> | Acceptor of cholesterol | References |
|----------------------------------|-----------------------------|----------------|------------------------|------------|
| Apelin-13                        | An adipocytokine, a ligand for the cognate G-protein coupled receptor APJ | THP-1 | ApoA-I | [85] |
| CXCL5                            | A chemokine that signals through the CXCR2 receptor | MPM | ApoA-I | [86] |
| IL-8-neutralizing antibody       | IL-8 is a proinflammatory chemokine that induces chemotaxis and phagocytosis | THP-1 | ApoA-I | [87] |
| IL-10                            | An anti-inflammatory cytokine | THP-1 | ApoA-I, HDL2, serum (FBS) | [88] |
| IL-12 with IL-18                  | IL-12 and IL-18 synergize for the production of IFNγ | THP-1 | ApoA-I | [89] |
| IL-27                            | An anti-inflammatory cytokine | THP-1 | ApoA-I | [90] |
| TGFβ<sup>b</sup>                  | An anti-inflammatory cytokine | MPM from WT or apoE KO mice | ApoA-I, HDL | [91] |
| TNFα<sup>b</sup>                  | Proinflammatory cytokine | MPM | ApoA-I | [92] |
| Inhibition                       | CCL2                        | HCAEC, HUVEC | ApoA-I (HCAEC), HDL | [93] |
|                                  | IFNβ                         | mBMDM | ApoA-I | [94] |
| Substance used for cell treatment | Description of the substance | Cells | Acceptor of cholesterol | References |
|----------------------------------|------------------------------|-------|-------------------------|------------|
| IL-1β                            | Pro-inflammatory cytokine    | HepG2, primary mouse hepatocytes | ApoA-I     | [95]                   |
| IL-6                             | Pro-inflammatory cytokine    | THP-1 | ApoA-I                  | [96]       |
| INFγ                             | Pro-inflammatory cytokine, has a variety of proatherogenic effects | MPM, THP-1 | ApoA-I                  | [91, 97–99]|
| TNFαb                            | Pro-inflammatory cytokine    | THP-1, HepG2, mouse primary hepatocytes, podocytes (kidney cells) | ApoA-I | [95, 96, 100] |
| TNF-like protein 1A (TL1A; TNFSF15) | Binds to DR3; highly expressed in atherosclerotic plaques | THP-1, hPBMC | ApoA-I | [99] |
| Visfatin (pre-B cell colony-enhancing factor 1) | A nicotinamide phosphoribosyltransferase | RAW 264.7 | ApoA-I, HDL | [101] |

**Hormones, hormone receptor ligands (excluding ligands of nuclear receptors), hormone metabolism and growth factors**

**Stimulation**

| Substance used for cell treatment | Description of the substance | Cells | Acceptor of cholesterol | References |
|----------------------------------|------------------------------|-------|-------------------------|------------|
| 17β-estradiol                    | A steroid sex hormone       | VSMC, MAC-T | ApoA-I, HDL (VSMC) | [34, 102] |
| Angiotensin-(1–7)                | Produced by ACE2; ACE2-deficient mice have an increased risk of heart failure | THP-1, RAW 264.7 | ApoA-I or HDL (THP-1) | [43, 103] |
| Exendin-4                        | A GLP-1 mimetic affecting insulin regulation | 3T3-L1 adipocytes | No acceptor | [104] |
| FGF-21                           | Mitogenic and cell survival activities | THP-1 | ApoA-I, HDL | [105] |
| Ghrelin                          | An endocrine peptide mainly identified in stomach epithelium; stimulates food intake in humans | THP-1 | ND | [106] |
| GDP-15                           | A 12-kDa secreted protein, also named macrophage inhibitory cytokine-1 | THP-1 | No acceptor | [107] |
| Hydrocortisone (i.e. cortisol)   | A steroid hormone, stimulates gluconeogenesis, suppresses the immune system | MAC-T | ApoA-I | [34] |
| IGF-1                            | Regulates metabolism, growth, and cell differentiation and survival | INS-1 cells originated from a rat insulinoma cell line | ND | [108] |
| Insulinb)                        | A peptide hormone, regulates glucose metabolism | MAC-T | ApoA-I | [34] |
| Progesterone                     | A steroid sex hormone       | MAC-T | ApoA-I | [34] |
| Prolactin                        | A peptide hormone; initiates milk production | MAC-T | ApoA-I | [34] |
| Vildagliptin                     | An antidiabetic drug, an inhibitor of DPP-4, thus prolonging the half-life of GLP-1 | 3T3-L1 adipocytes | No acceptor | [104, 109] |

**Inhibition**

| Substance used for cell treatment | Description of the substance | Cells | Acceptor of cholesterol | References |
|----------------------------------|------------------------------|-------|-------------------------|------------|
| Adiponectin (Acrp30)             | An adipokine secreted by adipocytes that functions as an insulin sensitizer | hPBMC | ApoA-I | [110] |
| Substance used for cell treatment | Description of the substance                                                                 | Cellsᵃ            | Acceptor of cholesterol | References |
|----------------------------------|-----------------------------------------------------------------------------------------------|-------------------|-------------------------|------------|
| Angiotensin-II                   | A peptide produced by the enzyme ACE; ACE inhibitors are used for the treatment of CVDs       | THP-1             | ApoA-I or HDL           | [103]      |
| CRH                              | A peptide that links psychological stress to pathophysiological responses                     | MPM               | ApoA-I                  | [111]      |
| Dexamethasone                    | A corticosteroid, agonist of GR                                                               | THP-1             | ApoA-I                  | [112]      |
| EGF                              | Activates MAP kinases ERK1/2                                                                   | RAW 264.7         | ApoA-I                  | [113]      |
| Hydrocortisone                   | A corticosteroid, agonist of GR                                                               | THP-1             | Human serum             | [114]      |
| Insulinᵇ                        | A peptide hormone, regulates glucose metabolism                                               | HepG2, HEK293     | ApoA-I, ABCA1           | [110, 115] |
| Raloxifene                       | A benzothiophene derivative that is used for the treatment of osteoporosis in postmenopausal women; a selective ER modulator: stimulates ER in bone and inhibits ER in the uterus and breast | THP-1, MPM        | ApoA-I, HDL             | [116]      |
| Tamoxifen                        | A medication for treating breast cancer; a prodrug that is metabolized in the liver into an ER antagonist | THP-1, MPM        | ApoA-I, HDL             | [116]      |
| Toremifene                       | A selective ER modulator; a medication for treating breast cancer                            | THP-1, MPM        | ApoA-I, HDL             | [116]      |

**Lipid metabolism—intracellular and extracellular**

**Stimulation**

| Substance used for cell treatment | Description of the substance | Cellsᵃ            | Acceptor of cholesterol | References |
|----------------------------------|------------------------------|-------------------|-------------------------|------------|
| Ibrolipim                        | An LPL activator             | THP-1             | ApoA-I, HDL             | [117]      |
| MCC-147                          | An inhibitor of ACAT         | MPM               | ApoA-I                  | [118]      |
| Myriocin                         | An inhibitor of SPTLC1       | Primary human fibroblasts, mBMDM | ApoA-I      | [119]      |
| NTE-122 (trans-1,4-bis [1-cyclohexyI-3-(4-dimethylamino phenyl)ureido]methyl)cyclohexane) | An inhibitor of ACAT | THP-1                 | HDL         | [120]      |
| PLTPᵇ                           | Transfers phospholipids between lipoproteins, remodels HDL                                 | J774, BHK expressing ABCA1 | HDL, trypinized HDL    | [121]      |
| PLTPᵇ                           | Relatively lipophilic statin; type II statinᵇ                                               | BHK expressing ABCA1 | No acceptor, LDL, phospholipid vesicles | [121] |
| Pitavastatinᵇ                    | Relatively lipophilic statin; type I statinᵇ                                               | Fu5AH              | ApoA-I                  | [122]      |
| Simvastatinᵇ                     |                                             | THP-1              | ApoB-depleted plasma    | [57]       |

**Inhibition**

| Substance used for cell treatment | Description of the substance                                              | Cellsᵃ            | Acceptor of cholesterol | References |
|----------------------------------|--------------------------------------------------------------------------|-------------------|-------------------------|------------|
| LPL                              | A secreted enzyme facilitating the hydrolysis of triglycerides in chylomicrons | THP-1             | ApoA-I                  | [123]      |
| PLTPᵇ                           | Transfers phospholipids between lipoproteins, remodels HDL               | BHK expressing ABCA1 | ApoA-I                  | [121]      |
| PCSK9                            | A subtilisin family-serine protease that degrades LDL receptor in liver   | MPM               | ApoA-I                  | [53]       |
| Substance used for cell treatment | Description of the substance | Cellsa | Acceptor of cholesterol | References |
|-----------------------------------|-------------------------------|--------|-------------------------|------------|
| Simvastatinb (0.01 µM)           | Relatively lipophilic statin; type I statinc | J774   | ApoA-I                  | [124]      |
|                                   |                               | THP-1, hPBMC | HDL                  |            |
| Atorvastatin (10 µM)             | Relatively lipophilic statin; type II statinc | J774, RAW 264.7 | ApoA-I              | [124, 126] |
|                                   |                               | THP-1, hPBMC | HDL, ApoA-I (THP-1)  | [125, 127] |
| Rosuvastatin (10 µM)             | Relatively hydrophilic statin; type II statinc | J774   | ApoA-I                  | [124]      |
| Pitavastatinb) (0.1 or 1 µM for J774, RAW—depends on the paper) | Relatively lipophilic statin; type II statinc | J774, MPM, RAW 264.7 | ApoA-I              | [124, 126, 128] |
| Pravastatin                       | Relatively hydrophilic statin; type I statinc | 3T3-L1 adipocytes | No acceptor           | [109]      |
| Mevasstatin (Compactin; 10 uM)   | Relatively lipophilic statin; type I statinc | MPM    | ApoA-I                  | [128]      |

Fatty acids and lipid membrane-disturbing agents

**Stimulation**

|                        | Description of the substance                        | Cellsa | Acceptor of cholesterol | References |
|------------------------|------------------------------------------------------|--------|-------------------------|------------|
| α-Linolenic acid conjugated to BSA | An omega-3 PUFA                                     | THP-1  | No acceptor             | [67]       |
| Cholesterolb           |                                                      | GM3468A normal human skin fibroblasts, primary cerebellar astroglia | ApoA-I | [129, 130] |
| Edelfosineb (1-O-octadecyl-2-O-methyl-rac-glycero-3-phosphocholine) | An alkyl-phospholipid with amphiphilic properties | HepG2  | No acceptor (the compound itself might perform as the acceptor) | [131] |
| Eruceylphosphocholine ([([Z]-docos-13-enyl) 2-(trimethylazaniumyl)ethyl phosphate) | An alkyl-phospholipid with amphiphilic properties | HepG2  | No acceptor (the compound itself might perform as the acceptor) | [131] |
| Miltefosine,b i.e. hexadecylphosphocholine (hexadecyl12-(trimethylazaniumyl)ethyl phosphate) | An alkyl-phospholipid with amphiphilic properties | HepG2  | No acceptor (the compound itself might perform as the acceptor) | [131] |
| Imipramine             | An amphipathic amine                                 | MPM    | ApoA-I                  | [132]      |
| Perifosineb (1,1-dimethylpiperidin-1-ium-4-y1) octadecyl phosphate | An alkyl-phospholipid with amphiphilic properties | HepG2  | No acceptor (the compound itself might perform as the acceptor) | [131] |
| U18666A                | An amphipathic amine                                 | MPM    | ApoA-I, HDL2            | [132]      |

**Inhibition**

|                        | Description of the substance                        | Cellsa | Acceptor of cholesterol | References |
|------------------------|------------------------------------------------------|--------|-------------------------|------------|
| 1,2-dioleoyl-sn-glycero-3-phospho-rac-1-glycerol [a precursor of bis(monoacylglycerophosphate)] | Bis(monoacylglycerophosphate (lysobisphosphatidic acid), a phospholipid highly abundant in the internal membranes of multi-vesicular late endosomes, in which it forms specialized lipid domains | RAW 264.7 | Mβ-CD, ApoA-I, HDL | [133] |
| Cholesterolb           |                                                      | MPM    | ApoA-I, HDL2            | [132]      |
Table 1 (continued)

| Substance used for cell treatment | Description of the substance | Cellsa | Acceptor of cholesterol | References |
|----------------------------------|------------------------------|--------|-------------------------|------------|
| Edelfosineb (1-O-octadecyl-2-O-methyl-rac-glycero-3-phosphocho-line) | An alkyl-phospholipid with amphiphilic properties | THP-1 | ApoA-I | [134] |
| Eicosapentaenoic acid [20:5(n-3)] | Omega-3 PUFA | RAW 264.7, THP-1 | ApoA-I | [49, 135] |
| Linoleic acid 18:2 omega-6 PUFA | mBMDM | HDL | | [136] |
| Miltefosineb, i.e. hexadecylphosphocholine [hexadecyl 2-(trimethylazaniumyl)ethyl phosphate] | An alkyl-phospholipid with amphiphilic properties | THP-1 | ApoA-I | [134] |
| Perifosineb (1,1-dimethylpiperidin-1-ium-4-yl) octadecyl phosphate | An alkyl-phospholipid with amphiphilic properties | THP-1 | ApoA-I | [134] |
| Oleic acid (18:1) | Monounsaturated fatty acid | J774, RAW 264.7 | ApoA-I | [49, 137] |

**Effectors of Akt, mTOR, PI-PLC**

**Stimulation**

| Substance | Description | Cells | Acceptor of cholesterol | References |
|-----------|-------------|-------|-------------------------|------------|
| Akt1/2 kinase inhibitor | An inhibitor of Akt | BHK expressing ABCA1 | ApoA-I | [137] |
| DEPC (10-[4‘-(N,N-Diethylamino)butyl]-2-chlorophenoxazine hydrochloride) | An inhibitor of Akt; supresses mTORC1 activity | RAW 264.7, Min6, HepG2, BHK expressing ABCA1 | ApoA-I | [138] |
| K3-0063794 | mTOR inhibitor | ABCA1-expressing BHK cells | ApoA-I | [35] |
| LY294002 | An inhibitor of PI3 kinase; supresses mTORC1 activity | HepG2, HEK293 expressing ABCA1, BHK expressing ABCA1 | ApoA-I | [115, 138] |
| Rapamycin (at 10–100 nM; inhibition over 10 μM) | mTOR inhibitor | BHK expressing ABCA1 | ApoA-I | [35, 138] |
| Torin-1 | An inhibitor of mTORC1 | BHK expressing ABCA1 | ApoA-I | [138] |

**Inhibition**

| Substance | Description | Cells | Acceptor of cholesterol | References |
|-----------|-------------|-------|-------------------------|------------|
| PI-PLC | Hydrolyzes PIP2 to inositol triphosphate and diacylglycerol | RAW264.7, HEK293 expressing ABCA1 | ApoA-I | [139] |

**Ceramide signaling**

**Stimulation**

| Substance | Description | Cells | Acceptor of cholesterol | References |
|-----------|-------------|-------|-------------------------|------------|
| C2-dihydroceramide | Ceramide analog that is not associated with apoptosis | CHO | ApoA-I | [140] |
| Ceramide | A lipid signaling molecule, a product of the digestion of sphingomyelin, an activator of cathepsin D (a lysosomal proteinase) | J774, CHO, CHO expressing ABCA1, HeLa expressing ABCA1 | ApoA-I | [140, 141] |
| MAPP [(1S,2R)-D-erythro-2-(N-myristoylamino)-1-phenyl-1-propanol | An inhibitor of alkaline ceramidase; elevates the level of endogenous ceramide | CHO | ApoA-I | [140] |
| Substance used for cell treatment | Description of the substance | Cells | Acceptor of cholesterol | References |
|---------------------------------|-------------------------------|-------|-------------------------|------------|
| **MAP kinase and non-receptor tyrosine kinase signaling** | | | | |
| **Stimulation** | | | | |
| PD98059<sup>b</sup> | An inhibitor of MAP kinases MEK1 and MEK2 | RAW 264.7, MPM | ApoA-I, HDL | [113, 142] |
| PP2 (i.e. AG 1879) | An inhibitor of Src family kinase | Jurkat cells (human acute T lymphocyte leukemia cell line) | ApoA-I | [143] |
| U0126 | An inhibitor of MAP kinases ERK1/2 | RAW 264.7, MPM | ApoA-I, HDL | [113, 142] |
| **Inhibition** | | | | |
| AG490 | Inhibitor of JAK-2 | MAC-T | ApoA-I | [34] |
| PD98059<sup>b</sup> | An inhibitor of MAP kinases MEK1 and MEK2 | MAC-T | ApoA-I | [34] |
| Raf1 kinase inhibitor I, i.e. GW5074 [3-(3,5-Dibromo-4-hydroxybenzyliden)-5-iodo-1,3-dihydroindol-2-one] | Inhibits signaling through the MAPK cascade | HEK293 expressing ABCA1 | ApoA-I | [115] |
| **Ion channels and Ca2+ regulation** | | | | |
| **Stimulation** | | | | |
| BAY-K8644 | An agonist of plasma membrane L-type Ca2+ channels | ABCA1-expressing BHK cells | ApoA-I | [44] |
| Digoxin | A cardioactive glycoside that inhibits Na+/K+/ATPase, activates the mevalonate pathway, and stimulates the mitochondrial respiratory chain and synthesis of ATP | H9c2 (rat cardiomyocyte cell line) | No acceptor, ApoA-I | [144] |
| Ouabain | A cardioactive glycoside that inhibits Na+/K+/ATPase, activates the mevalonate pathway, and stimulates the mitochondrial respiratory chain and synthesis of ATP | H9c2 (rat cardiomyocyte cell line) | No acceptor, ApoA-I | [144] |
| Nifedipine | A calcium channel blocker | RAW 264.7 | ApoA-I, HDL | [145] |
| **Inhibition** | | | | |
| BAPTA-AM | Intracellular Ca2+ chelator | ABCA1-expressing BHK cells, RAW 264.7 | ApoA-I | [44] |
| Benzamil (stimulation at 100 μM) | Blocks the epithelial sodium channel and sodium-calcium exchange | MAC-T | HDL | [34] |
| Cyclosporine A | Calcineurin inhibitor | ABCA1-expressing BHK cells, RAW 264.7, THP-1 | ApoA-I | [35, 44] |
| Disulphonic acid hydrate disodium salt | Chloride channel inhibitor | ABCA1-expressing BHK cells | ApoA-I | [44] |
| EDTA | Chelator of Ca2+ | ABCA1-expressing BHK cells | ApoA-I | [44] |
Table 1 (continued)

| Substance used for cell treatment | Description of the substance | Cells<sup>a</sup> | Acceptor of cholesterol | References |
|----------------------------------|------------------------------|------------------|------------------------|------------|
| EGTA                             | Chelator of Ca<sup>2+</sup>   | ABCA1-expressing BHK cells, RAW 264.7 | ApoA-I | [44] |
| Pimecrolimus                     | Calcineurin inhibitor        | ABCA1-expressing BHK cells | ApoA-I | [35] |
| FK506 (tacrolimus)               | Calcineurin inhibitor        | ABCA1-expressing BHK cells, RAW 264.7 | ApoA-I | [35, 44] |
| W-7                              | CaM antagonist (inhibits binding of Ca<sup>2+</sup>-bound CaM with its substrates) | ABCA1-expressing BHK cells | ApoA-I | [44] |

**Protein synthesis and degradation**

**Stimulation**

| ALLN (Calpain inhibitor I)       | Thiol protease inhibitors; increases ABCA1 level; reversibly blocks Ca-dependent neutral cysteine protease calpain I | THP-1 | ApoA-I | [146] |
| Bortezomib                       | A proteasome inhibitor       | THP-1, RAW 264.7, MPM | ApoA-I, HDL | [147] |
| Chloroquine                      | A lysosomal inhibitor        | HeLa expressing ABCA1 | ApoA-I | [24] |
| Epoxomicin                       | A proteasome inhibitor       | THP-1, RAW 264.7, MPM | ApoA-I, HDL | [147] |
| MG132                            | A proteasome inhibitor       | THP-1, RAW 264.7, MPM | ApoA-I, HDL | [147] |
| Leupeptin                        | Thiol protease inhibitor; increases the ABCA1 level; inhibits serine and cysteine proteases (plasmin, trypsin, papain, calpain, and cathepsin B) | THP-1 | ApoA-I | [146] |
| Pepstatin A                      | An inhibitor of cathepsin D, a lysosomal protease | mBMDM, MPM, J774, CHO | ApoA-I | [141] |

**Inhibition**

| Brefeldin A                      | Lactone antibiotic that alters the structure and function of the Golgi apparatus; inhibits protein processing through the Golgi | J774, RAW 264.7, human skin fibroblasts, 3T3 L-1-derived adipocytes | ApoA-I (J774, adipocytes), ApoE4 (RAW 264.7, HDL (fibroblasts), HDL3 (J774) | [23, 28, 148] |
| Cycloheximide                    | Protein synthesis inhibitor  | J774, MPM | ApoA-I | [29, 118] |
| Monensin                         | Polyether antibiotic that alters the structure and function of the Golgi apparatus; inhibits protein processing through the Golgi | RAW 264.7, human skin fibroblasts | ApoE4 (RAW 264.7), HDL (fibroblasts) | [36, 148] |

**Structural and trafficking proteins and their ligands**

**Stimulation**

| Colchicine                       | Inhibits microtubule polymerization, a metabolic and transport inhibitor, mitotic poison | Human skin fibroblasts | Plasma, albumin-depleted plasma, and ApoA-I-depleted plasma | [149] |
| Caveolin-1 expression            | Integral membrane protein that acts as a scaffolding protein | HepG2 stably transfected caveolin-1 | ApoA-I and plasma | [150] |
| Substance used for cell treatment | Description of the substance | Cells<sup>a</sup> | Acceptor of cholesterol | References |
|----------------------------------|-----------------------------|----------------|------------------------|------------|
| FGIN-1-27                        | A ligand for TSPO           | THP-1          | ApoA-I, HDL            | [151]      |
| Flunitrazepam                    | A ligand for TSPO           | THP-1          | ApoA-I                 | [151]      |
| GGTI-298                         | An inhibitor of prenyltransferase GGTase-I that post-translationally modifies proteins for association to the membrane | mBMDM, THP-1 | No acceptor, ApoA-I (mBMDM), HDL (mBMDM) | [152] |
| PK11195                          | A ligand for TSPO           | THP-1          | ApoA-I, HDL            | [151]      |

DNA-dependent processes

**Stimulation**

| Substance used for cell treatment | Description of the substance | Cells<sup>a</sup> | Acceptor of cholesterol | References |
|----------------------------------|-----------------------------|----------------|------------------------|------------|
| Etoposide (VP-16)                | DNA topoisomerase II inhibitor | MPM            | ApoA-I                 | [153]      |
| Pyrrole-imidazole polynamide targeting ABCA1 promoter | A nuclease-resistant compound that inhibits the transcription factor by binding to the minor groove of DNA | RAW 264.7 | ApoA-I | [154] |
| Teniposide (VM-26)               | DNA topoisomerase II inhibitor | MPM            | ApoA-I                 | [153]      |

**Inhibition**

| Substance used for cell treatment | Description of the substance | Cells<sup>a</sup> | Acceptor of cholesterol | References |
|----------------------------------|-----------------------------|----------------|------------------------|------------|
| Mithramycin A                    | A chemotherapeutic drug that binds to GC-rich DNA sequences and blocks the binding of the transcription factor Sp1 | RAW 264.7 | ApoA-I | [155] |

Other factors

**Stimulation**

| Substance used for cell treatment | Description of the substance | Cells<sup>a</sup> | Acceptor of cholesterol | References |
|----------------------------------|-----------------------------|----------------|------------------------|------------|
| Aspirin (up to 0.5 mM; inhibition over 1 mM) | NSAID and an antiplatelet drug (antiaggregant) used in CVD | RAW 264.7 | ApoA-I | [63] |
| Doxazosin                        | α1-selective alpha blocker used to treat high blood pressure | RAW 264.7 | ApoA-I | [154] |
| EP 80317                         | Selective CD36 ligand       | J774           | ApoA-I, HDL            | [156]      |
| IRAK1 and IRAK4 inhibitor        | IRAK1 participates in signaling via toll-like receptors/IL-1R | THP-1          | ApoA-I, HDL            | [157]      |
| L. acidophilus bacteria strain K301, heat killed | A component of the human gut microflora; used as probiotics | THP-1          | ApoA-I                 | [158]      |
| Paraoxonase-1                    | An HDL-associated enzyme that contributes to the antioxidant and anti-inflammatory capacities of HDLs | J774, THP-1    | No acceptor, HDL, ApoA-I (J774) | [159] |

**Inhibition**

| Substance used for cell treatment | Description of the substance | Cells<sup>a</sup> | Acceptor of cholesterol | References |
|----------------------------------|-----------------------------|----------------|------------------------|------------|
| Arsenic trioxide                 | Chronic arsenic exposure is associated with an increased risk of CVD mortality | HepG2          | HDL                    | [160]      |
| Celecoxib                        | COX-2-specific inhibitor for the treatment of pain and inflammation | THP-1          | ApoA-I                 | [161]      |
| Substance used for cell treatment | Description of the substance | Cells<sup>a</sup> | Acceptor of cholesterol | References |
|----------------------------------|-----------------------------|-----------------|------------------------|------------|
| *Chlamydia pneumoniae*, viable   | A Gram-negative obligate intracellular bacterium, a common cause of community-acquired pneumoniae | THP-1           | ApoA-I                 | [162]      |
| CRP                             | CRP in plasma are elevated in numerous disease states; CRP possesses proinflammatory and proatherogenic properties | THP-1, hPBMC    | ApoA-I, HDL (THP-1)    | [163]      |
| D-(+)-trehalose 6,6'-dibehenate | Synthetic Clec4e (macrophage inducible Ca2+ dependent lectin) ligand | mBMDM           | HDL, serum              | [164]      |
| HSP65                           | Binds to TCR and initiates immune responses, resulting in the production of proinflammatory cytokines | Jurkat cells (human acute T lymphocyte leukemia cell line), primary CD4+ T cells | ApoA-I | [143] |
| JNJ-26854165 (serdemetan)       | A proposed drug, activates p53 | HEK293T; mantle lymphoma cell lines: MAVER-1, JeKo-1; multiple myeloma cell lines: OPM-2, U266 | ApoA-I | [165] |
| Low pH (pH 5.5–6.5 compared with pH 7.5) | hPBMC | ApoA-I, HDL2, human plasma | [166] |
| Low temperature                 | Human skin fibroblasts | Plasma, albumin-depleted plasma, and ApoA-I-depleted plasma | [149] |
| LPS (i.e. endotoxins)           | A polysaccharide found in the outer membrane of Gram-negative bacteria that causes strong immune responses | RAW 264.7        | ApoA-I, HSA            | [167] |
|                                |                            | mBMDM, primary hepatocytes | Mβ-CD | [168] |
| Okadaic acid                   | An inhibitor of protein phosphatases that downregulates caveolin expression | Fibroblasts, SMC | ApoA-I | [26] |
| PAPP-A                          | A metalloproteinase detected in ruptured atherosclerotic plaques | THP-1           | ApoA-I, HDL            | [50] |
| Ritonavir                       | A human immunodeficiency virus protease inhibitor | hPBMC, THP-1    | ApoA-I, HDL (THP-1)    | [170] |
| Trypsin (pretreatment of the cells) | A protease | J774 | ApoA-I | [29] |
| Urotensin II                    | A vasoconstrictor peptide, a ligand of G protein-coupled receptor GPR14 | THP-1 | No acceptor | [171] |
| Vitamins, coenzymes and metabolites | | | | |
| **Stimulation**                 | | | | |
| 9-nitro oleic acid             | Found in human plasma; is generated by nitration of oleic acid by peroxynitrite and acidified nitrite | J774           | HDL                    | [172] |
| Calcitriol [1,25-dihydroxyvitamin D3 or 1,25-(OH)2D3] | Homonally active metabolite of vitamin D | THP-1           | ApoA-I                 | [173] |
| Substance used for cell treatment | Description of the substance                                                                 | Cells\(^a\)                                  | Acceptor of cholesterol | References                           |
|----------------------------------|-----------------------------------------------------------------------------------------------|---------------------------------------------|-------------------------|--------------------------------------|
| Citrulline                       | A precursor of arginine and a byproduct of arginine oxidation by nitric oxide synthase         | hPBMC, THP-1                                | ApoA-I, HDL             | [174]                                |
| Coenzyme Q10                     | A component of the electron transport chain and a natural antioxidant                          | hPBMC, THP-1, J774                         | HDL                     | [175, 176]                           |
| Ethanol                          | Astrocytes, HepG2 (conditioned media)                                                          |                                              | ApoA-I, HDL, ApoE, conditioned medium | [32, 177]                           |
| GSH (glutathione)                | A tripeptide, a thiol antioxidant                                                              | J774                                        | HDL                     | [178]                                |
| Nicotinic acid (niacin)          | Vitamin B3, lipid-lowering drug                                                                | MPM                                         | HDL3                    | [179], [180]                         |
| Spermidine                       | Endogenous polyamine that induces autophagy                                                    | VSMC                                        | ApoA-I                  | [181]                                |
| 7-Ketocholesterol (cholest-5-en-3beta-ol-7-one) | The major form of oxidized cholesterol that is present in oxidized LDL and atherosclerotic lesions | THP-1                                       | ApoA-I                  | [182]                                |
| Acetoacetate                     | A component of ketone bodies                                                                   | RAW 264.7                                   | ApoA-I                  | [49]                                 |
| Carbon monoxide                  | A component of the primary traffic emission; endogenously produced via heme degradation by heme oxygenase | J774                                        | HDL                     | [183]                                |
| Glucose, increased level (20–25 mM) |                                              | RAW 264.7, human glomerular endothelial cells | ApoA-I                  | [126, 184]                          |
| Neopterin                        | A catabolic product of GTP, mainly synthesized by activated macrophages upon stimulation with IFNy; a marker of inflammation | THP-1                                       | ApoA-I, HDL             | [185]                                |
| Alpinetin (7-hydroxy-5-methoxyflavanone) | A plant flavonoid abundantly present in Alpinia katsumadai Hayata                                   | THP-1, hPBMC                               | ApoA-I or HDL           | [186]                                |
| Anthocyanins (cyanidin-3-O-beta-glucoside and peonidin-3-O-beta-glucoside) | Plant pigments; phenolic compound rich in plants                                                | MPM                                         | ApoA-I                  | [73]                                 |
| Arctigenin                       | Antioxidant, antitumor and anti-inflammatory substance from Arctium lappa plant              | THP-1                                       | ApoA-I, HDL2, HDL3      | [187]                                |
| α-Asarone                        | Isolated from Purple perilla extract; known as a component of Acorus tatarinowii herb          | J774                                        | No acceptor             | [188]                                |
| Substance used for cell treatment | Description of the substance | Cells | Acceptor of cholesterol | References |
|----------------------------------|-----------------------------|-------|------------------------|------------|
| Astaxanthin                      | A carotenoid found in salmon, crab, and shrimp | RAW 264.7 | ApoA-I, HDL | [189] |
| BCD1                             | A compound designed for ABCA1 induction based on the structure of rutaecarpine | RAW 264.7 | HDL | [190] |
| Betulin                          | A pentacyclic triterpenoid from the bark of yellow and white birch trees | RAW 264.7 | ApoA-I, HDL | [191] |
| Dihydrocapsaicin                 | A component of capsaicinoids of pepper | THP-1 | ApoA-I | [192] |
| Chrysin                          | A flavonoid that is widely present in honey, propolis, and plant extracts | RAW 264.7 | HDL | [75] |
| Curcumin                         | A polyphenol derived from the rhizome of turmeric (curcuma longa) | Adipocytes | ApoA-I | [193] |
| Dehydroxytrichostatin A (i.e. 9179B) | A compound found by screening of microbial secondary metabolites on the ability to induce ABCA1 | RAW 264.7 | ApoA-I | [194] |
| Diosgenin                        | A steroidal sapogenin present in a variety of plants, including fenugreek, yam root and soy bean | MPM, THP-1 | ApoA-I | [195] |
| Emodin                           | Anthraquinone derivative from the roots of Rheum palmatum | THP-1 | ApoA-I | [196] |
| Ethanol extracts of Brazilian red propolis | Propolis, collected by honey bees from Dalbergia ecastaphyllum (L) Taub. (Leguminosae) | THP-1 | ApoA-I | [197] |
| Hesperetin                       | One of the major citrus flavonoids | THP-1 | ApoA-I | [198] |
| Leoligin                         | The major lignan from edelweiss (Leontopodium nivale subsp. alpinum) | THP-1 | ApoA-I, human plasma | [199] |
| Marrubium vulgare extract        | The plant is widely used in traditional medicine; extract is rich in phenolic compounds | THP-1 | HDL | [200] |
| Methyl protodioscin              | A compound isolated from Dioscorea nipponica makino | THP-1, HepG2 | ApoA-I | [78] |
| Nagilactone B                    | A novel compound, suppresses atherosclerosis in apoE−/− mice | RAW264.7 | ApoA-I, HDL | [201] |
| Paeonol                          | A phenolic component purified from Paonia suffrutiosa (Cortex Moutan) used in traditional Chinese medicine | J774 | ApoA-I | [202] |
| Phellinus linteus polysaccharide extract (at 5–20 μg/mL; inhibition at 100 μg/mL) | An immunomodulatory agent with a molecular weight of 153 Kd | THP-1 | ApoA-I | [203] |
| Piperine                         | The pungent ingredient of black pepper | THP-1 | ApoA-I, human plasma | [71] |
| Substance used for cell treatment | Description of the substance                                                                 | Cells<sup>a</sup> | Acceptor of cholesterol | References     |
|---------------------------------|----------------------------------------------------------------------------------------------|-------------------|-------------------------|----------------|
| Pomegranate peel polyphenols    | Gallic acid, ellagic acid, punicalagins are the main active substances                         | RAW 264.7         | ApoA-I                  | [204]          |
| Protocatechuic acid             | A metabolite of the flavonoid cyanidin-3-O-β-glucoside                                         | MPM, THP-1        | ApoA-I, HDL             | [205]          |
| Purple perilla extract          | Contains rosmarinic acid, methyl rosmarinic acid, caffeic acid, chlorogenic acid and luteolin | J774              | No acceptor             | [188]          |
| Rutaecarpine                    | A compound identified by screening of 20,000 compounds on the stimulation of the promoters of ABCAl and CLA1 (CD36 and lysosomal integral membrane protein II analogous 1) | RAW 264.7         | ApoA-I, HDL             | [206]          |
| Quercetin                       | A natural flavonoid found in red wine, fruits and other natural sources with antioxidant, anti-inflammatory and antiatherosclerosis activities | J774, THP-1, RAW 264.7 | ApoA-I, HDL (J774, RAW 264.7) | [178, 207, 208] |
| Quercetin 7-O-sialic acid       | Combines the cardioprotective effect of quercetin and N-acetyleneuraminic acid                 | RAW 264.7         | ApoA-I, HDL             | [208]          |
| Resveratrol                     | A stilbene with cardioprotective and anti-inflammatory properties                              | THP-1             | Human plasma            | [209]          |
| Riccardin C                     | Non-sterol natural product isolated from liverworts                                             | THP-1             | ApoA-I, no acceptor     | [77]           |
| Sage (Salvia plebeia) weed extract | Contains antioxidants royleanonic acid, hispidulin and eupatorin                             | J774 | No acceptor (just medium) | [210]          |
| Saikosaponin A                  | One of the most active saikosaponins of Radix Bupleuri, a triterpenoid glycoside             | THP-1             | ApoA-I, HDL             | [74]           |
| Salvianolic acid B              | A compound isolated from the Danshen root (Salvia miltiorrhiza Bunge)                        | THP-1             | ApoA-I, HDL2, HDL3      | [62]           |
| Sesame oil                      | Oil from Sesamum indicum                                                                      | MPM               | ApoA-I                  | [211]          |
| Sesamin                         | The most abundant lignan in sesame oil                                                         | RAW 264.7         | HDL                     | [212]          |
| Sesamol                         | A lignan found in sesame oil                                                                   | MPM               | ApoA-I                  | [211]          |
| Tanshinone IIA                  | A lipophilic compound derived from Danshen (Salvia miltiorrhiza)                             | THP-1             | ApoA-I, HDL             | [213]          |
| VAO-PE                          | Unsaponifiable fraction of the oil contains tocopherols, squalene, sterols (schottenol and spinasterol) and phenols (ferulic, syringic and vanillic acid) | THP-1 | HDL, Ox-HDL pre-incubated with VAO-PE | [214]          |
| Walnut oil                      | Walnuts contain high levels of PUFA, both linoleic acid and α-linolenic acid                  | THP-1             | No acceptor             | [67]           |
| Substance used for cell treatment | Description of the substance | Cells<sup>a</sup> | Acceptor of cholesterol | References |
|----------------------------------|-----------------------------|------------------|------------------------|------------|
| Wogonin                          | A component of *Scutellaria baicalensis* Georgi extracts | J774             | No acceptor            | [215]      |
| Zerumbone                        | A cyclic sesquiterpene isolated from Zingiber zerumbet Smith | THP-1            | ApoA-I                 | [216]      |
| **Inhibition**                   |                             |                  |                        |            |
| Cigarette smoke                  | Smoking a cigarette with a filter containing 14 mg of tar and 0.9 mg of nicotine was passed through 50 ml of culture medium | J774             | HDL                    | [217]      |
| Nicotine                         | Considered a pro-atherogenic component in tobacco | hPBMC            | ApoA-I                 | [218]      |

<sup>a</sup> In many cases, cells were treated with substances to differentiate to macrophages (e.g. by phorbol 12-myristate 13-acetate, macrophage colony-stimulating factor, or granulocyte/macrophage colony-stimulating factor), to induce expression of ABCA1 (e.g. by cpt-cAMP, TO-901317, or 22-OH + 9cRA), and transformed to foam cells (e.g. by Ac-LDL).

<sup>b</sup> The same factor stimulates and inhibits, depending on the cells, acceptor, and cholesterol depletion.

<sup>c</sup> Statin description is given according to McFarland et al. [219]
The distribution of activators and inhibitors between particular pathways is shown in Fig. 2. Importantly, the substances are distributed non-uniformly among different pathways; the ‘biological oxidations’ pathway includes mostly substances with an activating effect on cholesterol efflux (all-trans retinoic acid, ethanol, 17β-estradiol, progesterone, hydrocortisone, resveratrol), while signaling by the G protein-coupled receptor and protein tyrosine kinase 6 pathways include substances with an inhibiting effect (oleic and eicosapentaenoic acids). ‘Biological oxidations’ include biotransformation of xenobiotics and endogenous compounds in the liver, kidneys, gut and lungs. As far as chemicals that undergo functionalization, the electrophilic or nucleophilic species can be detrimental to biological systems. Electrophiles can react with electron-rich macromolecules such as proteins, DNA and RNA by covalent interaction, while nucleophiles have the potential to interact with biological receptors [221].

Thus, in addition to nuclear receptor ligands and their precursors activating cholesterol efflux and lipoprotein metabolism, and widely used in clinics (bezafibrate and fenofibric acid [222], pioglitazone [223], telmisartan [224]), targeting biological oxidation processes looks promising for the correction of inefficient reverse cholesterol transport in humans. For instance, the stimulating effect was described for chloroquine [225], diosgenin [226], 17β-estradiol [227], all-trans retinoic acid [228], ethanol [229], spermidine [230, 231], resveratrol [232] and 9-cis-retinoic acid [233].

### 3 Conclusions

We performed a comprehensive analysis of the various substances influencing cholesterol efflux, with pathway enrichment using the Reactome database. The activators and inhibitors of cholesterol efflux are non-uniformly distributed among different pathways. The substances influencing biological oxidation activate cholesterol efflux, and the substances influencing signaling by GPCR and PTK6 inhibit efflux. This analysis may be useful in the targeted therapy of structural and functional HDL deficiency.
Table 2 Substances and pathways influencing cellular cholesterol efflux (ChEBI and Reactome pathway indexes are included)

| Activator                                                                 | R-HSA-112316 | R-HSA-381340 | R-HSA-1428517 | R-HSA-163685 | R-HSA-196854 | R-HSA-211859 | R-HSA-897868 | R-HSA-400206 | R-HSA-8957322 | R-HSA-71291 | R-HSA-446728 | R-HSA-166520 | R-HSA-195721 | R-HSA-2187338 | R-HSA-372790 | R-HSA-5362517 |
|--------------------------------------------------------------------------|--------------|--------------|---------------|--------------|--------------|--------------|--------------|--------------|--------------|-------------|--------------|--------------|--------------|--------------|--------------|--------------|
| 2981 Baicalin                                                            |●●●           |●●●           |               |●            |●            |●            |●            |●●           |●●●          |●●          |●●●          |●●●          |●●●          |●●●          |●●●          |●●●          |
| 3086 Betulin                                                             |●●●          |●●●          |               |●●           |●            |●            |●            |●●●          |●●●          |●●●          |●●          |●●●          |●●●          |●●●          |●●          |●●●          |
| 3638 Chloroquine                                                         |●●●          |●            |               |●●           |●●●          |●●          |●●          |●●          |●●●          |●●●          |●●          |●            |●            |●●          |●●          |●            |
| 4551 Digoxin                                                            |●            |●●●          |               |●            |●●●          |●            |●●          |●●          |●●●          |●●●          |●●●          |●●●          |●●●          |●●●          |●●          |
| 4629 Diosgenin                                                           |●●●          |●●●          |               |●●            |●●●          |●            |●●          |●            |●●●          |●●●          |●●●          |●●●          |●●●          |●●●          |●●          |
| 4708 Doxazosin                                                          |●●●          |●●●          |               |●●●          |●●●          |●            |●            |●           |●●●          |●●●          |●●●          |●●●          |●●●          |●●●          |●●          |
| 6426 Leupeptin                                                          |●            |●●          |               |●            |●            |●●          |●            |●            |●●●          |●●●          |●●●          |●●●          |●●●          |●●●          |●           |
| 15365 Aspirin                                                           |●●●          |●●●          |               |●●             |●            |●●          |●            |●            |●●●          |●●●          |●●●          |●●●          |●●●          |●●●          |●●●          |
| 15367 All-trans retinoic acid (tretinoin)                               |●●●          |●●●          |               |●●●          |●●●          |●            |●●          |●            |●●●          |●●●          |●●●          |●●●          |●●●          |●●●          |●●          |
| 15940 Nicotinic acid (niacin)                                           |●            |●●          |               |●            |●            |●●          |●            |●            |●●●          |●●●          |●●●          |●●●          |●●●          |●●●          |●●          |
| 16236 Ethanol                                                           |●●●          |●●●          |               |●●●          |●●●          |●            |●●          |●            |●●●          |●●●          |●●●          |●●●          |●●●          |●●●          |●●          |
| 16243 Quercetin                                                         |●            |●●          |               |●            |●●●          |●            |●●          |●            |●●●          |●●●          |●●●          |●●●          |●●●          |●●●          |●           |
| 16469                                                                   |●●●          |●●●          |               |●●            |●            |●●          |●            |●●          |●●●          |●●●          |●●●          |●●●          |●●●          |●●●          |●●          |
| 17β-estradiol                                                           |●●●          |●●●          |               |●●●          |●●●          |●            |●●          |●            |●●●          |●●●          |●●●          |●●●          |●●●          |●●●          |●●          |
| 16610 Spermidine                                                        |●●●          |●●●          |               |●●●          |●●●          |●            |●●          |●            |●●●          |●●●          |●●●          |●●●          |●●●          |●●●          |●●          |
| 16856 GSH (glutathione)                                                 |●            |●●●          |               |●●            |●            |●●          |●            |●●          |●●●          |●●●          |●●●          |●●●          |●●●          |●●●          |●●          |
| 17026 Progesterone                                                      |●●●          |●●●          |               |●●●          |●●●          |●            |●●          |●            |●●●          |●●●          |●●●          |●●●          |●●●          |●●●          |●●          |
| 17351 α-Linolenic acid                                                 |●●●          |●●●          |               |●●●          |●●●          |●            |●●          |●            |●●●          |●●●          |●●●          |●●●          |●●●          |●●●          |●●          |
| 17579 All-trans β-carotene                                              |●●●          |●●●          |               |●●            |●            |●●          |●            |●●          |●●●          |●●●          |●●●          |●●●          |●●●          |●●●          |●●          |
| 17650 Hydrocortisone (i.e. cortisol)                                    |●●●          |●●●          |               |●●●          |●●●          |●            |●●          |●            |●●●          |●●●          |●●●          |●●●          |●●●          |●●●          |●           |
Table 2 (continued)

| R-HSA-112316 | R-HSA-381340 | R-HSA-1428517 | R-HSA-163685 | R-HSA-196854 | R-HSA-211859 | R-HSA-897886 | R-HSA-400206 | R-HSA-8957322 | R-HSA-71291 | R-HSA-446728 | R-HSA-166520 | R-HSA-195721 | R-HSA-2187338 | R-HSA-372790 | R-HSA-5362517 |
|--------------|--------------|---------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|
| Neuronal System | Neuronal System | Neuronal System | Neuronal System | Neuronal System | Neuronal System | Neuronal System | Neuronal System | Neuronal System | Neuronal System | Neuronal System | Neuronal System | Neuronal System | Neuronal System | Neuronal System | Neuronal System |
| R-HSA-381340 | R-HSA-1428517 | R-HSA-163685 | R-HSA-196854 | R-HSA-211859 | R-HSA-897886 | R-HSA-400206 | R-HSA-8957322 | R-HSA-71291 | R-HSA-446728 | R-HSA-166520 | R-HSA-195721 | R-HSA-2187338 | R-HSA-372790 | R-HSA-5362517 |
| Integration of energy metabolism | The citric acid (TCA) cycle and respiratory electron transport | Metabolism of vitamins and cofactors | Metabolism of lipids by PPAR-α | Regulation of lipid metabolism by PPAR-α | Metabolism of steroids | Metabolism of amino acids and derivatives | Cell junction organization | Signaling by NGF | Signaling by Wnt | Signaling by GPCR | Signaling by retinoic acid |

17823 Calcitriol
18211 Citrulline
23359 Colchicine
27881 Resveratrol
36062 Protocathecruic acid
46245 Coenzyme Q10
47499 Imipramine
50122 Rosiglitazone
50648 9-cis-retinoic acid
63892 Zerumbone
65329 LY294002
84612 cpt-cAMP

**Inhibitor**
8772 Raloxifene
9635 Toremifene
15344 Acetoacetate
16196 Oleic acid
16551 D-(-)-trehalose
6,6'-dibehenate
17245 Carbon monoxide
25675 Oligomycin
| R-HSA-112316 | R-HSA-381340 | R-HSA-1428517 | R-HSA-163685 | R-HSA-196854 | R-HSA-211859 | R-HSA-8978868 | R-HSA-400206 | R-HSA-8957322 | R-HSA-71291 | R-HSA-446728 | R-HSA-166520 | R-HSA-195721 | R-HSA-2187338 | R-HSA-372790 | R-HSA-5362517 |
|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
| R-HSA-381340   | Neuronal System | Transcriptional regulation of white adipocyte differentiation | The citric acid (TCA) cycle and respiratory electron transport | Integration of energy metabolism | Metabolism of vitamins and cofactors | Fatty acid metabolism | Regulation of lipid metabolism by PPAR-α | Metabolism of steroids | Metabolism of amino acids and derivatives | Cell junction organization | Signaling by NGF | Signaling by Wnt | Visual phototransduction | Signal by GPCR | Signaling by retinoic acid |

| 28364 Eicosapentaenoic acid | ● | ● | ● | ● |
| 30740 EGTA | ● | ● | ● | ● |
| 34159 15d-PGJ2 | ● | ● | ● | ● |
| 38545 Rosuvastatin | ● | ● | ● | ● |
| 41423 Celecoxib | ● | ● | ● | ● |
| 41774 Tamoxifen | ● | ● | ● | ● |
| 41879 Dexamethasone | ● | ● | ● | ● |

| R-HSA-73887 | R-HSA-8848021 | R-HSA-5619115 | R-HSA-5663202 | R-HSA-5579029 | R-HSA-5663084 | R-HSA-168256 | R-HSA-174824 | R-HSA-425366 | R-HSA-425397 | R-HSA-392499 | R-HSA-400253 | R-HSA-5653656 | R-HSA-73857 | R-HSA-8963743 |
|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
| R-HSA-73887   | Death receptor signaling | PTK6 | Disorders of transmembrane transporters | Diseases of signal transduction | Metabolic disorders of biological oxidation enzymes | Diseases of carbohydrate metabolism | Immune system | Plasma lipoprotein assembly, remodeling, and clearance | Transport of bile salts and organic acids, metal ions and amine compounds | Transport of vitamins, nucleosides, and related molecules | Metabolism of proteins | Circadian Clock | Vesicle-mediated transport | RNA Polymerase II Transcription | Digestion and absorption |

**Activator**

| 2981 Baicalin | ● | ● | ● | ● |
| 3086 Betulin | ● | ● | ● | ● |
| 3638 Chloroquine | ● | ● | ● | ● |
| 4551 Digoxin | ● | ● | ● | ● |
| 4629 Diosgenin | ● | ● | ● | ● |
| 4708 Doxazosin | ● | ● | ● | ● |
| R-HSA-73887 Death receptor signaling | R-HSA-8848021 Signaling by PTK6 | R-HSA-5619115 Disorders of trans-membrane transporters | R-HSA-5663084 Diseases of signal transduction | R-HSA-5579029 Metabolic disorders of biological oxidation enzymes | R-HSA-168256 Immune system | R-HSA-174824 Plasma lipo-protein assembly, remodeling, and clearance | R-HSA-425366 Transport of bile salts and organic acids, metal ions and amine compounds | R-HSA-425397 Transport of vitamins, nucleosides, and related molecules | R-HSA-392499 Metabolism of proteins | R-HSA-400253 Circadian Clock | R-HSA-5653656 Vesicle-mediated transport | R-HSA-73857 RNA Polymerase II Transcription | R-HSA-8963743 Digestion and absorption |
|-----------------------------------|---------------------------------|------------------------------------------------|---------------------------------|---------------------------------|-------------------------------|------------------------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| 6426 Leupeptin                    |                                 |                                                |                                 |                                 |                               |                                                |                                 |                                 |                                 |                                 |                                 |                                 |                                 |
| 15365 Aspirin                     |                                 |                                                |                                 |                                 |                               |                                                |                                 |                                 |                                 |                                 |                                 |                                 |                                 |
| 15367 All-trans retinoic acid (retinoin) |                                 |                                                |                                 |                                 |                               |                                                |                                 |                                 |                                 |                                 |                                 |                                 |                                 |
| 15940 Nicotinic acid (niacin)     |                                 |                                                |                                 |                                 |                               |                                                |                                 |                                 |                                 |                                 |                                 |                                 |                                 |
| 16236 Ethanol                     |                                 |                                                |                                 |                                 |                               |                                                |                                 |                                 |                                 |                                 |                                 |                                 |                                 |
| 16243 Quercetin                   |                                 |                                                |                                 |                                 |                               |                                                |                                 |                                 |                                 |                                 |                                 |                                 |                                 |
| 16469 17β-estradiol               |                                 |                                                |                                 |                                 |                               |                                                |                                 |                                 |                                 |                                 |                                 |                                 |                                 |
| 16610 Spermidine                  |                                 |                                                |                                 |                                 |                               |                                                |                                 |                                 |                                 |                                 |                                 |                                 |                                 |
| 16856 GSH (glutathione)           |                                 |                                                |                                 |                                 |                               |                                                |                                 |                                 |                                 |                                 |                                 |                                 |                                 |
| 17026 Progesterone                |                                 |                                                |                                 |                                 |                               |                                                |                                 |                                 |                                 |                                 |                                 |                                 |                                 |
| 17351 α-Linolenic acid            |                                 |                                                |                                 |                                 |                               |                                                |                                 |                                 |                                 |                                 |                                 |                                 |                                 |
| 17579 All-trans β-carotene        |                                 |                                                |                                 |                                 |                               |                                                |                                 |                                 |                                 |                                 |                                 |                                 |                                 |
| 17650 Hydrocortisone (i.e. cortisol) |                                 |                                                |                                 |                                 |                               |                                                |                                 |                                 |                                 |                                 |                                 |                                 |                                 |
| 17823 Calcitriol                  |                                 |                                                |                                 |                                 |                               |                                                |                                 |                                 |                                 |                                 |                                 |                                 |                                 |
| 18211 Citrulline                  |                                 |                                                |                                 |                                 |                               |                                                |                                 |                                 |                                 |                                 |                                 |                                 |                                 |
| 23359 Colchicine                  |                                 |                                                |                                 |                                 |                               |                                                |                                 |                                 |                                 |                                 |                                 |                                 |                                 |
Table 2 (continued)

| R-HSA-73887 Death receptor signaling | R-HSA-884021 Signaling by PTK6 | R-HSA-5619115 Disorders of transmembrane transporters | R-HSA-5663202 Diseases of signal transduction | R-HSA-5579029 Metabolic disorders of biological oxidation enzymes | R-HSA-5663084 Diseases of carbohydrate metabolism | R-HSA-168256 Immune system | R-HSA-174824 Plasma lipoprotein assembly, remodeling, and clearance | R-HSA-425366 Transport of bile salts and organic acids, metal ions and amine compounds | R-HSA-425397 Transport of vitamins, nucleosides, and related molecules | R-HSA-392499 Metabolism of proteins | R-HSA-400253 Circadian Clock | R-HSA-5653656 Vesicle-mediated transport | R-HSA-73857 RNA Polymerase II Transcription | R-HSA-8963743 Digestion and absorption |
|-------------------------------------|--------------------------------|---------------------------------------------------|-----------------------------------------------|--------------------------------------------------|---------------------------------------------|--------------------------------|-----------------------------------------|-----------------------------------------------|-----------------------------------------------|----------------------------------------------|----------------------------------|--------------------------------------------|----------------------------------|----------------------------------|
| 27881 Resveratrol                   | ⬤                             |                                                   |                                               |                                                 |                                             |                                             |                                        |                                               |                                              |                                              |                                             |                                           |                                             |
| 36062 Protocatechuc acid            | ⬤                             |                                                   |                                               |                                                 |                                             |                                             |                                        |                                               |                                              |                                              |                                             |                                           |                                             |
| 46245 Coenzyme Q10                  |                               |                                                   |                                               |                                                 |                                             |                                             |                                        |                                               |                                              |                                              |                                             |                                           |                                             |
| 47499 Imipramine                    |                               |                                                   |                                               |                                                 |                                             |                                             |                                        |                                               |                                              |                                              |                                             |                                           |                                             |
| 50122 Rosiglitazone                 |                               |                                                   |                                               |                                                 |                                             |                                             |                                        |                                               |                                              |                                              |                                             |                                           |                                             |
| 50649 9-cis-retinoic acid           |                               |                                                   |                                               |                                                 |                                             |                                             |                                        |                                               |                                              |                                              |                                             |                                           |                                             |
| 63892 Zerumbone                     | ⬤                             |                                                   |                                               |                                                 |                                             |                                             |                                        |                                               |                                              |                                              |                                             |                                           |                                             |
| 65329                                |                               |                                                   |                                               |                                                 |                                             |                                             |                                        |                                               |                                              |                                              |                                             |                                           |                                             |
| LY294002                             |                               |                                                   |                                               |                                                 |                                             |                                             |                                        |                                               |                                              |                                              |                                             |                                           |                                             |
| 84612 cpt-cAMP                       |                               |                                                   |                                               |                                                 |                                             |                                             |                                        |                                               |                                              |                                              |                                             |                                           |                                             |
| **Inhibitor**                       |                               |                                                   |                                               |                                                 |                                             |                                             |                                        |                                               |                                              |                                              |                                             |                                           |                                             |
| 8772 Raloxifene                      | ⬤                             |                                                   |                                               |                                                 |                                             |                                             |                                        |                                               |                                              |                                              |                                             |                                           |                                             |
| 9635                                 |                               |                                                   |                                               |                                                 |                                             |                                             |                                        |                                               |                                              |                                              |                                             |                                           |                                             |
| Toremifene                           |                               |                                                   |                                               |                                                 |                                             |                                             |                                        |                                               |                                              |                                              |                                             |                                           |                                             |
| 15344 Acetoacetate                  |                               |                                                   |                                               |                                                 |                                             |                                             |                                        |                                               |                                              |                                              |                                             |                                           |                                             |
| 16196 Oleic acid                    |                               |                                                   |                                               |                                                 |                                             |                                             |                                        |                                               |                                              |                                              |                                             |                                           |                                             |
| 16551 D-(-)-trehalose                |                               |                                                   |                                               |                                                 |                                             |                                             |                                        |                                               |                                              |                                              |                                             |                                           |                                             |
| 6,6’-dibehenate                     |                               |                                                   |                                               |                                                 |                                             |                                             |                                        |                                               |                                              |                                              |                                             |                                           |                                             |
| 17245 Carbon monoxide                |                               |                                                   |                                               |                                                 |                                             |                                             |                                        |                                               |                                              |                                              |                                             |                                           |                                             |
Table 2 (continued)

| R-HSA-73887 | R-HSA-884021 | R-HSA-5619115 | R-HSA-5579029 | R-HSA-5663084 | R-HSA-168265 | R-HSA-174824 | R-HSA-425366 | R-HSA-425397 | R-HSA-392499 | R-HSA-400253 | R-HSA-565365 | R-HSA-73857 | R-HSA-896374 |
|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
| Death receptor signaling | Signaling by PTK6 | Disorders of transmembrane transporters | Metabolic disorders of biological oxidation enzymes | Diseases of carbohydrate metabolism | Immune system | Plasma lipoprotein assembly, remodeling, and clearance | Transport of bile salts and organic acids, metal ions and amine compounds | Transport of vitamins, nucleosides, and related molecules | Metabolism of proteins | Circadian Clock | Vesicle-mediated transport | RNA Polymerase II Transcription | Digestion and absorption |

25675 Oligomycin  
28364 Eicosapentaenoic acid  
30740 EGTA  
34159 15d-PGJ2  
38545 Rosuvastatin  
41423 Celecoxib  
41774 Tamoxifen  
41879 Dexamethasone

GPCR G protein-coupled receptor, NGF nerve growth factor, PPAR peroxisome proliferator-activated receptor, black circle (●) denotes the action of a particular substance
Compliance with Ethical Standards

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