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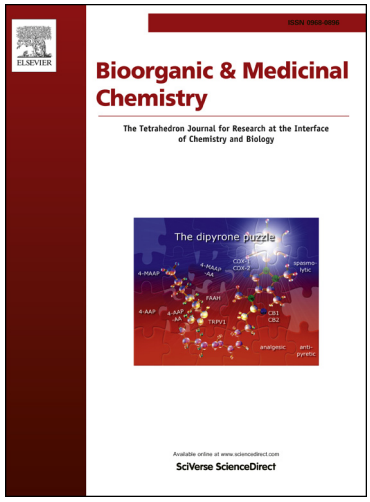

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Design, synthesis and biological evaluation of N, N-3-phenyl-3-benzylaminopropanamide derivatives as novel Cholesteryl Ester Transfer Protein inhibitor

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ABSTRACT

A series of N,N-3-phenyl-3-benzylaminopropanamide derivatives were identified as novel CETP (Cholesteryl ester transfer protein) inhibitors. In our previous study, lead compound **L10** was discovered by pharmacophore-based virtual screening (Dong-Mei Zhao et al, Chin. Chem. Lett, 25, 299). Based on **L10** (IC_{50} 8.06 μM), compound **HL6** (IC_{50} 10.7 μM) was discovered following systematic structure variation and biological tests. Further optimization of the structure−activity relationship (SAR) resulted in N,N-3-phenyl-3-benzylaminopro panamides derivatives as novel CETP inhibitors. They were synthesized and evaluated against CETP by BODIPY-CE fluorescence assay. Among them, **HL16** (IC_{50} 0.69 μM) was a highly potent CETP inhibitor *in vitro*. In addition, **HL16** exhibited favorable HDL-C enhancement and LDL-C reduction *in vivo* by hamster. The molecular docking of **HL16** into the CETP was performed. The binding mode demonstrated that **HL16** occupied the CETP binding site and formed interactions with the key amino acid residues.

Keywords: CETP inhibitor; N,N-3-phenyl-3-benzylaminopropanamides derivatives; Molecular docking

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1. Introduction

Cardiovascular disease (CVD) is the leading cause of death and morbidity in developed nations.[1-3] Elevated levels of low density lipoprotein-cholesterol (LDL-C) and decreased levels of high density lipoprotein-cholesterol (HDL-C) are considered to be the major risk factors for cardiovascular events.[4,5] Plasma cholesteryl ester transfer protein (CETP) is the key modulator of cholesterol ester inverse transport, facilitating the transfer of cholesteryl esters from high density lipoprotein to low density lipoprotein cholesterol and very low density lipoprotein-cholesterol (VLDL-C). CETP, secreted mainly from the liver, has 476 amino acid residues. It is a 74-kDa hydrophobic glycoprotein which circulates in plasma, primary bound to HDL-C.[12,13] CETP acts to elevated LDL-C levels and reduced HDL-C levels therefore it is considered to be a proatherogenic factor. Inhibition of CETP activities is considered to be one of the most effective mechanisms to elevate the level of HDL-C.[6-8] Epidemiological studies showed that for each 1.0 mmol/dL decrease in plasma LDL-C, there is approximately 22% decrease in cardiovascular risk[3]. The statins, which are HMG-CoA reductase inhibitors, have been used to reduce LDL-C levels in patients at risk for cardiovascular disease in clinical treatment. However, many patients on statins and other lipid lowering treatments remain at an unacceptably high risk of having a future CVD event.[8-11] Development of novel cholesterol lowering drugs is of utmost importance for treating cardiovascular diseases.

Torcetrapib is the first inhibitor into phase III clinical trial with potent CETP inhibition (IC_{50} 50 nM). However, it was prematurely terminated due to more mortality in the torcetrapib/atorvastatin group than the atorvastatin group.[14-16] Dalcetrapib showed modest potency, whose phase III clinical trial was also terminated due to the failure to show a clinically meaningful reduction in cardiovascular (CV) events.[17,18] In recent years, potential CETP inhibitors anacetrapib and evacetrapib have also entered phase III clinical trials. The clinical trial data showed that both anacetrapib and evacetrapib led to elevated HDL-C and lowered LDL-C while avoiding torcetrapib's side effects.[19-22] TA-8995, a newly-developed CETP inhibitor, has successfully completed phase IIb trial in 2014. The phase II clinical trial data showed that TA-8995 reduced LDL-C levels by 45. 3%, whereas increased HDL-C levels by up to 179. 1%, and without serious adverse events or signs of liver toxic effects.[24,25] It remains to be seen whether these drug candidates will prevail eventually.

Despite the setbacks from the terminations of torcetrapib and dalcetrapib, great progress has been made in illuminating the inhibition mechanism of CETP. A co-crystal structure of CETP with

torcetrapib was published in 2012.[14] It was reported that the mechanism of lipid transfer is through the hydrophobic tunnel between HDL-C and LDL-C, demonstrating the interactions of small molecule compounds with CETP at the atomic level. In our previous study, based on this structure (compounds 1-4 shown in Scheme 1), a pharmacophore-based virtual screening campaign was carried out several years ago and a lead compound **L10** was identified to show modest inhibitory activity against CETP. In this study, using **L10** as a starting point, we attempted to identify better lead compounds with more potency and novel structure as small-molecule CETP inhibitors as a therapy for atherosclerosis.

(**Scheme 1.** should be listed here)

Following the structure-activity relationship (SAR) of compound **L10**, **HL6** of N-cyclohexyl-3-(3,4-dichlorophenyl-4-fluorobenzyl)amino propanamide was discovered. It was shown to have a mild CETP inhibition (IC_{50} 10.7 μM). Molecular docking showed that **HL6** are located at the binding site cavity of CETP but cannot match with sub-pockets very well. Based on the result, our subsequent studies focused on exploring the propionamide scaffold. Different from most of disclosed inhibitors which require a central core ring for activity, the propionamide is a flexible scaffold as an unusually simple class of CETP inhibitors. This novel class thereby represents a flexibility families exhibiting inhibitory activity against CETP. We hypothesized that propionamide acted as a link to connect potential pharmacophore, thus the formation of modified amide terminus and aniline moiety (Scheme 2) are important to improve CETP inhibition.

We chose preponderant CETP inhibition drug fragments reported in literature as substituents for hybrids. As an initial strategy we studied the replacement of the amide terminus of the propionamide by different heterocycles, naphthene base and alkyl with the aim to achieve CETP affinity and mitigate lipophicility. After the biological evaluation, compound **HL3** with 1-phenylpiperazine as amide terminus scaffold showed the most promising results. Further optimization of **HL3** led to the discovery of compound **HL16** (IC_{50} 0.69 μM) in vitro by BODIPY-CE fluorescence assay, as shown in Scheme 2. Herein, we described the design, synthesis and biological evaluation N,N-3-phenyl-3-benzylaminoprop anamide as novel CETP inhibitors.

(**Scheme 2.** should be listed here)

2. Results and discussion

2.1. Chemistry

Compounds **HL1-HL17** were prepared according to Scheme 3. Overall, they were prepared in 5

steps. The first step was synthesizing the linker of the scaffold by commercially corresponding aniline with acrylic acid through michael reaction at 40 ^{o}C. In this reaction, we found the yield of product from the solvent of acrylic acid was higher than some literature reported acetonitrile or toluene as solvent. The next step **L2** was treated with HOBT, EDCI and DIEA in DMF at 0 °C for 2 h, followed by various substituent aliphatic amine or arylpiperazines by condensation reaction to obtain the key intermediate **L3**. These intermediates were used to in the next step to furnish the desired target compounds **HL1-HL17** by substitution reaction with 4-fluorobenzyl bromide and K_2CO_3 in DMF at 90 ^{o}C. The amide terminus scaffold was synthesized by two steps. Thionyl chloride and 2,2'-azanediyl bis(ethan-1-ol) were used as starting materials to give bis(2-chloroethyl)amine hydrochloride by chlorination, and then the corresponding aryl piperazines were obtained by cyclization.

(**Scheme 3.** should be listed here)

2.2. In vitro activity and Structure-Activity Relationships

(**Table 1.** should be listed here)

Structure−Activity Relationship (SAR) of **N,N-3-phenyl-3-benzylamino propanamides** derivatives **HL1-HL17**

In an attempt to evaluate the ability of various N,N-3-phenyl-3-benzylaminopropanamide derivatives to inhibit CETP, all these new synthetic compounds and reference compound anacetrapib were initially assayed for their inhibitory effects against CETP by BODIPY-CE fluorescence assay with CETP RP Activity Assay Kit (Catalog # RB-RPAK; Roar). The results of compound assay are shown in Table 1. Most of the target compounds exhibit good CETP inhibition activity, while two compounds have especially unexpected activity with IC_{50} >50 μM, indicating that the introduction of propionamide scaffold to fit into the large pocket of CETP increased the inhibition activity. As summarized below, several key structural changes provided critical insights into the general SAR of this series. First, the effect of the N-substituted amide terminus on the inhibition of CETP was examined. Compounds with N-cycloproryl and N-butyl have no inhibition activity, but these with N-tert-butyl **HL7** exhibit IC_{50} of 29.6 μM while IC_{50} of **HL6** with N-hexamethylene is nearly 2.8 fold higher than that of **HL7**. Thus we could conclude that the shape of the hexamethylene moiety seems to influence the potency. **HL3** with 1-phenylpiperazine exhibits nearly two times higher than **HL1** and **HL6**. These results indicate that the improvement of potency is related with the increase in the N-substituted space volume. However, the potency of the 2-(piperazin-1-yl) pyrimidine compound **HL2** is weaker than **HL3**, indicating that

further improvement in potency may increase N-substituted lipophilicity. Then, we were particularly interested in extended linker of 1-phenylpiperazine with 4-methoxyl or 4-ethoxycarbonyl. The results showed that **HL12** or **HL13** salient improved CETP inhibition activities, further indicating that the structure of ethyl 4-(piperazin-1-yl)benzoate is more important to improve CETP inhibition than 1-(4-methoxyphenyl)piperazine.

Next, the modified aniline moiety was examined as shown in Table 1. The small-group substituted aniline moiety caused loss of activity compared with compound **HL3**. When we increased the space volume of aniline with 3-biphenyl or 3-phenoxyl molecules, the result exhibited that **HL16** with 3-phenoxyaniline has especially outstanding activity with IC_{50} of 0.69 μM. Therefore we can conclude that 3-phenoxyaniline provided an important contribution to the potency.

2.3. In vivo study in hamsters

Based on the result of *in vitro* CETP inhibitory assay, potent inhibitor **HL16** was selected for the *in vivo* assay. Male Golden Syrian hamster (8 weeks old, weight 120-130 g) were randomly divided into control and treated groups (n = 6) by weight. Hamsters were placed on high cholesterol and lipid diet for 5 weeks, and dyslipidemia model was induced. After oral administration of **HL16** (formulation ethanol/cremophor/salin=5:5:90) at dose of 30 mg/kg/day for two weeks, the blood samples were drawn from orbit and the serum lipid levels were measured. The weights of hamsters were also observed during the dosing process. The results indicated that LDL-C was reduced by 24.6% and HDL-C was increased by 21.7%. The results were presented in Figure 1, confirming that **HL16** had significant lipid regulating potency.

(**Figure 1.** should be list here)

2.4. Molecular docking of compound HL16 in CETP

To further elucidate the binding pattern observed, molecular docking of the most potent inhibitor **HL16** were performed in the binding site cavity of CETP. Crystal structure of CETP (PDB ID: 4EWS) and inhibitors were both pretreated by Discovery Studio 3.5. All docking runs were utilizing LigandFit Dock protocol of Discovery Studio 3.5. The image files are generated by the Accelrys DS visualizer 4.0 systems. The binding modes of compound **HL16** and CETP were depicted in Figure 2 A and B, which revealed that the inhibitor is well occupied in the binding pocket. As showed in Figure 2 A, flexibility of 3-phenoxyaniline occupied the important sub-pocket, ethyl 4-(piperazin-1-yl)benzoate located at the deep of CETP. The amino acid residues which had interaction with inhibitor were labeled. As

illustrated in Figure 2 B, hydrogen atom on the piperazidine and the oxygen atom on the main chain of Ser230 contribute to the hydrogen bonding interaction together, being a probable explanation for its activity. One hydrophobic interaction is formed between the 3-phenoxyl and Ile15. Two hydrophobic bonding are formed between the aniline ring of **HL16** and Leu23 and Cys13. One π-π interaction is formed between the benzene ring of the compound **HL16** and phe441, and one hydrophobic reaction is formed between Leu261 and benzene ring. Two hydrophobic interactions are formed between ethoxycarbonyl and Leu29 and Val136, which may be helpful to improve its activity.[14]

(**Figure 2 A.** should be list here)

(**Figure 2 B.** should be list here)

3. Conclusion

In the present study, we report a novel CETP inhibitor and biological evaluation *in vitro* by BODIPY-CE fluorescence assay. Most of the synthetic compounds showed mild inhibition activity, fortunately, several representatives of N,N-3-phenyl-3-benzylaminopropanamides derivatives were identified to exhibit remarkable potent CETP inhibition. After limited further structure-activity relationship study, compounds **HL16** with ethyl 4-(piperazin-1-yl)benzoate and 3-phenoxyaniline were found to have potent CETP inhibition. **HL16** exhibits an IC_{50} of 0.69 μM *in vitro* and significant lipid regulating activity *in vivo* in hamster. In addition, Molecular docking of **HL16** into the CETP was performed, demonstrating that **HL16** occupies the CETP binding site, and forms interaction with key amino acid residues. In summary, these results demonstrate that the newly synthetic compounds have the potential to be developed as leads and novel scaffold. It is highly expected that through further structural modifications, the novel scaffold will produce promising CETP inhibition agents.

4. Experimental

4.1. Chemistry

4.1.1. Materials

All solvents were purchased from Aladdin (Shanghai China) and used without further purification. All the chemicals were purchased from commercial sources with purity>98%, and melting points (mp.) were determined in open capillaries on a Buchi 353 melting point apparatus (Buchi Labortechnik, Flawil, Switzerland) without further correction. The solvents used for moisture sensitive reactions were distilled and performed under argon atmosphere. The purity and homogeneity of the compounds were assessed by TLC and HPLC chromatography either on a glass column using silica gel(100-200 mesh).

Mass spectra were taken in ESI mode on Agilent 1100 LC-MS (Agilent, Palo Alto, CA, USA). High resolution accurate mass determinations (HRMS) for all final target compounds were obtained on a Bruker Micromass Time of Flight mass spectrometer equipped with electrospray ionisation (ESI). NMR spectra were recorded at 600 MHz for ^{1}H and 600 MHz for ^{13}C on a Bruker spectrometer with TMS as an internal standard, $CDCl_3$ or DMSO-d_6 as solvent. The chemical shifts (d) were reported in ppm relative to internal tetramethylsilane. Peak multiplicities were expressed as follows: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublet; m, multiplet.

4.1.2. 3-(3,4-Dichlorophenylamino) propanoic acid

A mixture of 3,4-dichloroaniline (4.6 g, 28.4 mmol), acrylic acid (15.0 mL) and 10% hydrochloric acid(0.5 mL) was added to a 250 mL three-necked round bottom flask. The solution was heated to 40 ^{o}C for 2 h and then cooled to room temperature.[23] The reaction mixture was poured into ice water. The precipitate was filtered, washed with water, and then purified by column chromatography (silica gel) to give target product (3.5 g, 72.1% yield) as a yellow solid. mp: 49.5-51.2 ^{o}C.

4.1.3. 4- substituted -phenylpiperazine (L7)

In a solution of 2,2'-azanediylbis(ethan-1-ol) (11.0 g, 104.7 mmol), dissolved in dry DCM (100.0 mL), thionyl chloride (37.4 g, 314.0 mmol) was added in a slow stream at below 5 ^{o}C with ice bath, and then the mixture was heated at reflux for 4.5 h, and then cooled to room temperature. The precipitate was filtered, washed with ethanol, dried in infrared lamp and obtained as a white solid bis(2-chloroethyl)aminehydrochloride, mp: 212-216 ^{o}C.

A mixture of bis(2-chloroethyl)aminehydrochloride (7.3 g, 41.0 mmol), K_2CO_3 (5.7 g, 41.3 mmol), dissolved in 1-butanol, the substituted aniline (41.0 mmol) was added. The solution was heated at reflux for 8 h and then cooled to room temperature. The precipitate was filtered, washed with water, dried in infrared lamp and obtained as a white solid used directly in the next step without further purification.

4.1.4. 3-(3,4-Dichlorophenylamino)propanamides

In a solution of 3-(3,4-dichlorophenylamino) propanoic acid (0.7 g, 3.0 mmol) dissolved in dry DMF (10.0 mL)1-hydroxybenzotrizole (HOBt, 0.4 g, 3.0mmol) and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDCI, 0.6 g, 3.0 mmol) was added. The mixture was stirred at room temperature for 1.5 h, and then the DIEA (0.8 g, 6.0 mmol) and the corresponding amine (3.0 mmol) were added. The reaction mixture was stirred at room temperature for 2 h and poured into ice water.

The precipitate was filtered, washed with water, dried in infrared lamp and obtained as a white solid used directly in the next step without further purification.

4.1.4. General procedure for the synthesis of HL1-HL17

To a solution of 3-(3,4-dichlorophenylamino) propanamides (1.0 mmol) in dry DMF (10.0 mL) was added potassium carbonate (2.0 mmol) and 1-(bromomethyl)-4-fluorobenzene (2.0 mmol). The solution was heated to 90 ^{o}C for 10 h and then cooled to room temperature. The reaction mixture was poured into ice water. The mixture was extracted with ethyl acetate. The organic layer was washed with water, and then dried over Na_2SO_4. Solvent was removed under reduced pressure and the resulting residue was purified by column chromatography (10% EtOAc/petroleum ether, silica) or recrystallization (petroleum ether/ethyl acetate) to provide the title **HL1** to **HL17** as a white to yellow solid.

4.1.4.1. 3-(3,4-dichlorophenyl-4-fluorobenzyl)amino-1-morpholinopropan-1-one (HL1)

Compound HL1 was obtained as a light white solid. Yield: 35.4%; mp: 133.4-134.2 ^{o}C. ^{1}H NMR(600 MHz, $CDCl_3$): δ 7.25-7.19 (m, 3H), 7.16-7.01 (m, 2H), 6.98(d, 2H, J = 2.97 Hz), 6.73 (dd, 1H, J_1 = 2.97 Hz, J_2 = 8.97 Hz),6.51 (m, 1H), 4.51 (s, 2H), 3.77 (t, 2H, J = 7.08 Hz), 3.64-3.58 (m, 6H), 3.37-3.36 (m, 2H), 2.60-2.55 (d, 2H, J = 6.93 Hz). ^{13}C NMR (150 MHz, DMSO-d_6): δ 30.18, 39.99, 47.47, 52.91, 66.44, 66.48, 112.42, 112.90, 113.55, 115.72, 115.86, 117.39, 128.73, 128.78, 131.00, 132.01, 148.11, 160.32, 161.94, 169.90. ESI-MS (m/z): 411.1$[M+H]^+$. HRMS calcd for $C_{20}H_{21}Cl_2FN_2O_2Na$, $[M+Na]^+$, 433.0862; found 433.0861.

4.1.4.2. 3-(3,4-dichlorophenyl-4-fluorobenzyl)amino-1-(4-(pyrimidin-2-yl)piperazin-1-yl)propan-1-one (HL2)

Compound HL2 was obtained as a light white solid. Yield: 34.69%; mp: 151.1-151.7 ^{o}C. ^{1}H NMR (600MHz, $CDCl_3$) δ 8.33(d, J = 4.74Hz, 2H), 7.19(d, J = 8.94Hz, 1H), 7.16-7.11(m, 2H), 7.03-6.96(m, 2H), 6.75(d, J = 2.94Hz, 1H), 6.57-6.49(m, 2H), 4.54(s, 2H), 3.83-3.79(m, 6H), 3.71-3.67(m, 2H), 3.47-3.44(m, 2H), 2.66(t, J = 7.05Hz, 2H). ^{13}C NMR (600 MHz, DMSO-d_6): δ 169.78, 159.06, 147.99, 137.99, 134.61, 131.94, 130.93, 128.68, 117.30, 115.78, 115.64, 113.63, 113.47, 112.82, 107.59, 52.84, 47.44, 44.96, 44.75, 41.04, 40.25, 40.05, 39.91, 39.77, 39.63, 39.49, 30.30. ESI-MS (m/z): 488.1$[M+H]^+$. HRMS calcd for $C_{24}H_{24}Cl_2FN_5ONa$, $[M+Na]^+$, 510.1240; found 510.1240.

4.1.4.3. 3-(3,4-dichlorophenyl-4-fluorobenzyl)amino-1-(4-phenylpiperazin-1-yl)propan-1-one (HL3)

Compound HL3 was obtained as a light white solid. Yield: 32.43%; mp: 135.0-135.8 ^{o}C. ^{1}H NMR(600MHz, $CDCl_3$) δ 7.28-7.26(d, 1H, J = 7.95Hz), 7.22-7.19(d, 1H, J = 9.0Hz), 7.14-7.09(m, 2H), 7.00-6.95(t, 2H, J = 8.61Hz), 6.79-6.78(m, 3H), 6.56-6.55(d, 1H, J = 2.97Hz), 6.54-6.53(dd, 1H, J = 3.0, 9.0Hz), 4.52(s, 2H), 3.83-3.80(m, 4H), 2.65-2.60(t, 2H, J = 4.89Hz), 3.17-3.08(m, 4H), 2.68-2.61(t, 2H, J = 6.75Hz). ^{13}C NMR (150 MHz, DMSO-d_6): δ 169.62, 162.32, 160.72, 151.16, 148.05, 134.62, 131.94, 130.92, 129.36, 128.68, 119.70, 117.31, 116.24, 115.78, 115.64, 113.49, 112.83, 52.84, 48.99, 48.61, 47.45, 45.06, 41.26, 40.33, 40.19, 40.05, 39.91, 39.77, 39.63, 39.49, 30.24. ESI-MS(m/z): 486.4$[M+H]^+$. HRMS calcd for $C_{26}H_{26}Cl_2FN_3ONa$, $[M+Na]^+$, 508.1331; found 508.1331.

4.1.4.4. N-(cyclopropylmethyl)-3-(3,4-dichlorophenyl-4-fluorobenzyl)amino-N-butylpropanamide (HL4)

Compound HL4 was obtained as a light white solid. Yield: 32.61%; mp: 115.7-116.3 ^{o}C. ^{1}H NMR (600MHz, $CDCl_3$): δ 7.41(d, *J* = 8.61Hz, 2H), 7.16-7.11(m, 2H), 7.01-6.95(m, 2H), 6.71(d, *J* = 8.55Hz, 2H), 4.60(s, 2H), 3.90-3.84(m, 2H), 3.38(t, *J* = 7.23Hz, 1H), 3.24-3.19(m, 2H), 3.07(d, *J* = 6.45Hz, 1H), 2.68-2.62(m, 2H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 25.22, 28.43, 34.19, 47.72, 49.88, 52.52, 112.49, 113.11, 114.72, 115.21, 116.93, 128.18, 130.38, 131.42, 134.09, 147.62, 160.31, 161.94, 169.91. ESI-MS(m/z): 451.1$[M+H]^+$. HRMS calcd for $C_{24}H_{29}Cl_2FN_2ONa$, $[M+Na]^+$, 473.1641; found 473.1639.

4.1.4.5. N-cyclopropyl-3-(3,4-dichlorophenyl-4-fluorobenzyl)aminopropanamide (HL5)

Compound HL5 was obtained as a light white solid. Yield: 31.59%; mp: 125.5-127.0 ^{o}C. ^{1}H NMR (600MHz, $CDCl_3$): δ 7.19-7.16(m, 1H), 7.13-7.08(m, 2H), 7.01-6.95(m, 2H), 6.73(d, 1H), 6.50(dd, J = 2.97,8.91Hz, 1H), 4.50(s, 2H), 3.74(t, J = 6.66Hz, 2H), 2.72-2.61(m, 1H), 2.41(t, J = 6.66Hz, 2H), 0.80-0.73(m, 2H), 0.49-0.41(m, 2H). ^{13}C NMR: (150 MHz, DMSO-d_6): δ 5.51, 22.24, 33.22, 47.49, 52.61, 112.54, 113.09, 115.18, 115.32, 116.92, 128.24, 130.48, 131.51, 134.09, 147.52, 160.33, 161.91. ESI-MS(m/z): 381.2 $[M+H]^+$. HRMS calcd for $C_{19}H_{19}Cl_2FN_2ONa$, $[M+Na]^+$, 403.0756; found 403.0755.

4.1.4.6. N-cyclohexyl-3-(3,4-dichlorophenyl-4-fluorobenzyl)aminopropanamide (HL6)

Compound HL6 was obtained as a white solid. Yield: 33.3%; mp: 132.5-134.0 ^{o}C. ^{1}H NMR(600 MHz, $CDCl_3$): δ 7.20 (d, 1H, J = 9.0 Hz), 7.13-7.01 (m, 2H), 6.98 (t, 2H, J = 8.61 Hz), 6.74 (d, 1H, J = 2.76 Hz), 6.51 (dd, 1H, J1 = 2.85 Hz, J2 = 8.82 Hz), 5.32-5.23 (m, 1H), 4.50 (s, 2H), 3.77-3.72 (m, 3H), 2.42 (t, 2H, J = 6.66 Hz), 1.89-1.86 (m, 2H), 1.71-1.57(m, 3H), 1.15-1.26 (m, 2H), 1.21-0.99(m, 3H).

^{13}C NMR (150 MHz, DMSO-d_6): δ 24.52, 25.23, 32.31, 33.49, 47.42, 47.58, 52.60, 112.52, 113.09, 115.21, 115.32, 116.89, 128.29, 130.42, 131.49, 134.12, 147.63, 160.34, 161.91, 169.23. ESI-MS (m/z): 423.3 $[M+H]^+$. HRMS calcd for $C_{22}H_{25}Cl_2FN_2ONa$, $[M+Na]^+$, 445.1226; found 445.1226.

4.1.4.7. N-tert-butyl-3-(3,4-dichlorophenyl-4-fluorobenzyl)amino-propanamide (HL7)

Compound HL7 was obtained as a white solid. Yield: 33.2%; mp: 135.4-136.7 °C. ^{1}H NMR(600 MHz, $CDCl_3$): δ 7.19-7.15 (m, 1H), 7.13-7.08 (m, 2H), 6.78 (t, 2H, J = 4.26 Hz), 6.75-6.70 (m, 1H), 6.50 (dd, 1H, J1 = 9.0 Hz, J2 = 2.88 Hz), 4.49 (s, 2H), 3.71 (t, 2H, J = 6.73 Hz), 2.37 (t, 2H, J = 6.77 Hz), 1.32 (s, 9H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 28.42, 34.24, 47.67, 49.92, 52.51, 112.54, 113.09, 114.67, 115.22, 116.91, 128.23, 130.42, 131.39, 134.12, 147.61, 160.32, 161.89, 169.92. ESI-MS (m/z): 397.1 $[M+H]^+$. HRMS calcd for $C_{20}H_{23}Cl_2FN_2ONa$, $[M+Na]^+$, 419.1069; found 419.1067.

4.1.4.8. 3-((4-chloro-3-(trifluoromethyl)phenyl)(4-fluorobenzyl)amino)-1-(4-phenylpiperazin-1-yl)propan-1-one (HL8)

Compound HL8 was obtained as a white solid. Yield: 42.79; mp: 137.1-138.4 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31-7.27 (m, 2H), 7.26 (dd, J = 8.6, 5.3 Hz, 1H), 7.19-7.16 (m, 4H), 6.93 (dd, J = 8.9, 3.1 Hz, 1H), 4.62 (s, 2H), 3.87 (dd, J = 17.6, 10.4 Hz, 2H), 3.79 (dd, J = 15.2, 9.3 Hz, 2H), 3.76 (s, 2H), 3.24 – 3.11 (m, 4H), 2.69 (t, J = 7.0 Hz, 2H). ^{13}C NMR(150 MHz, DMSO-d_6): δ 29.81, 40.82, 44.78, 47.03, 48.19, 48.56, 52.40, 112.43, 113.12, 115.24, 115.39, 115.79, 116.92, 119.31, 128.23, 128.28, 128.89, 130.51, 131.53, 134.24, 134.29, 147.71, 150.82, 160.31, 161.89, 169.22. ESI-MS (m/z): 519.2$[M+H]^+$. HRMS calcd for $C_{27}H_{26}ClF_4N_3ONa$, $[M+Na]^+$, 542.9584; found 542.9584.

4.1.4.9. 3-([1,1'-biphenyl]-3-yl(4-fluorobenzyl)amino)-1-(4-phenylpiperazin-1-yl)propan-1-one (HL9)

Compound HL9 was obtained as a white solid. Yield: 37.42%; mp: 140.7-141.5 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.52- 7.50 (t, 2H), 7.43 (m, J = 7.5 Hz, 8H), 7.36-7.28 (dd, J = 8.4, 3.7 Hz, 2H), 7.20 – 7.17 (m, 5H), 6.94 (t, J = 8.7 Hz, 1H), 4.66 (s, 2H), 3.95-3.91 (t, J = 7.1 Hz, 2H), 3.79 (d, J = 5.0 Hz, 2H), 3.57 (d, J = 5.0 Hz, 2H), 3.16-3.08 (m, 4H), 2.75 (s, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.84, 163.18, 160.74, 150.77, 148.06, 142.68, 134.29, 129.87, 129.28, 128.74, 127.24, 120.74, 116.74, 115.62, 115.41, 111.38, 77.33, 77.07, 76.75, 54.24, 49.58, 47.33, 45.48, 41.52, 30.44, 29.72. ESI-MS (m/z): 494.2$[M+H]^+$. HRMS calcd for $C_{32}H_{32}FN_3ONa$, $[M+Na]^+$, 516.2427; found 516.2423.

4.1.4.10. 3-((4-chloro-3-ethylphenyl)(4-fluorobenzyl)amino)-1-(4-phenylpiperazin-1-yl)propan-1-one (HL10)

Compound HL10 was obtained as a white solid. Yield: 37.42%; mp: 138.3-138.9 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 (s, 2H), 7.30 – 7.14 (m, 3H), 7.01 (t, J = 8.1 Hz, 2H), 6.93 (d, J = 6.9 Hz, 3H), 6.57 (s, 1H), 6.49 (d, J = 8.0 Hz, 1H), 4.53 (s, 2H), 3.81 (d, J = 15.0 Hz, 4H), 3.54 (s, 2H), 3.13 (d, J = 19.0 Hz, 4H), 2.67 (d, J = 7.1 Hz, 4H), 1.18 (t, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.58, 162.37, 159.80, 150.98, 146.76, 133.53, 131.23, 129.21, 128.10, 125.8, 125.55, 120.58, 116.62, 115.91, 115.50, 115.36, 111.78, 77.18, 76.97, 76.76, 54.04, 49.58, 49.32, 47.15, 45.40, 41.46, 38.41, 30.22, 29.63, 21.45. ESI-MS (m/z): 480.2$[M+H]^+$. HRMS calcd for $C_{28}H_{31}ClFN_3ONa$, $[M+Na]^+$, 502.2037; found 502.2038.

4.1.4.11. 3-((4-bromo-3-methylphenyl)(4-fluorobenzyl)amino)-1-(4-phenylpiperazin-1-yl)propan -1-one (HL11)

Compound HL11 was obtained as a white solid. Yield: 37.42%; mp: 143.8-144.6 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.21 (d, *J* = 9.2 Hz, 2H), 7.08 (s, 2H), 6.95-6.91 (d, *J* = 9.4 Hz, 3H), 6.83 (s, 4H), 6.47 (d, *J* = 8.2 Hz, 1H), 4.42 (s, 2H), 3.69 (s, 4H), 3.45 (s, 2H), 3.04 (d, *J* = 15.4 Hz, 4H), 2.57 (s, 2H), 2.19 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.62, 162.64, 161.02, 150.77, 146.89, 133.83, 131.16, 129.19, 128.05, 125.83, 125.55, 120.58, 116.62, 115.91, 115.50, 115.36, 111.78, 77.18, 76.97, 76.76, 54.04, 49.58, 49.32, 47.15, 45.40, 41.46, 30.22, 29.63, 21.45. ESI-MS (m/z): 510.1$[M+H]^+$. HRMS calcd for $C_{27}H_{29}BrFN_3ONa$, $[M+Na]^+$, 532.1376; found 532.1376.

4.1.4.12. 3-((3,4-dichlorophenyl)(4-fluorobenzyl)amino)-1-(4-(4-methoxyphenyl)piperazin-1-yl) propan-1-one (HL12)

Compound HL12 was obtained as a white solid. Yield: 39.87%; mp: 142.5-143.2 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.21 (d, J = 9.0 Hz, 1H), 7.15 (dd, J = 8.5, 5.4 Hz, 2H), 7.01 (t, J = 8.6 Hz, 2H), 6.87 (t, J = 8.8 Hz, 4H), 6.77 (d, J = 3.0 Hz, 1H), 6.53 (dd, J = 9.0, 3.0 Hz, 1H), 4.54 (s, 2H), 3.82 (d, J = 6.7 Hz, 2H), 3.79 (s, 5H), 3.55 (s, 2H), 3.02 (dd, J = 11.2, 4.9 Hz, 4H), 2.66 (t, J = 7.0 Hz, 2H). ^{13}C NMR(150 MHz, $CDCl_3$) δ 169.33, 163.23, 160.79, 147.27, 133.16, 130.76, 128.00, 119.59, 119.13, 115.77, 115.56, 114.62, 113.66, 112.04, 77.28, 77.02, 76.70, 55.57, 54.05, 47.32, 30.24. ESI-MS (m/z): 516.1$[M+H]^+$. HRMS calcd for $C_{27}H_{28}Cl_2FN_3O_2Na$, $[M+Na]^+$, 538.1440; found 538.1438.

4.1.4.13. Ethyl 4-(4-(3-((3,4-dichlorophenyl)(4-fluorobenzyl)amino)propanoyl)piperazin-1-yl) benoate (HL13)

Compound HL13 was obtained as a white solid. Yield: 41.52%; mp: 150.2-150.9 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.9 Hz, 1H), 7.12 (d, *J* = 9.0 Hz, 1H), 7.07 (dd, *J* = 8.5, 5.4 Hz, 2H),

6.95 (t, *J* = 8.6 Hz, 3H), 6.77 (d, *J* = 9.0 Hz, 2H), 6.69 (d, *J* = 3.0 Hz, 2H), 6.46 – 6.42 (m, 1H), 4.46 (s, 2H), 4.28 – 4.26 (m, 2H), 3.74 (dd, *J* = 12.7, 6.0 Hz, 4H), 3.47 (d, *J* = 5.4 Hz, 2H), 3.27 – 3.17 (m, 4H), 2.58 (t, *J* = 7.0 Hz, 2H), 1.30 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.47, 166.48, 163.23, 160.79, 153.50, 147.19, 133.18, 131.25, 130.78, 128.05, 127.97, 115.78, 118.69, 115.57, 114.12, 113.82, 112.07, 77.34, 77.03, 76.71, 60.50, 54.12, 47.76, 47.59, 47.25, 45.01, 41.19, 30.26, 19.19, 14.42. ESI-MS (m/z): 558.1[M+H]$^+$. HRMS calcd for $C_{29}H_{30}Cl_2FN_3O_3Na$, [M+Na]$^+$, 580.1546; found 580.1546.

4.1.4.14. 3-([1,1'-biphenyl]-3-yl(4-fluorobenzyl)amino)-1-(4-(4-methoxyphenyl)piperazin-1-yl) propan-1-one (HL14)

Compound HL14 was obtained as a white solid. Yield: 41.52%; mp: 148.9-149.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.68 (d, *J* = 7.7 Hz, 1H), 7.58 (s, 1H), 7.53 (d, *J* = 7.7 Hz, 1H), 7.29 (s, 3H), 7.24 (dd, *J* = 8.2, 5.6 Hz, 2H), 7.03 (s, 2H), 6.92 (d, *J* = 8.0 Hz, 5H), 6.79 (s, 1H), 4.63 (s, 2H), 3.93 (d, *J* = 7.1 Hz, 2H), 3.79 (s, 2H), 3.74 (d, *J* = 40.7 Hz, 3H), 3.57 (s, 2H), 3.18 – 3.03 (m, 4H), 2.74 (s, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 169.84, 158.87, 156.57, 142.68, 132.08, 129.87, 129.28, 128.70, 127.24, 120.74, 116.74, 115.62, 115.41, 111.38, 77.39, 77.07, 76.75, 49.69, 49.47, 45.48, 41.52, 30.44, 29.72. ESI-MS (m/z): 524.2[M+H]$^+$. HRMS calcd for $C_{33}H_{34}FN_3O_2Na$, [M+Na]$^+$, 546.2533; found 546.2532.

4.1.4.15. Ethyl 4-(4-(3-([1,1'-biphenyl]-3-yl(4-fluorobenzyl)amino)propanoyl)piperazin-1-yl)ben zoate (HL15)

Compound HL15 was obtained as a white solid. Yield: 43.61%; mp: 156.2-156.9 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.54 – 7.51 (m, 2H), 7.40 (t, *J* = 7.7 Hz, 2H), 7.31 (s, 1H), 7.29 – 7.25 (m, 2H), 7.20 (s, 1H), 7.14 (t, *J* = 8.9 Hz, 2H), 6.89 – 6.83 (m, 4H), 6.80 (d, *J* = 9.1 Hz, 2H), 6.67 (dd, *J* = 8.3, 2.4 Hz, 1H), 4.63 (s, 2H), 3.76 (t, *J* = 7.0 Hz, 2H), 3.67 (s, 3H), 3.61 – 3.49 (m, 4H), 2.95 – 2.86 (m, 4H), 2.72 (s, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 169.85, 166.01, 157.94, 157.10, 153.87, 149.67, 131.07, 130.68, 130.15, 128.67, 128.61, 123.34, 119.06, 118.66, 115.66, 115.52, 113.79, 107.83, 106.27, 103.12, 60.28, 40.32, 40.18, 40.04, 39.90, 39.76, 39.62, 39.48. ESI-MS (m/z): 566.6 [M+H]$^+$. HRMS calcd for $C_{35}H_{36}FN_3O_3Na$, [M+Na]$^+$, 588.2638; found 588.2638.

4.1.4.16. Ethyl 4-(4-(3-((4-fluorobenzyl)(3-phenoxyphenyl)amino)propanoyl)piperazin-1-yl)ben zoate (HL16)

Compound HL16 was obtained as a yellow solid. Yield: 42.59%; mp: 162.7-163.9 °C. ^{1}H NMR

(600 MHz, DMSO-d_6) δ 7.29 (d, J = 9.0 Hz, 2H), 7.28 – 7.26 (m, 2H), 7.13 (dd, J = 8.5, 5.6 Hz, 2H), 7.11 (dd, J = 16.0, 8.5 Hz, 3H), 7.06 (t, J = 7.4 Hz, 1H), 6.95 (d, J = 9.1 Hz, 2H), 6.91 – 6.86 (m, 2H), 6.47 (dd, J = 8.4, 2.3 Hz, 1H), 6.27 (t, J = 2.3 Hz, 1H), 6.17 (dd, J = 7.9, 2.0 Hz, 1H), 4.53 (s, 2H), 4.23 (d, J = 7.1 Hz, 2H), 3.67 (t, J = 7.0 Hz, 2H), 3.60 – 3.49 (m, 4H), 3.32 (s, 4H), 2.68 (d, J = 7.0 Hz, 2H), 1.28 (t, J = 7.1 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) d 169.85, 166.01, 162.24, 160.64, 157.94, 157.10, 153.87, 149.67, 135.24, 131.07, 130.68, 130.15, 128.67, 128.61, 123.34, 119.06, 118.66, 115.66, 115.52, 113.79, 107.83, 106.27, 103.12, 60.28, 40.32, 40.18, 40.04, 39.90, 39.76, 39.62, 39.48, 30.39, 14.68.ESI-MS (m/z): 582.2$[M+H]^+$. HRMS calcd for $C_{35}H_{36}FN_3O_4Na$, $[M+Na]^+$, 604.2588; found 604.2687.

4.1.4.17. 3-((4-fluorobenzyl)(3-phenoxyphenyl)amino)-1-(4-(4-methoxyphenyl)piperazin-1-yl) propan-1-one (HL17)

Compound HL17 was obtained as a yellow solid. Yield: 46.15%; mp: 155.4-156.2 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79 (d, J = 9.0 Hz, 2H), 7.29 (m, 2H), 7.12 (dd, J = 8.5, 5.6 Hz, 2H), 7.10(dd, J = 16.0, 8.5 Hz, 3H), 6.96 (t, J = 7.4 Hz, 2H), 6.95 (d, J = 9.1 Hz, 2H), 6.91 – 6.86 (m, 2H), 6.48 (dd, J = 8.4, 2.3 Hz, 1H), 6.16 (dd, J = 7.9, 2.0 Hz, 1H), 4.53 (s, 2H), 3.83 (d, J = 7.1 Hz, 2H), 3.79 (s, 3H), 3.55 (m, 2H), 3.03 (m, 2H), 2.68 (d, J = 7.0 Hz, 4H), 2.64 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.87, 166.01, 160.66, 153.87, 147.07, 140.43, 139.94, 131.06, 129.51, 128.43, 119.06, 118.22, 115.66, 115.57, 114.94, 113.80, 113.15, 60.28, 52.99, 47.44, 46.69, 44.66, 30.35. ESI-MS (m/z): 540.2$[M+H]^+$. HRMS calcd for $C_{33}H_{34}FN_3O_3Na$, $[M+Na]^+$, 562.2482; found 562.2481.

4.2. Biology

4.2.1. In Vitro CETP inhibitory assay

The CETP RP Activity Assay Kit (Catalog # RB-RPAK;Roar) uses a donor molecule containing a fluorescent self-quenched neutral lipid that is transferred to an acceptor by CETP(Catalog # R8899;Roar). CETP-mediated transfer of the fluorescence neutral lipid to the acceptor molecule results in an increase in fluorescence (ExEm = 465/535 nm). Inhibitor of CETP will inhibit the lipid transfer and therefore decrease the fluorescence intensity. The testing compounds are dissolved using 100% DMSO. It is important to make sure that each compound is dissolved totally. It is recommended to vibrate the solution on oscillator for more than 30 seconds then store them at nitrogen cabinet. Dilute the stocking compounds (10 mM) with DMSO for 8 points titration (1:5 serial dilutions) in 96-well dilution plate. The assay was performed according to the instruction for the CETP inhibitor screening

kit and recombinant CETP.

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Scheme and figure legends

Scheme 1. Structure of CETP inhibitors

Scheme 2. Optimization of **L10** led to discovery **HL16**

Scheme 3. Synthetic routes. Reagents and conditions: (a) 10% HCl, acrylic acid, 40 ^{o}C; (b) substituted amines, HOBt, EDCI, DIEA, RT; (d) DCM, reflux; (e) n-BuOH, K_2CO_3, reflux; (c) 4-fluorobenzyl bromide, K_2CO_3, DMF, 90 ^{o}C.

Table 1. Structure−Activity Relationship (SAR) of **N,N-3-phenyl-3-benzylamino propanamides** derivatives **HL1-HL17**

Figure 1. The in vivo analysis of hamster treated with **HL16** for 2 weeks. (ig). Control: high-fat diet-fed group untreated with **HL16; HL16**: high-fat diet-fed hamster treated with **HL16** (30 mg/kg/d). n=6.

Figure 2. The proposed binding mode of compound **HL16** and CETP. (A) **HL16** occupy the pocket of CETP-inhibitor binding site. (B) **HL16** interactions with amino acid. **HL16** with carbon atoms colored green light magenta, oxygen atoms colored red, nitrogen atoms colored blue, fluorine colored light blue. Amino acid carbon atoms are colored gray, oxygen colored red, hydrogen atoms colored light gray, nitrogen atom colored blue, the name of amino acid colored geen. Hydrogen bond colored pistachio green.

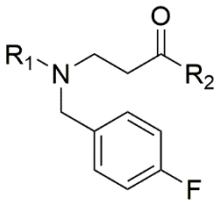
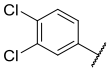
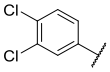
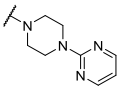
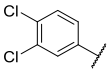
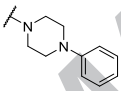
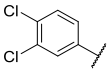
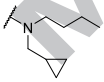
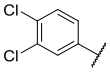
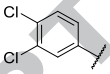
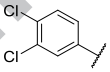
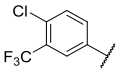
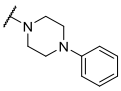
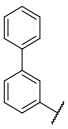
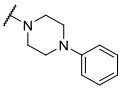
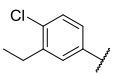
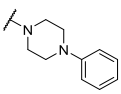
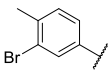
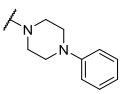
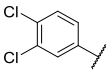
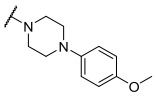
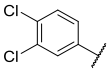
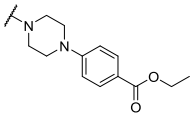
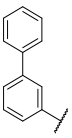
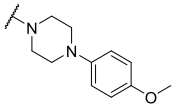
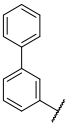
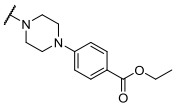
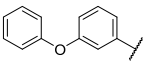
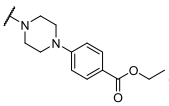
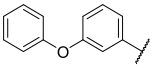
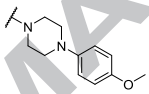


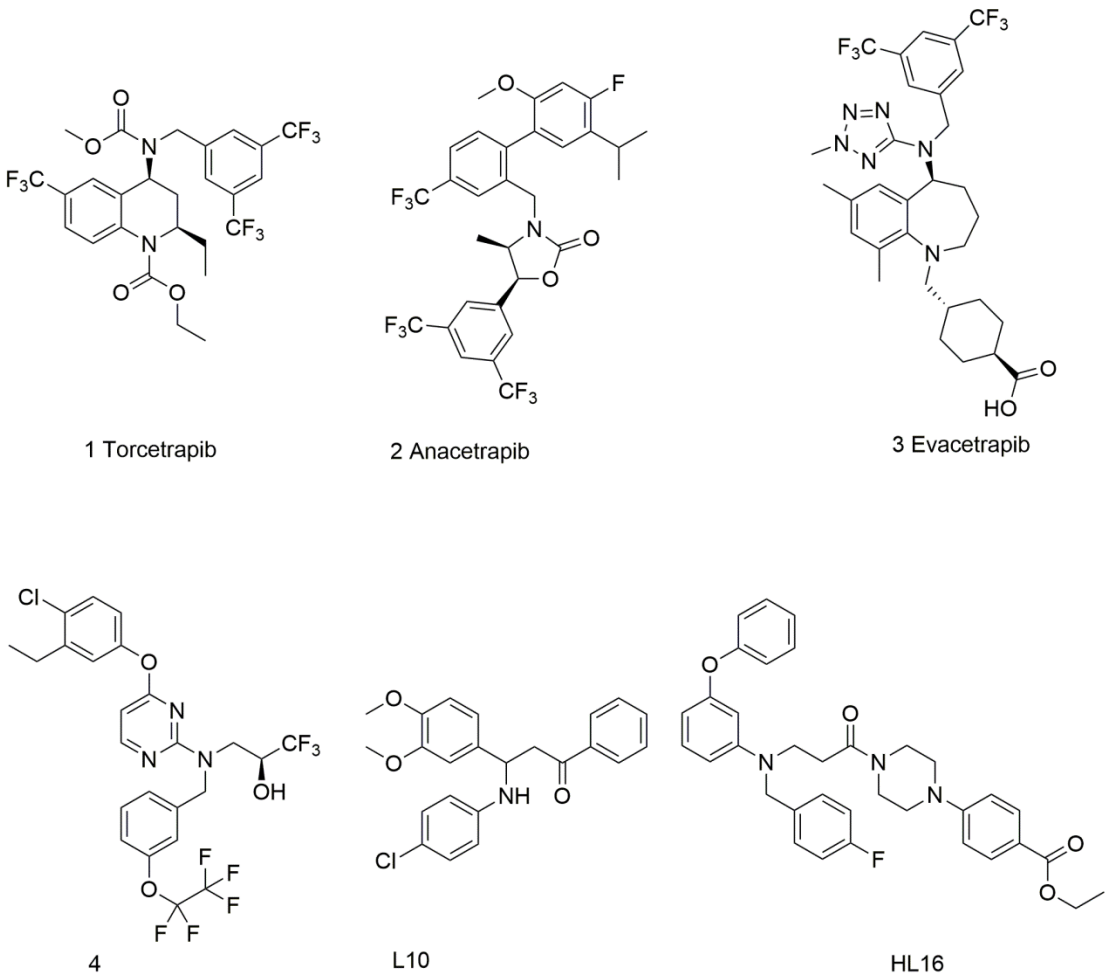
Table 1.

Structure−Activity Relationship (SAR) of **N,N-3-phenyl-3-benzylamino propanamides** derivatives **HL1-HL17**

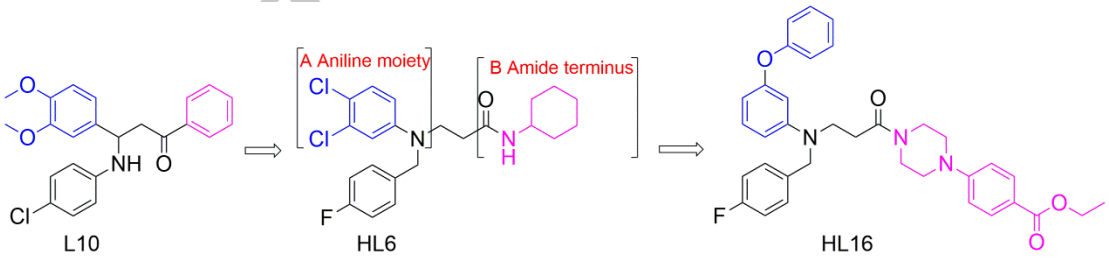
Compd	R_1	R_2	IC_{50} μM
HL1			14.2
HL2			11.8
HL3			5.2
HL4			>50[c]
HL5			>50[c]
HL6			10.7
HL7			29.6
HL8			37.8
HL9			11.3
HL10			19.5
HL11			13.9

HL12			3.5
HL13			2.8
HL14			7.3
HL15			3.1
HL16			0.69
HL17			2.8
anacetrapib[b]			0.06

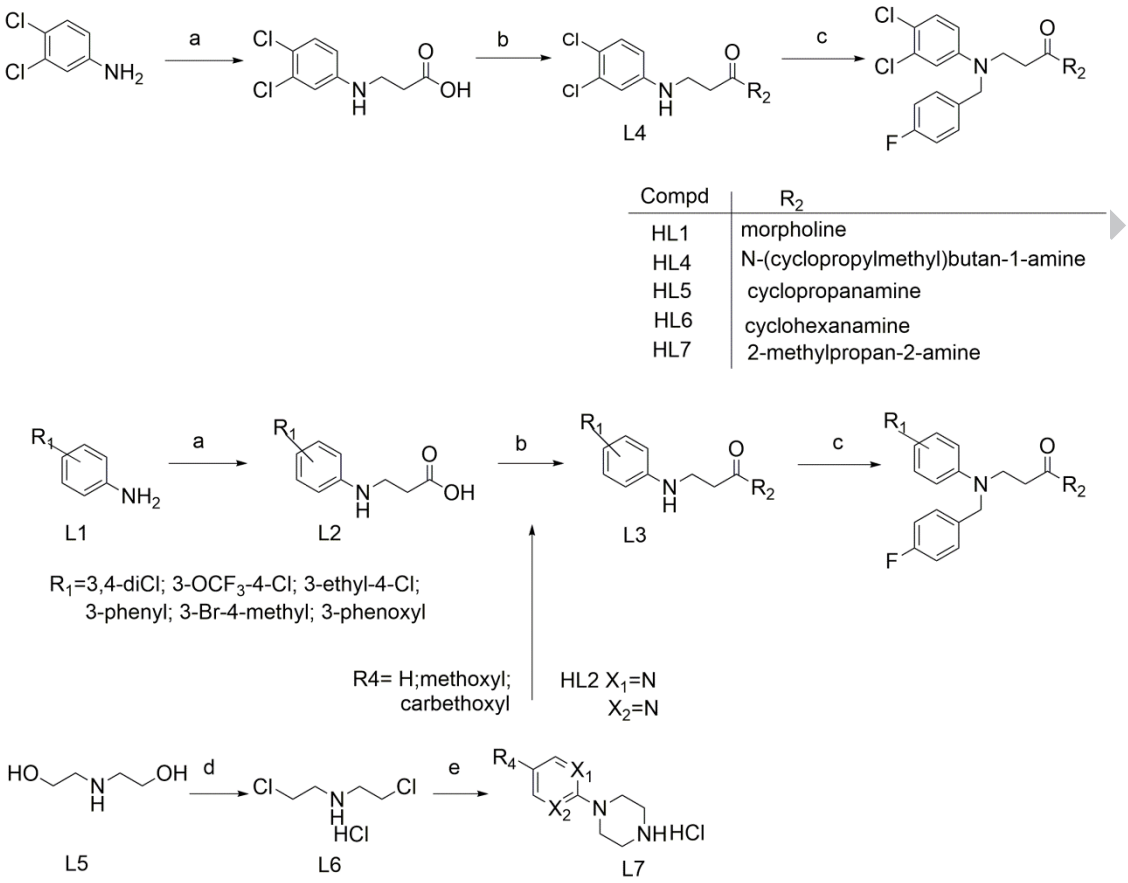
b The positive control; c considered with no CETP inhibition activity



Scheme 1. Structure of CETP inhibitors



Scheme 2. Optimization of **L10** led to discovery **HL16**



Scheme 3. Synthetic routes. Reagents and conditions: (a) 10% HCl, acrylic acid, 40 ^{o}C; (b) substituted amines, HOBt, EDCI, DIEA, RT; (d) DCM, reflux; (e) n-BuOH, K_2CO_3, reflux; (c) 4-fluorobenzyl bromide, K_2CO_3, DMF, 90 ^{o}C.

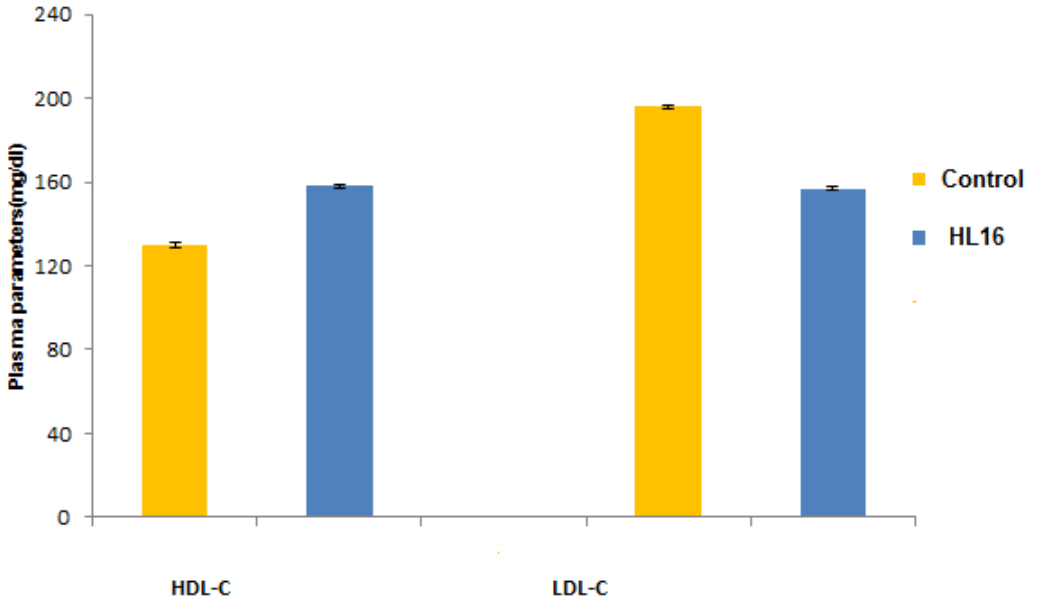
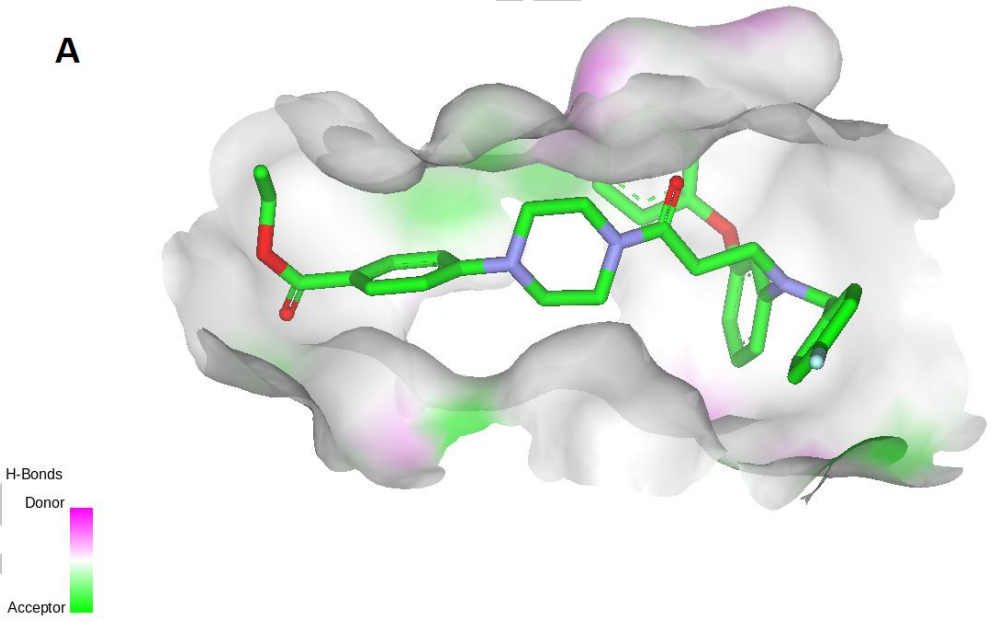


Figure 1. The in vivo analysis of hamster treated with **HL16** for 2 weeks. (ig). Control: high-fat diet-fed group untreated with **HL16**; **HL16**: high-fat diet-fed hamster treated with **HL16** (30 mg/kg/d). n=6.



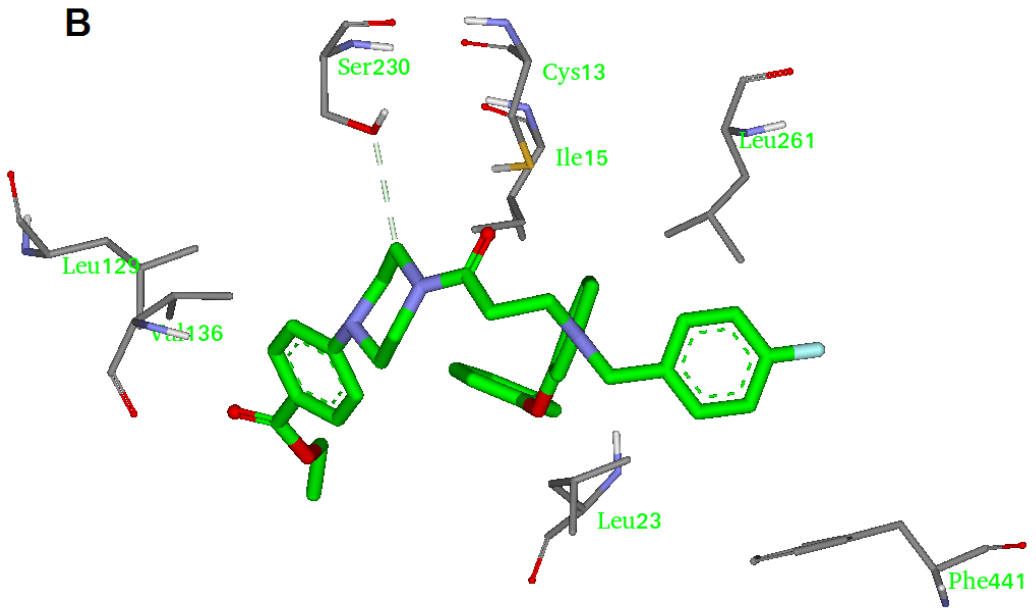


Figure 2. The proposed binding mode of compound **HL16** and CETP. (A) **HL16** occupy the pocket of CETP-inhibitor binding site. (B) **HL16** interactions with amino acid. **HL16** with carbon atoms colored green light magenta, oxygen atoms colored red, nitrogen atoms colored blue, fluorine colored light blue. Amino acid carbon atoms are colored gray, oxygen colored red, hydrogen atoms colored light gray, nitrogen atom colored blue, the name of amino acid colored geen. Hydrogen bond colored pistachio green.

Graphical Abstract