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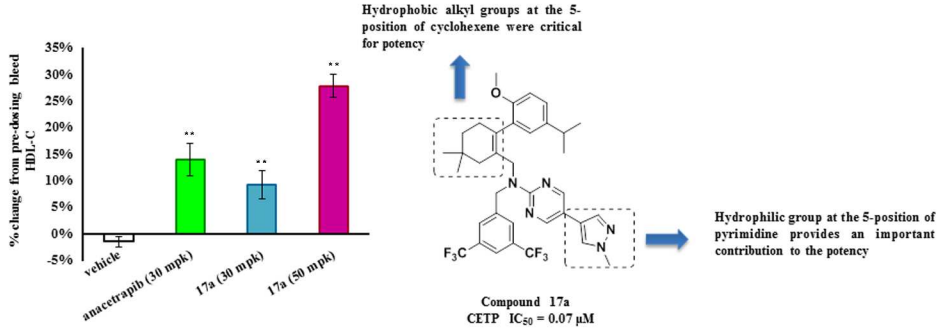

Design, synthesis and biological evaluation of novel cholesteryl ester transfer protein inhibitors bearing a cycloalkene scaffold

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Abstract

Cholesteryl ester transfer protein (CETP) is a potential target for cardiovascular disease therapy as inhibition of CETP leads to increased HDL-C in humans. Based on the structure of Merck's biphenyl CETP inhibitor, we designed novel *N*,*N*-substituted-cycloalkenyl-methylamine scaffold derivatives by utilizing core replacement and conformational restriction strategies. Consequently, twenty-eight compounds were synthesized and evaluated for their inhibitory activity against CETP. Their preliminary structure-activity relationships (SARs) studies indicate that polar substituents were tolerated in moiety A and hydrophobic alkyl groups at the 5-position of cyclohexene were critical for potency. Among them, compound **17a**, bearing an *N*-(5-pyrazolyl-pyrimidin-2-yl)-cycloalkenyl- methylamine scaffold, exhibited excellent CETP inhibitory activity (IC_{50} = 0.07 μM) *in vitro*. Furthermore, it showed an acceptable pharmacokinetic profile in S-D rats and efficient HDL-C increase in high-fat fed hamsters.

Keywords: Synthesis; *N*,*N*-substituted-cycloalkenyl-methylamine derivatives; CETP inhibitors; HDL-C; Cardiovascular disease

1. Introduction

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality worldwide. Epidemiological studies have indicated that low levels of high-density lipoprotein-cholesterol (HDL-C) are considered to be a major risk factor for CVD, independent of high levels of low-density lipoprotein-cholesterol (LDL-C) [1-4]. Each 1 mg/dL increase in HDL-C reduces cardiovascular events by 2-3% on the basis of clinical studies [5]. Cholesteryl ester transfer protein (CETP) is a 476-residue glycoprotein, secreted mainly from the liver, that facilitates the transfer of cholesteryl esters (CEs) from high-density lipoprotein (HDL) to low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) in exchange for triglycerides (TGs) [6, 7]. It has been shown that CETP plays a proatherogenic role due to raising LDL-C levels and reducing HDL-C levels [8, 9]. Therefore, the inhibition of CETP should result in increased HDL-C levels and reduce the risk of CVD [6, 10].

Several small molecular CETP inhibitors have been reported, and some of them have been through phase III clinical trials (Fig. 1) [11]. Torcetrapib (**1**) was the first CETP inhibitor to reach phase III clinical trials, exhibiting a very potent inhibitory activity. Unfortunately, the

ILLUMINATE study was prematurely halted due to unexpected effects that led to more mortality in the torcetrapib/atorvastatin group than in the atorvastatin group [12-14]. Subsequently, the dalcetrapib (**2**) phase III clinical trial was terminated, as the inhibitor did not decrease the risk of cardiovascular events [15]. Recently, Lilly announced that the phase III ACCELERATE study of evacetrapib (**3**) was terminated, but the precise explanation for the failure has not been published in any journal article. Anacetrapib (**4**) is currently being studied in a phase III clinical trial, and the data shows an effective increase in HDL-C and decrease in LDL-C, without the side effects of torcetrapib [16, 17].

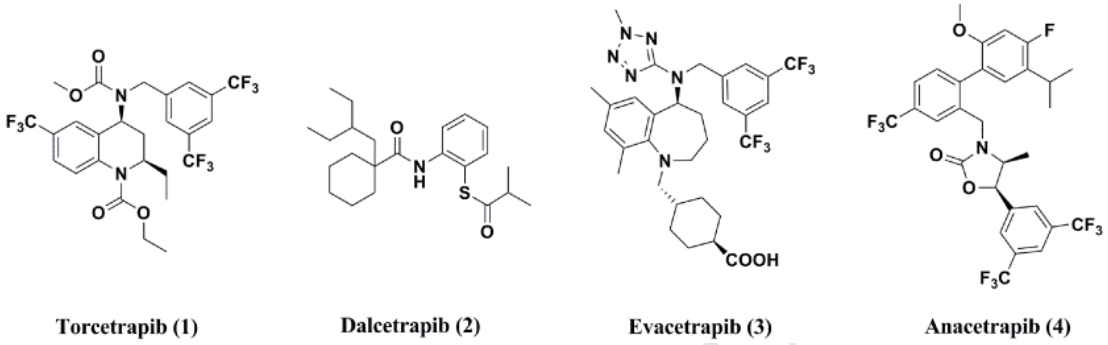


Figure 1. Representative CETP inhibitors

Compound **5** (IC_{50} = 0.11 μM, Fig. 2), developed by Merck, showed significant lipid-regulating activity *in vivo* [18, 19]. Its simple scaffold and favourable pharmacodynamic properties encouraged us to explore novel and potent structures based on this compound. As shown in Figure 2, the replacement of a substituted phenyl ring with a substituted cyclohexenyl ring resulted in weak micromolar activity (**10a**, IC_{50} = 20.97 μM), and efforts to enhance the pharmacological activity through alternative substitutions on the carbamate were largely unsuccessful. Next, our group investigated the cyclization of the carbamate using a conformational constraint strategy to attempt to increase the CETP inhibitory activity. To avoid instability and the generation of chiral centres, we focused on the introduction of aromatic rings onto moiety A. Fortunately, the compound containing a pyrimidine ring (**16**, IC_{50} = 3.52 μM) on moiety A showed increased inhibitory activity. We chose compound **16** as the lead compound, and a series of novel *N*,*N*-substituted-cycloalkenyl-methylamine derivatives were synthesized. Optimization efforts on moiety A and ring B are discussed in this study.

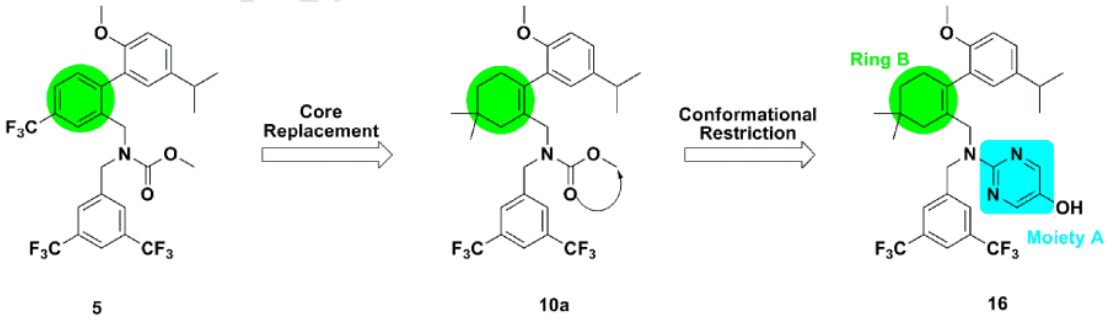


Figure 2. Design of new structures based on compound **5**

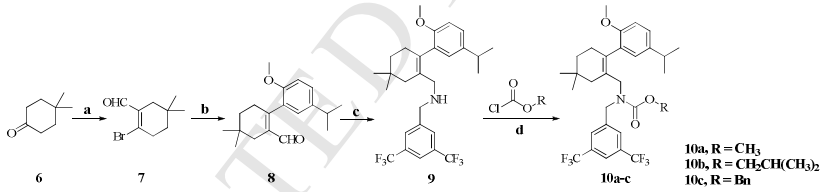
2. Results and discussion

2.1. Chemistry

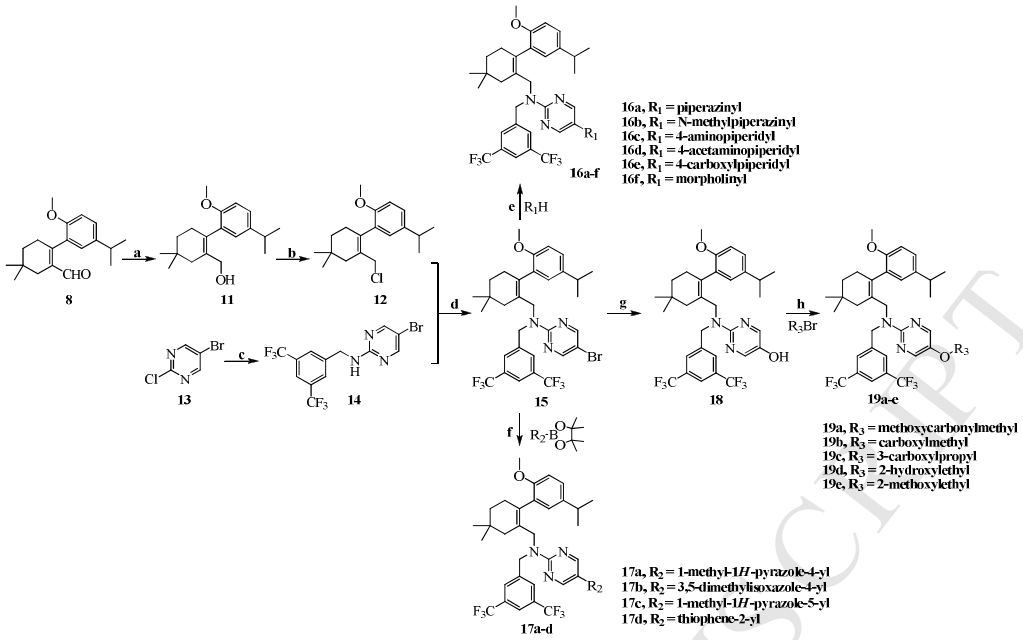
Compounds **10a-c** were prepared according to the procedure in Scheme 1. The commercially available 4,4-dimethylcyclohexanone (**6**) underwent a Vilsmeier-Haack-Arnold reaction to produce **7**. The treatment of **7** with 5-isopropyl-2-methoxyphenylboronic acid under Suzuki coupling conditions achieved **8** in good yield. Then, the -CHO of the resulting 2-phenylcyclohex-1-enecarbaldehyde scaffold was subjected to reductive amination with 3,5-bis(trifluoromethyl)benzyl amine to produce **9**. The obtained intermediate **9** was treated with corresponding chloroformates to give compounds **10a-c**.

Compounds **15**, **16a-f, 17a-d, 18** and **19a-e** were prepared according to the procedure in Scheme 2. The resulting **8** was reacted with $NaBH_4$ and subsequently, $SOCl_2$ to afford intermediate **12**. The treatment of starting material **13** with 3,5-bis(trifluoromethyl)benzyl amine provided **14**. Compound **15** was obtained by the nucleophilic substitution of **9** and **11** in the presence of NaH at 0°C. This compound was subjected to Buchwald-Hartwig coupling reactions with corresponding amines to yield compounds **16a-f** and Suzuki coupling reactions with corresponding borate esters to furnish compounds **17a-d**. In compound **15**, –Br was replaced with –OH to give compound **18** which was subjected to substitution reactions with various substituted alkyl bromides to yield compounds **19a-e.**

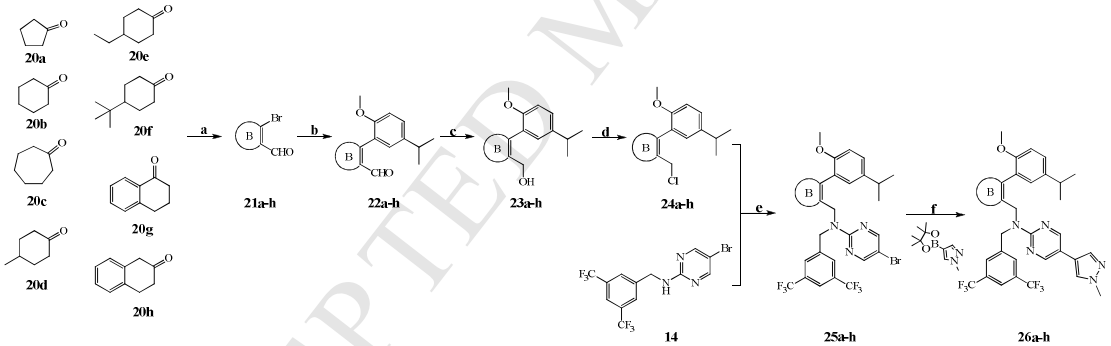
As illustrated in Scheme 3, compounds **26a-h** were synthesized from the corresponding starting material ketones. Intermediates **21a-h** were generated by Vilsmeier-Haack-Arnold reactions and treated with 5-isopropyl-2-methoxyphenylboronic acid to provide **22a-h**. These compounds were reacted with $NaBH_4$ and subsequently, $SOCl_2$ to afford intermediates **24a-h**, and key intermediates **25a-h** were obtained by nucleophilic substitution**.** The conventional Suzuki coupling of **25a-h** with 1-methylpyrazole-4-boronic acid pinacol ester afforded compounds **26a-h**.



Scheme 1. Synthesis of target compounds **10a–c**. Reagents and conditions: (a) DMF, PBr_3, $CHCl_3$, rt, 36.4%; (b) 5-isopropyl-2-methoxyphenylboronic acid, $Pd(OAc)_2$, K_2CO_3, acetylacetone, EtOH, 80°C, 78.3%; (c) 3,5-bis(trifluromethyl)benzyl amine, $NaBH(OAc)_3$, 1,2-dichloroethane, rt, 48.8%; (d) DIEA, DCM, rt, 87.0%-91.2%.



Scheme 2. Synthesis of target compounds **15**, **16a-f, 17a-d, 18** and **19a-e**. Reagents and conditions: (a) $NaBH_4$, MeOH, rt, 97.7%; (b) $SOCl_2$, DMF, rt, 75.3%; (c) 3,5-bis(trifluromethyl)benzyl amine, DIEA, 1,4-dioxane, 105°C, 75.8%; (d) NaH, DMF, 0°C, 64.7%; (e) $Pd_2(dba)_3$, 2-(di-tert-butylphosphino)biphenyl, NaOt-Bu, toluene, reflux, 39.3-53.1%; (f) $Pd(PPh_3)_4$, Na_2CO_3, DME/H_2O, 90°C, 58.3-66.9%; (g) (i) bis(pinacolato)diboron, $PdCl_2$(dppf)-CH_2Cl_2, AcOK, DMSO, 80°C; (ii) 30% H_2O_2, THF, 0℃, 46.4%; (h) K_2CO_3, DMF, rt, 56.5-84.3%.



Scheme 3. Synthesis of target compounds **26a-h**. Reagents and conditions: (a) DMF, PBr_3, $CHCl_3$, rt, 36.4%; (b) 5-isopropyl-2-methoxyphenylboronic acid, $Pd(OAc)_2$, K_2CO_3, acetylacetone, EtOH/H_2O, 80°C, 78.3%; (c) $NaBH_4$, MeOH, rt, 97.7%; (d) $SOCl_2$, DMF, rt, 75.3%; (e) NaH, DMF, 0°C, 64.7%; (f) $Pd(PPh_3)_4$, Na_2CO_3, DME/H_2O, 90°C, 43.8-58.0%.

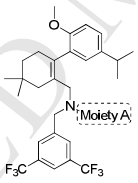
2.2. In vitro activity against Cholesteryl Ester Transfer Protein

The *N*,*N*-substituted-cycloalkenyl-methylamine derivatives and reference compound anacetrapib (**4**) were screened for their *in vitro* activity against CETP by a BODIPY-CE fluorescence assay with the CETP RP Activity Assay Kit (Catalog # RB-RPAK; Roar). The results are shown in Table 1 and Table 2. The IC_{50} values reveal that most of the compounds exhibit potent CETP inhibitory activity.

As shown in Table 1, moiety A is critical for the pharmacological activity *in vitro*, and replacement of a carbamate (**10a**, IC_{50} = 20.97 μM) with a pyrimidine ring (**18**, IC_{50} = 3.52 μM)

caused a significant increase in the activity. Next, we investigated the relationship between various substituents at the 5-position of the pyrimidine ring (moiety A) and the CETP inhibitory activity. The introduction of bromine (**15**) dramatically reduced the activity due to the hydrophobic effect. Interestingly, the potency of piperazine group **16a** (IC_{50} = 0.35 μM) was nearly 10-fold stronger than that of a free hydroxyl group (**18**, IC_{50} = 3.52 μM), and *N*-methyl piperazine (**16b**, IC_{50} = 2.07 μM) was 6-fold less potent than piperazine (**16a**). Replacing the free NH of piperazine (**16a**) with an oxygen atom (morpholine, **16f**, IC_{50} = 0.86 μM) caused a weak decrease in the activity. Nevertheless, the nitrogen atom of piperazine (**16a**) moved outside to construct exocyclic amine **16c** (IC_{50} = 0.17 μM), exhibiting 2-fold higher potency than compound **16a**, while a substitution of the amine of **16c** with an acetyl group (**16d**, IC_{50} = 0.52 μM) somewhat decreased the potency. Changing the 5-NH_2 group (**16c**) to a 5-COOH group (**16e**, IC_{50} = 0.37 μM) showed no advantage. Aromatic heterocycles attached at the 5-position of the pyrimidine ring were also examined, and of these, the 1-menthylpyrazole fragment was the most potent (**17a**, IC_{50} = 0.07 μM), although the other compounds also exhibited obvious decreases in activity. Interestingly, the potency of straight chain saturated carboxylic acids **19b** (IC_{50} = 0.36 μM) and **19c** (IC_{50} = 0.30 μM) were nearly 10-fold stronger than that with a free hydroxyl group (**18**, IC_{50} = 3.52 μM), but the corresponding ester (**19a**, IC_{50} = 0.91 μM) exhibited low potency *vs* **19b**. Meanwhile, a straight chain saturated alcohol (**19d**, IC_{50} = 0.19 μM) showed potent inhibitory activity, but the corresponding ether (**19e**, IC_{50} = 0.42 μM) exhibited almost 2-fold weaker potency. According to these results, we could speculate that the hydrophilic group at the 5-position of pyrimidine provides an important contribution to the potency due to interaction with the hydrophilic area.

Table 1 Structures and activities of compounds **10a-c**, **15**, **16a-f**, **17a-d**, **18**, **19a-e**



NO.	Moiety A	R	IC_{50} (μM)	NO.	Moiety A	R	IC_{50} (μM)
10a			20.97	**17a**			0.07
10b			>50[b]	**17b**			>50[b]
10c			>50[b]	**17c**			>50[b]
15			>50[b]	**17d**			>50[b]
16a			0.35	**18**			3.52
16b			2.07	**19a**			0.91
16c			0.17	**19b**			0.36

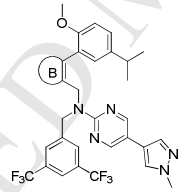
16d			0.52	**19c**			0.30
16e			0.37	**19d**			0.19
16f			0.86	**19e**			0.42
				Anacetrapib[a]			0.04

[a] Used as a positive control.

[b] Considered with no CETP inhibition activity

To further study the relationship between ring B and the CETP inhibitory activity, another eight compounds **26a-h** were prepared and evaluated for their activity (Table 2). Compounds containing hydrophobic alkyl groups at the 5-position of cyclohexene (**26d**, IC_{50} = 0.06 μM; **26e**, IC_{50} = 0.08 μM; **26f**, IC_{50} = 0.07 μM) showed better inhibitory activity than their counterparts lacking these groups (**26b**, IC_{50} = 0.93 μM). However, replacing the cyclohexene ring with a cyclopentene ring (**26a**, IC_{50} = 2.76 μM) or cycloheptene ring (**26c**, IC_{50} = 1.62 μM) resulted in an obvious decrease in activity. The incorporation of a benzene ring onto the cyclohexene to form a 1,2-dihydronaphthalene group (**26g**, **26h**) resulted in a decrease of activity due to the steric effect. These results indicate that hydrophobic alkyl groups at the 5-position of cyclohexene are critical for potency.

Table 2. Structures and activities of compounds **26a-h**



NO.	B ring	IC_{50} (μM)	NO.	B ring	IC_{50} (μM)
26a		2.76	**26e**		0.08
26b		0.93	**26f**		0.07
26c		1.62	**26g**		0.22
26d		0.06	**26h**		6.63
17a		0.07	**anacetrapib**[a]		0.04

[a] Used as a positive control.

*2.3. In vivo test of compound **17a** in high-fat fed hamsters*

Based on the result of the *in vitro* CETP inhibitory assay, potent inhibitor **17a** was selected for the *in vivo* assay. The high-fat fed hamster model was our primary animal model to measure the compound's ability to elevate HDL-C by CETP inhibition. As shown

in Figure 3, compound **17a** dose-dependently elevates HDL-C. Multiple oral dosing of **17a** at 30 mg/kg for 5 days in hamsters (n=6) produced a 9.3% elevation of HDL-C at similar levels to that observed for **4** (anacetrapib). A 50 mg/kg dose of **17a** showed a statistically significant 27.9% elevation of HDL-C. The results indicate that **17a** demonstrates a potent dose-dependent HDL-C elevation in hamsters.

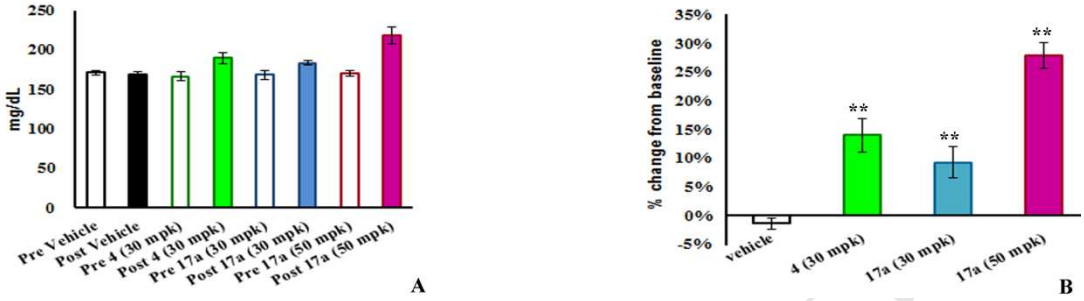


Figure 3. Elevation in HDL-C for compounds **4** and **17a** in moderately fat-fed hamsters. Predose blood samples were collected by retro-orbital bleed. Compounds were formulated in ethanol/hydrogenated castor oil/water at a 1:1:8 ratio and dosed at 30mg/kg, 50mg/kg (po, q.d.) for 5 days. Blood was drawn 2 h after the last dose and HDL-C levels were measured in the predose and postdose samples using chemistry analyser. (**A**) Predose and postdose plasma HDL-C levels and (**B**) percent changes in HDL-C after dosing compounds for 5 days are reported as the mean±SEM (n = 6), (**) $p < 0.01$ vs vehicle.

*2.4. Pharmacokinetic characterization of **17a***

The pharmacokinetic parameters of **17a** were determined in Sprague-Dawley rats (n = 4) dosed at 50 mg/kg, using a solution of 10% ethanol, 10% hydrogenated castor oil, and 80% water as the vehicle for the peros route. As shown in Table 3, observed maximal plasma concentration following oral dosing is 697.4 ng/mL, and time to reach C_{max} is 2.5 h; in rats, terminal half-life of compound **17a** is 2.5 h; area under curve (AUC) is 6994.4 ng·h/mL. On the basis of pharmacokinetic parameters, we can know that compound **17a** exhibited an acceptable pharmacokinetic profile in S-D rats.

Table 3. Pharmacokinetic parameters for **17a** in rats

Compound	Species（n = 4）	C_{max} (ng/mL)	T_{max} (h)	$T_{1/2}$ (h)	AUC (ng·h/mL)
17a	Rat (50 mpk)	697.4	2.5	11.1	6994.4

3. Conclusions

In summary, an *N*,*N*-substituted-cycloalkenyl-methylamine scaffold was designed from a reported CETP inhibitor by utilizing core replacement and conformational restriction. New compounds were synthesized and evaluated for their inhibitory activity against CETP by a BODIPY-CE fluorescence assay. An initial SAR revealed that polar substituents were tolerated in moiety A and hydrophobic alkyl groups at the 5-position of cyclohexene were critical for potency. Compound **17a** was identified as a promising CETP inhibitor with good inhibitory activity (IC_{50} = 0.07 μM), and based on its excellent *in vitro* property, it was selected for *in vivo* evaluation. Compound **17a** demonstrated a dose-dependent HDL-C elevation in hamsters and an acceptable pharmacokinetic profile in S-D rats. Future studies of **17a** are currently underway in our

laboratory.

4. Experimental

4.1. Chemistry

All chemicals were obtained from commercial sources and were used without purification unless otherwise specified. Solvents were distilled and dried using standard methods. TLC was performed on silica gel plates (Indicator F-254) and visualized by UV-light. NMR spectra were recorded on Bruker 400 MHz and 600MHz instruments, and the chemical shifts were reported in terms of parts per million with TMS as the internal reference. 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). Column chromatography was performed with silica gel (200-300 mesh) purchased from Qingdao Haiyang Chemical Co. Ltd. The purities of target compounds were ≥95%, measured by HPLC, performed on a Waters 1525-2489, eluting with 100%CH_3OH or a mixture of solvents H_2O (A) and MeOH (B) (V_A : V_B = 5 : 95). Peaks were detected at λ 254 nm with a flow rate of 1.0 mL/min.

*4.2. 2-Bromo-5,5-dimethylcyclohex-1-enecarbaldehyde (**7**).*

PBr_3 (2.8 mL, 27.0 mmol) was added slowly to a solution of DMF (2.1 mL, 30.0 mmol) in $CHCl_3$ (10 mL) that was cooled to 0°C. After stirring for 1 h at 0°C, 4,4-dimethylcyclohexanone (1.3 g, 10.0 mmol) was added to the mixture. The reaction mixture was again stirred at room temperature for 8 h and then poured into ice water (60 mL) and neutralized slowly with solid $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (20 mL×3), and the combined organic layers were washed with water (20 mL×3) and brine (20 mL×3), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by chromatography on silica gel (petroleum ether : EtOAc = 8:1) to give **7** (0.8 g, 36.4%), which was used immediately for the next step because of its instability.

*4.3. 2-(5-Isopropyl-2-methoxyphenyl)-5,5-dimethylcyclohex-1-enecarbaldehyde (**8**).*

5-Isopropyl-2-methoxyphenylboronic acid (1.6 g, 8.0 mmol) was dissolved in water (20 mL) and ethanol (20 mL), and intermediate **7** (1.7 g, 8.0 mmol), potassium carbonate (2.2 g, 16.0 mmol), acetylacetone (0.2 mL, 2.0 mmol) and $Pd(OAc)_2$ (0.02 g, 0.08 mmol) were added. The reaction mixture was heated to reflux for 4 h and then cooled to room temperature. After concentration, the residue was dissolved in EtOAc (20 mL), washed with water (20 mL×3) and brine (20 mL×3), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (petroleum ether : EtOAc = 8:1) to give **8** (1.8 g, 78.3%) as a pale yellow oil. ^{1}H NMR (400 MHz, DMSO-*d*6) *δ*: 9.21 (s, 1H), 7.13 (dd, *J* = 8.5Hz, 2.2Hz, 1H), 6.92-6.90 (m, 2H), 3.64 (s, 3H), 2.80-2.73 (m, 1H), 2.56 (m, 1H), 2.29-2.28 (m, 1H), 1.94-1.91 (m, 2H), 1.38 (t, *J* = 6.4 Hz, 2H), 1.09 (d, *J* = 6.9 Hz, 6H), 0.89 (s, 6H). MS (ESI) *m/z* 309.4 $[M+Na]^+$.

4.4. N-(3,5-Bis(trifluoromethyl)benzyl)-1-(2-(5-isopropyl-2-methoxyphenyl)-5,5-dimethylcyclohex

*-1-enyl)methanamine (**9**).*

Under an argon atmosphere, intermediate **8** (0.2 g, 0.8 mmol), 3,5-bis(trifluromethyl)benzyl amine (0.2 g, 0.8 mmol) and Na_2SO_4 (0.2 g) were dissolved in 1,2-dichloroethane (2 mL). After stirring for 1 h at room temperature, $NaBH(OAc)_3$ (0.2 g, 1.0 mmol) was added to the mixture. The reaction mixture was stirred at room temperature overnight and then poured into saturated sodium bicarbonate solution (10 mL). The mixture was extracted with CH_2Cl_2 (20 mL×3) and the combined organic layers were washed with water (20 mL×3) and brine (20 mL×3), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (petroleum ether : EtOAc = 4:1) to give **9** (0.2 g, 48.8%) as a pale yellow oil. ^{1}H NMR (400 MHz, DMSO-*d*6) δ: 7.86 (s, 3H), 6.98 (dd, *J* = 8.4 Hz, 2.3 Hz, 1H), 6.79 (d, *J* = 8.4 Hz, 1H), 6.75 (d, *J* = 2.3 Hz, 1H), 3.65 (s, 3H), 3.64 (s, 2H), 2.87-2.79 (m, 2H), 2.73-2.66 (m, 1H), 2.32-2.28 (m, 2H), 1.95 (s, 3H), 1.37 (t, *J* = 6.3 Hz, 2H), 1.07 (d, *J* = 6.9 Hz, 6H), 0.96 (s, 6H). MS (ESI) *m/z* 514.2 $[M+H]^+$.

*4.5. N-(3,5-Bis(trifluoromethyl)benzyl)-N-methoxycarbonyl-(2-(5-isopropyl-2-methoxyphenyl)-5,5 -dimethylcyclohex-1-enyl)methanamine (**10a**).*

Intermediate **9** (0.2 g, 0.4 mmol) was dissolved in CH_2Cl_2 (5 mL) and methyl chloroformate (0.1 mL, 0.6 mmol) and *N*,*N*-diisopropylethylamine (0.2 mL, 1.4 mmol) were added. The reaction mixture was stirred at room temperature for 30 min and then poured into H_2O (10 mL), and extracted with CH_2Cl_2 (10 mL×3). The combined organic layers were washed with H_2O (10 mL×3) and brine (10 mL×3), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (petroleum ether : EtOAc = 8:1) to give **10a** (0.2 g, 87.0%) as a white solid. mp 77.4-83.2°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.67 (s, 1H), 7.46 (s, 1H), 7.35 (s, 1H), 7.04-7.00 (m, 1H), 6.74-6.67 (m, 2H), 4.46-4.33 (m, 1H), 4.24-4.17 (m, 1H), 4.10-3.90 (m, 1H), 3.73-3.65 (m, 7H), 2.73 (s, 1H), 2.47-2.41 (m, 1H), 2.09-2.05 (m, 1H), 1.83-1.77 (m, 2H), 1.46-1.40 (m, 2H), 1.12 (d, *J* = 3.6 Hz, 6H), 0.98 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.15(×2), 141.12, 140.97(×2), 130.44(×2), 128.01(×2), 127.34(×2), 125.82(×2), 124.63, 121.91, 120.85, 110.84, 55.33, 52.85, 40.21, 35.47, 33.09(×2), 29.04, 28.17(×2), 24.05(×2), 24.00(×2). HRMS calcd for $C_{30}H_{36}F_6NO_3$, $[M+H]^+$, 572.2594; found 572.2592. HPLC: t_R = 6.500 min, 95.23%.

*4.6. N-(3,5-Bis(trifluoromethyl)benzyl)-N-isopropoxycarbonyl-(2-(5-isopropyl-2-methoxyphenyl)-5,5-dimethylcyclohex-1-enyl)methanamine (**10b**).*

Colourless oil; yield 89.3%; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.67 (d, *J* = 4.7 Hz, 1H), 7.43 (m, 2H), 7.02 (d, *J* = 6.9 Hz, 1H), 6.75-6.68 (m, 2H), 4.44-4.19 (m, 2H), 3.95-3.87 (m, 3H), 3.74-3.64 (m, 4H), 2.74 (d, *J* = 5.3 Hz, 1H), 2.44-2.42 (m, 1H), 2.09-2.07 (m, 1H), 1.85-1.82 (m, 3H), 1.42 (t, *J* = 6.5 Hz, 2H), 1.13-1.11 (m, 6H), 0.98-0.97 (m, 9H), 0.80-0.79 (m, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 157.14, 154.17(×2), 141.54, 141.00(×2), 135.41, 131.29, 130.51, 128.05, 127.96, 127.33, 125.79, 124.18, 122.37, 120.78, 110.93, 71.96(×2), 55.31, 48.83, 47.27, 40.36, 35.49, 33.08(×2), 29.02, 28.20, 28.02(×2), 24.01(×2), 18.87. HRMS calcd for $C_{33}H_{42}F_6NO_3$, $[M+H]^+$, 614.3063; found 614.3072. HPLC: t_R = 7.913 min, 95.46%.

*4.7. N-(3,5-Bis(trifluoromethyl)benzyl)-N-benzyloxycarbonyl-(2-(5-isopropyl-2-methoxyphenyl)-5 ,5- dimethylcyclohex-1-enyl)methanamine (**10c**).*

Colourless oil; yield 91.2%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.67 (d, J = 5.5 Hz, 1H), 7.46 (s, 1H), 7.39-7.33 (m, 5H), 7.22-7.20 (m, 1H), 7.04-7.01 (m, 1H), 6.75-6.69 (m, 2H), 5.20-5.12 (m, 2H), 4.46-4.21 (m, 1H), 4.17-4.16 (m, 1H), 4.14-3.98 (m, 1H), 3.93-3.64 (m, 4H), 2.74 (t, *J* = 6.8 Hz, 1H), 2.52-2.50 (m, 1H), 2.06-2.05 (m, 1H), 1.86-1.74 (m, 2H), 1.44-1.40 (m, 2H), 1.12 (d, *J* = 6.9 Hz, 6H), 0.99-0.93 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.25, 154.99(×2), 154.24, 141.66, 140.90, 138.34, 135.06, 131.30, 130.98, 130.73, 128.18, 128.08(×2), 127.77, 125.66(×2), 124.23(×2), 122.21(×2), 117.80, 110.71, 55.34, 48.75, 47.51, 40.38, 35.57, 33.12, 29.16, 29.11(×2), 28.26, 28.10, 24.06(×2). HRMS calcd for $C_{36}H_{39}F_6NO_3Na$, $[M+Na]^+$, 670.2726; found 670.2750. HPLC: t_R = 7.774 min, 97.13%.

*4.8. (2-(5-Isopropyl-2-methoxyphenyl)-5,5-dimethylcyclohex-1-enyl)methanol (**11**).*

Intermediate **8** (114.5 mg, 0.4 mmol) was dissolved in ethanol (5 mL), and thereto was added sodium borohydride (19.0 mg, 0.5 mmol). After being stirred at room temperature for 30 min, the reaction mixture was poured into H_2O (20 mL) and extracted with EtOAc (10 mL×3). The combined organic layers were washed with H_2O (10 mL×3) and brine (10 mL×3), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (petroleum ether : EtOAc = 2:1) to give **11** (112.7 mg, 97.7%) as a colourless oil. ^{1}H NMR (400 MHz, DMSO-*d*6) δ: 7.06 (dd, *J* = 8.4 Hz, 2.2 Hz, 1H), 6.88-6.85 (m, 2H), 4.25 (t, *J* = 5.3 Hz, 1H), 3.67 (s, 3H), 3.64-3.53 (m, 2H), 2.85-2.75 (m,1H), 2.35-2.31 (m, 1H), 2.04-1.86 (m, 3H), 1.38 (t, *J* = 6.5 Hz, 2H), 1.16 (d, *J* = 6.9 Hz, 6H), 0.96 (d, *J* = 3.0 Hz, 6H). MS (ESI) *m/z* 311.4$[M+Na]^+$.

*4.9. 2-(2-(Chloromethyl)-4,4-dimethylcyclohex-1-enyl)-4-isopropyl-1-methoxybenzene (**12**).*

$SOCl_2$ (0.1 mL, 1.4 mmol) was added to a solution of intermediate **11** (115.3 mg, 0.4 mmol) in DMF (2 mL) cooled to 0°C. After being stirred at room temperature for 1 h, the reaction mixture was poured into H_2O (10 mL) and was extracted with EtOAc (5 mL×3). The combined organic layers were washed with H_2O (10 mL×3) and brine (10 mL×3), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (petroleum ether : EtOAc = 10:1) to give **12** (92.5 mg, 75.3%), which was used immediately for the next step because of its instability.

*4.10. N-(3,5-Bis(trifluoromethyl)benzyl)-5-bromopyrimidin-2-amine (**14**).*

3,5-Bis(trifluromethyl)benzyl amine (5.0 g, 20.6 mmol) and 5-bromo-2-chloropyrimidine (3.9 g, 20.3 mmol) were dissolved in 1,4-dioxane (25 mL) and DIEA (5.2 mL, 30.5 mmol) was added. The reaction mixture was heated to reflux for 10 h and then cooled to room temperature. After concentration, the residue was dissolved in EtOAc (50 mL), washed with H_2O (20 mL×3) and brine (20 mL×3), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (petroleum ether : EtOAc = 10:1) to give **14** (6.2 g, 75.8%) as a

white solid. mp 127.1-131.1°C. ^{1}H NMR (600 MHz, DMSO-*d*6) δ: 8.41 (s, 2H), 8.18 (t, *J* = 6.3 Hz, 1H), 7.98 (d, *J* = 3.8 Hz, 3H), 4.64 (d, *J* = 6.3 Hz, 2H). MS (ESI) *m/z* 398.0[M-H]$^-$.

*4.11. N-(3,5-Bis(trifluoromethyl)benzyl)-5-bromo-N-((2-(5-isopropyl-2-methoxyphenyl)-5,5-di methylcyclohex-1-enyl)methyl)pyrimidin-2-amine (**15**).*

NaH (20 mg, 0.5 mmol, 60% in oil) was added to a solution of intermediate **14** (120.0 mg, 0.3 mmol) in DMF (2 mL) cooled to 0°C. After stirring at 0°C for 30 min, a solution of intermediate **12** (92.1 mg, 0.3 mmol) in DMF (2 mL) was added. The reaction mixture was allowed to warm to room temperature and stirred for 30 min, and then it was poured onto crushed ice. The mixture was diluted with EtOAc (15 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (5 mL×3), and the combined organic layers were washed with H_2O (10 mL×3) and brine (10 mL×3), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (petroleum ether : EtOAc = 20:1) to give **15** (129.9 mg, 64.7%) as a white solid. mp 120.1-123.7°C. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.26 (s, 2H), 7.64 (s, 1H), 7.47 (s, 2H), 7.01 (dd, *J* = 8.5 Hz, 2.3 Hz, 1H), 6.75 (d, *J* = 2.2 Hz, 1H), 6.69 (d, *J* = 8.4 Hz, 1H), 4.76-4.73 (m, 1H), 4.56-4.50 (m, 2H), 4.01-3.99 (m, 1H), 3.67 (s, 3H), 2.76-2.70 (m, 1H), 2.48-2.45 (m, 1H), 2.11-2.08 (m, 1H), 1.80-1.71 (m, 2H), 1.45-1.40 (m, 2H), 1.12 (d, *J* = 6.8 Hz, 6H), 0.95 (d, *J* = 10.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.43, 157.86(×4), 154.23, 141.38, 140.93, 135.16, 131.35, 131.01, 130.68, 128.25(×2), 128.05(×2), 127.81, 125.71(×2), 110.74, 55.33, 48.96, 47.62, 40.39, 35.54, 33.12, 29.17, 29.09, 28.23, 28.12, 24.05(×2). HRMS calcd for $C_{32}H_{35}BrF_6N_3O$, $[M+H]^+$, 670.1862; found 670.1847. HPLC: t_R = 13.921 min, 99.30%.

*4.12. N-(3,5-Bis(trifluoromethyl)benzyl)-N-((2-(5-isopropyl-2-methoxyphenyl)-5,5-dimethylcyclo hex-1-enyl)methyl)-5-(piperazin-1-yl)pyrimidin-2-amine (**16a**).*

Under an argon atmosphere, intermediate **15** (133.8 mg, 0.2 mmol) was dissolved in toluene (2 mL), and *N*-Boc-piperazine (55.9 mg, 0.3 mmol), NaOt-Bu (28.8 mg, 0.3 mmol), $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol), and 2-(di-tert-butylphosphino)biphenyl (6.0 mg, 0.02 mmol) were added. The reaction mixture was heated to reflux for 4 h and then cooled to room temperature and poured into saturated sodium bicarbonate solution. The mixture was diluted with EtOAc (5 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (5 mL×3), and the combined organic layers were washed with H_2O (5 mL×3) and brine (5 mL×3), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was immediately dissolved in saturated trifluoroacetic acid–CH_2Cl_2 (1:1) solution (2 mL) and stirred at room temperature overnight. After concentration, the residue was dissolved in EtOAc (5 mL), washed with H_2O (5 mL×3) and brine (5 mL×3), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (petroleum ether : EtOAc = 2:1) to give **16a** (65.3 mg, 48.3%) as a yellow solid. mp 61.8-64.2°C. ^{1}H NMR (400 MHz, DMSO-*d*6) δ: 9.45 (brs, 1H), 8.22 (s, 2H), 7.87 (s, 1H), 7.59 (s, 2H), 6.97 (dd, *J* = 8.4 Hz, 1.9 Hz, 1H), 6.74-6.73 (m, 2H), 4.75-4.62 (m, 2H), 4.30-4.16 (m, 2H), 3.63 (s, 3H), 3.25 (t, *J* = 3.1 Hz, 4H), 3.19 (t, *J* = 2.2 Hz, 4H), 2.66-2.60 (m, 1H), 2.37-2.33 (m, 1H), 2.04-2.00 (m, 1H), 1.75 (s, 2H), 1.37 (t, *J* = 6.1 Hz, 2H), 1.00 (d, *J* = 6.9 Hz, 6H), 0.91 (d, *J* = 3.9 Hz, 6H). ^{13}C NMR (100 MHz, DMSO-*d*6) δ: 157.88, 154.53, 148.29(×2), 143.40, 140.51, 136.41, 133.97, 130.61(×2), 130.30, 128.57, 127.75, 127.59(×2), 125.73, 125.08, 122.37, 120.61,

111.33, 55.75, 52.51, 46.82(×2), 42.97(×2), 35.52, 32.81, 29.27, 29.13, 28.62, 28.17, 24.28(×2), 24.21(×2). HRMS calcd for $C_{36}H_{44}F_6N_5O$, $[M+H]^+$, 676.3445; found 676.3436. HPLC: t_R = 25.670 min, 95.99%.

*4.13. N-(3,5-Bis(trifluoromethyl)benzyl)-N-((2-(5-isopropyl-2-methoxyphenyl)-5,5-dimethylcyclo hex-1-enyl)methyl)-5-(4-methylpiperazin-1-yl)pyrimidin-2-amine (**16b**).*

Colourless oil; yield 43.5%; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.07 (s, 2H), 7.62 (s, 1H), 7.49 (s, 2H), 6.98 (dd, *J* = 8.4 Hz, 2.1 Hz, 1H), 6.75 (d, *J* = 2.1 Hz, 1H), 6.66 (d, *J* = 8.5 Hz, 1H), 4.77-4.74 (m, 1H), 4.55-4.52 (m, 2H), 4.02-4.00 (m, 1H), 3.65 (s, 3H), 3.06 (t, *J* = 4.6 Hz, 4H), 2.71 (t, *J* = 6.9 Hz, 1H), 2.60 (d, *J* = 4.0 Hz, 4H), 2.47-2.44 (m, 1H), 2.35 (s, 3H), 2.09-2.06 (m, 1H), 1.79 (d, *J* = 7.5 Hz, 2H), 1.44-1.38 (m, 2H), 1.11 (d, *J* = 6.9 Hz, 6H), 0.93 (d, *J* = 12.2 Hz, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 158.19, 154.27, 148.41(×2), 142.43, 140.78, 136.48, 134.47, 130.88, 128.68, 128.18(×2), 127.62(×2), 125.48(×2), 124.32, 122.51, 120.25, 110.64, 55.28, 54.83(×2), 50.25(×2), 48.76, 47.61, 45.77, 40.36, 35.61, 33.08, 29.12, 29.07, 28.28, 28.03, 24.03(×2). HRMS calcd for $C_{37}H_{46}F_6N_5O$, $[M+H]^+$, 690.3601; found 690.3632. HPLC: t_R = 28.113 min, 97.71%.

*4.14. 5-(4-Aminopiperidin-1-yl)-N-(3,5-bis(trifluoromethyl)benzyl)-N-((2-(5-isopropyl-2-methoxy phenyl)-5,5-dimethylcyclohex-1-enyl)methyl)pyrimidin-2-amine (**16c**).*

Red oil; yield 53.1%; ^{1}H NMR (400 MHz, DMSO-*d*6) δ: 8.35 (s, 2H), 8.14 (s, 2H), 7.85 (s, 1H), 7.57 (s, 2H), 6.94 (dd, *J* = 6.4 Hz, 1.2 Hz, 1H), 6.73 (d, *J* = 6.4 Hz, 1H), 6.71 (d, *J* = 1.2 Hz, 1H), 4.70-4.60 (m, 2H), 4.25-4.13 (m, 2H), 3.60 (s, 3H), 3.40 (d, *J* = 8.0 Hz, 2H), 2.90-2.84 (m, 1H), 2.62-2.60 (m, 2H), 2.59 (s, 1H), 2.34-2.31 (m, 1H), 2.01-1.98 (m, 1H), 1.86 (d, *J* = 7.2 Hz, 2H), 1.72 (s, 2H), 1.51-1.49 (m, 2H), 1.34 (t, *J* = 4.3 Hz, 2H), 0.98 (d, J = 4.6 Hz, 6H), 0.88 (d, *J* = 4.6 Hz, 6H).^{13}C NMR (150 MHz, DMSO-*d*6) δ: 157.47, 154.54, 148.27(×2), 143.56, 140.53, 137.17, 133.85, 130.68, 130.56, 130.34, 128.68, 127.75, 127.58(×2), 125.72, 124.63, 122.82, 120.54, 111.38, 55.77, 48.48(×2), 47.74(×2), 45.80(×2), 35.54, 32.79, 29.71(×2), 29.11(×2), 28.62, 28.17, 24.27, 24.20. HRMS calcd for $C_{37}H_{46}F_6N_5O$, $[M+H]^+$, 690.3601; found 690.3611. HPLC: t_R = 26.614 min, 96.55%.

*4.15. N-(1-(2-((3,5-Bis(trifluoromethyl)benzyl)((2-(5-isopropyl-2-methoxyphenyl)-5,5-dimethyl cyclohex-1-enyl)methyl)amino)pyrimidin-5-yl)piperidin-4-yl)acetamide (**16d**).*

Brown solid; yield 46.1%; mp 143.5-147.3°C. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.06 (s, 2H), 7.61 (s, 1H), 7.48 (s, 2H), 6.97 (dd, *J* = 8.5 Hz, 2.2 Hz, 1H), 6.73 (d, *J* = 2.2 Hz, 1H), 6.66 (d, *J* = 8.4 Hz, 1H), 5.71 (d, *J* = 7.8 Hz, 1H), 4.76-4.73 (m, 1H), 4.54-4.51 (m, 2H), 4.01-3.99 (m, 1H), 3.90-3.84 (m, 1H), 3.65 (s, 3H), 3.31-3.29 (m, 2H), 2.78 (t, *J* = 11.8 Hz, 2H), 2.70 (t, *J* = 6.9 Hz, 1H), 2.47-2.44 (m, 1H), 2.08-2.06 (m, 1H), 2.03 (d, *J* = 13.0 Hz, 2H), 1.97 (s, 3H), 1.78 (d, *J* = 8.2 Hz, 2H), 1.58-1.56 (m, 2H), 1.42-1.39 (m, 2H), 1.10 (d, *J* = 7.0 Hz, 6H), 0.92 (d, *J* = 12.0 Hz, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 169.52, 158.21, 154.26, 148.85(×2), 142.33, 140.79, 134.57, 131.10, 130.85, 128.58, 128.17(×2), 127.62(×2), 125.50(×2), 124.31, 122.50, 120.28, 110.65, 55.28(×2), 50.55, 48.79, 47.60, 46.00, 40.35, 35.59, 33.08, 31.98, 29.11, 29.06, 28.27, 28.02,

24.02(×2), 23.44. HRMS calcd for $C_{39}H_{48}F_6N_5O_2$, $[M+H]^+$, 732.3707; found 732.3714. HPLC: t_R = 29.532 min, 97.18%.

*4.16. 1-(2-((3,5-Bis(trifluoromethyl)benzyl)((2-(5-isopropyl-2-methoxyphenyl)-5,5-dimethylcyclo hex-1-enyl)methyl)amino)pyrimidin-5-yl)piperidine-4-carboxylic acid (**16e**).*

Brown solid; yield 39.3%; mp 72.0-75.5°C. ^{1}H NMR (600 MHz, DMSO-*d*6) δ: 8.14 (s, 2H), 7.87 (s, 1H), 7.56 (s, 2H), 6.95 (dd, *J* = 8.5 Hz, 2.2 Hz, 1H), 6.74-6.71 (m, 2H), 4.67-4.63 (m, 2H), 4.21-4.13 (m, 2H), 3.61 (s, 3H), 2.64-2.59 (m, 3H), 2.33-2.28 (m, 2H), 2.01-1.98 (m, 1H), 1.88-1.86 (m, 2H), 1.72 (s, 2H), 1.65-1.62 (m, 2H), 1.34 (t, *J* = 6.5 Hz, 2H), 1.22 (s, 2H), 0.99 (d, *J* = 6.9 Hz, 6H), 0.89 (d, *J* = 8.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 179.68, 158.02, 154.26, 148.83(×2), 142.39, 140.78, 137.08, 134.53, 131.14, 130.86, 130.81, 128.64, 128.19(×2), 127.57, 125.49, 124.78, 122.07, 120.63, 110.62, 55.29(×2), 50.79, 50.71, 48.76, 47.57, 40.31, 35.61, 33.09(×2), 29.08(×2), 28.29, 28.05(×2), 24.06(×2). HRMS calcd for $C_{38}H_{43}F_6N_4O_3$, $[M-H]^-$, 717.3239; found 717.3205. HPLC: t_R = 22.183 min, 95.13%.

*4.17. N-(3,5-Bis(trifluoromethyl)benzyl)-N-((2-(5-isopropyl-2-methoxyphenyl)-5,5-dimethylcyclo hex-1-enyl)methyl)-5-morpholinopyrimidin-2-amine (**16f**).*

Colourless oil; yield 46.0%; ^{1}H NMR (600 MHz, DMSO-*d*6) δ: 8.10 (s, 2H), 7.63 (s, 1H), 7.48 (s, 2H), 6.98 (dd, *J* = 8.4 Hz, 2.3 Hz, 1H), 6.75 (d, *J* = 2.3 Hz, 1H), 6.67 (d, *J* = 8.4 Hz, 1H), 4.82-4.76 (m, 1H), 4.57-4.53 (m, 2H), 4.05-4.02 (m, 1H), 3.86 (t, *J* = 4.6 Hz, 4H), 3.66 (s, 3H), 3.02 (t, *J* = 4.6 Hz, 4H), 2.76-2.69 (m, 1H), 2.50-2.42 (m, 1H), 2.10-2.04 (m, 1H), 1.80-1.78 (m, 2H), 1.43 (s, 2H), 1.12 (d, *J* = 6.9 Hz, 6H), 0.94 (d, *J* = 8.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.25(×2), 140.82(×2), 134.72, 131.19, 130.86, 130.80, 128.48, 128.19(×2), 127.60(×2), 125.53(×2), 124.76, 122.05, 120.35, 110.64(×2), 66.76(×2), 55.31, 50.76, 48.85, 47.60, 40.35, 35.59, 33.10(×2), 29.12, 29.09, 28.29, 28.05, 24.07, 24.03. HRMS calcd for $C_{36}H_{43}F_6N_4O_2$, $[M+H]^+$, 677.3285; found 677.3272. HPLC: t_R = 23.472 min, 97.80%.

*4.18. N-(3,5-Bis(trifluoromethyl)benzyl)-N-((2-(5-isopropyl-2-methoxyphenyl)-5,5-dimethylcyclo hex-1-enyl)methyl)-5-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine (**17a**).*

Under an argon atmosphere, intermediate **15** (0.2 g, 0.3 mmol), 1-methylpyrazole-4-boronic acid pinacol ester (0.1 g, 0.5 mmol), $Pd(PPh_3)_4$ (34.7 mg, 0.03 mmol), Na_2CO_3 (63.6 mg, 0.6 mmol), DME (5 mL), and H_2O (0.5 mL) were added to a three-necked bottle containing a stirring bar. After being stirred at 90°C for 12 h, the reaction mixture was cooled to room temperature, and H_2O (20 mL) was added. The aqueous layer was extracted with EtOAc (10 mL×3), and the combined organic layers were washed with H_2O (10 mL×3) and brine (10 mL×3), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (petroleum ether : EtOAc = 2:1) to give **17a** (125.6 mg, 62.8%) as a white solid. mp 45.4-49.1°C. ^{1}H NMR (600 MHz, DMSO-*d*6) δ: 8.58 (s, 2H), 8.06 (s, 1H), 7.89 (s, 1H), 7.80 (s, 1H), 7.60 (s, 2H), 6.96 (dd, *J* = 8.4 Hz, 1.8 Hz, 1H), 6.76-6.74 (m, 2H), 4.78-4.66 (m, 2H), 4.32-4.20 (m, 2H), 3.84 (s, 3H), 3.62 (s, 3H), 2.64-2.59 (m, 1H), 2.35-2.32 (m, 1H), 2.03-2.00 (m, 1H), 1.74 (s, 2H), 1.36 (t, *J* = 6.4 Hz, 2H), 0.99-0.98 (m, 6H), 0.91 (d, *J* = 2.9 Hz, 6H). ^{13}C NMR (150 MHz,

DMSO-*d*6) δ: 160.37, 154.50(×2), 154.41, 142.63, 140.20, 135.40(×2), 133.76, 130.20, 130.02, 127.98, 127.35, 127.23(×2), 126.89, 125.40, 124.21, 122.41, 120.35, 116.05, 115.96, 111.03, 55.42, 48.18, 47.28, 38.69, 35.12, 32.41(×2), 28.92, 28.74, 28.23, 27.80, 23.89, 23.82. HRMS calcd for $C_{36}H_{40}F_6N_5O$, $[M+H]^+$, 672.3132; found 672.3164. HPLC: t_R = 8.010 min, 98.72%.

*4.19. N-(3,5-bis(trifluoromethyl)benzyl)-5-(3,5-dimethylisoxazol-4-yl)-N-((2-(5-isopropyl-2-methoxyphenyl)-5,5-dimethylcyclohex-1-enyl)methyl)pyrimidin-2-amine (**17b**).*

Pale yellow oil; yield 58.3%; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.21 (s, 2H), 7.65 (s, 1H), 7.51 (s, 2H), 7.01 (dd, *J* = 8.5 Hz, 2.2 Hz, 1H), 6.78 (d, *J* = 2.2 Hz, 1H), 6.70 (d, *J* = 8.5 Hz, 1H), 4.85-4.82 (m, 1H), 4.67-4.64 (m, 1H), 4.61-4.58 (m, 1H), 4.08-4.06 (m, 1H), 3.67 (s, 3H), 2.76-2.72 (m, 1H), 2.50-2.47 (m, 1H), 2.39 (s, 3H), 2.25 (s, 3H), 2.13-2.10 (m, 1H), 1.88-1.79 (m, 2H), 1.47-1.42 (m, 2H), 1.13 (d, *J* = 6.9 Hz, 6H), 0.97 (d, *J* = 10.6 Hz, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 154.85(×2), 154.23, 141.45, 140.95, 138.01, 135.25, 131.30, 131.08, 130.70, 128.15(×2), 128.09(×2), 127.74(×2), 125.68(×2), 124.39, 122.38, 120.60, 117.85, 110.76, 55.35(×2), 48.95, 47.59, 40.43, 35.55, 33.09(×2), 29.18(×2), 28.25(×2), 24.04(×2). HRMS calcd for $C_{37}H_{41}F_6N_4O_2$, $[M+H]^+$, 687.3128; found 687.3128. HPLC: t_R = 8.026 min, 99.84%.

*4.20. N-(3,5-bis(trifluoromethyl)benzyl)-N-((2-(5-isopropyl-2-methoxyphenyl)-5,5-dimethylcyclohex-1-enyl)methyl)-5-(1-methyl-1H-pyrazol-5-yl)pyrimidin-2-amine (**17c**).*

White solid; yield 66.9%; mp 97.8-102.8°C. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.35 (s, 2H), 7.66 (s, 1H), 7.53 (d, *J* = 1.9 Hz, 1H), 7.51 (s, 2H), 7.02 (dd, *J* = 8.3 Hz, 2.2 Hz, 1H), 6.78 (d, *J* = 2.2 Hz, 1H), 6.71 (d, *J* = 8.5 Hz, 1H), 6.29 (d, *J* = 1.8 Hz, 1H), 4.87-4.84 (m, 1H), 4.68-4.66 (m, 1H), 4.62-4.59 (m, 1H), 4.09-4.07 (m, 1H), 3.88 (s, 3H), 3.68 (s, 3H), 2.75-2.72 (m, 1H), 2.50-2.47 (m, 1H), 2.13-2.10 (m, 1H), 1.86-1.78 (m, 2H), 1.47-1.42 (m, 2H), 1.13 (d, *J* = 6.9 Hz, 6H), 0.97 (d, *J* = 9.8 Hz, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 161.56, 157.07(×2), 154.23, 140.96, 138.70, 138.21, 135.35, 131.08, 130.68, 128.12(×2), 127.82(×2), 125.73(×2), 124.24, 122.43, 120.62, 113.43, 110.79, 106.00(×2), 55.34, 48.84, 47.53, 40.46, 37.31, 35.55, 33.10, 29.18, 29.10, 28.23, 28.08, 24.02(×2). HRMS calcd for $C_{36}H_{40}F_6N_5O$, $[M+H]^+$, 672.3132; found 672.3130. HPLC: t_R = 7.777 min, 99.74%.

*4.21. N-(3,5-bis(trifluoromethyl)benzyl)-N-((2-(5-isopropyl-2-methoxyphenyl)-5,5-dimethylcyclohex-1-enyl)methyl)-5-(thiophen-2-yl)pyrimidin-2-amine (**17d**).*

White solid; yield 62.1%; mp 53.2-57.3°C. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.53 (s, 2H), 7.65 (s, 1H), 7.50 (s, 2H), 7.27 (s, 1H), 7.17 (d, *J* = 3.5 Hz, 1H), 7.09-7.07 (m, 1H), 7.00 (dd, *J* = 8.4 Hz, 2.2 Hz, 1H), 6.77 (d, *J* = 2.2 Hz, 1H), 6.70 (d, *J* = 8.4 Hz, 1H), 4.88-4.86 (m, 1H), 4.67-4.65 (m, 1H), 4.61-4.59 (m, 1H), 4.10-4.07 (m, 1H), 3.68 (s, 3H), 2.76-2.72 (m, 1H), 2.49-2.46 (m, 1H), 2.12-2.09 (m, 1H), 1.86-1.75 (m, 2H), 1.45-1.41 (m, 2H), 1.13 (d, *J* = 6.9 Hz, 6H), 0.96 (d, *J* = 10.5 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.25, 154.99(×2), 154.24, 141.66, 140.90, 138.34, 135.06, 131.30, 130.98, 130.73, 128.18(×2), 128.08(×2), 127.77, 125.66(×2), 124.23(×2), 122.21(×2), 117.80, 110.71, 55.34, 48,75, 47.51, 40.38, 35.57, 33.12, 29.16, 29.10, 28.26, 28.10, 24.06(×2). HRMS calcd for $C_{36}H_{38}F_6N_3OS$, $[M+H]^+$, 674.2634; found 674.2657. HPLC: t_R =

14.710 min, 99.27%.

*4.22. 2-((3,5-Bis(trifluoromethyl)benzyl)((2-(5-isopropyl-2-methoxyphenyl)-5,5-dimethylcyclohex-1-enyl)methyl)amino)pyrimidin-5-ol (**18**).*

Under an argon atmosphere, intermediate **15** (3.6 g, 5.4 mmol), $PdCl_2$(dppf)-CH_2Cl_2 (0.9 g, 1.1 mmol), AcOK (1.6 g, 16.2 mmol), bis(pinacolato) diboron (2.7 g, 10.8 mmol), and DMSO (40 mL) were added to a three-necked bottle containing a stirring bar. After being stirred at 80°C for 1 h, the reaction mixture was cooled to room temperature, and H_2O (200 mL) was added. The aqueous layer was extracted with EtOAc (50 mL×3), and the combined organic layers were washed with H_2O (50 mL×3) and brine (50 mL×3), dried over $NaSO_4$, and concentrated *in vacuo*. 30% H_2O_2 (15 mL) was added to a solution of the residue in THF (100 mL) cooled to 0°C, and the resultant mixture was stirred at 0℃ for 1 h prior to the addition of saturated sodium thiosulfate solution (10 mL). The mixture was extracted with EtOAc (20 mL×3), and the combined organic layers were washed with H_2O (20 mL×3) and brine (20 mL×3), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (petroleum ether : EtOAc = 2:1) to give **18** (1.5 g, 46.4%) as a white solid. mp 43.8-47.4°C. ^{1}H NMR (600 MHz, DMSO-*d*6) δ: 9.18 (s, 1H), 7.98 (s, 2H), 7.86 (s, 1H), 7.56 (s, 2H), 6.96 (dd, *J* = 8.3 Hz, 2.0 Hz, 1H), 6.75-6.72 (m, 2H), 4.68-4.58 (m, 2H), 4.21-4.11 (m, 2H), 3.62 (s, 3H), 2.64-2.60 (m, 1H), 2.34-2.31 (m, 1H), 2.01-1.98 (m, 1H), 1.72 (s, 2H), 1.35 (t, *J* = 6.4 Hz, 2H), 1.00 (d, *J* = 6.9 Hz, 6H), 0.89 (d, *J* = 7.4 Hz, 6H). ^{13}C NMR (150 MHz, DMSO) δ: 156.61, 154.18, 145.47(×2), 143.72, 143.24, 140.15, 133.25, 130.35, 130.14, 129.93, 128.44, 127.39, 127.23(×2), 125.33, 124.27, 122.46, 120.15, 111.01, 55.41(×2), 48.47, 47.55, 35.17, 32.42, 28.91, 28.74, 28.25, 27.80, 23.92, 23.85. HRMS calcd for $C_{32}H_{36}F_6N_3O_2$, $[M+H]^+$, 608.2706; found 608.2707. HPLC: t_R = 6.600min, 97.53%.

*4.23. Methyl2-(2-((3,5-bis(trifluoromethyl)benzyl)((2-(5-isopropyl-2-methoxyphenyl)-5,5-dimethyl cyclohex-1-enyl)methyl)amino)pyrimidin-5-yloxy)acetate (**19a**).*

Intermediate **18** (0.1 g, 0.2 mmol) and methyl bromoacetate (45.9 mg, 0.3 mmol) were dissolved in DMF (2 mL), followed by the addition of K_2CO_3 (41.5 mg, 0.3 mmol). After being stirred at room temperature for 2 h, the reaction mixture was poured into H_2O (10 mL) and extracted with EtOAc (5 mL×3), and the combined organic layers were washed with H_2O (5 mL×3) and brine (5 mL×3), dried over $NaSO_4$, and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (petroleum ether : EtOAc = 8:1) to give **19a** (101.8 mg, 74.9%) as a colourless oil. ^{1}H NMR (600 MHz, DMSO-*d*6) δ: 8.13 (s, 2H), 7.82 (s, 1H), 7.51 (s, 2H), 6.90 (dd, *J* = 8.5 Hz, 2.2 Hz, 1H), 6.69-6.66 (m, 2H), 4.72 (s, 2H), 4.65-4.55 (m, 2H), 4.20-4.09 (m, 2H), 3.61 (s, 3H), 3.55 (s, 3H), 2.57-2.53 (m, 1H), 2.28-2.25 (m, 1H), 1.96-1.93 (m, 1H), 1.67 (s, 2H), 1.30 (t, *J* = 6.4 Hz, 2H), 0.93 (d, *J* = 6.9 Hz, 6H), 0.84 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (150 MHz, DMSO-*d*6) δ: 169.15, 157.71, 154.13, 146.15(×2), 144.84, 142.86, 140.15, 133.59, 130.19, 128.11, 127.34(×2), 127.16(×2), 125.36(×2), 124.22, 122.41, 120.25, 110.98, 66.20, 55.38, 51.82(×2), 48.55, 47.55, 35.13, 32.40, 28.90, 28.74, 28.23, 27.78, 23.88, 23.82. HRMS calcd for $C_{35}H_{40}F_6N_3O_4$, $[M+H]^+$, 680.2918; found 680.2919. HPLC: t_R = 6.696 min, 98.50%.

*4.24. 2-(2-((3,5-Bis(trifluoromethyl)benzyl)((2-(5-isopropyl-2-methoxyphenyl)-5,5-dimethylcyclo hex-1-enyl)methyl)amino)pyrimidin-5-yloxy)acetic acid (**19b**).*

Colourless oil; yield 84.3%; ^{1}H NMR (600 MHz, DMSO-*d*6) *δ*: 12.95 (s, 1H), 8.18 (s, 2H), 7.87 (s, 1H)**,** 7.58 (s, 2H), 6.96 (dd, *J* = 8.4 Hz, 2.2 Hz, 1H), 6.76-6.73 (m, 2H), 4.72-4.62 (m, 1H), 4.26-4.24 (m, 1H), 4.17-4.15 (m, 1H), 3.62 (s, 3H), 2.65-2.60 (m, 1H), 2.35-2.32 (m, 1H), 2.03-2.01 (m, 1H), 1.74 (s, 2H), 1.36 (t, *J* = 6.2 Hz, 2H), 1.00 (d, *J* = 6.9 Hz, 6H), 0.91 (d, *J* = 7.1 Hz, 6H). ^{13}C NMR (150 MHz, DMSO-*d*6) *δ*: 170.50, 158.00, 154.54, 146.40(×2), 145.35, 143.30, 140.57, 133.96, 130.65, 128.55, 127.75(×2), 127.58(×2), 125.77(×2), 124.63, 122.82, 120.64, 111.40, 66.45, 55.80(×2), 48.95, 47.96, 35.54, 32.80, 29.31, 29.15, 28.63, 28.19, 24.29, 24.23. HRMS calcd for $C_{34}H_{36}F_6N_3O_4$, $[M-H]^+$, 664.2610; found 664.2579. HPLC: t_R = 17.043 min, 99.35%.

*4.25. 4-(2-((3,5-Bis(trifluoromethyl)benzyl)((2-(5-isopropyl-2-methoxyphenyl)-5,5-dimethylcyclo hex-1-enyl)methyl)amino)pyrimidin-5-yloxy)butanoic acid (**19c**).*

Colourless oil; yield 72.1%; ^{1}H NMR (600 MHz, DMSO-*d*6) *δ*: 12.11 (s, 1H), 8.16 (s, 2H), 7.87 (s, 1H), 7.58 (s, 2H), 6.96 (dd, *J* = 8.5 Hz, 2.1 Hz, 1H), 6.76-6.73 (m, 2H), 4.72-4.62 (m, 2H), 4.25-4.15 (m, 2H), 3.96 (t, *J* = 6.4 Hz, 2H), 3.62 (s, 3H), 2.63-2.60 (m, 1H), 2.37-2.34 (m, 2H), 2.32 (s, 1H), 2.03 (s, 1H), 2.01-1.86 (m, 2H), 1.73 (s, 2H), 1.36 (t, *J* = 6.4 Hz, 2H), 1.00 (d, *J* = 7.0 Hz, 6H), 0.91 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 178.34, 154.25, 145.66, 145.35, 142.26, 140.80, 134.59, 131.17, 130.84(×2), 128.58, 128.19(×2), 127.56, 125.51(×2), 124.76, 122.06, 120.27, 110.63(×2), 68.59, 55.30, 49.00, 47.73, 40.35, 35.59, 33.10, 30.22, 29.13, 29.08, 28.28, 28.05, 24.45, 24.06, 24.02. HRMS calcd for $C_{36}H_{40}F_6N_3O_4$, $[M-H]^+$, 692.2923; found 692.2943. HPLC: t_R = 17.508 min, 99.67%.

*4.26. 2-(2-((3,5-Bis(trifluoromethyl)benzyl)((2-(5-isopropyl-2-methoxyphenyl)-5,5-dimethylcyclo hex-1-enyl)methyl)amino)pyrimidin-5-yloxy)ethanol (**19d**).*

White solid; yield 56.5%; mp 85.5-89.9°C. ^{1}H NMR (600 MHz, DMSO-*d*6) *δ*: 8.18 (s, 2H), 7.88 (s, 1H), 7.57 (s, 2H), 6.96 (dd, *J* = 8.5 Hz, 2.1 Hz, 1H), 6.76-6.73 (m, 2H), 4.88 (t, *J* = 5.5 Hz, 1H), 4.72-4.62 (m, 2H), 4.25-4.15 (m, 2H), 3.98 (t, *J* = 4.8 Hz, 2H), 3.66 (t, *J* = 4.9 Hz, 2H), 3.62 (s, 3H), 2.64-2.59 (m, 1H), 2.35-2.32 (m, 1H), 2.03-2.00 (m, 1H), 1.74 (s, 2H), 1.36 (t, *J* = 6.4 Hz, 2H), 1.00 (d, *J* = 6.9 Hz, 6H), 0.91 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 158.22, 154.27, 145.86(×2), 145.34, 142.28, 140.81, 134.56, 130.85(×2), 128.60, 128.19(×2), 127.63, 125.53(×2), 124.77, 122.06, 120.32, 110.64, 71.34, 61.43, 55.30, 48.97, 47.74, 40.36, 35.59, 33.10, 29.13, 29.08, 28.28, 28.06, 24.06, 24.03. HRMS calcd for $C_{34}H_{40}F_6N_3O_3$, $[M+H]^+$, 652.2968; found 652.2968. HPLC: t_R = 14.536 min, 98.18%.

*4.27. N-(3,5-Bis(trifluoromethyl)benzyl)-N-((2-(5-isopropyl-2-methoxyphenyl)-5,5-dimethylcyclo hex-1-enyl)methyl)-5-(2-methoxyethoxy)pyrimidin-2-amine (**19e**).*

Colourless oil; yield 68.7%; ^{1}H NMR (600 MHz, DMSO-*d*6) *δ*: 8.18 (s, 2H), 7.88 (s, 1H),

7.58 (s, 2H), 6.96 (dd, *J* = 8.5 Hz, 2.2 Hz, 1H), 6.75-6.73 (m, 2H), 4.72-4.62 (m, 2H), 4.25-4.15 (m, 2H), 4.09-4.07 (m, 2H), 3.62 (s, 3H), 3.61-3.59 (m, 2H), 3.27 (s, 3H), 2.63-2.61 (m, 1H), 2.35-2.32 (m, 1H), 2.03-1.99 (m, 1H), 1.73 (s, 2H), 1.36 (t, *J* = 6.4 Hz, 2H), 1.00 (d, *J* = 6.9 Hz, 6H), 0.91 (d, *J* = 7.1 Hz, 6H). ^{13}C NMR (150 MHz, DMSO-*d*6) *δ*: 157.82, 154.54, 146.17(×2), 145.90, 143.37, 140.55, 133.88, 130.65, 130.36, 128.60, 127.75(×2), 127.55(×2), 125.75, 124.63, 122.83, 120.62, 111.39, 70.91, 69.04, 58.54(×2), 55.80, 48.88, 47.92, 35.54, 32.80, 29.30, 29.14, 28.65, 28.18, 24.30, 24.23. HRMS calcd for $C_{35}H_{42}F_6N_3O_3$, $[M+H]^+$, 666.3125; found 666.3136. HPLC: t_R = 8.043 min, 96.90%.

*4.28. N-(3,5-bis(trifluoromethyl)benzyl)-N-((2-(5-isopropyl-2-methoxyphenyl)cyclopent-1-enyl) methyl)-5-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine (**26a**).*

The title compound was obtained in a manner similar to that described for the preparation of **17a**. Colourless oil; yield 43.8%; ^{1}H NMR (600 MHz, $CDCl_3$) *δ*: 8.43 (s, 2H), 7.67 (s, 2H), 7.54-7.53 (m, 3H), 7.07 (dd, *J* = 8.3 Hz, 1.6 Hz, 1H), 6.85 (d, *J* = 1.7 Hz, 1H), 6.81 (d, *J* = 8.4 Hz, 1H), 4.69 (s, 2H), 4.41 (s, 2H), 3.95 (s, 3H), 3.75 (s, 3H), 2.78-2.76 (m, 1H), 2.74-2.71 (m, 2H), 2.39 (t, *J* = 7.1 Hz, 2H), 1.89-1.84 (m, 2H), 1.13 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) *δ*: 160.93, 155.15, 154.88(×2), 141.21, 136.07(×2), 135.33, 133.63, 131.33, 129.80, 127.65, 127.11, 126.61, 126.57, 126.06, 125.42, 124.25, 122.44, 120.57, 117.23, 115.91, 111.00, 55.50(×2), 48.73, 48.17, 39.12, 33.09, 28.08, 25.07, 24.04(×2). HRMS calcd for $C_{33}H_{34}F_6N_5O$, $[M+H]^+$, 630.2662; found 630.2658. HPLC: t_R = 6.493 min, 97.66%.

*4.29. N-(3,5-bis(trifluoromethyl)benzyl)-N-((2-(5-isopropyl-2-methoxyphenyl)cyclohex-1-enyl) methyl)-5-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine (**26b**).*

Colourless oil; yield 51.3%; ^{1}H NMR (600 MHz, $CDCl_3$) *δ*: 8.39 (s, 2H), 7.66-7.64 (m, 2H), 7.59 (s, 2H), 7.51 (s, 1H), 7.02 (dd, *J* = 8.4 Hz, 2.2 Hz, 1H), 6.80 (d, *J* = 2.2 Hz, 1H), 6.73 (d, *J* = 8.4 Hz, 1H), 4.80-4.77 (m, 1H), 4.63-4.58 (m, 2H), 4.07-4.05 (m, 1H), 3.94 (s, 3H), 3.70 (s, 3H), 2.76-2.73 (m, 1H), 2.44-2.41 (m, 1H), 2.09-2.00 (m, 3H), 1.69-1.67 (m, 2H), 1.63-1.61 (m, 2H), 1.13 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) *δ*: 161.00, 154.75(×2), 154.23, 141.98, 140.84, 136.04(×2), 135.84, 131.07(×2), 129.63, 128.22, 127.97(×2), 125.99, 125.62, 124.32, 122.50, 120.50, 117.34, 115.54, 110.78, 55.28, 48.93, 48.06, 39.07, 33.10, 31.26, 26.70, 24.03(×2), 22.98, 22.58. HRMS calcd for $C_{34}H_{36}F_6N_5O$, $[M+H]^+$, 644.2819; found 644.2830. HPLC: t_R = 6.735 min, 95.77%.

*4.30. N-(3,5-bis(trifluoromethyl)benzyl)-N-((2-(5-isopropyl-2-methoxyphenyl)cyclohept-1-enyl) methyl)-5-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine (**26c**).*

Colourless oil; yield 48.5%; ^{1}H NMR (600 MHz, $CDCl_3$) *δ*: 8.40 (s, 2H), 7.65-7.64 (m, 2H), 7.54 (s, 2H), 7.51 (s, 1H), 6.99 (dd, *J* = 8.4 Hz, 2.2 Hz, 1H), 6.74 (d, *J* = 2.2 Hz, 1H), 6.71 (d, *J* = 8.4 Hz, 1H), 4.86-4.84 (m, 1H), 4.81-4.78 (m, 1H), 4.59-4.56 (m, 1H), 3.94 (d, *J* = 3.6 Hz, 3H), 3.91-3.89 (m, 1H), 3.72 (s, 3H), 2.75-2.73 (m, 1H), 2.50-2.46 (m, 1H), 2.34-2.30 (m, 1H), 2.15-2.14 (m, 2H), 1.74-1.71 (m, 3H), 1.51-1.49 (m, 3H), 1.13 (dd, *J* = 6.8 Hz, 2.6 Hz, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) *δ*: 160.98, 154.82(×2), 154.11, 142.91, 141.88, 140.53, 136.03(×2),

135.48, 132.47, 131.08, 130.87, 128.33, 128.01, 126.01, 125.42, 124.32, 122.51, 120.39, 117.33, 115.57, 110.69, 55.22, 49.21, 47.59, 39.10, 35.97, 33.11, 32.69, 30.76, 26.43, 24.85, 24.05(×2). HRMS calcd for $C_{35}H_{38}F_6N_5O$, $[M+H]^+$, 658.2975; found 658.2970. HPLC: t_R = 7.483 min, 96.73%.

*4.31. N-(3,5-bis(trifluoromethyl)benzyl)-N-((2-(5-isopropyl-2-methoxyphenyl)-5-methylcyclohex-1-enyl)methyl)-5-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine (**26d**).*

Colourless oil; yield 46.8%; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.40 (s, 2H), 7.65 (s, 2H), 7.58 (s, 2H), 7.52 (s, 1H), 7.01 (t, J = 8.6 Hz, 1H), 6.78 (s, 1H), 6.73 (dd, J = 8.4 Hz, 3.8 Hz, 1H), 4.85-4.64 (m, 2H), 4.56-4.54 (m, 1H), 4.15-3.99 (m, 1H), 3.94 (s, 3H), 3.69 (s, 3H), 2.77-2.72 (m, 1H), 2.54-2.40 (m, 1H), 2.12-2.05 (m, 2H), 1.72-1.62 (m, 4H), 1.13 (t, J = 7.5 Hz, 6H), 0.93 (d, J = 5.5 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 160.93, 154.83(×2), 154.31, 141.99, 140.80, 136.04, 135.70, 131.19, 130.79, 129.07, 128.19, 127.95(×2), 126.00(×2), 125.67, 124.31, 122.50, 120.46, 117.32, 115.56, 110.78, 55.28, 49.04, 48.00, 39.09, 35.32, 33.10, 31.18, 31.11, 28.70, 24.02(×2), 21.80. HRMS calcd for $C_{35}H_{38}F_6N_5O$, $[M+H]^+$, 658.2975; found 658.2982. HPLC: t_R = 7.098 min, 98.23%.

*4.32. N-(3,5-bis(trifluoromethyl)benzyl)-N-((5-ethyl-2-(5-isopropyl-2-methoxyphenyl)cyclohex-1-enyl)methyl)-5-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine (**26e**).*

Colourless oil; yield 50.5%; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.40 (s, 2H), 7.66-7.65 (m, 2H), 7.61 (d, J = 8.9 Hz, 2H), 7.52 (s, 1H), 7.03-7.00 (m, 1H), 6.79 (s, 1H), 6.73 (d, J = 8.4 Hz, 1H), 4.85-4.67 (m, 2H), 4.57-4.55 (m, 1H), 4.16-3.99 (m, 1H), 3.94 (s, 3H), 3.70 (d, J = 7.3 Hz, 3H), 2.76-2.73 (m, 1H), 2.54-2.40 (m, 1H), 2.16-2.09 (m, 2H), 1.80-1.78 (m, 1H), 1.63-1.58 (m, 1H), 1.46-1.37 (m, 1H), 1.27-1.24 (m, 3H), 1.14 (t, J = 7.2 Hz, 6H), 0.87-0.82 (m, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 161.07, 154.77(×2), 154.32, 142.10, 140.77, 136.02(×2), 131.17, 130.96, 129.18, 128.23, 127.99(×2), 125.99(×2), 125.68, 124.33, 122.53, 120.47, 117.37, 115.53, 110.75, 55.26, 49.09, 48.00, 39.08, 35.52, 33.12(×2), 31.51, 29.07, 28.65, 24.04(×2), 11.43. HRMS calcd for $C_{36}H_{40}F_6N_5O$, $[M+H]^+$, 672.3132; found 672.3137. HPLC: t_R = 7.096 min, 95.18%.

*4.33. N-(3,5-bis(trifluoromethyl)benzyl)-N-((5-tert-butyl-2-(5-isopropyl-2-methoxyphenyl)cyclohex-1-enyl)methyl)-5-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine (**26f**).*

Colourless oil; yield 51.7%; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.41 (s, 2H), 7.67-7.66 (m, 4H), 7.53 (s, 1H), 7.02 (t, J = 9.1 Hz, 1H), 6.80-6.79 (m, 1H), 6.74 (t, J = 7.7 Hz, 1H), 4.76-4.55 (m, 3H), 4.16-3.97 (m, 1H), 3.95 (s, 3H), 3.71 (d, J = 2.9 Hz, 3H), 2.77-2.74 (m, 1H), 2.58-2.45 (m, 1H), 2.15-1.95 (m, 2H), 1.84-1.80 (m, 1H), 1.73-1.71 (m, 1H), 1.66 (s, 1H), 1.45-1.31 (m, 1H), 1.14 (t, J = 5.6 Hz, 6H), 0.77 (d, J = 12.6 Hz, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 161.02, 154.67(×2), 154.37, 142.21, 140.78, 136.03(×2), 131.21, 130.99, 129.78, 128.31, 128.12(×2), 126.02(×2), 125.70, 124.33, 122.52, 120.55, 117.32, 115.54, 110.75, 55.23(×2), 49.77, 48.31, 44.29, 43.81, 39.10, 33.10, 32.80, 32.12, 28.60, 27.13(×2), 24.02(×2). HRMS calcd for $C_{38}H_{44}F_6N_5O$, $[M+H]^+$, 700.3445; found 700.3443. HPLC: t_R = 8.819 min, 96.65%.

*4.34. N-(3,5-bis(trifluoromethyl)benzyl)-N-((1-(5-isopropyl-2-methoxyphenyl)-3,4-dihydronaphth alen-2-yl)methyl)-5-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine (**26g**).*

White solid; yield 53.8%; mp 56.5-60.6°C. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.42 (s, 2H), 7.66 (s, 2H), 7.54-7.53 (m, 3H), 7.14-7.09 (m, 3H), 7.04-7.02 (m, 1H), 6.87 (d, J = 1.7 Hz, 1H), 6.81 (d, J = 8.5 Hz, 1H), 6.59 (d, J = 7.7 Hz, 1H), 4.88-4.86 (m, 1H), 4.79-4.77 (m, 1H), 4.70-4.68 (m, 1H), 4.28-4.25 (m, 1H), 3.95 (s, 3H), 3.59 (s, 3H), 2.81-2.76 (m, 3H), 2.39-2.37 (m, 2H), 1.13 (d, J = 6.8 Hz, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 160.71, 154.86(×4), 141.79, 140.73, 139.95, 136.05(×2), 135.24, 131.30, 131.08, 128.17(×2), 127.94(×2), 126.48, 126.03(×4), 124.27, 122.46, 120.69, 117.33, 115.69, 110.77(×2), 55.32, 48.49, 44.54, 39.10, 37.71, 34.82, 33.13, 24.03, 22.14. HRMS calcd for $C_{38}H_{36}F_6N_5O$, $[M+H]^+$, 692.2819; found 692.2821. HPLC: t_R = 6.323 min, 95.44%.

*4.35. N-(3,5-bis(trifluoromethyl)benzyl)-N-((2-(5-isopropyl-2-methoxyphenyl)-3,4-dihydronaphth alen-1-yl)methyl)-5-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine (**26h**).*

White solid; yield 58.0%; mp 70.1-73.3°C. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.45 (s, 2H), 7.68 (s, 1H), 7.54 (s, 1H), 7.51 (s, 1H), 7.46-7.45 (m, 1H), 7.27 (s, 2H), 7.11 (dd, J = 8.5 Hz, 2.1 Hz, 1H), 7.06-7.05 (m, 2H), 6.97-6.96 (m, 1H), 6.84 (d, J = 2.1 Hz, 1H), 6.81 (d, J = 8.5 Hz, 1H), 5.55-5.52 (m, 1H), 4.83-4.80 (m, 1H), 4.52-4.49 (m, 1H), 4.45-4.42 (m, 1H), 3.95 (s, 3H), 3.80 (s, 3H), 2.83-2.81 (m, 1H), 2.49-2.44 (m, 3H), 2.33-2.31 (m, 1H), 1.21 (d, J = 7.0 Hz, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 160.52, 154.83(×2), 154.52, 142.09, 140.98, 140.88, 136.15, 136.04(×2), 133.84, 130.69, 130.47, 130.08, 128.89, 128.33, 127.27, 126.95(×2), 126.33(×2), 126.07, 124.25, 123.85, 122.44, 120.02, 117.22, 115.87, 110.84, 55.37, 48.70, 44.80, 39.11, 33.16, 30.44, 28.07, 24.86, 24.00. HRMS calcd for $C_{38}H_{36}F_6N_5O$, $[M+H]^+$, 692.2819; found 692.2813. HPLC: t_R = 6.586 min, 97.78%.

4.2. Biology

4.2.1. In vitro test for CETP inhibitory activity

The CETP RP Activity Assay Kit (Catalog #RB-RPAK; Roar) used a donor molecule containing a fluorescent self-quenched neutral lipid that was transferred to an acceptor by CETP (Catalog #R8899; Roar). The CETP-mediated transfer of the fluorescence neutral lipid to the acceptor molecule resulted in an increase in fluorescence (Ex/Em = 465/535 nm). The inhibitor of CETP inhibited the lipid transfer and thereby decreased the fluorescence intensity. Tested compounds were dissolved in DMSO. The solution was vibrated on an oscillator for more than 30 seconds and then stored in a nitrogen cabinet. The stock solutions (10 mM) were diluted with DMSO for an 8 point titration (1:5 serial dilutions) in a 96-well dilution plate. The assay was performed according to the instruction for the CETP inhibitor screening kit and recombinant CETP. Compounds were tested at eight concentrations, and the concentration required to inhibit 50% of the activity (IC_{50}) was determined from a curve fit of the data with each concentration tested for one time.

4.2.2. In vivo test of compound 17a in high-fat fed hamsters

Male golden (Syrian) hamsters were placed on a high-fat diet containing 10% lard oil and 3% cholesterol for 4 weeks. Source of the animals: Beijing Vital River. Age and weight of the animals: 8 weeks old. Weight: approximately 110−120 g. The test animals were randomly divided into four groups, each consisting of 6 animals. On the first day of dosing, the hamsters were bled to determine the baseline HDL-C. Compound **17a** (30 mg/kg, 50 mg/kg) and compound **4** (anacetrapib, 30 mg/kg) were administered orally to the animals. Each test compound was suspended in a solvent vehicle that was a solution of 10% ethanol, 10% hydrogenated castor oil, and 80% water. To the control group, the solvent vehicle alone was administered. The animals were dosed once a day for 5 days according to the groups (n = 5 for each group), and they were fasted for 16 hours prior to bleeding. Two hours after the final dose, blood specimens were retrieved from all hamsters (retro-orbital puncture) and collected in 500 μL EP tubes containing heparin sodium. The collected blood was centrifuged at 3000 rpm for 15 min, and the plasma lipid value in the separated serum (HDL-C) was determined using a MINDRAY BS-120 chemistry analyser.

4.2.3. Pharmacokinetic study of compound 17a

Four adult male Sprague-Dawley rats were fasted for 16 hours before the study. Compound **17a** (50 mg/kg) was administered orally to the animals. Test compound was suspended in a solvent vehicle that was a solution of 10% ethanol, 10% hydrogenated castor oil, and 80% water. Blood samples (~ 0.5 mL) were collected into tubes containing heparin sodium at the following time points: 0.5 h, 1 h, 2 h, 3 h, 4 h, 4.5 h, 5 h, 5.5 h, 6 h, 7 h, 8 h, 10 h, 12 h, 24 h, 36 h. The collected blood was centrifuged at 3000 rpm for 15 min, plasma was stored at -70^{o}C until analysis.

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- A series of *N*,*N*-substituted-cycloalkenyl-methylamine scaffold derivatives were designed and synthesized.
- Most compounds showed potent CETP inhibitory activity.
- Compound **17a** demonstrated a dose-dependent HDL-C elevation in hamsters.
- Compound **17a** exhibited an acceptable pharmacokinetic profile in S-D rats.