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Cholesteryl Ester Transfer Protein Inhibitory Activity of New 4-Bromophenethyl Benzamides

Reema Abu Khalaf [1]*, Areej NasrAllah[1], Ghadeer AlBadawi[1]

[1] Department of Pharmacy, Faculty of Pharmacy, Al-Zaytoonah University of Jordan, Jordan.

ABSTRACT

Cardiovascular diseases, as coronary heart disease, heart failure, and hypertension are the first leading cause of death in the United States and the third globally. CETP is a glycoprotein excreted mainly from the liver and found in plasma. Normal plasma CETP concentration is 1-4 µg/ml, while the ratio increased 70-80% in dyslipidemic patients. There is a growing need for new CETP inhibitors which encourages us to conduct this research. In this work, synthesis and *in vitro* study for four new 4-bromophenethylbenzamides 9a-d were carried out. *In vitro* study showed that the targeted compounds 9a-d exhibit acceptable activity against CETP, where compound 9a has a % inhibition of 40.7 at 10 µM concentration. It was found that the presence of the oxy group in both 9a and 9c enhances their activity which could be attributed to Hydrogen-bond formation with the amino acid residues of the CETP binding site.

Keywords: Benzamides, 4-Bromophenethyl, CETP, Hypercholesterolemia, Inhibitors.

INTRODUCTION

Cardiovascular diseases (CVD), like coronary heart disease, heart failure, and hypertension are the first leading cause for death in the United States and the third globally [1, 2]. The lipoproteins that carry cholesterol through the blood are chylomicrons, very low-density lipoproteins (VLDL), low-density lipoproteins (LDL) and high-density lipoproteins (HDL). Chylomicrons are triglyceride-loaded particles, which function in transferring dietary lipids from the intestine to the liver and tissues; VLDL is also a triglyceride loaded particle, whose function is to carry endogenous triglyceride from the liver to peripheral tissues [3]. It is suggested that VLDL triglyceride is processed to LDL *via* hepatic lipase or lipoprotein lipase [4, 5].

HDL are diverse group of lipoprotein particles. Most of the HDL particles contain apolipoprotein A-I, which is the most common apolipoprotein in plasma. HDL also contains apolipoprotein A-II, the second most common protein in HDL [4]. Many researchers found that elevated level of HDL in blood decreases the opportunity of CVD, *vice versa* high level of LDL and VLDL increases the incidence of CVD [2].

CETP is a glycoprotein excreted mainly from the liver and found in plasma. Normal plasma CETP concentration is 1-4 µg/ml, while it increased 70-80 % in people with dyslipidemia [6]. Lipid control has considerable scope for improvement in patients with dyslipidemia [7]. There are two hypothesized mechanisms for CETP activity: the shuttle model, and the ternary complex model. In the shuttle model, CETP can bind to cholesteryl ester and triglycerides and fills the stores that can be then exchanged with lipoproteins. The ternary complex model assumes that CETP can bind two lipoproteins one on each side, followed by the transfer of lipids between the two lipoproteins. Therefore, CETP raises LDL levels and decreases HDL levels and the inhibition of

[*]***Corresponding author: Reema Abu Khalaf***
reema.abukhalaf@zuj.edu.jo
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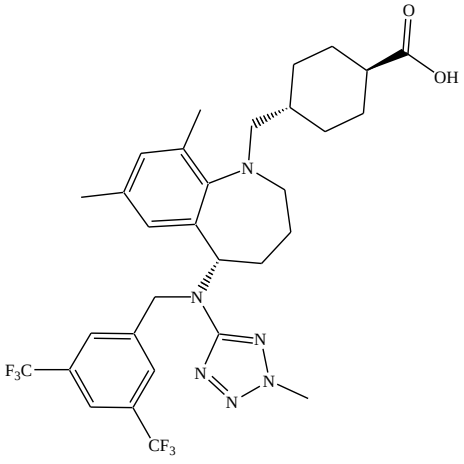
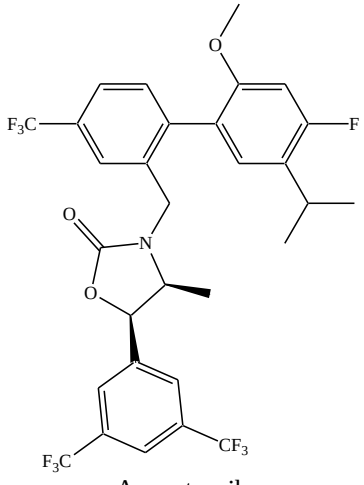
the CETP results in raising the concentration of cholesterol ester in HDL and decreasing its concentration in VLDL and LDL particles. High level of HDL has an atheroprotective effect against CVD [8]. Hyperlipidemia management with statin drugs still the most proper treatment despite of their side effect [9]. While CETP inhibitors are promising drugs that increase HDL cholesterol, and decrease LDL cholesterol in the blood with fewer side effects than statins [10, 11].

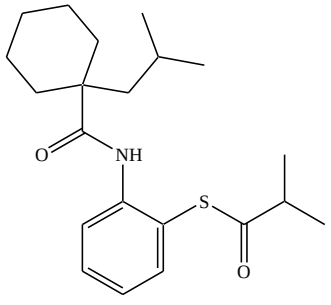
However, the first trials with the CETP inhibitors (Figure 1) torcetrapib and dalcetrapib failed to show a reduction in cardiovascular events. Torcetrapib has an effect on the aldosterone level that increases blood pressure, while dalcetrapib had a low enhancement of lipid profile [6, 12]. Besides, evacetrapib study was terminated due to its low efficacy, while anacetrapib is still under further investigation[12].



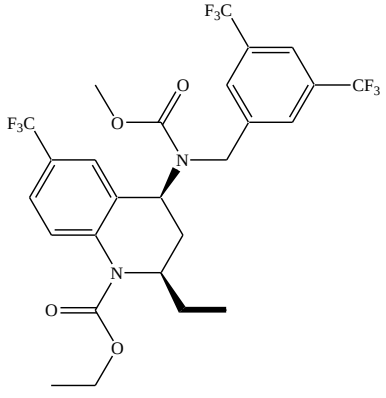
Evacetrapib



Anacetrapib



Dalcetrapib



Torcetrapib

Figure 1: Structures of some known CETP inhibitors.

Earlier our group design and synthesize different potential CETP inhibitors (Figure 2) such as: benzylidene-amino methanones [13], benzyl- amino-methanones [14], *N*-(4-benzyloxyphenyl)-4-methyl-benzenesulfonamides, *N*-(4-benzylamino- phenyl)-toluene-4-sulfonic acid esters [15], chlorobenzyl benzamides [16], fluorinated benzamides [17, 18], substituted benzyl benzamides [19, 20] and aryl sulfonamides [21, 22].

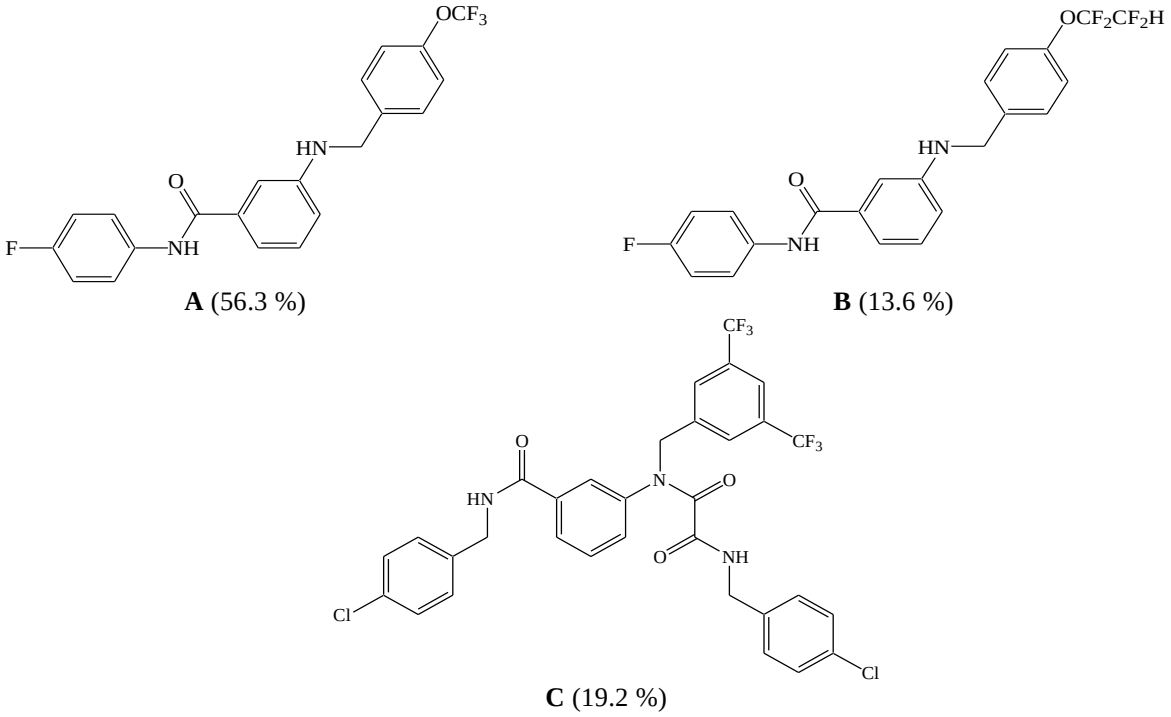


Figure 2: Our previously synthesized potential CETP inhibitors leads (% inhibition of CETP at 10 µM concentration) [16-20]

Our study aims to synthesize new benzamide analogues **9a-d** by varying the substitution with different groups such as -OCF_3, -CF_3, and-CF_2CF_2H, in addition to altering the chain length at the benzyl amine side, followed by *in vitro* biological evaluation of the targeted compounds as CETP inhibitors.

MATERIALS AND METHODS

General

All chemicals, reagents and solvents were of analytical grade. Chemicals and solvents were purchased from the corresponding companies (Alfa Aesar, Acros Organics, Sigma-Aldrich, Fluka, SD fine ChemLimite, and Tedia and Fisher Scientific).

3-Aminobenzoic acid was purchased from (Alfa Aesar materials, Karlsruhe, Germany). Dichloromethane (DCM), triethylamine (TEA), acetone, cyclohexane, ethanol, ethyl acetate, and methanol (CH_3OH) were obtained from (Tedia company, INC, USA). Chloroform, and dimethylformamide (DMF) were purchased from (Fisher Scientific UK limited, UK). Sodium sulfate anhydrous, hydrochloric acid (HCl, 37%), 2-(4-bromophenyl) ethylamine, oxalyl chloride $(COCl)_2$, and sodium borohydride ($NaBH_4$) were obtained from (Sigma-Aldrich, Germany). 1-Bromomethyl-4-trifluromethoxy benzene, 1-bromomethyl-4-trifluromethyl benzene, 4-(1,1,2,2-tetrafluoroethoxy) benzaldehyde, and 1-(bromomethyl)-3,5-bis (trifluoromethyl) benzene were obtained from (Aldrich chemistry, USA). Sodium hydroxide (NaOH) was purchased from (SD fine Chem Limited, India).

Melting points were measured using Gallenkamp melting point apparatus. Infrared (IR) spectra were recorded using Shimadzu IR Affinity1 FTIR spectrophotometer. All samples were prepared with potassium bromide and pressed into a disc. 1H and 13C Nuclear Magnetic Resonance (NMR) spectra were measured on Bruker, Avance DPX- 300, and 500 spectrometers, at The University of Jordan. Chemical

shifts are given in δ (ppm) using TMS as internal reference; the samples were dissolved in deuterated DMSO. High resolution mass spectrometry (HR-MS) was performed using LC Mass Bruker Apex-IV mass spectrometer utilizing an electrospray interface, at The University of Jordan. AFLX800TBI Microplate Fluorimeter (BioTek Instruments, Winooski, VT, USA) was used for the in vitro bioassay.

Thin Layer Chromatography (TLC) was performed on 20 x 20 cm with layer thickness of 0.2 mm aluminum cards pre-coated with fluorescent silica gel GF254 DC-alufolien-kieselgel (Fluka analytical, Germany), and visualized by UV light indicator (at 254 and/ or 360 nm). CETP inhibitory bioactivities were assayed employing a commercially available kit (Fluorometric) (BioVision, Linda Vista Avenue, USA).

Synthesis of the targeted compounds 9a-d

The methyl benzoate intermediates **5a-d** were synthesized as previously described [16-20] and purified by column chromatography using different concentrations of cyclohexane and ethyl acetate. The preparation of the acyl intermediates **7a-d** from methyl esters **5a-d** was carried out as formerly stated [16-20].

*3-(4-(Trifluoromethoxy)benzylamino)-N-(4-bromophenethyl)benzamide **(9a)***

2-(4-Bromophenyl)ethylamine (**8**, 0.48 ml, 2.91 mmol) together with 5 ml of triethylamine and 10 ml of dichloromethane were added to **7a** (0.97 mmol), then the reaction mixture was stirred at room temperature for 5 days. The crude product was purified by column chromatography using chloroform: methanol (98:2) as eluent.

White powder was achieved (0.1gm, % yield = 21%); m.p. = 184-185 ºC; Rf = 0.69 (Chloroform: methanol, 8.5:1.5); 1H-NMR (300 MHz, DMSO): δ 4.09 (s, 2H, CH2), 4.41 (s, 2H, CH2), 4.98 (s, 2H, CH2), 6.78 (s, 1H, CH2NH), 7.26-7.31 (m, 8H, Ar-H), 7.46 (s, 2H, Ar-H), 7.77 (s, 2H, Ar-H), 9.23 (s, 1H, CONH); 13C-NMR (75 MHz, DMSO): δ 41.4 (1C, CH2), 42.6 (1C, CH2), 50.8 (1C, CH2), 120.4 (1C, Ar-C), 121.5 (2C, Ar-C), 127.4 (1C, Ar-C), 128.7 (1C, Ar-C), 129.7 (1C, Ar-C), 130.0 (2C, Ar-C), 130.3 (2C, Ar-C), 131.7 (2C, Ar-C), 133.8 (1C, Ar-C), 136.4 (1C, Ar-C), 138.1 (1C, Ar-C), 139.5 (1C, Ar-C), 143.2 (1C, Ar-C), 148.1 (1C, Ar-C), 163.5 (1C, Ar-C), 165.8 (1C, CONH) ppm; IR (KBr): 3325, 3086, 2924, 2855, 1659, 1528, 1404, 1258 cm-1; HR-MS (ESI, positive mode) m/z [M-Br]+ 413.26614 (C23H20 F3N2O2 requires 413.06602).

*3-(3,5-Bis(trifluoromethyl)benzylamino)-N-(4-bromophenethyl)benzamide **(9b)***

2-(4-Bromophenyl)ethylamine (**8**, 0.18 ml, 1.18 mmol) together with 5 ml of triethylamine and 10 ml of dichloromethane were added to **7b** (0.34 mmol), then the reaction mixture was stirred at room temperature for 5 days. The crude product was purified by column chromatography using cyclohexane: ethyl acetate (6:4) as eluent.

Off white powder was achieved (0.164 gm, % yield = 82 %); m.p. = 87-89 ºC; Rf = 0.71 (Cyclohexane: ethyl acetate, 6:4); 1H-NMR (500 MHz, DMSO): δ 2.79 (s, 2H, CH2), 3.43 (s, 2H, CH2), 4.53 (s, 2H, CH2), 6.62 (s, 1H, CH2NH), 6.73 (s, 1H, Ar-H), 6.99 (s, 1H, Ar-H), 7.06 (s, 1H, Ar-H), 7.14-7.19 (m, 2H, Ar-H), 7.45 (s, 3H, Ar-H), 7.98 (s, 1H, Ar-H), 8.07 (s, 2H, Ar-H), 8.35 (s, 1H, CONH); 13C-NMR (125 MHz, DMSO):δ 34.9 (1C, CH2), 40.9 (1C, CH2), 45.9 (1C, CH2), 111.8 (1C, Ar-C), 115.3 (1C, CF3), 115.5 (1C, CF3), 119.6 (1C, Ar-C), 121.0 (1C, Ar-C), 122.8 (1C, Ar-C), 125.0 (1C, Ar-C), 128.4 (1C, Ar-C), 129.3 (1C, Ar-C), 129.7 (1C, Ar-C), 130.2 (1C, Ar-C), 130.5 (1C, Ar-C), 130.8 (1C, Ar-C), 131.0 (1C, Ar-C), 131.4 (2C, Ar-C), 131.5 (2C, Ar-C), 136.0 (1C, Ar-C), 139.5 (1C, Ar-C), 144.6 (1C, Ar-C), 148.5 (1C, Ar-C), 167.2 (1C, CONH) ppm; IR (KBr): 3318, 3063, 2932, 2870, 1651, 1589, 1543, 1489, 1381, 1327 cm-1; HR-MS (ESI, positive mode) m/z [M-Br]+ 465.12052 (C24H19 F6N2Orequires 465.05849).

*3-(4-(1,1,2,2-Tetrafluoroethoxy)benzylamino)-N-(4-bromophenethyl)benzamide **(9c)***

2-(4-Bromophenyl) ethylamine (**8**, 0.38 ml, 2.25 mmol) together with 5 ml of triethylamine and 10 ml of dichloromethane were added to **7c** (0.75 mmol), then the reaction mixture was stirred at room temperature for 5 days.

Then the crude product was purified by column chromatography using chloroform: methanol (98:2) as eluent.

Viscous yellow liquid was achieved (0.07 gm, % yield = 39.2 %); R_f = 0.71 (Chloroform: methanol, 98:2); H^1-NMR (300 MHz, DMSO): δ 2.65 (s, 2H, CH_2), 3.10 (s, 2H, CH_2), 3.45 (s, 2H, CH_2), 4.95 (s, 1H, CH_2N*H*), 6.56 (s, 1H, CF_2-*H*), 6.74 (s, 1H, Ar-*H*), 6.91-7.13 (m, 5H, Ar-*H*), 7.28-7.40 (m, 5H, Ar-*H*), 7.64-7.70 (m, 1H, Ar-*H*), 8.85 (s, 1H, CON*H*); ^{13}C-NMR (75 MHz, DMSO):δ 34.8 (1C, *C*H_2), 42.0 (1C, *C*H_2), 51.0 (1C,*C*H_2), 119.7 (1C, *C*F_2), 122.0 (2C, Ar-*C*), 126.2 (1C, *C*F_2), 126.4 (1C, Ar-*C*), 128.5 (1C, Ar-*C*), 129.3 (1C, Ar-*C*), 129.7 (2C, Ar-*C*), 130.0 (2C, Ar-*C*), 131.3 (2C, Ar-*C*), 131.4 (1C, Ar-*C*), 135.8 (1C, Ar-*C*), 138.9 (1C, Ar-*C*), 139.4 (1C, Ar-*C*), 141.2 (1C, Ar-*C*), 147.7 (1C, Ar-*C*), 163.3 (1C, Ar-*C*), 165.7 (1C, *C*ONH)ppm; IR (KBr): 3325, 3071, 2924, 2855, 1651, 1528, 1304, 1273 cm^{-1}.

*3-(4-(Trifluoromethyl)benzylamino)-N-(4-bromophenethyl)benzamide **(9d)***

2-(4-Bromophenyl)ethylamine (**8**, 0. 44ml, 2.63mmol) together with 5 ml of triethylamine and 10 ml of dichloromethane were added to **7d** (0.88mmol), then the reaction mixture was stirred at room temperature for 5 days. The crude product was purified by column chromatography using chloroform: methanol (95:5) as eluent.

Off white powder was achieved (0.199 gm, % yield = 47.8 %); m.p. = 88-90 ºC; Rf = 0.79 (Chloroform: methanol, 95: 5); 1H-NMR (300 MHz, DMSO): δ 2.76 (s, 2H, CH2), 3.13 (s, 2H, CH2), 4.09 (br s, 1H, CH2NH), 5.04 (s, 2H, CH2), 6.94-7.21 (m, 4H, Ar-H), 7.39-7.41 (d, J = 6.6 MHz, 6H, Ar-H), 7.63 (s, 1H, Ar-H), 8.61-8.68 (d, J = 7.0 MHz, 1H, Ar-H), 8.92 (s, 1H, CONH); 13C-NMR (75 MHz, DMSO):δ 35.2 (1C, CH2), 42.0 (1C, CH2), 52.5 (1C, CH2), 119.7 (1C, CF3), 122.9 (1C, Ar-C), 125.8 (1C, Ar-C), 126.5 (1C, Ar-C), 127.2 (1C, Ar-C), 128.2 (1C, Ar-C), 129.0 (2C, Ar-C), 129.8 (1C, Ar-C), 131.4 (2C, Ar-C), 131.4 (2C, Ar-C), 135.9 (1C, Ar-C), 138.9 (1C, Ar-C), 139.4 (2C, Ar-C), 141.1 (1C, Ar-C), 141.9 (1C, Ar-C), 165.7 (1C, CONH)ppm; IR (KBr): 3325, 3071, 2963, 2862, 1651, 1543, 1404, 1265 cm-1; HR-MS (ESI, positive mode) m/z [M-Br]+ 397.29759 (C23H20 F3N2Orequires 397.07111).

***In vitro* determination of CETP inhibition**

The assay kit is composed of a donor molecule harboring a self-quenched neutral lipid, an acceptor molecule, and CETP extracted from rabbit serum. The transfer of the fluorescent neutral lipid to the acceptor molecule induces fluorescence. The inhibition of CETP prohibits lipid transfer and thus decreases fluorescence intensity. The assay protocol is described as follows: an aliquot of rabbit serum (1.5 μL) was mixed with a testing sample (160 μL). Next, the donor and acceptor molecules in the assay buffer were added, mixed well, and the volume was adjusted to 203 μL using the assay buffer. Then the mixture was incubated at 37°C for 1 hour. The fluorescence intensity (Excitation λ: 465 nm; Emission λ: 535 nm) was read in a FLX800TBI Microplate Fluorimeter (BioTek Instruments, Winooski, VT, USA).

The synthesized molecules were dissolved in DMSO yielding 10 mM stock solutions. Then the solutions were diluted to the required concentration using distilled deionized water. DMSO concentration was adjusted to 0.1%. The percentage of residual CETP activity was identified in the presence and absence of the tested molecules. Torcetrapib was used as a positive inhibitor. CETP activity is not affected by DMSO. The negative control samples missing rabbit serum were used as a contrast background. The experimental protocol and measurements were carried out in duplicates.

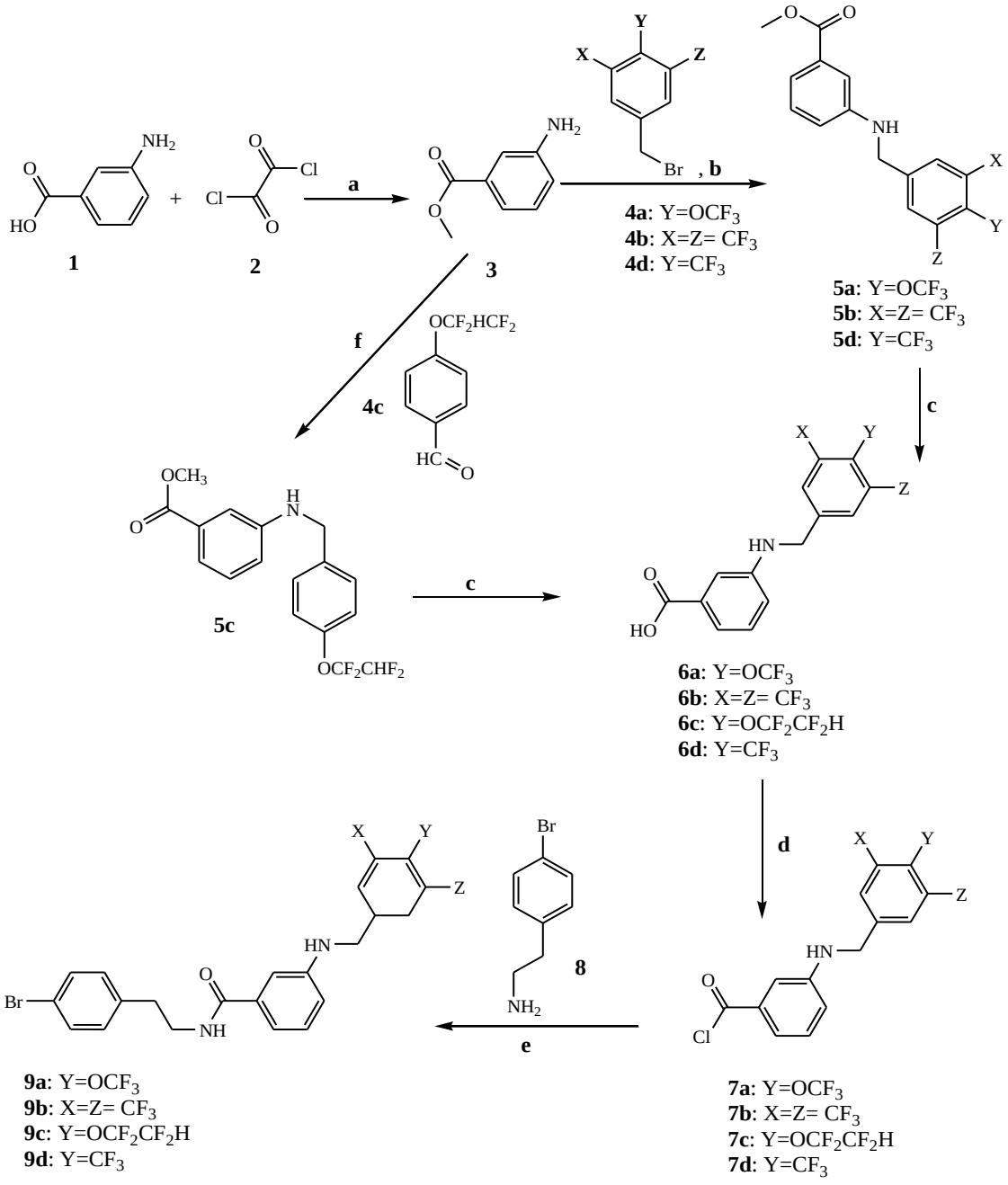
The % inhibition of CETP by the synthesized compounds was calculated using the following equation[13]:

$$\% \text{ Inhibition} = \left[1 - \frac{\text{Inhibitor read - Blank read}}{\text{Positive control- Negative control}} \right] * 100\%$$

RESULTS AND DISCUSSION

Chemistry

Novel series of 4-bromophenethyl benzamides **9a-d** was synthesized (Scheme 1).



Scheme 1: Synthesis of the targeted 4-bromophenethyl benzamides 9a-d. Reagents and conditions:
(a) CH_3OH/reflux (60-70°C), 24 hours, (b) DCM, TEA, RT, 5 days, (c) (1) 1M NaOH (100°C), overnight, (2) 1M HCl, (d) $(COCl)_2$ /reflux (60-70°C), DCM, 4 days, (e) TEA, DCM, RT, 5 days, (f) DMF/reflux (100-140°C), 7 days/ HCl after 24 hours, CH_3OH, $NaBH_4$, RT, 3 days

The synthesis started with the activation of the carboxylic acid moiety of 3-aminobenzoic acid (**1**) using oxalyl chloride (**2**) in the presence of methanol producing the methyl ester protecting group **3**. Next, the amine nitrogen of 3-amino benzoic acid methyl ester (**3**) attacked the partially positive methylene group of the benzyl bromide **4a**, **4b**, or **4d** in the presence of DCM as a solvent to produce substituted 3-benzylamino benzoic acid methyl ester intermediates **5a**, **5b**, or **5d**. Triethylamine was used as an acid scavenger (HBr).

Imine formation was attained by the nucleophilic attack of the amine nitrogen of 3-aminobenzoic acid methyl ester **3** on the partially positive carbonyl carbon of the 4- (1,1,2,2-tetrafluoroethoxy) benzaldehyde **4c** followed by the elimination of a molecule of water resulting in the acid-catalyzed formation of the imine intermediate. Afterward, reduction of the imine was carried out by sodium borohydride ($NaBH_4$) where a hydride ion attacks the electrophilic carbon of the imine functional group and the anion that forms is then protonated to generate the secondary amine **5c** using methanol as a solvent at room temperature for 3 days.

Afterward, deprotection of the carboxylic acid group of 3-aminobenzoic acid methyl ester intermediates **5a-d** was carried out by alkaline hydrolysis using 1M NaOH under reflux followed by neutralization with concentrated HCl. Then, reactivation of the carboxylic acid moiety of 3-benzylamino benzoic acid intermediates **6a-d** was performed using oxalyl chloride (**2**) to produce acyl chloride derivatives **7a-d** in the presence of DCM and the tetrahedral structure leaves as HCl, CO_2 and CO gases.

Subsequently, amide formation was attained by the nucleophilic attack of the amine moiety of 2-(4-bromophenyl) ethylamine (**8**) on the partially positive carbonyl carbon of the previously produced acyl chloride **7a-d** to get the targeted 4-bromophenethyl benzamide derivatives **9a-9d** (as shown in scheme I). The best yield of 82% was found for compound **9b**, while compound **9a** has the lowest yield of 21%.

***In vitro* determination of CETP inhibition**

The results of CETP inhibition bioassay, presented in Figure 3, demonstrated that compounds **9a-d** exhibited acceptable activity against CETP at 10 µM concentration. The preliminary CETP inhibitory activity of the synthesized compounds was evaluated at 10 µM concentration which is considered a suitable concentration for capturing possible CETP inhibitors as hit compounds that can later undergo further optimization [13].

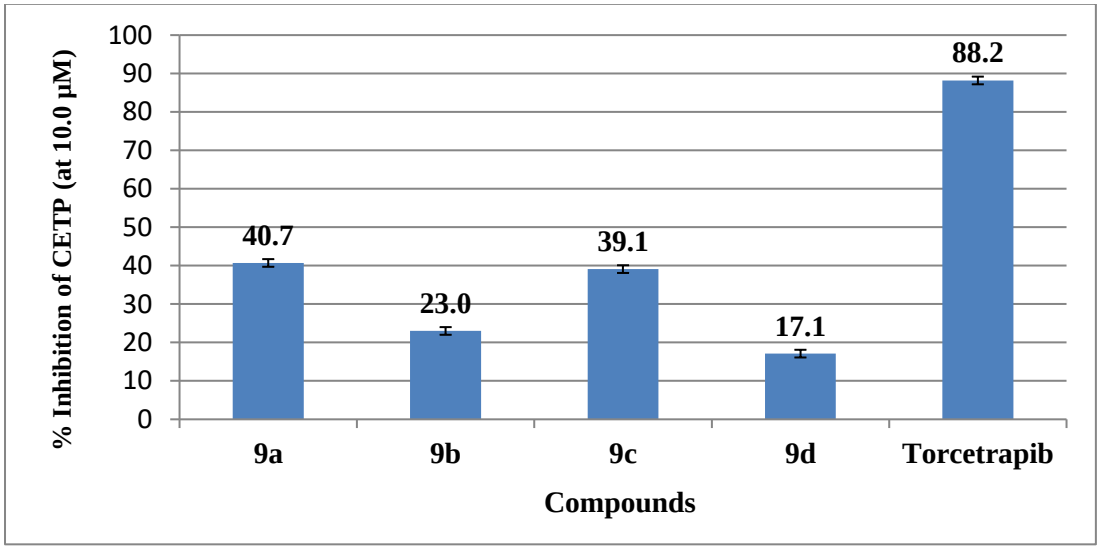


Figure 3. *In vitro* bioactivities of the synthesized 4-bromophenethyl benzamides 9a-d (at 10 µM concentration) and the positive inhibitor Torcetrapib (at 0.08 µM concentration)

As can be seen from Figure 3, compound **9a** with 4-trifluromethoxy group exhibits the highest activity with a % inhibition of 40.7 at 10 µM concentration. Compound **9c** was found to exhibit comparable activity to that of **9a** with a 39.1% inhibition at the same concentration. It is expected that the presence of the oxy group in both compounds, **9a** and **9c**, enhances their activity that can be involved in H-bond formation with the amino acid residues of CETP binding site. On the other hand, compounds **9b** (with 3, 5- ditrifluoromethyl) and **9d** (with 4-trifluoromethyl) showed similar CETP inhibition (23.0% and 17.1% respectively).

CONCLUSION

This work identified 4-bromophenethyl benzamide as a new scaffold targeting CETP activity. Benzamide **9a** showed the highest inhibitory activity with a % inhibition of 40.7 at 10 µM concentration. The study found that presence of oxy moiety such in compounds **9a** and **9c** enhances the activity which can be attributed to H-bond formation with CETP binding site.

Acknowledgments

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Conflict of interest

No conflict of interest is associated with this work.

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النشاط المثبط للبروتين الناقل للكوليستريل استر ل 4-بروموفينيثيل بنزاميدات الجديدة

ريما أبو خلف[1]*، أريج نصر الله[1]، غدير البدوي[1]

[1] قسم الصيدلة، كلية الصيدلة، جامعة الزيتونة الأردنية، عمان، الأردن.

ملخص

تعد أمراض القلب والأوعية الدموية، مثل أمراض القلب التاجية وفشل القلب وارتفاع ضغط الدم، السبب الرئيسي الأول للوفاة في الولايات المتحدة والثالث على مستوى العالم. CETP هو بروتين سكري يفرز بشكل رئيسي من الكبد ويوجد في البلازما. تركيز CETP في البلازما الطبيعي هو 1-4 ميكروغرام / مل، بينما زادت النسبة بين 70-80٪ في مرضى اضطراب دهنيات الدم. هناك حاجة متزايدة لمثبطات CETP الجديدة التي تشجعنا على إجراء هذا البحث. في هذا العمل، تم إجراء التوليف والدراسة في المختبر لأربعة 4-بروموفينيثيل بنزاميدات جديدة 9a-d. أظهرت دراسة في المختبر أن المركبات المستهدفة 9a-d تظهر نشاطًا مقبولًا ضد CETP، حيث يكون للمركب 9a تثبيط بنسبة 40.7 عند تركيز 10 ميكرومولار. وجد أن وجود مجموعة أوكسي في كل من 9a و9cيعزز نشاطها الذي يمكن أن يعزى إلى تكوين رابطة هيدروجينية مع بقايا الأحماض الأمينية في موقع ربط CETP.

الكلمات الدالة: بنزاميدات، 4-بروموفينيثيل، CETP، ارتفاع كوليسترول الدم، مثبطات.

* ***المؤلف المراسل: ريما أبو خلف***

reema.abukhalaf@zuj.edu.jo

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