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Synthesis of a series of novel 2,4,5-trisubstituted selenazole compounds as potential PLTP inhibitors

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ABSTRACT

Based on a homology-modeled structure of PLTP and characteristic structural features of reported cholesteryl ester transfer protein (CETP) inhibitors, we designed and synthesized a novel series of 2,4,5-trisubstituted selenazole compounds. Biological evaluation reveals that compounds **12** and **17** exhibit favorable PLTP activity, and their IC_{50}s are 8 μM and 10 μM, respectively.

Complications of atherosclerosis are among the most common causes of death in Western societies. Lipid imbalances are thought to be important contributors to the progression of this complex disease. It is generally accepted that elevated levels of LDLc increase the risk of developing atherosclerosis, whereas HDLc appears to be protective. Plasma phospholipid transfer protein (PLTP), a secreted plasma protein with 476 amino acid residues, plays an essential role in HDL metabolism.[1] As one of the extracellular lipid transfer proteins, PLTP has three distinct functions: (1) mediating the transfer of remaining phospholipids and free cholesterol to HDL during the lipolysis of triglyceride-rich lipoproteins; (2) modulating the conversion of HDL subfractions; and (3) regulating the secretion of ApoB-containing lipoproteins from the liver.[2]

The relationship between PLTP and human atherosclerosis is still under investigation. Studies indicate that systemic PLTP deficiency is atheroprotective in different strains of hypercholesterolemic mice and that sustained over-expression of plasma PLTP in PLTP-transgenic or bone marrow-transplanted mice leads to an increased risk of atherosclerosis.[3–7] In further support of the proatherogenic potential of plasma PLTP in vivo, a positive correlation between PLTP activity and the risk of coronary artery disease was observed in humans.[8] After assessing the current evidence on the role of PLTP under all conditions, Vergeer et al. came to the conclusion that PLTP could be an attractive therapeutic target.[9] Although presently known risk factors have some predictive value for coronary artery disease (CAD), a major part of the variability in this process remains unexplained.[10] Therapies aimed at lowering LDL cholesterol only reduce a fraction (roughly 30%) of the burden of atherosclerotic disease.[11] It is extremely important to improve our understanding and treatment of the disease. Exploration of the PLTP inhibition is one such approach.

Since there are no reported three dimensional structures of PLTP, molecular design based directly on protein structure is impossible. Also, when this project started, there were no reported structures of PLTP inhibitors, which could have provided potential lead compounds. Our goal in this Letter is to describe our efforts to discover compounds that exhibit PLTP inhibiting activity in vitro.

PLTP displays sequence homology to three other proteins: bactericidal permeability increasing protein (BPI) (25%), lipopolysaccharide binding protein (LBP), (24%) and cholesteryl ester transfer protein (CETP) (19%). These proteins belong to the LPS-binding/lipid transfer protein family. Among these family members, human BPI and human CETP have X-ray 3-D structures reported.[12,13] Both PLTP and CETP are important HDL modulators. Moreover, models of PLTP and CETP are similar to the structure of BPI.[14,15] Several CETP inhibitors have been reported, and some of them exhibit both CETP and PLTP inhibition.[16–20] Based on these results, a molecular model of PLTP has been constructed. Taking our constructed model and characteristics of reported CETP inhibitors into consideration, we designed a library of 2,4,5-trisubstituted thiazole compounds[21] and selenazole compounds. After synthesis, their PLTP inhibiting activities were evaluated. Selenazole compounds **12** and **17** exhibited PLTP inhibiting activities of IC_{50} 8 μM and 10 μM, respectively (Table 1). Since compound **12** is the most potent PLTP inhibitor, it might be considered the lead compound. The general formula of 2,4,5-trisubstituted selenazole compounds is shown in Figure 1.

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Table 1
Results of the biological assay

Compound	R^1	R^2	R^3	CETP IC_{50} (μM)	PLTP IC_{50} (μM)
1	Ethyl-	*p*-Hydroxyl-phenyl-	3,4,5-Trihydroxyl-phenyl-	No	32
2	Ethyl-	*p*-Methoxyl-phenyl-	3,4-Dimethoxyl-phenyl-	No	100
3	Ethyl-	*p*-Hydroxyl-phenyl-	*p*-Chloro-phenyl-	No	60
4	Ethyl-	*p*-Methoxyl-phenyl-	3,4,5-Trimethoxyl-phenyl-	No	No
5	Ethyl-	*p*-Methoxyl-phenyl-	*p*-Chloro-phenyl-	No	No
6	Benzyl-	*p*-Methoxyl-phenyl-	3,4-Dimethoxyl-phenyl-	No	80
7	Benzyl-	*p*-Hydroxyl-phenyl-	3,4,-Dihydroxyl-phenyl-	30	35
8	Benzyl-	*p*-Methoxyl-phenyl-	*p*-Nitro-phenyl-	No	85
9	Benzyl-	*p*-Methoxyl-phenyl-	3,4,5-Trimethoxyl-phenyl-	No	No
10	Benzyl-	*p*-Hydroxyl-phenyl-	3,4,5-Trihydroxyl-phenyl-	25	32
11	Benzyl-	*p*-Hydroxyl-phenyl-	Pentyl-	No	60
12	Phenyl-	Phenyl-	3,4-Dihydroxyl-phenyl-	25	8
13	Phenyl-	Phenyl-	3,4,5-Trihydroxyl-phenyl-	No	25
14	Phenyl-	Phenyl-	Phenyl-	No	No
15	Phenyl-	Phenyl-	3,4,5-Trimethoxyl-phenyl-	No	No
16	Phenyl-	Phenyl-	3,4,5-Trifluoro phenyl-	No	No
17	Butyl-	*p*-Hydroxyl-phenyl-	3,4,5-Trihydroxyl-phenyl-	No	10
18	Butyl-	*p*-Hydroxyl-phenyl-	Methyl-	No	60
19	Butyl-	*p*-Hydroxyl-phenyl-	*p*-Chloro-phenyl-	No	60
20	Butyl-	*p*-Methoxyl-phenyl-	3,4,5-Trimethoxyl-phenyl-	No	150
21	Butyl-	*p*-Methoxyl-phenyl-	3,4-Dimethoxyl-phenyl-	No	80

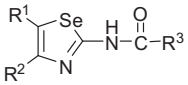
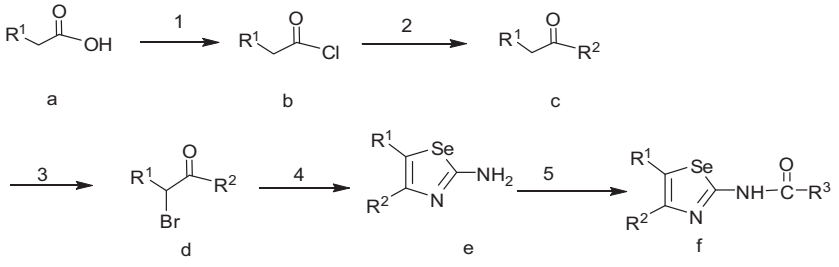


Figure 1. The general formula of 2,4,5-trisubstituted selenazole compounds.

As shown in Scheme 1, the starting carboxylic acid **a** was treated with $SOCl_2$ to yield compound **b**, which, without further purification, was reacted with aromatic compounds to give compound **c**. Then compound **c** was treated with bromine to give compound **d**. A suspension of compound **d**, $KSeCN/SiO_2$, and CH_3COONH_4/Al_2O_3 was heated in toluene at 80 °C for 12 h to afford compound **e**.[22] Then, compound **e** was acetylated to give compound **f**. If compound **f** had the methoxyl group, the compound was treated with BBr_3 to provide phenolic compounds as additional analogs for testing.[23] The structure data of MS and ^1H NMR were shown in the reference.[24]

After comparing the structure and PLTP activity assay results, it is conceivable that the hydroxyl group is the key determinant for PLTP inhibition, regardless of whether it is on $\mathbf{R}^2$ or $\mathbf{R}^3$. For example, compounds **4**, **5**, and **9** showed no or weak inhibition, while **1**, **3**, and **10** showed much stronger inhibition. Compounds with hydroxyl group substitution on $\mathbf{R}^3$ were more potent than those with a hydroxyl at $\mathbf{R}^2$. Compounds **12** and **13** exhibited good inhibition without any methoxy or hydroxyl substitution in $\mathbf{R}^2$. At $\mathbf{R}^1$, butyl- and phenyl-groups had better PLTP inhibition than benzyl- and ethyl-groups. To give some examples, compounds **13** and **17** had much stronger PLTP inhibition than compounds **1** and **10**.

In conclusion, a novel serial of 2,4,5-trisubstituted selenazoles were synthesized as potent PLTP inhibitors. Among them, compounds **12** and **17** exhibited favorable PLTP inhibiting activity, and they could be the potential new lead compounds in the search for useful PLTP inhibitors.



Scheme 1. General synthesis route for PLTP inhibitors. Reagents and conditions: (1) $SOCl_2$, CH_2Cl_2, reflux, 1 h; (2) CH_2Cl_2, $AlCl_3$, room temperature, 2 h; (3) $AlCl_3$, CH_2Cl_2, Br_2, 0 °C, 2 h; (4) $KSeCN/SiO_2$, CH_3COONH_2/Al_2O_3, toluene, 80 °C, 12 h.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.07.017.

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24. *Selected data for compounds* **12**: ^{1}H NMR (400 MHz, CD_3Cl) δ = 12.76 (s, 1H), 7.55–7.56 (d, 1H), 7.54 (s, 1H), 7.41–7.42 (d, 2H), 7.28–7.32 (m, 8H), 6.82–6.84 (d, 1H). MS (FAB) $[M+1]^+$: m/z = 437.1. *Compound* **17**: ^{1}H NMR (400 MHz, CD_3Cl) δ = 12.33 (s, 1H), 9.52 (s, 1H), 9.23 (s, 2H), 9.01 (s, 1H), 7.34–7.36 (d, 2H), 7.09 (s, 2H), 6.79–6.81 (d, 2H), 2.80–2.81 (t, 2H), 1.58–1.62 (m, 2H), 1.33–1.35 (m, 2H), 0.84–0.88 (t, 3H). MS (FAB) $[M+1]^+$: m/z = 449.