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Bioorganic & Medicinal Chemistry Letters 14 (2004) 2589–2591
Bioorganic & Medicinal Chemistry Letters

S-(2-(Acylamino)phenyl) 2,2-dimethylpropanethioates as CETP inhibitors

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Received 9 February 2004; accepted 20 February 2004

Abstract—Studies on the relationship between the structure of the benzene moiety of *S*-(2-(acylamino)phenyl) 2,2-dimethylpropanethioates and CETP inhibitory activity were performed. Substituents on the benzene moiety influenced CETP inhibitory activity in a type and position dependent manner, and electron-withdrawing groups at the 4- or 5-position increased the activity. The most potent compound showed 50% inhibition of CETP activity in human plasma at a concentration of 2 μM.

A high level of low-density lipoprotein (LDL) cholesterol is well known to be a major risk factor for atherosclerosis and coronary heart disease, and 3-hydroxy-3-methylglutaryl co-enzyme A (HMG-CoA) reductase inhibitors (statins) are widely used to decrease LDL cholesterol levels.[1] On the other hand, a low level of high-density lipoprotein (HDL) cholesterol is also an important risk factor.[2,3] HDL cholesterol plays a role in the transfer of excess cholesterol from the peripheral tissues to the liver (reverse cholesterol transport)[4,5] and in the inhibition of lipoprotein oxidation,[6,7] so HDL cholesterol is protective against atherosclerosis. Therefore, convenient drugs that can significantly increase the HDL cholesterol level would be useful.[8,9] Cholesteryl ester transfer protein (CETP) is a plasma glycoprotein that plays a role in the exchange of cholesteryl esters (CE) in HDL for triglycerides in very low-density lipoprotein (VLDL).[10,11] This process reduces the level of antiatherogenic HDL cholesterol and increases the level of proatherogenic VLDL and LDL cholesterol. Indeed, the atherogenicity of CETP has been supported by many studies,[12–16] and we showed that a CETP inhibitor, JTT-705, was able to inhibit the progression of atherosclerosis in rabbits through marked elevation of HDL cholesterol and slight reduction of non-HDL cholesterol.[17] The suggestion that CETP inhibitors are potentially antiatherogenic agents has led to their development as therapeutic drugs and two compounds, JTT-705 and torcetrapib, have reached clinical studies (Fig. 1).[18]

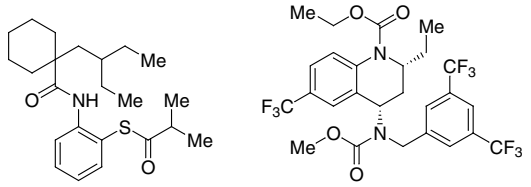

Figure 1. Structures of JTT-705 and torcetrapib.

We previously reported on the structure–activity relationships of *S*-(2-(acylamino)phenyl) alkanethioate derivatives, which are CETP inhibitors.[19] By performing structural changes and modification of both the acylamino moiety and the thioester moiety, the structural requirements for inhibition of CETP have been elucidated and the optimum compound, *S*-(2-((1-(2-ethylbutyl)cyclohexane)carbonylamino)phenyl) 2-methylpropanethioate (JTT-705), has been developed that shows 50% inhibition of CETP activity in human plasma at a concentration of 6 μM and is currently in phase II clinical studies.[18] Here we describe new data on the relationship between the structure of the central benzene moiety and CETP inhibitory activity, as well as the discovery of compound **18**, which is more potent than JTT-705.

The compounds for evaluation were synthesized from 2-aminothiophenols (Scheme 1) or 2-nitrophenols[20] (Scheme 2). Diacylation at both nitrogen and sulfur atoms of the 2-aminothiophenols with 2 equiv of the corresponding acyl chlorides,[21] followed by selective

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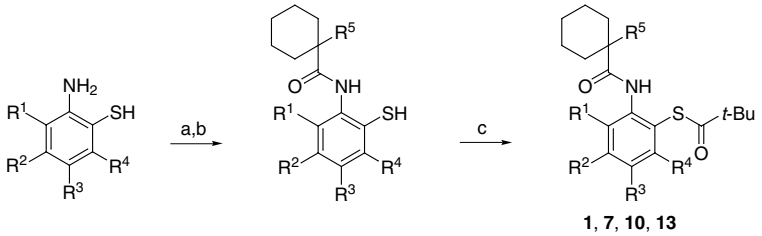
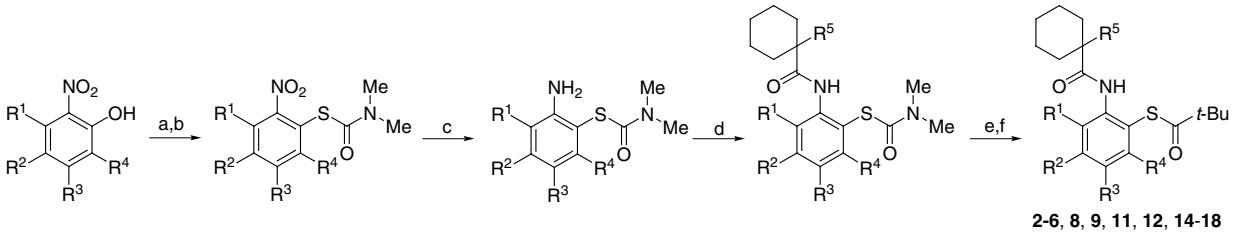
doi:10.1016/j.bmcl.2004.02.071



Scheme 1. Reagents: (a) 1-methylcyclohexanecarbonyl chloride (R^5=Me) or 1-(3-methylbutyl)cyclohexanecarbonyl chloride (R^5=isopentyl), pyridine, $CHCl_3$; (b) KOH, THF–MeOH–H_2O; (c) pivaloyl chloride, pyridine, $CHCl_3$.



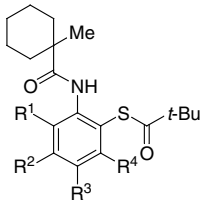
Scheme 2. Reagents and conditions: (a) *N*,*N*-dimethylthiocarbamoyl chloride, NaH, DMF; (b) diphenyl ether, 120–200 °C; (c) $SnCl_2{\cdot}2H_2O$, AcOEt; (d) 1-methylcyclohexanecarbonyl chloride (R^5=Me) or 1-(3-methylbutyl)cyclohexanecarbonyl chloride (R^5=isopentyl), pyridine; (e) KOH, THF–MeOH–H_2O; (f) pivaloyl chloride, pyridine, $CHCl_3$.

hydrolysis of the thioester bond, yielded the acylaminothiophenols. Coupling between these thiophenols and pivaloyl chloride gave the *S*-(2-(acylamino)phenyl) 2,2-dimethylpropanethioates (Scheme 1). The 2-nitrophenols were reacted with *N*,*N*-dimethylthiocarbamoyl chloride to give *O*-aryl dimethylthiocarbamates, and were subsequently transformed to *S*-aryl thiocarbamates by Newman–Kwart rearrangement.[22] After these nitro compounds were converted to aniline derivatives by reduction with tin(II) chloride, acylation was done with the corresponding acyl chlorides. Hydrolysis of the resulting *S*-acylaminophenyl dimethylthiocarbamates to thiols and subsequent acylation with pivaloyl chloride produced the *S*-(2-(acylamino)phenyl) 2,2-dimethylpropanethioates (Scheme 2).

In vitro inhibition of CETP activity was assessed by measuring the rate of [^{3}H] cholesteryl ester transfer from HDL to apoprotein B-containing lipoproteins in human plasma, as described previously.[17,19] The effect of each substituent on the central benzene moiety of compounds **1** and **10** was investigated and the results are summarized in Tables 1 and 2. For comparison, the inhibitory activity of JTT-705 is also shown in Table 2.

First, the introduction of one or two fluoro groups into the benzene moiety of compound **1** was tested. Although the 5-fluoro compound **3** and the 4-fluoro compound **5** maintained CETP inhibitory activity, the 6-fluoro compound **2** and the 3,5-difluoro compound **4** showed loss of activity. Since the 4- and 5-positions tolerated the introduction of a fluoro group, various groups were introduced into the 4-position on the benzene moiety of compounds **1** and **10**. Although introduction of electron-donating groups (**9**, and **15**–**16**) caused loss of CETP inhibitory activity, introduction of electron-withdrawing groups either maintained the inhibitory activity (**8**, and **11**) or caused it to increase (**6**, **7**, and **12**–**14**) compared with that of the parent compounds (**1** and **10**). Among various electron-withdrawing groups, the chloro group showed the greatest enhancement of activity. The 4-chloro compound **12** was about 5-fold more potent than the parent compound **10**. Because the active forms of this series are free thiols, as described previously,[19] the effect of electron-withdrawing groups, especially at the 4-position, may be partly due to acceleration of hydrolysis of the thioester. A chloro group was also substituted at the 5-position on the

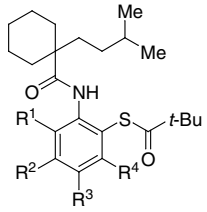
Table 1. Inhibition of CETP activity by the 1-methylcyclohexanecarbonylamino compounds



Compounds	R^1	R^2	R^3	R^4	CETP inhibition in human plasma IC_{50} (μM)[a]
1	H	H	H	H	72
2	H	H	H	F	>300
3	H	H	F	H	78
4	F	H	F	H	>300
5	H	F	H	H	70
6	H	Cl	H	H	28
7	H	CF_3	H	H	40
8	H	CN	H	H	102
9	H	OMe	H	H	>300

[a] Concentration achieving 50% inhibition of CETP-mediated CE transfer from HDL to VLDL and LDL.

Table 2. Inhibition of CETP activity by the 1-(3-methylbutyl)cyclohexanecarbonylamino compounds



Compounds	R^1	R^2	R^3	R^4	CETP inhibition in human plasma IC_{50} (μM)[a]
10	H	H	H	H	61
11	H	F	H	H	60
12	H	Cl	H	H	13
13	H	CF_3	H	H	13
14	H	CN	H	H	25
15	H	OMe	H	H	>300
16	H	Me	H	H	>300
17	H	H	Cl	H	10
18	H	Cl	Cl	H	2
JTT-705					6

[a] Concentration achieving 50% inhibition of CETP-mediated CE transfer from HDL to VLDL and LDL.

benzene moiety of **10**, which was another position tolerating the introduction of substituents. The 5-chloro compound **17** showed markedly increased activity and was about 6-fold more potent than **10**. On the basis of these results, we were able to obtain the 4,5-dichloro compound **18** with the highest potency, which was about 30-fold more potent than **10**. The effect of substituting two chloro groups at the 4- and 5-positions on the benzene moiety seemed to be synergistic (about 30-fold enhancement of activity) compared with the effect of a single chloro group at the 4- or 5-position (about 5- or 6-fold enhancement).

In summary, studies on the relationships between the structure of the benzene moiety of *S*-(2-(acylamino)phenyl) 2,2-dimethylpropanethioates and CETP inhibitory activity revealed that the effect of each substituent depended on its nature and position. Although electron-donating groups were not effective, substitution of electron-withdrawing groups at the 4- or 5-positions caused an increase in activity. Moreover, the introduction of chloro groups at both positions induced synergistic enhancement of inhibitory activity, and the most potent 4,5-dichloro compound **18** achieved 50% inhibition of CETP activity in human plasma at a concentration of 2 μM making it about three times more potent than JTT-705.

Acknowledgements

We would like to thank Shigeo Ishiguro, Jun-ichi Haruta, Itsuo Uchida, Noriaki Shimoyama, Takao Ito, and Takahiro Yamasaki for their helpful support.

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