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2-(4-Carbonylphenyl)benzoxazole inhibitors of CETP: Attenuation of hERG binding and improved HDLc-raising efficacy

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ABSTRACT

The development of 2-phenylbenzoxazoles as inhibitors of cholesteryl ester transfer protein (CETP) is described. Efforts focused on finding suitable replacements for the central piperidine with the aim of reducing hERG binding: a main liability of our benchmark benzoxazole (**1a**). Replacement of the piperidine with a cyclohexyl group successfully attenuated hERG binding, but was accompanied by reduced in vivo efficacy. The approach of substituting a piperidine moiety with an oxazolidinone also attenuated hERG binding. Further refinement of this latter scaffold via SAR at the pyridine terminus and methyl branching on the oxazolidinone led to compounds **7e** and **7f**, which raised HDLc by 33 and 27 mg/dl, respectively, in our transgenic mouse PD model and without the hERG liability of previous series.

For years, cardiovascular disease (CD) has remained the leading cause of mortality in the world. Noteworthy is the fact that despite the wide-spread use of methods for treatment (i.e., HMG-CoA reductase inhibitors), there remains a large unmet medical need due to the continued and prevalent impact of this disease on human health. For some time, it has been known that an inverse correlation exists between levels of high-density lipoprotein cholesterol (HDLc) and the relative risk for developing atherosclerosis (and hence CD).[1] Epidemiological studies have indicated that a 1 mg/dl increase in HDLc is associated with a 6% reduction in the risk of death from coronary heart disease (CHD).[2] Despite this, the current primary therapy for HDLc elevation has remained unchanged for years (niacin), and achieves only modest efficacy (~20%).

In the search for modern approaches to HDLc-raising therapy, cholesteryl ester transfer protein (CETP) has risen to the forefront of potential targets. CETP is a plasma glycoprotein that facilitates exchange of cholesteryl ester from HDL to low-density- and very-low-density lipoproteins (LDL and VLDL). This transfer is accompanied by a reverse exchange of triglycerides. As such, inhibition of CETP has been proposed as an approach for raising plasma levels of HDLc.[3] Indeed, clinical studies have been conducted for small-molecule inhibitors validating this approach in humans.[4] Hence, there is ongoing and continued interest in the development of small-molecule inhibitors of CETP, particularly if clinical studies determine that this approach to HDLc treatment results in reduced risk for development of CHD.

Previously, we have disclosed the discovery and development of a 2-phenylbenzoxazole class of CETP inhibitors.[5] This work lead to the development of a series of benzoxazoles containing the 2-arylpyridyl moiety in the eastern half of the molecule (Fig. 1). These compounds were potent (<50 nM) inhibitors of CETP and demonstrated robust elevation of HDLc (>20 mg/dl at 10 mpk) in our transgenic mouse PD model.[5b,6] Unfortunately, these compounds were also plagued by severe human ether-a-go-go-related gene (hERG) binding as reported in our MK499 assay.[7] Compound **1** inhibited hERG with an I_{Kr} binding IC_{50} of 56 nM. Our approach to address this issue focused on finding a suitable modification to the piperidine core. Ultimately, this led to the discovery of oxazolidinones **7e** and **7f,** which possessed improved efficacy in vivo, reduced log *D* value,[8] and no hERG liability.

Recent literature has provided a wealth of information on successful tactics to deal with the issue of hERG binding.[9] There have been thorough analyses of the types of chemical moieties and physical properties that molecules with this liability generally

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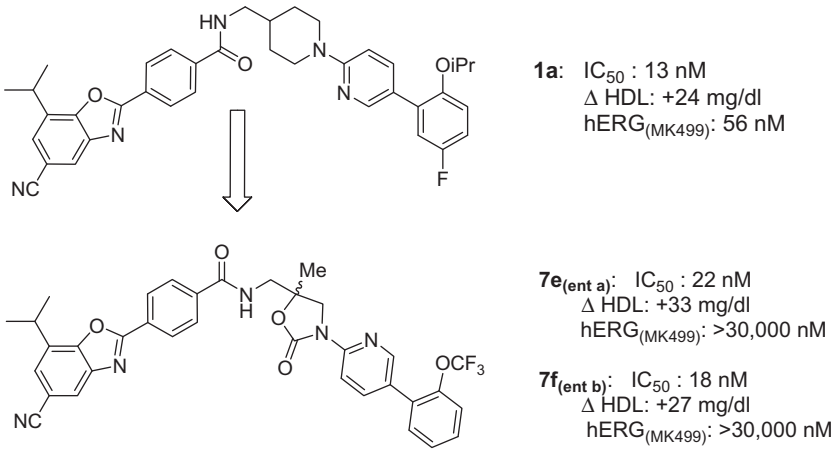


Figure 1. 2-Phenylbenzoxazole CETP inhibitors.

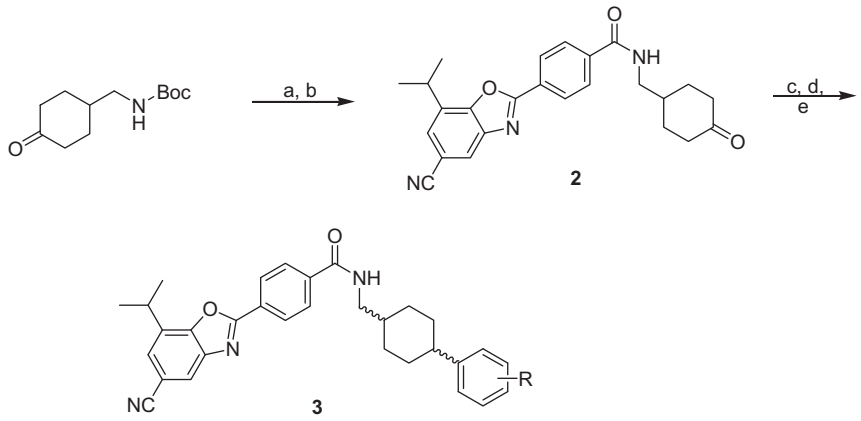
have.[10] In the previously discovered bi-aryl piperidine subclass (**1**), the source of the hERG liability was believed to be the piperidine moiety since the hERG binding issue only became serious after its introduction in our prior SAR work. As a result, our approach to address this liability centered on finding a suitable replacement for this embedded unit. The first approach was to remove the nitrogen and employ a cyclohexyl group as a replacement. Our second approach utilized an oxazolidinone replacement as inspired by the success of its use in clinical compound MK-0859.[11]

The synthesis of the cyclohexyl replacement began with 4-*N*-Boc-aminomethyl-cyclohexanone. Removal of the Boc group with TFA followed by amide formation with the previously synthesized 2-arylbenzoxazole fragment provided the elaborated cyclohexanone **2**. Vinyl triflate formation with trifluoromethanesulfonic anhydride in the presence of 2,6-lutidine allowed for further elaboration via Suzuki cross-coupling with various aryl boronic acids. Finally, hydrogenation of the cycloalkene furnished both cis- and trans- isomers of all compounds evaluated in this series (Scheme 1).

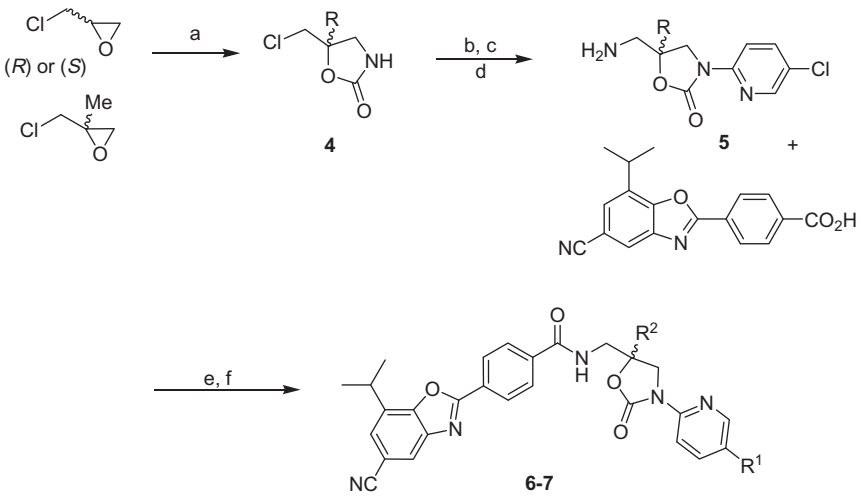
Our approach towards incorporation of an oxazolidinone replacement commenced with epichlorohydrin (*R*- or *S*-) or 2-chloromethyl-2-methyl-oxirane. Potassium cyanate-mediated ring expansion furnished the corresponding chloromethyl oxazolidinones **4**.[12] This intermediate was coupled to 2-bromo-4-chloropyridine via a palladium/Xanthphos-catalyzed amidation.[13] The chloride was then converted to the primary amine via the two-step approach of azide displacement and reduction with triphenylphosphine which provided pyridyl oxazolidinones **5**. This was coupled to the left-hand fragment, 4-(5-cyano-7-isopropyl-benzooxazol-2-yl)-benzoic acid, via the intermediate acyl chloride. Finally, the terminal 4-chloropyridine on the right-hand terminus of the molecule was used as a handle for further elaboration via Suzuki cross-coupling reactions to give final compounds **6**–**7** (Scheme 2).

The initial survey into the cyclohexyl class of molecules focused on simple substitution of the terminal phenyl ring rather than the more-elaborated biphenyl unit found in benchmark compound **1** in order to quickly determine the feasibility of this approach to address hERG.[14] As shown in Table 1, CETP inhibition prefers the trans isomer in general, with the *para* *t*-Bu group being the best among the initial group of substituents. This strategy proved successful in addressing hERG binding. However, the two most potent compounds, **3a** and **3b**, showed only modest efficacy towards raising HDLc in our mouse PD model (17 and 18 mg/dl, respectively). In addition, the removal of the nitrogen from the original piperidine led to an even more lipophilic class of molecules as evidenced by high log *D* values (7.1–7.3). For these reasons, we did not envision the strategy of piperidine-to-cyclohexane replacement as a viable one going forward, and we shifted our focus towards evaluating the oxazolinone class of molecules.

Our strategy to incorporate the oxazolidinone fragment did not look promising at first. The chloro-pyridine analog **6a** showed minimal CETP inhibition (19 μM) leading us to question the

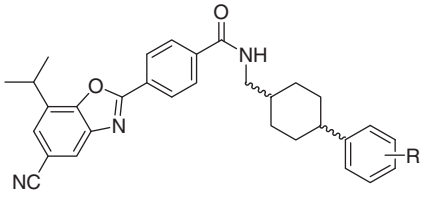


Scheme 1. Synthesis of benzoxazoles **3a–k**. Reagents and conditions: (a) triflouroacetic acid, CH_2Cl_2; (b) HBTU, HOBT, $(i\text{-Pr})_2NEt$, 4-(5-cyano-7-isopropylbenzooxazol-2-yl)-benzoic acid (71%); (c) Tf_2O, 2,6-lutidine (60%); (d) $ArB(OH)_2$, K_2CO_3, 1,1′-bis(di *t*-butylphosphino)ferrocene palladium dichloride (58–89%); (e) 10% Pd/C, H_2 (1 atm), MeOH, THF (31–77%).



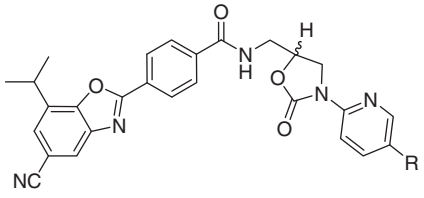
Scheme 2. Synthesis of benzoxazoles **6–8**. Reagents and conditions: (a) potassium cyanate, water, reflux (48–60%); (b) cesium carbonate, Pd_2dba_3, Xanthphos, 2-bromo-5-chloropyridine, dioxane, 80 °C (54–61%); (c) sodium azide, DMF (88–96%); (d) triphenylphosphine, THF/H_2O (84–89%); (e) oxalyl chloride, DMF, di-*iso* propylethylamine (78–86%); (f) $ArB(OH)_2$, K_2CO_3, 1,1′-bis(di-*t*-butylphosphino)ferrocene palladium dichloride (48–93%).

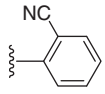
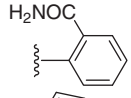
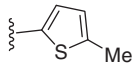
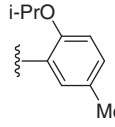
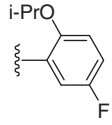
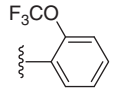
Table 1
SAR of the aryl-cyclohexyl class of benzoxazole CETP inhibitors



Entry	R	Config.	IC_{50} (nM)	I_{Kr} IC_{50} (MK499) (nM)	
1	4-*t*-Bu	*cis*	37	>30,000	**3a**
2	4-*t*-Bu	*trans*	38	>30,000	**3b**
3	4-CF_3	*cis*	134	>30,000	**3c**
4	4-CF_3	*trans*	40	>30,000	**3d**
5	3-CF_3	*cis*	78	2372	**3e**
6	3-CF_3	*trans*	100	>30,000	**3f**
7	3-CH_3	*cis*	145	11,330	**3g**
8	3-CH_3	*trans*	133	>30,000	**3h**
9	3,5-bis-CF_3	*cis*	1038	>30,000	**3i**
10	3,5-bis-CF_3	*trans*	84	>30,000	**3j**
11	4-Cl	*trans*	77	>30,000	**3k**

Table 2
SAR analysis of racemic aryl-oxazolidinones

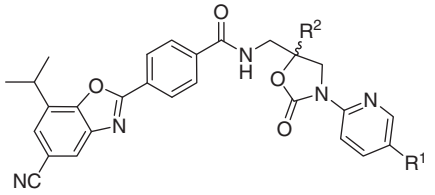


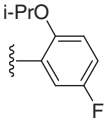
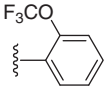
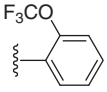
Entry	R	IC_{50} (nM)	I_{Kr} IC_{50} (nM) (MK499)	Log *D*	
1		19,160	>30,000	5.8	**6a**
2		2342	>30,000	5.4	**6b**
3		829	1188	5.1	**6c**
4		–	>30,000	4.8	**6d**
5		955	12,650	6.2	**6e**
6		171	>30,000	6.9	**6f**
7		124	>30,000	6.6	**6g**
8		67	>30,000	6.4	**6h**

likelihood of success via this approach (Table 2). Upon elaborating the terminus with an additional aryl group, potency began to increase to the sub-micromolar range (entries 3 and 5) although slightly polar groups such as the primary amide **6d** were not tolerated. Modifying the aryl group to resemble the substituent pattern found in our initial potent compound (**1a**) led to a series of potent compounds: **6f**, **6g**, and **6h** (entries 6–8). In addition, hERG binding was minimal for most of these compounds. These encouraging results, coupled with the slightly reduced log *D* values of this class of compounds (5.1–6.9) led to further evaluation of the individual enantiomers of the more potent compounds.

The enantiomers of the 2-isopropoxy-5-fluoro analog clearly showed a preference for *R*-configuration in our primary assay (Table 3, entries 1–2). This configuration was also preferred for the 2-trifluoromethoxy analog (entries 3–4). The potent configurations of both also showed reasonable response on our mouse PD assay: raising HDLc by 24 and 19 mg/dl, respectively. Finally, the methyl-substituted oxazolidinone was evaluated with the 2-trifluoromethoxy substitution pattern (entries 5 and 6). The addition of the branching methyl group enhanced potency >2-fold and resulted in a much more robust HDLc elevation of 33 and

Table 3
Analysis of enantiopure aryl-oxazolidinones for CETP inhibition and HDLc raising efficacy



Entry	R^1	R^2	Config.	IC_{50} (nM)	I_{Kr} IC_{50} (nM) (MK499)	ΔHDLc mg/dl	
1	i-PrO 	H	*R*	66	>30,000	24	**7a**
2		H	*S*	154	>30,000		**7b**
3	F_3CO 	H	*R*	46	>30,000	19	**7c**
4		H	*S*	140	3580		**7d**
5	F_3CO 	Me	*R*	22	>30,000	33	**7e**
6		Me	*S*	18	>30,000	27	**7f**

27 mg/dl, respectively. In addition, the hERG binding was also attenuated for both enantiomers.

In summary, we have highlighted a dual strategy to address the issue of hERG binding that plagued our benchmark compound **1a**. By replacing the piperidine moiety with a cyclohexyl group, hERG binding was successfully attenuated. The most potent compounds from a brief survey of analogs showed only modest efficacy in HDLc raising (17 and 18 mg/dl for compounds **3a** and **3b**) and possessed high log *D* values (7.1–7.3). Replacement of the piperidine moiety with an oxazolidinone also led to a successful attenuation of hERG binding. SAR optimization resembled that for the piperidine class, resulting in 2-alkoxyphenyl-pyridine substituted compounds **7a**–**7d** which were all potent inhibitors of CETP. The potency was generally enhanced for the *R* enantiomer, and both **7a** and **7c** led to an increase in HDLc in our mouse PD assay. Finally, methyl substitution on the oxazolidinone led to improved potency in compounds **7e** and **7f** (22 and 18 nM), robust HDLc-raising efficacy (33 and 27 mg/dl, respectively), and no hERG liability. Further optimization of this class of compounds in the context of CETP inhibition will be reported in due course.

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