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2-(4-Carbonylphenyl)benzoxazole inhibitors of CETP: Scaffold design and advancement in HDLc-raising efficacy

Ramzi F. Sweis [a,*], Julianne A. Hunt [a], Florida Kallashi [a], Milton L. Hammond [a], Ying Chen [b], Suzanne S. Eveland [b], Qiu Guo [b], Sheryl A. Hyland [b], Denise P. Milot [b], Anne-Marie Cumiskey [c], Melanie Latham [c], Raymond Rosa [c], Larry Peterson [c], Carl P. Sparrow [b], Samuel D. Wright [b], Matt S. Anderson [b], Peter J. Sinclair [a]

[a] Department of Medicinal Chemistry, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA
[b] Department of Cardiovascular Diseases, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA
[c] Department of Pharmacology, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA (ES)

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ABSTRACT

The development of 2-phenylbenzoxazoles as inhibitors of cholesteryl ester transfer protein (CETP) is described. Initial efforts aimed at engineering replacements for the aniline substructures in the benchmark molecule. Reversing the connectivity of the central aniline lead to a new class of 2-(4-carbonylphenyl)benzoxazoles. Structure–activity studies at the C-7 and terminal pyridine ring allowed for the optimization of potency and HDLc-raising efficacy in this new class of inhibitors. These efforts lead to the discovery of benzoxazole **11v**, which raised HDLc by 24 mg/dl in our transgenic mouse PD model.

Cholesteryl ester transfer protein (CETP) inhibitors have garnered intense interest as a possible treatment for atherosclerosis.[1] The inverse correlation between CETP activity and high-density lipoprotein cholesterol (HDLc) levels suggests that CETP inhibition may be an effective way to elevate levels of anti-atherogenic HDLc in humans. Noteworthy are epidemiological studies correlating a 1 mg/dl increase in plasma HDLc concentration to a 6% decrease in the risk of death from cardiovascular disease.[2] Accordingly, small-molecule CETP inhibitors have recently been reported in these[3] and other laboratories.[4]

In continuation of our ongoing studies on the development of 2-phenylbenzoxazoles as inhibitors of CETP, we focused on further refining this class of inhibitor to address its existing liabilities. The benchmark compound in this class, **1a**, is a potent inhibitor of CETP (IC_{50}: 16 nM) and elevates HDL cholesterol levels by 24 mg/dl in our transgenic mouse PD model.[5] However, the physicochemical properties (such as aqueous solubility) of this compound and others in its class are not ideal. In addition, aniline substructures are embedded in the molecule, and one of these forms part of a potentially labile amide bond. Since aniline is a toxic substance that is classified by the EPA as a Group B2 probable human carcinogen,[6] we strove to find suitable replacements for the aniline moieties in **1a** and **1b** while maintaining the in vitro potency and in vivo efficacy of these compounds (Fig. 1).

This goal was achieved through reversal of the central amide moiety to remove the aniline, installation of a C-7 isopropyl group

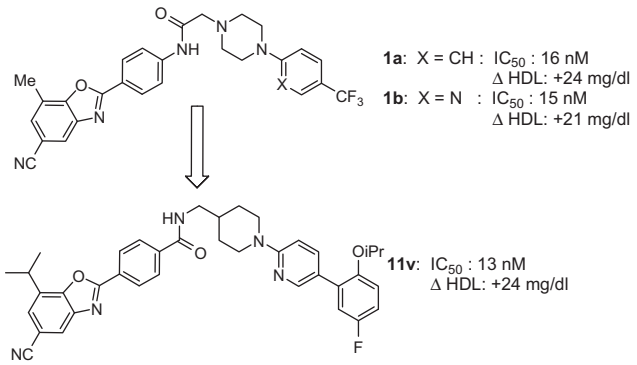

Figure 1. 2-Phenylbenzoxazole CETP inhibitors.

* Corresponding author. Tel.: +1 732 594 2742.
E-mail address: ramzi.sweis@merck.com (R.F. Sweis).

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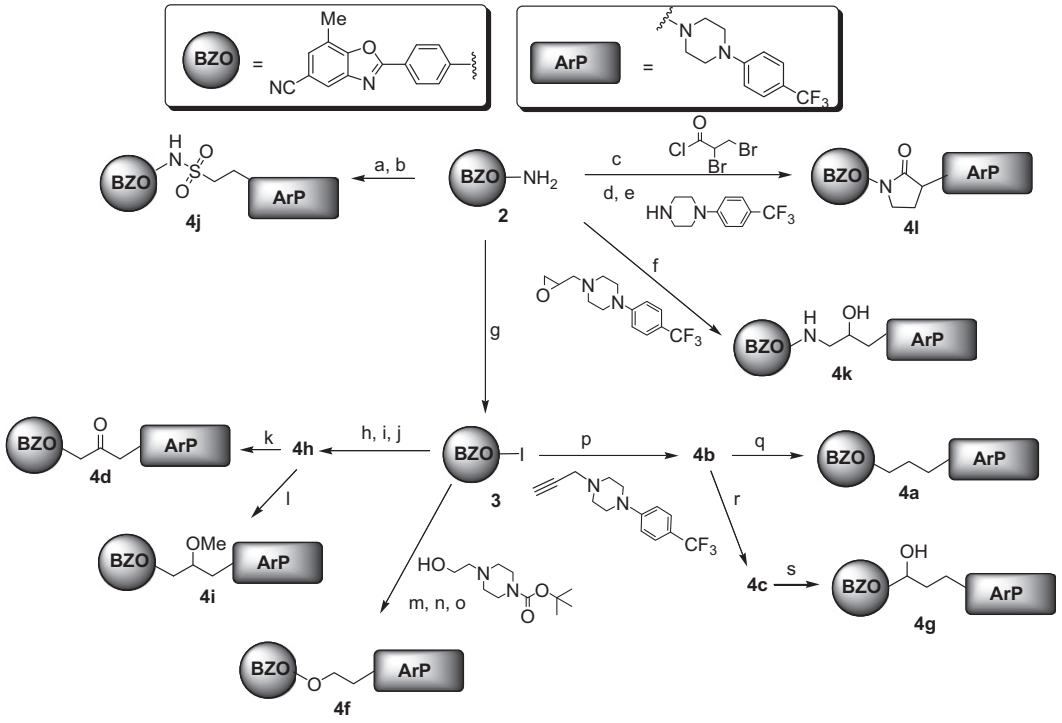
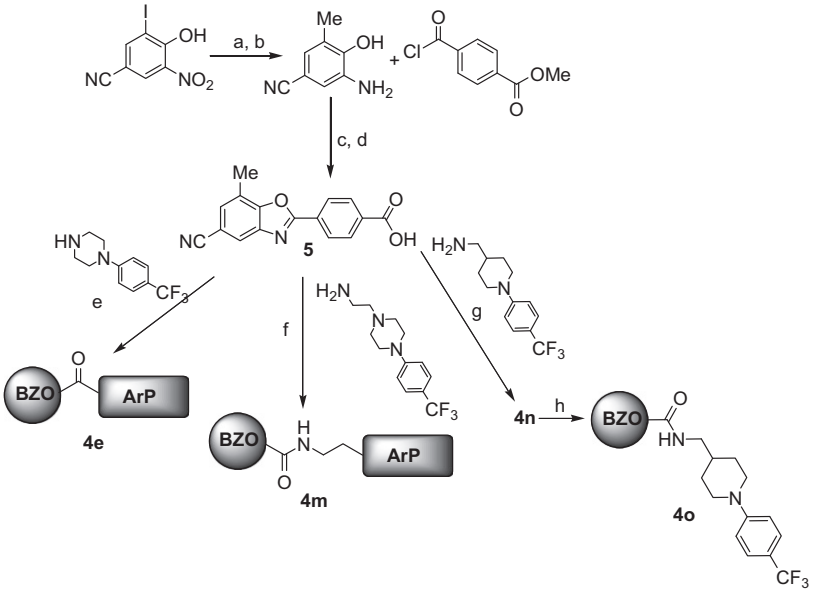


Scheme 1. Synthesis of benzoxazoles **4a**–**l**. Reagents and conditions: (a) 2-chloroethanesulfonyl chloride, pyridine, CH_2Cl_2 (99%); (b) 4-trifluoromethylphenylpiperidine, EtOH, 70 °C (86%); (c) Na_3PO_4, CH_3CN (97%); (d) K_2CO_3, MeOH 80 °C (96%); (e) MeOH, 140 °C, microwave (44%); (f) $CeCl_3$ (0.3 equiv), NaI (0.3 equiv), EtOH, microwave 150 °C (15%); (g) *n*-amylnitrite, I_2, $CHCl_3$ (76%); (h) allyltributyltin, $Pd(PPh_3)_2Cl_2$ (10 mol %), dioxane (87%); (i) H_2O_2, CH_3CN, CH_2Cl_2 (91%); (j) 4-trifluoromethylphenyl piperidine, EtOH (91%); (k) Dess–Martin periodinane, CH_2Cl_2 (95%); (l) NaH, MeI, dioxane (40%); (m) NaH, Pd_2dba_3 (10 mol %), BINAP (10 mol %) toluene, 90 °C (79%); (n) HCl, dioxane (98%); (o) 4-trifluoromethyl-iodobenzene, NaOtBu (1.5 equiv), Pd_2dba_3 (10 mol %), BINAP (20 mol %), toluene, 90 °C (75%); (p) triethylamine, $Pd(PPh_3)_2Cl_2$ (5 mol %), CuI, dioxane 50 °C (90%); (q) H_2, 10% Pd/C (79%); (r) $HgSO_4$, HCO_2H, 60 °C (16%); (s) $NaBH_4$, methanol (45%).

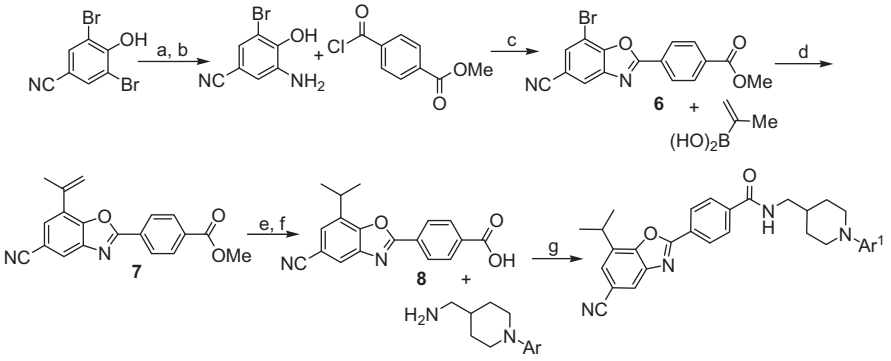


Scheme 2. Synthesis of 2-(4-carbonylphenyl)benzoxazoles **4e**, **4m**–**o**. Reagents and conditions: (a) $MeB(OH)_2$ (5 equiv), Cs_2CO_3, Pd_2dba_3 (10 mol %), DMF, 130 °C (53%); (b) $FeCl_3$–$6H_2O$ (5 mol %), hydrazine (5 equiv) charcoal, MeOH, 70 °C (89%); (c) TsOH, dioxane, toluene 110 °C (59%); (d) LiOH, THF/MeOH/H_2O (97%); (e) HOBT–H_2O, EDC, $(i\text{-Pr})_2$EtN, dioxane, 50 °C (36%); (f) $(COCl)_2$, DMF, $(i\text{-Pr})_2$EtN, CH_2Cl_2 (44%); (g) $(COCl)_2$, DMF, $(i\text{-Pr})_2$EtN, CH_2Cl_2 (73%); (h) NaH (10 equiv), MeI (2 equiv), THF (73%).

on the benzoxazole to restore in vitro potency, and evaluation of various aryl piperidines at the terminus of the molecule to achieve effective HDLc elevation. These efforts culminated in three potent CETP inhibitors (**11k**, **11p**, and **11v**), which produced robust elevations of HDLc levels (>20 mg/dl).

The synthesis of the various 2-phenylbenzoxazoles reported herein followed three main approaches. The first focused on modification of the central 'linker' region of the molecule, the second evaluated the C-7 position of the benzoxazole, and the third targeted changing the substitution pattern at the terminal pyridine ring.

As shown in Scheme 1, the common intermediate 2-(4-aminophenyl)benzoxazole **2** was used as a divergent starting point for a wide variety of linker modifications, including sulfonamide **4j**, cyclic



Scheme 3. Synthesis of 'reversed amide' benzoxazoles **9e**, **10**, **11a–i**. Reagents and conditions: (a) $NaNO_2$, AcOH (82%); (b) $FeCl_3$–$6H_2O$, hydrazine (78%); (c) TsOH, toluene, 110 °C (69%); (d) 2 M Na_2CO_3 (3 equiv), $Pd(PPh_3)_4$ (5 mol %), toluene/H_2O/EtOH (81%); (e) H_2, Pd/C (10%) THF/MeOH 2:1 (85%); (f) LiOH, THF/MeOH/H_2O (80%); (g) $(COCl)_2$, DMF, $(i\text{-}Pr)_2EtN$, CH_2Cl_2 (31–85%).

amide **4l**, β-hydroxyamine **4k**,[7] and 2-(4-iodophenyl)benzoxazole **3**. The latter served as the starting point for further analog generation via Stille cross-coupling, palladium-catalyzed C–O cross-coupling, and Sonogashira coupling. Further, synthetic manipulations of the products of the cross-coupling reactions provided compounds **4a–d** and **4f–i**.

Our most successful series of linker modifications derived from a reversal of the amide connectivity in compound **1**. 2-(4-Carboxyphenyl)benzoxazoles such as **5** were the key intermediates in the synthesis of the reverse amides, as shown in Scheme 2. Beginning with commercially available 4-hydroxy-3-iodo-5-nitrobenzonitrile, a Suzuki cross-coupling with methylboronic acid followed by iron(III) chloride-mediated reduction of the nitro-group with hydrazine furnished the desired aminophenol, which was condensed with methyl 4-chlorocarbonylbenzoate to provide the required benzoxazole. Basic hydrolysis of the ester gave rise to the key 2-(4-carboxyphenyl)benzoxazole intermediate, **5**, which could be then be coupled with a variety of amines under standard conditions.

Our second approach to improving the 2-phenylbenzoxazole class of CETP inhibitors involved an evaluation of analogs at the C-7 position of the benzoxazole ring. Bromobenzoxazole **6** provided a handle for the introduction of functionality at the C-7 position of the benzoxazole in the reverse amide scaffold. As shown in Scheme 3, this intermediate resulted from selective nitration of 3,5-dibromo-4-hydroxybenzonitrile,[8] followed by iron(III) chloride-mediated hydrazine reduction to the amino alcohol, which was then coupled with methyl 4-chlorocarbonylbenzoate and cyclized to the corresponding benzoxazole.

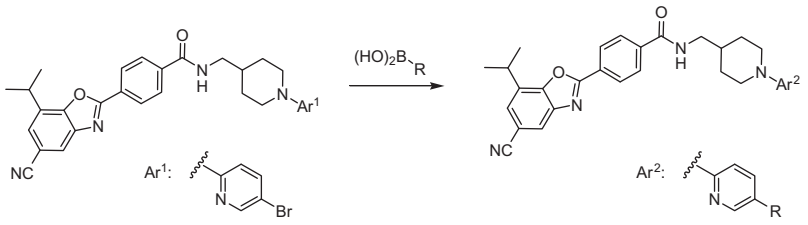
A Suzuki coupling reaction installed the desired isopropenyl group at C-7, and Pd-catalyzed reduction provided the isopropyl-substituted benzoxazole **8**, which was condensed with a variety of amines to furnish aminopiperidine-substituted analogs.

Finally, our third approach utilized 3-bromopyridine as the aryl functionality attached to the piperidine (Scheme 4). Further manipulation of the bromide, via palladium-catalyzed N-arylation reactions, was utilized to evaluate SAR at C3 of the pyridine ring.

Work in these laboratories showed that the terminal aniline in **1a** could be replaced by an aminopyridine (as in **1b**) without a significant effect on potency (IC_{50}: 15 nM vs 16 nM; see Fig. 1). However, employing this strategy to address the central aniline was unsuccessful, as replacement with an aminopyridyl ring led to a significant reduction in potency.[9] Therefore, we turned to modifying the 'linker' region of the molecule in order to address the removal of the central aniline, and the results of this approach are highlighted in Table 1.

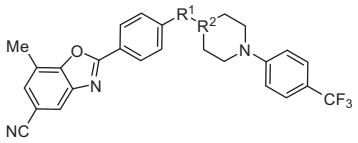
The importance of the central amide unit in the benchmark phenylbenzoxazole structures **1a** and **1b** became apparent by the significant attenuation in potency observed with seemingly simple substitutions. For example, potency was reduced by approximately two orders of magnitude when the amide was replaced with either a propyl or propynyl group (entries 1 and 2), a keto- or alkoxy-group (entries 3–5 and 7–8), or an ether linkage (entry 6). Other modifications such as 2-methoxypropyl linkages (entry 9), sulfonamides (entry 10), and β-hydroxyamines (entry 11) were also not well-tolerated. Even the relatively conservative substitution of a cyclic amide (entry 12) was deleterious to in vitro potency. These results may point to the participation of the amide in a hydrogen donor/acceptor interaction with the transfer protein. Ultimately, our only successful modification of the linker region was the reversed amide series, in which the necessary amide bond is maintained, but the aniline substructure is eliminated.

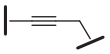
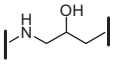
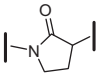
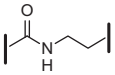
Our first foray into this series necessitated extending the 'linker' region by one carbon unit to avoid introduction of a potentially labile hemiaminal (entry 13), resulting in a severe attenuation of in vitro potency. In order to determine whether this reduced potency was due to the reversed amide, or simply to the greater degree of rotational freedom introduced by the extra carbon, the piperidine reversed amide analog of **1a** (without the extra methylene unit) was synthesized next (entry 14). Although the IC_{50} of this compound, **4n**, was still greatly reduced (300 nM) compared to that of **1a**, the potency showed nearly an order of magnitude improvement over all the other compounds in Table 1. Methylation of this amide had a strong deleterious effect on potency (entry 15),



Scheme 4. Synthesis of various aryl pyridines at the terminus of benzoxazoles **11j–v**. Reagents and conditions: 2 M Na_2CO_3 (3 equiv), $Pd(PPh_3)_4$ (5 mol %), toluene/H_2O/EtOH (25–59%).

Table 1
Effect of various linker groups on inhibition of CETP



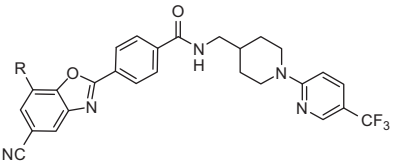
Entry	R^1	R^2	IC_{50}	
1		N	975	**4a**
2		N	2172	**4b**
3		N	2053	**4c**
4		N	5741	**4d**
5		N	4029	**4e**
6		N	4554	**4f**
7		N	2249	**4g**
8		N	874	**4h**
9		N	8940	**4i**
10		N	–	**4j**
11		N	18,760	**4k**
12		N	2742	**4l**
13		CH	11,600	**4m**
14		CH	300	**4n**
15		CH	2612	**4o**

once again highlighting the sensitivity of the SAR in the linker region.

Having identified the reversed amide as our most promising linker modification, we shifted the direction of our efforts towards improving the potency of **4n**. Prior SAR at the C-7 position of benzoxazole **1a** suggested that surveying substituents at this position could help us regain some of the potency that was lost by removing the aniline substructures.[3b] The C-7 methyl was known to be a potency-enhancing group in the previous amide class. Consequently, a series of alkyl substitutions at this position was evaluated in the reversed amide series (Table 2).

Replacing the C-7 methyl with a cyclopropyl group did not result in any improvement in IC_{50} value (entry 1). Similarly, substitution with a trifluoromethyl (entry 2) and *tert*-butyl group (entry 3) were either deleterious or lacked any significant enhancement in potency. Substitution with a C-7 isopropenyl group did, however, show some promise as the IC_{50} was reduced to 131 nM. Subsequent reduction of the alkene in compound **9d** to form the C-7 isopropyl group of compound **9e** (entry 5) brought the potency of this benzoxazole back to the range of compounds **1a** and **1b** (40 nM).

Table 2
Effect of benzoxazole C-7 substitution on CETP inhibition



Entry	R	IC_{50} (nM)	
1		243	**9a**
2		3186	**9b**
3		198	**9c**
4		131	**9d**
5		40	**9e**

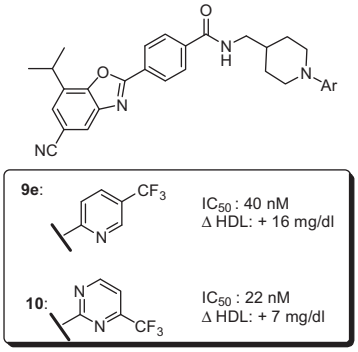


Figure 2. Isopropyl-substituted 'reversed amide' CETP inhibitors and their effect on HDLc elevation.

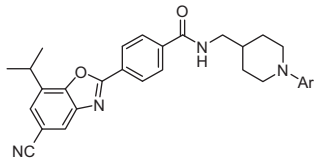
Benzoxazole **9e** was subsequently evaluated in our mouse PD assay along with a similar compound, pyrimidine **10** (Fig. 2). Both of these compounds showed only modest effects in raising HDLc. There also was substantial variability in this assay, presumably owing to the poor solubility of these compounds in many solvents, including DMSO and water.

Our strategy then shifted to evaluating substitution at the terminal pyridine of the molecule, since initial studies revealed that a variety of groups could be incorporated at this site without severely impeding in vitro potency. A series of pyridine analogs were studied, as shown in Table 3.

The potency of the unsubstituted pyridine (entry 1) dropped almost threefold compared to **9e**, demonstrating the importance of the CF_3 moiety on the pyridine ring; the 2-CF_3- and 4-CF_3-substituted pyridines (entries 2 and 4) were comparable in potency to **9e**. However, the reduced potency of the 2-methoxy- (entry 3), 2-methylcarboxy- (entry 6), and 3-methylcarboxy- (entry 5) variants revealed the superiority of nonpolar substituents, and variants with highly polar substituents such as 2-carboxy- (entry 7) and 3-nitro- (entry 8) showed no inhibition of CETP activity.

The 3-bromopyridine **11i** (entry 9) was synthesized in order to pursue more nonpolar substituents on the pyridine ring. While small groups such as isopropenyl (entry 10) led to insufficient potency, larger groups such as phenyl (entry 11) 4-methylphenyl (entry 12), and 3-methylphenyl (entry 13) drove the IC_{50} values to below 50 nM. When we discovered that ortho-substitution on the phenyl ring was well-tolerated (entry 14), we became intrigued by the possibility of incorporating a 2-methoxy-4-fluoro-5-isopro-

Table 3
Effect of pyridine substitution on inhibition of CETP



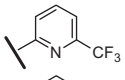
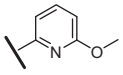
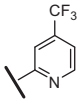
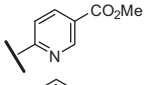
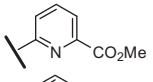
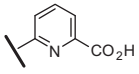
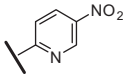
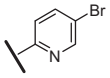
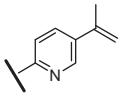
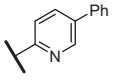
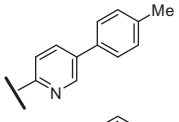
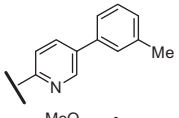
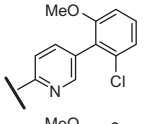
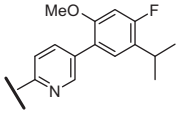
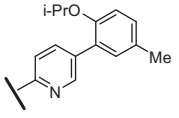
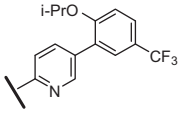
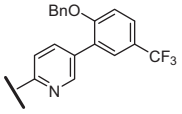
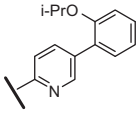
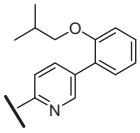
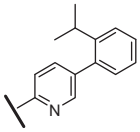
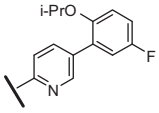
Entry	Ar	IC_{50} (nM)	
1		114	**11a**
2		37	**11b**
3		110	**11c**
4		61	**11d**
5		114	**11e**
6		306	**11f**
7		>10,000	**11g**
8		>10,000	**11h**
9		223	**11i**
10		229	**11j**
11		43	**11k**
12		48	**11l**
13		39	**11m**
14		47	**11n**
15		24	**11o**
16		22	**11p**
17		28	**11q**

Table 3 (*continued*)

Entry	Ar	IC_{50} (nM)	
18		413	**11r**
19		29	**11s**
20		31	**11t**
21		19	**11u**
22		13	**11v**

pylphenyl group onto the pyridine ring (entry 15), based on the use of this substitution pattern in our clinical CETP inhibitor, anacetrapib.[10] Similar compounds with an ortho-alkoxy, meta-alkyl substitution pattern were then prepared: 2-isopropoxy analogs (entries 16 and 17) showed comparable potency, but a further increase in the size of the alkoxy group proved deleterious (entry 18).

The complexity of the substitution pattern was then scaled back to simple 2-substituted aryl groups without the meta-alkyl substituents (entries 19, 20, and 21). Finally, replacement of the meta-alkyl group with a fluoro led to the most potent compound in the series (entry 22).

Three compounds in the arylpiperidine series were evaluated in our mouse PD assay. Compounds **11k**, **11p**, and **11v** (Table 3) raised HDLc levels by 22, 28, and 24 mg/dl at 10 mpk. These compounds, in addition to producing robust elevations of HDLc levels, were not plagued by the irreproducibility previously observed with compounds **9e** and **10**.

In summary, our efforts to develop a 2-phenyl benzoxazole CETP inhibitor devoid of aniline substructures began with an initial evaluation of the central amide portion of our lead compound **1a**. This work revealed that reversal of the amide connectivity was the most viable path forward towards this objective. The lost potency of **4n** was recovered via installation of an isopropyl group at the C-7 position of the benzoxazole (**9e**). The resultant IC_{50} of 40 nM was comparable to our benchmark compound **1a**, although the HDLc elevation in our mouse PD model remained inadequate. Further refinement via substitution on the terminal pyridine ring led to a class of arylpyridine inhibitors. From this class, three compounds (**11k**, **11p**, and **11v**) were evaluated and found to strongly elevate HDLc levels (>20 mg/dl). Continuing work on this class of compounds to address off-target activities will be reported in due course.

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