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2-Arylbenzoxazoles as CETP inhibitors: Substitution of the benzoxazole moiety

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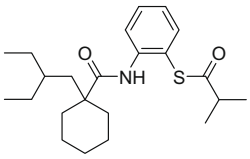
ABSTRACT

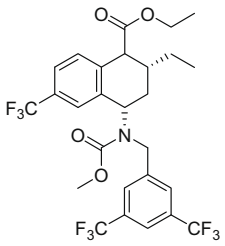
A series of 2-arylbenzoxazole inhibitors of the cholesterol ester transfer protein (CETP) is described. Structure–activity studies focused on variation of the substitution of the benzoxazole moiety. Substitution at the 5- and 7-positions of the benzoxazole moiety was found to be beneficial for CETP inhibition. Compound **47** was found to be the most potent inhibitor in this series and inhibited CETP with an IC_{50} of 28 nM.

Coronary heart disease (CHD) is now the leading cause of death of people in developed countries. Elevated levels of low-density lipoprotein-cholesterol (LDL-C) has been identified as a major risk factor for CHD. The development of the statins has significantly helped to reduce LDL-C levels in patients at risk for CHD.[1,2] There is now a growing body of epidemiological evidence linking increased levels of high density lipoprotein-cholesterol (HDL-C) with decreased risk of development of CHD.[3–6] Some cholesterol lowering drugs, including niacin, fibrates and statins, have a modest effect on increasing HDL-C levels.[7–10] Regardless, niacin remains the front line therapy for raising HDL-C levels despite its modest efficacy (~20% increase). Consequently there is a need for better therapies to address this problem.

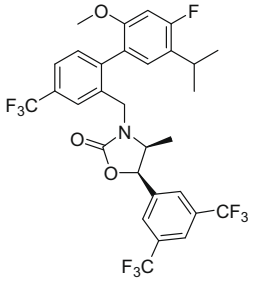
The beneficial effects of high density lipoprotein (HDL) are thought to arise from its participation in reverse cholesterol transport (RCT) as well as its anti-inflammatory and anti-oxidant properties.[11,12] Cholesteryl ester transfer protein (CETP) mediates the exchange of cholesteryl ester (CE) from HDL with triglycerides primarily from very low-density lipoprotein (VLDL).[11,12] Inhibition of CETP would therefore be expected to increase serum HDL-C levels. Clinical studies in humans with the CETP inhibitors, dalcetrapib (JTT-705),[13,14] torcetrapib,[15–19] and anacetrapib[20–22] established that pharmacological inhibition of CETP leads to significant increases in HDL-C concentrations. Despite this observation, imaging studies with torcetrapib showed the compound had no effect on the progression of atherosclerosis.[23–25] Additionally, the torcetrapib phase III trial was prematurely halted after the observation of



dalcetrapib (JTT-705)



torcetrapib



anacetrapib

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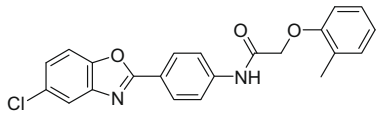
increased mortality in patients receiving torcetrapib and atorvastatin relative to the atorvastatin-only group.[19] This adverse effect may have been related to the observation of an increase in mean systolic blood pressure in the torcetrapib treated arm. There is currently significant debate over whether the adverse effects observed with torcetrapib were caused by mechanism based factors or off-target activities.[26–28] Despite the uncertainty regarding the viability of CETP inhibitors, there is continued interest in the development of a cardiovascular drug against this target. This communication details the identification and optimization of a series of 2-arylbenzoxazole based CETP inhibitors.

Inhibition of CETP mediated CE transfer was characterized in vitro using a fluorescence transfer assay.[29] The assay uses synthetic HDL donor particles that contain self-quenching BODIPY labeled CE along with an additional fluorescence quencher. As the BODIPY labeled CE is transferred from the donor particle to an acceptor lipoprotein by CETP, fluorescence is observed and quantified. Inhibition of CETP mediated CE transfer was characterized by a decrease in levels of fluorescence observed relative to control.

A high throughput screen of compounds in the Merck collection at 2 μM using the above assay was conducted and hits were confirmed by titration. 2-Arylbenzoxazole **1** was identified as a screening hit. This lead class was also independently identified by researchers at Bristol–Myers Squibb and published subsequent to our studies.[30] Their work showed the importance of substitution at the benzoxazole 5-position on potency of CETP inhibition. The work described in this publication is consistent with that described by BMS, but also shows that further substitution of the benzoxazole moiety at the 7-position leads to compounds with additional enhancement of CETP inhibition.



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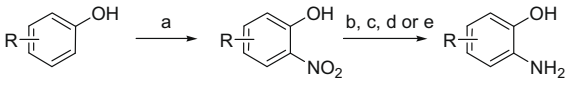
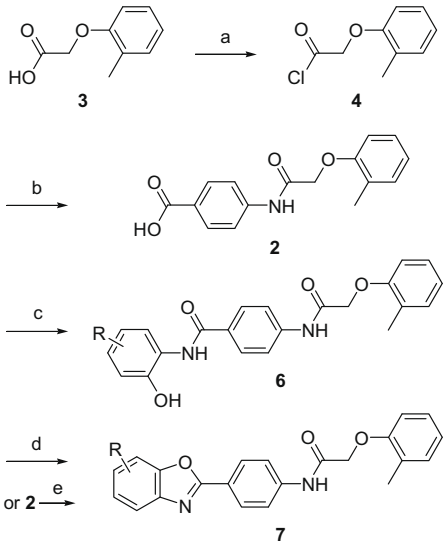
The development of lead compound **1** began with the investigation of the effect of variation of the substitution of the benzoxazole moiety. The synthetic approach used is shown in Scheme 1. Key carboxylic acid **2** was synthesized from phenoxyacetic acid **3** by first treating with oxalyl chloride to form the corresponding acid chloride **4**. Coupling with 4-aminobenzoic acid afforded carboxylic acid **2**. Benzoxazoles were then synthesized by one of three methods.[31] Activation of **2** as the corresponding acid chloride using oxalyl chloride followed by coupling with a range of substituted 2-aminophenols afforded amides of the general structure **6**. A solution of amides **6** in xylene was heated at reflux in a Dean–Stark apparatus with either *p*-tolenesulfonic acid or pyridinium *p*-toluenesulfonic acid, to afford 2-arylbenzoxazoles of general structure **7**. Alternatively, a solution of carboxylic acid **2**, a 2-aminophenol and boric acid in xylene could be heated at reflux or subjected to microwave irradiation at 270 °C to afford the corresponding 2-arylbenzoxazole. 2-Aminophenols were either commercially available or obtained by reduction of the corresponding 2-nitrophenol using either heterogeneous palladium or platinum oxide catalyzed hydrogenation or treatment with tin (II) chloride (Scheme 2). Some 2-nitrophenols were obtained by nitration of the corresponding phenols.

The CETP inhibition data for a series of compounds of different benzoxazole phenyl ring substitution is shown in Table 1 and it can be seen that substitution of this ring appreciably alters CETP inhibitory activity. The unsubstituted benzoxazole (**8**) was 10-fold less active than lead compound **1**. A survey of a series of benzoxazole substituents (compounds **9**–**22**) showed a clear preference for substitution at the 5-position. In particular the 5-nitro and 5-cyano

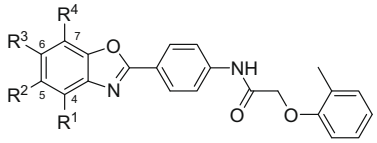


Scheme 2. Reagents and conditions: (a) 90% HNO_3, AcOH, 40 °C to room temperature, 1 h, 16–70%; (b) H_2, 10% Pd/C, EtOH, room temperature, 5–15 h, 97–99%; (c) HCO_2NH_4, 10% Pd/C, MeOH, room temperature, 15 h, quant.; (d) H_2, PtO_2, EtOH, room temperature, 2–15 h, 99%; (e) $SnCl_2{\cdot}2H_2O$, concd HCl, MeOH, room temperature, 15 h, 38–97%.



Scheme 1. Reagents and conditions: (a) $(COCl)_2$, cat. DMF, CH_2Cl_2, room temperature, 1 h, quant.; (b) 4-aminobenzoic acid, *i*-Pr_3NEt, CH_2Cl_2, room temperature, 30 min, 87%; (c) (i) $(COCl)_2$, cat. DMF, CH_2Cl_2, room temperature, 2 h; (ii) 2-aminophenol derivative, 1,4-dioxane, reflux, 2 h; (d) cat. TsOH or PPTS, xylene, reflux under Dean–Stark, 16 h, 10–53%; (e) 2-aminophenol derivative, boric acid, xylene, reflux, 24 h, 7–37%, or microwave irradiation, 270 °C, 1 h, 7–33%.

Table 1
SAR of 2-arylbenzoxazoles



Compd	R^1	R^2	R^3	R^4	CE[a]	
					IC_{50}[a] (μM)	% Max
8	H	H	H	H	13	79
1	H	Cl	H	H	1.1	94
9	H	H	Cl	H	n.d.[b]	32
10	H	H	H	Cl	21	71
11	Me	H	H	H	23	62
12	H	Me	H	H	2.0	89
13	H	H	Me	H	n.d.[b]	34
14	NO_2	H	H	H	n.d.[b]	42
15	H	NO_2	H	H	0.94	79
16	H	H	NO_2	H	3.2	71
17	H	F	H	H	1.9	91
18	H	H	F	H	7.5	50
19	H	H	H	F	n.d.[b]	36
20	H	CN	H	H	0.13	90
21	H	H	CN	H	0.41	97
22	H	H	H	CN	5.2	89

[a] Data reported is derived from duplicate wells and three independent experiments. Mean IC_{50} values were determined from 10-point, one-third log concentration response curves and standard errors were ⩽10%.

[b] IC_{50} not determined if % max inhibition was <50%.

derivatives **15** and **20** were found to be the most potent CETP inhibitors with IC_{50}s of 0.94 and 0.13 μM, respectively. Compounds **23**–**29** (Table 2) represent a series of substitutions that are tolerated at the 5-position with only methoxy (compound **24**) showing better potency than the original lead **1**. Other 5-substituents such as larger alkyl, trifluoromethyl, methyl ester, carboxylic acid, amides, carbamates, sulfonamides, sulfones, hydroxyl, anilino, amidine, tetrazole and substituted phenyl were found to have little or no inhibitory activity (data not shown). The best 5-substituted derivative found was therefore 5-cyano derivative **20** and this represented an early benchmark compound. This was consistent with the work published by researchers at Bristol–Myers Squibb.[30]

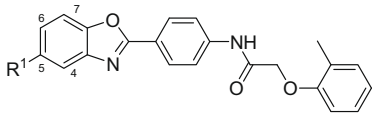
Holding the cyano group constant, the SAR of additional benzoxazole substitution was then explored (Table 3). The three possible regioisomeric methyl derivatives **31**, **33** and **35** were prepared via palladium catalyzed cyanation of the corresponding aryl halides **30**, **32** and **34**, respectively. The CETP inhibition data clearly shows that incorporation of a methyl group is preferred at the 7-position and affords a twofold increase in potency (compare **35** to **20** and **34** to **23**). Compound **35** has a CETP IC_{50} of 60 nM. Compounds **36**–**41** show that a number of other substituents are tolerated at the 7-position in combination with either 5-cyano or 5-halo the most potent being 5-cyano-7-fluoro derivative **39** with a CETP IC_{50} of 62 nM.

The substitution of the 7-position was further investigated by the synthesis of a series of alcohols (compounds **44**–**57**, Table 4). These compounds were synthesized from acetophenone **40** as shown in Scheme 3. Treatment of ketone **40** with sodium borohydride or a Grignard reagent afforded secondary or tertiary alcohols respectively of general structure **42**. These compounds were then transformed into nitriles of general structure **43** via palladium catalyzed cyanation. By and large, potency of CETP inhibition is inversely proportional to the size of the alkyl group added to acetophenone **40**, the best compound being methyl derivative **47** with a CETP IC_{50} of 28 nM. Replacement of the 5-cyano group of **47** with a hydrogen to give compound **57** results in a 10-fold loss in potency of CETP inhibition confirming the importance of substitution at both the 5- and 7-positions.

Compounds **20**, **35** and **47** were evaluated in a pharmacodynamic model in mice expressing cynomolgus monkey CETP and did not show an increase in HDL-C levels. This may be attributed to the lack of oral bioavailability observed with these compounds in mouse PK studies.

In summary, after high throughput screening of the Merck compound collection identified 2-arylbenzoxazole **1** as a lead, it was developed into compounds **35** and **47** using a modular synthetic approach that showed the importance of substitution at the 7-position for potency enhancement over the 5-position alone. These compounds represent important leads for further development of this structure class as CETP inhibitors. Further modifications of the amide and aryloxy moieties will be reported.

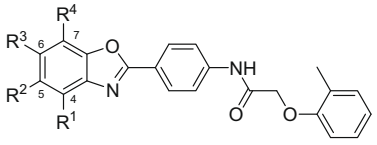
Table 2
SAR of 5-substituted-2-arylbenzoxazoles



Compd	R^1	CE[a] IC_{50}[a] (μM)
8	H	13
20	CN	0.13
23	Br	1.3
24	OMe	0.84
25	SMe	2.9
26	COMe	1.3
27[b]	CH(OH)Me	3.4
28[c]	Vinyl	2.8
29[d]	Ethynyl	2.0

[a] Data reported is derived from duplicate wells and three independent experiments. Mean IC_{50} values were determined from 10-point, one-third log concentration response curves and standard errors were ⩽10%.
[b] Synthesized by reduction of **26**; $NaBH_4$, MeOH, room temperature, 1 h, quant.
[c] Synthesized from **23** by Stille coupling; vinyltributyl tin. $(Ph_3P)_4Pd$, DMF, 80 °C, 12 h, 13%.
[d] Synthesized from **23** by Sonagashira coupling; (i) TMS acetylene, $Pd(PPh_3)_2Cl_2$, CuI, Ph_3P, Et_2NH, DMF, microwave irradiation, 120 °C, 75 min, (ii) aq NaOH, THF, room temperature, 1 h, 32%.

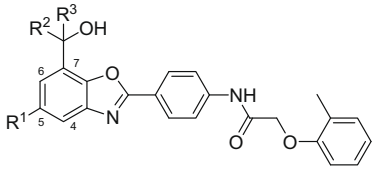
Table 3
SAR of disubstituted-2-arylbenzoxazoles



Compd	R^1	R^2	R^3	R^4	CE[a] IC_{50} (μM)
30	Me	Br	H	H	>100
31	Me	CN	H	H	38
32	H	Cl	Me	H	>100
33	H	CN	Me	H	1.9
34	H	Br	H	Me	0.51
35	H	CN	H	Me	0.060
36	H	CN	H	CN	0.27
37	H	Cl	H	NO_2	0.57
38	H	Br	H	F	0.91
39	H	CN	H	F	0.062
40	H	Br	H	COMe	0.38
41	H	CN	H	COMe	0.086

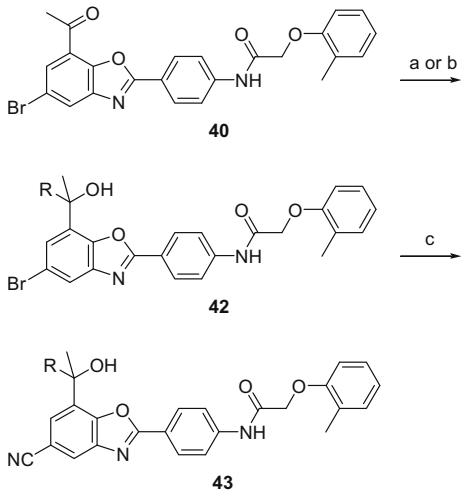
[a] Data reported is derived from duplicate wells and three independent experiments. Mean IC_{50} values were determined from 10-point, one-third log concentration response curves and standard errors were ⩽10%.

Table 4
SAR of 5,7-disubstituted-2-arylbenzoxazoles



Compd	R^1	R^2	R^3	CE[a] IC_{50} (μM)
44[b]	Br	H	Me	0.059
45	CN	H	Me	0.046
46	Br	Me	Me	0.044
47	CN	Me	Me	0.028
48	Br	Me	Et	0.11
49	CN	Me	Et	0.031
50	Br	Me	*n*-Pr	0.20
51	CN	Me	*n*-Pr	0.058
52	Br	Me	*i*-Pr	0.21
53	CN	Me	*i*-Pr	0.080
54	Br	Me	Ethynyl	0.094
55	Br	Me	1-Propynyl	0.21
56	CN	Me	1-Propynyl	0.16
57[c]	H	Me	Me	0.44

[a] Data reported is derived from duplicate wells and three independent experiments. Mean IC_{50} values were determined from 10-point, one-third log concentration response curves and standard errors were ⩽10%.
[b] Synthesized by reduction of **40**; $NaBH_4$, MeOH, room temperature, 1 h, quant.
[c] Synthesized from **46**; $LiAlH_4$, THF, room temperature, 1.5 h, 14%.



Scheme 3. Reagents and conditions: (a) R = alkyl, RMgX, THF, −20 °C to room temperature, 4 h, 40–75%; (b) R = H, $NaBH_4$, MeOH, room temperature, 1 h, quant.; (c) $Zn(CN)_2$, Pd_2dba_2, dppf, dimethylacetamide, microwave irradiation, 60 W, 200 °C, 1 h, 37–73%.

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31. *Benzoxazole synthesis—General method 1*: A mixture of **2** (1.05 mmol), 2-aminophenol derivative (1.05 mmol) and boric acid (1.37 mmol) in *o*-xylene (60 mL) was heated at reflux under a Dean–Stark apparatus overnight. After this time the reaction mixture was diluted with EtOAc (50 mL), washed successively with saturated $NaHCO_3$ (50 mL), H_2O (50 mL), and brine (50 mL), dried (Na_2SO_4) and concentrated in vacuo to afford the crude product. This was purified by flash chromatography and/or reversed phase HPLC to afford the desired benzoxazole.
General method 2: A mixture of **2** (0.307 mmol), 2-aminophenol derivative (0.430 mmol) and boric acid (0.430 mmol) in *o*-xylene (2.5 mL) was subjected to microwave irradiation (300 W, 270 °C, 60 min). The reaction mixture was diluted with EtOAc (25 mL), washed successively with saturated $NaHCO_3$ (25 mL), H_2O (25 mL), and brine (25 mL), dried ($MgSO_4$) and concentrated in vacuo to afford the crude product. This was purified by flash chromatography and/or reversed phase HPLC to afford the desired benzoxazole.
General method 3: A solution of oxalyl chloride (2 M in CH_2Cl_2, 1.40 mmol) was added to a stirred suspension of **2** (0.702 mmol) in CH_2Cl_2 (11 mL) followed by a few drops of DMF at room temperature under N_2. The reaction was stirred at room temperature for 4 h after which time the suspension dissolved. The reaction mixture was concentrated in vacuo and azeotroped with toluene (10 mL). The crude acid chloride and 2-aminophenol (1.05 mmol) were dissolved in 1,4-dioxane (20 mL) and heated at reflux for 4 h under N_2. The reaction was diluted with EtOAc (50 mL) and water (50 mL) and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4) and concentrated in vacuo to afford the crude amide product. A mixture of the crude amide and pyridinium *p*-toluenesulfonate (0.0702 mmol) in *o*-xylene (30 mL) was heated at reflux under a Dean–Stark apparatus overnight under N_2. The reaction was diluted with EtOAc (100 mL) and washed successively with saturated $NaHCO_3$ (50 mL), water (50 mL) and brine (50 mL), dried (Na_2SO_4) and concentrated in vacuo to afford the crude product. This was purified by flash chromatography and/or reversed phase HPLC to afford the desired benzoxazole.