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2-Arylbenzoxazoles as novel cholesteryl ester transfer protein inhibitors: Optimization via array synthesis

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Abstract—2-Arylbenzoxazole **5** was identified as a hit from a fluorescence-based high-throughput screen for CETP inhibitors. The synthesis and SAR investigation employing array synthesis of the A- and B-rings are described.

Lipid modifying therapies for the treatment of coronary heart disease (CHD) have principally focused on lowering circulating levels of low-density lipoprotein cholesterol (LDL-C).[1] With the recognition that there exists an inverse relationship between high-density lipoprotein cholesterol (HDL-C) and the risk of CHD,[2] drug discovery efforts now also focus on investigating mechanisms which have the potential for raising HDL-C in plasma. Current therapies such as fibrates or niacin exert only a modest effect on increasing HDL-C levels while displaying considerable side effects.[3] The need, therefore, exists for safer and more efficacious methods of increasing HDL-C levels.

Cholesteryl ester transfer protein (CETP) is a 74-kDa plasma glycoprotein secreted principally by the liver. CETP facilitates the transfer of cholesterol ester from HDL to LDL and VLDL in exchange for triglycerides.[4] Recent data have shown that CETP inhibition leads to increased HDL-C in humans.[5] As HDL particles are capable of accepting cholesterol from peripheral tissues including macrophages, CETP inhibitors could promote reverse cholesterol transport and therefore be anti-atherogenic.[6] Interest in this target by the pharmaceutical community has been widespread as evidenced by the number of clinical and/or pre-clinical lead compounds in various stages of development (Fig. 1).[7] In this com-

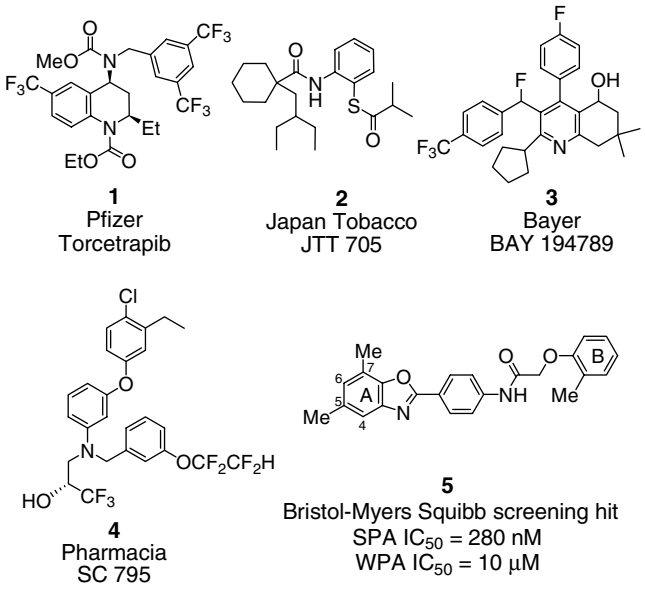

Figure 1. CETP inhibitors.

Keywords: CETP; HDL; Parallel synthesis; Benzoxazole; Cholesteryl ester transfer protein; CETP inhibitor; Coronary heart disease; CHD; SAR.
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munication, the identification and optimization of a novel series of 2-arylbenzoxazole-based CETP inhibitors are described.

A screening campaign was carried out on the BMS compound collection using a BODIPY fluorescence assay.[8] Retest positives in the fluorescence assay were directly followed by reconfirmation in a dose–response mode using a scintillation proximity assay (SPA).[9] Potent compounds in SPA were then evaluated for activity in a human whole plasma assay (WPA).[10] The 2-arylbenzoxazole **5** (Fig. 1) was one of the most potent analogs identified in the HTS (SPA IC_{50} = 0.28 μM) which also possessed a reasonable level of activity in human plasma (WPA IC_{50} = 10 μM).

The 2-arylbenzoxazole hit **5** is structurally dissimilar from published CETP inhibitors (Fig. 1). The relatively linear core of the 2-arylbenzoxazole shows a structural similarity to the molecular framework of cholesterol, the esters of which are known to bind in equimolar ratios with CETP.[11] Molecular modeling of an energy minimized conformation of **5** with cholesterol (Fig. 2) shows that the planar 2-arylbenzoxazole moiety (Alignment 1) overlays well with the tetracyclic core of cholesterol, with the 3β-hydroxyl group in the A-ring of cholesterol being positioned in a similar orientation as the 5-Me substituent on the benzoxazole of **5**. In the alternative Alignment 2, the 2-aryloxyacetamide group traverses the tetracyclic cholesterol core overlaying the A-ring of the steroid core with the phenyl ether. Both overlays suggest that substitution at the terminal rings A and B of **5** might be anticipated to modulate CETP inhibitory activity. The modular structure of this chemotype made it well suited for rapid exploration of the SAR of these terminal rings by applying array synthesis. The SAR strategy involved developing chemistry that allowed exploration of substitutions on either the fused phenyl of the benzoxazole (A) or the phenyl ether (B). Initial results of these studies are presented in this communication.

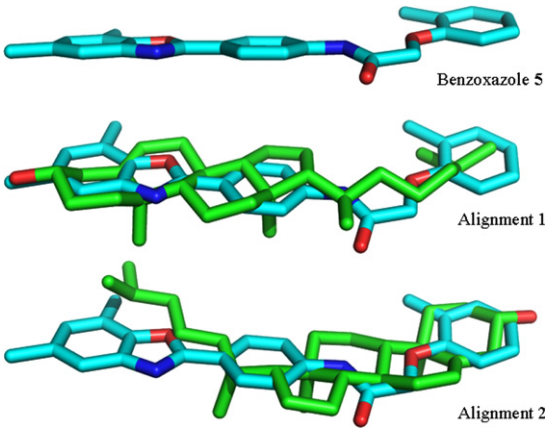
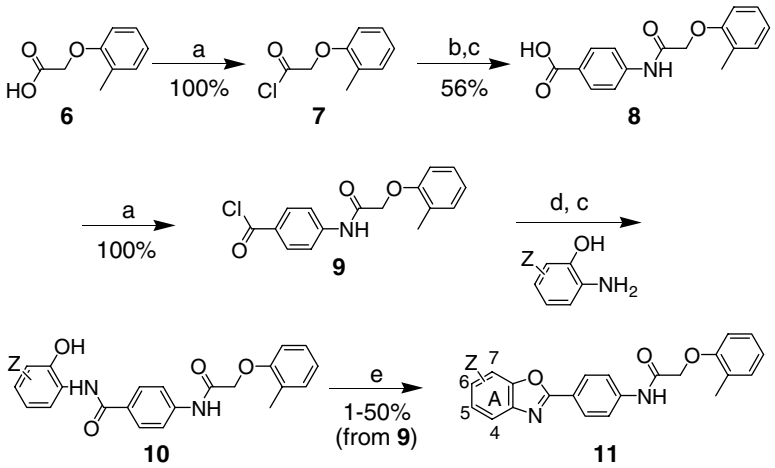


Figure 2. Energy minimized conformation of **5** (blue) and overlays with cholesterol (green).

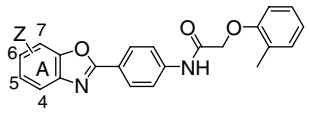
The synthetic approach employed to assess various A-ring substitutions is outlined in Scheme 1. Aryloxyacetic acid **6** was treated with oxalyl chloride to provide the corresponding acid chloride **7** in quantitative yield. Coupling of **7** with 4-carbomethoxy aniline, followed by saponification of the resulting ester gave carboxylic acid **8** in 56% overall yield. Activation of **8** with oxalyl chloride provided the acid chloride **9** in quantitative yield, which was subsequently coupled with various commercially available substituted amino phenols in an array format to afford intermediate amides of the general structure **10**. Conversion of the amides **10** to benzoxazoles **11** was achieved by microwave-mediated cyclization employing catalytic *p*-toluenesulfonic acid. The cyclizations typically proceed within 30 min, and the isolated yields ranged from 1% to 50% (from acid **8**).[12] The average purity (by HPLC-UV) of the final products was 94%.

The structure–activity relationships for a variety of A-ring substitutions are shown in Table 1. Consistent with Alignment 1, substitution on the A-ring significantly modulates CETP inhibitory activity. Removal of both



Scheme 1. General synthetic route to access A-ring variants. Reagents and conditions: (a) $(COCl)_2$, DCM, cat. DMF; (b) methyl 4-aminobenzoate, Et_3N, DCM; (c) LiOH, THF; (d) DIPEA, DCM; (e) cat. TsOH, toluene, 185 °C, μ-wave, 30 min.

Table 1. SAR for benzoxazole A-ring substitutions against human CETP



Compound	Z	SPA IC_{50} (μM)	WPA IC_{50}[a] (μM)
4	SC 795 (Fig. 1)	0.003	0.036
12		>32	NT
13	4-Me	>32	NT
14	4-NO_2	>32	NT
15	5-Me	1.1	31
16	5-COOMe	>32	NT
17	5-COOH	>32	NT
18	5-F	>32	NT
19	5-OMe	>32	NT
20	5-OCF_3	11	71
21	5-SO_2Et	9.3	NT
22	5-Ph	1.9	NT
23	5-CH_2OH	1.3	27
24	5-Ac	1.2	18
25	5-*t*Bu	>32	NT
26	5-CF_3	0.59	51
27	5-Cl	0.47	21
28	5-Br	0.44	28
29	5-NO_2	0.12	18
30	5-CN	0.057	3.3
31	6-Me	13	NT
32	6-Cl	>32	NT
33	6-OMe	>32	NT
34	6-NO_2	>32	NT
35	6-COOMe	>32	NT
36	6-F	>32	NT
37	6-(Piperidin-1-yl)	>32	NT
38	7-Me	1.7	100
39	7-COOMe	3.5	80
40	7-COOH	>32	NT
5	5,7-DiMe	0.28	8.9
41	5-Me-7-Ac	0.24	27
42	5-Cl-7-Br	0.097	26
43	5,7-DiCl	0.088	11
44	5,7-BisCF_3	0.092	9.1
45	5-CN-7-Cl	0.052	2.5
46	5-Cl-7-NO_2	0.049	18

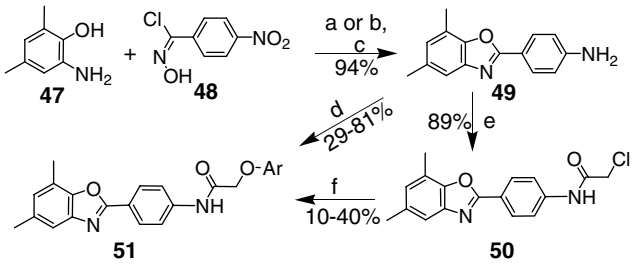
[a] NT, not tested.

A-ring methyl groups from **5** led to a loss of activity. Reintroduction of a single methyl substitution at the 4 position also led to an inactive analog. However, the activity was partially recovered by methyl substitution at the 5, 6, or 7 positions. Incorporation of amino phenols allowed more extensive surveying of the 5, 6, and 7 positions of the benzoxazole. The data indicate that mono substitution at the 5 position is preferred, with smaller nitro and cyano groups (**29** and **30**) exhibiting enhanced SPA and WPA activities. Disubstitution at the 5 and 7 positions was also examined further, and provided a modest improvement in inhibitory potency in the SPA assay, although no significant improvement was seen in the physiologically more relevant WPA which takes into consideration off-target interactions in plasma. The 5-cyano compound **30** and the 5-cyano-7-chloro compound **45** exhibited the best potencies across both SPA and WPA.

The synthetic approach utilized to examine the B-ring in the 2-arylbenzoxazole series is detailed in Scheme 2. Condensation of aminophenol **47** with chlorooxime **48** followed by reduction gave the aminobenzoxazole **49** in 94% yield. From intermediate **49**, the B-ring was explored in an array format using one of the two procedures. Acylation with a range of commercially available aryloxyacetyl chlorides provided the product amides **51** directly in 29–81% isolated yield.[12] Alternatively, to facilitate more extensive exploration of the B aryl ring, aniline **49** was acylated with chloroacetyl chloride to obtain the α-chloro amide **50** in 89% yield. Displacement of the chlorine of **50** with phenols in an array format yielded the resulting purified phenyl ethers **51** in 10–40% isolated yield.[12] The average purity (by HPLC-UV) of the final products was 98%.

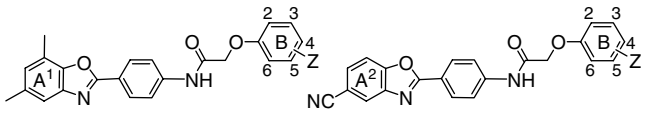
Select results from exploration of the substitution on the 2-arylbenzoxazole B-ring are provided in Table 2. Mono-substitution at the 2, 3, or 4 positions with a variety of substituents revealed that small alkyl groups and halogens are generally well-tolerated, although halogenation at the 2 position appears to lead to less active analogs (**55** and **64**). Several disubstituted analogs (**80**–**85**) provided further improvements in inhibitory potency both in the SPA and WPA. However, disubstitution at the 2,5-, 2,6-, or 3,5-positions led to a significant loss of activity (**86**–**90**) suggesting that substitutions were permitted along only one edge of the phenyl ring. A limited set of 2,3,4-trisubstituted analogs was also examined (e.g., **91**–**94**, **97**, **99**, and **100**). These proved to be well tolerated, exhibiting comparable SPA activity to the best di-substituted compounds. Among them, compounds **99** and **100**, which contain the best A-ring mono-substitution (5-CN) and the best B-ring trisubstitutions, had low nM SPA IC_{50}s and were the most potent in WPA (WPA IC_{50} ca. 1 μM) in the series.

In summary, high-throughput screening of the BMS sample collection identified 2-arylbenzoxazole **5** with submicromolar SPA and modest WPA in vitro activities. An array synthesis approach was taken to rapidly



Scheme 2. Synthetic route to vary B-ring. Reagents and conditions: (a) EtOH, rt, 1 day; (b) EtOH, 100 °C, μ-wave, 5 min; (c) Zn, HOAc, MeOH; (d) Aryloxyacetylchloride, pyridine, DCM; (e) Chloroacetylchloride, Na_2CO_3, DCM; (f) ArXH, Na_2CO_3, cat. KI, acetone, MeCN, DMSO, 75 °C, 12 h.

Table 2. SAR for benzoxazole B-ring substitutions against human CETP



A-sub	Compound	2	3	4	5	6	SPA IC_{50} (μM)	WPA IC_{50}[a] (μM)
A^1	**52**						0.70	30
A^1	**5**	Me					0.28	8.9
A^1	**53**		Me				0.69	18
A^1	**54**			Me			0.24	26
A^1	**55**	F					>10	NT
A^1	**56**		F				1.1	51
A^1	**57**			F			7.3	31
A^1	**58**	CN					>10	NT
A^1	**59**		CN				>10	NT
A^1	**60**			CN			>10	NT
A^1	**61**	OMe					8.3	NT
A^1	**62**		OMe				>10	NT
A^1	**63**			OMe			>10	NT
A^1	**64**	Cl					>10	NT
A^1	**65**		Cl				1.3	11
A^1	**66**			Cl			0.38	20
A^1	**67**	*i*-Pr					>10	NT
A^1	**68**		*i*-Pr				0.9	67
A^1	**69**	COOMe					0.22	NT
A^1	**70**		COOMe				>10	NT
A^1	**71**	CF_3					1.9	91
A^1	**72**		CF_3				>10	32
A^1	**73**			CF_3			>10	NT
A^1	**74**	Ph					3.3	NT
A^1	**75**		Ph				2.3	NT
A^1	**76**			Ph			>10	NT
A^1	**77**	OCF_3					0.20	NT
A^1	**78**		OCF_3				3.6	61
A^1	**79**			OCF_3			>10	NT
A^1	**80**		Cl	Cl			0.20	13
A^1	**81**	Me		Me			0.14	4.5
A^1	**82**		CF_3	Cl			0.12	4.9
A^1	**83**	Me		Cl			0.096	2.7
A^1	**84**	Me		Br			0.031	3.2
A^1	**85**	Me		F			0.023	4.9
A^1	**86**	Me			Me		>10	NT
A^1	**87**	Cl			Cl		>10	NT
A^1	**88**	Me				Cl	>10	NT
A^1	**89**	Cl				Cl	>10	NT
A^1	**90**		Me		Me		>10	NT
A^1	**91**		$-(CH_2)_3-$	Me			0.085	3.5
A^1	**92**		$-(CH_2)_3-$	Cl			0.056	2.5
A^1	**93**	Me	COOMe	Cl			0.042	2.8
A^1	**94**	Me	Me	Cl			0.040	1.7
A^2	**95**	Me		Cl			0.085	40
A^2	**96**		CF_3	Cl			0.018	4.3
A^2	**97**		$-(CH_2)_3-$	Cl			0.015	3.2
A^2	**98**	Me		Br			0.011	4.3
A^2	**99**	Me	COOMe	Cl			0.018	1.3
A^2	**100**	Me	Me	Cl			0.010	0.91

[a] NT, not tested.

optimize the in vitro CETP inhibition profile for this novel series of compounds. In accordance with the predictions derived from molecular modeling of **5** with cholesterol, substitutions on either the A- or B-ring resulted in modulation of CETP inhibitory potency. In particular, the 5-CN on the A-ring, and di- or trisubstitution with small hydrophobic groups on the B-ring provided improvements in potency. Finally, combinations

of preferred substitutions on both the A- and B-rings of this chemotype resulted in analogs demonstrating further improvements in SPA binding activity, with some trisubstituted B-ring analogs showing improvement in WPA activity. Further enhancement in WPA activity for this chemotype may require more extensive exploration of the structure–activity relationship.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2008.03.030.

References and notes

1. Bucher, H. C.; Griffith, L. E.; Guyatt, G. H. *Arterioscler. Thromb. Vasc. Biol.* **1999**, *19*, 187.
2. (a) Rhoads, G. G.; Gulbrandsen, C. L.; Kagan, A. *N. Engl. J. Med.* **1976**, *294*, 293; (b) Castelli, W. P.; Garrison, R. J.; Wilson, P. W.; Abbott, R. D.; Kalousdian, S.; Kannel, W. B. *J. Am. Med. Assoc.* **1986**, *256*, 2835; (c) Kannel, W. B. *Am. J. Cardiol.* **1995**, *76*, 69c.
3. Barter, P.; Kastelein, J.; Nunn, A.; Hobbs, R. *Atherosclerosis* **2003**, *168*, 195.
4. Barter, P. J.; Brewer, H. B.; Chapman, M. J.; Hennekens, C. H.; Rader, D. J.; Tall, A. R. *Arterioscler. Thromb. Vasc. Biol.* **2003**, *23*, 160.
5. Clark, R. W.; Sutfin, T. A.; Ruggeri, R. B.; Willauer, A. T.; Sugarman, E. D.; Magnus-Aryitey, G.; Cosgrove, P. G.; Sand, T. M.; Wester, R. T.; Williams, J. A.; Perlman, M. E.; Bamberger, M. J. *Arterioscler. Thromb. Vasc. Biol.* **2004**, *24*, 490.
6. Linsel-Nitschke, P.; Tall, A. R. *Nat. Rev. Drug Discov.* **2005**, *4*, 193, and references therein.
7. (a) Ruggeri, R. B. *Curr. Top. Med. Chem.* **2005**, *5*, 257, and references cited therein; (b) Sikorski, J. A. *J. Med. Chem.* **2006**, *49*, 1; (c) Krishna, R. et al. *Lancet* **2007**, *370*, 1907.
8. Based on the following reference using LDL as acceptor: Bisgaier, C. L.; Minton, L. L.; Essenburg, A. D.; White, A.; Homan, R. *J. Lipid Res.* **1993**, *34*, 1625.
9. Details of scintillation proximity assay will be published in due course.
10. Details of whole plasma assay will be published in due course.
11. Clark, R. W.; Ruggeri, R. B.; Cunningham, D.; Bamberger, M. J. *J. Lipid Res.* **2006**, *47*, 537.
12. For a general synthetic procedure, please see Supplemental information.