Bioorganic & Medicinal Chemistry Letters 20 (2010) 1019–1022

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

2-Arylbenzoxazoles as CETP inhibitors: Substitution and modification of the α-alkoxyamide moiety

Julianne A. Hunt *, Silvia Gonzalez, Florida Kallashi, Milton L. Hammond, James V. Pivnichny, Xinchun Tong, Suoyu S. Xu, Matt S. Anderson, Ying Chen, Suzanne S. Eveland, Qiu Guo, Sheryl A. Hyland, Denise P. Milot, Carl P. Sparrow, Samuel D. Wright, Peter J. Sinclair

Merck Research Laboratories, Rahway, NJ 07065, United States

ARTICLE INFO

Article history:
Received 28 October 2009
Revised 6 December 2009
Accepted 10 December 2009
Available online 14 December 2009

Keywords:
CETP
Cholesteryl ester transfer protein
High-density lipoprotein cholesterol
Low-density lipoprotien cholesterol
Reverse cholesterol transport
2-Arylbenzoxazole

ABSTRACT

The development of a series of 2-arylbenzoxazole α-alkoxyamide and β-alkoxyamine inhibitors of cholesteryl ester transfer protein (CETP) is described. Highly fluorinated α-alkoxyamides proved to be potent inhibitors of CETP in vitro, and the highly fluorinated 2-arylbenzoxazole β-alkoxyamine **4** showed a desirable combination of in vitro potency (IC_{50} = 151 nM) and oral bioavailability in the mouse.

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in developed countries. Therapies targeting elevation of high-density lipoprotein cholesterol (HDL-C) levels may reduce cardiovascular risk by slowing the development of atherosclerosis.[1] Epidemiological studies indicate that each 1 mg/dl increase in plasma HDL-C concentration is associated with a 6% decrease in the risk of death from CVD, independent of low-density lipoprotein cholesterol (LDL-C) concentration.[2]

One approach to treating CVD via elevation of HDL-C levels is to inhibit cholesteryl ester transfer protein (CETP).[3] CETP, a hydrophobic plasma glycoprotein that is physically associated with lipoprotein particles, facilitates the transfer of cholesteryl esters and triglycerides between HDL and the apo B-containing lipoproteins. Since the net effect of CETP activity is a reduction in plasma HDL-C levels, inhibition of CETP activity is expected to result in increased HDL-C levels. In turn, elevation of HDL-C is expected to reduce cardiovascular risk.

Our co-workers have recently communicated the discovery of a series of 2-arylbenzoxazole inhibitors of CETP.[4] Structure–activity optimization of the substituents on the benzoxazole moiety of screening lead **1** resulted in the identification of compound **2** as a potent CETP inhibitor (see Fig. 1).[4]

In this Letter, we describe optimization of the α-aryloxyamide moiety of the screening lead **1**, resulting in identification of potent alkyl-substituted analogs such as **3**. However, both the α-aryloxyamides and the β-alkyloxyamides showed extremely limited bioavailability. Further optimization of **3** was undertaken to improve the pharmacokinetic properties of this series, leading to the replacement of the central α-alkoxyamide with a β-alkoxyamine, as in compound **4**, a potent and orally bioavailable CETP inhibitor.

We began our optimization of the α-aryloxyamide moiety of **1** with a straightforward survey of replacements for the *o*-cresol substructure (Table 1). While removal of the *o*-methyl substituent resulted in only a fourfold loss of inhibitor potency (**5**), transposition of the methyl substituent to the *meta* (**1m**) or *para* (**1p**) positions

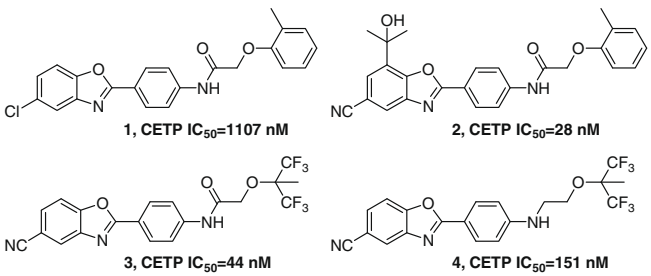
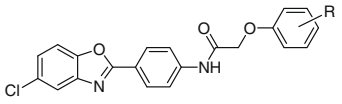


Figure 1. 2-Arylbenzoxazole CETP inhibitors.

* Corresponding author. Tel.: +1 732 594 0463; fax: +1 732 594 9473.
E-mail addresses: julianne_hunt@merck.com, huntjuli1205@gmail.com (J.A. Hunt).

0960-894X/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2009.12.046

Table 1
Inhibition of CETP activity by compounds of the formula



Compd	R	IC_{50}[a] (nM)		
		Ortho	*Meta*	*Para*
1	Me	1107	19,310	$>3 \times 10^4$
5	H	4230		
6	Et	2587	nd	Nd
7	Pr	2700	nd	Nd
8	CF_3	6390	1773	810
9	Cl	2150	1248	6810
10	CN	$>3 \times 10^4$	$>3 \times 10^4$	$>3 \times 10^4$
11	F	$>3 \times 10^4$	1994	1774
12	OMe	$>3 \times 10^4$	12,880	4570
13	NO_2	4396	26,490	2206

[a] Assay conditions have been described.[5]

caused a significant decline in potency. Larger alkyl substituents (**6** and **7**) were tolerated, but did not improve potency. Similarly, trifluoromethyl (**8**), halo (**9** and **11**), nitrile (**10**), methoxy (**12**), and nitro (**13**) substituents were either detrimental to potency or neutral. Not only were we unable to improve the potency of our lead via simple modification of the *o*-cresol substructure, we were also unable to determine an optimal potency-enhancing position for substituents on the phenyl ring, although it should be noted that a number of these compounds suffered from a severe lack of aqueous solubility, so it is possible that some of the inhibition constants shown in Table 1 reflect this problem rather than the true inhibitor potency.

Having encountered problems with compound solubility in our initial survey of phenyl substituents, we turned next to replacing the α-alkoxyamide, or 'linker', region of the molecule, reasoning that the amide bond might be contributing to the poor physicochemical properties of our lead series. Unfortunately, most of the linker variations we surveyed were not successful; in fact, every variation resulted in an analog that was a less potent inhibitor than the lead compound **1**. As shown in Table 2, reversal of the α-alkoxyamide to the carbamate (**17**), replacement of the amide with a urea (**18**), replacement of the α-oxygen with a carbon (**19**) or a sulfur (**20**), reversal of the amide (**21**), and replacement of the amide with a sulfonamide (**22**) all resulted in compounds with poor activity in our in vitro assay, as did methylation of the amide nitrogen (**23**), or of the carbon adjacent to the amide carbonyl (**24**).

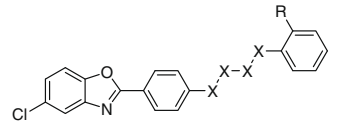
Only a few of the more conservative linker variations were fairly neutral in their effect on inhibitor potency. Replacement of the α-oxygen with a nitrogen (**14**) led to only a twofold decrease in potency, as compared to the analogous α-aryloxyamide **5**. Similarly, addition of a methylene unit between the α-oxygen and the phenyl ring (**15**) resulted in less than a twofold decrease in potency as compared to **5**.

Inspired by the nearly equivalent potencies of the phenyl (**5**) and benzyl (**15**) analogs in Table 2, we next turned to an exploration of benzyl and other alkyl substituents on the α-oxygen. At this point in our research, our co-workers had demonstrated the dramatically increased potency of the 5-cyanobenzoxazoles as compared to the analogous 5-chloro compounds (cf. compound **25** vs compound **1**),[4] so we continued the remainder of our SAR exploration in the 5-cyano series (see Table 3).

Although **26**, the benzyl analog of **25** was nearly 10-fold less potent, replacement of the methyl substituent on the phenyl ring with a trifluoromethyl (**27**) moved the potency back in the right direction. Similarly, **28**, the ethyl analog of **25** was tenfold less potent, but elaboration to the isopropyl (**29**) and *tert*-butyl (**30**) analogs restored potency. Combining the branched-alkyl strategy with the trifluoromethyl strategy led to the series of compounds shown at the bottom of Table 3, with the 1,1-bistrifluoromethylethyl analog **3** emerging as the most potent inhibitor in the series.

Unfortunately, although we had significantly improved the in vitro potency of our lead compound **1**, we were still challenged by the poor physicochemical properties of the 2-arylbenzoxazole amide series. For example, the bioavailability (in mouse) of compound **31** was less than 4%. Not surprisingly, even the most potent inhibitors among the compounds shown in Tables 1–3 lacked any appreciable activity when we tested them in vivo.[6]

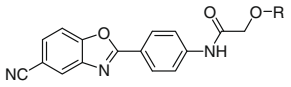
Table 2
Inhibition of CETP activity by compounds of the formula

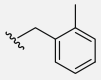
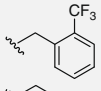


Compd	R	X–X–X–X	IC_{50}[a] (nM)
1	Me	NH–C(O)–CH_2–O	1107
5	H	NH–C(O)–CH_2–O	4230
14	H	NH–C(O)–CH_2–NH	8132
15	H	NH–C(O)–CH_2–O–CH_2	6537
16	H	NH–C(O)–CH_2–NH–CH_2	18,080
17	H	NH–C(O)–O–CH_2	$>3 \times 10^4$
18	H	NH–C(O)–NH–CH_2	$>3 \times 10^4$
19	H	NH–C(O)–CH_2–CH_2	$>3 \times 10^4$
20	H	NH–C(O)–CH_2–S	$>3 \times 10^4$
21	Me	C(O)–NH–CH_2	$>3 \times 10^4$
22	H	NH–SO_2–CH_2	$>3 \times 10^4$
23	Me	NMe–C(O)–CH_2–O	$>3 \times 10^4$
24	H	NH–C(O)–CH(Me)–O	$>3 \times 10^4$

[a] Assay conditions have been described.[5]

Table 3
Inhibition of CETP activity by compounds of the formula



Compd	R	IC_{50}[a] (nM)
25		130
26		1182
27		505
28		1375
29		613
30		132
31		94
32		51
3		44
33		151

[a] Assay conditions have been described.[5]

Early in our lead optimization efforts, we had prepared **34**, a β-aryloxyamine (or 'reduced amide') analog of our lead compound **1**, but we had been discouraged by its poor in vitro activity (Table 4). However, in light of the improved potency of the compounds shown in Table 3, we decided to revisit the reduced amide series. As shown in Table 4, with optimized substituents in place on either end of the 2-arylbenzoxazole scaffold, we finally succeeded in identifying a compound (**4**) with both in vitro potency and acceptable pharmacokinetic properties (for compound **4**: AUC-N_{iv} = 1.2 μM h kg/mg, Cl = 31 ml/min/kg, $t_{1/2}$ = 7.3 h).

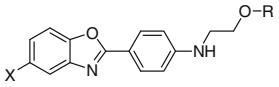
As shown in Figure 2, one-step assembly[7] of the 2-arylbenzoxazole amine **36** followed by formation of the key bromoacetamide intermediate **37** allowed rapid access to the α-aryloxyamide analogs shown in Table 1 via S_N2 displacement of the α-bromine of **37**.

As shown in Figure 3, nearly all of the linker variants in Table 2 were prepared from either aniline **36** or bromoacetamide **37** using standard synthetic transformations and commercially available starting materials. Reverse amide **21** was prepared from 2-methylbenzylamine and 2-arylbenzoxazole **42**[8] in 74% yield. Finally, tertiary amide **23** was prepared in 95% yield by deprotonation of compound **1** with lithium hexamethyldisilazide and subsequent alkylation with methyl iodide.

The key 5-cyano moiety in 2-arylbenzoxazole amine **38** proved labile to the conditions shown for formation of **36** (Fig. 2), so a milder, two-step protocol was developed for the assembly of this arylbenzoxazole core (Fig. 4). Similarly, the alkyl substituents shown in Table 3 were not generally amenable to the S_N2 reaction conditions shown in Figure 2, so α-alkyloxy acid chlorides **39** were prepared from α-bromoacetic acid and the appropriate alcohols. The acid chlorides **39** were then coupled with aniline **38** under standard conditions.

Synthesis of the β-alkoxyamines shown in Table 4 required a different arylbenzoxazole component, the bromide **40**, which was

Table 4
Inhibition of CETP activity by compounds of the formula



Compd	X	R	IC_{50}[a] (nM)	*F*%[b]
34	H		75,900	nd
35	CN		890	30
4	CN		151	20

[a] Assay conditions have been described.[5]
[b] In mouse.

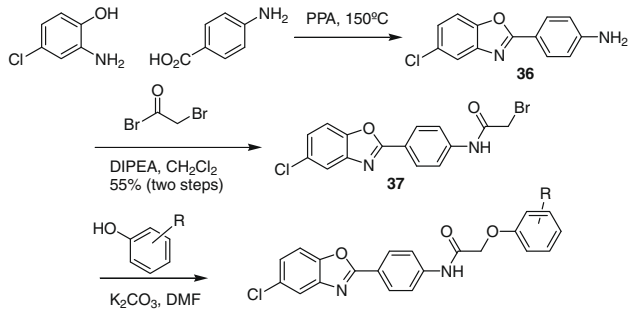


Figure 2. Synthesis of 2-arylbenzoxazole α-aryloxyamides **1** and **5**–**13**.

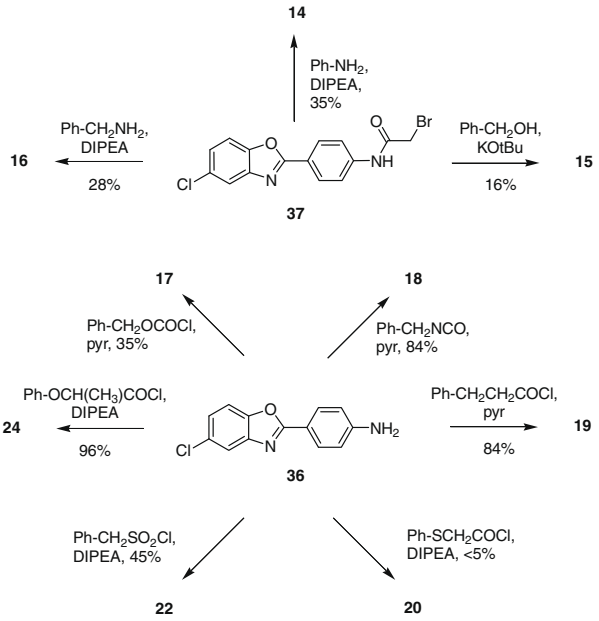


Figure 3. Synthesis of 2-arylbenzoxazoles **14**–**20**, **22**, and **24**.

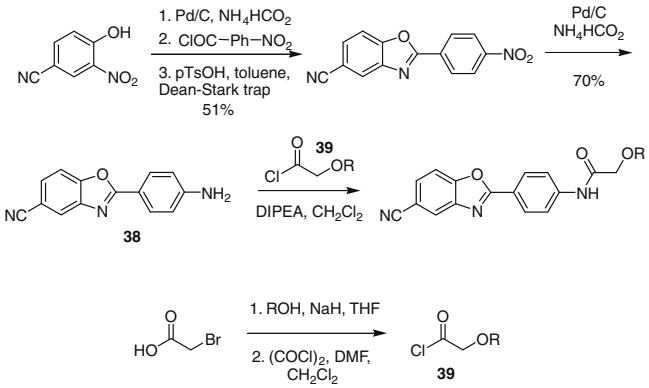


Figure 4. Synthesis of 2-arylbenzoxazole α-alkyloxyamides **3** and **25**–**33**.

prepared using the same two-step sequence shown in Figure 5 for aniline **38**. Palladium-catalyzed amination of **40** provided the desired 2-arylbenzoxazole β-alkoxyamines, as shown for

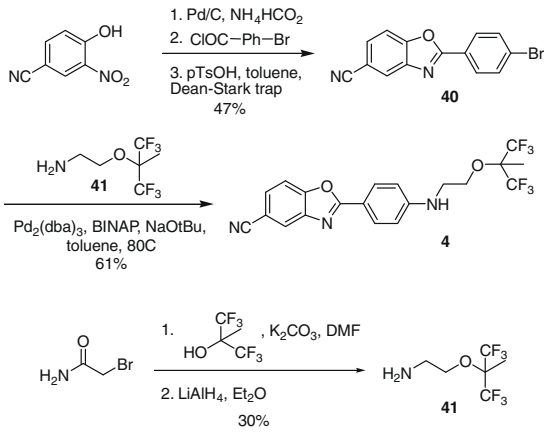
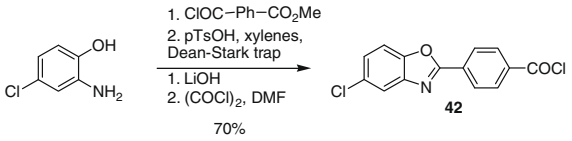


Figure 5. Synthesis of 2-arylbenzoxazole β-alkyloxyamine **4**.

compound **4**. While some β-alkoxyamines were commercially available, compound **41** was prepared from α-bromoacetamide and bistrifluoromethyl-*tert*-butanol via nucleophilic substitution of the α-bromide followed by reduction of the amide to the amine (Fig. 5).

Our group[4] and others[9] have shown that 2-arylbenzoxazole α-aryloxyamides such as **1** and **2** can inhibit CETP activity in vitro. However, the poor physicochemical properties of most compounds in this structure class represent a barrier to the development of analogs with in vivo activity. By reducing the central amide to the corresponding amine and replacing the aryloxy moiety with highly fluorinated alkyloxy substructures, we have identified new, potent CETP inhibitors with significantly improved pharmacokinetic properties. Unfortunately, despite the in vitro potency and moderate bioavailability of 2-arylbenzoxazole β-alkoxyamine **4**, this compound (and others in the same structure class) did not show activity in our in vivo assays.[6] Nevertheless, the α-alkyloxyamide and β-alkyloxyamine compounds shown in Tables 3 and 4 serve as leads for continuing development of this structure class. We will report further modifications of this class of CETP inhibitors aimed at improving in vivo activity in due course.

References and notes

1. Singh, I. M.; Shishehbor, M. H.; Ansell, B. J. *J. Am. Med. Assoc.* **2007**, *298*, 786.
2. Gordon, D. J.; Rifkind, B. M. *N. Eng. J. Med.* **1989**, *321*, 1311.
3. Barter, P. J.; Kastelein, J. J. P. *J. Am. Coll. Cardiol.* **2006**, *47*, 492.
4. Smith, C. J.; Ali, A.; Chen, L.; Hammond, M. L.; Anderson, M. S.; Chen, Y.; Eveland, S. S.; Guo, Q.; Hyland, S. A.; Milot, D. P.; Sparrow, C. P.; Wright, S. B.; Sinclair, P. J. *Bioorg. Med. Chem. Lett.* **2009**. *Available online 29-Oct-09*.
5. Eveland, S. S.; Milot, D. P.; Guo, Q.; Chen, Y.; Hyland, S. A.; Peterson, L. B.; Jezequel-Sur, S.; O'Donnell, G. T.; Zuck, P. D.; Ferrer, M.; Strulovici, B.; Wagner, J. A.; Tanaka, W. K.; Hilliard, D. A.; Laterza, O.; Wright, S. D.; Sparrow, C. P.; Anderson, M. S. *Anal. Biochem.* **2007**, 368.
6. Data not shown.
7. Hein, D. W.; Alheim, R. J.; Leavitt, J. J. *J. Am. Chem. Soc.* **1957**, *79*, 427.
8. 

9. Harikrishnan, L. S.; Kamau, M. G.; Herpin, T. F.; Morton, G. C.; Liu, Y.; Cooper, C. B.; Salvato, M. E.; Qiao, J. X.; Wang, T. C.; Adam, L. P.; Taylor, D. S.; Chen, A. Y. A.; Yin, X.; Seethala, R.; Peterson, T. L.; Nirschl, D. S.; Miller, A. V.; Weigelt, C. A.; Appiah, K. K.; O'Connell, J. C.; Lawrence, R. M. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2640.