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Identification of a potent and metabolically stable series of fluorinated diphenylpyridylethanamine-based cholesteryl ester transfer protein inhibitors

Michael M. Miller [a,*], Yalei Liu [a], Ji Jiang [a], James A. Johnson [a], Muthoni Kamau [a], David S. Nirschl [b], Yufeng Wang [a], Lalgudi Harikrishnan [a], David S. Taylor [c], Alice Ye A. Chen [c], Xiaohong Yin [c], Ramakrishna Seethala [d], Tara L. Peterson [d], Tatyana Zvyaga [e], Jun Zhang [b], Christine S. Huang [f], Ruth R. Wexler [a], Michael A. Poss [a], R. Michael Lawrence [a], Leonard P. Adam [c], Mark E. Salvati [a]

[a] Discovery Chemistry, Research and Development, Bristol-Myers Squibb, PO Box 4000, Princeton, NJ 08543-4000, USA
[b] Synthesis & Analysis Technology Team, Research and Development, Bristol-Myers Squibb, PO Box 4000, Princeton, NJ 08543-4000, USA
[c] Discovery Biology, Research and Development, Bristol-Myers Squibb, PO Box 4000, Princeton, NJ 08543-4000, USA
[d] Lead Evaluation, Research and Development, Bristol-Myers Squibb, PO Box 4000, Princeton, NJ 08543-4000, USA
[e] Lead Profiling, Research and Development, Bristol-Myers Squibb, PO Box 4000, Princeton, NJ 08543-4000, USA
[f] PCO MAP, Research and Development, Bristol-Myers Squibb, PO Box 4000, Princeton, NJ 08543-4000, USA

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ABSTRACT

A novel series of diphenylpyridylethanamine-based inhibitors of cholesteryl ester transfer protein is described. Optimization of the urea moiety, particularly by incorporation of fluorine, is explored to balance in vitro metabolic stability with CETP potency in the whole plasma assay.

Atherosclerosis is characterized by the accumulation of lipid-rich, rupture-prone plaques within arterial walls, and can lead to coronary heart disease (CHD) which afflicts over 17.6 million individuals in the United States.[1] Current clinical strategies of lipid lowering for the treatment of atherosclerosis have primarily focused on lowering circulating levels of low-density lipoprotein cholesterol (LDL-C)[2] via the use of agents such as statins.[3] It is also recognized that high-density lipoprotein cholesterol (HDL-C) is a powerful independent inverse predictor of CHD risk.[4] Importantly, elevation of plasma HDL-C has been shown to decrease CHD risk,[5,6] in large part by facilitating the transport of cholesterol from the arterial wall to the liver for excretion (a process termed 'reverse cholesterol transport', or RCT). Current approaches to increase HDL-C include the use of fibrates[7] and niacin[8–10] that have limited effects on increasing HDL-C levels[11] (i.e., 10% and 16%, respectively). Due to the limited efficacy of current HDL-C increasing therapies,[12] and the role of HDL-C in reducing CHD risk, additional approaches to increase HDL-C are being investigated.

Cholesteryl ester transfer protein (CETP) is a plasma glycoprotein that mediates the net transfer of cholesterol ester (CE) from HDL to LDL and very low-density lipoprotein (VLDL) in exchange for triglyceride (TG).[13] Inhibition of CETP activity leads to increased plasma HDL-C levels in both animals and humans.[13] Despite its role in HDL-C regulation, CETP has been proposed to have both pro- and anti-atherosclerotic properties, and defining the absolute role of CETP in atherosclerosis has been a subject of debate.[14–20] The beneficial HDL raising and anti-atherosclerotic effects of CETP inhibition have been supported by animal studies in hamsters[21] and rabbits.[22–24] However, despite increasing HDL-C in humans[25] to a similar extent as in animals, the first CETP inhibitor did not progress beyond phase III clinical trials, although it is likely this was due, at least in part, to off-target toxicities.[26] Despite the ongoing controversies surrounding CETP, widespread interest in discovering and developing inhibitors of this protein as a potential new therapeutic approach to treat CHD is evident by the numerous reports describing preclinical and clinical lead compounds (Fig. 1).[27–33]

* Corresponding author. Tel.: +1 609 252 3238.
E-mail address: michael.miller@bms.com (M.M. Miller).

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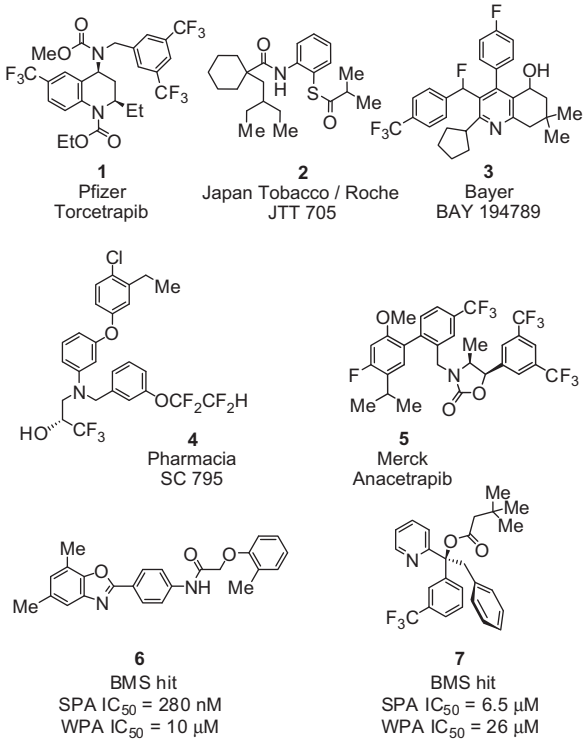


Figure 1. Reported CETP inhibitors.

In previous communications we[31] and others[32] described a novel series of 2-arylbenzoxazole-based (**6**) and diphenylpyridyl ethanol-based (**7**)[33] CETP inhibitors identified by leveraging the BMS compound collection via a screening campaign.[34] These two scaffolds are architecturally unique from other reported chemotypes in this target area and were deemed to have suitable SAR to warrant follow up exploration.

Early SAR exploration of screening hit **7** led to the identification of compound **8**, wherein the ester moiety was converted to an urea linkage with refined substitution of the groups off the quaternary center. These changes resulted in a lead exhibiting increased activity in the program's scintillation proximity assay (SPA)[35] with a determined IC_{50} of 20 nM. Although **8** demonstrated that SPA potency could be improved in this chemotype, other parameters also required attention: potency in the human whole plasma assay (WPA),[36] solubility, metabolic stability, PXR activation, *h*ERG inhibition, and oral bioavailability. To improve on these properties, discrete areas of exploration (i.e., modifications of the A-, B-, and/or C-rings, varying the amine capping fragments, and constraining the scaffold's molecular framework) were defined as outlined in Figure 2. This communication describes the optimization of the urea fragment of the diphenylpyridylethanamine (DPPE) based lead (**8**).[37]

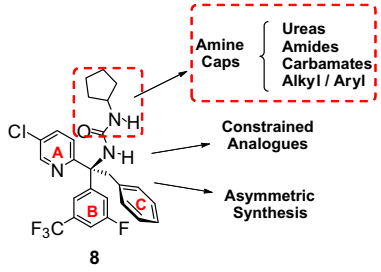


Figure 2. DPPE lead and strategy for optimization.

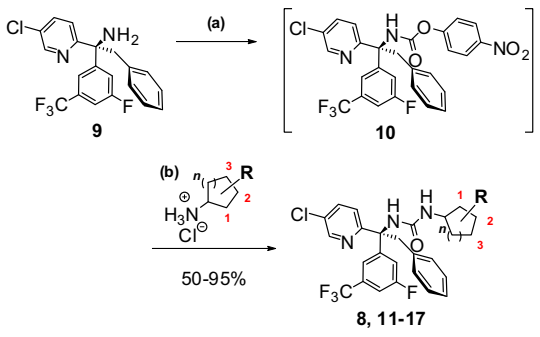
Initial SAR optimization of the urea moiety was carried out with both enantiomers and confirmed that the activity resided predominantly in the *S*-antipode (**8a** compared to **8b**) as shown previously.[33] Subsequent exploration utilized the chiral amine **9** prepared from the corresponding chiral sulfinylimine.[38] Profiling of **8a** demonstrated the analogue had poor in vitro metabolic stability in human, mouse and rat liver microsomes.[39] To investigate whether the urea was responsible for this liability, additional SAR of the urea alkyl group was desired.

Starting with **9**, a robust method to prepare urea analogues was utilized wherein an in situ generated *para*-nitrophenyl carbamate was directly treated with a variety of amines (Scheme 1, Table 1). From this study it was shown that incorporation of a heteroatom into the cyclopentyl ring was tolerated with respect to potency (**11a**), but resulted in a further decrease in metabolic stability (**8a** vs **11a**). However, the corresponding lactone analogue **12a**, although showing reduced CETP inhibitory potency, did provide some indications of improved in vitro metabolic stability. This observation coupled with a biotransformation analysis of the parent compound **8** suggested that the cyclopentyl ring system was the principal site of oxidative metabolism for these analogues and a potential area for continued optimization. In order to resolve this liability, a strategy was implemented to not only modulate metabolic stability,[40] but also to increase biological activity.

The profound effect and role of fluorine in drug discovery has been well documented.[41] Selective installation of fluorine into a target molecule has been shown to favorably influence a number of pharmacokinetic, physicochemical, and physical properties, including binding affinity (potency, selectivity), metabolic stability, ADME, molecular conformation, and safety issues. In particular, it was recently reported that fluorine substitution of CETP inhibitors during the development of **1** provided a beneficial effect in refining the activity of this series by influencing the lipophilicity of the molecules.[42] In addition, it was observed that although a variety of structurally diverse scaffolds have been developed as small molecule CETP inhibitors (Fig. 1), these are generally highly fluorinated lipophilic compounds.

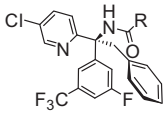
To this end, fluorine incorporation was explored extensively in the alkyl urea functionality of **8**. Examination of fluorination at the 3-position of the cyclopentyl ring (**13a**) provided a modest enhancement in WPA activity (**13a** vs **8a**), while exhibiting an overall improvement in metabolic stability (Table 1). Fluorine incorporation in the corresponding cyclohexylurea (**14–17** vs **8a**) failed to improve WPA activity, but **17** showed an improvement in its in vitro liver microsomal stability compared to **14**.

Parallel SAR development on the B-ring identified a 3,5-disubstituted aryl fragment which was subsequently utilized for the optimization of fluorinated ureas (Table 2).[33] Specifically, it was observed that in some instances the addition of a tetrafluorinated

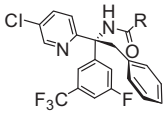


Scheme 1. General synthetic route to DPPE analogues. Reagents (a) *para*-nitrophenyl chloroformate, K_2CO_3, CH_2Cl_2; (b) amine, DIPEA, dioxane.

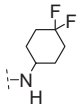
Table 1
SAR for substituted cycloalkyl ring against human CETP



S



R

R	Cmpd #	Core	SPA, IC_{50} (μM)	WPA, IC_{50} (μM)	MTS (% remaining)
	**8a**	S	0.02	1.57	9(h), 8(m), 10(r)
	8b	R	0.48	33.33	
	**11a**	S	0.05	4.88	1(h), 1(m), 9(r)
	11b	R	---	44.59	
	**12a**	S	0.27	7.10	28(h), 29(m), 61(r)
	12b	R	14.46	---	
	**13a**	S	0.006	0.67	61(h), 59(m), 47(r)
	13b	R	0.34	32.75	
	**14a**	S	0.09	8.89	9(h), 4(m), 6(r)
	14b	R	---	91.82	
	**15a**	S	0.02	4.23	
	**16a**	S	0.14	17.15	
	**17a**	S	0.13	13.07	37(h), 57(m), 62(r)

MTS: 3 μM metabolic stability (human, mouse, rat), $n = 4$ (Ref. 39).

ethoxy group demonstrated an enhancement in potency (i.e., **18** vs **8a**). Combination of the 3-fluoro-5-(1,1,2,2-tetrafluoro-ethoxy)benzene B-ring fragment of **18** and the 3,3-difluoro cyclopentanamine unit of **13** resulted in **19** as a mixture of diastereomers. Separation of the corresponding isomers showed that the activity resided in the *S,R*-isomer **20** which, with a WPA IC_{50} of 76 nM, was 36-fold more potent than *R,S*-isomer **21** and 21-fold more potent that the initial starting point **8**.

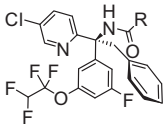
Although **20** proved to be quite active in whole plasma, it still was found to be rapidly metabolized by liver microsomes across species (h, m, r). While the difluorocyclopropyl analogue **22** provided excellent metabolic stability, a 20-fold drop off in WP activity was observed versus **20**. However, the corresponding difluorocyclobutyl variant **23** addressed metabolic stability in addition to maintaining an excellent level of CETP inhibitory potency. This 3,3-difluoro-substituted cyclobutyl fragment was of interest, not only because of its increased potency but for its symmetry which resulted in a simplified structure possessing only one chiral center.

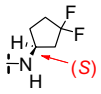
An alternate structural variation explored in an attempt to resolve the poor metabolic stability exhibited by **8** involved determining whether the urea nitrogen could be moved into the cycloalkyl ring (Table 3). These pyrrolidine-based urea analogues were furnished utilizing the route developed for the initial template represented by **9**.[37] The parent pyrrolidinyl urea **24** was found to have significantly reduced potency compared to the corresponding cyclopentyl urea **18**. Incorporation of fluorine to prepare **25**, provided an increase in potency relative to the parent **24** but remained significantly less potent than the corresponding **19**. Selective placement of additional fluorine atoms provided analogues, such as **28**, with enhanced potency and improved metabolic stability over initial pyrrolidine compounds (i.e., **24** vs **28**). In addition, there was an observed stereochemical preference for substitution as observed upon comparison of **26** with **27**. While (trifluoromethyl)pyrrolidine systems (i.e., **29**) were also tolerated, stereochemical considerations still played a role in affecting activity (**30** vs **31**). In general, although modest improvement was found within the series, compounds **20** and **23** showed superior WPA potency and metabolic stability compared to the pyrrolidine analogues.

The SAR of the fluoro-substituted alkyl urea was further extended by incorporation of acyclic fluorinated amine variants (Table 4). As observed previously, addition of fluorine into the alkyl chain of **32** provided an enhancement of CETP inhibition (i.e., **33**). Inclusion of two additional fluorine atoms into this urea fragment (**34**) enhanced potency and provided very good metabolic stability. Ultimately, truncation of **34** to analogue **36** afforded a compound that was equivalently potent in whole plasma to the best of the cyclic systems, while also demonstrating good metabolic stability.

In order to determine their effectiveness as inhibitors of CETP activity in vivo, compounds were evaluated in a CETP/apoB100

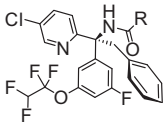
Table 2
SAR for optimized fluorinated cycloalkyl rings against human CETP

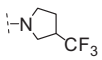


R	Cmpd #	SPA, IC_{50} (μM)	WPA, IC_{50} (μM)	MTS (% remaining)
	**18**	0.006	0.63	
	**19**	0.005	0.62	
	**20**	0.001	0.076	9(h), 20(m), 26(r)
	**21**	0.007	2.72	
	**22**	0.01	1.65	100(h), 84(m), 81(r)
	**23**	0.007	0.18	99(h), 99(m), 81(r)

MTS: 3 μM metabolic stability (human, mouse, rat), $n = 4$ (Ref. 39).

Table 3
SAR for substituted pyrrolidines against human CETP

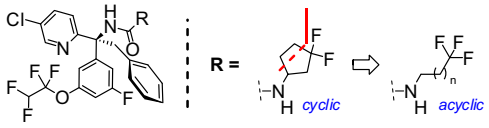


R	Cmpd #	SPA, IC_{50} (μM)	WPA, IC_{50} (μM)	MTS (% remaining)
	**24**	1.27	92.53	3(h), 0.4(m), 1(r)
	**25**	0.34	19.14	
	**26**	3.30	66.64	11(h), 0.2(m), 3(r)
	**27**	0.97	41.30	2(h), 0.4(m), 1(r)
	**28**	0.009	1.68	84(h), 7(m), 90(r)
	**29**	0.13	8.15	73(h), 5(m), 26(r)
	**30**	24.04	---	
	**31**	0.05	4.63	

MTS: 3 μM metabolic stability (human, mouse, rat), $n = 4$ (Ref. 39).

transgenic mouse model (Table 5).[43] Compound **20** was found to have activity in the transgenic mouse WPA comparable to its activity in the human WPA. At an oral dose of 30 mpk, **20** was found to have plasma exposures that exceeded or were nearly equivalent to its WPA IC_{50} for up to 8 h. This resulted in significant reduction of in vivo CETP activity at all time points examined with a 44% reduc-

Table 4
SAR for acyclic fluorinated alkyl ureas against human CETP



R	Cmpd #	SPA, IC_{50} (μM)	WPA, IC_{50} (μM)	MTS (% remaining)
	**32**	0.008	1.74	1(h), 4(m), 7(r)
	**33**	0.002	0.69	88(h), 43(m), 51(r)
	**34**	0.006	0.22	100(h), 100(m), 85(r)
	**35**	0.027	7.03	13(h), 6(m), 20(r)
	**36**	0.003	0.17	100(h), 91(m), 100(r)

MTS: 3 μM metabolic stability (human, mouse, rat), $n = 4$ (Ref. 39).

Table 5
Comparison of CETP pharmacodynamics and pharmacokinetics for compound **20** in transgenic mouse model (30 mpk, po)

Cmpds #	CETP hWPA IC_{50}, μM[a]	CETP TgWPA IC_{50}, μM[a]	AUC (0–8) nM h	2 h Levels nM[b]	CETP % of pre-dose 2 h[b]	4 h Levels nM[b]	CETP % of pre-dose 4 h[b]	8 h Levels nM[b]	CETP % of pre-dose 8 h[b]
20	0.076	0.11	3201	1070 (±222)	34 (±1)	249 (±38)	38 (±2)	112 (±21)	44 (±2)

[a] 2–4 Point determinations.
[b] Values are means of five experiments, standard deviation is given in parentheses.

tion of plasma CETP activity (versus pre-dose levels) observed 8 h after the oral dose.

In conclusion, although the addition of fluorine did not universally improve inhibitory potency, selective fluorination on the cyclopentyl urea fragment of **8** did provide CETP inhibitors with excellent potency in whole plasma (i.e., **20** and **23**). Optimization of the cyclopentyl moiety resulted in the preparation of acyclic variants (i.e., **34** and **36**) which retained CETP inhibitory potency with improved liver microsome stability. Finally, treatment of CETP/apoB100 dual transgenic mice with **20** led to potent suppression of CE transfer activity demonstrating in vivo efficacy in this chemotype. The effect of this CETP inhibition on modulation of plasma lipoprotein levels will be reported in due course.

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36. WPA: To the test compound in DMSO (1 μl) was added 29 μl of human plasma containing 0.15 μl ^{3}H-CE/HDL. The reaction was incubated at 37 °C and terminated by the addition of 6 μl of precipitation reagent (2:1:1 of water:1 M $MgCl_2$:2% Dextralip 50), to precipitate LDL and VLDL. After 10 min at room temperature, 15 μl of the reaction was transferred to filter plates (Millipore, #MHVBN45) pre-wetted with 100 μl phosphate buffered saline. The plates were centrifuged (1800 rpm) at room temperature for 10 min, and 50 μl Microscint-20 was added. The plates were then sealed and read. Background activity was determined with plasma samples incubated at 4 °C. The level of inhibition was determined by comparing the readings in wells that contain compound to the readings in control wells containing DMSO.
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