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Diphenylpyridylethanamine (DPPE)-based aminoheterocycles as cholesteryl ester transfer protein inhibitors

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ABSTRACT

A series of diphenylpyridylethanamine-based inhibitors of cholesteryl ester transfer protein with aminoheterocycles appended onto the N-terminus of the chemotype were explored as urea mimetics. Potent compounds were discovered and were further optimized to improve metabolic stability and PXR transactivation profile.

Atherosclerosis is characterized by the accumulation of lipid rich plaques within the walls of arteries, and is a key contributor to coronary heart disease (CHD), cerebrovascular disease and peripheral arterial disease. These diseases are the leading cause of mortality in industrialized nations and are a major health concern worldwide.[1] Studies have shown that low levels of high-density lipoprotein cholesterol (HDL-C) in the bloodstream are associated with a higher risk of CHD, and HDL-C was recognized as an inverse indicator for risk of developing atherosclerosis.[2] Because of this relationship, the discovery of compounds to increase HDL-C for the treatment of atherosclerosis has been an active area for drug discovery research.

Cholesteryl ester transfer protein (CETP) facilitates the transfer of cholesterol ester from HDL to LDL and VLDL in exchange for triglycerides. Several studies have demonstrated that CETP inhibition leads to increased HDL-C in animals and humans;[3] therefore, pharmacological inhibition of CETP has been proposed to raise HDL-C and reduce cardiovascular risk.[4] Intensive efforts have been undertaken to discover efficacious CETP inhibitors,[5] and compounds are currently being evaluated in clinical trials (e.g., anacetrapib[6a] and evacetrapib[6b]). Recently, however, the CETP inhibitor dalcetrapib (that increases HDL-C by ~30%) failed to demonstrate a cardiovascular benefit.[7] This result, coupled with the lack of cardiovascular benefit with niacin treatment[8] (that raised HDL-C to a lesser extent), has raised concerns about the potential beneficial effects of raising HDL-C, in general, and by CETP inhibition, in particular. However, the effects of the relatively weak CETP inhibitor dalcetrapib, on HDL-C were small in comparison to the effects of anacetrapib and evacetrapib. In addition, anacetrapib and evacetrapib reduce low-density lipoprotein cholesterol (LDL-C) levels, whereas dalcetrapib did not. As a result, the potential benefit of potent pharmacological inhibition of CETP has not been adequately tested in the clinic. The results of ongoing clinical trials are eagerly anticipated, and the discovery of new CETP inhibitors remains of interest to the cardiovascular field.

Recently, we reported on the discovery of a series of diphenylpyridylethanamine (DPPE) derivatives as CETP inhibitors.[9] In that disclosure, compounds **1** and **2** were identified as active CETP inhibitors in the scintillation proximity assay (SPA)[10] and human whole plasma assay (WPA),[10] and served as lead compounds for further optimization. Liabilities associated with this class of ureas generally include poor liver microsomal stability (LMS) and potent PXR activity in vitro. Biotransformation studies indicated that the cyclopentyl urea was the principal site of metabolism. Therefore to improve liver microsomal stability, replacement of the cyclopentyl urea with amides or installation of fluorine onto the cyclopentyl urea to block metabolism were explored and reported.[9,10] Described in this manuscript is a concomitant approach (Fig. 1), whereby aminoheterocycles were appended to the N-terminus of

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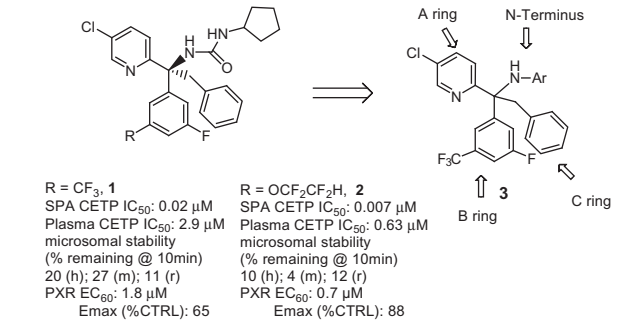
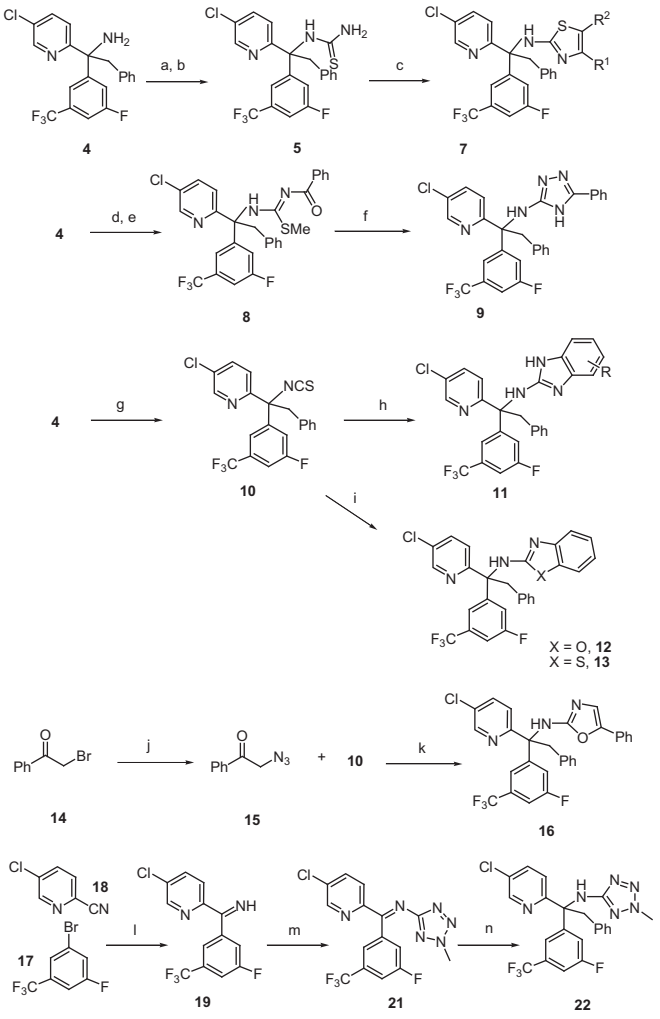


Figure 1. N-terminus aminoheterocycles as replacements for cyclopentyl urea.

3 and were explored as urea mimetics. Potent compounds were discovered with improved metabolic stability and PXR transactivation profile.



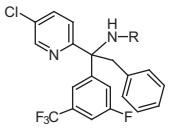
Scheme 1. Synthesis of N-terminal aminoheterocycles. Reagents and conditions: (a) PhCONCS, DCM, 40 °C, 2 h, 71%; (b) LiOH, MeOH/THF, reflux, 2 h, 78%; (c) **6**: R^1COCHR^2Br, MeOH, 80 °C, 16 h, 31–78%; (d) PhCONCS, DCM, 100%; (e) MeI, DMF, 63%; (f) H_2NNH_2, NEt_3, $AgNO_3$, ACN, 56 °C, 6 h, 25%; (g) $CSCl_2$, $NaHCO_3$, $CHCl_3/H_2O$, 50%; (h) 1,2-dianilines, TEA, EDCI, DCM, 35–85%; (i) X = O, 2-aminophenol, TEA, EDCI, DCE, 30%; X = S, 2-aminobenzenethiol, TEA, EDCI, DCM, 80%; (j) NaN_3, acetone, H_2O, 90%; (k) PPh_3, dioxane, 90 °C, 50%; (l) *n*-BuLi, ether, −78 °C, 100%; (m) 2-methyl-2*H*-tetrazol-5-amine **20**, xylene, 150 °C, 16 h, 44%; (n) BnMgCl, −78 °C to rt, DCM, 78%.

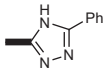
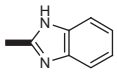
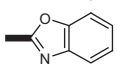
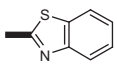
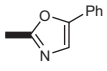
Shown in Scheme 1 are the syntheses of N-terminal aminoheterocycles prepared as urea mimetics.

Thiourea **5** was synthesized by treating the racemic diphenylpyridylethanamine (DPPE)[11] core **4** with isothiocyanate, followed by hydrolysis with lithium hydroxide. Intermediate **5** was then coupled with α-bromoketones **6** to provide the aminothiazoles **7**. Aminotriazole **9** was prepared by treatment of DPPE **4** with benzoyl isothiocyanate, followed by methyl iodide to yield intermediate **8**, which was then treated with hydrazine and silver nitrate. Aminobenzimidazoles **11**, aminobenzoxazoles **12** and aminobenzothiazoles **13** were prepared in a similar way by coupling of the isothiocyanate **10** derived from DPPE **4** to 2-aminothiophenols, 2-aminophenols and 2-aminoanilines, respectively. When isothiocyanate **10** reacted with 2-azido-1-phenylethanone **15** (prepared from 2-bromo-1-phenylethanone **14**), aminoxazole **16** was obtained. Aminotetrazole posed a synthetic challenge since there were no previous references of aminotetrazole synthesis on a tertiary carbon reported. We envisioned that aminotetrazole **22** could be prepared from imine **21** by Strecker reaction with BnMgCl. While we could not obtain imine **21** by treating 2-methyl-2*H*-tetrazol-5-amine **20** with ketone analog of **19** under elevated temperature and/or prolonged reaction time, we were gratified to see imine **21** could be obtained by heating 2-methyl-2*H*-tetrazol-5-amine **20** with imine **19** in xylene at 150 °C with continued heating for 16 h. Imine **19** was synthesized by lithiation of **17**, followed by reaction with commercially available **18** at −78 °C. This imine-Strecker route could potentially be applied to the synthesis of other aminoheterocycles.

A number of different aminoheterocycles were prepared with racemic core **4** to survey which might hold promise as a suitable replacement for the terminal cyclopentyl urea (Table 1). Among the aminoheterocycles tested, aminothiazole **7a**, aminobenzimidazole **11a** and aminobenzothiazole **13** provided the best potency. Aminobenzoxazole **12** only showed moderate activity, while aminotriazole **9**, aminooxazole **16** and aminotetrazole **22** were significantly less active. As a result, further SAR study was focused on the aminothiazole and aminobenzimidazole series.

Table 1
Aminoheterocycles as urea replacements



Compds	R	CETP SPA IC_{50} (μM)	CETP WPA IC_{50} (μM)
7a		0.4	29.5
9		>32	ND
11a		0.2	19.6
12		2.0	ND
13		0.5	23
16		12	ND
22		11	ND

A follow-up SAR study on aminothiazoles was conducted and the effect of substitutions on the thiazole is summarized in Table 2. Generally, small hydrophobic groups (Me, Et, CF_3, Br) were favored, with compounds **7a**, **7c**, **7e**, **7g** having sub-micromolar potency in the SPA assay. Compound **7g** was the most potent compound in this assay with an IC_{50} = 0.1 μM. The bulky *t*-butyl substituted compound **7d** resulted in about a 10 fold loss in SPA potency when compared to its ethyl counterpart **7c** (7.5 vs 0.7 μM). Polar/hydrophilic groups such as CO_2Me were not tolerated. In comparing the 5-Me compound **7a** to the methyl ester compound **7h**, an 80 fold loss in SPA potency (32 vs 0.4 μM) was observed. Extending the SAR to disubstituted thiazoles, we observed that 4,5-disubstituted thiazole **7a** was more potent than compound **7b** (0.4 vs 1.1 μM) and that **7g** was more potent than mono-CF_3 compound **7f** (0.1 vs 1.2 μM). Cyclohexyl compound **7e** in which positions 4 and 5 were linked to form a hydrophobic 6-carbon ring, further improved SPA potency over its 4,5-dimethyl counterpart **7a** by two fold (0.2 vs 0.4 μM).

Initial SAR studies with racemic DPPE amine enabled us to quickly identify thiazoles to further optimize. To identify the stereochemical preference of the aminoheterocycle series, two pairs of enantiomers, (**7i**/**7j**) of **7a** and (**7k**/**7l**) of **7e**, were prepared from the chiral amines and tested. CETP inhibitory activity was found to reside primarily in one enantiomer. Surprisingly the stereochemical preference of the aminoheterocycles was *R*- in contrast to the corresponding urea/amide analogs where the more active enantiomer configuration was *S*- (Fig. 2). The absolute stereochemistry of the quaternary center was determined by ^1H NMR analysis of the corresponding Mosher's amide.[12] The reversal of stereochemical preference was also consistent for other aminoheterocycles surveyed.[13]

For head-to-head comparison, aminothiazole **7k** and urea **1** were selected for PK/PD study in *h*CETP/apo B-100 transgenic mice, both dosed orally at 30 mpk. As shown in Table 3, compound **7k** achieved slightly better exposure and higher plasma concentrations at 2 and 4 h than urea **1**, likely due to its slightly improved liver microsomal stability in mice. However, because of weaker WPA potency, **7k** showed a lower PD effect (26% inhibition vs 56% inhibition at 8 h). Further improvement in potency was needed for the aminothiazole series.

Parallel SAR studies developed in our program on the B-ring identified a further optimized 3,5-disubstituted phenyl fragment which was subsequently utilized for the optimization of fluorinated ureas.[9,10] Specifically, it was observed that addition of a tetrafluorinated ethoxy group demonstrated a significant enhancement in WPA potency (i.e., **2** vs **1**). The DPPE with a tetrafluorinated ethoxy group was then utilized to carry out SAR studies on the terminal aminoheterocyclic series. Summarized in Tables 4 and 5 are potency and profiling data of selected aminothiazoles and aminobenzimidazoles with incorporation of the optimized B-ring. In Table 4, aminothiazoles combined with the tetrafluorinated ethoxy B ring in general achieved improved potency compared with the CF_3 substituted B ring (**7n** vs **7g**, **7o** vs **7k**). Although **7i** and **7m** had the same SPA potency, **7m** was more potent in the WPA assay. Compared to urea lead **2**, aminothiazole compounds in Table 4 in general were 3–30 fold less potent. However, **7n**, **7p** and **7q** all showed improvements on PXR, CYP and liver microsomal stability over urea lead **2**.

Aminoimidazoles in Table 5 demonstrated similar improvements on PXR, CYP and liver microsomal stability, compared to

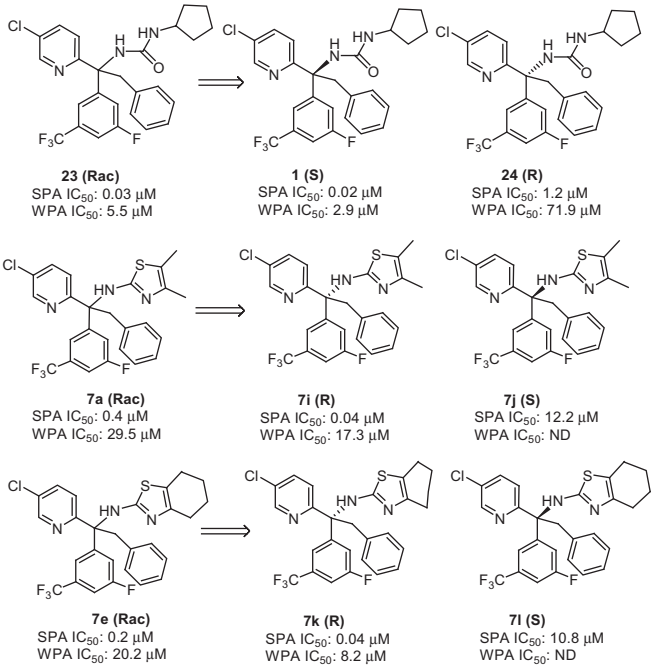
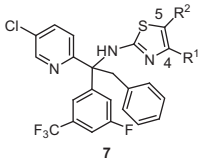


Figure 2. Reversal of stereochemical preference between aminoheterocycles and urea.

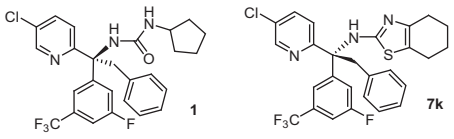
Table 2
SAR of substituted aminothiazoles against human CETP



7

Compds	R^1, R^2	SPA IC_{50} (μM)
7a	Me, Me	0.4
7b	H, Me	1.1
7c	Et, H	0.7
7d	*t*Bu, H	7.5
7e	$-CH_2CH_2CH_2CH_2-$	0.2
7f	CF_3, H	1.2
7g	CF_3, Br	0.1
7h	Me, CO_2Me	32

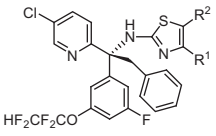
Table 3
PK/PD comparison of urea **1** and aminothiazole **7k**



	Compd **1**	Compd **7k**
SPA IC_{50} (μM)	0.02	0.04
WPA IC_{50} (μM)	2.9	8.2
LM stability (%remaining @10 min)	20(h), 27(m), 11(r)	73(h), 33(m), 56(r)
*AUC (nM h)	5713	8179
Plasma Conc. (nM) @2, 4, 8 h[a]	1754, 1012, na[b]	2531, 1241, 142
Inhibition of CETP activity@ 8 h[a]	56%	26%

[a] 30 mpk PO dose in *h*CETP/apo B-100 transgenic mice.
[b] na = Not available.

Table 4
SAR and profiling of aminothiazoles with optimized B-ring

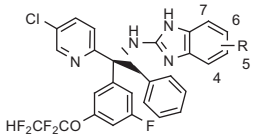


7

Compds	N-terminus R^1, R^2	SPA IC_{50} (μM)	WPA IC_{50} (μM)	PXR[a] EC_{60} (μM) (E_{max}% CTRL)	CYP IC_{50} (μM) 1A2, 2C9, 2C19, 2D6, 3A4 (BZRes), 3A4 (BFC)	LM stability (%remaining @10 min) (h, m, r)
2	Urea	0.007	0.63	0.7 (88)	40, 4.4, 17, 15, 3.6, 8.8	11, 11, 26
7m	Me, Me	0.04	5.5	na	na	na
7n	CF_3, Br	0.04	6.5	>5.6 (37)	All >40	100, 100, 95
7o	$-CH_2CH_2CH_2CH_2-$	0.02	4.2	na	na	na
7p	CF_3, H	0.22	14.8	>17 (45)	40, 40, 13, 40, 40, 40	98, 78, 83
7q	CF_3, Me	0.02	3.2	>5.6 (44)	All >40	82, 59, 55

[a] Compounds were tested at 10 concentrations (0.0025–50 μM) using 10 μM rifampicin as positive control. PXR activity of compounds is expressed as % of Control Activity (% CTRL), where control activity is the response observed with 10 μM rifampicin.

Table 5
SAR and profiling of aminobenzimidazoles



11

Compds	N-terminus R	SPA IC_{50} (μM)	WPA IC_{50} (μM)	PXR[a] EC_{60} (μM) (E_{max}% CTRL)	CYP IC_{50} (μM) 1A2, 2C9, 2C19, 2D6, 3A4(BZRes), 3A4(BFC)	LM stability (%remaining @10 min) (h, m, r)
2	Urea	0.007	0.63	0.7 (88)	40, 4.4, 17, 15, 3.6, 8.8	11, 11, 26
11b	R = H	0.09	15	>17 (70)	40, 19, 3, 40, 13, 40	na
11c	R = 5-F	0.05	9.5	>17 (56)	40, 40, 2, 29, 40, 32	56, 62, 95
11d	R = 5,7-diF	0.04	6.4	>5.6 (25)	40, 15, 3, 40, 19, 24	68, 72, 100

[a] Compounds were tested at 10 concentrations (0.0025–50 μM) using 10 μM rifampicin as positive control. PXR activity of compounds is expressed as % of Control Activity (% CTRL), where control activity is the response observed with 10 μM rifampicin.

urea lead **2**. However, similar to the observation in the aminothiazole series, compared to lead **2**, compounds **11**(**b**–**d**) lost around 5–10 fold in potency in the SPA and WPA assays.

In conclusion, N-terminus aminoheterocycles were synthesized as cyclopentyl urea replacements in the CETP program. Of the aminoheterocycles surveyed, aminothiazole and aminobenzimidazole provided the best in vitro potency. SAR studies of these two series identified compounds with comparable SPA potency to the urea, and with improved metabolic stability, PXR transactivation and CYP inhibition profiles. Further efforts in the DPPE series to identify novel compounds with improvements on WPA potency will be reported in due course.

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