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Novel Heteroaryl Replacements of Aromatic 3-Tetrafluoroethoxy Substituents in Trifluoro-3-(tertiaryamino)-2-propanols as Potent Inhibitors of Cholesteryl Ester Transfer Protein

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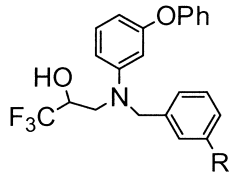
Abstract—A series of novel *N*,*N*-disubstituted trifluoro-3-amino-2-propanols has been prepared as potent inhibitors of cholesteryl ester transfer protein (CETP). Modifying the aromatic 3-tetrafluoroethoxy group in the lead molecule **1a** with various heteroaryl moieties produced new 2-furyl analogues **2a**,**b** with submicromolar potency in vitro.

Cholesteryl ester transfer protein is a plasma glycoprotein that mediates the transfer of cholesteryl ester (CE) from high-density lipoprotein (HDL) to very low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) with a balanced exchange of triglyceride (TG). The transfer of CE from HDL to LDL increases LDL-cholesterol (LDL-C) and decreases HDL-cholesterol (HDL-C).[1] Epidemiological studies have demonstrated an inverse relationship between serum HDL-C levels and the incidence of coronary heart disease (CHD).[2] Low levels of HDL-C represent a significant independent risk factor in CHD whether or not these patients have elevated plasma LDL-C.[3] CETP helps lower HDL-C by moving CE from HDL, which is thought to be atheroprotective to the more proatherogenic VLDL and LDL particles. The inhibition of CETP activity thus represents a potential new therapeutic approach to raise HDL-C.[4]

While a number of small molecule CETP inhibitors are known, few have been identified with submicromolar potency in vitro or with demonstrable potency in the presence of human plasma.[4] A new simple class of tertiary trifluoro-3-amino-2-propanols has recently been identified as potent CETP inhibitors.[5] The discovery of **1a** ($IC_{50} = 0.2$ μM) and the importance of its chiral alcohol center have been reported.[5] This communication summarizes our efforts to expand the SARs for the 3-tetrafluoroethoxy (TFE) substituent on the benzylic group in **1a**.



1a: R = OCF_2CF_2H
1b: R = OCH_2CH_3

A simple change to the nonhalogenated ethoxy group, **1b**, resulted in an 8-fold loss of potency ($IC_{50} = 1.6$ μM) indicating that the TFE group provided an important interaction for CETP binding. Molecular modeling (ab initio) experiments suggested that, in contrast to the ethoxy group, the TFE moiety prefers an out of plane orientation with respect to the phenyl ring. In an effort to explore this unusual spatial interaction as a possible contribution to the potency of **1a**, methodologies were developed to replace the TFE group with various heteroaryl substituents. The out of plane twisting of the two aromatic systems was seen as a possible route to mimic the spatial interactions provided by the TFE system. The syntheses of several of these compounds using Pd-catalyzed C–C bond formation is presented below along with their CETP inhibitory data.

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Most of the target compounds were easily assembled from three simple components: an appropriately substituted benzaldehyde, 3-phenoxyaniline, and commercially available 1,1,1-trifluoro-2,3-epoxypropane, of unspecified enantiomeric composition (Scheme 1).[5] Reductive amination of the benzaldehydes with 3-phenoxyaniline provided the secondary amines needed for the epoxide ring opening reactions. By using $Yb(OTf)_3$ as a catalyst[6] the amine reactions with this volatile epoxide were facilitated so that they could be performed at lower temperature and near stoichiometry (Scheme 1, route a). The indicated regioisomers were the only products detected prior to workup.

Examples of the various methods used to prepare the substituted benzaldehydes are illustrated in Scheme 2. The 3-(2-furyl)benzaldehydes (**3a**–**d**) were prepared from the corresponding 3-bromobenzaldehydes by Stille coupling[7] with 2-(tributylstannyl)furan. Suzuki coupling[8] of the boronic acid with 2-bromopyridines allowed the preparation of various 3-(2-pyridyl)benzaldehydes (**3e**–**g**). Similarly, 2-bromopyrimidine underwent Suzuki coupling to give 3-(2-pyrimidinyl)benzaldehyde, **3h**. In order to prepare 3-(1-methylpyrrol-2-yl)benzaldehyde, **3i**, 2-lithio-1-methylpyrrole was prepared in situ and then coupled with 3-bromobenzaldehyde using Pd(II).

In the cases where R = pyridyl in compound **4**, the epoxide reaction proceeded poorly, possibly due to competition from the basic nitrogen in the pyridine ring. This difficulty was avoided if the epoxide was first opened with the aniline to give intermediate **5** followed by reductive amination with the appropriately substituted pyridyl-benzaldehyde (Scheme 1, route b).

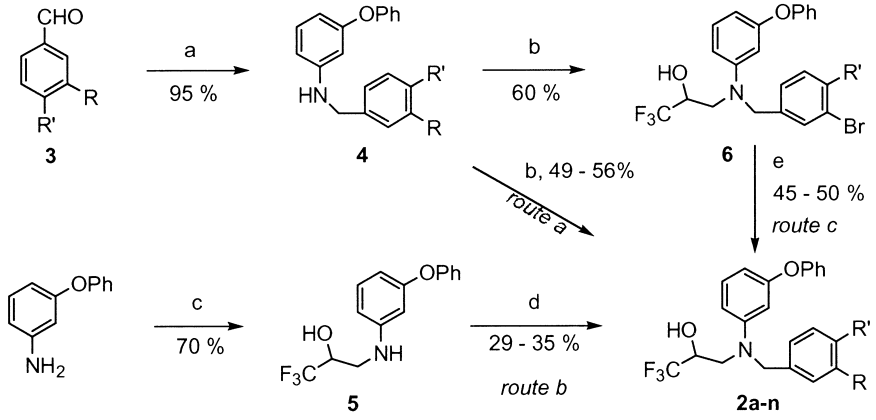
An alternative, more convergent method utilized the (tertiaryamino)propanol, **6**, having a 3-bromo substituent on the benzylic group. Intermediate **6** underwent Pd-catalyzed cross-coupling with aryl Grignard reagents or heteroaryl stannanes to give the desired final products (Scheme 1, route c).

All of the amino alcohol products were obtained from the ring opening of 1,1,1-trifluoro-2,3-epoxypropane from the same commercial source, resulting in final products as an unequal mixture of enantiomers.[5] All final products had satisfactory ^1H NMR, HR-MS, and microanalyses,[9] and the biological evaluations were performed on the resulting enantiomeric mixtures.

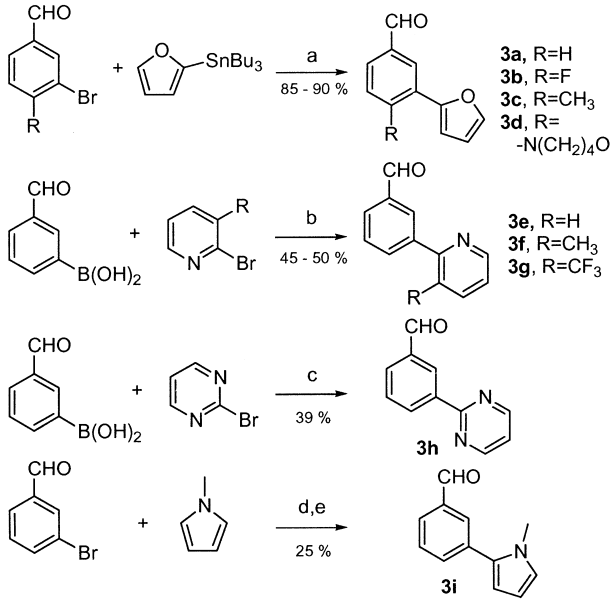
Several analogues of **1a** were prepared in which the TFE group was replaced in order to explore the SAR at this position. The resulting compounds were initially assessed in a buffered in vitro transfer assay (Table 1).[10] Compounds having comparable potency to **1a** in this assay were also evaluated in the presence of human serum to determine their IC_{50} (Table 2).[11] The serum transfer assay is presumably more representative of their activity in the desired target tissue, human blood.

Since no structural data exists for CETP with or without bound substrates, the rationale for changes made to the TFE group came from molecular modeling insights. Ab initio calculations with Gaussian 94[12] predict that the TFE group preferred a nearly perpendicular ($\sim 90°$) orientation to the phenyl ring in $PhOCF_2CF_2H$.[13] In contrast, PhOEt was predicted to adopt a more co-planar orientation. As a possible mimic of the TFE spatial interaction, 2-phenyl furan was also modeled and was shown to have a similar, energetically favorable, out of plane orientation with a smaller torsion angle ($\sim 30°$) (Fig. 1).[14,15] Substitutions in the 4-position of the benzyl ring combined with the 2-furyl ring were explored to provide a more perpendicular torsion angle.

The resulting 2-furyl substitution product, **2a**, displayed submicromolar activity as a CETP inhibitor. However, the introduction of additional substituents at the 4-position of the benzylic group led to decreased potency as the size of the substituent increased (IC_{50} R = H < F < CH_3 < *N*-morpholino). All of the 2-pyridyl substitutions (**2e**–**g**) showed significant loss of potency. Since the least basic compound, **2g**, exhibited the most potency in this series, it is likely that substituents with hydrogen-bond accepting character are disfavored at this position. In addition, comparison of **2e**, **2m**, and **2n** as the 2-, 3-, and 4-pyridyl substituents showed the 4-pyridyl, **2n**, to be the most potent suggesting that a basic



Scheme 1. Synthesis of trifluoro-3-(tertiaryamino)-2-propanols. Reaction conditions: (a) 3-phenoxyaniline, $NaBH(OAc)_3$, AcOH, 1,2-dichloroethane, rt; (b) 1,1,1-trifluoroepoxypropane, $Yb(CF_3SO_3)_3$, CH_3CN, 50 °C, 2 h; (c) 1,1,1-trifluoroepoxypropane, neat, 100 °C, 18 h; (d) **3**, $NaBH(OAc)_3$, AcOH, 1,2-dichloroethane, rt; (e) ArMgBr, $Pd(PPh_3)_4$, THF, reflux, 18 h or $HetSnBu_3$, $Pd(PPh_3)_2Cl_2$, dioxane, reflux, 18 h. R and R′ defined in Table 1.



Scheme 2. Synthesis of substituted benzaldehydes. Reaction conditions: (a) $Pd(PPh_3)_2Cl_2$, dioxane, reflux, 18 h; (b) $Pd(PPh_3)_4$, toluene/DMF (2:1), K_2CO_3, reflux, 18 h; (c) *n*-BuLi, TMEDA, Et_2O, $SnMe_3Cl$, −78 °C to rt; (d) $Pd(PPh_3)_2Cl_2$, dioxane, reflux,18 h.

nitrogen located near the benzyl ring was not well tolerated.

The most potent pyridyl compounds **2g** and **2n** were comparable to a simple phenyl substitution, **2l**, or the weakly basic nitrogen heterocycle, 2-pyrimidinyl, **2h**. The 3-furyl, **2j**, and 2-thienyl, **2k**, compounds were slightly less potent than 2-furyl, **2a**. However, both were more potent than any six-membered ring analogue suggesting that a smaller ring was favored. Of the compounds prepared in this series, the 2-furyl displayed the best activity in the buffer assay.

Table 1. CETP inhibitory data for (tertiaryamino)propanols **2a**–**n** using a buffer transfer assay[8]

Compd	Route	R	R′	IC_{50} (μM) Buffer
2a	A	2-Furyl	H	0.48
2b	A	2-Furyl	F	0.72
2c	A	2-Furyl	CH_3	3.96
2d	A	2-Furyl	$-N(CH_2)_4O$	45.8
2e	B	2-Pyridyl	H	22.9
2f	B	2-Pyridyl, 3-CH_3	H	15
2g	B	2-Pyridyl, 3-CF_3	H	4.08
2h	A	2-Pyrimidinyl	H	6.72
2i	A	*N*-Me-2-Pyrrolyl	H	6.79
2j	A	3-Furyl	H	0.91
2k	C	2-Thienyl	H	1.12
2l	C	Phenyl	H	4.42
2m	B	3-Pyridyl	H	14.3
2n	B	4-Pyridyl	H	6.24

Several of the more potent compounds were also assayed in the serum transfer assay (Table 2). Whereas **1a** exhibits a 30-fold shift of CETP inhibition in serum versus buffer, a 70- to 100-fold shift was observed with the TFE replacement analogues.

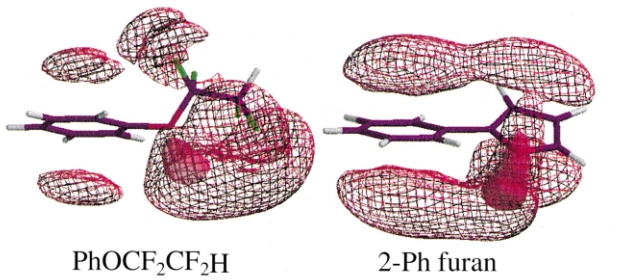


Figure 1. Comparison of negative electrostatic potential for $PhOCF_2CF_2H$ and 2-Ph Furan.[14,15]

Synthetic methodology was developed to replace TFE with various carbon-linked heteroaryl groups. The 2-furyl replacement, **2a**, exhibited submicromolar potency 2- to 3-fold less potent than the TFE analogue, **1a**, but showed improvement over the ethoxy analogue, **1b**. The potency may be influenced by the ability of the 2-furyl group to twist out of the plane of the benzyl ring. Figure 1 suggests the 2-furyl group prefers a twisted orientation similar to TFE with two important differences. The torsion angle of minimum energy in 2-phenylfuran is smaller than in $PhOCF_2CF_2H$. Further twisting will require energy, and therefore reduce potency, if that conformation is required for binding. Secondly, heteroaryl groups distribute electron density above and below the phenyl ring, while the TFE group has electron density generally directed to only one face of the benzene ring. These properties make haloalkoxy groups like TFE unique tools to probe substituent space around a phenyl ring asymmetrically.

Table 2. Serum transfer inhibitory data for selected (tertiaryamino)propanols

Compound	IC_{50} serum (μM)[9]
1b	6
2a	52
2b	49
2k	83
2l	47

The heteroaryl substitutions also had an unexpected increase in ratio of the CETP inhibition in serum versus buffer compared to the TFE group. This decreased inhibition in human plasma is possibly due to increased nonspecific protein binding.

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9. Analytical data for **2a**: Anal. calcd for $C_{26}H_{21}NO_3F_3 \cdot 0.5EtOH \cdot 0.3H_2O$: C, 67.30; H, 5.35; N, 2.91. Found: C, 67.12; H, 5.12; N, 2.89. HRMS calcd 454.1630 (M + H), found 454.1635. ^1H NMR (C_6D_6) δ 2.15 (d, 1H), 3.21 (dd, 1H), 3.50 (dd, 1H), 3.81 (m, 1H), 4.24 (s, 2H), 6.09 (dd, 1H), 6.33 (d, 1H), 6.35 (d, 1H), 6.44 (dd, 1H), 6.52 (t, 1H), 6.79 (m, 1H), 6.81 (s, 1H), 6.9–7.0 (m, 7H), 7.44 (d, 1H), 7.47 (s, 1H).
10. The ability of compounds to inhibit CETP activity was assessed using a reconstituted buffered in vitro assay that measures the rate of CETP-mediated transfer of radiolabeled cholesteryl ester ([^{3}H]CE) from HDL donor particles to LDL acceptor particles with recombinant human CETP. Alternatively the transfer activity from ([^{3}H]CE)-HDL donor particles could be measured in the presence of human serum, which provided the source of the LDL, VLDL and human CETP as described in detail in ref 11.
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13. Calculations were performed using the RHF/6-311G**//MP2/6-311G** ab initio level of Gaussian 94. The Ph–C torsional angle for $PhOCF_2CF_2H$ was 90° for the low energy conformation with a predicted barrier of 0.91 kcal/mol. The Ph–C torsional angle for PhOEt was 0° for the low energy conformation with a predicted barrier of 2.07 kcal/mol.
14. *Spartan 5.0.1*, Wavefunction Inc., Irvine, CA, USA.
15. Electrostatic potential calculations were performed using RHF/6-31G*//RHF/6-31G* ab initio level of Spartan 5.0.1. The hatched electrostatic potential surfaces are at −10 kcal/mol and the solid surfaces are at −20 kcal/mol.