Journal of Medicinal Chemistry

Article

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Diphenylpyridylethanamine (DPPE) Derivatives as Cholesteryl Ester Transfer Protein (CETP) Inhibitors

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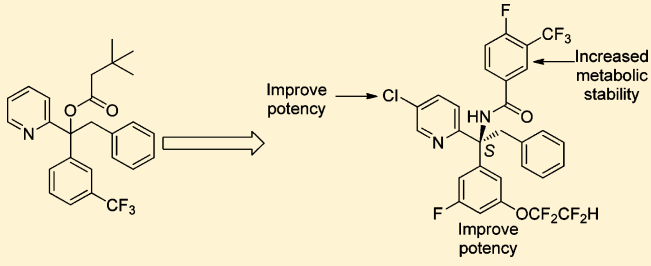
Supporting Information

ABSTRACT: A series of diphenylpyridylethanamine (DPPE) derivatives was identified exhibiting potent CETP inhibition. Replacing the labile ester functionality in the initial lead **7** generated a series of amides and ureas. Further optimization of the DPPE series for potency resulted in the discovery of cyclopentylurea **15d**, which demonstrated a reduction in cholesterol ester transfer activity (48% of predose level) in hCETP/apoB-100 dual transgenic mice. The PK profile of **15d** was suboptimal, and further optimization of the N-terminus resulted in the discovery of amide **20** with an improved PK profile and robust efficacy in transgenic hCETP/apoB-100 mice and in hamsters. Compound **20** demonstrated no significant changes in either mean arterial blood pressure or heart rate in telemeterized rats despite sustained high exposures.



INTRODUCTION

Lipid modifying therapies for the treatment of coronary heart disease (CHD) have 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 that 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] Therefore, the need exists for safer and more efficacious methods of increasing HDL-C levels.

Cholesteryl ester transfer protein (CETP) is a 74 kDa plasma glycoprotein secreted predominantly 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 antiatherogenic.[6] Interest in this target by the pharmaceutical community has been widespread as evidenced by the number of clinical and/or preclinical lead compounds in various stages of development (Figure 1).[7] In this manuscript the identification and optimization of a novel series of diphenylpyridylethanamine-based CETP inhibitors are described.

RESULTS AND DISCUSSION

In an effort to identify potential CETP inhibitor leads, a virtual screen was undertaken based on the published structures of three noncovalent modulators of CETP (compounds **1**, **3**, and **4** shown in Figure 1). Similarity searches and molecule shape-matching techniques were used to identify compounds for initial screening[8] using a BODIPY fluorescence assay.[9] Compounds that demonstrated activity in the BODIPY assay were followed up in concentration−response mode using a scintillation proximity assay (SPA).[10] Validated leads were then checked for activity in a human whole plasma assay (WPA).[11] This led to identification of racemic DPPE ester **7** with a measurable IC_{50} in the human whole plasma assay.

Developing a parallel high throughput synthetic method to access various analogues was challenging because of the quaternary carbon center. However, an efficient sequence was identified and utilized to generate compounds with diversity in the A, B, and C rings (Scheme 1).

Ketone **10** was obtained by the addition of substituted benzyl Grignard reagent **8** to ethyl picolinate.[12] Alternatively, ketone

Received: May 2, 2012
Published: May 31, 2012

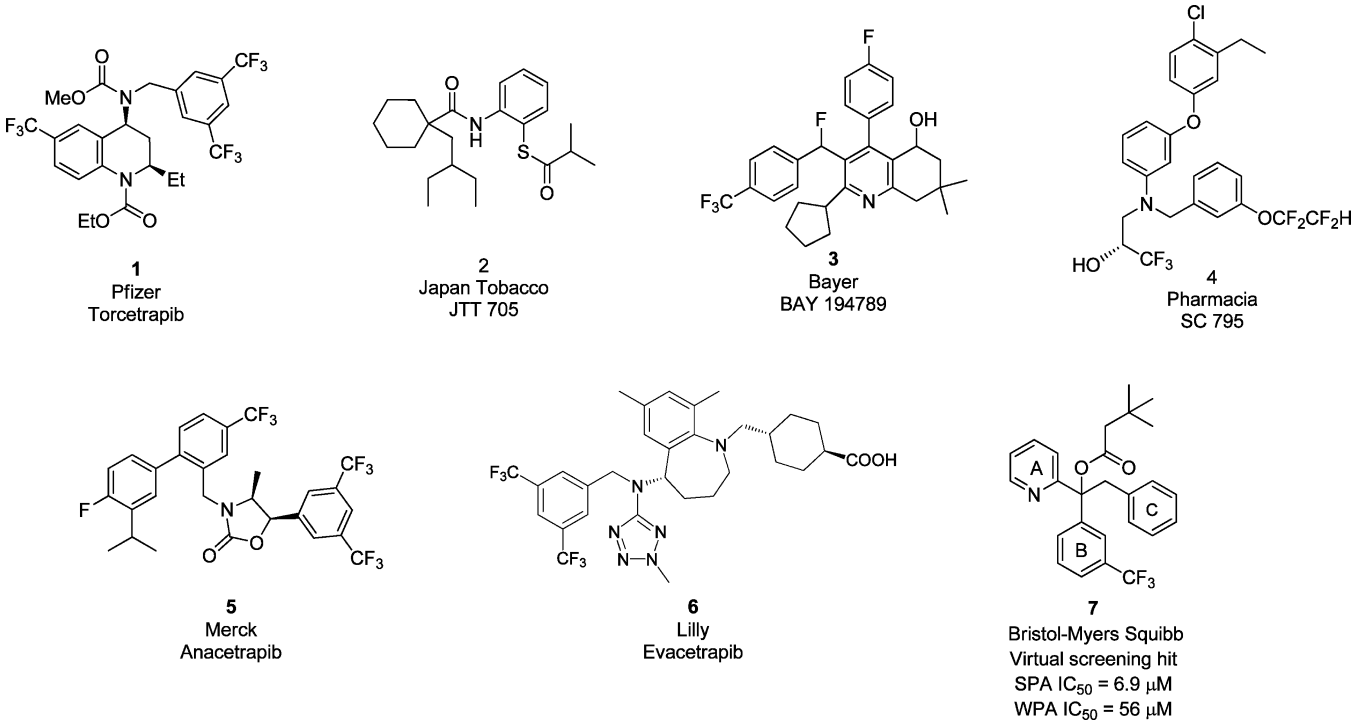
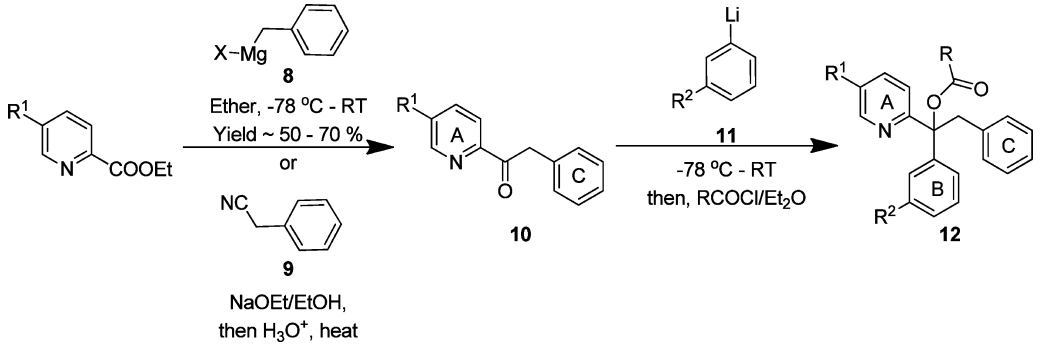


Figure 1. Reported CETP inhibitors.

Scheme 1. Synthetic Route to Analogues of Ester 7

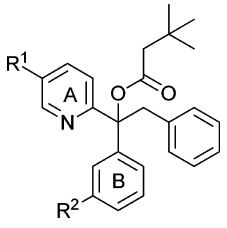


10 was obtained by the addition of the anion of substituted benzylic nitrile **9** to ethyl picolinate, followed by hydrolysis of the cyanide and decarboxylation of the resultant carboxylic acid (Scheme 1).[13] Addition of aryllithium **11** to ketone **10** yielded the lithium alkoxide, which was quenched with various acyl chlorides to generate ester **12**. Substituted A and B rings were employed to synthesize the compounds shown in Table 1.

The enantiomers of ester **7** were resolved, and it was determined that CETP activity resided primarily in one enantiomer (compound **12a**, Table 1). A racemic synthesis of this complex core was initially employed to synthesize analogues, and the SAR with the racemates demonstrated that a 5-chloro substituent on the A-ring increased potency (compound **12c**) and an alternative substitution such as tetrafluoroethoxy was tolerated in the B-ring (compound **12d**).

Ester functionalities can be hydrolyzed rapidly in vivo,[14] and as a result, replacement of this ester with a potentially more metabolically stable amide was targeted. A series of intermediate amines was generated and converted to the corresponding amides and ureas. An efficient one-pot parallel synthesis of the corresponding primary amine has been

Table 1. SAR of Ester Series

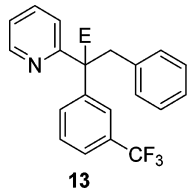


compd	R^1	R^2	quaternary chiral center	IC_{50} (μM)[a] CETP SPA	CETP WPA
12a	H	CF_3	enantiomer 1[b]	6.7	26
12b	H	CF_3	enantiomer 2[b]	44	>97
12c	Cl	CF_3	racemic	1.3	9.4
12d	H	OCF_2CF_2H	racemic	1.1	28

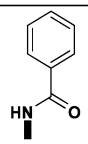
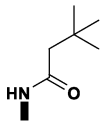
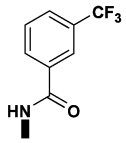
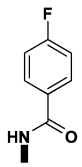
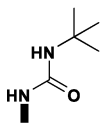
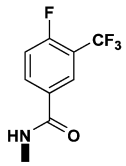
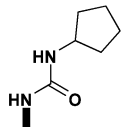
[a]SPA and WPA percent inhibitions were measured in duplicate at six concentrations and the mean values used to calculate IC_{50} values. [b]Absolute stereochemistry was not determined.[14]

dx.doi.org/10.1021/jm300611v | J. Med. Chem. 2012, 55, 6162–6175

Table 2. Optimization of N-Substituents



13

Compound Number	E	CETP SPA IC_{50} (μM)[a]	CETP WPA IC_{50} (μM)[a]
13a		>96	ND
13b		27	ND
13c		12	ND
13d		8.9	ND
13e		3.8	83
13f		2.9	15
13g		0.70	25

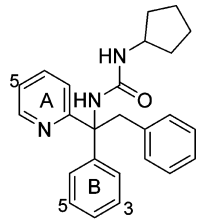
[a]SPA and WPA percent inhibitions were measured in duplicate at six concentrations and the mean values used to calculate IC_{50} values.

described previously and was used to generate extensive SAR in this series.[15]

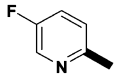
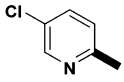
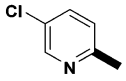
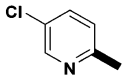
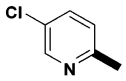
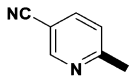
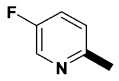
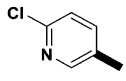
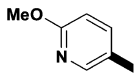
An initial survey of N-substituents showed that a variety of amides and ureas were tolerated (Table 2). The amide analogue **13b** resulted in a decrease in CETP inhibition compared to its ester counterpart **7**. A survey of additional amides showed that while unsubstituted benzamide **13a** demonstrated no measurable inhibition of CETP at 96 μM (highest concentration tested), certain monosubstituted phenylamides, for example, **13c** and **13d**, resulted in measurable activity in the SPA assay. The combination of the two substituents (**13f**) resulted in increased WPA potency. The urea analogue **13e** showed potency comparable to ester **7**. Cyclopentyl urea **13g** was identified with improved SPA potency as well as good WPA potency (comparable to **13f**), and this moiety was used in the further optimization of the A, B, and C rings.

dx.doi.org/10.1021/jm300611v | J. Med. Chem. 2012, 55, 6162−6175

Table 3. Optimization of A-Ring



14

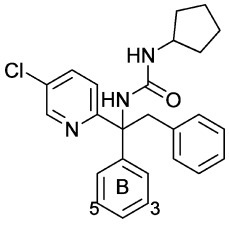
Compound Number	A-ring	B-ring 3-	B-ring 5-	Quaternary center chirality	CETP SPA IC_{50} (μM)[a]	CETP WPA IC_{50} (μM)[a]
14a		CF_3	H	rac	0.24	6.9
14b		CF_3	H	rac	0.31	16
14c		CF_3	F	rac	0.031	5.5
14d		CF_3	F	*R*[b]	1.2	72
14e		CF_3	F	*S*[b]	0.020	2.9
14f		CF_3	F	*S*	0.036	12
14g		CF_3	F	*S*	0.026	7.6
14h		CF_3	F	rac	0.031	12
14i		CF_3	F	*S*	0.015	3.4

[a]SPA and WPA percent inhibitions were measured in duplicate at six concentrations and the mean values used to calculate IC_{50} values. [b]These compounds were synthesized as racemates and resolved by chiral HPLC, and the stereochemistry was determined by X-ray analysis of Mosher's amide.[16]

dx.doi.org/10.1021/jm300611v | J. Med. Chem. 2012, 55, 6162−6175

Examples of A- and B-ring analogues are shown in Tables 3 and 4, respectively. Small electron withdrawing groups at the 5-position of the A-ring led to improvements in potency (**14a–g** compared to **13g**) as noted earlier in the ester series. Regioisomeric 3-pyridyl compounds (**14h** and **14i**) demonstrated reduced potency. With the optimized 5-chloropyridine A-ring, addition of fluorine at the 5-position of the B-ring led to a further increase in potency (**14c** versus **14b**). Consistent with the ester series, the *S* enantiomer was the more potent antipode. Extending the fluoroalkyl groups at the 5-position farther from the B-ring led to a progressive improvement in potency (compare **14b**, **15a**, and **15b**). Incorporating the SAR at the 3-position of the B-ring from the ester series (compound **12d**) and 3,5-disubstitution SAR from Table 3 (compounds **14d–i**) led to urea **15d** and yielded one of the first analogues in this series with submicromolar WPA potency.

Table 4. Optimization of B-Ring



15

	B-ring			IC_{50} (μM)[a]	
compd	3-	5-	quaternary center chirality	CETP SPA	CETP WPA
15a	OCF_3	H	rac	0.031	2.7
15b	OCF_2CF_2H	H	rac	0.025	0.84
15c	OCF_2CF_2H	F	*R*	0.43	36
15d	OCF_2CF_2H	F	*S*	0.0069	0.63

[a]SPA and WPA percent inhibitions were measured in duplicate at six concentrations and the mean values used to calculate IC_{50} values.

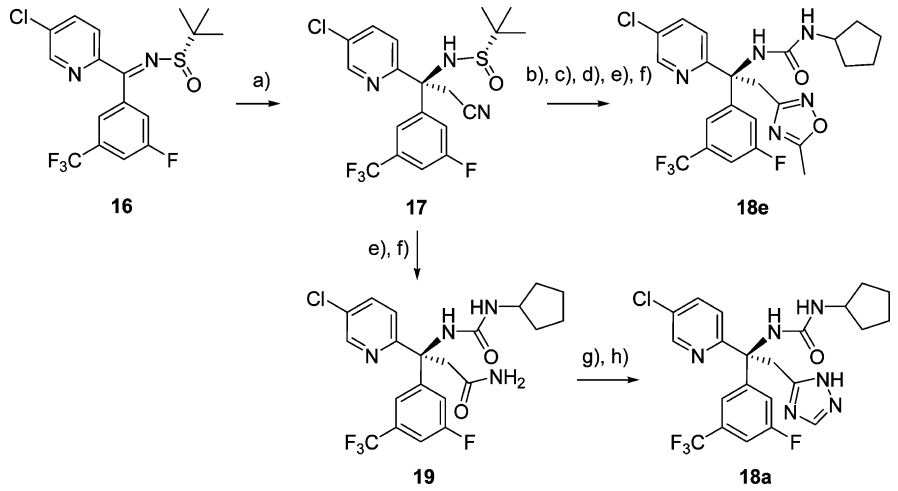
Although the one-pot synthetic methodology allowed rapid access to racemic analogues, a chiral route to the *S* amine intermediates was developed to further drive the SAR in this series and to enable subsequent scale up of compounds for in vivo studies (Scheme 2).[15] This route was then utilized to explore the SAR of the C-ring.

Examples of C-ring analogues are shown in Table 5. Triazole **18a** and oxadiazole **18e** were prepared as shown in Scheme 2 from the corresponding nitrile obtained by the addition of the anion of acetonitrile to the key (*R*)-sulfinamide followed by direct conversion to the oxadiazole. Compounds **18b–d** were prepared from the corresponding intermediate primary amines described previously.[15] Addition of Grignard reagents to sulfinamide **16** followed by deprotection and acylation afforded compounds **18f–i**.[15] Heterocyclic replacement of the C-ring was not tolerated (examples **18a**, **18b**, **18d**, and **18e**), and small substitutions at the C-ring phenyl were less potent than the corresponding unsubstituted phenyl compound **14e** (examples **18f**, **18h**, and **18i**). Therefore, an unsubstituted phenyl ring was chosen as the C-ring for further SAR studies. Urea **15d** proved to be the most potent compound resulting from concomitant optimization of the A, B, and C rings of the DPPE chemotype and was advanced to in vivo studies.

Compound **15d** inhibited cholesterol ester transfer from ^{3}H-CE/HDL to LDL to 48% of predose activity after 2 h in hCETP/apoB-100 transgenic mice when dosed at 30 mg/kg orally (po) (Table 6).[17] Maximal inhibition of CETP in this model reduces CE transfer to between ~30% and 35% of control. The area under the curve (AUC) of the plasma concentration vs time profile, AUC (0–8 h), of **15d** was 9.7 μM·h, demonstrating only moderate exposure in the mouse pharmacodynamic (PD) model.

The mouse liver microsomal stability of urea **15d** was poor (10% remaining after 10 min; rate of 0.27 (nmol/min)/mg protein),[18] and biotransformation studies indicated that the cyclopentyl urea was the principal site of metabolism.[19] Liver microsomal stability of earlier compounds revealed that the profile of amide **13f** (68% remaining after 10 min incubation) was superior to that of the urea **13g** (2% remaining after 10 min

Scheme 2. Synthetic Route to Heterocyclic C-Ring Analogues[a]

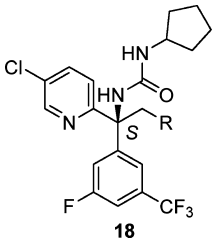


16 **17** **18e** **19** **18a**

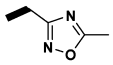
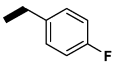
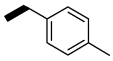
[a]Reagents and conditions: (a) 2 equiv of CH_3CN, LDA, BF_3Et_2O, THF, −78 °C (28% *S*,*R* and 11% *S*,*S* yield); (b) NH_2OH, EtOH 70 °C, 2 h; (c) Ac_2O TEA, DCM 0 °C to rt, 14 h; (d) Cs_2CO_3, THF, 105 °C to dryness 3 h (44% yield for three steps); (e) 4 M HCl/dioxane (100% and 100% yield); (f) cyclopentyl isocyanate, DCE, catalytic citric acid, rt, 14 h (41% yield for **18e** and 36% for **19**); (g) DMF/DMA, rt (100% yield); (h) hydrazine, AcOH, 60 °C, 2 h (21% yield).

dx.doi.org/10.1021/jm300611v | *J. Med. Chem.* 2012, 55, 6162–6175

Table 5. Optimization of C-Ring



18

Compound Number	R	CETP SPA IC_{50} (μM)[a]	CETP WPA IC_{50} (μM)[a]
18a		>96	ND
18b		27	ND
18c		2.4	ND
18d		1.1	24
18e		1.07	34
18f		0.087	10
18g		0.085	7.1
18h		0.023	3.4
18i		0.016	6.4

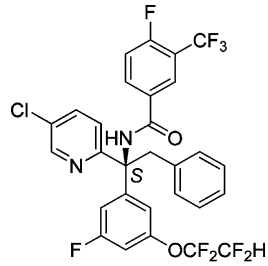
[a]SPA and WPA percent inhibitions were measured in duplicate at six concentrations and the mean values used to calculate IC_{50} values.

Table 6. Pharmacodynamic (PD) Data in hCETP/apoB-100 Tg Mice for Advanced Compounds

	IC_{50} (μM)[a]			CETP activity (% of predose)		
compd	CETP hWPA	CETP mWPA	AUC (0–8 h) (μM·h)	2 h	4 h	8 h
torcetrapib	0.11	0.16	65	31	31	25
15d	0.63	0.94	9.7	48	58	65
20	3.6	9.0	93	55	48	40

[a]SPA and WPA percent inhibitions were measured in duplicate at six concentrations and the mean values used to calculate IC_{50} values.

incubation). Therefore, the cyclopentylurea moiety in compound **15d** was replaced with the metabolically stable amide to obtain compound **20** (Figure 2).[15] Compound **20** demonstrated significantly improved mouse liver microsomal stability (100% remaining after 10 min; rate of 0.0025 (nmol/min)/mg protein), as well as a superior pharmacokinetic profile in mice (Table 6). Compound **20** was advanced to PD evaluation and inhibited CETP mediated transfer of ^{3}H-CE/HDL to LDL to 32% of predose activity after 8 h in h-CETP/apoB-100 transgenic mice when dosed at 30 mg/kg, po (Table 6).[20] The AUC (0–8 h) of amide **20** was 93 μM·h.



20
SPA IC_{50} = 0.036 μM
hWPA IC_{50} = 2.8 μM
TgWPA IC_{50} = 9.0 μM

Figure 2. Optimized amide resulting in metabolically stable compound **20**.

Although amide **20** inhibited CETP in h-CETP/apoB-100 transgenic mice, it remained to be evaluated in a species that naturally expresses CETP. Since hamsters (unlike mice and rats) express CETP, compound **20** was tested in a hamster PD model. Compound **20** was dosed in moderately fat-fed hamsters at 30 mg/kg, once-a-day (q.d.), and 21 μM plasma exposures were achieved at 2 h after dosing on day 3.[21] An increase of 40% in HDL-C was also observed after 3 days (Figure 3), demonstrating robust efficacy for the compound in hamsters.

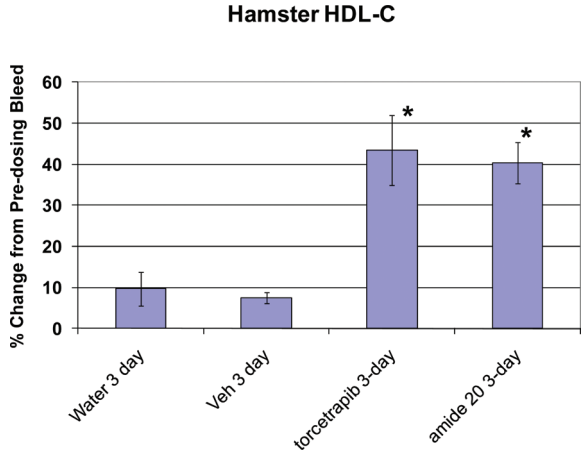


Figure 3. In vivo efficacy data for amide **20** in hamsters. Male Golden Syrian hamsters 12 weeks of age were used. Predose blood samples were collected by retro-orbital bleed. Compounds were formulated in ethanol/Cremophor/water at a 1:1:8 ratio and dosed at 30 mg/kg, po, q.d., for 3 days. Blood was drawn 2 h postdose on day 3, and HDL-C levels were measured in the predose and postdose samples using an automated lipid analyzer (COBAS). Percentage increases in HDL-C with treatment are reported as the mean ± SEM (N = 6).

Torcetrapib was reported to increase blood pressure in humans,[22] as well as in telemeterized rats.[23] Since rats do not express CETP, the elevation in blood pressure was due to an off-target effect.[24] To ensure that amide **20** did not cause effects on blood pressure, it was also evaluated in rat telemetry studies. Significantly, unlike torcetrapib, amide **20** did not produce changes in mean arterial blood pressure (MABP) or heart rate (HR) in telemeterized rats at doses up to 60 mg/kg with sustained high exposure (C_{max} = 25 μM; $T_{1/2}$ = 14 h).

In summary, ester **7** was identified from virtual screening as a CETP inhibitor. Initial SAR in the ester series led to

dx.doi.org/10.1021/jm300611v | J. Med. Chem. 2012, 55, 6162–6175

optimization of the A-ring and B-ring. Replacement of the metabolically labile ester group led to the discovery of N-terminal ureas and amides which were further optimized in the A-, B-, and C-ring positions. A one-pot route was developed to access the precursor amines via parallel synthesis, and an enantioselective route was subsequently developed to scale up the desired *S*-enantiomers. The DPPE series SAR was further extended to achieve over 1000-fold improvement in in vitro potency and in vivo activity in h-CETP/apoB-100 transgenic mice and hamsters. Improved metabolic stability was achieved by replacing the cyclopentylurea group in compound **15d** with an optimized amide to yield **20** which had an improved pharmacokinetic profile, demonstrated the ability to inhibit CETP mediated cholesterol transfer in both h-CETP/apoB-100 transgenic mice and hamsters, and provided a 40% increase in HDL levels in hamsters. No significant changes in MABP and HR were observed in telemeterized rats when compound **20** was administered orally at sustained high exposures. The studies described herein demonstrate that the DPPE chemotype shows promise as a novel scaffold for development of a potent CETP inhibitor. Further efforts to optimize this series will be reported in subsequent disclosures.

EXPERIMENTAL SECTION

General Information. All reactions were carried out under a static atmosphere of argon or nitrogen and stirred magnetically unless otherwise stated. All reagents used were of commercial quality and were obtained from Aldrich Chemical Co., Sigma Chemical Co., Lancaster Chemical Co., Oakwood Chemical Co., and Matrix Chemical Co. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a JEOL GSX400 spectrometer using tetramethylsilane as an internal standard unless otherwise stated. ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra were recorded on a JEOL JNM-ECP500 spectrometer. Chemical shifts are given in parts per million (ppm) downfield from internal reference trimethylsilane in δ units, and coupling constants (J) are given in hertz (Hz). Selected data are reported in the following manner: chemical shift, multiplicity, coupling constants. All reactions were carried out using commercially available anhydrous solvents from Aldrich Chemical Co. or EM Science Chemical Co. unless otherwise stated. All flash chromatographic separations were performed using E. Merck silica gel (particle size, 0.040−0.063 mm). Reactions were monitored by TLC using 0.25 mm E. Merck silica gel plates (60 F_{254}) and were visualized with UV light, with 5% phosphomolybdic acid in 95% EtOH, or by sequential treatment with 1 N HCl/MeOH followed by ninhydrin staining. LC−MS data were recorded on a Shimadzu LC-10AT equipped with a SIL-10A injector, a SPD-10AV detector, normally operating at 220 nm, and interfaced with a Micromass ZMD mass spectrometer. LC−MS or HPLC retention times, unless otherwise noted, are reported using a Phenomenex Luna C-18 4.6 mm × 50 mm column, and elution was with a 4 min gradient from 0% to 100% B, where A is 10% MeOH−90% H_2O−0.1% TFA and B is 90% MeOH−10% H_2O−0.1% TFA. All solvents were removed by rotary evaporation under vacuum using a standard rotovap equipped with a dry ice condenser. All filtrations were performed with a vacuum unless otherwise stated. Unless otherwise specified the purity of all intermediates and final compounds was determined to be >95% by Sunfire C18 3.5 μm, 3.0 mm × 150 mm, 1.0 mL/min, gradient 10−100% 95:5 AcCN in H_2O (0.05% TFA) in 5:95 AcCN in H_2O (0.05% TFA) (method A), Xbridge Phenyl 3.5 μm, 4.6 mm × 150 mm, 1.0 mL/min, gradient 10−100% 95:5 AcCN in H_2O (0.05% TFA) in 5:95 AcCN in H_2O (0.05% TFA) (method B), Phenomenex Luna 5 μm, 4.6 mm × 50 mm, 4.0 mL/min, gradient 10−100% 95:5 MeOH in H_2O (0.1% HP_3O_4) in 5:95 MeOH in H_2O (0.1% HP_3O_4) (method C), Sunfire 5 μm, 4.6 mm × 50 mm, 4.0 mL/min, gradient 10−100% 90:10 MeOH in H_2O (0.1% TFA) in 10:90 MeOH in H_2O (0.1% TFA) (method D) and/or elemental analyses.

General Procedure A for Synthesis of DPPE Esters. To a solution of aryl bromide (1 mmol) in ether (10 mL) under nitrogen at −78 °C was added *n*-BuLi (1.6 M in hexane, 0.63 mL, 1 mmol), and the mixture was stirred for 10 min. Then a solution of ketone **10** (1 mmol) in THF (0.5 mL) was added. The reaction mixture was stirred at −78 °C for 30 min. An aliquot of the resultant alkoxide (1.1 mL, 0.10 mmol) was added into an array of vials containing freshly prepared solutions of various acid chlorides (0.11 mmol) in ether (0.5 mL). The mixtures were warmed to room temperature. The crude products were purified by reverse phase HPLC to obtain the desired products in 18−60% yield.

General Procedure B for Synthesis of DPPE Ureas (40 μmol Scale). To an array of vials containing various isocyanates (0.2 M in dioxane, 400 μL, 80 μmol) was added primary amine **14**[15] (0.5 M in dioxane, 80 μL, 40 μmol). The reaction mixture was agitated at room temperature for 18 h. The solvents were evaporated, and the crude product was purified by reverse phase HPLC.

General Procedure C for Synthesis of DPPE Amides. To an array of vials containing various acid chlorides (0.2 M in DCM, 400 μL, 80 μmol) and pyridine (8 μL, 98 μmol) was added primary amine **14**[15] (0.5 M in DCM, 80 μL, 40 μmol). The reaction mixture was agitated at room temperature for 18 h. The solvents were evaporated, and the crude product was purified by reverse phase HPLC.

2-Phenyl-1-(pyridin-2-yl)-1-(3-(trifluoromethyl)phenyl)ethyl 3,3-Dimethylbutanoate, 7. Ester **7** was obtained using general procedure A, in 49% yield. The racemic 2-phenyl-1-(pyridin-2-yl)-1-(3-(trifluoromethyl)phenyl)ethyl 3,3-dimethylbutanoate **7** (100 mg, 22.6 μmol) was separated by chiral HPLC using Chiralpak AD column, eluting with 2% EtOH/MeOH (1:1) in heptane to give (*R*)-2-phenyl-1-(pyridin-2-yl)-1-(3-(trifluoromethyl)phenyl)ethyl 3,3-dimethylbutanoate **12b** (45.3 mg, white solids) as the faster eluting enantiomer (analytical Chiralpak AD 10 μm, 4.6 mm × 250 mm, SN AD00CE-DD007 column, 2% EtOH/MeOH (1:1) in heptane, 0.5 mL/min, retention time of 9.29 min) and (*S*)-2-phenyl-1-(pyridin-2-yl)-1-(3-(trifluoromethyl)phenyl)ethyl 3,3-dimethylbutanoate **12a** (43 mg, white solids) as the slower eluting enantiomer (analytical Chiralpak AD 10 μm, 4.6 mm × 250 mm; SN AD00CE-DD007 column, 2% EtOH/MeOH (1:1) in heptane, 0.5 mL/min, retention time of 11.36 min). Data for ester **6**: LC−MS ESI 464.5 (M + Na), retention time of 2.1 min (10−90% MeOH in H_2O with 0.1% TFA in a 2 min gradient). ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.60−8.69 (m, 1H), 7.63 (dt, J = 1.76, 7.68 Hz, 1H), 7.34−7.57 (m, 5H), 7.06−7.22 (m, 4H), 6.62 (d, J = 7.05 Hz, 2H), 4.42 (d, J = 13.60 Hz, 1H), 4.10 (d, J = 13.60 Hz, 1H), 2.27 (s, 2H), 1.02 (s, 9H). ^{13}C NMR (126 MHz, chloroform-*d*) δ 170.5, 162.0, 148.9, 144.6, 136.5, 135.7, 130.2, 130.3 (q, J = 32.9 Hz, 1C), 129.5, 128.5, 127.7, 126.5, 124.17−123.70 (m, 1C), 123.1, 122.3, 120.9, 125.3 (q, J = 271.3 Hz, 1C), 86.5, 48.4, 41.9, 30.7, 29.5. Orthogonal HPLC purity: 95%, retention time of 11.84 min (HPLC method A); 98%, retention time of 13.12 min (HPLC method B).

1-(5-Chloropyridin-2-yl)-2-phenyl-1-(3-(trifluoromethyl)-phenyl)ethyl 3,3-Dimethylbutanoate, 12c. Ester **12c** was obtained using general procedure A, in 60% yield. LC−MS ESI 476.13 (M + H), retention time of 4.23 min (10−90% MeOH in H_2O with 0.1% TFA in a 4 min gradient). ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.58 (d, J = 2.22 Hz, 1H), 7.60 (dd, J = 2.50, 8.60 Hz, 1H), 7.47−7.53 (m, 3H), 7.39−7.45 (m, 1H), 7.30 (d, J = 8.60 Hz, 1H), 7.08−7.19 (m, 3H), 6.61 (d, J = 7.21 Hz, 2H), 4.35 (d, J = 13.87 Hz, 1H), 4.06 (d, J = 13.59 Hz, 1H), 2.26 (s, 2H), 1.02 (s, 9H). ^{13}C NMR (126 MHz, chloroform-*d*) δ 170.5, 160.3, 147.8, 144.2, 136.3, 135.4, 130.6, 130.2 (s, 2C), 130.85−129.96 (m, J = 33.6, 33.6, 33.6 Hz, 1C), 129.4, 128.6, 127.8 (s, 2C), 126.7, 124.29−124.04 (m, 1C), 123.08−122.83 (m, 1C), 121.8, 86.2, 48.4, 41.9, 30.7, 29.5 (s, 3C). Orthogonal HPLC purity: 92%, retention time of 12.70 min (HPLC method A)[25]

2-Phenyl-1-(pyridin-2-yl)-1-(3-(1,1,2,2-tetrafluoroethoxy)-phenyl)ethyl 3,3-Dimethylbutanoate, 12d. Ester **12d** was obtained using general procedure A, in 27% yield. LC−MS ESI 490.17 (M + H), retention time of 3.38 min (10−90% MeOH in H_2O with 0.1% TFA in a 4 min gradient). ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.59−8.67 (m, 1H), 7.56−7.66 (m, 1H), 7.34 (d, J = 8.05 Hz,

dx.doi.org/10.1021/jm300611v | J. Med. Chem. 2012, 55, 6162−6175

1H), 7.21−7.32 (m, 2H), 7.17 (ddd, J = 0.97, 4.86, 7.49 Hz, 1H), 7.03−7.15 (m, 5H), 6.60−6.68 (m, 2H), 4.39 (d, J = 13.59 Hz, 1H), 4.06 (d, J = 13.87 Hz, 1H), 2.24 (d, J = 1.39 Hz, 2H), 1.00 (s, 9H). ^{13}C NMR (126 MHz, chloroform-d) δ 170.4, 162.2, 148.6, 145.7, 136.6, 135.8, 130.3 (s, 2C), 129.2, 127.7 (s, 2C), 126.5, 124.3, 122.3, 121.0, 120.1, 119.7, 116.4 (tt, J = 271.8, 28.6 Hz, 1C), 107.6 (tt, J = 251.8, 41.0 Hz, 1C), 86.4, 48.4, 42.0, 30.6, 29.5 (s, 3C). Orthogonal HPLC purity: 93%, retention time of 11.7 min (HPLC method A); 95%, retention time of 13.44 min (HPLC method B).

***N*-(2-Phenyl-1-(pyridin-2-yl)-1-(3-(trifluoromethyl)phenyl)-ethyl)benzamide, 13a.** Amide **13a** was obtained using general procedure C, in 31% yield. LC−MS ESI 446.99 (M + H), retention time of 3.89 min (10−90% MeOH in H_2O with 0.1% TFA in a 4 min gradient). ^{1}H NMR (500 MHz, chloroform-d) δ 9.43 (br s, 1H), 8.36−8.40 (m, 1H), 7.76−7.82 (m, 3H), 7.69−7.75 (m, 2H), 7.42−7.56 (m, 5H), 7.18−7.23 (m, 2H), 7.06−7.11 (m, 1H), 6.96−7.02 (m, 2H), 6.57−6.62 (m, 2H), 4.70 (d, J = 12.76 Hz, 1H), 3.71 (d, J = 12.76 Hz, 1H). ^{13}C NMR (126 MHz, chloroform-d) δ 166.4, 160.3, 146.5, 146.0, 137.6, 135.5, 135.1, 131.5, 130.7 (q, J = 31.5 Hz, 1C), 130.2 (m, 3C, two overlapping peaks), 128.9, 128.5, 127.7, 127.0, 126.69−126.46 (m, 1C), 124.17−124.00 (m, 1C), 123.3 (q, J = 3.8 Hz, 1C), 122.9, 122.5, 124.1 (q, J = 270.8 Hz, 1C), 64.0, 41.7. Orthogonal HPLC purity: 94%, retention time of 11.39 min (HPLC method A); 99%, retention time of 12.75 min (HPLC method B).

3,3-Dimethyl-*N*-(2-phenyl-1-(pyridin-2-yl)-1-(3-(trifluoromethyl)phenyl)ethyl)butanamide, 13b. Amide **13b** was obtained using general procedure C, in 55% yield. LC−MS ESI 441.07 (M + H), retention time of 4.00 min (10−90% MeOH in H_2O with 0.1% TFA in a 4 min gradient). ^{1}H NMR (500 MHz, chloroform-d) δ 8.58 (s, 1H), 8.35−8.39 (m, 1H), 7.71 (dt, J = 1.94, 7.77 Hz, 1H), 7.68 (d, J = 7.49 Hz, 1H), 7.59 (s, 1H), 7.49−7.53 (m, 1H), 7.43−7.49 (m, 1H), 7.17−7.24 (m, 2H), 7.10−7.15 (m, 1H), 7.03−7.08 (m, 2H), 6.53−6.58 (m, 2H), 4.46 (d, J = 12.76 Hz, 1H), 3.67 (d, J = 12.76 Hz, 1H), 2.69 (br s, 1H), 2.10−2.21 (m, 2H), 0.97 (s, 9H). ^{13}C NMR (126 MHz, chloroform-d) δ 171.4, 160.4, 146.5, 146.2, 137.6, 135.7, 130.7 (q, J = 31.5 Hz, 1C), 130.2, 130.0, 128.7, 127.7, 126.6, 124.08−123.63 (m, 2C), 122.4, 124.1 (q, J = 271.8 Hz, 1C), 64.0, 50.7, 41.7, 34.9, 31.1, 29.8. Orthogonal HPLC purity: 94%, retention time of 11.49 min (HPLC method A); 95%, retention time of 13.24 min (HPLC method B).

***N*-(2-Phenyl-1-(pyridin-2-yl)-1-(3-(trifluoromethyl)phenyl)-ethyl)-3-(trifluoromethyl)benzamide, 13c.** Amide **13c** was obtained using general procedure C, in 65% yield. LC−MS ESI 515.02 (M + H), retention time of 4.08 min (10−90% MeOH in H_2O with 0.1% TFA in a 4 min gradient). ^{1}H NMR (500 MHz, chloroform-d) δ 9.53 (s, 1H), 8.39−8.44 (m, 1H), 8.06 (s, 1H), 7.92 (d, J = 7.77 Hz, 1H), 7.72−7.84 (m, 4H), 7.54−7.62 (m, 2H), 7.47−7.53 (m, 1H), 7.21−7.27 (m, 2H), 7.10−7.15 (m, 1H), 6.99−7.05 (m, 2H), 6.55−6.61 (m, 2H), 4.70 (d, J = 12.76 Hz, 1H), 3.74 (d, J = 12.76 Hz, 1H). ^{13}C NMR (126 MHz, chloroform-d) δ 165.1, 160.0, 146.4, 145.2, 138.2, 135.7, 135.1, 130.9 (q, J = 32.4 Hz, 1C), 131.2 (q, J = 32.7 Hz, 1C), 130.2, 130.1 (s, 2C, 129.2, 129.1, 128.2 (q, J = 3.8 Hz, 1C), 127.8 (s, 2C), 126.9, 124.58−124.22 (m, J = 3.8, 3.8, 3.8, 3.8 Hz, 1C), 123.4 (q, J = 3.8 Hz, 1C), 123.2, 123.99−122.99 (m, 1C), 122.8, 124.0 (q, J = 272.8 Hz, 1C), 127.09−120.28 (m, 1C), 64.2, 41.9. Orthogonal HPLC purity: 95%, retention time of 11.87 min (HPLC method A); 100%, retention time of 13.47 min (HPLC method B).

4-Fluoro-*N*-(2-phenyl-1-(pyridin-2-yl)-1-(3-(trifluoromethyl)-phenyl)ethyl)benzamide, 13d. Amide **13d** was obtained using general procedure C, in 50% yield. LC−MS ESI 465.01 (M + H), retention time of 3.93 min (10−90% MeOH in H_2O with 0.1% TFA in a 4 min gradient). ^{1}H NMR (500 MHz, chloroform-d) δ 9.40 (s, 1H), 8.34−8.42 (m, 1H), 7.76−7.83 (m, 3H), 7.68−7.75 (m, 2H), 7.51−7.57 (m, 1H), 7.43−7.50 (m, 1H), 7.18−7.24 (m, 2H), 7.06−7.15 (m, 3H), 6.95−7.03 (m, 2H), 6.52−6.61 (m, 2H), 4.68 (d, J = 12.76 Hz, 1H), 3.70 (d, J = 12.76 Hz, 1H). ^{13}C NMR (126 MHz, chloroform-d) δ 165.6, 164.8 (d, J = 252.7 Hz, 1C), 160.1, 146.3, 145.3, 138.1, 135.2, 131.0 (d, J = 2.9 Hz, 1C), 130.8 (q, J = 32.2 Hz, 1C), 130.1, 129.5 (d, J = 8.6 Hz), 129.0, 127.8, 126.7, 124.37−124.16 (m, 1C), 123.4 (q, J = 3.8 Hz), 123.2, 122.7, 124.0 (q, J = 271.8 Hz, 1C), 115.6 (d, J = 21.9 Hz, 2C), 64.1, 41.9. Orthogonal HPLC purity: 97%, retention time of 11.53 min (HPLC method A); 98%, retention time of 12.91 min (HPLC method B).

1-*tert*-Butyl-3-(2-phenyl-1-(pyridin-2-yl)-1-(3-(trifluoromethyl)phenyl)ethyl)urea, 13e. Urea **13e** was obtained using general procedure B, in 81% yield. LC−MS ESI 442.2 (M + H), retention time of 2.3 min (10−90% MeOH in H_2O with 0.1% TFA in a 4 min gradient). ^{1}H NMR (500 MHz, chloroform-d) δ 8.52 (d, J = 4.44 Hz, 1H), 8.11 (t, J = 7.21 Hz, 1H), 7.95 (br s, 1H), 7.81 (br s, 1H), 7.47−7.58 (m, 2H), 7.41 (t, J = 7.91 Hz, 1H), 7.27−7.37 (m, 2H), 7.14−7.21 (m, 1H), 7.06−7.14 (m, 2H), 6.56−6.70 (m, 2H), 4.12 (d, J = 12.21 Hz, 1H), 3.83 (d, J = 11.37 Hz, 1H), 1.27 (s, 9H). ^{13}C NMR (126 MHz, chloroform-d) δ 161.6, 157.0, 144.3, 143.3, 141.5, 134.5, 130.6, 130.8 (q, J = 32.4 Hz, 1C), 130.1, 129.1, 127.9, 127.1, 124.77−124.53 (m, J = 3.8 Hz, 1C), 124.4, 123.6, 123.61−123.50 (m, J = 3.8 Hz, 1C), 123.9 (q, J = 270.8 Hz, 1C), 64.6, 50.6, 43.7, 29.1. Orthogonal HPLC purity: 95%, retention time of 9.79 min (HPLC method A); 97%, retention time of 10.56 min (HPLC method B).

4-Fluoro-*N*-(2-phenyl-1-(pyridin-2-yl)-1-(3-(trifluoromethyl)-phenyl)ethyl)-3-(trifluoromethyl)benzamide, 13f. Amide **13f** was obtained using general procedure C, in 48% yield. LC−MS ESI 533.03 (M + H), retention time of 4.12 min (10−90% MeOH in H_2O with 0.1% TFA in a 4 min gradient). ^{1}H NMR (500 MHz, chloroform-d) δ 9.49 (s, 1H), 8.37−8.42 (m, 1H), 8.06 (dd, J = 1.94, 6.66 Hz, 1H), 7.91 (ddd, J = 2.22, 4.58, 8.46 Hz, 1H), 7.69−7.80 (m, 3H), 7.54−7.58 (m, 1H), 7.46−7.52 (m, 1H), 7.20−7.27 (m, 3H), 7.08−7.13 (m, 1H), 6.97−7.04 (m, 2H), 6.50−6.58 (m, 2H), 4.66 (d, J = 13.04 Hz, 1H), 3.72 (d, J = 12.76 Hz, 1H). ^{13}C NMR (126 MHz, chloroform-d) δ 163.8, 162.83−160.35 (m, J = 261.3, 1.9 Hz, 1C), 160.0, 146.5, 145.6, 137.9, 135.3, 132.6 (d, J = 9.5 Hz, 1C), 131.6 (d, J = 3.8 Hz, 1C), 130.9 (q, J = 32.1 Hz, 1C), 130.1, 130.0 (s, 2C), 129.1, 127.8 (s, 2C), 127.10−126.87 (m, J = 1.9 Hz, 1C), 126.8, 124.48−124.23 (m, 1C), 123.44−123.24 (m, 1C), 123.0, 122.7, 124.0 (q, J = 272.8 Hz, 1C), 122.2 (q, J = 273.2 Hz, 1C), 118.8 (qd, J = 33.4, 13.4 Hz, 1C), 117.1 (d, J = 21.0 Hz, 1C), 64.1, 41.7. Orthogonal HPLC purity: 98%, retention time of 12.00 min (HPLC method A); 100%, retention time of 13.60 min (HPLC method B).

1-Cyclopentyl-3-(2-phenyl-1-(pyridin-2-yl)-1-(3-(trifluoromethyl)phenyl)ethyl)urea, 13g. Urea **13g** was obtained using general procedure B, in 45% yield. LC−MS ESI 454.05 (M + H), retention time of 1.9 min (10−90% MeOH in H_2O with 0.1% TFA in a 4 min gradient). ^{1}H NMR (500 MHz, chloroform-d) δ 8.27−8.30 (m, J = 0.96, 0.96, 0.96, 4.89 Hz, 1H), 7.73 (s, 1H), 7.70 (d, J = 7.77 Hz, 1H), 7.64 (dt, J = 1.66, 7.77 Hz, 1H), 7.47−7.51 (m, 1H), 7.42−7.47 (m, 1H), 7.38 (br s, 1H), 7.09−7.16 (m, 3H), 7.02−7.07 (m, 2H), 6.58−6.62 (m, 2H), 4.53 (d, J = 12.48 Hz, 1H), 3.94 (br s, 1H), 3.60 (d, J = 12.76 Hz, 1H), 1.98−2.06 (m, 1H), 1.82−1.91 (m, 1H), 1.51−1.70 (m, 4H), 1.43 (dd, J = 6.38, 12.76 Hz, 1H), 1.25−1.31 (m, 1H). ^{13}C NMR (126 MHz, chloroform-d) δ 160.7, 157.6, 145.5, 145.2, 139.1, 135.0, 130.7 (q, J = 32.0 Hz, 1C), 130.3, 127.7, 126.8, 124.3 (q, J = 3.6 Hz, 1C), 123.4 (q, J = 3.8 Hz, 1C), 123.9 (q, J = 273.0 Hz, 1C), 122.9, 64.0, 52.6, 43.0, 33.1, 32.9, 23.6, 23.5. Orthogonal HPLC purity: 97%, retention time of 9.95 min (HPLC method A); 98%, retention time of 10.77 min (HPLC method B).

1-Cyclopentyl-3-(1-(5-fluoropyridin-2-yl)-2-phenyl-1-(3-(trifluoromethyl)phenyl)ethyl)urea, 14a. Urea **14a** was obtained using general procedure B, in 25% yield. LC−MS ESI 472.20 (M + H), retention time of 3.38 min (10−90% MeOH in H_2O with 0.1% TFA in a 4 min gradient). ^{1}H NMR (500 MHz, chloroform-d) δ 8.15 (d, J = 2.77 Hz, 1H), 7.66−7.74 (m, 2H), 7.49−7.54 (m, 1H), 7.43−7.49 (m, 1H), 7.35−7.42 (m, 1H), 7.05−7.17 (m, 5H), 6.58−6.65 (m, 2H), 4.53 (d, J = 12.48 Hz, 1H), 4.37 (d, J = 6.66 Hz, 1H), 3.88−3.99 (m, 1H), 3.58 (d, J = 12.48 Hz, 1H), 1.96−2.07 (m, 1H), 1.82−1.92 (m, 1H), 1.51−1.73 (m, 4H), 1.37−1.48 (m, 1H), 1.23−1.33 (m, 1H). ^{13}C NMR (126 MHz, chloroform-d) δ 157.33−157.25 (m, 1C), 158.3 (d, J = 261.3 Hz, 1C), 155.9, 147.4, 136.1, 134.4 (d, J = 23.8 Hz, 1C), 130.7 (q, J = 31.5 Hz, 1C), 130.3 (s, 2C), 130.1, 128.8, 127.6 (s, 2C), 126.4, 124.2 (d, J = 19.1 Hz, 1C), 123.9 (q, J = 3.8 Hz, 1C), 123.8 (d, J = 4.8 Hz, 1C), 123.4 (q, J = 3.8 Hz, 1C), 124.2 (q, J = 271.8 Hz, 1C), 63.4,

dx.doi.org/10.1021/jm300611v | J. Med. Chem. 2012, 55, 6162−6175

52.2, 42.8, 33.8, 33.3, 23.6 (s, 2C). Orthogonal HPLC purity: 84%, retention time of 11.11 min (HPLC method A); 97%, retention time of 12.45 min (HPLC method B).

1-(1-(5-Chloropyridin-2-yl)-2-phenyl-1-(3-(trifluoromethyl)-phenyl)ethyl)-3-cyclopentylurea, 14b. Urea **14b** was obtained using general procedure B, in 34% yield. LC−MS ESI 488.30 (M + H), retention time of 3.32 min (10−90% MeOH in H_2O with 0.1% TFA in a 4 min gradient). ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.26 (dd, *J* = 2.5, 0.6 Hz, 1H), 7.76−7.66 (m, 2H), 7.63 (dd, *J* = 8.6, 2.5 Hz, 1H), 7.55−7.50 (m, 1H), 7.49−7.43 (m, 1H), 7.19−7.02 (m, 5H), 6.67−6.60 (m, 2H), 4.54 (d, *J* = 12.8 Hz, 1H), 4.27 (d, *J* = 6.9 Hz, 1H), 3.99−3.89 (m, *J* = 6.7, 6.7, 6.7, 6.7, 6.7 Hz, 1H), 3.58 (d, *J* = 12.5 Hz, 1H), 2.08−1.97 (m, 1H), 1.93−1.83 (m, 1H), 1.74−1.56 (m, 4H), 1.48−1.38 (m, 1H), 1.34−1.23 (m, 1H). ^{13}C NMR (126 MHz, chloroform-*d*) δ 159.6, 155.9, 147.3, 145.4, 136.8, 136.0, 130.6, 130.8 (q, *J* = 32.4 Hz, 1C), 130.4 (s, 2C), 130.1, 128.9, 127.7 (s, 2C), 126.5, 124.09−123.88 (m, 1C), 123.7, 123.50−123.29 (m, *J* = 3.8 Hz, 1C), 124.2 (q, *J* = 271.8 Hz, 1C), 63.5, 52.2, 42.7, 33.8, 33.3, 23.6 (s, 2C). Orthogonal HPLC purity: 97%, retention time of 11.55 min (HPLC method A); 97%, retention time of 13.00 min (HPLC method B).

1-(1-(5-Chloropyridin-2-yl)-1-(3-fluoro-5-(trifluoromethyl)-phenyl)-2-phenylethyl)-3-cyclopentylureas 14c, 14d, and 14e. Urea **14c** was obtained using general procedure B, in 40% yield. The precursor amine was resolved by chiral SFC and acylated according to procedure B to obtain (*R*)-1-(1-(5-chloropyridin-2-yl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)-3-cyclopentylurea **14d** (SFC conditions, chiral OJ column, 5% methanol, 2 mL/min, 35 °C, 100 bar, t_R = 5.42 min) as the faster eluting enantiomer and (*S*)-1-(1-(5-chloropyridin-2-yl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)-3-cyclopentylurea **14e** (SFC conditions, chiral OJ column, 5% methanol, 2 mL/min, 35 °C, 100 bar, t_R = 7.60 min) as the slower eluting enantiomer. Data for urea **14e**: LC−MS ESI 506.06 (M + H), retention time of 3.59 min (10−90% MeOH in H_2O with 0.1% TFA in a 4 min gradient). ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.27 (d, *J* = 2.2 Hz, 1H), 7.66 (dd, *J* = 8.6, 2.5 Hz, 1H), 7.55 (s, 1H), 7.39 (d, *J* = 9.7 Hz, 1H), 7.22 (d, *J* = 8.0 Hz, 1H), 7.19−7.13 (m, 1H), 7.12−7.02 (m, 4H), 6.63 (d, *J* = 7.2 Hz, 2H), 4.51 (d, *J* = 12.5 Hz, 1H), 4.36 (d, *J* = 6.9 Hz, 1H), 3.99−3.88 (m, *J* = 6.5, 6.5, 6.5, 6.5, 6.5 Hz, 1H), 3.55 (d, *J* = 12.8 Hz, 1H), 2.09−1.97 (m, 1H), 1.94−1.83 (m, 1H), 1.72−1.54 (m, 4H), 1.50−1.39 (m, 1H), 1.35−1.24 (m, *J* = 13.6, 6.6, 6.6, 6.6 Hz, 1H). ^{13}C NMR (126 MHz, chloroform-*d*) δ 162.6 (d, *J* = 248.0 Hz, 1C), 158.9, 155.8, 150.5, 150.4, 145.6, 137.0, 135.6, 132.4 (qd, *J* = 32.4, 7.6 Hz, 1C), 130.9, 130.3 (s, 2C), 127.8 (s, 2C), 123.57−123.33 (m, 1C), 127.13−119.80 (m, *J* = 273.7, 273.7, 273.7, 2.9 Hz, 1C), 119.15−118.99 (m, 1C), 117.5 (d, *J* = 21.9 Hz, 1C), 111.5 (dq, *J* = 24.8, 3.8 Hz, 1C), 63.4, 52.2, 42.6, 33.8, 33.3, 23.6 (s, 2C). Orthogonal HPLC purity: 97%, retention time of 11.72 min (HPLC method A); 98%, retention time of 13.30 min (HPLC method B).

(*S*)-1-(1-(5-Cyanopyridin-2-yl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)-3-cyclopentylurea, 14f. 1-(1-(5-Bromopyridin-2-yl)-1-(3-fluoro-5-(trifluoromethyl)-phenyl)-2-phenylethyl)-3-cyclopentylurea was obtained by using general procedure B. This bromide (100 mg, 0.18 mmol), $K_4Fe(CN)_6$ (45 mg, 0.107 mmol), $Pd(OAc)_2$ (catalytic amount, spatula tip), and Na_2CO_3 (31 mg, 0.29 mmol) were stirred in DMAC (0.4 mL) at room temperature. The reaction mixture was degassed several times and was stirred and heated at 120 °C for 6 h. After the mixture was cooled, EtOAc was added. The mixture was filtered through Celite, washed with H_2O, 5% NH_4OH, dried over $MgSO_4$, filtered, and concentrated to dryness. The residue was purified by by flash chromatography (silica gel, hexanes/EtOAc, came out 50% EtOAc) and was then further purified by RP HPLC (20−100% CH_3CN in H_2O with 0.1 TFA in a 18 min run, came out at 13.38−13.88 min) to give pure racemic mixture of the titled compound as white solids (16 mg, yield 18%). LC−MS ESI 494.9 (M-H), retention time of 3.93 min (10−90% MeOH in H_2O with 10 mM NH_4Cl in a 4 min run). The racemates were separated by chiral preparative HPLC using AD column (20% iPA/heptane/DEA, isocratic) to give (*R*)-1-(1-(5-cyanopyridin-2-yl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)-3-cyclopentylurea as the fast eluting enantiomer (analytical chiral HPLC AD (25% iPA/heptane/DEA, isocratic), retention time of 5.30 min) and (*S*)-1-(1-(5-cyanopyridin-2-yl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)-3-cyclopentylurea **14f** as the slow eluting enantiomer: analytical chiral HPLC AD (25% iPA/heptane/DEA, isocratic), retention time of 9.72 min. Data for the *S*-isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.62 (d, *J* = 1.4 Hz, 1H), 7.96 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.55 (s, 1H), 7.40 (d, *J* = 9.6 Hz, 1H), 7.31 (d, *J* = 8.3 Hz, 1H), 7.29 (s, 1H), 7.26 (d, *J* = 8.0 Hz, 1H), 7.19 (t, *J* = 7.4 Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 2H), 6.99 (br s, 1H), 6.60 (d, *J* = 7.2 Hz, 2H), 4.55 (d, *J* = 12.8 Hz, 2H), 3.95 (br s, 1H), 3.59 (d, *J* = 12.8 Hz, 1H), 2.19−2.00 (m, 1H), 1.91 (td, *J* = 12.8, 6.8 Hz, 1H), 1.82−1.65 (m, 2H), 1.65−1.55 (m, 2H), 1.55−1.39 (m, 1H), 1.33 (dt, *J* = 20.3, 6.5 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.01, 162.87 (d, *J* = 249.3 Hz, 1C), 155.99, 150.18, 149.62 (d, *J* = 6.7 Hz), 140.10, 135.24, 130.37, 128.16, 127.14, 123.43 (d, *J* = 275.5 Hz, 1C), 123.17, 119.32 (m, 1C), 117.84 (d, *J* = 22.6 Hz, 1C), 116.27, 112.21 (dd, *J* = 24.6, 3.7 Hz, 1C), 108.94, 64.36, 52.51, 42.92, 34.00, 33.52, 23.78. ^{19}F NMR (471 MHz, $CDCl_3$) δ −62.54, −109.77. Orthogonal HPLC purity: 97.7%, retention time of 13.386 min (method A); 100.0%, retention time of 12.376 min (method B). HRMS $(M + H)^+$ calcd for $C_{27}H_{25}F_4N_4O$ 497.1959, found 497.1946.

(*R*)-1-Cyclopentyl-3-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(5-fluoropyridin-2-yl)-2-phenylethyl)urea, 14g. Urea **14g** was obtained using general procedure B, in 55% yield. LC−MS ESI 490.55 (M + H), retention time of 3.97 min (10−90% MeOH in H_2O with 0.1% TFA in a 4 min gradient). ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.16 (d, *J* = 2.77 Hz, 1H), 7.55 (s, 1H), 7.36−7.46 (m, 2H), 7.22 (d, *J* = 8.32 Hz, 1H), 7.06−7.18 (m, 5H), 6.56−6.65 (m, 2H), 4.51 (d, *J* = 12.48 Hz, 1H), 4.32 (d, *J* = 6.94 Hz, 1H), 3.90−4.00 (m, *J* = 6.50, 6.50, 6.50, 6.50, 6.50 Hz, 1H), 3.54 (d, *J* = 12.48 Hz, 1H), 1.98−2.10 (m, 1H), 1.84−1.95 (m, 1H), 1.53−1.74 (m, 4H), 1.40−1.50 (m, 1H), 1.27−1.34 (m, 1H). ^{13}C NMR (126 MHz, chloroform-*d*) δ 162.6 (d, *J* = 248.9 Hz, 1C), 158.5 (d, *J* = 256.5 Hz, 1C), 156.6 (d, *J* = 2.9 Hz, 1C), 155.8, 150.7 (d, *J* = 7.6 Hz, 1C), 135.7, 134.6 (d, *J* = 23.8 Hz, 1C), 132.4 (qd, *J* = 32.4, 7.6 Hz, 1C), 130.3 (s, 2C), 127.8 (s, 2C), 126.6, 124.5 (d, *J* = 19.1 Hz, 1C), 123.7 (d, *J* = 4.8 Hz, 1C), 126.76−119.76 (m, *J* = 275.6, 275.6, 275.6, 3.8 Hz, 1C), 119.26−119.04 (m, *J* = 2.9 Hz, 1C), 117.6 (d, *J* = 21.9 Hz, 1C), 111.76−111.25 (m, 1C), 63.3, 52.3, 42.8, 33.9, 33.4, 23.6 (s, 2C). Orthogonal HPLC purity: 98%, retention time of 11.22 min (HPLC method A); 96%, retention time of 12.63 min (HPLC method B).

1-(1-(6-Chloropyridin-3-yl)-1-(3-fluoro-5-(trifluoromethyl)-phenyl)-2-phenylethyl)-3-cyclopentylurea, 14h. Urea **14h** was obtained using general procedure B, in 91% yield. LC−MS ESI 506.1(M + H), retention time of 2.25 min (MeOH/H_2O/TFA, Phenomenex Luna C18, 50 mm × 4.6 mm, 2 min gradient). ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.33−8.22 (d, *J* = 2.7 Hz, 1H), 7.78−7.65 (dd, *J* = 8.5, 2.7 Hz, 1H), 7.61−7.50 (d, *J* = 8.3 Hz, 1H), 7.46−7.45 (m, 1H), 7.45−7.42 (dd, *J* = 8.4, 0.6 Hz, 2H), 7.19−7.07 (qd, *J* = 5.2, 1.8 Hz, 3H), 6.76−6.66 (dd, *J* = 7.4, 2.0 Hz, 2H), 6.47−6.39 (d, *J* = 7.1 Hz, 1H), 3.96−3.86 (m, 2H), 3.84−3.69 (dq, *J* = 12.9, 6.7 Hz, 1H), 1.83−1.66 (m, 2H), 1.66−1.56 (td, *J* = 7.3, 3.1 Hz, 2H), 1.55−1.41 (m, 2H), 1.39−1.21 (dt, *J* = 11.6, 5.3 Hz, 2H). ^{13}C NMR (126 MHz, DMSO) δ 161.73 (d, *J* = 245.8 Hz), 156.84, 148.37, 148.26, 140.37, 138.28, 136.11, 130.63, 131.10−130.04 (m), 127.59, 126.44, 123.48, 123.30 (d, *J* = 272.5 Hz), 119.39, 118.46, 118.29, 111.07 (d, *J* = 25.6 Hz), 62.56, 59.78, 50.81, 42.39, 32.95, 32.80, 23.07, 20.78, 14.10. Orthogonal HPLC purity: 94%, retention time of 12.09 min (HPLC method A); 94%, retention time of 10.62 min (HPLC method B).

(*S*)-1-Cyclopentyl-3-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(6-methoxypyridin-3-yl)-2-phenylethyl)urea, 14i. By use of general procedure B, 1-cyclopentyl-3-(1-(3-fluoro-5-(trifluoromethyl)-phenyl)-1-(6-methoxypyridin-3-yl)-2-phenylethyl)urea (62 mg, 62%) was obtained as white solids from 1-(3-fluoro-5-(trifluoromethyl)-phenyl)-1-(6-methoxypyridin-3-yl)-2-phenylethanamine[15] (75 mg) and cyclopentyl isocyanate (0.075 mL). The racemic compound (50 mg) was separated by chiral HPLC using chiral AD column, eluting with 20% IPA/heptane/0.1%DEA to give (*R*)-1-cyclopentyl-3-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(6-methoxypyridin-3-yl)-2-phenylethyl)urea (26 mg, white solids) as the faster eluting

dx.doi.org/10.1021/jm300611v | *J. Med. Chem.* 2012, 55, 6162−6175

enantiomer (analytical chiral AD, 10% isopropanol/heptane/0.1% DEA, retention time of 4.60 min) and (*S*)-1-cyclopentyl-3-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(6-methoxypyridin-3-yl)-2-phenylethyl)urea **14j** (18 mg, white solids) as the slower eluting enantiomer (analytical chiral AD, 10%isopropanol/heptane/0.1%DEA, retention time of 7.68 min). Data for the *S*-isomer: LC−MS ESI 502.18 (M + H), retention time of 3.99 min (10−90% MeOH in H_2O with 0.1% TFA in a 4 min run). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.89 (d, *J* = 2.6 Hz, 1H), 7.30 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.24 (s, 1H), 7.22−7.04 (m, 5H), 6.64 (m, 3H), 4.99 (s, 1H), 4.44 (br s, 1H), 3.86 (s, 3H), 3.81 (d, *J* = 12.9 Hz, 1H), 3.77 (m, 1H), 3.66 (d, *J* = 13.0 Hz, 1H), 1.79 (m, 2H), 1.61−1.33 (m, 4H), 1.22 (m, 2H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 163.81, 162.58 (d, *J* = 250 Hz), 156.62, 149.45, 144.71, 138.76, 135.33, 132.85, 132.38 (qd, *J* = 33, 8 Hz, 1C), 131.06, 128.25, 127.34, 123.42 (q, *J* = 274 Hz, 1C), 119.60, 118.20 (d, *J* = 23 Hz, 1C), 111.77 (d, *J* = 26 Hz, 1C), 110.64, 63.02, 54.20, 52.39, 45.04, 33.69, 33.64, 23.69. ^{19}F NMR (376 MHz, chloroform-*d*) δ −62.46, −109.84, −109.87. Orthogonal HPLC purity: 97.2%, retention time of 12.481 min (method A); 96.4%, retention time of 11.166 min (method B). HRMS (M + H)$^+$ calcd for $C_{27}H_{28}F_4N_3O_2$ 502.2112, found 502.2100.

1-(1-(5-Chloropyridin-2-yl)-2-phenyl-1-(3-(trifluoromethoxy)phenyl)ethyl)-3-cyclopentylurea, 15a. Urea **15a** was obtained using general procedure B, in 57% yield. LC−MS ESI 504.07 (M + H), retention time of 3.59 min (10−90% MeOH in H_2O with 0.1% TFA in a 4 min gradient). ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.26 (d, *J* = 1.94 Hz, 1H), 7.63 (dd, *J* = 2.50, 8.60 Hz, 1H), 7.42−7.48 (m, 1H), 7.37 (t, *J* = 8.05 Hz, 1H), 7.29 (s, 1H), 7.07−7.18 (m, 5H), 7.04 (br s, 1H), 6.61−6.68 (m, 2H), 4.49 (d, *J* = 12.76 Hz, 1H), 4.31 (d, *J* = 5.55 Hz, 1H), 3.88−4.00 (m, 1H), 3.55 (d, *J* = 12.76 Hz, 1H), 1.96−2.07 (m, 1H), 1.82−1.93 (m, 1H), 1.52−1.71 (m, 4H), 1.37−1.47 (m, 1H), 1.23−1.35 (m, 1H). ^{13}C NMR (126 MHz, chloroform-*d*) δ 159.7, 155.9, 149.4, 148.6, 145.4, 136.8, 136.0, 130.5, 130.3 (s, 2C), 129.7, 127.7 (s, 2C), 126.5, 124.9, 123.6, 119.5, 119.2, 120.4 (q, *J* = 256.5 Hz, 1C), 63.4, 52.2, 42.7, 33.8, 33.3, 23.6 (s, 2C). Orthogonal HPLC purity: 98%, retention time of 11.65 min (HPLC method A); 91%, retention time of 13.17 min (HPLC method B).

1-(1-(5-Chloropyridin-2-yl)-2-phenyl-1-(3-(1,1,2,2-tetrafluoroethoxy)phenyl)ethyl)-3-cyclopentylurea, 15b. Urea **15b** was obtained using general procedure B, in 21% yield. LC−MS ESI 536.09 (M + H), retention time of 4.00 min (10−90% MeOH in H_2O with 0.1% TFA in a 4 min gradient). ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.26 (d, *J* = 2.22 Hz, 1H), 7.62 (dd, *J* = 2.50, 8.60 Hz, 1H), 7.41 (d, *J* = 8.05 Hz, 1H), 7.34 (t, *J* = 7.91 Hz, 1H), 7.29 (s, 1H), 7.02−7.18 (m, 6H), 6.66 (d, *J* = 7.21 Hz, 2H), 5.88 (tt, *J* = 2.20, 53.00 Hz, 1H), 4.39−4.54 (m, 2H), 3.87−4.01 (m, 1H), 3.58 (d, *J* = 12.76 Hz, 1H), 1.94−2.04 (m, 1H), 1.82−1.92 (m, 1H), 1.50−1.70 (m, 4H), 1.35−1.45 (m, 1H), 1.23−1.33 (m, 1H). ^{13}C NMR (126 MHz, chloroform-*d*) δ 159.7, 156.0, 149.0, 148.3, 145.3, 136.7, 136.1, 130.4, 130.3 (s, 2C), 129.5, 127.6 (s, 2C), 126.4, 124.6, 123.5, 120.0, 119.8, 118.91−113.71 (m, *J* = 271.8, 271.8, 27.7, 27.7 Hz, 1C), 107.6 (tt, *J* = 252.7, 42.0 Hz, 1C), 63.5, 52.1, 42.7, 33.7, 33.3, 23.5, 23.5. Orthogonal HPLC purity: 95%, retention time of 11.55 min (HPLC method A); 95%, retention time of 12.77 min (HPLC method B).

(*R*)-1-(1-(5-Chloropyridin-2-yl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-cyclopentylurea, 15c, and (*S*)-1-(1-(5-Chloropyridin-2-yl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-cyclopentylurea, 15d. A solution of 1-bromo-3,5-difluorobenzene (20.0 g, 104 mmol) was cooled in a water bath, and 2-(methylsulfonyl)ethanol (26.0 g, 207 mmol) in DMSO (100 mL) was added. KO^{t}Bu (29.0 g, 260 mmol) was added to this reaction mixture in portions. The reaction mixture turned dark. After the addition was complete, the water bath was removed and the mixture was stirred at room temperature for 1 h. The pH was adjusted to 1 using 1 N HCl, and extraction was with ether (3 × 200 mL). The combined organic portions were washed with aqueous 1 N NaOH (2 × 200 mL). The NaOH layer was acidified to pH 1 and extracted with ether (3 × 200 mL). The combined organic layers were dried over sodium sulfate and filtered. The filtrate was concentrated and used directly in the next step without further purification. To a solution of 3-bromo-5-fluorophenol (104 mmol crude) and iodo-1,1,2,2,-tetrafluoroethane (28.4 g, 125 mmol) in DMSO (80 mL) was added K_2CO_3 (57.0 g, 420 mmol). The reaction mixture was sealed in a thick walled glass pressure round-bottom flask and heated at 70 °C for 18 h. The reaction mixture was allowed to cool to room temperature, diluted with water (500 mL), and extracted with ether (3 × 200 mL). The combined ether layers were washed with 1 N NaOH (2 × 200 mL), water (2 × 200 mL), and brine (200 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated. The residue was dissolved in ether (150 mL) and filtered through a plug of activated basic alumina. The filtrate was concentrated to give 1-bromo-3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)benzene as a pale yellow oil (27.2 g, 88% for two steps) which was used without further purification. HPLC: 3.76 min (4 min gradient, MeOH/H_2O 0.2% polyphosphoric acid), purity 100%. By use of this aryl bromide urea, **15c** and **15d** were obtained employing general procedure B, in 94% yield. The penultimate primary amine was resolved by chiral SFC, and the faster eluting antipode was used in the final acylation to obtain urea **15c**, while the slower eluting antipode was used to obtain urea **15d** (analytical Chiralpak AD 10 μm, 4.6 mm × 250 mm column, 5% MeOH/95% carbobdioxide/0.1% diethylamine, 0.5 mL/min, retention time of 10.36 and 11.23 min). Data for urea **15d**: LC−MS ESI 554.28 (M + H), retention time of 4.09 min (10−90% MeOH in H_2O with 0.1% TFA in a 4 min gradient). ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.26 (d, *J* = 1.92 Hz, 1H), 7.66 (d, *J* = 6.41 Hz, 1H), 7.00−7.22 (m, 7H), 6.88 (d, *J* = 7.90 Hz, 1H), 6.63 (br s, 2H), 5.74−6.03 (m, 1H), 3.83−4.66 (m, 3H), 3.51 (br s, 1H), 2.05 (br s, 1H), 1.90 (br s, 1H), 1.69 (br s, 4H), 1.28−1.49 (m, 2H). ^{13}C NMR (126 MHz, chloroform-*d*) δ 162.8 (d, *J* = 248.0 Hz, 1C), 158.4, 157.2, 149.74−149.07 (m, 1C), 145.5, 137.2, 135.2, 131.0, 130.1 (s, 2C), 127.9 (s, 2C), 126.8, 123.4, 115.67−115.36 (m, 1C), 119.55−113.31 (m, 1C), 112.0 (d, *J* = 23.7 Hz, 1C), 108.60−107.96 (m, 1C), 107.35−107.27 (m, 1C), 107.5 (tt, *J* = 252.5, 41.2 Hz, 1C), 63.4, 52.6, 42.6, 33.3, 32.9, 23.6, 23.6. Orthogonal HPLC purity: 94%, retention time of 11.69 min (HPLC method A); 97%, retention time of 13.04 min (HPLC method B).

(*S*)-1-(1-(5-Chloropyridin-2-yl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-(1*H*-1,2,4-triazol-5-yl)ethyl)-3-cyclopentylurea, 18a. Compound **17** (41 mg, 0.096 mmol) was dissolved in MeOH (1 mL), and HCl (4.0 M in dioxanes, 1.5 mL) was added. The solution was diluted with DCM, washed with saturated $NaHCO_3$, dried, and concentrated under reduced pressure to yield a white residue that was taken on directly to the cyclopentylurea as described for compound **18b**. Intermediate **19** was isolated in 36% yield by preparative HPLC (retention time of 3.75 min, purity 96%). LC−MS: [M + 1] 473.2. Compound **19** (10 mg, 0.021 mmol) was dissolved in DMF−DMA (0.5 mL) and the solution stirred at room temperature for 1.5 h. The solvents were removed under reduced pressure, and the residue was azeotroped with hexanes (10 mL). The resulting oil was dissolved in AcOH (0.5 mL) and hydrazine hydrate added (30 mg). The reaction mixture was heated to 55 °C for 30 min and allowed to cool. MeOH was added and the solution filtered. The filtrate was purified by preparative HPLC, yielding compound **18a** as a colorless oil (2.1 mg, 21% yield). ^{1}H NMR (400 MHz,) δ 8.44 (d, *J* = 2.0 Hz, 1H), 8.19 (s, 1H), 7.70 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.39 (s, 1H), 7.28 (m, 1H), 7.24 (s, 1H), 7.22 (s, 1H), 4.59 (d, *J* = 14.8 Hz, 1H), 4.33 (d, *J* = 14.4 Hz, 1H), 1.89 (m, 2H), 1.62 (m, 4H), 1.38 (m, 2H). LCMS: [M + 1] 497.2. HPLC: method C, purity 90% retention time 3.69 min.

(*S*)-1-(1-(5-Chloropyridin-2-yl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-(pyridin-2-yl)ethyl)-3-cyclopentylurea, 18b. To a solution of (*S*)-1-(5-chloropyridin-2-yl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-(pyridin-2-yl)ethanamine[15] (15 mg, 0.029 mmol) in DCE (0.5 mL) were added 4 N HCl (0.5 mL), MeOH (0.5 mL), cyclopentyl isocyanate (17 μL, 0.15 mmol), and citric acid (1 mg, catalytic). The reaction mixture was stirred at room temperature for 18 h, then concentrated to a volume of 0.5 mL under reduced pressure and the residue applied to a preparative silica gel TLC plate (1 mm thickness, 25 mm × 25 mm). Elution was with

dx.doi.org/10.1021/jm300611v | *J. Med. Chem.* 2012, 55, 6162−6175

hexane/EtOAc, 1:1. Compound **18b**, R_f = 0.3, was isolated from the silica as a white solid (9.5 mg, 65% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 8.38 (s, 1H), 8.23 (s, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.65 (m, 2H), 7.54 (d, J = 11.2 Hz, 2H), 7.34 (s, 2H), 7.16 (s, 1H), 7.08 (d, J = 6.5 Hz, 1H), 4.40 (d, J = 12.7 Hz, 1H), 3.99 (d, J = 13.3 Hz, 1H), 3.94 (s, 1H), 2.03−1.81 (m, 2H), 1.73 (s, 2H), 1.61 (s, 2H), 1.54−1.28 (m, 2H). ^{19}F NMR (376 MHz, CD_3OD) δ −60.56, −109.00. ^{13}C NMR (101 MHz, CD_3OD) δ 165.21, 162.76, 160.18, 158.82, 158.10, 151.97, 149.32, 146.77, 138.03, 137.54, 131.86, 126.80, 125.30, 123.09, 120.35 (m), 118.86, 118.75 (d, J = 22.9 Hz), 111.95 (dd, J = 24.9, 3.5 Hz), 65.13, 52.80, 46.09, 34.39, 34.39, 34.09, 24.54, 24.51. LC−MS: [M + 1] 507.1. HPLC: method A, purity 97% retention time of 6.65 min; method B, purity 99%, retention time of 7.29 min. HRMS (ESI) calcd for $C_{25}H_{24}N_4ClF_4O$ $(M + H)^+$ = 507.156 926, found 507.156 42.

(*S*)-Methyl 3-Amino-3-(5-chloropyridin-2-yl)-3-(3-fluoro-5-(trifluoromethyl)phenyl)propanoate, 18c. Compound **18c** was prepared from (*S*)-methyl 3-amino-3-(5-chloropyridin-2-yl)-3-(3-fluoro-5-(trifluoromethyl)phenyl)propanoate[15] using the procedure described for compound **18b** as a white solid in 70% isolated yield. R_f = 0.3, hexanes/EtOAc, 4:1. ^{1}H NMR (400 MHz, CD_3OD) δ 8.51 (d, J = 2.4 Hz, 1H), 7.74 (dd, J = 8.7, 2.5 Hz, 1H), 7.59 (s, 1H), 7.51 (s, 1H), 7.45 (d, J = 10.1 Hz, 1H), 7.38 (d, J = 8.6 Hz, 1H), 7.27 (d, J = 8.4 Hz, 1H), 6.74 (s, 1H), 4.06 (dd, J = 14.9, 2.0 Hz, 1H), 3.87 (m, 1H), 3.80 (d, J = 14.9 Hz, 1H), 3.51 (s, 3H), 1.85 (m, 2H), 1.70 (m, 2H), 1.56 (m, 2H), 1.40 (m, 2H). ^{19}F NMR (376 MHz, CD_3OD) δ −64.39, −112.25. ^{13}C NMR (101 MHz, MeOD) δ 172.21, 160.65, 158.89, 147.51, 138.28, 132.07, 131.90, 123.89, 119.73 (m), 118.05 (d, J = 33.9 Hz), 117.88, 63.30, 52.79, 52.06, 42.40, 34.25, 24.60. LCMS: [M + 1] 488.2. HPLC: method A, purity 97% retention time of 10.13 min; method B, purity 96%, retention time of 9.04 min. HRMS (ESI) calcd for $C_{22}H_{23}N_3ClF_4O_3$ $(M + H)^+$ = 488.135 856, found 488.135 51.

(*S*)-1-(1-(5-Chloropyridin-2-yl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-(4-methylthiazol-2-yl)ethyl)-3-cyclopentylurea, 18d. Compound **18d** was prepared from (*S*)-1-(5-chloropyridin-2-yl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-(4-methylthiazol-2-yl)ethanamine[15] using the procedure described for compound **18b** as a white solid in 70% isolated yield. R_f = 0.5, hexanes/EtOAc, 1:1. ^{1}H NMR (400 MHz, CD_3OD) δ 8.44 (s, 1H), 7.76 (dd, J = 8.6, 1.4 Hz, 1H), 7.52 (s, 2H), 7.49−7.44 (m, 1H), 7.39 (d, J = 8.7 Hz, 1H), 7.31 (d, J = 7.9 Hz, 1H), 6.91 (s, 1H), 4.68 (d, J = 13.6 Hz, 1H), 4.35 (d, J = 14.2 Hz, 1H), 3.98−3.78 (m, 1H), 2.24 (s, 3H), 1.88 (m, 2H), 1.71 (m, 2H), 1.58 (m, 2H), 1.48 (m, 1H), 1.39 (m, 1H). ^{19}F NMR (376 MHz, CD_3OD) δ −64.40, −112.19. ^{13}C NMR (101 MHz, CD_3OD) δ 166.41, 159.77, 152.46, 147.30, 138.29, 132.22 (m), 124.66, 120.13, 115.76, 64.48, 53.05, 40.37, 34.48, 33.74, 24.64, 15.95. LC−MS: [M + 1] 527.2. HPLC: method A, purity 99% retention time of 9.40 min; method B, purity 96%, retention time of 8.65 min. HRMS (ESI) calcd for $C_{25}H_{24}N_4ClF_4OS$ $(M + H)^+$ = 527.128 996, found 527.128 55.

(1-(5-Chloropyridin-2-yl)-1-(3-fluoro-5-(trifluoromethyl)-phenyl)-2-(5-methyl-1,2,4-oxadiazol-3-yl)ethyl)-3-cyclopentylurea, 18e. To a solution of acetonitrile (150 mg, 3.7 mmol) in ether (10 mL) at −78 °C under argon was added LDA (2.0 M in cyclohexane, 1.8 mL, 3.7 mmol). The yellow solution was stirred for 20 min. In a separate flask at 0 °C under argon, (*S*,*E*)-*N*-((5-chloropyridin-2-yl)(3-fluoro-5-(trifluoromethyl)phenyl)methylene)-2-methylpropane-2-sulfinamide[15] (0.75 g, 1.8 mmol) was dissolved in ether (2 mL), and $BF_3{\cdot}Et_2O$ (0.26 mg, 1.8 mmol) was added. This solution was taken up via syringe and added to a solution of acetonitrile pretreated with LDA. After 30 min, 1.0 M HCl (5 mL) was added to the solution at −78 °C and the reaction mixture allowed to reach room temperature, transferred to a separatory funnel, and extracted with EtOAc. The combined extracts were dried over Na_2SO_4, decanted, and concentrated, and the diastereomers were separated by ISCO chromatography, 120 g from elution with hexane/EtOAc, 1:1. (*S*)-*N*-((*R*)-1-(5-Chloropyridin-2-yl)-2-cyano-1-(3-fluoro-5-(trifluoromethyl)phenyl)ethyl)-2-methylpropane-2-sulfinamide was isolated as the major diastereomer (230 mg), R_f = 0.8 (hexane/EtOAc, 1:1). (*S*)-*N*-((*S*)-1-(5-Chloropyridin-2-yl)-2-cyano-1-(3-fluoro-5-(trifluoromethyl)phenyl)ethyl)-2-methylpropane-2-sulfinamide was isolated as the minor diastereomer (88 mg), R_f = 0.6 (hexane/EtOAc, 1:1). Analytical data for (*S*)-*N*-((*S*)-1-(5-chloropyridin-2-yl)-2-cyano-1-(3-fluoro-5-(trifluoromethyl)phenyl)ethyl)-2-methylpropane-2-sulfinamide: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, J = 2.6 Hz, 1H), 7.73 (dd J = 8.8 Hz and J = 2.6 Hz, 1H), 7.37 (s, 1H), 7.32 (d, J = 7.9 Hz, 1H), 7.21 (s, 1H), 7.19 (s, 1H), 5.87 (s, 1H), 3.75 (d, J = 16.7 Hz, 1H), 3.67 (d, J = 16.7 Hz, 1H), 3.45 (br s, 1H), 1.36 (s, 9H). LC−MS: [M + 1] 448.0. HPLC: purity 97%, retention time of 3.57 min (method C).

To (*S*)-*N*-((*S*)-1-(5-chloropyridin-2-yl)-2-cyano-1-(3-fluoro-5-(trifluoromethyl)phenyl)ethyl)-2-methylpropane-2-sulfinamide (30 mg, 0.067 mmol) solution in EtOH (1 mL) was added NH_2OH (1 mL, 50% solution in water). The solution was heated to 70 °C for 3 h, allowed to cool, and diluted with DCM, and the layers were separated. The aqueous layer was extracted with DCM, and the combined extracts were dried and concentrated to yield a tan solid which was dissolved directly in DCM (1 mL) and cooled to 0 °C. Acetic anhydride (11 μL) and TEA (25 μL) were added. The reaction mixture was stirred for 14 h. Then additional acetic anhydride (20 μL) and TEA (50 μL) were added. After 30 min, the reaction mixture was diluted with DCM, washed with saturated NaCl, dried, and concentrated under reduced pressure. LCMS [M + 1] 523.1. The residue was dissolved in THF (2 mL), and Cs_2CO_3 (63 mg, mmol) was added. The slurry was heated to 65 °C under reflux for 14 h, whereupon the solvent evaporated leaving a residual solid which was redissolved in methanol and purified using preparative HPLC. Intermediate (*S*)-*N*-((*S*)-1-(5-chloropyridin-2-yl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-(5-methyl-1,2,4-oxadiazol-3-yl)ethyl)-2-methylpropane-2-sulfinamide was isolated as a colorless oil (15 mg). HPLC: retention time of 3.80 min, purity 96%, method C. LC−MS: [M + 1] 505.1. The sulfinamide was deprotected using HCl/MeOH[15] and converted directly to compound **18e** as described for compound **18b** and isolated as a white solid in 43% isolated yield. R_f = 0.2 hexanes/EtOAc, 2:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, J = 1.7 Hz, 1H), 7.61 (dd, J = 8.6, 2.4 Hz, 1H), 7.48 (s, 1H), 7.36 (d, J = 9.8 Hz, 1H), 7.16 (s, 1H), 7.09 (d, J = 8.6 Hz, 1H), 4.64 (d, J = 14.0 Hz, 1H), 4.46 (d, J = 2.4 Hz, 1H), 4.07−3.86 (m, 1H), 3.80 (d, J = 14.0 Hz, 1H), 2.45 (s, 3H), 1.96 (m, 2H), 1.61 (m, 4H), 1.42 (m, 2H). ^{19}F NMR (376 MHz, CD_3OD) δ −62.23, −110.03. ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.79, 166.32, 158.07, 156.09, 146.27, 137.56, 131.70, 122.95, 118.79, 118.78 (m), 117.39, 117.02 (d, J = 37.4 Hz), 62.60, 52.36, 34.20, 33.42, 22.86, 11.78. LCMS: [M + 1] 512.2. HPLC: method A, purity 95%, retention time of 9.98 min; method B, purity 95%, retention time of 8.93 min. HRMS (ESI) calcd for $C_{23}H_{23}N_5ClF_4O_2$ $(M + H)^+$ = 512.147 096, found 512.146 76.

(*S*)-1-(1-(5-Chloropyridin-2-yl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-(4-fluorophenyl)ethyl)-3-cyclopentylurea, 18f. Urea **18f** was obtained using general procedure B, in 65% yield. LC−MS ESI 524.2 (M + H), retention time of 4.2 min (10−90% MeOH in H_2O with 0.1% TFA in a 4 min gradient). ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.29 (d, J = 2.19 Hz, 1H), 7.66 (dd, J = 2.44, 8.52 Hz, 1H), 7.52 (s, 1H), 7.37 (d, J = 9.74 Hz, 1H), 7.21 (d, J = 8.04 Hz, 1H), 7.11 (br s, 1H), 7.08 (d, J = 8.52 Hz, 1H), 6.75−6.83 (m, J = 8.60, 8.60 Hz, 2H), 6.58 (dd, J = 5.60, 8.52 Hz, 2H), 4.50 (d, J = 12.91 Hz, 1H), 4.44 (d, J = 6.57 Hz, 1H), 3.87−3.98 (m, J = 6.50, 6.50, 6.50, 12.60 Hz, 1H), 3.51 (d, J = 12.91 Hz, 1H), 1.98−2.08 (m, 1H), 1.84−1.94 (m, 1H), 1.51−1.76 (m, 4H), 1.38−1.48 (m, 1H), 1.29 (qd, J = 6.72, 13.70 Hz, 1H). ^{13}C NMR (126 MHz, chloroform-*d*) δ 163.91−161.36 (m, 1C), 161.8 (d, J = 245.2 Hz, 1C), 158.7, 155.8, 150.3 (d, J = 6.4 Hz, 1C), 145.7, 137.1, 132.4 (qd, J = 33.6, 8.2 Hz, 1C), 131.7 (d, J = 8.2 Hz, 2C), 131.3 (d, J = 2.7 Hz, 1C), 131.0, 123.51−123.23 (m, 1C), 126.64−119.88 (m, J = 272.5, 272.5, 272.5, 1.8 Hz, 1C), 119.0 (br s, 1C), 117.5 (d, J = 22.7 Hz, 1C), 114.82−114.44 (m, 2C), 111.83−111.44 (m, 1C), 63.3, 52.2, 41.8, 33.8, 33.3, 23.6 (s, 2C). Orthogonal HPLC purity: 95%, retention time of 11.69 min (HPLC method A); 95%, retention time of 13.20 min (HPLC method B).

(*S*)-1-(1-(5-Chloropyridin-2-yl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)but-3-enyl)-3-cyclopentylurea, 18g. Urea **18g** was obtained using general procedure B, in 21% yield.

LC−MS ESI 456.53 (M + H), retention time of 4.00 min (10−90% MeOH in H_2O with 0.1% TFA in a 4 min gradient). ^1H NMR (500 MHz, chloroform-*d*) δ 8.49 (dd, *J* = 0.55, 2.50 Hz, 1H), 7.61 (dd, *J* = 2.50, 8.60 Hz, 1H), 7.46 (s, 1H), 7.28−7.36 (m, 2H), 7.18 (d, *J* = 8.05 Hz, 1H), 6.97 (dd, *J* = 0.55, 8.60 Hz, 1H), 5.39 (tdd, *J* = 7.14, 9.99, 17.06 Hz, 1H), 4.97−5.08 (m, 2H), 4.36 (d, *J* = 6.94 Hz, 1H), 3.90−4.02 (m, 2H), 3.04 (dd, *J* = 6.94, 13.32 Hz, 1H), 1.92−2.07 (m, 2H), 1.57−1.70 (m, 4H), 1.32−1.45 (m, 2H). ^{13}C NMR (126 MHz, chloroform-*d*) δ 162.6 (d, *J* = 248.0 Hz, 1C), 159.1, 155.7, 150.0 (d, *J* = 6.7 Hz, 1C), 146.0, 137.3, 132.89−131.80 (m, *J* = 32.4, 32.4, 32.4, 7.6 Hz, 1C), 132.0, 131.0, 122.9, 126.92−119.76 (m, *J* = 270.8, 270.8, 270.8, 3.8 Hz, 1C), 119.5, 119.14−118.79 (m, *J* = 3.8 Hz, 1C), 117.4 (d, *J* = 21.9 Hz, 1C), 111.82−111.22 (m, 1C), 62.6, 52.4, 41.4, 33.8, 33.6, 23.7 (s, 2C). Orthogonal HPLC purity: 97%, retention time of 11.12 min (HPLC method A); 100%, retention time of 12.75 min (HPLC method B).

(*S*)-1-(1-(5-Chloropyridin-2-yl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-*p*-tolylethyl)-3-cyclopentylurea, 18h. Urea **18h** was obtained using general procedure B, in 60% yield. LC−MS ESI 520.48 (M + H), retention time of 4.21 min (10−90% MeOH in H_2O with 0.1% TFA in a 4 min gradient). ^1H NMR (500 MHz, chloroform-*d*) δ 8.28 (d, *J* = 2.14 Hz, 1H), 7.66 (dd, *J* = 2.24, 8.43 Hz, 1H), 7.54 (br s, 1H), 7.38 (d, *J* = 9.39 Hz, 1H), 7.21 (d, *J* = 7.69 Hz, 1H), 7.08 (d, *J* = 8.54 Hz, 1H), 6.91 (d, *J* = 6.19 Hz, 2H), 6.50 (d, *J* = 6.83 Hz, 2H), 4.47 (d, *J* = 8.75 Hz, 1H), 4.34 (br s, 1H), 3.99 (br s, 1H), 3.50 (d, *J* = 10.89 Hz, 1H), 2.27 (s, 3H), 2.04 (br s, 1H), 1.90 (br s, 1H), 1.60−1.73 (m, 4H), 1.46 (br s, 1H), 1.30 (br s, 1H). ^{13}C NMR (126 MHz, chloroform-*d*) δ 162.6 (d, *J* = 248.0 Hz, 1C), 159.0, 150.6, 150.56−150.51 (m, 1C), 145.6, 137.0, 136.2, 132.44−132.32 (m, 1C), 132.74−131.90 (m, *J* = 31.0, 31.0, 31.0 Hz, 1C), 130.8, 130.2 (s, 2C), 128.5 (s, 2C), 123.5, 123.3 (q, *J* = 273.7 Hz, 1C), 119.26−118.96 (m, *J* = 3.8 Hz, 1C), 117.81−117.35 (m, 1C), 111.77−111.28 (m, 1C), 63.3, 52.2 (br s, 1C), 42.3, 33.9 (br s, 1C), 33.4 (br s, 1C), 23.6, 23.6, 21.0. Orthogonal HPLC purity: 94%, retention time of 11.92 min (HPLC method A); 95%, retention time of 13.55 min (HPLC method B).

(*S*)-1-(1-(5-Chloropyridin-2-yl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-(2-fluorophenyl)ethyl)-3-cyclopentylurea, 18i. Urea **18i** was obtained using general procedure B, in 40% yield. LC−MS ESI 524.20 (M + H), retention time of 4.10 min (10−90% MeOH in H_2O with 0.1% TFA in a 4 min gradient). ^1H NMR (500 MHz, chloroform-*d*) δ 8.22 (d, *J* = 2.14 Hz, 1H), 7.60 (dd, *J* = 2.46, 8.65 Hz, 1H), 7.55 (s, 1H), 7.36−7.43 (m, *J* = 9.80 Hz, 1H), 7.20−7.25 (m, *J* = 8.10 Hz, 1H), 7.11−7.19 (m, 2H), 7.07 (dt, *J* = 1.81, 7.53 Hz, 1H), 6.97−7.04 (m, 2H), 6.72−6.80 (m, *J* = 9.30, 9.30 Hz, 1H), 4.31−4.41 (m, 2H), 3.90−4.01 (m, 1H), 3.76 (d, *J* = 12.81 Hz, 1H), 2.00−2.10 (m, 1H), 1.87−1.96 (m, 1H), 1.54−1.73 (m, 4H), 1.42−1.50 (m, 1H), 1.28−1.37 (m, 1H). ^{13}C NMR (126 MHz, chloroform-*d*) δ 162.5 (d, *J* = 248.9 Hz, 1C), 161.1 (d, *J* = 246.1 Hz, 1C), 158.4, 155.8, 150.3 (d, *J* = 6.4 Hz, 1C), 145.2, 136.8, 133.2 (d, *J* = 4.5 Hz, 1C), 132.90−131.77 (m, *J* = 32.7, 32.7, 32.7, 8.2 Hz, 1C), 131.0, 128.6 (d, *J* = 8.2 Hz, 1C), 124.0 (d, *J* = 2.7 Hz, 1C), 123.6 (d, *J* = 3.6 Hz, 1C), 122.5 (d, *J* = 15.4 Hz, 1C), 126.80−119.95 (m, *J* = 272.5, 272.5, 272.5, 2.7 Hz, 1C), 119.23−118.92 (m, *J* = 3.6 Hz, 1C), 117.6 (d, *J* = 21.8 Hz, 1C), 114.8 (d, *J* = 23.6 Hz, 1C), 111.93−111.44 (m, 1C), 63.0, 52.2, 35.7, 33.8, 33.3, 23.6 (s, 2C). Orthogonal HPLC purity: 96%, retention time of 11.60 min (HPLC method A); 95%, retention time of 13.16 min (HPLC method B).

(*S*)-*N*-(1-(5-Chloropyridin-2-yl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl)benzamide, 20. Amide **20** was obtained using general procedure C in 49% yield. LC−MS ESI 633.3 (M + H), retention time of 2.21 min (10−90% MeOH in H_2O with 0.1% TFA in a 2 min gradient). ^1H NMR (500 MHz, chloroform-*d*) δ 9.11 (s, 1H), 8.36 (d, *J* = 2.14 Hz, 1H), 8.01−8.06 (m, 1H), 7.88 (ddd, *J* = 2.24, 4.70, 8.43 Hz, 1H), 7.75 (dd, *J* = 2.46, 8.65 Hz, 1H), 7.25−7.31 (m, 1H), 7.22 (d, *J* = 8.54 Hz, 1H), 7.11−7.17 (m, 3H), 7.04 (t, *J* = 7.69 Hz, 2H), 6.93 (d, *J* = 8.75 Hz, 1H), 6.55 (d, *J* = 7.05 Hz, 2H), 5.89 (tt, *J* = 2.80, 53.00 Hz, 1H), 4.56 (d, *J* = 13.02 Hz, 1H), 3.62 (d, *J* = 12.81 Hz, 1H). ^{13}C NMR (126 MHz, chloroform-*d*) δ 163.6, 164.03−161.74 (m, 1C), 162.82−160.17 (m, *J* = 248.0 Hz, 1C), 158.0, 149.7 (d, *J* = 11.4 Hz, 1C), 148.5 (d, *J* = 7.6 Hz, 1C), 145.8, 137.5, 134.9, 132.5 (d, *J* = 9.5 Hz, 1C), 131.5 (d, *J* = 3.8 Hz, 1C), 131.4, 130.0 (s, 2C), 128.0 (s, 2C), 127.0, 126.92−126.74 (m, *J* = 4.3, 2.4 Hz, 1C), 123.4, 122.1 (q, *J* = 272.8 Hz, 1C), 119.61−118.19 (m, *J* = 32.4, 32.4, 32.4 Hz, 1C), 117.3 (d, *J* = 21.9 Hz, 1C), 115.5 (d, *J* = 3.8 Hz, 1C), 112.0 (d, *J* = 21.9 Hz, 1C), 108.5 (d, *J* = 24.8 Hz, 2C), 107.5 (tt, *J* = 252.7, 40.1 Hz, 1C), 63.7 (d, *J* = 1.9 Hz, 1C), 41.6. Orthogonal HPLC purity: 98%, retention time of 12.59 min (HPLC method A); 100%, retention time of 14.25 min (HPLC method B).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Determination of absolute stereochemistry, crystal structure analysis, and crystal data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank Dr. James Johnson, Dr. Wu Yang, and Yufeng Wang for the resynthesis of amide **20**, Sarah C. Traeger for the NMR support, Atsu Apedo for resolution of enantiomers by chiral HPLC and SFC, and Dr. Jonathan Josephs and Ming Chang for conducting the biotransformation studies. The authors also thank the Discovery Analytical Sciences, Compound Management, Lead Evaluation, and Lead Profiling groups for their contributions.

■ ABBREVIATIONS USED

CETP, cholesteryl ester transfer protein; DPPE, diphenylpyridylethanamine; RCT, reverse cholesterol transport; SPA, scintillation proximity assay; WPA, whole plasma assay; ND, not determined; MABP, mean arterial blood pressure; HR, heart rate

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(8) Virtual screening details are as follows. A single low energy structure for each of the reference compounds **1**, **3**, and **4** was generated using *Macromodel*, version 7.2008; Schrodinger, LLC: New York, 2002 , followed by SAM1 quantumchemical energy calculations (*AMPAC*, version 6.55; Semichem (P.O. Box 1649, Shawnee Mission, KS 66222), 1997).For each reference compound, a four-point pharmacophore search (ChemX,Chemical Design, Ltd., flexible option on) was performed against theBMS in-house deck, and the top 1000 (reference molecules **1** and **3**) and 3000 (reference molecule **4**)hits were retained. The lowest energy conformation of reference molecule **3** was also used as input to an in-house molecule shape-matchingtool in which BMS deck compounds were scored based on 3D matchingto specific features including hydrophobes, aromatic rings, fluorineatoms, and an acceptor atom. The assay yielded an initial hit thatcould be traced back to the four-point similarity search around referencecompound **3**, and subsequent similarity searching aroundthis hit yielded compound **7**.

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(10) CETP activity was measured by scintillation proximity assay (SPA) as the amount of ^{3}H-cholesteryl ester transferred from HDL (^{3}H-CE/HDL) to biotinylated LDL and captured on avidin-SPA beads. Reactions were initiated by the addition of purified human recombinant CETP (∼5.5 nM final concentration) and incubated at 37 °C. Reactions were terminated by the addition of LEADseeker beads (GE Healthcare, no. RPNQ0261, 2 mg/mL in buffer containing 1 mg/mL BSA and 0.05 mg protein/mL HDL). The beads were allowed to settle overnight at room temperature before reading. Compounds were tested at multiple concentrations, and the concentration required to inhibit 50% of the activity (IC_{50}) was determined from a curve fit of the data with each concentration tested in duplicate. Background activity was determined in a set of wells that received buffer but not CETP. All data were background-subtracted.

(11) CE transfer activity was measured in a "whole plasma assay" (WPA) as follows. Compound (1 μL) was added to 29 μL of human plasma containing ^{3}H-cholesterol ester in HDL (^{3}H-CE/HDL). The mixture was incubated for 2.5 h at 37 °C and terminated with the addition of 6 μL of water/1 M $MgCl_2$/2% Dextralip 50 (2:1:1) to precipitate LDL and VLDL. After 10 min at room temperature, the mixture was transferred to filter plates (Millipore, no. MHVBN45) that were prewet with phosphate buffered saline. The plates were centrifuged (1800 rpm) at room temperature for 10 min. Scintillation fluid was added and the amount of radioactivity determined using a scintillation counter. Background activity was determined with plasma samples incubated for 2.5 h at 4 °C. All concentrations of compounds were tested in duplicate and the IC_{50} values calculated from a curve fit of the data.

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(16) Absolute stereochemistry of active antipode was determined by X-ray crystal structure of Mosher's amide. See Supporting Information for details.

(17) For the transgenic mouse PD study, ^{3}H-CE transfer activity was measured in plasma obtained from hCETP/apoB-100 dual transgenic mice before and at several time points after dosing. Briefly, ^{3}H-CE/HDL (refs 10 and 11) was added to the samples, and the amount of radioactivity incorporated into LDL/VLDL after precipitation with water/1 M $MgCl_2$/2% Dextralip 50 (2:1:1) was determined. The activities measured in samples obtained after dosing were normalized to the activity in the plasma sample taken from the same animal before dosing.

(18) Liver microsomal stability was determined by incubating compound (3 μM) with microsomal protein (1 mg/mL) for 10 min followed by quantitative determination of the remaining compound by UV absorbance.

(19) Biotransformation studies were carried out by incubating the compound (30 μM) with microsomal protein (1 mg/mL) for 60 min followed by metabolite identification by LC/MS/MS using a Thermo LTQ mass spectrometer.

(20) For the transgenic mouse pharmacodynamic assay, transgenic mice expressing human CETP and apoB-100 were used. Predose blood samples were collected by retro-orbital bleed. Compounds were formulated in ethanol/Cremophor/water at a 1:1:8 ratio and dosed at 30 mg/kg, po. At 2, 4, and 8 h after dosing, blood samples were collected. Cholesterol ester transfer activity was measured in all blood samples and normalized by the activity measured in the same animal at baseline (mean of four or five mice per dose).

(21) For the hamster study, plasma HDL-C was measured in male Golden Syrian hamsters initially fed a moderately fat diet (2.5% coconut oil, 0.25% cholesterol) for 2 weeks. The hamsters were then dosed with vehicle, torcetrapib, or amide 20, po, q.d. At 2 h after dosing on day 3, plasma samples were obtained and HDL-C was measured and compared to the values measured before dosing.

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