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5-Carboxamido-1,3,2-dioxaphosphorinanes, potent inhibitors of MTP

Richard Sulsky,[a,*] Jeffrey A. Robl,[a] Scott A. Biller,[a] Thomas W. Harrity,[b] John Wetterau,[b] Fergal Connolly,[b] Kern Jolibois[b] and Lori Kunselman[b]

[a]*Department of Discovery Chemistry, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ 08543-4000, USA*
[b]*Department of Metabolic Disease, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ 08543-4000, USA*

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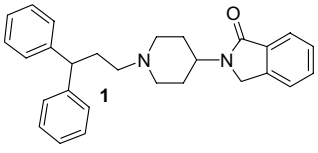
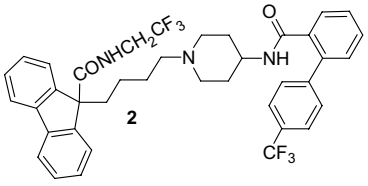
Abstract—5-Carboxamido-1,3,2-dioxaphosphorinanes have been identified as potent inhibitors of microsomal triglyceride-transfer protein. The 1,3,2-dioxaphosphorine functionality acted as a neutral and stable replacement for piperidine and piperidine N-oxide.

Isoindolylpiperidine BMS-188063 (**1**) was identified by high-throughput screening in our laboratories as an inhibitor of microsomal triglyceride-transfer protein (MTP).[1] Inhibiting the function of MTP, a protein necessary to the assembly and secretion of lipoproteins, has been shown to be an effective method for reducing serum cholesterol.[1]

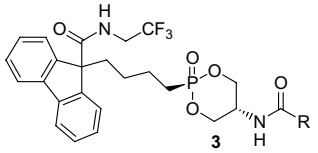


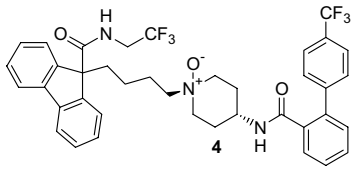


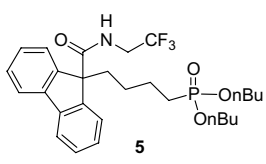
Intense efforts, by both conventional and combinatorial synthetic methods,[2] led to BMS-201038 (**2**), which had advanced as a clinical candidate in the treatment of hypercholesterolemia. To expand the SAR of this series, structurally diverse chemotypes were developed with the aim of preparing potent MTP inhibitors that did not contain the piperidine (or other basic amine) functionality. Described here is the identification of one such chemotype, the cyclophosphonates of general structure **3**.

In the course of exploring the SAR of **2**, we synthesized the N-oxide **4**,[3] a compound equipotent (in its ability to inhibit the secretion of lipoproteins from HepG2 cells) with **2** in vitro and slightly less potent in vivo (Table 1). In addition, we prepared simple phosphonates such as **5**, with somewhat diminished intrinsic potency and in vivo activity.[4] We hypothesized that the phosphonates and piperidines, having greatly different structures, do not bind to the protein at precisely the same site.

On the other hand, N-oxides are isoelectronic with phosphonate esters, although the N–O bond is somewhat shorter than the P–O bond.[5] As a challenge to our initial hypothesis, we conjectured that a hybrid structure,







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* Corresponding author. Tel.: +1 609 8184730; fax: +1 609 8186810; e-mail: sulskyr@bms.com

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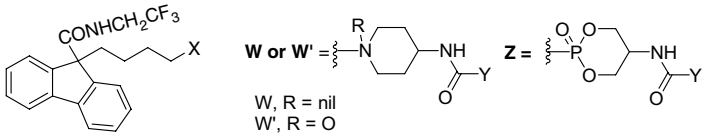
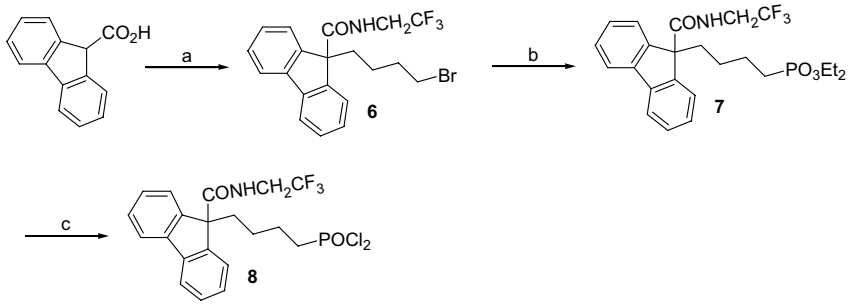
Table 1. MTP inhibition profile of selected compounds

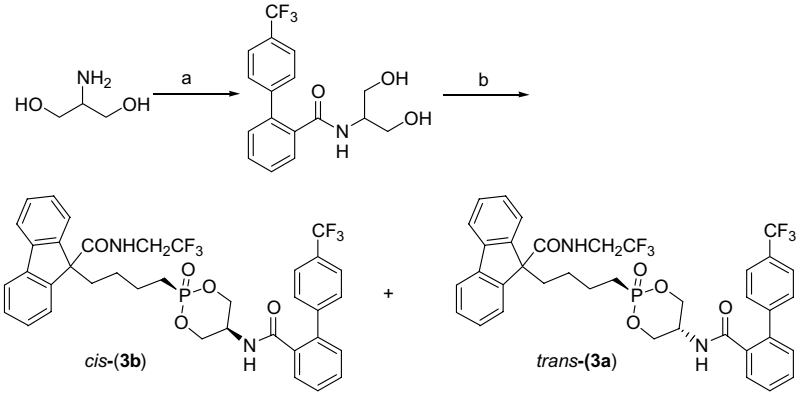


Compound	X	Y	IC_{50} in vitro (nM)[a]	HepG2 apo B ED_{50} (nM)[b]	Δ% Serum cholesterol (mpk)[c]
2	W	2-(4′-Trifluorobiphenyl)	8	0.8	−92 (30)[e]
4	W′	2-(4′-Trifluorobiphenyl)	5	0.9	−77 (15)
5	PO_3Bu_2	—	22	7	−5 (30)
3a	*trans*-Z	2-(4′-Trifluorobiphenyl)	7	0.65	−73 (30)[f]
3b	*cis*-Z	2-(4′-Trifluorobiphenyl)	44	18	−4 (20)
3c	*trans*-Z[d]	$-OCH_2C_6H_5$	14	40	ND
3e	*trans*-Z	C_6H_5-	11	23	−12 (15)
3f	*trans*-Z	2-(N-Benzyl)piperidinyl	9	ND	−22 (30)
3g	*trans*-Z	2-(2′-Pyridyl)phenyl	<10	79	−19 (15)
3h	*trans*-Z	2-(2′-Benzothiazolyl)phenyl	9	7.5	−76 (15)[g]
3i	*trans*-Z	2-(1′-Morpholino)phenyl	12	ND	−3 (15)
3j	*trans*-Z	2-(2′-Benzoxazolyl)phenyl	3	ND	−13 (30)

[a] In vitro values of triglyceride transfer of human MTP.
[b] Inhibition of secretion of apoB and apoA1 from HepG2 cells.
[c] Change in serum HDL cholesterol from control, after 3 day study in male Golden Syrian hamsters dosed once daily.[1]
[d] For corresponding *cis*-isomer, I_{50} = 210 nM.
[e] ED_{50} = 2.0 mpk.
[f] ED_{50} = 3.3 mpk.
[g] ED_{50} = 4.0 mpk.

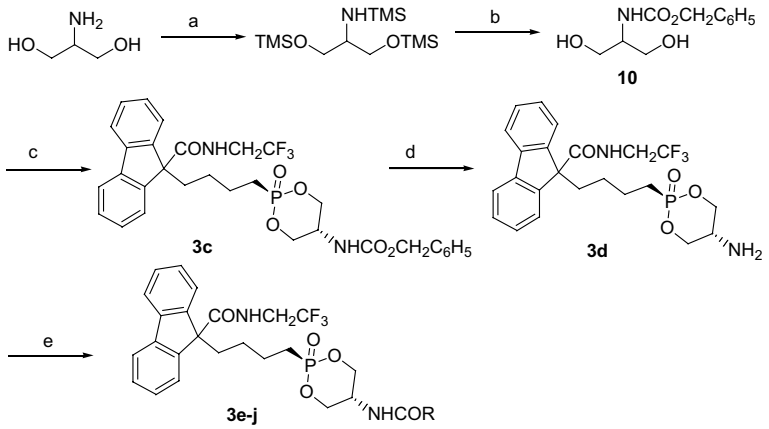


Scheme 1. Reagents and conditions: (a) (i) 2*n*-BuLi/THF, (ii) $Br(CH_2)_4Br$, (iii) $(COCl)_2$, DMF/CH_2Cl_2, (iv) $CF_3CH_2NH_2$·HCl, Et_3N/CH_2Cl_2, 71%; (b) $P(OEt)_3$, 110 °C, 79%; (c) (i) TMSBr/CH_2Cl_2, (ii) $(COCl)_2$, DMF/CH_2Cl_2, 88%.



Scheme 2. Reagents: (a) EDCI, HOBT, 2-(4′-trifluoromethylphenyl)benzoic acid/THF, 72%; (b) **8**, Et_3N/CH_2Cl_2.

containing both phosphonate and piperidine N-oxide structural features, would have a synergistic effect on binding potency. Thus we set about preparing compounds of structural type **3**.[6] Preparation of the necessary phosphoryl chloride (**8**) (Scheme 1), proceeded in three steps from 9-fluorenylcarboxylic acid. Carbodiimide coupling of serinol with 2-(trifluoromethylphenyl)benzoic acid provided **9a**, which was then reacted with **8** to give the



Scheme 3. Reagents and conditions: (a) $(Me_3Si)_2NH$, TMSBr, 180 °C, 86%; (b) (i) CbzCl, Et_3N/CH_2Cl_2, (ii) 4 N HCl/dioxane, 92%; (c) (**8**), Et_3N/CH_2Cl_2, 23%; (d) H_2, 10% Pd–C/EtOH, 95%; (e) EDCI, HOBt, Et_3N, RCO_2H/CH_2Cl_2.

trans-(**3a**) and *cis*-(**3b**) isomers, obtained in a 63:37 ratio in 44% yield. Separation of the isomers was readily accomplished by normal phase silica gel chromatography, and structural assignments were made by ^1H, ^{13}C, and ^{31}P NMR spectroscopy[7] (Scheme 2).

The *trans*-isomers were consistently more active in vitro than the *cis*-isomers (see Table 1). A more efficient technique for obtaining a variety of desired *trans*-analogs of **3a** is described in Scheme 3. Serinol was exhaustively silylated and the resulting tris-silylated compound was protected with CbzCl, followed by acidolysis (Scheme 3) to give **10**. This diol was then reacted with phosphoryl dichloride **8** to give carbamate **3c** (isolated and separated from the *cis*-analog in 23% yield). Hydrogenolysis of **3c** gave amine **3d**, a common intermediate, which was acylated to provide compounds **3e**–**j**.

Biological data. The compounds were assayed in vitro, in a cell-based assay and in a whole-animal model. Initial assay results showed that the *trans*-compounds were 5–6-fold more potent in vitro than the *cis*-isomers (Table 1).[1] The acyl analogs of **3** revealed little difference in the triglyceride transfer human MTP assay, with IC_{50} in the range of 3–14 nM for the *trans*-isomers and somewhat less potent than piperidine **2**.

Apolipoprotein B (apoB)-containing lipoproteins promote coronary artery atherosclerosis. We used a human liver-derived cell line, HepG2, which secrete apoB, as a cell-based assay to further characterize these compounds. Lipoprotein secretions of apo B in HepG2 cells were inhibited by the cyclophosphonate analogs, the most potent being **3a** (ED_{50} = 0.65 nM). This compares favorably to clinical candidate BMS-201038, which also possesses subnanomolar potency in the cell assay.

The compounds were tested in vivo in a three-day po hamster study. Hamsters, unlike other rodents, transport a substantial proportion of their cholesterol on LDL, thus providing a useful animal model of the human system.[1] Analogs **3a** (ED_{50} = 3.3 mpk) and **3g**, (ED_{50} = 4 mpk) exhibited in vivo efficacy similar to that of BMS-201038 (ED_{50} = 2.0 mpk).

We have prepared a series of cyclophosphonate analogs of the MTP inhibitor BMS-201038, a clinical candidate. The compounds are comparatively rigid structural mimics of the presumed bioactive chair form of the piperidine contained by BMS-201038. The cyclophosphonate compounds are essentially equipotent in vitro with the piperidine-containing MTP inhibitors. Two of the cyclophosphonates are equipotent with the clinical candidate in an in vivo model of cholesterol transport. Contrary to our initial hypothesis, no synergistic effect of the phosphonate was uncovered. The cyclophosphonate functionality neither helps nor interferes with the binding affinity of molecules to MTP. However, the cyclophosphonate structure itself may serve as a useful, stable, neutral surrogate for piperidines, their N-oxides, and additional nonaromatic six-member rings in other drug targets.

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6. Sulsky, R. U.S. Patent 5,962,440. Included are experimentals for all cyclophosphonate compounds and intermediates described in this paper.
7. Assignments of stereochemistry were made on the basis of ^{1}H NMR spectroscopy and comparison to literature examples of cyclophosphonates (see, Yee, K. C.; Bentrude, W. G. *Tetrahedron Lett*. **1971**, *12*, 2775) NMR data: Compound **3a** (*trans*): ^{1}H 300 MHz NMR ($CDCl_3$): δ 7.2–7.8 (m, 17H, *ArHs*, *NHCOAr*); 5.37 (t, 1H, $J = 6.5$ Hz, *CONHCH*$_2$*CF*$_3$); 4.21 (dt, 1H, $J = 4.1$ Hz, O*CH*$_2$*CHNH*); 3.96 (dd, 4H, $J = 4.1$, 11.1 Hz, O*CH*$_2$*CHNH*); 3.68 (dq, 2H, $J = 6.9$, 9.0 Hz, *NHCH*$_2$*CF*$_3$); 2.35 (m, 2H, *CH*$_2$(*CH*$_2$)$_3$*PO*); 1.4 (m, 4H, *CH*$_2$(*CH*$_2$)$_2$*CH*$_2$*PO*); 0.71 (m, 2H, (*CH*$_2$)$_3$*CH*$_2$*PO*). Compound **3b** (*cis*): ^{1}H 300 MHz NMR ($CDCl_3$): δ 7.2–7.8 (m, 16H, *ArHs*, *NHCOAr*); 6.27 (d, 1H, $J = 7.9$ Hz, *NHCOAr*); 5.44 (t, 1H, $J = 6.3$ Hz, *CONHCH*$_2$*CF*$_3$); 4.54 (d, 2H, $J = 11.4$ Hz, *equatorial* O*CH*$_2$*CHNH*); 4.07 (d, 1H, $J = 6.1$ Hz, O*CH*$_2$*CHNH*); 3.79 (dd, 2H, $J = 6.1$, 11.8 Hz, *axial* O*CH*$_2$*CHNH*); 3.65 (m, 2H, *NHCH*$_2$*CF*$_3$); 2.28 (m, 2H, *CH*$_2$(*CH*$_2$)$_3$*PO*); 1.4 (m, 4H, *CH*$_2$(*CH*$_2$)$_2$*CH*$_2$*PO*); 0.80 (m, 2H, (*CH*$_2$)$_3$-*CH*$_2$*PO*).