Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 6, No. 7, pp. 919-922, 1996

0960-894X/96 $15.00 + 0.00

S0960-894X(96)00145-X

SUBSTITUTED 1,3,5-TRIAZINES AS CHOLESTERYL ESTER TRANSFER PROTEIN INHIBITORS

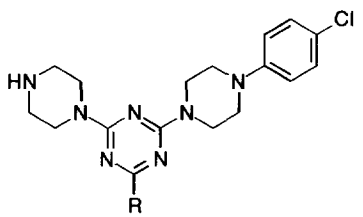
Yan Xia,* Bita Mirzai, Samuel Chackalamannil, Michael Czarniecki, Suke Wang, Anthony Clemmons, Ho-Sam Ahn, and George C. Boykow

Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033, U.S.A.

Abstract. A series of substituted 1,3,5-triazines (represented by **2**) were synthesized and evaluated for their cholesteryl ester transfer protein (CETP) inhibitory activities. Among the most potent compounds were those with R = benzyl (IC_{50} = 9 μM) and R = [(2-naphthalenyl)methyl] (IC_{50} = 5 μM).

Plasma lipoprotein profiles play an important role in the development of atherosclerosis, a major cause for cardiovascular mortality. Proper maintenance of the "good" HDL level and reduction of the "bad" LDL level has been a major goal in treating cardiovascular diseases. Many therapeutic approaches have been undertaken toward this goal.[1] Cholesteryl ester transfer protein (CETP),[2] a hydrophobic glycoprotein with a molecular weight of 74 kDa, transfers cholesteryl ester (CE) from HDL to LDL and in return transfers triglyceride (TG) back to HDL. The net result is a reduction of the beneficial HDL concentration and an increase in the detrimental LDL concentration.[3] Therefore, inhibition of CETP presented a potential therapeutic approach for treating atherosclerosis.

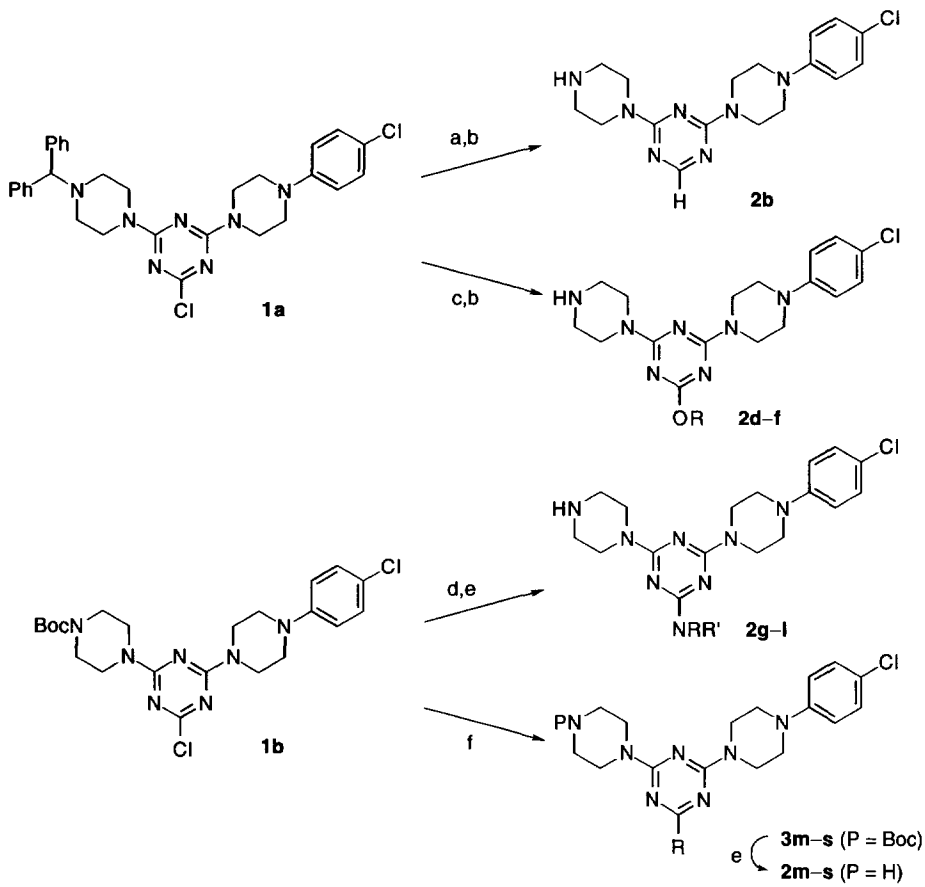
We, and others, have recently described several CETP inhibitors.[4-6] Here we disclose a new class of CETP inhibitors, namely, the 2,4,6-trisubstituted 1,3,5-triazine derivatives represented by structure **2**. Our initial lead structure (**2a**)[7] was discovered by random screening. In the subsequent SAR development we replaced the hydrazone group in **2a** with a variety of isosteric substituents (*vide infra*). The resulting triazine compounds display a range of in vitro CETP inhibitory activities with the most potent ones having low μM IC_{50} values.



2

2a: R = NHN=CHPh

Compounds represented by structure **2** were prepared from the key intermediates **1a** or **1b** (Scheme 1).[7] The disubstituted triazine derivative **2b** was obtained by chemoselective hydrogenolysis of **1a** with HI and PI_3[8] followed by TFA treatment. The displacement of the chlorine atom of **1a,b** by oxygen and nitrogen nucleophiles went as described in the literature.[7] For the introduction of carbon nucleophiles, we found that palladium-mediated cross coupling reactions of organozinc and organotin reagents to triazinyl chloride **1b** gave the carbon-substituted products (**3m–s**) efficiently and in good yields (**3m**, 73%; **3n**, 51%; **3o**, 83%; **3p**, 40%; **3q**, 84%; **3r**, 90%; and **3s**, 81%).[9,10] To our knowledge, these are the first examples of Pd-mediated cross coupling reactions of organozinc and organotin reagents to triazinyl chloride.[11] In the absence of $Pd(PPh_3)_4$, tributylphenyltin does not react with **1b** and *p*-chlorobenzylzinc bromide[12] react partially with **1b** to form **3r** (52% conversion by HPLC) under the same reaction conditions.

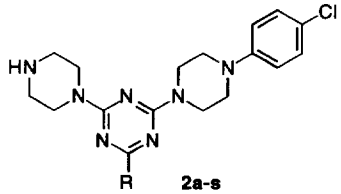


Scheme 1. (a) HI, PI_3, rt, 42%; (b) TFA, 75 °C; (c) ROH, NaOH; (d) NHRR', K_2CO_3, *n*-BuOH, reflux; (e) TFA, 0 °C to rt; (f) $RSnBu_3$ or RZnBr, $Pd(PPh_3)_4$.

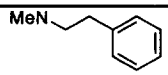
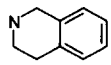
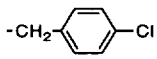
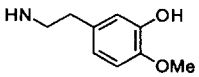
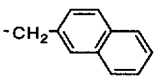
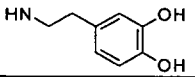
The CETP inhibitory activities of these compounds were measured using an in vitro Scintillation Proximity Assay (SPA).[4] The results are listed in Table 1. Clearly, the hydrazone group in **2a** can be replaced by several groups to give the same activities. There is a size requirement for activity at this hydrazone substitution site: the H and OH substituted compounds (**2b** and **2d**) showed little inhibition at 50 μM, whereas increasing size resulted in increasing inhibition (**2d→2e→2f**). For nitrogen substituted compounds, secondary amine substituted compounds (**2k** and **2l**) gave more potent inhibitors than primary amine substituted compounds (**2g–2j**). Most carbon substituted compounds displayed low μM CETP inhibitory activities except the small vinyl group substituted compound (**2n**).

In conclusion, a new class of 1,3,5-triazine derived CETP inhibitors was discovered by random screening and SAR development. These compounds exhibit low μM inhibition of CETP in vitro and may have potential use in treating cardiovascular diseases caused by low HDL levels.

Table 1.



2a-s

Entry	R	IC_{50} (μM)	% Inhibition (@ 50 μM)	Entry	R	IC_{50} (μM)	% Inhibition (@ 50 μM)
2a	NHN=CHPh	10		**2k**		6	
2b	H		14	**2l**		5	
2c	Cl		37	**2m**	Ph	11	
2d	OH		11	**2n**	-CH=CH$_2$	-	48
2e	OBun		57	**2o**	—C≡C—Ph	12	
2f	OCH_2CH_2Ph		66	**2p**	Bun	11	
2g	$NHCH_2CH_2Ph$	45		**2q**	-CH_2-Ph	9	
2h	$NHCH_2Ph$		52	**2r**		9	
2i		16		**2s**		5	
2j		21					

Acknowledgment. We thank Drs. M. Tong and M. Green for helpful discussions and Dr. Puar for the NMR structural determinations.

References and Notes

1. McCarthy, P. A. *Med. Res. Rev.* **1993**, *13*, 139.
2. For a review on CETP, see: Tall, A. R. *J. Lipid Res.* **1993**, *34*, 1255.
3. For atherogenic effect of CETP on transgenic mice, see: Marotti, K. R.; Castle, C. K.; Boyle, T. P.; Lin, A. H.; Murray, R. W.; Melchior, G. W. *Nature* **1993**, *364*, 73.
4. Coval, S. J.; Conover, M. A.; Mierzwa, R.; King, A.; Puar, M. S.; Phife, D. W.; Pai, J.-K.; Burrier, R. E.; Ahn, H.-S.; Boykow, G. C.; Patel, M.; Pomponi, S. A. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 605.
5. Chackalamannil, S.; Xia, Y.; Wang, Y.; Tsai, H.; Czarniecki, M.; Wang, S.; Clemmons, A.; Ahn, H.-S.; Boykow, G. C. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2005.
6. Kuo, M. S.; Zielinski, R. J.; Cialdella, J. I.; Marschke, C. K.; Dupuis, M. J.; Li, G. P.; Kloosterman, D. A.; Spilman, C. H.; Marshall, V. P. *J. Am. Chem. Soc.* **1995**, *117*, 10629; Kwon, B.-M.; Nam, J.-Y.; Lee, S.-H.; Jeong, T.-S.; Kim, S.-U.; Son, K.-H.; Kim, Y.-K.; Han, K.-H.; Kim, S.-K.; Bok, S.-H. *Tetrahedron Lett.* **1995**, *36*, 6487; Kim, H.-S.; Oh, S.-H.; Kim, D.-I.; Kim, I.-C.; Cho, K.-H.; Park, Y.-B. *Bioorg. Med. Chem.* **1995**, *3*, 367.
7. Compounds **2a** and **1a,b** were prepared from cyanuric chloride by stepwise displacements with appropriate amines: Quirke, J. M. E. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Pergamon: Oxford, 1984; Vol 3, pp 457-530. All the triazines mentioned in this paper are 1,3,5-triazines.
8. Modest, E. J. In *Heterocyclic Compounds*; Elderfield, R. C., Ed.; John Wiley & Sons: New York, 1961; Vol 7, p 671; Diels, O. *Chem. Ber.* **1899**, *32*, 691.
9. For reviews on Pd-mediated cross coupling reactions with various organometallic reagents, see: Stille, J. K. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508; Negishi, E.-I. *Acc. Chem. Res.* **1982**, *15*, 340; Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117; Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457; Undheim, K.; Benneche, T. *Acta Chem. Scand.* **1993**, *47*, 102; Kalinin, V. N. *Synthesis* **1992**, 413.
10. Procedure and analytical data for Pd-mediated coupling of tributylphenyltin to triazinyl chloride **1b**: A mixture of **1b** (258 mg, 0.522 mmol), tributylphenyltin (0.50 mL, 1.6 mmol), $Pd(PPh_3)_4$ (60 mg, 0.052 mmol), and PPh_3 (27 mg, 0.10 mmol) were heated in *N*-methylpyrrolidinone (4 mL) at 100 °C under N_2 for 28 h. The reaction solvent was distilled off and the residue was dissolved in CH_2Cl_2-MeOH (9-1), washed with saturated $NaHCO_3$ solution, dried ($MgSO_4$), and concentrated. Flash chromatography on a silica gel column with EtOAc-hexane (15–85) as eluent gave 204 mg (73%) product **3m** as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$): δ 1.48 (s, 9 H), 3.16–3.24 (m, 4 H), 3.47–3.54 (m, 4 H), 3.78–4.08 (m, 4 H), 3.90–4.18 (m, 4 H), 6.87 (d, 2 H, J = 8.8 Hz), 7.22 (d, 2 H, J = 8.9 Hz), 7.40–7.51 (m, 3 H), 8.38 (d, 2 H, J = 7.9 Hz); FAB MS 536 (100%); Anal. ($C_{28}H_{34}N_7O_2Cl$) C, H, N.
Procedure and analytical data for Pd-mediated coupling of *p*-chlorobenzylzinc to triazinyl chloride **1b**:[12] A solution of *p*-chlorobenzylzinc bromide in THF (1.7 mL, ca 3.0 mmol) was heated with a mixture of **1b** (300 mg, 0.607 mmol), $Pd(PPh_3)_4$ (70 mg, 0.061 mmol), PPh_3 (32 mg, 0.12 mmol), and *N*-methylpyrrolidinone (4 mL) in a pressure tube at 100 °C under N_2 for 20 h. The mixture was concentrated and the residue was dissolved in CH_2Cl_2-MeOH (9-1), washed with saturated $NaHCO_3$ solution, dried ($MgSO_4$), and concentrated. Flash chromatography on a silica gel column with EtOAc-hexane (15–85) as eluent gave 319 mg (90%) product **3r** as a solid. ^1H NMR (400 MHz, $CDCl_3$): δ 1.48 (s, 9 H), 3.11–3.19 (m, 4 H), 3.42–3.49 (m, 4 H), 3.74–3.81 (m, 4 H), 3.77 (s, 2 H), 3.89–3.98 (m, 4 H), 6.86 (d, 2 H, J = 9.0 Hz), 7.22 (d, 2 H, J = 8.9 Hz), 7.25 (d, 2 H, J = 9 Hz), 7.31 (d, 2 H, J = 9 Hz); FAB MS 584 (100%); Anal. ($C_{29}H_{35}N_7O_2Cl_2$) C, H, N.
11. There was a recent report of Pd-mediated coupling reactions of phenylboronic acid to 2-substituted 4,6-dichloro-1,3,5-triazines: Janietz, D.; Bauer, M. *Synthesis* **1993**, 33.
12. The zinc reagent was prepared by Knochel's procedure: Berk, S. C.; Knochel, P.; Yeh, M. C. P. *J. Org. Chem.* **1988**, *53*, 5789.

(*Received in USA* 2 *February* 1996; *accepted* 11 *March* 1996)