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A SERIES OF CONFORMATIONALLY AND STERICALLY CONSTRAINED ANALOGS OF N-PHENYL-N'-ARALKYLUREA ACAT INHIBITORS.[1]

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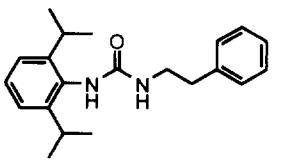
Abstract: A series of conformationally and sterically constrained analogs of N-phenyl-N'-aralkylureas has been synthesized and evaluated as potential ACAT inhibitors. Most of these analogs are potent inhibitors of ACAT *in vitro* and lower plasma cholesterol in an acute *in vivo* model of hypercholesterolemia.

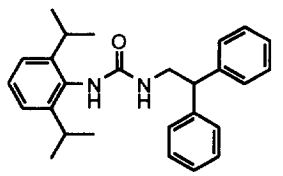
In recent years, there has been a tremendous surge in the literature delineating a wide range of structurally diverse ACAT inhibitors as potentially useful therapeutic agents. The plethora of literature, which is summarized extensively in recent review articles,[2-5] relates to the design and development of ACAT inhibitors as potential hypocholesterolemic and/or antiatherosclerotic agents. This is primarily due to the observations that ACAT may not only play an important role in the regulation of lipoprotein secretion in the liver[6,7], but may also be equally important in the development of atherosclerosis.[8,9] Due to this potential for therapeutic utility, we have continued our efforts to identify potent inhibitors of ACAT. We recently described a series of N-phenyl-N'-aralkylureas and N-phenyl-N'-(1-phenylcycloalkyl)ureas as potent ACAT inhibitors *in vitro* having excellent hypocholesterolemic activity *in vivo*.[10,11] In this article we will discuss the effect of conformational and steric constraint for these analogs on ACAT inhibition *in vitro* and hypocholesterolemic activity *in vivo*.

We recently described compounds **1-4** having a rather simple structural template for the inhibition of ACAT. We were intrigued by the observation that a simple compound such as **1**, having the optimized 2,6-diisopropylphenyl moiety, inhibited ACAT with an IC_{50} value of 88 nM. Additionally, incorporation of a phenyl group in the ß-position (**2**) improved the *in vitro* ACAT inhibitory activity

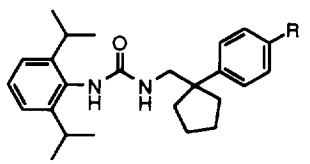
four fold.[9] These observations provided the basis for the SAR study which led to the identification of PD-132301-2 (**4**). In order to further define the structural motif required for potency at the N'-nitrogen we synthesized several analogs as shown in Table 1. Synthesis of these analogs is straightforward, as described previously.[10,11]



1 IC_{50} = 88 nM



2 IC_{50} = 24 nM

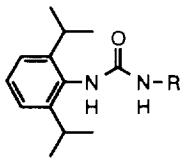


3 R = H IC_{50} = 17 nM

4 R = NMe_2 IC_{50} = 52 nM

Initially we synthesized a series of analogs of **1** having regioisomeric tetralin (**5, 6**) and indanyl (**7, 8**) functionalities. In both cases, the regioisomeric 2-substituted analogs were almost an order of magnitude more potent than the corresponding 1-substituted analogs confirming our earlier observation that for optimal ACAT inhibition, a phenyl moiety two atoms away from the urea N'-nitrogen was necessary. This activity was further optimized by introduction of a methoxy group in the 5-position. Thus compound **9** inhibited ACAT with an IC_{50} of 17 nM. Homologs of the 1-tetralin and 1-indanyl derivatives were synthesized to install the optimal two carbon spacer between the N'-nitrogen and the hydrophobic phenyl residue. As anticipated, both of the higher homologs (**13, 15**) showed a significant increase in potency with IC_{50} values of 27 and 36 nM, respectively. Interestingly the corresponding ß-hydroxy substituted analogs (**11, 14**) lacked activity both *in vitro* as well as *in vivo*. The 1-naphthylmethyl (**16**) and 1-naphthylethyl (**17**) analogs showed excellent *in vitro* activity with IC_{50} values of 34 and 41 nM, respectively. The regioisomeric 2-naphthylethyl derivative (**18**) was also a potent inhibitor with an IC_{50} value of 39 nM. It is interesting to note that insertion of an additional phenyl moiety into the 2,2,-diphenylethyl analog (**2**) produced **19** which was four fold less active *in-vitro*. However, compound **19** represents one of the most lipophilic compounds of this series which maintained acute *in vivo* efficacy by lowering total cholesterol 68% when dosed at 30 mg/kg. Furthermore, conformationally constrained analogs (**20, 21**) of the parent compound **2** provided ACAT inhibitors with IC_{50} values of 27 and 42 nM, respectively. These data suggest that for this series of

Table 1. ***In-vitro*** **and** ***in-vivo*** **activity**



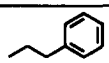
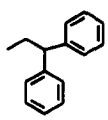
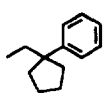
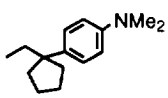
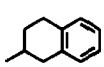
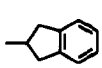
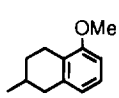
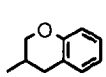
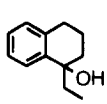
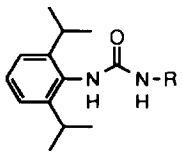
Compound	R	IAI[a] IC_{50} (uM)	APCC % Change in TC[b]
1		0.088	-16
2		0.024	-73
3		0.017	-70
4		0.052	-76
5		0.85	N.C.
6		0.063	-26
7		0.91	N.C.
8		0.096	-8
9		0.017	-39
10		0.11	-20
11		0.35	N.C.

Table 1. Continued.



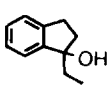
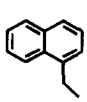
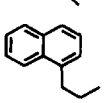
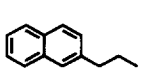
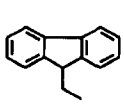
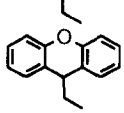
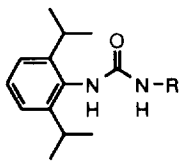
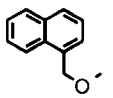
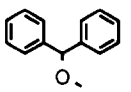
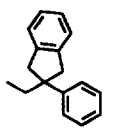
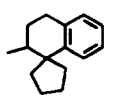
Compound	R	IAI[a] IC_{50} (uM)	APCC % Change in TC[b]
12		0.029	-33
13		0.036	-47
14		0.81	N.C.
15		0.027	-49
16		0.034	-53
17		0.041	-32
18		0.039	-54
19		0.091	-68
20		0.027	-41
21		0.042	-25

Table 1. Continued.



Compound	R	IAI[a] IC_{50} (uM)	APCC % Change in TC[b]
22		0.092	-32
23		0.030	-67
24		0.053	-30
25		0.027	-67
26		0.031	-49

[a]in-vitro ACAT inhibition, determined in rabbit intestinal microsome from cholesterol-fed animals. [b]Reported as percent change of total cholesterol as compared to controls. Animals were administered a single dose (30 mg/kg) of compound and then fed a single meal containing cholic acid (0.5%), cholesterol (1.5%), and peanut oil (5.5%). N.C. = no change.

compounds, there is a significant bulk tolerance at the N'-nitrogen of the inhibitor to interact optimally with the enzyme. A few hydroxylamine derivatives were also prepared (**22-24**). These analogs also showed excellent ACAT inhibitory activity *in vitro*, and compound **23** lowered plasma cholesterol by 67% when dosed at 30 mg/kg in the *in vivo* screen. Although **23** maintained the *in vivo* efficacy of the

parent compound **2**, similar modification for compound **19** provided compound **24** which was less efficacious *in vivo*. Similar observations have recently been made for a different class of ACAT inhibitors.[12] Finally, compounds **25** and **26** were synthesized based on **3**, in which both steric bulk (**25**) and conformational constraint (**26**) were incorporated. Both the compounds, surprisingly, maintained excellent ACAT inhibitory activity *in vitro* as well as cholesterol lowering activity *in vivo*.

In conclusion, a series of conformationally and sterically constrained analogs has been developed as potent ACAT inhibitors. The *in vitro* data reconfirms our earlier observation that for potency, an aromatic residue five atoms away from the N-phenyl moiety is required. A polar hydrogen bonding function such as a hydroxyl group (**11, 14**) at the ß-carbon is detrimental to activity. Furthermore, for this class of ACAT inhibitors significant bulk is tolerated at the N'-nitrogen. The SAR presented here will provide further insight into the design of potent ACAT inhibitors as potential therapeutic agents for the treatment of hypercholesterolemia and atherosclerosis.

References:

1. Inhibitors of Acyl-CoA:Cholesterol Acyl Transferase. Part 16. Presented in part at the 201st National ACS Meeting, Atlanta, Georgia,1991, MEDI 112. Stoeber, T. L.; Holmes A.; Essenburg, A. D.; Hamelehle, K. L.; Shaw, M. K.; Stanfield, R. L.; Krause, B. R.; Trivedi, B. K. A Series of Novel Disubstituted Ureas as ACAT Inhibitors: Chemistry and SAR Studies.
2. O'Brien, P. M. and Sliskovic, D. R. *Current Op. Ther. Patents* **1992**, 2, 507.
3. Picard, J. A. *Current Op. Ther. Patents* **1993**, 3, 151.
4. Sliskovic, D. R. and Trivedi, B. K. *Current Med. Chem.* **1994**, 1, 204.
5. Matsuda, K. *Medicinal Res. Rev.* **1994**, 14, 271.
6. Carr, T. P.; Parks, J. S.; Rudel, L. L. *Arterioscler. Thromb.* **1992**, 12, 1274.
7. Tanaka, M.; Jingami, H.; Otani, H.; Cho, M.; Ueda, Y.; Arai, H.; Nagano, Y.; Doi, T.; Yokode, M.; Kita, T. *J. Biol. Chem.* **1993**, 268, 12713.
8. Bocan, T. M. A.; Bak Muller, S.; Uhlendorf, P. D.; Newton, R. S.; Krause, B. R. *Arterioscler. Thromb.* **1991**, 11, 1830.
9. Bocan, T. M. A.; Bak Muller, S.; Uhlendorf, P. D.; Brown, E. Q.; Mazur, M. J.; Black, H. E. *Atherosclerosis* **1993**, 99, 175.
10. Trivedi, B. K.; Holmes, A.; Stoeber, T. L.; Blankley, C. J.; Roark, W. H.; Picard, J. A.; Shaw, M. K.; Essenburg. A. D.; Stanfield, R. L.; Krause, B. R. *J. Med. Chem.* **1993**, 36, 3300.
11. Trivedi, B. K.; Purchase, T. S.; Holmes, A.; Augelli-Szafran, C. E.; Essenburg, A. D.; Hamelehle, K. L.; Stanfield, R. L.; Bousley, R. F.; Krause, B. R. *J. Med. Chem.* **1994**, 37, 1652.
12. Clader, J. W.; Berger, J. G.; Burrier, R. E.; Davis, H. R.; Domalski, M.; Dugar, S.; Kogan, T. P.; Salisbury, B.; Vaccaro, W. *J. Med. Chem.* **1995**, 38, 1600.

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