Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 6, No. 1, pp. 47-50, 1996

0960-894X/96 $15.00 + 0.00

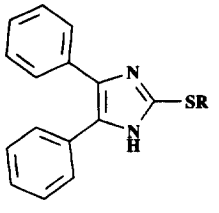
0960-894X(95)00555-2

RP 73163: A BIOAVAILABLE ALKYLSULPHINYL-DIPHENYLIMIDAZOLE ACAT INHIBITOR[1]

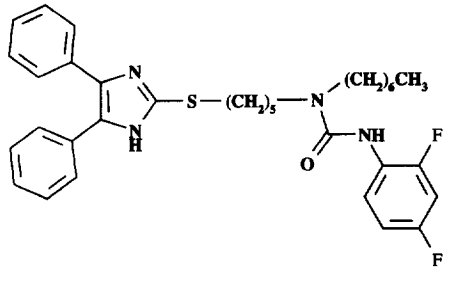
C.Smith*, M.J.Ashton, R.C.Bush, V.Facchini, N.V.Harris, T.W.Hart, R.Jordan, R.MacKenzie, D.Riddell,
Rhone-Poulenc Rorer, Central Research, Dagenham Research Centre, Dagenham, Essex, RM10 7XS (UK)

Abstract: RP 73163 **5** the major metabolite of the ACAT inhibitor RP 76076 **3** retains ACAT activity. This alkylsulphinyl-4,5-diphenyl-1H-imidazole has higher systemic bioavailability than the parent thioether, with plasma levels of parent compound in certain species exceeding the IC_{50} required for inhibition of hepatic, intestinal, artery, adrenal and macrophage ACAT for up to twelve hours after oral dosing.

2-(Alkylthio)-4,5-diphenyl-1H-imidazoles **1**[2,3,4,5] are one of the growing number of structurally diverse classes of potent inhibitors of acyl-CoA:cholesterol O-acyl transferase (ACAT, EC 2.3.1.26) that have been shown to be hypocholesterolaemic agents in cholesterol-fed animal models. A recent review on ACAT inhibitors by Sliskovic[6] chronicles the quest from non-absorbed intestinal ACAT inhibitors (efficacy for compounds whose action is restricted to inhibition of intestinal ACAT in humans remains to be shown), to bioavailable inhibitors capable of hepatic, arterial and macrophage ACAT inhibition. Studies carried out in the DuPont laboratories, directed towards systemically available ACAT inhibitors, concerning modification of their lead compound DuP 128 **2** were described in a recent series of papers.[7,8,9]

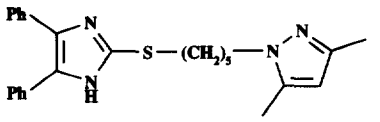


1



2

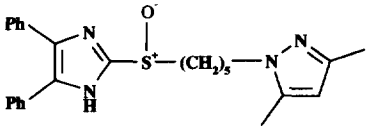
Compounds which are systemically available and which inhibit hepatic ACAT, arterial wall ACAT and/or macrophage ACAT could well provide novel anti-atherosclerotic drugs by virtue of their action at sites that could effect incorporation of cholesterol into VLDL particles, and deposition of cholesterol esters in atherosclerotic lesions. We have previously demonstrated[4] that the dimethylpyrazolyl derivative RP 70676 **3** was a potent inhibitor of ACAT obtained from a number of tissues of several species. Furthermore, RP 70676 **3**, given orally at a dose of 10mg/kg to New Zealand White (NZW) rabbits, was well absorbed with plasma levels of parent compound being of the order of 500nM over a period of 6 hours post dose.



3

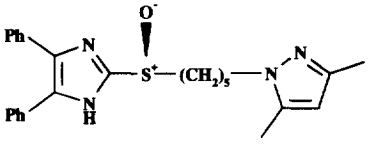
RP 70676 **3** was subsequently demonstrated to be an effective oral hypocholesterolaemic agent in both the rabbit and the marmoset. However, further efficacy studies in minipigs and dogs showed that the compound was emetic after oral dosing at 10mg/kg. The emetic effect was observed 5 minutes after dosing in minipigs and approximately 1 hour after dosing in dogs. Intravenous administration of the hydrochloride salt of RP 70676 to dogs caused emesis at 3mg/kg, with a delay of onset of 35-40 minutes.

Disposition studies in the rat and marmoset showed that RP 70676 was metabolised to the corresponding racemic sulphoxide **4**. Metabolism was also shown to be slightly stereoselective, with formation of the (S)-enantiomer predominating in both species (rat, ratio of enatiomers 77:33; marmoset, ratio of enantiomers 70:30).



4

The racemic sulphoxide **4**, synthesised by oxidation of RP 70676 with meta-chloroperbenzoic acid, showed ACAT inhibitory properties, but with an IC_{50} of 350nM for inhibition of rat liver ACAT was 14 times less potent then RP 70676. I.v. administration of the sulphoxide RP 72514 **4** at 10mg/kg to dogs caused immediate and prolonged (25 minutes) emesis. The enantiomeric sulphoxides were separated by HPLC using a chiral stationary phase derived from cellulose[10]. The emetic properties associated with the racemic sulphoxide **4** were shown to reside with the (R)-enantiomer and the ACAT inhibitory activity to reside predominantly with the (S)-enantiomer RP 73163 **5** (the IC_{50} for inhibition of rat liver ACAT for the (S)-enantiomer was 63nM compared to 1453nM for the (R)-enantiomer). To enable further profiling and possible development an asymmetric synthesis[11] of RP 73163 was established capable of providing multikilogramme quantities of RP 73163 in 99% enantiomeric excess.



5

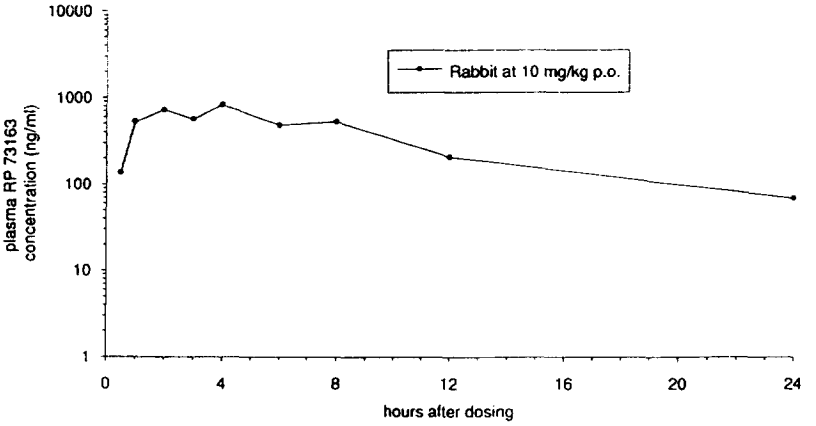
Compared to RP 70676 **3** the sulphoxide RP 73163 **5** was consistently some 3 to 4 fold less active against ACAT from a variety of tissues and species - see Table 1.

Table 1 Comparison of activity of RP 73163 and RP 70676 against ACAT in microsomes from various species / tissues, IC_{50}'s

	RP 73163	RP 70676
RAT LIVER	86nM	25nM
RABBIT LIVER	122nM	44nM
RABBIT INTESTINE	370nM	108nM
RABBIT ARTERY	245nM	40nM
RABBIT ADRENAL	208nM	80nM
HEP G2 CELLS	108nM	
THP-1 CELLS	164nM	

Figure 1 shows the plasma levels of RP 73163, after oral dosing to fed NZW rabbits at 10mg/kg. Levels of drug substance were found to be three times higher than those observed for the corresponding sulphide RP 70676. The highest levels (C_{max} 2100nM) were seen 4 hours after dosing and the plasma levels were still in excess of the IC_{50}'s for inhibition of hepatic, arterial and macrophage ACAT after 12 hours. The product has also been demonstrated to be highly bioavailable in the male dog (F=76.5%) and in male and female rats (F=39.1 and 70.8%, repectively) following single administration at a level of 10mg/kg.[12]

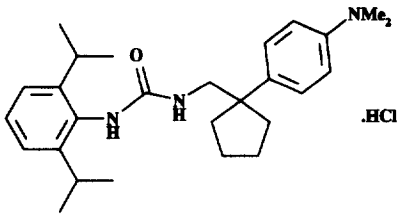
Figure 1 Drug levels of RP 73163 after oral dosing to rabbits @ 10mg/kg



In cholesterol fed NZW rabbits, RP 73163 given orally at 1mg/kg, produced a reduction in plasma cholesterol levels comparable to that observed by returning the animals to a normal diet. This is similar to the results observed with RP 70676.

RP 73163 was considered for development as a hypocholesterolaemic agent which was expected to have lipid lowering properties by virtue of possessing inhibitory activity at the level of intestinal and hepatic ACAT as well as having direct disease (atherosclerotic) modifying activity by preventing ACAT induced cholesteryl ester formation within the arterial wall/macrophage thereby reducing foam cell formation. In one month oral toxicology trials in the dog (30 - 300mg/kg/day) drug induced adrenal necrosis was observed[13]. This adrenal toxicity may well have been the result of inhibition of adrenal ACAT, or inhibition of

mitochondrial respiration in adrenal cells causing atrophy of the *zona fusciculata*[14, 15] as reported by the Parke-Davis group for their bioavailable urea, PD-132301-2 **6**.



6

It will be interesting to see how the challenge in design and development of bioavailable ACAT inhibitors for the treatment of atherosclerosis progresses. The question of adrenotoxicity has been addressed by Parke-Davis where minor changes to PD-132301-2 **6** have given compounds devoid of such toxicities.[6] Further developments at the Rhone-Poulenc Rorer Laboratories on new diphenyl-1H-imidazoles, potent ACAT inhibitors with novel 2-substituents, will be reported shortly.[16]

Acknowledgements: The authors gratefully acknowledge the valuable contributions of the following colleagues to the work described in this letter: A. Al-Shaar, J. Archer, M. Birrell, B. Burton, J. Casey, D.Chatterjee, J. Davison, P.E.Gunraj, S. Heather, D. Hele, T.A.Hoff, G.Jahn, P. Joannou, G. Jones, L. King, S. Lammin, J. Lloyd, S. Man, K. Naik, D. Neighbour, B. Pedgrift, S. Roberts, G. Stevenson, J. Webb, and E. White.

References and Notes

1. Presented in part at the *RSC-SCI 7th Medicinal Chemistry Symposium Cambridge* 12-15th September, P45, **1993**
2. *Eur.Pat.* 391796 (10 October **1990**).
3. *Eur.Pat.* 372445 (13 June **1990**).
4. Ashton, M.J.; Bridge, A.W.; Bush, R.C.; Dron, D.I.; Harris, N.V.; Jones, G.D.; Lythgoe, D.J.; Riddell, D.; Smith, C. *Bioorg. Med. Chem. Lett.*, **1992**, *2*, 375.
5. Harris, N.V.; Smith, C.; Ashton, M.J.; Bridge, A.W.; Bush, R.C.; Coffee, E.J.; Dron, D.I.; Harper, M.F.; Lythgoe, D.J.; Newton, C.G.; Riddell, D. *J. Med. Chem.*,**1992**, *35*, 4384.
6. Sliskovic, D.R.; Trivedi, B.K. *Current Med. Chem.*,**1994**, *1* , 204.
7. Wilde, R.G.; Billheimer, J.T.; Germain, S.J.; Gillies, P.J.; Higley, A.; Kezar III, H.S.; Maduskuie, T.P.; Shimshick, E.S.; Wexler, R.R. *Bioorg. Med. Chem. Lett.*, **1995**, *5*, 167.
8. Wilde, R.G.; Billheimer, J.T. *Bioorg. Med. Chem. Lett.*, **1995**, *5*, 173.
9. Wilde, R.G.; Klaczkiewicz, J.D.; Billheimer, J.T.; Wexler, R.R. *Bioorg. Med. Chem. Lett.*, **1995**, *5*, 177.
10. Separation of the enantiomers of RP 75214 was carried out using a "chiracel OD" column. Typical conditions were: methanol, isopropanol and n-heptane 5:2:93, v/v.
11. Pitchen, P. *Chemistry & Industry*, **1994**, 636. Pitchen. P.; France, C.J.; McFarlane, I.M.; Newton, C.G.; Thompson, D.M. *Tet. Letters*, **1994**, *35*, 485.
12. Chauhan, P.B.; Facchini, V.; Gunraj, P.E.; Hoff, T.A.; Jones, G.D.; Acott, S. *Fifth European ISSX Meeting Tours, France*. September 26-29, **1993**.
13. Warne, P. *Society of Pharmaceutical Medicine : Antiatherosclerotic & Lipid Modifying Drugs in the 1990's, London* 28-29th October **1993**.
14. Dominick, M.A.; Bobrowski, W.A.; MacDonald, J.R.; Roth, B.D.; Wilson, M.W.; Hamelehe, K.L.; Krause, B.R.; Stanfield, R.L. *Toxicol. Pathol.*,**1993**, *21*, 54.
15. O'Brien, P.M.; Sliskovic, D.R.; Blankley, C.J.; Gough, A.W.. *J. Med. Chem.*, **1994**, *37*, 1810.
16. Astles, P., submitted to *J. Med. Chem.*

(*Received in Belgium* 30 *August* 1995; *accepted* 22 *November* 1995)