Bioorganic & Medicinal Chemistry Letters, Vol.2, No.2, pp. 181-184, 1992
Printed in Great Britain

0960-894X/92 $3.00 + .00

SYNTHESIS AND BIOLOGICAL ACTIVITY OF THE PLATELET-ACTIVATING FACTOR ANTAGONIST (±)-*trans*-2-(3-METHOXY-4-PHENYLSULFONYLETHOXY-5-*n*-PROPYLSULFONYLPHENYL)-5-(3,4,5-TRIMETHOXYPHENYL)TETRAHYDROFURAN (L-671,284) AND ITS ANALOGS

Robert L. Bugianesi,* Mitree M. Ponpipom, William H. Parsons, San-Bao Hwang, Thomas W. Doebber, My-Hanh Lam, Margaret S. Wu, Alfred W. Alberts and John C. Chabala

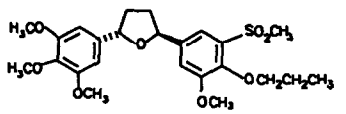
Merck Sharp and Dohme Research Laboratories, Rahway, New Jersey 07065 (U.S.A.)

(*Received* 22 *November* 1991)

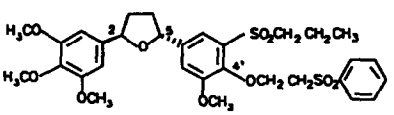
ABSTRACT: (±)-*trans*-2-(3-Methoxy-4-phenylsulfonylethoxy-5-*n*-propylsulfonylphenyl)tetrahydrofuran (**L-671,284**) is a highly potent, selective, competitive PAF-receptor antagonist with a K_i of 1.0 n*M* for inhibition of binding of [^{3}H]C_{18}-PAF to human platelets and exhibits little or no gender differences in bioactivities in rats. Several 4' positional analogs of **L-671,284** have been synthesized and evaluated *in vitro*.

Platelet activating factor (PAF), chemically identified as 1-*O*-alkyl-2-*O*-acetyl-*sn*-glycero-3-phosphocholine[1], has been implicated as a mediator of pathophysiological reactions in various animal models as well as in human disease[2]. PAF is produced by a variety of inflammatory cells such as basophils, neutrophils, platelets, macrophages, endothelial cells, and IgE-sensitized bone marrow mast cells[3]. PAF induces smooth-muscle contraction, neutrophil degranulation and platelet aggregation[4]. In various animal models, PAF induces bronchoconstriction, systemic hypotension, neutropenia, increased vascular permeability, and elevated plasma lysosomal hydrolase levels. It is the most potent mediator able to elicit a recruitment of eosinophils in allergic subjects[5]. PAF may also play a major role in asthma[6,7]. Thus potent and specific PAF-receptor antagonists are not only useful tools for defining the biological roles of PAF and conformational properties of PAF receptor sites, but are also potential therapeutic agents for asthma and other immune disorders such as endotoxic shock and graft rejection.

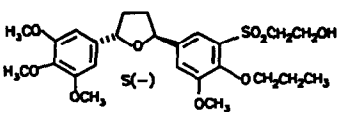
In 1982 a program was initiated in these laboratories to identify and develop novel PAF receptor antagonists. This research has led to the discovery of **L-659,989**[8] with a K_i of 14.3 n*M* and **MK 287**[9] with a K_i of 6.0 n*M* in inhibiting the binding of [^{3}H]C_{18} PAF to human platelet membrane PAF receptors. An objective of the ongoing Merck PAF program is to identify derivatives of **MK 287** that not only are more potent, but also do not exhibit gender dependent oral activity in rats. It was previously determined that position 4' of the 2-aryl group (see table 1) tolerated lipophilic sidechains and research was undertaken to exploit this observation. Of the various heteroatoms inserted into the 4'-position, the thioethoxy group showed the most promise, and arylthioethoxy substituents were found to be superior to alkylthioethoxy substituents in intrinsic potency. Herein is disclosed a class of novel potent 4'-arylthioethoxy and 4'-arylsulfonylethoxyltetrahydrofuran PAF antagonists typified by **L-671,284** [(±)-*trans*-2-(3-methoxy-4-phenylsulfonylethoxy-5-propylsulfonylphenyl)-5-(3,4,5-trimethoxyphenyl) tetrahydrofuran] (**9a**), which exhibits minimal gender-dependent oral activity in rats.



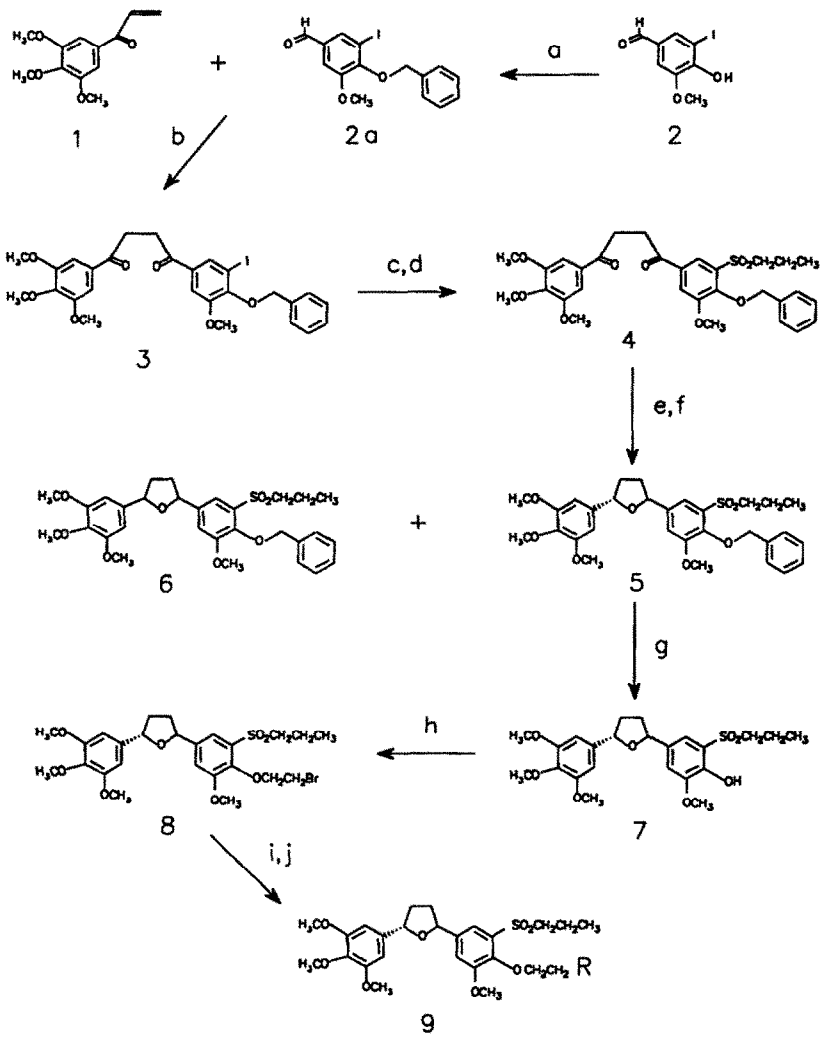
L-659,989



L-671,284



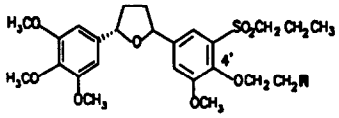
MK 287



a = benzyl chloride, K_2CO_3, DMF, 1.5 h, 80°C, 87%
b = Et_3N, DMF, 2 h, 70%
c = Cu, $(CH_3CH_2CH_2S)_2$, DMF, reflux, 24 h, 60%
d = mCPBA, CH_2Cl_2, rt, 2 h, 90%
e = $NaBH_4$, EtOH, 70°C, 15 min, 100%
f = 5% CF_3COOH in $CHCl_3$, rt, 1.5 h, 52% *trans* + 20% *cis*
g = H_2, 10% Pd/C, EtOAc rt, 1 h, 100%
h = 1,2-dibromoethane, K_2CO_3, DMF, 1 h, 80°C, 75%
i = Appropriate thiophenol, NaH, DMF, 20 min, 60-80%
j = *m*CPBA, CH_2Cl_2, rt, 2 h, ~80%

The method of synthesis employed incorporation a benzyl protecting group at the 4' position of iodovanillin (**2**) and then selective removal to expose the phenol **7**, for subsequent alkylation. The vinylketone (**1**)[9] was condensed with 4-O-benzyl-5-iodovanillin (**2a**) to yield the iododiketone **3**. Iododiketone **3** was treated with propyldisulfide and copper powder in DMF to provide the propylthio derivative which was oxidized to the sulfone (**4**) with *m*-chloroperbenzoic acid. Compound **4** was then reduced with $NaBH_4$ in EtOH in quantitative yield and the resulting diol was cyclized with 5% triflouroacetic acid in $CHCl_3$ to provide a mixture of *trans*- and *cis*- 2,5-diaryltetrahydrofurans (**5** and **6**, respectively), separable by chromatography (SiO_2; hexane-ethyl acetate, 2:1 [v/v]). The benzyl protecting group of **5** was then removed by hydrogenolysis in quantitative yield to give **7**, which was alkylated with 1,2-dibromoethane in DMF to afford the versatile 2-bromoethoxy intermediate **8**. 4'-Arylthioethoxy derivatives **9** were prepared from **8** and sodium thioaryloxide in DMF. These products can be further oxidized with *m*-chloroperbenzoic acid to give 4'-arylsulfenylethoxy and 4'-arylsulfonylethoxy analogs[10].

Table 1. Bioactivity (in vivo and in vitro) of L-671,284 and analogs



		R		% INH		
				5nM in vitro[a]	NAGA	HEMO[b]
L-671,284	9a	$SO_2C_6H_5$		72	94	94
	9b	S C_6H_5		93	84	95
	9c	S C_6H_4	4-CN	93	39	33
	9d	SO C_6H_4	4-CN	74	0	5
	9e	$SO_2C_6H_4$	4-CN	69	1	0
	9f	S C_6H_4	2-OH	58	ND	ND[c]
	9g	S C_6H_4	3-OH	61	29	27
	9h	S C_6H_4	4-OH	100	76	63
	9i	SO C_6H_4	4-OH	73	44	25
	9j	$SO_2C_6H_4$	4-OH	88	13	7
	9k	S C_6H_4	2-NH_2	57	ND	ND
	9l	S C_6H_4	3-NH_2	80	4	7
	9m	S C_6H_4	4-NH_2	60	58	56
	9n	SO C_6H_4	4-NH_2	0	ND	ND
	9o	$SO_2C_6H_4$	4-NH_2	41	ND	ND
	9p	S C_6H_4	4-$N(CH_3)_2$	66	57	66
	9q	S C_6H_4	4-$CONH_2$	70	32	26
	9r	S C_6H_4	4-COOH	38	23	11
	9s			60	13	11
	9t			73	15	15
	9u			45	5	0

[a]Inhibition of [^{3}H]C_{18} PAF binding to human platelet membranes.[8] [b]Inhibition of 10 nmole/kg PAF-induced plasma N-acetyl-β-glucosaminidase (NAGA) and hemoconcentration (HEMO) at 1 mg/kg *p.o.* in rats.[11] [c]ND = not done.

The *in vitro* inhibition of [^{3}H]C_{18} PAF binding to human platelet membrane PAF receptors is shown in Table 1. Aryl sulfides tend to be more potent than sulfones and sulfoxides (*e.g.* **9b,c,h,m,t > 9a,d,e,i,j,n,o,u**). In the case of the positional isomers of the hydroxy substituted arylthio deravites, the 4 isomer **9h** (100%) is more potent than either the 2 or 3 isomer. This relationship is not absolute, however, since in the case of the amino substituted compounds the 3 isomer **9l** (80%) is the most potent. The heteroarylthio derivatives are less potent *in vitro* and *in vivo* (*e.g.* **9b>9t>9s**). The unsubsituted phenyl derivatives **9a** and **9b** exhibit the greatest potency *in vivo* while **9m,9h** and **9p** exhibit moderate *in vivo* activity, all other compounds are much less active. **L-671,284** was chosen for further study since it was the most potent compound *in vivo*, the sulfone moiety was expected to enhance oxidative metabolic stability. **L-671,284** inhibits the binding of [^{3}H]C_{18} PAF to human platelet membranes with an IC_{50} value of 1 n*M*. In human PMNs **L-671,284** inhibits 3 x 10^{-7}M PAF-induced degranulation of PAF as measured by myeloperoxidase secretion with an IC_{50} value of 0.78 n*M*. When administered orally to male and female rats, **L-671,284** inhibits 10 nmole/kg PAF-induced hemoconcentration and plasma N-acetyl-β-glucosaminidase (NAGA) increase with average ED_{50} values of 0.22 mg/kg and 0.26 mg/kg in female and male rats, respectively. When administered intravenously to male rats, a 0.2 mg/kg dose of **L-671,284** reverses a 5 nmole/kg PAF-induced 84 mm Hg drop in blood pressure by 79 mm 15 minutes after administration.

References and Notes

1. Demopoulos, C. A.; Pinckard, R. N.; and Hanahan, D.J. *J. Biol. Chem.* **1979**, *254*, 9355; Benveniste, J.; Tence, M.; Bidault, J.; Boullet, C.; Varence, P. and Polonsky, J. *C. R. Seances Acad. Sci., Ser. D.* **1979**, *289*, 1037.

2. Braquet, P.; Touqui, L.; Shen T. Y. and Vargaftig, B. B. *Pharmacol. Rev.* **1987**, *39*, 97.

3. Vargaftig, B. B.; Benveniste J. *Trends Pharmacol. Sci.* **1983**, 341.

4. Snyder, F. *Med. Res. Rev.* **1985**, *5*, 107; Venuti, M. C. *Annu. Rep. Med. Chem.* **1985**, *20*, 193.

5. Benveniste, J.; Arnoux, B. Eds., *Platelet-Activating Factor and Structurally Related Ether Lipids*, Inserm Symposium, Elsevier Science Publishers; Amsterdam, 1983; No.23.pp. 26-29

6. Peplow, P.V.; Mikhalidis, D.P., *Prostaglandins Leukotrienes and Essential Fatty Acids* **1990**, *41*, 71.

7. Patterson, R.; Bernstein, P. R.; Harris, K. E.; Krell, R. D. *Lab. Clin. Med.* **1984**, *104*, 340.

8. Ponpipom, M.M.; Hwang, S.-B.; Doebber,T. W.; Acton, J.J.; Alberts, A. W.; Biftu, T.; Brooker, D. R.; Bugianesi R. L.; Chabala, J. C.; Gamble, N. L.; Graham, D. W.; Lam, M.-H. and Wu, M. S. *Biochem. Biophys. Res. Commun.* **1988**, *150*, 1213.

9. Sahoo, S.P.; Graham, D.W.; Acton J.; Biftu, T.; Bugianesi, R.L.; Girotra, N.N.; Kuo, C.-H.; Ponpipom, M.M.; Doebber, T.W.; Wu, M.S.; Hwang, S.-B.; Lam, M.-Hanh; MacIntyre, D. E.; Bach, T.J.; Luell, S.; Meurer, R.; Davies, P.; Alberts, A.W. and Chabala, J.C., *Bioorganic and Med. Chem. Let.*, **1991**, *1*, 327.

10. **L-671,284** physical constants: 1H NMR [$CDCl_3$]: d 0.94 [t,$CH_3CH_2CH_2$], 1.62 [m,$CH_3CH_2CH_2$], 1.96 and 2.47 [2m, H-3 and H-4], 3.16 [m, $CH_3CH_2CH_2SO2$], 3.69 [t,$CH_2CH_2SO_2$], 3.82,3.86,3.90 [3s, 3 OCH_3], 4.47 [t,CH_2CH_2O], 5.20 [m, H-2 and H-5], 6.59 [s,C5ArH], 7.24, 7.41 [2d, ArH] 7.59 [m, C2ArH] 7.98 [d, $HArSO_2$]. MS, m/e 634, mp 124-125°. *Anal.* Calc. for $C_{31}H_{38}O_{10}S_2$: C,58.66; H,6.03; S,10.10. Found: C,58.56; H,5.97; S,10.19. All other compounds gave NMR, MS and analytical data consistent with thier structures.

11. Doebber, T.W., Wu, M.S., and Shen, T.Y. *Biochem. Biophys. Res. Commun.* **1984**, *125*, 980.