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CYCLIC ETHER ACETAL PLATELET ACTIVATING FACTOR (PAF) RECEPTOR ANTAGONISTS I: 3-PYRIDYL DERIVATIVES

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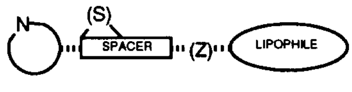
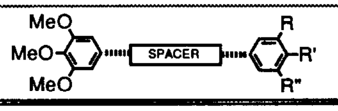
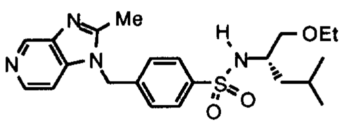
Abstract: A novel series of 2-(3-pyridyl)alkoxy-5-aryltetrahydrofuran PAF antagonists has been identified and the effect of variation of the alkoxy chain length, aryl substitution and stereochemistry about the tetrahydrofuran ring studied. The optimal compound, *cis*-(±)-2-(3-(3-pyridyl)propanoxy)-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran (**27a**), inhibits [^{3}H]-PAF receptor binding to washed human platelet membranes with an IC_{50} value of 100 nM.

Platelet activating factor (PAF) is the bioactive phospholipid 1-*O*-hexadecyl/octadecyl-2-acetyl-*sn*-glyceryl-3-phosphoryl choline[1,2] that appears to be involved in many inflammatory disorders including asthma and endotoxin shock.[3,4] There is considerable interest in the design of PAF receptor antagonists since they may be of clinical benefit in such diseases. The diverse range of compounds that are PAF antagonists can be grouped into three main structural classes (Table 1).[5]

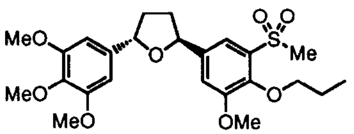
Table 1: Classification of PAF antagonists

Classification	Examples	Schematic Representation
1) Quaternary nitrogen compounds: X is a phosphate isostere, Y an ether isostere.	CV-6209,[6] E-5880,[7] UR-11353.[8]	
2) Heterocyclic sp2 nitrogen compounds: Z is carbonyl or sulphonyl.	WEB 2086,[9] RP 59227,[10] Ro 24-0238,[11] UK-74,505,[12] BB-823,[13] SDZ 64-412[14]	
3) Diaryl compounds: R, R', R" are alkoxy or sulphonyl.	L-652,731,[15] L-659,989.[16]	

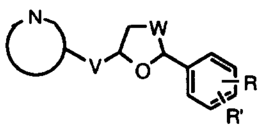
We recently reported the identification of an extremely potent PAF antagonist, BB-823;[13] a member of the second class of PAF antagonists for which an sp2 nitrogen atom plays a crucial role in receptor binding.[5,17] In this letter we describe a further series of PAF antagonists, as exemplified by general structure **I**, which combine key features of the sp2 nitrogen class with diaryl compounds such as L-659,989.



BB-823



L-659,989

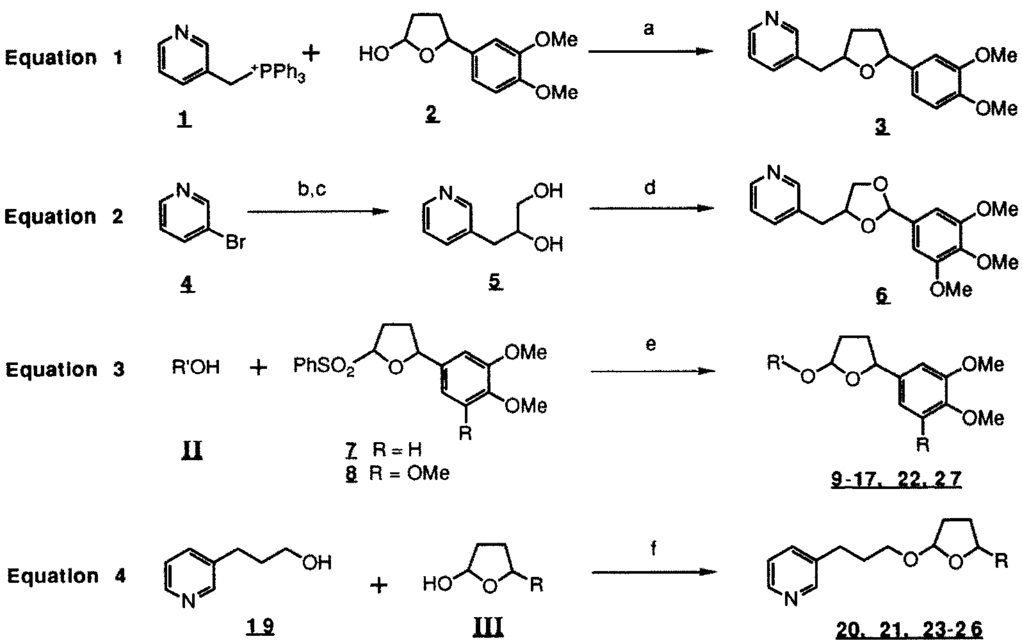


I

Chemistry

The tetrahydrofuran **3** was prepared as a 1:1 mixture of diastereoisomers by a Wittig reaction of a 3-picolyl phosphonium salt **1** with the lactol **2** (Equation 1). The 1,3-dioxolane derivative **6** was prepared as a 1:1 mixture of diastereoisomers by condensation of 3,4,5-trimethoxybenzaldehyde with the diol **5**, which in turn could be readily obtained from 3-bromopyridine (Equation 2).

Synthesis of cyclic ether PAF antagonists



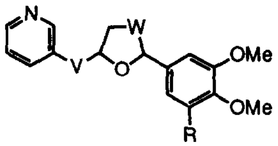
Reagents: (a) NaH, DMSO, 20-50°C, 3h, 27% (+ 44% 1-(3,4-dimethoxyphenyl)-6-(3-pyridyl)-5-hexen-1-ol); (b) CH_2=$CHCH_2MgBr$, [1,2-bis(diphenylphosphino)ethane]nickel(II) chloride, THF, 0°C-Δ, 6h, 72%; (c) OsO_4 NMMO, acetone/H_2O, 0-20°C, 3h, 50%; (d) 3,4,5-trimethoxybenzaldehyde, *p*-toluenesulphonic acid, toluene, DMF, 4Å molecular sieves, Δ, 3 days, 33%; (e) $MgBr_2.Et_2O$, $NaHCO_3$, THF, 20°C, 18h, 44-92%; (f) TFAA, Et_3N, CH_2Cl_2, 0-20°C, 1-6h, 53-94%. Satisfactory analytical and spectral data were obtained for new compounds.

The 2-alkoxytetrahydrofurans were obtained initially from Lewis acid catalysed condensation of the alcohols **II** with the phenylsulphones **7** and **8** (Equation 3).[18,19] However, this procedure was not generally applicable to a series of 5-aryltetrahydrofuran derivatives and we developed an alternative method. We found that the readily prepared lactols **III** could be coupled under mild conditions with the heterocyclic alcohol **19** in a reaction mediated by trifluoroacetic anhydride to give the 2-alkoxytetrahydrofurans **20**, **21**, **23-26** (Equation 4).[20] For 2-alkoxytetrahydrofurans **11** and **22-27** the *cis* and *trans* diastereoisomers were separated by chromatography over silica gel. A small NOE enhancement was observed between the protons at the 2- and 5- positions of the tetrahydrofuran ring for the *cis* but not the *trans* diastereoisomers. Diastereoisomeric ratios were determined by integration of the ^1H NMR signal for the proton at the 2-position of the *cis* and *trans* 2-alkoxytetrahydrofurans (*cis*; d at ca. δ 5.2 ppm: *trans*; dd at ca. δ 5.3 ppm). The N-methyl-3-pyridyl derivatives **18a** and **18b** were obtained in quantitative yield by treatment of the diastereoisomers **11a** and **11b** with methyl iodide.

Results and Discussion

Compounds were evaluated *in vitro* for the inhibition of [^{3}H]-PAF receptor binding to washed human platelet membranes and an IC_{50} value determined.[21] Since IC_{50} values are not absolute constants, SDZ 64-412[14] and L-659,989[16] were assayed as comparators and found to possess IC_{50} values, of 40 nM and 13 nM respectively, similar to the literature values. We decided to incorporate the 3-pyridyl group into our initial targets since this heterocycle is a feature of a number of members of the sp2 nitrogen heterocycle class of PAF antagonists.[5] The tetrahydrofuran derivative **3** proved to be a weak inhibitor of [^{3}H]-PAF receptor binding as was the dioxolane derivative **6** (Table 2).

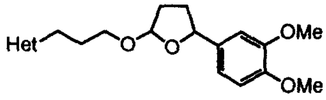
Table 2: Activities for variation of the cyclic ether and the spacer chain length



Compound	-V-	-W-	-R	Stereochemistry	IC_{50} nM
3	$-CH_2-$	$-CH_2-$	-H	1:1 *cis/trans*	60% @ 10,000 nM
6	$-CH_2-$	-O-	-OMe	1:1 *cis/trans*	35% @ 1,000 nM
9	$-CH_2O-$	$-CH_2-$	-H	1:1 *cis/trans*	25,000
10	$-(CH_2)_2O-$	$-CH_2-$	-H	1:1 *cis/trans*	15,000
11	$-(CH_2)_3O-$	$-CH_2-$	-H	1:1 *cis/trans*	300
11a	$-(CH_2)_3O-$	$-CH_2-$	-H	*cis*	150
11b	$-(CH_2)_3O-$	$-CH_2-$	-H	*trans*	4,000
12	$-(CH_2)_4O$	$-CH_2-$	-H	1:1 *cis/trans*	6,000
13	$-(CH_2)_5O-$	$-CH_2-$	-H	1:1 *cis/trans*	3,000
14	*E* $-CH{=}CHCH_2O-$	$-CH_2-$	-H	1:1 *cis/trans*	300
15	$-C{\equiv}CCH_2O-$	$-CH_2-$	-H	1:1 *cis/trans*	18,000
	SDZ 64-412			-	40
	L-659,989			*trans*	13

From a comparison with other sp2 nitrogen heterocycle PAF antagonists we reasoned that a greater distance would be required between the sp2 nitrogen heterocycle and the 'lipophilic' aryl group. We prepared the acetal derivatives **9-13** and found that compound **11** (IC_{50} 300 nM) with the 4 atom spacer between the 3-pyridyl and the THF moiety was more potent than either the shorter chain compounds **9** and **10** or the longer chain compounds **12** and **13** (Table 2). The individual diastereoisomers of **11** were assayed with the *cis* diastereoisomer **11a** exhibiting 25 fold greater potency than the *trans* diastereoisomer **11b** (Table 2). This is in contrast to the structure activity relationship (SAR) for the diastereoisomers of L-652,731,[15] L-659,989[16] and the Corey 2,5-diaryl-1,3-dioxolanes[22] for which the active diastereoisomer is *trans*, and suggests that compound **11a** is interacting with the PAF receptor in a different manner to the 2,5-diaryltetrahydrofuran derivatives.

Table 3: Activities for variation of the heterocycle



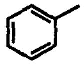
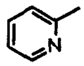
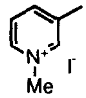
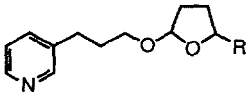
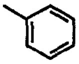
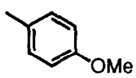
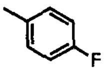
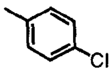
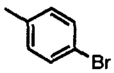
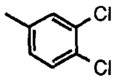
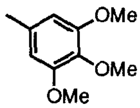
Compound	Het-	Stereochemistry	IC_{50} nM
16		1:1 *cis/trans*	0% @ 10,000 nM
17		1:1 *cis/trans*	20% @ 10,000 nM
18a		*cis*	1,000
18b		*trans*	3,000

Table 4: Activities for variation of the tetrahydrofuryl substituent

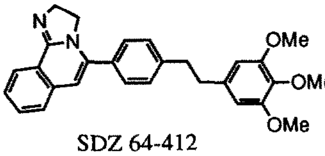


Compound	-R	Stereochemistry	IC_{50} nM
20	$-(CH_2)_6CH_3$	1:1 *cis/trans*	15% @ 10,000 nM
21		*trans*	6,000
22a		*cis*	2,000
22b		*trans*	4,000
23a		*cis*	230
23b		*trans*	4,000
24a		*cis*	1,000
24b		*trans*	5,000
25a		*cis*	800
25b		*trans*	4,000
26a		*cis*	200
26b		*trans*	2,500
27a		*cis*	100
27b		*trans*	1,500

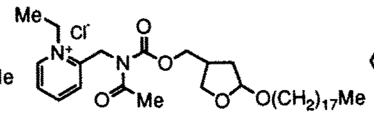
The effects of chain length suggested that there is a specific receptor interaction with the 3-pyridyl group. Further support for this came from the observation that the *E*-alkene **14**, which can place the sp2 nitrogen in a similar position to that in compound **11**, was active but the acetylene **15**, which cannot, was inactive. Confirmation of this specific interaction came from the observation that activity was lost when the 3-pyridyl group of compound **11** was replaced by phenyl or 2-pyridyl as in compounds **16** and **17** (Table 3).

We examined the effect on activity of changes to the 5-substituent of the THF ring for a series of compounds derived from 3-(3-pyridyl)propan-1-ol (**19**). For most of these compounds the diastereoisomers were separated and in all cases the *cis* was found to be more potent than the *trans* diastereoisomer (Table 4). Activity is lost when an aliphatic group (compound **20**) was employed instead of an aryl moiety as the 5-substituent. A brief exploration of aryl substituents revealed the following activity trend: 3,4,5-trimethoxy > 3,4-dimethoxy > 4-fluoro >> 4-bromo > 4-chloro >> 4-methoxy. Greater potency for trimethoxy over dimethoxy substitution is observed for the 2,5-diaryltetrahydrofurans,[15] and it is possible that the aryl group of the compounds described here is binding to a similar region of the PAF receptor as one of the aryl groups of the 2,5-diaryl-tetrahydrofurans.[5]

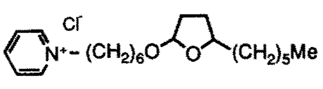
The SAR for the compounds reported here is similar to that reported for SDZ 64-412 and analogues[14] in that 3,4,5-trimethoxyphenyl is the preferred aryl group and that there is an optimal distance between this group and the sp2 nitrogen heterocycle. Indeed a comparison of molecular models for **27a** and SDZ 64-412 indicates that the distances from the sp2 nitrogens to the centroid of the aryl rings are similar for these two molecules. The SAR observed in this study for changes to the 3-pyridyl group is similar to that reported by Tilley and co-workers for a series of pyridoquinazoline carboxamide PAF antagonists,[23] and provides further evidence for a heterocyclic sp2 nitrogen atom being important for PAF antagonist activity. Quaternisation of the 3-pyridyl heterocycle leads to a reduction in activity for the N-methyl derivatives **18a** and **18b** (Table 3) suggesting that the sp2 nitrogen pharmacophoric group does not bind to the same region of the PAF receptor as the quaternised heterocycle moiety of the quaternised nitrogen class of PAF antagonists. Indeed, 2-alkoxytetrahydrofuran PAF antagonists reported in the literature[8,24] that belong to the quaternary nitrogen class[5] exhibit different SAR trends to the compounds reported here.[25] UR-11353, the lead compound in a series reported by Forn and co-workers, inhibits PAF-induced rabbit platelet aggregation with an IC_{50} value of 12 nM.[8] For this series the *trans* diastereoisomer is more potent than the *cis* and activity is lost when the long aliphatic chain is shortened. In a series of compounds reported by Godfroid and co-workers,[24] compound **30** is one of the more potent and inhibits PAF-induced rabbit platelet aggregation with an IC_{50} value of 1,600 nM.[24] Although the *cis* diastereoisomer is more potent than the *trans*, other diastereoisomers in the series show no significant difference in activities.[24] In contrast to the SAR for the 5-substituent observed here, an n-hexyl 'hydrophobic tail' was sufficient to provide 'potent antagonistic activity' and similar biological activity was obtained when this group was replaced by 3,4,5-trimethoxyphenyl.[24]



SDZ 64-412



UR-11353



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In conclusion, we have shown that for our series of cyclic ether acetal PAF antagonists the sp2 nitrogen atom of the 3-pyridyl group is a crucial requirement for good potency. A 4-atom linker between the heterocycles and *cis* stereochemistry is required in order to correctly orientate the nitrogen heterocycle with respect to the tetrahydrofuran ring and the optimal 3,4,5-trimethoxyphenyl substituent. In the following letter we report on the further optimisation of this series of PAF antagonists.

Acknowledgements: NOE determinations on diastereomeric 2-alkoxytetrahydrofurans were carried out by the late Dr Andy Derome. PAF antagonists were kindly provided by Sandoz (SDZ 64-412) and Merck, Sharp & Dohme (L-659,989).

References and Notes

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25. It should be noted that the comparison of SAR trends is complicated by the use of different *in vitro* assay systems.