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CYCLIC ETHER ACETAL PLATELET ACTIVATING FACTOR (PAF) RECEPTOR ANTAGONISTS II: IMIDAZO[4,5-c]PYRIDYL DERIVATIVES

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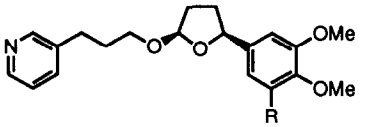
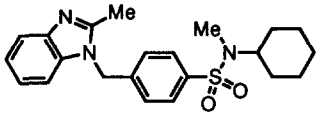
Abstract: The 1H-2-methylimidazo[4,5-c]pyridyl group has been found to be the optimal heterocycle for a series of cyclic ether acetal PAF antagonists. A lead compound **8** inhibits [^{3}H]-PAF receptor binding to washed human platelets with an IC_{50} value of 15 nM, and both PAF-induced hypotension and endotoxin-induced hypotension in anaesthetised rats with ED_{50} values of 1.4 μg/kg *i.v.* and 19 μg/kg *i.v.* respectively.

There is considerable interest in receptor antagonists of platelet activating factor (PAF) as this phospholipid appears to be involved in many inflammatory disorders.[1-3] For example PAF, with other mediators, is released during endotoxin shock and administration of PAF mimics the shock state in animals causing hypotension.[4] In the preceding letter we reported a series of 3-pyridyl cyclic ether acetal PAF antagonists that included compounds **1** and **2**.[5] This series of compounds can be viewed as consisting of a nitrogen heterocycle linked by a spacer group to an aryl substituted tetrahydrofuran. The *in vitro* activity data for this series indicate that the sp2 nitrogen atom of the 3-pyridyl heterocycle is crucial for potency, that the optimal spacer length is 4 atoms, the preferred aryl group is 3,4,5-trimethoxyphenyl, and the *cis* diastereoisomers are more potent than the *trans*.[4] At the same time that compounds **1** and **2** were identified we were also working on another series of PAF antagonists, the lead compound of which was BB-182 (**3**).[6] We were interested in the relationship between these two series, in particular the possibility that the 3-pyridyl moiety and alkyl spacer in compound **1** could be replaced with the benzimidazolyl heterocycle and benzyl spacer of BB-182. We report here on the synthesis, structure activity relationships (SARs) and preliminary *in vivo* results for these novel PAF antagonists which have led to the identification of potent imidazo[4,5-c]pyridyl derivatives.



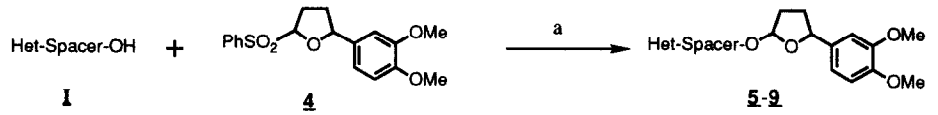
1 R = H IC_{50} 150 nM
2 R = OMe IC_{50} 100 nM



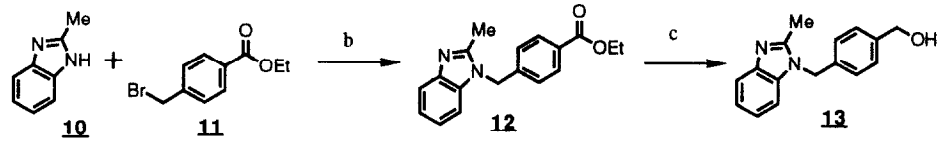
3 (BB-182) IC_{50} 300 nM

Synthesis of cyclic ether PAF antagonists

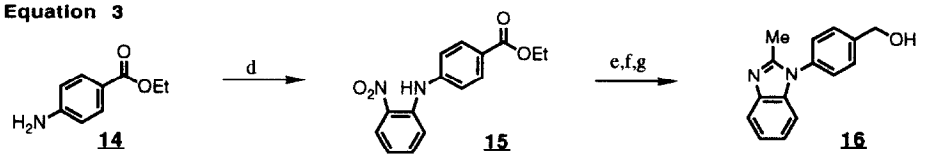
Equation 1



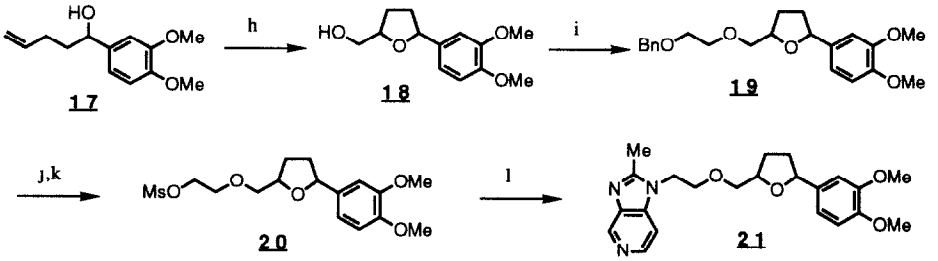
Equation 2



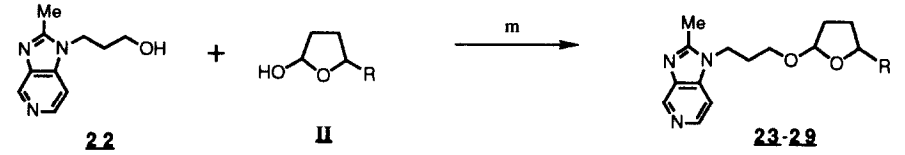
Equation 3



Equation 4



Equation 5



Reagents: (a) $MgBr_2.Et_2O$, $NaHCO_3$, THF, 20°C, 18h, 44-92%; (b) NaH, THF, 0-20°C, 18h, 34%; (c) $LiAlH_4$, THF, -20-20°C, 18h, 93%; (d) 1-fluoro-2-nitrobenzene, KF, 180°C, 48h, 22%; (e) $Na_2S_2O_4$, EtOH, Δ, 0.75h, 71%; (f) MeC(=NH)OEt.HCl, EtOH, 20°C, 2h, 16%; (g) $LiAlH_4$, THF, -20-20°C, 18h, 97%; (h) mCPBA, CH_2Cl_2, 0-20°C, 18h, 29%; (i) NaH, $MsO(CH_2)_2OBn$, DMF, 0-20°C, 5 days, 65%; (j) H_2, Pd-C, EtOH, 20°C, 8h, 26%; (k) MsCl, Et_3N, CH_2Cl_2, 0°C, 1.75h, 100%; (l) 2-methylimidazo[4,5-c]pyridine, NaH, THF/DMF, 0-20°C, 18h, 2%; (m) TFAA, Et_3N, CH_2Cl_2, 0-20°C, 1-6h, 53-94%. Satisfactory analytical and spectral data were obtained for new compounds.

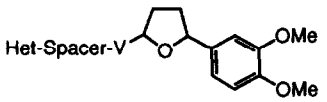
Chemistry

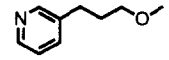
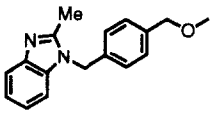
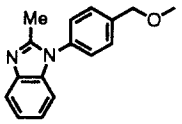
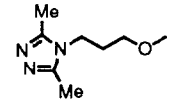
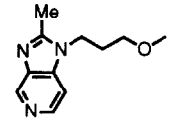
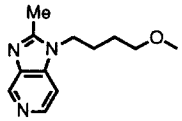
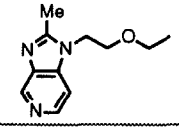
2-Alkoxy-5-(3,4-dimethoxyphenyl)tetrahydrofurans (**5-9**) were obtained by Lewis acid catalysed condensation of the alcohols **I** with the phenylsulphone **4** (Equation 1).[7,8] The alcohols **I** were prepared by a variety of methods. Alcohol **13** was prepared by the alkylation of 2-methylbenzimidazole (**10**) followed by reduction (Equation 2) and **16** was obtained by arylation of the amine **14**[9] followed by a sequence of reduction of the nitro group, benzimidazole formation and reduction of the ester (Equation 3). The alcohols required for the preparation of cyclic acetals **7**, **8** and **9** were obtained by methods analogous to those reported by Cooper.[10] The tetrahydrofuran derivative **21** was prepared by oxidative cyclisation of **17** followed by chain extension and alkylation of 2-methylimidazo[4,5-c]pyridine (Equation 4). This last reaction gives a mixture of three regioisomers from which the desired 1H-regioisomer was separated in low yield by chromatography. Cyclic acetals **23-29** were prepared by condensation of the lactols **II** with the alcohol **22** mediated by trifluoroacetic anhydride.[11] Cyclic ether acetals were obtained as mixtures of diastereoisomers.[5] The *cis* and *trans* diastereoisomers of **8** were separated by preparative reverse phase hplc.

Results and Discussion

Compounds were evaluated *in vitro* as inhibitors of [^{3}H]-PAF receptor binding to washed human platelet membranes and an IC_{50} value determined.[12] Selected compounds were tested *in vivo* for their ability to reverse the hypotension induced in anaesthetised rats by an infusion of PAF and an ED_{50} value determined.[12] From the synthesis of analogues of BB-182 it was apparent that the unsubstituted sp2 nitrogen of the benzimidazole was required for activity and that methyl was the optimal substituent in the 2-position.[6] However, the cyclic ether acetal **5** incorporating both the 2-methybenzimidazole and the benzyl spacer moiety of BB-182 was significantly less active *in vitro* than the 3-pyridyl derivative **1** (Table 1). We reasoned that this poor activity was probably due to the longer length and inflexibility of the spacer for **5**. Although shortening the spacer chain as in **6** did give a modest improvement in activity *in vitro*, the compound was essentially inactive *in vivo*. A review of PAF antagonists indicates that certain other sp2 nitrogen heterocycles have been used in place of a 3-pyridyl group.[3] We therefore decided to prepare a series of heterocycles connected to the tetrahydrofuryl moiety by the flexible alkyl spacer group found in compound **1**. Replacement of the 3-pyridyl group with 3,5-trimethyl-1,2,4-triazol-4-yl in compound **7**, gave a similar level of *in vitro* potency, but the 2-methylimidazo[4,5-c]pyridyl moiety (**8**) resulted in a significant increase in activity both *in vitro* and *in vivo* (Table 1). As observed for the 3-pyridyl derivative **1**[5] the *cis* diastereoisomer **8a** is more potent than the *trans* diastereoisomer **8b**, but the difference is not as pronounced (Table 1). As expected from the SAR for the 3-pyridyl derivative **1**[5], elongation of the spacer chain as in **9** significantly reduced *in vitro* activity. Interestingly, the tetrahydrofuran derivative **21**, which has the same spacer length as **8** was also less potent. This could be due either to the effect the acetal grouping has on the conformation of the side chain and/or a receptor interaction with the acetal moiety itself that is not satisfied by the tetrahydrofuran derivative **21**. We recently reported on a molecular modelling comparison of five members of the sp2 nitrogen heterocycle class of PAF antagonists that possess a carbonyl (or sulphonyl) group and suggested that this group provides an interaction with the receptor by a hydrogen bond.[13] It is possible that the acetal function of the series of 2-alkoxytetrahydrofuran PAF antagonists reported here may provide such an interaction.

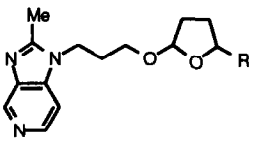
Table 1: Activities for variation of the heterocycle

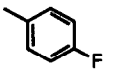
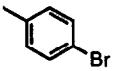
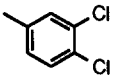
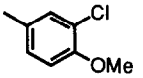
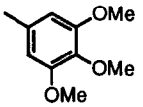


Compound	Het-Spacer-V-	Stereochemistry	*In vitro* (IC_{50} nM)	*In vivo* (ED_{50} μg/kg *i.v.*)
1		*cis*	150	7.8±0.7
5		1:1 *cis/trans*	2,000	-
6		1:1 *cis/trans*	900	11% @ 10 mg/kg
7		1:1 *cis/trans*	250	-
8 BB-654		1:1 *cis/trans*	15	1.4±0.5
8a		*cis*	7	-
8b		*trans*	25	-
9		1:1 *cis/trans*	500	2.8±0.8
21		1:1 *cis/trans*	500	-
	L-659,989	*trans*	13	6.9±0.6

Compound **8**, although equipotent with the 2,5-diaryltetrahydrofuran compound L-659,989[14] *in vitro*, was found to possess greater activity *in vivo*. We therefore decided to concentrate on this lead and examined the effect of varying substituents on the aryl group. Activity was reduced for the alkyl derivative **23** and the unsubstituted phenyl derivative **24** (Table 2). The trend in *in vitro* activity for aryl substitution (3-chloro-4-methoxy > 3,4-dichloro > 4-fluoro > 4-bromo >3,4-dimethoxy > 3,4,5-trimethoxy) is different to that observed for the corresponding 3-pyridyl derivatives for which 3,4,5-trimethoxy substitution is optimal.[5] The optimal compound *in vivo* was the 4-fluorophenyl derivative **25** (Table 2).

Table 2: Activities for variation of the tetrahydrofuryl substituent



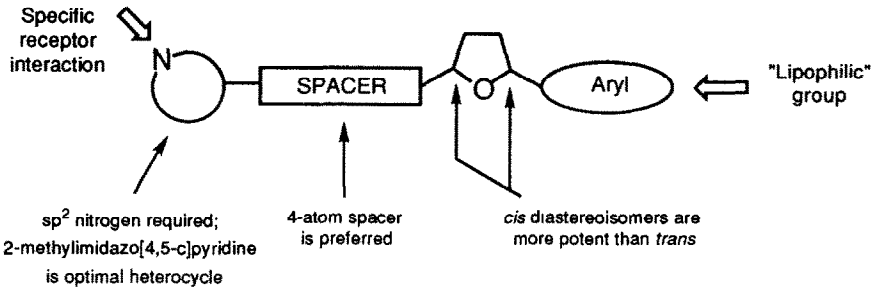
Compound	-R	Stereochemistry	*In vitro* (IC_{50} nM)	*In vivo* (ED_{50} μg/kg *i.v.*)
23	$-(CH_2)_6CH_3$	1:1 *cis/trans*	120	2.1±0.9
24		1:1 *cis/trans*	190	-
25		1:1 *cis/trans*	7	1.1±0.1
26		1:1 *cis/trans*	10	-
27		1:1 *cis/trans*	5	1.9±0.2
28		1:1 *cis/trans*	3	1.8±0.2
29		1:1 *cis/trans*	20	3.2±0.5

A comparison of the activities of the 3-pyridyl derivatives, described in the preceding communication,[5] with those of the corresponding 2-methylimidazo[4,5-c]pyridine compounds indicates that the latter heterocycle consistently confers greater potency. We have also found that 2-methylimidazo[4,5-c]pyridine analogues of BB-182 are particularly potent and we recently identified a PAF antagonist (BB-823) with picomolar activity.[13,15]

As a result of this study, **8** (BB-654) has been selected for further pharmacological testing and the compound shows promising activity in a model of septic shock. Endotoxin (*E. coli* acetone powder 100 mg/kg *i.v.*) gave a reproducible sustained fall in blood pressure when administered to anaesthetised rats.[12] Intravenous administration of BB-654 resulted in a transient reversal of the endotoxin-induced hypotension that was dose dependent (ED_{50} 19 μg/kg). That the ED_{50} value is greater than that obtained for the inhibition of PAF-induced hypotension may reflect differences in the effects of PAF released endogenously to those of PAF applied exogenously.

In conclusion, we have identified a novel series of cyclic ether acetal PAF antagonists that consist of a nitrogen heterocycle linked by a spacer group to an aryl substituted tetrahydrofuran (Figure). The structure activity relationships presented here and in the preceding letter indicate that an sp2 nitrogen atom correctly orientated with respect to the THF aryl substituent is a crucial requirement for activity. The preferred nitrogen heterocycle is 2-methylimidazo[4,5-c]pyridine, the optimal spacer length is 4 atoms and the *cis* diastereoisomers are more potent than the *trans*.

Figure: Schematic representation of cyclic ether acetal PAF antagonists



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References and Notes

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12. Protocols for the *in vitro* and *in vivo* assays used in this study are given in reference 15. Receptor binding assays were conducted in triplicate and results given here are means of 2-4 separate experiments. Results for inhibition of PAF-induced hypotension are given as mean ± SEM for n=4-8.
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