Development of a Novel Series of Trialkoxyaryl Derivatives as Specific and Competitive Antagonists of Platelet Activating Factor

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The synthesis and structure–activity relationship (SAR) analysis of a novel series of trialkoxyaryl derivatives, as specific and competitive inhibitors of platelet activating factor (PAF), are described. Molecular modeling comparisons of PAF with the known antagonists Ginkgolide B and L-652731 led to the selection of *N*-[2-[(3,4,5-trimethoxybenzoyl)oxy]ethyl]-*N*,*N*,*N*-trimethylammonium iodide (**1**) from the Wellcome registry of compounds and to the synthesis of the lead compound *N*-[2-[[4-(hexyloxy)-3,5-dimethoxybenzoyl]oxy]ethyl]-*N*,*N*,*N*-trimethylammonium iodide (**3**, pK_b 5.43). Further SAR considerations directed the design to 2-(hexyloxy)-1,3-dimethoxy-5-[4-(4-methylthiazol-5-yl)butyl]benzene (**38**) (pK_b 7.14), a novel, specific, and competitive inhibitor of the PAF receptor in rabbit-washed platelets.

Introduction

Platelet activating factor (1-*O*-alkyl-2-acetyl-*sn*-glyceryl-3-phosphorylcholine; PAF)[1–4] has been shown to be the most powerful inducer of platelet aggregation yet described and its isolation and/or activity in a diversity of animal models of human disease[5] has implicated the compound as a powerful mediator of inflammation. In recent years these studies have been extended such that PAF is now thought to play a major role in a number of pathological disease states in humans, such as bronchial asthma,[6] inflammatory bowel disease,[7] septic shock,[8] and brain injury.[9] The ether lipid is thought to exert its effects by interaction with specific receptors[10] located on a diversity of cell types, and the significance of PAF in human disease has led to the development of a number of compounds which are purported to antagonize the interaction of PAF with these receptors.[11]

In this study we now describe the synthesis and development of a novel series of selective PAF receptor antagonists, together with the methods for their evaluation.

Chemistry

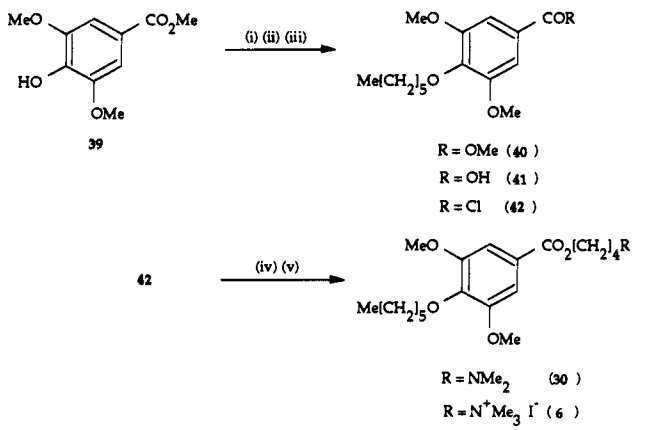
All compounds described in Tables 1–3, except **1**, are novel, and their syntheses are outlined in Schemes 1–7.

Scheme 1 illustrates the synthesis of quaternary amine **6** but has also been applied to others indicated in the tables. Thus, using a phase transfer catalyst, methyl syringate **39** was readily alkylated to triether **40** and then subsequently hydrolyzed, under basic conditions, to acid **41**. Treatment of **41** with thionyl chloride gave acid chloride **42**. Tertiary amine **30** was obtained from **42** by esterifying with 4-(dimethylamino)-butanol and then was quaternized with MeI to yield **6**.

The tertiary amines **30** were sometimes difficult to purify, so the opportunity was taken to examine other syntheses which did not proceed through tertiary amines. In particular, esterification of acid chloride **43** with THF in the presence of zinc chloride (Scheme 2) gave the chloro compound **44** which, by standard methods, was converted to the readily purified iodo analogue **45**. Trimethylamine then gave crystalline **20** which was easily separated from **45**.

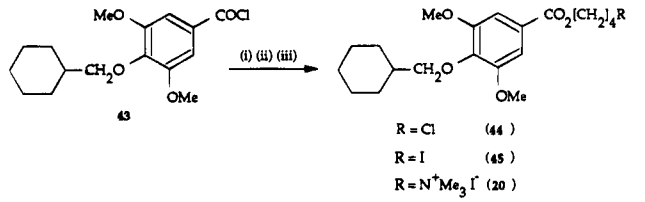
Scheme 3 illustrates the synthesis of the phenol **49** and its conversion into the quaternary amine **21** with its reversed ester configuration. Syringaldehyde **46** was alkylated, as before, to **47**, and the resultant aldehyde was oxidized, with *m*-chloroperoxybenzoic acid, to formate **48** before basic hydrolysis to phenol **49**. Dicyclo-

Scheme 1[a]



[a] Reagents: (i) Me[CH_2]$_5$Br, Bu_4NHSO_4, K_2CO_3, toluene; (ii) NaOH, EtOH; (iii) $SOCl_2$; (iv) $Me_2N[CH_2]_4OH$, toluene; (v) MeI, MeOH.

Scheme 2[a]



[a] Reagents: (i) THF, $ZnCl_2$; (ii) NaI, MeCOEt; (iii) Me_3N, EtOH, MeCOEt.

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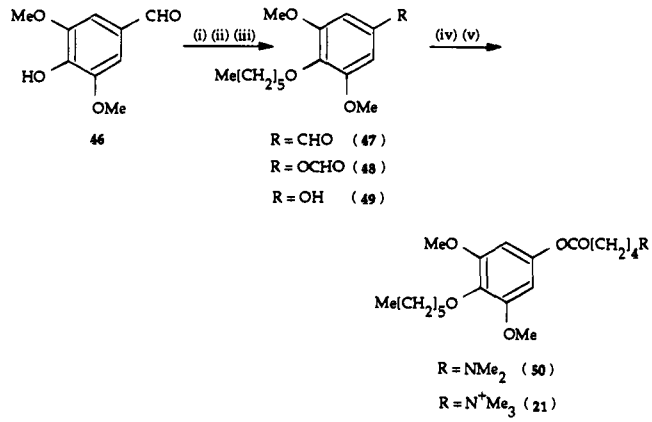
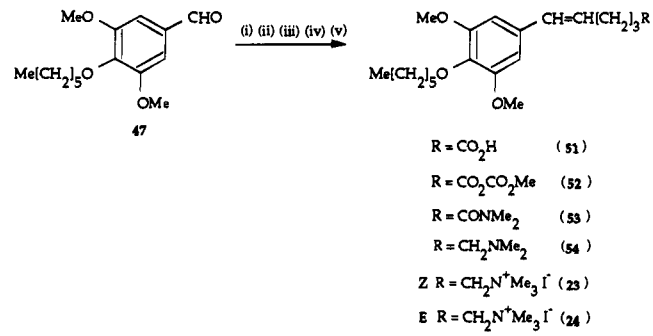
Scheme 3[a]



[a] Reagents: (i) $Me[CH_2]_5Br$, K_2CO_3, Bu_4NHSO_4, toluene; (ii) *m*-CPBA, DCM; (iii) KOH, H_2O, MeOH; (iv) $Me_2N[CH_2]_4CO_2H$, DMAP, DCCI, DMF; (v) MeI, Me_2CO.

Scheme 4[a]



[a] Reagents: (i) $Ph_3P^+[CH_2]_4CO_2H\ Br^-$, PhH, *t*-BuOK; (ii) Et_3N, MeOCOCl, THF; (iii) Me_2NH, EtOH, THF; (iv) $LiAlH_4$, Et_2O; (v) MeI, Me_2CO.

hexylcarbodiimide coupling of the phenol with 5-(dimethylamino)pentanoic acid led to **50** which on methylation with methyl iodide gave a low yield of the quaternary base **21**.

Analogues without the ester moiety, but with some conformational restriction, were synthesized *via* the route illustrated by Scheme 4. The Wittig reaction of (4-carboxybutyl)triphenylphosphorane with aldehyde **47** yielded olefinic acid **51**. Methyl chloroformate at low temperature gave mixed anhydride **52**, and the action of dimethylamine on this gave a mixture of the *E* and *Z* isomers of amide **53**. Flash chromatography separated the two isomers, and each was taken through the rest of the synthesis in turn. Lithium aluminum hydride reduction of the amide group of *Z*-**53** proceeded, without concomitant reduction of the olefin, to give tertiary amine *Z*-**54** which was then quaternized as usual giving **23**. The *E* isomer **26** was obtained similarly.

Purification problems attended the synthesis of **25** by reduction of the olefinic moiety of **23** or **24**; hence, its preparation *via* Scheme 5 was examined. The olefinic alcohol **55**, obtained from aldehyde **47** by a standard Wittig reaction, was hydrogenated over 10% palladium on charcoal to give the hexanol **56**. Tosylation followed by reaction with lithium iodide gave a readily purifiable iodo derivative **58**. Trimethylamine then yielded the quaternary base **25** as an oil.

The incorporation of a phenyl ring into the link between ester and quaternary amine was achieved by the synthesis described in Scheme 6. Here the phenolic alcohol **61** was made by reduction of the mixed anhydride **60** derived from 2-hydroxyphenylacetic acid **59** and ethyl chloroformate. The phenol was then reacted with acid chloride **42** to give ester **62** which was converted, as described above, to the desired compound **26**.

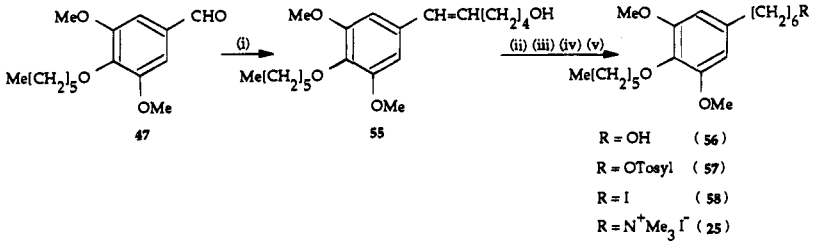
Finally, the synthesis of **38**, a compound made to avoid problems associated with quaternary bases, is shown in Scheme 7. One intermediate, phosphonium salt **67**, was readily prepared following sodium borohydride reduction of aldehyde **47** to alcohol **65**, bromination to **66**, and subsequent treatment with triphenylphosphine. The other intermediate, aldehyde **71**, was unstable and hence was used immediately on synthesis. This was achieved by reductive hydrolysis of nitrile **70**, which itself was made from alcohol **68** *via* mesylate **69**. The reaction of aldehyde **71** and phosphonium salt **67** gave a 2:1 mixture of the *E* and *Z* isomers of olefin **72**. The stereoisomeric mixture was hydrogenated over 10% palladium on charcoal to give **38**.

Results and Discussion

In a preliminary modeling exercise, employing conventional three-dimensional computer-graphic techniques, we were able to overlay the PAF molecule and two known PAF antagonists, Ginkgolide B and L-652731 (Figure 1).[12] By superimposing the common features of the PAF molecule and the antagonists, several overlays were possible, and from one such overlay an initial target structure (compound **1**) was selected from the Wellcome registry of compounds. This compound, *N*-[2-[(3,4,5-trimethoxybenzoyl)oxy]ethyl]-*N*,*N*,*N*-trimethylammonium iodide (**1**),[13] exhibited weak PAF antagonist activity. The modeling exercise also indicated that replacement of the 4-methoxy moiety of **1** with a long alkoxy chain would mimic the PAF molecule more closely and, indeed, as the chain was extended (**2** and **3**), the antagonist potency did increase. However, the longer chain molecule (**4**) also inhibited the aggregation of platelets induced by ADP and U46619, indicating a nonspecific effect on platelet function. Nevertheless, these preliminary studies had generated a lead compound (**3**) which was a novel, specific, competitive inhibitor of PAF-induced platelet aggregation with an acceptable level of activity ($pK_b = 5.43$).

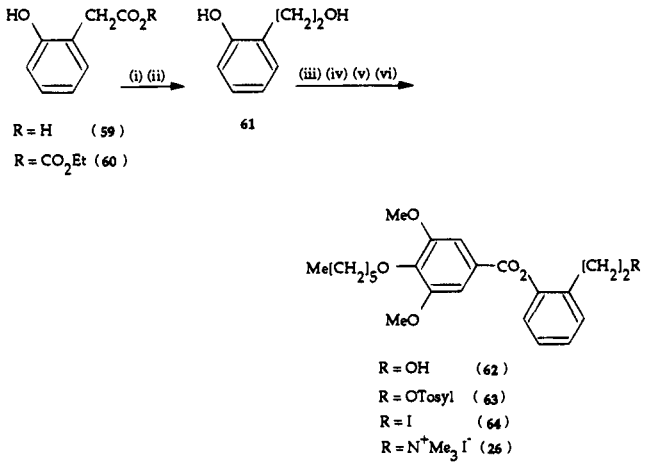
At this stage a conventional chemical approach to examine SAR was employed. Table 1 shows the compounds synthesized to explore the methylene chain length between the ester and quaternary amine moieties. Optimal activity and selectivity was obtained with four methylenes (**6**) (pK_b 6.01). As this was an increase in potency, albeit modest, this aspect of the inhibitor molecule was retained and other alkoxy substituents were examined more thoroughly (Table 2). The longer 4-alkoxy substituents (**10**, **11**, and **12**), as with compound **4** (Table 1), again introduced nonspecificity into the antagonist molecule's actions. The highest affinity, with specificity, was found with hexyloxy **6**. The position of the hexyloxy chain on the phenyl ring was found to be important; *para* to the ester group gave a compound with higher affinity than its *meta* analogue (**17**). Antagonist activity was also reduced when this hexyl chain was replaced by either an aliphatic (**19** and **20**) or aromatic (**18**) ring system. Replacement of the methoxyl moieties by hydrogen, methyl or chlorine (**13**,

Scheme 5[a]



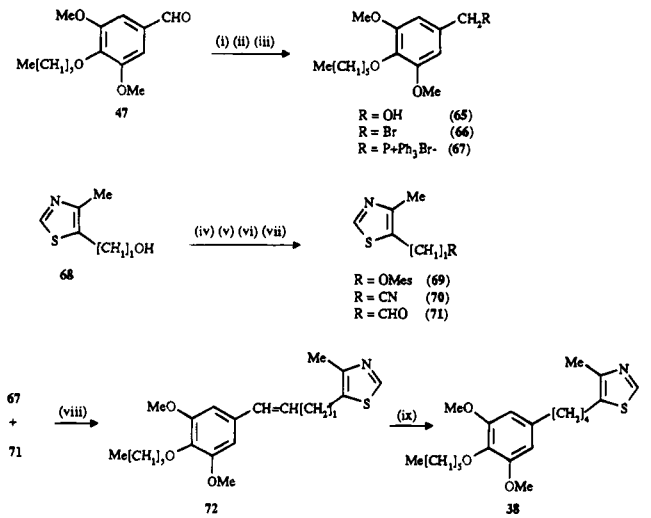
[a] Reagents: (i) $Ph_3P^+[CH_2]_5OH\ Br^-$, PhH, *t*-BuOK; (ii) H_2, Pd/C, MeOH; (iii) *p*-TsCl, pyridine; (iv) LiI, Me_2CO; (v) Me_3N, EtOH, MeOH.

Scheme 6[a]



[a] Reagents: (i) Et_3N, EtOCOCl, THF; (ii) $NaBH_4$, H_2O, THF; (iii) **42**, THF, 2 M NaOH; (iv) *p*-TsCl, pyridine; (v) LiI, Me_2CO; (vi) Me_3N, EtOH, MeOH.

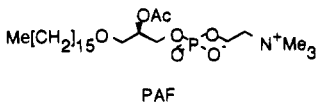
Scheme 7[a]



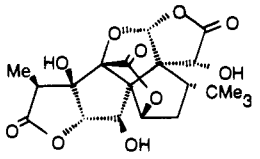
[a] Reagents: (i) $NaBH_4$, Me_2CHOH: (ii) HBr, $CHCl_3$; (iii) Ph_3P, toluene; (iv) MesCl, DCM; (v) KCN, 18-crown-6, DMF; (vi) DIBAL-H, toluene; (vii) 2 M HCl; (viii) *t*-BuOK, THF; (ix) H_2, Pd/C EtOAc.

14, **15**, and **16**) was unfavorable, with the more lipophilic compounds (**14**, **15**, and **16**) showing nonspecificity as well as reduced antagonist potency. These initial results suggested that 4-(hexyloxy)-3,5-dimethoxy (as in **6**) was the optimum substituent pattern for this part of the molecule.

Examination of the variations to the spacer chain, between the phenyl ring and nitrogen-containing moiety, and to the nitrogen-containing group itself, were carried out concurrently (Table 3). A lowering in affinity was seen when the ester group was "reversed" (**21**) or moved within the chain (**22**). Similarly the introduction



PAF



Ginkgolide B

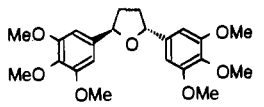


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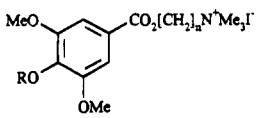
Figure 1.

Table 1. *N*-[ω-[[4-(Alkyloxy)-3,5-dimethoxybenzoyl]oxy]alkyl]-*N*,*N*,*N*-trimethylammonium Iodides



compd	R	*n*	synthetic method	mp (°C)	formula	analyses
1	Me	2	A	180–181[a]	$C_{15}H_{24}NO_5I$	C, H, N
2	$Me[CH_2]_3$	2	A	185	$C_{18}H_{30}NO_5I$	C, H, N
3	$Me[CH_2]_5$	2	A	187–189	$C_{20}H_{34}NO_5I$	C, H, N
4	$Me[CH_2]_9$	2	A	186	$C_{24}H_{42}NO_5I$	C, H, N
5	$Me[CH_2]_5$	3	A	154–155	$C_{21}H_{36}NO_5I$	C, H, N
6	$Me[CH_2]_5$	4	A	137–138	$C_{22}H_{36}NO_5I$	C, H, N
7	$Me[CH_2]_5$	6	A	68–71	$C_{24}H_{42}NO_5I \cdot H_2O$	C, H, N

[a] Literature[13] mp 175–178 °C.

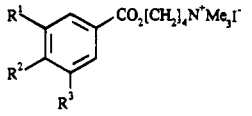
of a benzene ring into the chain (**26**, **27**, and **28**) also reduced activity, but in these cases nonspecificity also appeared.

An apparent increase in affinity was seen when the ester group of **6** was replaced by two methylenes, **25**; however, handling and solubility problems prevented accurate biological measurements. The *E*-olefin intermediate to this compound (**24**) had a higher activity (pK_b 6.21) than either its *Z*-analogue (**23**) or the ester analogue (**6**), suggesting that conformational constraints on the molecule might lead to improved potency.

A number of nitrogen-containing end groups were examined (Table 3) and a variety of quaternary nitrogen-containing "bulky" systems could not only be accommodated by the receptor (**29**, **31**, **32**, and **33**), but in some cases their affinity was increased. Even higher affinities were achieved by the introduction of both conformational constraints and bulk into the "spacer chain" as well as the end group (**34**, **35**, and **37**).

Although simple tertiary amines such as **30** lowered affinity by 1 order of magnitude, the thiazole **36** had an affinity equal to the corresponding quaternary amine **6**. Combination of this end group with a tetramethylene "spacer chain" gave **38** (pK_b 7.14), a novel, potent,

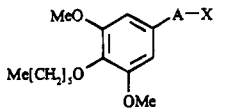
Table 2. *N*-[4-[(Substituted-benzoyl)oxy]butyl]-*N,N,N*-trimethylammonium Iodides



compd	R^1	R^2	R^3	synthetic method	mp °C	formula	analyses
8	MeO	$Me[CH_2]_4O$	MeO	A	142–142.5	$C_{21}H_{36}NO_5I$	C, N; H[a]
9	MeO	$Me[CH_2]_6O$	MeO	A	139.5–140.5	$C_{23}H_{40}NO_5I$	C, H, N
10	MeO	$Me[CH_2]_7O$	MeO	A	138.5–140	$C_{24}H_{42}NO_5I$	C, H, N
11	MeO	$Me[CH_2]_9O$	MeO	A	144–146	$C_{26}H_{46}NO_5I$	H, N; C[b]
12	MeO	$Me[CH_2]_{15}O$	MeO	A	142–144	$C_{32}H_{58}NO_5I$	C, H, N
13	MeO	$Me[CH_2]_5O$	H	A	140–141	$C_{21}H_{36}NO_4I$	C, H, N
14	H	$Me[CH_2]_5O$	H	A	179–180	$C_{20}H_{34}NO_3I$	C, H, N
15	MeO	$Me[CH_2]_5O$	Cl	B	113–114	$C_{21}H_{35}NO_4ClI$	C, H, N
16	Me	$Me[CH_2]_5O$	Me	B	163–164	$C_{22}H_{38}NO_3I$	C, H, N
17	$Me[CH_2]_5O$	MeO	MeO	A	83–85	$C_{22}H_{36}NO_5I \cdot {}^3/_4H_2O$	C, H, N
18	MeO	$PhCH_2O$	MeO	A	158–162[c]	$C_{23}H_{32}NO_5I$	C, H, N
19	MeO	$C_5H_9[CH_2]_2O$	MeO	A	135–137	$C_{23}H_{38}NO_5I$	C, N; H[d]
20	MeO	$C_6H_{11}CH_2O$	MeO	B	148–150	$C_{23}H_{38}NO_5I$	C, H, N, I

[a] H: calcd, 7.07; found, 6.57. [b] C: calcd, 53.89; found, 53.28. [c] Decomposed. [d] H: calcd, 7.10; found, 7.67.

Table 3. 4-(Hexyloxy)-3,5-dimethoxyphenyl Derivatives



compd	A	X	synthetic method	mp (°C)	formula	analyses
21	$OCO(CH_2)_4$	N^+Me_3	C	75–77	$C_{22}H_{38}NO_5I \cdot {}^1/_2H_2O$	C, H, N
22	$CH_2CO_2(CH_2)_3$	N^+Me_3	C	100–102	$C_{22}H_{38}NO_5I$	C, H, N
23	*Z*[a] $CH{=}CH(CH_2)_4$	N^+Me_3	D	85–87	$C_{23}H_{40}NO_3I$	C, H, N
24	*E*[b] $CH{=}CH(CH_2)_4$	N^+Me_3	D	148–150	$C_{23}H_{40}NO_3I \cdot {}^1/_3H_2O$	C, H, N
25	$(CH_2)_6$	N^+Me_3	E	c	$C_{23}H_{42}NO_3I$	
26	$CO_2C_6H_4$-2-$(CH_2)_2$	N^+Me_3	F	181–182.5	$C_{26}H_{38}NO_5I$	C, H, N
27	$CO_2C_6H_4$-4-$(CH_2)_2$	N^+Me_3	F	205–206	$C_{26}H_{38}NO_5I$	C, H, N
28	$CO_2CH_2C_6H_4$-2-CH_2	N^+Me_3	A	189[d]	$C_{26}H_{38}NO_5I$	C, H, N
29	$CO_2(CH_2)_4$	N^+Et_3	A	*e*	$C_{25}H_{44}NO_5I \cdot H_2O$	C, H, N
30	$CO_2(CH_2)_4$	NMe_2	A	113–114	$C_{21}H_{35}NO_5 \cdot HCl \cdot {}^1/_2H_2O$	C, H, N
31	$CO_2(CH_2)_4$	pyridinium	B	104–104.5	$C_{24}H_{34}NO_5I$	H, N; C[f]
32	$CO_2(CH_2)_4$	quinolinium	B	98.5–100	$C_{28}H_{36}NO_5Cl \cdot {}^2/_3H_2O$	C, H, N
33	$CO_2(CH_2)_4$	thiazolium	B	113–115	$C_{22}H_{32}NO_5SCl$	C, H, N
34	CO_2	*g*	A	141–143	$C_{25}H_{30}NO_5I$	C, H, N
35	CO_2	*h*	A	151–153	$C_{25}H_{30}NO_5I \cdot C_2H_5OH$	C, H, N
36	$CO_2(CH_2)_2$	*i*	A	138.5–140.5	$C_{21}H_{29}NO_5S \cdot HBr$	C, H, N
37	$CO_2(CH_2)_2$	*j*	A	132.5–134.5	$C_{22}H_{32}NO_5SI$	C, H, N
38	$(CH_2)_4$	*i*	G	98–99.5	$C_{22}H_{33}NO_3S \cdot HBr$	C, H, N

[a] 3% of *E* isomer. [b] 5% of *Z* isomer. [c] Oil. [d] Decomposed. [e] Pasty solid. [f] C: calcd, 53.04; found, 53.54. [g] *N*-Methylquinolinium-6-yl. [h] *N*-Methylquinolinium-8-yl. [i] 4-Methylthiazol-5-yl. [j] 3,4-Dimethylthiazol-5-yl.

specific, and competitive inhibitor of the PAF receptor in rabbit-washed platelets.

Biological Assay Methods

1. Preparation of Platelet Suspensions. Blood was withdrawn from the carotid artery of anaesthetized male New Zealand White rabbits (2–3 kg) into polycarbonate tubes containing sodium citrate [final concentration 0.315% (w/v)]. Platelet-rich plasma was prepared by the immediate centrifugation of the blood at 220*g* for 15 min at room temperature. Washed platelet (WP) suspensions were prepared as previously described,[14] using prostacyclin to protect the cells from activation during isolation procedures. The final platelet suspension was prepared in prostacyclin-free Tyrodes solution (3×10^8 platelets/mL) and stored at room temperature for at least 2 h in order to achieve maximum sensitivity to aggregatory agonists.

2. Aggregation Assays. i. Primary Assay: Estimation of IC_{50} Ratio. Platelet aggregation was monitored in a dual-channel Payton aggregometer according to the light transmission method of Born.[15] A dose–response curve to PAF was established and the ED_{50} concentration determined. Aggregations to this dose of PAF in the presence of a range of concentrations of antagonist were measured, and the IC_{50} for the antagonist was estimated. In each experiment the IC_{50} value for an internal reference compound (**3**) was also determined such that the IC_{50} ratio for each antagonist could be calculated according to the formula IC_{50} ratio = 1000 (IC_{50} new compound)/(IC_{50} of reference compound **3**) This simple system determined the relative antagonist potency of each compound, thereby allowing rapid selection of potent compounds for further screening. The range of IC_{50} values obtained for the reference compound was 0.65–7.25 μM: mean = 2.41 ± 0.14. (n = 85).

ii. Secondary Assay: Determination of pK_b. Full dose-response curves for PAF-induced platelet aggregation in the presence of a range of concentrations of a

Table 4. Biological Results

compd	PAF-induced aggregation IC50 ratio[a]	PAF-induced aggregation pKb	PAF binding pKi	ADP aggregation IC50, μM
1	15000			
2	3371			NE[b] at 50
3	1000	5.43		NE at 50
4	153		5.8	2
5	7000			NE at 50
6	164	6.01	6.57	NE at 50
7	270			
8	540			NE at 50
9	199			NE at 50
10	103			13.8
11	33		6.73	2.1
12	35		6.85	2.9
13	1735		5.33	NE at 50
14	1403		4.88	22.5
15	263		5.58	9.6
16	265			12
17			6.31	
18	533		5.92	NE at 50
19	203			
20	443			c
21	833			NE at 20
22	820			c
23	200	5.71		NE at 20
24	133	6.21	6.99	NE at 20
25	65		7.48	
26	507			d
27	200			11.8
28	144		5.67	16
29	115	6.0	6.72	NE at 50
30	1500		5.64	NE at 50
31	107	6.07	7.08	NE at 20
32	57.3	6.37		NE at 20
33	48	6.16	7.6	NE at 20
34	13	6.73	7.21	NE at 20
35	11.7	6.73		NE at 20
36	116	6.01	7.38	
37	114	6.07		NE at 20
38	14.7	7.14	8.59	13.5
L652731[7]		6.75		
WEB 2086[7]		7.42	8.15	

[a] IC_{50} ratio is 1000 × the IC_{50} of the test compound divided by the IC_{50} of a standard (**3**). [b] NE, no effect. [c] U46619 aggregation NE at 20 μM. [d] U46619 aggregation IC_{50} 22 μM.

selected antagonist were established. The data obtained were evaluated according to the methods described by Schild,[16] and the pK_b was determined.

iii. Selectivity Assay. Every compound with potential PAF-antagonist activity was evaluated for activity against other aggregatory agonists, principally adenosine diphosphate (ADP) and the thromboxane mimetic, U46619. The ED_{50} concentration for each agonist was determined, and an IC_{50} value for each antagonist was obtained. In the majority of cases the antagonists had little inhibitory effects at concentrations below the exclusion value of 50 μM.

3. PAF-Binding Assay. Platelet suspensions were prepared as outlined above, except that the anticoagulant used was ACD, aspirin was omitted from the washing buffer, and the platelets were finally suspended in a Tris-HCl buffer (10 mM; pH 7.4) containing EDTA (2 mM) and $MgCl_2$ (5 mM) to a cell concentration of 5 × 10^8/mL. The suspensions were incubated with [^{3}H]PAF (90 mCi/mol), without stirring, at 0 °C. Under these conditions there was no evidence of aggregation of the cells, and the [^{3}H]PAF was not metabolized or incorporated into platelet membranes. Maximum specific binding was achieved after 90 min incubation and specific binding represented 55–75% of the total binding. Scatchard analysis of the data indicated one class of specific binding site (K_d = 1 nM; B_{max} = 9.3 fmol/10^7 cells, indicating 559 binding sites per cell).

Experimental Section

Melting points were taken on either an Electrothermal or Gallenkamp digital melting point apparatus and are uncorrected. Proton magnetic resonance spectra were taken on either a JEOL JNM PMX60SI or Bruker AC200 spectrometer. NMR spectra were obtained for each compound reported and are consistent with the assigned structures. CHN microanalyses were obtained with a Carlo Erba 1106 elemental analyser. Flash chromatography used Merck silica gel 60 (230–400 mesh ASTM). All solvents, except ether, were dried over molecular sieves 3A. Ether was dried using Na/Pb alloy. Temperatures quoted are in °C and are uncorrected.

Method A. 4-(Hexyloxy)-3,5-dimethoxybenzoic Acid (41).[17] A mixture of methyl syringate (**39**) (2.12 g, 10 mmol), Bu_4NHSO_4 (0.34 g, 1 mmol), anhydrous K_2CO_3 (1.38 g, 10 mmol), and 1-bromohexane (1.68 g, 12 mmol) in dry toluene (50 mL) was stirred and heated to reflux for 6 h. The mixture was treated with H_2O (100 mL), and the aqueous layer was extracted with toluene. The toluene extracts were combined, dried (Na_2SO_4), filtered, and evaporated *in vacuo* to give **40** (2.6 g) which was used directly in the next step.

A solution of **40** (2.6 g) in industrial methylated spirits (IMS) (25 mL) was heated to reflux with 2 M NaOH (25 mL) for 15 min. The IMS was removed *in vacuo*, and the residue was treated with H_2O and then acidified with concentrated HCl. The precipitated solid was separated by filtration, washed with H_2O, and dried to give **41** (2.37 g, 84% from **39**), mp 112–113.

***N*-[4-[[4-(Hexyloxy)-3,5-dimethoxybenzoyl]oxy]butyl]-*N*,*N*-dimethylamine (30).** A solution of **41** (1.41 g, 5 mmol) in thionyl chloride (1.25 mL) was heated to reflux for 2 h. The thionyl chloride was removed *in vacuo* as an azeotrope with dry toluene (3 × 20 mL) to give crude **42**.

A solution of **42** in dry toluene (10 mL) was added dropwise to a stirred solution of (*N*,*N*-dimethylamino)ethanol (0.575 g, 5 mmol) in dry toluene (20 mL). The solution was stirred and heated to reflux for 2 h and then evaporated *in vacuo*. The residual oil was triturated with dry ether (20 mL) to give a white solid which was separated by filtration, washed with dry ether, and dried giving **30**·HCl (1.55 g, 74%), mp 113–114.

***N*-[4-[[4-(Hexyloxy)-3,5-dimethoxybenzoyl]oxy]butyl]-*N*,*N*,*N*-trimethylammonium Iodide (6).** A solution of **30**·HCl (1.03 g, 2.5 mmol) in H_2O (20 mL) was basified with 2 M NaOH (5 mL) and then extracted with ether. The ether extracts were combined, dried (Na_2SO_4), filtered, and evaporated *in vacuo* to give **30** (900 mg, 2.36 mmol). A solution of **30** (450 mg, 1.28 mmol) in MeOH was treated with MeI (1 mL), left at 21 °C overnight, and then evaporated *in vacuo*. The residual solid was purified by recrystallization (IMS/ether) to give **6** (400 mg, 82%): mp 138–140; NMR (DMSO-d_6, 200 MHz) δ 0.9 (3 H, t, CH_3), 1.2–1.9 (12 H, m, 6 CH_2), 3.05 (9 H, s, 3 CH_3), 3.4 (2 H, m, CH_2N^+), 3.83 (6 H, s, 2 CH_3), 3.95 (2 H, t, CH_2O), 4.3 (2 H, t, CH_2OCO), 7.25 (2 H, s, ArH).

Method B. *N*-[4-[[4-(Cyclohexylmethoxy)-3,5-dimethoxybenzoyl]oxy]butyl]-*N*,*N*,*N*-trimethylammonium Iodide (20). Acid chloride **43** was prepared by essentially the same methodology described for **42** (method A), but using cyclohexylmethyl bromide as the alkylating agent for methyl syringate **39**, and was used directly in the next step.

A stirred mixture of **43** (1.56 g, 5 mmol) and zinc chloride (250 mg) in dry THF (20 mL) was heated to reflux for 1.5 h, and then evaporated to dryness *in vacuo*. The residue was partitioned between H_2O (50 mL) and ether (100 mL), and the organic layer was separated, washed with H_2O, dried (Na_2SO_4), filtered, and evaporated *in vacuo* to give **44** as a pale yellow oil (1.94 g) which was not purified further.

A stirred mixture of **44** (1.94 g, 5 mmol) and NaI (2.27 g, 15.1 mmol) in dry butanone (30 mL) was heated to reflux for 3.5 h and then was cooled and filtered. The filtrate was evaporated *in vacuo*, and the resultant oil was purified by flash

chromatography (eluant hexane:ether, 1:1) to give **45** as a clear oil (1.75 g, 73% from **43**).

A 33% solution of trimethylamine in EtOH (1 mL) was added to a solution of **45** (0.75 g, 1.58 mmol) in butanone (5 mL). The reaction was left at 21 °C overnight, and the solvent was removed *in vacuo*. The residual solid was triturated with ether, separated by filtration, and purified by recrystallization (acetone/petroleum ether (bp 40–60 °C)) to afford **20** (692 mg, 82%): mp 148–150; NMR ($CDCl_3$, 200 MHz) δ 0.9–2.1 (15 H, m, 7 CH_2, CH), 3.45 (9 H, s, 3 CH_3), 3.75–3.95 (10 H, m, 2 CH_3, CH_2O, CH_2N^+), 4.4 (2 H, t, CH_2OCO), 7.25 (2 H, s, ArH).

Method C. 4-(Hexyloxy)-3,5-dimethoxybenzaldehyde (47). The alkylation of syringaldehyde **46** (34.5 g, 0.189 mol) with 1-bromohexane (38 mL, 0.27 mol) was as described in method A for the alkylation of methyl syringate (**39**). The reaction mixture was treated with H_2O (500 mL) and extracted with toluene. The toluene extracts were combined, washed with 2 M NaOH (3 × 50 mL) and H_2O (3 × 50 mL), then dried ($MgSO_4$), filtered, and evaporated *in vacuo*. The residual oil was purified by distillation to give **47** (46.4 g, 92%), bp 130–135 °C/0.2 mmHg.

4-(Hexyloxy)-3,5-dimethoxyphenol (49). A solution of **47** (26.6 g, 0.1 mol) in dry DCM (400 mL) was treated with 85% *m*-chloroperbenzoic acid (25.3 g, 0.125 mol) at 21 °C. The mixture was stirred and heated to reflux for 72 h, the solvent was removed *in vacuo*, and the residue was digested in EtOAc (300 mL). The organic layer was washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), and evaporated *in vacuo* to leave formate **48** which was used in the next step without purification.

A solution of formate **48**, MeOH (30 mL), and 10% aqueous KOH (54 mL, 96 mmol) was heated to reflux for 2 h and then left for 16 h at 21 °C. H_2O (500 mL) was added, and the mixture was extracted with ether (3 × 200 mL). The ethereal extracts were combined and extracted with 2 M NaOH (2 × 20 mL). All the aqueous material was combined, acidified with citric acid (pH 6), and then extracted with ether (3 × 200 mL). These ether extracts were combined, dried (Na_2SO_4), filtered, and evaporated *in vacuo* to give **49** (16.1 g, 63% from **47**), mp 87–89.

***N*-[4-[[4-(Hexyloxy)-3,5-dimethoxyphenoxy]carbonyl]-butyl]-*N,N,N*-trimethylammonium Iodide (21).** A mixture of **49** (0.51 g, 2 mmol), DMAP (200 mg), 5-(*N,N*-dimethylamino)valeric acid (0.39 g, 2.1 mmol), and DCCI (0.41 g, 2 mmol) in dry DMF (25 mL) was stirred at 21 °C for 72 h. The DMF was removed *in vacuo*, and the residual paste was partially digested in DCM (50 mL). The solid was removed by filtration, and the filtrate yielded **50** on evaporation (0.3 g, 39%).

A solution of **50** (0.3 g) in dry acetone (10 mL) was treated with MeI (0.5 mL) and left at 21 °C for 16 h. Ether (5 mL) precipitated **21** as a hemihydrate (50 mg, 12%): mp 75–77; NMR (DMSO-d_6, 200 MHz) δ 0.9 (3 H, t, CH_3), 1.25–1.9 (12 H, m, 6 CH_2), 2.65 (2 H, t, CH_2CO), 3.07 (9 H, s, 3 CH_3), 3.3 (s, HOD), 3.3 (2 H, m, CH_2N^+), 3.75 (6 H, s, 2 CH_3), 3.80 (2 H, t, CH_2O), 6.47 (2 H, s, ArH).

Method D. 6-[4-(Hexyloxy)-3,5-dimethoxyphenyl]hex-5-enoic Acid (51). A mixture of (4-carboxybutyl)triphenylphosphonium bromide (5.02 g, 11.3 mmol) in benzene (500 mL) was stirred and heated to reflux under a Dean–Stark apparatus for 30 min. Potassium *tert*-butoxide (3.13 g, 11.3 mmol) was added, and the mixture was stirred and heated to reflux for 2 h and then cooled to 10 °C. A solution of **47** (3.01 g, 11.3 mmol) in dry benzene (40 mL) was then added dropwise, the resulting suspension was left at 21 °C for 16 h, and the reaction mixture was extracted with 1 M NaOH (3 × 500 mL). The aqueous extracts were combined, washed with ether (2 × 500 mL), acidified with citric acid (pH 6), and extracted with ether (3 × 200 mL). The ether extracts were combined, dried ($MgSO_4$), filtered, and evaporated *in vacuo* to give **51** (2.31 g, 58%) which was used without further purification.

(*E*)- and (*Z*)-*N,N*-Dimethyl-6-[4-(Hexyloxy)-3,5-dimethoxyphenyl]hex-5-enamide (53). Methyl chloroformate (0.61 mL, 7.92 mmol) was added to a stirred and cooled (0–5 °C) solution of **51** (2.31 g, 6.6 mmol) and Et_3N (2.1 mL, 13.2 mmol) in dry THF (50 mL). The solution was stirred at 0–5 °C for 2 h, treated with a 33% solution of dimethylamine in EtOH (20 mL), and then left at 21 °C for 72 h. The solvent was removed *in vacuo*, and the residual oil was separated by flash chromatography, giving *Z*-**53** (250 mg, 10%) [NMR ($CDCl_3$, 200 MHz) δ 0.9 (3 H, t, CH_3), 1.2–1.9 (10 H, m, 5 CH_2), 2.25–2.5 (4 H, m, CH_2CH=, CH_2CO), 2.95 (6 H, d, $CON(CH_3)_2$), 3.85 (6 H, s, 2 CH_3), 3.95 (2 H, t, CH_2O), 5.5–5.68 (1 H, 2 t, =$CHCH_2$), 6.35 (1 H, d, ArCH=CH, J = 11.55 Hz), 6.45 (2 H, s, ArH)] and *E*-**53** (680 mg, 27%); NMR ($CDCl_3$, 200 MHz) δ 0.9 (3 H, s, CH_3), 1.2–1.9 (10 H, m, 5 CH_2), 2.25–2.35 (4 H, m, CH_2CH=, CH_2CO), 2.95 (6 H, d, $CON(CH_3)_2$), 3.85 (6 H, s, 2 CH_3), 3.95 (2 H, t, CH_2O), 6.0–6.18 (1 H, 2 t, =$CHCH_2$), 6.33 (1 H, d, ArCH=CH, J = 15.55 Hz), 6.55 (2 H, s, ArH).

(*Z*)-*N*-[6-[4-(Hexyloxy)-3,5-dimethoxyphenyl]hex-5-en-1-yl]-*N,N*-dimethylamine (*Z*-54). A solution of *Z*-**53** (250 mg, 0.66 mmol) in dry ether (20 mL) was added dropwise to a stirred suspension of lithium aluminum hydride (1 g, 17 mmol) in dry ether (100 mL). The suspension was stirred and heated to reflux for 1.5 h and then was cooled and decomposed by careful addition of H_2O (1 mL), 2 M NaOH (1 mL), and then H_2O (1 mL). The suspension was stirred for a further 30 min and then filtered. The filtrate was dried (K_2CO_3), filtered, and evaporated *in vacuo* to give an oil which was purified using preparative TLC plates (eluant butanol:acetic acid:H_2O, 3:1:1) giving *Z*-**54** (100 mg, 41%).

Methylation as before gave **23** (90 mg, 65%): mp 85–87, softens at 83; NMR ($CDCl_3$, 200 MHz) δ 0.9 (3 H, s, CH_3), 1.2–1.9 (12 H, m, CH_2), 2.45 (2 H, q, CH_2CH=), 3.35 (9 H, s, 3 CH_3), 3.6 (2 H, m, CH_2N^+), 3.85 (6 H, s, 2 CH_3), 3.95 (2 H, t, CH_2O), 5.5–5.62 (1 H, 2 t, CH=$CHCH_2$), 6.4 (1 H, d, ArCH=CH), 6.47 (2 H, s, ArH).

Method E. 6-[4-(Hexyloxy)-3,5-dimethoxyphenyl]hex-5-en-1-ol (55). The Wittig reaction of aldehyde **47** (1.33 g, 11 mmol) with (5-hydroxypentyl)triphenylphosphonium bromide (2.36 g, 5.5 mmol) was as described for the preparation of acid **51** in method D. Workup differed in that the reaction mixture was poured onto H_2O (200 mL) and extracted with ether (3 × 50 mL). The ether extracts were combined, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (eluant hexane:ether, 1:1), giving **55** as an oil (0.8 g, 43%).

6-[4-(Hexyloxy)-3,5-dimethoxyphenyl]hexan-1-ol (56). A suspension of **55** (0.8 g, 2.38 mmol) and 10% palladium on carbon (50 mg) in MeOH (100 mL) was hydrogenated at atmospheric pressure for 30 min. The catalyst was removed by filtration, the filtrate was evaporated *in vacuo*, and the residue was purified by flash chromatography (eluant hexane:ether, 4:1) to give **56** as an oil (0.4 g, 50%).

6-[4-(Hexyloxy)-3,5-dimethoxyphenyl]-1-iodohexane (58). *p*-Toluenesulfonyl chloride (0.5 mL) was added dropwise to a stirred and cooled (0 °C) solution of **56** (0.4 g, 1.18 mmol) in dry pyridine (10 mL), the reaction mixture was stirred at 0 to −5 °C for 2 h, and then stored at −18 °C for 96 h. The solution was treated with H_2O (100 mL) and extracted with ether (3 × 25 mL). The ether extracts were combined, washed with H_2O, dried (Na_2SO_4), filtered, and evaporated *in vacuo* to give tosylate **57** (0.48 g).

A mixture of **57** (0.48 g) and anhydrous LiI (1 g) in dry acetone (50 mL) was stirred at 21 °C for 16 h and then evaporated *in vacuo*. The residual oil was treated with H_2O (20 mL) and extracted with ether (3 × 15 mL). The ether extracts were combined, washed with 1 M NaOH (2 × 10 mL), H_2O (2 × 10 mL), 1 M HCl (2 × 10 mL), and H_2O (2 × 10 mL), dried (Na_2SO_4), filtered, and evaporated *in vacuo*. Purification by flash chromatography (eluant hexane:ether, 4:1) gave **58** (0.28 g, 53% from **56**).

***N*-[6-[4-(Hexyloxy)-3,5-dimethoxyphenyl]hexyl]-*N,N,N*-trimethylammonium Iodide (25).** A solution of **58** (0.28 g) and 33% ethanolic trimethylamine (1 mL) in MeOH (10 mL) was left at 21 °C for 96 h and then evaporated *in vacuo* to give **25** (0.3 g, 95%) as a clear oil: NMR ($CDCl_3$, 200 MHz) δ 0.9 (3 H, t, CH_3), 1.2–1.85 (16 H, m, 8 CH_2), 2.5 (2 H, t, CH_2Ar), 3.35 (9 H, s, 3 CH_3), 3.6 (2 H, m, CH_2N^+), 3.83 (6 H, s, 2 CH_3), 3.9 (2 H, t, CH_2O), 6.4 (2 H, s, ArH).

Method F. 2-(2-Hydroxyphenyl)ethanol (61).[18] A stirred and cooled (0 °C) solution of **59** (2.90 g, 19 mmol) in dry THF (50 mL) was treated dropwise with Et_3N (2.12 g, 21 mmol) and then ethyl chloroformate (2.07 g, 19 mmol). The mixture was stirred at 0 °C for 1 h and then was filtered, and the filtrate was added dropwise to a stirred and cooled (0 °C) solution of sodium borohydride (1.08 g, 28.5 mmol) in 50% aqueous THF. The reaction mixture was stirred at 0 °C for 45 min and then at 21 °C for 2 h. The solvent was removed in *vacuo*, and the residue was digested in H_2O (50 mL) and ether (100 mL). The ethereal layer was separated, washed with 2 M Na_2CO_3, H_2O, 1 M citric acid, and H_2O, dried ($MgSO_4$), filtered, and evaporated *in vacuo* to give **61** as an oil (2.3 g, 87%) which was used without further purification.

2-[2-[[4-(Hexyloxy)-3,5-dimethoxybenzoyl]oxy]phenyl]-ethanol (62). A solution of acid chloride **42**, from acid **41** (4.71 g, 16.7 mmol), in dry THF (50 mL) was added dropwise over 10 min to a stirred and cooled (0–5 °C) solution of **61** (2.30 g, 16.6 mmol) in 2 M NaOH (8.3 mL). The reaction mixture was stirred at 0 °C for 30 min and 21 °C for 1 h, and then the THF was removed *in vacuo*. The residue was treated with 2 M NaOH (20 mL) and extracted with ether (3 × 20 mL). The ethereal extracts were combined, washed with H_2O (2 × 20 mL), dried ($MgSO_4$), filtered, and evaporated *in vacuo* to give **62** as a yellow oil (5.7 g, 85%).

2-[2-[[4-(Hexyloxy)-3,5-dimethoxybenzoyl]oxy]phenyl]-1-iodoethane (64). Method E describes the general method used in the conversion of alcohol **62** (2.61 g, 6.5 mmol) *via* tosylate **63** to iodo compound **64**. Purification by flash chromatography (eluant petroleum ether (bp 40–60 °C):ether, 3:1) gave **64** (2.31 g, 69%), mp 65.5–66.

***N*-[2-[2-[[4-(Hexyloxy)-3,5-dimethoxybenzoyl]oxy]-phenyl]ethyl]-*N,N,N*-trimethylammonium Iodide (26).** Method E also describes the general method for the alkylation of trimethylamine with **64** (0.7 g, 1.36 mmol). The precipitated solid was recrystallized from H_2O to give **26** (0.347 g, 44%): mp 181–182.5; NMR ($CDCl_3$, 200 MHz) δ 0.9 (3 H, t, CH_3), 1.25–1.85 (8 H, m, 4 CH_2), 3.05 (2 H, m, CH_2Ar), 3.35 (9 H, s, 3 CH_3), 3.85–3.95 (8 H, m, 2 CH_3, CH_2N^+), 4.1 (2 H, t, CH_2O), 7.05–7.75 (6 H, m, ArH).

Method G. 4-(Hexyloxy)-3,5-dimethoxybenzyl Bromide (66). A stirred solution of **47** (42 g, 0.158 mol) in propan-2-ol (300 mL) was treated portionwise over 5 min with sodium borohydride (2.996 g, 79 mmol). The reaction mixture was left at 21 °C for 2 h then was concentrated *in vacuo*. H_2O (200 mL) was added to the residue which was then extracted with ether (3 × 100 mL). The ethereal extracts were combined, washed with H_2O (2 × 50 mL), dried ($MgSO_4$), filtered, and evaporated *in vacuo* to leave **65** as a pale oil (40.2 g, 95%).

HBr was bubbled through a cooled (5 °C) solution of **65** (40.2 g, 0.15 mol) in chloroform (400 mL) over 45 min. The resulting solution was washed with 2 M $NaHCO_3$ and H_2O, dried ($MgSO_4$), filtered, and evaporated *in vacuo*. The residue was purified by flash chromatography (eluant petroleum ether (bp 60–80 °C): EtOAc, 4:1) to give **66** (47.9 g, 96%).

[4-(Hexyloxy)-3,5-dimethoxybenzyl]triphenylphosphonium Bromide (67). A stirred solution of **66** (45 g, 0.135 mol) and triphenylphosphine (36 g, 0.137 mol) in toluene (300 mL) was heated to reflux for 3 h. On cooling to 21 °C, a solid was precipitated which was isolated by filtration, giving **67** (72 g, 90%), mp 167–169.

3-(4-Methylthiazol-5-yl)propionitrile (70).[19] Methanesulfonyl chloride (48.6 g, 0.42 mol) was added dropwise over 30 min to a stirred and cooled (−50 to −20 °C) solution of **68** (50.6 g, 0.35 mol) in dry DCM (150 mL). The reaction mixture was stirred at (−10 to 0 °C) for 2 h and 21 °C for 2 h, washed with H_2O (2 × 50 mL), dried ($MgSO_4$), filtered, and evaporated *in vacuo* to give **69**[20] which was used directly in the next step.

A suspension of **69**, potassium cyanide (23 g, 0.35 mol), and 18-crown-6 (400 mg) in dry DMF (300 mL) was stirred at 21 °C for 16 h and then at 80 °C for 1 h. The cooled reaction mixture was treated with H_2O (500 mL) and extracted with chloroform (4 × 150 mL). The organic extracts were combined, washed with H_2O (3 × 100 mL) , dried ($MgSO_4$), filtered, and evaporated *in vacuo* to give a dark oil which was purified by distillation giving **70** (15.53 g, 36%), bp 104–112 °C/0.2 mmHg.

2-(Hexyloxy)-1,3-dimethoxy-5-[4-(4-methyl-5-thiazolyl)but-1-enyl]benzene (72). Diisobutylaluminum hydride (38 mL, 0.21 mol) was added dropwise over 20 min to a stirred and cooled (−5 to 0 °C) solution of **70** (28 g, 0.184 mol) in dry toluene (400 mL). The solution was stirred at 21 °C for 1 h, and then MeOH (20 mL) was added dropwise. The solution was stirred at 21 °C for 45 min, and then 2 M HCl (250 mL) was added with cooling at 21–30 °C. The reaction mixture was stirred at 21 °C for 1 h, and the MeOH was removed *in vacuo*. The aqueous phase was separated, basified with 10 M NaOH (pH 10), and extracted with chloroform (4 × 100 mL). The chloroform extracts were combined, washed with H_2O (2 × 100 mL), dried ($MgSO_4$), filtered, and evaporated *in vacuo* to give **71** (36 g) as an orange oil which was used immediately.

Potassium *tert*-butoxide (13.6 g, 0.12 mol) was added to a stirred and cooled (0–5 °C) solution of **67** (72 g, 0.13 mol) in dry THF (350 mL). After stirring for 1 h at 0–5 °C a solution of **71** (36 g, 0.23 mol) in dry THF (70 mL) was added dropwise over 30 min at 0–5 °C, and the resultant mixture was left at 21 °C for 72 h. The THF was removed *in vacuo*, and the residue was partitioned between 1 M citric acid (300 mL) and ether (500 mL). The ethereal extract was washed with H_2O (2 × 100 mL), dried ($MgSO_4$), filtered, and evaporated *in vacuo*. The residue was purified by flash chromatography (eluant petroleum ether (bp 60–80 °C): EtOAc 3:1) to give **72** (9.2 g, 13% from **70**) as a mixture of isomers (*E*:*Z*, 2:1).

2-(Hexyloxy)-1,3-dimethoxy-5-[4-(4-methylthiazol-5-yl)butyl]benzene (38). A suspension of **72** (1.2 g, 3.1 mmol) and 10% palladium on carbon (200 mg) in EtOAc (20 mL) was hydrogenated at atmospheric pressure for 7 h. The catalyst was removed by filtration, and the filtrate was evaporated *in vacuo*. The resultant oil was dissolved in ether and treated with a solution of HBr in acetic acid to precipitate a solid. Recrystallization from EtOAc gave **38**·HBr (0.933 g, 64%): mp 98–99.5 °C; NMR (DMSO-d_6, 200 MHz) δ 0.9 (3 H, t, CH_3-CH_2), 1.2–1.7 (12 H, m, 6 CH_2), 2.37 (3 H, s, CH_3-thiazole), 2.55 (2 H, t, CH_2-thiazole), 2.85 (2 H, t, CH_2Ar), 3.75 (9 H, s, 3 CH_3), 3.8 (2 H, t, CH_2O), 6.5 (2 H, s, ArH), 9.57 (1 H, s, thiazole H), 10.6–11 (1 H, bs, exchangeable).

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