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Potent, Orally Active Inhibitors of Lipoprotein-Associated Phospholipase A_2: 1-(Biphenylmethylamidoalkyl)-pyrimidones

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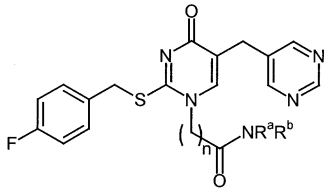
Abstract—A series of 1-(biphenylmethylamidoalkyl)-pyrimidones has been designed as nanomolar inhibitors of recombinant lipoprotein-associated phospholipase A_2 with high potency in whole human plasma. 5-(Pyrazolylmethyl) derivative **16** and 5-(methoxypyrimidinylmethyl) derivative **27** demonstrated excellent pharmacodynamic profiles which correlated well with their pharmacokinetic effects.

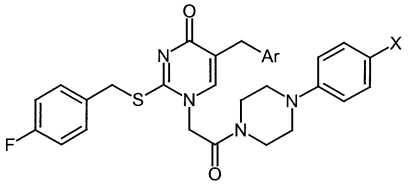
The regulation of plasma lipid levels, particularly LDL cholesterol, represents the focus of current therapy for atherosclerosis. Whilst the statins have achieved both medical and commercial success in this role,[1] they are only particularly effective in about 30% of patients. With the aim of treating many more of the at risk population, we have focussed our attention on treating the inflammatory nature of the disease[2] and, in particular, targeted the enzyme lipoprotein-associated phospholipase A_2 (Lp-PLA_2). This enzyme has been shown to release pro-inflammatory mediators from oxidatively modified phosphatidylcholines.[3] Furthermore, a strong positive correlation has been shown between Lp-PLA_2 levels and coronary events in asymptomatic hypercholesterolemic males, suggesting that Lp-PLA_2 is a new independent marker of coronary heart disease.[4] We therefore wished to identify potent, orally effective inhibitors of this enzyme in order to assess its role in the atherosclerotic disease process.

In two recent reports,[5,6] we described the identification of a series of 1-((amidolinked)-alkyl)-pyrimidones **1** and a related series of 1-(arylpiperazinylamidoalkyl)-pyrimidones **2** as inhibitors of Lp-PLA_2 which showed activity in the Watanabe hereditable hyperlipidaemic rabbit (WHHL rabbit). In the belief that additional enhancements in oral performance could be achieved through further modification of the pyrimidone N-1 substituent, we investigated the replacement of this group with a series of biarylmethyl amides and now



1 n = 1 or 3

R^a = long chain alkyl, R^b = H, Me



2 Ar = e.g. 5-(2-MeO-pyrimidin-5-yl)

X = e.g. 4-Cl

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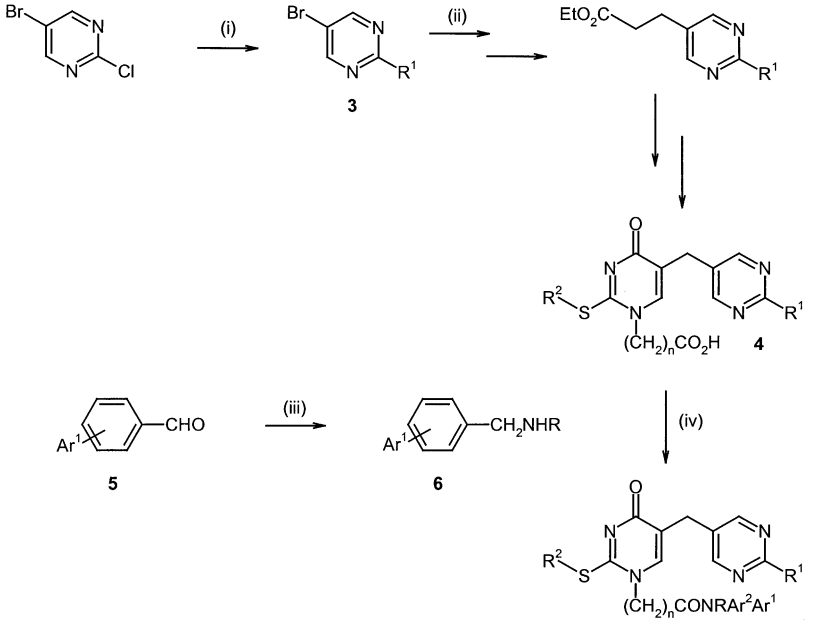
report the result of these studies alongside the effect of introducing some novel 5 substituents into the pyrimidone ring.

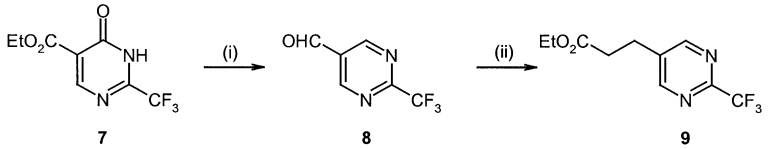
The synthesis of inhibitors **10**–**13**, **26**–**29** and **34**–**38** started from substituted pyrimidines **3** and used methods similar to those previously reported (Scheme 1).[5,6] The related 2-trifluoromethyl derivative **43** was prepared via aldehyde **8** which was itself prepared in three steps from pyrimidone ester **7** (Scheme 2).[7] Knoevenagel reaction, esterification and reduction gave the propionic ester **9** which was converted through to acid **4** as before. The corresponding 1-methylpyrazol-4-yl derivatives **14**–**25** and **30**–**33** were prepared in a similar fashion from 1-methylpyrazole-4-carboxaldehyde.[8] Biarylmethylamines **6** were prepared via reductive amination of the corresponding aldehydes **5** (R = Me) or by reduction of **5** followed by Mitsonobu reaction with phthalimide and deprotection (R = H). Subsequent carbodiimide coupling proceeded smoothly. All compounds in Tables 1–3 were evaluated using recombinant human Lp-PLA_2 (rhLp-PLA_2). In order to include non-specific binding effects in plasma, compounds were assessed against the plasma enzyme in both whole human and WHHL rabbit plasma.[5] Good activity in rabbit and human plasma was required before compounds were evaluated in vivo in WHHL rabbits.[9]

We initially investigated the biphenyl moiety and the effect of substitution of this group in the pyrimidone acetamide and butyramide series (Tables 1 and 2, respectively). Although secondary amides were initially prepared, they proved particularly insoluble and as a result, we quickly moved to the corresponding *N*-methyl derivatives. For similar solubility issues, much of the SAR was developed in the 5-(1-methylpyrazol-4-yl)methyl and 5-(2-methoxypyrimidin-5-yl)methyl series. Preliminary work indicated the 4-biaryl substitution pattern to be preferred over either 3- or 2-substitution (cf. **10** vs **12** and **13**). Substitution of the 4-biphenyl moiety proved advantageous (e.g., **16** vs **14**) with 4-substitution being somewhat favoured over the 2- or 3-substituted derivatives (cf. **16** with **20** and **21**). A lipophilic 4-substituent proved optimal for potency against rhLp-PLA_2 with the more bulky bromo and trifluoromethyl groups the most potent. More polar electron withdrawing or strongly donating groups were less well tolerated (see **16**, **18**, **19** and **22**–**25**).

In contrast to our previous work with long-chain amides at the pyrimidone N-1 position,[5] activity in the related butyramide series proved somewhat disappointing (Table 2). In this series, no additional advantage was seen on increasing the size of the 4-substituent from fluoro to chloro and although secondary amides showed



Scheme 1. Reagents and conditions: (i) (a) NaOMe, MeOH or (b) amine, CH_2Cl_2; (ii) for elaboration to acid **4**, see ref 6; (iii) for R = H: (a) $NaBH_4$, EtOH; (b) phthalimide, DEAD, PPh_3, THF; (c) NH_2NH_2, EtOH; for R = Me (a) $MeNH_2$, 4 Å molecular sieves, CH_2Cl_2; (b) $NaBH_4$, EtOH; (iv) EDC, HOBT, CH_2Cl_2 or DMF; for subsequent transformations within Ar (Ar = 2-oxo-pyrimidin-5-yl and derivatives), see ref 6.

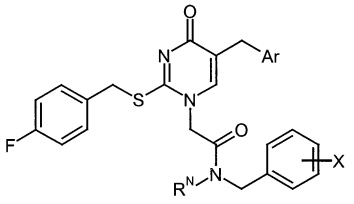


Scheme 2. Reagents and conditions: (i) (a) $(COCl)_2$, CH_2Cl_2; (b) H_2, Pd/C, *i*Pr_2NEt, EtOH; (c) iBu_2AlH, THF; (ii) (a) $CH_2(CO_2H)_2$, piperidine, pyridine; (b) EtOH, H_2SO_4; (c) H_2, Pd/C, EtOH.

better activity in whole human plasma than their tertiary counterparts (see **31** and **32**, **37** and **38**), activity was reduced when compared with the best acetamide derivatives (cf. **16** with all compounds in Table 2).

With these results in hand, we decided to concentrate our efforts on the pyrimidone acetamide series and, conscious of the rather lipophilic nature of these molecules, we targeted the 4-chlorobiphenyl derivatives as a

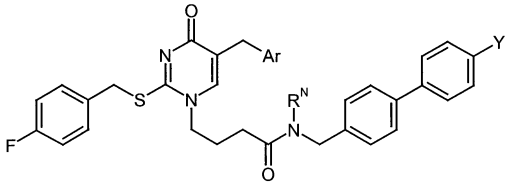
Table 1. Acetamides: biaryl variation



No.[a]	X	R^N	Ar	% Inhibition in plasma			
				IC_{50} (nM)	Human (10 nM)	Human (100 nM)	Rabbit (100 nM)
10	4-Ph	H	Pyrimidin-5-yl	4	8	50	42
11	4-Ph	Me	Pyrimidin-5-yl	8		66	41
12	3-Ph	H	Pyrimidin-5-yl	24		23	18
13	2-Ph	H	Pyrimidin-5-yl	194		NT[b]	NT
14	4-Ph	Me	1-Me-pyrazol-4-yl	5	4		9
15	4-(4-F-Ph)	Me	1-Me-pyrazol-4-yl	2.7		78	44
16	4-(4-Cl-Ph)	Me	1-Me-pyrazol-4-yl	1	43	88	55
17	4-(4-Cl-Ph)	H	1-Me-pyrazol-4-yl	1.6	28	83	50
18	4-(4-Br-Ph)	Me	1-Me-pyrazol-4-yl	0.5	53		53
19	4-(4-CF_3-Ph)	Me	1-Me-pyrazol-4-yl	0.7	70	96	69
20	4-(3-Cl-Ph)	Me	1-Me-pyrazol-4-yl	1.6	13	65	40
21	4-(2-Cl-Ph)	Me	1-Me-pyrazol-4-yl	1.6	18	70	35
22	4-(4-Me-Ph)	Me	1-Me-pyrazol-4-yl	0.9	43		44
23	4-(4-MeO-Ph)	Me	1-Me-pyrazol-4-yl	17	13	64	23
24	4-(4-NC-Ph)	Me	1-Me-pyrazol-4-yl	2.6	43		42
25	4-(4-MeO_2S-Ph)	Me	1-Me-pyrazol-4-yl	5	8		12
26	4-(4-F-Ph)	Me	2-MeO-pyrimidin-5-yl	0.6	37	84	51
27	4-(4-Cl-Ph)	Me	2-MeO-pyrimidin-5-yl	0.2	51	93	65
28	4-(4-Cl-Ph)	H	2-MeO-pyrimidin-5-yl	0.5	42	90	52
29	4-(4-CF_3-Ph)	Me	2-MeO-pyrimidin-5-yl	0.2	75	97	78

[a]All new compounds gave satisfactory analytical/spectral data.[10]
[b]Not tested.

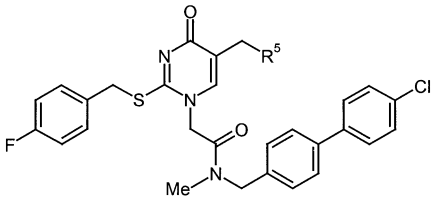
Table 2. Biaryl butyramides



No.[a]	Y	R^N	Ar	% Inhibition in plasma			
				IC_{50} (nM)	Human (10 nM)	Human (100 nM)	Rabbit (100 nM)
30	H	H	1-Me-pyrazol-4-yl	5	6	28	18
31	F	H	1-Me-pyrazol-4-yl	4	19	69	33
32	F	Me	1-Me-pyrazol-4-yl	8	8	36	25
33	Cl	Me	1-Me-pyrazol-4-yl	5	8	36	15
34	H	H	2-MeO-pyrimidin-5-yl	4	4	55	22
35	F	H	2-MeO-pyrimidin-5-yl	3	27	83	36
36	F	Me	2-MeO-pyrimidin-5-yl	15	12	52	34
37	Cl	H	2-MeO-pyrimidin-5-yl	4	29	81	31
38	Cl	Me	2-MeO-pyrimidin-5-yl	5	3	46	20

[a]All new compounds gave satisfactory analytical/spectral data.[10]

Table 3. Effect of pyrimidone 5-substituent variation



No.[a]	R^5	% Inhibition in plasma		
		IC_{50} (nM)	Human (10 nM)	Rabbit (100 nM)
16	1-Me-pyrazol-4-yl	1	43	55
27	5-(2-MeO-pyrimidin-5-yl)	0.2	51	65
39	2-Morpholinylpyrimidin-5-yl	1	48	48
40	2-Me_2N-pyrimidin-5-yl	0.8	41	47
41	2-(4-Me-piperazin-1-yl)pyrimidin-5-yl	1.7	59	76
42	2-(Piperazin-1-yl)pyrimidin-5-yl	0.2	64	55
43	2-CF_3-pyrimidin-5-yl	5	14	16
44	2-Oxo-1*H*-pyrimidin-5-yl	1	48	63
45	1-Et-2-oxo-pyrimidin-5-yl	0.5	33	43

[a]All new compounds gave satisfactory analytical/spectral data.[10]

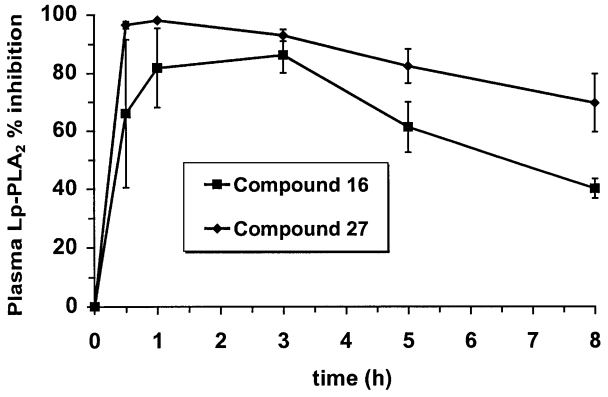


Figure 1. Inhibition of plasma Lp-PLA_2 in the WHHL rabbit @ 10 mg/kg ($n=2$) po.

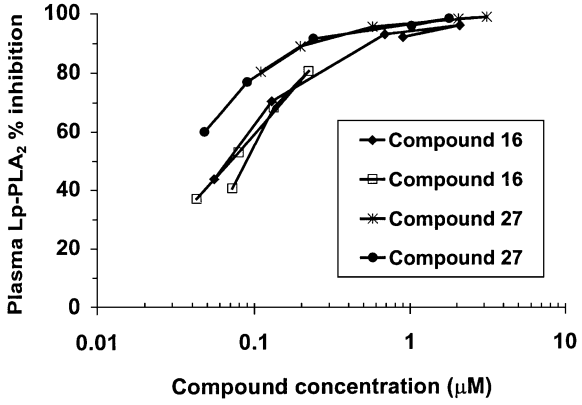


Figure 2. Correlation of pharmacodynamic and pharmacokinetic effects in the WHHL rabbit @ 10 mg/kg ($n=2$) po.

compromise between potency and lipophilicity/molecular weight (**16** vs **18** and **19**) or reduced potential for metabolic liability (**16** vs **22**). We then investigated the effect of varying the pyrimidone 5-substituent in these biphenyl derivatives and showed that high potency could be achieved with a wide variety of pyrimidine substituents (Table 3).

Based on these encouraging results, all compounds from Table 3 (with the exception of trifluoromethyl derivative **43**) were evaluated in WHHL rabbits at 10 mg/kg po.[9] From this study, compounds **16** and **27** proved of most interest, displaying prolonged inhibition ($>$ 8 h) (Fig. 1) with an excellent correlation of pharmacodynamic effect with pharmacokinetic effect (Fig. 2). Furthermore, the inhibition profiles of **16** and **27** (clogP[11] 5.5 and 5.9 respectively) match or better the best previously reported in the WHHL rabbit (compound **1**, $R^a=C_{18}H_{35}$, $R^b=H$, $n=3$, clogP 9.2).[5] These very promising results alongside a much greater activity in human rather than in rabbit plasma would suggest that compounds **16** and **27** have the potential for potent inhibition of Lp-PLA_2 in man.

In conclusion, we have shown that compounds of high potency against rhLp-PLA_2 may be obtained by replacing the long lipophilic chain present in our previously described orally active inhibitors[5] with a series of 4-biphenylacetamide derivatives. Compounds **16** and **27** show excellent activity in vivo and possess enhanced physicochemical properties over our previously described orally active leads (in particular a reduced clogP). These compounds should be of considerable value in our evaluation of the role of Lp-PLA_2 in atherosclerosis.

References and Notes

1. Farnier, M.; Davignon, J. *Am. J. Cardiol.* **1998**, *82*, 3J, and references therein.
2. Macphee, C. H. *Curr. Opin. Pharmacol.* **2001**, *1*, 121.
3. Also known as PAF acetyl hydrolase, this enzyme has much broader substrate specificity than this name implies. See: Tew, D. G.; Southan, C.; Rice, S. Q. J.; Lawrence, M. P.; Haodong, L.; Boyd, H. F.; Moores, K.; Gloger, I. S.; Macphee, C. H. *Atheroscler. Thromb. Vasc. Biol.* **1996**, *16*, 591.

4. Packard, C. J.; O'Reilly, D. St. J.; Caslake, M. J.; McMahon, A. D.; Ford, I.; Cooney, J.; Macphee, C. H.; Suckling, K. E.; Krishna, M.; Wilkinson, F. E.; Rumley, A.; Lowe, G. D. O. *N. Engl. J. Med.* **2000**, *343*, 1148.
5. Boyd, H. F.; Fell, S. C. M.; Flynn, S. T.; Hickey, D. M. B.; Ife, R. J.; Leach, C. A.; Macphee, C. H.; Milliner, K. J.; Moores, K. E.; Pinto, I. L.; Porter, R. A.; Rawlings, D. A.; Smith, S. A.; Stansfield, I. G.; Tew, D. G.; Theobald, C. J.; Whittaker, C. M. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2557, and references therein.
6. Bloomer, J. C.; Boyd, H. F.; Hickey, D. M. B.; Ife, R. J.; Leach, C. A.; Macphee, C. H.; Milliner, K. J.; Pinto, I. L.; Rawlings, D. A.; Smith, S. A.; Stansfield, I. G.; Stanway, S. J.; Taylor, M. A.; Theobald, C. J.; Whittaker, C. M. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1925, and references therein.
7. Suto, M. J.; Gayo, L. M.; Palanki, M. S. S.; Ransome-Fong, L. J. WO Patent 9838171, 1998; *Chem. Abstr.* **1998**, *129*, 216625.
8. Finar, I. L.; Lord, G. H. *J. Chem. Soc.* **1957**, 3314.
9. The method of ref 5 was used. Compounds were administered in a 9:1 mixture of polyethylene glycol 300/Pharmasolve®. Additionally, blood levels of compound were measured: serial blood samples were collected over 8 h post dose and compound concentration analysed by LC/MS/MS.
10. Representative examples: Compound **16** (250 MHz) ^{1}H NMR (DMSO) δ 2.95 and 3.08 (3H, 2×s), 3.61 (2H, m), 3.86 (3H, m), 4.46–4.61 (6H, m), 6.74 and 6.80 (1H, 2×s), 6.91–6.99 (2H, m), 7.21–7.49 (12H, m); MS (APCI+) found (M+1) = 602; $C_{32}H_{29}ClFN_5O_2S$ requires 601. Compound **27** (250 MHz) ^{1}H NMR (DMSO) δ 2.87 and 2.95 (3H, 2×s), 3.54 (2H, m), 3.88 (3H, s), 4.37–4.62 (4H, m), 4.9–5.0 (2H, m), 7.05–7.75 (13H, m), 8.49 (2H, bd); MS (APCI+) found (M+1) = 630; $C_{33}H_{29}ClFN_5O_3S$ requires 629.
11. Daylight CIS, Mission Viejo, CA, USA version 4.71.