Antitumor Activity of 5-Aryl-2,3-dihydroimidazo[2,1-*a*]isoquinolines

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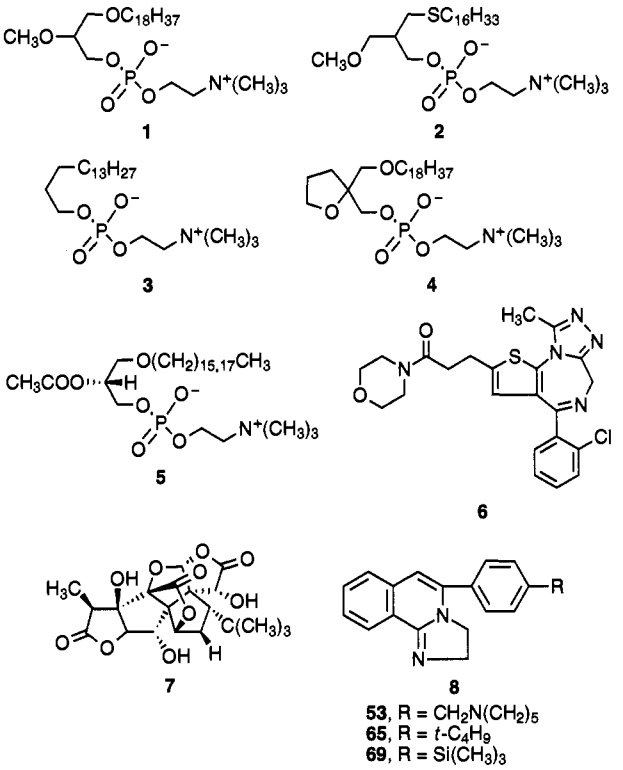
A series of 5-aryl-2,3-dihydroimidazo[2,1-*a*]isoquinolines previously reported to be platelet activating factor (PAF) receptor antagonists were evaluated for potential antitumor activity. Several compounds, such as the 5-(4′-*tert*-butylphenyl) (**65**), 5-[4′-(trimethylsilyl)phenyl] (**69**), and 5-(4′-cyclohexylphenyl) (**71**) analogs showed very good cytotoxicity against several tumor cell lines. 5-[4′-(Piperidinomethyl)phenyl]-2,3-dihydroimidazo[2,1-*a*]isoquinoline (SDZ 62-434, **53**) was more effective on a milligram per kilogram basis than the clinical cytostatic agent edelfosine (**1**) in increasing survivors and decreasing tumor volume in the oral mouse Meth A fibrosarcoma assay. It was selected for further development and is currently in phase I clinical trials in cancer patients.

Introduction

A number of phospholipids, such as edelfosine[1] (ET-18-OCH_3, **1**), ilmofosine[2] (BM41-440, **2**), miltefosine[3] (**3**), and (±)-2-[[hydroxy[[tetrahydro-2-[(octadecyloxy)methyl]furan-2-yl]methoxy]phosphinyl]oxy]-*N,N,N*-trimethylethaniminium hydroxide, inner salt[4] SRI62-834, **4**), that are structurally related to platelet activating factor[5,6] (PAF, **5**) have been shown to exhibit antitumor activity against a variety of murine and human tumor cell lines and in murine tumor models.[7] These phospholipids exert a wide range of pharmacological activities such as direct cytotoxic effects against tumor cells,[8] macrophage activation,[9] changes in membrane structure and permeability,[10,11] alteration of signal transduction,[12,13] and the rate of uptake by endocytosis[14,15] that may contribute to their antitumor activity. No direct correlation between direct or macrophage-induced cytotoxic effects and binding to the PAF receptor or other PAF-induced effects has been reported.[16-18] Furthermore, the cytotoxic effects of edelfosine (**1**) and **4** on most human tumor cell lines could not be blocked by PAF receptor antagonists.[19-22]

In our laboratories we have been evaluating the potential antitumor activity of noncharged PAF receptor antagonists, that is, those that do not contain a phospholipid moiety. We previously reported that there is no apparent relationship between PAF receptor antagonist activity and direct or macrophage-induced tumor cytotoxicity. Very potent noncharged PAF receptor antagonists such as the *s*-triazolo[3,4-*c*]thieno[2,3-*e*][1,4]-diazepine (**6**), WEB 2086) and ginkgolide B (**7**) failed to exhibit any activity when examined in several tumor cell lines.[23] However, one series of noncharged PAF receptor antagonists, the 5-aryl-2,3-dihydroimidazo[2,1-*a*]isoquinolines[24,25] (**8**), gave antitumor activity, with the 4′-(trimethylsilyl)[23,26] (**69**), 4′-*tert*-butyl[26] (**65**), and 4′-(piperidinomethyl)[26-29] (**53**) analogs displaying an *in vitro* cytotoxicity profile similar to edelfosine (**1**).

In this paper we report on the *in vitro* and *in vivo* antitumor activity of a series of 5-aryl-2,3-dihydroimidazo[2,1-*a*]isoquinolines.



Chemistry

The synthesis of the 5-aryl-2,3-dihydroimidazo[2,1-*a*]isoquinolines was carried out by the procedures given in Scheme 1. The 2-aryl-2(*1H*)-imidazolines **9a-d**, prepared from the appropriate benzonitrile and (2-aminoethyl)ammonium *p*-toluenesulfonate, were lithiated[30,31] to the dilithio derivatives and then treated with a methyl aryl ester **10** to give the 5-aryl-2,3,5,6-tetrahydroimidazo[2,1-*a*]isoquinolin-5-ols **11-37** (Table 1). Dehydration to the 5-aryl-2,3-dihydroimidazo[2,1-*a*]-isoquinolines **38-79** (Table 2) was accomplished by refluxing in toluene in the presence of a catalytic amount of *p*-toluenesulfonic acid or refluxing acetic acid. When the 3′,4′-dimethoxybenzyl ether **11** was dehy-

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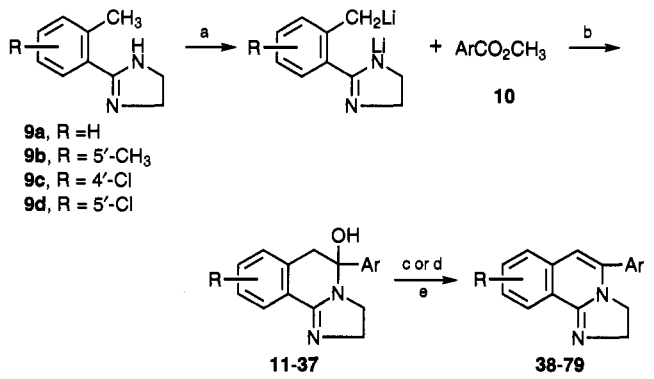
Scheme 1[a]



[a] Reagents/conditions: (a) *n*-BuLi, THF, 35 °C, 4 h; (b) −20±5 to 0 °C, *ca.* 4 h; (c) HOAc, reflux, 5 h; (d) *p*-toluenesulfonic acid, toluene, reflux; (e) HCl, EtOH.

drated, cleavage of the ether occurred to give the 4'-hydroxyphenyl derivative **46**.

Results and Discussion

***In Vitro* Studies.** The direct cytotoxicity on Abelson 8.1 tumor cells for the 5-aryl-2,3-dihydroimidazo[2,1-*a*]-isoquinolines **38**–**79** at doses of 1, 3, and 5 μg/mL is given in Table 3.

Introduction of one or more F or Cl atoms (**39**–**45**), an OH (**46**), one to three OCH_3 groups (**47**–**49**), or a OCH_2O (**50**) failed to increase the cytotoxicity at the lowest dose (1 μg) relative to the unsubstituted 5-phenyl compound **38**. At the highest dose (5 μg), the 4'-Cl and 2',4'- and 3',4'-Cl_2 derivatives **43**–**45** appeared to show increased cytotoxicity relative to **38** based on reduction of viable cells.

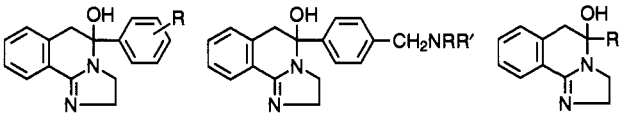
Several members of the 4'-substituted aminomethylene analogs **51**–**56** (type B, Table 3) showed a good level of cytotoxicity at both the 3 and 5 μg/mL doses with the diallylamino (**51**), pyrrolidino (**52**), piperidino (**53**), 2-methylpiperidino (**54**), and thiomorpholino (**56**) analogs giving a profile of activity similar to edelfosine (**1**).

A progressive increase in cytotoxicity was found as the size of the 4'-alkyl group increased from CH_3 to *t*-C_4H_9 (**58, 60**–**65**) with 3'- and 4'-*t*-C_4H_9 having nearly identical activity at all doses. Addition of a Cl at the 8- or 9-position or a CH_3 at the 9-position (**66**–**68**) of the 4'-*tert*-butyl derivative **65** gave compounds of similar activity. Replacing the CH_3 by the CF_3 group (**59**) resulted in loss of activity while substitution of the 4'-*t*-C_4H_9 by the lipophilic $Si(CH_3)_3$ (**69**), cyclopentyl (**70**), cyclohexyl (**71**), or phenyl (**72**) groups resulted in similar or slightly improved cytotoxicity.

Replacement of the phenyl group in **38** by 2'-furyl (**73**), 2'-thienyl (**74**), 1'- or 2'-naphthyl (**77**, **78**) or tetramethyltetralin **79**, which can be regarded as a cyclic mimic of a 3',4'-di-*tert*-butylphenyl group, gave an increase in cytotoxicity, especially at the 3 and 5 μg/mL doses.

These findings suggest that introduction of a lipophilic group (cf. **60, 64, 69, 70,** etc.) in the phenyl ring of **38**

Table 1. 5-Aryl-2,3,5,6-tetrahydroimidazo[2,1-*a*]isoquinolin-5-ols (11–37)



no.[a]	type	R or NRR'	yield, %	mp, °C (recryst solv)[b]	formula[d]	anal.[c]
11	A	4'-$OCH_2C_6H_3$3,4$(OCH_3)_2$	36	144–147 (A)	$C_{26}H_{26}N_2O_4$	C,H,N
12	A	3',4'-$(OCH_3)_2$	46	194–196 (A)	$C_{19}H_{20}N_2O_3$	C,H,N
13	A	3',4',5'-$(OCH_3)_3$	40	152 (B)	$C_{20}H_{22}N_2O_4$	C,H,N
14	B	$N(CH_2CH{=}CH_2)_2$	36	150–151 (C)	$C_{24}H_{27}N_3O$	C,H,N
15	B	$N(CH_2)_4$	37	171–173 (D)	$C_{22}H_{25}N_3O$	C,H,N
16	B	$N(CH_2)_5$	43	168–170 (E)	$C_{23}H_{27}N_3O$	C,H,N
17	B	(±)-2-methylpiperidyl	42	oil	$C_{24}H_{29}N_3O$	C,H,N
18	B	morpholino	61	167–169 (C)	$C_{19}H_{26}N_3O$	C,H,N
19	B	thiomorpholino	49	oil	$C_{19}H_{26}N_3OS$	–[d]
20	B	$N(C_6H_{11})_2$	45	180 (C)	$C_{30}H_{39}N_3O$	C,H,N
21	A	4'-C_2H_5	48	177–179 (A)	$C_{19}H_{20}N_2O$	C,H,N
22	A	4'-*n*-C_3H_7	26	183–185	$C_{26}H_{22}N_2O$	C,H,N
23	A	4'-*i*-C_3H_7	56	179–181 (F)	$C_{20}H_{22}N_2O$	C,H,N
24	A	4'-*n*-C_4H_9	43	179–180 (G)	$C_{21}H_{24}N_2O$	C,H,N
25	A	3'-*t*-C_4H_9	42	172–174 (C)	$C_{21}H_{24}N_2O$	C,H,N
26	A	4'-*t*-C_4H_9	48	187–188 (C)	$C_{21}H_{24}N_2O$	C,H,N
27	A	4'-*t*-C_4H_9,8-Cl	46	198 (D)	$C_{21}H_{23}ClN_2O$	C,H,Cl,N
28	A	4'-*t*-C_4H_9,9-Cl	38	189 (C)	$C_{21}H_{23}ClN_2O$	C,H,Cl,N
29	A	4'-*t*-C_4H_9,9-CH_3	35	168 (C)	$C_{22}H_{26}N_2O$	C,H,N
30	A	4'-$Si(CH_3)_3$	44	163 (C)	$C_{20}H_{24}N_2OSi$	C,H,N
31	A	4'-cyclopentyl	37	198–200 (A)	$C_{23}H_{26}N_2O$	C,H,N
32	A	4'-cyclohexyl	35	214 (A)	$C_{23}H_{26}N_2O$	C,H,N
33	A	4'-C_6H_5	41	167–169 (H)	$C_{23}H_{20}N_2O$	C,H,N
34	C	2'-furyl	46	160–162 (G)	$C_{15}H_{14}N_2O_2$	C,H,N
35	C	1'-naphthyl	38	202 (H)	$C_{21}H_{18}N_2O$	C,H,N
36	C	2'-naphthyl	75	214 (H)	$C_{21}H_{18}N_2O$	C,H,N
37	C	1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphth-6'-yl	38	182–184 (G)	$C_{25}H_{30}N_2O$	C,H,N

[a] The physical properties and ^{2}H-NMR of type A where R = H, 2'-F, 4'-F, 2'-Cl, 3'-Cl, 4'-Cl, 2',4'-Cl_2, 3',4'-Cl_2, 4'-OCH_3, 3',4'-OCH_2O-, 4'-CH_3, 3'-CF_3 and type C where R = 2'-thiophenyl, 3'-pyridyl and 4'-pyridyl are given in ref 31. [b] Recrystallization solvents: A, EtOH; B, Et_2O–petroleum ether; C, CH_2Cl_2–pentane; D, CH_2Cl_2–petroleum ether, E, CH_2Cl_2; f, Et_2O–MeOH; G, EtOH–pentane; H, CH_2Cl_2–EtOH. [c] Unless otherwise stated, the analysis are within ±0.4% of the theoretical values. [d] All compounds had ^{1}H-NMR and MS consistent with assigned structures. Some representative ^{1}H-NMR are given in ref 41.

Table 2. Physical Properties of Compounds Listed in Table 3

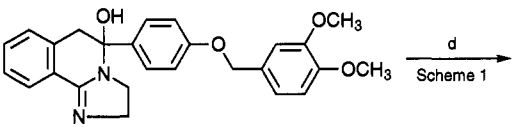
no.	method, yield, %	mp, °C (recryst solv)[a]	formula[c]	anal.[b]
38	D, 65	>250 (A)	$C_{17}H_{14}N_2$·HCl	C,H,Cl,N
39	D, 70	>250 (A)	$C_{17}H_{13}FN_2$·HCl	C,H,Cl,N
40	D, 62	150–151 (B)	$C_{17}H_{13}FN_2$	C,H,N
41	D, 62	134–136 (B)	$C_{17}H_{13}ClN_2$	C,H,Cl,N
42	D, 75	>250 (A)	$C_{17}H_{13}ClN_2$·HCl	C,H,Cl,N
43	D, 88	>250 (A)	$C_{17}H_{13}ClN_2$·HCl	C,H,Cl,N
44	D, 60	150–152 (B)	$C_{17}H_{12}Cl_2N_2$	C,H,Cl,N
45	D, 53	158–160 (C)	$C_{17}H_{12}Cl_2N_2$	C,H,Cl,N
46	D, 68	>260 (D)	$C_{17}H_{14}N_2O$·$2H_2O$	C,H,N
47	D, 40	126–128 (C)	$C_{18}H_{16}N_2O$	C,H,N
48	D, 45	158–160 (C)	$C_{19}H_{18}N_2O_2$	C,H,N
49	D, 46	>250 (D)	$C_{20}H_{20}N_2O_3$·HCl	C,H,Cl,N
50	D, 53	128–130 (B)	$C_{18}H_{13}N_2O_2$	C,H,N
51	D, 72	228 (E)	$C_{24}H_{25}N_3$·2HCl	C,H,Cl,N
52	D, 60	106–108 (F)	$C_{22}H_{23}N_3$	C,H,N
53	D, 75	>250 (E)	$C_{23}H_{25}N_3$·2HCl	C,H,Cl,N
54	D, 63	>250 (E)	$C_{24}H_{27}N_3$·2HCl	C,H,Cl,N
55	D, 85	160–162 (C)	$C_{22}H_{23}N_3O$	C,H,N
56	D, 83	275–278 (D)	$C_{22}H_{23}N_3S$·2HCl	C,H,Cl,N,S
57	D, 80	273 (E)	$C_{30}H_{37}N_3$·2HCl	C,H,Cl,N
58	D, 86	>250 (A)	$C_{18}H_{16}N_2$·HCl	C,H,Cl,N
59	D, 70	>250 (A)	$C_{18}H_{13}F_3N_2$·HCl	C,H,Cl,N
60	E, 75	>275 (E)	$C_{19}H_{18}N_2$·HCl	C,H,Cl,N
61	E, 63	>260 (E)	$C_{20}H_{20}N_2$·HCl	C,H,Cl,N
62	E, 52	>270 (E)	$C_{20}H_{20}N_2$·HCl	C,H,Cl,N
63	E, 81	272–274 (E)	$C_{21}H_{22}N_2$·HCl	C,H,Cl,N
64	E, 75	>275 (E)	$C_{21}H_{22}N_2$·HCl	C,H,Cl,N
65	E, 82	>250 (E)	$C_{21}H_{22}N_2$·HCl	C,H,Cl,N
66	E, 84	>250 (E)	$C_{21}H_{21}ClN_2$·HCl	C,H,Cl,N
67	E, 65	>275 (E)	$C_{21}H_{21}ClN_2$·HCl	C,H,Cl,N
68	E, 65	>275 (E)	$C_{22}H_{24}N_2$·HCl	C,H,Cl,N
69	E, 74	>275 (E)	$C_{20}H_{22}N_2Si$·HCl	C,H,Cl,N
70	E, 39	>270 (E)	$C_{22}H_{22}N_2$·HCl	C,H,Cl,N
71	E, 80	>270 (A)	$C_{23}H_{24}N_2$·HCl	C,H,Cl,N
72	E, 58	>250 (E)	$C_{23}H_{18}N_2$·HCl	C,H,N
73	D, 47	>315 (E)	$C_{15}H_{12}N_2O$·HCl	C,H,Cl,N
74	D, 46	98–100 (B)	$C_{15}H_{12}N_2S$	C,H,N
75	D, 58	>250 (E)	$C_{16}H_{13}N_3$·HCl	C,H,Cl,N
76	D, 47	>250 (E)	$C_{16}H_{13}N_3$·HCl	C,H,Cl,N
77	E, 70	>250 (E)	$C_{21}H_{16}N_2$·HCl	C,H,Cl,N
78	E, 56	>250 (E)	$C_{21}H_{16}N_2$·HCl	C,H,Cl,N
79	E, 81	>250 (A)	$C_{25}H_{28}N_2$·HCl	C,H,Cl,N

[a] Recrystallization solvents: A, CH_2Cl_2–EtOH; B, Et_2O–pentane; C, Et_2O; D, EtOH–Et_2O; E, EtOH; F, CH_2Cl_2–pentane. [b] Unless otherwise stated, the analyses are within ±0.4% of the theoretical values. [c] Satisfactory mass spectrum and ^{1}H-NMR were obtained for all compounds. Some representative ^{1}H-NMR are given in ref 41.

leads to more of an increase in cytotoxicity than adding one or more electron-rich substituents (cf. **40, 44, 48, 49**). A straight or branched alkyl group or a cycloalkyl group with four to six carbon atoms (cf. **63, 65, 70, 71**) or a phenyl group (**72**) confers good cytotoxicity while an increase in the liphophilic bulk to 10 or 14 carbon atoms (**78, 79**) leads to a decline in cytotoxicity.

Several of the compounds that showed good cytotoxicity on the Abelson 8.1 tumor cells were evaluated on the YAC-1 tumor cell line (Table 4). The cytotoxicity on the YAC-1 tumor cells parallels that found on the Abelson 8.1 tumor cells. The 4′-*n*-C_4H_9 (**63**), 3′- and 4′-*t*-C_4H_9 (**64, 65**), and 4′-cyclohexyl (**71**) analogs increased cytotoxicity relative to that of edelfosine (**1**) at 1 μg/mL.

The inhibition of [^{3}H]PAF receptor binding on human platelets for a representative grouping of 5-aryl-2,3-dihydroimidazo[2,1-*a*]isoquinolines is given in Table 3. Best inhibition (IC_{50} 1–3 μM) occurred with the 4′-*t*-C_4H_9 (**65**) thiomorpholinomethyl (**56**), 4′-*t*-C_4H_9, 8-Cl (**66**), and morpholinomethyl (**55**) derivatives. No obvious correlations between these activities and direct cytotoxicity exist. A most striking lack of correlation



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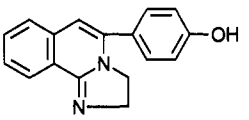

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is the 4′-*t*-C_9H_9 (**65**), 4′-*t*-C_4H_9, 8-Cl (**66**), 4′-*t*-C_4H_9, 9-Cl (**67**), and 4′-*t*-C_4H_9, 9-CH_3 (**68**) analogs that have about the same cytotoxicity (2.0–4.2% viable cells at 1 μg/mL) but have IC_{50} values of 0.9, 2.2, 40.4, and 31.8 μM respectively.

***In Vivo* Study.** The 4′-piperidinomethyl (**53**) and 4′-*t*-C_4H_9 (**65**) analogs, representatives of the more cytotoxic polar and lipophilic compounds, were evaluated orally (po) in the mouse Meth A fibrosarcoma tumor model (Table 5). At a daily dose of 5 μg/mouse/day (ca. 0.25 mg/kg) both compounds showed a positive effect in increasing the number of survivors and decreasing tumor volume relative to controls. When the dose was increased to 50 μg/mouse/day (2.5 mg/kg), compound **53** gave a 100% (10/10 mice) survivor rate with all mice being tumor free, while **65** was less effective at the 5 μg/mouse dose in both the number of survivors and tumor volume on day 28 after tumor inoculation. In comparison with edelfosine (**1**), compound **53** appears to be more effective in both decreasing tumor size and increasing survivors.

Conclusion

The 5-aryl-2,3-dihydroimidazo[2,1-*a*]isoquinolines, originally designed as PAF receptor antagonists, also represent a novel class of potential antitumor agents.

Several members, such as the 3′- and 4′-*t*-C_4H_9, 4′-$Si(CH_3)_3$, 4′-cyclopentyl, and 4′-cyclohexylphenyl (**64, 65, 69–71**), gave an *in vitro* cytotoxicity against two tumor cell lines that was considerably more effective than edelfosine (**1**).

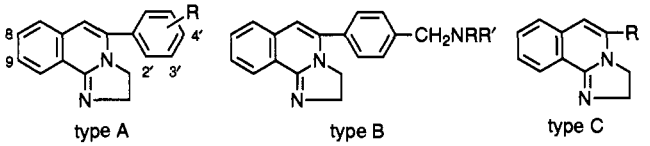
The 4′-piperidinomethyl analog **53** was more effective, on a milligram per kilogram basis, than edelfosine (**1**) in increasing survivors and decreasing tumor volume in the oral mouse Meth A fibrosarcoma assay.

Compound **53** (SDZ 62–434) has now entered phase I clinical trials under the auspice of the Cancer Research Campaign (CRC) of Great Britain. Further investigations to profile the potential antitumor activity of (**53**) have been completed,[32] and additional studies on the 4′-*t*-C_4H_9 analog **65** are in progress. No obvious correlations between inhibition of [^{3}H] PAF binding to human platelets and direct tumor cell cytotoxicity were found.

Experimental Section

General. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Nuclear magnetic resonance (NMR) data for ^{1}H-NMR were taken on JEOL-FX-90 (90 MHz) or Bruker (200 MHz) spectrometers and are reported in δ (ppm) downfield from tetramethylsilane (TMS). Mass spectra (MS) were obtained on a Finnigan MAT 4600 GC/MS instrument applying a desorption chemical ionization method using ammonia (or isobutane) as the reagent gas. Elemental analyses for carbon, hydrogen, and nitrogen were determined with a Carlo Erba Instruments Model

Table 3. Direct Cytotoxicity on Abelson 8.1 Tumor Cells and Inhibition of [^{3}H]PAF Binding to Human Platelet Receptor



no.[a]	type	R or NRR'	% viable cells at 72 h,[b,c] μg/mL 1	3	5	[^{3}H]PAF binding IC_{50} μM[d]
38	A	H	90	70	48	11.2
39	A	2'-F	85	62	31	5.7
40	A	4'-F	82	58	30	14.2
41	A	2'-Cl	72	17	4	8.1
42	A	3'-Cl	85	60	30	5.4
43	A	4'-Cl	80	19	1	37.2
44	A	2',4'-Cl_2	68	5.0	1.2	82.0
45	A	3',4'-Cl_2	68	5.3	1.4	17.0
46	A	4'-OH	80	68	53	7.2
47	A	4'-OCH_3	72	28	25	55.0
48	A	3',4'-$(OCH_3)_2$	78	59	37	22.0
49	A	3',4',5'-$(OCH_3)_3$	110	124	120	>100
50	A	3',4'-OCH_2O-	68	32	10	19.0
51	B	$N(CH_2CH{=}CH_2)_2$	39	2.0	1.2	9.2
52	B	$N(CH_2)_4$	62	10	1.3	59.4
53	B	$N(CH_2)_5$	72	12	3	7.5
54	B	(±)-2-methylpiperidyl	51	3.1	2.4	29.4
55	B	morpholino	73	46	28	2.8
56	B	thiomorpholino	51	3.1	2.4	1.1
57	B	$N(C_6H_{11})_2$	100	80	51	13.1
58	A	4'-CH_3	81	38	7	5.4
59	A	3'-CF_3	92	50	23	19.2
60	A	4'-C_2H_5	36	3.0	2.0	6.3
61	A	4'-*n*-C_3H_7	2.8	1.5	1.3	nt
62	A	4'-*i*-C_3H_7	4.6	1.4	1.4	nt
63	A	4'-*n*-C_4H_9	2.0	1.4	1.3	nt
64	A	3'-*t*-C_4H_9	2.0	0.5	0.5	4.0
65	A	4'-*t*-C_4H_9	3.3	1.4	1.3	0.9
66	A	4'-*t*-C_4H_9,8-Cl	3.7	1.7	1.5	2.2
67	A	4'-*t*-C_4H_9,9-Cl	4.2	2.0	1.9	40.4
68	A	4'-*t*-C_4H_9,9-CH_3	2.0	2.0	2.0	31.8
69	A	4'-$Si(CH_3)_3$	2.0	0.5	0.5	6.5
70	A	4'-cyclopentyl	1.5	1.3	1.2	nt
71	A	4'-cyclohexyl	1.4	1.3	1.3	nt
72	A	4'-C_6H_5	2.1	1.6	1.4	3.4
73	C	2'-furyl	24	3.1	2.3	100
74	C	2'-thienyl	83	29	2.3	15.2
75	C	3'-pyridyl	100	95	93	100
76	C	4'-pyridyl	100	96	98	47.9
77	C	1'-naphthyl	60.7	1.6	1.4	nt
78	C	2'-naphthyl	56.1	3.8	1.7	nt
79	C	1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphth-6'-yl	100	2.8	1.8	nt
1	edelfosine		70.0	9.5	2.8	

[a] Compounds **40**, **44**, **45**, **47**, **48**, **50**, **52**, **55**, and **74** are free bases; all other compounds are HCl salts. [b] Values are averages of quadruplicate assays. Average errors: ±0.6% at 0.5–10% viable cells, ±1.5% at 11–25% viable cells and ±4.2% at >25% viable cells. [c] Viable cells were measured by alkaline phosphatase activity. [d] nt denotes not tested.

EA1108 elemental analyzer and are within ±0.4% of theory unless noted otherwise. If not otherwise specified, chemicals and reagents were obtained from the Aldrich Chemical Co. Solvents were of reagent grade and dried prior to use. Reaction progress and purity of final products were determined on E. Merck silica gel 60 chromatography plates. Column chromatography was carried out using E. Merck silica gel CH83 (0.06–0.20 mesh) with the indicated eluents.

Cell Lines. The tumor cell line Abelson 8.1 was obtained from A. W. Harris (Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia) and the YAC-1 from G. Klein (Department of Tumor Biology, Karolinska Institute, Stockholm, Sweden). The cells were grown in stationary suspension culture in Dulbecco Modified Eagle's Medium (DMEM) and 10% heat-inactivated fetal calf serum (FCS) supplemented with 50 μM 2-mercaptoethanol, 100 units of penicillin, and 1 μg of streptomycin. The Meth A fibrosarcoma cells were originally induced in Balb/c mice by administering methylcholanthrene according to the procedure of Old *et al.*[33]

Tumor Cell Cytotoxicity. Abelson 8.1 tumor cells (1×10^3 cells/well) in DMEM and 10% FCS were placed in flat-bottom microtiter plastic plates (Nunc Roskieide Denmark) and incubated with 1–3 μg/mL of test substance dissolved in water for 24–72 h. The number of tumor cells present was determined by measuring alkaline phosphatase activity by a modified procedure of Culvenor,[34] the tumor cell plates were centrifuged at 500*g* for 10 min, and the supernatant was flicked off. Without further washing, 100 μL of buffer containing 20 μL of diethanolamine, 2 μM magnesium chloride hexahydrate, 2.5 μM *p*-nitropenyl phosphate, and 10 mg of Triton X-100 was added. The samples were incubated for 60 min at room temperature, and the enzymatic activity was terminated by the addition of 100 μL of 0.5 N sodium hydroxide. The absorbance was then measured at 405 nM using a Titertak Multiskan apparatus and compared to non-drug-treated cells. The same assay procedure was used to determine YAC-1 tumor cells.

Table 5. Mouse Meth A Fibrosarcoma Assay:[a] Oral Administration

no.	dose, μg/mouse, po ($n = 10$)	tumor volume, % control				survivors[b]
		day 7	day 14	day 21	day 28	day 28
control		100	100	100	100	0/10
53	5.0	102	32	19	27	5/10
	50.0	70	14	0.3	0	10/10
65	5.0	80	43	26	44	3/10
	50.0	90	53	41	61	1/10
1	5.0	86	27	12	18	6/10
	50.0	64	18	9	9	7/10

[a] At an average weight of 20 g/mouse: 5.0 μg/mouse is ca. 0.25 mg/kg and 50 μg/mouse is ca. 2.5 mg/kg. [b] All survivors are tumor free as measured by calipers and were observed for 120 days after completion of the assay.

Table 4. Direct Cytotoxicity on YAC-1 Tumor Cells[a]

no.	R or NRR'[b]	% viable cells at 72 h, μg/mL		
		1	3	5
61	4'-*n*-C_3H_7	18.0	1.0	0.9
62	4'-*i*-C_3H_7	46.0	3.9	2.1
63	4'-*n*-C_4H_9	4.0	1.6	1.1
64	3'-*t*-C_4H_9	4.2	1.7	1.0
65	4'-*t*-C_4H_9	3.4	2.7	2.2
69	4'-$Si(CH_3)_3$	11.6	2.6	2.3
70	4'-cyclopentyl	10.5	1.7	1.6
71	4'-cyclohexyl	3.6	1.6	1.4
72	4'-C_6H_5	10.8	3.5	2.8
53	$CH_2N(CH_2)_5$	92.0	53.0	21.0
1	edelfosine	68.0	8.4	2.5

[a] See footnotes *b* and *c* in Table 3. [b] See formulas type A and type B in Table 3.

Mouse Meth A Fibrosarcoma Assay. Ten CBF_1 mice, 10–12 weeks of age, were implanted with 10^5 Meth A sarcoma cells to serve as control. Ten other CBF_1 mice were implanted with 10^5 Meth A sarcoma cells and on day 1 after implant were each treated per os (po) with 5.0 or 50 μg/mouse of 1, **53**, or **65**, and daily drug treatment continued for 27 days. On days 7, 15, 21, and 28 after tumor implant, the entire tumor volume was calculated by the equation $V = {}^2/_3\pi AB(AB + B/2)$, where A and B are measured tumor diameters.

PAF Receptor Assay. Methodology for evaluation in PAF receptor binding studies has previously been described.[35] Human platelets prepared for the receptor binding were incubated with [9,10-$^3H_2$]PAF (49 Ci mM^{-1}) at a final concentration of 1.5 nM for 1 h at 24 °C. Free ligand was separated by centrifugation, and the platelets were counted for 1 min in a liquid scintillation counter. Specific binding was calculated as the difference in counts per minute between bound and nonspecifically (calculated using 0.37 mM cold PAF) bound [^{3}H]PAF.

2-Aryl-2-(1*H*)-imidazolines[36] 9a-d: 2-(2',5'-Dimethylphenyl)imidazoline(9b). A mixture of 2,5-dimethylbenzonitrile (7.87 g, 0.06 mol) and (2-aminoethyl)ammonium *p*-toluenesulfonate (13.96 g, 0.06 mol) was refluxed for ca. 6 h, allowed to cool to ca. 40 °C, poured with stirring into H_2O (100 mL), treated with 6 N NaOH (80 mL, 0.48 mol), and then allowed to stir overnight at room temperature. The resultant solid was filtered off, dissolved in CH_2Cl_2, washed with H_2O (twice with 100 mL), filtered through Celite, and then concentrated *in vacuo* to give 7.84 g (75%) of **9b**: mp 108–110 °C (CH_2Cl_2/petroleum ether); MS *m/z* 175 (MH^+). Anal. ($C_{11}H_{14}N_2$) C, H, N.

2-(4'-Chloro-2'-methylphenyl)imidazoline (9c): obtained as a white solid (45%); mp 97–98 °C (CH_2Cl_2/pentane); MS *m/z* 195 (MH^+). Anal. ($C_{10}H_{11}ClN_2$) C, H, Cl, N.

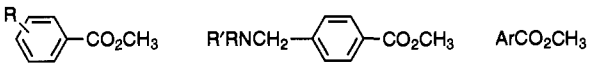
2-(5'-Chloro-2'-methylphenyl)imidazoline (9d): obtained as a white solid (60%); mp 96–97 °C (C_2H_5OH/pentane); MS *m/z* 195 (MH^+). Anal. ($C_{10}H_{11}ClN_2$) C, H, Cl, N.

Methyl Aryl Esters 10a-s. The 3,4-dimethoxy- and 3,4,5-trimethoxybenzoic acid methyl esters, methyl furoate, 4-isopropyl-, 4-*tert*-butyl, and 4-phenylbenzoic acid, 4-ethyl-, 4-propyl-, and 4-butylbenzoyl chloride, and 1- and 2-naphthoyl chloride were obtained from Aldrich. The 4-(trimethylsilyl)-,[37] 4-cyclopentyl-,[38] and 4-cyclohexylbenzoic[39] acids and 5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthoic acid[40] were prepared by cited procedures.

Method A (10a-g). A stirred mixture of methyl *p*-toluate (67.5 g, 0.45 mol), anhydrous $NaHCO_3$ (45.3 g, 0.54 mol), and CCl_4 (750 mL) was irradiated with a high-intensity light source (150 W reflector Westinghouse lamp) and treated dropwise with a solution of Br_2 (23.05 mL, 0.45 mol) in CCl_4 (100 mL) at such a rate that color faded immediately. The mixture was then refluxed for ca. 2 h, allowed to stand overnight at room temperature, filtered, and then concentrated *in vacuo* to give 104.3 g of crude methyl 4-(bromomethyl)toluate (80% CH_2 Br by ^{1}H-NMR).

A stirred solution of crude bromo ester (22.9 g, ca. 0.08 mol as CH_2Br) in THF (200 mL) was treated dropwise at room temperature with a solution of piperidine (13.6 g, 0.16 mol) in

Table 6. Methyl Aryl Esters **10**



type A type B type C

no.	type	R or NRR'	method,[a] yield, %	mp or bp (mmHg), °C	formula	anal.
10a	B	$N(CH_2CH{=}CH_2)_2$	A, 52	145–147 (0.2)	$C_{15}H_{19}NO_2$	C,H,N
10b	B	$N(CH_2)_4$	A, 65	130–135 (0.3)	$C_{13}H_{17}NO_2$	C,H,N
10c	B	$N(CH_2)_5$	A, 70	128–133 (0.3)	$C_{14}H_{19}NO_2$	C,H,N
10d	B	(±)-2-methylpiperidyl	A, 42	135–140 (0.2)	$C_{15}H_{21}NO_2$	C,H,N
10e	B	morpholino	A, 61	130–132 (0.3)	$C_{13}H_{17}NO_3$	C,H,N
10f	B	thiomorpholino	A, 46	134–138 (0.3)	$C_{13}H_{17}NO_2S$	C,H,N
10g	B	$N(C_6H_{11})_2$	A, 56	99–101	$C_{21}H_{31}NO_2$	C,H,N
10h	A	4'-C_2H_5	B, 75	90–93 (0.13)[b]	$C_{10}H_{12}O_2$	
10i	A	4'-*n*-C_3H_7	B, 95	138–140 (16)	$C_{11}H_{14}O_2$	
10j	A	4'-*i*-C_3H_7	B, 80	135–138 (18)	$C_{11}H_{14}O_2$	
10k	A	4'-*n*-C_4H_9	B, 82	146–148 (18)[c]	$C_{12}H_{16}O_2$	
10l	A	3'-*t*-C_4H_9	B, 63	69–72 (0.2)	$C_{12}H_{16}O_2$	
10m	A	4'-$Si(CH_3)_3$	B, 79	80–82 (0.2)	$C_{11}H_{16}O_2Si$	
10n	A	4'-cyclopentyl	B, 82	oil	$C_{13}H_{16}O_2$	
10o	A	4'-cyclohexyl	B, 50	45–46[d]	$C_{14}H_{18}O_2$	C,H
10p	A	4'-C_6H_5	B, 61	111–112[e]	$C_{14}H_{12}O_2$	
10q	C	1-naphthyl	B, 75	128–130 (0.2)	$C_{12}H_{10}O_2$	
10r	C	2-naphthyl	B, 72	76–78	$C_{12}H_{10}O_2$	
10s	C	1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphth-6'-yl	B, 93	75–77 (0.1)[f]	$C_{16}H_{22}O_2$	

[a] See the Experimental Section for a detailed description of the general methods A and B. [b] Lit.[42] oil. [c] Lit.[43] bp 69–70 °C (0.13 mm). [d] Lit.[44] mp 47–48 °C. [e] Lit.[45] mp 112 °C. [f] Lit.[40] bp 161–164 °C (7.8 mm).

THF (20 mL) and then stirred ca. 48 h. The solids were filtered off, the filtrate was concentrated *in vacuo*, and the residue was dissolved in CH_2Cl_2 (300 mL) and washed with 2 N HCl (300 mL). The acid layer was treated with 2 N NaOH until basic to litmus paper, extracted with CH_2Cl_2 (400 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*, and the residue was distilled to give 13.1 g of methyl 4-(1-piperidinylmethyl)benzoate (**10c**) (Table 6).

Method B. A solution of 4-(trimethylsilyl)benzoic acid (8.8 g, 0.045 mol), thionyl chloride (8.0 g, 0.073 mol), and CH_2Cl_2 was stirred and refluxed for ca. 8 h and then concentrated *in vacuo*. The residue was added to sodium methoxide (0.054 mol) in CH_3OH (80 mL), stirred at room temperature for ca. 48 h, and concentrated *in vacuo*, and the residue was treated with H_2O (20 mL) and CH_2Cl_2 (50 mL). The organic layer was separated, dried ($MgSO_4$), filtered, and concentrated *in vacuo*, and the residue was distilled to give 7.4 g of methyl 4-(trimethylsilyl)benzoate (**10m**, Table 6).

Method C. Methyl 4-[[(3′,4′-Dimethoxyphenyl)methyl]oxy]benzoate (10t). A stirred mixture of methyl 4-hydroxybenzoate (19.8 g, 0.13 mol), 50% NaH (7.5 g, 0.16 mol), and 3,4-dimethoxybenzyl chloride (21.2 g, 0.16 mol) in DMF (500 mL) under N_2 was heated at 60 °C for 4 h and concentrated *in vacuo*, and the residue was treated with H_2O (50 mL) and CH_2Cl_2 (200 mL). The organic layer was washed with H_2O, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give 24.0 g (62%) of **10t**: mp 94–5 °C (C_2H_5OH/pentane); MS *m/z* 303 (MH^+). Anal. ($C_{17}H_{18}O_5$) C, H.

5-Aryl-2,3,5,6-tetrahydroimidazo[2,1-*a*]isoquinolin-5-ols (11–37). A stirred solution of 2-(*o*-methylphenyl)imidazoline (8.0 g, 0.05 mol) in THF (200 mL) under N_2 was treated dropwise with 1.6 M *n*-BuLi in hexane (105 mL, 0.15 mol) and then heated at 35 °C for ca. 4 h. The mixture was then immersed in a dry ice–acetone bath, cooled to an internal temperature of −25 °C, and treated dropwise with a solution of methyl aryl ester (0.10 mol) in THF (50 mL) at such a rate than the internal temperature did not exceed −20 °C. After an additional 3 h at −25 °C, the reaction mixture was allowed to warm to 0 °C, treated with saturated NH_4Cl solution (30 mL), and allowed to stand overnight at room temperature. The mixture was then concentrated *in vacuo* and treated with CH_2Cl_2 (200 mL) and H_2O (100 mL), the CH_2Cl_2 layer was separated, washed with H_2O, dried ($MgSO_4$), and filtered, and the filtrate was concentrated *in vacuo*. The resultant residue was then crystallized from the appropriate solvent given in Table 1.

5-Aryl-2,3-dihydroimidazo[2,1-*a*]isoquinolines (38–79). Method D. A solution of 5-aryl-2,3,5,6-tetrahydroimidazo[2,1-*a*]isoquinolin-5-ol (0.01 mol) in acetic acid (40 mL) was stirred and refluxed under N_2 for ca. 5 h. The acetic acid was removed *in vacuo*, and the residue was treated with H_2O (50 mL) and then made alkaline with 2 N Na_2CO_3 (35 mL). The mixture was extracted with CH_2Cl_2 (2 × 100 mL), and the organic layer was washed with H_2O (50 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give the free base. The HCl salt was prepared by dissolving the base in saturated H Cl/EtOH, evaporating *in vacuo*, and crystallizing from the appropriate solvent (cf. Table 2).

Method E. A mixture of 5-aryl-2,3,5,6-tetrahydroimidazo-[2,1-*a*]isoquinolin-5-ol (2 g), *p*-toluenesulfonic acid (0.2 g), and toluene (50 mL) were stirred and refluxed for ca. 12 h with continuous removal of H_2O (Dean–Stark trap). The toluene was removed *in vacuo*, and the residue was dissolved in CH_2Cl_2, washed with H_2O, saturated NaH CO_3 solution, and saturated NaCl solution, dried ($MgSO_4$), filtered, and evaporated *in vacuo* to give the free base. The HCl salt was prepared as given in method D.

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(41) ^{1}H-NMR data of selected compounds from Tables 1 and 2. The solvent is DMSO-d_6, unless indicated otherwise. **23**: δ 1.21 (d, 6H), 2.80–3.78 (m, 6H), 6.15 (s, 1H), 7.11–7.55 (m, 7H), 7.98 (d, 1H). **31**: δ 1.44–2.15 (m, 8H), 3.00 (m, 1H), 3.01–3.96 (m, 6H), 7.38–7.96 (m, 7H), 8.30 (d, 1H). **32**: δ 1.05–1.76 (m, 10H), 3.80–4.36 (m, 6H), 7.30–7.86 (m, 8H). **36**: δ 3.06–3.87 (m, 6H), 6.32 (s, 1H), 7.12–8.11 (m-11H). **37**: δ 1.31 (s, 12H) 1.72 (s, 4H), 3.03–3.93 (m, 6H), 7.05–7.55 (m, 6H), 8.08 (s, 1H). **39**: (D_2O): δ 3.90 (t, 2H), 4.30 (t, 2H), 7.02 (s, 1H), 7.15–8.18 (m, 8H). **42**: (CF_3CO_2D) δ 3.98 (m, 2H), 4.35 (m, 2H), 6.86 (s, 1H), 7.03–8.13 (m, 8H). **58**: (CF_3CO_2D) δ 2.52 (s, 3H), 4.35 (μ, 2H), 5.65 (μ, 2H), 7.17 (s, 1H), 7.42 (s, 4H), 7.65–8.28 (μ, 4H). **61**: δ 0.95 (t, 3H), 1.67 (m, 2H), 2.68 (t, 2H) 7.18 (s, 1H), 7.47 (A_2B_2, 4H), 7.63–8.02 (m, 3H), 8.48 (d, 1H). **62**: (D_2O) δ 1.18 (d, 6H), 2.92 (quintet, 1H), 3.95 (t, 2H), 4.37 (t, 2H), 6.83 (s, 1H), 7.33 (s, 4H), 7.52–7.95 (m, 4H). **63**: 0.98 (t, 3H), 1.17–1.72 (m, 4H), 2.65 (t, 2H), 4.02 (t, 2H), 4.48 (t, 2H), 7.13 (s, 1H), 7.43 (A_2B_2, 4H), 7.50–7.82 (m, 3H), 8.48 (d, 1H). **70**: 1.43–2.11 (m, 8H), 3.05 (m, 1H), 4.02 (t, 2H), 4.53 (t, 2H), 7.12 (s, 1H), 7.46 (A_2B_2, 4H), 7.52–7.96 (m, 3H) 8.51 (d, 1H). **71**: (D_2O) 1.08–1.82 (m, 10H), 3.08 (m, 1H), 3.98 (t, 2H), 4.38 (t, 3H), 6.92 (s, 1H), 7.38 (s, 4H), 7.58–8.00 (m, 4H). **77**: (D_2O) δ 3.92 (m, 4H), 6.87 (s, 1H), 7.32–8.05 (m, 11H). **78**: δ 4.11 (t, 2H), 4.63 (t, 2H), 7.35 (s, 1H), 7.56–8.32 (m, 10H), 8.68 (d, 1H). **79**: δ 1.28 (s, 12H), 1.75 (s, 4H), 4.09 (t, 2H), 4.60 (t, 2H), 7.17 (s, 1H), 7.20–7.82 (m, 6H), 8.43 (d, 1H).
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