carbonate (6.1 g, 44.2 mmol) in DMF (50 mL) was heated at 60 °C for 0.5 h. Then 3-(2-chloroethyl)-2-oxazolidinone[9] (6.6 g, 44.2 mmol) was added and heating was continued for 18 h at 60 °C. The reaction was allowed to cool to room temperature and concentrated under reduced pressure and the resulting solid partitioned between $CHCl_3$ and H_2O. The organic layer was dried ($MgSO_4$), filtered, and concentrated to a solid which was recrystallized to provide compound **7** (3.5 g, 35%): mp 103–104 °C; ^1H NMR ($CDCl_3$) δ 3.43 (m, 2 H), 3.70 (m, 2 H), 4.14 (m, 2 H), 4.61 (t, 2 H), 7.20 (s, 2 H); MS (M + 1) 227. Anal. ($C_8H_{10}N_4O_4$) C, H, N.

3-[3-(2-Nitro-1*H*-imidazol-1-yl)propyl]-2-oxazolidinone (8). Compound **8** was prepared as described above starting with 2-nitroimidazole and 3-(3-chloropropyl)-2-oxazolidinone[10] in a yield of 42%: mp 89–91 °C (recrystallized from ethanol); ^1H NMR ($CDCl_3$) δ 2.13 (m, 2 H), 3.38 (m, 2 H), 3.60 (m, 2 H), 3.60 (m, 2 H), 4.41 (q, 4 H), 7.18 (d, 1 H), 7.39 (d, 1 H); MS (M + 1) 241. Anal. ($C_9H_{12}N_4O_4$) C, H, N.

***N*-(2-Bromoethyl)-2-nitro-1*H*-imidazole-1-ethanamine Monohydrobromide (9).** A mixture of **7** (3.5 g, 15.5 mmol) and 31% hydrogen bromide/acetic acid[9] (30 mL) was stirred at 25 °C for 18 h. The dark solution was diluted with ether and methanol and provided compound **9** (3.0 g, 54%): mp 103–104 °C; ^1H NMR (DMSO-d_6) δ 3.45 (m, 4 H), 3.70 (m, 2 H), 4.66 (t, 2 H), 7.28 (s, 1 H), 7.71 (s, 1 H), 8.90 (bs, 2 H); MS m/e = 263, (M + 2) 265. Anal. ($C_7H_{11}N_4Br_2O_2 \cdot H_2O \cdot HBr$) C, H, N, Br.

***N*-(2-Bromoethyl)-2-nitro-1*H*-imidazole-1-propanamine Monohydrobromide (10).** Compound **10** was prepared as described above for compound **9**, starting with **8**, in a yield of 80%: mp 164–168 °C dec (recrystallized from ethanol); ^1H NMR (DMSO-d_6) δ 2.24 (m, 2 H), 3.00 (m, 2 H), 3.41 (m, 2 H), 3.70 (t, 2 H), 4.48 (t, 2 H), 7.23 (d, 1 H), 7.75 (d, 1 H), 8.70 (bs, 2 H); MS m/e = 277, (M + 2) 279. Anal. ($C_8H_{13}N_4BrO_2 \cdot HBr \cdot 0.5H_2O$) C, H, N, Br.

3-[2-Hydroxy-3-(2-nitro-1*H*-imidazol-1-yl)propyl]-2-oxazolidinone (4). A suspension of 2-nitroimidazole (8.8 g, 78 mmol) and cesium carbonate (0.9 g, 2.8 mmol) in absolute ethanol (180 mL) was heated under reflux for 20 min. Then 1-glycidyl-2-oxazolidinone (21.2 g, 160 mmol) was added and the suspension was heated at reflux for 6 h. The mixture was cooled and filtered, and the residue was washed with ethanol to provide compound **4** (16.3 g, 85%): mp 216–218 °C; ^1H NMR (DMSO-d_6) δ 3.22 (t, 2 H), 3.63 (t, 2 H), 3.99 (m, 1 H), 4.27 (m, 3 H), 4.55 (dd, 1 H), 5.43 (d, 1 H), 7.17 (s, 1 H), 7.62 (s, 1 H); MS m/e = 256. Anal. ($C_9H_{12}N_4O_5$) C, H, N.

α-[[(2-Bromoethyl)amino]methyl]-2-nitro-1*H*-imidazole-1-ethanol Monohydrobromide (2, RB 6145). A mixture of **4** (0.5 g, 1.9 mmol) and 31% hydrogen bromide/acetic acid (5 mL) was stirred at room temperature. After 20 min a solution resulted and stirring was continued for 20 h. The reaction was concentrated under reduced pressure and the resulting dark solid was recrystallized from methanol (2×) to provide compound **2** (0.40 g, 54%): mp 159–160 °C dec; ^1H NMR (DMSO-d_6) δ 3.00 (m, 1 H), 3.29 (m, 1 H), 3.42 (m, 2 H), 3.69 (t, 2 H), 4.25 (m, 1 H), 4.39 (m, 1 H), 4.53 (m, 1 H), 5.97 (bs, 1 H), 7.22 (s, 1 H), 7.66 (s, 1 H), 8.83 (bs, 2 H); MS m/e = 293, (M + 2) 295. Anal. ($C_8H_{13}N_4BrO_3$) C, H, N, Br.

3-[(2,3-Dihydroimidazol[2,1-*b*]oxazol-2-yl)methyl]-2-oxazolidinone (12). A mixture of 2-nitroimidazole (3.0 g, 26.5 mmol), potassium carbonate (7.3 g, 52.8 mmol), and 18-crown-6 (0.6 g, 2.7 mmol) in DMF (30 mL) was heated at 60 °C for 3 h. To the resulting solution was added 1-glycidyl-2-oxazolidinone (4.0 g, 27 mmol) and heating was continued at 60 °C for 28 h. TLC indicated that no 2-nitroimidazole remained. The mixture was concentrated under reduced pressure and the residue was dissolved in $CHCl_3$. The solution was washed with brine, dried ($MgSO_4$), filtered, and concentrated to provide 3.8 g of an oil. Chromatography (SiO_2, $CHCl_3$/methanol, 98:2) provided **12** (1.8 g, 32%) which was recrystallized from ethyl acetate: mp 140–141.5 °C; ^1H NMR ($CDCl_3$) δ 3.63 (m, 4 H), 4.00 (m, 1 H), 4.27 (m, 3 H), 5.30 (m, 1 H), 6.55 (dd, 2 H); MS (M + 1) 210. Anal. ($C_9H_{11}N_3O_3$) C, H, N.

Conversion of 2 to 1. To a solution of **2** (3.74 mg, 1×10^{-5} mol) in saline (2 mL) was added Et_3N (3 μL, 2.1×10^{-5} mol). The solution was stirred at 25 °C and monitored by HPLC (Alltech CN column, 0.1 M KH_2PO_4/methanol, 9/1, 313 mm). After 30 min complete conversion to **1** had occurred (identified by co-injection with an authentic sample of **1**). This provided a 5-mmol stock solution of **1**.[13]

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Triazolobenzo- and Triazolothienodiazepines as Potent Antagonists of Platelet Activating Factor

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A series of [1,2,4]triazolo[4,3-*a*][1,4]benzodiazepines bearing an ethynyl functionality at the 8-position and the isosteric thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepines were prepared and evaluated as antagonists of platelet activating factor. The effects of substitution were explored in in vitro and in vivo test systems designed to measured PAF-antagonistic activity. Results are discussed and compared with previously published data. Many of the compounds had activity superior to WEB 2086, compound **1**. In general, the thieno analogues exhibited better oral activity than the corresponding benzodiazepines. The duration of activity upon oral administration was modulated by the substitution on the acetylenic side chain. Compounds **71** and **81** were selected for further pharmacological evaluation as a result of their good oral potency and exceptionally long duration of action.

Antagonists of platelet activating factor (PAF) have been discovered by several laboratories among classes of compounds with quite different structures.[1] The triazolothienodiazepines[2] have emerged as one of the more important series of PAF-antagonists, because of their selectivity, potency, and bioavailability, three properties which are essential to assess the clinical utility of a PAF antagonist in allergic and inflammatory diseases.

When we were confronted with the task of preparing compound **1** (WEB 2086)[3] for pharmacological comparison

† Department of Pharmacology.

(1) Cooper, K.; Parry, M. J. In *Annual Report in Medical Chemistry*; Allen, R. C., Ed.; Academic Press, Inc.: New York, 1989, p 81.
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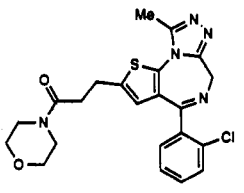
Table I. Triazolobenzodiazepines

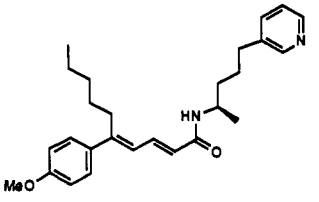
compd	X	R_1	R_2	R_3	inhibition of PAF-binding: IC_{50},[a] nM	guinea pig bronchoconstriction assay: intravenous % inhibn 1 mg/kg[b]	intravenous ID_{50},[a,b] mg/kg	oral % inhib 1 mg/kg[c]	oral ID_{50},[a,c] mg/kg
1					200	99 ± 1	0.03	42 ± 11	1.2
2					40	99 ± 1	0.05	12 ± 14	4
10a, 8-I	2-Cl	Me	H		1000	19 ± 3			
10b, 8-I	2-F	Me	H		1000	19 ± 4			
12					1000	10 ± 8			
16, 8-sub.	2-F	H	H	A	1000	95 ± 1	0.3		
17, 8-sub.	2-F	Me	H	A	10	99 ± 0	0.01	93 ± 4	0.5
18, 8-sub.	2-Cl	Me	H	A	20	99 ± 0	0.02	32 ± 4	
19, 8-sub.	2-F	Et	H	A	100	99 ± 1	0.05	30 ± 3	
20, 8-sub.	2-F	CF_3	H	A	5	97 ± 1	0.4	9 ± 1	
21, 9-sub.	2-F	Me	H	A	inact.[d]	3 ± 12			
22, 8-sub.	2-F	Me	(5,6-H_2)	A	110	100 ± 0	0.02	0 ± 0	
23, 8-sub.	2-F	Me	H	CH_2A	45	100 ± 0	0.02	96 ± 1	0.3
24, 8-sub.	2-F	Me	H	B_1	20	100 ± 0	0.02	81 ± 5	0.4
25, 8-sub.	2-F	Me	Me (*S*)	B_1	6	100 ± 0	0.008	100 ± 0	0.1
26, 8-sub.	2-F	Me	Me (*R*)	B_1	1000	49 ± 6			
27, 8-sub.	2-F	Me	OH	B_1	50	99 ± 1	0.003	0 ± 0	
28, 8-sub.	2-F	Me	OMe	B_1	100	99 ± 1	0.004	21 ± 11	
29, 8-sub.	2-F	CF_3	H	B_1	200	100 ± 0	0.03	0 ± 0	
30, 8-sub.	4-Cl	Me	H	B_1	100	98 ± 0	0.03	38 ± 5	
31, 8-sub.	4-Cl	CF_3	H	B_1	1000	97 ± 0	0.2	12 ± 5	
32, 8-sub.	2-Cl	Me	H	C_1	130	99 ± 0	0.005	0 ± 0	
33, 8-sub.	2-Cl	Me	H	D_1	15	100 ± 0	0.02	59 ± 4	0.6
34, 8-sub.	2-F	Me	H	E	7	99 ± 0	0.02	98 ± 1	0.3
35, 8-sub.	2-F	Me	H	F_1	5	100 ± 0	0.01	30 ± 7	
94					300	1 ± 6			
98					500	99 ± 1	0.04	0 ± 0	

[a] IC_{50} and ID_{50} values were determined by linear regression analysis; the correlation coefficient for each regression line was >0.95. [b] One-minute pretreatment time. [c] Two-hour pretreatment time. [d] Inact. = no significant inhibition at 1000 nM.

with PAF antagonists of the pentadienyl carboxamide series represented by compound **2**,[4] we investigated the



1



2

palladium-catalyzed coupling of acetylenes with aryl iodides or aryl bromides as a possible synthetic route. The pilot reaction, in which *N*-propargylphthalimide was coupled with 8-iodotriazolobenzodiazepine **10b**, resulted in compound **17**, which surprisingly was found to have excellent activity as a PAF antagonist, surpassing WEB 2086 in our screening tests[5] (Table I). Encouraged by these findings we embarked on a search for even more potent PAF antagonists. Initially, we tried to establish some structure–activity relationship (SAR) in the series of benzodiazepines which we found easier to synthesize than the thienodiazepines. It was thought that key elements necessary for PAF-antagonist activity identified in this study could be applied to the isosteric thienodiazepine series. However, it soon became apparent that the thieno analogues exhibited about 10-fold greater oral potency than the benzodiazepines. Thus our major focus shifted to this class of compounds.

The question of why the thienodiazepines are more potent orally than the corresponding benzodiazepines has not yet been resolved. One obvious difference of the two isoesters is the higher flexibility of the thienodiazepine ring system, evident from the NMR data. Thienotriazolodiazepines exhibit a broad singlet for the methylene group in the diazepine ring, while the corresponding benzodiazepines show an AB system for the corresponding protons. In the triazolobenzodiazepines the ring inversion is impeded by the steric interaction of the methyl group in position 1 with the proton in position 10. Of course we do not imply a connection between ring flexibility and oral potency.

The compounds prepared and tested in the benzodiazepine series allowed us to derive some qualitative SAR which agree well with, and complement the studies reported by, Tahara et al.[6] and by Weber and Heuer.[2] The results are discussed in more detail below.

Since the phthalimido functionality of our lead compound **17** was considered to be an undesirable feature of a possible drug candidate, this group was replaced by a variety of other heterocyclic moieties. Although a large degree of freedom of substitution of the 2-position of the thienotriazolodiazepine system was found by Weber[2] and confirmed by our work, high oral potency and long duration of action appears to be limited to a few select compounds. Phenanthridinone **71** and tetrahydrocarbazole **81** are two prominent members of this group.

Chemistry

The target compounds were synthesized by the palladium-catalyzed coupling of 8(9)-iodotriazolobenzo-

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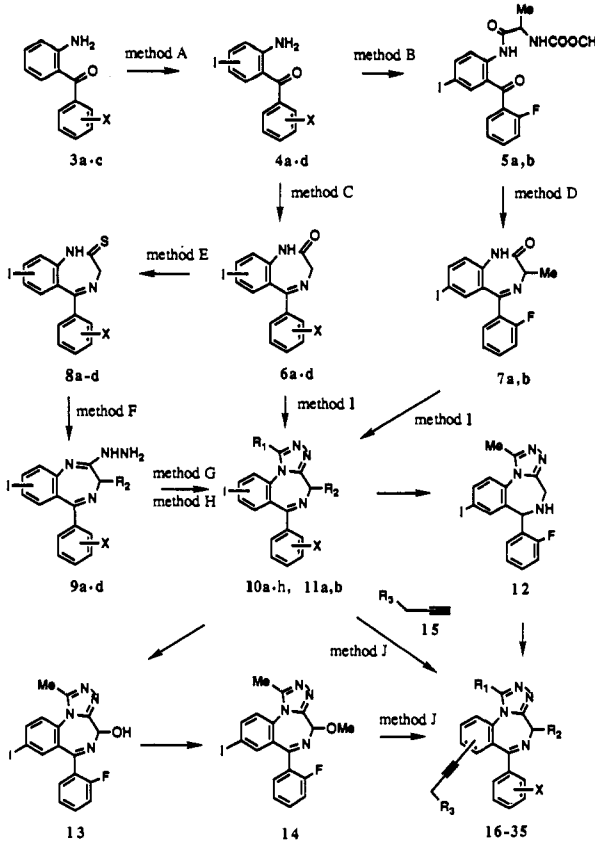
(6) Tahara, T.; Mikashima, H.; Terasawa, M.; Maruyama, Y. *Chem. Pharm. Bull.* **1987**, *35*, 2119.

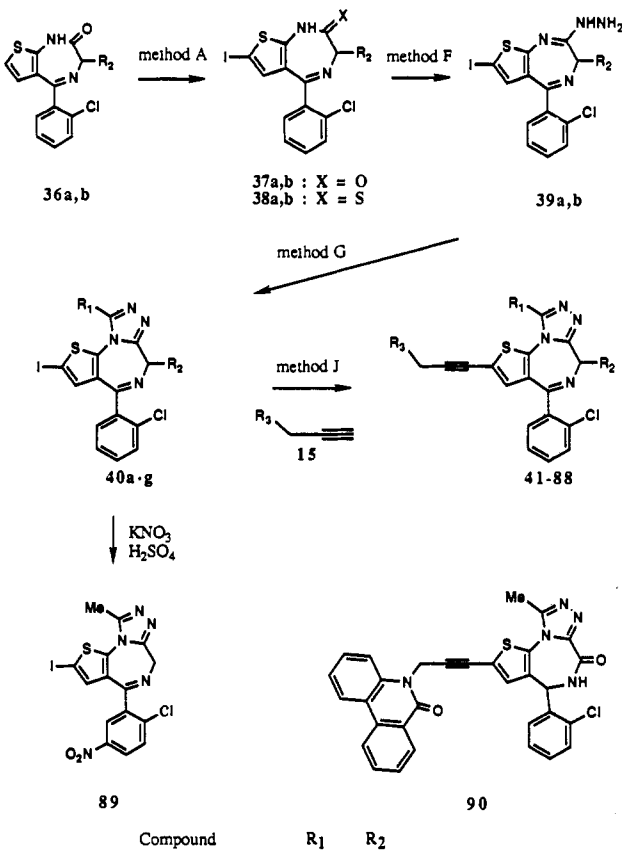
Scheme I



Compound		X	1	R_1	R_2	
4	a	2-Cl	5-I			
	b	2-F	5-I			
	c	4-Cl	5-I			
	d	2-F	4-I			
5,7	a					(S-enantiomer)
	b					(R-enantiomer)
6,8,9	a	2-Cl	7-I			
	b	2-F	7-I			
	c	4-Cl	7-I			
	d	2-F	8-I			
10	a	2-Cl	8-I	Me	H	
	b	2-F	8-I	Me	H	
	c	4-Cl	8-I	Me	H	
	d	2-F	9-I	Me	H	
	e	2-F	8-I	H	H	
	f	2-F	8-I	Et	H	
	g	2-F	8-I	CF_3	H	
	h	4-Cl	8-I	CF_3	H	
11	a	2-F	8-I	Me	Me	(S-enantiomer)
	b	2-F	8-I	Me	Me	(R-enantiomer)

diazepines **10**–**14** (Scheme I) or 2-iodothienotriazolodiazepines **40** (Scheme II) with terminal acetylenes **15** (method J). These reaction components were prepared according to, or analogous to, procedures previously described in the literature. Iodinated aminobenzophenones **4a**,b,**c** were accessible by iodination (method A) of the corresponding parent compounds **3**. 5-Iodo analogue **4d** was obtained by the acylation of 3-iodoaniline with 2-fluorobenzonitrile. The conversion of these aminobenzophenones to diazepinones **6** was carried out by reaction with bromoacetyl bromide followed by amination in liquid ammonia and cyclization by heating in ethanol containing acetic acid (method C). The optically active 3-methyl analogues **7** resulted from cleavage and ring closure of the carbobenzoxyalanine derivatives **5** (method D). Amides **5a**,b were accessible by reaction of aminobenzophenone **4b** with carbobenzoxyalanine using phosphorus pentachloride in THF at low temperature (method B). Diazepinones **6** were elaborated into the triazolo derivatives **10** preferably via the corresponding thiones **8** (method E) and 2-hydrazino compounds **9** (method F). Treatment of hydrazines **9** with orthoesters in situ led to the triazolo compounds **10** (method G). Activation of the lactam by

Scheme II

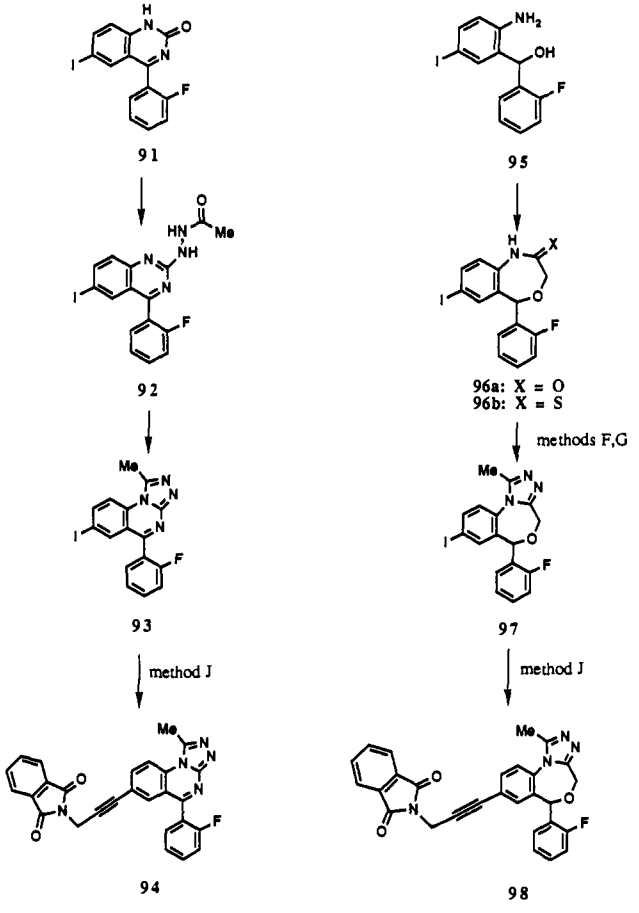


Compound		R_1	R_2	
36,37,38,39	a		H	
	b		Me	
40	a	Me	H	
	b	Me	Me	
	c	CH_2Cl	H	
	d	CH_2OH	H	
	e	Me	H	5-oxide
	f	OAc	H	
	g	OH	H	

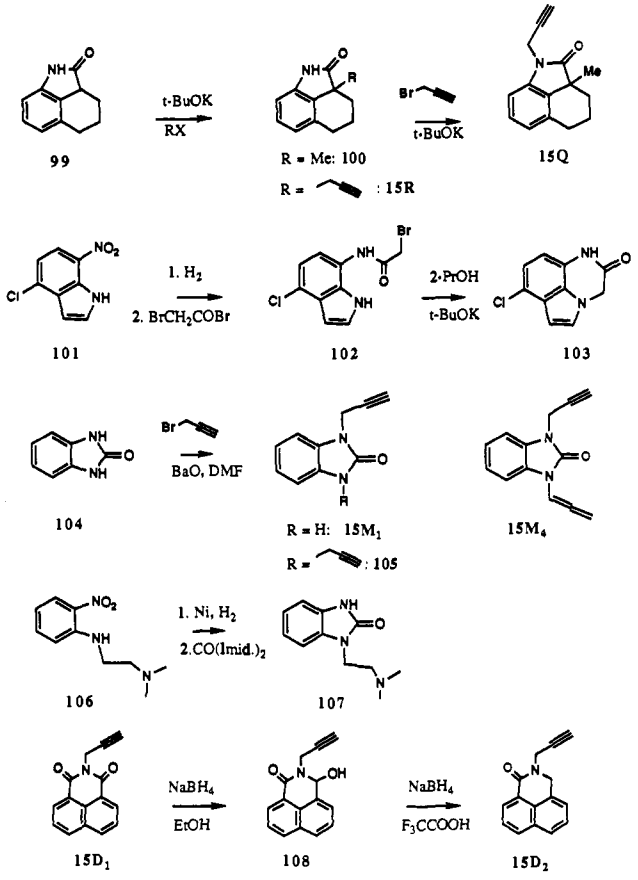
conversion to the phosphorylimidate and subsequent reaction with acetylhydrazine provided another approach to the triazolo compounds, in particular the optically active 4-methyl compounds **11** (method I). 1-Trifluoromethyl-substituted analogues **10g**,**h** were obtained by reaction of hydrazine **9** with trifluoroacetic anhydride in trifluoroacetic acid (method H). Oxidation of compound **10b** with oxygen in the presence of strong base and triethylphosphite yielded racemic 4-hydroxy analogue **13**. This compound was converted to 4-methoxy derivative **14** by reaction with thionyl chloride and subsequent treatment of the intermediate chloride with methoxide. Reduction of **10b** with zinc and acetic acid allowed the preparation of racemic 5,6-dihydro derivative **12**.

The synthesis of the 2-iodothienotriazolodiazepines **40** (Scheme II) follows a similar sequence, but we found it easier to introduce the iodine at the stage of diazepinones **36**. In contrast to the benzo series the 3-methyl compound was not obtained in optically active form, although the carbobenzoxyalanine precursor still had a rotation. Racemization most likely occurred during the cleavage and cyclization process. The conversion of lactams **37** to fused triazoles **40** was achieved via thiones **38** and hydrazines **39**. 1-Chloromethyl derivative **40c** was prepared in lower yield by reaction of hydrazine **39a** with chloroacetyl chloride in acetic acid. This chloride was transformed into 1-hydroxymethyl compound **40d** via the corresponding acetate. Iodo compound **40a** was nitrated in the 5′-position by potassium nitrate in concentrated sulfuric acid to give **89**, which was subjected to the coupling reaction with **15B**$_1$

Scheme III



Scheme IV



to form compound **43**. Coupling with acetylenes **15** proceeded in every case with good retention of the other functionalities. The yields, however, were quite variable, mainly because of the chromatographic workup and the often difficult crystallization process. Oxidation of the coupling product **71** with *m*-chloroperoxybenzoic acid led to *N*-oxide **72**, which could be rearranged to the 6-acetoxy derivative by treatment with acetic anhydride. Mild hydrolysis of this acetate yielded 6-hydroxy analogue **73** together with rearranged amide **90**. Compounds **71–73** could also be obtained by coupling the appropriately functionalized diazepines **40e,f,g** with propargylphenanthridinone **15O$_1$**.

In order to determine the importance of the nonplanar seven-membered ring for PAF-antagonist activity, we synthesized triazoloquinazoline **94** as illustrated in Scheme III. Iodoquinazolinone **91**, prepared by boiling aminobenzophenone **3b** with urea in acetic acid, was converted to acetylhydrazine **92** by reacting it first with potassium *tert*-butoxide and diethyl chlorophosphate to form the intermediate 2-(phosphoryloxy)quinazoline and then treating it in situ with acetylhydrazine. Ring closure of **92** to **93** by dehydration was effected by heating in polyphosphoric acid up to 190 °C. The standard coupling of **93** with propargylphthalimide (**15A**) then led to the target compound **94**.

Racemic triazolobenzoxazepine **98**, the oxygen isoester of the 5,6-dihydro compound **22**, was prepared by the sequence of steps also shown in Scheme III. Aminobenzhydrol **95**, obtained by reduction of the corresponding benzophenone **3b** with diborane in THF, was bromoacetylated and the product was subjected to ring closure by treatment with potassium *tert*-butoxide in 2-propanol. Benzoxazepinone **96** was converted to the triazolo derivative **97** by the standard route via the thione and the hydrazino compound. The final coupling reaction with propargylphthalimide gave triazolobenzoxazepine **98**.

The acetylenic reaction partners **15A–X** were generally prepared by alkylation of the parent heterocycles with propargyl bromide using potassium *tert*-butoxide in DMF (method N). Tetrahydrobenzindole **99** (Scheme IV) alkylated on carbon to give tertiary propargyl compound **15R**. Consequently, methylation with methyl iodide under similar conditions gave compound **100**, which was then alkylated with propargyl bromide on the amide nitrogen to yield **15Q**. Monoalkylation of the benzimidazolone **104** to **15M$_1$** was carried out with propargyl bromide and barium oxide in DMF. This reaction gave in addition dialkylated compound **105** and isomeric allene **15M$_4$**. The latter was isolated in low yield by chromatography. Pyrroloquinoxaline **103** was prepared from 4-chloro-7-nitroindole (**101**) by catalytic hydrogenation to the aminoindole and subsequent reaction with bromoacetyl bromide to form bromoacetyl derivative **102**. This compound was cyclized with potassium *tert*-butoxide in 2-propanol to yield the desired tricyclic system **103**, which was alkylated with propargyl bromide in the standard fashion (method N). The benzimidazolone with a basic side chain (compound **107**) was prepared by catalytic reduction of substituted nitroaniline **106** and reaction of the product with carbonyldiimidazole. The conversion of the propargyl naphthalimide **15D$_1$** to the lactam **15D$_2$** was achieved by reduction with sodium borohydride in ethanol to form carbinol **108**, which was then further reduced by the same reagent in trifluoroacetic acid. The 6,8-dichloro-3,4-dihydroquinolin-2(1*H*)-one required for the synthesis of **15B$_2$** was obtained by chlorination.

Results and Discussion

The compounds listed in Tables I and II were tested for

Table II. Thienotriazolodiazepines

compd	R_1	R_2	R_3	other	inhibn of PAF-binding: IC_{50},[a] nM	guinea pig bronchoconstriction assay: intravenous ID_{50},[a,b] mg/kg	guinea pig bronchoconstriction assay: oral ID_{50},[a,c] mg/kg	guinea pig bronchoconstriction assay: % inhibn 0.03 mg/kg[e]
1 (WEB 2086)					200	0.03	1.2	
40a	Me	H			370	0.2	inact.[d]	
40b	Me	Me			120	0.05	inact.	
41	Me	H	B_1		0.2	0.004	0.02	
42	Me	H	B_1	5-oxide	80	0.008	inact.	
43	Me	H	B_1	5′-NO_2	75	0.01	inact.	
44	Me	H	B_2		9	0.006	0.02	
45	Me	H	B_3		12	0.003	0.03	
46	Me	H	B_4		2	0.006	0.02	
47	Me	H	B_5		7	0.002	0.1	
48	Me	H	C_1		4	0.0003	0.2	
49	Me	H	C_2		3	0.006	0.1	
50	Me	H	D_1		12	0.01	0.03	
51	Me	H	D_2		4	0.01	0.009	60 ± 3[f]
52	Me	H	F_1		0.7	0.007	0.02	
53	Me	H	F_2		5	0.004	0.05	
54	Me	H	F_3		4	0.005	0.02	
55	Me	H	G_1		4	0.007	0.08	
56	Me	H	G_2		6	0.003	0.05	
57	Me	H	H_1		0.6	0.007	0.02	
58	Me	H	H_2		150	0.03	0.3	
59	Me	H	I		3	0.004	0.05	
60	Me	H	J		7	0.01	0.06	
61	Me	H	K		5	0.009	0.1	
62	Me	H	L		1	0.002	0.02	
63	Me	H	M_1		9	0.0007	0.2	
64	Me	H	M_2		0.3	0.004	0.04	
65	Me	H	M_3		1	0.008	0.02	
66	Me	H	M_4		6	0.003	0.03	
67	Me	H	M_5		30	0.005	0.2	
68	Me	H	N_1		5	0.008	0.03	
69	Me	H	N_2		1	0.007	0.03	
70	Me	H	N_3		25	0.02	0.05	
71	Me	H	O_1		13	0.02	0.01	75 ± 10
72	Me	H	O_1	5-oxide	15	0.02	0.08	
73	Me	Me	O_1		250	0.02	0.03	
74	Me	OH	O_1		25	0.02	0.07	
75	CH_2OH	H	O_1		75	0.004	0.3	
76	Me	H	O_2		30	0.008	0.03	
77	Me	H	P		5	0.003	0.04	
78	Me	H	Q		12	0.01	0.03	
79	Me	H	R		0.7	0.008	0.3	
80	Me	H	S_1		120	0.02	0.02	
81	Me	H	S_2		7	0.005	0.006	75 ± 3
82	Me	H	S_3		90	0.02	0.04	
83	Me	H	T_1		15	0.003	0.004	8 ± 1
84	Me	H	T_2		70	0.004	0.3	
85	Me	H	U		25	0.01	0.02	
86	Me	H	V		6	0.008	0.03	
87	Me	H	W		51	0.01	0.02	
88	Me	H	X		15	0.02	0.003	0 ± 0
89					360	0.3	inact.	
90					560	inact.	inact.	

[a,b,c] Same as in Table I. [d] Inact. = no significant inhibition at 1 mg/kg. [e] Twenty-four hour pretreatment time. [f] Values are means ± SEM.

PAF-antagonistic activity in a PAF-binding assay using dog platelets as previously described.[5] IC_{50} values (nanomoles) were determined by linear-regression analysis, the correlation coefficient for each regression line being >0.95. Following this in vitro assay, most compounds were evaluated in vivo in the guinea pig bronchoconstriction model for their ability to prevent PAF-induced bronchoconstriction. In this model, guinea pigs were administered 1 mg/kg of the drug substance intravenously 1 min prior to iv challenge with a maximally constrictory dose of PAF (1 μg/kg), and the ability of the drug (n = 3) to inhibit the ensuing bronchoconstriction relative to control animals (n = 3) was determined. Compounds which caused a 50% or greater inhibition of the response were further evaluated at lower doses to determine an intravenous ID_{50}. They were also tested orally at a trial dose of 1 mg/kg, administered 2 h before PAF challenge, and compounds which caused a 50% or greater inhibition of the response in the initial screen were further profiled by determining oral ID_{50} values. The duration of action after oral administration was determined only for selected potent compounds.

From our earlier work[4,5] with other chemical series of PAF antagonists, we had found that the PAF binding assay employing dog platelets is useful for the identification of potential PAF antagonists, but not for predicting relative potencies of compounds in the guinea pig bronchoconstriction test. The results obtained with these benzo- and thienodiazepines are consistent with this observation. The structure–activity relationships for the triazolobenzodiazepines determined by the data presented in Table I have led to the following conclusions.

With respect to the substituent on the triazole ring (1-position), a methyl group appears to be optimal. In the PAF binding assay, 1-methyl compound **17** was 100-fold

Table III. Data of Compounds Not Described in the Experimental Section

1. Benzodiazepine Series

compd	X	R_1	R_2	R_3	method	% yield	mp, °C	solvent[a]	[a]*D*, deg	formula[a]
4c, 5-I	4-Cl				A	63	137–9	T/H		$C_{13}H_9ClINO$
5b, *R*					B	77	159–61	D/E	+15.68	$C_{24}H_{20}FIN_2O_4$
6c, 7-I	4-Cl				C	66	246–8	D/E		$C_{15}H_{10}ClIN_2O$
6d, 8-I	2-F				C	54	238–40	E		$C_{15}H_{10}FIN_2O$
7b, *R*					D	52	223–5	D/EA	−100.4	$C_{16}H_{12}FIN_2O$
8c, 7-I	4-Cl				E	52	260–2	THF/E		$C_{15}H_{10}ClIN_2S$
8d, 8-I	2-F				E	80	198–200	EA		$C_{15}H_{10}FIN_2S$
9c, 7-I	4-Cl				F	85	250–2	THF/E		$C_{15}H_{12}ClIN_4$
10c, 8-I	4-Cl	Me	H		G	68	358–60	THF/E		$C_{17}H_{12}ClIN_4$
10d, 9-I	2-F	Me	H		E,F,G	38	197–8	E		$C_{17}H_{12}FIN_4 \cdot 0.33W$
10e, 8-I	2-F	H	H		G	88	220–2	EA		$C_{16}H_{10}FIN_4$
10f, 8-I	2-F	Et	H		G	97	209–11	M/EA		$C_{18}H_{14}FIN_4$
10h, 8-I	4-Cl	CF_3	H		H	55	243–5	EA		$C_{17}H_9ClF_3IN_4$
11b, 8-I	2-F	Me	Me (*R*)		I	18	141–4	EA/H	−53.0	$C_{18}H_{14}FIN_4$
16, 8-sub.	2-F	H	H	A	J	63	207–9	M/EA		$C_{27}H_{16}FN_5O_2 \cdot 0.5W$
17, 8-sub.	2-F	Me	H	A	J	84	253–5	D/EA		$C_{28}H_{18}FN_5O_2$
18, 8-sub.	2-Cl	Me	H	A	J	61	248–50	M/EA		$C_{28}H_{18}ClN_5O_2 \cdot 0.5W$
19, 8-sub.	2-F	Et	H	A	J	83	216–9	EA		$C_{29}H_{20}FN_5O_2 \cdot 0.5W$
21, 9-sub.	2-F	Me	H	A	J	46	248–50	EA		$C_{28}H_{18}FN_5O_2 \cdot 0.33W$
22, 8-sub.	2-F	Me	5,6-H_2	A	J	76	235–40 d	EA		$C_{28}H_{20}FN_5O_2 \cdot 0.25EA$
23, 8-sub.	2-F	Me	H	CH_2A	J	20	128–30	E		$C_{29}H_{20}FN_5O_2 \cdot E$
24, 8-sub.	2-F	Me	H	B_1	J	80	236–9	EA		$C_{29}H_{22}FN_5O$
25, 8-sub.	2-F	Me	Me (*S*)	B_1	J	36	155–60	E/Et_2O	+87.5	$C_{30}H_{24}FN_5O \cdot W + E$
26, 8-sub.	2-F	Me	Me (*R*)	B_1	J	57	amor.		−83.6	$C_{30}H_{24}FN_5O \cdot W$
27, 8-sub.	2-F	Me	OH	B_1	J	46	253–5	M/EA		$C_{29}H_{22}FN_5O_2 \cdot W$
28, 8-sub.	2-F	Me	OMe	B_1	J	51	155–60 d	EA/Et_2O		$C_{30}H_{24}FN_5O_2 \cdot 0.33W$
29, 8-sub.	2-F	CF_3	H	B_1	J	58	193–6	EA		$C_{29}H_{19}F_4N_5O$
30, 8-sub.	4-Cl	Me	H	B_1	J	48	215–7	EA		$C_{29}H_{22}ClN_5O \cdot 0.33W$
31, 8-sub.	4-Cl	CF_3	H	B_1	J	43	220–2	EA		$C_{29}H_{19}ClF_3N_5O \cdot 0.5W$
32, 8-sub.	2-Cl	Me	H	C_1	J	41	128–30	E/Et_2O		$C_{25}H_{18}ClN_5O \cdot 0.66W$
33, 8-sub.	2-Cl	Me	H	D_1	J	45	213–5	THF/E		$C_{32}H_{20}ClN_5O_2 \cdot 0.66W$
34, 8-sub.	2-F	Me	H	E	J	51	203–6	EA		$C_{28}H_{20}FN_5OS \cdot 0.16EA$
35, 8-sub.	2-F	Me	H	F_1	J	56	238–40	EA		$C_{28}H_{20}FN_5O_2 \cdot 0.16EA$
94, triazoloquinazoline					J	54	263–6 d	THF/E		$C_{27}H_{16}FN_5O_2 \cdot W$
98, triazolobenzoxazepine					J	61	183–5	EA		$C_{28}H_{19}FN_4O_3 \cdot 0.16EA$

2. Thienodiazepine Series

compd	R_1	R_2	R_3	other	method	% yield	mp, °C	solvents[a]	formula[a]
36b		Me			D	79	200–3	Et_2O	$C_{14}H_{11}ClN_2OS$
37b		Me			A	43	235–7	M/EA	$C_{14}H_{10}ClIN_2OS$
40b	Me	Me			E,F,G	39	262–4	D/M	$C_{16}H_{12}ClIN_4S$
42	Me	H	B_1	5-oxide	K	45	225–30 d	M/EA	$C_{27}H_{20}ClN_5O_2S \cdot 0.16EA$
43	Me	H	B_1	5′-NO_2	J	28	258–60	D/E/EA	$C_{27}H_{19}ClN_6O_3S$
44	Me	H	B_2		J	33	163–5	EA	$C_{27}H_{18}Cl_3N_5OS$
45	Me	H	B_3		J	73	203–6	EA/Et_2O	$C_{29}H_{24}ClN_5OS$
46	Me	H	B_4		J	23	162–5	M/EA	$C_{27}H_{18}ClN_5OS \cdot 0.5W$
47	Me	H	B_5		J	49	224–6	M/EA	$C_{27}H_{19}Cl_2N_5OS$
48	Me	H	C_1		J	60	amor.		$C_{23}H_{16}ClN_5OS$
49	Me	H	C_2		J	38	148–51	E/EA	$C_{24}H_{17}ClN_4OS \cdot 2HCl \cdot W$
50	Me	H	D_1		J	53	188–92	THF/EA	$C_{30}H_{18}ClN_5O_2S$
51	Me	H	D_2		J	36	205–10 d	M/EA	$C_{30}H_{20}ClN_5OS \cdot 0.66W$
52	Me	H	F_1		J	45	190–2	EA	$C_{26}H_{18}ClN_5O_2S$
53	Me	H	F_2		J	24	202–5	EA	$C_{26}H_{17}Cl_2N_5O_2S$
54	Me	H	F_3		J	63	215–7	EA	$C_{26}H_{17}ClFN_5O_2S$
55	Me	H	G_1		J	22	173–6	M/EA	$C_{26}H_{18}ClN_5O_2S \cdot 0.33W$
56	Me	H	G_2		J	59	237–40	E	$C_{26}H_{19}ClN_6OS$
57	Me	H	H_1		J	18	167–70	E	$C_{27}H_{19}ClN_6O_2S \cdot 0.5W$
58	Me	H	H_2		J	52	223–5	M/EA	$C_{30}H_{26}ClN_7O_2S$
59	Me	H	**I**		J	50	203–6	EA	$C_{26}H_{18}ClN_5OS \cdot 0.66W$
60	Me	H	**J**		J	22	185–90	EA	$C_{26}H_{16}ClN_5O_2S \cdot EA$
61	Me	H	**L**		J	28	170–3	EA/Et_2O	$C_{25}H_{17}ClN_6S$
62	Me	H	**K**		J	20	215–7	E/H	$C_{26}H_{17}ClN_6S \cdot 0.66W$
63	Me	H	M_1		J	73	295–8	D/E/EA	$C_{25}H_{17}ClN_6OS \cdot 0.33W$
64	Me	H	M_2		J	25	188–91	E	$C_{26}H_{19}ClN_6OS$
65	Me	H	M_3		J	78	176–9	M	$C_{31}H_{21}ClN_6OS \cdot 0.66W$
66	Me	H	M_4		J	44	>200 d	EA/Et_2O	$C_{28}H_{19}ClN_6OS$
67	Me	H	M_5		J	49	amor.	THF/H	$C_{29}H_{26}ClN_7OS$
68	Me	H	N_1		J	45	164–6	EA	$C_{27}H_{20}ClN_5OS$
69	Me	H	N_2		J	33	148–50	E/EA	$C_{27}H_{18}ClN_5OS \cdot 0.66W$
70	Me	H	N_3		J	66	138–41	THF/Et_2O	$C_{29}H_{24}ClN_5O_3S$
71	Me	H	O_1		J	76	247–9	THF/EA	$C_{31}H_{20}ClN_5OS$
72	Me	H	O_1	5-oxide	K	79	260–70 d	THF/M/EA	$C_{31}H_{20}ClN_5O_2S$
73	Me	Me	O_1		J	75	182–6	E	$C_{32}H_{22}ClN_5OS \cdot W$

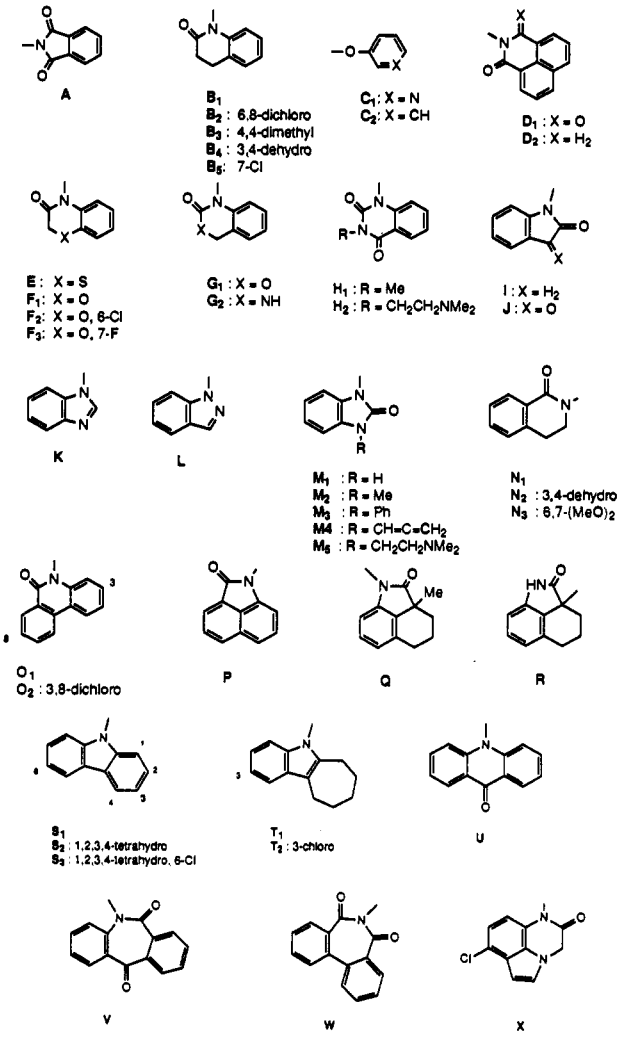
Table III (Continued)

2. Thienodiazepine Series

compd	R_1	R_2	R_3	other	method	% yield	mp, °C	solvents[a]	formula[a]
74	Me	OH	O_1		L,M	28	255–8	M/EA	$C_{31}H_{20}ClN_5O_2S$
75	CH_2OH	H	O_1		J	35	235–8	D/E	$C_{31}H_{20}ClN_5O_2S·0.66W$
76	Me	H	O_2		J	46	218–20	EA/THF	$C_{31}H_{18}Cl_3N_5OS$
77	Me	H	**P**		J	58	202–5	EA	$C_{29}H_{18}ClN_5OS·0.75W$
78	Me	H	**Q**		J	70	175–8	E/EA	$C_{30}H_{24}ClN_5OS·2HCl·0.33W$
79	Me	H	**R**		J	78	215–7	EA/Et_2O	$C_{29}H_{22}ClN_5OS$
80	Me	H	S_1		J	31	180–4	E/EA	$C_{30}H_{20}ClN_5S·2HCl$
81	Me	H	S_2		J	63	164–6	E	$C_{30}H_{24}ClN_5S·0.66E$
82	Me	H	S_3		J	47	181–4	E/EA	$C_{30}H_{23}Cl_2N_5S·2HCl·W$
83	Me	H	T_1		J	38	188–90	EA/Et_2O	$C_{31}H_{26}ClN_5S$
84	Me	H	T_2		J	58	176–80	E/EA	$C_{31}H_{25}Cl_2N_5S·2HCl$
85	Me	H	**U**		J	42	175–80	E	$C_{31}H_{20}ClN_5OS·W$
86	Me	H	**V**		J	50	245–7	EA/Et_2O	$C_{32}H_{20}ClN_5O_2S·0.3EA$
87	Me	H	**W**		J	59	220–3	E/EA	$C_{32}H_{20}ClN_5O_2S·0.2EA$
88	Me	H	**X**		J	81	220–2	D/E	$C_{28}H_{18}Cl_2N_6OS·W$
90					L,M	18	225–30	M/EA	$C_{31}H_{20}C_2N_5O_2S·0.3W$

[a] Solvents: D = dichloromethane, E = ethanol, EA = ethyl acetate, H = hexane, M = methanol, W = water.

Chart I



more potent than 1-unsubstituted analogue **16** and 10-fold more potent than 1-ethyl derivative **19**. In vivo, by the intravenous route, these compounds exhibited a similar rank order of potency (compound **17** was 30-fold more potent than compound **16** and 5-fold more potent than **19**. This result is in agreement with the SAR work reported by Weber[2] and Tahara.[6] Comparison, particularly of the in vivo intravenous data, of several pairs of 1-trifluoro-

Table IV. Data of Acetylenes **15**

R_3	method	% yield	mp, °C	solvents[a]	formula	ref
B_1	N	64	82–4	Et_2O	$C_{12}H_{11}NO$	14
B_2		31	92–5	Et_2O/H	$C_{12}H_9Cl_2NO$	
B_3	N	56	96–8	Et_2O/H	$C_{14}H_{15}NO$	
B_4	N	49	137–9	EA/H	$C_{12}H_9NO$	14
B_5	N	54	88–90	Et_2O/H	$C_{12}H_{10}ClNO$	
D_1	N	84	235–7	EA	$C_{15}H_9NO_2$	
D_2		27	139–40	EA/H	$C_{15}H_{11}NO$	
E	N	62	112–5	Et_2O	$C_{11}H_9NOS$	18
F_1	N	75	119–22	E	$C_{11}H_9NO_2$	14
F_2	N	83	100–01	H	$C_{11}H_8ClNO_2$	17
F_3	N	26	98–100	Et_2O/H	$C_{11}H_8FNO_2$	
G_1	N	46	123–5	M	$C_{11}H_9NO_2$	
G_2	N	8.5	172–5	E	$C_{11}H_{10}N_2O$	
H_1	N	21	192–4	D/Et_2O	$C_{12}H_{10}N_2O_2$	19
H_2	N	44	140–2	THF/Et_2O/H	$C_{15}H_{17}N_3O_2$	
I	N	34	101–3	E	$C_{11}H_9NO$	14
J	N	56	158–60	EA	$C_{11}H_7NO_2$	14
K	N	26	45–7	Et_2O	$C_{10}H_8N_2$	19
L	N	25	38–40	H	$C_{10}H_8N_2$	20
M_1		14	177–9	EA/H	$C_{10}H_8N_2O$	
M_2	N	63	110–2	EA/H	$C_{11}H_{10}N_2O$	
M_3	N	48	145–7	D/EA	$C_{16}H_{12}N_2O$	
M_4		3.5	110–2	Et_2O/H	$C_{13}H_{10}N_2O$	
M_5	N	31	70–2	EA/H	$C_{14}H_{17}N_3O$	
N_1	N	26	57–9	Et_2O/H	$C_{12}H_{11}NO$	25
N_2	N	58	104–5	Et_2O	$C_{12}H_9NO$	
N_3	N	34	104–7	EA/H	$C_{14}H_{15}NO_3$	
O_1	N	85	167–9	M	$C_{16}H_{11}NO$	23
O_2	N	65	248–50	E	$C_{16}H_9Cl_2NO$	
P	N	77	185–7	E	$C_{14}H_9NO$	
Q	N	60	127–30	EA/H	$C_{15}H_{15}NO$	
R	N	38	177–80	EA	$C_{14}H_{13}NO$	
S_1	N	30	108–10	E	$C_{15}H_{11}N$	22
S_2	N	40	74–6	H	$C_{15}H_{15}N$	
S_3	N	57	97–9	H	$C_{15}H_{14}ClN$	
T_1	N	27	56–8	H	$C_{16}H_{17}N$	
T_2	N	51	99–102	H	$C_{16}H_{16}ClN$	
U	N	75	222–5	D/THF/E	$C_{16}H_{11}NO$	26
V	N	40	117–8	Et_2O/H	$C_{17}H_{11}NO_2$	
W	N	76	175–8	D/M	$C_{17}H_{11}NO_2$	24
X	N	66	186–8	THF/E	$C_{13}H_9ClN_2O$	

[a] Solvents: D = dichloromethane, E = ethanol, EA = ethyl acetate, H = hexane, M = methanol.

methyl and 1-methyl analogues (compounds **20** and **17**, **29** and **24**, **31** and **30**) demonstrates that a methyl substituent on the triazole ring (1-position) is superior. Concerns about the possible teratogenic effects of compound **17** prompted us to prepare analogues replacing the phthalimido group with a variety of mono-, di-, and tricyclic ring systems as

exemplified by compounds **24** and **32–35**. Surprisingly, all of these compounds retained the high potency observed with compound **17**, suggesting that this position would tolerate additional bulk. 8-Iodo compounds **10a,b**, used as starting materials, have extremely low affinity according to the binding assay, suggesting that the large moiety in 8-position is required for high affinity and in vivo potency. The relative insensitivity to variation of the large 8-position substituent is further demonstrated by the homologous compound **23** which has an additional methylene group inserted into the side chain. This compound has in vitro and in vivo potency equivalent to **17**.

Exceptionally high intravenous potency was observed with 3-pyridyloxy compound **32** and with compounds **25**, **27**, and **28**, which are 4-substituted analogues of quinolinone **24**. An interesting result is the high enantiospecificity of both the binding and the in vivo activity found with 4-methyl enantiomers **25** and **26**. The enantiomer with the 4-*S* configuration, derived from L-alanine, is the active ligand. Interestingly, the same absolute configuration is also responsible for the central nervous system (CNS) activity of the benzodiazepines. It should be noted that attachment of a large moiety at the 8-position destroys the affinity of benzodiazepines for the central binding site, but increases the PAF-antagonist activity, as evidenced from comparison of **10** with **17**. It is well-known that the CNS effects of benzodiazepines and the binding to the central site can also be suppressed by substitution of the 6-phenyl group in the para (4′) position. 4′-Chloro compounds **30** and **31** retain activity as PAF antagonists, suggesting that binding at the "PAF-antagonist site" is not sensitive to substitution in the 4′-position. This freedom of substitution has been exploited by Hoon and Houlihan[7] and disclosed in a recent patent application showing good PAF-antagonist activity with 4′-phenethyl-substituted thienotriazolodiazepines.

Comparison of compounds **17** and **18** suggests that a fluorine in the 2′-position may be marginally superior to a chlorine.

Planar triazoloquinazoline **94** demonstrated weak PAF binding affinity in vitro and was inactive in vivo, indicating the need for a nonplanar orientation of the methyltriazole relative to the benzo ring. The racemic benzoxazepine **98** had poor binding affinity but good iv activity, comparable to that of the related racemic 5,6-dihydrobenzodiazepine **22**.

One major drawback of the benzoxazepine and many benzodiazepines is the low oral potency. The ratio of oral to intravenous ID_{50}s is between 1 and 3 orders of magnitude for most compounds. The optically active 4-methyl compound **25** showed the most potent oral activity of the benzodiazepine series and has a oral to intravenous ratio of about 12.

In order to probe the spacial limitations in the area occupied by the 8-position substituent, compound **21** was prepared which bears the substituent in position 9. Shifting the propargylphthalimide side chain from carbon 8 to 9 abolished both the binding and the in vivo activity. This sensitivity to bulk in the space around position 9 is corroborated by data collected with some thienotriazolodiazepines which will be the subject of a future paper.

The thienotriazolodiazepines listed in Table II were prepared to explore the effect of the heterocyclic moiety attached to the propynyl substituent at the 2-position. The 2-position in the thieno series may be considered roughly equivalent to the 8-position in the triazolobenzodiazepine system. It is apparent from the data gathered in Table II that many compounds are among the most potent orally active PAF antagonists yet described in the literature. The ratio of oral to intravenous ID_{50}s is typically less than 10. This ratio is about 4 for quinolinone **41**, while it is about 30 for the corresponding triazolobenzodiazepine **17**. The more lipophilic compounds **51**, **71**, **73**, **80**, **81**, and **83** have a ratio closer to 1.

However, there are a few compounds with poor oral bioavailability. In particular 3-pyridinyloxy compound **48**, which is the most active of the series by the intravenous route. Other examples are compounds **58**, **63**, **67**, and **77**, analogues bearing more hydrophilic substituents. The comparison of compounds **64–66** with the basic analogue **67** suggests that introduction of basic functionalities leads to loss of oral activity.

Compounds in Table II with an oral ID_{50} 0.01 mg/kg and below were selected for duration of action studies. The percent inhibition 24 h after a 0.03 mg/kg oral dose was determined for compounds **51**, **71**, **81**, **83**, and **88**. Compounds **51**, **71**, and **81** still gave considerable inhibition of PAF-induced bronchoconstriction 24 h after oral administration. The structural features responsible for the long duration of action may be associated with bulk and lipophilicity. Steric inhibition of oxidative metabolism may be a contributing factor, although we have no data as yet to support this hypothesis.

Oxidation of **41** to 5-oxide **42** was detrimental to the affinity and the oral activity but the intravenous potency was retained. The same transformation of **70** to **71** had little effect on all test parameters. The racemic 6-hydroxy compound **74** was active as expected from the results obtained in the analogous benzo series. The racemic 6-methyl derivative **73** exhibited about half the in vivo activity of the parent compound **71**. Since **73** is a racemate, this observation would suggest that one enantiomer may carry most or all of the activity, as we observed in the benzodiazepine series with enantiomers **25** and **26**. Introduction of a nitro group into the 5′-position led to some loss in affinity and activity as shown by the data for compound **43**. Hydroxylation of the 9-methyl group afforded **75**, an active compound with considerably reduced oral potency.

In conclusion, in this report we describe the structure–activity relationships among compounds of the triazolobenzo- and triazolothienodiazepine classes of PAF-antagonists. The thieno analogues exhibited generally better oral activity and bioavailability than the corresponding benzodiazepines. The duration of action upon oral administration was influenced by the substitution on the acetylenic side chain. The most interesting compounds to emerge from this work are **71** and **81**, each of which inhibits PAF-induced bronchoconstriction by 75%, 24 h after an oral dose of 0.03 mg/kg.

Experimental Section

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Proton magnetic resonance spectra were recorded on a Varian XL-200 spectrometer. Microanalyses were obtained for C, H, and N and were within 0.4% of the calculated values except as indicated for noncrystalline materials. Silica gel (Merck 70–230 mesh) was used for preparative column chromatography. Short-path distillations were carried out in a Büchi Kugelrohr oven. Anhydrous sodium sulfate was used for drying purposes. Dry ice and acetone were employed for low-temperature reactions.

Method A. (2-Amino-5-iodophenyl)(2-chlorophenyl)-methanone (4a). Iodine monochloride (15 mL, 21 g) was added to a solution of 23 g (0.1 mol) of (2-aminophenyl)(2-chlorophenyl)methanone[8] in 500 mL of CH_2Cl_2 cooled to −60 °C. After

(7) Cheon, S. H.; Houlihan, W. J. Eur. Pat. Appl. 0 338 993 A1, October 1989.

stirring with cooling for 5 h, the cooling bath was removed and the temperature of the reaction mixture was allowed to reach 0 °C. Following the addition of 300 mL of aqueous sodium bisulfite solution, the two-phase system was stirred for 10 min. The organic phase was separated, dried, and evaporated. The residue was crystallized from Et_2O/hexane to yield 20 g (56%) of yellow crystals with mp 120–122 °C. Anal. ($C_{13}H_9ClINO$): C, H, N.

(2-Amino-4-iodophenyl)(2-fluorophenyl)methanone (4d). Boron trichloride (11.6 g) was bubbled into 100 mL of dry tetrachloroethane cooled on ice. A solution of 18 g (0.082 mol) of 3-iodoaniline in 90 mL of tetrachloroethane was added over a period of 10 min. 2-Fluorobenzonitrile (10 g, 0.082 mol) was then added followed by 13.3 g (0.1 mol) of aluminum chloride. The mixture was stirred for 1 h, then heated to 130 °C over a 2-h period and maintained at this temperature for 14 hours. Hydrochloric acid (65 mL, 3 N) was slowly added to the cooled reaction mixture which was then heated to reflux for 1 h. After cooling, the two-phase system was filtered. The aqueous phase was extracted with CH_2Cl_2 and the extract was combined with the organic layer, which was dried and evaporated. The residue was repeatedly extracted by boiling with hexane. The hexane extracts were concentrated to give 6.5 g (23%) of yellow crystals. The analytical sample was recrystallized from hexane to give yellow crystals with mp 107–109 °C. Anal. ($C_{13}H_9FINO$): C, H, N.

Method B. (*S*)-[2-[[2-(2-Fluorobenzoyl)-4-iodophenyl]amino]-1-methyl-2-oxoethyl]carbamic Acid Phenylmethyl Ester (5a). A solution of 2.9 g (13 mmol) of *N*-(benzyloxycarbonyl)-L-alanine in 15 mL of THF was cooled to −40 °C. Phosphorus pentachloride (2.7 g, 13 mmol) was added and the mixture was stirred for 30 min at −30 °C. A solution of 3.41 g (10 mmol) of 2-(2-fluorobenzoyl)-4-iodoaniline in 50 mL of CH_2Cl_2 was then added and stirring was continued for 15 min at 0–10 °C. After addition of 10% aqueous Na_2CO_3 solution, the two-phase mixture was stirred at this temperature for 30 min. It was then extracted with ether. The extracts were washed with sodium carbonate solution and water, dried, and evaporated. The residue was passed over a plug of silica gel with methylene chloride. The filtrate was evaporated and the residue was crystallized from ethanol to give 5 g (91.5%) of colorless crystals with mp 159–161 °C; $[\alpha]_D = -10.35°$ ($c = 0.985$ in CH_2Cl_2). Anal. ($C_{24}H_{20}FIN_2O_4$): C, H, N.

Method C. 5-(2-Chlorophenyl)-1,3-dihydro-7-iodo-2*H*-1,4-benzodiazepin-2-one (6a). Bromoacetyl bromide (5 mL) was added to a solution of 52 g (0.145 mol) of **4a** in 300 mL of CH_2Cl_2 cooled to 0 °C. A 10% aqueous solution of Na_2CO_3 (150 mL) was added slowly with stirring. Following addition, the mixture was stirred in the cold for 30 min. The organic layer was separated, washed with water, dried, and evaporated. Crystallization of the residue from CH_2Cl_2/Et_2O yielded 61 g (90%) of 2-bromo-*N*-[2-(2-chlorobenzoyl)-4-iodophenyl]acetamide with mp 150–152 °C.

A solution of 50 g of this material in 1 L of CH_2Cl_2 was added to 800 mL of liquid ammonia with dry ice/acetone cooling. After refluxing for 16 h, the cooling was discontinued and the ammonia was allowed to evaporate. The remaining solution was washed with water, dried, and evaporated. The residue was dissolved in 1 L of ethanol and the solution was heated to reflux for 30 min after the addition of 15 mL of acetic acid. The crystals separated from the partially evaporated and cooled reaction mixture were collected to leave 38 g (89%) of colorless crystals. The analytical sample was recrystallized from THF/EtOH and had mp 260–262 °C. Anal. ($C_{15}H_{10}ClIN_2O$): C, H, N.

Method D. (*S*)-5-(2-Fluorophenyl)-1,3-dihydro-7-iodo-3-methyl-2*H*-1,4-benzodiazepin-2-one (7a). A mixture of 11 g of **5a** and 30 mL of acetic acid containing 30% of HBr was stirred at room temperature for 3 h. The reaction mixture was partitioned between water and ether. The aqueous phase was washed with ether and made alkaline by addition of ice and ammonia. The precipitated material was extracted with CH_2Cl_2, and the extracts were dried and evaporated. The residue was heated in 50 mL of ethanol containing 5 mL of acetic acid on the steam bath for 15 min. The solvent was evaporated under reduced pressure and the residue was partitioned between CH_2Cl_2 and 10% aqueous Na_2CO_3 solution. The organic phase was dried and evaporated and the residue was crystallized from EtOAc and recrystallized from CH_2Cl_2/EtOAc to yield 3.5 g (44%) of colorless crystals with mp 223–225 °C. $[\alpha]_D = +100.79°$ ($c = 0.9891$ in CH_2Cl_2). Anal. ($C_{16}H_{12}FIN_2O$): C, H, N.

Methods E–G. 6-(2-Fluorophenyl)-8-iodo-1-methyl-4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepine (10b).[9] A mixture of 31 g (0.08 mol) of 1,3-dihydro-5-(2-fluorophenyl)-7-iodo-2*H*-1,4-benzodiazepin-2-one (**6b**),[10] 20 g (0.09 mol) of phosphorus pentasulfide, 20 g of $NaHCO_3$, and 300 mL of diglyme was stirred and heated to 80–85 °C for 3 h. The reaction mixture was then poured onto ice and diluted with water. After stirring for 30 min, the precipitated yellow product was filtered off, washed with water, 2-PrOH, and a little ether. It was sucked dry in the funnel and further dried in vacuum to leave 26 g (80%) of 1,3-dihydro-5-(2-fluorophenyl)-7-iodo-2*H*-1,4-benzodiazepin-2-thione (**8b**), which was used for further transformation. An analytical sample was obtained by recrystallization from THF/EtOH and had mp 242–244 °C. Anal. ($C_{15}H_{10}FIN_2S$): C, H, N.

Hydrazine (3 mL) was added to a suspension of 8 g of the above thione in 40 mL of 2-PrOH and 100 mL of THF. After stirring for 15 min at room temperature, the reaction mixture was filtered over 20 g of silica gel using THF for elution. The filtrate was evaporated and the residue was crystallized from ether to yield 6.7 g (83%) of 5-(2-fluorophenyl)-2-hydrazino-7-iodo-3*H*-1,4-benzodiazepine (**9b**) with mp 179–181 °C.

A mixture of 4 g of the above hydrazino derivative **9b**, 20 mL of triethyl orthoacetate, 30 mL of toluene, and 4 g of silica gel was heated to reflux with stirring for 3 h. The silica gel was filtered off and washed with ethanol. The filtrate was evaporated and the residue was crystallized from CH_2Cl_2/EtOAc to yield 3.9 g (92%) of **10b** as colorless crystals with mp 235–238 °C. Anal. ($C_{17}H_{12}FIN_4$): C, H, N.

Method H. 6-(2-Fluorophenyl)-1-(trifluoromethyl)-8-iodo-4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepine (10g). A mixture of 5 g of 5-(2-fluorophenyl)-2-hydrazino-7-iodo-3*H*-1,4-benzodiazepine (**9b**), 20 mL of trifluoroacetic acid, 5 mL of trifluoroacetic anhydride, and 100 mL of CH_2Cl_2 was heated on the steam bath under a stream of nitrogen to distill off the CH_2Cl_2. Toluene (100 mL) was then added and heating on the steam bath was continued for 30 min. The mixture was partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$ solution. The organic phase was separated, dried, and evaporated. The residue was crystallized from ether and recrystallized from ethanol to yield 2.2 g (37%) of colorless crystals with mp 202–204 °C. Anal. ($C_{17}H_9F_4IN_4$): C, H, N.

Method I. 6-(2-Chlorophenyl)-8-iodo-1-methyl-4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepine (10a). A solution of 15.7 g (0.04 mol) of **6a** in 350 mL of THF was cooled to −30 °C. Potassium *tert*-butoxide (4.9 g, 0.044 mol) was added and stirring under N_2 was continued for 30 min at −10 to −5 °C. Diethyl chlorophosphate (6.6 mL) was then added and the mixture was stirred at this temperature for another 30 min. Following the addition of 3.4 g of acetic hydrazide, stirring without cooling was continued for 1 h and 150 mL of 1-butanol was added. The THF and part of the 1-butanol was distilled out of the reaction mixture over a period of 45 min. The residue was partitioned between toluene and water. The organic phase was washed with brine, dried, and evaporated down to a small volume. The precipitated crystals were collected to leave 14 g of crude product which was purified by chromatography over 250 g of silica gel using CH_2Cl_2 containing 5% (v/v) of ethanol. The clean fractions were combined and evaporated and the residue was crystallized from THF/EtOH to yield 8.5 g (49%) of colorless crystals with mp 290–292 °C. Anal. ($C_{17}H_{12}ClIN_4$): C, H, N.

(*S*)-6-(2-Fluorophenyl)-8-iodo-1,4-dimethyl-4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepine (11a). A solution of 2 g (5.07 mmol) of **7a** in 60 mL of THF was cooled to −30 °C and 0.57 g (5.7 mmol) of potassium *tert*-butoxide was added. The mixture was stirred under nitrogen for 30 min while the temperature was

(8) Reeder, E.; Sternbach, L. H. US patent 3,371,085, February 1968.

(9) Ning, R. Y., unpublished work, Hoffmann-LaRoche Inc., Nutley, NJ 07110.

(10) Field, G. F.; Sternbach, L. H. Swiss patents 561,706, May 1975; 562,222, April 1975.

allowed to climb to 5 °C. Diethyl chlorophosphate (1.03 g, 6.5 mmol) was added and stirring was continued for 30 min without cooling. After addition of 0.54 g (7.2 mmol) of acetic hydrazide the mixture was stirred for another 30 minutes at room temperature. Butanol (75 mL) was then added and the tetrahydrofuran was distilled out. A few drops of acetic acid were added, and part of the butanol was distilled over as well. The reaction mixture was evaporated under reduced pressure and the residue was partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$ solution. The organic layer was separated, dried, and evaporated and the residue was chromatographed over silica gel using 5% (v/v) of ethanol in CH_2Cl_2 for elution. Crystallization of the material obtained from the combined clean fractions from EtOAc/hexane gave colorless crystals with mp 142–145 °C. $[\alpha]_D$ = +50.38° (c = 0.9964 in CH_2Cl_2). Anal. ($C_{18}H_{14}FIN_4$): C, H, N.

***rac*-5,6-Dihydro-6-(2-fluorophenyl)-8-iodo-1-methyl-4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepine (12).** A mixture of 2 g of **10b**, 30 mL of CH_2Cl_2, 10 mL of AcOH, and 3 g of zinc dust was stirred at room temperature for 1 h. The inorganic material was filtered off and the residue was partitioned between aqueous ammonia and CH_2Cl_2. The organic phase was dried and evaporated and the residue was crystallized from EtOAc to give 1.6 g (80%) of product which was recrystallized twice from THF/EtOH to leave colorless crystals with mp 258–262 °C. Anal. ($C_{17}H_{14}FIN_4$): C, H, N.

***rac*-6-(2-Fluorophenyl)-4-hydroxy-8-iodo-1-methyl-4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepine (13).** A solution of 0.8 g of potassium *tert*-butoxide in 20 mL of THF and 15 mL of *tert*-butyl alcohol and 0.6 mL of triethyl phosphite was cooled to −30 °C with stirring under argon. A solution of 0.8 g of **10b** in 5 mL of DMF was added and stirring was continued for 1 h at −20 to −10 °C. A stream of oxygen was introduced while the mixture was stirred for an additional hour at this temperature. The reaction mixture was acidified by addition of acetic acid and was partitioned between Na_2CO_3 solution and CH_2Cl_2 containing 10% (v/v) of ethanol. The organic layer was dried and evaporated, and the residue was crystallized from CH_2Cl_2/EtOAc and recrystallized from ethanol to give 0.425 g (51%) of colorless crystals with mp 258–260 °C. Anal. ($C_{17}H_{12}FIN_4O$): C, H, N.

***rac*-6-(2-Fluorophenyl)-8-iodo-4-methoxy-1-methyl-4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepine (14).** A mixture of 0.435 g (1 mmol) of **13**, 3 mL of thionyl chloride, and 20 mL of CH_2Cl_2 was stirred at room temperature for 2 h. After evaporation under reduced pressure, the residue was dissolved in 20 mL of methanol and the solution was treated with 3 mL of triethylamine. After heating on the steam bath for 5 min, the mixture was evaporated to dryness and the residue was partitioned between CH_2Cl_2 and aqueous $NaHCO_3$ solution. The organic layer was dried and evaporated and the residue was crystallized from EtOAc to yield 350 mg (78%) of colorless crystals with mp 240–242 °C. The analytical sample was recrystallized from methanol/EtOAc and had mp 243–244 °C. Anal. ($C_{18}H_{14}FIN_4O$): C, H, N.

Method J. 2-[3-[6-(2-Fluorophenyl)-1-(trifluoromethyl)-4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepin-8-yl]-2-propynyl]-1*H*-isoindole-1,3(2*H*)-dione (20). A mixture of 0.94 (2 mmol) of **10g**, 0.55 g (3 mmol) of *N*-propargylphthalimide (**15A**), 80 mg of triphenylphosphine, 20 mg of curpous iodide, 0.6 mL of triethylamine, and 50 mL of DMF was degassed with argon for 10 min. Palladium acetate (25 mg) was then added and the mixture was stirred for 3 days at room temperature. The product was precipitated by dilution with $NaHCO_3$ solution and was collected by filtration. It was dissolved in CH_2Cl_2 and the solution was washed with $NaHCO_3$ solution, dried, and evaporated. The residue was chromatographed over 40 g of silica gel using 5% (v/v) of ethanol in CH_2Cl_2. The combined good fractions were evaporated, and the residue was crystallized from EtOAc to give colorless crystals with mp 204–206 °C. Anal. ($C_{28}H_{15}F_4N_5O_2$): C, H, N.

Method A. 5-(2-Chlorophenyl)-1,3-dihydro-7-iodo-2*H*-thieno[2,3-*e*][1,4]diazepin-2-one (37a).[11,12] A solution of 54.8 g (0.2 mol) of 5-(2-Chlorophenyl)-1,3-dihydro-2*H*-thieno[2,3-*e*][1,4]diazepin-2-one (**36a**)[11] in 350 mL of AcOH and 350 mL of MeOH was treated with 64.4 g (0.4 mol) of iodine monochloride and 16.2 g (0.2 mol) of sodium acetate. The mixture was stirred for 15 min at room temperature. A solution of 65 g of $NaHSO_3$ in 350 mL of water was then added and stirring was continued for 10 min. The mixture was neutralized by addition of 500 mL of concentrated NH_4OH and 1 kg of ice. The precipitated product was filtered off and washed with water and EtOH. It was recrystallized from THF/EtOH to yield 47.5 g (59%) of product with mp 229–231 °C.

Method E. 5-(2-Chlorophenyl)-1,3-dihydro-7-iodo-2*H*-thieno[2,3-*e*][1,4]diazepine-2-thione (38a). A mixture of 70 g (0.173 mol) of **37a**, 43.3 g of P_2S_5, 45 g of $NaHCO_3$, and 700 mL of diglyme was heated to 70–80 °C for 2 h with stirring under N_2. After cooling to room temperature, 2 L of water mixed with crushed ice was added and stirring was continued for 15 min. The precipitated product was collected by filtration, washed with water, and sucked dry to leave 64.4 g (89%) of yellow product which was used directly in the next step. An analytical sample was prepared by recrystallizing the crude material from CH_2Cl_2/MeOH to give yellow crystals with mp 220–222 °C. Anal. ($C_{13}H_8ClIN_2S_2$): C, H, N.

Method F. 5-(2-Chlorophenyl)-2-hydrazino-7-iodo-3*H*-thieno[2,3-*e*][1,4]diazepine (39a). A mixture of 64.4 g (0.1538 mol) of thione **38a**, 650 mL of THF, and 65 mL of hydrazine was stirred at room temperature for 30 min. The solvent was removed under reduced pressure at a bath temperature of below 50 °C. The residue was treated with 275 mL of water and 275 mL of CH_2Cl_2, and the two-phase suspension was stirred for 15 min. The crystalline product was collected by filtration and washed with water and ether. This material was used without further purification in the next step. An analytical sample was obtained by recrystallization from CH_2Cl_2/MeOH and had mp 191–194 °C. Anal. ($C_{13}H_{10}ClIN_4S$): C, H, N.

Method G. 4-(2-Chlorophenyl)-2-iodo-9-methyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepine (40a).[13] The above crude hydrazine **39a** was combined with 375 mL of EtOAc and 170 mL of triethyl orthoacetate and heated on the steam bath for 30 min after a few crystals of *p*-toluenesulfonic acid had been added. The product crystallized from the mixture and was filtered off after cooling and some dilution with EtOAc. The crystals were washed with EtOAc and sucked dry to leave 55.3 g (81%) of off-white product, which was recrystallized from CH_2Cl_2/EtOH to give 50.5 g (74.5%) of pure material with mp 254–256 °C.

Method H. 9-(Chloromethyl)-4-(2-chlorophenyl)-2-iodo-6*H*-thieno[3,2-*f*][1,2,4]-triazolo[4,3-*a*][1,4]diazepine (40c). Chloroacetyl chloride (1.8 mL) was added to a solution of 4 g (9.6 mmol) of **39a** in 40 mL of acetic acid. The mixture was heated on the steam bath for 10 min and was evaporated under reduced pressure. The residue was partitioned between 10% aqueous Na_2CO_3 solution and CH_2Cl_2. The organic layer was dried and evaporated and the residue was chromatographed over silica gel using 5% EtOH in CH_2Cl_2 for elution. The combined clean fractions were crystallized from CH_2Cl_2/EtOAc to leave 1.6 g (35%) of colorless crystals with mp 223–225 °C dec. NMR ($CDCl_3$): δ 4.9 (s, 2, CH_2Cl), 4.94 (br s, 2, C_6-H), 6.88 (s, 1, C_2-H), 7.2–7.5 (m, aromatic H). Anal. ($C_{15}H_9Cl_2IN_4S$): C, H, N.

4-(2-Chlorophenyl)-2-iodo-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepine-9-methanol (40d). A mixture of 1.3 g (2.73 mmol) of **40c**, 1.3 g of sodium acetate, 50 mg of NaI, and 25 mL of DMF was heated on the steam bath with stirring for 2 h. The solvent was removed under reduced pressure and the residue was partitioned between CH_2Cl_2 and water. The organic phase was dried and evaporated and the residue was crystallized from EtOAc to yield 0.9 g (66%) of 9-(acetoxymethyl)-4-(2-chlorophenyl)-2-iodo-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*]-[1,4]diazepine with mp 225–229 °C. NMR ($CDCl_3$): δ 2.12 (s, 3, Ac), 4.95 (br s, 2, C_6-H), 5.37 (s, 2, CH_2OAc), 6.87 (s, 1, C_3-H), 7.2–7.6 (m, 4, aromatic H).

(11) (a) Hromatka, O.; Binder, D. US patent 3,872,089; March 1975. (b) NL patent 7,205,730, November 1972; Hoffmann-LaRoche & Co., AG, Basle, Switzerland.

(12) Weber, K.-H.; Langbein, A.; Lehr, E.; Boeke, K.; Kuhn, F. J. German Offen. 2,701,752, July 1978.

(13) This compound was previously prepared by M. Gerecke, at Hoffmann-LaRoche & Co., AG, Basle, Switzerland.

The above acetoxy compound (0.9 g, 1.81 mmol), was dissolved in 150 mL of hot methanol. NaOH (3 N, 5 mL) was added and the mixture was heated on the steam bath for 10 min. The methanol was evaporated and the residue was partitioned between aqueous $NaHCO_3$ solution and CH_2Cl_2 containing 10% of EtOH. The organic layer was separated, dried, and evaporated and the residue was crystallized from MeOH to yield 0.45 g (54%) of colorless crystals with mp 244–246 °C dec. The analytical sample was recrystallized from CH_2Cl_2/EtOH and had the same melting point. NMR ($CDCl_3$): δ 4.62 (d, 2, J = 6 Hz, CH_2OH), 4.68 (br s, 2, C_6-H), 5.45 (t, 1, J = 6 Hz, OH), 6.6 (s, 1, C_3-H), 7.0–7.3 (m, 4, aromatic H). Anal. ($C_{15}H_{10}ClIN_4OS$): C, H, N.

Method K. **4-(2-Chlorophenyl)-2-iodo-9-methyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepine 5-Oxide (40e).** A mixture of 4.4 g (10 mmol) of **40a**, 200 mL of CH_2Cl_2, and 3.4 g of 3-chloroperoxybenzoic acid was allowed to sit at room temperature overnight. The solution was washed with 10% aqueous Na_2CO_3 solution, dried, and evaporated. The residue was crystallized from THF/MeOH/EtOAc to yield 3.3 g (72%) of product, which was purified by passing over silica gel using 10% (v/v) of methanol in CH_2Cl_2 followed by recrystallization from THF/MeOH to leave yellowish crystals with mp 280–283 °C dec. NMR ($CDCl_3$ + DMSO): δ 2.58 (s, 3, Me), 5.2 (AB system, J = 12 Hz, 2, C_6-H), 6.62 (s, 1, C_3-H), 7–7.4 (m, 4, aromatic H). Anal. ($C_{15}H_{10}ClIN_4OS$): C, H, N.

Method L. ***rac*-6-Acetoxy-4-(2-chlorophenyl)-2-iodo-9-methyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepine (40f).** A mixture of 1 g (2.19 mmol) of **40e**, 25 mL of pyridine, and 15 mL of acetic anhydride was heated on a steam bath for 4 h. The reagents were evaporated under reduced pressure, at the end azeotropically with xylene. The residue was chromatographed over 25 g of silica gel using 5% of EtOH in CH_2Cl_2 for elution. The combined clean fractions were evaporated and the residue was crystallized from EtOAc to yield 0.7 g (64%) of colorless product with mp 248–250 °C. The analytical sample was recrystallized from THF/MeOH/EtOAc. NMR ($CDCl_3$): δ 2.4 (s, 3, Ac), 2.72 (s, 3, Me), 6.8 (s, 1, C_6-H), 6.94 (s, 1, C_3-H) 7.3–7.6 (m, 4, aromatic H). Anal. ($C_{17}H_{12}ClIN_4O_2S$): C, H, N.

Method M. ***rac*-4-(2-Chlorophenyl)-2-iodo-6-hydroxy-9-methyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepine (40).** A mixture of 0.3 g (0.6 mmol) of **40f**, 30 mL of MeOH, 10 mL of water, and 1 mL of 3 N NaOH was allowed to sit at room temperature for 30 min. It was acidified by addition of acetic acid and partitioned between CH_2Cl_2 and $NaHCO_3$ solution. The organic layer was dried and evaporated and the residue was crystallized from MeOH/EtOAc to yield 0.21 g (76%) of product with mp 240–243 °C dec. NMR ($CDCl_3$): δ 2.7 (s, 3 Me), 5.76 (s, 1, C_6-H), 6.93 (s, 1, C_3-H), 7.3–7.6 (m, 4, aromatic H). Anal. ($C_{15}H_{10}ClIN_4OS$): C, H, N.

Method J. **1-[3-[4-(2-Chlorophenyl)-9-methyl-6*H*-thieno-[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-2-yl]-2-propynyl]-3,4-dihydro-2(1*H*)-quinolinone (41).** A mixture of 33 g (0.075 mol) of **40a**, 21 g (0.113 mol) of 3,4-dihydro-1-(2-propynyl)-2-(1*H*)-quinolinone,[14] 0.75 g of triphenylphosphine, 0.2 g of cuprous iodide, 60 mL of triethylamine, and 600 mL of DMF was stirred and degassed by a stream of argon for 30 min. At this time 0.225 g of palladium acetate was added and the mixture was stirred at room temperature under argon for 3 days. The mixture was poured into 2.5 L of saturated aqueous $NaHCO_3$ solution and ice. After stirring for 15 min, the precipitate was filtered off, washed with water, and sucked dry. This material was dissolved in CH_2Cl_2 and the solution was washed with bicarbonate solution and dried. The solvent was removed under reduced pressure and the residue was dissolved by warming in EtOAc. After seeding and cooling, the crystallized product was collected and recrystallized from methanol/EtOAc to leave 25.2 g (67%) of off-white crystals with mp 180–182 °C. NMR ($CDCl_3$): δ 2.72 (s, 3, Me), 2.68 and 2.94 (2 t, $j \simeq 6$ Hz, CH_2CH_2), 4.9 (s, 2, NCH_2), 4.94 (s, 2, C_6-H), 6.75 (s, 1, C_3-H), 7–7.5 (m, 8, aromatic H). Anal. ($C_{27}H_{20}ClN_5OS$): C, H, N.

4-(2-Fluorophenyl)-6-iodoquinazolin-2(1*H*)-one (91). A mixture of 5 g of **4a**, 5 g of urea, and 50 mL of acetic acid was heated to reflux for 30 min. The crystals which separated from the cooled reaction mixture were filtered off, washed with MeOH and Et_2O, and dried to leave 4.5 g (83%) of yellow needles with mp >350 °C. Anal. ($C_{14}H_8FIN_2O$): C, H, N.

5-(2-Fluorophenyl)-7-iodo[1,2,4]triazolo[4,3-*a*]quinazoline (93). Potassium *tert*-butoxide (0.7 g, 6.2 mmol) was added to a suspension of 1.83 g (5 mmol) of **91** in 50 mL of THF cooled to 0 °C. Diethyl chlorophosphate (2 mL) was added and the mixture was stirred under N_2 for 1 h at room temperature. After the addition of 1 g of acetic hydrazide stirring was continued with heating to reflux. Butanol (50 mL) was then added; the THF and some of the butanol was distilled over. The remaining mixture was evaporated and the residue was slurried with aqueous 10% Na_2CO_3 solution and a little CH_2Cl_2. The insoluble product was filtered off and dissolved in 30 mL of hot DMSO. This solution was diluted with 25 mL of 1 N NaOH and then with 100 mL of water. The precipitated material was collected and washed with water and MeOH to leave 0.9 g (42%) of 2-(acetylhydrazino)-4-(2-fluorophenyl)-6-iodoquinazoline (**92**) which was recrystallized from THF/EtOH/water to give colorless crystals with mp 293–296 °C dec. NMR (DMSO): δ 1.9 ppm (s, 3, Ac), 7.3–7.9 (m, 5, aromatic H), 8.0 (dd, 1, J = 8 Hz, 1.5 Hz, C_7-H), 9.37 (br s, 1, NH) 9.95 (br s, 1, NH).

A suspension of 0.8 g of this material in 10 mL of polyphosphoric acid was heated with stirring to 190 °C. The cooled mixture was partitioned between CH_2Cl_2 and ice and ammonia. The organic phase was separated, dried, and evaporated and the residue was crystallized from CH_2Cl_2/EtOH and from THF/EtOH to leave 0.45 g (58%) of colorless crystals with mp 323–325 °C. NMR ($CDCl_3$ + 3 drops of DMSO): δ 3.02 (s, 3, Me), 7.1–7.7 (m, 4, aromatic H), 7.94 (d, 1, J = 8 Hz, C_8-H), 8.0 (t, J = 1.5 Hz, C_5-H), 8.13 (dd, J = 8 and 1.5 Hz, C_7-H). Anal. ($C_{16}H_{10}FIN_4$): C, H, N.

2-Amino-α-(2-fluorophenyl)-5-iodobenzenemethanol (95). A solution of 5 g (14.66 mmol) of **4a** in 100 mL of THF was treated with 100 mL of a 1 M solution of borane in THF. After stirring for 45 min at room temperature, the excess borane was destroyed by the addition of water. The mixture was then extracted with CH_2Cl_2. The extracts were washed with 10% aqueous Na_2CO_3 solution, dried, and evaporated. Crystallization of the residue from Et_2O/hexane yielded 3.6 g (71%) of product which was directly used in the next step. An analytical sample was purified by chromatography over silica gel and crystallization from Et_2O/hexane to give colorless crystals with mp 110–112 °C. Anal. ($C_{13}H_{11}FINO$): C, H, N.

***rac*-5-(2-Fluorophenyl)-1,5-dihydro-7-iodo-4,1-benzoxazepin-2(3*H*)-one (96a).** A solution of 3.3 g (9.6 mmol) of crude **95** in 150 mL of CH_2Cl_2 was treated with 2.14 g (10.5 mmol) of bromoacetyl bromide and layered with 100 mL of 10% aqueous Na_2CO_3 solution. The mixture was stirred for 30 min and the organic layer was separated, dried, and evaporated. 2-PrOH (50 mL) was added and the solution was again evaporated. The residue was dissolved in 200 mL of 2-PrOH and the solution was treated with 2.86 g (25.3 mmol) of potassium *tert*-butoxide. This mixture was heated to boiling on a steam bath, was acidified by addition of acetic acid, and partially evaporated under reduced pressure. The product was crystallized by dilution with water. The crystals were collected, washed with water, and sucked dry. Recrystallization from THF/EtOH yielded 2.7 g (73%) of colorless crystals with mp 256–258 °C. NMR ($CDCl_3$ + 3 drops of DMSO): δ 4.47 (AB system, J = 16 Hz, C_3-H), 5.86 (s, 1, C_5-H), 6.7–7.5 (m, 7, aromatic H), 9.23 (br s, 1, NH). Anal. ($C_{15}H_{12}FINO_2$): C, H, N.

***rac*-5-(2-Fluorophenyl)-1,5-dihydro-7-iodo-4,1-benzoxazepine-2(3*H*)-thione (96b).** A mixture of 2.5 g (6.5 mmol) of **96a**, 1.6 g (3.6 mmol) of P_2S_5, and 100 mL of diglyme was heated to 70–80 °C for 2.5 h. It was poured into water and the precipitated product was collected, washed with water, and sucked dry. Recrystallization from CH_2Cl_2/THF/EtOH yielded 1.9 g (72%) of cream-colored crystals with mp 237–240 °C. Anal. ($C_{15}H_{11}FINOS$): C, H, N.

***rac*-6-(2-Fluorophenyl)-8-iodo-1-methyl-4*H*,6*H*-[1,2,4]triazolo[4,3-*a*][4,1]benzoxazepine (97).** Hydrazine (1 mL) was added to a solution of 1.8 g (4.5 mmol) of **96b** in 100 mL of THF. After stirring for 15 min, it was partitioned between CH_2Cl_2 and water. The organic layer was dried and evaporated. The residue

(14) Lindquist, A.; Lagerstroem, P.-O.; Dahlbom, R. *Acta Pharm. Suec.* **1972**, *9*, 99.

was treated with 50 mL of ethanol and 10 mL of triethyl orthoacetate and the mixture was heated to reflux for 15 min. It was then evaporated, at the end azeotropically with xylene. The residue was dissolved in 50 mL of acetic acid and this solution was heated to reflux for 15 min. After evaporation the residue was partitioned between CH_2Cl_2 and 10% aqueous Na_2CO_3 solution. The organic phase was dried and evaporated and the residue was crystallized from EtOAc to yield 1.4 g (73%) of product. For analysis it was recrystallized from CH_2Cl_2/EtOAc to leave colorless crystals with mp 237–240 °C. NMR ($CDCl_3$): δ 2.6 (s, 3, Me), 4.48 (d, 1) and 5.09 (d, 1) (AB-system, J = 13 Hz, C_4-H), 5.64 (s, 1, C_6-H), 6.9–7.9 (m, 7, aromatic H). Anal. ($C_{17}H_{13}FIN_3O$): C, H, N.

4-(2-Chloro-5-nitrophenyl)-2-iodo-9-methyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepine (89). Concentrated sulfuric acid (30 mL) was added to a solution of 2.2 g (5 mmol) of **40a** in 50 mL of CH_2Cl_2. After the addition of 2 g (20 mmol) of KNO_3 the two-phase mixture was stirred at room temperature for 4 h. It was poured onto ice and made alkaline by the addition of ice and ammonia. The product was extracted with CH_2Cl_2 and the extract was dried and evaporated. Crystallization of the residue from ethanol and recrystallization from CH_2Cl_2/ethanol gave 1.7 g (70%) of yellow crystals with mp 233–238 °C. The analytical sample was recrystallized again from THF/ethanol and had mp 243–246 °C. NMR ($CDCl_3$): δ 2.73 (s, 3, Me), 5.0 (s, 2, C_6-H), 6.88 (s, 1, C_3-H), 7.6 (d, 1, J = 8 Hz, $C_{3'}$-H), 8.25 (dd, 1, J = 8 and 2 Hz, $C_{4'}$-H), 8.33 (d, 1, J = 2 Hz, $C_{6'}$-H). Anal. ($C_{15}H_9ClIN_5O_2S$): C, H, N.

***rac*-2a,3,4,5-Tetrahydro-2a-methylbenz[*cd*]indol-2(1*H*)-one (100).** A solution of 6.92 g (40 mmol) of 2a,3,4,5-tetrahydrobenz[*c,d*]indol-2(1*H*)-one in 50 mL of DMF was stirred with 4.94 g (44 mmol) of potassium *tert*-butoxide for 15 min at room temperature. Methyl iodide (2.75 mL, 44 mmol) was then added and stirring was continued for 30 min. The mixture was diluted with ice and water and was extracted with CH_2Cl_2. The extracts were dried and evaporated and the residue was crystallized from ether to yield 1.7 g of product with mp 146–149 °C. Additional material (1.5 g, 43% total) was recovered by chromatography of the mother liquor using a 40-fold amount of silica gel and 10% of EtOAc in CH_2Cl_2 for elution. The analytical sample was recrystallized from ether to leave colorless crystals with mp 148–150 °C. Anal. ($C_{12}H_{13}NO$): C, H, N.

***rac*-2a,3,4,5-Tetrahydro-2a-(2-propynyl)benz[*cd*]indol-2-(1*H*)-one (15R).** Substituting methyl iodide in the above experiment with propargyl bromide yielded after crystallization from ethyl acetate 3.2 g (38%) of product. For analysis it was recrystallized from EtOAc to give colorless crystals from mp 177–180 °C. Anal. ($C_{14}H_{13}NO$): C, H, N.

Method N. *rac*-2a,3,4,5-Tetrahydro-2a-methyl-1-(2-propynyl)benz[*cd*]indol-2(1*H*)-one (15Q). Potassium *tert*-butoxide (1.65 g, 14 mmol) was added to a solution of 2.5 g (13.3 mmol) of **100** in 20 mL of DMF. After stirring for 10 min, 1.3 mL (14 mmol) of propargyl bromide was added and the mixture was stirred at room temperature for 30 min. It was then poured into ice water and saturated sodium bicarbonate solution. The precipitate was collected by filtration, washed with water, and sucked dry. The crude product was purified by filtering over 20 g of silica gel using CH_2Cl_2. The filtrate was evaporated and the residue was crystallized from EtOAc/hexane to yield 1.8 g (60%) of colorless crystals with mp 127–130 °C. Anal. ($C_{15}H_{15}NO$): C, H, N.

2-Bromo-*N*-(4-chloro-1*H*-indol-7-yl)acetamide (102). A mixture of 19.6 (0.1 mol) of 4-chloro-7-nitroindole,[15] 20 g of Raney nickel, 100 mL of THF, and 100 mL of ethanol was hydrogenated at atmospheric pressure for 6 h. The catalyst was filtered off and the filtrate was evaporated. The product was converted to the hydrochloride by treatment with ethanolic HCl to give crystals which were further reacted as follows.

Part of this hydrochloride (10.2 g, 0.05 mol) was suspended in 500 mL of CH_2Cl_2 and layered with saturated aqueous $NaHCO_3$ solution. Bromoacetyl bromide (6.6 mL, 0.075 mol), was added and the mixture was stirred for 15 min. The organic phase was separated, dried, and evaporated. The residue was crystallized from CH_2Cl_2/hexane to yield 10.8 g (75%) of product with mp 139–142 °C. The analytical sample was purified by filtration over silica gel using CH_2Cl_2 and was crystallized from CH_2Cl_2/hexane to give colorless crystals with the same melting point. Anal. ($C_{10}H_8BrClN_2O$): C, H, N.

7-Chloro-1,3-dihydro-2*H*-pyrrolo[1,2,3-*de*]quinoxalin-2-one (103). Compound **101** (11.5 g, 0.04 mol) was dissolved in 1200 mL of 2-propanol. Potassium *tert*-butoxide (13.5 g, 0.12 mol) was added with stirring under nitrogen. The mixture was stirred at room temperature for 1 h, acidified by addition of acetic acid, and partially evaporated. The product was precipitated by dilution with water. It was collected by filtration, washed with water and a little ethanol and recrystallized from THF/ethanol to leave 5.5 g (66%) of crystals with mp 275–275 °C. The analytical sample was recrystallized from the same solvents. Anal. ($C_{10}H_7ClN_2O$): C, H, N.

1,3-Dihydro-1-(1,2-propadienyl)-3-(2-propynyl)-2*H*-benzimidazol-2-one ($15M_4$) and 1,3-Dihydro-1-(2-propynyl)-2*H*-benzimidazol-2-one ($15M_1$). A mixture of 13.4 g (0.1 mol) of 2-hydroxybenzimidazole, 200 mL of DMF, 10 g of BaO, and 11 mL of propargyl bromide (80% in toluene) was heated with stirring at 100–103 °C for 15 min. The cooled reaction mixture was acidified with 20 mL of acetic acid and was diluted with water. The precipitate was filtered off, washed with water, and sucked dry. It was recrystallized from CH_2Cl_2/hexane to give 3.1 g (15%) of the 1,3-dipropargyl derivative with mp 157–159 °C. The evaporated mother liquor was chromatographed over 100 g of silica gel using CH_2Cl_2. The clean fractions were combined and evaporated and the residue was crystallized from Et_2O/hexane to leave 0.74 g (3.5%) of $15M_4$ with mp 110–112 °C. NMR ($CDCl_3$): δ 2.3 (t, 1, J = 2 Hz, acetylenic H), 4.7 (d, 2, J = 2 Hz, CH_2), 5.64 (d, 2, J = 6 Hz, olefinic H), 7–7.4 (m, 3, aromatic H) 7.55 (dd, 1, J = 8 and 1.5 Hz, C_7-H). Anal. ($C_{13}H_{10}N_2O$): C, H, N.

The original aqueous filtrate was extracted with EtOAc three times. The combined extracts were dried and evaporated. The residue was dissolved partially in hot EtOAc. The insoluble material was filtered off and the filtrate was evaporated. The residue was dissolved in CH_2Cl_2/EtOAc and the solution was passed over a plug of silica gel. The eluate was evaporated and crystallized from EtOAc/hexane to give 2.4 g (14%) of 1,3-dihydro-1-(2-propynyl)-2*H*-benzimidazol-2-one ($15M_1$) with mp 176–178 °C. Anal. ($C_{10}H_8N_2O$): C, H, N.

2,3-Dihydro-2-(2-propynyl)-1*H*-benz[*de*]isoquinolin-1-one ($15D_2$). A suspension of 2 g (8.5 mmol) of compound $15D_1$ and 0.75 g of $NaBH_4$ in 50 mL of THF and 50 mL of ethanol was heated on the steam bath until all was dissolved. An additional 0.25 g of $NaBH_4$ was added and heating on a steam bath was continued with distillation of the THF for 30 min. The cooled mixture was diluted with ice/water, buffered with acetic acid, and diluted with saturated $NaHCO_3$ solution. The precipitate was filtered after stirring for 30 min and was sucked dry. The collected material was dissolved in CH_2Cl_2 (ca. 250 mL) and the solution was dried and evaporated. The crystalline residue was slurried with CH_2Cl_2/Et_2O/hexane and collected to leave 0.67 g (33.5%) of 2,3-dihydro-3-hydroxy-2-(2-propynyl)-1*H*-benz[*de*]isoquinolin-1-one, which was used as is for further reduction.

This product (0.6 g, 2.5 mmol) was dissolved in 6 mL of trifluoroacetic acid. Sodium borohydride (0.3 g) was added in small portions and the mixture was stirred for 15 min at room temperature. It was partitioned between ice/water, ammonia, and CH_2Cl_2. The organic layer was dried and evaporated, and the residue was chromatographed over silica gel using CH_2Cl_2 containing 10% of EtOAc for elution. The clean fractions were combined and evaporated and the residue was crystallized from EtOAc/Et_2O to yield 0.45 g (80%) of colorless crystals with mp 139–140 °C. NMR ($CDCl_3$): δ 2.3 (t, 1, J = 2 Hz, acetylenic H), 4.6 (d, 2, J = 2 Hz, CH_2) 5.13 (s, 2, C_3-H) 7.3–8.4 (m, 6, aromatic H). Anal. ($C_{15}H_{11}NO$): C, H, N.

6,8-Dichloro-3,4-dihydro-1-(2-propynyl)-1*H*-quinolin-2-one ($15B_2$). Dichloroethane (75 mL) was saturated in the cold (ice/water) with chlorine. A solution of 6 g (0.04 mol) of 3,4-dihydroquinolin-2(1*H*)-one in 50 mL of formic acid and 50 mL of concentrated HCl was added and stirred over ice for 30 min. Chlorine was introduced for 5 min and stirring in the cold was continued for 2 h. The mixture was poured over ice, made alkaline

(15) Batcho, A. D. US patent 4,506,078, March 1985.

with ammonia, and extracted with CH_2Cl_2. The extracts were dried and evaporated, and the residue was crystallized from Et_2O to yield 3 g (34%) of colorless crystals with mp 248–250 °C.

A mixture of 1.5 g of this material, 40 mL of DMF, 1.3 g of BaO, and 0.8 mL of propargyl bromide was heated on the steam bath for 45 min. After cooling it was diluted with water and the precipitated product was filtered off and dissolved in CH_2Cl_2. The solution was dried and evaporated and the residue was crystallized from Et_2O/hexane to give 0.55 g (31%) of colorless crystals with mp 92–95 °C. NMR ($CDCl_3$): δ 2.14 (t, 1, J = 1.5 Hz, acetylenic H), 2.62 (t, 2, J = 6 Hz, CH_2), 2.86 (t, 2, J = 6 Hz, CH_2), 4.92 (d, 2, J = 1.5 Hz, CH_2), 7.12 (d, 1, J = 2 Hz, C_5-H), 7.32 (d, 1, J = 2 Hz, C_7-H). Anal. ($C_{12}H_9Cl_2NO$): C, H, N.

1,3-Dihydro-2-[2-(dimethylamino)ethyl]-2*H*-benzimidazol-2-one (107). A mixture of 10 g of *N*-(2-nitrophenyl)-2-(dimethylamino)ethylamine hydrochloride,[16] 1.5 g of palladium on carbon (5%), and 100 mL of methanol was hydrogenated at atmospheric pressure for 6 h. The catalyst was filtered off and the filtrate was evaporated. The residue was crystallized from 2-propanol to yield 7.5 g of *N*-(2-aminophenyl)-2-(dimethylamino)ethylamine hydrochloride which was further reacted as follows.

Part of this hydrochloride (6.5 g, 30 mmol), 5.3 g (32 mmol) of carbonyldiimidazole, and 5 mL of triethylamine in 100 mL of CH_2Cl_2 was heated to reflux for 1 h. The methylene chloride was evaporated and replaced by ethanol. The mixture was heated on the steam bath for 30 min and evaporated and the residue was partitioned between CH_2Cl_2 and 10% Na_2CO_3 solution. The organic layer was dried and evaporated and the residue was crystallized from ether and recrystallized from EtOAc/hexane to yield 3.1 g (50%) of colorless crystals with mp 108–110 °C. Anal. ($C_{11}H_{15}N_3O$): C, H, N.

PAF-Induced Bronchoconstriction Assay (in Vivo). Male guinea pigs (Hartley strain, Charles River) weighing 400–600 g were anesthetized with urethane (2g/kg) intraperitoneally, and a polyethylene cannula was inserted into the jugular vein for intravenous drug administration. Tracheal pressure (centimeters of H_2O) was recorded from a Statham pressure transducer (P 23 AA). Propanolol was administered 5 min before PAF. Two minutes later, spontaneous breathing was arrested with succinylcholine chloride (1.2 mg/kg) administered intravenously, and the animals were ventilated with a Harvard Model 680 small-animal respirator set at 40 breaths/min and 4.0 cm^3 stroke volume. For intravenous dosing, test drug or vehicle were administered through the cannula into the jugular vein 1 min before the animals were challenged with a maximal constrictory dose of PAF (1 μg/kg) given intravenously. For determination of oral activity, animals were dosed with the test compound or the vehicle 2 h prior to challenge with PAF (1 μg/kg iv). Compounds were initially evaluated at a dose of 1 mg/kg intravenously or orally. The change in tracheal pressure was averaged for three control and three drug-treated animals and percent inhibition was calculated. The median inhibitory dose values (ID_{50}) for active compounds were determined by linear-regression of log dose–response curves generated by at least three doses that caused statistically significant inhibition of the PAF-induced bronchoconstriction of between 10 and 90%. The correlation coefficient for the regression line of each antagonist was always greater than 0.95.

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Registry No. **4a**, 125030-09-3; **4b**, 30843-54-0; **4c**, 116725-41-8; **4d**, 131637-09-7; **5a**, 125030-96-8; **5b**, 131637-10-0; **6a**, 55500-87-3; **6b**, 30843-56-2; **6c**, 116725-43-0; **6d**, 131637-11-1; **7a**, 125133-61-1; **7b**, 131723-31-4; **8b**, 125030-06-0; **8c**, 125031-19-8; **8d**, 131637-12-2; **9b**, 125030-07-1; **9c**, 125031-20-1; **10a**, 125030-11-7; **10b**, 125030-08-2; **10c**, 125031-21-2; **10e**, 131637-13-3; **10f**, 125030-12-8; **10g**, 125030-94-6; **10h**, 125031-23-4; **11a**, 125030-97-9; **11b**, 131637-14-4; **12**, 131656-36-5; **13**, 125031-09-6; 14, 125031-10-9; **15A**, 7223-50-9; **15B$_1$**, 37994-16-4; **15B$_2$**, 125030-84-4; **15B$_3$**, 131637-15-5; **15B$_4$**, 35227-94-2; **15B$_5$**, 131637-16-6; **15D$_1$**, 125030-14-0; **15D$_2$**, 125030-63-9; **15E**, 6397-44-0; **15F$_1$**, 37988-92-4; **15F$_2$**, 118108-38-6; **15F$_3$**, 118108-43-3; **15G$_1$**, 73282-03-8; **15G$_2$**, 131637-17-7; **15H$_1$**, 1904-39-8; **15H$_2$**, 131637-18-8; **15I**, 37994-11-9; **15J**, 4290-87-3; **15K**, 42076-28-8; **15L**, 58412-92-3; **15M$_1$**, 131637-19-9; **15M$_2$**, 125030-66-2; **15M$_3$**, 125030-82-2; **15M$_4$**, 131637-20-2; **15M$_5$**, 131637-21-3; **15N$_1$**, 83451-17-6; **15N$_2$**, 125030-80-0; **15N$_3$**, 131637-22-4; **15O$_1$**, 37045-22-0; **15O$_2$**, 125031-29-0; **15P**, 125030-19-5; **15Q**, 125030-73-1; **15R**, 125030-67-3; **15S$_1$**, 4282-77-3; **15S$_2$**, 79629-22-4; **15S$_3$**, 131637-23-5; **15T$_1$**, 131637-24-6; **15T$_2$**, 131637-25-7; **15U**, 94707-28-5; **15V**, 51494-75-8; **15W**, 42996-70-3; **15X**, 131637-26-8; **16**, 131637-27-9; **17**, 125540-18-3; **18**, 125055-04-1; **19**, 125055-05-2; **20**, 125030-95-7; **21**, 131637-28-0; **22**, 131637-29-1; **23**, 125030-48-0; **24**, 125030-92-4; **25**, 125030-98-0; **26**, 131637-30-4; **27**, 125031-13-2; **28**, 125031-11-0; **29**, 125031-12-1; **30**, 125031-22-3; **31**, 125031-24-5; **32**, 125030-35-5; **33**, 125030-15-1; **34**, 125030-21-9; **35**, 125030-22-0; **36a**, 36811-58-2; **36b**, 131723-32-5; **37a**, 40017-66-1; **37b**, 131723-33-6; **38a**, 67860-47-3; **39a**, 67860-46-2; **40a**, 67860-41-7; **40b**, 125031-30-3; **40c**, 131637-31-5; **40d**, 131637-32-6; **40e**, 125031-15-4; **40f**, 125031-16-5; **40g**, 125031-17-6; 41, 125030-62-8; **42**, 125055-13-2; **43**, 131637-33-7; **44**, 125030-85-5; **45**, 131637-34-8; **46**, 125030-61-7; **47**, 131637-35-9; **48**, 125030-44-6; **49**, 125030-76-4; **50**, 125030-38-8; **51**, 125030-64-0; **52**, 125030-49-1; **53**, 131637-36-0; **54**, 131637-37-1; **55**, 125055-11-0; **56**, 131637-38-2; **57**, 125055-10-9; **58**, 131637-39-3; **59**, 125030-40-2; **60**, 125030-39-9; **61**, 125030-45-7; **62**, 125030-41-3; **63**, 131637-40-6; **64**, 131637-41-7; **65**, 125030-83-3; **66**, 131637-42-8; **67**, 131637-43-9; **68**, 125030-87-7; **69**, 125030-81-1; **70**, 131637-44-0; **71**, 125030-71-9; **72**, 125031-04-1; **73**, 125031-03-0; **74**, 125031-26-7; **75**, 131637-45-1; **76**, 125030-91-3; **77**, 125055-09-6; **78**, 125030-74-2; **79**, 125030-68-4; **80**, 125030-70-8; **81**, 125031-25-6; **82**, 131637-46-2; **83**, 131637-47-3; **84**, 131637-48-4; **85**, 125030-90-2; **86**, 125030-77-5; **87**, 125030-72-0; **88**, 131637-49-5; **89**, 131637-50-8; **90**, 125031-06-3; **91**, 131637-51-9; **92**, 131637-52-0; **93**, 131637-53-1; **94**, 131637-54-2; **95**, 131637-55-3; **96a**, 131637-56-4; **96b**, 131637-57-5; **97**, 131637-58-6; **98**, 131637-59-7; **99**, 125030-69-5; **100**, 125030-75-3; **101**, 96831-52-6; **102**, 131637-60-0; **103**, 131637-61-1; **104**, 615-16-7; **105**, 131637-62-2; **106**, 131637-63-3; **107**, 131637-64-4; **108**, 131637-65-5; **171**, 131637-66-6; (2-aminophenyl)(2-chlorophenyl)methanone, 2894-45-3; 3-iodoaniline, 626-01-7; 2-fluorobenzonitrile, 394-47-8; *N*-(benzyloxycarbonyl)-L-alanine, 1142-20-7; bromoacetyl bromide, 598-21-0; 2-bromo-*N*-[2-(2-chlorobenzoyl)-4-iodophenyl]acetamide, 125030-10-6; acetic hydrazide, 1068-57-1; triethyl orthoacetate, 78-39-7; 9-(acetoxymethyl)-4-(2-chlorophenyl)-2-iodo-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepine, 131637-67-7; propargyl bromide, 106-96-7; 3,4-dihydroquinolin-2(1*H*)-one, 553-03-7; 6,8-dichloro-3,4-dihydroquinolin-2(1*H*)-one, 125030-86-6; *N*-(2-aminophenyl)-2-(dimethylamino)ethylamine hydrochloride, 131637-68-8.

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