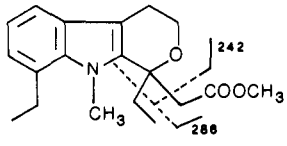
The methylated urine extracts were chromatographed by HPLC on a reverse-phase Microsorb C-18 column (Rainin Instruments; 25 cm X 4.6 mm) under isocratic conditions: 75% MeCN in H_2O mobile phase pumped through the column by a Rabbit HPX pressure module (Rainin Instruments) at a flow rate of 1.5 mL/min. The eluent was monitored at 226 nm by a Gilson Holochrome UV detector. A peak having the same t_R as authentic *N*-methyletodolac methyl ester was collected. The amount of radioactivity associated with this peak was 1–3% of the total urinary radioactivity.

GC–MS analysis on the isolated peak was carried out on a Varian Model 3000 GC instrument interfaced with a Finnigan 8230 mass spectrometer. The following GC conditions were used. The samples were injected onto a RPB 5 capillary column (15 m X 0.25 mm) with the injection temperature at 280 °C and the column temperature initially at 100 °C and then increased after injection at a rate of 25 °C/min to 280 °C. The He carrier gas flow rate was 1.0 mL/min. The interface and spectrometer settings were as follows: heat funnel (interface) temperature, 245 °C; line of sight temperature, 285 °C; MS source temperature, 200 °C; scan rate, 1 s/decade; interscan time, 0.3 s; CO_2 travel time at 100 °C, 18 s; analysis pressure at 100 °C, 9 X 10^{-7} Torr; ionization voltage, 70 eV. The spectrometer was set to monitor ion current for *m/e* 315, the molecular ion of *N*-methyletodolac methyl ester. The t_R of the *m/e* 315 ion current and the mass spectra of the GC peaks were identical for the authentic *N*-methyletodolac ester and the metabolite isolated by HPLC from human urine. The mass spectra showed the characteristic substituted pyranoindole fragmentation pattern: molecular ion (M^+, *m/e* 315), methylene methylacetate cleavage (*m/e* 242), ethyl cleavage (*m/e* 286).



Pharmacology. Adjuvant Edema Assay. Groups of 10 male Sprague–Dawley rats, each weighing 180–200 g, were injected intradermally in the left hindpaw with 0.1 mL of Freund's complete adjuvant (FCA; 0.5 mg of killed and dried *Mycobacterium butyricum* suspended in 0.1 mL of mineral oil). Test compounds or vehicle control (0.5% Tween 80 in distilled water) were administered by gastric lavage immediately before the FCA injection (day 0) and 24 and 48 h after the FCA (days 1 and 2). The volume of the injected hindpaw was measured both before the FCA injection and 24 h after the last drug administration (day 3) by means of a plethysmometer (Buxco Electronics, Sharon, CT). The mean hindpaw volume was calculated for each group, and the mean edema volume represents the difference between the volumes on days 0 and 3. The percent inhibition was calculated as follows:

$$100 \times (\text{mean control edema} - \text{mean drug-treated edema})/\text{mean control edema}$$

Statistical comparisons were performed for 1, 4, and **6** by using the unpaired *t* test with significance achieved at the $p < 0.05$ level.

In Vitro IC_{50} Determinations. The method for determining IC_{50} values for inhibition of prostaglandin production in stimulated chondrocyte cultures has been described in detail elsewhere.[34] IC_{50} values were estimated from a curve of log dose versus percent inhibition.

Registry No. 1, 87226-38-8; **2**, 101901-06-8; **3**, 101901-07-9; *cis*-4, 114719-97-0; *trans*-4, 114719-98-1; *cis*-4·$PhCH_2NH_2$, 114719-99-2; *trans*-4·$PhCH_2NH_2$, 114720-00-2; **5** (diastereomer 1), 114720-01-3; **5** (diastereomer 2), 114720-02-4; **5** (methyl ester, diastereomer 1), 114720-03-5; **5** (methyl ester, diastereomer 2), 114720-04-6; **6**, 111478-86-5; **7**, 114720-05-7; **8**, 41340-36-7; **9**, 114737-75-6; **9**·HCl, 114737-76-7; **10**, 114720-06-8; 11, 111478-90-1; (*Z*)-**12**, 114720-07-9; (*E*)-**12**, 114720-08-0; **13**, 111478-93-4; 14, 111478-94-5; **15**, 111478-95-6; **16**, 111478-96-7; *cis*-**17**, 111478-97-8; *trans*-**17**, 111479-03-9; *cis*-**18**, 111478-98-9; *trans*-**18**, 112059-19-5; *cis*-**19**, 114720-09-1; *trans*-**18**, 114720-10-4; *cis*-**20**, 111478-99-0; *trans*-**20**, 111479-00-6; *cis*-**21**, 114720-11-5; *trans*-**21**, 114720-12-6; *cis*-**22**, 114720-13-7; *trans*-**22**, 114720-14-8; **23**, 111478-84-3; **28**, 114737-77-8; **29**, 60481-34-7; **30**, 114720-15-9; **31**, 114720-16-0; **32**, 114720-17-1; **33**, 114720-18-2; **34** (diastereomer 1), 114720-19-3; **34** (diastereomer 2), 114720-20-6; $C_2H_5C(OCH_3)=CHCO_2CH_3$, 104065-67-0; *o*-$IC_6H_4NH_2$, 615-43-0; 6-hydroxyetodolac methyl ester, 114720-21-7; 7-ethylindole, 22867-74-9; 2,3-dihydrofuran, 1191-99-7.

(33) Hashimoto, N.; Aoyama, T.; Shiori, T. *Chem. Pharm. Bull.* **1981**, *29*, 1475.
(34) Neuman, R. G.; Wilson, B. D.; Barkley, M.; Kimball, E. S.; Weichman, B. M.; Wood, D. D. *Agents Actions* **1987**, *21*, 160.

3-[1-(2-Benzoxazolyl)hydrazino]propanenitrile Derivatives: Inhibitors of Immune Complex Induced Inflammation[1]

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Abbott Laboratories, Abbott Park, Illinois 60064. *Received July 6, 1987*

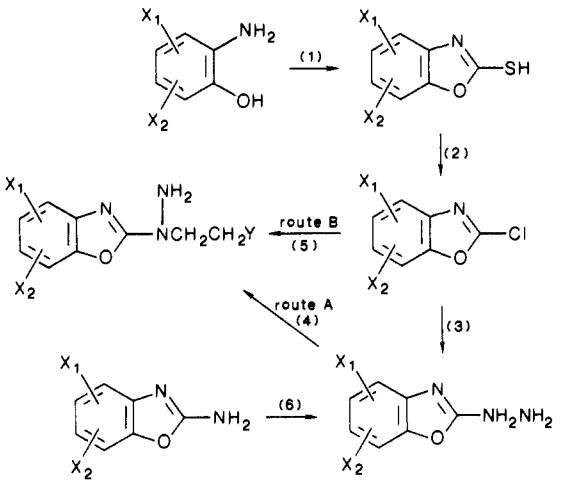
3-[1-(2-Benzoxazolyl)hydrazino]propanenitrile derivatives were evaluated in the dermal and pleural reverse passive Arthus reactions in the rat. In the pleural test these compounds were effective in reducing exudate volume and accumulation of white blood cells. This pattern of activity was similar to that of hydrocortisone and different from that of indomethacin. The structural requirements for inhibiting the Arthus reactions were studied by systematic chemical modification of 1. These structure–activity relationship studies revealed that nitrogen 1′ of the hydrazino group is essential for activity and must be electron rich, whereas chemical modifications of other sites of 1 had only a modest effect on activity.

Immune complexes have been implicated in the pathogenesis of rheumatoid arthritis (RA) and other inflammatory diseases.[2-4] The reverse passive Arthus reaction (RPAR) represents a well-characterized experimental model of acute immune complex induced inflammation and tissue injury. The close similarities between the pathogenesis of the Arthus reaction and RA makes it an attractive model to search for new drugs to treat RA and related diseases. Therefore, the Arthus model was chosen to screen for novel antiarthritic agents. This reaction is inhibited by hydrocortisone and other corticosteroids but

(1) This paper has been presented: see *Abstracts of Papers*; 189th National Meeting of the American Chemical Society, Miami, April 29–May 2, 1985, American Chemical Society: Washington, DC, 1985; MEDI 62.
(2) Zvaifler, N. J. *Adv. Immunol.* **1973**, *16*, 265.
(3) Ziff, M. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1973**, *32*, 131.
(4) Zvaifler, N. J. *Arthritis Rheum.* **1974**, *17*, 297.

0022-2623/88/1831-1719$01.50/0

Scheme I[a]



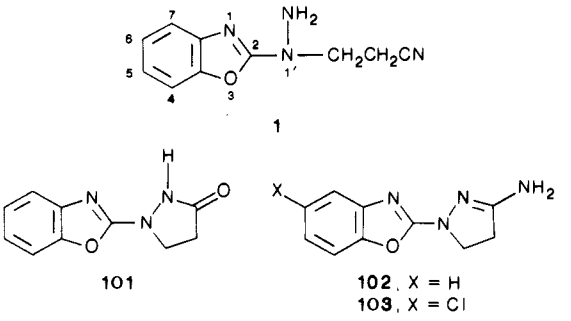
[a] (1) KSCSEt; (2) PCl_5; (3) $NH_2NH_2 \cdot H_2O$; (4) CH_2=CHCN and NaOH; (5) Et_3N, $NH_2NHCH_2CH_2Y$; (6) a. $NaNO_2$/HCl, b. $SnCl_2$/HCl, c. NaOH.

is insensitive to inhibition by traditional nonsteroidal antiinflammatory drugs (NSAID), such as indomethacin.

During the course of screening with the rat dermal RPAR, the inhibitory activity of the 3-[1-(2-benzoxazolyl)hydrazino]propanenitrile series was identified. This report describes the synthesis and structure–activity relationship (SAR) of this novel chemical series.

Synthesis

The 3-[1-(2-benzoxazolyl)hydrazino]propanenitrile derivatives **1–30** were prepared either by reacting 2-hydrazinobenzoxazole with acrylonitrile in the presence of base (methods A or C), or by reacting 2-chlorobenzoxazole with 3-hydrazinopropane nitrile (prepared in situ) in the presence or absence of base (method B) (Scheme I). The stability of compound 1, whose structure was confirmed by single-crystal X-ray analysis (Figure 1),[5] was investigated under acidic and basic conditions. When heated in ethanolic hydrochloric acid solution for 2 h, compound 1 was stable and no cyclization to 1-(2-benzoxazolyl)-3-amino-pyrazol-2-ene (**102**) was observed. However, the chloro analogue **8** cyclized to the 1-(6-chloro-2-benzoxazolyl)-3-aminopyrazol-2-ene (**103**) under the same conditions. To prove the structure of **103**, we synthesized the related 1-(2-benzoxazolyl)-3-amino-3-pyrazol-2-ene (**102**) by direct alkylation of 3-aminopyrazol-2-ene with 2-chlorobenzoxazole in the presence of base. The IR and NMR spectra of **102** and **103** were similar. Also, base hydrolysis of methyl 3-[1-(2-benzoxazolyl)hydroazino]propanoate hydrochloride (**34**) afforded 1-(2-benzoxazolyl)-3-pyrazolone (**101**) as a byproduct.



1

101 102, X = H; 103, X = Cl

(5) X-ray analysis was performed by Molecular Structure Corporation, College Station, Texas.

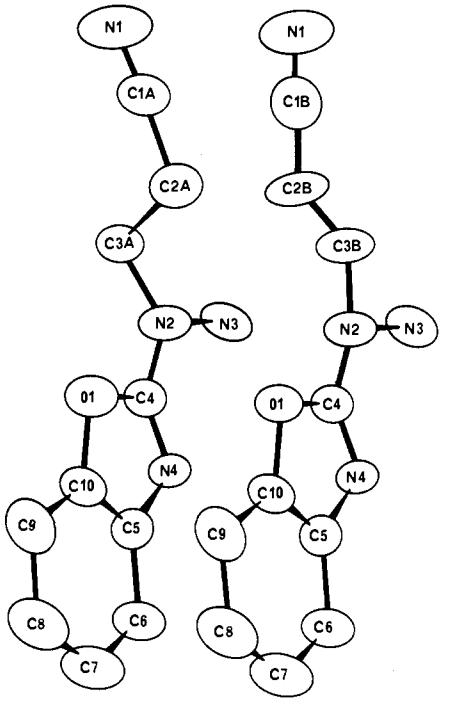
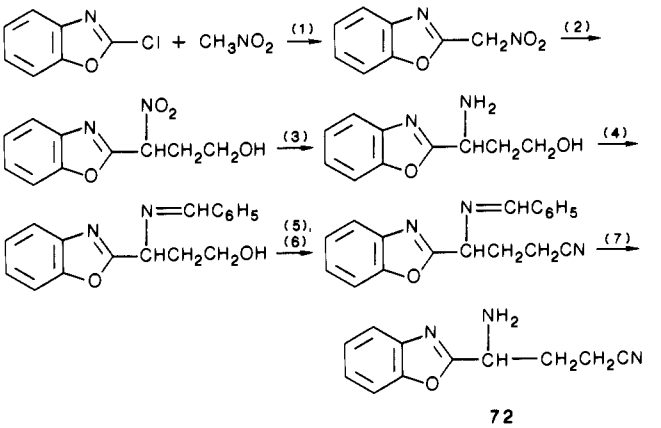


Figure 1. Representation of the structure of two conformers of 3-[1-(2-benzoxazolyl)hydrazino]propanenitrile (1) as determined by single-crystal X-ray analysis.[5]

Scheme II[a]

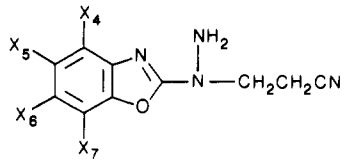


72

[a] (1) NaH; (2) LDA, ethylene oxide; (3) H_2, Adams' catalyst; (4) benzaldehyde, TsOH, (5) PBr_3; (6) KCN, DMF; (7) hydrazine hydrate.

Compounds **31**, **32**, and **37–56** were synthesized by alkylation of appropriate derivatives of 3-hydrazinopropane with 2-chlorobenzoxazole in the presence of triethylamine. Similar reaction conditions were used for alkylation of 3-aminopropanenitrile to give compound **73**. Compounds **57–71** were prepared from 1 by using conventional synthetic methods. Compound **72**, the carbon isostere of 1, was synthesized by a seven-step procedure outlined in Scheme II. The most crucial step in this synthesis was the identification of a suitable protecting group for the amino moiety. Conventional protecting groups such as acetyl, phthalyl, and *tert*-butoxycarbonyl could not be removed without decomposing the final product. Only the benzylidene group gave satisfactory results. This group was stable through the entire synthesis and could be easily removed upon mild treatment with hydrazine hydrate at room temperature for 2 h. The same reaction conditions failed to remove the benzylidene group from **81** (the dideuterio derivative of 1), which was previously obtained upon treatment of the benzylidene derivative of 1 with

Table I. The Activities of Ring Substituted 3-[1-(2-Benzoxazolyl)hydrazino]propanenitrile Derivatives in the Dermal Reverse Passive Arthus Reaction



compd	X_4	X_5	X_6	X_7	yield, % (synth method)	formula	mp, °C	ED_{40},[a] μmol/kg po
1	H	H	H	H	85 (A)	$C_{10}H_{10}N_4O$	169–170	84 (54, 119)
2	H	CH_3	H	H	64 (A)	$C_{11}H_{12}N_4O$	105–107	83 (65, 97)
3	H	CH_2CH_3	H	H	66 (A)	$C_{12}H_{14}N_4O$	110–111	330 (161, 6726)
4	H	OCH_3	H	H	81 (A)	$C_{11}H_{12}N_4O_2$	124–126	59 (6, 115)
5	H	$C(CH_3)_3$	H	H	71 (C)	$C_{14}H_{18}N_4O$	105–106	345 (236, 639)
6	H	SCH_3	H	H	60 (A)	$C_{11}H_{12}N_4OS$	91–92	399 (274–714)
7	H	CF_3	H	H	62 (A)	$C_{11}H_9F_3N_4O$	146–147	26 (19, 33)
8	H	Cl	H	H	90 (C)	$C_{10}H_9ClN_4O$	143–144	177 (93, 575)
9	H	F	H	H	86 (A)	$C_{10}H_9FN_4O$	112–114	141 (118, 168)
10	H	CN	H	H	66 (A)	$C_{11}H_9N_5O$	159–160	66 (53, 79)
11	H	$COOCH_2CH_3$	H	H	61 (A)	$C_{13}H_{14}N_4O_3$	99–100	inactive[b]
12	H	C_6H_5	H	H	43 (A)	$C_{16}H_{14}N_4O$	127–128	inactive[b]
13	H	$OCH_2C_6H_5$	H	H	74 (A)	$C_{17}H_{16}N_4O_2$	134–136	inactive[b]
14	H	$OC\text{-}C_6H_5$	H	H	66 (A)	$C_{17}H_{15}ClN_4O_2$[d]	>250	inactive[b]
15	H	SO_2CH_3	H	H	35 (Ex)[e]	$C_{11}H_{12}N_4O_3S$	165–167	407 (325, 554)
16	H	$SOCH_3$	H	H	35 (Ex)[e]	$C_{11}H_{12}N_4O_2S$	124–126	607[c]
17	H	OC_6H_5	H	H	29 (B)	$C_{16}H_{14}N_4O_2$	137–139	inactive[b]
18	H	H	CH_3	H	88 (A)	$C_{11}H_{12}N_4O_2$	172–173	216 (148, 375)
19	CH_3	H	H	H	88 (A)	$C_{11}H_{12}N_4O$	106–107	356 (176, 6037)
20	H	H	H	CH_3	80 (A)	$C_{11}H_{12}N_4O$	113–114	250 (185, 389)
21	H	H	OCH_3	H	84 (A)	$C_{11}H_{12}N_4O_2$	109–111	388 (254, 815)
22	H	H	H	Cl	74 (C)	$C_{10}H_9ClN_4O$	114–115	275 (186, 545)
23	H	Cl	CH_3	H	84 (A)	$C_{11}H_{11}ClN_4O$	151–152	36 (29, 44)
24	H	Cl	H	CH_3	73 (A)	$C_{11}H_{11}ClN_4O$	140–142	191 (139, 287)
25	H	CH_3	H	CH_3	66 (A)	$C_{12}H_{14}N_4O$	103–105	161 (126, 209)
26	H	CH_3	CH_3	H	84 (A)	$C_{12}H_{14}N_4O$	162–164	413 (257, 1039)
27	CH_3	CH_3	H	CH_3	75 (A)	$C_{13}H_{16}N_4O$	146–147	115 (86, 148)
28	CH_3	CH_3	CH_3	H	93 (A)	$C_{13}H_{16}N_4O$	143–144	139 (119, 164)
29	H	OCH_3	OCH_3	H	35 (A)	$C_{12}H_{14}N_4O_3$	122–124	650[c]
30	H	$C(CH_3)_3$	H	SCH_3	34 (C)	$C_{15}H_{20}N_4OS$	106–108	801[c]
hydrocortisone					33			33 (25, 47)
indomethacin								inactive[f]

[a] The dose estimated to produce 40% inhibition (ED_{40}) with 95% confidence limits shown in parentheses, calculated by least-squares regression analysis. [b] Compounds that did not produce statistically significant activity ($p > 0.05$) are listed as inactive. [c] An estimated ED_{40} value was extrapolated from the regression analysis of the prototype compound 1 for compounds producing significant inhibition of less than 40%. [d] Isolated as hydrochloride. [e] Ex = experimental procedure described. [f] The highest dose tested for indomethacin was 56 μmol/kg.

lithium diisopropylamide and deuterium oxide. For the synthesis of **81** the formylidene group was found to be a more suitable protecting group, being rapidly removed upon mild treatment with hydrazine hydrate for 10 min. Compounds **92–100** were prepared from the appropriate hydrazino heterocycles or chloro heterocycles by using synthetic methods similar to those described in Scheme I.

Biological Results and Discussion

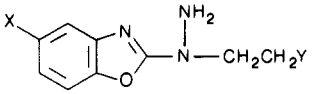
One of the most interesting members of the series was 3-[1-(2-benzoxazolyl)]propanenitrile (**1**). This compound inhibited the dermal RPAR with an ED_{40} value of 84 μmol/kg (Table I). As this compound represents a relatively simple prototype of the series, it was subjected to an extensive structure–activity relationship investigation to optimize its potency.

The influence of various substituents on the benzoxazoyl ring of **1** on inhibitory activity in RPAR was investigated, and the results are shown in Table I. At position 5, which was the site most investigated, small groups such as methyl (**2**), methoxy (**4**), trifluoromethyl (**7**), fluoro (**9**), and nitrile maintained or improved activity.[6] The most potent derivative of this type (**7**) had an ED_{40} of 26 μmol/kg, which was approximately 3 times more potent than **1**. Introducing bulky groups at position 5 reduced or eliminated activity. In general, inhibitory activity in RPAR was inversely related to the size of the substituent at position 5. Substitution at other sites on the benzoxazolyl ring generally resulted in compounds which were less active than **1**. However, the 5-chloro-6-methyl analogue **23** was substantially more potent than **1**. Partition coefficients and pK_a values were determined for these benzoxazolyl ring substituted derivatives, but no correlation was found between these physical parameters and biological activity in RPAR.[6]

Replacement of the nitrile group of **1** by methyl (**31**), hydrogen (**32**), acetylene (**33**), carbomethoxyl (**34**), carboxyl (**35**), amide (**36**), hydroxyl (**37**), methoxyl (**38**), and other groups generally decreased activity (Table II). The ED_{40} of the methoxyl analogue **38** was 300 μmol/kg. Interestingly, the potency of **38** was improved nearly sevenfold when another methoxyl (**52**) or a trifluoromethyl (**51**) group was introduced at position 6 of the benzoxazolyl ring. Alkylation of the hydrazino moiety with methyl (**58**) or ethyl (**59**) reduced activity two- to threefold. Similarly, substitution at this site with electron-withdrawing groups such as acyl (**57**), amide (**65** and **66**), thioamide (**67**), ester

(6) QSAR studies of this series by Kim, K. H.; Martin, Y. C.; Norris, B.; Haviv, F. will be published elsewhere.

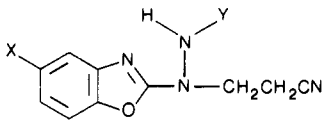
Table II. The Activities of 3-[1-(2-Benzoxazolyl)hydrazino]propanenitrile Analogues, Modified at the Nitrile Site, in the Dermal Reverse Passive Arthus Reaction



compd	X	Y	yield, % (synth method)	formula	mp, °C	ED_{40},[a] μmol/kg po
31	H	CH_3	44 (D)	$C_{10}H_{14}ClN_3O$[d]	179–181	400 (246, 1076)
32	H	H	63 (D)	$C_9H_{11}N_3O$	79–81	254 (226, 288)
33	H	C≡CH	90 (Ex)[e]	$C_{11}H_{11}N_3O$	129–131	348 (194, 1791)
34	H	$COOCH_3$	40 (Ex)[e]	$C_{11}H_{14}ClN_3O$[d,f]	145–146	1208[c]
35	H	COOH	17 (Ex)[e]	$C_{10}H_{12}ClN_3O_3$[d,f]	158–160	inactive[b]
36	H	$CONH_2$	68 (Ex)[e]	$C_{10}H_{13}ClN_4O_2$[d]	185–186	1009[c]
37	H	OH	31 (D)	$C_9H_{10}N_3O_2$[g]	110–111	1247[c]
38	H	OCH_3	58 (D)	$C_{10}H_{13}N_3O_2$	84–86	300 (203, 546)
39	H	CH_2OH	49 (D)	$C_{10}H_{13}N_3O_2$	91–93	576[c]
40	H	SO_2CH_3	95 (D)	$C_{10}H_{13}N_3O_3S$[h]	114–115	278 (220, 385)
41	H	OC_6H_5	26 (D)	$C_{15}H_{15}N_3O_2$	76–78	457 (338, 710)
42	H	SOC_6H_5	47 (D)	$C_{15}H_{15}N_3O_2S$[f]	134–135	719[c]
43	H	C_6H_5	65 (D)	$C_{15}H_{15}N_3O$	80–82	962[c]
44	H	SC_6H_5	57 (D)	$C_{15}H_{15}N_3OS$	133–134	inactive[b]
45	H	$SO_2C_6H_5$	42 (D)	$C_{15}H_{15}N_3O_3S$	114–116	inactive[b]
46	H	Morpholinyl	50 (D)	$C_{13}H_{18}N_4O_2$	60–61	825[c]
47	H	OC_6H_4-4-F	37 (D)	$C_{15}H_{14}FN_3O_2$	79–80	800[c]
48	H	2-Pyridinyl	89 (D)	$C_{14}H_{14}N_4O$	88–90	258 (146, 762)
49	H	SCH_3	30 (D)	$C_{10}H_{13}N_3OS$	81–82	913[c]
50	H	$N(CH_2CH_3)_2$	25 (D)	$C_{13}H_{20}N_4O$	oil	611[c]
51	CF_3	OCH_3	39 (D)	$C_{11}H_{13}ClF_3N_3O_2$[d]	148–150	47 (40, 55)
52	OCH_3	OCH_3	39 (D)	$C_{11}H_{16}ClN_3O_3$[d]	152–154	43 (0, 122)
53	CN	OCH_3	35 (D)	$C_{11}H_{12}N_4O_2$	107–111	181 (147, 224)
54	Cl	OCH_3	40 (D)	$C_{10}H_{12}ClN_3O_2$	92–95	136 (79, 248)
55	CH_3	OCH_3	35 (D)	$C_{11}H_{15}N_3O_2$	48–51	127 (104, 154)
56	OCH_3	OCH_2CH_3	38 (D)	$C_{12}H_{12}ClN_3O_3$[f]	136–138	149 (111, 208)

[a] The dose estimated to produce 40% inhibition (ED_{40}) with 95% confidence limits shown in parentheses, calculated by least-squares regression analysis. [b] Compounds that did not produce statistically significant activity ($p > 0.05$) are listed as inactive. [c] Estimated ED_{40} value extrapolated from the regression analysis of the prototype compound 1 for compounds producing significant inhibition of less than 40%. [d] Isolated as hydrochloride. [e] Ex = experimental procedure described. [f] Isolated as $0.25H_2O$. [g] Isolated as $0.8H_2O$. [h] Isolated as monohydrate.

Table III. The Activities of N-Substituted 3-[1-(2-Benzoxazolyl)hydrazino]propanenitrile Derivatives in the Dermal Reverse Passive Arthus Reaction



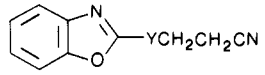
compd	X	Y	yield, %	formula	mp, °C	ED_{40},[a] μmol/kg po
58	H	$COCH_3$	95	$C_{12}H_{12}N_4O_2$[c]	137–139	402 (316, 557)
58	H	CH_3	12	$C_{11}H_{12}N_4O$	89–92	250 (213, 301)
59	H	CH_2CH_3	60	$C_{12}H_{14}N_4O$	liquid[d]	196 (152, 265)
60	H	COH	49	$C_{11}H_{10}N_4O_2$[e]	87	142 (113, 176)
61	CH_3	COH	86	$C_{12}H_{12}N_4O_2$	115–117	168 (152, 193)
62	OCH_3	COH	57	$C_{12}H_{12}N_4O_3$	110–112	200 (181, 219)
63	CF_3	COH	46	$C_{12}H_9F_3N_4O_2$	135–136	87 (40, 151)
64	H	$=CHCH_3$	89	$C_{12}H_{12}N_4O$	159–161	625 (316, 4331)
65	H	$CONHCH_3$	96	$C_{12}H_{13}N_5O_2$	202–203	inactive[b]
66	H	$CONH_2$	60	$C_{11}H_{11}N_5O_2$	194–195	inactive[b]
67	H	$CSNHCH_3$	40	$C_{12}H_{13}N_5SO$	198–200	inactive[b]
68	H	$COOCH_3$	41	$C_{12}H_{12}N_4O_3$	150–152	695[f]
69	H	SO_2CH_3	65	$C_{11}H_{12}N_4O_3S$	152–153	inactive[b]
70	H	$CONHC_6H_{11}$	96	$C_{17}H_{20}N_5O_2$	179–180	inactive[b]
71	H	$=CH_2$	72	$C_{11}H_{10}N_4O$	144–146	845[f]

[a] The dose estimated to produce 40% inhibition (ED_{40}) with 95% confidence limits shown in parentheses, calculated by least-squares regression analysis. [b] Compounds that did not produce statistically significant activity ($p > 0.05$) are listed as inactive. [c] Isolated as $^3/_4H_2O$. [d] bp 140–160 °C at 0.6 mm/kg. [e] Isolated as monohydrate. [f] Estimated ED_{40} extrapolated from the regression analysis of the prototype compound 1 for compounds producing significant inhibition of less than 40%.

(**68**), and sulfone (**69**) significantly decreased or eliminated activity (Table III). An exception was the *N*-formyl derivative **60**, which was only slightly less active than **1**. The *N*-formyl derivative **63**, which also contained trifluoromethyl at position 5, had the same activity as **1**. It is quite possible that the activity of these formyl derivatives is the result of deformylation in vivo to yield **1** or **7**, respectively.

The importance of nitrogen 1′ for biological activity is indicated by the finding that replacing this atom with carbon (**72**) or sulfur (**77**) leads to inactive or weakly active compounds (Table IV). Furthermore, for optimal activity it appears that this nitrogen should be electron-rich since analogues substituted at nitrogen 1′ with electron-withdrawing groups such as carbomethoxyl (**74**), formyl (**76**),

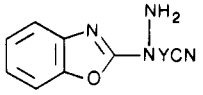
Table IV. The Activities of 3-[1-(2-Benzoxazolyl)hydrazino]propanenitrile Analogues, Modified at the Hydrazino Site, in the Dermal Reverse Passive Arthus Reaction



compd	Y	yield, %	formula	mp, °C	ED_{40},[a] μmol/kg
72	$CHNH_2$	29	$C_{11}H_{11}N_3O$	128–129	inactive[b]
73	NH	61	$C_{10}H_9N_3O$	127–129	1302[c]
74	$NCOOCH_3$	40	$C_{12}H_{11}N_3O_8$	121–123	inactive[b]
75	$NCOCH_3$	76	$C_{12}H_{11}N_3O_2$	81–82	inactive[b]
76	NCOH	80	$C_{11}H_9N_3O_2$	156–159	inactive[b]
77	S	47	$C_{10}H_8N_2OS$	46–47	1268[c]

[a] The dose estimated to produce 40% inhibition (ED_{40}) with 95% confidence limits shown in parentheses, calculated by least-squares regression analysis. [b] Compounds that did not produce statistically significant activity ($p > 0.05$) are listed as inactive. [c] Estimated ED_{40} extrapolated from the regression analysis of the prototype compound 1 for compounds producing significant inhibition of less than 40%.

Table V. The Activities of 3-[1-2-Benzoxazolyl)hydrazino]propanenitrile Analogues, Modified at the Ethylene Site, in the Dermal Reverse Passive Arthus Reaction



compd	Y	yield, % (synth method)	formula	mp, °C	ED_{40},[a] μmol/kg po
78	$CH_2CH(CH_3)$	47 (A)	$C_{11}H_{12}N_4O$	101–103	210 (87, 1827)
79	$(CH_3)CHCH_2$	65 (A)	$C_{11}H_{12}N_4O$	94–96	245 (139, 768)
80	$COCH_2$	63 (Ex)[c]	$C_{10}H_8N_4O_2$	195–197	inactive[b]
81	CH_2CD_2	18 (Ex)[c]	$C_{10}H_8D_2N_4O$	168–170	255 (157, 534)

[a] The dose estimated to produce 40% inhibition (ED_{40}) with 95% confidence limits shown in parentheses, calculated by least-squares regression analysis. [b] Compounds that did not produce statistically significant activity ($p > 0.05$) are listed as inactive. [c] Ex = experimental procedure described.

or acyl (**75** and **80**) were completely inactive. The desamino analogue **73** was only marginally active. Methyl substitution of the propanenitrile side chain at position 2 (**78**) or 3 (**79**), or deuteriation of position 2 (**81**) reduced activity approximately threefold compared to that of 1 (Table V).

The benzoxazolyl ring of 1 was replaced by various heterocyclic rings described in Table VI. 2-Thiazolyl (**82**), 5-phenyl-2-pyrimidinyl (**88**), 4-quinolinyl (**91**), and 4-phenyl-2-oxazolyl (**95**) analogues were the most active compounds in this group, with ED_{40}'s in the range of 120–180 μmol/kg. These benzoxazolyl ring replacement analogues share the common structural feature of an aromatic ring fused or linked to a heterocyclic moiety. The heterocyclic ring generally contains a nitrogen at position 2 (or 4) with respect to and in conjugation with the hydrazino group, a feature that may influence the electron density at nitrogen 1′ and, possibly, the biological potency of the molecule.

In addition to testing analogues **1–94** in the dermal RPAR, the inhibitory activity of these compounds was also evaluated by using the pleural RPAR. This latter assay has the advantage that the inhibitory effects of compounds on both neutrophil accumulation and edema formation can be assessed. Compounds that inhibited the dermal RPAR were also found to inhibit the pleural RPAR; however, they were generally less potent against the pleural reaction. The activities of selected analogues (**1**, **2**, **4**, **7**) in the pleural RPAR are shown in Table VII along with the effects of reference agents hydrocortisone and indomethacin. The test compounds were effective inhibitors of both exudate volume and inflammatory cell accumulation and, thus, were similar but less potent than hydrocortisone. In contrast, indomethacin was inactive in this model, even at very high doses. The inhibitory activity of 1 is not the result of the compound stimulating the release of endogenous steroids because 1 produced significant inhibition of the pleural RPAR in bilaterally adrenalectomized animals (data not shown). In the conventional pleural carrageenin test compound 1 inhibited both exudate volume and cell accumulation. Hydrocortisone also affected both parameters, while indomethacin had an effect on exudate volume only (Table VIII). The abilities of analogues **1**, **2**, **4**, and **7** to inhibit inflammatory cell accumulation is of particular interest, since these cells are believed to be responsible for the tissue damage observed in immune complex diseases. By modulating the numbers of inflammatory white blood cells (neutrophils) that reach the sites of immune complex deposition, these inhibitors of immune complex induced inflammation have the potential to interrupt the joint and tissue destruction associated with RA.

Conclusions

A series of 3-[1-(2-benzoxazolyl)hydrazino]propanenitrile derivatives has been synthesized, and their inhibitory activities have been evaluated by using the dermal and pleural RPAR. Structure–activity studies have indicated that the hydrazino moiety is important for activity and that substitution of the benzoxazolyl ring at position 5 with small groups, such as trifluoromethyl, increases potency. Chemical modification of other regions either decreased or had only a modest effect on activity. This novel series of compounds exhibits an exciting profile of activity that resembles hydrocortisone but which differs from that of indomethacin and other NSAID. The ability of these compounds to inhibit the accumulation of inflammatory cells, which are thought to be responsible for producing the tissue injury associated with immune-complex diseases such as RA, suggests that these compounds have the potential to arrest the destructive processes at work in these debilitating and disabling diseases.

Experimental Section

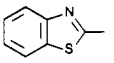
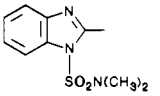
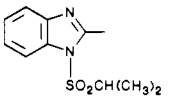
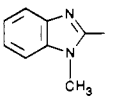
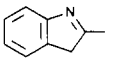
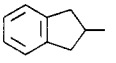
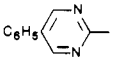
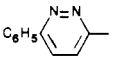
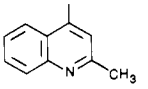
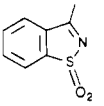
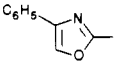
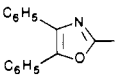
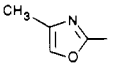
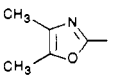
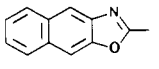
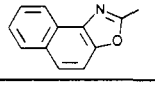
All melting points were taken on a Thomas-Hoover apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 521 spectrophotometer, ^1H NMR spectra on a QE-300 (General Electric) spectrometer. All new compounds had NMR and IR consistent with their assigned structures and also satisfactory C, H, and N analyses in the range of ±0.5% from the calculated values. All the organic phases were dried over anhydrous Na_2SO_4.

General Synthetic Methods for the Preparation of 3-[1-(2-Benzoxazolyl)hydrazino]propanenitrile Derivatives Described in Table I. A. A mixture of *o*-aminophenol (87 mmol) and potassium ethyl xanthate (87 mmol) in ethanol (150 mL) was heated under reflux overnight. The solvent was removed in vacuo, and the residue was dissolved in water. The solution was acidified to pH 5 with glacial acetic acid. The 2-mercaptobenzoxazole product was filtered and crystallized.

A suspension of 2-mercaptobenzoxazole (100 mmol) in dry benzene (150 mL) was stirred at room temperature while being treated portionwise with phosphorus pentachloride (120 mmol). After the addition was completed the mixture was heated under reflux for 2 h and then concentrated in vacuo. The 2-chlorobenzoxazole residue was purified either by crystallization or by distillation. A solution of 2-chlorobenzoxazole (70 mmol) in dioxane (50 mL) was added dropwise and with stirring to hy-

Table VI. The Activities of 3-[1-(2-Benzoxayolyl)hydrazino]propanenitrile Analogues, Modified at the Benzoxazole Site, in the Dermal Reverse Passive Arthus Reaction

$RN(NH_2)CH_2CH_2CN$

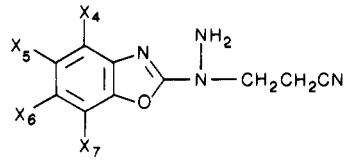
compd	R	yield, %	formula	mp, °C	ED_{40},[a] μmol/kg po
82		28	$C_{10}H_{10}N_4S$	114–115	128 (55, 225)
83		56	$C_{12}H_{16}N_6O_2$	164–165	inactive[b]
84		17	$C_{13}H_{17}N_5O_2S$	160–162	inactive[b]
85		70	$C_{11}H_{13}N_5$	118–119	349 (274, 474)
86		47	$C_{11}H_{12}N_4$	120–122	265 (185, 455)
87		59	$C_{12}H_{15}N_3$	110–111	565 (314–2413)
88		50	$C_{13}H_{13}N_5$	111–115	121 (100, 138)
89		38	$C_7H_9N_5$	135–137	760 (36, 1779)
90		32	$C_{13}H_{13}N_5$	107–108	672[c]
91		49	$C_{13}H_{14}N_4$	118–120	177 (137, 239)
92		29	$C_{10}H_{10}N_4O_2S$	228–229	643[c]
93		74	$C_6H_9ClN_4O$	160–162	360 (270, 561)
94		33	$C_6H_9ClN_4S$	158–160	390 (298, 576)
95		51	$C_{12}H_{13}ClN_4O$	170–172	119 (75, 174)
96		56	$C_{18}H_{17}ClN_4O$	168–170	332 (156, 761)
97		35	$C_7H_{11}ClN_4O$	155–157	705[c]
98		50	$C_8H_{13}ClN_4O$	162–164	519[c]
99		61	$C_{14}H_{12}N_4O$	197–199	306 (242, 409)
100		40	$C_{14}H_{12}N_4O$	115–118	346 (195, 1498)

[a] The dose estimated to produce 40% inhibition (ED_{40}) with 95% confidence limits shown in parentheses, calculated by least-squares regression analysis. [b] Compounds that did not produce statistically significant activity ($p > 0.05$) are listed as inactive. [c] Estimated ED_{40} extrapolated from the regression analysis of the prototype compound 1 for compounds producing significant inhibition of less than 40%.

drazine hydrate (400 mmol) cooled at 5 °C. The addition was made at such a rate that the internal temperature did not rise above 10 °C. After the addition was completed, the reaction mixture was stirred at room temperature for 30 min and then diluted with cold water (100 mL). The 2-hydrazinobenzoxazole product was collected, washed with water, dried, and recrystallized.

To a suspension of 2-hydrazinobenzoxazole (370 mmol) in THF (800 mL) was added acrylonitrile (796 mmol) at room temperature and with stirring. A solution of 2 N sodium hydroxide (5 mL) was added dropwise at 30 °C. The temperature was raised to 60 °C, and stirring was continued for 15 min. The heating bath was removed, and the reaction mixture was stirred for additional 15

Table VII. The Activities of Selected 3-[1-(2-Benzoxazolyl)hydrazino]propanenitrile Derivatives in the Rat Pleural Reverse Passive Arthus Reaction



compd	X_4	X_5	X_6	X_7	ED_{50},[a] μmol/kg po exudate volume	ED_{50},[a] μmol/kg po exudate WBC[b]
1	H	H	H	H	238 (183, 362)	243 (192, 330)
2	H	CH_3	H	H	148 (69, 208)	175 (125, 222)
4	H	OCH_3	H	H	155 (112, 211)	116 (69, 168)
7	H	CF_3	H	H	70 (22, 107)	92 (44, 144)
hydrocortisone					38 (33, 44)	50 (44, 58)
indomethacin					inactive[c]	inactive[c]

[a] The dose estimated to produce 50% inhibition (ED_{50}) with 95% confidence limits shown in parentheses, calculated by least-squares regression analysis. [b] WBC = white blood cells. [c] Indomethacin produced no significant inhibition at the highest dose (56 μmol/kg) tested.

Table VIII. Effect of 3-[1-(2-Benzoxazolyl)hydrazino]propanenitrile and Standard Agents in the Rat Pleural Carrageenin Test

compd	ED_{50},[a] μmol/kg po exudate volume	ED_{50},[a] μmol/kg po exudate WBC[b]
1	105 (80, 145)	171 (126, 278)
hydrocortisone	12 (8, 19)	9 (7, 11)
indomethacin	1.1 (0.7, 1.6)	NA

[a] The dose estimated to produce 50% inhibition (ED_{50}) with 95% confidence limits shown in parentheses, calculated by least-squares regression analysis. NA = nonactive; indomethacin produced no significant effect at 28 μmol/kg. [b] WBC = white blood cells.

min at ambient temperature. Water (1500 mL) was added, and the mixture was cooled to 5 °C. The precipitate was filtered, washed with water, dried, and crystallized to give the desired product.

B. To acrylonitrile (200 mmol) cooled at 0 °C and rapidly stirred was added dropwise hydrazine hydrate (200 mmol). After the addition was completed the solution was heated in an oil bath to an internal temperature of 50 °C for 45 min. The reaction mixture was then cooled at 0 °C and diluted with dioxane (30 mL). A solution of 2-chlorobenzoxazole (50 mmol) in dioxane (30 mL) was added dropwise. The mixture was filtered and concentrated in vacuo. The residue was washed with water, dried, and crystallized to give the desired product.

C. 2-Hydrazinobenzoxazole (500 mmol) was dissolved in THF (500 mL) at 40 °C. To the solution was added dropwise acrylonitrile (600 mmol) followed by 10 drops of 50% choline–methanol solution. Stirring was continued for 15 min, and the reaction mixture was heated at 65 °C for 5 h and then concentrated in vacuo. The residue was washed several times with water, dried, and crystallized to give the desired product.

General Synthetic Method for the Preparation of 3-[1-(2-Benzoxazolyl)hydrazino]propanenitrile Analogues, Modified at the Nitrile Site. D. The compounds described in Table II were prepared by reacting hydrazino derivatives with general structure ($H_2NHNCH_2CH_2Y$) with 2-chlorobenzoxazole in dioxane and in the presence of triethylamine by using a procedure similar to method B described above for 3-hydrazinopropanenitrile. The hydrazines $H_2NNHCH_2CH_2Y$, wherein Y is OCH_3, OC_6H_5, $N(Et)_2$, OCH_2CH_3, OC_6H_4-4-F, SC_6H_5, SCH_3, and morpholinyl, were prepared upon heating under reflux the corresponding bromides $BrCH_2CH_2Y$ with excess of hydrazine hydrate in ethanol overnight. The products were purified by distillation. Sulfoxide **42** and sulfones **40** and **45** were prepared from the corresponding mercaptans 44 and **49** upon treatment with *m*-chloroperbenzoic acid as described for **15**.

General Synthetic Method for the Preparation of 3-[1-(2-Benzoxazolyl)-2-formylhydrazino]propanenitrile (60) and Derivatives Described in Table III. E. A mixture of compound 1 (or its analogue) (10.1 g, 50 mmol) and 97% formic acid (10 mL) in benzene (190 mL) was heated under reflux overnight with use of a water separator. The solvent and excess of reagent were removed in vacuo. The residue was washed with water. The formed solid was crystallized from ethyl acetate–petroleum ether to give compound **60** (5.66 g).

3-[1-[6-(Methylthio)-2-benzoxazolyl]hydrazino]propanenitrile Sulfoxide (16) and 3-[1-[6-(Methylthio)-2-benzoxazolyl]hydrazino]propanenitrile Sulfone (15). Sulfoxide **16** was obtained upon oxidation of **6** with 1 equiv of *m*-chloroperbenzoic acid in methylene chloride at 0 °C for 15 min. By use of the same conditions and 2 equiv of the oxidizing agent, sulfone **15** was obtained.

4-[1-(2-Benzoxazolyl)hydrazino]-1-butyne (33). To a solution of hydrazine (0.3 g, 10 mmol) in dioxane (50 mL) stirred and cooled at 10 °C was added dropwise 4-bromo-1-butyne (1.33 g, 10 mmol). After completion of the addition the reaction was stirred at room temperature for 20 min. Water was added, and the solution was extracted with chloroform. The extracts were dried and concentrated in vacuo, and the residue was purified by silica gel column chromatography (1:1 ether–hexane) to give 4-hydrazino-1-butyne (1.14 g). This was reacted with 2-chlorobenzoxazole by using method **B** to give **33**.

Methyl 3-[1-(2-Benzoxazolyl)hydrazino]propanoate Hydrochloride (34). A mixture of 2-hydrazinobenzoxazole (4.48 g, 30 mmol) and methyl acrylate (3.44 g, 40 mmol) in THF (30 mL) was heated under reflux in the presence of 4 drops of 50% choline methanol overnight. The solvent and excess reagent were removed in vacuo. The residue was treated with ethanolic hydrogen chloride solution. Upon addition of ether an oil separated. The ether was decanted, and the oil was crystallized from 2-propanol to give compound **34** (3.24 g).

1-(2-Benzoxazolyl)pyrazolidin-3-one (101) and 3-[1-(2-Benzoxazolyl)hydrazino]propionic Acid Hydrochloride (35). To a solution of potassium hydroxide (2.06 g, 36.8 mmol) in absolute ethanol (45 mL) was added compound **34** (4.0 g, 14.7 mmol). The suspension was heated under reflux with stirring for 2 h. The solution was cooled to room temperature and treated with ethanolic hydrogen chloride to pH 6. The inorganic solid was filtered, and the filtrate was concentrated in vacuo. The residue was crystallized from ethanol to give 1-(2-benzoxazolyl)-3-pyrazolidinone (**101**) (1.05 g), $C_{10}H_9N_3O_2$: mp 190–191 °C; ^1H NMR (DMSO-*d*) δ 11.66 (br s, 1 H, exchangeable), 7.8–7.0 (m, 4 H, aromatic), 4.30 (t, 2 H, 8 Hz), 2.70 (t, 2 H, 8 Hz); IR (KBr), ν_{max} (cm^{-1}) 3600–3400 (m), 3100 (m), 1720 (s), 1660 (s), 1640 (s). Upon standing compound **35** (0.66 g) crystallized from the mother liquor.

3-[1-(2-Benzoxazolyl)hydrazino]propionamide Hydrochloride (36). To a stirred mixture of 1 (2.02 g, 10 mmol) and borane tribromide (0.25 g, 1 mmol) in THF (50 mL) was added water (0.070 g, 3 mmol). The mixture was stirred at room temperature for 1 h. Boronic acid crystals precipitated first and were filtered. Afterward the product precipitated. This was filtered and chromatographed over a silica gel column, eluting with methylene chlonide. The product was treated with ethanolic hydrochloric acid and precipitated as the hydrochloride upon addition of ether to give **36** (1.8 g).

3-[1-(2-Benzoxazolyl)-2-acetylhydrazino]propanenitrile (57). A mixture of compound 1 (4.57 g, 22 mmol) and anhydrous sodium acetate (2.05 g, 25 mmol) in acetic anhydride (45 mL) was stirred at room temperature for 1 h. The excess reagent was removed in vacuo, and the residue was treated with water and cooled with ice for 30 min. The white solid was collected and crystallized from hot water to give the acetamido derivative **57** (4.48 g).

3-[1-(2-Benzoxazolyl)-2-methylhydrazino]propanenitrile (58), 3-[1-(2-Benzoxazolyl)-2-ethylhydrazino]propanenitrile (59), and Intermediates 71 and 64. A mixture of compound 1 (4.04 g, 20 mmol) and 37% formalin (20 mL) in benzene (50 mL) was stirred at room temperature for 1 h. During this period the mixture went from a suspension to a nearly clear two-phase system and then to the appearance of another solid phase. The solid was collected, washed with water, dried, and crystallized from ethanol to give compound **71** (3.09 g).

A solution of compound **71** (21.4 g, 100 mmol) in dioxane (500 mL) and ethanol (500 mL) was cooled to 2 °C and treated with glacial acetic acid (9 mL). Sodium borohydride (37.8 g, 1 mol) was added, and the mixture was stirred in ice for 1.5 h and then at room temperature overnight. The reaction mixture was poured into 3% acetic acid (2000 mL) and extracted with methylene chloride three times. The extracts were washed with water, dried, and concentrated in vacuo. The residue was dissolved in benzene and insoluble material was filtered. The benzene filtrate was diluted with hexane to give compound **58** (2.8 g). Compounds **64** and **59** were prepared by using an analogous procedure to the one described above. The only difference was that the Schiff base **64** was obtained upon heating (with azeotropic removal of water) compound 1 with a threefold excess of acetaldehyde in benzene overnight.

Compounds 65, 70, and 67. To a stirred suspension of compound 1 (4 g, 20 mmol) in dry pyridine (50 mL) was added methyl isocyanate (2.0 g, 35 mmol). After 45 min all the solid went in solution. The reaction solution was stirred at room temperature overnight. Ether was added, and the solid was filtered, washed several times with additional ether, and dried to give compound **65** (5.0 g). Compound **70** was prepared by using the same synthetic method. Compound **67** was prepared by using a synthetic procedure similar to that used for **65**, the only difference being that the reaction was carried out at 75 °C for 48 h.

Compound 66. Compound 1 (6.0 g, 30 mmol) was dissolved in acetic acid (90 mL) and then diluted with water (60 mL). To the solution was added dropwise a solution of potassium cyanate (5.0 g, 62 mmol) in water (60 mL). The solution was stirred at room temperature overnight and then concentrated in vacuo. The residue was diluted with water (800 mL), and on cooling a mixture of the product and starting material crystallized. The solid mixture was treated with boiling benzene. The insoluble solid was filtered to give compound **66** (5.88 g).

3-[1-(2-Benzoxazolyl)-2-(methoxycarbonyl)hydrazino]-propanenitrile (68) and 3-[1-(2-Benzoxazolyl)-2-(methylsulfonyl)hydrazino]propanenitrile (69). To a solution of compound 1 (2.02 g, 10 mmol) in pyridine (40 mL) was added dropwise methyl chloroformate (1.223 g, 12.9 mmol). The reaction mixture was kept at 5 °C overnight and then poured into ice. The precipitate was filtered, washed with water, and dried. The solid was crystallized from benzene–hexane to give methyl carbamate **68** (1.06 g). A similar synthetic procedure, wherein methyl chloroformate was replaced by methanesulfonyl chloride, was used for **69**.

4-(2-Benzoxazolylamino)butanenitrile (72). To a mixture of nitromethane (1.22 g, 20 mmol) and sodium hydride (0.48 g, 20 mmol) in dry THF (20 mL) was added dropwise a solution of 2-chlorobenzoxazole (3.08 g, 20 mmol) in THF (20 mL) under nitrogen and at 0 °C. The reaction mixture was stirred for 2 h at 0 °C and for 1 h at room temperature. A cold saturated solution of ammonium chloride was added, and the mixture was extracted with methylene chloride. The extracts were dried and concentrated in vacuo. The residue was purified by silica gel column chromatography (1:1 pentane–ether) to give benzoxazolylnitromethane (2.4 g), mp 90–91 °C.

To a solution of diisopropylamine (1.6 g, 16 mmol) in THF (20 mL) was added, at −78 °C and under nitrogen, a solution of 2.6 M *n*-butyllithium in hexane (6 mL, 15.6 mmol). After 20 min the solution was cannulated over and added dropwise to a solution of benzoxazolylnitromethane (24 g, 15 mmol) in THF (80 mL) at −78 °C under nitrogen. After 30 min a solution of 1 M ethylene oxide in ether (15 mL) was added, and stirring was continued for 1 h at the same temperature. Then the reaction mixture was stirred at room temperature overnight. A cold saturated solution of ammonium chloride was added, and the mixture was diluted with water and extracted with methylene chloride. The extracts were dried and concentrated in vacuo. The residue was purified by silica gel column chromatography (2:3 hexane–ether) to afford 3-benzoxazolyl-3-nitropropanol (2.4 g).

3-Benzoxazolyl-3-nitropropanol (2.4 g, 12 mmol) in methanol (25 mL) was hydrogenated in the presence of Adams' catalyst (0.25 g) and under atmospheric pressure to give 3-benzoxazolyl-3-aminopropanol (2.3 g).

A solution of 3-benzoxazolyl-3-aminopropanol (2.3 g, 11.9 mmol) and benzaldehyde (1.4 g, 12 mmol) in benzene (100 mL) was heated under reflux in the presence of *p*-toluenesulfonic acid (0.05 g) for 5 h with use of a water separator. The solution was cooled at room temperature, washed with water, dried, and concentrated in vacuo. The residue was crystallized from hexane–ether to give 3-benzoxazolyl-3-(benzylideneamino)propanol (2.9 g), mp 164–165 °C.

A solution of phosphorus tribromide (0.9 g, 3.3 mmol) in methylene chloride (10 mL) was added dropwise to a solution of 3-benzoxazolyl-3-(benzylideneamino)propanol (2.8 g, 10 mmol) in methylene chloride (100 mL) at 0 °C and under nitrogen. The reaction mixture was heated under reflux for 4 h and then cooled to room temperature, washed with water, dried, and concentrated in vacuo. The crude 3-benzoxazolyl-3-(benzylideneamino)-1-bromopropane (3.9 g) was dissolved in DMF (50 mL) and treated with a solution of potassium cyanide (2.4 g, 40 mmol) in DMF (10 mL). The reaction mixture was stirred at room temperature for 1 h, heated at 40 °C for 5 h, cooled to ambient temperature, poured into water, and extracted with methylene chloride. The combined extracts were dried and concentrated in vacuo. The residue was purified by silica gel column chromatography (1:1 hexane–ether) and crystallized from ethanol–ether to give 4-(2-benzoxazolyl)-4-(benzylideneamino)butanenitrile (1.85 g, 6.4 mmol).

A solution of 4-(2-benzoxazolyl)-4-(benzylideneamino)butanenitrile (1.45 g, 50 mmol) and hydrazine hydrate (1.25 g 250 mmol) in ethanol (120 mL) was stirred at room temperature for 2 h. The reaction mixture was poured into water (2000 mL) and extracted with methylene chloride. The extracts were dried and concentrated in vacuo. The residue was purified by silica gel column chromatography (1:1 hexane–ether) and crystallized from ethanol–hexane to give compound **72** (1.0 g), mp 128–129 °C.

3-(2-Benzoxazolylamino)propanenitrile (73). To a cold solution of sodium hydroxide (3.2 g, 40 mmol) in water (2.1 mL) and dioxane (50 mL) was added 3-aminopropionitrile fumarate (5.12 g, 40 mmol) at 12 °C. The solution was stirred for 15 min. A solution of 2-chlorobenzoxazole (3.07 g, 20 mmol) in dioxane (10 mL) was introduced dropwise over a period of 30 min. The reaction mixture was stirred at room temperature overnight and then heated under reflux for 2 h. The mixture was poured into water. After 30 min the solution began to deposit a crystalline product. This was filtered and dried to give compound **73** (2.27 g).

3-[2-Benzoxazolyl(methoxycarbonyl)amino]propanenitrile (74). A solution of compound **73** (3.74 g, 20 mmol), methyl chloroformate (4.72 g, 50 mmol), and triethylamine (2.252 g, 25 mmol) in methylene chloride (50 mL) was heated under reflux overnight. The reaction mixture was cooled to room temperature and then extracted with 2 N hydrochloric acid. The organic phase was dried and concentrated in vacuo. The residue was crystallized from benzene–hexane to give **74** (1.64 g).

3-(2-Benzoxazolylacetylamino)propanenitrile (75). A mixture of compound **73** (3.74 g, 20 mmol), sodium acetate (3.4 g, 25 mmol), and acetic anhydride (50 mL) was stirred at room temperature overnight. The excess reagent was removed in vacuo, and the residue was washed with cold water, dried, and crystallized from benzene–petroleum ether to give compound **75** (3.48 g).

3-(2-Benzoxazolylformylamino)propanenitrile (76). Anhydrous formic acid (2.1 g, 45 mmol) was added dropwise to a cold solution of acetic anhydride. The mixture was heated at 55

°C for 15 min and then cooled to 5 °C. Compound **73** (3.74 g, 20 mmol) was added portionwise over a period of 10 min. The reaction mixture was stirred at room temperature overnight and then diluted with ether. The crystalline product was filtered, dried, and crystallized from benzene to give **76** (3.45 g).

3-(2-Benzoxazolylthio)propanenitrile (77). To a mixture of 2-mercaptobenzoxazole (15.1 g, 100 mmol) and anhydrous potassium carbonate (13.8 g, 100 mmol) in dry DMF (250 mL) was added dropwise a solution of 3-bromopropionitrile (17.4 g, 130 mmol) in DMF (100 mL). The mixture was stirred at room temperature for 48 h, filtered, and concentrated in vacuo at 75 °C. The residue was dissolved in methylene chloride. Insoluble solid was filtered, and the filtrate was washed with 10% sodium hydroxide solution and twice with water. The organic phase was dried and concentrated in vacuo. The solid residue was crystallized from petroleum ether to give **77** (9.58 g).

1-(2-Benzoxazolyl)-1-(2-cyanoacetyl)hydrazine (80). To a mixture of 2-hydrazinobenzoxazole (6.0 g, 40.2 mmol) and cyanoacetic acid (3.42 g, 40.2 mmol) in methylene chloride (90 mL) was added a solution of dicyclohexylcarbodiimide (9.26 g, 44.9 mmol) in methylene chloride (90 mL) over a period of 30 min. The reaction mixture was stirred at room temperature for 17 h and then concentrated in vacuo. The residue was subjected to column chromatography (silica gel, methylene chloride–ethanol–ammonium hydroxide (20:3:3.1 v/v)) to give **80** (5.7 g).

3-[1-(2-Benzoxazolyl)hydrazino]-2,2-dideuteriopropanenitrile (81). A 10% solution of lithium diisopropylamide in hexane (8.0 mL) was diluted with THF (50 mL), and deuterium oxide (20 mL) was added at −60 °C. To the mixture, compound **71** (4.28 g, 20 mmol) in THF (160 mL) was added dropwise over a period of 40 min. The reaction mixture was stirred at the same temperature for 1 h and then at room temperature for 4 h. The solution was acidified to pH 6 with glacial acetic acid and then concentrated in vacuo. The residue was dissolved in warm THF (70 mL), petroleum ether was added, and the solution was cooled with ice. The precipitate was filtered and dried to give the dideuterio compound **71** (1.63 g).

To a suspension of compound **71** (1.45 g, 6.7 mmol) in ethanol (30 mL) was added dropwise at room temperature hydrazine hydrate (1.5 mL, 30 mmol). A solution was obtained within 10 min, followed by the separation of a precipitate within another 5 min. A solution of glacial acetic acid (3.6 mL, 60 mmol) in water (10 mL) was added. Upon cooling the reaction mixture, a solid separated. This was filtered, dried, and crystallized from boiling ethanol to give compound **81** (0.713 g).

3-[1-(2-Benzthiazolyl)hydrazino]propanenitrile (82) and 3-[1-(2-methyl-4-quinolyl)hydrazino]propanenitrile (91) were prepared from 2-hydrazinobenzthiazole and 2-methyl-4-hydrazinoquinoline by using a synthetic procedure similar to method A described above.

3-[1-[1-(Dimethylsulfamoyl)-2-benzimidazolyl]hydrazino]propanenitrile (83). To a stirred mixture of 2-aminobenzimidazole (13.3 g, 100 mmol) and triethylamine (10.1 g, 100 mmol) in chloroform (300 mL) was added dimethylsulfamoyl chloride (14.3 g, 100 mmol) at room temperature. The reaction mixture was heated under reflux for 1 h and then cooled to ambient temperature, washed with water, dried, and concentrated in vacuo. The residue was crystallized from benzene to give 1-(dimethylsulfamoyl)-2-aminobenzimidazole (20.4 g), mp 185–186 °C. To a stirred suspension of 1-(dimethylsulfamoyl)-2-aminobenzimidazole (2.4 g, 10 mmol) in 50% hydrochloric acid (16 mL) and water (16 mL) was added at 0 °C a solution of sodium nitrite (0.7 g, 10 mmol) in water (4 mL). The resulting solution was added dropwise to stannous chloride (4.75 g, 25 mmol) in concentrated hydrochloric acid (10 mL) at 0 °C. Stirring was continued for 30 min. The reaction mixture was basified to pH 9 with sodium hydroxide pellets and extracted with methylene chloride. The extracts were washed with water, dried, and concentrated in vacuo to give 1-(dimethylsulfamoyl)-2-hydrazinobenzimidazole (2.1 g). This was reacted with acrylonitrile by using method A to afford compound **83**.

3-[1-[1-(Isopropylsulfonyl)-2-benzimidazolyl]hydrazino]propanenitrile (84). Compound **84** was obtained by using a synthetic method similar to that described above for **83**, wherein isopropylsulfonyl chloride was used instead of dimethylsulfamoyl chloride.

3-[1-(1-Methyl-2-benzimidazolyl)hydrazino]propanenitrile (85). A solution of sodium nitrite (0.69 g, 10 mmol) in water (5 mL) was added dropwise to a suspension of 1-methyl-2-aminobenzimidazole (1.23 g, 10 mmol) in 25% hydrochloric acid (32 mL) at −10 °C. The cold diazonium salt solution was added dropwise to a solution of stannous chloride (4.5 g, 20 mmol) in 12 N hydrochloric acid (10 mL) at −10 °C. The reaction mixture was stirred for 1 h, neutralized with sodium hydroxide, and extracted with methylene chloride. The organic extracts were dried and concentrated in vacuo. The residue was crystallized from ethanol–pentane to give 1-methyl-2-hydrazinobenzimidazole (1.1 g). This was reacted with acrylonitrile by using method A to afford compound **85**.

3-[1-(2-Indolenyl)hydrazino]propanenitrile (86). A mixture of oxindole (1.33 g, 10 mmol), phosphorus oxychloride (4.5 g, 30 mmol), and triethylamine (1.01 g, 10 mmol) was heated under reflux for 4 h. The excess reagent was removed in vacuo. The residue was dissolved in dioxane (50 mL) and added dropwise to hydrazine hydrate (2.5 g, 50 mmol) in dioxane (50 mL). The reaction mixture was heated under reflux for 10 h and concentrated in vacuo. The residue was crystallized from ether–ethanol to give 2-hydrazinoindolenine (1.68 g), mp 165–167 °C. This was reacted with acrylonitrile by using method A to afford **86**.

3-[1-(2-Indanyl)hydrazino]propanenitrile (87) was obtained from 2-aminoindan by using a synthetic method analogous to that described above for **85**.

3-[1-(5-Phenyl-2-pyrimidinyl)hydrazino]propanenitrile (88). 2-Hydrazino-5-phenylpyrimidine[7] was reacted with acrylonitrile by using method A.

3-[1-(2-Pyrazinyl)hydrazino]propanenitrile (89). A mixture of 2-chloropyrazine (23 g, 200 mmol) and anhydrous hydrazine (32 mL) in absolute ethanol (100 mL) was refluxed for 4 h. The solvent and excess reagent were removed in vacuo. The residue was washed with cold ethanol and dried to give 2-hydrazinopyrazine (14.68 g). This was reacted with acrylonitrile by using method A to give **89**.

3-[1-(3-Phenyl-6-pyridazinyl)hydrazino]propanenitrile (90). 2-Hydrazinopyridazine was reacted with acrylonitrile according to method A to give **90**.

3-[1-(2,3-Dihydro-3-benzisosulfonazolyl)hydrazino]propanenitrile (92). A mixture of 1,2-benzisothiazolin-3-one 1,1-dioxide (18.3 g, 100 mmol) and phosphorus oxychloride (100 mL) was heated under reflux for 48 h and then concentrated in vacuo. The residue was washed with ether and dried to give crude 2,3-dihydro-1,2-benzisothiazole chloride (15.9 g).

To hydrazine hydrate (15.0 g, 300 mmol) stirred and cooled to 0 °C was added dropwise acrylonitrile (15.9 g, 300 mmol). The resulting product was dissolved in dioxane (100 mL) and treated with 2,3-dihydro-3-benzisosulfonazolyl chloride (14.1 g, 70 mmol) in dioxane (100 mL). After the mixture was allowed to stand overnight at room temperature, a solid precipitated. This was filtered, washed with water, dried, and crystallized from DMF to give compound **92** (5.04 g).

3-[1-(2-Oxazolyl)hydrazino]propanenitrile (93). 2-Chlorooxazole (1.3 g, 10 mmol) was added dropwise to a solution of hydrazine hydrate (5 g, 100 mmol). The reaction mixture was heated under reflux for 12 h. The solvent and excess reagent were removed in vacuo to give 2-hydrazinooxazole (0.792 g). This was reacted with acrylonitrile by using method A.

3-[1-(2-Thiazolyl)hydrazino]propanenitrile (95) was prepared from 2-aminothiazole by using a synthetic method analogous to that described above for **85**.

3-[1-(5-Phenyl-2-oxazolyl)hydrazino]propanenitrile (95), 3-[1-(4,5-Dimethyl-2-oxazolyl)hydrazino]propanenitrile (98), and 3-[1-(5-Methyl-2-oxazolyl)hydrazino]propanenitrile (97). A mixture of 1-bromoacetophenone (19.9 g, 100 mmol), semicarbazide (10.7 g, 100 mmol), and 10 N hydrochloric acid (1 mL) in ethanol (300 mL) was heated under reflux for 30 h. The solvent was removed in vacuo. The residue was crystallized from ether–ethanol to give 4-phenyl-2-hydrazinooxazole hydrochloride. This salt was suspended in 10% ammonium chloride solution, stirred, filtered, and dried to give 4-phenyl-2-hydrazinooxazole

(7) Coppola, G. M.; Hartmann, G. E.; Huegi, B. S. *J. Heterocycl. Chem.* **1980**, *17*, 1479.

(1.85 g), mp 158–160 °C. This compound was reacted with acrylonitrile according to method A to give **95**.

Compounds **98** and **97** were prepared from 4-bromo-2-butanone and 1-bromo-2-propanone, respectively, by using a synthetic method analogous to that used for **95**.

3-[1-(4,5-Diphenyl-2-oxazolyl)hydrazino]propanenitrile (96) was prepared from 4,5-diphenyl-4-oxazolin-2-one by using a synthetic method analogous to that used for **86**.

3-[1-(2,3-Naphthoxazol-2-yl)hydrazino]propanenitrile (99) and 3-[1-(1,2-naphthoxazol-2-yl)hydrazino]propanenitrile (100) were prepared from 3-amino-2-naphthol and 1-amino-2-naphthol by using a synthetic procedure analogous to method A.

1-(6-Chloro-2-benzoxazolyl)-3-aminopyrazol-2-ene (103). To compound **8** (3.0 g, 12.7 mmol) suspended in ethanol (10 mL) was added an ethanolic hydrochloric acid solution (10 mL). The mixture was heated under reflux for 30 min and then cooled to room temperature. The crystalline solid was filtered, suspended in sodium bicarbonate solution, stirred for 30 min at room temperature, filtered again, washed with water, and dried to give **103** (1.98 g): mp 252–253 °C; ^{1}H NMR (DMSO-*d*) δ 7.35 (d, 1 H, 9 Hz), 7.25 (d, 1 H, 3 Hz), 6.95 (dd, 1 H, 9 Hz and 3 Hz), 6.30 (br s, 2 H, exchangeable), 3.92 (t, 2 H, 9 Hz), 2.92 (t, 2 H, 9 Hz); IR (KBr) ν_{max} (cm^{-1}) 3480 (s), 3300 (m), 3150 (s), 1750 (s), 1680 (s), 1600 (s).

1-(2-Benzoxazolyl)-3-aminopyrazol-2-ene (102). To a suspension of 1*H*-3-aminopyrazol-2-ene hydrosulfate (2.68 g, 20 mmol) in benzene (50 mL) was added at room temperature with vigorous stirring 2-chlorobenzoxazole (3.07 g, 20 mmol) and tetrabutylammonium chloride (0.3 g, 1.08 mmol) followed by the dropwise addition of a 50% sodium hydroxide solution (2.6 mL). The mixture was stirred at room temperature for 1 h. The solid was filtered and dissolved in warm water. Upon addition of sodium bicarbonate to pH 8, compound **102** (2.54 g) precipitated: mp 268–271 °C; ^{1}H NMR (DMSO-*d*) δ 7.35 (d, 1 H, 7.5 Hz), 7.23 (d, 1 H, 7.5 Hz), 7.12 (t, 1 H, 7.5 Hz), 6.95 (t, 1 H, 7.5 Hz), 6.20 (br s, 2 H, exchangeable), 3.88 (t, 2 H, 9 Hz), 2.90 (t, 2 H, 9 Hz); IR (KBr) ν_{max} (cm^{-1}) 3460 (s), 3280 (m), 3270 (m), 3180 (m), 1680 (s), 1650 (s), 1580 (s).

Biological Testing Methods. Fasted, male rats were injected intravenously with bovine serum albumin (BSA) and challenged approximately 1 h later with an injection of rabbit anti-BSA either intradermally or intrapleurally. Compounds were administered orally (po) 30 min prior to the challenge. The rats were sacrificed 4 h later, and the dermal lesion size or the accumulation of exudate fluid and white blood cells, intrapleurally, were determined. A more detailed description of these methods can be found in previous publications.[8,9]

Registry No. 1, 93794-06-0; **2**, 93794-10-6; **3**, 93794-17-3; 4, 93794-08-2; **5**, 114997-06-7; **6**, 93794-12-8; **7**, 93794-18-4; 8, 93794-07-1; **9**, 93794-14-0; **10**, 93794-15-1; 11, 114997-07-8; **12**, 114997-08-9; **13**, 114997-09-0; 14, 114997-10-3; 14·HCl, 114997-11-4; **15**, 93794-34-4; **16**, 93794-33-3; **17**, 114997-12-5; **18**, 93794-22-0; **19**, 93794-20-8; **20**, 93794-19-5; **21**, 93794-09-3; **22**, 86691-35-2; **23**, 93794-13-9; **24**, 93794-21-9; **25**, 93794-16-2; **26**, 114997-13-6; **27**, 93794-25-3; **28**, 93794-26-4; **29**, 114997-14-7; **30**, 114997-15-8; **31**, 114997-16-9; **31**·HCl, 114997-17-0; **32**, 114997-18-1; **33**, 114997-19-2; **34**, 114997-20-5; **34**·HCl, 114997-21-6; **35**, 86691-33-0; **35**·HCl, 114997-22-7; **36**, 114997-23-8; **36**·HCl, 114997-24-9; **37**, 114997-25-0; **38**, 114997-26-1; **39**, 114997-27-2; **40**, 114997-28-3; 41, 114997-29-4; **42**, 114997-30-7; **43**, 15166-44-6; **44**, 114997-31-8; **45**, 114997-32-9; **46**, 114997-33-0; **47**, 114997-34-1; **48**, 114997-35-2; **49**, 114997-36-3; **50**, 114997-37-4; **51**, 114997-38-5; **51**·HCl, 114997-39-6; **52**, 114997-40-9; **52**·HCl, 114997-41-0; **53**, 114997-42-1; **54**, 114997-43-2; **55**, 114997-44-3; **56**, 114997-45-4; **56**·HCl, 114997-62-5; **57**, 114997-46-5; **58**, 114997-47-6; **59**, 114997-48-7; **60**, 114997-49-8; **61**, 114997-50-1; **62**, 114997-51-2; **63**, 114997-52-3; **64**, 114997-53-4; **65**, 114997-54-5; **66**, 114997-55-6; **67**, 114997-56-7; **68**, 114997-57-8; **69**, 114997-58-9; **70**, 114997-59-0; **71**, 114997-60-3; **71** (dideuterio compd), 114997-61-4; **72**, 115017-56-6; **73**, 74180-62-4; **74**, 114997-63-6; **75**, 114997-64-7; **76**, 114997-65-8; **77**, 25176-73-2; **78**, 86691-36-3; **79**, 86691-37-4; **80**, 114997-66-9; **81**, 114997-67-0; **82**, 86691-41-0; **83**, 114997-68-1; **84**, 114997-69-2; **85**, 114997-70-5; **86**, 114997-71-6; **87**, 114997-72-7; **88**, 114997-73-8; **89**, 114997-74-9; **90**, 114997-75-0; **91**, 114997-76-1; **92**, 114997-77-2; **93**, 95458-78-9; **93**·HCl, 95458-67-6; **94**, 95458-75-6; **94**·HCl, 95458-68-7; **95**, 95458-76-7; **95**·HCl, 95458-70-1; **96**, 95458-74-5; **96**·HCl, 95458-73-4; **97**, 114997-78-3; **97**·HCl, 95458-71-2; **98**, 95458-79-0; **98**·HCl, 95458-72-3; **99**, 114997-79-4; **100**, 114997-80-7; **101**, 114997-81-8; **102**, 114997-82-9; **103**, 114997-83-0; H_2NNHPr, 5039-61-2; H_2NNHEt, 624-80-6; $H_2NNH(CH_2)_2OH$, 109-84-2; $H_2NNH(CH_2)_2OMe$, 3044-15-3; $H_2NNH(CH_2)_3OH$, 40440-12-8; $H_2NNH(CH_2)_2OPh$, 3184-38-1; $H_2NNH(CH_2)_2Ph$, 51-71-8; $H_2NNH(CH_2)_2SPh$, 55459-98-8; *p*-$FC_6H_4O(CH_2)_2NHNH_2$, 114997-84-1; $H_2NNH(CH_2)_2SMe$, 114997-85-2; $H_2NNH(CH_2)_2NEt_2$, 924-29-8; $H_2NNH(CH_2)_2OEt$, 39556-67-7; $H_2N(CH_2)_2CN{\cdot}C_4H_4O_4$, 1119-28-4; *o*-aminophenol, 95-55-6; potassium ethyl xanthate, 140-89-6; 2-amino-4-methylphenol, 95-84-1; 2-amino-4-ethylphenol, 94109-11-2; 2-amino-4-methoxyphenol, 20734-76-3; 2-amino-4-(methylthio)phenol, 98547-24-1; 2-amino-4-(trifluoromethyl)phenol, 454-81-9; 2-amino-4-fluorophenol, 399-97-3; 2-amino-4-cyanophenol, 14543-43-2; ethyl 3-amino-4-hydroxybenzoate, 13052-92-1; 2-amino-4-phenylphenol, 1134-36-7; 2-amino-4-(benzyloxy)phenol, 102580-07-4; 2-amino-4-benzoylphenol, 42404-41-1; 2-amino-5-methylphenol, 2835-98-5; 2-amino-3-methylphenol, 2835-97-4; 2-amino-6-methylphenol, 17672-22-9; 2-amino-5-methoxyphenol, 40925-70-0; 2-amino-4-chloro-5-methylphenol, 53524-27-9; 2-amino-4-chloro-6-methylphenol, 80526-44-9; 2-amino-4,6-dimethylphenol, 41458-65-5; 2-amino-4,5-dimethylphenol, 6623-41-2; 2-amino-3,4,6-trimethylphenol, 93794-37-7; 2-amino-3,4,5-trimethylphenol, 114997-86-3; 2-amino-4,5-dimethoxyphenol, 7107-04-2; 2-chloro-5-phenoxybenzoxazole, 114997-87-4; 5-*tert*-butyl-2-hydrazinobenzoxazole, 114997-88-5; 5-chloro-2-hydrazinobenzoxazole, 64037-22-5; 7-chloro-2-hydrazinobenzoxazole, 114997-89-6; 5-*tert*-butyl-2-hydrazino-7-(methylthio)-benzoxazole, 114997-90-9; 2-chlorobenzoxazole, 615-18-9; 2-chloro-5-(trifluoromethyl)benzoxazole, 114997-91-0; 2-chloro-5-methoxybenzoxazole, 49559-34-4; 2-chloro-5-cyanobenzoxazole, 114997-92-1; 2,5-dichlorobenzoxazole, 3621-81-6; 2-chloro-5-methylbenzoxazole, 3770-60-3; 4-bromo-1-butyne, 38771-21-0; 2-hydrazinobenzoxazole, 15062-88-1; methyl acrylate, 96-33-3; *N*-(2-hydrazinoethyl)morpholine, 2154-24-7; 2-(2-hydrazinoethyl)pyridine, 2587-15-7; benzoxazolylnitromethane, 24998-80-9; 3-benzoxazalyl-3-nitropropanol, 115017-57-7; 3-benzoxazalyl-3-aminopropanol, 115017-58-8; 3-benzoxazalyl-3-(benzylideneamino)propanol, 115017-59-9; 4-(2-benzoxazolyl)-4-(benzylideneamino)butanenitrile, 115017-60-2; 2-mercaptobenzoxazole, 2382-96-9; 3-bromopropionitrile, 2417-90-5; 2-aminobenzimidazole, 934-32-7; 1-(dimethylsulfamoyl)-2-aminobenzimidazole, 43066-94-0; 1-(dimethylsulfamoyl)-2-hydrazinobenzimidazole, 114997-93-2; 1-methyl-2-aminobenzimidazole, 1622-57-7; oxindole, 59-48-3; 2-hydrazinoindolenine, 86691-39-6; 2-aminoindan, 2975-41-9; 2-hydrazino-5-phenylpyrimidine, 75175-43-8; 2-chloropyrazine, 14508-49-7; 2-hydrazinopyridazine, 114997-94-3; 1,2-benzisothiazolin-3-one 1,1-dioxide, 81-07-2; 2-chlorooxazole, 95458-77-8; 2-aminothiazole, 96-50-4; 1-bromoacetophenone, 70-11-1; 4-bromo-2-butanone, 28509-46-8; 1-bromo-2-propanone, 598-31-2; 4-phenyl-2-hydrazinooxazole, 95458-69-8; 4,5-diphenyl-4-oxazolin-2-one, 5014-83-5; 3-amino-2-naphthol, 5417-63-0; 1-amino-2-naphthol, 2834-92-6; 1*H*-3-aminopyrazol-2-ene hydrosulfate, 28793-69-3.

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