and the reaction was treated with 200 mL of $CHCl_3$. The organic layer was decanted and washed with 1% $NaHCO_3$ and H_2O. Removal of solvent yielded an oil, which was chromatographed on a Florisil column (200 g, acid-washed and impregnated with 10% boric acid, w/w) with cyclohexane–EtOAc, 3:1: yield 9 g (68%) of amorphous material; TLC R_f 0.41 (cyclohexane–EtOAc, 3:1); NMR ($CDCl_3$) δ 2.38 (s, 6 H, 2 × $NCCH_3$), 3.7 (s, 4 H, 2 × CH_2CO), 3.82 (s, 6 H, 2 × OCH_3), 4.15 (s, 4 H, 2 × CH_2O), 6.5–7.8 (m, 14 H, 4 × Ph); MS *m/e* 770 (M^+).

1,2,3-Tris[1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetyl]glyceride (16). Compound **2** (4.14 g, 0.011 mol) was added to a solution of **15** (7.69 g, 0.01 mol) and pyridine (0.87 g, 0.011 mol) in CH_2Cl_2 (200 mL). The reaction mixture was stirred for 4 days at room temperature. The insoluble material was filtered off and the organic layer washed with H_2O. Removal of the solvent yielded 1.7 g of solid (15%); mp 118–120 °C. This solid was chromatographed on a Florisil (200 g) column with cyclohexane–EtOAc (9:1 and then 8:2): TLC R_f 0.73 (cyclohexane–EtOAc, 1:1); mp 123–124 °C (after treatment with acetone); NMR ($CDCl_3$) δ 2.32 (s, 9 H, 3 × $NCCH_3$), 3.55 (s, 6 h, 3 × CH_2CO), 3.8 (s, 9 H, 3 × OCH_3), 4.2 (m, 4 H, 2 × CH_2O), 5.25 (d, 1 H, OCH), 6.5–7.8 (m, 21 H, 6 × Ph); MS *m/e* 1109 (M^+).

Method E (Scheme V). 1,3-Dialkanoyl-2-[1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetyl]glycerides (18). General Procedure. Synthesis of the compounds in Table II is exemplified by the preparation of 1,3-dipalmitoyl-2-[1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetyl]glyceride (**18f**).

1,3-Dipalmitoylglyceride (5.7 g, 0.010 mol) was dissolved in 50 mL of freshly distilled $CHCl_3$. Pyridine (0.95 g, 0.012 mol) and compound **2** (4.5 g, 0.011 mol) were added at once; the reaction mixture was stirred for 40 h at room temperature and treated with 100 mL of H_2O. The aqueous layer was decanted and extracted with 2 × 25 mL of $CHCl_3$. The $CHCl_3$ extracts were combined, washed with 1% HCl and H_2O, dried over $MgSO_4$, and evaporated to dryness. The solid obtained was purified by chromatography on a Florisil column (180 g). Compound **18f** was eluted with petroleum ether–ether (50:50): yield 5.2 g (68%); mp 65–66 °C (after one crystallization from petroleum ether); NMR ($CDCl_3$) δ 2.40 (s, 3 H, $NCCH_3$), 3.7 (s, 2 H, CH_2CO), 3.82 (s, 3 H, OCH_3), 4.20 (m, 4 H, 2 × CH_2O), 5.3 (m, 1 H, OCH), 6.6–7.6 (m, 7 H, 2 × Ph); MS *m/e* 908 (M^+).

1,3-Dilinoleoyl-2-[1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetyl]glyceride (19). Compound **19** was prepared by the general procedure described for compounds **18**, using linoleic acid instead of the saturated fatty acids in positions 1 and 3. A viscous oil was obtained in 65% yield: NMR ($CDCl_3$) δ 2.40 (s, 3 H, $NCCH_3$), 3.7 (s, 2 H, CH_2CO), 3.85 (s, 3 H, OCH_3), 4.25 (m, 4 H, 2 × CH_2O), 5.4 (m, 8 H, 4 × CH=CH), 6.5–7.8 (m, 7 H, 2 × Ph); MS *m/e* 955 (M^+).

Acknowledgment. We are indebted to Mr. G. Nettleship for ^1H NMR spectra. We also thank Dr. R. Egan and Ms. R. Stanaszek, and Dr. M. Levenberg and Ms. S. Mueller of Abbott Laboratories, North Chicago, for ^{13}C NMR and mass spectra, respectively, and to the staff of the Microanalytical Department of Abbott Laboratories for elemental analyses.

Basic Antiinflammatory Compounds. N,N′,N″-Trisubstituted Guanidines

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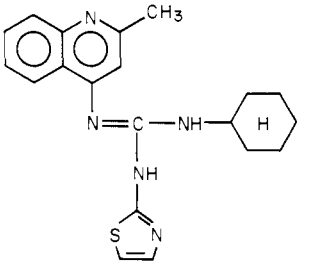
A variety of basic N,N′,N″-trisubstituted guanidines was prepared and tested for antiinflammatory activity. Compounds with a thiazolylguanidine moiety linked to the 4 position of the 2-methylquinoline ring exhibited fairly high antiinflammatory activity. Optimal activity was associated with the presence of *N*-cycloalkyl substituents on *N*″-4-(2-methylquinolyl)-*N*′-2-thiazolylguanidine. Pharmacological data on *N*-cyclohexyl-*N*″-4-(2-methylquinolyl)-*N*′-2-thiazolylguanidine (SR 1368, **44**) are presented and discussed.

The majority of clinically useful antiinflammatory agents are carboxylic acids, such as aroic, heteroaroic, arylalkanoic, and heteroarylalkanoic acids, and enolic acids. There are few examples of basic antiinflammatory compounds, among these, benzydamine[1,2] [1-benzyl-3-[3-(dimethylamino)propoxy]-1*H*-indazole]. Some amidine[3] and guanidine derivatives have been reported to exhibit antiinflammatory activity in animals, e.g., aminoguanidine[4] and trisubstituted[5] and tetrasubstituted[6] guanidines. During our investigations on biological activity of guanidine derivatives,[7] it was observed that certain thiazolyl-substituted guanidines containing other heteroaryl groups showed antiinflammatory activity. Variations in substituents around the guanidine moiety were made, and the results of pharmacological investigations eventually led to the selection of *N*-cyclohexyl-*N*″-4-(2-methylquinolyl)-*N*′-2-thiazolylguanidine (**44**, SR 1368) for further study.



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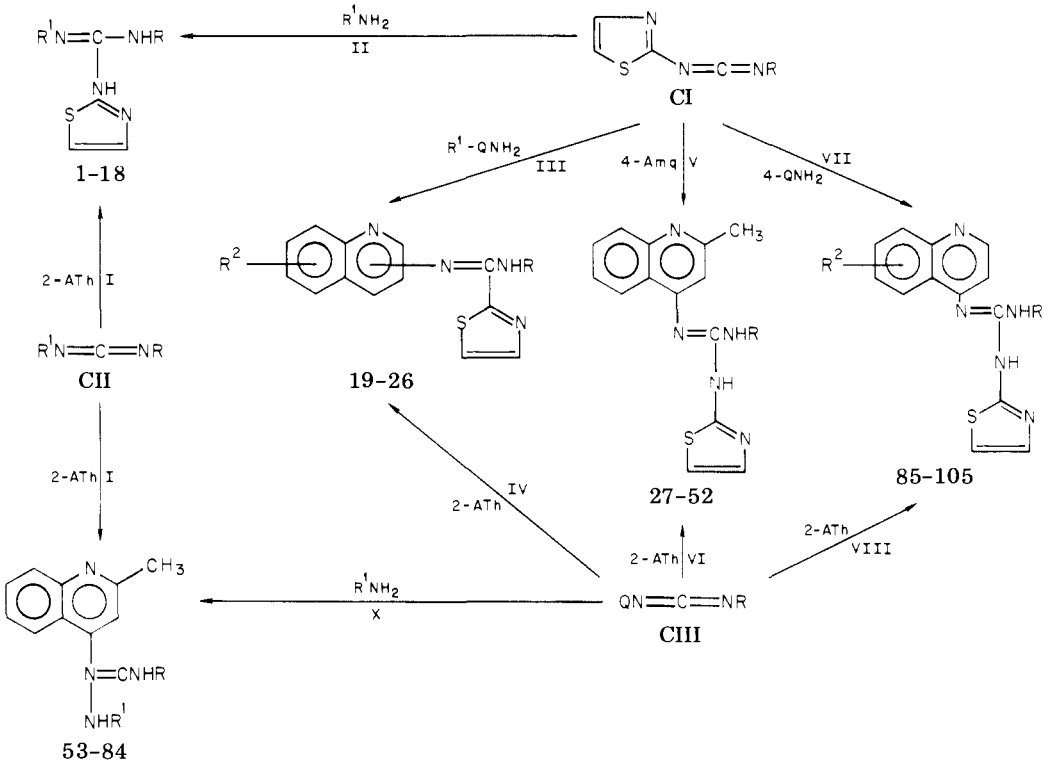
Scheme I. Synthetic Routes for the Preparation of N,N',N''-Trisubstituted Guanidines[a]



[a] For R, R^1, and R^2, see Tables I–V. 2-ATh = 2-aminothiazole; Q = quinolyl moiety; 4-Amq = 4-amino-2-methylquinoline. [b] In routes VI and X, Q = 4-(2-methylquinolyl).

Chemistry. The synthetic routes for the preparation of guanidine derivatives are illustrated in Scheme I. Methods for preparing N,N′,N″-trisubstituted guanidines are well known from the literature.[8] Ureas and thioureas, used as starting materials for the carbodiimides CI, CII, and CIII, were prepared by standard procedures[9] from the corresponding isocyanates, isothiocyanates, and dithiocarbamic acid esters[10] by reaction with appropriate primary amines. Data on these ureas and thioureas have previously been reported.[7,11] The ureas and thioureas were converted into the respective carbodiimides CI, CII, and CIII by the method of Appel,[12] which gave good yields of crude carbodiimides. These could be reacted without further purification with primary amines to afford the trisubstituted guanidines (Scheme I). The amines could be added to the carbodiimides in the absence of solvent (method A). Some reactions were exothermic; in other cases, the reaction mixture was treated further on a steam bath. Alternatively, the reaction was run in refluxing toluene (method B), or the reaction was performed in DMF at room temperature with the addition of 1 mol of sodium hydride (method C). All compounds in Tables I–V could be prepared by using two routes from two different carbodiimides and the requisite amines.

N,N′,N″-Trisubstituted guanidines are very strong bases, comparable in strength with inorganic hydroxides.[13] Most guanidines were isolated as free bases, but some of them were converted into mono- or dihydrochlorides and mono- or dinitrates (from EtOH–concentrated HNO_3 + Et_2O).

Pharmacology. Structure–Activity Discussion. Assessment of antiinflammatory activity depended upon inhibition of edema formation in the hind paw of the rat in response to subplantar injection of carrageenan and of prostaglandin biosynthesis by bovine seminal vesicles microsomes. The results are listed in Tables I–V.

Substantial inhibition of prostaglandin biosynthesis and moderate inhibition of carrageenan edema development was achieved when the thiazolylguanidino moiety was linked to the 4 position of the 2-methylquinoline ring (**16**, Table I). The attachment of the thiazolylguanidino moiety to other positions of the quinoline ring resulted in inactive compounds (Table II). The influence of different N substitutions in *N″*-4-(2-methylquinolyl)-*N′*-2-thiazolylguanidine was then examined (Table III). High activity in prostaglandin and carrageenan assays was found when R = $C(Me)_2Et$ (**32**), cyclopentyl (**42**), cyclohexyl (**44**), cyclooctyl (**49**), and phenyl (**51**). Among the cycloalkyl-substituted compounds, the highest activity was observed with unsubstituted cyclohexyl (**44**), smaller or larger rings resulting in less pronounced activity in one or both of the biological assays. The cycloalkyl-substituted compounds also displayed lower acute toxicity than the derivatives with lower alkyl side chains. Attempts were made to further enhance the antiinflammatory activity of **44** and to reduce the toxicity and to enhance the activity of **16** by substituting other groups, mainly heterocyclic rings, for thiazole (Table IV). Reduction of the toxicity was achieved in most of the cases, but no substantial improvement of the antiinflammatory activity was obtained. It is noteworthy that all the compounds endowed with marked antiedema activity have a sulfur-containing five-membered ring with or without nitrogen. Saturation of a double bond of the thiazole ring led to almost complete disappearance of the inhibitory effect on prostaglandin synthetase (**55** and

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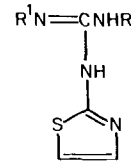
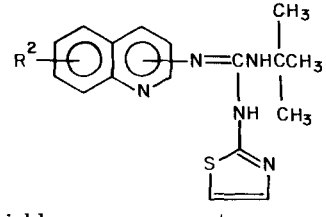
Table I. Chemical and Pharmacological Data on N,N''-Disubstituted *N'*-2-Thiazolylguanidines



no.	R	R^1	mp, °C	method and route	yield, %	recrystn solvent	formula	LD_{50} in mice, mg/kg, po	carrageenan edema:[b] inhibn, %	10^{-5} M PGS inhibn, %	score[c]
1	t-C_4H_9	H	138–140	B-II	47	H_2O	$C_8H_{14}N_4S$ maleate	600	54	29.0	2–1
2	t-C_4H_9	phenyl	140–142	A-II	58	H_2O	$C_{14}H_{18}N_4S$·HCl·0.5H_2O	>1000	24	6.4	1–0
3	t-C_4H_9	3-Cl-2-Me-Ph	106–108	A-II	78	EtOH–H_2O	$C_{15}H_{18}ClN_4S$	>1000	17	9.5	0–0
4	t-C_4H_9	1-naphthyl	129–131	A-II	37	EtOH–H_2O	$C_{18}H_{20}N_4S$	>1000	19[f]	6.9	0–0
5	t-C_4H_9	5-OH-napht-1-yl	190–192	B-II	16	EtOH–H_2O	$C_{18}H_{20}N_4OS$·HNO_3	>1000	22	nd[e]	0–[e]
6	t-C_4H_9	2-naphthyl	114–116	B-II	45	EtOH–H_2O	$C_{18}H_{20}N_4S$	>1000	17[f]	1.7	0–0
7	t-C_4H_9	2-thiazolyl	100–102	B-II	48	EtOH–H_2O	$C_{11}H_{15}N_5S_2$	>1000	49[a]	13.1	2–0
8	t-C_4H_9	2-pyridyl	166–168	A-II	54	EtOH–Et_2O	$C_{13}H_{17}N_5S$·HNO_3	>1000	83[a]	6.9	3–0
9	t-C_4H_9	5-Cl-pyrid-2-yl	92–94	A-II	44	EtOH	$C_{13}H_{16}ClN_5S$	>1000	31	1.0	2–0
10	t-C_5H_{11}	3-pyridyl[d]	87–88	C-I	53	DMF–H_2O	$C_{14}H_{19}N_5S$	>1000	82[a]	0	3–0
11	t-C_4H_9	2-Cl-pyrid-3-yl	121–123	A-II	38	EtOH	$C_{13}H_{16}ClN_5S$	>1000	19	10.1	0–0
12	t-C_4H_9	4-pyridyl	120–122	A-I	21	Et_2O	$C_{13}H_{17}N_5S$	300	15	nd[e]	0–[e]
13	$C(Me_2)CH_2$-$CHMe_2$	4-pyridyl	108–110	A-I	31	pet. ether	$C_{16}H_{23}N_5S$	800	22	1.1	1–0
14	t-C_4H_9	2-Me-pyrid-4-yl	155 dec	B-II	53	n-PrOH	$C_{14}H_{19}N_5S$·2HNO_3	250	13	14.9	0–0
15	t-C_5H_{11}	2-pyrimidyl	129–131	C-I	33	EtOH	$C_{13}H_{18}N_6S$	>1000	20	27.5	1–1
16	t-C_4H_9	4-(2-Me-quinolyl)	194–196	A-II	47	benzene	$C_{18}H_{21}N_5S$	200	34	100	1–3
17	t-C_4H_9	5-isoquinolyl	173–175	B-II	39	toluene + pet. ether	$C_{17}H_{19}N_5S$	>1000	21	8.8[g]	1–0
18	t-C_4H_9	1-isoquinolyl	92–94	B-II	51	EtOH–H_2O	$C_{17}H_{19}N_5S$	>1000	18	3.4	0–1

[a] Hypotensive. [b] Percent inhibition of carrageenan paw edema (3 h) in rats administered orally with a dose of each compound corresponding to one-tenth of the oral LD_{50} in mice. [c] Carrageenan edema inhibition percent: 0–19% = 0; 20–39% = 1; 40–59% = 2; ≥60% = 3. Prostaglandin synthetase inhibition percent, 10^{-5} M: 0–25% = 0; 26–50% = 1; 51–75% = 2; ≥76% = 3. [d] Compound 98, ref 7. [e] Not determined. [f] Percent enhancement of the edema. [g] Percent enhancement of PG synthesis.

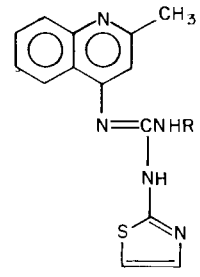
Table II. Chemical and Pharmacological Data on N''-Substituted Quinolyl-*N*-*tert*-butyl-*N'*-2-thiazolylguanidines



no.	Q[a]	R^2	mp, °C	method and route	yield, %	recrystn solvent	formula	LD_{50} in mice, mg/kg, po	carrageenan edema: 3-h inhibn, %	10^{-5} M PGS inhibn %	score[b]
19	2	H	97–99	A-IV	57	EtOH + H_2O	$C_{17}H_{19}N_5S$	>1000	32[c]	nd[e]	0–[e]
20	3	H	112–114	B-III	36	EtOH + H_2O	$C_{17}H_{19}N_5S$	>1000	36[c]	1.0[d]	0–0
21	3	2-Me	148–150	B-III	44	toluene	$C_{18}H_{21}N_5S$	>1000	24[c]	2.3	0–0
22	5	H	151–152	B-III	45	toluene	$C_{17}H_{19}N_5S$	>1000	21[c]	9.0	0–0
23	6	2-Me	155–157	B-III	35	toluene	$C_{18}H_{21}N_5S$	>1000	43	3.7	2–0
24	8	H	143–145	B-III	45	toluene	$C_{17}H_{19}N_5S$	>1000	8	4.3	0–0
25	8	2-Me	120–121	B-III	32	i-Pr_2O	$C_{18}H_{21}N_5S$	>1000	4[c]	7.0	0–0
26	8	6-MeO	137–139	B-III	31	toluene	$C_{18}H_{21}N_5OS$	>1000	nd[e]	5.0	[e]–0

[a] Q = position of guanidine moiety. [b] See Table I, footnote *c*. [c] See Table I, footnote *f*. [d] See Table I, footnote *g*. [e] Not determined.

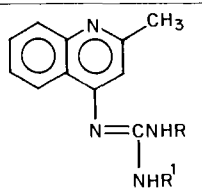
Table III. Chemical and Pharmacological Data on N-Substituted *N''*-4-(2-Methylquinolyl)-*N'*-2-thiazolylguanidines



no.	R	mp, °C	method and route	yield, %	recrystn solvent	formula	LD_{50} in mice, mg/kg, po	carrageenan edema: 3-h inhibn, %	10^{-5} M PGS inhibn, %	score[a]
27	C_2H_5	183-185	A-VI	32	EtOAc	$C_{16}H_{17}N_5S$	100	56	8.0	2-0
28	n-C_4H_9	156-158	B-VI	27	EtOH-H_2O	$C_{18}H_{21}N_5S$	800	89	0.6	3-0
29	i-C_4H_9	146-147	B-VI	20	toluene	$C_{18}H_{21}N_5S$	1000	57	18.0	2-0
30	sec-C_4H_9	152-154	A-VI	58	Et_2O	$C_{18}H_{21}N_5S$	400	57	10.5	2-0
31	n-C_5H_{11}	134-136	B-VI	14	i-PrOH	$C_{19}H_{23}N_5S \cdot 2HNO_3$	400	62	37.0[b]	3-0
32	$C(Me)_2Et$	164-165	A-VI	39	EtOAc	$C_{19}H_{23}N_5S$	400	53	100	2-3
33	CH_2CMe_3	176-178	B-VI	36	toluene	$C_{19}H_{23}N_5S$	600	66	31.1	3-1
34	$CHMeCMe_3$	184-185	B-VI	43	toluene	$C_{20}H_{25}N_5S$	>1000	36	4.0	1-0
35	n-C_6H_{13}	132-134	B-VI	14	i-PrOH	$C_{20}H_{25}N_5S \cdot 2HNO_3$	nd[c]	8[d]	23.8[b]	0-0
36	$CH_2CHEt(CH_2)_3Me$	127-129	B-VI	23	i-PrOH	$C_{22}H_{29}N_5S \cdot 2HNO_3$	>1000	28	2.1	1-0
37	$CHMe(CH_2)_3CHMe_2$	130-131	B-VI	14	i-PrOH	$C_{22}H_{29}N_5S \cdot 2HNO_3$	>1000	25	1.7	1-0
38	$CMe_2CH_2CMe_3$	173-175	A-V	37	EtOH-H_2O	$C_{22}H_{29}N_5S$	>1000	25[e]	49.3	1-1
39	n-$C_{10}H_{21}$	130 dec	B-VI	19	i-PrOH	$C_{24}H_{33}N_5S \cdot 2HNO_3$	>1000	4[d]	4.5	0-0
40	n-$C_{18}H_{37}$	145-148	A-VI	27	MeOH-Et_2O	$C_{32}H_{49}N_5S \cdot 2HCl$	>1000	5	7.0	0-0
41	cyclopropyl	143 dec	B-VI	23	EtOH	$C_{17}H_{17}N_5S \cdot 2HNO_3$	600	65	15.8	3-0
42	cyclopentyl	196-198	B-VI	37	toluene	$C_{19}H_{21}N_5S$	600	52	58.7	2-2
43	1-Me-cyclopentyl	183-185	B-VI	58	toluene	$C_{20}H_{23}N_5S$	600	46	100	2-3
44	cyclohexyl	194-195	B-VI	76	toluene	$C_{20}H_{23}N_5S$	>1000	68	100	3-3
45	4-Me-cyclohexyl	170-171	C-VI	34	Et_2O	$C_{21}H_{25}N_5S$	>1000	39	12.6	1-0
46	2,3-Me_2-cyclohexyl	168-170	B-VI	44	MeOH-EtOAc	$C_{22}H_{27}N_5S \cdot HCl$	>1000	47	7.0	2-0
47	cyclohexylmethyl	131-132	B-VI	43	EtOH	$C_{21}H_{25}N_5S \cdot 2HNO_3$	>1000	50	21.0	2-0
48	cycloheptyl	167-169	B-VI	47	toluene	$C_{21}H_{25}N_5S$	>1000	19	34.8	0-1
49	cyclooctyl	145-147	B-VI	29	Et_2O	$C_{22}H_{25}N_5S$	>1000	62	55.1	3-2
50	1-adamantyl	210-212	B-VI	67	MeOH	$C_{24}H_{27}N_5S$	>1000	17	32.0	0-1
51	phenyl	208-210	A-VI	21	MeOH	$C_{20}H_{17}N_5S$	>1000	59	83.8	2-3
52	2-Me-Ph	177-179	A-VI	37	toluene	$C_{21}H_{19}N_5S$	>1000	53	14.8	2-0

[a] See Table I, footnote *c*. [b] See Table I, footnote *g*. [c] Not determined. [d] See Table I, footnote *f*. [e] Hypotensive.

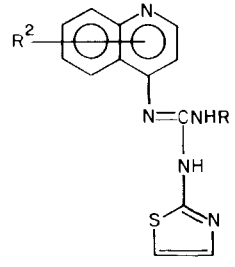
Table IV. Chemical and Pharmacological Data on N,N'-Disubstituted *N''*-4-(2-Methylquinolyl)guanidines



no.	R	R^1	mp, °C	method and route	yield, %	recrystn solvent	formula	LD_{50} in mice, mg/kg, po	carrageenan edema: 3-h inhibn, %	10^{-5} M PGS inhibn, %	score[d]
53	*t*-C_4H_9	H	232-234	B[a]-X	78	EtOH-Et_2O	$C_{15}H_{20}N_4$	100	5	11.7	0-0
54	*t*-C_4H_9	$HOCH_2CH_2$	154-156	A-X	83	EtOAc	$C_{17}H_{24}N_4O$	600	40	2.8	2-0
55	*t*-C_4H_9	2-thiazolinyl	195-197	A-X	36	EtOAc	$C_{18}H_{23}N_5S$	200	41	1.3	2-0
56	*t*-C_4H_9	4-Me-thiazol-2-yl	203-205	A-X	53	Et_2O	$C_{19}H_{23}N_5S$	600	31	95.1	1-3
57	*t*-C_4H_9	4,5-Me_2-thiazol-2-yl	190-192	C-X	74	Et_2O	$C_{20}H_{25}N_5S$	>1000	19	64.2	0-2
58	*t*-C_4H_9	4-carbethoxythiazol-2-yl	174-176	B-X	46	EtOH	$C_{21}H_{25}N_5O_2S$	>1000	36[f]	71.8	0-2
59	*t*-C_4H_9	5-carbethoxythiazol-2-yl	188-190	B-X	39	EtOH-H_2O	$C_{21}H_{25}N_5O_2S$	>1000	16	15.8	0-0
60	*t*-C_4H_9	2-benzothiazolyl	200-202	A-X	45	Et_2O	$C_{22}H_{23}N_5S$	>1000	18	51.8	0-[e]
61	*t*-C_4H_9	5-Me-1,3,4-thiadiazol-2-yl	216-218	A-X	30	MeOH	$C_{18}H_{22}N_6S$	>1000	85	33.0	3-1
62	*t*-C_4H_9	5-SH-1,3,4-thiadiazol-2-yl	150-152	B-X	52	MeOH	$C_{17}H_{20}N_6S_2$MeOH	>1000	16	6.0	0-0
63	*t*-C_4H_9	1,3,4-triazol-1-yl	264-266	A-X	46	MeOH	$C_{17}H_{21}N_7$	>1000	9[f]	nd[e]	0-[b]
64	*t*-C_4H_9	2-thienyl	193-195	B-IX	29	DMF-H_2O	$C_{19}H_{22}N_4S$	>1000	73	37.2	3-1
65	*t*-C_4H_9	phenyl	188-190	A-X	60	EtOH-H_2O	$C_{21}H_{24}N_4$	40	34	43.9	1-1
66	*t*-C_4H_9	2-pyridyl	224-226	A-IX	89	EtOH-H_2O	$C_{20}H_{23}N_5$	>1000	36	30.1	1-1
67	*t*-C_4H_9	2-pyrazinyl	201-203	A-IX	28	*i*-PrOH	$C_{19}H_{22}N_6$	>1000	39	16.6	1-0
68	cyclohexyl	H	198-200	B[a]-X	67	MeOH-Et_2O	$C_{17}H_{22}N_4$	>1000	33	12.6	1-0
69	cyclohexyl	2-thiazolinyl	129-131	A-X	62	Et_2O	$C_{20}H_{25}N_5S$	>1000	33	12.6	1-0
70	cyclohexyl	4-Me-thiazol-2-yl	180-182	A-X	70	Et_2O	$C_{21}H_{25}N_5S$	>1000	38	89.3	1-3
71	cyclohexyl	4,5-Me_2-thiazol-2-yl	180-182	A-X	47	Et_2O	$C_{22}H_{27}N_5S$	>1000	54	87.9	2-3
72	cyclohexyl	4-carbethoxythiazol-2-yl	170-172	B-X	57	EtOH-H_2O	$C_{23}H_{27}N_5O_2S$	>1000	1[f]	89.8	0-3
73	cyclohexyl	4-carboxythiazol-2-yl	238-240	*b*	93	H_2O	$C_{21}H_{23}N_5O_2S$	>1000	9	2.9	0-0
74	cyclohexyl	5-carbethoxythiazol-2-yl	228-230	B-X	27	EtOH-H_2O	$C_{23}H_{27}N_5O_2S$	>1000	16[f]	15.6	0-0
75	cyclohexyl	5-carboxythiazol-2-yl	198-200	*b*	53	H_2O	$C_{21}H_{23}N_5O_2S\cdot 2H_2O$	>1000	30	8.4	1-0
76	cyclohexyl	2-benzothiazolyl	184-186	A-X	42	EtOAc	$C_{24}H_{25}N_5S$	>1000	1	76.1	0-3
77	cyclohexyl	3-methylisothiazol-5-yl	226-228	C-X	32	EtOAc	$C_{21}H_{25}N_5S$	>1000	48	83.2	2-3
78	cyclohexyl	1,3,4-thiadiazol-2-yl	217-219	B[c]-X	15	EtOH	$C_{19}H_{22}N_6S$	250	40	15.1	2-0
79	cyclohexyl	5-Me-1,3,4-thiadiazol-2-yl	246-248	B[c]-X	44	MeOH	$C_{20}H_{24}N_6S$	>1000	56	36.2	2-1
80	cyclohexyl	5-SH-1,3,4-thiadiazol-2-yl	172-174	B[a]-X	59	MeOH	$C_{19}H_{22}N_6S_2\cdot 2H_2O$	>1000	36	7.0	1-0
81	cyclohexyl	3,5-Me_2-isoxazol-4-yl	218-220	A-X	78	EtOH-H_2O	$C_{22}H_{27}N_5O$	>1000	17	19.3	0-0
82	cyclohexyl	2-benzimidazolyl	199-201	A-X	64	EtOH	$C_{24}H_{26}N_6$	>1000	13[f]	7.2	0-0
83	cyclohexyl	phenyl	191-193	A-X	47	Et_2O	$C_{23}H_{26}N_4$	300	38	10.0	1-0
84	cyclohexyl	2-pyridyl	206-208	B-X	23	toluene	$C_{22}H_{25}N_5$	>1000	23	0.4	1-0

[a] MeOH instead of toluene. [b] Hydrolysis of esters 72 and 74. [c] Dioxane instead of toluene. [d] See Table I, footnote *c*. [e] Not determined. [f] See Table I, footnote *f*.

Table V. Chemical and Pharmacological Data on N-Substituted *N''*-4-(Substituted quinolyl)-*N'*-2-thiazolylguanidines



no.	R	R^2	mp, °C	method and route	yield, %	recrystn solvent	formula	LD_{50} in mice, mg/kg po	carrageenan edema: 3-h inhibn, %	10^{-5} M PGS inhibn, %	score[a]
85	*t*-C_4H_9	H	172-174	A-VIII	46	Et_2O	$C_{17}H_{19}N_5S$	>1000	29	23.8	1-0
86	*t*-C_4H_9	2-*n*-C_3H_7	175-176	B-VIII	32	toluene	$C_{20}H_{25}N_5S$	600	51	74.1	2-2
87	*t*-C_4H_9	2-*i*-C_3H_7	162-164	B-VIII	34	EtOH	$C_{20}H_{25}N_5S \cdot 2HNO_3$	>1000	31	12.4	1-0
88	*t*-C_4H_9	2-*i*-C_4H_9	159-160	A-VIII	25	Et_2O	$C_{21}H_{27}N_5S$	600	33	20.0	1-0
89	*t*-C_4H_9	2-C_6H_5	181-183	B-VIII	31	Et_2O	$C_{23}H_{23}N_5S$	>1000	40[b]	<10.0	0-0
90	*t*-C_4H_9	6-CH_3O	162-164	B-VIII	13	benzene	$C_{18}H_{21}N_5OS$	>1000	42	12.7	2-0
91	*t*-C_4H_9	2-C_2H_5O	122-124	B-VII	18	EtOH	$C_{19}H_{23}N_5OS \cdot 2HNO_3$	800	39	88.9	1-3
92	*t*-C_4H_9	7-Cl	180-182	B-VIII	65	toluene	$C_{17}H_{18}ClN_5S$	>1000	61	5.5	3-0
93	*t*-C_4H_9	2-CF_3	185-187	C-VII	53	MeOH	$C_{18}H_{18}F_3N_5S$	>1000	28	75.4	1-3
94	*t*-C_4H_9	7-CF_3	200-202	B-VII	36	toluene	$C_{18}H_{18}F_3N_5S$	>1000	32	nd[c]	1-[c]
95	*t*-C_4H_9	2,6-Me_2	180-182	B-VIII	46	toluene	$C_{19}H_{23}N_5S$	>1000	42	7.5[d]	2-0
96	cyclohexyl	H	195-197	B-VIII	48	Et_2O	$C_{19}H_{21}N_5S$	>1000	46	21.2	2-0
97	cyclohexyl	2-C_2H_5	185-187	B-VIII	52	toluene	$C_{21}H_{25}N_5S$	>1000	24	67.0	1-2
98	cyclohexyl	2-*n*-C_3H_7	174-176	B-VIII	40	MeOH	$C_{22}H_{27}N_5S$	>1000	54	56.0	2-2
99	cyclohexyl	2-*i*-C_3H_7	168-170	B-VIII	35	MeOH	$C_{22}H_{27}N_5S$	>1000	36	0	1-0
100	cyclohexyl	2-*i*-C_4H_9	169-171	A-VIII	33	MeOH	$C_{23}H_{29}N_5S$	>1000	40	11.0	2-0
101	cyclohexyl	2-C_6H_5	149-151	B-VIII	20	Et_2O	$C_{25}H_{25}N_5S$	>1000	5	14.0	0-0
102	cyclohexyl	2,6-Me_2	195-197	B-VIII	43	toluene	$C_{21}H_{25}N_5S$	>1000	65	0.6	3-0
103	cyclohexyl	6-CH_3	168-170	B-VIII	33	toluene	$C_{20}H_{23}N_5OS$	>1000	12	7.2	0-0
104	cyclohexyl	7-Cl	196-197	B-VIII	39	toluene	$C_{19}H_{20}ClN_5S$	>1000	56	21.6	2-0
105	cyclohexyl	2-CH_3-3-Cl	244-245	B-VIII	35	dioxane	$C_{20}H_{22}ClN_5S$	>1000	19	8.1	0-0

[a] See Table I, footnote *c*. [b] See Table I, footnote *f*. [c] Not determined. [d] See Table I, footnote *g*.

Table VI. Effect of Selected Compounds on Adjuvant Polyarthritis and Assessment of Antiinflammatory Efficacy

table	no.	day + 28: % inhibn[a] inj paw	noninj paw	arthr score[b]	tox score[c]	carr-PGS score[d]	total score[e]
I	16	56	60	3	1	1-3	8
III	28	4	34	1	2	3-0	6
	31	19	4[f]	1	3	3-0	7
	32	59	55	3	1	2-3	9
	33	31	29	1	2	3-1	7
	41	53	30	2	2	3-0	7
	43	nd[g]	nd[g]		2	2-3	(7)
	44	53	63	3	3	3-3	12
	49	21	8[f]	1	3	3-2	9
	51	46	47	2	3	2-3	10
IV	56	53	59	3	3	1-3	9
	61	45	51	2	3	3-1	9
	64	16	26	1	3	3-1	8
	70	15[f]	23[f]	0	3	1-3	7
	71	7	63[f]	0	3	2-3	8
	72	4	24	1	3	0-3	7
	76	7[f]	4[f]	0	3	0-3	6
	77	1	21	1	3	2-3	9
V	91	8	13	0	2	1-3	6
	92	26	8	1	3	3-0	7
	93	6[f]	2	0	3	1-3	7
	102	21[f]	0	0	3	3-0	6

[a] Daily oral dosing from the day of adjuvant injection to day 28. Compounds with oral LD_{50} in mice ≥ 1000 mg/kg were administered at the dose of 10 (mg/kg)/day. Compounds with oral LD_{50} in mice <1000 mg/kg were administered at the dose of 5 (mg/kg)/day. [b] Assessment of activity; average percent inhibition of the swelling of both injected and noninjected paw: $<10\% = 0$; 10-29% = 1; 30-49% = 2; $\geq 50\% = 3$. [c] LD_{50} oral mice: mg/kg $>1000 = 3$; 500-1000 = 2; $<500 = 1$. [d] carr = carrageenan edema; PGS = prostaglandin synthetase; see also Tables I-V. [e] Sum of the scores obtained in the adjuvant arthritis, acute toxicity, carrageenan edema, and prostaglandin synthetase assay. [f] Enhancement of the edema. [g] Not determined.

69 as compared to 16 and 44, respectively). Other modifications of the thiazole ring (56, 70–72, 76, and 77) did not affect the activity in the prostaglandin assay. Other substituents than methyl in position 2 of the quinoline ring as well as substitutions in other positions of this ring, although reducing the acute toxicity when R = *t*-Bu, did not result in any improvement of the antiinflammatory activity (Table V).

The compounds with the highest activity in one or both of the biological assays, i.e., carrageenan edema and prostaglandin synthetase inhibition, were tested for their effects on a model of chronic experimental inflammation, the adjuvant polyarthritis in rats (Table VI). Although the dosage used in this assay was remarkably low, corresponding to $^1/_{40}$ to $^1/_{100}$ of the acute oral LD_{50} in mice, several compounds exhibited a substantial inhibitory effect. Table VI also includes the assessment of antiinflammatory efficacy (adjuvant arthritis, carrageenan, and prostaglandin synthetase assay) and acute toxicity (oral dosing, mice) of these compounds that led to the selection of 44 for more extensive pharmacological investigations. In addition to the potent antiinflammatory activity, no other biological action, such as hypotensive activity, has been detected. A summary of the more relevant findings obtained in these studies with 44 in comparison with indomethacin is reported in Table VII. It can be seen that 44, in addition to low acute toxicity and gastroulcerogenic effect, is characterized by a very potent inhibitory activity in the adjuvant arthritis assay. Some features of this activity deserve mention. 44 chiefly inhibits the secondary manifestations of the disease when administered according to the continuous-dosing regimen and it prevents their development—without evidence of "escape" phenomena—when given prophylactically. In the latter condition, the primary lesions are only marginally affected. No evidence of cytotoxic–immunosuppressive activity has been obtained.

On the basis of these findings and a favorable long-term safety evaluation, clinical evaluation of 44 has been initiated.

Experimental Section

Pharmacology. Acute Toxicity. Median lethal dose (LD_{50}) was calculated by the method of Litchfield and Wilcoxon[14] using four mice per dose.

Carrageenan Edema. The method of Winter et al.[15] was used. The compounds (suspended in carboxymethylcellulose, 0.5%) were orally administered to 18-h fasting Sprague–Dawley rats 1 h before the injection of 0.1 mL of a 1% suspension of carrageenan into the plantar tissue of the right hind paw. The swelling was determined in treated and control animals 3 h after carrageenan injection by mercury-displacement plethismometry.

Prostaglandin Synthetase Inhibition. Bovine seminal vesicle microsomes, 0.3 mg of protein/mL; *l*-epinephrine bitartrate, 75 μg/mL; reduced glutathione, 75 μg/mL; [1-^{14}C]arachidonic acid (Amersham, G.B.), 0.18 μCi/mL; with or without 10^{-5} M concentration of the compound under investigation in a final volume of 200 μL of 0.05 M KH_2PO_4/NaOH, pH 7.4, were incubated with shaking on a water bath at 37 °C for 10 min. To the incubation mixture was added 3 volumes of *n*-hexane–ethyl acetate (2:1). After the solution was vigorously mixed, the aqueous layer was obtained by centrifugation and the [1-^{14}C]prostaglandin formed was counted in a Beckman liquid scintillation counter.

Adjuvant Arthritis. Inbred female Lewis rats (Charles River, U.K.) were used in groups of six after 2 weeks of acclimatization in our animal quarters. The arthritis was induced by injecting into the plantar tissues of the right hind paw 0.1 mL of a suspension of *M. butyricum* (Difco) in mineral oil (3 mg/mL). The assessment of the severity of the disease was performed 28 days later by measuring (mercury-displacement plethismometry) the swelling of the injected and of the noninjected hind paws. The compounds were administered orally once daily from the day of

(14) J. T. Litchfield, Jr., and F. Wilcoxon, *J. Pharmacol. Exp. Ther.*, **96**, 99 (1949).
(15) C. A. Winter, E. A. Risley, and C. W. Nuss, *Proc. Soc. Exp. Biol. Med.*, 111, 544 (1962).

Table VII. Comparison of Pharmacological Activity of 44 and Indomethacin

	44	indomethacin
LD_{50} in mice, mg/kg, po	>1000	24.3
LD_{50} in rats, mg/kg, po	1215	12.0
PG synthetase inhibn, IC_{50}, μM	2.5	1.0
carrageenan edema, ED_{50}, mg/kg, po	29.6	3.5
nystatin edema, ED_{50}, mg/kg, po[a]	26.5	>6.0
analgesic act., ED_{50}, mg/kg, po[b]	68.5	6.5
antipyretic act., MED, mg/kg, po[c,d]	12.4	1.6
gastroulcerogenic effect, ED_{50}, mg/kg, po[e,f]	170.0	4.6
adjuvant arthritis, MED, mg/kg, po[g]		
continuous dosing[h]	3.0	1.0
therapeutic dosing[i]	10.0	<1.0
prophylactic dosing[j]	10.0	2.0[k]

[a] E. Arrigoni-Martelli, P. Schiatti, and D. Selva, *Pharmacology*, 5, 215 (1971). [b] K. F. Swingle, T. J. Grant, and D. C. Kvam, *Proc. Soc. Exp. Biol. Med.*, 127, 536 (1971). [c] R. D. Sofia, W. Diamantis, R. Gordon, and M. Kletzkin, *Eur. J. Pharmacol.*, 26, 51 (1974). [d] MED = minimal effective dose; i.e., the lowest dose preventing any further increase of body temperature. [e] Groups of six Sprague-Dawley rats dosed orally once daily for 3 days. Examination for lesions of the internal surface of the stomachs 24 h after the last dose. [f] ED_{50} = dose causing lesions macroscopically appreciable in 50% of rats. [g] MED = minimal effective dose, i.e., the lowest dose causing significant ($p < 0.05$) inhibition of the swelling of the noninjected paw on day 28 post-adjuvant. [h] Daily dosing from the day of adjuvant injection to day 28. [i] Daily dosing from day 16 to day 28 postadjuvant. [j] Daily dosing from day 5 preadjuvant to day 5 postadjuvant. [k] Not active at 2.0.

adjuvant injection to day 28 postadjuvant, unless otherwise indicated.

Synthesis. Melting points were uncorrected and recorded with a Büchi 510 apparatus. Elemental analyses for C, H, N, S, halogen, and H_2O were performed by G. Cornali and W. Egger and were within ±0.4% of the calculated values, unless otherwise noted. IR and NMR spectra were obtained for all compounds and were consistent with assigned structures. A Perkin-Elmer 457 spectrophotometer was used to obtain IR spectra. NMR spectra were obtained with Varian A 60 A, JEOL JNM-PMX 60, and JEOL JNM-FX 100 spectrometers.

***N*-Cyclohexyl-*N'*-4-(2-methylquinolyl)carbodiimide.** A mixture of *N*-cyclohexyl-*N'*-4-(2-methylquinolyl)urea[11] (142.0 g, 0.50 mol), Ph_3P (150.0 g, 0.57 mol), CCl_4 (50.0 mL, 0.52 mol), and Et_3N (75.0 mL, 0.53 mol) in CH_2Cl_2 (1.0 L) was refluxed for 2 h. After evaporation of all solvent, the residue was triturated with four portions of petroleum ether (2.0 L). The combined extracts were evaporated in vacuo to yield the crude carbodiimide (110.0 g, 83.0%) as a yellow oil, which was not further characterized.

Method A. *N-tert*-Butyl-*N''*-4-(2-methylquinolyl)-*N'*-2-thiazolylguanidine (16, Table I). 4-Amino-2-methylquinoline (0.6 g, 5 mmol) was added to crude *N-tert*-butyl-*N'*-2-thiazolylcarbodiimide[7] (1.2 g, 6.6 mmol). The mixture was heated on a steam bath for 30 min and allowed to cool to room temperature. After 12 h, the mixture was triturated with Et_2O. The crystalline precipitate of **16** was collected.

Method B. *N*-Cyclohexyl-*N''*-4-(2-methylquinolyl)-*N'*-2-thiazolylguanidine (44, Table III). To crude *N*-cyclohexyl-*N'*-4-(2-methylquinolyl)carbodiimide (4.0 g, 15 mmol) in toluene (10 mL) was added 2-aminothiazole (1.0 g, 10 mmol), and the solution was refluxed for 1 h. After the solution was left standing at room temperature overnight, the precipitate (sometimes the addition of petroleum ether induced crystallization) was filtered off and washed with toluene and Et_2O.

Method C. *N-tert*-Butyl-*N'*-2-thiazolyl-*N''*-4-[2-(trifluoromethyl)quinolyl]guanidine (93, Table V). 4-Amino-2-(trifluoromethyl)quinoline (2.0 g, 9.1 mmol) was stirred in dry DMF (25 mL). NaH (50% in mineral oil dispersion; 0.5 g, 10 mmol) was added, followed by *N-tert*-butyl-*N'*-2-thiazolylcarbodiimide (1.9 g, 10.5 mmol). The mixture was stirred overnight at room temperature, and ice-water was added (100 mL). The precipitate was filtered and washed with H_2O and petroleum ether.

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Adaptive Least-Squares Method Applied to Structure–Activity Correlation of Hypotensive *N*-Alkyl-*N''*-cyano-*N'*-pyridylguanidines

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A method using an adaptive least-squares (ALS) technique has been developed for the discrimination of ordered categorical data. The method (ALS method) has the advantages of simultaneously considering any number of classes and of producing a single discriminant function which can place patterns in several classes. The ALS method was compared with linear discriminant analysis (LDA) in application to the problem of discriminating three-class hypotensive therapeutic indices of 76 *N*-alkyl-*N''*-cyano-*N'*-pyridylguanidines using nine descriptor variables. With the full data set and in the five leave-out runs, it was shown that the ALS method was superior and more stable in recognition and prediction. The structure–activity relationship is discussed on the basis of discriminant functions formulated.

The strength of drug action has been often recorded in a form of activity rating. To such ordered categorical data, linear discriminant analysis (LDA) has been applied for the structure–activity correlation.[1-4] For this purpose,

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