Synthesis and Quantitative Structure-Activity Relationship Analysis of *N*-Triiodoallyl- and *N*-Iodopropargylazoles. New Antifungal Agents

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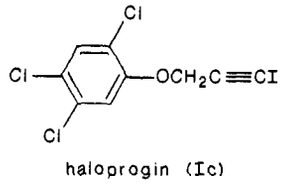
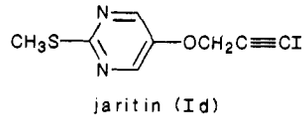
New series of *N*-(2,3,3-triiodoallyl) and *N*-(3-iodopropargyl) azole derivatives (100 compounds) involving pyrrole, pyrazole, imidazole, triazole, and tetrazole nuclei were synthesized successively with the aid of quantitative structure-activity relationship (QSAR) analysis to obtain potent antifungal agents. Starting from the derivatives of nitropyrrole-containing antibiotics, the QSAR analysis of the pyrrole derivatives against *Candida albicans* and *Trichophyton mentagrophytes* strains indicated the positive contribution of the nitro group and negative effect of the size of molecule. Further application of the QSAR analysis on the multi-azole derivatives revealed the importance of hydrophobicity and electronegativity as well as steric effect to the activities and led to the synthesis of one of the most potent iodo compounds, 2-(2,3,3-triiodoallyl)tetrazole (**67**, ME1401).

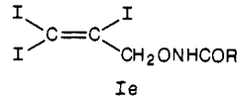
A number of iodine-containing compounds have been reported or claimed as antifungal agents. Among them, iodo alcohols such as 3-iodopropyn-2-yl alcohol (Ia; iodopropargyl alcohol) and 2,3,3-triiodopropen-2-yl alcohol (Ib; triiodoallyl alcohol) have been extensively studied. Further development of the iodo alcohol derivatives, as seen in haloprogin (Ic),[1] jaritin (Id),[2] and Ie,[3] has been limited because the structural modification methods available were rather a few. However, one of the authors, Kai,[4] found that triiodoallyl 4-methylbenzenesulfonate (If) and iodopropargyl 4-methylbenzenesulfonate (Ig) were useful reagents for the introduction of the bioactive triiodoallyl or iodopropargyl function to various molecules.



haloprogin (Ic)



jaritin (Id)

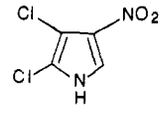


Ie

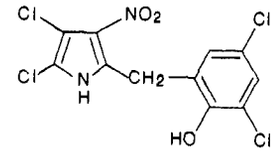
The first hint for a new series of iodo compounds came from natural antibiotics pyrrolomycins[5-7] which were found in our screening program for novel antibiotics. The stability and chemical reactivity of the nitropyrrole nucleus of pyrrolomycins[5] seemed to be fitted to further studies and, moreover there were few reports on *N*-triiodoallyl or *N*-iodopropargyl heterocycles. Although previous studies have revealed that N-alkylation of pyrrolomycin A (IIa) caused considerable reduction of the antimicrobial activity,[5] N-iodoalkylation caused an enhancement of the potency.

Indeed, *N*-(iodopropargyl)pyrrolomycin A (1) and *N*-(triiodoallyl)pyrrolomycin A (8) exhibited more potent antifungal activity than those of IIa and known antifungal agents used in the clinic such as Ic and clotrimazole. In particular, the high activity against *Candida* and *Trichophyton* species and low toxicity (LD_{50} > 1000 mg/kg, po in mice) of 1 and 8 were noted. This result encouraged us to synthesize 16 additional compounds (**2-7, 9-18**) from pyrrolomycin B (IIb),[5] pyrrolnitrin (IIc),[8] and other synthetic pyrroles.

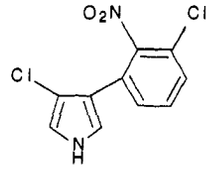
The quantitative structure-activity relationship (QSAR) analysis of the above 18 pyrrole compounds revealed that bulky substituents on the pyrrole ring weakened the activity whereas the nitro group caused a potency-enhancing



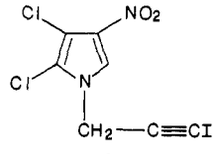
IIa



IIb



IIc



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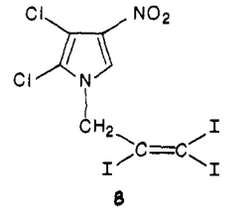

8

effect. The optimum compound among those initially synthesized was found to be 8. However, it was difficult to develop large-scale manufacture[5] of the nitropyrrole nucleus. Therefore, this study was expanded to include other five-membered azole derivatives that could replace the nitropyrrole moiety of 8.

The QSAR analysis of 32 iodo compounds synthesized from many simple azoles and nitropyrroles indicated that the effect of the nitro group on the antifungal activity came from its electronegativity and that the function of the nitro group could be mimicked by the introduction of other electronegative groups such as nitrogen atoms into the heteroaromatic moiety. In fact, 2-(triiodoallyl)tetrazole

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(1) Seki, S.; Nomiya, B.; Koeda, T.; Umemura, K.; Oda, M.; Ogawa, H. *Antimicrob. Agents Chemother.* **1964**, 569.
(2) Budesinsky, Z.; Bruna, L.; Capek, A. *Collect. Czech. Chem. Commun.* **1975**, *40*, 1078.
(3) Sankyo Chemical Ltd. JP 56-40659; *Chem. Abstr. 94*, P174372*d*.
(4) Meiji Seika Kaisha Ltd. JP 49-24445; *Chem. Abstr. 82*, P30942*u*.
(5) Koyama, M.; Kodama, Y.; Tsuruoka, T.; Ezaki, N.; Niida, T.; Inouye, S. *J. Antibiot.* **1981**, *34*, 1569.
(6) Koyama, M.; Nakamura, S.; Ezaki, N.; Iitaka, Y. *J. Antibiot.* **1981**, *34*, 1366.
(7) Koyama, M.; Ezaki, N.; Tsuruoka, T.; Inouye, S. *J. Antibiot.* **1983**, *36*, 1483.
(8) Imanaka, H.; Kousaka, M.; Tamura, G.; Arima, K. *J. Antibiot.* **1965**, *18*, 207.

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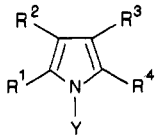
Table I. Structures, Synthetic Routes, and Physical Properties of *N*-(Iodopropargyl)- and *N*-(Triiodoallyl)pyrroles



compd	Y	R^1	R^2	R^3	R^4	method	% yield	mp, °C	solvent	formula	anal.
1	$CH_2C{\equiv}CI$	Cl	Cl	NO_2	H	A′	41	132–134	MeOH	$C_7H_3Cl_2IN_2O_2$	C, H, N, Cl + I
2	$CH_2C{\equiv}CI$	H	NO_2	H	H	A	43	133–138	MeOH	$C_7H_5IN_2O_2$	C, H, N, I
3	$CH_2C{\equiv}CI$	NO_2	H	H	H	A	82	102–104	DMF–H_2O	$C_7H_5IN_2O_2$	C, H, N, I
4	$CH_2C{\equiv}CI$	$COOCH_3$	H	H	H	A	71	oil		$C_9H_8INO_2$	C, H, N, I
5	$CH_2C{\equiv}CI$	CH_3	$COCH_3$	CH_3	H	A	10	135–138	MeOH	$C_{11}H_{12}INO$	C, H, N
6	$CH_2C{\equiv}CI$	H	Cl	*b*	H	A	46	126–128	MeOH	$C_{13}H_7Cl_2IN_2O_2$	C, H, N, Cl + I
7	$CH_2C{\equiv}CI$	Cl	Cl	NO_2	*c*	A	26	oil		$C_{14}H_7Cl_4IN_2O_3$	C, H, N
8	$CH_2CI{=}CI_2$	Cl	Cl	NO_2	H	A′	95	126–127	DMF–H_2O	$C_7H_3Cl_2I_3N_2O_2$	C, H, N, Cl + I
9	$CH_2CI{=}CI_2$	H	NO_2	H	H	A	56	107–109	MeOH	$C_7H_5I_3N_2O_2$	C, H, N, I
10	$CH_2CI{=}CI_2$	NO_2	H	H	H	A	78	122–123	MeOH	$C_7H_5I_3N_2O_2$	C, H, N, I
11	$CH_2CI{=}CI_2$	$COCH_3$	H	H	H	A	71	105–107	DMF–H_2O	$C_9H_8I_3NO$	C, H, N
12	$CH_2CI{=}CI_2$	$COOCH_3$	H	H	H	A	51	88–90	MeOH	$C_9H_8I_3NO_2$	C, H, N, I
13	$CH_2CI{=}CI_2$	COC_6H_5	H	H	H	A	63	127–130	DMF–H_2O	$C_{14}H_{10}I_3NO$	C, H, N
14	$CH_2CI{=}CI_2$	Cl	Cl	COOEt	H	A	44	117–119	hexane	$C_{10}H_8Cl_2I_3NO_2$	C, H, N, Cl + I
15	$CH_2CI{=}CI_2$	*a*	H	H	H	A	72	132–134	MeOH	$C_{15}H_{11}ClI_3NO_2$	C, H, N
16	$CH_2CI{=}CI_2$	$COOCH_3$	H	NO_2	H	A	28	88–90	C_6H_6–MeOH	$C_9H_7I_3N_2O_4$	C, H, N
17	$CH_2CI{=}CI_2$	H	Cl	*b*	H	A	88	102–104	MeOH	$C_{13}H_7Cl_2I_3N_2O_2$	C, H, N
18	$CH_2CI{=}CI_2$	Cl	Cl	NO_2	*c*	A	45	foam		$C_{14}H_7Cl_4I_3N_2O_3$	C, H, N

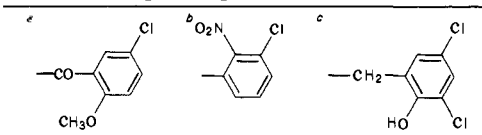
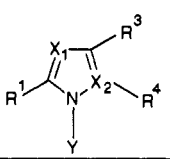


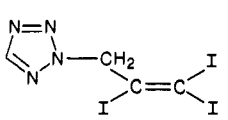
Table II. Structures, Synthetic Routes, and Physical Properties of *N*-(Iodopropargyl)- and *N*-(Triiodoallyl)imidazoles, -pyrazoles, and -1,2,4-triazoles



compd	Y	X_1	X_2	R^1	R^3	R^4	method	% yield	mp, °C	solvent	formula	anal.
19	$CH_2C{\equiv}CI$	—N=	—CH=	H	H	H	C	24	111–113	EtOAc	$C_6H_5IN_2$	C, H, N, I
20[a]	$CH_2C{\equiv}CI$	—N=	—CH=	H	NO_2 or H		A	26	157–159	EtOAc	$C_6H_4IN_3O_2$	C, H, N, I
21	$CH_2CI{=}CI_2$	—N=	—CH=	H	H	H	C	98	127–128 dec	DMF–H_2O	$C_6H_5I_3N_2$	C, H, N, I
22	$CH_2CI{=}CI_2$	—N=	—CH=	NO_2	H	H	A	92	156–158	MeOH	$C_6H_4I_3N_3O_2$	C, H, N, I
23[a]	$CH_2CI{=}CI_2$	—N=	—CH=	H	NO_2 or H		A	71	134–136	EtOAc	$C_6H_4I_3N_3O_2$	C, H, N, I
24[a]	$CH_2CI{=}CI_2$	—N=	—CH=	H	H or CH_3		C	90	111–113 dec		$C_7H_7I_3N_2$	C, H, N
25	$CH_2CI{=}CI_2$	—N=	—CH=	CH_3	H	H	C	91	116–117 dec		$C_7H_7I_3N_2$	C, H, N
26	$CH_2C{\equiv}CI$	—CH=	—N=	H	H	H	A	70	94–95	MeOH–H_2O	$C_6H_5IN_2$	C, H, N
27[a]	$CH_2C{\equiv}CI$	—CH=	—N=	CH_3 or H		H	B	63	82–85	C_6H_6–hexane	$C_7H_7IN_2$	C, H, N
28	$CH_2C{\equiv}CI$	—CH=	—N=	CH_3	CH_3	H	B	27	oil		$C_8H_9IN_2$	C, H, N
29	$CH_2C{\equiv}CI$	—N=	—N=	H	H	H	A	62	126–128	MeOH–H_2O	$C_5H_4IN_3$	C, H, N
30[a]	$CH_2C{\equiv}CI$	—N=	—N=	NO_2 or H		H	B	68	oil		$C_5H_3IN_4O_2$	C, H, N
31	$CH_2CI{=}CI_2$	—N=	—N=	H	H	H	A	61	134–135	MeOH	$C_5H_4I_3N_3$	C, H, N
32[a]	$CH_2CI{=}CI_2$	—N=	—N=	NO_2 or H		H	B	46	127–128	MeOH	$C_5H_3I_3N_4O_2$	C, H, N

[a] The positions of the substituents (R^1, R^3, and R^4) were not determined.

(**67**), which has four azole nitrogens, showed marked antifungal activity.



67 (ME1401)

In general, tetrazoles can be readily prepared from various nitriles,[9] and the discovery of the highly active compound **67** led us to concentrate our effort on the (triiodoallyl)- and (iodopropargyl)tetrazoles at the final stage of this work.

(9) Finnegan, W. G.; Henry, R. A.; Lofguist, R. *J. Am. Chem. Soc.* **1958**, *80*, 3908.

Chemistry. The synthetic routes, yields, and physicochemical properties of 100 iodo compounds synthesized in this work are listed in Tables I–V.

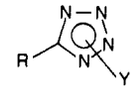
N-Iodopropargyl and *N*-triiodoallyl derivatives of the pyrrole, imidazole, pyrazole, triazole, and 5-alkyltetrazole nuclei were synthesized according to Schemes I and II. The 4-methylbenzenesulfonates If and Ig[4] were good reagents for this alkylation. In cases where N-alkylation proceeded poorly with If and Ig, new alkylating agents, 4-nitrobenzenesulfonates (Ih and Ii), and 2,3,3-triiodoallyl iodide (Ij) were used. These new reagents showed higher reactivity and were more easily handled than If and Ig (see Experimental Section).

In the synthesis of the imidazole (**19**, **21**) and alkylimidazole derivatives (**24**, **25**), the appropriate imidazoles were employed in excess as the base catalyst. The (tri-

Table III. Structures, Synthetic Routes, and Physical Properties of *N*-(Iodopropargyl)- and *N*-(Triiodoallyl)-1,2,3-triazoles

compd	Y	method	% yield	mp, °C	solvent	formula	anal.
33	1-$CH_2C{\equiv}CI$	B	40	148–152	MeOH–H_2O	$C_5H_4IN_3$	C, H, N
34	2-$CH_2C{\equiv}CI$	B′	18	88–89	hexane	$C_5H_4IN_3$	C, H, N
35	1-$CH_2CI{=}CI_2$	B	62	126–127	MeOH–H_2O	$C_5H_4I_3N_3$	C, H, N
36	2-$CH_2CI{=}CI_2$	B	16	135–136	MeOH	$C_5H_4I_3N_3$	C, H, N

Table IV. Structures, Synthetic Routes, and Physical Properties of *N*-(Iodopropargyl)- and *N*-(Triiodoallyl)-5-alkyltetrazoles



compd	Y	R	method	% yield	mp, °C	solvent	formula	anal.
37	1-$CH_2C{\equiv}CI$	H	B	55	95–96	hexane	$C_4H_3IN_4$	C, H, N
38	1-$CH_2C{\equiv}CI$	CH_3	B	58	90–93	hexane	$C_5H_5IN_4$	C, H, N
39	1-$CH_2C{\equiv}CI$	*n*-C_3H_7	B′	28	96–98	MeOH–H_2O	$C_7H_9IN_4$	C, H, N
40	1-$CH_2C{\equiv}CI$	*i*-C_3H_7	B	47	89–91	MeOH–H_2O	$C_7H_9IN_4$	C, H, N
41	1-$CH_2C{\equiv}CI$	c-C_3H_5	B	51	128–129	MeOH–H_2O	$C_7H_7IN_4$	C, H, N
42	1-$CH_2C{\equiv}CI$	*i*-C_4H_9	B	50	75–77	MeOH	$C_8H_{11}IN_4$	C, H, N
43	1-$CH_2C{\equiv}CI$	*t*-C_4H_9	B	34	80–82	MeOH	$C_8H_{11}IN_4$	C, H, N
44	1-$CH_2C{\equiv}CI$	*n*-C_5H_{11}	B	58	oil		$C_9H_{13}IN_4$	C, H, N, I
45	1-$CH_2C{\equiv}CI$	*n*-C_7H_{15}	B′	60	oil		$C_{11}H_{17}IN_4$	C, H, N
46	1-$CH_2C{\equiv}CI$	$CH_2C_6H_5$	B	57	oil		$C_{11}H_9IN_4$	C, H, N
47	2-$CH_2C{\equiv}CI$	H	B	39	92–95	hexane	$C_4H_3IN_4$	C, H, N
48	2-$CH_2C{\equiv}CI$	CH_3	B	24	112–114	hexane	$C_5H_5IN_4$	C, H, N, I
49	2-$CH_2C{\equiv}CI$	*n*-C_3H_7	B′	18	60–62	hexane	$C_7H_9IN_4$	C, H, N
50	2-$CH_2C{\equiv}CI$	*i*-C_3H_7	B	39	53–54	hexane	$C_7H_9IN_4$	C, H, N
51	2-$CH_2C{\equiv}CI$	c-C_3H_5	B	33	87–89	MeOH–H_2O	$C_7H_7IN_4$	C, H, N
52	2-$CH_2C{\equiv}CI$	*i*-C_4H_9	B	22	oi		$C_8H_{11}IN_4$	C, H, N
53	2-$CH_2C{\equiv}CI$	*t*-C_4H_9	B	54	86–88	MeOH–H_2O	$C_8H_{11}IN_4$	C, H, N
54	2-$CH_2C{\equiv}CI$	*n*-C_5H_{11}	B	37	oil		$C_9H_{13}IN_4$	C, H, N, I
55	2-$CH_2C{\equiv}CI$	*n*-C_7H_{15}	B′	34	oil		$C_{11}H_{17}IN_4$	C, H, N
56	2-$CH_2C{\equiv}CI$	$CH_2C_6H_5$	B	28	68–70	MeOH–H_2O	$C_{11}H_9IN_4$	C, H, N
57	1-$CH_2CI{=}CI_2$	H	B	56	118–120	MeOH	$C_4H_3I_3N_4$	C, H, N, I
58	1-$CH_2CI{=}CI_2$	CH_3	B	34	162–167 dec	MeOH	$C_5H_5I_3N_4$	C, H, N, I
59	1-$CH_2CI{=}CI_2$	C_2H_5	B	53	184–186 dec	EtOAc	$C_6H_7I_3N_4$	C, H, N
60	1-$CH_2CI{=}CI_2$	*n*-C_3H_7	B′	55	130–133	MeOH	$C_7H_9I_3N_4$	C, H, N, I
61	1-$CH_2CI{=}CI_2$	*i*-C_3H_7	B′	50	173–176	MeOH	$C_7H_9I_3N_4$	C, H, N
62	1-$CH_2CI{=}CI_2$	c-C_3H_5	B	56	187–188 dec	MeOH	$C_7H_7I_3N_4$	C, H, N
63	1-$CH_2CI{=}CI_2$	*n*-C_5H_{11}	B	51	105–107	MeOH	$C_9H_{13}I_3N_4$	C, H, N
64	1-$CH_2CI{=}CI_2$	*n*-C_7H_{15}	B′	51	69–70	MeOH–H_2O	$C_{11}H_{17}I_3N_4$	C, H, N
65	1-$CH_2CI{=}CI_2$	$CH_2C_6H_5$	B	52	142–144	C_6H_6–MeOH	$C_{11}H_9I_3N_4$	C, H, N
66	1-$CH_2CI{=}CI_2$	$(CH_2)_2OEt$	B	46	oil		$C_8H_{11}I_3N_4O$	C, H, N
67	2-$CH_2CI{=}CI_2$	H	B	34	94–96	MeOH	$C_4H_3I_3N_4$	C, H, N, I
68	2-$CH_2CI{=}CI_2$	CH_3	B	25	110–111	MeOH–H_2O	$C_5H_5I_3N_4$	C, H, N, I
69	2-$CH_2CI{=}CI_2$	C_2H_5	B	31	103–105	MeOH–H_2O	$C_6H_7I_3N_4$	C, H, N
70	2-$CH_2CI{=}CI_2$	*n*-C_3H_7	B′	32	85–87	MeOH–H_2O	$C_7H_9I_3N_4$	C, H, N
71	2-$CH_2CI{=}CI_2$	*i*-C_3H_7	B′	38	113–115	MeOH–H_2O	$C_7H_9I_3N_4$	C, H, N
72	2-$CH_2CI{=}CI_2$	c-C_3H_5	B	31	115–118	MeOH	$C_7H_7I_3N_4$	C, H, N
73	2-$CH_2CI{=}CI_2$	*t*-C_4H_9	B′	52	108–111	MeOH	$C_8H_{11}I_3N_4$	C, H, N
74	2-$CH_2CI{=}CI_2$	*n*-C_5H_{11}	B	27	oil		$C_9H_{13}I_3N_4$	C, H, N
75	2-$CH_2CI{=}CI_2$	*n*-C_7H_{15}	B′	29	oil		$C_{11}H_{17}I_3N_4$	C, H, N
76	2-$CH_2CI{=}CI_2$	$(CH_2)_2OEt$	B	25	81–84		$C_8H_{11}I_3N_4O$	C, H, N

iodoallyl)imidazole derivatives (**21**, **24**, **25**) were obtained in good yield under these conditions, but the yield of (iodopropargyl)imidazole derivative (**19**) was low. The positions of the substituents in some of the imidazole and pyrazole derivatives were not determined owing to the difficulty in assigning the structures.

In the synthesis of 1,2,3-triazole and 5-alkyltetrazole derivatives, two positional isomers were obtained as shown in Scheme II. The ratio of 1- and 2-substituted derivatives was approximately 2:1, and these isomers were separated by silica gel chromatography or fractional crystallization. The structures of these isomers were determined by ^1H NMR spectra.[10] The NMR data and R_f values on TLC of representative compounds are summarized in Table VI.

Some of the 5-aryltetrazole derivatives were prepared by a new iodination reaction of the terminal acetylenes using crystalline morpholine–iodine complex, as shown in Scheme III. Use of excess morpholine[11] caused considerable decomposition of the starting *N*-propargyltetrazoles. In contrast to the N-substitution of 5-alkyltetrazoles, N-alkylation or N-iodoalkylation of 5-aryltetrazoles occurred preferentially at the 2-position. The low yield (11%) of the 1-substituted 5-aryltetrazoles precluded their isolation in many cases.

Biological Assays. Antifungal activities of the iodo compounds were determined in vitro by the agar dilution

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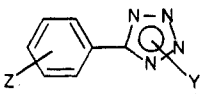
(11) Southwick, P. L.; Kirchner, J. R. *J. Org. Chem.* **1962**, *27*, 3305.

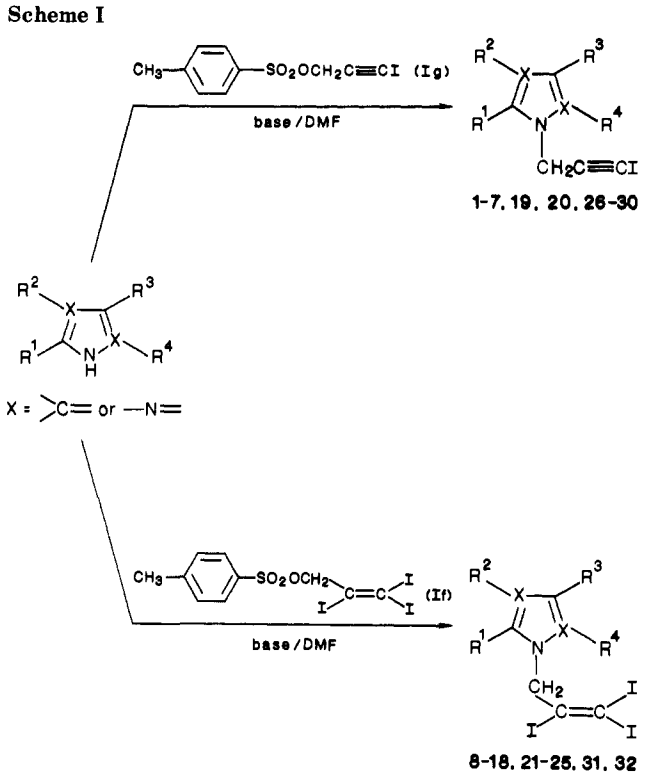
Table V. Structures, Synthetic Routes, and Physical Properties of *N*-(Iodopropargyl)- and *N*-(Triiodoallyl)-5-aryltetrazoles



compd	Y	Z	method	% yield	mp, °C	solvent	formula	anal.
77	2-$CH_2C{\equiv}CI$	H	D	55	128–129	MeOH	$C_{10}H_7IN_4$	C, H, N, I
78	2-$CH_2C{\equiv}CI$	4-Cl	D	65	127–129	MeOH	$C_{10}H_6ClIN_4$	C, H, N, Cl + I
79	1-$CH_2C{\equiv}CI$	4-Cl	D	11	140–141	MeOH	$C_{10}H_6ClIN_4$	C, H, N, Cl + I
80	2-$CH_2C{\equiv}CI$	4-CH_3	D	37	139–141	MeOH	$C_{11}H_9IN_4$	C, H, N, I
81	2-$CH_2C{\equiv}CI$	4-NO_2	A	51	188–190	MeOH-DMF	$C_{10}H_6IN_5O_2$	C, H, N
82	2-$CH_2C{\equiv}CI$	4-OCH_3	D	40	147–150	MeOH	$C_{11}H_9IN_4O$	C, H, N
83	1-$CH_2C{\equiv}CI$	4-OCH_3	D	low	118–119	MeOH	$C_{11}H_9IN_4O$	C, H, N
84	2-$CH_2C{\equiv}CI$	3-Cl	D	57	92–93	MeOH-H_2O	$C_{10}H_6ClIN_4$	C, H, N
85	2-$CH_2C{\equiv}CI$	2-Cl	D	39	93–94	IPE	$C_{10}H_6ClIN_4$	C, H, N
86	2-$CH_2C{\equiv}CI$	3-CF_3	D	68	70–72	MeOH	$C_{11}H_6F_3IN_4$	C, H, N
87	2-$CH_2C{\equiv}CI$	4-F	D	73	105–106	hexane-C_6H_6	$C_{10}H_6FIN_4$	C, H, N
88	2-$CH_2C{\equiv}CI$	4-CN	D	74	180–185 dec	acetone	$C_{11}H_6IN_5$	C, H, N, I
89	2-$CH_2C{\equiv}CI$	4-OH	A	32	187–188 dec	IPA	$C_{10}H_7IN_4O$	C, H, N, I
90	2-$CH_2C{\equiv}CI$	3,5-Cl_2	D	83	102–104	hexane	$C_{10}H_5Cl_2IN_4$	C, H, N, Cl + I
91	2-$CH_2C{\equiv}CI$	4-$CONH_2$	D	37	193–194 dec	acetone	$C_{11}H_8IN_5O$	C, H, N, I
92	2-$CH_2C{\equiv}CI$	4-tetrazole[a]	A	61	168–173 dec	DMF-H_2O	$C_{11}H_7IN_8$	C, H, N
93	2-$CH_2C{\equiv}CI$	4-$N(CH_3)_2$	A	43	165–166 dec	MeOH	$C_{12}H_{12}IN_5$	C, H, N
94	2-$CH_2C{\equiv}CI$	4-COOH	A	low	211–212 dec		$C_{11}H_7IN_4O_2$	C, H, N
95	2-$CH_2CI{=}CI_2$	H	B	77	188–189	C_6H_6-MeOH	$C_{10}H_7I_3N_4$	C, H, N
96	2-$CH_2CI{=}CI_2$	4-OCH_3	B′	48	177–178	C_6H_6-MeOH	$C_{11}H_9I_3N_4O$	C, H, N
97	2-$CH_2CI{=}CI_2$	4-F	B′	31	136–137	MeOH	$C_{10}H_6FI_3N_4$	C, H, N
98	2-$CH_2CI{=}CI_2$	4-NO_2	B′	64	200–201	C_6H_6-MeOH	$C_{10}H_6I_3N_5O_2$	C, H, N
99	2-$CH_2CI{=}CI_2$	4-CH_3	B′	63	196–197	C_6H_6-MeOH	$C_{11}H_9I_3N_4$	C, H, N
100	1-$CH_2CI{=}CI_2$	4-OCH_3	B′	low	148–150	MeOH	$C_{11}H_9I_3N_4O$	C, H, N

[a] 

Scheme I



test method, with Sabouraud dextrose agar (Difco Laboratories) as a medium. Compounds to be tested were dissolved in ethanol at a concentration of 10 mg/mL, and the solution was serially diluted to 100 or 25–0.1 μg/mL with the melted Sabouraud dextrose agar containing 0.5% ethanol. Ethanol was added to avoid precipitating the water-insoluble iodo compounds during dilution. The final ethanol concentration was 0.5–1.5%, and no influence of ethanol was observed against the growth of test fungi under this conditions.

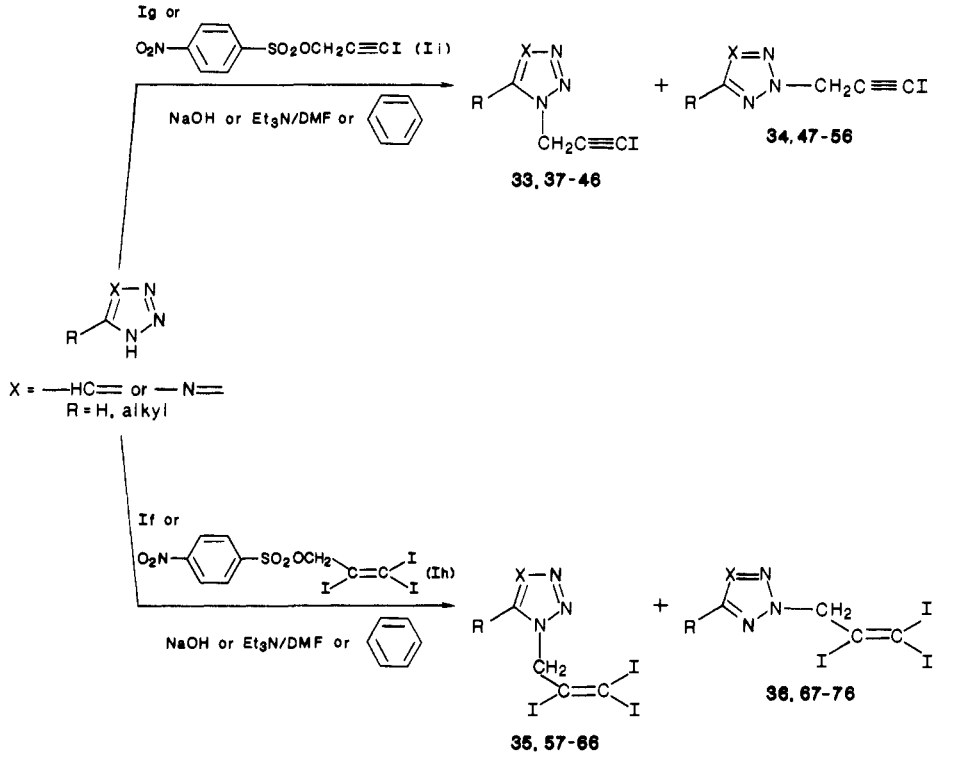
Table VI. ^1H NMR Data and R_f Values of 1,2,3-Triazole and Tetrazole Derivatives

	chemical shift[a]			
compd	CH_2	H-5	H-4	R_f[b]
33	5.35	8.15	7.77	0.10
34	5.41	7.66	7.66	0.46
35	5.41	8.22	7.83	0.13
36	5.32	7.90	7.90	0.55
37	5.30	8.66		0.11
47	5.50	8.45		0.42
57	5.40	8.67		0.13
67	5.63	8.53		0.50
58	5.20	(2.56)[c]		0.10
68	5.50	(2.55)[c]		0.45
79	5.33			0.35
78	5.52			0.60
100	5.33			0.26
96	5.70			0.59

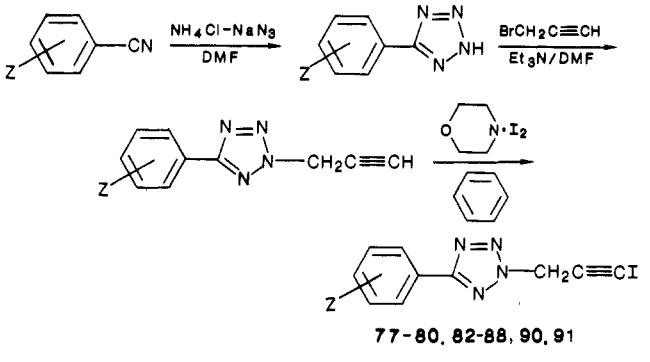
[a] In $CDCl_3$. [b] TLC; silica gel 60 F-254 (Merck), C_6H_6/EtOAc (9:1). [c] Figures in parentheses are chemical shifts of methyl protons.

Fungal strains used were *Candida albicans* C-A-24 (*C.A.*), *Cryptococcus neoformans* Cr-1 (*C.N.*), *Trichophyton mentagrophytes* 530324 (*T.M.*), *Trichophyton interdigitale* (*T.I.*), and *Aspergillus fumigatus* Saito (*A.F.*). The inoculum size of the yeast or conidium suspension of the test strain was ca. 10^6 cells/mL, and 0.003 mL of each suspension was applied on solidified agar plates. The growth of the test fungi was observed after 2-day (yeast) or 7-day incubation (molds) at 27–28 °C. The MIC (minimum inhibitory concentration) was defined as the lowest drug concentration that inhibited development of visible growth on agar. Further details of in vitro evaluation of **67** were reported separately.[12] The MICs of 100

Scheme II



Scheme III



iodo compounds are summarized in Table VII. In every bioassay, Ic and clotrimazole were used as reference compounds, the MICs of which were quite reproducible.

QSAR Analysis. The activities against *C.A.* and *T.M.* were chosen for QSAR analysis because *Candida* and *Trichophyton* species are the most prevailing pathogens of dermatophytes, which were our primary target for the development of a new antifungal agent. The MIC values for *C.A.* and *T.M.* were converted to the respective log $(1/C)$ (*C.A.*) and log $(1/C)$ (*T.M.*).

The parameters used were hydrophobic factors ($\sum\pi$ and log k'), steric factors ($\sum$Vw, $\sum$Vw$_\alpha$ and $\sum$Vw$_\beta$), and indicator variables (I_{NO_2}, I_{CH_3}, I_{I_3}, and N_α). The $\sum\pi$ values are the sum of Hansch's[13] aromatic standard constants of the substituents on the five-membered heteroaromatic rings. The parameter log k',[14] representing the hydrophobic nature of the whole molecule, was calculated from the retention time of each individual compound on the reversed-phase HPLC. Details of the measurement and calculation of log k' are described in the Experimental Section.

The steric parameter Vw is the van der Waals volume of the substituent calculated by the known method.[15] The $\sum$Vw value is the sum of the van der Waals volume over α- and β-positions. In some analyses, the Vw was separately calculated according to the substituted position α or β ($\sum$Vw$_\alpha$ or $\sum$Vw$_\beta$). The indicator variable I_{NO_2} was assigned a value of 1 when the nitro group was attached on the azole ring, and the I_{CH_3} was assigned also a value of 1 for the presence of methyl group on the azole ring. The term N_α represents the number of nitrogen atoms located in the α-position of the N-substituted azole ring. All data and residuals of the QSAR analysis are shown in Tables VIII–XI.

Results and Discussion

From the multiple regression analysis on the initially synthesized 18 pyrrole derivatives (Table VIII), eq 1 and 2 were obtained. In each equation, t = t statistics, n =

$$\log (1/C)\ (C.A.) = -0.95\sum\text{Vw} + 0.75I_{NO_2} + 0.43I_{I_3} + 5.37 \quad (1)$$
$$(t = 4.46^{**})\quad (5.97^{**})\quad (2.54^{*})$$

$$n = 18,\ r = 0.910,\ s = 0.352,\ F = 22.40^{**}$$

$$\log (1/C)\ (T.M.) = -0.87\sum\text{Vw} + 0.60I_{NO_2} + 6.24 \quad (2)$$
$$(t = 6.44^{**})\quad (4.27^{**})$$

$$n = 18,\ r = 0.906,\ s = 0.297,\ F = 34.34^{**}$$

number of points, s = standard deviation, r = correlation coefficient, and F = overall F test for significance of re-

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(13) Hansch, C.; Leo, A.; Unger, S. H.; Kim, K. H.; Nakatani, D.; Lien, E. J. *J. Med. Chem.* **1973**, *16*, 1207. Hansch, C.; Rockmell, S. D.; Jow, P. Y.; Leo, A.; Steller, E. E. *J. Med.Chem.* **1977**, *20*, 304.
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Table VII. Antifungal Activities of 100 Iodo Compounds and Reference Compounds against Five Fungal Strains

	MIC, μg/mL						MIC, μg/mL				
compd	*C.A.*[a]	*C.N.*[b]	*T.M.*[c]	*T.I.*[d]	*A.F.*[e]	compd	*C.A.*[a]	*C.N.*[b]	*T.M.*[c]	*T.I.*[d]	*A.F.*[e]
1	0.78	1.56	0.10	0.39	0.39	**53**	3.13	25	0.78	0.78	1.56
2	0.78	0.10	0.20	0.78	0.10	**54**	3.13	3.13	0.10	0.10	0.78
3	0.78	0.39	0.10	0.39	0.39	**55**	12.5	6.25	0.10	0.10	0.78
4	3.13	6.25	1.56	1.56	1.56	**56**	6.25	6.25	0.10	0.10	0.78
5	25	25	1.56	6.25	3.13	**57**	3.13	3.13	0.39	0.39	0.78
6	25	25	6.25	6.25	12.5	**58**	3.13	6.25	0.78	0.78	0.78
7	25	3.13	3.13	3.13	12.5	**59**	>25	>25	1.56	3.13	25
8	0.39	0.20	0.20	1.56	0.20	**60**	6.25	6.25	0.10	0.10	0.78
9	0.20	0.39	0.20	0.39	0.20	**61**	12.5	6.25	3.13	1.56	12.5
10	0.39	6.25	0.20	0.10	0.39	**62**	25	>25	0.78	1.56	1.56
11	12.5	>25	1.56	0.39	12.5	**63**	12.5	>25	0.10	0.10	0.39
12	1.56	3.13	0.78	0.39	3.13	**64**	>25	>25	0.78	0.10	3.13
13	6.25	6.25	1.56	3.13	6.25	**65**	>25	>25	0.10	0.10	25
14	25	25	3.13	3.13	25	**66**	6.25	6.25	0.78	1.56	3.13
15	25	25	12.5	12.5	25	**67**	0.20	0.78	0.10	0.10	0.20
16	3.13	3.13	0.39	0.39	1.56	**68**	0.78	1.56	0.20	0.20	0.39
17	12.5	12.5	3.13	6.25	12.5	**69**	0.78	0.78	0.20	0.10	0.20
18	>25	>25	25	25	>25	**70**	1.56	0.78	0.10	0.10	0.39
19	12.5	6.25	6.25	6.25	12.5	**71**	6.25	12.5	0.78	0.78	3.13
20	6.25	0.10	0.20	0.78	0.78	**72**	3.13	3.13	0.20	0.20	0.39
21	1.56	6.25	1.56	3.13	1.56	**73**	>25	>25	0.39	0.39	6.25
22	0.78	25	0.78	1.56	0.78	**74**	3.13	0.78	0.10	0.20	0.78
23	3.13	6.25	0.78	0.39	0.39	**75**	12.5	6.25	0.78	0.78	6.25
24	12.5	12.5	1.56	1.56	3.13	**76**	3.13	1.56	0.20	0.39	0.78
25	12.5	25	6.25	3.13	6.25	**77**	0.78	1.56	0.20	0.39	0.20
26	3.13	0.78	0.39	0.39	0.78	**78**	0.78	0.78	0.10	0.20	0.78
27	6.25	1.56	0.39	0.78	0.78	**79**	1.56	0.78	0.20	0.39	0.39
28	6.25	3.13	0.78	0.78	0.78	**80**	0.78	1.56	0.20	0.39	1.56
29	3.13	0.78	0.78	0.78	0.39	**81**	25	3.13	0.20	0.39	6.25
30	3.13	0.78	0.39	0.78	0.39	**82**	12.5	25	0.10	0.10	1.56
31	1.56	6.25	0.78	0.39	0.20	**83**	25	25	0.10	0.20	0.78
32	12.5	0.78	0.39	0.20	0.39	**84**	0.78	0.39	0.10	0.10	0.78
33	3.13	1.56	0.78	0.78	0.78	**85**	1.56	1.56	0.10	0.10	0.78
34	1.56	1.56	0.39	0.78	0.78	**86**	3.13	1.56	0.10	0.10	3.13
35	3.13	6.25	0.39	0.78	0.78	**87**	0.78	0.78	0.10	0.10	0.20
36	0.78	1.56	0.20	0.39	0.39	**88**	50	50	3.13	1.56	6.25
37	3.13	0.78	1.56	1.56	1.56	**89**	6.25	12.5	0.20	0.10	0.39
38	6.25	3.13	3.13	3.13	6.25	**90**	1.56	0.39	0.10	0.10	1.56
39	6.25	3.13	0.78	1.56	3.13	**91**	>100	12.5	6.25	3.13	>100
40	12.5	25	3.13	1.56	6.25	**92**	>100	>100	1.56	1.56	>100
41	12.5	12.5	1.56	3.13	3.13	**93**	50	50	0.78	0.78	50
42	12.5	6.25	1.56	1.56	3.13	**94**	>100	100	25	6.25	>100
43	12.5	25	3.13	0.78	6.25	**95**	12.5	12.5	1.56	3.13	6.25
44	3.13	3.13	0.20	0.10	0.39	**96**	>100	>100	25	>100	25
45	6.25	1.56	0.20	0.10	0.78	**97**	>100	>100	0.10	0.78	>100
46	12.5	12.5	0.78	0.39	1.56	**98**	>100	>100	>100	>100	>100
47	1.56	0.39	0.78	0.78	0.39	**99**	>100	>100	>100	>100	>100
48	1.56	0.78	0.78	0.78	0.78	**100**	6.25	0.78	0.10	0.39	0.78
49	0.78	0.78	0.10	0.10	0.10	IIa	100	25	6.25	3.13	25
50	1.56	3.13	0.78	0.78	0.78	Ic	3.13	1.56	0.39	0.39	3.13
51	1.56	1.56	0.39	0.78	0.39	CTZ[f]	6.25	1.56	0.39	0.39	1.56
52	3.13	3.13	0.39	0.39	0.78						

[a] *Candida albicans* C-A-24. [b] *Cryptococcus neoformans* Cr-1. [c] *Trichophyton mentagrophytes* 530324. [d] *Trichophyton interdigitale*. [e] *Aspergillus fumigatus* Saito. [f] Clotrimazole.

gression. The asterisked terms were significant at ≥99% (**) or ≥95% (*) confidence level.

Equations 1 and 2 showed that the bulky substituent on the pyrrole ring decreased the antifungal activities and that the nitro group increased the activities. Equation 1 showed also the superiority of the triiodoallyl derivatives to the iodopropargyl derivatives in the anti-*Candida* activity, but this relation was not observed in the anti-*Trichophyton* activity (eq 2). No improvement of the correlation was obtained by using the parameters $\sum\pi$ and log k', and accordingly, the effect of hydrophobicity on the activities was not clarified in a series of the pyrrole derivatives.

Equations 1 and 2 indicated that the optimum compounds among the pyrrole derivatives were rather simple nitropyrrole derivatives such as **8–10**. Since the pyrrole nucleus of **8** was derived from natural antibiotic IIa and since the large-scale chemical synthesis of nitropyrrole proved difficult,[5] replacement of nitropyrrole by other nuclei was sought.

It was likely that the enhancing effect of nitropyrrole on the antifungal activities could be ascribed to the electronegativity of a nitro group that is transmitted through the pyrrole ring. If so, alternative electron-withdrawing groups such as an azole nitrogen atom might induce a similar effect to that of a nitro group. According to this hypothesis, a new series of *N*-iodopropargyl and *N*-triiodoallyl azoles were synthesized. For the purpose of the QSAR analysis, our synthesis was focused on simple azoles without substituent or substituted with an electronegative nitro group or an electron-donating methyl group.

From the QSAR analysis of six nitropyrrole analogues and 26 simple azole analogues (Table IX), the following equations were obtained:

$$\log (1/C)\ (C.A.) = 0.42 \log k' + 0.54N_\alpha + 0.81I_{NO_2} - 0.36I_{CH_3} + 0.45I_{I_3} + 4.45 \quad (3)$$
$$(t = 2.41^*)\quad (5.10^{**})\quad (5.01^{**})\quad (2.50^*)\quad (3.01^{**})$$

$$n = 31,\ r = 0.874,\ s = 0.304,\ F = 16.23^{**}$$

$$\log (1/C)\ (T.M.) = 0.56 \log k' - 0.58(\log k')^2 + 0.30N_\alpha + 0.52I_{NO_2} - 0.31I_{CH_3} + 5.67 \quad (4)$$
$$(t = 4.54^{**})\quad (2.82^{**})\quad (2.90^{**})\quad (3.32^{**})\quad (2.34^*)$$

$$n = 31,\ r = 0.840,\ s = 0.280,\ F = 11.97^{**}$$

In eq 3 and 4, N_α values appeared at a significant level, and these results suggested that the introduction of nitrogen atoms in the α-position of N-substituted heteroaromatic systems caused an increase in the antifungal activities. The positive sign of I_{NO_2} and the negative sign of I_{CH_3} in eq 3 and 4 showed that the presence of an electronegative nitro group increased potency whereas that of an electron-donating methyl group decreased it.

The difference between the two types of iodo compounds was shown only in eq 3, indicating that the triiodoallyl derivatives were more active than the iodopropargyl derivatives against *C.A.*, whereas the two types of compounds were equally active against *T.M.* The contribution of hydrophobicity to the antifungal activities was evident in eq 3 and 4. The correlation of hydrophobicity was parabolic ($\log k'_0 = 0.48$) with the anti-*Trichophyton* activity and positively linear with the anti-*Candida* activity. From the above results, it was concluded that a high potency was expected not only in nitropyrroles but also in other azoles containing multi-nitrogen atoms.

Among the compounds analyzed, **67** was one of the most potent triiodoallyl derivatives and exhibited a broad activity against *C.A.*, *C.N.*, *T.M.*, *T.I.*, *A.F.* (Table VII), and other fungal species.[12]

Although an extension of the azole system from nitropyrrole to imidazole, triazole, and tetrazole provided new types of active compounds, it caused a decrease in the hydrophobicity owing to an increase in the number of nitrogen atoms. For example, the hydrophobicity of the tetrazole derivatives **67** ($\log k' = 0.086$), **57** (−0.190), **47** (−0.514), and **37** (−0.781) were lower than that of nitropyrroles **8** (1.005) and **1** (0.547). The lower activities of 1*H*-tetrazole derivatives than those of the corresponding 2*H* derivatives and the lower activities of the iodopropargyl derivatives than those of the corresponding triiodoallyl derivatives may be attributed to their decreased hydrophobicity.

If the hydrophobicity was increased by the introduction of hydrophobic substituents, an increase in the activities would be expected. Therefore, for the final optimization study of iodo compounds, our effort was concentrated on the synthesis and QSAR analysis of various 5-alkyl- and 5-aryltetrazole derivatives.

Equations 5 and 6 were derived from the QSAR analysis of the 5-alkyltetrazole derivatives shown in Table X.

$$\log (1/C)\ (C.A.) = 1.48 \log k' - 0.48(\log k')^2 + 2.25\sum Vw - 0.52I_{I_3} - 0.23I_{br} + 6.43 \quad (5)$$
$$(t = 8.45^{**})\quad (4.29^{**})\quad (10.23^{**})\quad (4.45^{**})\quad (2.09^*)$$

$$n = 38,\ r = 0.896,\ s = 0.241,\ F = 25.91^{**}$$

$$\log (1/C)\ (T.M.) = 1.10 \log k' - 0.70(\log k')^2 - 0.44\sum Vw_\alpha - 0.69I_{br} + 6.20 \quad (6)$$
$$(t = 9.24^{**})\quad (5.29^{**})\quad (5.64^{**})\quad (3.40^{**})$$

$$n = 38,\ r = 0.890,\ s = 0.289,\ F = 31.50^{**}$$

From eq 5 and 6, the parabolic effect of hydrophobicity and the negative effect of the bulkiness of substituents were apparent on the activities of the alkyltetrazole derivatives. The significance of the bulkiness was indicated by the fact that the correlations were improved by the introduction of an additional indicator variable I_{br}, which represents the presence of a branched side chain in the alkyl groups.

In general, the antifungal activities of the (iodopropargyl)tetrazole derivatives were enhanced by introducing the hydrophobic alkyl groups at C-5, and the activities of **49** were two- to eightfold as high as those of the nonsubstituted parent compound (**47**). However, the steric effect caused by alkyl substituents contributed oppositely, and this effect was more remarkable in the triiodoallyl derivatives than in the iodopropargyl derivatives.

The QSAR of the 2-substituted 5-aryltetrazole derivatives shown in Table XI were explained by eq 7 and 8. In

$$\log (1/C)\ (C.A.) = 0.85\sum\pi_{(Z\text{-}\phi\text{-})} - 4.30\sum Vw_{(Z\text{-}\phi\text{-})} - 1.33I_{I_3} + 7.27 \quad (7)$$
$$(t = 8.39^{**})\quad (7.16^{**})\quad (8.23^{**})$$

$$n = 20,\ r = 0.955,\ s = 0.299,\ F = 54.68$$

$$\log (1/C)\ (T.M.) = 0.50\sum\pi_{(Z\text{-}\phi\text{-})} - 2.65\sum Vw_{(Z\text{-}\phi\text{-})} - 2.37I_{I_3} + 7.82 \quad (8)$$
$$(t = 4.79^{**})\quad (2.34^*)\quad (7.44^{**})$$

$$n = 20,\ r = 0.907,\ s = 0.555,\ F = 24.78$$

this analysis, the use of the parameter $\log k'$ did not improve the correlation, but the $\sum\pi$ was found to be effective. The cross-correlation of $\sum\pi$ and $\sum Vw$ in this analysis was very low level ($r^2 = 0.00$ in eq 7 and $r^2 = 0.01$ in eq 8[16]).

Equations 7 and 8 clearly indicated the positive contribution of the hydrophobicity and the negative contribution of the bulkiness of 5-aryl group. The term of I_{I_3} in both equations suggested that the potent activity could not be expected for any of the (triiodoallyl)-5-aryltetrazoles. In fact, as shown in Table VII, the activities of all the 2-substituted triiodoallyl derivatives (**95–99**) were markedly decreased owing to the steric effects.

However, in contrast to the triiodoallyl derivatives, many of the *N*-(iodopropargyl)-5-aryltetrazoles (**77**, **78**, **80**, **84**, **85**, **87**, **90**) possessed high activity in spite of a bulky aryl substituent at C-5. The optimum structure of this aryltetrazole series was found in the most simple **77** and its halogenated analogues (**78** and in particular **84**). Notably, these compounds exhibited potent activity not only against *C.A.* and *T.M.* but against *C.N.*, *T.I.*, and *A.F.* The high activity of these compounds may be ascribed to the presence of the conjugated system involving the aryl substituents, and this effect is probably cancelled by the steric effect in the more bulky triiodoallyl derivatives.

The 1-substituted 5-aryltetrazole derivatives (**79**, **83**, **100**) were not subjected to the QSAR analysis, because of their small number.

The fact that the QSAR of each series of triiodoallyl and iodopropargyl compounds could be explained by the same equations suggests a similar mechanism of action against fungi between these two types of iodo compounds.

In conclusion, the *N*-iodopropargyl and *N*-triiodoallyl azoles showed the highest antifungal activity under the following structural requirements: (i) presence of electronegative groups or heteroaromatic nucleus, (ii) proper hydrophobicity, and (iii) the minimized size of molecule.

(16) Detailed examinations on the cross-correlations in eq 1–8 are shown in Table XII (Experimental Section).

Table VIII. Data and Residuals for Eq 1 and 2: Activities of Pyrrole Derivatives against *C. albicans* and *T. mentagrophytes* Strains

					log (1/C) (C.A.)			log (1/C) (T.M.)		
compd	ΣVw	log k′	I_{NO_2}	I_{I_3}	calcd[a]	found	error	calcd[b]	found	error
1	0.809	0.547	1	0	5.35	5.64	−0.29	6.14	6.54	−0.40
2	0.433	−0.073	1	0	5.71	5.54	0.17	6.46	6.14	0.32
3	0.433	0.062	1	0	5.71	5.54	0.17	6.46	6.44	0.02
4	0.669	0.395*[c]	0	0	4.73	4.97	−0.24	5.66	5.27	0.12
5	0.966	0.236	0	0	4.45	4.08	0.37	5.40	5.28	0.11
6	1.493	0.929	0	0	3.95	3.92	0.03	4.94	4.83	0.11
7	2.090	1.284	1	0	4.13	4.32	−0.19	5.02	5.22	−0.20
8	0.809	1.005	1	1	5.78	6.18	−0.40	6.14	6.48	−0.34
9	0.433	0.488	1	1	6.14	6.42	−0.28	6.46	6.42	0.04
10	0.433	0.558	1	1	6.14	6.13	0.01	6.46	6.42	0.04
11	0.588	0.689	0	1	5.24	4.62	0.62	5.73	5.53	0.20
12	0.669	0.924	0	1	5.16	5.54	−0.38	5.66	5.84	−0.18
13	1.128	1.194	0	1	4.73	4.97	−0.24	5.26	5.58	−0.32
14	1.199	1.280	0	1	4.66	4.39	0.27	5.20	5.30	−0.10
15	1.528	0.582	0	1	4.35	4.42	−0.07	4.91	4.72	0.19
16	0.878	0.798	1	1	5.72	5.27	0.45	6.08	6.18	−0.10
17	1.493	1.506	0	1	4.38	4.73	−0.35	4.94	5.39	−0.45
18	2.090	1.779*	1	1	4.56	4.19	0.37	5.02	4.49	0.53

[a] Calculated from eq 1. [b] Calculated from eq 2. [c] (*) see Experimental Section.

Table IX. Data and Residuals for Eq 3 and 4: Activities of Nitropyrrole and Multi-Azole Derivatives against *C. albicans* and *T. mentagrophytes* Strains

						log (1/C) (C.A.)			log (1/C) (T.M.)		
compd	log k′	N_a	I_{NO_2}	I_{CH_3}	I_{I_3}	calcd[a]	found	error	calcd[b]	found	error
1	0.547	0	1	0	0	5.49	5.64	−0.15	6.33	6.54	−0.21
2	−0.073	0	1	0	0	5.23	5.55	−0.32	6.15	6.14	0.01
3	0.062	0	1	0	0	5.29	5.55	−0.26	6.22	6.44	−0.22
8	1.005	0	1	0	1	6.13	6.18	−0.05	6.18	6.48	−0.30
9	0.488	0	1	0	1	5.92	6.42	−0.50	6.33	6.42	−0.09
10	0.558	0	1	0	1	5.94	6.13	−0.19	6.33	6.42	−0.09
19	0.230	0	0	0	0	4.55	4.26	0.29	5.77	4.57[d]	1.20
20	−0.558	0	1	0	0	5.03	4.65	0.38	5.70	6.14	−0.44
21	0.558	0	0	0	1	5.13	5.49	−0.36	5.81	5.49	0.32
22	0.124	0	1	0	1	5.76	5.83	−0.07	6.25	5.83	0.42
23	0.050	0	1	0	1	5.73	5.23	0.50	6.22	5.83	0.39
24	0.841	0	0	1	1	4.89	4.60	0.29	5.43	5.51	−0.08
25	1.007	0	0	1	1	4.96	4.60	0.36	5.35	4.90	0.45
26	−0.296	1	0	0	0	4.87	4.87	0.00	5.75	5.77	−0.02
27	−0.070	1	0	1	0	4.60	4.59	0.01	5.62	5.80	−0.18
28	0.055	1	0	1	0	4.65	4.62	0.03	5.69	5.52	0.17
29	−0.590	1	0	0	0	4.74	4.87	−0.13	5.44	5.48	−0.04
30	−0.514	1	1	0	0	5.58	4.95	0.63	6.05	5.85	0.20
31	−0.036	1	0	0	1	5.42	5.49	−0.07	5.95	5.79	0.16
32	0.051	1	1	0	1	5.82	4.63[c]	1.19	6.52	6.13	0.39
33	−0.688	1	0	0	0	4.70	4.87	−0.17	5.31	5.48	−0.17
34	−0.360	2	0	0	0	5.38	5.17	0.21	5.99	5.78	0.21
35	−0.076	1	0	0	1	5.41	5.19	0.22	5.92	6.10	−0.18
36	0.280	2	0	0	1	6.10	5.80	0.30	6.38	6.39	−0.01
37	−0.781	1	0	0	0	4.66	4.87	−0.21	5.18	5.18	0.00
47	−0.514	2	0	0	0	5.31	5.18	0.13	5.83	5.48	0.35
38	−0.717	1	0	1	0	4.33	4.60	−0.27	4.97	4.90	0.07
48	−0.325	2	0	1	0	5.03	5.20	−0.17	5.72	5.50	0.22
57	−0.190	1	0	0	1	5.36	5.19	0.17	5.84	6.09	−0.25
67	0.086	2	0	0	1	6.02	6.39	−0.37	6.31	6.69	−0.38
58	−0.155	1	0	1	1	5.01	5.20	−0.19	5.56	5.81	−0.25
68	0.255	2	0	1	1	5.71	5.81	−0.10	6.06	6.40	−0.34

[a] Calculated from eq 3. [b] Calculated from eq 4. [c] Not used in the derivation of eq 3. [d] Not used in the derivation of eq 4.

The unsubstituted (triiodoallyl)tetrazole (**67**, ME1401) satisfied these requirements and appears to be a promising candidate as a new antifungal agent.

Experimental Section

Melting points were determined on the recrystallized samples with a Yamato MP-21 glass capillary apparatus and are uncorrected. For the compounds in which solvent was not given in Tables I–V, melting points were recorded on the amorphous solids. TLC was carried out by using Kieselgel 60 F_{254} (Merck) and a mixture of benzene–ethyl acetate (9:1). Column chromatography was carried out by using Wako gel C-200 (Wako Chemicals) and the same solvent system as used for TLC. ^1H NMR spectra were determined on a Varian T-60 system and mass spectra on a Hitachi M-80 mass spectrometer. Most of starting materials were obtained commercially, but a few of them were synthesized by the following methods.

2-Acylpyrroles. Pyrrole was converted to pyrrylmagnesium bromide by the addition of ethylmagnesium bromide in diethyl ether followed by reaction with appropriate esters.[6] A yield in this synthesis was rather low (20–30%), but the 2-acylpyrroles were easily purified by column chromatography.

5-Substituted Tetrazoles. 5-Substituted tetrazoles except the 5-dimethylamino derivative were synthesized by the known method.[9] Thus a nitrile (0.1 mol) was dissolved in 100 mL of DMF containing 0.11 mol of NH_4Cl and 0.11 mol of NaN_3. The reaction mixture was heated at 100–110 °C for 4–18 h and then cooled and acidified with dilute HCl. The 5-substituted tetrazole that pre-

Table X. Data and Residuals for Eq 5 and 6: Activities of 5-Alkyltetrazole Derivatives against *C. albicans* and *T. mentagrophytes* Strains

						log (1/C) (C.A.)			log (1/C) (T.M.)		
compd	log k'	$\sum$Vw	$\sum$Vw$_\alpha$	I_{1_3}	I_{br}	calcd[a]	found	error	calcd[b]	found	error
37	−0.781	0.056	0.056	0	0	4.86	4.87	−0.01	4.89	5.18	−0.29
38	−0.717	0.245	0.245	0	0	4.57	4.60	−0.03	4.94	4.90	0.04
39	−0.359	0.553	0.553	0	0	4.59	4.65	−0.06	5.47	5.55	−0.08
40	−0.450*[e]	0.553	0.553	0	1	4.19	4.34	−0.15	4.63	4.95	−0.32
41	−0.461	0.527	0.527	0	0	4.46	4.34	0.12	5.31	5.24	0.07
42	−0.193	0.707	0.707	0	0	4.54	4.37	0.17	5.65	5.27	0.38
43	−0.221	0.707	0.707	0	1	4.26	4.37	−0.11	4.92	4.97	−0.05
44	0.056*	0.861	0.861	0	0	4.57	4.99	−0.42	5.88	6.18	−0.30
45	0.479*	1.169	1.169	0	0	4.40	4.73	−0.33	6.05	6.22	−0.17
46	−0.126*	0.939	0.939	0	0	4.12	4.41	−0.29	5.64	5.62	0.02
47	−0.514	0.056	0	0	0	5.42	5.18	0.24	5.45	5.48	−0.03
48	−0.325	0.245	0	0	0	5.35	5.20	0.15	5.77	5.50	0.27
49	0.106	0.553	0	0	0	5.34	5.55	−0.21	6.31	6.74	−0.43
50	0.110	0.553	0	0	1	5.11	5.15	−0.04	5.62	5.55	0.07
51	−0.032	0.527	0	0	0	5.20	5.24	−0.04	6.16	5.85	0.31
52	0.305	0.707	0	0	0	5.25	4.97	0.28	6.47	5.87	0.60
53	0.301*	0.707	0	0	1	5.01	4.97	0.04	5.78	5.57	0.21
54	0.576*	0.861	0	0	0	5.19	4.99	0.20	6.60	6.78	−0.18
55	1.065	1.169	0	0	0	4.83	4.42	0.41	6.58	6.81	−0.23
56	0.280	0.939	0	0	0	4.69	4.71	−0.02	6.45	6.81	−0.36
57	−0.190	0.056	0.056	1	0	5.49	5.19	0.30	5.94	6.10	−0.16
58	−0.155	0.245	0.245	1	0	5.12	5.20	−0.08	5.90	5.81	0.09
59	−0.015	0.399	0.399	1	0	4.99	4.01[c]	0.98	6.01	5.52	0.49
60	0.180	0.553	0.553	1	0	4.92	4.93	−0.01	6.13	7.02[d]	−0.89
61	0.112	0.553	0.553	1	1	4.60	4.63	−0.03	5.38	5.23	0.15
62	0.063	0.527	0.527	1	0	4.82	4.32	0.50	6.03	5.83	0.20
63	0.598	0.861	0.861	1	0	4.69	4.65	0.04	6.23	6.75	−0.52
64	1.005	1.169	1.169	1	0	4.28	4.07	0.21	6.08	5.88	0.20
65	0.423	0.939	0.939	1	0	4.34	4.06	0.28	6.13	7.06[d]	−0.93
66	0.214	0.576	0.576	1	0	4.91	4.95	−0.04	6.15	5.86	0.29
67	0.086	0.056	0	1	0	5.91	6.39	−0.48	6.29	6.69	−0.40
68	0.225	0.245	0	1	0	5.67	5.81	−0.14	6.41	6.40	0.01
69	0.435	0.399	0	1	0	5.57	5.82	−0.25	6.55	6.41	0.14
70	0.620	0.553	0	1	0	5.40	5.53	−0.13	6.61	7.02	−0.41
71	0.637	0.553	0	1	1	5.18	4.93	0.25	5.93	5.82	0.11
72	0.510	0.527	0	1	0	5.35	5.23	0.12	6.58	6.42	0.16
73	0.834	0.707	0	1	1	5.00	4.04[c]	0.95	5.94	6.14	0.20
74	1.098	0.861	0	1	0	5.02	5.25	−0.23	6.56	6.75	−0.19
75	1.568	1.169	0	1	0	4.42	4.67	−0.25	6.20	5.88	0.32
76	0.422	0.576	0	1	0	5.15	5.25	−0.10	6.54	6.45	0.09

[a] Calculated from eq 5. [b] Calculated from eq 6. [c] Not used in the derivation of eq 5. [d] Not used in the derivation of eq 6. [e] (*) see Experimental Section.

Table XI. Data and Residuals for Eq 7 and 8: Activities of 5-Aryltetrazole Derivatives against *C. albicans* and *T. mentagrophytes* Strains

					log (1/C) (C.A.)			log (1/C) (T.M.)		
compd	$\pi_{(Z-\phi-)}$	Vw$_{(Z-\phi-)}$	log k'	I_{1_3}	calcd[a]	found	error	calcd[b]	found	error
77	1.96	0.785	0.450	0	5.56	5.60	−0.04	6.72	6.20	0.52
78	2.67	0.950	0.822	0	5.45	5.64	−0.19	6.64	6.84	−0.20
80	2.52	0.939	0.683	0	5.37	5.63	−0.26	6.59	6.23	0.36
81	1.68	0.972	−0.071*[e]	0	4.52	4.16	0.26	6.08	6.56	−0.47
82	1.94	1.020	0.444*	0	4.53	4.44	0.09	6.09	6.84	−0.75
84	2.67	0.950	0.799	0	5.45	5.64	−0.19	6.64	6.84	−0.20
85	2.67	0.950	0.406	0	5.45	5.34	0.11	6.64	6.54	0.10
86	2.84	1.077	0.830	0	5.05	5.08	−0.03	6.39	6.88	−0.49
87	2.10	0.831	0.533	0	5.48	5.63	−0.15	6.67	6.53	0.14
88	1.39	0.962	0.246	0	4.31	3.82	0.49	5.97	5.02	0.95
89	1.29	0.853	−0.074	0	4.70	4.71	−0.01	6.20	6.22	−0.02
90	3.38	1.115	1.274	0	5.35	5.39	−0.04	6.56	6.59	−0.03
91	0.47	1.059	−0.297	0	3.12	3.25	−0.23	5.25	4.75	0.50
92	1.15	1.184	0.436	0	3.16	3.28	−0.12	5.26	5.38	−0.12
93	2.14	1.208	0.577	0	3.89	3.85	0.04	5.69	5.66	0.03
94	−2.40	1.028	−1.979	0	1.96	3.24[c]	−1.28	3.90	4.14	−0.24
95	1.96	0.785	0.980	1	4.23	4.66	−0.43	4.34	5.56	−1.22
96	1.94	1.020	1.006	1	3.20	3.47	−0.27	3.70	3.47	0.24
97	2.10	0.831	1.057	1	4.15	3.76	0.39	4.30	6.46[d]	−2.16
98	1.68	0.972	0.476	1	3.19	3.48	−0.29	3.70	3.48	0.22
99	2.52	0.939	1.204	1	4.04	3.46	0.58	4.21	3.46	0.75

[a] Calculated from eq 7. [b] Calculated from eq 8. [c] Not used in the derivation of eq 7. [d] Not used in the derivation of eq 8. [e] (*)see Experimental Section.

Table XII. Squared Cross-Correlation Matrixes of Parameters

(a) for eq 1 and 2

	$\sum$Vw	I_{NO_2}	I_{I_3}
$\sum$Vw	1.00		
I_{NO_2}	0.02	1.00	
I_{I_3}	0.00	0.01	1.00

(b) for eq 3

	log k'	N_α	I_{NO_2}	I_{CH_3}	I_{I_3}
log k'	1.00				
N_α	0.23	1.00			
I_{NO_2}	0.05	0.39	1.00		
I_{CH_3}	0.02	0.03	0.17	1.00	
I_{I_3}	0.39	0.02	0.00	0.00	1.00

(c) for eq 4

	log k'	(log k')^2	N_α	I_{NO_2}	I_{CH_3}
log k'	1.00				
(log k')^2	0.10	1.00			
N_α	0.22	0.11	1.00		
I_{NO_2}	0.06	0.00	0.40	1.00	
I_{CH_3}	0.02	0.02	0.02	0.19	1.00

(d) for eq 5

	log k'	(log k')^2	$\sum$Vw	I_{I_3}	I_{br}
log k'	1.00				
(log k')^2	0.39	1.00			
$\sum$Vw	0.46	0.19	1.00		
I_{I_3}	0.23	0.03	0.01	1.00	
I_{br}	0.01	0.02	0.00	0.01	1.00

(e) for eq 6

	log k'	(log k')^2	$\sum$Vw$_\alpha$	I_{br}
log k'	1.00			
(log k')^2	0.42	1.00		
$\sum$Vwα	0.01	0.02	1.00	
I_{br}	0.00	0.01	0.00	1.00

(f) for eq 7

	$\sum\pi_{(Z-\phi-)}$	$\sum$Vw$_{(Z-\phi-)}$	I_{I_3}
$\sum\pi_{(Z-\phi-)}$	1.00		
$\sum$Vw$_{(Z-\phi-)}$	0.00	1.00	
I_{I_3}	0.00	0.09	1.00

(g) for eq 8

	$\sum\pi_{(Z-\phi-)}$	$\sum$Vw$_{(Z-\phi-)}$	I_{I_3}
$\sum\pi_{(Z-\phi-)}$	1.00		
$\sum$Vw$_{(Z-\phi-)}$	0.01	1.00	
I_{I_3}	0.01	0.05	1.00

cipitated was collected by filtration or extracted with ethyl acetate.

5-[4-(Dimethylamino)phenyl]tetrazole. This compound was synthesized by the reductive alkylation[17] method using 5% Pd–C catalyst, HCHO, and 5-(4-nitrophenyl)tetrazole in ethanol.

2,3,3-Triiodoallyl 4-Methylbenzenesulfonate (If). To a cooled (10–12 °C) solution of 2,3,3-triiodoallyl alcohol (10.0 g, 0.023 mol) and 4-methylbenzenesulfonyl chloride (8.79 g, 0.046 mol) in dioxane (20 mL) was added dropwise an aqueous NaOH solution (1.26 g in 5.0 mL of H_2O) during which time the solution was kept at 10–15 °C. The reaction mixture was stirred at 15–25 °C for 2 h. Diethyl ether (100 mL) and water were added, and the ether extract was washed with water, dried over anhydrous Na_2SO_4, and concentrated. The residual solid was crystallized from hot carbon tetrachloride to give If: yield 11.1 g (82%); colorless crystals; mp 114–116 °C. Anal. ($C_{10}H_9I_3O_3S$) C, H, N.

3-Iodopropargyl 4-Methylbenzenesulfonate (Ig). 3-Iodopropargyl alcohol (18.2 g, 0.1 mol) and 4-methylbenzenesulfonyl chloride (19.1 g, 0.1 mol) were dissolved in 200 mL of dry dioxane, and the mixture was cooled. Triethylamine (10.1 g, 0.1 mol) was added dropwise, and the reaction mixture was stirred at 10–15 °C for 2 h. The solution was evaporated to dryness and the residual solid was extracted with benzene (200 mL) and water (200 mL). Evaporation of the benzene layer followed by crystallization from hot isopropyl ether gave Ig as colorless crystals: yield 24.2 g (72%); mp 79–81 °C. Anal. ($C_{10}H_9IO_3S$) C, H, N.

CAUTION: *It is suspected that If and Ig cause delayed type hypersensitivity on contact with skin because a skin reaction sometimes occurred after repeated handling for a few weeks. Although the stability of the 4-methylbenzenesulfonates for storage was superior to that of the 4-nitrobenzenesulfonates, the authors recommend the use of the less irritating latter compounds. In any case, these compounds should not be handled without appropriate precaution.*

2,3,3-Triiodoallyl 4-Nitrobenzenesulfonate (Ih). This compound was synthesized in a manner similar to that for Ig: yield 87%; mp 159–161 °C (recrystallized from ethyl acetate). Anal. ($C_9H_6I_3NO_5S$) C, H, N.

3-Iodopropargyl 4-Nitrobenzenesulfonate (Ii). This compound was synthesized in a manner similar to that for Ig: yield 81%; mp 117–119 °C (recrystallized from isopropyl ether). Anal. ($C_9H_6INO_5S$) C, H, N.

2,3,3-Triiodoallyl Iodide (Ij). Ten grams (0.023 mol) of 2,3,3-triiodoallyl alcohol and 8.73 g (0.046 mol) of 4-methylbenzenesulfonyl chloride were dissolved in 50 mL of dioxane (solution A). Potassium iodide (6.0 g, 0.036 mol) and NaOH (93% pellet, 2.96 g, 0.069 mol) were dissolved in 30 mL of water (solution B). To cooled solution A (10–15 °C), alkaline solution B was added dropwise, during which time the temperature was maintained at 10–15 °C. After the addition was completed, the mixture was kept at 25–26 °C for 4 h. A yellow oil was gradually solidified on cooling and Ij was obtained by filtration: yield 11.7 g (94%); mp 80–81 °C.

Morpholine–Iodine Complex. To a stirred solution of iodine (25.4 g, 0.1 mol) in 400 mL of methanol was added dropwise morpholine (8.7 g, 0.1 mol). The reaction mixture was stirred at 20–25 °C for 1 h. Orange crystals were filtered and washed with cold methanol: yield 28 g (82%). This complex was stored in a refrigerator and used without further purification.

1-(3-Iodopropargyl)-2,3-dichloro-4-nitropyrrole (1) (Method A: 4-Methylbenzenesulfonate and NaOH). 2,3-Dichloro-4-nitropyrrole (IIa; 181 mg, 0.001 mol) was dissolved in DMF (10 mL), and powdered NaOH (45 mg, 0.0013 mol) was added. The reaction mixture was stirred at 20–25 °C for 4 h and cooled to 5 °C. To this solution was added 340 mg (0.001 mol) of Ig in one portion and the mixture was stirred at 0–5 °C for 6 h. This was extracted with ethyl acetate (50 mL) and water (50 mL). The organic layer was washed with water (30 mL × 2), dried over Na_2SO_4, and concentrated. Crystallization of the residual solid from 2 mL of methanol afforded 198 mg (41%) of 1 as pale yellow crystals: mp 132–134 °C; EI mass spectrum, m/z 344, 346, 348 (M^+); NMR ($CDCl_3$) 4.92 (2 H, CH_2), 7.76 ppm (1 H, pyrrole).

1-(2,3,3-Triiodoallyl)-2,3-dichloro-4-nitropyrrole (8) (Method A′: 4-Methylbenzenesulfonate and Et_3N). To a solution of 2,3-dichloro-4-nitropyrrole (220 mg, 0.0012 mol) and Et_3N (101 mg, 0.001 mol) in DMF (10 mL) was added 590 mg (0.001 mol) of If. The mixture was heated at 60 °C for 30 min. After cooling, 8 was crystallized by the addition of ice–water (20 mL): yield 567 mg (95%); mp 126–127 °C (recrystallized from DMF–H_2O); EI mass spectrum, m/z 598, 600, 602 (M^+); NMR ($CDCl_3$) 5.01 (2 H, CH_2), 7.69 ppm (1 H, pyrrole).

1-(2,3,3-Triiodoallyl)imidazole (21) (Method C: Excess Imidazole as Base). A solution of imidazole (340 mg, 0.005 mol) and If (590 mg, 1 mmol) in 5 mL of dry DMF was kept at 20–25 °C for 5 h. Water (20 mL) was added, and the yellow crystals that precipitated were separated by filtration. Yield 440 mg (98%); mp 127–128 °C dec (recrystallized from DMF–H_2O).

2-(2,3,3-Triiodoallyl)tetrazole (67) and 1-(2,3,3-Triiodoallyl)tetrazole (57) (Method A). A mixture of 1*H*-tetrazole (420 mg, 0.006 mol), powdered NaOH (240 mg, 0.006 mol), and 20 mL of dry DMF was stirred at 20–25 °C and cooled to 5 °C. To this solution was added 2.95 g (0.005 mo) of If in one portion, and the solution was stirred at 20–25 °C for 4 h. The reaction mixture was poured into a mixture of ice–water (100 mL) and ethyl acetate (100 mL) with vigorous stirring. The ethyl acetate layer was separated, washed with water saturated with NaCl, and dried over Na_2SO_4. After evaporation, a crude product (2.31 g, 95%) was obtained as a mixture of two isomers. This was purified by silica gel column chromatography eluting with benzene–ethyl acetate (7:1) to give pure isomers. **67**: 830 mg (34%); pale yellow crystals;

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mp 94–96 °C (recrystallized from MeOH); EI mass spectrum, m/z 488 (M^+). **57**: 1370 mg (56%); yellow crystals; mp 118–120 °C (recrystallized from MeOH); EI mass spectrum, m/z 488 (M^+).

2-(2,3,3-Triiodoallyl)-5-heptyltetrazole (75) and 1-(2,3,3-Triiodoallyl)-5-heptyltetrazole (64) (Method B′: 4-Nitrobenzenesulfonate and Et_3N). To a solution of 5-heptyltetrazole (6.83 g, 0.041 mol) in 200 mL of dry benzene were added 23.8 g (0.038 mol) of Ih and 4.0 g (0.04 mol) of Et_3N. The solution was allowed to react at room temperature for 1.5 h. The benzene solution was washed with saturated $NaHCO_3$ solution, dried over Na_2SO_4, and concentrated. A crude mixture of two isomers (22.4 g, 98%) was obtained as dark solid. Two grams of this mixture was separated by silica gel column chromatography eluting with benzene–ethyl acetate (10:1) to give pure isomers. **75**: 0.68 g (29%); amber oil; EI mass spectrum, m/z 586 (M^+). **64**: 1.19 g (51%); colorless crystals; mp 69–70 °C (recrystallized from MeOH–H_2O); EI mass spectrum, m/z 586 (M^+).

2-(3-Iodopropargyl)-5-phenyltetrazole (77) (Method D). 5-Phenyltetrazole (4.38 g, 0.03 mol), Et_3N (3.03 g, 0.03 mol), and propargyl bromide (3.57 g, 0.03 mol) were dissolved in 50 mL of DMF. The mixture was kept at 20–25 °C for 3 h and then extracted with ethyl acetate (200 mL) and water (200 mL). The ethyl acetate layer was separated, washed with saturated NaCl solution, and dried over Na_2SO_4. Evaporation of ethyl acetate gave 2-propargyl-5-phenyltetrazole as a crude oil (4.80 g, 87%). The oil (4.80 g, 0.026 mol) was dissolved in 150 mL of benzene and 9.62 g (0.028 mol) of morpholine–iodine complex was added. The mixture was stirred at 20–25 °C for 16 h and then washed with water containing a small amont of $Na_2S_2O_3$. Evaporation of the benzene solution followed by repeated recrystallization from methanol gave **77** as colorless crystals: yield 5.11 g (55%); mp 128–129 °C; EI mass spectrum, m/z 310 (M^+).

2-(2,3,3-Triiodoallyl)tetrazole (67) (Method E). To a solution of tetrazole (1.54 kg, 22 mol) in 50 L of DMF was added K_2CO_3 (1.38 kg, 10 mol), and the mixture was stirred at 60–70 °C for 1 h. The clear solution was cooled to 24 °C, Ij (10.9 kg, 20 mol) was added portionwise, and the mixture was stirred at 24–29 °C for 4 h. The reaction mixture was poured with vigorous stirring into a mixture of toluene (48 L) and water (144 L) and then cooled. Insoluble material (1*H* isomer) was removed by filtration, and the toluene layer was separated and concentrated to dryness. The residual solid was recrystallized two times from hot methanol to give **67**: yield 3.15 kg (20.2%); mp 94–96 °C.

log *k′* Values. The retention time of the iodo compounds on HPLC was measured under the following conditions with compound **67** as an internal standard [HPLC apparatus, JEOL model BIP-I; column, Develosil ODS-7 (Nomura Chemicals), 4.6 × 250 mm; solvent system, MeOH–H_2O (2:1); flow rate, 1.0 mL/min]. log k' values were calculated from the retention time according to the following equation:

$$\log k' = \log [(t_R - t_0)/t_0]$$

where t_R = retention time of a compound and t_0 = retention time of the solvent front. Since the log k' values of the iodopropargyl derivatives (log $k'_{(I)}$) were found to be highly correlated with the values of the corresponding triiodoallyl derivatives (log $k'_{(T)}$), the asterisked log k' values in Tables VIII–XI were calculated from those of the corresponding iodopropargyl or triiodoallyl compounds by using the following equation:

$$\log k'_{(I)} = 1.040 \log k'_{(T)} + 0.557$$

$$n = 18, r = 0.998$$

Internal Correlations among Parameters Used in the QSAR Study. The squared cross-correlation matrixes of parameters used in the regression equations are given in Table XII. No problematic collinearity was recognized.

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Registry No. 1, 87427-31-4; **2**, 87427-32-5; **2** (Y = H), 5930-94-9; **3**, 87427-35-8; **3** (Y = H), 5919-26-6; 4, 87427-34-7; 4 (Y = H), 1193-62-0; **5**, 106191-69-9; **5** (Y = H), 2386-25-6; **6**, 87427-33-6; **7**, 106191-70-2; **8**, 87427-19-8; **9**, 87427-20-1; **10**, 106191-71-3; **11**, 106191-72-4; 11 (Y = H), 1072-83-9; **12**, 87427-42-7; **13**, 106191-73-5; **13** (Y = H), 7697-46-3; **14**, 87427-21-2; **14** (Y = H), 39205-30-6; **15**, 106191-74-6; **15** (Y = H), 39205-06-6; **16**, 106191-75-7; **16** (Y = H), 13138-74-4; **17**, 87427-22-3; **18**, 106191-76-8; **19**, 87427-37-0; **19** (Y = H), 288-32-4; **20**, 106192-03-4; **20** (Y = H), 3034-38-6; **21**, 87427-23-4; **22**, 87427-24-5; **22** (Y = H), 527-73-1; **23**, 106192-04-5; **24**, 106192-05-6; **24** (Y = H), 822-36-6; **25**, 106191-77-9; **25** (Y = H), 693-98-1; **26**, 87427-36-9; **26** (Y = H), 288-13-1; **27**, 106192-06-7; **27** (Y = H), 1453-58-3; **28**, 106191-78-0; **28** (Y = H), 67-51-6; **29**, 87427-38-1; **29** (Y = H), 288-88-0; **30**, 106192-07-8; **30** (Y = H), 24807-55-4; **31**, 106191-79-1; **32**, 106192-08-9; **33**, 106191-80-4; **34**, 106191-81-5; **35**, 106191-82-6; **36**, 106191-83-7; **37**, 87427-40-5; **37** (Y = H), 288-94-8; **38**, 92712-02-2; **38** (Y = H), 4076-36-2; **39**, 92712-06-6; **39** (Y = H), 14389-13-0; **40**, 92712-08-8; **40** (Y = H), 6280-28-0; **41**, 106191-84-8; **41** (Y = H), 27943-07-3; **42**, 106191-85-9; **42** (Y = H), 106192-01-2; **43**, 92712-10-2; **43** (Y = H), 92712-46-4; **44**, 92712-12-4; **44** (Y = H), 25717-82-2; **45**, 92712-14-6; **45** (Y = H), 92712-47-5; **46**, 106191-86-0; **46** (Y = H), 18489-25-3; **47**, 87427-39-2; **48**, 92712-01-1; **49**, 92712-05-5; **50**, 92712-07-7; **51**, 106191-87-1; **52**, 106191-88-2; **53**, 92712-09-9; **54**, 92712-11-3; **55**, 92712-13-5; **56**, 106191-89-3; **57**, 87427-26-7; **58**, 87427-28-9; **59**, 92712-42-0; **59** (Y = H), 16687-59-5; **60**, 92712-38-4; **61**, 92712-40-8; **62**, 106191-90-6; **63**, 92712-34-0; **64**, 92712-32-8; **65**, 92731-72-1; **66**, 106191-91-7; **66** (Y = H), 106192-02-3; **67**, 87427-25-6; **68**, 87427-27-8; **69**, 92712-41-9; **70**, 92712-37-3; **71**, 92712-39-5; **72**, 106191-92-8; **73**, 92712-35-1; **74**, 92712-33-9; **75**, 92712-31-7; **76**, 106191-93-9; **77**, 92712-15-7; **77** (Y = H), 18039-42-4; **78**, 92712-17-9; **78** (Y = H), 16687-61-9; **79**, 92712-18-0; **80**, 92712-23-7; **80** (Y = H), 24994-04-5; **81**, 92712-28-2; **81** (Y = H), 16687-60-8; **82**, 92712-16-8; **82** (Y = H), 6926-51-8; **83**, 106191-94-0; **84**, 92712-20-4; **84** (Y = H), 41421-28-7; **85**, 92712-19-1; **85** (Y = H), 50907-46-5; **86**, 92712-24-8; **86** (Y = H), 92712-48-6; **87**, 92712-21-5; **87** (Y = H), 50907-21-6; **88**, 92712-25-9; **88** (Y = H), 14389-10-7; **89**, 92712-44-2; **89** (Y = H), 51517-88-5; **90**, 92712-22-6; **90**, 92712-49-7; **91**, 92712-27-1; **91** (Y = H), 92712-51-1; **92**, 106191-95-1; **92** (Y = H), 6926-49-4; **93**, 92712-30-6; **93** (Y = H), 51449-84-4; **94**, 92712-29-3; **94** (Y = H), 34114-12-0; **95**, 87427-29-0; **96**, 106191-96-2; **97**, 106191-97-3; **98**, 106191-98-4; **99**, 106191-99-5; **100**, 106192-00-1; **Ia**, 1725-82-2; **Ib**, 42778-72-3; **If**, 42778-73-4; **Ig**, 71984-04-8; **Ih**, 92712-52-2; **Ii**, 92712-45-3; **Ij**, 42778-71-2; **IIa**, 79763-01-2; **IIb**, 1018-71-9; **IIc**, 79763-00-1; 4-$H_3CC_6H_4SO_2Cl$, 98-59-9; 4-$O_2NC_6H_4SO_2Cl$, 98-74-8; $BrCH_2C{\equiv}CH$, 106-96-7; C_6H_5CN, 100-47-0; 4-ClC_6H_4CN, 623-03-0; 4-$H_3CC_6H_4CN$, 104-85-8; 4-$O_2NC_6H_4CN$, 619-72-7; 4-$MeOC_6H_4CN$, 874-90-8; 3-ClC_6H_4CN, 766-84-7; 2-ClC_6H_4CN, 873-32-5; 3-$F_3CC_6H_4CN$, 368-77-4; 4-FC_6H_4CN, 1194-02-1; 4-NCC_6H_4CN, 623-26-7; 4-HOC_6H_4CN, 767-00-0; 3,5-$Cl_2C_6H_3CN$, 6575-00-4; 4-$H_2NCOC_6H_4CN$, 3034-34-2; 4-$HO_2CC_6H_4CN$, 619-65-8; 4-$tetC_6H_4CN$, 14389-10-7; morpholine, 110-91-8; 2-propargyl-5-phenyltetrazole, 78909-96-3; 5-(4-nitrophenyl)tetrazole, 16687-60-8; 1,2,3-triazole, 27070-49-1; morpholine–iodine complex, 60840-15-5.