to 6 with concentrated HCl. The product was isolated by centrifugation and washed with 3 × 40 mL of H_2O. After drying, there was obtained 1.2 g (73%) of white crystalline powder: mp 339–341 °C dec; TLC, R_f 0.58 (Whatman KC18F-reverse phase, EtOH–MeCN, 8:2); NMR (300 MHz, CF_3COOD) δ 4.56 (br s, 2, CH_2S) 7.59 (br s, 2, 3′, 5′), 7.64 (br s, 1, H_8), 8.21 (br s, 2, 2′, 6′ + br s, 1, H_7), 8.48 (br s, 1, H_5). Anal. ($C_{16}H_{13}N_3O_3S\cdot0.5H_2O$) C, H, N.

Di-*tert*-butyl 10-Thia-5,8-dideazafolate (12). To a suspension of **10** (0.2 g, 0.6 mmol) in 10 mL of DMF were added di-*tert*-butyl L-glutamate hydrochloride, **11** (0.195 g, 0.66 mmol), and diethyl phosphorocyanidate (0.108 g, 0.66 mmol) in 1.0 mL of DMF. The suspension was treated with 0.134 g (1.32 mmol) of Et_3N in 2 mL of DMF, and the resulting mixture was stirred under N_2 at ambient temperature for 1.5 h. It was then poured into a mixture of EtOAc–C_6H_6 (3:1) and the organic layer washed successively with 50 mL of H_2O, 60 mL of saturated aqueous Na_2CO_3, 50 mL of H_2O, and 60 mL of saturated NaCl. After drying over $MgSO_4$, the solvent was removed under vacuum. The crude product was applied to a silica gel column and eluted with $CHCl_3$–MeOH, 9:1. Fractions homogeneous by TLC were pooled and evaporated to obtain an off-white powder, which was recrystallized from $CHCl_3$-*n*-hexane, 1:3. The precipitate was separated by centrifugation to yield 0.27 g (81%) of crystalline white powder: mp 190–192 °C; TLC, R_f 0.79 ($CHCl_3$–MeOH, 4:1); HPLC, 47.5 min; NMR (300 MHz, Me_2SO-d_6) δ 1.37 (s, 9, $C(CH_3)_3$), 1.40 (s, 9, $C(CH_3)_3$), 1.70–2.05 (m, 2, glu β-CH_2), 2.32 (t, 2, glu γ-CH_2, J = 7.4 Hz), 4.26–4.33 (m, 1, glu α-CH), 4.39 (s, 2, CH_2S), 6.44 (br s, 2, NH_2), 7.14 (d, 1, H_8, $J_{7,8}$ = 8.45 Hz), 7.42 (d, 2, 3′, 5′, J_o = 8.46 Hz), 7.59 (dd, 1, H_7, $J_{7,8}$ = 8.45 Hz, $J_{5,7}$ = 2.03 Hz), 7.78 (d, 2, 2′, 6′, J_o = 8.46 Hz), 7.92 (d, 1, H_5, $J_{5,7}$ = 2.03 Hz), 8.54 (d, 1, CON*H*, J = 7.53 Hz). Anal. ($C_{29}H_{36}N_4O_6S\cdot H_2O$) C, H, N.

10-Thia-5,8-dideazafolic Acid (5d). Compound **12** (0.217 g, 0.40 mmol) was dissolved in CF_3COOH (10 mL). After the reaction mixture was stirred under N_2 at ambient temperature for 1 h, the solution was evaporatd under reduced pressure. The yellow oily residue was treated with 40 mL of Et_2O, and the off-white precipitate was separated by centrifugation and washed with 3 × 30 mL of Et_2O. The crude product was dissolved in 30 mL of H_2O, and the resulting white suspension was basified to pH 11 with 1 N NaOH. Traces of insoluble material were removed by filtration, and the filtrate was brought to pH 3.5 with 1 N HCl. The white precipitate was separated by centrifugation, washed three times with H_2O, and dried under vacuum at 80 °C for 6 h, yielding 0.138 g (79%) of white crystalline powder: mp 224–225 °C (lit.[13] mp > 220 °C dec); TLC, R_f 0.62; HPLC, 34.6 min; NMR (300 MHz, Me_2SO-d_6) δ 1.85–2.12 (m, 2, glu, β-CH_2), 2.49 (t, 2, glu γ-CH_2), 4.31–4.37 (m, 1, glu α-CH), 4.37 (s, 2, CH_2S), 6.39 (br s, 2, NH_2), 7.12 (d, 1, H_8, $J_{7,8}$ = 8.46 Hz), 7.42 (d, 2, 3′, 5′, J_o = 8.46 Hz), 7.58 (dd, 1, H_7, $J_{7,8}$ = 8.46 Hz, $J_{5,7}$ = 2.10 Hz), 7.78 (d, 2, 2′, 6′, J_o = 8.46 Hz), 7.90 (d, 1, H_5, $J_{5,7}$ = 2.10 Hz), 8.56 (d, 1, CON*H*, J = 7.63 Hz). Anal. ($C_{21}H_{20}N_4O_6S$) C, H, N.

Acknowledgment. This investigation was supported by PHS Grants CA 25014 (J.B.H.) and CA 41461 (J.H.F.) awarded by the National Cancer Institute, DHHS. One of us (A.K.) was the recipient of a Postdoctoral Fellowship from the College of Graduate Studies, Medical University of South Carolina, 1983–1984. We thank Kevin Ballard of the Mass Spectrometry Laboratory, Department of Pharmacology, Medical University of South Carolina for the FAB/MS spectral determinations.

Registry No. 1a, 56239-21-5; **1b**, 56277-35-1; **1c**, 102743-78-2; **1d**, 87614-69-5; **1e**, 87597-82-8; **1f**, 87539-56-8; **2a**, 88050-25-3; **2b**, 87597-85-1; **2c**, 88050-31-1; **3a**, 76858-74-7; **3b**, 111718-80-0; **3c**, 111718-81-1; **3d**, 111742-50-8; **3e**, 111742-51-9; **4a**, 76849-19-9; **4b**, 111718-82-2; **4c**, 111718-83-3; **4d**, 111742-52-0; **4e**, 111742-53-1; **5a**, 2854-11-5; **5b**, 5854-12-6; **5c**, 61038-31-1; **5d**, 64088-74-0; **5e**, 64088-76-2; **6a**, 56239-22-6; **6b**, 56277-34-0; **6c**, 97541-74-7; **6d**, 93502-95-5; **6e**, 93502-96-6; **6f**, 18921-68-1; **6g**, 27244-49-1; **6h**, 20242-62-0; **6i**, 61075-41-0; **7**, 58677-08-0; **9**, 111718-84-4; **10**, 111718-85-5; 11, 32677-01-3; **12**, 111718-86-6; TS, 9031-61-2; DHFR, 9002-03-3; $BrCH_2C{\equiv}CH$, 106-96-7; $BrCH_2CH{=}CH_2$, 106-95-6; EtOCO-*p*-$C_6H_4SSC_6H_4$-*p*-COOEt, 20057-83-4.

Supplementary Material Available: Table V containing high-resolution ^1H NMR data for compounds presented in Table I (3 pages). Ordering information is given on any current masthead page.

Synthesis and Potential Antipsychotic Activity of 1*H*-Imidazo[1,2-*c*]pyrazolo[3,4-*e*]pyrimidines

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The synthesis of a series of 1*H*-imidazo[1,2-*c*]pyrazolo[3,4-*e*]pyrimidines is reported along with the effects of these compounds in preclinical tests for antipsychotic activity. Certain of these compounds displayed antipsychotic-like effects in conditioned avoidance tests, but unlike currently used antipsychotic drugs, they did not have affinity for brain dopamine receptors. These compounds also did not cause dystonias predictive of extrapyramidal side effects in monkeys at doses that produced behavioral effects. On the basis of this unique biological profile, a member of this series, 7,8-dihydro-8-ethyl-1,3,5-trimethyl-1*H*-imidao[1,2-*c*]pyrazolo[3,4-*e*]pyrimidine (**19**, CI-943), has been selected for clinical evaluation as an antipsychotic agent.

Although dopamine antagonist antipsychotic drugs continue to be the preferred method for the treatment of schizophrenia, the need exists for a new generation of agents with improved efficacy and reduced neurological side effects.[1] Available antipsychotics are effective in controlling the positive symptoms of schizophrenia such as delusions, hallucinations, and loose associations but are ineffective in treating the negative symptoms including social withdrawal and blunted affect. Moreover, these agents cause side effects such as extrapyramidal syndrome and tardive dyskinesia. In recent years research has been focused on identifying compounds with improved clinical profiles. However, despite the desire for novel antipsychotics, many of these so-called "atypical" agents are dopamine antagonists that have profiles similar to those of existing agents.[2]

† Department of Chemistry.
‡ Department of Pharmacology.

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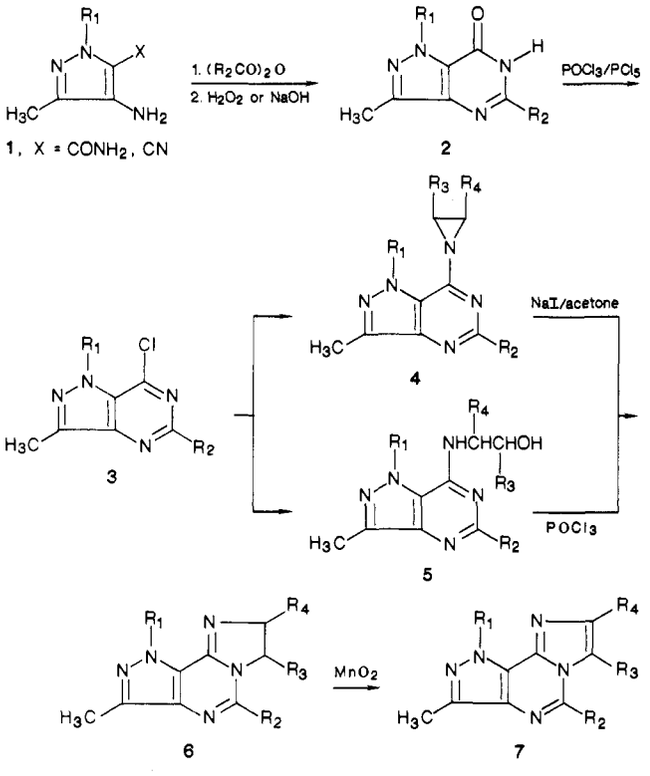
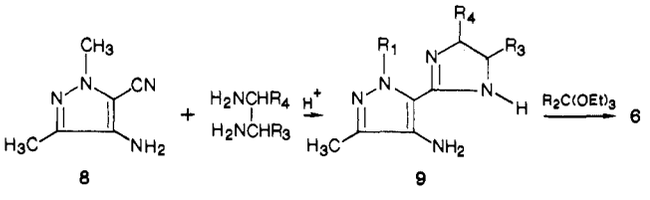
Scheme I



1, X = $CONH_2$, CN

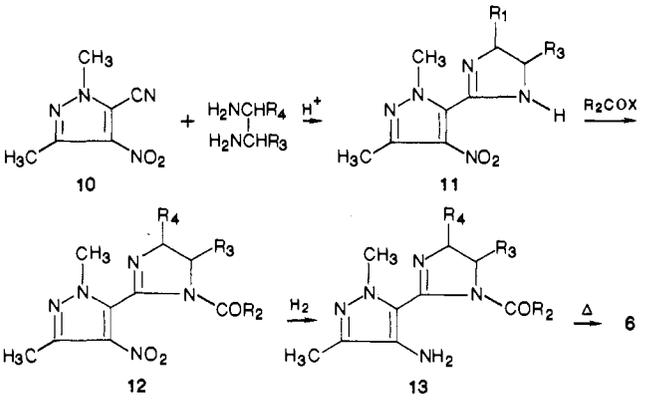
Scheme II



8 9 6

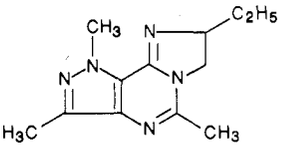
In previous papers we described two series of compounds that lack dopamine antagonist activity and exhibit preclinical profiles suggestive of antipsychotic efficacy without extrapyramidal side effect potential.[3,4] As part of this continuing effort, we now report the investigation of a series of novel imidazopyrazolopyrimidines with preclinical effects that resemble those of antipsychotic drugs. This work was based, in part, on our earlier observations that use of a pyrazole ring as an isoelectronic equivalent to a fused benzene ring provided compounds with interesting central nervous system (CNS) activity.[5-7] Encouraged by the early discovery that several of the original imidazopyrazolopyrimidines selectively suppressed conditioned avoidance responding in rats, an effect characteristic of antipsychotic agents,[8] we continued to synthesize and evaluate analogues of this new heterocyclic system and

Scheme III



10 11 12 13 6

identified compound **19**, CI-943, as an antipsychotic clinical candidate.



19

Chemistry

Preparation of the tricyclic system **6** is depicted in Scheme I–III. In Scheme I acylation of the readily available 4-amino-pyrazole-5-carbonitriles **1**,[9] followed by ring closure using hydrogen peroxide in aqueous sodium hydroxide,[10] provided the corresponding 7*H*-pyrazolo-[4,3-*d*]pyrimidin-7-ones, **2**, in high yields (Table I). Alternatively, cyclization could also be effected by simply heating the acylated *o*-amino carboxamides[9] in 1 N sodium hydroxide at 80 °C. Treatment of the pyrazolopyrimidinones **2** with phosphorus pentachloride in phosphorus oxychloride furnished the chloropyrazolopyrimidines **3**, which could be further converted to the various substituted pyrazolopyrimidinamines **4** and **5** by reaction with aziridines or 2-amino alcohols, respectively.

Rearrangement of the aziridines **4** with sodium iodide in acetone or ring closure of the amino alcohols **5** with phosphorus oxychloride afforded the 7,8-dihydro-1*H*-imidazo[1,2-*c*]pyrazolo[3,4-*e*]pyrimidines **6**. Rearrangement of an unsymmetrical aziridine **4** appeared to be fairly regiospecific and similar to that previously observed in the isomerization of 4-(1-aziridinyl)quinazolines to 2,3-dihydroimidazo[1,2-*c*]quinazolines.[11] For example, when 2-methylaziridine was employed, only compound **16** where R_3 = H and R_4 = CH_3 was obtained. in addition to a characteristic NMR hydrogen pattern for the proton at C-7,8, the structures of these products were confirmed by comparison with those obtained via cyclization of the amino alcohol **5**. This latter procedure provided a convenient synthesis of the positional isomers (e.g., compound **27** where R_3 = CH_3 and R_4 = H). Optically active C-8 compounds **20** and **21**, were obtained by the same sequence **3** → **5** → **6** from readily available optically active amino alcohols.

Schemes II and III illustrate shorter, more versatile, and higher yielding reaction sequences to **6**. These routes feature construction of the pyrimidine ring from (1*H*-

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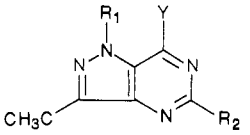
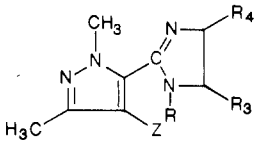
Table I. 3-Methyl-1*H*-pyrazolo[4,3-*d*]pyrimidines



no.	R_1	R_2	Y	mp, °C	recrystn solvent[a]	meth	yield, %	formula[b]
2a	CH_3	H	OH	299–301	z	A	58	$C_7H_8N_4O \cdot 0.1H_2O$
2b	CH_3	CH_3	OH	258–260	z	B	75	$C_8H_{10}N_4O \cdot H_2O$
2c	CH_3	C_2H_5	OH	220–222	x	A	70	$C_9H_{12}N_4O$
2d	CH_3	c-C_3H_5	OH	238–240	p	A	68	$C_{10}H_{12}N_4O \cdot 0.2H_2O$
2e	CH_3	*i*-C_3H_7	OH	264–266	x	A	77	$C_{10}H_{14}N_4O$
2f	CH_3	C_6H_5	OH	272–274	x	A	66	$C_{13}H_{12}N_4O$
2g	CH_3	$CH_2C_6H_5$	OH	248–250	z	A	87	$C_{14}H_{14}N_4O$
2h	C_2H_5	CH_3	OH	222–224	x	A	80	$C_9H_{12}N_4O$
2i	C_2H_5	C_2H_5	OH	192–194	z	A	92	$C_{10}H_{14}N_4O$
2j	*n*-C_3H_7	CH_3	OH	272–274	x	A	66	$C_{10}H_{14}N_4 \cdot 0.1H_2O$
4a	C_2H_5	CH_3		66–69	w	C	90	$C_{11}H_{15}N_5 \cdot 0.25H_2O$
4b	CH_3	CH_3		oil	z	C	92	$C_{11}H_{15}N_5 \cdot 0.1H_2O$
4c	CH_3	C_6H_5		119–121	v	C	74	$C_{16}H_{17}N_5$
5a	CH_3	H	$NHCH_2CH_2OH$	200–202	t	D	64	$C_9H_{13}N_5O \cdot 0.5H_2O$
5b	CH_3	CH_3	$NHCH(C_2H_5)CH_2OH$	166–168	p	D	68	$C_{12}H_{19}N_5O$
5c	CH_3	CH_3	$NHCH(C_2H_5)CH_2OH$[c]	180–182	t	D	50	$C_{12}H_{19}N_5O$
5d	CH_3	CH_3	$NHCH(C_2H_5)CH_2OH$[d]	188–190	t	D	82	$C_{12}H_{19}N_5O \cdot 0.5H_2O$
5e	CH_3	CH_3	$NHCH(i\text{-}C_3H_7)CH_2OH$[e]	166–168	r	D	45	$C_{13}H_{21}N_5O$
5f	CH_3	CH_3	$NHC(CH_3)_2CH_2OH$	185–187	v	D	53	$C_{12}H_{19}N_5O$
5g	CH_3	C_2H_5	$NHCH(C_2H_5)CH_2OH$	166–168	p	D	87	$C_{13}H_{21}N_5O \cdot H_2O$
5h	CH_3	C_2H_5	$NHCH_2CH(CH_3)OH$	116–119	v	D	76	$C_{12}H_{19}N_5O \cdot 0.5H_2O$
5i	C_2H_5	CH_3	$NHCH_2CH_2OH$	181–183	v	D	56	$C_{11}H_{17}N_5O$
5j	C_2H_5	CH_3	$NHCH_2CH(C_6H_5)OH$	162–164	t	D	60	$C_{17}H_{21}N_5O$[f]

[a] Recrystallization solvents are abbreviated as follows: p = water, q = 2-propanol, r = acetonitrile, s = ether, t = toluene, v = ethyl acetate, w = petroleum ether, x = ethanol, y = acetone, z = not recrystallized. [b] Analytical results from C, H, and N are within ±0.4% of theoretical values except where noted. [c] From L-2-amino-1-butanol. [d] From D-2-amino-1-butanol. [e] From L-valinol ($NaBH_4$ reduction of L-valine methyl ester). [f] N: calcd, 22.49; found, 20.07.

Table II. 4-Substituted 5-(1*H*-Imidazol-2-yl)-1,3-dimethyl-1*H*-pyrazoles



no.	Z	R	R_3	R_4	mp, °C	recrystn solvent[a]	yield, %	meth	formula[b]
9a	NH_2	H	H	H	65–68	vw	65	F	$C_8H_{13}N_5 \cdot HCl$
9b	NH_2	H	H	CH_3	243–245	qv	86	F	$C_9H_{15}N_5 \cdot HCl$
9c[c]	NH_2	H	CH_3	CH_3	252–255	z	68	F	$C_{10}H_{17}N_5 \cdot 2HCl$
11a	NO_2	H	H	H	143–145	v	61	H	$C_8H_{11}N_5O_2$
11b	NO_2	H	H	CH_3	101–103	v	84	H	$C_9H_{13}N_5O_2$
11c[d]	NO_2	H	CH_3	CH_3	94–96	v	70	H	$C_{10}H_{15}N_5O_2$[e]
13a[c]	NH_2	$COCH_3$	CH_3	CH_3	141–143	vw	60	I	$C_{12}H_{19}N_5O \cdot CH_3CO_2H$
13b[f]	NH_2	$COCH_3$	CH_3	CH_3	145–146	vw	85	I	$C_{12}H_{19}N_5O \cdot 0.5CH_3CO_2H \cdot H_2O$
13c	NH_2	$COCH_2CO_2Et$	H	CH_3				I	$C_{14}H_{21}N_4O_3$[g]

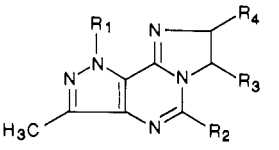
[a,b] See footnotes *a* and *b*, Table I. [c] R_3 and R_4 are trans. [d] Mixture of cis and trans isomers. [e] H: calcd, 6.37; found, 5.91. [f] R_3 and R_4 are cis. [g] Intermediate used directly without characterization.

imidazol-2-yl)-1*H*-pyrazoles **9** and **11** (Table II) as the ultimate step instead of from the imidazole moiety as in Scheme I.

The reaction of 1,2-diamines with 5-cyano-1,3-dimethyl-1*H*-pyrazol-4-amine[9] (**8**) in the presence of *p*-toluenesulfonic acid at 120–160 °C gave 5-(imidazol-2-yl)-1,3-dimethyl-1*H*-pyrazol-4-amines **9** (see Scheme II). Subsequent cyclizations were carried out with ortho esters to furnish **6**. A modified version, especially useful for unsymmetrical 1,2-diamines, employed 5-cyano-1,3-dimethyl-4-nitropyrazole (**10**)[9] as the starting material (see Scheme III). The intermediate 4-nitro-5-(1*H*-imidazol-2-yl)-1*H*-pyrazole **11**, obtained in high yield under mild conditions, could be reduced to compound **9** and then cyclized to **6**. However, it proved more advantageous to acylate compound **11** and then reduced to compound **13**, which often cyclized to **6** on evaporation of the solvent.

When a monoalkyldiamine ($H_2NCHRCH_2NH_2$) was employed in Scheme II, the isomer in which the R group was attached at C-8 was isolated. The isomer of **6** in which R was at C-7 was also formed in this procedure, although in minor amounts. Its presence was readily detected by gas chromatography, but separation and isolation by preparative chromatography was not practical. While both

Table III. Substituted 7,8-Dihydro-3-methyl-1*H*-imidazo[1,2-*c*]pyrazolo[3,4-*e*]pyrimidines



no.	R_1	R_2	R_3	R_4	mp, °C	recrystn solvent[a]	yield, %	meth	formula[b]	ED_{50}, mg/kg mouse ip[c] inhibn of LMA	mouse ip[c] ataxia	rat po,[d] inhibn of cond avoid.
14	CH_3	H	H	H	305	qv	64	E	$C_9H_{11}N_5$·HCl	39.3	>100	18
15	CH_3	H	H	CH_3	116–118	vw	47	C	$C_{10}H_{13}N_5$	49.2	>100	18
16	CH_3	CH_3	H	CH_3	169–172	vw	56	C	$C_{11}H_{15}N_5$·0.1H_2O	32.1	>100	10
17[e]	CH_3	CH_3	CH_3	CH_3	290–292	qv	95	G, J	$C_{12}H_{17}N_5$·HCl	69.1	>100	20
18[f]	CH_3	CH_3	CH_3	CH_3	190	qs	95	J	$C_{12}H_{17}N_5$·HCl·0.5H_2O	37.8	>100	26
19	CH_3	CH_3	H	C_2H_5	123–124	r	70	E	$C_{12}H_{17}N_5$	23.7	>100	7.5
20[g]	CH_3	CH_3	H	C_2H_5	125–127	sw	27	E	$C_{12}H_{17}N_5$	42.8	>100	38
21[h]	CH_3	CH_3	H	C_2H_5	124–127	s	33	E	$C_{12}H_{17}N_5$	61.1	>100	12
22[i]	CH_3	CH_3	H	i-C_3H_7	185–187	qv	37	E	$C_{13}H_{19}N_5$·2HCl·0.2H_2O	57.3	>100	20
23	CH_3	CH_3	H	$(CH_3)_2$	148–150	tw	65	E	$C_{12}H_{17}N_5$·0.1H_2O	22.7	>100	18
24	CH_3	C_2H_5	H	H	165–167	v	75	G	$C_{11}H_{15}N_5$	22.8	>100	17
25	CH_3	C_2H_5	H	CH_3	154–156	w	32	G	$C_{12}H_{17}N_5$	21.6	>100	6.4
26	CH_3	C_2H_5	H	C_2H_5	134–137	vw	83	E	$C_{13}H_{19}N_5$	21.7	>100	32
27	CH_3	C_2H_5	CH_3	H	105–107	vw	65	E	$C_{12}H_{17}N_5$	28.3	>100	35
28	CH_3	c-C_3H_5	H	CH_3	107–110	s	30	C	$C_{13}H_{17}N_5$	46.1	>100	12
29	CH_3	i-C_3H_7	H	CH_3	96–97	v	54	C	$C_{13}H_{19}N_5$	>100	>100	41
30	CH_3	CH_2CO_2Et	H	CH_3	152–154	vw	40	J	$C_{14}H_{19}N_5O_2$	>100	>100	>100
31	CH_3	C_6H_5	H	CH_3	132–134	r	80	C	$C_{16}H_{17}N_5$	62.5	>100	65
32	CH_3	$CH_2C_6H_5$	H	CH_3	232–234	qs	68	C	$C_{17}H_{19}N_5$·HCl·0.1H_2O	21.9	>100	62
33	C_2H_5	CH_3	H	H	168–170	y	82	C, E	$C_{11}H_{15}N_5$	27.7	>100	10
34	C_2H_5	CH_3	H	CH_3	145–147	vw	71	C	$C_{12}H_{17}N_5$·0.3H_2O	25.7	>100	5
35	C_2H_5	C_2H_5	H	CH_3	120–122	r	55	C	$C_{13}H_{19}N_5$·0.1H_2O	27.2	>100	9
36	C_2H_5	CH_3	C_6H_5	H	108–110	s	30	E	$C_{17}H_{19}N_5$[j]	75.5	>100	>100
37	n-C_3H_7	CH_3	H	CH_3	85–90	vw	63	C	$C_{13}H_{19}N_5$·0.2H_2O	37.7	>100	37

[a,b] See footnotes *a* and *b*, Table I. [c] Compounds were evaluated for inhibition of locomotor activity (LMA) and for induction of ataxia. ED_{50}'s were determined from at least three doses (N = 9). [d] Compounds were evaluated for inhibition of shelf-jump avoidance in rats. ED_{50}'s were determined from at least three doses (N = 10). [e] R_3 and R_4 are trans. [f] R_3 and R_3 are cis. [g] *S* configuration. [h] *R* configuration. [i] *S* configuration. [j] N: calcd, 23.87; found, 23.34.

this route and the aziridine route in Scheme I favored the formation of the isomer with the alkyl substituent on the imidazole ring distal to ring juncture (i.e., C-8), the formation of this isomer predominated in Scheme III. The structures of these products were readily established by comparison with the compounds made by the amino alcohol route in Scheme I. When a mixture of 2,3-diaminobutane stereoisomers was used in Scheme III, the resulting isomeric mixture was separated by column chromatography at compound **12** stage, and each isomer was separately converted to **6** (i.e., compounds **17**, **18**) by reduction and cyclization. The trans stereochemistry of **17** was established by preparing the identical compound via Scheme II by starting with DL-*threo*-2,3-diaminobutane.

A number of imidazoline derivatives **6** were oxidized to the corresponding imidazoles **7** with manganese dioxide in refluxing toluene (Scheme I).

Results and Discussion

The potential antipsychotic activity of the target compounds was first identified by using the inhibition of spontaneous locomotor activity test in mice[12] and the inhibition of one-way shelf-jump conditioned avoidance responding in rats[a] (Tables III and IV). Secondary testing of these compounds involved determination of their ability to inhibit continuous (Sidman) avoidance responding in rats[13] (Table V). Selected compounds were also evaluated for ability to bind to D_2 dopamine receptors in vitro by measuring their affinity for displacing [^{3}H]haloperidol from rat striatal membranes.[14] Although many of the compounds exhibited some weak effects in the locomotor activity test (Tables III and IV), compounds **19**, **24**, **25**, **33–35**, and **43** inhibited both shelf-jump and Sidman avoidance with oral potency comparable to that of thioridazine (Table V).

In general, many substitution combinations where R_1, R_2, R_3, and R_4 are hydrogen, methyl, or ethyl gave compounds of similar potency in rodent avoidance paradigms. Optimum potency seemed to emerge when at least one substituent was an ethyl group (cf. **19**, **25**, **33–35**, and **43**). Larger substituents resulted in compounds of lesser potency, e.g., **29**, R_2 = isopropyl; **32**, R_2 = benzyl; **37**, R_1 = *n*-propyl; **40**, R_4 = benzyl. Substituents other than alkyl were deleterious, e.g., **36**, R_3 = phenyl; **44**, R_4 = Cl; **45**, R_2 = CH_2CO_2H. Only modest differences in potency were obtained between the optical isomers. Thus, the *R* isomer **21** appeared to be about 3 times as active as the *S* form **20** in the conditioned avoidance screen. Similarly, the geometric isomers **17** and **18**, where the R_3 and R_4 methyl substituents have a trans and cis relationship, respectively, were not appreciably different in the avoidance test.

Most significantly, these compounds were inactive in the D_2 dopamine receptor binding assay. Compounds **16**, **17**, **19**, **25**, **33**, and **43** displayed no appreciable affinity for brain dopamine receptors ($IC_{50} > 10^{-5}$ M) in contrast to the high affinity of the standard antipsychotic, thioridazine (IC_{50} = 4 nM).

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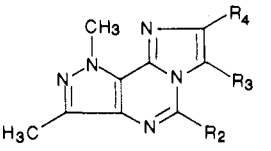
Table IV. Substituted 1,3-Dimethyl-1*H*-imidazo[1,2-*c*]pyrazolo[3,4-*e*]pyrimidines



no.	R_2	R_3	R_4	mp, °C	recrystn solvent[a]	yield, %	meth	formula[b]	ED_{50}, mg/kg mouse ip[c] inhibn of LMA	ED_{50}, mg/kg mouse ip[c] ataxia	ED_{50}, mg/kg rat po,[d] inhibn of cond avoid.
38	CH_3	H	CH_3	196–198	t	75	K	$C_{11}H_{13}N_5 \cdot 0.1H_2O$	73.0	>100	<32
39	CH_3	CH_3	CH_3	175–177	r	20	K	$C_{12}H_{15}N_5$	39.7	>100	10
40	CH_3	H	$CH_2C_6H_5$	173–175	vw	24	K	$C_{17}H_{17}N_5 \cdot 0.1H_2O$	83.3	>100	86
41	C_2H_5	H	H	192–195	t	59	K	$C_{11}H_{13}N_5$	34.2	>100	15
42	C_2H_5	CH_3	H	134–136	tw	51	K	$C_{12}H_{15}N_5$	35.5	>100	11
43	C_2H_5	H	CH_3	182–184	vw	77	K	$C_{12}H_{15}N_5$	36.8	>100	8
44	C_2H_5	Cl	CH_3	172–174	t	55	L	$C_{12}H_{14}ClN_5$	>100	>100	100
45	CH_2CO_2H	H	CH_3	192–194	p	62	K	$C_{12}H_{13}N_5O_2 \cdot 0.25H_2O$	>100	>100	>100
46	C_2H_2	H	C_2H_5	145–147	tw	78	K	$C_{13}H_{17}N_5$	20.6	>30	16
thioridazine									4.40	>10	5.8
haloperidol									0.27	>3	0.3

[a,b] See footnotes *a* and *b*, Table I. [c,d] See footnotes *c* and *d*, Table III.

Table V. Effects of Selected Compounds in the Sidman Avoidance Test in Rats and in the Extrapyramidal Side Effect Test in Monkeys

no.	inhibn Sidman avoid. in rats: ED_{50},[a] mg/kg po	EPS in *Cebus* monkeys at 32 mg/kg po[b]
19	19.2 ± 2.3	N
23	53.7 ± 14.1	N
24	24.4 ± 4.1	N
25	15.7 ± 3.4	N
33	15.3 ± 2.2	N
34	14.8 ± 0.6	N
35	15.8 ± 2.3	N
43	11.4 ± 1.1	N
thioridazine	14.4 ± 0.6	A (at 2.5 mg/kg)
haloperidol	0.8 ± 0.6	A (at 0.125 mg/kg)
clozapine	14.4 ± 0.6	N

[a] At least three doses of each drug were tested in four animals at each dose. Values expressed as ± SEM. [b] Signs of extrapyramidal syndrome (EPS) were measured in at least four haloperidol-sensitized *Cebus* monkeys. A: EPS signs observed in one or more monkeys; N: EPS not observed.

The clinically available dopamine antagonist antipsychotics all induce extrapyramidal side effects (EPS). To estimate this liability for the present series, we employed a test in which *Cebus* monkeys were sensitive to the dystonic effects of haloperidol by its chronic administration.[15] Subsequent acute administration of dopamine antagonists such as thioridazine to these sensitized monkeys at doses comparable to their ED_{50}'s in Sidman avoidance in rats induced dyskinetic movements and dystonic postures. The profile of the imidazopyrazolopyrimidines in this test was in sharp contrast to that of the clinically available antipsychotic drugs in that the present compounds did not produce dystonias at doses that reduced avoidance responding in rats.

On the basis of these results, as well as those obtained from additional preclinical toxicology, pharmacokinetic, and pharmaceutic studies, compound **19** (CI-943) was selected for further clinical evaluation as an antipsychotic agent. As shown in Table VI, **19**, like thioridazine, inhibited spontaneous locomotor activity in rats at doses that did not cause ataxia (ED_{50} = 15.5 mg/kg po) and inhibited high base line self-stimulation in rats (ED_{50} = 10.8 mg/kg po).[16] In squirrel monkeys, **19** inhibited Sidman avoidance responding with an ED_{50} of 7.25 mg/kg po. Compound **19**, unlike known antipsychotics, e.g., thioridazine, did not exhibit any significant in vitro affinity for D_1 or D_2 dopamine receptors.[17] In addition, it did not bind to other CNS receptors such as muscarinic,[18] adrenergic,[19,20] sero-

Table VI. Additional Behavioral Effects of **19**

test	**19**	thioridazine
inhibn of locomotion in rats: ED_{50} ± SEM, mg/kg po	15.5 ± 0.6	13.3 ± 0.32
inhibn of self-stimulation in rats: ED_{50}, mg/kg po	10.8	28.3
inhibn of Sidman avoid. in squirrel monkeys: ED_{50} ± SEM, mg/kg po	7.25 ± 0.33	3.90 ± 0.02

Table VII. Affinity of **19** for Various Neurotransmitter Receptors in Rat Brain[a]

receptor	[^{3}H] ligand	**19**	thioridazine
dopamine D_2	haloperidol	>10	0.004
dopamine D_1	*cis*-flupenthixol	>10	0.080[b]
muscarinic	QNB[c]	>10	0.002
α_1-adrenergic	WB4101[d]	>10	0.017
α_2-adrenergic	clonidine	>10	1.3
β_1-adrenergic	DHA[e]	>10	>10
β_2-adrenergic	DHA[e]	>10	>10
serotonin-1	5-HT[f]	>10	8.70
serotonin-2	spiroperidol	>10	0.060
adenosine A_1	CHA[g]	>10	>10
benzodiazepine	flunitrazepam	>1	>10
Ca^{2+} channel	nitrendipine	>10	–

[a] Reported as IC_{50}'s (μM) to displace the following ligands. These values were determined from four or five concentrations by a nonlinear regression analysis. [b] Obtained from ref 17. [c] Quinuclidinyl benzilate. [d] 2-[[[2-(2,6-Dimethoxyphenoxy)ethyl]-amino]methyl]-2,3-dihydro-1,4-benzodioxin. [e] Dihydroalprenolol. [f] 5-Hydroxytryptamine creatinine sulfate. [g] N^6-Cyclohexyladenosine.

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tonergic,[21] adenosine A_1,[22] or benzodiazepine receptors[23] (Table VII). Finally, unlike all clinically available antipsychotic drugs which increase serum prolactin levels by virtue of their blockade of anterior pituitary dopamine receptors, **19** at doses of 5, 25, and 50 mg/kg ip did not alter serum prolactin levels (e.g., 2 h after dosing: vehicle = 5.3 ± 1.0 ng/mL, mean ± SEM; **19** = 4.4 ± 1.1 ng/mL at 50 mg/kg vs haloperidol = 109 ± 20.0 ng/mL at 1 mg/kg).[24]

In summary, **19**, like known antipsychotics, exhibited activity in a number of behavioral tests predictive of antipsychotic efficacy; however, in contrast to known agents, **19** did not bind to dopamine receptors (or to a number of other CNS receptor binding sites). The fact that **19** did not alter serum prolactin levels in vivo supports the in vitro radioligand binding data and indicates that it does not block dopamine receptor in vivo at behaviorally effective doses. In addition to these tests, **19** has been examined in a wide variety of other biochemical, electrophysiological, and behavioral tests, all of which support the above data. These results will be the subject of forthcoming pharmacological papers.

Experimental Section

Melting points were determined in a Thomas-Hoover melting point apparatus in open capillary tubes and are uncorrected. The structures of the compounds were confirmed by elemental analysis and infrared, mass, and NMR spectrometry. Infrared spectra were recorded on a Digilab FTP-14 infrared spectrometer or a Nicolet MX-1/360 FT-IR instrument, and NMR spectra were obtained on a Varian EM 390 90-MHz or Brucker WH 90 spectrometer. Mass spectra were obtained on a Finnigan 4500 and were consistent with the proposed structures. Where analyses are indicated by the symbols of the elements, the results are within 0.4% of the theoretical values. TLC was carried out with 0.25-mm silica gel 60 F254 (E. Merck) glass plates. GLC was carried out on a Shimadzu GC-Mini 2. Unless otherwise noted, starting materials were obtained from Aldrich Chemical Co. and were used without further purification. Representative general procedures for the synthesis illustrated in Schemes I–III are as follows.

5-Ethyl-1,6-dihydro-1,3-dimethyl-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (2c). General Procedure A. A mixture of 14 g (0.1 mol) of 4-amino-1,3-dimethyl-1*H*-pyrazole-5-carbonitrile[9] and 14 g (0.11 mol) of propionic anhydride in 120 mL of ethyl acetate was stirred under reflux for 3.5 h and evaporated in vacuo. The residue was treated with ether and filtered to give 18 g (94%) of ***N*-(5-cyano-1,3-dimethyl-1*H*-pyrazol-4-yl)propanamide**, mp 153–155 °C from ethanol.

The above compound (18 g, 0.094 mol) was added in portions to a solution prepared by adding 24 mL of 30% hydrogen peroxide to 250 mL of water containing 6 g (0.15 mol) of sodium hydroxide. The mixture was stirred at 80 °C for 5 h, cooled, and acidified with acetic acid. The product was collected to yield 12.7 g (70%) of **2c**, mp 220–222 °C from ethanol.

1,6-Dihydro-1,3,5-trimethyl-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (2b). General Procedure B. A solution of 42 g (0.23 mol) of **1,3-dimethyl-4-nitro-1*H*-pyrazole-5-carboxamide**[9] in 300 mL of 95% ethanol and 50 mL of water was treated with 50 g of iron powder (reduced) and 4 mL of concentrated hydrochloric acid. The mixture was stirred under reflux for 3.5 h; the mixture was filtered, and the filtrate was evaporated to dryness. The resulting amino carboxamide 1 ($R_1 = CH_3$) was suspended in 300 mL of dichloromethane, and 30 mL of acetic anhydride was added dropwise with stirring. After being stirred overnight, the mixture was diluted with 100 mL of petroleum ether and filtered to yield 38 g (85%) of ***N*-[5-(aminocarbonyl)-1,3-dimethylpyrazol-4-yl]acetamide**, mp 247–249 °C. This solid (38 g, 0.19 mol) was stirred with 365 mL of 1 N sodium hydroxide at 80–90 °C for 3 h, cooled, and acidified with 30 mL of glacial acetic acid. The mixture was filtered to yield 28.5 g (75%) of **2b**, mp 258–260 °C.

7,8-Dihydro-1,3,5,8-tetramethyl-1*H*-imidazo[1,2-*c*]pyrazolo[3,4-*e*]pyrimidine (16). General Procedure C. A mixture of 30.5 g (0.17 mol) of **2b** and 37 g (0.18 mol) of phosphorus pentachloride in 350 mL of phosphorus oxychloride was stirred under reflux for 7 h. The resulting solution was evaporated in vacuo. The solid residue was redissolved in 300 mL of dichloromethane and stirred with 200 mL of saturated aqueous sodium bicarbonate solution. The organic layer was dried over magnesium sulfate and evaporated in vacuo to yield 30 g (98%) of **7-chloro-1,3,5-trimethyl-1*H*-pyrazolo[4,3-*d*]pyrimidine** (**3**; $R_1 = R_2 = CH_3$), mp 91–93 °C from ethyl acetate–petroleum ether.

A solution of 30 g (0.153 mol) of the above chloro compound was dissolved in 300 mL of dichloromethane, cooled in an ice bath, and treated dropwise with a mixture of 28 mL (0.2 mol) of triethylamine and 17 g (0.3 mol) of 2-methylaziridine. After standing at 20 °C for 2 days, the solution was washed with a sodium bicarbonate solution, dried over magnesium sulfate, and evaporated in vacuo to give 34 g of **1,3,5-trimethyl-7-(2-methyl-1-aziridinyl)-1*H*-pyrazolo[4,3-*d*]pyrimidine**, **4b**, as an oil.

A solution of 4.4 g of **4b** (0.02 mol) in 50 mL of acetone was stirred under reflux with 3.5 g of sodium iodide for 3 h and evaporated in vacuo. The residue was partitioned between 150 mL of dichloromethane and 50 mL of 20% aqueous sodium carbonate solution. The organic layer was separated, dried over magnesium sulfate, and evaporated in vacuo. The resulting solid was crystallized from acetonitrile to give 2.5 g (56%) of **16**, mp 169–172 °C from ethyl acetate–petroleum ether.

***N*-(1,3-Dimethyl-1*H*-pyrazolo[4,3-*d*]pyrimidin-7-yl)-2-aminoethanol (5a). General Procedure D.** A mixture of 5.0 g (0.03 mol) of **2a** and 6 g (0.03 mol) of phosphorus pentachloride in 100 mL of phosphorus oxychloride was stirred under reflux for 3 h. The resulting solution was evaporated in vacuo. The solid residue was redissolved in dichloromethane and stirred with saturated aqueous sodium bicarbonate solution. The organic layer was dried over magnesium sulfate and evaporated in vacuo to yield 5.5 g of **7-chloro-1,3-dimethyl-1*H*-pyrazolo[4,3-*d*]pyrimidine** (**3**; $R_1 = CH_3$, $R_2 = H$), mp 87–90 °C.

To a solution of 5.5 g (0.03 mol) of the chloro compound in 100 mL of dichloromethane were added 3 g (0.05 mol) of 2-aminoethanol and 6 mL of triethylamine. The mixture was refluxed for 2 h and allowed to stand for 18 h. The solvent was removed in vacuo. The residue was dissolved in dichloromethane and washed with concentrated ammonium hydroxide. The organic extracts were dried over magnesium sulfate and evaporated to afford 4.1 g (64%) of **5a**, mp 200–202 °C.

7,8-Dihydro-1,3-dimethyl-1*H*-imidazo[1,2-*c*]pyrazolo[3,4-*a*]pyrimidine (14). General Procedure E. A solution of 5.0 g (0.021 mol) of **5a** (hydrochloride) in 70 mL of phosphorus oxychloride was refluxed for 2 h. The excess phosphorus oxychloride was evaporated in vacuo. The residue was taken up in 200 mL of dichloromethane and washed with 70 mL of 20% aqueous sodium carbonate. The organic extracts were dried over magnesium sulfate and evaporated. The residue was slurried with ether and collected to afford 3.2 g (64%) of 14, mp 305 °C.

5-(4,5-Dihydro-4(or 5)-methyl-1*H*-imidazol-2-yl)-1,3-dimethyl-1*H*-pyrazol-4-amine (9b). General Procedure F. *p*-Toluenesulfonic acid (38 g, 0.2 mol) was added portionwise to 16 g (0.2 mol) of 1,2-diaminopropane at 70–90 °C. To the clear melt was added 27 g (0.2 mol) of 4-amino-1,3-dimethyl-1*H*-pyrazole-5-carbonitrile[9] (8) in portions with stirring under nitrogen. The mixture was heated at 190–200 °C for 3 h. The melt was stirred into a mixture of 400 mL of dichloromethane and 100 mL of concentrated ammonium hydroxide. The organic layer was separated, dried over anhydrous magnesium sulfate, and evaporated in vacuo to yield 27 g of a viscous red-brown gum. A sample of **9b** was characterized as the hydrochloride salt from 2-propanolic hydrogen chloride and ethyl acetate, mp 243–245 °C.

5-Ethyl-7,8-dihydro-1,3,8-trimethyl-1*H*-imidazo[1,2-*c*]pyrazolo[3,4-*e*]pyrimidine (25). General Procedure G. A mixture of 13.5 g (0.07 mol) of **9b** and 20 g (0.14 mol) of triethyl orthopropionate in 200 mL of toluene and 10 mL of glacial acetic acid was refluxed for 3 h. The mixture was extracted with 200 mL of 2 N hydrochloric acid. The aqueous layer was made alkaline

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with 50% aqueous sodium hydroxide and extracted with dichloromethane. The organic extracts were dried over magnesium sulfate and evaporated in vacuo to afford 14 g of a semisolid. The crude product was crystallized from ethyl acetate–petroleum ether to yield 5.3 g (32%) of **25**, mp 154–156 °C.

5-(4,5-Dihydro-4,5-dimethyl-1*H*-imidazol-2-yl)-1,3-dimethyl-4-nitro-1*H*-pyrazole (Cis and Trans Mixture) (11c). General Procedure H. A pea-sized piece of sodium was dissolved in 200 mL of absolute methanol. To this solution was added 41.5 g (0.25 mol) of 1,3-dimethyl-4-nitro-1*H*-pyrazole-5-carbonitrile.[9] After standing at room temperature for 18 h, the methanolic solution was added slowly to a melt (70–90 °C) of a salt of 2,3-diaminobutane prepared by adding 48 g (0.25 mol) of *p*-toluenesulfonic acid monohydrate to 23 g (0.25 mol) of 2,3-diaminobutane (a mixture of meso and DL-threo forms). The mixture was stirred and heated slowly to 130 °C, with removal of the methanol by distillation. The cooled melt was dissolved in 200 mL of 4 N hydrochloric acid and extracted with toluene. The aqueous solution was mixed with dichloromethane, and excess concentrated ammonium hydroxide was added to a resultant pH of 11. The organic layer was separated, dried over anhydrous magnesium sulfate, and evaporated in vacuo. There remained 18 g (70%) of **11c** as an oil, which was essentially a two-component mixture by gas chromatography (56:44).

***trans*- and *cis*-1-[2-(4-Amino-1,3-dimethyl-1*H*-pyrazol-5-yl)-4,5-dihydro-4,5-dimethyl-1*H*-imidazol-1-yl]ethanone (13a and 13b). General Procedure I.** A solution of 26 g (0.11 mol) of isomeric mixture **11c** in 250 mL of dichloromethane was treated with 30 g (0.11 mol) of acetyl chloride and 15 mL of triethylamine at 5–10 °C. After being stirred for 4 h at room temperature, the reaction mixture was washed with saturated sodium bicarbonate solution. The organic layer was separated, dried over magnesium sulfate, and evaporated in vacuo to yield 27 g of an oil containing a mixture of isomers. This mixture was separated into two components by flash chromatography over ca. 2.5 L of SiO_2 [MC/B silica gel 60 (230–400 mesh)] in ethyl acetate with rechromatography of the central fractions. By this procedure, there were obtained 12 g of the trans form and 7.5 g of the cis form of **1-[2-(1,3-dimethyl-4-nitro-1*H*-pyrazol-5-yl)-4,5-dihydro-4,5-dimethyl-1*H*-imidazol-1-yl]ethanone (12)**, each as an oil with an isomeric purity of 90–95% by gas chromatography.

A solution of 12 g (0.043 mol) of the trans isomer (**12** above) in 120 mL of glacial acetic acid was hydrogenated over a catalytic amount of 10% Pd/C at an initial pressure of 50 psi. The catalyst was removed, and the solvent was evaporated. The residue was recrystallized from ethyl acetate–petroleum ether to afford 7.9 g (23%) of **13a** as an acetate salt, mp 141–143 °C.

A solution of 7.5 g (0.027 mol) of the cis isomer (**12** above) in 120 mL of glacial acetic acid was likewise hydrogenated. The residue was recrystallized from ethyl acetate–petroleum ether to afford 5.3 g (17%) of **13b** as an acetate salt, mp 145–146 °C.

***trans*-7,8-Dihydro-1,3,5,7,8-pentamethyl-1*H*-imidazo[1,2-*c*]pyrazolo[3,4-*e*]pyrimidine Hydrochloride (17). General Procedure J.** A solution of 24 g (0.09 mol) of **13a** in 150 mL of toluene containing 20 mL of acetic acid and 20 mL of triethyl orthoacetate was refluxed for 18 h. The toluene solution was extracted with 200 mL of 3 N hydrochloric acid. The aqueous extract was mixed with dichloromethane and made alkaline with excess concentrated ammonium sulfate. The organic layer was separated, dried over magnesium sulfate, and evaporated in vacuo to give 17.5 g of an oil. This oil was dissolved in 30 mL of 2-propanol and 40 mL of ethyl acetate and treated with 15 mL of a 20% 2-propanolic hydrogen chloride. There was obtained 14.5 g of **17** as the hydrochloride salt, mp 290–292 °C.

The configuration of the 7,8-dimethyl groups of **17** was established as trans on the bais of an independent synthesis starting from DL-*threo*-2,3-diaminobutane employing procedures G and H via intermediate **9c**.

5-Ethyl-1,3,8-trimethyl-1*H*-imidazo[1,2-*c*]pyrazolo[3,4-*e*]pyrimidine (43). General Procedure K. Manganese dioxide (45 g) was dried by stirring vigorously in 400 mL of refluxing toluene for 1.5 h and using a Dean–Stark trap to remove water. After cooling to about 90 °C, 15 g (0.065 mol) of **25** was added. The mixture was stirred and refluxed for 5 h and filtered while hot. The filtrate was concentrated in vacuo, and the concentrate was diluted with 70 mL of petroleum ether, cooled, and filtered to yield 11.5 g (77%) of **43**, mp 182–184 °C.

7-Chloro-5-ethyl-1,3,8-trimethyl-1*H*-imidazo[1,2-*c*]pyrazolo[3,4-*e*]pyrimidine (44). General Procedure L. To a solution of 4.4 g (0.02 mol) of **43** in 150 mL of chloroform was added 2.7 g (0.02 mol) of *N*-chlorosuccinimide. The mixture was refluxed for 1.5 h. After the reaction mixture was washed with several portions of 2 N sodium hydroxide, the organic extracts were dried over anhydrous magnesium sulfate and evaporated in vacuo. The resulting solid was recrystallized from toluene to yield 3.7 g (55%) of **44**, mp 172–174 °C.

Pharmacological Methods. The following procedures were used as described in a previous paper:[3] the locomotor activity and ataxia test in mice and rats,[12] the one-way shelf-jump conditioned avoidance test in rats,[8] the Sidman avoidance procedure in rats and monkeys,[13] the extrapyramidal side effect test in *Cebus* monkeys,[15] the receptor binding assays,[14,17–23] and the serum prolactin assay.[24] The suppression of high base line self-stimulation test[16] was also described in an earlier paper.[25]

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Registry No. 1 (R_1 = CH_3,X = $(CONH_2)$, 59023-32-4; 1 (R_1 = C_2H_5,X = CN), 26308-60-1; 1 (R_1 = C_3H_7,X = CN), 111770-08-2; **2a**, 51222-27-6; **2b**, 59023-33-5; **2c**, 89239-43-0; **2d**, 89257-69-2; **2e**, 89239-54-3; **2f**, 104393-31-9; **2g**, 104393-21-7; **2h**, 89239-59-8; **2i**, 89239-67-8; **2j**, 89239-71-4; **3** (R_1 = R_2 = CH_3), 89239-22-5; **3** (R_1 = CH_3,R_2 = H), 89239-18-9; **4a**, 89239-61-2; (±)-**4b**, 111770-10-6; (±)-**4c**, 111770-11-7; (±)-**4** (R_1 = R_4 = CH_3,R_2 = R_3 = H), 111770-63-9; (±)-**4** (R_1 = R_4 = CH_3,R_2 = c-C_3H_5,R_3 = H), 111770-64-0; (±)-**4** (R_1 = R_4 = CH_3,R_2 = c-C_3H_7,R_3 = H), 111770-65-1; (±)-**4** (R_1 = R_4 = CH_3,R_2 = $CH_2C_6H_5$,R_3 = H), 111770-66-2; (±)-**4** (R_1 = C_2H_5,R_2 = R_4 = CH_3,R_3 = H), 111770-67-3; (±)-**4** (R_1 = R_2 = C_2H_5,C_3 = H,R_4 = CH_3), 111770-68-4; (±)-**4** (R_1 = C_3H_7,R_2 = R_4 = CH_3,R_4 = H), 111770-69-5; **5a**, 111770-29-7; **5a**·HCl, 111770-34-4; (±)-**5b**, 111770-30-0; (±)-**5b**·HCl, 111770-35-5; **5c**, 111821-34-2; **5c**·HCl, 111821-36-4; **5d**, 111821-35-3; **5d**·HCl, 111900-58-4; **5e**, 89239-36-1; **5e**·HCl, 111770-36-6; **5f**, 89239-41-8; **5f**·HCl, 111770-37-7; (±)-**5g**, 111770-31-1; (±)-**5g**·HCl, 111770-38-8; (±)-**5h**, 111770-32-2; (±)-**5h**·HCl, 111770-39-9; **5i**, 89239-64-5; **5i**·HCl, 111770-40-2; (±)-**5j**, 111770-33-3; (±)-**5j**·HCl, 111770-41-3; 8, 32183-14-5; **9a**, 89239-15-6; **9a**·HCl, 111770-42-4; (±)-**9b**, 111770-45-7; (±)-**9b**·HCl, 111770-43-5; (±)-**9c**, 111770-46-8; (±)-**9c**·HCl, 111770-44-6; **10**, 32183-13-4; 11a, 89239-14-5; (±)-**11b**, 111770-47-9; (±)-*cis*-**11c**, 111770-48-0; (±)-*trans*-**11c**, 111770-49-1; (±)-*cis*-**12**, 111770-51-5; (±)-*trans*-**12**, 111770-50-4; (±)-**13a**, 111770-53-7; (±)-**13b**, 111770-55-9; (±)-**13c**, 111770-56-0; 14, 89239-16-7; **14**·HCl, 111770-70-8; (±)-**15**, 111770-12-8; (±)-**16**, 111821-31-9; (±)-**17**, 111770-13-9; (±)-**17**·HCl, 111770-71-9; (±)-**18**, 111770-14-0; (±)-**18**·HCl, 111770-72-0; (±)-**19**, 111770-15-1; **20**, 111821-32-0; **21**, 111821-32-0; **22**, 89239-37-2; **22**·2HCl, 111770-73-1; **23**, 89239-42-9; **24**, 89239-46-3; (±)-**25**, 111770-16-2; (±)-**26**, 111770-17-3; (±)-**27**, 111770-18-4; (±)-**28**, 111770-19-5; (±)-**29**, 111770-20-8; (±)-**30**, 111770-21-9; (±)-**31**, 111770-22-0; (±)-**32**, 111770-23-1; (±)-**32**·HCl, 111770-74-2; (±)-**33**, 111770-24-2; (±)-**34**, 111770-25-3; (±)-**35**, 111770-26-4; (±)-**36**, 111770-27-5; (±)-**37**, 111770-28-6; **38**, 89239-94-1; **39**, 89239-89-4; **40**, 111770-57-1; **41**, 111770-58-2; **42**, 111770-58-2; **43**, 89239-93-0; **44**, 111770-60-6; **45**, 111770-61-7; **46**, 111770-62-8; $(HCO)_2O$, 1558-67-4; $(H_3CCO)_2O$, 108-24-7; $(C_2H_5CO)_2O$, 123-62-6; (*c*-$C_3H_5CO)_2O$, 33993-24-7; (*i*-$C_3H_7CO)_2O$, 97-72-3; $(C_6H_5CO)_2O$, 93-97-0; $(C_6H_5CH_2CO)_2O$, 1555-80-2; $H_2N(CH_2)_2NH_2$, 107-15-3; $H_2NCH(CH_3)CH_2NH_2$, 78-90-0; *meso*-$H_2NCH(CH_3)CH(CH_3)NH_2$, 20759-15-3; (±)-*threo*-$H_2NCH(CH_3)CH(CH_3)NH_2$, 20699-48-3; $H_3CC(OC_2H_5)_3$,

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78-39-7; $C_2H_5C(OC_2H_5)_3$, 78-39-7; $ClCOCH_2CO_2C_2H_5$, 36239-09-5; $NH(CH_2)_2OH$, 141-43-5; (±)-$NHCH(C_2H_5)CH_2OH$, 13054-87-0; $NHCH(C_2H_5)CH_2OH$, 5856-62-2; $NHCH(C_2H_5)CH_2OH$, 5856-63-3; (S)$NHCH(i\text{-}C_3H_7)CH_2OH$, 2026-48-4; $NHC(CH_3)_2CH_2OH$, 124-68-5; (±)-$NHCH_2CH(CH_3)OH$, 1674-56-2; (±)-$NHCH_2CH(C_6H_5)OH$, 1936-63-6; aziridine, 151-56-4; 2-methylaziridine, 75-55-8; *N*-(5-cyano-1,3-dimethyl-1*H*-pyrazo-4-yl)propanamide, 111770-09-3; 1,3-Dimethyl-4-nitro-1*H*-pyrazole-5-carboxamide, 78208-58-9; *N*-(5-aminocarbonyl)-1,3-dimethylpyrazol-4-yl) acetamide, 89239-25-8.

Imidazole–Pyridine Bioisosterism: Comparison of the Inotropic Activities of Pyridine- and Imidazole-Substituted 6-Phenyldihydropyridazinone Cardiotonics

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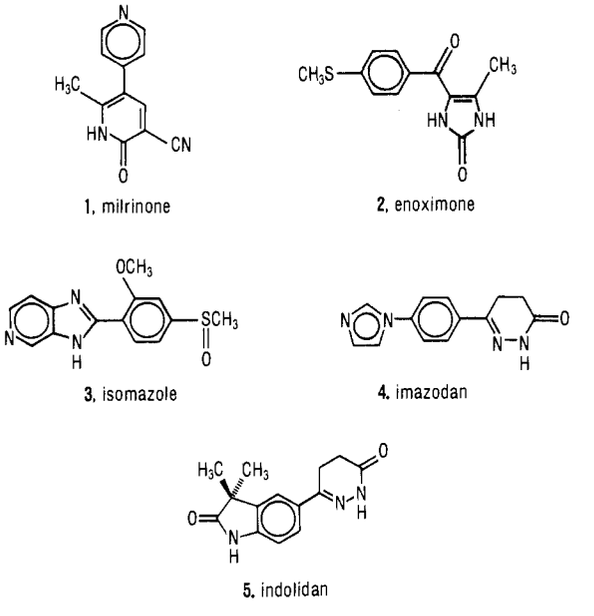
We previously reported the structure–activity relationships (SAR), molecular structure, pharmacology, and molecular pharmacology of indolidan (LY195115), a potent and long-acting dihydropyridazinone cardiotonic. Our 6-phenyldihydropyridazinone SAR studies revealed the critical nature of the substituent at the para position of the phenyl ring. An acetamido substituent provided potent cardiotonic activity and we hypothesized that this may relate to the ability of the acetamide carbonyl to function as a hydrogen-bond acceptor. To further address this question, we prepared **15** (4,5-dihydro-6-[4-(3-pyridinyl)phenyl]-3(2*H*)-pyridazinone), the 3-pyridyl analogue of imazodan. As is the case with imazodan, this (pyridylphenyl)dihydropyridazinone possesses a nitrogen three atoms removed from the phenyl ring, but the molecular framework through which it is attached to the phenyldihydropyridazinone moiety is altered. After iv administration to pentobarbital-anesthetized dogs, inotropic ED_{50} values of **15**, imazodan, and the parent compound, 4,5-dihydro-6-phenyl-3(2*H*)-pyridazinone, were 19.4, 50.1, and 6330 μg/kg, respectively. Thus, **15** is over 2-fold more potent than imazodan and 326-fold more potent than the parent, unsubstituted compound. These data, as well as data obtained with other congeners, are consistent with the hypothesis that a suitably oriented hydrogen-bond-acceptor site contributes to the high degree of inotropic potency observed with these dihydropyridazinone cardiotonics.

During the past decade there has been a resurgence of interest in development of agents for treatment of congestive heart failure (CHF).[1,2] Traditional pharmacological therapy, including digitalis and diuretics, has been supplemented with use of vasodilators to alleviate the excessive vascular tone that characterizes this disease state.[3,4] The long-term benefit of preload and afterload reduction in CHF patients has recently been confirmed with the demonstration that a combination of hydralazine and isosorbide dinitrate resulted in a decrease in mortality.[5] Moreover, the pathophysiological role of the renin–angiotensin cascade in CHF is now well-appreciated, and captopril has been approved for CHF therapy on the basis of its favorable effects on exercise tolerance.[6] Effects of the angiotensin converting enzyme inhibitor enalapril on mortality was recently addressed in a long-term, multicenter clinical trial and the drug prolonged survival in severely ill CHF patients.[7]

Several representatives of a class of cardiotonics that simultaneously express inotropic and vasodilator activities have been studied clinically. These include milrinone, enoximone, imazodan, isomazole, and indolidan (LY195115, Chart I).[8,9] Use of this class of drugs, which

Chart I



appear to exert their pharmacological effects via inhibition of a specific isozyme of phosphodiesterase,[10,11] has resulted in considerable controversy. These compounds have been studied primarily in severely ill CHF patients who are refractory to established therapy, and although they produce hemodynamic and functional improvements, mortality has been high in the small, uncontrolled clinical studies published to date. There is concern that these

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