1,3-Dialkyl-4-(iminoarylmethyl)-1*H*-pyrazol-5-ols. A Series of Novel Potential Antipsychotic Agents

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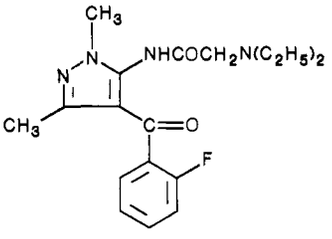
2-(Diethylamino)-*N*-[4-(2-fluorobenzoyl)-1,3-dimethyl-1*H*-pyrazol-5-yl]acetamide (1) was recently found to have an antipsychotic-like profile in behavioral animal tests but, unlike clinically available antipsychotic agents, did not interact with dopamine receptors. Compound 1 was apparently metabolized to (5-amino-1,3-dimethyl-1*H*-pyrazol-4-yl)(2-fluorophenyl)methanone (2), which was both active in the behavioral animal tests and toxic. The synthesis and pharmacological evaluation of a series of 1,3-dialkyl-4-(iminoarylmethyl)-1*H*-pyrazol-5-ols are described in which the hydroxy and imine functionalities were selected as possible isosteric replacements for the amino and ketone groups of the earlier series. The initial target, 1,3-dimethyl-4-(iminophenylmethyl)-1*H*-pyrazol-5-ol (28), like known antipsychotics, reduced spontaneous locomotion in mice at doses that did not cause ataxia, and unlike known agents, it did not bind to D_2 dopamine receptors in vitro. An examination of the SAR of related compounds indicated that maximal activity was obtained with analogues containing methyl groups at the 1- and 3-positions on the pyrazole ring and with a 3-chloro substituent on the phenyl ring. Replacement of the hydrogen atom of the imine moiety with various substituents led to loss of activity. Attempts to synthesize the 2-fluorophenyl compound analogous to 2 resulted in ring-closure to 1,3-dimethyl[1]benzopyrano[2,3-*c*]pyrazol-4(1*H*)-one (65). 4-[(3-Chlorophenyl)iminomethyl]-1,3-dimethyl-1*H*-pyrazol-5-ol (41) was evaluated in additional tests. It inhibited conditioned avoidance responding in both rats and monkeys but, unlike available antipsychotic drugs, did not elicit dystonic movements in a primate model of antipsychotic-induced extrapyramidal side effects.

The discovery of antipsychotic or neuroleptic drugs three decades ago revolutionized the treatment of schizophrenia.[1] These drugs control the most disruptive symptoms of the disease (delusions, hallucinations, loose associations) and have allowed patients to be moved from a hospital environment back into the community. Unfortunately, these agents have serious limitations. While they control the more commonly known positive symptoms of schizophrenia, they are less effective against the insidious and debilitating negative symptoms (e.g., social withdrawal, blunted affect, anhedonia).[2] In addition, antipsychotic drugs carry a high liability for causing neurological side effects such as the extrapyramidal syndrome (EPS) and tardive dyskinesia.[3]

Although there are now several distinct chemical classes of antipsychotic drugs available clinically, none of these agents offers a significant advancement in the treatment of schizophrenia.[4] The clinical efficacy of these drugs is commonly attributed to their blockade of brain dopamine receptors, and it is also this mechanism that is thought to be responsible for their neurological side effects.[5]

These clinical limitations of dopamine receptor blockers have prompted the search for new agents with improved clinical profiles that do not owe their efficacy to a dopaminergic mechanism of action. One approach to finding such drugs would be to identify compounds that have antipsychotic-like profiles in recognized preclinical behavioral tests but that do not act via the brain dopamine receptors.

In a recent paper we described a series of 2-(substituted amino)-*N*-[4-(2-fluorobenzoyl)-1,3-dimethyl-1*H*-pyrazol-5-yl]acetamides as potential non-dopaminergic antipsychotic agents.[6] These compounds shared the behavioral profile of antipsychotics but were not dopamine antagonists. For example, the diethylamino analogue 1 produced behavioral effects similar to those produced by known antipsychotic drugs in both rodent and monkey tests for antipsychotic efficacy but did not have affinity for brain dopamine receptors. It also did not produce signs of EPS in a highly predictive primate model. Unfortunately, mammary carcinomas observed with these compounds prevented the possibility of clinical verification of this activity.[7]



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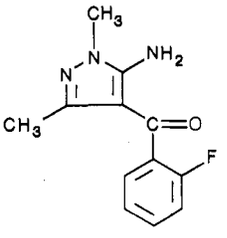

2

Preliminary studies suggested that 1 was metabolized to the unsubstituted 5-aminopyrazole 2, which also had antipsychotic-like preclinical activity but was toxic.[7,8] Because of this we became interested in examining potential isosteric replacements for the functionalities on the pyrazole ring of 2 in order to obtain compounds free of this toxicity. In this paper we describe the results of our investigation of one such series, the 4-(iminoarylmethyl)-1*H*-pyrazol-5-ols.

Chemistry

The general routes for the synthesis of the 1,3-dialkyl-4-(iminoarylmethyl)-1*H*-pyrazol-5-ols as well as the N-substituted imines (28–62) are illustrated in Scheme I. The starting 1,3-dialkylpyrazolones were either synthesized

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(3) (a) Klein, D. F.; Davis, J. M. *Diagnosis and Treatment of Psychiatric Disorders*; Williams & Wilkins: Baltimore, 1969. (b) Crane, G. E. *Handbook of Psychopharmacology*; Iversen, L. L., Iversen, S. D., Snyder, S. H., Eds.; Plenum: New York, 1978; Vol. 10, Chapter 5.
(4) Enna, S. J.; Coyle, J. T. *Neurochemical, Behavioral, and Clinical Perspectives*; Coyle, J. T., Enna, S. J., Eds.; Raven: New York, 1983; p 1.
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(8) Butler, D. E.; Wise, L. D.; DeWald, H. A. *J. Med. Chem.* **1984**, *27*, 1396.

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Scheme I

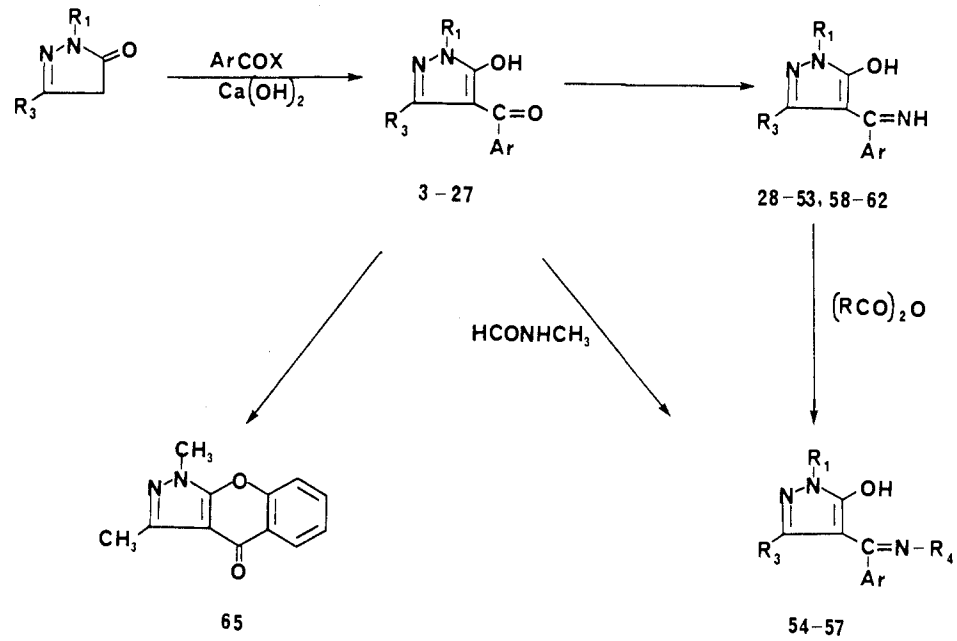
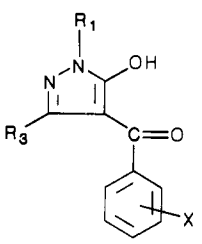


Table I. (Aryl)(1,3-dialkyl-5-hydroxy-1*H*-pyrazol-4-yl)methanones



no.	R_1	R_3	X	yield,[a] %	mp, °C	formula[b]
3[c]	CH_3	CH_3	H			
4	C_2H_5	CH_3	H	43	109–110	$C_{13}H_{14}N_2O_2$
5	C_3H_7	CH_3	H	41	103–104	$C_{14}H_{16}N_2O_2$
6	C_4H_9	CH_3	H	25	87–88	$C_{15}H_{18}N_2O_2$
7	CH_3	CH_3	4-F	57	178–180	$C_{12}H_{11}FN_2O_2$
8	CH_3	CH_3	4-CF_3	95	214–215	$C_{13}H_{11}F_3N_2O_2$
9	CH_3	CH_3	4-CH_3	81	145–147	$C_{13}H_{14}N_2O_2$
10	CH_3	CH_3	4-NO_2	64	202–205	$C_{12}H_{11}N_3O_4$
11	CH_3	CH_3	3,4-Cl_2	61	246–248	$C_{12}H_{10}Cl_2N_2O_2$
12	CH_3	CH_3	3-Cl	62	167–168	$C_{12}H_{11}ClN_2O_2$
13	CH_3	CH_3	3-F	47	139–141	$C_{12}H_{11}FN_2O_2$
14	CH_3	CH_3	3-CF_3	63	153–155	$C_{13}H_{11}F_3N_2O_2$
15	CH_3	CH_3	3-CH_3	65	131–133	$C_{13}H_{14}N_2O_2 \cdot 0.1H_2O$
16	CH_3	CH_3	3-NO_2	61	286–287	$C_{12}H_{11}N_3O_4$
17	CH_3	CH_3	3,5-Cl_2	51	245–248	$C_{12}H_{10}Cl_2N_2O_2$
18	C_2H_5	CH_3	3-Cl	30	97–98	$C_{13}H_{13}ClN_2O_2$
19	C_3H_7	CH_3	3-Cl	41	116–117	$C_{14}H_{15}ClN_2O_2$
20	*i*-Pr	CH_3	3-Cl	92	168–172	$C_{14}H_{15}ClN_2O_2 \cdot H_2O$[d]
21	C_4H_9	CH_3	3-Cl	19	95–96	$C_{15}H_{17}ClN_2O_2$
22	CH_3	C_2H_5	3-Cl	14	185–187	$C_{13}H_{13}ClN_2O_2 \cdot 0.1H_2O$
23	CH_3	CH_3	2-F	47	153–155	$C_{12}H_{11}FN_2O_2$
24	CH_3	CH_3	2-OCH_3	42	159–162	$C_{13}H_{14}N_2O_3$
25	CH_3	CH_3	(2-thienyl)[e]	93	157–160	$C_{10}H_{10}N_2O_2S$
26	CH_3	CH_3	(2-furanyl)[e]	71	88–89	$C_{10}H_{10}N_2O_3$
27	CH_3	CH_3	(2-naphthenyl)[e]	83	195–196	$C_{16}H_{14}N_2O_2$

[a] No attempts were made to maximize yields. [b] All compounds were analyzed for C, H, N. Except where noted, values agreed with calculated values within ±0.4%. [c] Synthesized as described in ref 21. [d] H: calcd, 5.77; found, 5.23. [e] Replacement for phenyl group.

as described in the literature or prepared by the method of Butler and DeWald[9] (see Experimental Section). Reaction of the pyrazolones with the appropriately substituted aroyl chlorides and calcium hydroxide in dioxane under reflux gave good yields of the requisite hydroxy ketones **3–27** (Table I). Conversion of these ketones to the corresponding imines (**28–53, 58–62**) was carried out by several methods (Table II). The most general method (A) involved refluxing the hydroxy ketones with formamide. Several imines were prepared by the above reaction sequence without isolation of the intermediate hydroxy ketones (method B). Alternatively, the desired hydroxy imines were synthesized by pyrolysis of the hydroxy ketones with ammonium carbonate in a pressure vessel at 110 °C (method C) or by heating the hydroxy ketones with

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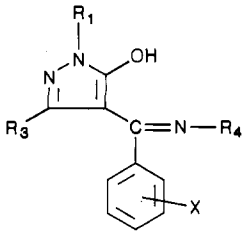
Table II. 1,3-Dialkyl-4-(iminoarylmethyl)-1*H*-pyrazol-5-ols



no.	R_1	R_3	R_4	X	method	yield,[a] %	mp, °C	formula[b]	inhibn of LMA/ataxia:[c] ED_{50}, mg/kg ip		inhibn of [^{3}H]haloperidol binding:[d] IC_{50}, nM
28	CH_3	CH_3	H	H	A	39	228–230	$C_{12}H_{13}N_3O$	13.9	30.2	>10000
29	C_2H_5	CH_3	H	H	A	53	213–214	$C_{13}H_{15}N_3O$	11.8	21.5	>10000
30	C_3H_7	CH_3	H	H	A	67	185–187	$C_{14}H_{17}N_3O$	11.6	25.2	
31	C_4H_9	CH_3	H	H	A	59	218–220	$C_{15}H_{19}N_3O$	48.7	>100	
32	CH_3	H	H	H	B	7.5	227–229	$C_{11}H_{11}N_3O$	49.1	>100	
33	CH_3	CH_3	H	4-Cl	B	56	248–250	$C_{12}H_{12}ClN_3O$	18.9	>56	
34	CH_3	CH_3	H	4-F	A	80	224–226	$C_{12}H_{12}FN_3O$	15.0	>30	>10000
35	CH_3	CH_3	H	4-CF_3	A	69	283–284	$C_{13}H_{12}F_3N_3O$	31.4	>30	>10000
36	CH_3	CH_3	H	4-OCH_3	B	73	178–179	$C_{13}H_{15}N_3O_2$	>100	>100	
37	CH_3	CH_3	H	4-CH_3	A	76	218–219	$C_{13}H_{15}N_3O$	>100	>100	
38	CH_3	CH_3	H	4-NO_2	A	58	299–301	$C_{12}H_{12}N_4O_3$	>90	>90	
39	CH_3	CH_3	H	4-NHz	G	64	82–85	$C_{12}H_{14}N_4O\cdot 2H_2O$	>100	>100	
40	CH_3	CH_3	H	3,4-Cl_2	A	64	283–285	$C_{12}H_{11}Cl_2N_3O$	26.4	>30	
41	CH_3	CH_3	H	3-Cl	A,D	82	236–238	$C_{12}H_{12}ClN_3O$	15.2	>100	>10000
42	CH_3	CH_3	H	3-Br	B	61	222–223	$C_{12}H_{12}BrN_3O$	20.5	>30	>10000
43	CH_3	CH_3	H	3-F	A	83	252–254	$C_{12}H_{12}FN_3O$	35.6	63.6	>10000
44	CH_3	CH_3	H	3-CF_3	A	74	245–247	$C_{13}H_{12}F_3N_3O$	>30	>30	
45	CH_3	CH_3	H	3-CH_3	A	50	204–206	$C_{13}H_{15}N_3O$	33.1	79.3	
46	CH_3	CH_3	H	3-NO_2	A	99	286–287	$C_{12}H_{12}N_4O_3$	38.8	>100	
47	CH_3	CH_3	H	3,5-Cl_2	A	38	256–257	$C_{12}H_{11}Cl_2N_3O$	34.9	>100	
48	C_2H_5	CH_3	H	3-Cl	A	54	163–164	$C_{13}H_{14}ClN_3O$	16.0	45.3	>10000
49	C_3H_7	CH_3	H	3-Cl	A	48	183–184	$C_{14}H_{16}ClN_3O$	21.5	>30	>10000
50	*i*-Pr	CH_3	H	3-Cl	A	26	164–165	$C_{14}H_{16}ClN_3O$	~25	>30	>10000
51	C_4H_9	CH_3	H	3-Cl	A	36	175–176	$C_{15}H_{18}ClN_3O$	88.3	62.5	
52	CH_3	H	H	3-Cl	B	8.5	214–215	$C_{11}H_{10}ClN_3O\cdot 0.1H_2O$	47.8	>100	
53	CH_3	C_2H_5	H	3-Cl	A	80	165–167	$C_{13}H_{14}ClN_3O$	60.6	47.6	
54	CH_3	CH_3	CH_3	3-Cl	E	55	152–153	$C_{13}H_{14}ClN_3O$	50.5	73.1	
55	CH_3	CH_3	$COCF_3$	3-Cl	F	86	99–101	$C_{14}H_{11}ClF_3N_3O_2$	17.9	>100	>10000
56	CH_3	CH_3	$COCH_3$	3-Cl	F	76	167–169	$C_{14}H_{14}ClN_3O_2$	25.1	>100	>1000
57	CH_3	CH_3	$COCHCl_2$	3-Cl	F	72	120–122	$C_{14}H_{12}Cl_3N_3O_2$	35.5	>100	>1000
58	CH_3	CH_3	H	2-Cl	B	12	207–210	$C_{12}H_{12}ClN_3O$	31.1	50.8	
59	CH_3	CH_3	H	2-OCH_3	A	80	183–185	$C_{13}H_{15}N_3O_2$	46.6	87.9	
60	CH_3	CH_3	H	(2-thienyl)[e]	A	35	172–174	$C_{10}H_{11}N_3OS$	40.5	>90	
61	CH_3	CH_3	H	(2-furanyl)[e]	A	34	189–191	$C_{10}H_{11}N_3O_2$	33.6	>100	
62	CH_3	CH_3	H	(2-naphthenyl)[e]	A	88	234–235	$C_{16}H_{15}N_3O$	65.6	>100	
63	thioridazine								2.9	>100	2.8
64	clozapine								5.65	~10	38.0

[a,b] See footnotes *a,b*, respectively, in Table I. [c] Compounds were evaluated for inhibition of locomotor activity (LMA) and ataxia. Nine mice were used for each drug dose. ED_{50}'s were generated from at least three doses. [d] IC_{50}'s were calculated from four or more concentrations done in triplicate. [e] Replacement for phenyl group.

hexamethyldisilazane at ca. 200 °C (method D). Unfortunately, all attempts to prepare the 2-fluorophenyl hydroxy imine analogous to **2** were unsuccessful. Under a variety of reaction conditions, only the tricyclic ring-closed product **65** was formed. The structure of **65** was confirmed by an unambiguous synthesis from (1,3-dimethyl-5-chloro-1*H*-pyrazol-4-yl)(2-hydroxyphenyl)methanone (**67**). The *N*-methyl imine **54** was prepared by refluxing **12** with *N*-methylformamide while the methylene acetamides **55–57** were obtained by reaction of **41** with the appropriate anhydrides. Catalytic hydrogenation of the 4-nitrophenyl compound **38** afforded the 4-aminophenyl analogue **39**.

This series of hydroxy imines appeared to be quite stable, possibly due to intramolecular hydrogen bonding between the hydroxyl and imine groups.

Results and Discussion

Target compounds were evaluated in mice for their effects on spontaneous locomotion and motor coordination. This test is based on the observation that known antipsychotic drugs inhibit spontaneous exploratory activity at doses that do not cause impaired motor function or ataxia.[10] As a measure of their ability to bind to D_2 dopamine receptors in vitro, these compounds were also tested for their affinity for displacing [^{3}H]haloperidol from rat striatal membranes.[11]

The initial synthetic target, **28**, produced an antipsychotic-like profile in the behavioral test, with ED_{50}'s of 13.9 mg/kg for inhibiting exploratory locomotion and 30.2 mg/kg for causing ataxia. Interestingly, **28** did not bind appreciably to D_2 dopamine receptors (IC_{50} > 10000 nM), which suggested that this compound did not owe its antipsychotic-like effects in the locomotor activity/ataxia test

(10) Coughenour, L. L.; McLean, J. R.; Parker, R. B. *Pharmacol., Biochem. Behav.* **1977**, *6*, 351.
(11) Burt, D. R.; Creese, I.; Snyder, S. H. *Mol. Pharmacol.* **1976**, *12*, 800.

to an interaction with D_2 dopamine receptors.

In order to maximize this activity, structural modifications of **28** were examined, beginning with the groups at the 1- and 3-positions on the pyrazole ring. As shown in Table II, inhibition of locomotor activity was maintained for analogues with either an ethyl or *n*-propyl group at R_1, **29** and **30**, respectively, although they caused slightly more ataxia. Increasing the size of R_1 to a butyl group (compound **31**) resulted in a very significant decrease of potency in inhibiting locomotion. Replacement of the methyl group at R_3 with a hydrogen atom likewise decreased this activity significantly. As with the previously described amino ketone series (e.g., **1** and **2**), these results suggest that optimal activity might be obtained with methyl substituents on the 1- and 3-positions of the pyrazole ring.[6,8]

A second group of analogues of **28** was examined to determine the effects of various substituents on the phenyl ring. The initial group of compounds to be synthesized contained substituents at the 4-position. The 4-chloro and 4-fluoro analogues, **33** and **34**, respectively, were similar in potency to **28**, but their locomotor activity/ataxia selectivities were improved. With the exception of 4-trifluoromethyl **35**, none of the other 4-substituted analogues exhibited appreciable activity. The 3,4-dichloro analogue **40** was active but much less so than **28**.

The inability to enhance potency with substituents at the 4-position of the phenyl ring might be the result of unfavorable steric effects. Thus, attention was next focused on 3-substituted compounds. The 3-chloro analogue **41** was comparable to **28** in inhibiting locomotor activity (ED_{50} = 15.2 mg/kg) but had a much-improved profile. No significant ataxia was seen even at 100 mg/kg. The 3-bromo analogue **42** was almost as active as **41** while 3-fluoro **43**, 3-methyl **45**, and 3,5-dichloro **47** were less active. Interestingly, 3-trifluoromethyl **44** lacked significant activity at 30 mg/kg. Finally, to complete this aspect of the SAR study, the 2-chloro and 2-methoxy analogues **58** and **59**, respectively, were examined; neither had significant activity. Unfortunately, the lack of stability of the 2-fluoro analogue made a direct comparison with compound **2** of the amino ketone series impossible.

Because of the selectivity seen with **41**, several 3-chlorophenyl analogues were examined. Although the *N*-methyl analogue of **41**, compound **54**, had little activity, simple acetylimines were active. *N*-Trifluoroacetyl imine **55** produced activity similar to that produced by **41** while the methyl and dichloromethyl analogues **56** and **57**, respectively, were less potent. Finally, the examination of analogues of **41** with other alkyl groups at R_1 and R_3 of the pyrazole ring supported earlier findings with analogues of **28** that maximal activity was obtained with methyl substituents.

None of the compounds with behavioral activity displayed significant binding to the D_2 dopamine receptor in vitro.

The 3-chlorophenyl analogue **41** was selected for a more complete evaluation on the basis of its efficacy and selectivity in the locomotor activity/ataxia test. The pharmacological profile of this compound was compared with that of the widely used antipsychotic drug thioridazine (Table III). Compound **41** was orally active in the Sidman avoidance and self-stimulation tests in rats, with ED_{50} values comparable to those of thioridazine.[12,13] In addition, **41** was active in the squirrel monkey Sidman avoidance procedure, with an ED_{50} of 16.3 mg/kg po.

Table III. Pharmacological Profile of 41

test	41	thioridazine
inhibn of Sidman avoidance in rats (ED_{50} ± SEM, mg/kg po)	17.0 ± 2.35	14.4 ± 0.6
inhibn of self-stimulation in rats (ED_{50} ± SEM, mg/kg po)	23.7[a]	28.3 ± 1.2
inhibn of Sidman avoidance in squirrel monkeys (ED_{50} ± SEM, mg/kg po)	16.3 ± 0.33	4.0 ± 0.1
EPS signs in cebus monkeys (MED, mg/kg po)[b]	>100	2.5
effect on serum prolactin level (% control ± SEM at 23.7 and 27.0 mg/kg po respectively)[c]	−25.0 ± 8.6	+918 ± 254
displacement of [^{3}H]SCH23390 binding (IC_{50}, nM)[d,e]	>10000	
displacement of [^{3}H]WB4101 binding (IC_{50}, nM)[d]	>10000	17.3
displacement of [^{3}H]clonidine binding (IC_{50}, nM)[d]	>10000	1300

[a] Two doses of drug were tested in four animals at each dose. [b] Minimal effective doses (MED) were measured in at least three animals. [c] Rats were sacrificed at 1 h after administration of compound. The value is a mean from groups of five animals. Control values: 7.5 ± 2.2 and 8.8 ± 0.9 ng/mL (mean ± SEM). [d] These values were determined from four or five concentrations by a nonlinear regression analysis. [e] Reference standard SCH23390 IC_{50} ± SEM = 0.55 ± 0.09 nM.

Interestingly, **41** did not produce any dystonic signs in the haloperidol-sensitized cebus monkey model for EPS at 100 mg/kg, 6 times its ED_{50} in the monkey Sidman avoidance test.[14] Thioridazine, which causes EPS clinically, produced dystonias and dyskinesias at a dose that was less than its Sidman avoidance ED_{50}.[15] In addition to its lack of affinity for D_2 dopamine receptors, **41** did not exhibit any significant in vitro affinity for D_1 receptors (labeled by [^{3}H]SCH23390).[16] Also, the fact that **41** did not increase serum prolactin levels in rats indicates that it lacks dopamine antagonist effects in vivo.[17] Finally, **41** did not bind to α-adrenergic receptors, which suggests that its activity in the behavioral tests was not due to an adrenergic mechanism and that it should have a low liability for adrenergic-mediated cardiovascular side effects.[18]

In summary, the activity seen with this series demonstrates that it is possible to identify compounds with antipsychotic-like profiles in preclinical tests in animals that are not brain dopamine receptor antagonists. The results in the haloperidol-sensitized cebus monkey model predict that compound **41** should not cause EPS like the clinically available antipsychotic drugs. The pharmacological profiles of these compounds are being examined in more detail to elucidate their mechanism of action.

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, infrared spectrometry, and NMR spectrometry. Infrared spectra were recorded on a Digilab FTP-14 infrared spectrometer, and NMR spectra were obtained on a Varian EM 390 90-MHz or Brucker 90 spectrometer and were consistent with the proposed structures. Where analyses are indicated by the symbols of the

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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 with a Shimadzu GC Mini 2 gas chromatograph equipped with fid.

Pyrazolones. 2,4-Dihydro-2,5-dimethyl-3*H*-pyrazol-3-one,[19] 2-ethyl-2,4-dihydro-5-methyl-3*H*-pyrazol-3-one,[20] 2,4-dihydro-5-methyl-2-propyl-3*H*-pyrazol-3-one,[20] 2,4-dihydro-5-methyl-2-(2-methylethyl)-3*H*-pyrazol-3-one,[20] and 5-ethyl-2,4-dihydro-2-methyl-3*H*-pyrazol-3-one[9] were synthesized as described in the references cited. The 2,4-dihydro-2-methyl-3*H*-pyazol-3-one (mp 119–124 °C) and 2-butyl-5-ethyl-2,4-dihydro-3*H*-pyrazol-3-one (mp 85–88 °C) were synthesized by using the route of Butler and DeWald.[9]

(3-Chlorophenyl)(5-hydroxy-1,3-dimethyl-1*H*-pyrazol-4-yl)methanone (12). To a suspension of 112 g (1.0 mol) of 2,4-dihydro-2,5-dimethyl-3*H*-pyrazol-3-one in 700 mL of dioxane was added 148 g (2.0 mol) of calcium hydroxide powder. With vigorous stirring, 175 g (1.0 mol) of 3-chlorobenzoyl chloride was added in a slow stream as the temperature increased to 80 °C. The mixture was refluxed for an additional 1.5 h and poured into 2.5 L of ice water containing 250 mL of concentrated hydrochloric acid. The resulting mixture was stirred for 1 h, and the precipitate was collected. The solid was treated with 1 L of methanol; the mixture was cooled, and the product was collected to yield 170 g (62%) of **12**, mp 167–168 °C. Anal. ($C_{12}H_{11}ClN_2O_2$) C, H, N.

Method A. 4-[(3-Chlorophenyl)iminomethyl]-1,3-dimethyl-1*H*-pyrazol-5-ol (41). A solution of 25 g (0.01 mol) of **12** in 100 mL of formamide was stirred and heated to boiling for 20 min. The solution was cooled to 130 °C and poured into a solution of 30 mL of ammonium hydroxide and 500 mL of ice water. The resulting solid was collected, dried, and recrystallized from acetonitrile to afford 20.5 g (82%) of **41**, mp 236–238 °C. Anal. ($C_{12}H_{12}ClN_3O$) C, H, N.

Method B. 4-(Iminophenylmethyl)-1-methyl-1*H*-pyrazol-5-ol (32). To a slurry of 2.95 g (0.03 mol) of 1-methyl-5-pyrazolone and 4.6 g (0.05 mol) of calcium hydroxide powder in 50 mL of dioxane was added 4.2 g (0.03 mol) of benzoyl chloride. The mixture was refluxed for 0.5 h and poured into an excess of cold dilute hydrochloride acid. The mixture was extracted with chloroform, dried over magnesium sulfate, and evaporated in vacuo. The resulting oil was refluxed with 20 mL of formamide for 20 min; the solution was poured into water and extracted with methylene chloride. The organic extracts were evaporated, and the residue was crystallized from ethyl acetate to yield 0.32 g (7.5%) of **32**, mp 227–229 °C. Anal. ($C_{11}H_{11}N_3O$) C, H, N.

Method C. 4-(Iminophenylmethyl)-1,3-dimethyl-1*H*-pyrazol-5-ol (28). A mixture of 32.4 g (0.15 mol) of **3**, 39 g of ammonium carbonate, 300 mL of methanol, and 15 mL of water was heated in a steel bomb for 24 h at 110 °C. The reaction mixture was cooled to room temperature, and the solvent was evaporated in vacuo. The residue was stirred with 200 mL of water; the solid was collected and recrystallized from water to yield 12.7 g (39%) of **28**, mp 228–230 °C. Anal. ($C_{12}H_{13}N_3O$) C, H, N.

Method D. 4-[(3-Chlorophenyl)iminomethyl]-1,3-dimethyl-1*H*-pyrazol-5-ol (41). A solution of 10 g (0.04 mol) of **12** in 100 mL of hexamethyldisilazane was heated in a bomb at 190 °C for 0.5 h. The solvent was evaporated in vacuo, and the residue was stirred in 200 mL of 2 N ammonium hydroxide. The solid was collected to give rise to 1.0 g (10%) of **41**, mp 233 °C. Anal. ($C_{12}H_{12}ClN_3O$) C, H, N.

Method E. 4-[(3-Chlorophenyl)(methylimino)methyl]-1,3-dimethyl-1*H*-pyrazol-5-ol (54). A solution of 8.0 g (0.032 mol) of **12** in 32 mL of *N*-methylformamide was refluxed for 10 min. The solution was cooled to room temperature and diluted with 100 mL of water. The product was extracted into dichloromethane; the organic extracts were dried over magnesium sulfate and evaporated. The residue was crystallized from ethyl acetate to yield 4.4 g (55%) of **54**, mp 152.5–153.5 °C. Anal. ($C_{13}H_{14}ClN_3O$) C, H, N.

Method F. Dichloro-*N*-[(3-chlorophenyl)(1,3-dimethyl-5-hydroxy-1*H*-pyrazol-4-yl)methylene]acetamide (57). A mixture of 5.0 g (0.02 mol) of **41** and 5 g (0.02 mol) of dichloroacetic anhydride in 120 mL of ethyl acetate was refluxed for 4 h. The mixture was cooled and filtered. The filtrate was washed with saturated sodium bicarbonate solution, dried over magnesium sulfate, and evaporated in vacuo. The residue was crystallized from ether to afford 5.2 g (72%) of **57**, mp 120–122 °C. Anal. ($C_{14}H_{12}Cl_3N_3O_2$) C, H, N.

Method G. 4-[(4-Aminophenyl)iminomethyl]-1,3-dimethyl-1*H*-pyrazol-5-ol (39). A solution of 6.3 g (24 mmol) of **38** in 200 mL of methanol was hydrogenated over Raney nickel at 50 psi. The catalyst was removed by filtration, and the filtrate was evaporated. The residue was crystallized from methanol–water to give 4.0 g (64%) of **39** as a yellow solid, mp 82–85 °C. Anal. ($C_{12}H_{14}N_4O$) C, H, N.

1,3-Dimethyl[1]benzopyrano[2,3-*c*]pyrazol-4(1*H*)-one (65). Reaction of 18.0 g (0.075 mol) of **23** with formamide as described in method A afforded 12.5 g (78%) of **65**, mp 178–180 °C. Anal. ($C_{12}H_{10}N_2O_2 \cdot 2H_2O$) C, H, N.

(1,3-Dimethyl-5-chloro-1*H*-pyrazol-4-yl)(2-hydroxyphenyl)methanone (67). A solution of 20 g (0.079 mol) of (1,3-dimethyl-5-hydroxy-1*H*-pyrazol-4-yl)(2-hydroxyphenyl)-methanone (**66**)[9] in 50 mL of 48% hydrobromic acid and 20 mL of glacial acetic acid was heated at 100 °C for 18 h. The solvent was removed in vacuo, and the residue was made alkaline with concentrated ammonium hydroxide solution. The solution was extracted with dichloromethane. The organic extracts were dried over magnesium sulfate and evaporated. The residue was distilled through a short-path column to yield 16.0 g (84%) of **67**, bp 133–135 °C (0.2 mm). Anal. ($C_{12}H_{11}ClN_2O_2$) C, H, N.

1,3-Dimethyl[1]benzopyrano[2,3-*c*]pyrazol-4(1*H*)-one (65). To 14.0 g (0.056 mol) of **67** in 100 mL of DMSO was added 2.32 g (0.056 mol) of 57% sodium hydride. The mixture was slowly heated to 130 °C for 1 h and poured into 600 mL of water. The product crystallized and was collected. Recrystallization from ethanol afforded 7.0 g (58%) of analytical **65**, mp 176–178 °C. Anal. ($C_{12}H_{10}N_2O_2$) C, H, N.

Pharmacological Methods. The following methods were used as described in our previous paper:[6] locomotor activity and ataxia test,[10] [^{3}H]haloperidol receptor binding assay,[11] Sidman avoidance procedure,[12] extrapyramidal side effect test in cebus monkeys,[14] prolactin assay,[17] [^{3}H]WB4101 receptor binding assay,[18] and [^{3}H]clonidine receptor binding assay.[18] The suppression of high base line self-stimulation test[13] also was used as described in an earlier paper.[21] The [^{3}H]SCH23390 receptor binding assay was carried out by using the method of Billard et al.[16]

Registry No. **3**, 37704-89-5; **4**, 109803-04-5; **5**, 109803-05-6; **6**, 109803-06-7; **7**, 58011-27-1; **8**, 76089-43-5; **9**, 58011-03-3; **10**, 37704-91-9; **11**, 58011-02-2; **12**, 58011-00-0; **13**, 109803-07-8; **14**, 109803-08-9; **15**, 58011-04-4; **16**, 58011-06-6; **17**, 58011-09-9; **18**, 109803-09-0; **19**, 109803-10-3; **20**, 109803-11-4; **21**, 109803-12-5; **22**, 109838-72-4; **23**, 58011-12-4; **24**, 58011-05-5; **25**, 72619-93-3; **26**, 109803-13-6; **27**, 72619-94-4; **28**, 109803-14-7; **29**, 109803-15-8; **30**, 109803-16-9; **31**, 109803-17-0; **32**, 109803-18-1; **33**, 109803-19-2; **34**, 109803-20-5; **35**, 109803-21-6; **36**, 109803-22-7; **37**, 109803-23-8; **38**, 63124-47-0; **39**, 109803-24-9; **40**, 109803-25-0; **41**, 109803-26-1; **42**, 109803-27-2; **43**, 109803-28-3; **44**, 109803-29-4; **45**, 109838-73-5; **46**, 109803-30-7; **47**, 109803-31-8; **48**, 109803-32-9; **49**, 109803-33-0; **50**, 109803-34-1; **51**, 109803-35-2; **52**, 109838-74-6; **53**, 109803-36-3; **54**, 109803-37-4; **55**, 109803-38-5; **56**, 109803-39-6; **57**, 109803-40-9; **58**, 109803-41-0; **59**, 109803-42-1; **60**, 109803-43-2; **61**, 109803-44-3; **62**, 109803-45-4; **63**, 50-52-2; **64**, 5786-21-0; **65**, 37703-63-2; **67**, 109803-46-5; 4-FC_6H_4COCl, 403-43-0; 4-$F_3CC_6H_4COCl$, 329-15-7; 4-$H_3CC_6H_4COCl$, 874-60-2; 4-$O_2NC_6H_4COCl$, 122-04-3; 3,4-$Cl_2C_6H_3COCl$, 3024-72-4; 3-ClC_6H_4COCl, 618-46-2; 3-FC_6H_4COCl, 1711-07-5; 3-$F_3CC_6H_4COCl$, 2251-65-2; 3-$H_3CC_6H_4COCl$, 1711-06-4; 3-$F_3CC_6H_4COCl$, 2251-65-2; 3-$H_3CC_6H_4COCl$, 1711-06-4; 3-$O_2NC_6H_4COCl$, 121-90-4; 3,5-$Cl_2C_6H_3COCl$, 2905-62-6; 2-FC_6H_4COCl, 393-52-2; C_6H_5COCl, 98-88-4; 2-$H_3COC_6H_4COCl$,

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Thromboxane Synthase Inhibitors. Synthesis and Pharmacological Activity of (*R*)-, (*S*)-, and (±)-2,2-Dimethyl-6-[2-(1*H*-imidazol-1-yl)-1-[[(4-methoxyphenyl)-methoxy]methyl]ethoxy]hexanoic Acids

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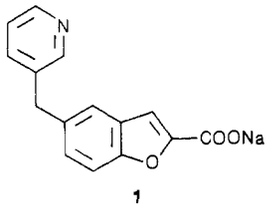
A series of substituted ω-[2-(1*H*-imidazol-1-yl)ethoxy]alkanoic acid derivatives were synthesized and evaluated for their ability to inhibit thromboxane synthase both in vitro and in vivo. Compound **13** was identified as a potent and selective competitive inhibitor of human platelet thromboxane synthase having a K_i value of 9.6×10^{-8} M. In collagen-treated human whole blood, **13** potentiated levels of 6-keto$PGF_{1\alpha}$. Enantiospecific syntheses afforded the *R* and *S* enantiomers of **13**, of which the *S* enantiomer **13b** was the more potent. Compounds **13** and **13b** were potent in vivo inhibitors of thromboxane synthase with good oral activity and duration of action.

Thromboxane A_2 (TxA_2), discovered by Hamberg et al.[1] and unequivocably characterized through synthesis by Still and co-workers,[2] is an unstable molecule derived from thromboxane synthase catalyzed rearrangement of the prostaglandin endoperoxide PGH_2.[3] TxA_2, formed by platelets and locally in tissues such as vascular smooth muscle and cardiac muscle cells, has been implicated in a variety of circulatory disorders, including unstable angina, coronary artery vasospasm, trauma- or endotoxin-induced shock, and acute myocardial infarction. Recent pharmacological data obtained with the selective TxA_2 synthase inhibitors furegrelate (**1**)[4] and OKY 0046/1581 (**2a,b**)[5-7] has demonstrated potential clinical utility for these compounds. Thus, when administered either alone or in combination with other agents such as cyclosporin, calcium channel blockers, and TxA_2 receptor antagonists, significant protection against unstable angina, allograft rejection, tumor proliferation, and coronary thrombosis has been observed in animal models.



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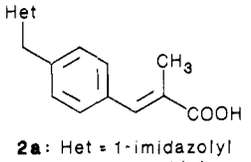
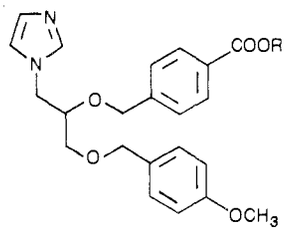
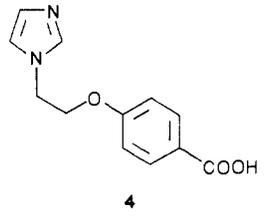


2a: Het = 1-imidazolyl
b: Het = 3-pyridyl

We recently reported on the structural requirements for a novel series of selective, imidazole-based TxA_2 synthase inhibitors.[8] However, on either intravenous or oral administration the lead compound from this series, **3a**, was rapidly metabolized to acid **3b** and excreted as the glucuronide. These findings prompted further structural modifications with the aim of improving the pharmacokinetic properties of the series while maintaining potent inhibitory activity against TxA_2 synthase in vitro and in vivo.



3a: R = Et
b: R = H



4

Whereas there are many examples of the glucuronidation of aryl acids, simple alkanoic acids are rarely conjugated.[9] Moreover, there is considerable precedent for the inhibition of TxA_2 synthase by molecules containing alkanoic and alkenoic acid groups.[10,11] Initially analogues of compounds **3a** and **3b** were prepared with incorporation of alkyl spacer groups designed to enable the molecules to adopt conformations in which the imidazole and carboxylate pharmacophores occupied similar regions of space to those in the more rigid benzoic acid derivatives (**3a,b**).

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