Perhaps complexes with pyridine and amine ligands have different biodistributions or the greater reactivity of the trans isomer may result in more rapid inactivation in the animal. Whatever the mechanism, our results raise questions concerning the general validity of in vitro criteria for antitumor activity of Pt(II) compounds based on the results of amine complexes.

In summary, we report *trans*-Pt(II) complexes with unusual biological activity that are significantly more cytostatic than their corresponding cis isomers. The metabolism and biodistribution of these compounds is of considerable interest. These molecules should be useful for investigating the detailed mechanism of isomeric selectivity of platinum antitumor compounds and the design of structurally novel platinum antitumor agents.

* Authors to whom correspondence should be addressed.
† University of Vermont.
‡ Laboratoire de Pharmacologie et de Toxicologie Fondamentales du CNRS.

Nicholas Farrell,*,† Tam T. B. Ha‡
Jean-Pierre Souchard,‡ Franz L. Wimmer‡
Suzy Cros,‡ Neil P. Johnson*,‡

Department of Chemistry
University of Vermont
Burlington, Vermont 05405
and Laboratoire de Pharmacologie et de Toxicologie
Fondamentales du CNRS
205 Route de Narbonne
Toulouse 31400, France

Received February 16, 1989

Articles

5-Piperazinylalkyl-2(3*H*)-oxazolones with Neuroleptic Activity

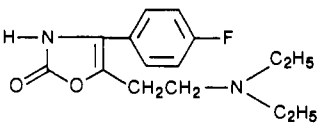
Giuseppe Cascio,* Elso Manghisi, and Giancarlo Fregnan

Lusofarmaco,† Research Division, Milan, Italy. *Received December 14, 1988*

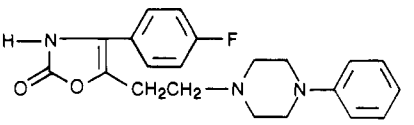
A series of new 4-aryl-5-[ω-(4-aryl-1-piperazinyl)alkyl]-2(3*H*)-oxazolones was synthesized and tested for neuroleptic activity in mice and rats. Several compounds exhibited interesting neuroleptic activity with very low liability to the extrapyramidal side effects. In particular the activity of 4-(4-fluorophenyl)-5-[2-[4-(3,5-dichlorophenyl)-1-piperazinyl]ethyl]-2(3*H*)-oxazolone (**14**) was greater than that of butropipazone and fluanisone, while of the same order of that of chlorpromazine; however, the product showed a longer lasting activity and minor ability to produce catalepsy as compared with the reference drugs.

2(3*H*)-Oxazolones have received little attention as molecules of potential pharmacological interest; however, sedative and muscle relaxant activity were found to be associated with some 4-aryl-2(3*H*)-oxazolones.[1] As part of a program aimed at discovering new series of therapeutically active compounds, a number of 4-aryl-2(3*H*)-oxazolones bearing an aminoethyl group in the 5-position have been synthesized in our laboratories; pharmacological evaluation of such compounds revealed the pronounced antiarrhythmic activity of 4-(4-fluorophenyl)-5-[2-(diethylamino)ethyl]-2(3*H*)-oxazolone (**1**).[2,3] Substitution of the diethylamino group of **1** with 4-phenylpiperazine was subsequently shown to result in compound **2** (Table I) exhibiting central nervous system (CNS) depressant activity in mice and rats. This result prompted us to prepare a number of 4-arylpiperazine derivatives **3–41** (listed in Table I), which being mostly prepared from the corresponding 2-hydroxy-4-aminobutyrophenones (**2a–29a**), might be considered structurally related to well-known 4-aminobutyrophenones endowed with neuroleptic activity. Therefore, it was of some interest to ascertain the biological activity of analogues in which the butanone side chain was modified and partially incorporated into a heterocyclic structure.

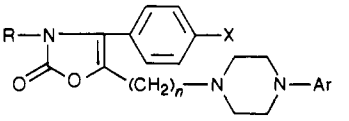
The structure–activity relationships of the above oxazolones are discussed herein. Also a detailed pharmacological profile of two selected compounds, **5** and **14**, is reported (Table II).



1



2



3-41

Chemistry

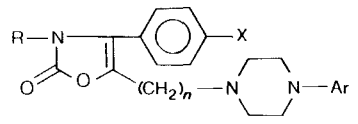
Oxazolones **2–29** were obtained by cyclization of the corresponding ketols **2a–29a** with phosgene and NH_3 (method A). Similarly, cyclization of ketol **2a** with phosgene and the proper substituted amine provided the oxazolones **31–35** (method A). Alternatively, compounds

† A company linked to "A. Menarini–Industrie Farmaceutiche Riunite s.r.l.".

(1) Bottari, F.; Nannipieri, E.; Saettone, M. F.; Serafini, M. F.; Tellini, N. *J. Med. Chem.* **1972**, *15*, 39.
(2) Cascio, G.; Fregnan, G. B.; Manghisi, E. In *La ricerca scientifica nell'industria farmaceutica in Italia*; Ferro, Ed.; Milan, 1977; p 635.
(3) Fregnan, G. B.; Prada, G.; Subissi, A. In *La ricerca scientifica nella industria farmaceutica in Italia*; Ferro, Ed.; Milan, 1977; p 645.

0022-2623/89/1832-2241$01.50/0

Table I. Physical Properties and Pharmacological Activities of 4-Aryl-5-[ω-(4-aryl-1-piperazinyl)alkyl]-2(3*H*)-oxazolones



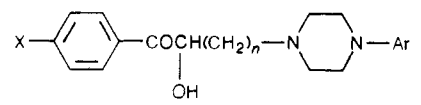
										ED_{50},[b] mg/kg po			
										mice		rats	
compd	X	R	Ar	*n*	method	mp,[a] °C	formula	anal.	approximate LD_{50}, mg/kg ip, mice	inhibn of SMA	inhibn of amphetamine-induced motility	inhibn of apomorphine-induced stereotypy	cataleptic activity
2	F	H	C_6H_5	2	A, B	191–192	$C_{21}H_{22}FN_3O_2$	C,H,N	>2000	3.6	5.4	47.5	87
3	F	H	2-$CH_3C_6H_4$	2	A, B	161–176	$C_{22}H_{24}FN_3O_2 \cdot HCl \cdot H_2O$	C,H,N	250	6.3	8.6	(60 = 0)	(60 = 0)
4	F	H	3-$CH_3C_6H_4$	2	A, B	170–173	$C_{22}H_{24}FN_3O_2$	C,H,N	>1000	13.4	7.3	(50 = 0)	(50 = 0)
5	F	H	2-$OCH_3C_6H_4$	2	A, B	155–157	$C_{22}H_{24}FN_3O_3$	C,H,N	>2000	4.6	4	10.4	55.6
6	F	H	3-$OCH_3C_6H_4$	2	A, B	158–165	$C_{22}H_{24}FN_3O_3 \cdot HCl$	C,H,N	500	10.8	7.6	(50 = 0)	(50 = 30)
7	F	H	4-$OCH_3C_6H_4$	2	A, B	244–246	$C_{22}H_{24}FN_3O_3$	C,H,N	>1000	(100 = 33)	(100 = 0)	(100 = 0)	(100 = 0)
8	F	H	3-$CF_3C_6H_4$	2	A, B	125–128	$C_{22}H_{21}F_4N_3O_2$	C, H, N	>1000	16.9	11.6	(100 = 0)	(100 = 0)
9	F	H	2-ClC_6H_4	2	A, B	150–152	$C_{21}H_{21}ClFN_3O_2$	C,H,N,Cl	>1000	14.2	15	(100 = 0)	(100 = 30)
10	F	H	3-ClC_6H_4	2	A, B	175–176	$C_{21}H_{21}ClFN_3O_2$	C,H,N,Cl	>1000	58.5	54.1	80	(100 = 0)
11	F	H	4-ClC_6H_4	2	A, B	207–209	$C_{21}H_{21}ClFN_3O_2$	C,H,N,Cl	>1000	200	(100 = 0)	(100 = 0)	(100 = 0)
12	F	H	2,5-$Cl_2C_6H_3$	2	A, B	286–287	$C_{21}H_{20}Cl_2FN_3O_2 \cdot HCl$	C,H,N,Cl	750	(90 = 45)	10	(90 = 0)	(90 = 0)
13	F	H	3,4-$Cl_2C_6H_3$	2	A, B	260–262	$C_{21}H_{20}Cl_2FN_3O_2 \cdot HCl$	C,H,N	1000	(100 = 21)	(100 = 62)	(100 = 0)	(100 = 0)
14	F	H	3,5-$Cl_2C_6H_3$	2	A, B	283–286	$C_{21}H_{20}Cl_2FN_3O_2 \cdot HCl$	C,H,N	>2000	2.7	1.5	(100 = 0)	(200 = 0)
15	F	H	2,4-$Cl_2C_6H_3$	2	A, B	264–267	$C_{21}H_{20}Cl_2FN_3O_2 \cdot HCl$	C,H,N	1000	(40 = 45)	23.9	(40 = 0)	(40 = 0)
16	F	H	2,3-$Cl_2C_6H_3$	2	A, B	259–262	$C_{21}H_{20}Cl_2FN_3O_2 \cdot HCl \cdot H_2O$	C,H,N	90	12.5	(20 = 69)	(20 = 0)	(20 = 0)
17	F	H	3,5-$Br_2C_6H_3$	2	A, B	276–278	$C_{21}H_{20}Br_2FN_3O_2 \cdot HCl$	C,H,N	1000	15	5.4	(100 = 0)	(100 = 0)
18	F	H	2,3,4-$Cl_3C_6H_2$	2	A, B	282–284	$C_{21}H_{19}Cl_3FN_3O_2 \cdot HCl$	C,H,N,Cl	750	(20 = 0)	(20 =0)	(20 = 0)	(20 = 0)
19	F	H	2,4,5-$Cl_3C_6H_2$	2	A, B	271–272	$C_{21}H_{19}Cl_3FN_3O_2 \cdot HCl$	C,H,N	750	(20 = 0)	(20 =0)	(20 = 0)	(20 = 0)
20	F	H	3,4,5-$Cl_3C_6H_2$	2	A, B	283–285	$C_{21}H_{19}Cl_3FN_3O_2 \cdot HCl$	C,H,N	>1000	(100 = 0)	(100 = 0)	(100 = 0)	(100 = 0)
21	F	H	2-pyridyl	2	A, B	172–174	$C_{20}H_{21}FN_4O_2$	C,H,N	>1000	38	(100 = 0)	(200 = 30)	(100 = 0)
22	Cl	H	2-pyridyl	2	A, B	270–273	$C_{20}H_{21}ClN_4O_2 \cdot 2HCl$	C,H,N	375	14.1	14.3	(50 = 0)	47
23	F	H	C_6H_5	3	A, B	249–251	$C_{22}H_{24}FN_3O_2 \cdot HCl$	C,H,N	170	8	(10 = 69)	(40 = 0)	(40 = 0)
24	H	H	C_6H_5	2	A, B	188–190	$C_{21}H_{23}N_3O_2$	C,H,N	>1000	60	51	200	63
25	CH_3	H	C_6H_5	2	A, B	190–191	$C_{22}H_{25}N_3O_2 \cdot C_4H_4O_4$	C,H,N	400	6.4	2	(100 = 0)	(100 = 0)
26	CH_3O	H	C_6H_5	2	A, B	188–189	$C_{22}H_{25}N_3O_3$	C,H,N	350	(70 = 26)	(.. 27)	47	(70 = 0)
27	CH_3S	H	C_6H_5	2	A, B	261–262	$C_{22}H_{25}N_3O_2S \cdot HCl$	C,H,N	250	(70 = 47)	(70 = 0)	(70 = 0)	(70 = 0)
28	C_6H_5	H	C_6H_5	2	A, B	236–237	$C_{27}H_{27}N_3O_2 \cdot 2HCl$	C,H,N	750	(10 = 32)	(10 = 33)	(20 = 0)	(20 = 0)
29	Cl	H	C_6H_5	2	A, B	194–195	$C_{21}H_{22}ClN_3O_2$	C,H,N,Cl	>1000	3	4.7	(400 = 0)	(150 = 0)
30	Cl	H	C_6H_5	1	E	170–171	$C_{20}H_{20}ClN_3O_2 \cdot HCl$	C,H,N	>1000	(100 = 15)	(100 = 0)	(100 = 0)	(100 = 0)
31	F	CH_3	C_6H_5	2	A, C	104–106	$C_{22}H_{24}FN_3O_2$	C,H,N	750	19.5	21	112	(100 = 0)
32	F	C_2H_5	C_6H_5	2	A, C	84–85	$C_{23}H_{26}FN_3O_2$	C,H,N	750	15.4	17	75	(150 = 0)
33	F	*n*-C_4H_9	C_6H_5	2	A, C	70–71	$C_{25}H_{30}FN_3O_2Cl$	C,H,N	750	16	15.4	(150 = 40)	(150 = 0)
34	F	$(C_2H_5)_2$-$N(CH_2)_2$	C_6H_5	2	A	70–71	$C_{27}H_{35}FN_4O_2$	C,H,N	350	60	(60 = 27)	35	(70 = 0)
35	F	$C_6H_5CH_2$	C_6H_5	2	A	119–121	$C_{28}H_{28}FN_3O_2$	C,H,N	>1000	51	(100 = 40)	200	(200 = 0)
36	F	C_6H_5	C_6H_5	2	C	165–168	$C_{27}H_{26}FN_3O_2$	C,H,N	>1000	(125 = 0)	(100 = 0)	(100 = 0)	(100 = 0)
37	F	CH_3CO	C_6H_5	2	D	107–109	$C_{23}H_{24}FN_3O_8$	C,H,N	350	2.7	4.7	44	30.5
38	F	CH_3CO	2-$OCH_3C_6H_4$	2	D	221–222	$C_{24}H_{26}FN_3O_4 \cdot HCl$	C,H,N	190	4.3	3.5	14.5	30
39	F	CH_3CO	3,5-$Cl_2C_6H_3$	2	D	238–239	$C_{23}H_{22}Cl_2FN_3O_3 \cdot HCl$	C,H,N,Cl	1000	4.5	2.7	(100 = 10)	(100 = 0)
40	F	CH_3NHCO	C_6H_5	2	D	214–215	$C_{23}H_{25}FN_4O_3 \cdot HCl$	C,H,N	750	16.5	9.9	(180 = 30)	(100 = 0)
41	F	C_6H_5CO	C_6H_5	2	D	231–233	$C_{28}H_{26}FN_3O_3 \cdot HCl$	C,H,N	750	4	9.3	(150 = 40)	(150 = 0)
butropipazone[c]									95	6.5	11.7	41.9	102.5
fluanisone[d]									180	7.7	16.4	63.2	18
clozapine									100	4.2	4.5	(80 = 30)	(26 = 37)[e]

[a] All compounds were crystallized from EtOH. [b] Numbers in parentheses indicate the maximal dose administered and the related percent activity. [c] 4-(4-Phenyl-1-piperazinyl)-1-(4-fluorophenyl)-1-butanone. [d] 4-[4-(2-Methoxyphenyl)-1-piperazinyl]-1-(4-fluorophenyl)-1-butanone. [e] At higher doses muscle relaxation was observed.

Table II. Pharmacological Profile of Compounds **5** and **14** in Comparison to That of Known Neuroleptics

tests	animal species	ED_{50},[a] mg/kg po or IC_{50},[b] nM													
		5		**14**		butropipazone		fluoanisone		chlorpromazine		haloperidol		clozapine	
		1 h	5 h	1 h	5 h	1 h	5 h	1 h	5 h	1 h	5 h	1 h	5 h	1 h	5 h
aggressive behavior	mouse	4.7	4.7	23.8	8.5	2.5	5.2	6.1	20.1	2.7	3.1	0.23	0.29	3.5	(10 = 0)
spontaneous locomotor activity	mouse	4.6	20.3	2.7	2.5	6.5	26.5	7.7	15.7	2.9	4.8	0.16	0.35	4.2	23.0
amphetamine-induced hypermotility	mouse	4.0	15.0	1.5	1.9	11.7	35.0	16.4	18.0	4.1	2.4	0.12	0.28	4.5	20.1
amphetamine-induced stereotypy	rat	5.3	12.4	13.5	4.2	60.7	(100 = 0)	17.8	50.0	19.4	13.6	0.27	0.39	(20 = 20)	(20 = 0)
apomorphine-induced stereotypy	rat	10.4	60.7	(100 = 0)	106.0	41.9	(100 = 0)	63.2	(100 = 0)	28.9	41.6	1.1	1.8	(80 = 30)	(80 = 0)
apomorphine-induced emesis	dog	0.7	1.5	4.0	2.5	NT	7.5	NT	8.6	NT	7.5	NT	0.04	NT	NT
apomorphine-induced climbing	mouse	0.42	4.0	0.37	0.21	12.4	20.0	5.0	15.0	2.0	2.2	0.12	0.045	12.0	NT
apomorphine-induced turning	mouse	15.9	20.0	0.84	1.0	38.2	(100 = 0)	14.7	NT	4.4	NT	0.32	NT	16.4	NT
conditioned avoidance response (CAR)	rat	3.5	11.6	(40 = 44)	6.4	32.0	(90 = 36)	25.0	50.0[c]	6.8	10.3	0.23	0.32	8.6	(20 = 0)
body weight gain (ΔW test)	rat	7.1[d]	NT	2.2[d]	NT	27.8[d]	NT	6.0[d]	NT	6.0[d]	NT	0.30[d]	NT	8.0	NT
pentobarbital-induced sleeping	mouse	41.1	37.3	(100 = 30)	(100 = 0)	21.3	NT	20.7	NT	3.2	3.3	7.0	3.1	6.6	NT
tryptamine-induced convulsions	mouse	9.8	(40 = 0)	(40 = 0)	(40 = 0)	9.9	NT	12.5	NT	3.4	NT	1.1	NT	10.3	(40 = 0)
pentylenetetrazol-induced convulsions	mouse	(100 = 0)	(100 = 0)	(100 = 0)	(100 = 0)	(100 = 0)	(100 = 0)	(40 = 0)	(40 = 0)	(15 = 0) (50 = 30)	NT NT	(9.4 = 0) (20 = 0)	NT NT	(40 = 0) (40 = 0)	(40 = 0) NT
electroshock-induced convulsions	mouse	(100 = 0)	(100 = 0)	(100 = 0)	(100 = 0)	(100 = 20)	(100 = 0)	(40 = 0)	(40 = 0)	19.2	10.0	1.9	0.38	(26 = 37)[e]	NT
catalepsy	rat	55.6	21.5	(200 = 0)	24.3	102.5	115.5	18.0	13.9	10.3	NT	15.4	NT	34.0	(40 = 10)
inclined screen	mouse	91.0	(100 = 0)	(100 = 0)	(100 = 0)	30.0	(60 = 0)	49.0	(60 = 0)	5.4	7.0	6.8	6.5	9.3	18.8
skeletal muscle contractile force	mouse	179.2	62.5	200[c]	200[c]	10.3	20[c]	20.0	50[c]	36.5	10.3	(30 = 0)	15	40.0	(40 = 10)
skeletal muscle tone	mouse	(200 = 0)	75.0	(200 = 10)	(200 = 0)	(100 = 0)	(100 = 0)	(100 = 30)	(100 = 0)	2.7	7.5	17.1	(20 = 23)	9.2	30.0
tremorine-induced tremors	mouse	(60 = 10)	(60 = 0)	(60 = 0)	(60 = 0)	(60 = 0)	(60 = 0)	(60 = 0)	(60 = 0)	(7.5 = 0)	(7.5 = 15)	(20 = 0)	20[c]	30.0	30.0
tremorine-induced salivation	mouse	(60 = 0)	(60 = 0)	(60 = 0)	(60 = 0)	(60 = 0)	(60 = 0)	(60 = 0)	(60 = 0)	2.5	2.0	4.0	21.6	6.9	NT
norepinephrine-induced lethality	rat	3.2	8.2	(40 = 10)	(40 = 0)	0.75	3.5	1.9	5.6						
[^{3}H]spiroperidol displacement binding on striatal membranes	rat	250[b]		68[b]		NT		NT		180[b]		10[b]		NT	

[a] Numbers in parentheses indicate the maximal administered dose and the related percent activity. NT = not tested. [b] IC_{50} after 15 min of incubation in vitro at 37 °C. [c] Approximate values. [d] After 2-h-period of conditioned feeding. [e] At higher doses muscle relaxation was observed.



2a-29a

2–29 and 31–33 were prepared from the corresponding ketols with isocyanic acid (method B) or alkyl isocyanate (method C). Compound **36** was obtained according to method C with phenyl isocyanate. 4-Hydroxy-2-oxazolidones were often isolated as intermediates of the reactions run according to methods A and C; they were quantitatively dehydrated to oxazolones by acidic treatment (boiling AcOH or aqueous HCl). Acylation of the oxazolones with acetyl chloride, methyl isocyanate, or benzoyl chloride (method D) gave the respective *N*-acyl compounds (**37–41**). Compound **30** was obtained from 4-(4-chlorophenyl)-2(3*H*)-oxazolone by Mannich-type condensation with formaldehyde and phenylpiperazine in the presence of $ZnCl_2$ (method E).[4]

Pharmacological Results and Discussion

All the new compounds were evaluated for their ability to inhibit spontaneous motor activity (SMA) and amphetamine-induced hypermotility in mice, to antagonize apomorphine-induced stereotypy, and to evoke catalepsy in rats after oral treatment; these tests were selected in order to evaluate potential sedative and neuroleptic activities and to exclude possible extrapyramidal side effects[5-7] (Table I). The acute toxicity was tested in mice. Butropipazone, fluanisone (two butyrophenone-type neuroleptics derived from 4-phenylpiperazine), and clozapine were included in the pharmacological assays as appropriate standards.

Among the compounds bearing substituents on the phenyl group of the piperazine moiety (**3–20**), oxazolones **3**, **5**, **14**, and **17** were the most active in inhibiting SMA and amphetamine-induced hypermotility; however, oxazolone **2** showed practically the same activity. Aromatic substitution showed the following order of increasing activity: $OCH_3 \geq H > CH_3 > Cl$. It is interesting to note that a substitution on the 4-position of the phenyl ring diminished the activity. Disubstitution with halogens was favorable only in the 3- and 5-position (compounds **14**, **17**). The trichloro-substituted compounds (**18–20**) were inactive. Compounds **21** and **22**, with a 2-pyridyl group at the 4-position of the piperazine, showed only mild CNS depressant activities. Replacement of the fluorine of compound **2** with chlorine or methyl resulted in equipotent, or slightly less active, compounds. Homologation of the alkyl chain of **2** and **29** negatively influenced the toxicity or the activity of the parent compound. Alkylation of the oxazolone ring nitrogen (compound **31–36**) resulted in minor activities. N-Acylated oxazolones **37–41** retained some of the activity of the unsubstituted analogues (**2**, **5**, and **14**), possibly due to in vivo deacylation. With the exception of compounds **2**, **5**, **37**, and **38**, all the other oxazolones were generally inactive or slightly active in antagonizing the apomorphine-induced stereotypy and in evoking catalepsy. These findings indicate that the substitutions on the phenyl ring of piperazine moiety results in compounds that may not produce extrapyramidal effects in man, although they are active as neuroleptics. It is of interest that the active compounds were less toxic in mice as compared with the reference drugs.

Oxazolones **5** and **14** were selected for further pharmacological studies in order to better define their profiles as CNS depressants and to verify the duration of the pharmacological actions. A comparative evaluation with butropipazone, fluanisone, haloperidol, chlorpromazine, and clozapine was carried out (see Table II). The two oxazolones were very effective in a number of tests for neuroleptic activity: in fact, they reduced aggressive behaviors, spontaneous locomotion, and conditioned responses, while they prevented a number of effects due to pharmacological stimulation of central dopaminergic receptors. Compound **5** (but not compound **14**) and the reference drugs showed antiadrenergic, antitryptaminergic, and prohypnotic activities.

Compound **14** elicited a much longer lasting action than compound **5** and the reference drugs. Its peak effects generally appeared by the fifth hour and some effects were still detected 24 h after treatment (unpublished observations). Both the new compounds were also able to inhibit the [^{3}H]spiroperidol binding in striatum rat membranes in vitro. By comparing the IC_{50}'s in this test, it appears that compound **14** is more active than **5** and chlorpromazine but less active than haloperidol. The two oxazolones were devoid of central and peripheral anticholinergic, anticonvulsive, and skeletal muscle relaxant properties, while butropipazone, fluanisone, haloperidol, chlorpromazine, and clozapine caused loss of the contractile force. Finally, the high ratios calculated at the fifth hour between the ED_{50}'s in some tests indicative for extrapyramidal symptoms (catalepsy and apomorphine-induced stereotypy) and ED_{50}'s in others indicative for neuroleptic activity (amphetamine-induced hypermotility or stereotypy, apomorphine-induced emesis or climbing and CAR) (Table III) suggest that compound **14** might alleviate certain psychotic manifestations in man without evoking extrapyramidal side effects. In contrast, chlorpromazine and especially haloperidol have low ratios and frequently induce extrapyramidal symptoms. It also appears that the lack of cataleptogenic property in compound **14** is not due to an hypothetical central anticholinergic activity (which is absent, as it can be seen from the data presented in Table II concerning tremorine-induced tremors) but probably to a more specific action on certain central dopaminergic structures.

Experimental Section

Chemistry. Melting points were determined on a Büchi capillary apparatus and are uncorrected. Analytical results for indicated elements were within ±0.4% of the theoretical values. The IR and UV spectra were obtained on Perkin-Elmer 237 and Beckman DB-GT spectrophotometers. NMR spectra were recorded on a Perkin-Elmer R-24 instrument (Me_4Si internal standard). Only significant spectral data are reported. For purity tests, TLC was performed on silica gel 60 F254 plates (Merck) with 5–20% MeOH–$CHCl_3$ as developing solvent.

General Synthesis of Oxazolones 2–29 and 31–35. Method A. 4-(4-Fluorophenyl)-5-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-2(3*H*)-oxazolone (5) was synthesized according to Gompper.[8] A solution of **5a** (23 g, 0.0619 mol) and triethylamine (8.1 g, 0.0802 mol) in dry chloroform (200 mL) was added during 15 min at 0 °C, with stirring, to a 20% solution of phosgene in toluene (37 mL, 0.074 mol). Stirring was continued 2 h after the addition, and then the solution was saturated with dry NH_3. The mixture was allowed to warm up to room temperature and then washed with H_2O. The dried solution was evaporated to an oil which was dissolved in acetone and converted

(4) Ganapathi, K.; Venkataraman, A. *Proc. Indian Acad. Sci.* **1945**, *21*, 34.
(5) Fog, R. *Acta Neurol. Scand.* **1972**, *50*, Suppl. 1.
(6) Marsden, C. D. In *Modern trends in neurology*; Williams, D., Ed.; London: Butterworths, 1975; Vol. 6, p 141.
(7) Sjungberg, T.; Ungerstedt, U. *Psychopharmacology* **1978**, *56*, 239.
(8) Gompper, R. *Chem. Ber.* **1956**, *89*, 1748.

Table III. Ratios between ED_{50}'s in Some Tests Indicative for Extrapyrimidal Side Effects (A and B)[a] and ED_{50}'s in Other Tests Indicative for Antipsychotic Activity (C, D, E, F, G)[b] Calculated at the Fifth Hour

compd	A/C	B/C	A/D	B/D	A/E	B/E	A/F	B/F	A/G	B/G
14	55.8	12.8	25.2	5.8	42.4	9.7	504.8	115.7	16.6	3.8
chlorpromazine	17.3	4.2	3.1	0.7	5.5	1.3	18.9	4.5	4.0	0.97
haloperidol	6.4	1.4	4.6	0.97	45	9.5	40	8.4	5.6	1.2

[a] A = ED_{50} in apomorphine-induced stereotypy test; B = ED_{50} in catalepsy test. [b] C = ED_{50} in amphetamine-induced hypermotility test; D = ED_{50} in amphetamine-induced stereotypy test; E = ED_{50} in apomorphine-induced emesis test; F = ED_{50} in apomorphine-induced climbing test; G = ED_{50} in CAR test.

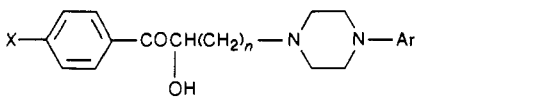
to its hydrochloride. Dissolution of the hydrochloride in EtOH (80 mL) followed by addition of NH_4OH (20 mL) gave the free base. Recrystallization from EtOH afforded 16 g (65%) of **5**: mp 155–157 °C; IR (Nujol) 1760 cm^{-1}; UV (EtOH) λ_{max} 252 nm (ϵ 13580); NMR ($CDCl_3$) δ 7.20 (m, 8 H, aromatic H), 3.82 (s, 3 H, CH_3), 2.75 (m, 12 H, CH_2). Anal. ($C_{22}H_{24}FN_3O_3$) C, H, N. With the appropriate ketols as starting materials, compounds **2–4** and **6–29** were similarly prepared. Yields varied from 35% to 75%. Oxazolones **31–35** were prepared in an analogous manner by substitution of NH_3 with the appropriate amines. Physical properties of ketols **2a–29a** are listed in Table IV. Some of these ketols have been reported in previous publications.[9,10]

Alternative Synthesis of Oxazolones 2–29. Method B. 4-(4-Fluorophenyl)-5-[2-[4-(3,5-dichlorophenyl)-1-piperazinyl]ethyl]-2(3*H*)-oxazolone hydrochloride (14) was prepared by an adaptation of the procedure described by Dziomko et al.[11] A mixture of **14a** (42.6 g, 0.103 mol), potassium cyanate (10.1 g, 0.124 mol), and DMF (130 mL) was heated to 55 °C, and with stirring, concentration HCl (11 mL) in DMF (20 mL) was added dropwise. The mixture was stirred at 60 C for 15 min and then concentrated HCl (11 mL) was added dropwise. The precipitate was stirred with EtOH (150 mL) at 50 °C. The mixture was made basic with NH_4OH (40 mL) and then cooled. The solid was collected by filtration and washed with H_2O. Dissolution of the solid in DMF, followed by addition of gaseous HCl, gave **14** (43 g): mp 283–286 °C; yield 88%; IR (Nujol) 1760 cm^{-1}; UV (EtOH) λ_{max} 263 (ϵ 23980); NMR (CD_3SOCD_3) δ 7.50 (m, 7 H, aromatic H), 350 (m, 12 H, CH_2). Anal. ($C_{21}H_{21}Cl_3FN_3O_2$) C, H, N.

Alternative Synthesis of Oxazolones 31–33. Method C. 3-Butyl-4-(4-fluorophenyl)-5-[2-(4-phenyl-1-piperazinyl)-ethyl]-2(3*H*)-oxazolone (33). A mixture of 10.0 g (0.029 mol) of **2a** and 3.50 g (0.035 mol) of butyl isocyanate was stirred at 100 °C for 2 h and then cooled. The mixture was dissolved in benzene (130 mL) and the hot solution filtered with animal charcoal. Hexane (60 mL) was added to the solution to give crystals, which were recrystallized from EtOH to obtain 6 g of 3-butyl-4-(4-fluorophenyl)-4-hydroxy-5-[2-(4-phenyl-1-piperazinyl)ethyl]-2-oxazolidone: mp 144 °C; IR (Nujol) 1760 cm^{-1}; NMR ($CDCl_3$) δ 9.4 (bs, exchangeable, 1 H, OH), 4.6 (dd, 1 H, CH). The oxazolidone was dissolved in acetic acid (50 mL) and refluxed for 1 h. The mixture was evaporated to dryness and the residue crystallized from EtOH to give 3 g (24.3%) of **33**: mp 71 °C; IR (Nujol) 1750 cm^{-1}; UV (EtOH) λ_{max} 250 nm (ϵ 16500); NMR ($CDCl_3$) δ 7.05 (m, 9 H, aromatic H), 0.80 (m, 3 H, CH_3). Anal. ($C_{25}H_{30}FN_3O_2$) C, H, N. Compounds **31** and **32** were prepared in an analogous manner.

Synthesis of Oxazolones 37–41. Method D. 3-Acetyl-4-(4-fluorophenyl)-5-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-2(3*H*)-oxazolone Hydrochloride (38). To a solution of 8 g of **5** (0.02 mol) in pyridine (40 mL) was added dropwise 4.4 g of acetyl chloride (0.056 mol), at 10–15 °C with stirring. After the addition, the reaction mixture was stirred at 80 °C for 3 h and then evaporated to dryness. The residue was taken up in acetone and filtered. The solid was recrystallized twice from EtOH to obtain 3.5 g (48%) of **38**: mp 222 °C; IR (Nujol) 1795 cm^{-1}; UV (EtOH) λ_{max} 245 nm (ϵ 16185); NMR (D_2O + CD_3SOCD_3) δ 7.00 (m, 8 H, aromatic H), 3.80 (s, 3 H, CH_3), 2.70 (m, 12 H, CH_2), 2.50 (s, 3 H, CH_3). Anal. ($C_{24}H_{27}ClFN_3O_4$) C, H, N.

Table IV. 1-Aryl-2-hydroxy-ω-(4-aryl-1-piperazinyl)-1-alkanones



compd	X	Ar	n	mp,[a] °C	formula[b]
2a	F	C_6H_5	2	202–203	$C_{20}H_{23}FN_2O_2$
3a	F	2-$CH_3C_6H_4$	2	128–130	$C_{21}H_{25}FN_2O_2$
4a	F	3-$CH_3C_6H_4$	2	130–132	$C_{21}H_{25}FN_2O_2$
5a	F	2-$OCH_3C_6H_4$	2	105–106	$C_{21}H_{25}FN_2O_3$
6a	F	3-$OCH_3C_6H_4$	2	198–199	$C_{21}H_{25}FN_2O_3$·HCl
7a	F	4-$OCH_3C_6H_4$	2	131–132	$C_{21}H_{25}FN_2O_3$
8a	F	3-$CF_3C_6H_4$	2	105–107	$C_{21}H_{22}F_4N_2O_2$
9a	F	2-ClC_6H_4	2	107–109	$C_{20}H_{22}ClFN_2O_2$
10a	F	3-ClC_6H_4	2	120–122	$C_{20}H_{22}ClFN_2O_2$
11a	F	4-ClC_6H_4	2	105–107	$C_{20}H_{22}ClFN_2O_2$
12a	F	2,5-$Cl_2C_6H_3$	2	92–93	$C_{20}H_{21}Cl_2FN_2O_2$
13a	F	3,4-$Cl_2C_6H_3$	2	92–94	$C_{20}H_{21}Cl_2FN_2O_2$
14a	F	3,5-$Cl_23C_6H_3$	2	84–85	$C_{20}H_{21}Cl_2FN_2O_2$
15a	F	2,4-$Cl_2C_6H_3$	2	111–113	$C_{20}H_{21}Cl_2FN_2O_2$
16a	F	2,3-$Cl_2C_6H_3$	2	107–108	$C_{20}H_{21}Cl_2FN_2O_2$
17a	F	3,5-$Br_2C_6H_3$	2	211-213	$C_{20}H_{21}Br_2FN_2O_2$·HCl
18a	F	2,3,4-$Cl_3C_6H_2$	2	163–166	$C_{20}H_{20}Cl_3FN_2O_2$
19a	F	2,4,5-$Cl_3C_6H_2$	2	178–180	$C_{20}H_{20}Cl_3FN_2O_2$
20a	F	3,4,5-$Cl_3C_6H_2$	2	182–183	$C_{20}H_{20}Cl_3FN_2O_2$
21a	F	2-pyridyl	2	103–105	$C_{19}H_{22}FN_3O_2$
22a	Cl	2-pyridyl	2	116–117	$C_{19}H_{22}N_3O_2$
23a	F	C_6H_5	3	182–184	$C_{21}H_{25}FN_2O_2$·HCl
24a	H	C_6H_5	2	144–146	$C_{20}H_{24}N_2O_2$
25a	CH_3	C_6H_5	2	207–208	$C_{21}H_{26}N_2O_2$·HCl
26a	OCH_3	C_6H_5	2	137–139	$C_{21}H_{26}N_2O_3$
27a	SCH_3	C_6H_5	2	155–156	$C_{21}H_{26}N_2O_2S$
28a	C_6H_5	C_6H_5	2	160–162	$C_{26}H_{28}N_2O_2$
29a	Cl	C_6H_5	2	150–152	$C_{20}H_{23}ClN_2O_2$

[a] All compounds were recrystallized from EtOH. [b] All compounds had analyses within ±0.4% for C, H, and N.

Method E. 4-(4-Chlorophenyl)-5-[(4-phenyl-1-piperazinyl)methyl]-2(3*H*)-oxazolone (30) was prepared according to Ganapathi et al.[4] To a hot solution of 25 g (0.127 mol) of 4-(4-chlorophenyl)-2(3*H*)-oxazolone[1] in anhydrous CH_3OH (1700 mL) were added 20.7 g of phenylpiperazine (0.127 mol), 3.83 g of paraformaldehyde, and 6.95 g of anhydrous $ZnCl_2$. The mixture was stirred at 60 °C for 3 h and then evaporated to dryness. Aqueous 5 N HCl (30 mL) and chloroform (150 mL) were added to the residue to give crystals which were collected by filtration. The solid was stirred for 1 h with NH_4OH solution (50 mL) and filtered. The crude free base was recrystallized twice from EtOH to give 9.9 g (21%) of **30**: mp 171 °C; IR (Nujol) 1750 cm^{-1}; UV (EtOH) λ_{max} 255 nm (ϵ 17920); NMR ($CDCl_3$ + CD_3SOCD_3) δ 7.30 (m, 9 H, aromatic H), 3.50 (s, 2 H, CH_2), 3.20 (m, 4 H, CH_2), 2.70 (m, 4 H, CH_2). Anal. ($C_{20}H_{20}ClN_3O_2$) C, H, N.

Pharmacological Methods. Male and female CF_1 mice (20–22 g of body weight), Sprague–Dawley rats (130–150 g of body weight), and beagle dogs (10–14 kg of body weight) born and raised in the Lusofarmaco animal quarters were used. The animals were fasted overnight before the treatment. Ten animals were used for each dose level of a given compound. In each experiment a group of control animals, receiving the vehicle alone, was included. The compounds were weighed as bases and kept in suspension with arabic gum in different concentrations in order to administer a constant volume of 10 mL/kg orally 1 h before the performance of the screening tests (Table I) or 1 and 5 h before the other tests

(9) Cascio, G.; Erba, R.; Manghisi, E.; Biazzi, A.; Ferni, G.; Fregnan, G. *Farmaco, Ed. Sci.* **1980**, *35*, 605.
(10) Cascio, G.; Manghisi, E.; Porta, R.; Fregnan, G. *J. Med. Chem.* **1985**, *28*, 815.
(11) Dziomko, V. M.; Ivashchenko, A. V. *Zh. Org. Khim.* **1973**, *9*, 2191.

(Table II). When subjective evaluations were to be performed, the experiments were carried out by trained unbiased technicians using coded solutions, the content of which was not disclosed before the end of the experimental sessions. ED_{50} and LD_{50} values were computed by using Finney's probit analysis.[12]

Suppression of Aggressive Behavior in Mice.[13] Fighting behavior was induced in male mice by isolation in individual black cages for about 1 month and by weekly treatment with testosterone cyclopentylpropionate (250 mg/kg sc). These isolated animals will attack a nonisolated male mouse placed in the same cage within 15 min. Pairs of mice were preselected for aggressiveness shortly prior to administration of the drugs. The dose of drug that supressed the aggressive behavior in 50% of the animals (ED_{50}) was determined.

Inhibition of Spontaneous Locomotor Activity (SMA) in Mice.[14] Groups of five animals each were given the test compounds, and their locomotor activity was measured for 10 min, by means of a photocell apparatus (Danuso's activity cage). These readings were performed in at least two groups of animals for each dose of a given drug. The dose of drug that caused 50% inhibition of the locomotor activity measured in control animals (ED_{50}) was determined.

Antagonism against Amphetamine-Induced Hypermotility in Mice.[14] Male animals, divided into groups of five mice each, received 4 mg/kg ip of amphetamine 30 min after treatment with the test compounds. Ten minutes later they were placed in an actophotometer, and their locomotor activity was registered for 15 min as described in the paragraph concerning the spontaneous locomotor activity in mice. The dose of drug that caused 50% reduction of the hypermotility measured in control animals (ED_{50}) was determined.

Antagonism against Amphetamine-Induced Stereotypy in Rats.[15] Male rats were treated intravenously with amphetamine (7.5 mg/kg) and 1 h later observed for the presence or absence of typical stereotyped movements. The dose of drug that inhibited stereotypes in 50% of the animals (ED_{50}) was determined.

Antagonism against Apomorphine-Induced Stereotypy in Rats. Male rats were injected intravenously with apomorphine (3 mg/kg) and 20 min later observed for stereotype behavior. The dose of drug that inhibited stereotypies in 50% of the animals (ED_{50}) was determined according to the method of Janssen.[16]

Antagonism against Apomorphine-Induced Emesis in Dogs. Apomorphine (0.3 mg/kg sc) induces vomiting in all control dogs. Male and female dogs were pretreated with the drugs 4 h before being challenged with apomorphine. Complete protection against emesis for 30 min after apomorphine was adopted as the criterion for drug effect. The dose of drug that inhibited emesis in 50% of the animals (ED_{50}) was determined according to the method of Janssen.[17]

Apomorphine-Induced Climbing in Mice.[18] Apomorphine (1 mg/kg sc) induces climbing behavior in all control mice put into cylindrical individual cages with walls of vertical metal bars. The behavior of mice pretreated with neuroleptics was scored as follows: four paws on the floor, 0; forefeet holding the wall, 1; four paws holding the wall, 2. The ED_{50} was considered the neuroleptic dose that caused a 50% reduction of the score determined in control mice.

Apomorphine-Induced Turning in Mice.[19] Unilateral destruction of nigrostriatal dopaminergic nerve terminals was produced in mice by direct injection of 6-hydroxydopamine (20 μg). Seven days later the mice showing strong contraversive turning 15 min after apomorphine administration (2 mg/kg ip) were selected. After another week the animals were pretreated with the neuroleptics and then challenged again with apomorphine. The mice showing less than six complete rotations in 2 min were considered protected. The ED_{50} was the neuroleptic dose that protected 50% of the animals.

Inhibition of Conditioned Avoidance Response (CAR) in Rats.[20] Male rats were trained to avoid an electrical shock, delivered through the grid floor in a Basile's shuttle box, by moving from one compartment to the other during a period of warning. Each cycle was organized as follows: 3 s of warning signal with turning on a light (conditioning stimulus), 3 s of light + shock (unconditioning stimulus), and 14-s intertrial. An experimental session consisted of 10 cycles for each rat. Rats were trained until at least 90% conditioned avoidance response was reached for each animal. The percent inhibition of CAR was calculated on the basis of a predosing level test and the ED_{50} reported as the dose causing 50% inhibition.

Effect on the ΔW Test in Rats.[21] Female rats (250–280 g of body weight), individually caged, were put on a 22-h food deprivation schedule, standard pellets being offered ad libitum between 10 and 12 a.m. Tap water was available at all times. Each rat was weighed before and after each eating period to determine weight gain (ΔW). After 30–40 days of training the animals were treated with test drugs just 1 h prior to the feeding period of 2 h. The values were then expressed as percentages of the average values for the two preceding control days, and the dose causng 50% reduction (ED_{50}) of those values for each drug was calculated.

Potentiation of Pentobarbital Sleeping Time in Mice.[22] Female mice received a subhypnotic dose of pentobarbital (10 mg/kg iv). A prohypnotic effect was attributed to the compounds when the animals, placed gently on their back 3 min later, showed complete loss of the righting reflex for at least 15 s. The neuroleptic dose that caused this effect in 50% of the mice (ED_{50}) was calculated.

Anticonvulsant Activity in Mouse.[23] Male animals were challenged with tryptamine (100 mg/kg iv), pentylenetetrazol (110 mg/kg ip), or maximal electroshock. The tested drugs were considered active when bilateral clonic seizures of the forepaws and head twitches (in the case of tryptamine) or tonic hind-limb extension (in the other cases) did not appear. The ED_{50} was determined as the dose that protected 50% of mice from convulsions.

Cataleptic Activity in Rats.[22] Symptoms of catalepsy were searched by placing each animal with their anterior legs on a horizontal bar at 7 cm from the floor for three times at 5-min intervals. The animals were considered cataleptic when they remained immobile for at least 15 s and were assigned a score of 0 (while the normal animals received a score of 1). The ED_{50} was defined as the dose that caused catalepsy in 50% of the animals.

Effects on Skeletal Muscles of Mice. Two experimental procedures were followed, which evaluated the tone, the force of contraction, and the coordination of the movements of the skeletal muscles.

(1) **Inclined Screen.**[24] Male mice, just after the treatment and 4 h later, were placed for 1 h on a wire screen (bent at an angle of 60° to the horizontal plane). Normal mice could move on the screen without difficulty, but ataxic or miorelaxed mice slid off.

(2) **Traction and Suspension.**[25] Male mice were suspended by means of their forepaws to a wire of 1.8 mm in diameter stretched horizontally at 15 cm from a plane. Trained normal

(12) Finney, D. J. In *Probit Analysis*; Cambridge University Press: London, 1964.
(13) Janssen, P. A. J.; Jageneau, A. H. M.; Niemegeers, C. J. E. *J. Pharmacol. Exp. Ther.* **1960**, *129*, 471.
(14) Honma, T.; Sasajima, K.; Ono, K.; Kitakawa, S.; Inaba, Sh.; Yamamoto, H. *Arzneim. Forsch.* **1974**, *24*, 1248.
(15) Simon, P.; Chermat, R. *J. Pharmacol.* **1972**, *3*, 235.
(16) Janssen, P. A. J.; Niemegeers, C. J. E.; Jageneau, A. H. M. *Arzneim. Forsch.* **1960**, *10*, 1003.
(17) Janssen, P. A. J.; Niemegeers, C. J. E.; Schellekens, K. H. L. *Arzneim. Forsch.* **1960**, *10*, 955.
(18) Protais, P.; Costentin, J.; Schwartz, J. C. *Psychopharmacology* **1976**, *50*, 1.
(19) Piycock, C. J.; Tarsy, D.; Marsden, C. D. *J. Pharm. Pharmacol.* **1975**, *27*, 445.
(20) Chieli, T.; Fregnan, G. B. *Pharmacol. Res. Commun.* **1979**, *11*, 617.
(21) Janssen, P. A. J.; Niemegeers, C. J. E.; Schellekens, K. H. L. *Arzneim. Forsch.* **1965**, *15*, 104.
(22) Niemegeers, C. J. E.; Van Nueten, J. M.; Janssen, P. A. J. *Arzneim. Forsch.* **1974**, *24*, 1798.
(23) Swinyard, E. A.; Brown, C. W.; Goodman, S. C. *J. Pharmacol. Exp. Ther.* **1952**, *106*, 319.
(24) Hoppe, J. O. *J. Pharmacol. Exp. Ther.* **1950**, *100*, 333.
(25) Couvoisier, S.; Ducrot, R.; Julou, L. In *Psychotropic drugs*; Garattini, S.; Ghetti, Eds.; Elsevier: Amsterdam, 1957; p 373.

animals touched the wire with at least one of the hind-paws within 2 s (traction) and remained hanging for at least 1 min (suspension). The ED_{50} for each test was the dose causing 50% of the mice to fall, without traction and suspension.

Antagonism against Tremorine-Induced Parasympathetic Stimulation in Mice.[26] Tremorine (20 mg/kg ip) was given to male mice 1 h after the test compounds, and the presence of central (tremor) and peripheral parasympathetic stimulation (salivation) was recorded thereafter. The ED_{50} was considered the neuroleptic dose protecting 50% of rats from tremorine-induced effects.

Antagonism against Catecholamine-Induced Lethality in Rats.[22] The rats (80–90 g of body weight) were injected with a dose of norepinephrine (0.5 mg/kg iv) that caused their death within 30 min when not protected with active drugs. The ED_{50} was the neuroleptic dose protecting 50% of rats from norepinephrine-induced lethality.

In Vitro Interaction with Dopamine Rat Striatum Receptors Labeled with [^{3}H]Spiroperidol.[27] The binding experiments were performed on crude membrane preparations of rat striata that were stored at −80 °C until used. Aliquots (2.5 mL) of thawed and freshly washed membrane fractions were incubated for 15 min at 37 °C with increasing concentrations (10^{-10} to 10^{-4} M) of drugs to be tested and with [^{3}H]spiroperidol (0.5 nM, 24.5 Ci/mmol; New England Nuclear Corp.) in the presence of 1 μM pargyline and of 0.1% ascorbic acid. The membranes were than filtered, washed three times, dried overnight in an oven, and counted in toluene–POPOP fluor. Specific binding was considered as that bound without the addition of 1 μM of haloperidol minus that bound in its presence. IC_{50} was considered as the concentration of drug causing 50% binding inhibition and was calculated from the displacement curve.

Acute Toxicity in Mice. The toxicity was evaluated by the intraperitoneal route and the LD_{50} was considered the dose causing the death in 50% of treated mice.

Registry No. **2**, 52867-87-5; **2a**, 51037-47-9; **3**, 120944-08-3; **3** base, 120944-47-0; **3a**, 120944-34-5; **4**, 120944-09-4; **4a**, 120944-35-6; **5**, 52867-74-0; **5a**, 51037-51-5; **6**, 120944-10-7; **6** base, 120944-48-1; **6a**, 120944-36-7; **7**, 120944-11-8; **7a**, 120944-37-8; **8**, 120944-12-9; **8a**, 95217-32-6; **9**, 120944-13-0; **9a**, 120944-38-9; **10**, 120944-14-1; **10a**, 95217-30-4; **11**, 120944-15-2; **11a**, 120944-39-0; **12**, 120944-16-3; **12** base, 120944-49-2; **12a**, 95217-34-8; **13**, 120944-17-4; **13** base, 120944-50-5; **13a**, 95217-33-7; **14**, 120944-18-5; **14** base, 72444-63-4; **14a**, 95217-35-9; **15**, 120944-19-6; **15** base, 120944-51-6; **15a**, 120944-40-3; **16**, 120944-20-9; **16** base, 120944-52-7; **16a**, 120944-41-4; **17**, 120944-21-0; **17** base, 120944-53-8; **17a**, 120944-42-5; **18**, 120944-22-1; **18** base, 120944-54-9; **18a**, 120944-43-6; **19**, 120944-23-2; **19** base, 120944-55-0; **19a**, 120944-44-7; **20**, 120944-24-3; **20** base, 120944-56-1; **20a**, 120944-45-8; **21**, 52867-80-8; **21a**, 51037-58-2; **22**, 120944-25-4; **22** base, 120944-57-2; **22a**, 120944-46-9; **23**, 120944-26-5; **23** base, 120944-58-3; **23a**, 95217-36-0; **24**, 52868-12-9; **24a**, 51037-52-6; **25**, 120944-28-7; **25** base, 120944-27-6; **25a**, 95217-25-7; **26**, 52868-09-4; **26a**, 51037-54-8; **27**, 120944-29-8; **27** base, 120944-59-4; **27a**, 95217-26-8; **28**, 120944-30-1; **28** base, 120944-60-7; **28a**, 95217-27-9; **29**, 52868-08-3; **29a**, 51037-53-7; **30**, 120944-31-2; **30** base, 120944-61-8; **31**, 52867-94-4; **32**, 52867-95-5; **33**, 52867-99-9; **34**, 52867-97-7; **35**, 52867-96-6; **36**, 120944-32-3; **37**, 52868-03-8; **38**, 52868-05-0; **38** base, 120944-62-9; **39**, 120944-33-4; **39** base, 120944-63-0; **40**, 52985-68-9; **40** base, 120944-64-1; **41**, 52868-06-1; **41** base, 120944-65-2; $MeNH_2$, 74-89-5; $EtNH_2$, 75-04-7; n-$C_4H_9NH_2$, 109-73-9; $(C_2H_5)_2N(CH_2)_2NH_2$, 100-36-7; $C_6H_5CH_2NH_2$, 100-46-9; MeNCO, 624-83-9; EtNCO, 109-90-0; n-C_4H_9NCO, 111-36-4; C_6H_5NCO, 103-71-9; 4-(4-chlorophenyl)-2(3*H*)-oxazolone, 36404-33-8; phenylpiperazine, 92-54-6.

(26) Christensen, J. A.; Hernestam, S.; Lassen, J. B.; Sterner, N. *Acta Pharmacol. Toxicol.* **1965**, *23*, 109.
(27) Fields, J. Z.; Reisine, T. D.; Yamamura, H. I. *Brain Res.* **1977**, *136*, 578.

Linear and Proximal Benzo-Separated Alkylated Xanthines as Adenosine-Receptor Antagonists

Stewart W. Schneller,*,† Augusto C. Ibay,† William J. Christ,† and Robert F. Bruns‡

Department of Chemistry, University of South Florida, Tampa, Florida 33620-5250 and Department of Pharmacology, Warner-Lambert/Parke-Davis Pharmaceutical Research, Ann Arbor, Michigan 48105. *Received October 21, 1988*

The linear and proximal benzo-separated derivatives of 8-phenyltheophylline, 1,3-diethyl-8-phenylxanthine, 1,3-dipropylxanthine, 1,3-dibutylxanthine, 3-isobutyl-1-methylxanthine, theophylline, caffeine, and isocaffeine have been synthesized and evaluated for affinity at the A_1 and A_2 adenosine receptors. Although structure–activity relationships in the benzo-separated series differed from the relationships in the simple xanthines, the most potent of the benzo-separated xanthines were about equal in affinity to the most potent of the corresponding xanthines. On the basis of the present results and the diverse structures reported in the literature as non-xanthine adenosine antagonists, it appears that the primary requirement for adenosine-receptor affinity in nonnucleosides is a flat, neutral, fused-ring heterocycle and that once this requirement is met there are numerous potential binding modes.

Membrane receptors sensitive to adenosine are receiving considerable attention[1-3] because of the role of adenosine in regulating a variety of physiological responses. Activation of these receptors by extracellular adenosine can cause inhibition or stimulation of the formation of intracellular adenosine 3′,5′-cyclic monophosphate from adenosine 5′-triphosphate by adenylate cyclase. The existence of two types of adenosine receptors has been proposed: an A_1 receptor, which mediates inhibition of adenylate cyclase, and an A_2 receptor, which stimulates the cyclase.[2] Antagonism of either the A_1 or A_2 receptor would permit the selective control of the effects caused by the binding of adenosine to that particular receptor. Included among the antagonists are various alkylated xanthines[4] (e.g., **1b**).

† University of South Florida.
‡ Present address: Fermentation Products Research Division, Lilly Research Laboratories, Indianapolis, IN 46285.

(1) Williams, M. *Annu. Rev. Pharmacol. Toxicol.* **1987**, *27*, 315–345.
(2) Hamprecht, B.; van Calker, D. *Trends Pharmacol. Sci.* **1985**, *6*, 153–154.
(3) (a) Daly, J. W.; Bruns, R. F.; Snyder, S. H. *Life Sci.* **1981**, *28*, 2083–2097. (b) Schwabe, U. *Trends Pharmacol. Sci.* **1981**, *2*, 299–303. (c) Bruns, R. F.; Daly, J. W.; Snyder, S. H. *Proc. Natl. Acad. Sci. U.S.A.* **1983**, *80*, 2077–2080. (d) Stiles, G. L.; Daly, D. T.; Olsson, R. A. *J. Biol. Chem.* **1985**, *260*, 10806–10811. (e) Olsson, R. A.; Kusachi, S.; Thompson, R. D.; Ukena, D.; Padgett, W.; Daly, J. W. *J. Med. Chem.* **1986**, *29*, 1683–1689. (f) Bruns, R. F.; Lu, G. H.; Pugsley, T. A. *Mol. Pharmacol.* **1986**, *29*, 331–346.

0022-2623/89/1832-2247$01.50/0