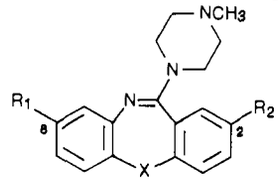
A Novel Class of Potential Central Nervous System Agents. 3-Phenyl-2-(1-piperazinyl)-5*H*-1-benzazepines

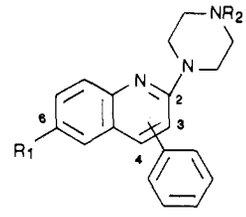
Katsuhiko Hino,* Yasutaka Nagai, Hitoshi Uno, Yoshinobu Masuda, Makoto Oka, and Tadahiko Karasawa

Research Laboratories, Dainippon Pharmaceutical Co., Ltd., 33-94, Enoki-cho, Suita, Osaka 564, Japan.
Received June 23, 1987

A series of 3-phenyl-2-piperazinyl-5*H*-1-benzazepines and related compounds were synthesized and evaluated for potential neuroleptic activity. The preparation of these compounds was carried out by 2,3-dichlorination of 3-phenyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-ones with phosphorus pentachloride followed by amination and concurrent dehydrochlorination. Compounds having the 4-chloro or 4-fluoro substituent in the 3-phenyl group were found to possess the neuroleptic-like activity. Among them, 2-(4-methyl-1-piperazinyl)-3-(4-fluorophenyl)-5*H*-1-benzazepine dihydrochloride (**23**) was comparable to chlorpromazine in inhibiting exploratory activity, conditioned avoidance response, and self-stimulation response and more potent than chlorpromazine in antagonizing apomorphine-induced emesis. These neuroleptic effects may be based on an antidopaminergic property of the compound. In causing catalepsy or ptosis, however, **23** was weaker than chlorpromazine. Therefore, this ring system is of interest as a novel class of neuroleptics. Some compounds having the 7-chloro or 7-bromo substituent showed potent anticonvulsant effects against maximal seizures induced by electroshock or pentylenetetrazole.

Among drugs acting on the central nervous system (CNS), some of those possessing a dibenzo structure joined to a central seven-membered ring with a basic side chain are of interest as neuroleptics. Examples are clothiapine (**1**) and loxapine (**2**), which are neuroleptics having a classical profile similar to that of chlorpromazine. In general, neuroleptic-induced extrapyramidal symptoms (EPS) limit the usefulness of most currently available antipsychotic drugs. An exception is clozapine (**3**), the first example of a new class of tricyclic neuroleptics (atypical antipsychotics), which in clincal use produces practically no EPS.[1] Since clozapine unfortunately displays agranulocytosis as a serious side effect,[2] efforts have been made to find new tricyclic epine derivatives with low EPS liability and no other toxic side effects. Emphasis has been placed on the replacement of the bridged atom in the central ring, or the basic side chain, and also on the alterations of the aromatic ring or substituents on it.[3]





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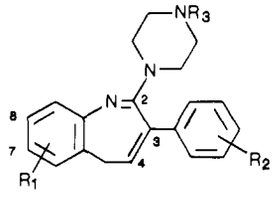
1: X = S; R_1 = H; R_2 = Cl; clothiapine
2: X = O; R_1 = H; R_2 = Cl; loxapine
3: X = NH; R_1 = Cl; R_2 = H; clozapine
4a: X = CH_2; R_1 = H; R_2 = H; perlapine
4b: X = CH_2; R_1 = F; R_2 = H; fluperlapine



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Recently, fluperlapine (**4b**) having a dibenz[*b*,*e*]azepine skeleton, was reported to have a pharmacological resemblance to clozapine.[4] It is of interest to design, synthesize, and pharmacologically test new compounds whose skeletons are derived from but do not belong to the above dibenzo–epines (**1**–**4**). A series of 4-phenyl-2-(1-piperazinyl)quinolines (**5**)[5] with potent antidepressant activity and 3-phenyl analogues (**5**)[6] with anticonvulsant effect are suggestive of a direction. These compounds have at least one phenyl ring as a substituent. A similar structural modification of the dibenz[*b*,*e*]azepine skeleton results in 3-phenyl-2-(1-piperazinyl)-5*H*-1-benzazepines (**6**), which possess one phenyl ring as a substituent at the 3-position in conjugation with the 3,4-double bond. At the same time, this ring system, if it bears a halogen atom at the 8-position, incorporates the [[(3-halophenyl)imino]-methyl]piperazine moiety. This is assumed to be the pharmacophore responsible for the clozapine-like activity[7] seen with fluperlapine (**4b**), doclothepine, and analogous compounds.[8] The object of our work is to clarify the problems of whether the new 2-amino-3-phenyl-5*H*-1-benzazepine system can exhibit an antipsychotic effect, and whether the resulting possible pharmacophore can make a similar contribution as in dibenzo–epine systems toward antipsychotic properties. This paper deals with the synthesis of a series of 3-phenyl-2-(1-piperazinyl)-5*H*-1-benzazepines and related compounds and the results of their CNS pharmacological evaluation. In order to investigate structure–activity relationships of these compounds, various modifications of the substituents in the aromatic rings and of the amine moiety at the 2-position have been made, and the results are also described.

Chemistry

The synthesis of 2-amino-3-aryl-5*H*-1-benzazepines was accomplished as illustrated in Scheme I. Compounds **15** could be prepared by the known methods as follows. Hydrolysis of readily available nitriles **7**, or reduction of keto acids **12**, which were obtainable from benzalacetophenones **9** by the addition of hydrogen cyanide followed by methanolysis and subsequent hydrolysis, afforded diphenylbutyric acids **8**. The Friedel–Crafts reaction of acid chlorides derived from **8** or the direct cyclization of **8** afforded 2-aryltetralones (**13**). The intermediates, 3-aryl-

(1) Gross, H.; Langner, E. *Arzneim.-Forsch.* **1969**, *19*, 496.
(2) Idänpään-Heikkilä, J.; Alhava, E.; Olkinoura, M.; Palva, I. P. *Eur. J. Clin. Pharmacol.* **1977**, *11*, 193.
(3) Steiner, G.; Franke, A.; Hädicke, E.; Lenke, D.; Teschendorf, H. J.; Hofmann, H. P.; Kreiskott, H.; Worstman, W. *J. Med. Chem.* **1986**, *29*, 1877 and references cited therein.
(4) Eichenberger, E. *Arzneim.-Forsch.* **1984**, *34*, 110.
(5) Hino, K.; Furukawa, K.; Nagai, Y.; Uno, H. *Chem. Pharm. Bull.* **1980**, *28*, 2618.
(6) Hino, K.; Nagai, Y.; Uno, H. *Chem. Pharm. Bull.* **1987**, *35*, 2819.
(7) Humber, L. G.; Sideridis, N.; Asselin, A. A.; Bruderlein, F. T. *J. Med. Chem.* **1978**, *21*, 1225.
(8) Jîleh, J. O.; Šindelář, K.; Rajšner, M.; Dlabăc, A.; Metyšovā, J.; Votava, Z.; Pomykaček, J.; Protiva, M. *Collect. Czech. Chem. Commun.* **1975**, *40*, 2887.

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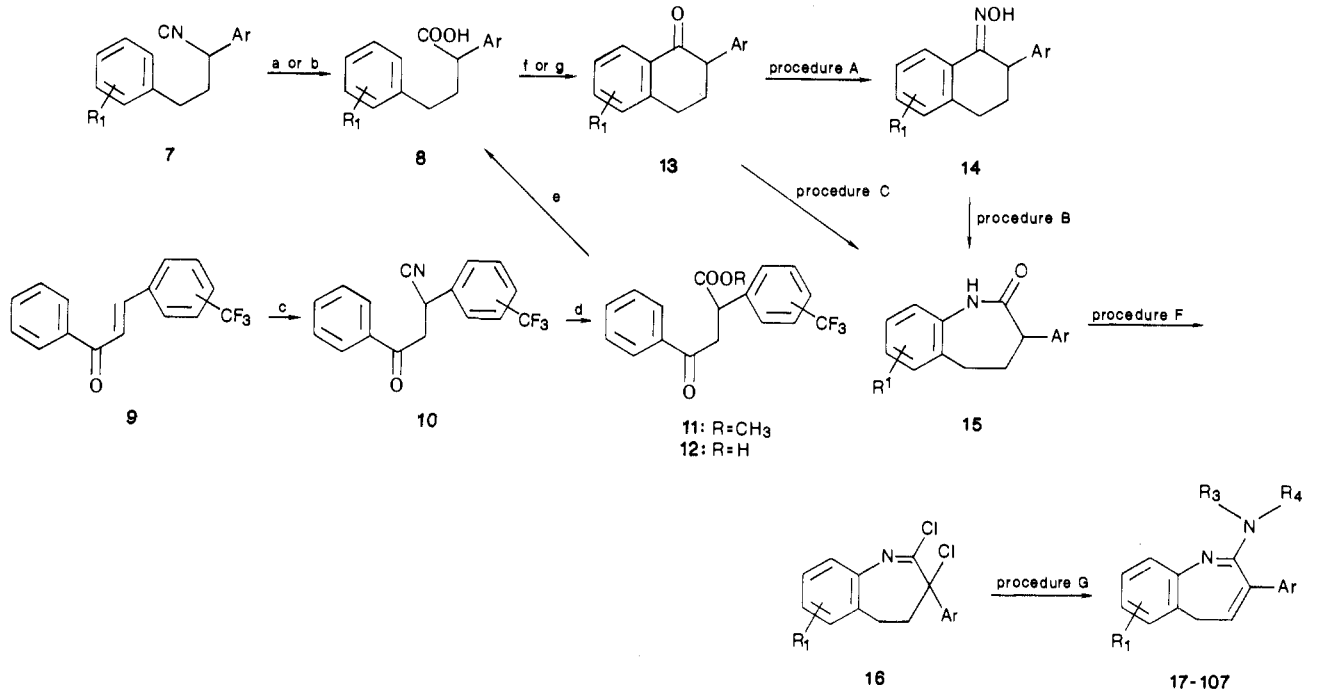
Scheme I[a]



[a] a; 70% H_2SO_4/AcOH. b; KOH/$HO(CH_2)_2OH$. c; KCN/AcOH. d; H_2SO_4/MeOH, 10% KOH. e; 5% Pd-C/AcOH. f; PCl_5, $AlCl_3/C_6H_6$. g; PPA. procedure A; H_2NOH·HCl/NaOAc. procedure B; PPA/120 °C. procedures C; NaN_3/H_2SO_4-AcOH/50 °C. procedure F; PCl_5/110 °C. procedure G; amine/130 °C.

2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-ones (**15**), were known to be obtainable by means of the Schmidt reaction (procedure C) of **13**. Besides this procedure (**15k,l,t,y**), we mostly employed an alternative one via the Beckmann reaction (procedure B) of the tetralone oxime (**14**), since higher yields of **15** were generally obtained via this route. Acetoxyphenyl isomer **15j** were prepared by the reaction of **15i** with acetic anhydride (procedure D). The reaction of **15a** with surfuryl chloride resulted in the nuclear substitution, affording the 7-chloride **15n**, while the reaction of **15a,c,e** with bromine gave 7-bromides **15o,v,w** (procedure E).

On treatment of **15** with 2 mol of PCl_5, the requisite intermediate 2,3-dichloro derivatives (**16**) were generally obtained in a fairly good yield (procedure F), although this depended on the stability of the products. A few compounds (**16i,j**) were not stable enough to isolate. In the case of **15h**, this reaction was unsuccessful. The reaction was in contrast with that of 3,4-dihydro-3-phenylcarbostyrils, which afforded three products including 2,3-dichlorides.[6] Caprolactam was known to give the 3,3-dichloro derivative when treated with an excess of PCl_5.[9] The above intermediate compounds (**14–16**) are listed in Table I. Preparation of the desired 2-amino-3-aryl-5*H*-1-benzazepines (**17–107**, Table II) was achieved by the reaction of **16** with appropriate piperazines or other amines (procedure G). This involved a nucleophilic substitution reaction at the 2-position and a concurrent formation of the 3,4-double bond due to the dehydrochlorination. Subsequent alkylations of the distal nitrogen on the piperazinyl moiety (procedure H, J) or of the 3-(4-hydroxy)phenyl group (procedure I) were then carried out.

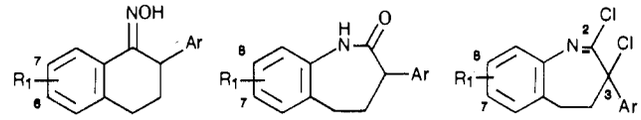
Pharmacological Results and Discussion

The CNS pharmacological profile of 2-amino-3-aryl-5*H*-1-benzazepine derivatives obtained in this study was examined by their effects on exploratory activity, reserpine-induced hypothermia, maximal electroshock seizure (MES), and tremorine-induced tremor in mice, and the results are summarized in Table II. Compound **18**, having the structure closely related to the hypnotic perlapine (**4a**), a defluoro analogue of fluperlapine (**4b**), showed slight to moderate effects on both exploratory activity and resperine-induced hypothermia as well as did **19**. Among compounds (**22–53** and **92–98**) having a substituted phenyl group at the 3-position of the benzazepine nucleus, the 4-fluorophenyl (**23–27**) and 4-chlorophenyl derivatives (**37** and **38**), which bear a lower alkyl, hydroxyalkyl, or cyclohexyl group on the piperazine distal nitrogen atom, were the most potent in suppressing exploratory activity. Another substitution on the 3-phenyl group with a 3-Cl, 4-CH_3, 4-OCH_3, or 3- or 4-CF_3 group led to inactivity. Compounds having a 2-chlorophenyl (**30** and **32**), 4-bromophenyl (**42**), or 4-hydroxyphenyl group (**47**) still retained some potency, while the introduction of a fluorine atom (**55** and **56**) or a methoxy group (**88**) into the 7-position of the benzazepine nucleus also suppressed the exploratory activity. Displacement of the 2-piperazinyl group with the other amines, however, led to inactivity (**103–105**).

Further studies on the CNS depressant activities of the 3-(4-halophenyl) derivatives (**23–27**, **38**, **41**, and **42**), including their effect on brain dopamine (DA) metabolites in mice, were examined in comparison with those of chlorpromazine and clozapine, and the results are shown in Table III. Apomorphine causes emesis by directly stimulating DA receptors; thus the antagonism against this behavior indicates DA receptor blocking activity. The 4-fluorophenyl (**23–27**) and 4-chlorophenyl (**38**) derivatives exhibited potent inhibition of both exploratory activity and apomorphine-induced emesis, although the 4-bromo isomers (**41** and **42**) showed some potency only in the emesis test. Standard antipsychotics are considered to increase brain DA turnover rate by blockade of dopaminergic receptor sites.[10] The above compounds also increased DA

(9) Francis, W. C.; Thornton, J. R.; Werner, J. C.; Hopkins, T. R. *J. Am. Chem. Soc.* **1958**, *80*, 6238.

Table I. Physical Properties of Intermediates 14, 15, and 16



14 15 16

14a–g,i,l,m,p–u,x; 15a–x, 16a,e,f,o,v–x: Ar = $C_6H_4(R_2)$; 14y, 15y: Ar = 3-C_5H_4N

no.	R_1	R_2	proced[a]	yield, %	mp, °C	recrystn[b]	formula[c]
14a	H	H	A	97	170–171	C-H	$C_{16}H_{15}NO$
14b	H	4-F	A	64	141–143	H	$C_{16}H_{14}FNO$
14c	H	2-Cl	A	60	169–170	C-H	$C_{16}H_{14}ClNO$
14d	H	3-Cl	A	69	116	C-H	$C_{16}H_{14}ClNO$
14e	H	4-Cl	A	98	117–120	E-H	$C_{16}H_{14}ClNO$
14f	H	4-Br	A	70	156–158	E-H	$C_{16}H_{14}BrNO$
14g	H	4-CH_3	A	98	163	C-H	$C_{17}H_{17}NO$
14i	H	4-OH	A	97	130	A-H	$C_{16}H_{15}NO_2$
14l	H	4-CF_3	A	23	97–98	E-H	$C_{17}H_{14}F_3NO$
14m	6-F	H	A	96	165–166	C-H	$C_{16}H_{14}FNO$
14p	6-CH_3	H	A	96	169–170	C-H	$C_{17}H_{17}NO$
14q	6-C_2H_5	H	A	89	187	C-H	$C_{18}H_{19}NO$
14r	6-*n*-C_3H_7	H	A	89	157	C-H	$C_{19}H_{21}NO$
14s	6-*i*-C_3H_7	H	A	75	162–163	C-H	$C_{19}H_{21}NO$
14t	6-OCH_3	H	A	38	186–189	C-H	$C_{17}H_{17}NO_2$
14u	7-Cl	H	A	93	219	D-HO	$C_{16}H_{14}ClNO$
14x	7-Cl	4-Cl	A	88	157–158	E-H	$C_{16}H_{13}Cl_2NO$
14y			A	67	177–178	C	$C_{15}H_{14}N_2O$
15a	H	H	B	97	195–197[d]	C-E	$C_{16}H_{15}NO$
15b	H	4-F	B	75	175	C-E	$C_{16}H_{14}FNO$
15c	H	2-Cl	B	93	254–255[e]	C-E	$C_{16}H_{14}ClNO$
15d	H	3-Cl	B	87	223[f]	C-E	$C_{16}H_{14}ClNO$
15e	H	4-Cl	B	85	198[g]	C-E	$C_{16}H_{14}ClNO$
15f	H	4-Br	B	75	203–205	C-E	$C_{16}H_{14}BrNO$
15g	H	4-CH_3	B	88	195–197[h]	C-E	$C_{17}H_{17}NO$
15h	H	4-OCH_3	B	36	187	C-E	$C_{17}H_{17}NO_2$
15i	H	4-OH	B	86	238–239	A-C	$C_{16}H_{15}NO_2$
15j	H	4-OAc	D	71	171–173	A-E	$C_{18}H_{17}NO_3$
15k	H	3-CF_3	C	12	190–191	C-E	$C_{17}H_{14}F_3NO$
15l	H	4-CF_3	C	35	187–188	C-E	$C_{17}H_{14}F_3NO$
15m	7-F	H	B	85	224–225	C-E	$C_{16}H_{14}FNO$
15n	7-Cl	H	E	76	245–247[i]	C	$C_{16}H_{14}ClNO$
15o	7-Br	H	E	97	251–252	C	$C_{16}H_{14}BrNO$
15p	7-CH_3	H	B	89	216–217	C-E	$C_{17}H_{17}NO$
15q	7-C_2H_5	H	B	91	186–187	C-E	$C_{18}H_{19}NO$
15r	7-*n*-C_3H_7	H	B	82	159	C-E	$C_{19}H_{21}NO$
15s	7-*i*-C_3H_7	H	B	72	202–203	C-E	$C_{19}H_{21}NO$
15t	7-OCH_3	H	C	40	190–194[j]	Al	$C_{17}H_{17}NO_2$
15u	8-Cl	H	B	78	234[k]	C	$C_{16}H_{14}ClNO$
15v	7-Br	2-Cl	E	92	247–248	C-E	$C_{16}H_{13}BrClNO$
15w	7-Br	4-Cl	E	97	240–242	C-E	$C_{16}H_{13}BrClNO$
15x	8-Cl	4-Cl	B	91	258–259	T-Al	$C_{16}H_{13}Cl_2NO$
15y			C	34	170–175[l]	C-E	$C_{15}H_{14}N_2O$
16a	H	H	F	87	123–124	C-Al	$C_{16}H_{13}Cl_2N$
16e	H	4-Cl	F	48	113–115	C-Al	$C_{16}H_{12}Cl_3N$
16f	H	4-Br	F	92	142	C-E	$C_{16}H_{12}BrCl_2N$
16o	7-Br	H	F	93	103–104	H	$C_{16}H_{12}BrCl_2N$
16v	7-Br	2-Cl	F	70	154–155	E	$C_{16}H_{11}BrCl_3N$
16w	7-Br	4-Cl	F	63	138–139	E-H	$C_{16}H_{11}BrCl_3N$
16x	8-Cl	4-Cl	F	85	106–107	Al-E	$C_{16}H_{11}Cl_4N$

[a] See the Experimental Section. [b] Recrystallization solvents used are as follows: C, $CHCl_3$; H, hexane; E, Et_2O; A, acetone; D, dioxane; HO, H_2O; Al, EtOH; T, toluene. [c] All compounds were analyzed for C, H, N, and, when present, for Br, Cl, and F. Values were within ±0.4% of the theoretical values. [d] Literature[17] mp 193–195 °C. [e] Literature[17] mp 245–247 °C. [f] Literature[17] mp 204–207 °C. [g] Literature[17] mp 193–195 °C. [h] Literature[17] mp 193–195 °C. [i] Literature[36] mp 248–250 °C. [j] Literature[36] mp 191–193 °C. [k] Literature[17] mp 228–230 °C. [l] Literature[36] mp 183–187 °C.

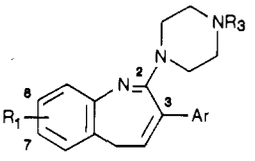
turnover rates at the dose of 50 and 10 mg/kg as shown by the increased brain levels of the major DA metabolites, homovanillic acid (HVA) and 3,4-dihydroxyphenylacetic acid (DOPAC). These results suggest that these compounds exert CNS depressant or antipsychotic effect through a possible antidopaminergic property.

Compounds **23** and **38** were selected for further examination on the basis of their CNS depression profiles. Table IV showed ED_{50} values of the compounds in the present tests in comparison with those of existing antipsychotics, chlorpromazine and clozapine. A suppression of conditioned avoidance response represents one of the characteristic properties of neuroleptics.[11] Catalepsy is

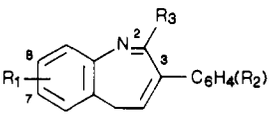
(10) Stawarz, R. J.; Hill, H.; Robinson, S. E.; Setler, P.; Dingell, J. V.; Sulser, F. *Psychopharmacologia* **1975**, *43*, 125.

(11) Oka, M.; Shimizu, M. *Jpn. J. Pharmacol.* **1975**, *25*, 121.

Table II. Physical and Pharmacological Data on 2-Amino-3-aryl-5*H*-1-benzazepines



17-98: Ar = $C_6H_4(R_2)$
99: Ar = 3-C_5H_4N



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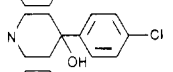
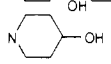
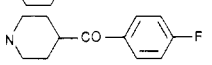
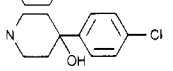
no.	R_1	R_2	R_3	proced[a] yield, %	mp, °C recrystn[b]	formula[c]	dose,[d] mg/kg	EXPL[e]	RES[f]	MES[g]	TRM[h]
17	H	H	H	G 55	155–160 Al	$C_{20}H_{21}N_3 \cdot C_4H_4O_4$[i]	100	–[k]	–	0/5[l]	–
18	H	H	CH_3	G 79	250–252 Al-E	$C_{21}H_{23}N_3 \cdot 2HCl$	100	++	+	0/5	–
19	H	H	CH_2CH_2OH	G 73	213–214 Al-E	$C_{22}H_{25}N_3O \cdot 2HCl \cdot {}^1/_2H_2O$	100	+	+	0/5	–
20	H	H	$CH_2C_6H_5$	H 54	167–170 C-E	$C_{27}H_{27}N_3$	100	–	++	0/5	–
21	H	H	C_6H_5	G 32	186–188 E	$C_{26}H_{25}N_3$	100	–	–	0/5	–
22	H	4-F	H	G 72	188–190 Al	$C_{20}H_{20}FN_3 \cdot C_4H_4O_4$[j]	50	+	+	NT[m]	NT
23	H	4-F	CH_3	G 56	247–252 Al	$C_{21}H_{22}FN_3 \cdot 2HCl$	10 50	+ +++	–	NT	NT
24	H	4-F	C_2H_5	H 62	253–256 Al	$C_{22}H_{24}FN_3 \cdot 2HCl \cdot {}^1/_4H_2O$	10 50	– +++	+	NT	NT
25	H	4-F	n-C_3H_7	H 16	182–185 Al	$C_{23}H_{26}FN_3 \cdot C_4H_4O_4$[j]	10 50	– ++	NT	NT	NT
26	H	4-F	CH_2CH_2OH	G 35	255–260 Al	$C_{22}H_{24}FN_3O \cdot 2HCl$	10 50	– ++	NT	NT	NT
27	H	4-F	C_6H_{11}	H 25	183–185 Al	$C_{26}H_{30}FN_3 \cdot 2(C_4H_4O_4)$[j]	10 50	++ +++	NT	NT	NT
28	H	4-F	$CH_2C_6H_5$	H 44	156–157 E	$C_{27}H_{26}FN_3$	50	–	NT	NT	NT
29	H	2-Cl	H	G 48	154–156 Al-Ac	$C_{20}H_{20}ClN_3 \cdot 2(C_4H_4O_4)$[j]	100	–	–	0/5	–
30	H	2-Cl	CH_3	G 40	248–251 Al-Ac	$C_{21}H_{22}ClN_3 \cdot 2HCl$	100	++	++	0/5	+
31	H	2-Cl	C_2H_5	H 54	254–258 Al-AE	$C_{22}H_{24}ClN_3 \cdot 2HCl \cdot H_2O$	100	–	–	0/5	+
32	H	2-Cl	CH_2CH_2OH	G 40	256–259 Al	$C_{22}H_{24}ClN_3O \cdot 2HCl$	100	++	–	0/5	+
33	H	3-Cl	CH_3	G 51	250–253 Al	$C_{21}H_{22}ClN_3 \cdot 2HCl \cdot {}^1/_2H_2O$	50	–	++	0/5	NT
34	H	3-Cl	CH_2CH_2OH	G 24	195–200 Al	$C_{22}H_{24}ClN_3O \cdot 2HCl \cdot H_2O$	50	–	+	0/5	NT
35	H	4-Cl	H	G 64	162–164 Al	$C_{20}H_{20}ClN_3 \cdot 2(C_4H_4O_4)$[j]	100	–	–	0/5	–
36	H	4-Cl	CH_3	G 73	225–230 Al-A	$C_{21}H_{22}ClN_3 \cdot 2HCl$	100	+	–	0/5	+
37	H	4-Cl	C_2H_5	H 70	232–235 Al-E	$C_{22}H_{24}ClN_3 \cdot 2HCl$	100	++	–	0/5	–
38	H	4-Cl	CH_2CH_2OH	G 84	220–224 Al-A	$C_{22}H_{24}ClN_3O \cdot 2HCl$	100	+++	–	0/5	+
39	H	4-Cl	$CH_2C_6H_6$	H 50	194–195 C-E	$C_{27}H_{26}ClN_3$	50	–	+	NT	NT
40	H	4-Cl	$(CH_2)_3COC_6H_4$-4-F	H 25	168–170 Al	$C_{30}H_{29}ClFN_3O \cdot 2(C_4H_4O_4)$[j]	50	+	–	NT	NT
41	H	4-Br	CH_3	G 69	265–275 Al	$C_{21}H_{22}BrN_3 \cdot 2HCl$	50	–	NT	NT	NT
42	H	4-Br	CH_2CH_2OH	G 75	235–245 Al	$C_{22}H_{24}BrN_3O \cdot 2HCl$	50	+	–	0/5	–
43	H	4-CH_3	CH_3	G 60	265–270 Al	$C_{22}H_{25}N_3 \cdot 2HCl$	100	–	+	0/5	+
44	H	4-CH_3	C_2H_5	H 15	240–245 Al	$C_{23}H_{27}N_3 \cdot 2HCl$	100	–	–	0/5	–
45	H	4-CH_3	CH_2CH_2OH	G 58	230–235 Al	$C_{23}H_{27}N_3O \cdot 2HCl$	100	–	–	0/5	–
46	H	4-OCH_3	CH_3	I 48	128–130 AE	$C_{22}H_{25}N_3O \cdot 2(C_4H_4O_4)$[j]	50	–	+	NT	NT
47	H	4-OH	CH_3	G[n] 78	254–256 E	$C_{21}H_{23}N_3O \cdot {}^1/_4H_2O$	50	++	++	NT	NT
48	H	4-OH	CH_2H_2OH	G[n] 46	211–212 A-E	$C_{22}H_{25}N_3O_2$	50	–	–	NT	NT
49	H	3-CF_3	CH_3	G 63	90–93 M-AE	$C_{22}H_{22}F_3N_3 \cdot 2(C_4H_4O_4) \cdot {}^1/_2H_2O$	100	–	NT	0/5	–
50	H	3-CF_3	CH_2CH_2OH	G 44	84–86 M-AE	$C_{23}H_{24}F_3N_3O \cdot 2(C_4H_4O_4) \cdot {}^1/_2H_2O$	100	–	NT	0/5	–
51	H	4-CF_3	CH_3	G 48	210–215 Al-AE	$C_{22}H_{22}F_3N_3 \cdot 2HCl$	50	–	–	NT	NT
52	H	4-CF_3	C_2H_5	G 18	210–215 Al-AE	$C_{23}H_{24}F_3N_3 \cdot 2HCl \cdot {}^1/_2H_2O$	50	–	–	NT	NT
53	H	4-CF_3	CH_2CH_2OH	G	185–190	$C_{23}H_{24}F_3N_3O \cdot 2HCl \cdot {}^1/_4H_2O$	50	–	–	NT	NT

Table II (Continued)

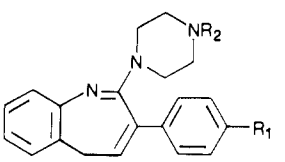
no.	R_1	R_2	R_3	proced[a] yield, %	mp, °C recrystn[b]	formula[c]	dose,[d] mg/kg	EXPL[e]	RES[f]	MES[g]	TRM[h]
				37	Al						
54	7-F	H	CH_3	G	242–247	$C_{21}H_{22}FN_3 \cdot 2HCl$	100	+	–	0/5	–
				61	Al						
55	7-F	H	C_2H_5	H	252–255	$C_{22}H_{24}FN_3 \cdot 2HCl$	100	++	–	0/5	–
				55	Al						
56	7-F	H	CH_2CH_2OH	G	170–173	$C_{22}H_{24}FN_3O \cdot 2HCl$	100	+++	–	0/5	–
				38	Al-E						
57	7-Cl	H	CH_3	G	252–257	$C_{21}H_{22}ClN_3 \cdot 2HCl \cdot {}^1/_4H_2O$	10			0/5	–
				60	HO-Al		100	–	–	4/5	+++
58	7-Cl	H	C_2H_5	H	253–256	$C_{22}H_{24}ClN_3 \cdot 2HCl$	10			0/5	+
				43	Al		100	–	–	4/5	+++
59	7-Cl	H	CH_2H_2OH	G	192–197	$C_{22}H_{24}ClN_3O \cdot 2HCl$	10			0/5	
				53	HO-Al		100	–	–	4/5	++
60	7-Cl	H	$CH_2C_6H_5$	G	204–207	$C_{27}H_{26}ClN_3$	100	–	+	0/5	–
				42	C-E						
61	7-Cl	H	$CONH_2$	H	163–164	$C_{21}H_{21}ClN_4O$	100	–	–	0/5	–
				49	A						
62	7-Br	H	H	G	192–195	$C_{20}H_{20}BrN_3 \cdot C_4H_4O_4$[i]	100	–	+	0/5	NT
				32	Al-AE						
63	7-Br	H	CH_3	G	255–260	$C_{21}H_{22}BrN_3 \cdot 2HCl$	100	–	–	5/5	+++
				53	HO-Al						
64	7-Br	H	C_2H_5	G	253–258	$C_{22}H_{24}BrN_3 \cdot 2HCl \cdot H_2O$	100	–	–	3/5	–
				51	Al						
65	7-Br	H	CH_2CH_2OH	G	162–163	$C_{22}H_{24}BrN_3O$	100	–	–	5/5	–
				75	Al-H						
66	7-Br	H	$CH_2CH{=}CH_2$	H	155–156	$C_{23}H_{24}BrN_3$	100	–	+	0/5	–
				61	E						
67	7-Br	H	$CH_2C{\equiv}CH$	H	83–85	$C_{23}H_{22}BrN_3$	100	–	–	0/5	–
				30	Al						
68	7-Br	H	$CH_2C_6H_4$-4-OCH_3	H	187–188	$C_{28}H_{28}BrN_3O$	100	–	–	0/5	–
				68	AE						
69	7-Br	H	$CH_2COC_6H_5$	H	144–146	$C_{28}H_{26}BrN_3O$	100	–	–	0/5	–
				47	E-M						
70	7-Br	H	$CH_2CH_2COC_6H_5$	J	163–164	$C_{29}H_{28}BrN_3O$	100	–	–	0/5	–
				30	E						
71	7-Br	H	C_6H_5	G	164–165	$C_{26}H_{24}BrN_3$	100	–	–	0/5	–
				19	E						
72	7-Br	H	$CONH_2$	H	161–162	$C_{21}H_{21}BrN_4O$	100	–	–	5/5	–
				53	A-E						
73	7-CH_3	H	CH_3	G	255–260	$C_{22}H_{25}N_3 \cdot 2HCl$	100	–	–	3/5	–
				62	Al						
74	7-CH_3	H	C_2H_5	H	260–265	$C_{23}H_{27}N_3 \cdot 2HCl$	10			0/5	–
				42	Al		100	–	–	4/5	+++
75	7-CH_3	H	CH_2CH_2OH	G	107–110	$C_{23}H_{27}N_3O \cdot 2(C_4H_4O_4) \cdot H_2O$	100	+	–	3/5	–
				51	Al-E						
76	7-C_2H_5	H	CH_3	G	255–260	$C_{23}H_{27}N_3 \cdot 2HCl \cdot {}^1/_2H_2O$	10			0/5	
				63	Al		100	NT	–	5/5	++
77	7-C_2H_5	H	C_2H_5	H	250–254	$C_{24}H_{29}N_3 \cdot 2HCl \cdot H_2O$	10			0/5	
				56	Al		100	+	–	5/5	++
78	7-C_2H_5	H	n-C_3H_7	H	130–132	$C_{25}H_{31}N_3 \cdot 2(C_4H_4O_4)$[j]	100	–	–	0/5	+
				45	Al-E						
79	7-C_2H_5	H	i-C_3H_7	H	102–104	$C_{25}H_{31}N_3 \cdot 2(C_4H_4O_4)$[j]	10			0/5	
				53	Al-E		100	–	–	5/5	++
80	7-C_2H_5	H	n-C_4H_9	H	155–157	$C_{26}H_{23}N_3 \cdot 2(C_4H_4O_4)$[j]	100	–	–	0/5	+
				49	Al-E						
81	7-C_2H_5	H	CH_2CH_2OH	G	232–237	$C_{24}H_{29}N_3O \cdot 2HCl$	10			0/5	
				63	Al-A		100	–	–	5/5	++
82	7-n-C_3H_7	H	CH_3	G	240–245	$C_{24}H_{29}N_3 \cdot 2HCl \cdot {}^1/_2H_2O$	100	–	–	0/5	++
				27	Al						
83	7-n-C_3H_7	H	C_2H_5	H	72–74	$C_{25}H_{31}N_3 \cdot 2(C_4H_4O_4) \cdot {}^1/_2H_2O$	100	–	–	0/5	–
				37	AE						
84	7-n-C_3H_7	H	CH_2CH_2OH	G	225–230	$C_{25}H_{35}N_3O \cdot 2HCl$	100	–	–	0/5	++
				48	Al						
85	7-i-C_3H_7	H	CH_3	G	188–190	$C_{24}H_{29}N_3 \cdot {}^5/_4(C_4H_4O_4) \cdot {}^1/_2H_2O$	100	–	–	0/5	++
				57	AE						
86	7-i-C_3H_7	H	C_2H_5	H	115–120	$C_{26}H_{31}N_3 \cdot 2(C_4H_4O_4) \cdot {}^3/_2H_2O$	100	–	–	0/5	+
				55	AE						
87	7-i-C_3H_7	H	CH_2CH_2OH	G	243–248	$C_{25}H_{31}N_3O \cdot 2HCl \cdot {}^1/_2H_2O$	100	–	–	0/5	–
				68	Al						
88	7-OCH_3	H	CH_3	G	240–250	$C_{22}H_{25}N_3O \cdot 2HCl$	10	–		0/5	
				39	Al-A		100	+++	++	4/5	++
89	8-Cl	H	H	G	174–177	$C_{20}H_{20}ClN_3 \cdot C_4H_4O_4$	100	+	+	0/5	–
				41	Al						
90	8-Cl	H	CH_3	G	248–251	$C_{21}H_{22}ClN_3 \cdot 2HCl$	100	–	–	0/5	++
				47	Al-E						
91	8-Cl	H	CH_2CH_2OH	G	210–215	$C_{22}H_{24}ClN_3O \cdot 2HCl \cdot {}^3/_4H_2O$	100	–	–	0/5	++
				41	Al						
92	8-Cl	4-Cl	H	G	202–203	$C_{20}H_{19}Cl_2N_3 \cdot C_4H_4O_4$[j]	100	–	+	0/5	++
				77	Al-E						
93	8-Cl	4-Cl	CH_3	G	223–225	$C_{21}H_{21}Cl_2N_3 \cdot 2HCl$	100	++	–	0/5	–
				50	Al						
94	8-Cl	4-Cl	CH_2CH_2OH	G	203–206	$C_{22}H_{23}Cl_2N_3O \cdot 2HCl$	100	–	–	0/5	–
				58	Al						
95	7-Br	2-Cl	H	G	163–164	$C_{20}H_{19}BrClN_3 \cdot C_4H_4O_4$[i]	100	–	–	0/5	–
				22	Al-AE						

Table II (Continued)

no.	R_1	R_2	R_3	proced[a] yield, %	mp, °C recrystn[b]	formula[c]	dose,[d] mg/kg	EXPL[e]	RES[f]	MES[g]	TRM[h]
96	7-Br	4-Cl	CH_3	G 72	229–233 Al-A	$C_{21}H_{21}BrClN_3 \cdot 2HCl$	100	–	–	0/5	–
97	7-Br	4-Cl	C_2H_5	H 63	195 Al-E	$C_{22}H_{23}BrClN_3 \cdot C_4H_4O_4$[j]	100	–	–	2/5	–
98	7-Br	4-Cl	CH_2CH_2OH	G 52	203–206 Al-A	$C_{22}H_{23}BrClN_3O \cdot 2HCl$	100	–	–	0/5	–
99			CH_3	G 23	139–140 E	$C_{20}H_{22}N_4$	100	–	+++	0/5	–
100	H	H		G 49	211–212 Al-E	$C_{20}H_{20}N_2O \cdot HCl$	100	–	–	0/5	–
101	H	H		G 42	193–197 A-E	$C_{21}H_{22}N_3 \cdot 2HCl$	100	+	–	0/5	–
102	H	H		G 34	165–167 E-H	$C_{27}H_{25}ClN_2O$	100	+	–	0/5	–
103	H	4-F		G 36	237–242 Al-AE	$C_{21}H_{21}FN_2O \cdot HCl$	50	–	–	0/5	–
104	H	4-Cl		G 35	124–125 H	$C_{21}H_{21}ClN_2$	50	–	–	0/5	–
105	H	4-Cl		G 28	149–150 E	$C_{28}H_{24}ClFN_2O$	50	–	–	0/5	–
106	7-Br	H		G 48	155–157 E	$C_{21}H_{21}BrN_2$	100	–	+	0/5	–
107	7-Br	H		G 43	240–243 M-Al	$C_{27}H_{24}BrClN_2O \cdot HCl$	100	–	–	0/5	–

[a] See the corresponding procedure under the Experimental Section. [b] Recrystallization solvents used are as follows: AE, AcOEt; M, MeOH. See also footnote *b* in Table I. [c] All compounds were analyzed for C, H, N, and, when present, Br, Cl, and F. Values were within ±0.4% of the theoretical values. [d] Test compounds were administered po. [e] EXPL = antiexploratory activity in mice. [f] RES = antireserpine activity in mice. [g] MES = antimaximal electroshock seizure activity in mice. [h] TRM = antitremorine activity in mice. [i] Fumarate. [j] Maleate. [k] The symbols have the following meanings: –, no inhibition (<30%); +, slight inhibition (31–50%); ++, moderate inhibition (51–70%); +++, potent inhibition (>71%). [l] Number of positive effects/number of mice tested. [m] NT = not tested. [n] The starting material is dichloroacetate (**16j**). During the process of usual workup and purification, the hydrolysis of an acetoxy group took place, affording the 4-hydroxyphenyl derivatives.

Table III. CNS Depressant Activities and Effects on Brain Monoamine Metabolites of 3-Phenyl-2-piperazinyl-5*H*-1-benzazepine Derivatives



			% inhibition			brain levels in mice, % of control			
			exploratory activity in mice			HVA		DOPAC	
no.	R_1	R_2	10 mg/kg[a]	50 mg/kg	apomorphine-induced emesis in dogs, 1 mg/kg	10 mg/kg	50 mg/kg	10 mg/kg	50 mg/kg
23	F	CH_3	43.3	79.3	100	197	400	188	306
24	F	C_2H_5	10.6	86.8	100	432	461	287	345
25	F	n-C_3H_7	18.5	61.4	100	328	557	166	317
26	F	CH_2CH_2OH	19.6	68.4	100	243	349	262	369
27	F	C_6H_{11}	61.4	84.6	46.0	295	343	244	334
38	Cl	CH_2CH_2OH	40.8	57.3[b]	95.5	265	382	186	289
41	Br	CH_3	11.4	13.2	72.5	162	294	161	233
42	Br	CH_2CH_2OH	31.9	36.1	72.5	181	335	106	291
chlorpromazine			46.3	90.1	22.2[c]	203	304	232	303
clozapine			50.6	87.8	27.4	106	274	128	324

[a] Administered po. [b] At 100 mg/kg. [c] At 2 mg/kg.

considered to be associated with antidopaminergic activity and to be an indicator of a compound's liability to produce undesirable EPS in clinical use.[12] Compound **23** exibited a marked suppression of locomotor activity, where the potency was nearly equal to that of chlorpromazine and clozapine. The potency of **23** for the inhibition of conditioned avoidance response, however, was slightly weaker than that of the above drugs. In the self-stimulation test, **23** is more active than chlorpromazine, whereas clozapine is much less effective. In the antagonism to apomorphine-induced emesis in dogs, **23** was about 16 and 45 times as potent as chlorpromazine and clozapine, respectively. On the other hand, the cataleptic effect of **23** was weak, and the potency is one-third that of chlorpromazine. The ptosis induced by many neuroleptics has been regarded as an animal model capable of predicting the unfavorable symptom such as oversedation and drowziness in man. The potency of **23** in this test was about a half and one-fourth that of chlorpromazine and clozapine, respectively. Compound **38** was less effective than **23** in all the tests except for the antiemetic test, in which **38** showed specifically potent activity. On the basis of above results,

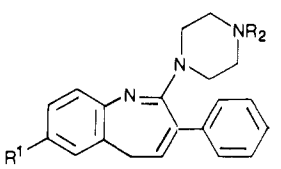
(12) Hornykiewicz, O.; Markham, C. M.; Clark, W. G.; Fleming, R. M. In *Principles of Psychopharmacology*; Clark, W. G., Ed.; Academic: New York, 1970; p 585.

Table IV. Pharmacological Profiles of 23 and 38

no.	ED_{50}, mg/kg, po: inhibn of exploratory activity in mice	inhibn of conditioned avoidance response in mice	inhibn of self-stimulation response in rats	inhibn of apomorphine-induced emesis in dogs	catelepsy in mice	ptosis in mice
23	8.15 (3.18–20.9)[a]	14.6 (5.35–39.6)	4.05 (1.31–12.6)	0.28 (0.14–0.55)	21.5 (11.7–39.6)	61.0 (32.5–114)
38	73.1 (37.3–20.9)	38.1 (13.4–108)	25.4 (18.1–35.5)	0.19 (0.06–0.60)	66.8 (36.5–123)	88.7 (35.8–220)
CPZ[b]	8.26 (4.27–16.0)	5.59 (3.75–8.34)	6.68 (4.88–9.15)	4.53 (1.49–13.8)	7.81 (3.58–17.0)	24.9 (12.0–51.4)
CLZ[c]	8.45 (5.26–13.6)	9.68 (6.28–14.9)	77.1 (40.6–146)	12.6 (4.40–36.2)	>100	15.8 (8.49–29.4)

[a] 95% confidence limits. [b] Chlorpromazine. [c] Clozapine.

Table V. Anticonvulsant Activities of 6-Substituted 3-Phenyl-2-piperazinyl-5*H*-1-benzazepine Derivatives



no.	R_1	R_2	ED_{50}, mg/kg, po, in mice: antimaximal electroshock seizure activity	antipentylenetetrazole activity
18	H	CH_3	>100	NT[a]
19	H	CH_2CH_2OH	>100	NT
54	F	CH_3	>500	>200
55	F	C_2H_5	>500	>100
56	F	CH_2CH_2OH	>500	>500
57	Cl	CH_3	89.4 (55.1–145)[b]	42.9 (23.5–78.2)
58	Cl	C_2H_5	93.1 (72.8–119)	34.7 (23.3–51.9)
59	Cl	CH_2CH_2OH	49.5 (37.8–65.0)	26.5 (19.2–36.6)
63	Br	CH_3	31.2 (22.1–44.0)	8.3 (5.3–13.0)
64	Br	C_2H_5	30.7 (21.5–44.0)	17.2 (13.0–22.8)
65	Br	CH_2CH_2OH	14.6 (11.5–18.4)	13.2 (8.9–19.6)
73	CH_3	CH_3	86.1 (57.6–129)	50.9 (33.5–77.4)
74	CH_3	C_2H_5	70.2 (56.3–87.6)	32.3 (26.7–39.1)
75	CH_3	CH_2CH_2OH	103 (77.5–137)	39.4 (23.7–65.6)
CMZ[c]			13.3 (9.6–17.6)	10.3 (6.7–15.8)
DBH[d]			7.9 (5.8–9.7)	3.7 (2.5–5.6)

[a] Not tested. [b] 95% confidence limits. [c] Carbamazepine. [d] Diphenylhydantoin.

23 is a compound with neuroleptic-like activity approximately as potent as chlorpromazine but with less cataleptic and ptotic potential and with much more potential in antagonizing emesis. However, as to the CNS depression profile, **23** seems to be substantially closer to chlorpromazine than to clozapine.

Compounds **89–94**, having a [[(halophenyl)imino]methyl]piperazine framework and being closely related in the structure to atypical antipsychotic fluperlapine (**4b**), did not show any suppression of exploratory activity (except for **93**). It is obvious that the forementioned supposed pharmacophore could not exert the effect in this ring system.

In contrast to 7-fluoro isomers (**55** and **56**) with suppressing exploratory activity, replacement of this fluorine atom by a chlorine, bromine, methyl, or ethyl group resulted in loss of the activity, but brought about potent anti-MES and moderate antitremorine activities (**57–59**, **63–65**, **72–77**, **79**, and **81**) at a 100 mg/kg dose. The potencies were, however, much decreased at 10 mg/kg. As to substituents on the distal nitrogen of the piperazinyl group, a lower alkyl or hydroxyalkyl group appeared to be preferable for exhibiting the activities, and bulky substituents or other amines diminished the potency. This was also decreased in the 7-propyl (**82–87**) and 7-bromo-3-chlorophenyl (**95–98**) derivatives. Antagonistic effects on convulsions induced electrically (MES) and chemically (pentylenetetrazole) were examined in more detail for some 7-substituted compounds, and the results were shown in Table V in comparison with those of the antiepileptics carbamazepine and diphenylhydantoin. Potent antagonism of MES in animals is considered to correlate positively with the clinical efficacy in controlling tonic-clonic (grad mal) and temporal lobe (psychomotor) seizures in man.[13] Drugs effective against grand mal epilepsy are known to be capable of preventing the tonic extenser component of maximal seizures induced by pentylenetetrazole, while exerting little effect on minimal seizures induced by the same analeptic.[14] The most potent compounds are **63** and **65**, and the potency is close to those of carbamazepine. Concerning the substituents in the 7-position, the order of increasing potency was H, F < CH_3, Cl < Br.

Many observations in neuroleptics possessing 6-6-6 or 6-7-6 tricyclic ring systems suggest that a specific spacial relationship between the phenyl group, which is closer to

(13) Millichap, J. G. *Epilepsia* **1969**, *10*, 315.
(14) Swinyard, E. A. In *Anticonvulsant Drugs*; Mercier, J., Ed.; Pergamon: New York, 1973; p 47.

the amino group, and the amino group is necessary for binding at receptor sites; that is, one phenyl group plays a more specific role than the another in the binding of tricyclic antipsychotics.[15] As to 5*H*-1-benzazepines in this study, the neuroleptic-like activities of **23** and **38** suggest that the property of the phenyl group at the 3-position, in combination with the 2-piperazinyl moiety, does a great deal for determining neuroleptic-like activity. Thus, more exactly, there is the need for a 4-fluoro- or 4-chlorophenyl group for the good activity. In this study, the above phenyl moiety, in conjugation with the 3,4-double bond, plays a role of a fused phenyl ring of the dibenzo–epine skeleton, and this structural requirement exhibited potent neuroleptic-like activity. The new ring system, 3-phenyl-2-piperazinyl-5*H*-1-benzazepine, offers a first instance of compounds that are derived from the dibenzo–epine skeleton and exhibit neuroleptic activity equipotent to or more potent than chlorpromazine and clozapine.

Experimental Section

Melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were measured on a Hitachi 260-10 infrared spectrometer. ^{1}H NMR spectra were taken in $CDCl_3$, DMSO-d_6, or D_2O solution with a Varian FT-80A or a Varian XL-300 spectrometer with TMS (Me_4Si) or DSS [$Me_3Si(CH_2)_3SO_3Na$] as an internal reference. Mass spectra (MS) were obtained with a JEOL JMS-D300 spectrometer. The IR, ^{1}H NMR, and MS data of all compounds were consistent with structure, and these data are presented only where required for structural assignment. Analytical results for compounds indicated by the molecular formula were within ±0.4% of calculated values. Organic extracts were dried over $MgSO_4$.

2,4-Diphenylbutyric Acids (8a–h,k–m,p–u,x) and 2-(3-Pyridyl)-4-phenylbutyric Acid (8y). According to the procedure described by Newman,[16] various phenethyl bromides were allowed to react with the appropriate benzyl cyanides or 3-pyridylacetonitrile in presence of sodium amide or sodium hydride to afford 2,4-diphenylbutyronitriles (**7a–h,m,p–u,x,y**). The above nitriles (**7a–g,m,p–s,u,x**) were subsequently subjected to hydrolysis with 70% sulfuric acid in acetic acid to give **8** (R_1, R_2, and mp): **8a** [H, H, mp 73 °C (lit.[16] mp 70–72 °C)], $C_{16}H_{16}O_2$; **8b** (H, 4-F, oil); **8c** [H, 2-Cl, oil (lit.[17] oil)]; **8d** [H, 3-Cl, oil (lit.[17] oil)]; **8e** [H, 4-Cl, mp 78–79 °C (lit.[17] mp 81–83 °C)], $C_{16}H_{15}ClO_2$; **8f** (H, 4-Br, oil); **8g** (H, 4-CH_3, oil); **8m** (3-F, H, oil); **8p** (3-CH_3, H, oil); **8q** (3-C_2H_5, H, oil); **8r** (3-*n*-C_3H_7, H, oil); **8u** [4-Cl, H, mp 78–79 °C (lit.[17] mp 78–79 °C)], $C_{16}H_{15}ClO_2$; **8x** (4-Cl, 4-Cl, mp 82–83 °C), $C_{16}H_{14}Cl_2O_2$. 2-(4-Methoxyphenyl)-4-phenylbutyric acid (**8h**), 4-(3-methoxyphenyl)-2-phenylbutyric acid (**8t**), and 4-phenyl-2-(3-pyridyl)butyric acid (**8y**) were obtained as an oil by the hydrolysis of the corresponding nitriles (**7h**, **7t**, or **7y**) with KOH in ethylene glycol. **4-Phenyl-2-[(trifluoromethyl)phenyl]-butyric acids (8k and 8l)** were obtained as an oil by hydrogenation of the corresponding oxocarboxylic acid (**12k** or **12l**) over 5% Pd–C in acetic acid at 50 °C.

1-Phenyl-3-[(trifluoromethyl)phenyl]-2-propen-1-ones (9k and 9l). The condensation[18] of acetophenone with 3- or 4-(trifluoromethyl)benzaldehyde afforded **9**: 1-phenyl-3-[(3-(trifluoromethyl)phenyl]-2-propen-1-one (**9k**), mp 110 °C ($CHCl_3$–hexane), $C_{16}H_{11}F_3O$, yield 77%; 1-phenyl-3-[4-(trifluoromethyl)phenyl]-2-propen-1-one (**9l**), mp 125 °C ($CHCl_3$–hexane), $C_{16}H_{11}F_3O$, yield 62%.

4-Oxo-4-phenyl-2-[(trifluoromethyl)phenyl]butyronitrile (10k and 10l). The addition[19] of hydrogen cyanide to the required benzalacetophenone (**9k** or **9l**) gave the following nitriles (**10**): 4-phenyl-2-[3-(trifluoromethyl)phenyl]butyronitrile (**10k**), mp 74 °C ($CHCl_3$–hexane), $C_{17}H_{12}F_3NO$, yield 80%; 4-phenyl-2-[4-(trifluoromethyl)phenyl]butyronitrile (**10l**), mp 97–98 °C ($CHCl_3$–hexane), $C_{17}H_{12}F_3NO$, yield 98%.

Methyl 4-Oxo-4-phenyl-2-[(trifluoromethyl)phenyl]-butyrates (11k and 11l). The methanolysis[19] of the corresponding nitriles (**10k** or **10l**) with methanol and concentrated sulfuric acid afforded the following methyl esters (**11**): methyl 4-oxo-4-phenyl-2-[3-(trifluoromethyl)phenyl]butyrate (**11k**), oil, yield 98%; methyl 4-oxo-4-phenyl-2-[4-(trifluoromethyl)-phenyl]butyrate (**11l**), mp 91–92 °C (Et_2O–hexane), $C_{18}H_{15}F_3O_3$, yield 95%.

4-Oxo-4-phenyl-2-[(trifluoromethyl)phenyl]butyric Acids (12k and 12l). Alkaline hydrolysis[19] of the above ester (**11k** or **11l**) gave the following oxocarboxylic acids (**12**): 4-oxo-4-phenyl-2-[3-(trifluoromethyl)phenyl]butyric acid (**12k**), mp 147 °C ($CHCl_3$–hexane), $C_{17}H_{13}F_3O_3$, yield 97%; 4-oxo-4-phenyl-2-[4-(trifluoromethyl)phenyl]butyric acid (**12l**), mp 152–153 °C (ether–hexane), $C_{17}H_{13}F_3O_3$, yield 94%.

2-Phenyl-1-tetralones (13a–i,k–m,p–u,x) and 2-(3-Pyridyl)-1-tetralone (13y). 2,4-Diphenylbutyric acids (**8a–h,k–m,p–u,x**) were converted into the acid chlorides, which were subjected to Friedel–Crafts cyclization according to the procedure described by Newman[16] to give **13** (R_1, R_2, yield, mp): **13a** [H, H, 94%, mp 76 °C (lit.[20] mp 76–77 °C)], $C_{16}H_{14}O$; **13b** [H, 4-F, 83%, mp 89 °C (lit.[17] mp 93–94 °C)], $C_{16}H_{13}FO$; **13c** [H, 2-Cl, 95%, mp 68 °C (lit.[17] mp 69–70 °C)], $C_{16}H_{13}ClO$; **13d** (H, 3-Cl, 59%, mp 100 °C), $C_{16}H_{13}ClO$; **13e** [4-Cl, 94%, mp 104–105 °C (lit.[21] mp 108–109 °C)], $C_{16}H_{13}ClO$; **13f** (H, 4-Br, 42%, mp 113–114 °C), $C_{16}H_{13}BrO$; **13g** (H, 4-CH_3, 83%, mp 70–71 °C), $C_{17}H_{16}O$; **13h** [H, OCH_3, 49%, mp 106–107 °C (lit.[22] mp 106–107.5 °C)], $C_{17}H_{16}O_2$; **13k** (H, 3-CF_3, 90%, mp 71 °C), $C_{17}H_{13}F_3O$; **13l** (H, 4-CF_3, 64%, mp 151 °C), $C_{17}H_{13}F_3O$; **13m** (6-F, H, 85%, mp 98–99 °C), $C_{16}H_{13}FO$; **13p** (6-CH_3, H, 77%, mp 89–90 °C), $C_{17}H_{16}O$; **13q** (6-C_2H_5, H, 85%, mp 70 °C), $C_{18}H_{18}O$; **13r** (6-*n*-C_3H_7, H, 90%, mp 95 °C), $C_{19}H_{20}O$; **13s** (6-*i*-C_3H_7, H, 85%, mp 71 °C), $C_{19}H_{20}O$; **13t** [6-OCH_3, H, 45%, mp 113–115 °C (lit.[23] mp 113–116 °C)], $C_{17}H_{16}O_2$; **13u** [7-Cl, H, 84%, mp 84–85 °C (lit.[17] mp 88–89 °C)], $C_{16}H_{13}ClO$; **13x** (7-Cl, 4-Cl, 90%, mp 108–109 °C), $C_{16}H_{12}Cl_2O$. 2-(4-Hydroxyphenyl)tetralone (**13i**) was prepared by demethylation of **13h** with hydrobromic acid in acetic acid: yield 87%; mp 138 °C; $C_{16}H_{14}O_2$. 2-(3-Pyridyl)tetralone (**13y**) was prepared by the cyclization of **8y** in polyphosphoric acid: yield 59%; mp 78 °C (lit.[24] mp 79–80 °C); $C_{15}H_{13}NO$.

2-Phenyl-1-tetralone Oxime (14a). Procedure A. A mixture of **13a** (33.3 g, 0.15 mol), hydroxylamine hydrochloride (31.5 g, 0.45 mol), sodium acetate (36.9 g, 0.45 mol), methanol (200 mL), and water (80 mL) was stirred and refluxed for 4 h. The reaction mixture was evaporated to about half its initial volume and diluted with water. The resulting crystals were collected, washed with water, and dried. Recrystallization from chloroform–hexane gave **14a** (34.6 g, 97%). Similarly prepared by this method were compounds **14b–i,l,m,p–u,x,y**. Among them, **14h** was obtained as an oil, yield 80%.

3-Phenyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (15a). Procedure B. The oxime **14a** (23.7 g, 0.1 mol) was added portionwise to a stirred polyphosphoric acid (300 g) preheated at 120 °C. After 15 min, the solution was poured onto ice and water. The resulting solid was collected and crystallized from chloroform–ether to give **15a** (23 g, 97%). Similarly prepared by this method were compounds **15b–i,m,p–s,u,x**. The reaction of **14l** by this method was unsuccessful, because the trifluoromethyl group was hydrolyzed to the carboxyl group under these conditions.

3-[3-(Trifluoromethyl)phenyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (15l). Procedure C. Concentrated sulfuric

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acid (15 mL) was added dropwise to a stirred mixture of 13l (15 g, 0.052 mol), acetic acid (100 mL), and sodium azide (6.7 g, 0.1 mol) over 30 min at 50 °C, and the reaction mixture was stirred at this temperature for additional 1 h. After being cooled, the reaction mixture was diluted with ice–water and extracted with chloroform. The organic layer was washed with dilute ammonia water and then with water, dried, and evaporated. The residue was crystallized from chloroform–ether to give **15a** (5.6 g, 35%). Also prepared by this method were compounds **15k,t,y**.

3-(4-Acetoxyphenyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (15j). Procedure D. A mixture of **15i** (11.9 g, 0.047 mol), acetic anhydride (24 mL), and pyridine (40 mL) was stirred for 30 min at room temperature. The reaction mixture was concentrated, and the residue was crystallized from acetone–ether to give **15j** (9.9 g, 71%).

Procedure E. (a) 7-Chloro-3-phenyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (15n). Sulfuryl chloride (14.9 g, 0.11 mol) was added dropwise to a stirred solution of **15a** (23.7 g, 0.1 mol) in chloroform (200 mL) at room temperature. After the addition was complete, the reaction mixture was refluxed for 20 min and concentrated to about half its initial volume. The resulting crystalline materials were collected and recrystallized from chloroform to give **15n** (20.7 g, 76%): ^{1}H NMR (Me_2SO-d_6) δ 2.2–3.0 (4 H, m, CH_2CH_2), 3.60 (1 H, m, 3-H), 7.05 (1 H, d, J = 8.5 Hz, 9-H), 7.34 (1 H, q, J = 8.5, 2.5 Hz, 6-H), 7.25 (5 H, s, C_6H_5), 9.73 (1 H, NH); MS (EI, 70 eV), m/z 271 and 273 (M^+).

(b) 7-Bromo-3-phenyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (15o). Bromine (3.2 g, 0.02 mol) was added dropwise to a stirred solution of **15a** (2.37 g, 0.01 mol) in acetic acid (35 mL) at room temperature, and the reaction mixture was left overnight and concentrated. The crystalline residue was washed with water and recrystallized from chloroform to give **15o** (3.06 g, 97%): ^{1}H NMR (Me_2SO-d_6) δ 2.2–3.0 (4 H, m, CH_2CH_2), 3.6 (1 H, m, 3-H), 6.99 (1 H, d, J = 8.5 Hz, 9-H), 7.47 (1 H, q, J = 8.5, 2.5 Hz, 8-H), 7.54 (1 H, d, J = 2.5 Hz, 6-H), 7.24 (5 H, s, C_6H_5), 9.75 (1 H, NH); MS (EI, 70 eV), m/z 315 and 317 (M^+). Compounds **15v,w** were prepared similarly by this method.

2,3-Dichloro-3-phenyl-4,5-dihydro-3*H*-1-benzazepine (16a). Procedure F. A mixture of **15a** (16.8 g, 0.069 mol) and phosphorus pentachloride (37.4 g, 0.18 mol) was heated to 110 °C for 1 h. The volatile materials were removed in vacuo, and the residue was partitioned between ice–water and ether. The organic layer was repeatedly washed with water quickly and thoroughly, dried, and evaporated to give a crystalline residue, which was recrystallized from chloroform–ethanol to give **16a** (16.5 g, 87%): ^{1}H NMR (Me_2SO-d_6) δ 2.43 (1 H, q, J = 15.4, 10.7 Hz, 4-H_a), 2.68 (1 H, q, J = 15.4, 7.8 Hz, 4-H_b), 2.87 (1 H, q, J = 15.6, 7.8 Hz, 5-H_a), 3.22 (1 H, q, J = 15.6, 10.7 Hz, 5-H_b), 7.0–7.6 (9 H, m, aromatic H); MS (EI, 70 eV), m/z (relative intensity) 291 [28, M^+ (^{37}Cl)], 289 [43, M^+ (^{35}Cl)], 256 (34, 291 - Cl), 254 (100, 289 - Cl), 219 (67, 254 - Cl), 218 (79, 254 - HCl). Similarly prepared by this method were compounds **16b–g,j–y**. Compounds obtained in a crystalline form were listed in Table I, and the other oily or unstable ones were used for the next step without purification. Compound **15h** did not afford a dichloro derivative. Compound **16i** was very unstable and decomposed in several minutes, and compound **16j** crystallized but was never obtained in a form pure enough to give satisfactory elemental analysis, due to its instability.

2-(4-Methyl-1-piperazinyl)-3-phenyl-5*H*-1-benzazepine Dihydrochloride (18). Procedure G. A mixture of **16a** (1.74 g, 0.006 mol) and *N*-methylpiperazine (1.5 g, 0.015 mol) was stirred at 130 °C for 1 h. The reaction mixture was cooled, diluted with water, basified with aqueous sodium hydroxide, and extracted with ethyl acetate. The organic layer was washed with water, dried, and evaporated. The residual oil was dissolved in chloroform and chromatographed on silica gel. The eluate with chloroform–methanol (100:1) was treated with ethanolic hydrogen chloride to form the hydrochloride. Crystallization with ethanol–ether gave **18** (1.85 g, 79%): ^{1}H NMR (D_2O) δ 2.97 (3 H, br s, NCH_3), 3.50 (1 H, dd, J = 13.7 Hz, 5-H_a), 3.66 (1 H, dd, J = 13, 8.5 Hz, 5-H_b), 3.1–4.2 (8 H, br, piperazine), 7.22 (1 H, t-like, J = ca. 8 Hz, 4-H), 7.3–7.7 (9 H, m, aromatic H); MS (EI, 70 eV), m/z 317 (M^+).

2-(4-Ethyl-1-piperazinyl)-3-(4-fluorophenyl)-5*H*-1-benzazepine Dihydrochloride (24). Procedure H. Compound **22** (2.19 g, 0.005 mol) was treated in a usual manner to give the free base, to which were added ethyl iodide (1.2 g, 0.0075 mol), sodium carbonate (0.8 g, 0.0075 mol), and toluene (30 mL). The reaction mixture was stirred and heated at 100 °C for 18 h. After the reaction mixture was cooled, the insoluble materials were removed, and the solution was evaporated in vacuo. The residue was chromatographed over silica gel. The eluates with chloroform–methanol (100:1) was treated with ethanolic hydrogen chloride. Crystallization with ethanol gave **24** (1.3 g, 62%).

3-(4-Methoxyphenyl)-2-(4-methyl-1-piperazinyl)-5*H*-1-benzazepine Dimaleate (46). Procedure I. To the suspension of 50% sodium hydride (270 mg, 0.0056 mol) in dimethylformamide (15 mL) was dropwise added **47** (1.7 g, 0.0056 mol), and the mixture was stirred for 1 h. After addition of a solution of methyl iodide (0.8 g, 0.0056 mol) in toluene (15 mL), the resulting mixture was stirred for 1 h at room temperature, diluted with water, and extracted with ether. The organic layer was washed with water, dried, and treated with a solution of maleic acid in ethyl acetate to form the maleate. Crystallization with ethyl acetate gave **46** (1.1 g, 48%).

7-Bromo-2-[4-(2-benzoylethyl)-1-piperazinyl]-3-phenyl-5*H*-1-benzazepine (70). Procedure J. Compound **62** (4.97 g, 0.01 mol) was treated in a usual manner to give the free base, to which were added ethanol (10 mL), 35% ethanolic hydrogen chloride (2 mL), acetophenone (1.2 g, 0.01 mol), and paraformaldehyde (0.36 g, 0.012 mol). The mixture was stirred under reflux for 3 h. After being cooled, the reaction mixture was partitioned between dilute hydrochloric acid and ether. The aqueous layer was basified with dilute sodium hydroxide and extracted with ether. The organic layer was washed with water, dried, and evaporated. The residue was chromatographed over silica gel. The eluates with chloroform were evaporated and crystallized with ether to give **70** (1.56 g, 30%).

Pharmacological Methods. Animals and Materials. Male Std-ddY mice (20–25 g), male Wister HLA rats (300–400 g), and beagle dogs (10–15 kg) were employed in the experiments. Test compounds were dissolved or suspended in 0.5% aqueous tragacanth and administered orally to groups of five mice. All doses of the compounds are expressed as the form (salt or base) indicated in Table II.

Statistics. The ED_{50} values were calculated according to the method of Litchfield and Wilcoxon.[25]

Effect on Exploratory Activity in Mice. The effect of the compounds on exploratory activity was examined in mice by using an Animex activity meter (Farad Ltd.) according to the modified method of Svensson and Thieme.[26] A group of five mice was used for each dose of the compounds. Two hours after oral administration of the compounds, each mouse was put into the cage, and the locomotor activity was measured for 3 min. The average suppression of the exploratory activity by each dose of test compound was expressed as percent inhibition of control, and the ED_{50} of each compound, which caused 50% inhibition, was calculated.

Effect on Hypothermia Induced by Reserpine in Mice. The antagonistic effect of the compounds on reserpine-induced hypothermia in mice was examined according to the method of Askew.[27] Each test compound was given orally, followed by an injection of reserpine, 5 mg/kg ip. The rectal temperature of each mouse was measured 4 h later with a thermister (Shibaura Electric, BMG III-130). Average inhibition of the reserpine-induced fall of rectal temperature was expressed as percent inhibition of control.

Effect on Maximal Electroshock Seizure in Mice. The antagonistic effect of the compounds on maximal electroshock seizure was examined in mice according to the method of Masuda et al.[28] Test compounds, administered orally to a group of five mice in each dose, were evaluated for their ability to prevent the hindlimb tonic extensor component of seizures induced by a 60-Hz, 25-mA current for 0.2 s, delivered through corneal electrodes 2

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h after dosing. The effect was considered to be positive if the above seizure component was completely antagonized by previous administration of the compounds, and the ED_{50} of each compound, defined as the dose that prevents seizures in 50% of animals was calculated.

Effect on Tremor Induced by Tremorine in Mice. Each test compound was given orally to a group of mice 2 h before administration of tremorine, 20 mg/kg ip. Half an hour after the injection of tremorine, each mouse was observed to determine the tremor severity according to a rating scale with scores of 0, 1, 2, and 3. Average suppression of the tremor by each dose of test compound was expressed as percent inhibition of control.

Effect on Seizure Induced by Pentylenetetrazole in Mice. The effect of the test compounds on maximal seizure induced chemically was examined by the method of Nakamura et al.[29] Test compounds, administered orally to a group of five mice in each dose, were evaluated for their ability to prevent the tonic extensor component induced by 175 mg/kg ip of pentylenetetrazole. Anticonvulsant activity was judged when the component was blocked. ED_{50}, the dose that showed anticonvulsant activity in 50% of animals, was calculated.

Effect of Emsis Induced by Apomorphine in Dogs. The antiemetic effect of the compounds was examined according to the method of Janssen et al.[30] Groups of three dogs were given the test compound po in a gelatin capsule, and 2 h later, they were injected sc with 0.3 mg/kg of apomorphine hydrochloride. Then, the vomiting rates were counted for 1 h. Average inhibition of the vomiting was expressed as percentage inhibition of control. ED_{50} was defined as the dose that produced 50% inhibition in this emetic response.

Effect on Monoamine Metabolites in Mouse Brain. The levels of homovanillic acid (HVA) in mouse brain were determined according to the method of Karasawa et al.[31] 3,4-Dihydroxyphenylacetic acid (DOPAC) was measured by the fluorometric procedure of Murphy et al.[32] after purification by column chromatography on Sephadex G-10 and QAE-Sephadex. Brains from five mice receiving each compound were pooled for the determination.

Effect on Conditioned Avoidance Response in Mice. Effect of test compounds on one-way active avoidance in mice was examined by using a box with two compartments, darkened and lightened, according to the method of Oka et al.[11] Mice were previously trained to avoid electroshock from the floor by moving from the darkened compartment to the lighted one in response to a warning stimulus. This test was carried out for each group with 10 mice that could avoid the shock at a rate more than 80% in 10 trials. The results are expressed as the ED_{50} values, defined as the dose that caused 50% inhibition in the rate of the avoidance response.

Effect on Self-Stimulation in Rats. The effect of test compounds on intracranial self-stimulation behavior was evaluated in rats with chronic implanted electrodes in the lateral posterior hypothalamus.[33] The rats that showed a constant lever-pressing response of 50–100/min were used. In the test, self-stimulation rates were counted for 10 min before and 2 h after po administration of test compounds. The ED_{50} is the dose that causes 50% or more inhibition of the rate of the self-stimulation in 50% of the rats.

Catalepsy in Mice. This test was carried out by the method of Ueki et al.[34] At 2 h after po administration of the test compound, each mouse was forced to put its foresteps on a horizontal rod of 4.5 cm in height. The mice that failed to remove their paws from the rod within 30 s in three successive trials were considered to be cataleptic. The ED_{50} is defined as the dose that causes catalepsy in 50% of the mice.

Ptosis in Mice. Each test compound was given orally to a group of five mice. Two hours later, the degree of eyelid closure (ptosis) was assessed on the basis of macroscopic scoring (8, no closure of the eyelid; 6, $^1/_4$ closure; 4, $^1/_2$ closure; 2, $^3/_4$ closure, 0, complete closure), essentially according to the method of Janssen.[35] The mean score for each group was used to construct the dose–response curve from which the dose required to reduce the mean score to 50% (ED_{50}) was calculated.

Acknowledgment. We thank Dr. M. Hashimoto, the director of this laboratory, and Drs. H. Nishimura (the late), J. Matsumoto, and S. Naruto for their encouragement throughout this work. Thanks are also due to the staff of the analytical section of this laboratory for elemental analyses and spectral measurements.

Registry No. **7a**, 5558-42-9; **7b**, 92615-42-4; **7c**, 92615-43-5; **7d**, 92615-45-7; **7e**, 4800-35-5; **7f**, 92874-15-2; **7g**, 92615-41-3; **7h**, 111026-47-2; **7m**, 111026-48-3; **7p**, 111026-49-4; **7q**, 111026-50-7; **7r**, 111026-51-8; **7s**, 111026-52-9; **7t**, 5020-40-6; **7u**, 109234-76-6; **7x**, 66246-26-2; **7y**, 6529-37-9; **8a**, 2901-34-0; **8b**, 111026-53-0; **8c**, 3300-71-8; **8d**, 15944-65-7; **8e**, 4800-36-6; **8f**, 88857-54-9; **8g**, 108974-22-7; **8h**, 3261-91-4; **8k**, 111026-54-1; **8l**, 111026-55-2; **8m**, 111026-56-3; **8p**, 111026-57-4; **8q**, 111026-58-5; **8r**, 111026-59-6; **8s**, 111026-60-9; **8t**, 1729-35-7; **8u**, 15944-67-9; **8x**, 111026-61-0; **8y**, 6529-39-1; **9k**, 621-16-9; **9l**, 61637-11-4; **10k**, 111026-62-1; **10l**, 111026-63-2; **11k**, 111026-64-3; **11l**, 111026-65-4; **12k**, 111059-95-1; **12l**, 111026-66-5; **13a**, 7498-87-5; **13b**, 111026-67-6; **13c**, 3300-72-9; **13d**, 15944-61-3; **13e**, 3300-73-0; **13f**, 92872-96-3; **13g**, 109037-07-2; **13h**, 3261-92-5; **13i**, 3261-93-6; **13j**, 111026-68-7; **13l**, 111026-69-8; **13m**, 111026-70-1; **13p**, 111026-71-2; **13q**, 111026-72-3; **13r**, 111026-73-4; **13s**, 111026-74-5; **13t**, 1769-84-2; **13u**, 14087-96-8; **13x**, 111026-75-6; **13y**, 653-56-5; **14a**, 20495-17-4; **14b**, 111026-76-7; **14c**, 111026-77-8; **14d**, 111026-78-9; **14e**, 111026-79-0; **14f**, 111026-80-3; **14g**, 111026-81-4; **14h**, 111027-07-7; **14i**, 111026-82-5; **14l**, 111026-83-6; **14m**, 111026-84-7; **14p**, 111026-85-8; **14q**, 111026-86-9; **14r**, 111026-87-0; **14s**, 111026-88-1; **14t**, 111026-89-2; **14u**, 111026-90-5; **14h**, 111027-07-7; **14x**, 111026-91-6; **14y**, 6733-61-5; **15a**, 3300-62-7; **15b**, 111026-92-7; **15c**, 3300-74-1; **15d**, 15944-49-7; **15e**, 3300-76-33; **15f**, 111026-93-8; **15g**, 15884-80-7; **15h**, 111026-94-9; **15i**, 111026-95-0; **15j**, 111026-96-1; **15k**, 111026-97-2; **15l**, 111026-98-3; **15m**, 111026-99-4; **15n**, 28717-84-2; **15o**, 111027-00-0; **15p**, 111027-01-1; **15q**, 111027-02-2; **15r**, 111027-03-3; **15s**, 111027-04-4; **15t**, 28717-78-4; **15u**, 3300-75-2; **15v**, 111059-96-2; **15w**, 111027-05-5; **15x**, 111027-06-6; **15y**, 28717-58-0; **16a**, 111027-08-8; **16b**, 111028-69-4; **16c**, 111028-70-7; **16d**, 111028-71-8; **16e**, 111027-09-9; **16f**, 111027-10-2; **16g**, 111028-72-9; **16j**, 111028-73-0; **16j** (dichloroacetate deriv), 111028-68-3; **16k**, 111028-74-1; **16l**, 111028-75-2; **16m**, 111028-76-3; **16n**, 111028-77-4; **16o**, 111027-11-3; **16p**, 111028-78-5; **16q**, 111028-79-6; **16r**, 111028-80-9; **16s**, 111028-81-0; **16t**, 111060-04-9; **16u**, 111028-82-1; **16v**, 111027-12-4; **16w**, 111027-13-5; **16x**, 111027-14-6; **16y**, 111028-83-2; **17**, 111027-16-8; **17**·$C_4H_4O_4$, 111028-02-5; **18**, 111059-48-4; **18**·2HCl, 111028-03-6; **19**, 111027-17-9; **19**·2HCl, 111028-04-7; **20**, 111027-18-0; **21**, 111027-19-1; **22**, 111027-20-4; **22**·$C_4H_4O_4$, 111028-05-8; **23**, 111027-21-5; **23**·2HCl, 111028-06-9; **24**, 111027-15-7; **24**·2HCl, 111028-07-0; **25**, 111027-22-6; **25**·$C_4H_4O_4$, 111028-08-1; **26**, 111027-23-7; **26**·2HCl, 111060-00-5; **27**, 111027-24-8; **27**·$2C_4H_4O_4$, 111028-09-2; **28**, 111027-25-9; **29**, 111027-26-0; **29**·$2C_4H_4O_4$, 111028-10-5; **30**, 111027-27-1; **30**·2HCl, 111028-11-6; **31**, 111027-28-2; **31**·2HCl, 111028-12-7; **32**, 111027-29-3; **32**·2HCl, 111028-13-8; **33**, 111027-30-6; **33**·2HCl, 111028-14-9; **34**, 111027-31-7; **34**·2HCl, 111028-15-0; **35**, 111027-32-8; **35**·$2C_4H_4O_4$, 111112-30-2; **36**, 111027-33-9; **36**·2HCl, 111028-16-1; **37**, 111027-34-0; **37**·2HCl, 111028-17-2; **38**, 111027-35-1; **38**·2HCl, 111028-18-3; **39**, 111027-36-2; **40**, 111027-37-3; **40**·$2C_4H_4O_4$, 111028-19-4; **41**, 111027-38-4; **41**·2HCl, 111028-20-7; **42**, 111027-39-5; **42**·2HCl, 111028-21-8; **43**, 111027-40-8; **43**·2HCl, 111028-22-9; **44**, 111027-41-9; **44**·2HCl, 111028-23-0; **45**, 111027-

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Evaluation of the Side Arm of (Naphthylvinyl)pyridinium Inhibitors of Choline Acetyltransferase

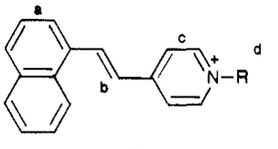
J. F. DeBernardis,[†] P. Gifford,[‡] M. Rizk,[‡] R. Ertel,[‡] D. J. Abraham,[†] and J. F. Siuda*[†,§]

Departments of Medicinal Chemistry, Pharmacology, and Pharmaceutical Sciences, School of Pharmacy, University of Pittsburgh, Pittsburgh, Pennsylvania 15261. *Received May 22, 1987*

A number of quaternary salts of *trans*-4-(β-1-naphthylvinyl)pyridine (NVP) were synthesized and evaluated as inhibitors of the enzymes choline acetyltransferase (ChAT) and acetylcholinesterase (AChE). Structural variations in the side arm attached to the pyridine nitrogen atom demonstrate that an inductive effect is small but significant for activity. Inhibition of ChAT by alkylated derivatives decreases when electron-withdrawing groups are placed in the side chain. Substitution of a methyl group on the pyridine ring only slightly affects activities toward ChAT and AChE. When the pyridinium moiety is replaced by an imidazolium ring, no ChAT inhibition was observed. The imidazolium compound, however, was a weak inhibitor of AChE. For design of affinity columns for purification of ChAT, the data also supports the use of long chain alkylated amide derivatives of NVP.

Choline acetyltransferase (EC 2.3.1.6, ChAT) is an enzyme that catalyzes the formation of acetylcholine in neurons and other tissues. Interest in ChAT has intensified recently as the enzyme has been studied as a marker for cholinergic neurons especially in Alzheimer's disease and related symptoms of dementia.[1,2] Furthermore, methods of purifying ChAT are required for studying properties of the enzyme. Drugs that affect ChAT might also be useful in the investigations of several neurological disease states. There have been a number of successful attempts in developing in vitro inhibitors of this enzyme. However, the control of synthesis, tissue levels, and release of acetylcholine in vivo is a much more complex issue.[3] The more potent inhibitors of ChAT suffer from inability to cross the blood–brain barrier, poor absorption from the GI tract, or low selectivity between ChAT and its enzyme cousin acetylcholinesterase (EC 3.1.1.7, AChE).

Among the most potent synthetic inhibitors of ChAT are quaternary derivatives of *trans*-4-(β-1-naphthylvinyl)pyridine (NVP), I. Despite several drawbacks, the parent drug NVP is still utilized as a pharmacological tool for the inhibition of ChAT.[3,4] In 1967, Cavallito et al. reported the first in a series of papers on the NVP analogues.[5-8] Structure–activity studies on NVP derivatives indicated that naphthyl substitution at area a was superior to a phenyl group; a single bond at b resulted in loss of



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[†] Department of Medicinal Chemistry.
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