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4-Phenyl-2-(1-piperazinyl)quinolines with Potent Antidepressant Activity

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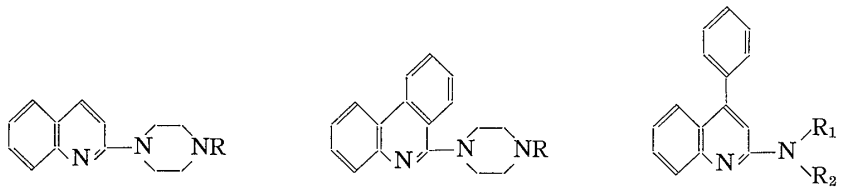
A series of 2-amino-4-phenylquinolines was synthesized and the effects of these compounds on the central nervous system were evaluated pharmacologically in mice. Among these compounds, many 2-(substituted piperazinyl) derivatives exhibited a potent antagonism to hypothermia and catalepsy induced by reserpine, as well as some inhibitory effect on locomotor activity. Some compounds were found to possess activity to inhibit tremorine-induced tremor.

Keywords——4-phenyl-2-piperazinylquinoline; antidepressants; neuroleptic-like activity; anti-tremorine activity; structure-activity relationship

Many drugs acting on the central nervous system (CNS) have tricyclic chemical structures, and among antidepressants, tricyclic systems[2] generally appear to show higher antidepressant activity. However, quipazine, 2-(1-piperazinyl)quinoline (I, R=H),[3] as well as its analogs[4] was reported to possess antidepressant activity as potent as that of imipramine, in spite of the lack of a third ring. It was expected that the introduction of an additional ring into quipazine derivatives would potentiate the antidepressant activity or modify the antidepressant profile. The corresponding fused tricyclic phenanthridine derivatives (II)[5] have been reported to exhibit antidepressant activity.



I II III

Chart 1

In a search for more active compounds with unique pharmacological profiles, we tried to introduce a phenyl group into the 4 position of the quinoline nucleus. The target system, 2-amino-4-phenylquinolines (III),[6–8] has already been synthesized and the compounds were reported to have antiinflammatory and diuretic activities,[8] though detailed pharmacological data are not available.

This paper describes the synthesis and the pharmacological activities on the CNS of 2-amino-4-phenylquinolines (III), especially those of 2-piperazinyl derivatives with potent

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4) Miles Lab., Ger. Patent 2006638 (1970) [*C.A.*, **73**, 98987 (1970)]; Ger. Patent 1923047 (1969) [*C.A.*, **72**, 31637 (1970)].
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6) G. Gast, J. Schmutz, and D. Sorg, *Helv. Chim. Acta*, **60**, 1644 (1977).
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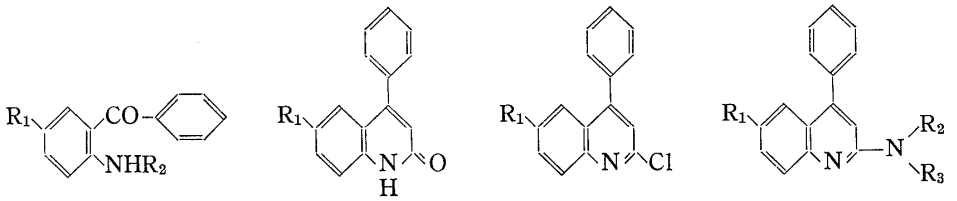
antidepressant activity. The structure-activity relationships of these compounds are also briefly discussed.

4-Phenylcarbostyrils (**3** and **4**), prepared by the acetylation of *o*-aminobenzophenones (**1a** and **2a**) and subsequent cyclization of the acetates (**1b** and **2b**) with sodium ethoxide, were converted into the 2-chloro-4-phenylquinolines (**5** and **6**) by treatment with phosphorus oxychloride. The reaction of the 2-chloro derivatives (**5** and **6**) with various secondary amines gave the desired 2-amino-4-phenylquinoline (**7a, b, d, i** and **8a, b, i—k**). Compounds **7a** and **8a** were further alkylated by reaction with various alkyl halides to give piperazinyl derivatives



1a: $R_1=R_2=H$
1b: $R_1=H$, $R_2=Ac$
2a: $R_1=Cl$, $R_2=H$
2b: $R_1=Cl$, $R_2=Ac$

3: $R_1=H$
4: $R_1=Cl$

5: $R_1=H$
6: $R_1=Cl$

7a—i: $R_1=H$
8a—c, i—k: $R_1=Cl$

Chart 2

TABLE I. 2-Amino-4-phenylquinolines (**7a—i** and **8a—c, i—k**)

Compd. No.	R_1	NR_2R_3	Method[a]	Yield (%)	mp (°C) (Recryst. solvent)	Formula	Analysis (%) Calcd (Found) C	H	Cl	N
7a	H	1-piperazinyl	A	87	133—134 (Et_2O)	$C_{19}H_{19}N_3$	78.86 (78.79	6.62 6.61		14.52 14.31)
7b	H	4-methyl-1-piperazinyl	A	85	121—122[b] (Et_2O)	$C_{20}H_{21}N_3$	79.17 (79.30	6.98 7.03		13.85 13.68)
7c	H	4-ethyl-1-piperazinyl	B	85[c]	225—230 (EtOH)	$C_{21}H_{23}N_3\cdot 2HCl$	64.61 (64.44	6.46 6.61	18.17 17.91	10.77 10.59)
7d	H	4-(2-hydroxyethyl)-1-piperazinyl	A	72	199—202[d] (EtOH–Me_2CO)	$C_{21}H_{23}N_3O\cdot 2HCl\cdot 7/4H_2O$	57.60 (57.47	6.56 5.82	16.19 16.37	9.60 9.43)
7e	H	4-propyl-1-piperazinyl	B	49[c]	225—230 (EtOH–Et_2O)	$C_{22}H_{25}N_3\cdot 2HCl$	65.34 (65.07	6.73 6.69	17.54 17.31	10.39 10.29)
7f	H	4-allyl-1-piperazinyl	B	71[c]	180—182 (EtOH–Et_2O)	$C_{22}H_{23}N_3\cdot C_8H_8O_8$[e]	64.16 (64.10	5.56 5.53		7.48 7.31)
7g	H	4-butyl-1-piperazinyl	B	59[c]	167—168 (Me_2CO)	$C_{29}H_{27}N_3\cdot C_8H_8O_8$[e]	64.46 (64.45	6.11 6.17		7.28 7.30)
7h	H	4-benzyl-1-piperazinyl	B	77[c]	165—167 (Me_2CO)	$C_{26}H_{25}N_3\cdot 1/6H_2O$	81.64 (81.61	6.67 6.56		10.99 10.99)
7i	H	$N(CH_3)_2$	C	42	122[f] (EtOH)	$C_{17}H_{16}N_2$	82.22 (82.04	6.50 6.32		11.28 11.27)
8a	Cl	1-piperazinyl	A	81	201—203[g] (EtOH–Et_2O)	$C_{19}H_{18}ClN_3\cdot C_4H_4O_4$[e]	62.80 (62.88	5.04 4.97	8.06 8.28	9.55 9.62)
8b	Cl	4-methyl-1-piperazinyl	A	90	266—267[h] (EtOH)	$C_{20}H_{20}ClN_3\cdot 2HCl$	58.48 (58.61	5.40 5.64	25.90 25.61	10.23 10.00)
8c	Cl	4-ethyl-1-piperazinyl	B	68[c]	268—273 (EtOH)	$C_{21}H_{22}ClN_3\cdot 2HCl$	59.38 (59.08	5.70 5.62	25.04 24.74	9.89 9.65)
8i	Cl	$N(CH_3)_2$	C	47	102[i] (EtOH)	$C_{17}H_{15}ClN_2$	72.21 (72.03	5.35 5.22	12.54 12.63	9.91 9.72)
8j	Cl	4-phenyl-1-piperazinyl	A	62	166—169[j] (Me_2CO)	$C_{25}H_{22}ClN_3$	75.08 (75.17	5.55 5.46	8.87 8.82	10.51 10.49)
8k	Cl	4-morpholinyl	A	65	120—122[k] (Me_2CO)	$C_{19}H_{17}ClN_2O$	70.26 (69.96	5.28 5.34	10.92 11.18	8.63 8.29)

a) See "Experimental." *b*) Ref. 6, 123—129°. *c*) Yield from **5** (or **6**) *via* **7a** (*or* **8a**). *d*) Base: 117° (Et_2O). *e*) Maleate salt. *f*) Ref. 7, 117—118°; ref. 8, 115—119°. *g*) Base 90—92° (Et_2O). *h*) Ref. 8, base: 94—96°. *i*) Ref. 8, 100—102°. *j*) Ref. 8, 165—167°. *k*) Ref. 7, 125°; ref. 8, 120—122°.

(**7c**, **e**—**h** and **8c**) substituted at the 4 position of the piperazinyl moiety. The synthesis of these compounds is shown in Chart 2, and their properties are given in Table I.

Some of these amino derivatives have been reported by Gast *et al.*[6] (**7b**), Ried *et al.*[7] (**7i** and **8k**) and in a patent[8] (**7i** and **8b**, **i**—**k**). However, their CNS activities have never been disclosed.

Pharmacological Results

All the compounds (**7a**—**i** and **8a**—c, **i**, **j**) prepared in this work were evaluated pharmacologically in mice to examine their CNS activities, and the results are summarized in Table II. Compounds (**7a**—**g**) exhibited extremely high potency in antagonizing hypothermia and catalepsy caused by reserpine. These anti-reserpine effects can be regarded as evidence of antidepressant activity. In antagonizing reserpine hypothermia, **7a** and **7c** were the most active, being 13.4 and 3.7 times as potent as imipramine, respectively. In antagonizing reserpine-induced catalepsy, **7c** possessed the most potent activity, being 25.6 times as potent as imipramine. The other compounds also exhibited high potency. Substitution

Table II. CNS Activities in Mice

Compd. No.	ED_{50}, mg/kg (95% CL)[a]				
	Anti-Reserpine activities		Spontaneous locomotor activity (*p.o.*)	Anti-methamphetamine activity (*i.p.*)	Anti-tremorine activity (*p.o.*)
	Hypothermia (*p.o.*)	Catalepsy (*p.o.*)			
7a	1.6 (0.1—20.1)	3.8 (1.9—7.3)	59.9 (25.6—140.0)	20.2 (12.6—32.3)	5.6 (2.6—12.3)
7b	13.9 (2.0—95.3)	4.7 (1.7—12.6)	56.4 (18.2—174.6)	12.9 (5.7—29.2)	100<
7c	5.8 (0.6—55.5)	1.5 (0.4—5.0)	58.7 (26.6—129.0)	8.0 (3.5—18.3)	9.7 (4.0—23.3)
7d	17.9 (2.5—129.0)	7.7 (2.2—27.4)	111.9 (39.4—317.6)	17.3 (10.8—27.9)	100<
7e	13.6 (3.2—59.0)	4.4 (2.0—9.9)	62.2 (35.3—110.0)	13.2 (2.5—35.2)	100<
7f	15.9 (3.7—68.6)	11.0 (1.9—62.9)	134.0 (53.0—342.0)	30<	100<
7g	13.7 (1.8—105.2)	6.3 (2.8—14.4)	50.6 (20.8—123.2)	16.4 (9.4—28.5)	100<
7h	30.4 (4.1—225.3)	45.3 (5.0—412.7)	95.0 (22.1—407.9)	30<	100<
7i	100<	61.0 (36.3—102.4)	200<	30<	100<
8a	17.3 (2.5—121.5)	28.5 (9.2—88.8)	150<	30<	60.0 (27.0—131.0)
8b	30.8 (3.9—245.6)	20.0 (10.3—54.9)	200<	30<	37.3 (11.7—118.6)
8c	24.2 (7.6—77.3)	16.8 (6.3—45.1)	150<	30<	12.5 (4.4—35.2)
8i	100<	100<	200<	30<	100<
8j	100<	100<	200<	30<	100<
8k	100<	61.0 (36.3—102.4)	200<	30<	100<
Imipramine	21.5 (5.4—85.3)	38.3 (23.2—63.2)	200<	30<	48.3 (26.0—89.7)
Quipazine	31.6 (1.0—1042.0)	24.4 (4.4—32.8)	200<	30<	100<
Chlorpromazine			7.4 (3.2—17.1)	1.0 (0.44—2.28)	
Biperiden					11.4 (4.0—32.8)

a) 95% confidence limits.

of the terminal piperazine nitrogen with a benzyl group caused a considerable decrease in both effects. The introduction of chlorine into the 6 position of the quinoline nucleus also decreased the potency. However, **8a**—**c** still possessed activity comparable to that of imipramine. Phenylpiperazinyl derivatives (**8j**) and compounds (**7i** and **8i, k**) without the piperazinyl moiety showed little or no activity. Thus, the antidepressant potency of the series of compounds was markedly influenced by the substituent of the terminal piperazine nitrogen, and the order of potency was $CH_2C_6H_5 < CH_2CH_2OH \approx CH_2CH{=}CH_2 < CH_3 \approx n\text{-}C_3H_7 \approx n\text{-}C_4H_9 < H \approx C_2H_5$.

Neuroleptic-like properties were exhibited by some of the compounds which showed marked antidepressant activity in the above tests, as disclosed by tests on locomotor activity. Compounds (**7a**—**e, g**) bearing a hydrogen or an alkyl group on the terminal piperazine nitrogen, inhibited both spontaneous and methamphetamine-induced locomotor activities. The potency of the most active compound (**7c**) was about one-eighth of that of chlorpromazine. The introduction of chlorine into the 6 position of the quinoline ring resulted in loss of the neuroleptic-like properties.

Antagonistic action against tremor induced by tremorine was also found with this series of compounds. Two compounds, **7a** and **7c**, exhibited a higher potency than biperiden, which is one of the most effective drugs for parkinsonism. This antagonism has been regarded as evidence of activity against parkinsonism, and is shared, to some extent, by some currently used antidepressant drugs. All the pharmacological results described above suggest that some of the compounds synthesized here, especially **7c**, may possess clinically useful antidepressant activity. The pharmacological properties of some of these compounds are now being studied in detail and will be reported elsewhere.

Experimental

Melting points were taken on a Yanagimoto micro melting point apparatus and are uncorrected. Proton magnetic resonance (PMR) spectra were recorded on a Varian A-60 spectrometer using tetramethylsilane as an internal standard. The following abbreviations are used: singlet (s), doublet (d) and multiplet (m).

4-Phenylcarbostyrils (3 and 4)——Using the method of Kwon *et al.*,[9] **3** was prepared from **1a** in a yield of 79%, mp 264—265° ($CHCl_3$–EtOH). *Anal.* Calcd for $C_{15}H_{11}NO$: C, 81.43; H, 5.01; N, 6.33. Found: C, 81.40; H, 5.05; N, 6.30. PMR (DMSO-d_6) δ: 6.44 (1H, s, 3-H), 7.0—7.6 (9H, m), 11.93 (1H, NH). The 6-chloro isomer (**4**) was prepared from **2a** in a yield of 64%, mp 262° ($CHCl_3$–EtOH). PMR (DMSO-d_6) δ: 6.53 (1H, s, 3-H), 7.32 (1H, d, J=2 Hz, 5-H), 7.4—7.8 (8H, m), 12.20 (1H, NH).

2-Chloro-4-phenylquinolines (5 and 6)——Using the procedure described by Stephenson,[10] **5** was obtained from **3** as a crystalline residue in quantitative yield. This material was used directly in the next step. In a similar manner, **6** was obtained from **4** in 87% yield, mp 105—107° (EtOH).

2-Amino-4-phenylquinolines (Table I)——Method A: A mixture of **5** (or **6**) (1 mol) and piperazine, an appropriate N-substituted piperazine or morpholine (3—5 mol) was heated at 130° for 5 hr with stirring. After cooling, the mixture was dissolved in MeOH, diluted with water, and extracted with AcOEt. The extract was washed with water, dried over Na_2SO_4 and concentrated. The residue was chromatographed on silica gel with $CHCl_3$–MeOH (100: 1—2). The eluate was concentrated and recrystallized or converted to the hydrochloride with ethanolic HCl, then recrystallized from a suitable solvent.

Method B: A mixture of **7a** (or **8a**) (0.01 mol), an appropriate alkyl halide (0.012 mol), Na_2CO_3 (0.01 mol) and toluene or methyl ethyl ketone (40 ml) was heated under reflux for 10—20 hr. The insoluble material was removed by filtration and the filtrate was treated as described in method A.

Method C: A mixture of **5** (or **6**) and excess of ethanolic dimethylamine was heated in a sealed tube at 130° for 9 hr. The mixture was then concentrated, diluted with water and extracted with ether. The extract was dried over Na_2SO_4 and concentrated. The residue was treated as described in method A.

Pharmacological Methods

Animals and Materials——Male STD-ddy strain mice, weighing 20—25 g, were employed in the experiments. Test compounds were dissolved or suspended in 0.5% aqueous tragacanth and administered.

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Statistics——ED_{50} values with 95% confidence limits were calculated according to Litchfield and wilcoxon.[11]

Antagonistic Effect on Hypothermia induced by Reserpine——This experiment was carried out according to the method of Askew.[12] Each test compounds was given orally to groups of 5 mice in 6 different doses, followed immediately by an injection of reserpine, 5 mg/kg *i.p.* The rectal temperature of each mouse was measured 4 hr later with a thermister (Shibaura Electric, BMG III-130). ED_{50} was defined as the dose that caused 50% inhibition of the reserpine-induced fall of rectal temperature.

Antagonistic Effect on Catalepsy induced by Reserpine——This experiment was carried out by a modification of method of Horst *et al.*[13] Each group of 10 mice was injected with reserpine, 5 mg/kg *i.p.*, 5 hr before oral administration of test compounds in 7 different doses. One hour after the treatment with test compounds, the mice were tested for catatonia for 1 min. ED_{50} was defined as the dose that protected 50% of the animals from reserpine-induced catatonia.

Inhibitory Effect on Spontaneous Locomotor Activity——This experiment was carried out according to a modification of method of Svensson *et al.*[14] Each test compounds was given orally to groups of 5 mice in 5 different doses. The spontaneous locomotor activity of each mouse was measured for 3 min with an Animex locomotor activity meter (Farad Electronics) 2 hr after medication. ED_{50} was defined as the dose that caused a 50% decrease of the locomotor activity.

Inhibitory Effect on Locomotor Activity induced by Methamphetamine——Groups of 10 mice were treated with methamphetamine, 4 mg/kg *i.p.*, 30 min before intraperitoneal injection of test compounds in 3 different doses. One hour after the treatment with methamphetamine, the locomotor activity of each mouse was measured for 10 min with an Animex locomotor activity meter. ED_{50} was defined as the dose that caused 50% inhibition of the methamphetamine-induced hyperactivity.

Antagonistic Effect on Tremor induced by Tremorine——Each test compound was given orally to groups of 5 mice in 5 different doses 2 hr before administration of tremorine, 20 mg/kg *i.p.* Half an hour after the injection of tremorine, each mouse was examined macroscopically to determine the tremor severity according to a rating scale with scores of 0, 1, 2 and 3. ED_{50} was defined as the dose which caused 50% inhibition of the tremorine-induced tremor severity.

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