# Novel 4-Substituted 2-Piperazinylquinazolines as Potent Anticonvulsive and Antihypoxic Agents[1)]

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**Several types of quinazoline derivatives were prepared and examined for anticonvulsive and antihypoxic activities. Many compounds showed potent anticonvulsive activity, and their anticonvulsive profile is similar to that of phenytoin. The analysis of quantitative structure–activity relationships indicated that the anticonvulsive activity was parabolically related to the lipophilicity of the compounds. Most of the 4-alkoxyquinazolines showed potent anticonvulsive and antihypoxic activities. It is confirmed that there is a good correlation between the potencies of these activities.**

**Keywords** quinazoline; anticonvulsive activity; neurotoxicity; antihypoxic activity; structure–activity relationship; lipophilicity

It was reported that several current antiepileptic agents showed protective effects against cerebral hypoxia.[2-4)] Phenytoin shows the most potent antihypoxic activity and has been clinically used as a cerebroprotective agent.[4)] It is still the drug of choice for the treatment of many seizure disorders, however, a number of side effects have limited its use.[5)] Therefore, phenytoin is not a satisfing compound as an antiepileptic agent or as an antihypoxic agent.

We started a project to find new antiepileptic and/or antihypoxic agents with more effective and/or fewer side effects. In a previous paper, we reported the syntheses and anticonvulsive and antihypoxic activities of 4-phenoxy-2-(1-piperazinyl)quinazolines (**1**).[1)] As a result, compound **1a** was selected as the most promising antiepileptic agent with fewer side effects. On the other hand, there was no potent antihypoxic agent with lower toxicity than phenytoin.

This paper deals with the syntheses of 4-alkoxy-, 4-alkylthio- and 4-alkylaminoquinazoline derivatives and their biological evaluations: anticonvulsive activity, neurotoxicity and antihypoxic activity. The structure–activity relationships are also discussed.

## Chemistry

Two methods were utilized to obtain compounds for biological evaluation as summarized in Chart 2. In method A, the 2-amino-4(3*H*)-quinazolinones (**3**) were treated with the alkyl halides in the presence of sodium hydride (NaH). It was reported that 4(3*H*)-quinazolinones were alkylated at the 3-nitrogen atom or the 4-oxygen atom and the steric hindrance of 2-position affected the ratio of the formations.[6)] We confirmed the alkylating position by comparing the structural analyses of **11** with those of 3-(2-ethoxyethyl)-2-(4-methyl-1-piperazinyl)-4(3*H*)-quinazolinone.[7)] As the alkylation selectively occurred at the oxygen atom, it was thought that the 2-piperazinyl moiety has enough steric effect to prevent the alkylation at 3-nitrogen atom. 4-Pentyloxy-2-(1-piperazinyl)quinazoline (**12**) was prepared by deprotection of the formyl derivative (**36**) prepared by method A. In method B, the 2-amino-4-chloroquinazolines (**4**) were treated with alcohols or thiols in the presence of NaH. The 4-pentylamino derivative (**35**) was prepared by the reaction of excess pentylamine with 4-chloro-2-(4-methyl-1-piperazinyl)quinazoline[1)] (Table I).

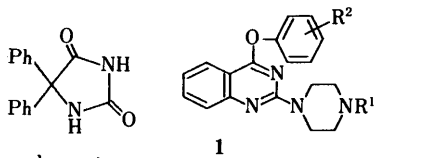



Chart 1

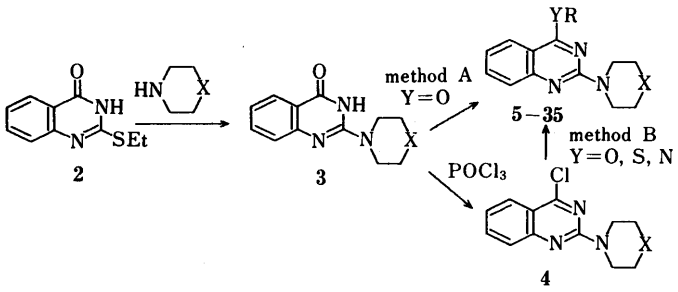



Chart 2

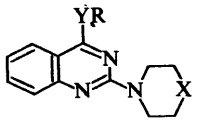
The 2-amino-4(3*H*)-quinazolinones (**3**) were prepared from 2-ethylthio-4(3*H*)-quinazolinone (**2**)[8)] and amines such as 1-substituted piperazines, 4-methylpiperidine and morpholine. The 2-amino-4-chloroquinazolines (**4**) were prepared by the reaction of phosphorus oxychloride ($POCl_3$) with compound **3**. The new derivatives (**3** and **4**) are summarized in Table II and the others were listed in our previous paper.[1)]

## Biological Results and Discussion

Anticonvulsive activity was determined by maximal electroshock seizure test (anti-MES) and subcutaneous pentylenetetrazol seizure threshold test (anti-PTZ).[9)] Neurotoxicity was determined by rotarod test.[10)] The compounds which showed significant anti-MES activity with lower neurotoxicity or acute toxicity compared to phenytoin were examined for antihypoxic activity by the gasping test.[11)] The results of these evaluations are summarized in Table III. The result of anti-PTZ activity of the test compounds was omitted because of their negligible activity at a dose of 200 mg/kg *p.o.* like that of phenytoin.

**Antiepileptic Properties** The methoxy and 2-ethoxyethyl derivatives (**7** and **11**) showed weak anticonvulsive activity, while the propyloxy, pentyloxy and heptyloxy derivatives (**8**, **9** and **10**) showed potent activity nearly equal to phenytoin. It seemed that the potency was affected by lipophilicity of the compound as in the case of 4-phenoxyquinazolines.[1)] The pentyloxy group is one of the most favorable substituents and, interestingly, it has a lipophilicity close to that of the phenoxy group; the $\pi$ value

TABLE I. 2,4-Disubstituted Quinazolines (5—35)



5—35

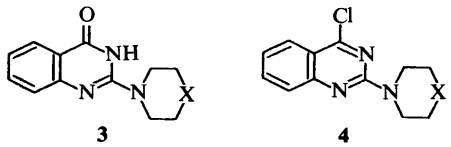
| No. | Compound structure X | Compound structure YR | Procedure | mp (°C) (Recryst. solvent)[a] | Formula | Yield[b] (%) | Analysis (%)[c] Calcd (Found) C | H | N |
|---|---|---|---|---|---|---|---|---|---|
| 5 | $NCH_3$ | $OCH_2Ph$ | B | 83.0— 85.0 (C) | $C_{20}H_{22}N_4O$ | 60 | 71.83 (72.00) | 6.63 6.66 | 16.75 16.78) |
| 6 | $NCH_3$ | $OCH_2CH_2Ph$ | B | 187.0—189.0 (A) | $C_{21}H_{24}N_4O \cdot C_4H_4O_4 \cdot 0.5H_2O$ | 80 | 63.41 (63.56 | 6.17 5.94 | 11.83 11.59) |
| 7 | $NCH_3$ | $OCH_3$ | B | 88.0— 90.5 (C) | $C_{14}H_{18}N_4O$ | 64 | 65.09 (65.34 | 7.02 7.08 | 21.69 21.82) |
| 8 | $NCH_3$ | $O(CH_2)_2CH_3$ | B | 171.5—174.0 (B) | $C_{16}H_{22}N_4O \cdot C_4H_4O_4$ | 92 | 59.69 (59.80 | 6.51 6.51 | 13.92 13.90) |
| 9 | $NCH_3$ | $O(CH_2)_4CH_3$ | A | 150.0—158.0 (B) | $C_{18}H_{26}N_4O \cdot C_4H_4O_4$ | 86 | 61.38 (61.37 | 7.02 6.96 | 13.01 12.95) |
| 10 | $NCH_3$ | $O(CH_2)_6CH_3$ | B | 152.5—155.0 (B) | $C_{20}H_{30}N_4O \cdot C_4H_4O_4$ | 98 | 62.86 (62.88 | 7.47 7.52 | 12.22 12.17) |
| 11 | $NCH_3$ | $OCH_2CH_2OCH_2CH_3$ | A | 177.5—180.5 (B) | $C_{17}H_{14}N_4O \cdot C_4H_4O_4 \cdot 0.5H_2O$ | 47 | 57.13 (56.89 | 6.62 6.31 | 12.69 12.29) |
| 12[d] | NH | $O(CH_2)_4CH_3$ | A | 176.5—178.0 (D) | $C_{17}H_{24}N_4O \cdot C_4H_4O_4$ | 71 | 60.56 (60.50 | 6.78 6.74 | 13.45 13.43) |
| 13 | $NCH_2CH_3$ | $O(CH_2)_4CH_3$ | B | 165.5—166.5 (B) | $C_{19}H_{28}N_4O \cdot C_4H_4O_4$ | 75 | 62.14 (62.10 | 7.26 7.27 | 12.60 12.56) |
| 14 | $NCH_2CH=CH_2$ | $O(CH_2)_4CH_3$ | A | 140.5—144.0 (B) | $C_{20}H_{28}N_4O \cdot 1.5C_4H_4O_4$ | 90 | 60.69 (60.47 | 6.66 6.67 | 10.89 10.86) |
| 15 | $N(CH_2)_2CH_3$ | $O(CH_2)_4CH_3$ | B | 160.5—162.0 (B) | $C_{20}H_{30}N_4O \cdot C_4H_4O_4$ | 74 | 62.86 (62.94 | 7.47 7.47 | 12.22 12.25) |
| 16 | $N(CH_2)_3CH_3$ | $O(CH_2)_4CH_3$ | B | 165.0—166.5 (B) | $C_{21}H_{32}N_4O \cdot C_4H_4O_4$ | 55 | 63.54 (63.40 | 7.68 7.66 | 11.86 11.90) |
| 17 | $N(CH_2)_4CH_3$ | $O(CH_2)_4CH_3$ | B | 154.0—156.0 (B) | $C_{22}H_{34}N_4O \cdot C_4H_4O_4$ | 62 | 64.18 (64.00 | 7.87 7.82 | 11.51 11.42) |
| 18 | NPh | $O(CH_2)_4CH_3$ | A | 101.0—103.0 (C) | $C_{23}H_{28}N_4O$ | 62 | 73.37 (73.56 | 7.50 7.55 | 14.88 14.85) |
| 19 | $NCH_2Ph$ | $O(CH_2)_4CH_3$ | B | 149.0—150.0 (B) | $C_{24}H_{30}N_4O \cdot C_4H_4O_4 \cdot 0.5H_2O$ | 64 | 65.23 (65.45 | 6.84 6.62 | 10.87 10.65) |
| 20 | $NCH_2CH=CH_2$ | $O(CH_2)_2CH_3$ | B | 152.5—155.0 (B) | $C_{18}H_{24}N_4O \cdot C_4H_4O_4$ | 86 | 61.67 (61.78 | 6.59 6.51 | 13.08 13.22) |
| 21 | $NCH_2CH=CH_2$ | $O(CH_2)_3CH_3$ | B | 142.0—144.0 (B) | $C_{19}H_{26}N_4O \cdot 1.5C_4H_4O_4$ | 87 | 59.99 (60.21 | 6.44 6.50 | 11.19 11.34) |
| 22 | $NCH_2CH=CH_2$ | $O(CH_2)_5CH_3$ | B | 153.0—154.5 (B) | $C_{21}H_{30}N_4O \cdot C_4H_4O_4$ | 65 | 63.81 (64.08 | 7.28 7.36 | 11.91 11.92) |
| 23 | $NCH_2CH=CH_2$ | $OCH_2CHCH_2CH_2CH_3$ (CH3 on CH) | B | 152.5—155.0 (B) | $C_{21}H_{30}N_4O \cdot C_4H_4O_4$ | 90 | 63.81 (63.89 | 7.28 7.23 | 11.91 11.96) |
| 24 | $NCH_2CH=CH_2$ | $OCHCH(CH_3)_2$ ($CH_2CH_3$ on CH) | B | 156.5—159.5 (A) | $C_{21}H_{30}N_4O \cdot C_4H_4O_4$ | 84 | 63.81 (63.89 | 7.28 7.33 | 11.91 11.93) |
| 25 | $NCH_2CH=CH_2$ | O-cyclopentyl | B | 183.5—186.0 (B) | $C_{20}H_{26}N_4O \cdot 2C_4H_4O_4$ | 75 | 58.94 (59.06 | 6.01 6.02 | 9.82 9.89) |
| 26 | $NCH_2CH=CH_2$ | O-cyclohexyl | B | 196.5—199.0 (B) | $C_{21}H_{28}N_4O \cdot 2C_4H_4O_4$ | 77 | 59.58 (59.32 | 6.21 6.31 | 9.58 9.63) |
| 27 | $NCH_2CH=CHCH_3$ | $O(CH_2)_4CH_3$ | A | 145.5—148.5 (B) | $C_{21}H_{30}N_4O \cdot C_4H_4O_4$ | 88 | 63.81 (63.72 | 7.28 7.35 | 11.91 11.86) |
| 28 | $NCH_2C(CH_3)=CH_2$ | $O(CH_2)_4CH_3$ | B | 153.5—155.5 (B) | $C_{21}H_{30}N_4O \cdot C_4H_4O_4$ | 71 | 63.81 (63.92 | 7.28 7.44 | 11.91 11.93) |
| 29 | $CHCH_3$ | $O(CH_2)_4CH_3$ | A | 126.5—128.5 (E) | $C_{19}H_{27}N_4O \cdot HCl$ | 98 | 65.22 (65.35 | 8.07 8.02 | 12.01 12.18) |
| 30 | O | $O(CH_2)_4CH_3$ | A | 137.0—139.0 (E) | $C_{17}H_{23}N_3O_2 \cdot HCl$ | 92 | 60.44 (60.25 | 7.16 7.24 | 12.44 12.46) |
| 31 | $NCH_3$ | $SCH_2CH_3$ | B | 183 (dec.) (A) | $C_{15}H_{20}N_4S \cdot C_4H_4O_4$ | 97 | 56.42 (56.60 | 5.98 6.08 | 13.85 13.81) |
| 32 | $NCH_3$ | $S(CH_2)_3CH_3$ | B | 154.5—156.5 (B) | $C_{17}H_{24}N_4S \cdot 1.5C_4H_4O_4$ | 98 | 56.31 (56.45 | 6.16 6.18 | 11.42 11.38) |
| 33 | $NCH_3$ | $S(CH_2)_4CH_3$ | B | 165.5—168.0 (B) | $C_{18}H_{26}N_4S \cdot C_4H_4O_4$ | 96 | 59.17 (59.39 | 6.77 6.90 | 12.55 12.42) |
| 34 | $NCH_3$ | $S(CH_2)_5CH_3$ | B | 175.0—177.5 (B) | $C_{19}H_{28}N_4S \cdot C_4H_4O_4$ | 92 | 59.98 (59.75 | 7.00 6.93 | 12.16 12.12) |

TABLE I. (continued)

| No. | Compound structure X | Compound structure YR | Procedure | mp (°C) (Recryst. solvent)[a] | Formula | Yield[b] (%) | Analysis (%)[c] Calcd (Found) C | H | N |
|---|---|---|---|---|---|---|---|---|---|
| **35** | $NCH_3$ | $NH(CH_2)_4CH_3$ | B | 190.0—195.0 (B) | $C_{18}H_{27}N_5 \cdot 2C_4H_4O_4$ | 91 | 57.24 (57.24 | 6.47 6.67 | 12.84 13.14) |

*a*) A. EtOH; B, EtOH–AcOEt; C, hexane; D, EtOH–MeOH; E, EtOH–EtOEt. *b*) Yield of free base. *c*) Analytical results are within ±0.4% of the theoretical values in C, H, N analysis. *d*) See experiment.

TABLE II. 4(3*H*)-Quinazolinones (**3**) and 4-Chloroquinazolines (**4**)



**3** **4**

| Compound | X | mp (°C) (Recryst. solvent)[a] | Formula | Yield (%) | Analysis (%)[b] Calcd (Found) C | H | N |
|---|---|---|---|---|---|---|---|
| **3a** | $N(CH_2)_3CH_3$ | 202.0—203.0 (A) | $C_{16}H_{22}N_4O$ | 60 | 67.11 (67.24 | 7.74 7.85 | 19.56 19.67) |
| **3b** | $N(CH_2)_4CH_3$ | 200.0—201.5 (A) | $C_{17}H_{24}N_4O$ | 70 | 67.97 (67.84 | 8.05 8.11 | 18.65 18.71) |
| **3c** | NPh | 265 (dec.) (B) | $C_{18}H_{18}N_4O$ | 94 | 70.57 (70.61 | 5.92 6.03 | 18.29 18.26) |
| **3d** | NCHO | 256.0—264.0 (A) | $C_{13}H_{14}N_4O_2$ | 49 | 60.45 (60.59 | 5.46 5.65 | 21.69 21.58) |
| **3e** | $NCH_2CH=CHCH_3$ | 220.0—224.0 (A) | $C_{16}H_{20}N_4O$ | 60 | 67.58 (67.51 | 7.09 6.99 | 19.70 19.69) |
| **3f** | $NCH_2C(CH_3)=CH_2$ | 180.5—183.0 (A) | $C_{16}H_{20}N_4O$ | 63 | 67.58 (67.60 | 7.09 6.95 | 19.70 19.69) |
| **3g** | $CHCH_3$ | 190.5—192.5 (C) | $C_{14}H_{17}N_3O$ | 83 | 69.11 (69.31 | 7.04 7.10 | 17.27 17.18) |
| **3h** | O | 245.0—248.5 (A) | $C_{12}H_{13}N_3O_2$ | 90 | 62.33 (62.58 | 5.67 5.63 | 18.17 18.16) |
| **4a** | $N(CH_2)_3CH_3$ | 143.0 (dec.) (A) | $C_{16}H_{21}ClN_4 \cdot C_4H_4O_4$[c] | 88[d] | 57.07 (57.18 | 5.99 5.99 | 13.31 13.35) |
| **4b** | $N(CH_2)_4CH_3$ | 63.5— 65.0 (D) | $C_{17}H_{23}ClN_4$ | 54 | 64.04 (63.94 | 7.27 7.10 | 17.57 17.62) |
| **4c** | $NCH_2C(CH_3)=CH_2$ | 78.0— 80.0 (D) | $C_{16}H_{19}ClN_4$ | 92 | 63.47 (63.48 | 6.32 6.25 | 18.50 18.43) |

*a*) A, EtOH–AcOEt; B, DMF–EtOH; C, benzene; D, hexane. *b*) Analytical results are within ±0.4% of the theoretical values in C, H, N analysis. *c*) Fumarate. *d*) Yield of free base.

of the pentyloxy group is 2.05 and that of the phenoxy group is 2.08.[12]

When the 4-position of the quinazoline ring was fixed with the most favorable pentyloxy group, the order of increasing potency of anticonvulsive activity by various substituents of piperazinyl moiety was as follows: $Ph \ll CH_2Ph < H$, pentyl < methyl, ethyl, allyl, propyl, butyl. In the most potent group (**9**, **13**, **14**, **15** and **16**), only the allyl derivative (**14**) showed lower neurotoxicity than phenytoin. So, in order to find more potent agents with low neurotoxicity, nine additional compounds which had similar structures to that of compound **14** were prepared (**20**—**28**). However, they did not draw our attention because they showed more reduced anticonvulsive activity than **14**.

The 4-methyl-1-piperidinyl derivative (**29**) and morpholino derivative (**30**) showed negligible anticonvulsive activity. This fact suggests that the nitrogen atom of 4-position of piperazinyl moiety plays an important role in the potent anticonvulsive activity.

The 4-alkylthioquinazolines (**31**—**34**) showed slightly weaker anticonvulsive activity than the corresponding 4-alkoxyquinazolines but 4-pentylaminoquinazoline (**35**) showed negligible activity.

In order to find more potent anticonvulsive agents, quantitative structure–activity relationship (QSAR) analyses were performed. Because of the negligible activity, compounds **18**, **24**, **29**, **30** and **35** were removed, and Eq. 1 was obtained as the best equation.

$$\log 1/ED_{50} = -0.127(\pm 0.055)(\Sigma\pi)^2 + 0.306(\pm 0.109)\Sigma\pi - 0.521(\pm 0.182)B_3 + 5.151(\pm 0.400) \quad (1)$$
$$n=26,\ r=0.85,\ s=0.190,\ F=19.6$$

In Eq. 1, the number in parentheses is the 95% confidence

TABLE III. Pharmacological Activities of 2,4-Disubstituted Quinazolines

| Compound | Anti-MES[a] $ED_{50}$ (mg/kg, *p.o.*) | Neurotoxicity $NTD_{50}$ (mg/kg, *p.o.*) | Antihypoxic % of control Found[b] | Calcd[c] | Acute toxicity $LD_{50}$ (mg/kg, *p.o.*) |
|---|---|---|---|---|---|
| **5** | 47 | | 154 | 139 | >800 |
| **6** | 18 | 63 | 200 | 211 | >800 |
| **7** | 100 | | | | |
| **8** | 10 | 54 | | | 283 |
| **9** | 10 | 71 | 251 | 231 | 429 |
| **10** | 10 | 35 | | | 325 |
| **11** | 100 | | | | |
| **12** | 23 | 46 | 210 | 199 | 746 |
| **13** | 10 | 71 | 258 | 231 | 424 |
| **14** | 13 | 132 | 185 | 224 | 979 |
| **15** | 13 | 72 | 263 | 223 | 857 |
| **16** | 18 | 53 | 225 | 211 | >1000 |
| **17** | 31 | <50 | 185 | 179 | >1000 |
| **18** | >100 | | | | |
| **19** | 62 | | | | |
| **20** | 20 | 71 | 184 | 206 | 429 |
| **21** | 18 | 115 | 155 | 211 | 650 |
| **22** | 27 | 115 | 175 | 189 | >1000 |
| **23** | 47 | | 139 | 139 | >1000 |
| **24** | >100 | | | | |
| **25** | 100 | | | | |
| **26** | 123 | | | | |
| **27** | 18 | <50 | 260 | 211 | >800 |
| **28** | 18 | 93 | 176 | 211 | >800 |
| **29** | >100 | | | | |
| **30** | >100 | | | | |
| **31** | 27 | 216 | 138 | | 650 |
| **32** | 18 | 200 | 217 | | 746 |
| **33** | 18 | 163 | 131 | | 970 |
| **34** | 20 | 100 | 139 | | >1000 |
| **35** | >100 | | | | |
| Phenytoin | 6.2 | 79 | 215 | | 373 |
| **1a** | 23 | 429 | 131 | | >1000 |

*a*) Anticonvulsive activity against maximal electroshock-induced seizure. *b*) Gasping duration at dose of 50 mg/kg *p.o.* *c*) Result of multiple regression analysis of relationship between the anti-MES and antihypoxic activities.

TABLE IV. Parameters and Results of QSAR Analysis

| No. | Compounds structure X | YR | $\Sigma\pi$[a] | $B_3$[b] | log 1/$ED_{50}$ Obs.[c] | Calcd |
|---|---|---|---|---|---|---|
| **5** | $NCH_3$ | $OCH_2Ph$ | 0.42 | 3.11 | 3.85 | 3.64 |
| **6** | $NCH_3$ | $OCH_2CH_2Ph$ | 0.86 | 1.90 | 4.29 | 4.33 |
| **7** | $NCH_3$ | $OCH_3$ | −1.26 | 1.90 | 3.41 | 3.57 |
| **8** | $NCH_3$ | $O(CH_2)_2CH_3$ | −0.19 | 1.90 | 4.46 | 4.10 |
| **9** | $NCH_3$ | $O(CH_2)_4CH_3$ | 0.81 | 1.90 | 4.50 | 4.32 |
| **10** | $NCH_3$ | $O(CH_2)_6CH_3$ | 1.81 | 1.90 | 4.52 | 4.30 |
| **11** | $NCH_3$ | $O(CH_2)_2OCH_2$-$CH_3$ | −1.48 | 1.90 | 3.50 | 3.43 |
| **12** | NH | $O(CH_2)_4CH_3$ | 0.31 | 1.90 | 4.12 | 4.24 |
| **13** | $NCH_2CH_3$ | $O(CH_2)_4CH_3$ | 1.31 | 1.90 | 4.52 | 4.34 |
| **14** | $NCH_2CH=CH_2$ | $O(CH_2)_4CH_3$ | 1.51 | 1.90 | 4.42 | 4.33 |
| **15** | $N(CH_2)_2CH_3$ | $O(CH_2)_4CH_3$ | 1.81 | 1.90 | 4.42 | 4.30 |
| **16** | $N(CH_2)_3CH_3$ | $O(CH_2)_4CH_3$ | 2.31 | 1.90 | 4.30 | 4.19 |
| **17** | $N(CH_2)_4CH_3$ | $O(CH_2)_4CH_3$ | 2.81 | 1.90 | 4.08 | 4.02 |
| **19** | $NCH_2Ph$ | $O(CH_2)_4CH_3$ | 2.56 | 1.90 | 3.80 | 4.11 |
| **20** | $NCH_2CH=CH_2$ | $O(CH_2)_2CH_3$ | 0.51 | 1.90 | 4.19 | 4.28 |
| **21** | $NCH_2CH=CH_2$ | $O(CH_2)_3CH_3$ | 1.01 | 1.90 | 4.26 | 4.34 |
| **22** | $NCH_2CH=CH_2$ | $O(CH_2)_5CH_3$ | 2.01 | 1.90 | 4.11 | 4.26 |
| **23** | $NCH_2CH=CH_2$ | $OCH_2\underset{CH_3}{C}HCH_2CH_2CH_3$ | 2.01 | 3.16 | 3.87 | 3.61 |
| **25** | $NCH_2CH=CH_2$ | O-cyclopentyl | 1.10 | 2.90 | 3.53 | 3.82 |
| **26** | $NCH_2CH=CH_2$ | O-cyclohexyl | 1.47 | 3.16 | 3.44 | 3.68 |
| **27** | $NCH_2CH=CHCH_3$ | $O(CH_2)_4CH_3$ | 2.01 | 1.90 | 4.29 | 4.26 |
| **28** | $NCH_2\underset{CH_3}{C}=CH_2$ | $O(CH_2)_4CH_3$ | 2.01 | 1.90 | 4.29 | 4.26 |
| **31** | $NCH_3$ | $S(CH_2)_2CH_3$ | 0.33 | 1.90 | 4.03 | 4.25 |
| **32** | $NCH_3$ | $S(CH_2)_3CH_3$ | 0.83 | 1.90 | 4.25 | 4.33 |
| **33** | $NCH_3$ | $S(CH_2)_4CH_3$ | 1.33 | 1.90 | 4.26 | 4.34 |
| **34** | $NCH_3$ | $S(CH_2)_5CH_3$ | 1.83 | 1.90 | 4.24 | 4.30 |

*a*) $\Sigma\pi$ was calculated according to references 12 and 13. *b*) From reference 14. *c*) These values were calculated from $ED_{50}$ in Table IV on a molar basis.

interval, $n$ is the number of data points used in deriving the equation, $r$ is the correlation coefficient, $s$ is the standard deviation and $F$ is the $F$ ratio between the variances of calculated and observed activities. $\Sigma\pi$ is a summation of the $\pi$ value[12,13] of substituents bonded at 2- and 4-position of the quinazoline ring. $B_3$ is a STERIMOL width parameter[14] of the substituent bonded at 4-position of the quinazoline ring. The electronic parameter ($\sigma$), steric parameters ($E_s$ and $MR$) or the other STERIMOL parameters ($B_1$, $B_2$, $B_4$ and $L$) did not give statistically significant equations. The values of parameters ($\Sigma\pi$ and $B_3$) and the result are summarized in Table IV.

The negative coefficient of $B_3$ indicates that a small value of the second largest width parameter $B_3$ is required for potent activity. So, the plane substituents of the straight alkyl chain are favorable. Iemura and Ohtaka reported that an antihistaminic activity of the benzimidazole derivatives was reversely correlated to the $B_3$ value of substituents.[15] They proposed an antihistaminic receptor model with a slit-shaped cavity to which the plane substituent fit. Similarly, it is proposed that the anticonvulsive receptor has a slit-like cavity.

The anticonvulsive activity is parabolically correlated to $\Sigma\pi$ and the optimum $\Sigma\pi$ value is calculated to be 1.20. The log $P$ value of the quinazoline ring is reported to be 1.01.[16] Therefore, the optimum log $P$ value is calculated to be 2.21. Jones and Woodbury assumed that the anticonvulsive activity of the current agents might be parabolically related to the log $P$ value.[17] Our result is consistent with their assumption in spite of the fact that our compounds have completely different structures from the agents. Moreover, it is interesting that our optimum log $P$ value is equal to that of phenytoin (log $P$=2.23),[17] which shows the most potent anti-MES activity in the current agents. The anticonvulsive profile of our quinazolines is similar to that of phenytoin as both compounds showed potent anti-MES and negligible anti-PTZ activities. From the above results, it is assumed that our quinazolines and phenytoin show anticonvulsive activity through the same receptor and mechanisms.

The study on structure–activity relationships indicates that piperazinyl group at 2-position, unbranched substituent at 4-position and suitable lipophilicity of the whole molecule are required for potent anticonvulsive activity. In the series of the 4-alkoxyquinazolines, the study on neurotoxicity indicates that the allyl group is the best substituent of the piperazinyl moiety. When the 2-position of the quinazoline ring is fixed with the 4-allyl-1-piperazinyl moiety for low neurotoxicity, the simple straight 4-alkoxy group of the most potent derivative calculated is limited to the butoxy or the pentyloxy group, which have already been prepared. All the 4-alkylthioquinazolines showed weaker activity than calculated. Because of the small number of derivatives we can not confirm it but there seem to be undesirable effects because of reduced anticonvulsive ac-

tivity. They showed equipotent activity to compound **1a** but showed much higher neurotoxicity. Thus, the 4-alkylthioquinazolines are not interesting because of anticonvulsive activity weaker than that of the 4-alkoxyquinazolines and neurotoxicity more potent than that of **1a**. From the above results, we concluded that further analogue synthesis was not necessary.

In the previous paper, we reported that the anticonvulsive activity of 4-phenoxyquinazolines was parabolically related to the $\pi$ value of substituent on the 4-phenoxy moiety.[1] The $\Sigma\pi$ value of the 4-phenoxyquinazolines was calculated and reanalysis was performed including these derivatives, and Eq. 2 was obtained.

$$\log 1/ED_{50} = -0.133(\pm 0.043)(\Sigma\pi)^2 + 0.314(\pm 0.089)\Sigma\pi - 0.526(\pm 0.152)B_3 - 0.352(\pm 0.122)D + 5.17(\pm 0.331)$$
$$n=42,\ r=0.84,\ s=0.160,\ F=22.3 \quad (2)$$

In Eq. 2, the dummy variable ($D$) indicates the presence of 4-phenoxy moiety ($D=1$) or not ($D=0$). The values of coefficient of each of the variables in the above two equations are consistent. Therefore, it is thought that these compounds show anti-MES activity through the same receptor. It is reported that the O-$CH_3$ bond of anisole is in, or nearly in, the plane of the benzene ring.[18] The other lower alkoxy groups can be regarded as in the same conformation. On the other hand, it was proposed that the two benzene rings of diphenyl ether were twisting.[19] So, it is expected that the conformations of 4-alkoxyquinazolines and 4-phenoxyquinazolines are not similar. The former showed stronger anticonvulsive activity than the latter. The phenoxy moiety is rotated to the plane conformation in order to fit the receptor cavity. The dummy variable may mean the rotating energy is, or is not, necessary. This receptor model was supported by the result that *ortho* substituents of the phenoxy moiety reduced the anticonvulsive activity[1]; the rotation would be prevented by the steric hindrance between the substituents and the quinazoline ring.

**Antihypoxic Activity** In the series of 4-alkoxyquinazolines, compounds **9**, **13**, **15**, **16** and **27** showed potent antihypoxic activity superior to phenytoin. As all of these compounds showed potent anti-MES activity, there seems to be some relationships between the antihypoxic and anticonvulsive activities. When the relationship between these potencies was examined without any treatment, a statistically significant equation was obtained.

$$\text{duration}\ (\%) = -2.48(\pm 1.53)ED_{50} + 256(\pm 37.9) \quad (3)$$
$$n=15,\ r=0.71,\ s=30.8,\ F=12.3,\ P<0.01$$

In Eq. 3, duration is the percent of gasping duration value compared to control and $ED_{50}$ was the median effective dose (mg/kg) of anticonvulsive activity. Except for the discussion of the biological meaning of the result, it became clear that the potency of antihypoxic activity is correlated to that of anticonvulsive activity at least in this series of quinazolines (Table III).

King reported that the antihypoxic activity was not correlated to the anticonvulsive activities in the current anticonvulsive agents.[3] His result is opposite from our finding. There are many mechanisms for an exhibition of the anticonvulsive activity.[20] Thus, it is not questionable that anticonvulsive agents of different structure show varied antihypoxic potencies.

In the series of 4-alkylthioquinazolines, the antihypoxic potency was not necessarily correlated to that of anticonvulsive activity. These compounds showed weaker antihypoxic activity than the corresponding 4-alkoxyquinazolines. The oxygen atom seems to play an important role in potent antihypoxic activity as well as in potent anticonvulsive activity.

In conclusion, as mentioned above, the QSAR analysis suggests that the most potent anticonvulsive derivatives with low neurotoxicity have already been prepared. As the antihypoxic activity is correlated to the anticonvulsive activity, the more potent antihypoxic compounds with low neurotoxicity can not be designed in this series. Compounds **9**, **13**, **15**, **16** and **27** are the most potent antihypoxic agents. Compounds **16** and **27** showed higher neurotoxicity than phenytoin. Compounds **9** and **13** were not approved due to acute toxicity compared to phenytoin. So we selected compound **15** as the most promising antihypoxic candidate agent in the series of our quinazolines.

## Experimental

Melting points were measured with a capillary melting point apparatus (Yamato MP-21) and are uncorrected. Infrared (IR) spectra were recorded on a Hitachi 270-50 spectrometer. Proton nuclear magnetic resonance ($^1$H-NMR) spectra were taken on a Hitachi R-24B NMR spectrometer with tetramethylsilane (TMS) as an internal standard. Chemical shifts are given as $\delta$ values (ppm): s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Elemental analyses were performed by the Analytical Department of Kanebo Research Center. For column chromatography, Silica gel 60 (Merck) was used.

2-(4-Formyl-1-piperazinyl)-4(3*H*)-quinazolinone (**3d**): A mixture of 2-ethylthio-4(3*H*)-quinazolinone[8] (**2**) (50 g, 0.24 mol) and *N*-formylpiperazine (69 g, 0.6 mol) was stirred at 150—165 °C for 4 h. The reaction mixture was treated with AcOEt and filtered. The resulting solid was chromatographed on silica gel with $CHCl_3$–MeOH (20:1) to give **3d** (31 g, 49%). IR (KBr) 1675, 1650 cm$^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 3.57 (8H, $NCH_2$), 7.0—8.1 (4H, Ar-H), 8.15 (1H, s, NCHO), 11.58 (1H, s, CONH). Compounds **3a**—**c** and **3e**—**h** were similarly prepared.

2-(4-Butyl-1-piperazinyl)-4-chloroquinazoline (**4a**): A mixture of **3a** (2.7 g, 9.5 mmol) and $POCl_3$ (2.7 ml, 29 mmol) was heated at 130 °C for 2 h. The reaction mixture was poured over ice, neutralized with 3 N NaOH and extracted with AcOEt. The organic layer was washed with water, dried over $MgSO_4$, and concentrated. The resulting oil was chromatographed on silica gel with hexane–$CHCl_3$ (1:3) to give **4a** (2.6 g, 88%). $^1$H-NMR ($CDCl_3$) $\delta$: 0.92 (3H, t, $J=6$ Hz, $CH_2CH_3$), 1.45 (4H, m, $CH_2(CH_2)_2CH_3$), 2.35 (2H, t, $J=7$ Hz, $NCH_2CH_2$), 2.48 (4H, t, $J=5$ Hz, $CH_2CH_2N$), 3.90 (4H, t, $J=5$ Hz, Ar-$NCH_2CH_2$), 7.0—8.0 (4H, Ar-H). Compounds **4b** and **4c** were similarly prepared. The oily compound **4a** was treated with a solution of fumaric acid in EtOH to form the fumarate for elemental analysis.

**Method A** 2-(4-Methyl-1-piperazinyl)-4-pentyloxyquinazoline (**9**): NaH (60% in oil) (0.65 g, 16 mmol) was added to a mixture of 2-(4-methyl-1-piperazinyl)-4(3*H*)-quinazolinone[1] (3.5 g, 14 mmol), 1-iodopentane (3.5 g, 18 mmol) and *N*,*N*-dimethylformamide (DMF, 20 ml) at 0 °C, and stirred at 60 °C for 4.5 h. The reaction mixture was diluted with water and extracted with AcOEt. The organic layer was washed with water, dried over $MgSO_4$, and concentrated. The resulting oil was chromatographed on silica gel with $CHCl_3$–MeOH (20:1) to give **9** (3.9 g, 86%). $^1$H-NMR ($CDCl_3$) $\delta$: 0.95 (3H, t, $J=6$ Hz, $CH_2CH_3$), 1.2—2.0 (6H, $OCH_2(CH_2)_3CH_3$), 2.34 (3H, s, $NCH_3$), 2.48 (4H, t, $J=5$ Hz), 3.96 (4H, t, $J=5$ Hz), 4.50 (2H, t, $J=6$ Hz, $OCH_2CH_2$), 7.0—8.0 (4H).

4-Pentyloxy-2-(1-piperazinyl)quinazoline (**12**): 2-(4-Formyl-1-piperazinyl)-4-pentyloxyquinazoline (**36**) was similarly prepared by method A. mp 80.0—83.0 °C. *Anal.* Calcd for $C_{18}H_{24}N_4O_2$: C, 65.83; H, 7.37; N, 17.06. Found: C, 65.70; H, 7.24; N, 17.05. $^1$H-NMR ($CDCl_3$) $\delta$: 0.95 (3H, t, $J=6$ Hz), 1.2—2.2 (6H), 3.3—3.7 (4H, $NCH_2CH_2$), 3.8—4.1 (4H, Ar-$NCH_2CH_2$), 4.45 (2H, t, $J=6$ Hz), 7.0—8.0 (4H, Ar-H), 8.12 (1H, NCHO). Compound **36** (2.6 g, 8.0 mmol) was added to 3 N HCl (20 ml) and

refluxed for 2.5 h. The reaction mixture was neutralized with 20% NaOH and extracted with AcOEt. The organic layer was washed with water, dried over $MgSO_4$, and concentrated. The resulting oil was chromatographed on silica gel with $CHCl_3$–MeOH (10:1) to give **12** (1.7 g, 71%). $^1$H-NMR ($CDCl_3$) $\delta$: 0.90 (3H, t, $J$=6 Hz), 1.1—2.0 (6H), 2.30 (1H, s, NH), 2.90 (4H, t, $J$=5 Hz), 3.85 (4H, t, $J$=5 Hz), 4.43 (2H, t, $J$=7 Hz), 6.9—8.0 (4H).

**Method B** 2-(4-Butyl-1-piperazinyl)-4-pentyloxyquinazoline (**16**): NaH (60% in oil) (0.64 g, 16 mmol) was added to a mixture of **4a** (3.2 g, 10 mmol), 1-pentanol (1.4 g, 16 mmol) and DMF (20 ml) at 0 °C and the mixture was stirred at r.t. for 1 h. The reaction mixture was diluted with water and extracted with AcOEt. The organic layer was washed with water, dried over $MgSO_4$, and concentrated. The resulting oil was chromatographed on silica gel with $CHCl_3$–MeOH (50:1) to give **16** (2.0 g, 55%). $^1$H-NMR ($CDCl_3$) $\delta$: 0.95 (3H, t, $J$=6 Hz), 1.1—2.0 (10H), 2.38 (2H, t, $J$=7 Hz), 2.5 (4H, t, $J$=5 Hz), 3.95 (4H, t, $J$=5 Hz), 4.50 (2H, t, $J$=6 Hz), 7.0—8.1 (4H). The oily compounds **6**, **8**—**17**, **19**—**28** and **31**—**35** were treated with a solution of fumaric acid in EtOH to form the fumarate. Compounds **29** and **30** were purified as the HCl salts.

**Pharmacological Method** Male ddy strain mice weighing 18—25 g were used in all experiments. All animals were fasted overnight before the experiments. Test compounds were dissolved or suspended in 1% acacia solution and administered orally to animals.

**Anticonvulsive Activity**[9] A group of five mice was used for each dose of test compound. Each animal was electroshocked (60 Hz, 80 mA, 0.2 s) through corneal electrodes 1 h after the administration of the test compounds. The prevention of hindlimb tonic extensor reaction was classified as an anticonvulsive effect. Median effective dose ($ED_{50}$) was calculated according to Weil's method.[21]

**Neurotoxicity**[10] Neurotoxicity was defined as the inability of the animals to remain on a horizontal rod (3.4 cm) rotating at 5 rpm. Mice had been trained to remain on the rotating rod for at least 60 s. A group of ten mice was used for each dose of test compound. Rotarod performance tests for 60 s were carried out repeatedly at intervals of 1 h for 6 h after the administration of a test compound. Median neurotoxic dose ($NTD_{50}$) was calculated according to Weil's method.

**Antihypoxic Activity**[11] A group of five mice was used for each dose of test compound. The animals were decapitated 1 h after the oral administration of the test compound. Then, the gasping duration was measured and expressed as a percent of the control value.

**Acute Toxicity** The mortality was observed and recorded for 7 d following the administration of each test compound, and the median lethal dose ($LD_{50}$) was calculated according to Weil's method.

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