**9f**, 86457-49-0; **9f**·HCl, 86495-79-6; **9g**, 86470-93-1; **9h**, 86457-50-3; **9h**·HCl, 86495-80-9; **9i**, 86457-51-4; **9j**, 86457-52-5; **9j**·HCl, 86495-81-0; **11a**, 86457-53-6; **11a**·HCl, 86495-82-1; **11b**, 86495-83-2; **11b**·HCl, 86540-86-5; **12a**, 86457-54-7; **12b**, 86457-55-8; **12b**·HCl, 86457-56-9; **12c**, 86457-57-0; **13**, 86457-58-1; **14**, 86457-59-2; **14**·HCl, 86495-84-3; **15**, 86457-60-5; **16**, 86457-61-6; **16**·HCl, 86495-85-4; **20** (R = H) (isomer 1), 86457-62-7; **20** (R = H) (isomer 2), 86495-86-5; **20** (R = H) (isomer 1) chlorohydrin derivative, 86457-63-8; **20** (R = H) (isomer 2) chlorohydrin derivative, 86495-87-6; **20** (R = Et) (isomer 1), 86457-64-9; **20** (R = Et) (isomer 2), 86495-88-7; diphenylpropylsulfonium tetrafluoroborate, 14264-05-2; *N*-(2-phenylpropyl)formamide, 85070-52-6; methyl vinyl ketone, 78-94-4; ethyl acetate, 141-78-6; 3-(phenylmethyl)-3-buten-2-one, 25522-79-6; 3-methyl-3-buten-2-one, 814-78-8; 3-ethyl-3-buten-2-one, 4359-77-7; 3-propyl-3-buten-2-one, 25409-10-3; 3-butyl-3-buten-2-one, 65818-30-6; 3-phenyl-3-buten-2-one, 32123-84-5; 2-(1-aminopropyl)-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizin-2-ol (isomer 1), 86496-35-7; 2-(1-aminopropyl)-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizin-2-ol (isomer 2), 86457-65-0.

# Synthesis and Antihypertensive Activity of Some New Quinazoline Derivatives

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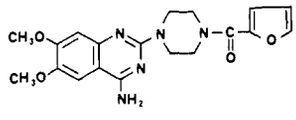
A series of substituted 2-piperidino-4-amino-6,7-dimethoxyquinazolines was synthesized and screened as potential antihypertensive agents. The hypotensive effect of all the new compounds was studied after intravenous administrations in urethane-anesthetized normotensive rats. The furoylpiperazine moiety in the prazosin molecule could be replaced by a more stable substituted piperidine group without loss of the blood pressure lowering activity. However, the nature of the substituent profoundly influenced the hypotensive potency as well as the duration of the hypotensive action. Some of the new compounds were found to be as potent as prazosin. On the basis of potency and the duration of the hypotensive action in the anesthetized rats, five of the most promising compounds were selected for further studies. Each of these agents exerted an antihypertensive effect upon oral administrations in conscious spontaneously hypertensive rats. At small doses, the new compounds appeared to be somewhat less potent than prazosin, but at the higher doses of 10–100 μmol/kg, two of them appeared to be even more efficacious antihypertensive agents than prazosin.

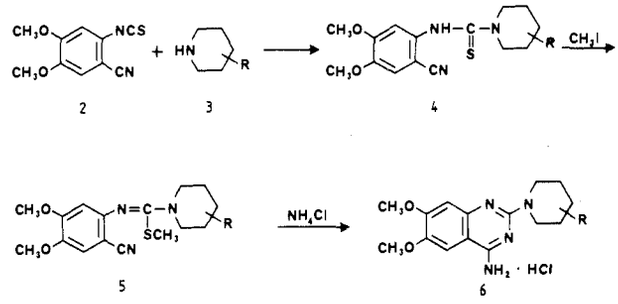
Prazosin, 2-[4-(2-furoyl)piperazin-1-yl]-4-amino-6,7-dimethoxyquinazoline (**1**), is a novel, highly active and selective antagonist of $\alpha_1$-adrenoceptors and can be considered an important advancement both pharmacologically and therapeutically, since this compound, in contrast to the classical $\alpha$-adrenoceptor blocking agents, is effective for the treatment of high blood pressure. Prazosin lacks direct smooth muscle relaxing properties, and, unlike many vasodilatators, in doses that decrease blood pressure it does not produce undesirable tachycardia or increases the heart rate only slightly. The most serious side effect of prazosin is known as the "first dose phenomenon", which can sometimes lead to syncope.[1] Prazosin is well absorbed from the gastrointestinal tract and entirely eliminated after undergoing extensive metabolism. The bioavailability of prazosin is rather low, and the elimination half-life is quite short, being only about 2–3 h. A typical metabolic pathway of prazosin is the easy elimination of the furoyl group from the piperazine ring, leading to metabolites of very low antihypertensive activity.[2] The piperazine ring is also very sensitive toward enzymatic hydroxylation.



1

The purpose of this investigation was to study the possibility of replacing the labile furoylpiperazine moiety in prazosin by a more stable piperidino group so that the antihypertensive activity of the new derivatives remains unaltered but possess longer duration of action due to the increased stability against enzymatic degradation.

Scheme I



Therefore, a series of new 2-piperidino-4-amino-6,7-dimethoxyquinazoline derivatives substituted with various chemical groups in the piperidino moiety was synthesized. The compounds synthesized and their hypotensive activity compared to prazosin are presented in Table IV.

**Chemistry.** The new quinazoline derivatives **6** can be synthesized in different ways as described previously.[3] However, the most practical route used in the synthesis of prazosin[4] is shown in Scheme I.

3,4-Dimethoxy-6-isothiocyanatobenzonitrile (**2**) was condensed first with the substituted piperidine derivatives **3** to give the thioureas **4**. After methylation of **4** with methyl iodide, the *S*-methylisothioureas (**5**) formed were cyclized to the quinazolines (**6**) with an excess of ammonium chloride. The overall yield from **2** to **6** is, in general,

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‡ University of Helsinki.

(1) Gavero, I.; Roach, A. G. *Life Sci.* **1980**, *27*, 1525.
(2) Hess, H. J. In "Prazosin—Evaluation of a New Antihypertensive Agent" (*Excerpta Med.*); Elsevier: Amsterdam, 1974; pp 3–15.
(3) Honkanen, E.; Hietava, M.; Kairisalo, P.; Nore, P.; Karppanen, H.; Paakkari, I. European Patent 34471, 1981.
(4) Honkanen, E.; Pippuri, A.; Kairisalo, P.; Thaler, H.; Koivisto, M.; Tuomi, S. *J. Heterocycl. Chem.* **1980**, *17*, 797.

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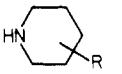
Table I. Synthetic Data and Physical Constants of Substituted Piperidines



| compd | R | synth scheme | yield, % | mp, °C | recrystn solv | formula | anal.[b] |
|---|---|---|---|---|---|---|---|
| 3e | 4-$COOCH_2C(CH_3)_3$ | *a* | 81 | ·HCl 216 | EtOH-$Me_2CO$ | $C_{11}H_{22}ClNO_2$ | C, H, Cl, N |
| 3g | 4-$CONHC(CH_3)_3$ | IIb | 88 | 128-131 | MeOH | $C_{10}H_{20}N_2O$ | C, H, N |
| 3i | 3-$CON(CH_2)_3CH_2$ (*d*) | IIb | 95 | oil | | $C_{10}H_{18}N_2O$ | |
| 3ii | 3-$CON(CH_2)_3CH_2$ (*l*) | IIb | 88 | oil | | $C_{10}H_{18}N_2O$ | |
| 3j | 4-$CON(CH_2)_3CH_2$ | IIab | 91 | oil | | $C_{10}H_{18}N_2O$ | |
| 3k | 4-$CON(CH_2)_4CH_2$ | IIab | 85 | oil | | $C_{11}H_{20}N_2O$ | |
| 3l | 4-$CON(CH_2)_5CH_2$ | IIb | 87 | oil | | $C_{12}H_{22}N_2O$ | |
| 3m | 4-$CON(CH_2)_6CH_2$ | IIb | 97 | oil | | $C_{13}H_{24}N_2O$ | |
| 3n | 4-$CONCHCH_3(CH_2)_2CHCH_3$ | IIb | 98 | oil | | $C_{12}H_{22}N_2O$ | |
| 3o | 4-$CONCHCH_3(CH_2)_3CH_2$ | IIb | 77 | oil | | $C_{12}H_{22}N_2O$ | |
| 3p | 4-$CONCHCH_3(CH_2)_3CHCH_3$ | IIb | 24 | oil | | $C_{13}H_{24}N_2O$ | |
| 3q | 4-$COCH_2CH_3$ | III | 90 | oil | | $C_8H_{15}NO$ | |
| 3r | 4-$CO(CH_2)_3CH_3$ | III | 82 | ·HCl 115 | EtOH-$Et_2O$ | $C_{10}H_{20}ClNO$ | C, H, Cl, N |
| 3s | 4-$COCH(CH_2)_3CH_2$ | III | 87 | 32-33 | $Et_2O$-pentane | $C_{11}H_{19}NO$ | C, H, N |
| 3t | 4-$COCH(CH_2)_4CH_2$ | III | 85 | 52-55 | $Et_2O$-pentane | $C_{12}H_{21}NO$ | C, H, N |
| 3u | 4-COC=CHCH=CHS | III | 41 | 98-100 | $Et_2O$-pentane | $C_{10}H_{13}NOS$ | C, H, N, S |
| 3w | 4-$CHOH(CH_2)_3CH_3$ | III | 97 | oil | | $C_{10}H_{21}NO$ | |
| 3x | 4-$CHOHCH(CH_2)_3CH_2$ | III | 72 | 123-125 | $Et_2O$-pentane | $C_{11}H_{21}NO$ | C, H, N |

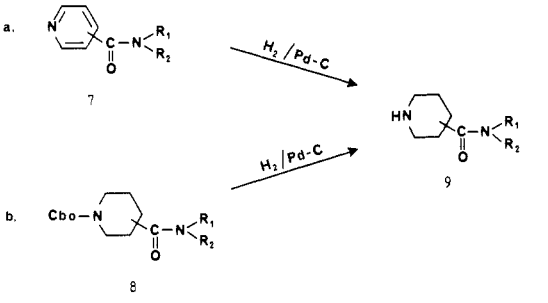
[a] Prepared by esterification of piperidine-4-carboxylic acid with neopentyl alcohol. [b] The oils were characterized by $^1H$ NMR spectrometry only.

60–80% of theoretical values. The hydrochlorides of **6** of high purity were obtained directly in the last step.

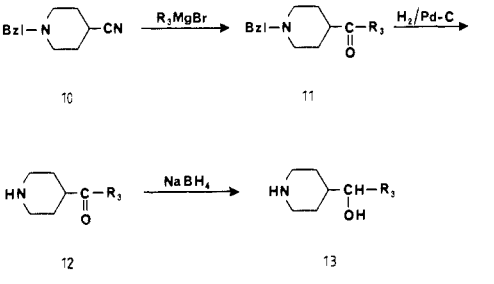
The intermediate piperidine derivatives **3** were prepared in different ways according to the nature of the substituent R. If R is 4-methyl, 4-benzyl, 3- or 4-ethoxycarbonyl, or 3- or 4-carboxamido, the compounds were obtained commercially.

Optically active 3-(ethoxycarbonyl)piperidines were prepared according to Akkerman et al.[5] 4-(1-Hydroxyethyl)piperidine (**3v**) was synthesized according to Wawzonek et al.[6] by catalytic hydrogenation of 4-acetylpyridine. If R is a substituted carboxamido group, the compounds **9** were prepared either from the corresponding pyridinecarboxamides **7** or from the *N*-Cbo-protected piperidinecarboxamides **8** by catalytic hydrogenation (Scheme II). If R is a 4-acyl or a substituted 4-hydroxymethyl group, the compounds (**12** and **13**) were synthesized as illustrated in Scheme III.

Scheme II




Scheme III

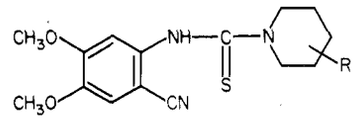



## Biological Results and Discussion

The hypotensive potencies of the new compounds in urethane-anesthetized normotensive rats are summarized in Table IV. $ED_{30}$ is defined as the dose that produced a 30% decrease in the mean blood pressure. To elucidate the duration of action of the compounds, we give the $LD_{30}$

(5) Akkerman, A.; DeJongh, D.; Veldstra, H. *Recl. Trav. Chim. Pays-Bas* **1951**, *70*, 899.
(6) Wawzonek, S.; Wilkinson, T. *J. Org. Chem.* **1966**, *31*, 1732.
(7) Paakkari, I. *J. Pharmacol. Methods* **1981**, *6*, 97.

Table II. Synthetic Data and Physical Constants of Substituted Thioureas



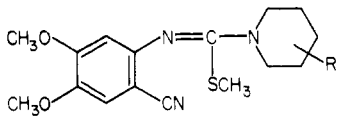
| compd | R | yield, % | mp,[a] °C | formula[b] |
|---|---|---|---|---|
| 4a | 4-$CH_3$ | 98 | 169-170 | $C_{16}H_{21}N_3O_2S$ |
| 4b | 4-$CH_2C_6H_5$ | 64 | 108-110 | $C_{22}H_{25}N_3O_2S$ |
| 4c | 3-$COOCH_2CH_3$ (*d*) | 80 | 141-145 | $C_{18}H_{23}N_3O_4S$ |
| 4cc | 3-$COOCH_2CH_3$ (*l*) | 82 | 142-146 | $C_{18}H_{23}N_3O_4S$ |
| 4d | 4-$COOCH_2CH_3$ | 76 | 154-158 | $C_{18}H_{23}N_3O_4S$ |
| 4e | 4-$COOCH_2C(CH_3)_3$ | 87 | 125-128 | $C_{21}H_{29}N_3O_4S$ |
| 4f | 4-$CONH_2$ | 95 | 235-239 | $C_{16}H_{20}N_4O_3S$ |
| 4g | 4-$CONHC(CH_3)_3$ | 89 | 190-192 | $C_{20}H_{28}N_4O_3S$ |
| 4i | 3-$CON(CH_2)_3CH_2$ (*d*) | 85 | 165-171 | $C_{20}H_{26}N_4O_3S$ |
| 4ii | 3-$CON(CH_2)_3CH_2$ (*l*) | 88 | 168-171 | $C_{20}H_{26}N_4O_3S$ |
| 4j | 4-$CON(CH_2)_3CH_2$ | 89 | 221-223 | $C_{20}H_{26}N_4O_3S$ |
| 4k | 4-$CON(CH_2)_4CH_2$ | 65 | 221-224 | $C_{21}H_{28}N_4O_3S$ |
| 4l | 4-$CON(CH_2)_5CH_2$ | 64 | 196-202 | $C_{22}H_{30}N_4O_3S$ |
| 4m | 4-$CON(CH_2)_6CH_2$ | 67 | 190-194 | $C_{23}H_{32}N_4O_3S$ |
| 4n | 4-$CONCHCH_3(CH_2)_2CHCH_3$ | 97 | 182-185 | $C_{22}H_{30}N_4O_3S$ |
| 4o | 4-$CONCHCH_3(CH_2)_3CH_2$ | 53 | 145-146 | $C_{22}H_{30}N_4O_3S$ |
| 4p | 4-$CONCHCH_3(CH_2)_3CHCH_3$ | 90 | 168-170 | $C_{23}H_{32}N_4O_3S$ |
| 4q | 4-$COCH_2CH_3$ | 60 | 158-160 | $C_{18}H_{23}N_3O_3S$ |
| 4r | 4-$CO(CH_2)_3CH_3$ | 62 | 162-165 | $C_{20}H_{27}N_3O_3S$ |
| 4s | 4-$COCH(CH_2)_3CH_2$ | 70 | 187-189 | $C_{21}H_{27}N_3O_3S$ |
| 4t | 4-$COCH(CH_2)_4CH_2$ | 95 | 185-190 | $C_{22}H_{29}N_3O_3S$ |
| 4u | 4-$COC{=}CHCH{=}CHS$ | 58 | 207-209 | $C_{20}H_{21}N_3O_3S_2$ |
| 4v | 4-$CHOHCH_3$ | 81 | 141-144 | $C_{17}H_{23}N_3O_3S$ |
| 4w | 4-$CHOH(CH_2)_3CH_3$ | 55 | 95-98 | $C_{20}H_{29}N_3O_3S$ |
| 4x | 4-$CHOHCH(CH_2)_3CH_2$ | 64 | 196-200 | $C_{21}H_{29}N_3O_3S$ |

[a] All compounds were recrystallized from AcOEt, except 4f and 4w, which were recrystallized from DMF and $Me_2CO$, respectively. [b] All compounds gave satisfactory C, H, N, and S analyses.

value both shortly (1–5 min) after the injection when the effect reached its maximum and at 30 min. Each of the new compounds, regardless of the nature of the substituent R in the piperidine ring, showed hypotensive activity. Among the esters **6c–e**, the one with the neopentyl group (**6e**) was considerably more active than those with ethyl groups. Among the amide compounds **6f–p**, those with the amido group in position 3 (**6i** and **6ii**) had only very low activity. The primary (**6f**) and secondary (**6g**) amides had about the same activity as the cyclic amides **6h,j,n–p**. However, the cyclic amides **6k–m** were distinctly more potent hypotensive agents than the other amide compounds. The activity of these compounds was comparable with that of prazosin. In the series of ketones **6g–u**, the compound **6g** had weak activity only, while the other ketones were about equally active as the corresponding cyclic amides **6l–n**. The hypotensive activity of the corresponding alcohols **6v–y** was, in general, equal to that of the ketones (see **6w** vs. **6r**, **6x** vs. **6s**, and **6y** vs. **6t**). The esters **6c–e**, which can be expected to be rapidly hydrolyzed in the organism, had a very short duration of action. As estimated on the basis of potency and the duration of the hypotensive action, the most promising compounds appeared to be **6m,s,y,t,r**. Therefore, these compounds were additionally tested upon oral administration in conscious spontaneously hypertensive rats (SHR) for their antihypertensive activity. Each of these compounds lowered the blood pressure of SHR (Table V). At small doses, the new compounds appeared to be somewhat less potent than prazosin. However, at higher doses, 10–100 μmol/kg, compounds **6m** and **6s** appeared to be even more efficacious antihypertensive compounds than prazosin. At the doses used, none of the compounds, including prazosin, produced any statistically significant changes in the heart rate of SHR.

The results of the present study show that the furoylpiperazine moiety in prazosin can be replaced by a piperidine group having various substituents, without loss of the blood pressure lowering effect. However, the nature of the substituent profoundly influences the potency and

Table III. Synthetic Data and Physical Constants of Substituted *S*-Methylisothioureas



| compd | R | yield, % | mp, °C | recrystn solv | formula | anal.[a] |
|---|---|---|---|---|---|---|
| 5a | 4-$CH_3$ | 83 | 118-121 | $Et_2O$ | $C_{17}H_{23}N_3O_2S$ | C, H, N, S |
| 5b | 4-$CH_2C_6H_5$ | 80 | 64-65 | $Et_2O$ | $C_{23}H_{27}N_3O_2S$ | C, H, N, S |
| 5c | 3-$COOCH_2CH_3$ (*d*) | 56 | oil | | $C_{19}H_{25}N_3O_4S$ | |
| 5cc | 3-$COOCH_2CH_3$ (*l*) | 57 | oil | | $C_{19}H_{25}N_3O_4S$ | |
| 5d | 4-$COOCH_2CH_3$ | 81 | oil | | $C_{19}H_{25}N_3O_4S$ | |
| 5e | 4-$COOCH_2C(CH_3)_3$ | 98 | oil | | $C_{22}H_{31}N_3O_4S$ | |
| 5f | 4-$CONH_2$ | 92 | 170-175 | AcOEt | $C_{17}H_{22}N_4O_3S$ | C, H, N, S |
| 5g | 4-$CONHC(CH_3)_3$ | 70 | 136-138 | AcOEt | $C_{21}H_{30}N_4O_3S$ | C, H, N, S |
| 5i | 3-$CON(CH_2)_3CH_2$ (*d*) | 44 | oil | | $C_{21}H_{28}N_4O_3S$ | |
| 5ii | 3-$CON(CH_2)_3CH_2$ (*l*) | 40 | oil | | $C_{21}H_{28}N_4O_3S$ | |
| 5j | 4-$CON(CH_2)_3CH_2$ | 94 | 132-135 | AcOEt | $C_{21}H_{28}N_4O_3S$ | C, H, N, S |
| 5k | 4-$CON(CH_2)_4CH_2$ | 85 | 145-147 | EtOH | $C_{22}H_{30}N_4O_3S$ | C, H, N, S |
| 5l | 4-$CON(CH_2)_5CH_2$ | 76 | oil | | $C_{23}H_{32}N_4O_3S$ | |
| 5m | 4-$CON(CH_2)_6CH_2$ | 97 | oil | | $C_{24}H_{34}N_4O_3S$ | |
| 5n | 4-$CONCHCH_3(CH_2)_2CHCH_3$ | 82 | oil | | $C_{23}H_{32}N_4O_3S$ | |
| 5o | 4-$CONCHCH_3(CH_2)_3CH_2$ | 96 | oil | | $C_{23}H_{32}N_4O_3S$ | |
| 5p | 4-$CONCHCH_3(CH_2)_3CHCH_3$ | 79 | oil | | $C_{24}H_{34}N_4O_3S$ | |
| 5q | 4-$COCH_2CH_3$ | 81 | oil | | $C_{19}H_{25}N_3O_3S$ | |
| 5r | 4-$CO(CH_2)_3CH_3$ | 91 | oil | | $C_{21}H_{29}N_3O_3S$ | |
| 5s | 4-$COCH(CH_2)_3CH_2$ | 79 | oil | | $C_{22}H_{29}N_3O_3S$ | |
| 5t | 4-$COCH(CH_2)_4CH_2$ | 89 | oil | | $C_{23}H_{31}N_3O_3S$ | |
| 5u | 4-COC=CHCH=CHS | 53 | 45-50 | $Et_2O$-pentane | $C_{21}H_{23}N_3O_3S_2$ | C, H, N, S |
| 5v | 4-$CHOHCH_3$ | 98 | oil | | $C_{18}H_{25}N_3O_3S$ | |
| 5w | 4-$CHOH(CH_2)_3CH_3$ | 83 | 41-44 | $Et_2O$-pentane | $C_{21}H_{31}N_3O_3S$ | C, H, N, S |
| 5x | 4-$CHOHCH(CH_2)_3CH_2$ | 86 | 41-45 | $Et_2O$-pentane | $C_{22}H_{31}N_3O_3S$ | C, H, N, S |

[a] The oils were characterized by $^1H$ NMR spectrometry only.

the duration of action of the compounds. Therefore, it is possible that the replacement of the furoylpiperazine moiety of prazosin with the more stable piperidine group, having appropriate substituents, might result in antihypertensive agents with a better pharmacological profile than prazosin itself. The results suggest that, at least for one improvement, it may be possible to prolong the short duration of action of prazosin by such manipulations of the molecule.

## Experimental Section

Melting points were determined on a Kofler block and are uncorrected. Elementary analyses were performed in Mikroanalytisches Laboratorium by Dr. Ilse Beetz, West Germany. All compounds analyzed within ±0.4% of theoretical values for C, H, Cl, N, and S. The $^1H$ NMR spectra of all new compounds were measured on Perkin-Elmer R 12 A spectrometer with $Me_4Si$ as internal standard and were in agreement with the assigned structures. The purity of all the compounds synthesized was checked by TLC on silica gel plates (Merck) using the solvent system EtOH/$Et_3N$ (98:2).

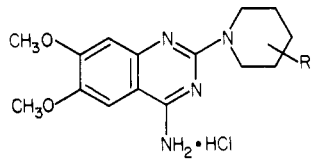
**Biological Test Procedures.** Normotensive male Wistar rats were anesthetized with urethane, 1.5 g/kg intraperitoneally. For the recording of blood pressure and heart rate, the left femoral artery was cannulated with a polyethylene tube that was connected to a pressure transducer (MP-15, Micron Instrument, Inc.). The arterial pulsations were amplified with a bioelectric amplifier (HP 8811D, Hewlett Packard) and analyzed on-line with a digital computer (PDP 11/34, Digital Equipment Corp.). The left femoral vein was cannulated with a polyethylene tube for intravenous injections of the compounds to be tested. Each of the compounds was injected in increasing doses (0.01, 0.1, 1, and 10 μmol/kg) at 30-min intervals. Each dose was administered in a volume of 1 mL/kg within 2 min. Control rats received the corresponding solvent instead of the drug solution. During the experiments the colonic temperature of the rats was kept at 38.0 ± 0.3 °C with a thermostatically controlled heating pad placed underneath the rats (Anitemp, Ab Aero-Tel). A detailed description of the recording system has been reported.

Systolic blood pressure of spontaneously hypertensive rats (SHR) was recorded by the tail-cuff method on a W + W instrument, Model 8008 (Basle, Switzerland). Before each measurement, the rats were warmed for 30 min at 36 °C to make the pulsations of the tail artery detectable. The drugs were administered by gavage in a volume of approximately 1 mL/rat.

The following typical examples illustrate the syntheses of the compounds listed in Tables I–IV.

***N*-(3,4-Dimethoxy-6-cyanophenyl)-*N'*,*N'*-(3-carboxamidopentamethylene)thiourea (4f).** To a solution of 3,4-

Table IV. Synthetic Data, Physical Constants, and Hypotensive Acitivity in Anesthetized Rats of Substituted Quinazolines



| compd | R | yield, % | mp,[d] °C | formula | anal. | hypotensive act.[e] $ED_{30}$ | hypotensive act.[e] $ED_{30}$ after 30 min |
|---|---|---|---|---|---|---|---|
| 6a | 4-$CH_3$ | 98 | 249-252 | $C_{16}H_{23}ClN_4O_2$ | C, H, Cl, N | 0.08 | 0 |
| 6b | 4-$CH_2C_6H_5$ | 72 | 254-255 | $C_{22}H_{27}ClN_4O_2$ | C, H, Cl, N | 0.06 | 0.07 |
| 6c | 3-$COOCH_2CH_3$ (*d*)[a] | 67 | 227-230 | $C_{18}H_{25}ClN_4O_4$ | C, H, Cl, N | 0.8 | 20 |
| 6cc | 3-$COOCH_2CH_3$ (*l*)[a] | 69 | 227-229 | $C_{18}H_{25}ClN_4O_4$ | C, H, Cl, N | 0.2 | 2 |
| 6d | 4-$COOCH_2CH_3$ | 50 | 260-265 | $C_{18}H_{25}ClN_4O_4$ | C, H, Cl, N | 0.3 | 30 |
| 6e | 4-$COOCH_2C(CH_3)_3$ | 81 | 285-289 | $C_{21}H_{31}ClN_4O_4$ | C, H, Cl, N | 0.03 | 2 |
| 6f | 4-$CONH_2$ | 88 | 280-286 | $C_{16}H_{22}ClN_5O_3$ | C, H, Cl, N | 0.1 | 0.8 |
| 6g | 4-$CONHC(CH_3)_3$ | 92 | 274-276 | $C_{20}H_{30}ClN_5O_3$ | C, H, Cl, N | 0.08 | 1 |
| 6h | 4-$CON(CH_2)_2CH_2$[b] | 86 | 263-264 | $C_{19}H_{26}ClN_5O_3$ | C, H, Cl, N | 0.07 | 0.4 |
| 6i | 3-$CON(CH_2)_3CH_2$ (*d*)[a] | 82 | 184-188 | $C_{20}H_{28}ClN_5O_3$ | C, H, Cl, N | 12 | 30 |
| 6ii | 3-$CON(CH_2)_3CH_2$ (*l*)[a] | 83 | 183-188 | $C_{20}H_{28}ClN_5O_3$ | C, H, Cl, N | 10 | 15 |
| 6j | 4-$CON(CH_2)_3CH_2$ | 85 | 201-203 | $C_{20}H_{28}ClN_5O_3$ | C, H, Cl, N | 0.2 | 0.4 |
| 6k | 4-$CON(CH_2)_4CH_2$ | 85 | 315-318 | $C_{21}H_{30}ClN_5O_3$ | C, H, Cl, N | 0.02 | 0.08 |
| 6l | 4-$CON(CH_2)_5CH_2$ | 65 | 283-289 | $C_{22}H_{32}ClN_5O_3$ | C, H, Cl, N | 0.01 | 0.05 |
| 6m | 4-$CON(CH_2)_6CH_2$ | 80 | 272-275 | $C_{23}H_{34}ClN_5O_3$ | C, H, Cl, N | 0.02 | 0.05 |
| 6n | 4-$CONCHCH_3(CH_2)_2CHCH_3$ | 19 | 248-252 | $C_{22}H_{32}ClN_5O_3$ | C, H, Cl, N | 0.08 | 0.2 |
| 6o | 4-$CONCHCH_3(CH_2)_3CH_2$ | 73 | 140-143 | $C_{22}H_{32}ClN_5O_3$ | C, H, Cl, N | 0.1 | 0.9 |
| 6p | 4-$CONCHCH_3(CH_2)_3CHCH_3$ | 16 | 270-274 | $C_{23}H_{34}ClN_5O_3$ | C, H, Cl, N | 0.08 | 0.2 |
| 6q | 4-$COCH_2CH_3$ | 32 | 167-170 | $C_{18}H_{25}ClN_4O_3$ | C, H, Cl, N | 5 | 30 |
| 6r | 4-$CO(CH_2)_3CH_3$ | 50 | 196-199 | $C_{20}H_{29}ClN_4O_3$ | C, H, Cl, N | 0.03 | 0.06 |
| 6s | 4-$COCH(CH_2)_3CH_2$ | 53 | 255-260 | $C_{21}H_{29}ClN_4O_3$ | C, H, Cl, N | 0.06 | 0.09 |
| 6t | 4-$COCH(CH_2)_4CH_2$ | 65 | 290-293 | $C_{22}H_{31}ClN_4O_3$ | C, H, Cl, N | 0.07 | 0.1 |
| 6u | 4-COC=CHCH=CHS | 65 | 258-261 | $C_{20}H_{23}ClN_4O_3S$ | C, H, Cl, N, S | 0.2 | 6 |
| 6v | 4-$CHOHCH_3$ | 74 | 268-269 | $C_{17}H_{25}ClN_4O_3$ | C, H, Cl, N | 0.5 | 0.7 |
| 6w | 4-$CHOH(CH_2)_3CH_3$ | 19 | 182-184 | $C_{20}H_{31}ClN_4O_3$ | C, H, Cl, N | 0.1 | 0.7 |
| 6x | 4-$CHOHCH(CH_2)_3CH_2$ | 66 | 269-273 | $C_{21}H_{31}ClN_4O_3$ | C, H, Cl, N | 0.1 | 0.7 |
| 6y | 4-$CHOHCH(CH_2)_4CH_2$[c] | 94 | 196-200 | $C_{22}H_{33}ClN_4O_3$ | C, H, Cl, N | 0.06 | 0.1 |
| prazosin | | | | | | 0.01 | 0.03 |

[a] $[\alpha]^{20}_D$ (water): for 6c, +94.2°; for 6cc −96.0°; for 6i +3.5°; for 6ii −3.9°. [b] Prepared by aminolysis of 6d with azacyclobutane. [c] Prepared by sodium borohydride reduction of 6t. [d] All compounds were recrystallized from EtOH/$H_2O$. [e] $ED_{30}$ is the dose (in micromoles per kilogram) that produced a 30% fall in mean blood pressure.

dimethoxy-6-isothiocyanatobenzonitrile (**2**;[4] 22.0 g, 0.1 mol) in DMF (100 mL) was added, with stirring and cooling (0–5 °C), a solution of piperidine-4-carboxamide (12.8 g, 0.1 mol) in DMF (50 mL). The mixture was stirred for 20 h at 0 °C, water (200 mL) was added slowly, and the precipitate was filtered, washed with water, and dried to yield 33.1 g (95%), mp 235–239 °C. Anal. ($C_{16}H_{20}N_4O_3S$) C, H, N, S.

***N*-(3,4-Dimethoxy-6-cyanophenyl)-*N'*,*N'*-(3-carboxamidopentamethylene)-*S*-methylisothiourea (5f).** A mixture of **4f** (17.4 g, 0.05 mol), methyl iodide (15.2 g, 0.1 mol), and calcium oxide (2.8 g, 0.05 mol) in chloroform (170 mL) was heated under reflux for 18 h at 60 °C. The solution was filtered, the filtrate was washed with water, and the solvent was evaporated to yield 16.7 g (92%), mp 170–175 °C. Anal. ($C_{17}H_{22}N_4O_3S$) C, H, N, S.

**2-(4-Carboxamidopiperidin-1-yl)-4-amino-6,7-dimethoxyquinazoline Hydrochloride (6f).** A mixture of **5f** (14.5 g, 0.04 mol) and ammonium chloride (43.0 g, 0.8 mol) in formamide (150 mL) was stirred for 20 h at 120 °C in a stream of nitrogen gas. The mixture was cooled to 80 °C, and water (75 mL) was added. The precipitate was filtered, and the filtrate was washed with cold water and acetone and dried to yield 13.1 g (88%), mp 280–286 °C. Anal. ($C_{16}H_{22}ClN_5O_3$) C, H, Cl, N.

**1-(4-Piperidinylcarbonyl)pyrrolidine (3j).** A solution of 1-(4-pyridylcarbonyl)pyrrolidine (25.1 g, 0.14 mol) in 1 N hydrochloric acid (140 mL) was hydrogenated at normal pressure and room temperature in the presence of platinum dioxide (1.0 g). After the theoretical amount of hydrogen was consumed (5–6 h), the solution was filtered and evaporated to dryness in vacuo. Sodium hydroxide, 5 N, was added to the residue, and the solution was extracted with dichloromethane. The solvent was evaporated,

Table V. Antihypertensive Activity of Quinazoline Derivatives in Spontaneously Hypertensive Rats

| compd | dose, μmol/kg po | fall in systolic BP, mmHg, at the following times after dosing: 1 h | 3 h | 5 h |
|---|---|---|---|---|
| 6m | 1 | 11 | NS | NS |
| | 10 | 29 | 29 | 26 |
| | 100 | 52 | 66 | 83 |
| 6r | 1 | 13 | 14 | NS |
| | 10 | 40 | 36 | 27 |
| 6s | 0.3 | NS | 11 | 11 |
| | 1 | 18 | 20 | 21 |
| | 3 | 34 | 34 | 35 |
| | 10 | 45 | 54 | 50 |
| 6t | 1 | 15 | 20 | NS |
| | 10 | NS | 54 | 51 |
| 6y | 1 | 12 | 17 | 19 |
| | 10 | 25 | 30 | 38 |
| prazosin | 1 | 29 | 30 | 26 |
| | 10 | 38 | 36 | 34 |
| | 100 | 38 | 30 | 26 |

[a] Values in the table indicate statistically significant decreases in blood pressure ($p \leq 0.05$) relative to control values. NS = nonsignificant change in blood pressure. The average systolic blood pressure before the administration of the compounds ranged in various experiments from 175 to 190 mmHg. Five rats were used to study the effect of each dose.

yielding 23.3 g (90%): $^1$H NMR ($CDCl_3$) δ 1.45–1.95 (m, 7 H), 2.40–3.60 (m, 10 H), 2.55 (s, 1 H).

**1-Benzyl-4-cyanopiperidine (10).** A mixture of 1-benzylpiperidine-4-carboxamide (14.3 g, 0.066 mol) in thionyl chloride (115 mL) was refluxed for 3 h. Excess thionyl chloride was evaporated in vacuo, and the residue was basified with sodium hydroxide solution and extracted with dichloromethane. The solvent was evaporated, and the residue was distilled in vacuo, yielding 9.6 g (73%) of a viscous oil: bp 130–132 °C (0.4–0.5 mmHg); $^1$H NMR ($CDCl_3$) δ 1.6–2.2 (m, 4 H), 2.2–2.8 (m, 5 H), 3.42 (s, 2 H), 7.21 (s, 5 H).

**1-Benzyl-4-(cyclopentylcarbonyl)piperidine.** To a solution of cyclopentylmagnesium bromide, prepared in the usual way from magnesium (4.8 g, 0.2 mol) and bromocyclopentane (29.8 g, 0.2 mol) in THF (100 mL), was added, with stirring and cooling (0–5 °C), **10** (34.0 g, 0.17 mol) in THF (100 mL). The mixture was refluxed for 3 h and allowed to stand overnight at room temperature. Hydrochloric acid (5 N, 300 mL) was added, and THF was evaporated in vacuo. The aqueous solution was made basic with 50% sodium hydroxide and extracted with dichloromethane. The solvent was evaporated, yielding 31.4 g (68%) of a viscous oil: $^1$H NMR ($CDCl_3$) δ 1.4–3.0 (m, 18 H), 3.40 (s, 2 H), 7.17 (s, 5 H).

**4-(Cyclopentylcarbonyl)piperidine (3s).** A solution of 1-benzyl-4-(cyclopentylcarbonyl)piperidine (18.7 g, 0.069 mol) in methanol (270 mL) and 1 N hydrochloric acid (85 mL) was hydrogenated at normal pressure and at room temperature in the presence of 10% Pd/C (5.0 g) until the theoretical amount of hydrogen was consumed. The solution was filtered, and the filtrate was evaporated to dryness in vacuo. The residue was made basic with 5 N sodium hydroxide and extracted with dichloromethane. The solvent was evaporated, yielding 12.5 g (87%): mp 32–33 °C; $^1$H NMR ($CDCl_3$) δ 1.5–1.9 (m, 10 H), 1.97 (s, 1 H), 2.4–3.2 (m, 8 H). Anal. ($C_{11}H_{19}NO$) C, H, N.

**Cyclopentyl-4-piperidinylcarbinol (3x).** To a solution of **3s** (4.7 g, 0.026 mol) in methanol (50 mL) was added, with stirring and cooling (0–5 °C), sodium borohydride (1.3 g) in water (15 mL). The mixture was stirred for 2 h at room temperature. The solvent was evaporated in vacuo, water was added to the residue, and the solution was extracted with chloroform. The solvent was evaporated yielding 3.4 g (72%) of a crystalline solid: mp 123–125 °C. Anal. ($C_{11}H_{21}NO$) C, H, N.

**Registry No.** 1, 19216-56-9; **2**, 43091-89-0; **3e**·HCl, 86542-85-0; **3g**, 86542-86-1; **3i**, 86542-87-2; **3ii**, 86542-88-3; **3j**, 35090-95-0; **3k**, 63214-58-4; **3l**, 86542-89-4; **3m**, 86542-90-7; **3n**, 86542-91-8; **3o**, 86542-92-9; **3p**, 86542-93-0; **3q**, 86542-94-1; **3r**·HCl, 86542-95-2; **3s**, 86542-96-3; **3t**, 86542-97-4; **3u**, 86542-98-5; **3v**, 24152-50-9; **3w**, 86542-99-6; **4a**, 86543-00-2; **4b**, 86543-01-3; **4c**, 86543-02-4; **4cc**, 86543-03-5; **4d**, 86543-04-6; **4e**, 86543-05-7; **4f**, 86543-06-8; **4g**, 86543-07-9; **4i**, 86543-08-0; **4ii**, 86543-09-1; **4j**, 86543-10-4; **4k**, 86543-11-5; **4l**, 86543-12-6; **4m**, 86543-13-7; **4n**, 86543-14-8; **4o**, 86543-15-9; **4p**, 86543-16-0; **4q**, 86543-17-1; **4r**, 86543-18-2; **4s**, 86543-19-3; **4t**, 86543-20-6; **4u**, 86543-21-7; **4v**, 86543-22-8; **4w**, 86543-23-9; **4x**, 86543-24-0; **5a**, 86543-25-1; **5b**, 86543-26-2; **5c**, 80030-55-3; **5cc**, 80030-56-4; **5d**, 80024-64-2; **5e**, 80030-53-1; **5f**, 80030-57-5; **5g**, 80030-58-6; **5i**, 80030-61-1; **5ii**, 80342-07-0; **5j**, 80030-52-0; **5k**, 80030-54-2; **5l**, 80030-60-0; **5m**, 80030-69-9; **5n**, 80030-62-2; **5o**, 80030-59-7; **5p**, 80030-63-3; **5q**, 80030-66-6; **5r**, 80030-67-7; **5s**, 86543-27-3; **5t**, 80030-68-8; **5u**, 86543-28-4; **5v**, 86543-29-5; **5w**, 86543-30-8; **5x**, 86543-31-9; **6a**, 86543-32-0; **6b**, 23673-00-9; **6c**, 86543-33-1; **6cc**, 86543-34-2; **6d**, 80024-65-3; **6e**, 80024-67-5; **6f**, 80024-72-2; **6g**, 86543-35-3; **6h**, 86543-36-4; **6i**, 80024-76-6; **6ii**, 80024-77-7; **6j**, 80024-63-1; **6k**, 86543-37-5; **6l**, 80024-75-5; **6m**, 80024-83-5; **6n**, 80024-78-8; **6o**, 80024-74-4; **6p**, 80030-64-4; **6q**, 80024-80-2; **6r**, 80024-81-3; **6s**, 86543-38-6; **6t**, 80024-82-4; **6u**, 65189-42-6; **6v**, 86543-39-7; **6w**, 86543-40-0; **6x**, 86543-41-1; **6y**, 86543-42-2; **10**, 62718-31-4; **11** ($R_3$ = cyclopentyl), 86542-84-9; 1-(4-pyridylcarbonyl)pyrrolidine, 86542-83-8; 1-benzylpiperidine-4-carboxamide, 62992-68-1; bromocyclopentane, 137-43-9.

# Autoxidation of the Antitumor Drug 9-Hydroxyellipticine and Its Derivatives[1]

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In aqueous solution and using molecular oxygen as electron acceptor, the antitumor drug 9-hydroxyellipticine (9-OH-E) undergoes a spontaneous oxidation to give hydrogen peroxide ($H_2O_2$), the quinone imine 9-oxoellipticine (9-oxo-E), and a dimer of 9-OH-E (9-OH-$E_2$). Electron paramagnetic resonance (EPR) experiments performed either in alkaline $Me_2SO$ or in phosphate buffer in the presence of the spin trap 5,5-dimethylpyrroline 1-oxide (DMPO) suggest that the oxidation process involves the initial formation of superoxide anion ($O_2^{-}\cdot$) and the free radical of the drug. In aqueous medium, this step is followed by the dismutation of both $O_2^{-}\cdot$ and free radicals of the drug generating, respectively, $H_2O_2$ and 9-oxo-E. 9-Oxo-E further reacts with the 9-OH-E remaining in the solution to form the dimer 9-OH-$E_2$ as the terminal product. The autoxidation process is strongly enhanced by superoxide dismutase and manganese ions. In the ellipticine series, all drugs that have an OH group in position 9 exhibit the ability to transfer one electron on molecular oxygen to generate $O_2^{-}\cdot$. This property may be involved in the cytotoxic activities of these drugs.

Two main hypotheses have been proposed concerning the mechanisms of action of the antitumor drugs derived from ellipticine (5,11-dimethyl-6*H*-pyrido[4,3-*b*]carbazole; see Table I). First, the possible interaction of these drugs

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