# 2,4-Diamino-6,7-dimethoxyquinazolines. 3. 2-(4-Heterocyclylpiperazin-1-yl) Derivatives as $\alpha_1$-Adrenoceptor Antagonists and Antihypertensive Agents

Simon F. Campbell* and Rhona M. Plews

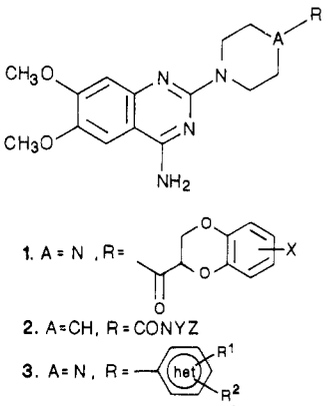
*Department of Discovery Chemistry, Pfizer Central Research, Sandwich, Kent, United Kingdom.* *Received March 2, 1987*

A series of 4-amino-6,7-dimethoxy-2-(4-heterocyclylpiperazin-1-yl)quinazolines (**3**) was prepared and screened for $\alpha$-adrenoceptor affinity and antihypertensive activity. These quinazoline derivatives showed high binding affinity (ca. $10^{-10}$ M) and selectivity (>10 000) for $\alpha_1$-adrenoceptors in vitro, with no relevant activity at $\alpha_2$ sites. Several compounds displayed similar activity to prazosin ($K_i = 1.9 \times 10^{-10}$ M) while the dimethoxytriazine derivative **30** ($K_i = 8 \times 10^{-11}$ M) was more potent. Like prazosin ($pA_2 = 8.37 \pm 0.24$), **30** proved to be a potent ($pA_2 = 8.63 \pm 0.15$), competitive antagonist of the $\alpha_1$-mediated vasoconstrictor action of norepinephrine. The high binding affinity of series **3** is most likely due to formation, at physiological pH, of the protonated, $\alpha_1$-adrenoceptor pharmacophore **33**, coupled with efficient hydrophobic interactions of the quinazoline 2-substituents. Computer-assisted superimposition of prazosin and **30** showed little structural correspondence between the furoyl and dimethoxytriazine moieties, and specific interactions of these molecular fragments with the receptor protein appear unlikely. Series **3** was evaluated for antihypertensive activity after oral administration (5 mg/kg) to spontaneously hypertensive rats, and blood pressure was recorded after 1 and 6 h. In vivo performance was markedly dependent on the nature of the distal heterocyclic system and various derivatives demonstrated superior or equivalent profiles to prazosin, with respect to both antihypertensive efficacy and duration of action.

In previous papers,[1,2] the design, synthesis, and structure–activity relationships (SARs) for two series of 2,4-diamino-6,7-dimethoxyquinazoline derivatives (**1**, **2**) were described. Many of these compounds proved to be potent, long-lasting antihypertensive agents in animals, and doxazosin[3,4] (**1**, X = H) was chosen for clinical development. High affinity and selectivity for $\alpha_1$-adrenoceptors is characteristic of these quinazoline derivatives and several members of series **2** proved equiactive with prazosin. It was suggested that the enhanced basicity of the quinazoline nucleus in **2**, as compared to **1**, and hydrophobic interaction of the carboxamide substituents (Y, Z) dominated receptor interactions.[2] Thus, it was apparent that the carbonyl functions in **1**, **2** occupied different spatial orientations that did not permit a common receptor recognition mode. In order to clarify further the importance and function of these $\pi$ systems, the preparation and pharmacological properties of a series of 2-(4-heterocyclylpiperazin-1-yl)quinazoline derivatives, **3**, are now reported. For these compounds, the carbonyl moiety common to series **1**, **2** is replaced by a heteroaromatic $\pi$ system,[5] which also allows the influence of dipole direction to be probed. In addition, modification of the heterocyclic substituents (**3**, $R^1$, $R^2$) permits optimization of hydrophobic interactions, by analogy with SARs developed around **2**.

## Chemistry

Compounds for biological evaluation were synthesized by either of the approaches summarized in Scheme I.[6] In route A, an appropriate *N*-(heterocyclyl)piperazine, **4**, was condensed with 4-amino-2-chloro-6,7-dimethoxyquinazoline (**5**) in butanol and products **14**, **16**, **17**, **25**, **29** isolated by conventional procedures. In a complementary approach, reaction of a chloro heterocycle, **6**, with 4-amino-6,7-dimethoxy-2-piperazin-1-ylquinazoline (**7**) under




similar conditions provided an efficient entry to **18**–**24**, **26**, **27**, **30**–**32** (route B). Products from route B that contained a labile chlorine atom in the heterocyclic ring could be further transformed by either hydrogenolysis (**15**, route C) or reaction with an appropriate amine (**28**, route D) as shown in Scheme II. Final compounds were often characterized as acid addition salts, although many proved to be hygroscopic, as confirmed by elemental analysis (Table I).

Most of the intermediates **4**, **6** employed in routes A and B either were known compounds or could be prepared by conventional means. For example, reaction of *N*-formylpiperazine (**8**) with 2,4-dichloropyrimidine (**9**) gave intermediate **10**, which on treatment with sodium phenate followed by acidic cleavage of the protecting group gave 2-phenoxy-4-piperazin-1-ylpyrimidine (**11**, route E, Scheme III). Alternatively, reaction of 3-chloro-6-piperazin-1-ylpyridazine (**12**) with sodium isopropoxide provided 3-isopropoxy-6-piperazin-1-ylpyridazine (**13**, route F) directly.

## Results and Discussion

**SARs for in Vitro $\alpha$-Adrenoceptor Activity.** In Table II, the effects of variation of the heterocyclic substituent in series **3** on $\alpha_1$- and $\alpha_2$-adrenoceptor binding affinities are presented. Initial inspection of these data confirms that no compounds display any relevant activity at $\alpha_2$-sites whereas $\alpha_1$-adrenoceptor binding affinity is generally within the $10^{-10}$ M range. Comparison of entries **14**–**17** indicates that these isomeric diaza aromatic derivatives show similar, prazosin-like potency and that the introduction of alkoxy (**18**, **19**, **23**, **24**, **26**, **29**) or amino (**20**, **28**) substituents is well tolerated. Activity was slightly

(1) Campbell, S. F.; Davey, M. J.; Hardstone, J. D.; Lewis, B. N.; Palmer, M. J. *J. Med. Chem.* **1987**, *30*, 49.
(2) Alabaster, V. A.; Campbell, S. F.; Danilewicz, J. C.; Greengrass, C. W.; Plews, R. M. *J. Med. Chem.* **1987**, *30*, 999.
(3) Campbell, S. F.; Davey, M. J. *Drug Des. Delivery* **1986**, *1*, 83.
(4) Reid, J. L., Davies, H. C., Eds. *Br. J. Clin. Pharmacol.* **1986**, *21*, Suppl. 1.
(5) Olson, G. L.; Cheung, H.-C.; Morgan, K. D.; Blount, J. F.; Todaro, L.; Berger, L.; Davidson, A. B.; Boff, E. *J. Med. Chem.* **1981**, *24*, 1026.
(6) Campbell, S. F.; Plews, R. M. European Patent 0055583, published 1982.

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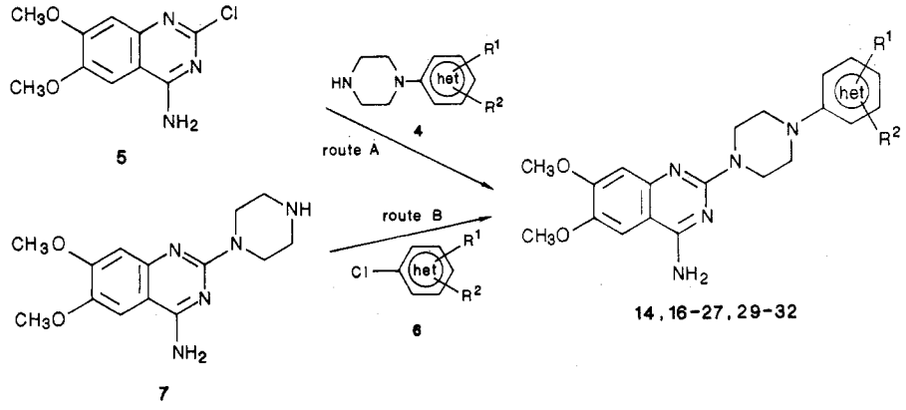
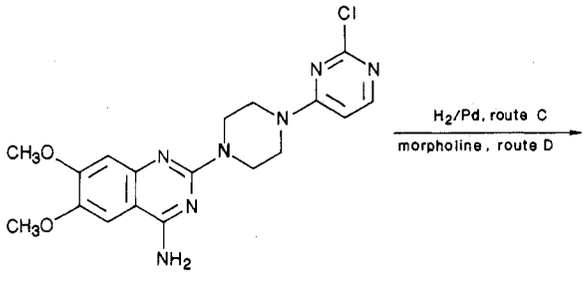
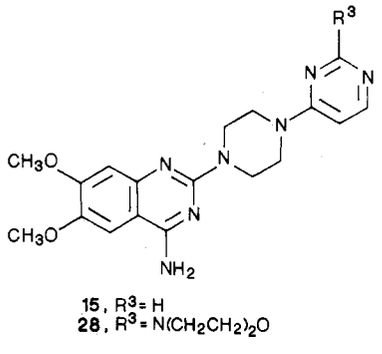
**Scheme I**

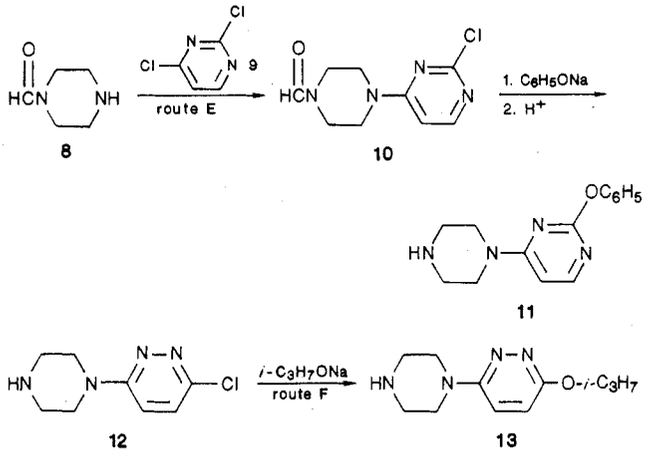



**Scheme II**




**Scheme III**



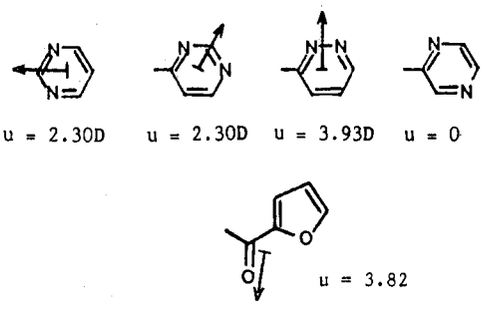
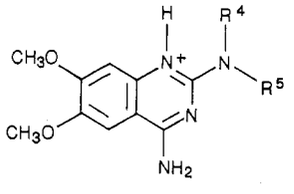




**Figure 1.** Calculated (CNDO) dipole moments for the heteroaryl fragments in **14–17** and the furoyl unit of prazosin.

reduced in the 4-methylpyrimidin-2-yl derivative (**21**) while incorporation of an aryl $\pi$ system (**22**) reduced potency some sixfold compared to the parent heterocycle, **14**. By contrast, activity was fully recovered with the phenoxy analogue **25**. Introduction of an additional nitrogen atom into the pyrimidinyl systems, **14**, **15**, appeared to be particularly beneficial and the dimethoxy-*s*-triazine derivative (**30**) was 2–3 times more potent than prazosin, with activity in the $10^{-11}$ M range. Unexpectedly, the diphenoxy and diamino analogues (**31**, **32**) were slightly less potent than the corresponding pyrimidines.

Apart from **26**, none of the novel compounds in Table II significantly displaced [$^3$H]clonidine from $\alpha_2$-adrenoceptor binding sites, even at concentrations up to $10^{-6}$ M. These binding data demonstrate that series **3** displays outstanding $\alpha_1/\alpha_2$ selectivity ratios (>10 000) and that any intrinsic affinity of the *N*-(heterocyclyl)piperazinyl moiety for $\alpha_2$-receptors[7] is completely overwhelmed by the $\alpha_1$-adrenoceptor pharmacophore **33**.[1,2]

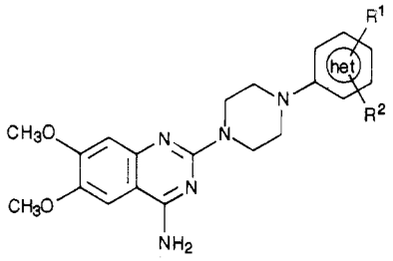


**33**

The data in Table II demonstrate that the heteroaryl moieties in **3** provide effective replacements for the carbonyl function present in prazosin. The similar potency shown by the isomeric derivatives **14–17** and prazosin suggests that neither the magnitude nor direction of the heteroaryl or carbonyl dipoles[8] (Figure 1) has any particular influence on $\alpha_1$-adrenoceptor interactions. However, comparison of the results in Table II with the unsubsti-

(7) Gueremy, C.; Audiau, F.; Renault, C.; Benavides, J.; Uzan, A.; LeFur, G. *J. Med. Chem.* **1986**, *29*, 1394.
(8) Dipoles given (CNDO) for parent heterocyclic and furoyl systems.[9] The influence of the piperazine nitrogen atom is assumed to be common although different degrees of $sp^2$ vs. $sp^3$ hybridization may exist.[10]
(9) For experimental values: *Tables of Experimental Dipole Moments*, A. L. McClellan, Ed.; W. H. Freeman: San Francisco, 1963.
(10) Lumma, W. C.; Hartmann, R. D.; Saari, W. S.; Engelhardt, E. L.; Hirschmann, R.; Clineschmidt, B. V.; Torchiana, M. L.; Stone, C. A. *J. Med. Chem.* **1978**, *21*, 536.

**Table I.** Synthetic Routes and Physical Data for Variation of Groups Het, $R^1$, and $R^2$




| no. | Het | $R^1$ | $R^2$ | route | mp, °C | solvent[e] | formula | anal. |
|---|---|---|---|---|---|---|---|---|
| 14 | pyrimidin-2-yl | H | H | A | 265–266 | E | $C_{18}H_{21}N_7O_2 \cdot 2HCl$ | C, H, N |
| 15 | pyrimidin-4-yl | H | H | C | 261 | E | $C_{18}H_{21}N_7O_2$ | C, H, N |
| 16 | pyridazin-3-yl | H | H | A | 214–215 | F | $C_{18}H_{21}N_7O_2 \cdot HCl \cdot 0.5H_2O$ | C, H, N[a] |
| 17 | pyrazin-2-yl | H | H | A | 291–293 | G | $C_{18}H_{21}N_7O_2 \cdot HCl$ | C, H, N |
| 18 | pyrimidin-2-yl | 4-$OCH_3$ | H | B | 202–203 | H | $C_{19}H_{23}N_7O_3$ | C, H, N |
| 19 | pyrimidin-2-yl | 4-$OC_3H_7$ | H | B | 265–269 | I | $C_{21}H_{27}N_7O_3 \cdot 2HCl \cdot H_2O$ | C, H, N[b] |
| 20 | pyrimidin-2-yl | 4-$N(CH_3)_2$ | H | B | 262–264 | J | $C_{20}H_{26}N_8O_2 \cdot HCl \cdot 0.5H_2O$ | C, H, N |
| 21 | pyrimidin-2-yl | 4-$CH_3$ | H | B | 225–226 | J | $C_{19}H_{23}N_7O_2$ | C, H, N[c] |
| 22 | pyrimidin-2-yl | 4-$C_6H_5$ | H | B | 250 | K | $C_{24}H_{25}N_7O_2 \cdot 0.5H_2O$ | C, H, N |
| 23 | pyrimidin-4-yl | 6-$OC_3H_7$ | H | B | 239–241 | J | $C_{21}H_{27}N_7O_3 \cdot 0.5H_2O$ | C, H, N |
| 24 | pyrimidin-4-yl | 6-O-*i*-$C_3H_7$ | H | B | 263–265 | K | $C_{21}H_{27}N_7O_3$ | C, H, N |
| 25 | pyrimidin-4-yl | 2-$OC_6H_5$ | H | A | 253–254 | J | $C_{24}H_{25}N_7O_3 \cdot 0.75H_2O$ | C, H, N |
| 26 | pyrimidin-4-yl | 2-$OCH_3$ | 6-$OCH_3$ | B | 194–195 | L | $C_{20}H_{25}N_7O_4$ | C, H, N |
| 27 | pyrimidin-4-yl | 6-$N(CH_3)_2$ | H | B | 187–188 | L | $C_{20}H_{26}N_8O_2 \cdot 0.5H_2O$ | C, H, N[d] |
| 28 | pyrimidin-4-yl | 2-$N(CH_2CH_2)_2O$ | H | D | 232–233 | L | $C_{22}H_{28}N_8O_3$ | C, H, N |
| 29 | pyridazin-3-yl | 6-O-*i*-$C_3H_7$ | H | A | 247–248 | J | $C_{21}H_{27}N_7O_3$ | C, H, N |
| 30 | *s*-triazin-2-yl | 4-$OCH_3$ | 6-$OCH_3$ | B | 225–226 | M | $C_{19}H_{24}N_8O_4 \cdot HCl \cdot H_2O$ | C, H, N |
| 31 | *s*-triazin-2-yl | 4-$OC_6H_5$ | 6-$OC_6H_5$ | B | 145–150 | J | $C_{29}H_{28}N_8O_4$ | C, H, N |
| 32 | *s*-triazin-2-yl | 4-$NH_2$ | 6-$NH_2$ | B | 276–277 | E | $C_{17}H_{22}N_{10}O_2$ | C, H, N |

[a] H: calcd, 5.9; found, 5.4. [b] H: calcd, 6.1; found 5.6. [c] Contains 0.33 mol of ethanol. [d] Contains 0.5 mol of ethyl acetate. [e] E, $CH_3OH$; F, DMF, G, $C_4H_9OH$; H, $C_3H_7OH$; I, $C_2H_5OH/CH_3OH$; J, $C_2H_5OH$; K, $DMF/(C_2H_5)_2O$; L, $CH_3CO_2C_2H_5$ M, $DMF/H_2O/(C_2H_5)_2O$.

**Table II.** Binding and Antihypertensive Activities for 4-Amino-2-(4-heterocyclylpiperazin-1-yl)-6,7-dimethoxyquinazoline Derivatives

| | $\alpha$-receptor binding affinity[a] | | % reduction in SHR ($n$ = 6) blood pressure[e] (dose, 5 mg/kg, po) | |
|---|---|---|---|---|
| no. | $\alpha_1$[b] | $\alpha_2$[c] | 1 h | 6 h |
| 14 | 0.26 ± 0.08 | NA | 40 | 28 |
| 15 | 0.27 ± 0.09 | NA | 21 | 12[f] |
| 16 | 0.40 ± 0.06 | NA | 22 | 20[f] |
| 17 | 0.18 ± 0.09 | NA | 7 | 8 |
| 18 | 0.19 ± 0.16 | NA | 15 | 14 |
| 19 | 0.32 ± 0.17 | NA | 34 | 22 |
| 20 | 0.27 ± 0.09 | NA | 7 | 13 |
| 21 | 0.92 ± 0.56 | NA | 28 | 15 |
| 22 | 1.66 ± 1.78 | NA | 17 | 17 |
| 23 | 0.36 ± 0.18 | NA | 39 | 22 |
| 24 | 0.18 ± 0.05 | NA | 55 | 49 |
| 25 | 0.24 ± 0.12 | NA | 19 | 24 |
| 26 | 0.16 | 54.2 ± 4.9 | 22 | 20 |
| 27 | NT | NT | 8 | 18 |
| 28 | 0.31 ± 0.10 | NA | 16 | 43[f] |
| 29 | 0.29 ± 0.09 | NA | 39 | 33[f] |
| 30 | 0.08 ± 0.03 | NA | 15 | 22 |
| 31 | 0.87 ± 0.03 | NA | 9 | 8 |
| 32 | 0.47 ± 0.07 | NA | 2 | 12 |
| prazosin | 0.19 ± 0.02 | 4830 ± 1280[d] | 33 | 29 |

[a] Rat brain homogenate preparation; all results are the mean ± SEM of at least three separate experiments performed in triplicate. [b] $K_i$ (nM) for displacement of [$^3$H]prazosin. [c] Percentage displacement of [$^3$H]clonidine at $10^{-6}$ M; NA indicates less than 50%. [d] $K_i$ (nM). [e] Falls in blood pressure below 10% are not significant. [f] Four-hour time point, dose 3 mg/kg, po.

tuted piperazin-1-ylquinazoline[11] **7** ($K_i$ = 3.3 × $10^{-8}$ M) shows an increase in $\alpha_1$-binding affinity of at least 100-fold, confirming that appropriate substituents in this area of the quinazoline molecule can have a profound effect on receptor affinity. The wide tolerance for a range of heterocyclic systems in series **3** supports the view that these substituents occupy a relatively open area on the $\alpha_1$-adrenoceptor, and the major contribution to binding affinity relies on the expulsion of water molecules from the receptor active site[1] (vide infra).

Previous studies suggested that the quinazoline cation **33** was essential for $\alpha_1$-adrenoceptor recognition, but diaminopyrimidine derivatives such as **20** do provide an alternative protonation site. Physicochemical measurements confirm the presence of two basic centers in **20** ($pK_a$ = 7.2, 5.9) corresponding to mono- and diprotonated species. Literature precedent suggests coincidental basicities for the quinazoline and pyrimidine fragments[12] and thus the N-1 protonated, $\alpha_1$-pharmacophore **33** would be expected to exist (ca. 20%) in equilibrium with the corresponding pyrimidinium species (ca. 20%) at physiological pH.[13] Dication formation will be much less favored (<-5%). The measured $pK_a$ (6.7) for **30** is almost identical with that for prazosin ($pK_a$ = 6.8), and both compounds also display high $\alpha_1$-adrenoceptor binding affinities (8 × $10^{-11}$ M, 1.9 × $10^{-10}$ M). In addition, **30** and prazosin are essentially equipotent, competitive antagonists ($pA_2$: **30**, 8.63 ± 0.15; prazosin, 8.37 ± 0.24) of the $\alpha_1$-mediated vasoconstrictor effects of norepinephrine.[14] However, while computer-assisted superimposition of **30** with prazosin

(11) Campbell, S. F. *X-Ray Crystallography and Drug Action*; Horn, A. S., De Ranter, C. J., Eds.; Clarendon: Oxford, 1984; p 347.
(12) *Dissociation Constants of Organic Bases in Aqueous Solution*, Perrin, D. D., Ed.; Butterworths: London, 1965, 1972.
(13) Monoprotonation of **20** at physiological pH should be approximately 40%.
(14) Rabbit pulmonary artery; slopes: **30**, 1.27 ± 0.12 ($n$ = 3); prazosin, 1.14 ± 0.31 ($n$ = 4).

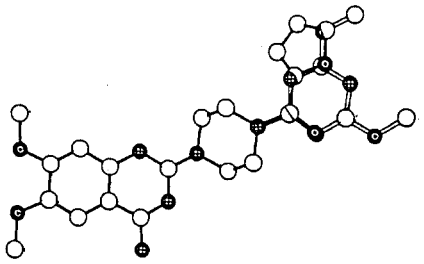


**Figure 2.** Computer-assisted superimposition of **30** (hollow bonds) and prazosin (solid bonds); hydrogen atoms omitted.

demonstrates the obvious equivalence of the piperazin-1-ylquinazoline nuclei, there appears to be little structural correspondence between the dimethoxytriazine and furoyl moieties[15] (Figure 2). Thus, while these molecular features are particularly well accepted by the $\alpha_1$-adrenoceptor, specific interaction with the receptor protein may be less important than efficient dislocation of water molecules from the active site.

**SARs for in Vivo Antihypertensive Activity.** The compounds in Table I were administered orally to spontaneously hypertensive rats (SHR), and reductions in blood pressure at 1 and 6 h are presented in Table II. The pyrimidin-2-yl derivative (**14**) displayed excellent, long-lasting efficacy with a similar profile to prazosin and was clearly superior to the isomeric diaza analogues **15–17**. Introduction of a range of 4-substituents into **14** was generally detrimental, although some activity was recovered with the propoxy derivative **19**. A similar modification of the pyrimidin-4-yl series was also beneficial (cf. **15**, **23**) and activity was markedly improved with the 6-isopropoxy analogue **24**. Indeed, this compound displayed superior antihypertensive efficacy to prazosin at both the 1- and 6-h time points. The outstanding in vivo performance of **24**, compared to **18**, **19**, and **23**, for example, may be due to a reduced susceptibility of the branched alkyl chain to metabolic O-dealkylation. In agreement, the 6-isopropoxypyridazine **29** displayed a similar in vivo profile to prazosin whereas **30** was only moderately active, despite demonstrating the highest $\alpha_1$-adrenoceptor binding affinity in vitro. The isomeric (dimethylamino)pyrimidines **20**, **27** showed modest activity in SHR, but incorporation of a 2-morpholino substituent (**28**) into the latter series led to a further improvement, particularly in duration of action.

In summary, the data in Table II demonstrate that many of the quinazoline derivatives **3** are potent, effective antihypertensive agents in SHR and that in vivo performance can be optimized by appropriate structural modification. Thus, **14**, **23**, **24**, **28**, **29** demonstrate equivalent or superior profiles to prazosin and most likely act by selective blockade of the postjunctional, vasoconstrictor effects of norepinephrine.

## Experimental Section

**Chemistry.** Melting points were determined in a Büchi apparatus in glass capillary tubes and are uncorrected. Spectroscopic data for all compounds were recorded on Perkin-Elmer 257 (IR), AEI MS12 or VG 7070F (MS), Perkin-Elmer R12B, Varian XL 100, or Nicolet QE300 (NMR) instruments and were consistent with assigned structures. Where analyses are indicated only by symbols of the elements, results obtained were within ±0.4% of the theoretical values.

(15) Compound **30** was built with use of appropriate bond lengths/angles obtained from related structures in the Cambridge Crystallographic Data Base. The triazine–piperazine torsion angle was set at 9° and further energy minimization was not undertaken.

**Route A. 4-Amino-6,7-dimethoxy-2-[4-(2-phenoxypyrimidin-4-yl)-piperazin-1-yl]quinazoline, 0.75-Hydrate (25).** 4-Amino-2-chloro-6,7-dimethoxyquinazoline (0.8 g, 3.3 mmol) and 2-phenoxy-4-piperazin-1-ylpyrimidine dihydrochloride (1.2 g, 4.7 mmol) were heated under reflux in butanol (50 mL) overnight. After cooling, the mixture was evaporated, and the residue was partitioned between chloroform/methanol/saturated aqueous sodium carbonate solution (300 mL:100 mL:50 mL). The chloroform/methanol layer was separated, dried ($Na_2SO_4$), and evaporated, and then the residue (1 g) was purified by chromatography on silica (85 g). Elution with chloroform/methanol (100:0 → 97.5:2.5) provided a solid product which was crystallized from ethanol to give 4-amino-6,7-dimethoxy-2-[4-(2-phenoxypyrimidin-4-yl)piperazin-1-yl]quinazoline, 0.75-hydrate (0.14 g, 9%), mp 253–254 °C. Anal. ($C_{24}H_{25}N_7O_3 \cdot 0.75H_2O$) C, H, N.

**Route B. 4-Amino-6,7-dimethoxy-2-[4-(4-phenylpyrimidin-2-yl)piperazin-1-yl]quinazoline, Hemihydrate (22).** 4-Amino-6,7-dimethoxy-2-piperazin-1-ylquinazoline (3.44 g, 12 mmol) and 2-chloro-4-phenylpyrimidine (2.5 g, 13 mmol) in butanol (250 mL) were heated under reflux for 6 h. After cooling, the solid product was collected, washed with ether, then partitioned between chloroform, and saturated sodium carbonate solution. The chloroform layer was separated, the aqueous phase was extracted with chloroform, and the combined organic layers were washed with water, dried ($Na_2SO_4$), and then evaporated. The residue (5.0 g) was purified by chromatography on silica gel with chloroform and chloroform/methanol (97.5:2.5) as eluants. The resulting solid product was crystallized from DMF/ether to give 4-amino-6,7-dimethoxy-2-[4-(4-phenylpyrimidin-2-yl)-piperazin-1-yl]quinazoline hemihydrate (2.28 g, 42%), mp 250 °C. Anal. ($C_{24}H_{25}N_7O_2 \cdot 0.5H_2O$) C, H, N.

**Route C. 4-Amino-6,7-dimethoxy-2-(4-pyrimidin-4-ylpiperazin-1-yl)quinazoline (15).** A sample (3.1 g, 7.75 mmol) of the product from route D (a) and triethylamine (1.6 g, 14.4 mmol) in dioxane (250 mL) was hydrogenated over Pd/C at 50 °C (50 psi) for 9 h. The mixture was filtered, the catalyst was washed with dioxane, and then the combined organic fractions were evaporated. The residue was partitioned between sodium hydroxide (5 N) and chloroform, and the organic layer separated, dried ($Na_2SO_4$), and evaporated. The residue was purified by chromatography on silica (32 g), eluting with chloroform/methanol (100:0 → 99.5:0.5) followed by crystallization from methanol to give 4-amino-6,7-dimethoxy-2-(4-pyrimidin-4-ylpiperazin-1-yl)-quinazoline (0.7 g, 25%), mp 261 °C. Anal. ($C_{18}H_{21}N_7O_2$) C, H, N.

**Route D. 4-Amino-6,7-dimethoxy-2-[4-(2-morpholinopyrimidin-4-yl)piperazin-1-yl]quinazoline (28).** (a) 4-Amino-6,7-dimethoxy-2-piperazin-1-ylquinazoline (30.0 g, 0.10 mol), 2,4-dichloropyrimidine (17.3 g, 0.12 mol), and triethylamine (20.5 g) in ethanol (1200 mL) were heated under reflux for 3 h. After cooling, the solid product was collected, washed with hot propan-2-ol and methanol, and then partitioned between aqueous sodium carbonate solution (10%) and dichloromethane/methanol (95:5). The organic layer was separated, washed with water, dried ($Na_2SO_4$), and evaporated. The residue was treated with hot propan-2-ol and then collected to give 4-amino-6,7-dimethoxy-2-[4-(2-chloropyrimidin-4-yl)piperazin-1-yl]quinazoline (20.0 g, 50%), mp 266 °C. Anal. ($C_{18}H_{20}ClN_7O_2$) C, H, N.

(b) A sample (2.0 g, 5.0 mmol) of the above product and morpholine (1.1 g, 12.6 mmol) in butanol (150 mL) were heated in a sealed bomb at 160 °C for 19 h. The mixture was then evaporated and the residue partitioned between sodium hydroxide (5 N) and chloroform/methanol (95:5). The organic layer was separated, washed with water, dried ($Na_2SO_4$), and evaporated. The residue was purified by chromatography on silica (20 g), and elution with chloroform followed by crystallization from ethyl acetate gave 4-amino-6,7-dimethoxy-2-[4-(2-morpholinopyrimidin-4-yl)piperazin-1-yl]quinazoline (0.8 g, 35%), mp 232–233 °C. Anal. ($C_{22}H_{28}N_8O_3$) C, H, N.

**2-Phenoxy-4-piperazin-1-ylpyrimidine (11).** (a) 1-Formylpiperazine (38.5 g, 0.385 mol) and triethylamine (34 g, 0.34 mol) in ethanol (500 mL) were added slowly to a stirred solution of 2,4-dichloropyrimidine (50 g, 0.33 mol) in ethanol (2500 mL) at room temperature. The mixture was stirred at room temperature for 24 h and then evaporated and the residue partitioned between chloroform and water. The organic phase was washed

with water and the aqueous phase extracted with chloroform. The combined chloroform extracts were dried ($Na_2SO_4$) and evaporated and the residue was crystallized from ethyl acetate to give 2-chloro-4-(4-formylpiperazin-1-yl)pyrimidine (24.0 g, 32%), mp 125–126 °C. Anal. ($C_9H_{11}ClN_4O$) C, H, N.

(b) A solution of sodium phenoxide (2.50 g, 22 mmol) in 1,2-dimethoxyethane (160 mL) was treated with a sample (5.0 g, 22 mmol) of the product from (a) and then heated under reflux for 24 h. The solvent was evaporated, the residue partitioned between chloroform (50 mL) and water (30 mL), and the aqueous phase extracted with chloroform. The combined chloroform extracts were dried ($Na_2SO_4$) and evaporated, and the residue was triturated with ether followed by crystallization from ethyl acetate to give 2-phenoxy-4-(4-formylpiperazin-1-yl)pyrimidine 0.25-hydrate (2.93 g, 47%), mp 149–151 °C. Anal. ($C_{15}H_{16}N_4O_2 \cdot 0.25H_2O$) C, H, N.

(c) A sample (2.6 g, 9.2 mmol) of the above product in methanol (27 mL) and 2 N hydrochloric acid (6.9 mL) was left at room temperature for 24 h and then heated on a steam bath for 0.5 h. The mixture was evaporated and the residue crystallized from propan-2-ol to give 2-phenoxy-4-piperazin-1-ylpyrimidine (1.5 g, 64%) characterized spectroscopically (**12**).

**3-Isopropoxy-6-piperazin-1-ylpyridazine (13).** 3-Chloro-6-piperazin-1-ylpyridazine (4.0 g, 20 mmol) and sodium isopropoxide [from sodium (0.7 g, 30 mmol) and propan-2-ol (70 mL)] were heated in a sealed bomb at 130–140 °C for 10 h. The mixture was then evaporated, the residue taken up in dichloromethane (300 mL), and the solution washed with water (2 × 50 mL). The organic layer was dried ($Na_2SO_4$) and evaporated to give 3-isopropoxy-6-piperazin-1-ylpyridazine (3.3 g, 74%). A sample of the product was converted to the dimaleate salt hemihydrate, which was recrystallized from ethanol, mp 144–145 °C. Anal. ($C_{11}H_{18}N_4O \cdot 2C_4H_4O_4 \cdot 0.5H_2O$).

2-Chloro-4-propoxypyrimidine, bp 101–103 °C (14 mm), was prepared in a similar manner from 2,4-dichloropyrimidine and sodium propoxide at 40 °C and characterized spectroscopically.

**Biology.** Experimental details for evaluation of α-adrenoceptor binding and antihypertensive activities have been detailed previously.[1] Okamoto SHR were used for the evaluation of **15**, **16**, **28**, **29** and New Zealand AS genetically hypertensive rats for the remaining compounds in Table II.

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**Registry No.** **4**·2HCl (het = pyrimidin-2-yl, $R^1 = R^2 = H$), 94021-22-4; **4**·2HCl (het = pyridazin-3-yl, $R^1 = R^2 = H$), 90434-90-5; **4**·2HCl (het = pyrazin-2-yl, $R^1 = R^2 = H$), 109467-19-8; **4**·2HCl (het = pyrimidin-3-yl, $R^1$ = 6-O-*i*-$C_3H_7$, $R^2 = H$), 109467-20-1; **5**, 23680-84-4; **6** (het = pyrimidin-2-yl, $R^1$ = 4-$OCH_3$, $R^2 = H$), 22536-63-6; **6** (het = pyrimidin-2-yl, $R^1$ = 4-$OC_3H_7$, $R^2 = H$), 83774-10-1; **6** (het = pyrimidin-2-yl, $R^1$ = 4-$N(CH_3)_2$, $R^2 = H$), 31058-81-8; **6** (het = pyrimidin-2-yl, $R^1$ = 4-$CH_3$, $R_2 = H$), 13036-57-2; **6** (het = pyrimidin-2-yl, $R^1$ = 4-$C_6H_5$, $R^2 = H$), 13036-50-5; **6** (het = pyrimidin-4-yl, $R^1$ = 6-$OC_3H_7$, $R^2 = H$), 83774-14-5; **6** (het = pyrimidin-4-yl, $R^1$ = 6-O-*i*-$C_3H_7$, $R^2 = H$), 83774-13-4; **6** (het = pyrimidin-4-yl, $R^1 = R^2$ = 2,6-$(OCH_3)_2$), 6320-15-6; **6** (het = pyrimidin-4-yl, $R^1$ = 6-$N(CH_3)_2$, $R^2 = H$), 31058-83-0; **6** (het = *s*-triazin-2-yl, $R^1 = R^2$ = 4,6-$(OCH_3)_2$), 3140-73-6; **6** (het = *s*-triazin-2-yl, $R^1 = R^2$ = 4,6-$(OC_6H_5)_2$), 2972-65-8; **6** (het = *s*-triazin-2-yl, $R^1 = R^2$ = 4,6-$(NH_2)_2$), 3397-62-4; **7**, 60547-97-9; **8**, 7755-92-2; **9**, 3934-20-1; **10**, 83774-24-7; **11**, 83774-15-6; **11** (4-formyl), 109467-27-8; **12**, 56392-83-7; **13**, 83774-20-3; **13**·2$C_4H_4O_4$, 83774-27-0; **14**, 109467-21-2; **14**·2HCl, 83773-87-9; **15**, 83774-07-6; **16**, 109467-22-3; **16**·HCl, 83773-96-0; **17**, 109467-23-4; **17**·HCl, 83773-99-3; **18**, 83773-65-3; **19**, 109467-26-7; **19**·2HCl, 83773-71-1; **20**, 109467-24-5; **20**·HCl, 83773-68-6; **21**, 83773-69-7; **22**, 83773-64-2; **23**, 83773-82-4; **24**, 83773-81-3; **25**, 83773-86-8; **26**, 83773-72-2; **13**·2$C_4H_4O_4$, 83774-27-0; **27**, 83773-80-2; **28**, 83774-03-2; **29**, 83773-93-7; **30**, 109467-25-6; **30**·HCl, 83773-76-6; **31**, 83773-73-3; **32**, 83773-75-5; 4-amino-6,7-dimethoxy-2-[4-(2-chloropyrimidin-4-yl)piperazin-1-yl]quinazoline, 83774-02-1.

# Effects of [(*N*-Alkyl-1,3-dioxo-1*H*,3*H*-isoindolin-5-yl)oxy]alkanoic Acids, [(*N*-Alkyl-1-oxo-1*H*,3*H*-isoindolin-5-yl)oxy]butanoic Acids, and Related Derivatives on Chloride Influx in Primary Astroglial Cultures

Steven D. Wyrick,* Forrest T. Smith, W. Evans Kemp, and Anne A. Grippo

*Division of Medicinal Chemistry and Natural Products, School of Pharmacy, University of North Carolina, Chapel Hill, North Carolina 27514.* *Received March 13, 1987*

It has been shown that agents that inhibit chloride influx and therefore lower intracellular chloride levels in a major cell type in cerebral gray matter, the astrocyte, inhibit astrocytic swelling in vitro and in vivo. In our laboratories, 4-[(*N*-alkyl-1,3-dioxo-1*H*,3*H*-isoindolin-5-yl)oxy]alkanoic acids and related derivatives have been synthesized and tested for ability to lower intracellular astrocytic chloride levels in an established in vitro cultured rat astrocyte model. In general, derivatives with nitrogen substituents such as relatively small alkyl groups are active at 0.1 mM and/or 0.5 mM levels whereas larger substituents such as cyclopentyl and cyclohexyl are less active. Halogen substitution on the aromatic ring did not enhance activity. Derivatives with acid side chains of four carbons demonstrated superior activity to those of two carbons.

It has been shown that cerebral swelling is due largely to swelling of the glial cell, the astrocyte, in the cerebral gray matter.[1] Astrocytic swelling is a consequence of increased chloride influx followed by passive influx of an osmotic equivalent of water. Loop diuretics such as ethacrynic acid and furosemide markedly inhibit the influx of chloride in both cultured rat astrocytes and those associated with intact cerebral tissue.[2,3] In addition to the increased intracranial pressure that results from such swelling, astrocytic swelling alters capillary–tissue interaction and is detrimental to capillary–tissue solute transfer since astrocytes are involved in the structure of the blood–brain barrier.[4]

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