7-(Trifluoromethyl)-4-aminoquinoline Hypotensives: Novel Peripheral Sympatholytics

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A family of 7-(trifluoromethyl)-4-aminoquinolines that are hypotensive agents and that act by a novel sympatholytic mechanism is described. Structure–activity relationships in this series have been elucidated. Some of the more potent hypotensives were evaluated for safety in the mouse. A candidate, 1-[(4-fluorophenyl)sulfonyl]-4-[4-[[7-(trifluoromethyl)-4-quinolinyl]amino]benzoyl]piperazine hydrochloride (losulazine hydrochloride) has been selected for clinical development. Losulazine hydrochloride is a hypotensive agent in the rat, cat, and dog. At acute effective hypotensive doses, it does not block the response of the sympathetic nervous system to stimuli. Both animal pharmacology and clinical experience suggest that losulazine hydrochloride may be free of the clinically limiting side effects that often plague compounds that decrease blood pressure by interfering with autonomic neurogenic function.

We have investigated the structure–activity relationships, pharmacology, and safety of a family of 7-(trifluoromethyl)-4-aminoquinolines that are hypotensive agents and that act by a novel sympatholytic mechanism. A candidate, 1-[(4-fluorophenyl)sulfonyl]-4-[4-[[7-(trifluoromethyl)-4-quinolinyl]amino]benzoyl]piperazine hydrochloride (losulazine hydrochloride, compound **3n**; see Table I) has been selected for clinical development. The cardiovascular pharmacology of losulazine in the rat, cat, and dog has been reported.[1] Both animal pharmacology and clinical experience suggest that losulazine hydrochloride may be free of the clinically limiting side effects of most peripheral sympatholytics.

Diverse biological activities have been reported for 4-aminoquinolines. For example, chloroquine, hydroxychloroquine, and amidoquine are well-known antimalarials that have 7-chloro-4-aminoquinolines as key structural features.[2-4] All of these antimalarials have a basic nitrogen in a chain that extends from the 4-amino group. Roussel-UCLAF is developing two analgesic 4-aminoquinolines, floctafenin and glafenine. Floctafenin bears an 8-trifluoromethyl group while glafenine has a 7-chloro quinoline substituent. Both compounds have a 4-amino group that is substituted by an aryl group.[5-7] In this respect, these two compounds are similar to the compounds of this paper, although their biological activites are very different.

In past work in our laboratories, 1-[4-[[7-(trifluoromethyl)-4-quinolinyl]amino]benzoyl]piperazine (**3a**)[8] was identified during random screening as an interesting hypotensive. This compound lowered blood pressure in rats but was associated with unacceptable toxicity in 90-day rat studies. Because of this, we sought a safer and more efficacious analogue of **3a**. This paper summarizes the search for such an analogue. Table I outlines the compounds that were prepared. Many of these are potent hypotensives. The chemistry, pharmacology, and safety data from this series are described below.

Chemistry. Scheme I depicts the various routes that we have followed to our 7-(trifluoromethyl)-4-aminoquinoline products. In method A, the 4-anilinoquinoline product **2** of the reaction of *p*-aminobenzoic acid and 7-(trifluoromethyl)-4-chloroquinoline[8] is a convenient starting material for a variety of amides of structure **3**. The acid was activated as the acid chloride, the imidazolide, or a mixed anhydride. In method B, compound **3a** was reacted with various reactive heterocyclic chlorides, acid chlorides, isocyanates, and sulfonyl chlorides to produce piperazines where the piperazine nitrogen is thus substituted by the various heterocyles, carbonyl, carboxamido, and sulfonyl groups that are shown in Table I. In method C, we first prepared the aniline side chain by the chemistry that is depicted in Scheme I. The starting materials for these *p*-carboxamido, *p*-sulfonamido, and *p*-aminomethyl anilines were prepared, respectively, from various secondary amines and *p*-nitrobenzoyl chloride, *p*-nitrobenzenesulfonyl chloride, or *p*-nitrobenzyl chloride. The nitro groups of the products of these reactions were reduced catalytically or by titanium trichloride and the resulting substituted anilines were reacted with 7-(trifluoromethyl)-4-chloroquinoline to yield final products of structures **3**, **4**, and **5** where W is carbonyl, sulfonyl, or methylene.

Pharmacology. The hypotensive activity, safety, and CNS side effect potential were evaluated for the 4-aminoquinolines that are described in this paper. Hypotensive activity was assessed in the conscious rat. Drug was administered orally at doses that ranged from 50 to 0.05 mg/kg. Blood pressure was measured at 0, 4, and 24 h. Blood pressure effects are expressed as change in mean arterial pressure in mmHg relative to the predrug blood pressure. The results of these tests are summarized in Table I. Not all test drugs were screened for hypotensive activity at the same dose level and ED_{50} values were not obtained. Because of this, our structure–activity relationship (SAR) conclusions are only rough. However, the apparent SAR is interesting. The hypotensive response is maintained with wide variation in the side chains of the aminoquinoline. However, certain generalizations can be made. In Table II, the series is divided into three groups. Group 1 shows the most dramatic potency and group 3 the least. Usually, the benzamides (W = carbonyl, Scheme I) where the amine function is a piperazine or piperidine are superior to the analogous sulfonamides (W = SO_2) while the analogous benzylpiperazines are only minimally active. The most active group of compounds consists of analogues

(1) Wendling, M. G.; DuCharme, D. W.; Johnson, G. A.; McCall, R. B.; Pals, D. T. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1983**, *42*, 162.
(2) Surrey, A. R.; Hammer, H. F. *J. Am. Chem. Soc.* **1946**, *68*, 113.
(3) Surrey, A. R.; Hammer, H. F. *J. Am. Chem. Soc.* **1950**, *72*, 1814.
(4) Burckhalter, J. H.; Tendick, F. H.; Jones, E. M.; Holcomb, W. F.; Rawlins, A. L. *J. Am. Chem. Soc.* **1948**, *70*, 1363.
(5) Anon., Belgian Patent 636381, 1964.
(6) Allais; et al. *Chim. Ther.* **1973**, *8*, 154.
(7) Pottier, J.; et al. *Eur. J. Drug Metab. Pharmacokinet.* **1979**, *4*, 109.
(8) Hsi, R. C. *J. Labelled Compd. Radiopharm.* **1976**, *12*, 601. McCall, J. M. U.S. Patent 4167567, 1979.
(9) Horn, H. J. *Biometrics* **1956**, *12*, 311.

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Table I. Physical Data and Hypotensive Activity [R = $CONR_2$ (3), SO_2NR_2 (4), CH_2NR_2 (5)]

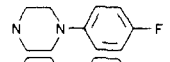
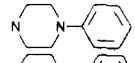
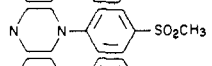
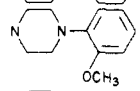
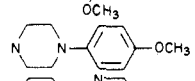
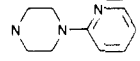
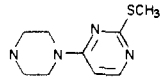
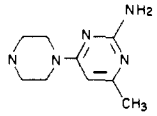
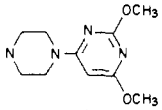
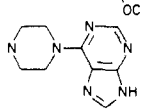
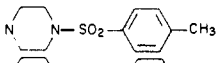
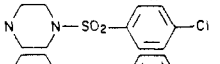
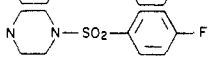
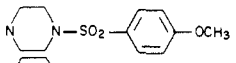
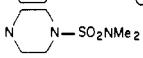
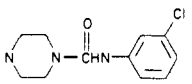
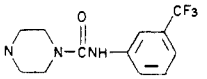
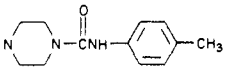
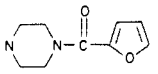
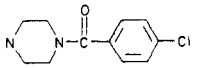
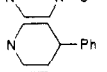
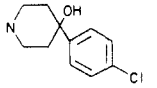
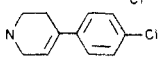
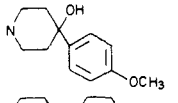
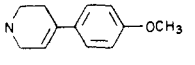
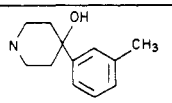
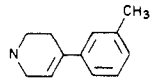
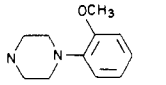
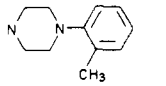
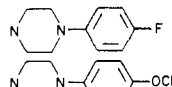
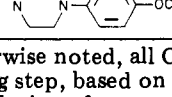
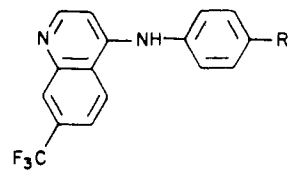
compd	NR_2	formula[a]	mp,[b] °C	method synth	yield,[d] %	ΔBP, mmHg [4 h/24 (dose)][e]
3a		ref 8				−15/−22 (50) −7/−8 (10) ia (3)
3b		$C_{27}H_{22}N_4OF_4$	213 dec[j]	C1	62	−11/−10 (5) −12/+1 (1)
3c		$C_{27}H_{23}N_4F_3O$[n]	199-201[j]	A3	30	+4/−13 (50)
3d		$C_{28}H_{25}F_3N_4O_3S$	277-278[k]	B1[n]	22	−10/−16 (5) −7/−5 (0.5)
3e		$C_{26}H_{25}F_3N_4O_2$	210-212[f]	A1	17	−13/−27 (50)
3f		$C_{28}H_{25}F_3N_4O_2$	198-199[f]	A3	31	−19/−18 (50)
3g		$C_{26}H_{22}N_5OF_3$	251-252.5	B1	73	−10/−13 (5) +2/−2 (0.5)
3h		$C_{26}H_{23}F_3N_6OS$	271-272[g]	B1	35	−8/−16 (5)
3i		$C_{26}H_{24}F_3N_7O$	283-286[g]	B1	80	−3/−4 (50)
3j		$C_{27}H_{25}F_3N_6O_3$	260-262[g]	B1	43	−13/−29 (50) −10/−24 (5) −2/−12 (0.5)
3k		$C_{27}H_{21}F_3N_8O$	>300[k]	B1	61	−4/−3 (50)
3l		$C_{26}H_{25}F_3N_4SO_3$	215-217[k]	B4	95	−42/−25 (5)
3m		$C_{27}H_{22}ClF_3N_4SO_3$	234-236[g]	B4	77	−20/−34 (5) −13/−15 (0.5)
3n		$C_{26}H_{22}F_4N_4SO_3$	251-253[g]	B4	92	−19/−25 (15) −17/−21 (1.5) −10/−15 (0.5) −12/−14 (0.15) −6/−2 (0.05)
3o		$C_{28}H_{25}F_3N_4SO_4$	221-223[g]	B4	53	−6/−3 (5)
3p		$C_{23}H_{24}F_3N_5O_3S$	223-224.5[f]	B4	88	−18/−6 (5) −6/−2 (0.5)
3q		$C_{28}H_{23}ClF_3N_5O_2$	266-268[g]	B3	90	−14/−5 (50)
3r		$C_{29}H_{23}F_6N_5O_2$[o]	198-200[k]	B3	68	−10/−8 (50)
3s		$C_{29}H_{26}F_3N_5O_2$	280-282[a]	B3	93	−3/−9 (50)
3t		$C_{26}H_{21}F_3N_4O_3$	268-269[m]	B2	93	−11/−14 (5) −8/−4 (0.5)
3u		$C_{28}H_{22}ClF_3N_4O_2$	>280[m]	B2	44	0/−16 (5) −1/+1 (0.5)
3v		$C_{28}H_{24}F_3N_3O$	232-235	A2	53	−4/−17 (50)
3w		$C_{28}H_{23}ClF_3N_3O_2$	245-247	A2	79	−19/−22 (0.5)
3x		$C_{28}H_{21}ClF_3N_3O$	225-226	A1	57	−7/−16 (5) −3/−11 (0.1)
3y		$C_{29}H_{26}F_3N_3O_3$	250-251	A2	100	−15/−5 (5)
3z		$C_{29}H_{24}F_3N_3O_2$	237-238.5	A2	46	−6/−2 (5)

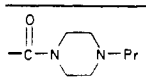
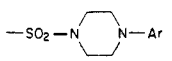
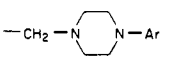
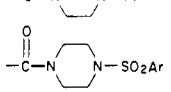
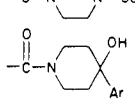
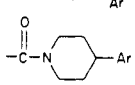
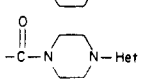
Table I (*Continued*)

compd	NR_2	formula[a]	mp,[b] °C	method synth	yield,[d] %	ΔBP, mmHg [4 h/24 (dose)][e]
3aa		$C_{29}H_{26}F_3N_3O_2$	236-238	A2	92	−10/−4 (5) −4/−1 (0.5)
3bb		$C_{29}H_{24}F_3N_3O$	233-234.5	A2	30	−8/−8 (5)
4a		$C_{27}H_{25}F_3N_4O_3S$	146-148[f]	C2	61	−1/−14 (5)
4b		$C_{27}H_{25}F_3N_4O_2S\cdot H_2O$	140-145[f]	C2	51	−10/−13 (5) −1/0 (0.5)
5a		$C_{27}H_{24}F_4N_4$	216-217[j]	C3	60	−4/−18 (50) −7/−9 (5)
5b		$C_{28}H_{27}F_3N_4O$	235-237[j]	C3	86	−5/−16 (150) +1/−1 (50)

[a] Unless otherwise noted, all C, H, and N analyses are ±0.4%. [b] In degrees centigrade. [c] See Scheme I. [d] Percent yield of product-forming step, based on isolated pure product. [e] Average change in mean arterial blood pressure in mmHg at 4 and 24 h after oral dosing of a conscious rat. Predrug pressure is 115–120 mm Hg. A change of 5 mm is significant (see Experimental Section). "ia" designates inactive. Data are presented in the form change at 4 h/change at 24 h (mg/kg dose tested). In this model, Prazosin, a standard compound, shows the following effects on blood pressure: −26/+2 (1.5), −24/+3 (0.5), −14/+1 (0.05). [f] From CH_2Cl_2/C_6H_{12}. [g] From CH_2Cl_2/CH_3OH. [h] From CH_2Cl_2. [i] From CH_3OH/EtOAc. [j] From EtOAc. [k] From CH_3OH. [l] From CH_2Cl_2/ether. [m] From CH_3OH/H_2O. [n] Calcd/found: C, 69.94/69.08; H, 4.65/5.19; N, 11.33/10.74. [o] Calcd/found: C, 66.78/66.26.

Table II. Hypotensive Structure-Activity Relationships



R substit		
group 1, best	group 2, moderate	group 3, minimal
		
		
		
		
		

3l–3p. These compounds possess a piperazine moiety with a benzoyl group at N-1 and a sulfonyl at N-4.

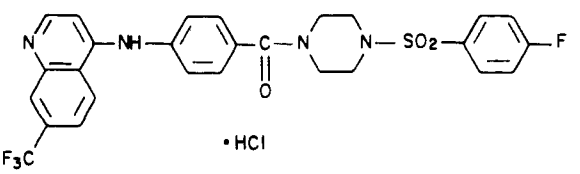
Safety. The most promising of these compounds were selected for further evaluation. The acute oral toxicity of nine potent hypotensive analogues of quinoline **3a** was determined in the mouse. Three observations—the LD_{50}, the lowest dose that was associated with untoward clinical signs (e.g., weight loss, nausea, diarrhea), and the lowest dose that caused no clinical signs—were noted. The compounds that were tested can be divided into four groups (see Table III). Group 1 contains four compounds. These are the safest analogues in a single-dose oral trial in the mouse. However, when the toxic doses of all nine trial compounds are contrasted to the amount of drug that will cause a hypotensive response, all of the test compounds have a good margin of safety in the rodent. Losulazine (**3n**)

Table III. Toxicity in Mice

group	compd[a]	LD_{50}[a,b]	clinical sign free dose[b,c]	dose/unacceptable clinical signs[b,d]
I	**3d**	3160	316	1000
	3m	>3160	<100	>3160
	3n	>3160	100	>3160
	3p	>3160	100	>3160
II	**3a**	1778	100	1000
III	**3g**	1395	<100	316
	3j	>3160	<100	<100
	3x	1000	<100	316
IV	**3w**	237	NAe	<100

[a] See Table I. [b] Milligrams/kilogram. [c] Lowest dose associated with clinical signs. [d] Lowest dose associated with unacceptable clinical signs. [e] Not acceptable.

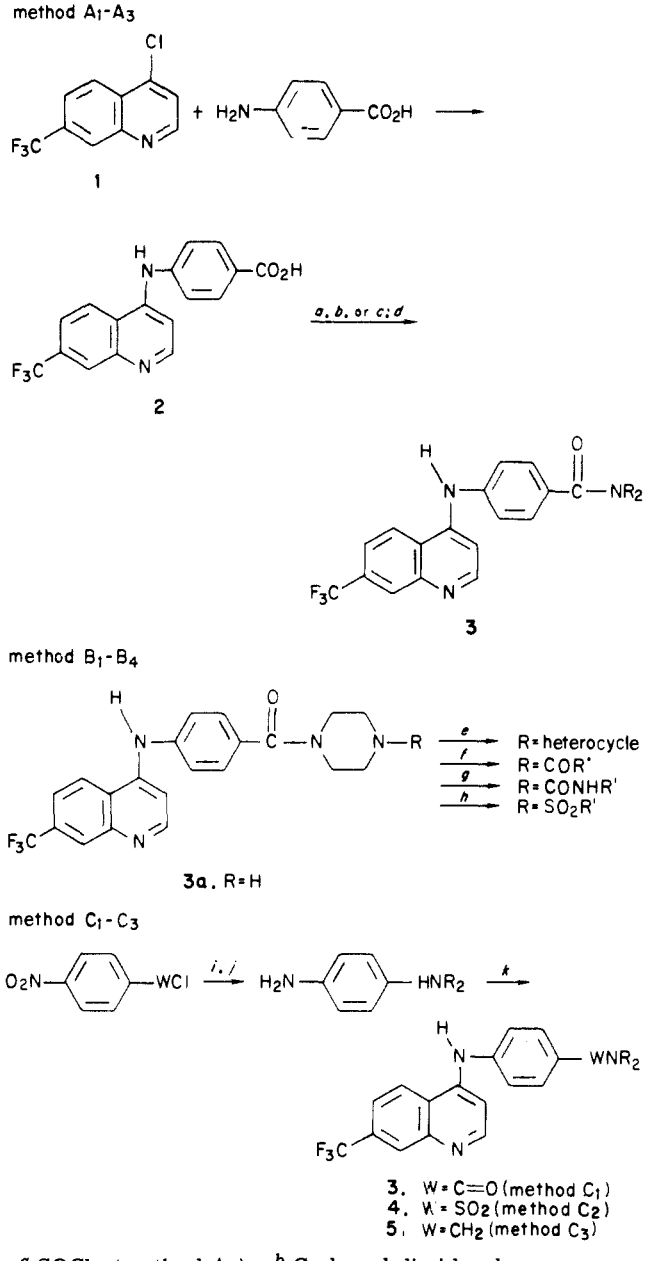
was clearly one of the safest compounds that emerged from this study. Because of this and because of its high degree of oral hypotensive activity in the rat, losulazine (active at 0.05 mg/kg) was selected for further study.



3n

Losulazine Pharmacology. The pharmacologic evaluation of losulazine has been reported.[1] Losulazine promotes a dose-related hypotensive response in conscious, spontaneously hypertensive and normotensive rats and in supine conscious monkeys (1–10 mg/kg in monkey). The drug was associated with dose-related decreases in norepinephrine levels in plasma and in cardiac and splenic tissue, whereas brain norepinephrine was unaltered. Although losulazine attenuated the vascular responses from electrical stimulation of sympathetic nerves, it did not impair the ability of monkeys to withstand orthostatic stress nor did it block the contraction of the nictitating

Scheme I. Methods of Synthesis



[a] $SOCl_2$ (method A_1). [b] Carbonyl dimidazole (method A_2). [c] $ClCO_2Et$/triethylamine (method A_3). [d] HNR_2. [e] Chloro-substituted heterocycle/EtOH (method B_1). [f] R'COCl (method B_2). [g] R'NCO (method B_3). [h] $R'SO_2Cl$ (method B_4). [i] Compound HNR_2. [j] $TiCl_3$ or H_2/PtO_2. [k] Compound 1/EtOH.

membrane after sympathetic stimulation in the cat. Also, the drug does not inhibit sympathetic nervous discharge from the CNS of the anesthetized cat. Thus, losulazine apparently alters peripheral sympathetic neurogenic function but does not act centrally. The drug is not associated with an orthostatic liability at hypotensive doses in the monkey.

Conclusion. We have prepared a group of 4-aminoquinoline hypotensives. One compound, losulazine, lowers blood pressure by a peripheral sympatholytic mechanism. We assume that its close analogues act by a similar mechanism. Losulazine is being evaluated clinically.

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus (capillary method) and are uncorrected. NMR spectra were recorded on a Varian HFT-80 instrument and are consistent with assigned structure. Medium-pressure liquid chromatographies were run on EM silica gel 60 silica gel. Table I denotes the procedures by which the final analogues of each method were prepared (see also Scheme I). Table I also gives the yields of the last step in the method and the melting points of the final products. Examples of the methods that are described in Scheme I are given below.

4-(4-Chlorophenyl)-1,2,3,6-tetrahydro-1-[4-[[7-(trifluoromethyl)-4-quinolinyl]amino]benzoyl]pyridine (3x). Method A1. A mixture of 3.90 g of 4-[[7-(trifluoromethyl)-4-quinolinyl]amino]benzoic acid and 15 mL of thionyl chloride was refluxed for 4.5 h. The mixture was concentrated, the residue was dissolved in 100 mL of pyridine, and 4.0 g of 4-(4-chlorophenyl)-1,2,5,6-tetrahydropyridine was added. The reaction was stirred overnight and then partitioned between chloroform and aqueous sodium carbonate. The organic phase was dried and concentrated. The residue was crystallized from methylene chloride. The crystalls were filtered and washed with ether; first crop, 2.99 g (57%), mp 225–226 °C (premelt at 188–189 °C and resolidified). Anal. ($C_{28}H_{21}N_3ClF_3O$) C, H, N.

4-(4-Chlorophenyl)-1-[4-[[7-(trifluoromethyl)-4-quinolinyl]amino]benzoyl]piperidinol (3w). Method A2. A solution of 2.10 g (5.69 mmol) of 4-[[7-(trifluoromethyl)-4-quinolyl]amino]benzoic acid hydrochloride in 15 mL of dry DMF was stirred under nitrogen with 0.92 g (5.69 mmol) of carbonyldiimidazole for 1 h. To this solution was added 1.00 g (4.74 mmol) of 4-(4-chlorophenyl)-4-piperidinol. The reaction was stirred for 20 h and then partitioned with methylene chloride and aqueous sodium bicarbonate. The organic phase was dried over sodium sulfate and concentrated. The product was crystallized from 5% methanol/methylene chloride to yield 1.65-g first crop, mp 245–247 °C, and a 330-mg second crop. Anal. ($C_{26}H_{23}N_3O_2ClF_3$) C, H, N, Cl.

1-Phenyl-4-[*p*-[[7-(trifluoromethyl)-4-quinolyl]amino]benzoyl]piperazine (3c). Method A3. Equimolar amounts of 4-chloro-7-(trifluoromethyl)quinoline and 4-aminobenzoic acid were refluxed in ethanol for 4 h to yield 4-[[7-(trifluoromethyl)-4-quinolinyl]amino]benzoic acid hydrochloride (2). A mixture of 2.00 g (5.43 mmol) of 4-[[7-(trifluoromethyl)-4-quinolinyl]amino]benzoic acid hydrochloride (2), 4 mL of triethylamine, and 0.56 mL (10.8 mmol) of ethyl chloroformate in 100 mL of chloroform was stirred at 0 °C for 3 h. To this solution were added 1.92 g of 1-phenylpiperazine dihydrochloride and 1.0 mL of triethylamine. The mixture was stirred for 2.5 h at room temperature. The mixture was partitioned with 1 N sodium hydroxide. The organic phase was dried over sodium sulfate and concentrated. The residue was chromatographed on silica gel (3% methanol, $^1/_2$% ammonium hydroxide in methylene chloride). The product was crystallized from hot ethyl acetate to yield 600 mg (22%) of product, mp 199–201 °C. In addition, 770 mg (25%) of the adduct of ethyl chloroformate and *N*-phenylpiperazine was isolated. Anal. ($C_{27}H_{23}N_4F_3O$) C, H, N.

1-(2-Amino-6-methyl-4-pyrimidinyl)-4-[4-[[7-(trifluoromethyl)-4-quinolinyl]amino]benzoyl]piperazine (3i). Method B1. A mixture of 4.00 g (10 mmol) of compound **3a**,[8] 1.43 g (10 mmol) of 2-amino-4-chloro-6-methylpyrimidine, 1.39 mL (100 mmol) of triethylamine, and 125 mL of ethylene glycol was stirred at 100 °C for 5 h. The reaction mixture was stirred overnight at room temperature. The mixture was then partitioned between methylene chloride and aqueous sodium carbonate. The organic phase was dried over sodium sulfate and concentrated. The residue was crystallized from methanol/methylene chloride to yield 4.06 g (80%) of product, mp 283–286 °C. Anal. ($C_{26}H_{24}F_3N_7O$) C, H, N.

1-(2-Furylcarbonyl)-4-[4-[[7-(trifluoromethyl)-4-quinolinyl]amino]benzoyl]piperazine (3t). Method B2. A solution of 0.4 g (3.05 mmol) of 2-furoyl chloride in 5 mL of dry methylene chloride was added to a solution of 1.0 g (2.5 mmol) of compound **3a** in 50 mL of pyridine at 0–10 °C. The mixture was stirred at 0 °C for 45 min and at room temperature for 20 h. The reaction was concentrated in vacuo. The residue was partitioned between 1 N sodium hydroxide and methylene chloride. The organic phase was dried over sodium sulfate and concentrated. The residue was crystallized from alcohol/water to yield 1.15 g (93%) of compound 3t, mp 268–269 °C. Anal. ($C_{26}H_{21}N_4O_3$) C, H, N.

1-[[(4-Methylphenyl)amino]carbonyl]-4-[4-[[7-(trifluoromethyl)-4-quinolinyl]amino]benzoyl]piperazine (3s). Method B3. To a suspension of 2.00 g of compound **3a** in 15 mL of methylene chloride was added dropwise a solution of 1.2 equiv of *p*-tolyl isocyanate in 10 mL of methylene chloride under nitrogen at room temperature. The resulting suspension was stirred for 2 h. The white solid was then filtered and washed with methylene chloride. The solid was recrystallized from methanol/methylene chloride to yield 2.5 g (93%) of product **3d**, mp 280–282 °C. Anal. ($C_{29}H_{26}F_3N_5O_2$) C, H, N, F.

1-[(4-Fluorophenyl)sulfonyl]-4-[4-[[7-(trifluoromethyl)-4-quinolinyl]amino]benzoyl]piperazine (3n). Method B4. To a suspension of 2.0 g (5.0 mmol) of compound **3a** and 0.5 g of triethylamine in 30 mL of tetrahydrofuran was added dropwise a solution of 0.97 g (5.0 mmol) of *p*-fluorobenzenesulfonyl chloride in 10 mL of tetrahydrofuran. The mixture was stirred for 1 h. The insoluble white product was filtered and washed with tetrahydrofuran. The residue was crystallized from methanol and methylene chloride to give 2.5 g (92%) of product **3n**, mp 251–253 °C. Anal. ($C_{26}H_{22}F_4N_4SO_3$) C, H, N, F, S.

1-(4-Fluorophenyl)-4-[4-[[7-(trifluoromethyl)-4-quinolinyl]amino]benzoyl]piperazine (3b). Method C1. To a mixture of 17 g (0.169 mol) of triethylamine and 25.43 g (0.141 mol) of 1-(4-fluorophenyl)piperazine in 340 mL of methylene chloride was added a methylene chloride solution of 31.43 g (0.169 mol) of *p*-nitrobenzoyl chloride. The mixture was stirred under nitrogen for 17 h and then was partitioned between methylene chloride and 1 N sodium hydroxide. The organic phase was filtered through sodium sulfate, concentrated, and recrystallized from hot ethyl acetate and cyclohexane to yield a 43.9-g first crop. This was dissolved in 300 mL of ether. An aqueous solution of titanium trichloride was added until the purple color no longer was discharged. The reaction mixture was partitioned between ether and ammonium hydroxide. The organic phase was washed with aqueous potassium carbonate, dried over sodium sulfate, and concentrated. The residue was chromatographed on silica gel (4% methanol in methylene chloride). The product was crystallized from ethyl acetate and cyclohexane to yield 17.49 g of 1-(4-aminobenzoyl)-4-(4-fluorophenyl)piperazine. Anal. ($C_{17}H_{18}FN_3O$) C, H, N.

A mixture of 3.10 g (13.4 mmol) of 4-chloro-7-(trifluoromethyl)quinoline, 4.00 g (13.4 mmol) of this 1-(4-fluorophenyl)-4-(4-aminobenzoyl)piperazine, and 4.46 mL (13.4 mmol) of concentrated HCl was heated at 100 °C in 40 mL of ethylene glycol for 24 h. The mixture was partitioned between methylene chloride and 1 N potassium hydroxide. The organic phase was dried over sodium sulfate and concentrated. The residue was triturated with boiling ethyl acetate to yield 4.12 g (62%) of product **3b**, 213 °C dec. Anal. ($C_{21}H_{22}F_4N_4O$) C, H, N.

1-(2-Methoxyphenyl)-4-[[4-[[7-(trifluoromethyl)-4-quinolinyl]amino]phenyl]sulfonyl]piperazine (4a). Method C2. 1-[(4-Aminophenyl)sulfonyl]-4-(2-methoxyphenyl)piperazine was prepared in a manner that is analogous with method C1. Thus, *p*-nitrobenzenesulfonyl chloride was reacted with 4-(2-methoxyphenyl)piperazine. The sulfonamide product was reduced with hydrogen over platinum oxide in chloroform and the product was crystallized from methanol/methylene chloride, mp 230–232 °C. To 1.73 g (4.98 mmol) of 1-[(4-aminophenyl)sulfonyl]-4-(2-methoxyphenyl)piperazine in 150 mL of ethanol was added 0.35 mL (4.88 mmol) of acetyl chloride in ethanol. The mixture was stirred for 10 min. Then, 1.15 g (4.97 mmol) of 4-chloro-7-(trifluorometnyl)quinoline was added. The mixture was refluxed for 3 h and was then stirred overnight at room temperature. The reaction mixture was concentrated. The residue was partitioned between methylene chloride and aqueous sodium bicarbonate. The organic phase was dried over sodium sulfate and concentrated. The residue was chromatographed over silica gel with methylene chloride. The product was crystallized from methylene chloride/hexane to yield 1.61 g (61%), mp 146–148 °C. Anal. ($C_{26}H_{22}N_4F_4SO_2 \cdot CH_3OH$).

4-[[4-[[4-(4-Fluorophenyl)piperazinyl]methyl]phenyl]amino]-7-(trifluoromethyl)quinoline (5a). Method C3. 1-[(4-Aminophenyl)methyl]-4-(4-fluorophenyl)piperazine was prepared in a manner that is analogous with method C1. Thus, *p*-nitorbenzoyl chloride was reacted with 1-(*p*-fluorophenyl)-piperazine. The product was reduced with titanium trichloride and the anilino product was crystallized from ethyl acetate and hexane, mp 130–132 °C. A solution of 762 mg (3.5 mmol) of 4-chloro-7-(trifluoromethyl)quinoline and 1 g (3.5 mmol) of 1-[(4-aminophenyl)methyl]-4-(4-fluorophenyl)piperazine with 1 equiv of HCl in 20 mL of ethanol was refluxed under nitrogen for 3 h. The mixture was partitioned between methylene chloride and aqueous sodium carbonate. The organic phase was washed with water, dried over sodium sulfate, and concentrated. The residue was crystallized from ethyl acetate to yield 1.0 g (60%) of **5a**, mp 216–217 °C. Anal. ($C_{27}H_{24}F_4N$) C, H, N, F.

Hypotensive Activity in Conscious Rat. The blood pressure of restrained conscious female Sprague–Dawley rats was measured directly from chronic indwelling aortic cannulas exteriorized from the nape of the neck. In order to obtain a high level of sympathetic tone, rats were restrained in a towel during the period of blood pressure measurement via a Statham transducer (P23G) and a Grass Model 5 polygraph.[5] Measurements were made before, as well as 4 and 24 h after, the oral administration of each compound suspended in a (carboxymethyl)cellulose vehicle at 10 mL/kg. Blood pressure values of two animals were averaged at each of the three measuremeht times. An average change of at least 5 mmHg was required posttreatment for statistical significance ($p < 0.05$) to be attained.

Toxicity in Mice. A single oral dose of each drug was administered to five groups of mice (two males and two females per group) at doses of 0, 100, 316, 1000, and 3160 mg/kg. The drugs were suspended in 0.25% methylcellulose. Mice were observed daily for 14 days following drug administration. LD_{50} values were calculated by the method of Horn.[9] The LD_{50} results are summarized in Table III.

Acknowledgment. We are indebted to Michael G. Wendling and John E. Rogers, who collected the hypotensive data in the conscious rat; to Lubomir Baczynskyj and James R. Boal, who ran and interpreted mass spectra; and to Upjohn's Physical and Analytical Chemistry Department for elemental analyses and IR spectroscopy.

Registry No. **1**, 346-55-4; **2**, 71916-45-5; **2**·HCl, 57975-84-5; **3a**, 72141-43-6; **3b**, 98859-09-7; **3c**, 98859-10-0; **3d**, 98859-11-1; **3e**, 98859-12-2; **3f**, 98874-76-1; **3g**, 72141-45-8; **3h**, 72141-50-5; **3i**, 72141-48-1; **3j**, 72141-49-2; **3k**, 98859-13-3; **3l**, 72141-55-0; **3m**, 72141-56-1; **3n**, 72141-57-2; **3o**, 72141-58-3; **3p**, 72141-54-9; **3q**, 72141-59-4; **3r**, 72141-61-8; **3s**, 72141-62-9; **3t**, 98859-14-4; **3u**, 98859-15-5; **3v**, 71916-53-5; **3w**, 71916-54-6; **3x**, 71916-44-4; **3y**, 71916-55-7; **3z**, 71916-59-1; **3aa**, 71916-56-8; **3bb**, 71916-51-3; **4a**, 71422-38-3; **4b**, 71422-41-8; **5a**, 70261-71-1; **5b**, 70261-72-2; 4-$H_2NC_6H_4CO_2H$, 150-13-0; *p*-$H_3CC_6H_4NCO$, 622-58-2; *p*-$FC_6H_4SO_2Cl$, 349-88-2; *p*-$O_2NC_6H_4COCl$, 122-04-3; *p*-$O_2NC_6H_4SO_2Cl$, 98-74-8; *p*-$H_3CC_6H_4SO_2Cl$, 98-59-9; *p*-$ClC_6H_4SO_2Cl$, 98-60-2; *p*-$H_3COC_6H_4SO_2Cl$, 98-68-0; Me_2NSO_2Cl, 13360-57-1; *m*-ClC_6H_4NCO, 2909-38-8; *m*-$F_3CC_6H_4NCO$, 329-01-1; *p*-ClC_6H_4COCl, 122-01-0; *p*-$H_3CSO_2C_6H_4Cl$, 15481-45-5; 4-(4-chlorophenyl)-1,2,5,6-tetrahydropyridine, 30005-58-4; 4-(4-chlorophenyl)-4-piperidinol, 39512-49-7; 1-phenylpiperazine dihydrochloride, 4004-95-9; 2-amino-4-chloro-6-methylpyrimidine, 5600-21-5; 2-furoyl chloride, 527-69-5; 1-(4-fluorophenyl)piperazine, 2252-63-3; 1-(4-aminobenzoyl)-4-(4-fluorophenyl)piperazine, 98859-16-6; 4-(2-methoxyphenyl)piperazine, 35386-24-4; 1-[(4-nitrophenyl)sulfonyl]-4-(2-methoxyphenyl)piperazine, 71422-91-8; 2-methoxyphenyl)piperazine, 71454-13-2; 1-(4-chlorophenyl)-piperazine, 38212-33-8; 1-[(4-aminophenyl)methyl]-4-(4-fluorophenyl)piperazine, 70261-76-6; 1-(2-methoxyphenyl)piperazine, 35386-24-4; 1-(4-methoxyphenyl)piperazine, 38212-30-5; 2-chloropyridine, 109-09-1; 2-(methylthio)-4-chloropyrimidine, 49844-90-8; 2,6-dimethoxy-4-chloropyrimidine, 6320-15-6; 6-chloro-9*H*-purine, 87-42-3; 4-(4-methoxyphenyl)-4-piperidinol, 50329-87-8; 4-(4-methoxyphenyl)-1,2,5,6-tetrahydropiperidine, 59954-73-3; 4-(3-methylphenyl)-4-piperidinol, 71916-57-9; 4-(3-methylphenyl)-1,2,5,6-tetrahydropyridine, 71916-52-4.