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# Studies on Positive Inotropic Agents. VI.[1] Synthesis of 1-Aromatic Ring Substituted 4-(3,4-Dimethoxybenzoyl)-piperazine Derivatives

HIDENORI OGAWA,* SHIGEHARU TAMADA, TAKAFUMI FUJIOKA, SHUJI TERAMOTO, KAZUMI KONDO, SHUJI YAMASHITA, YOUICHI YABUUCHI, MICHIAKI TOMINAGA, and KAZUYUKI NAKAGAWA

*Tokushima Research Institute, Otsuka Pharmaceutical Co., Ltd., Kagasuno 463–10, Kawauchi-cho, Tokushima-shi 771–01, Japan*

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A series of 1-aromatic ring substituted 4-(3,4-dimethoxybenzoyl)piperazines were synthesized and examined for positive inotropic activity on the canine heart. Among them, 6-[4-(3,4-dimethoxybenzoyl)-1-piperazinyl]-3-methyl-1*H*,3*H*-quinazolin-2,4-dione was found to have a potent activity.

**Keywords**——positive inotropic activity; congestive heart failure; 6-[4-(3,4-dimethoxybenzoyl)-1-piperazinyl]-3-methyl-1*H*,3*H*-quinazoline-2,4-dione; biological activity; hydrazine hydrate–Raney nickel; 1-aromatic ring substituted 4-(3,4-dimethoxybenzoyl)piperazine derivative

We have been searching for compounds having potent positive inotropic activity with little chronotropic effect for the treatment of congestive heart failure. At the outset of our studies, 3,4-dihydro-6-[4-(3,4-dimethoxybenzoyl)-1-piperazinyl]-2(1*H*)-quinolinone (I)[2] appeared to be the most promising agent with desirable biological activities.[3]

This judgement led us to investigate this molecule as a source of novel positive inotropic drugs. Therefore, we synthesized 4-(3,4-dimethoxybenzoyl)piperazines which were substituted lactam heterocyclic analogues of 2(1*H*)-quinolinone and examined their effects on the canine heart. Herein, we report the synthesis and the biological activities of these lactam analogues.

## Chemistry

Most analogues of I were efficiently synthesized from a nitro aldehyde intermediate (IV) which was readily available in two steps as shown in Chart 1. Treatment of the chloride (II)[4] with excess piperazine in dimethylformamide (DMF) followed by hydrolysis of the acetal with concentrated hydrochloric acid (HCl) gave the aldehyde (III). Acylation of III with 3,4-dimethoxybenzoyl chloride in the presence of triethylamine ($Et_3N$) in DMF afforded the nitro-aldehyde (IV) in 73% yield. Reduction of IV with sodium borohydride ($NaBH_4$) in methanol (MeOH) afforded the benzyl alcohol, which was converted to the corresponding amino-alcohol (V) by reduction with hydrazine hydrate ($N_2H_4 \cdot H_2O$)–Raney nickel[5] in MeOH. Treatment of V with potassium ethyl xanthate in refluxing 90% ethanol (EtOH) gave a mixture of the benzothiazine (VIa) and the benzoxazine (VIb),[6] which were readily separated by column chromatography over silica gel. Condensation of V with trichloroacetyl chloride in aqueous dichloromethane ($CH_2Cl_2$) in the presence of potassium carbonate provided the benzoxazine (VIc)[7] in 41% yield.

Oxidation of IV with potassium permanganate in acetone gave the acid (VII) in 63% yield. Reduction of VII with $N_2H_4 \cdot H_2O$–Raney nickel, followed by esterification with diazomethane gave the ester (VIII) in 54% yield. Treatment of VIII with potassium isocyanate

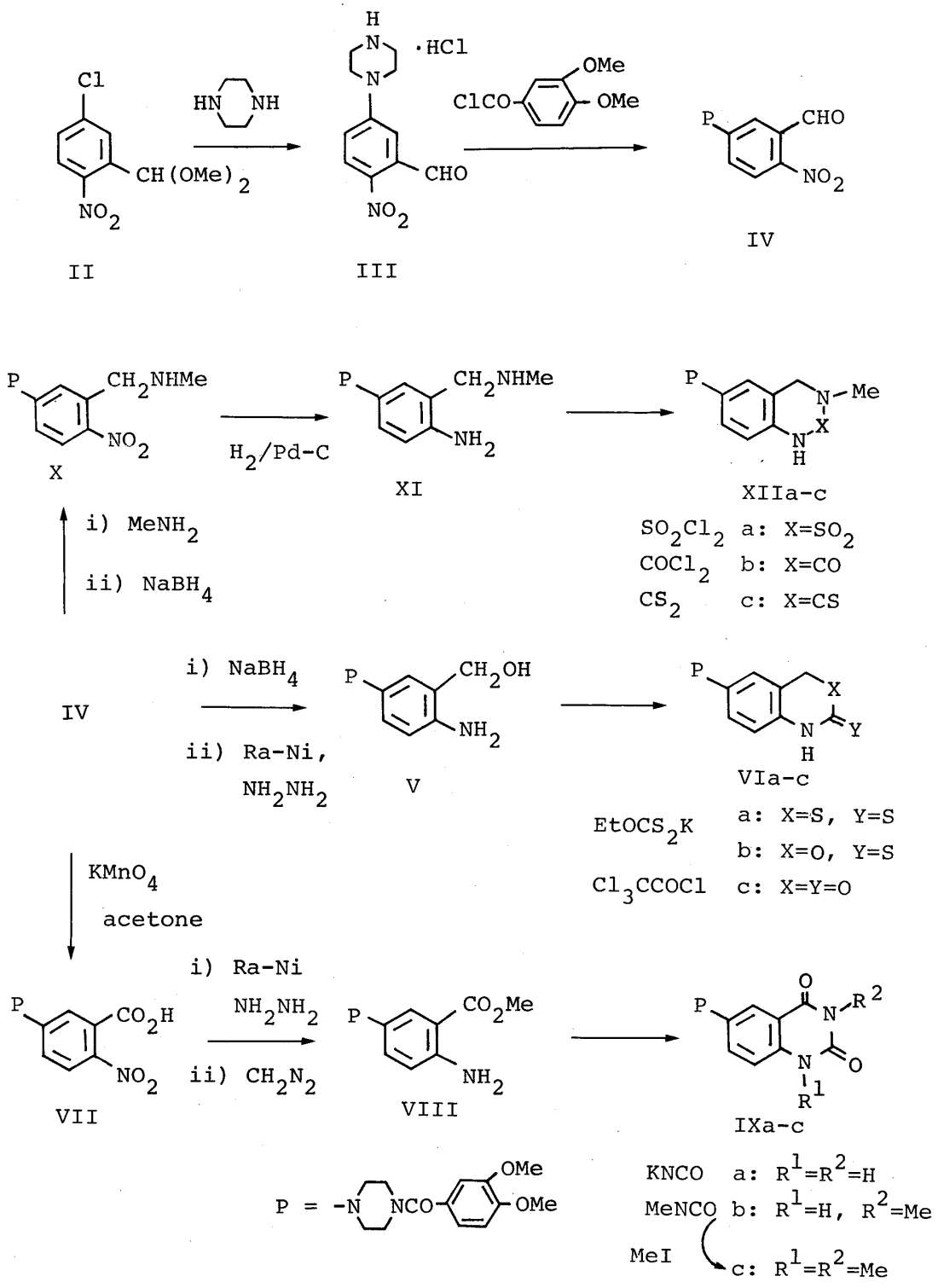



Chart 1

(KNCO) in water, followed by heating of the urea intermediate in the presence of sodium methoxide in MeOH provided the quinazoline-2,4-dione (IXa). Compound IXb, the 3-methyl analogue of IXa, was obtained in a similar fashion from VIII by the reaction with methyl isocyanate in place of KNCO. The 1,3-dimethyl analogue (IXc) was prepared from IXb by the reaction with methyl iodide in the presence of sodium hydride in DMF.

The nitroamine (X) was obtained from IV by the standard reductive amination with

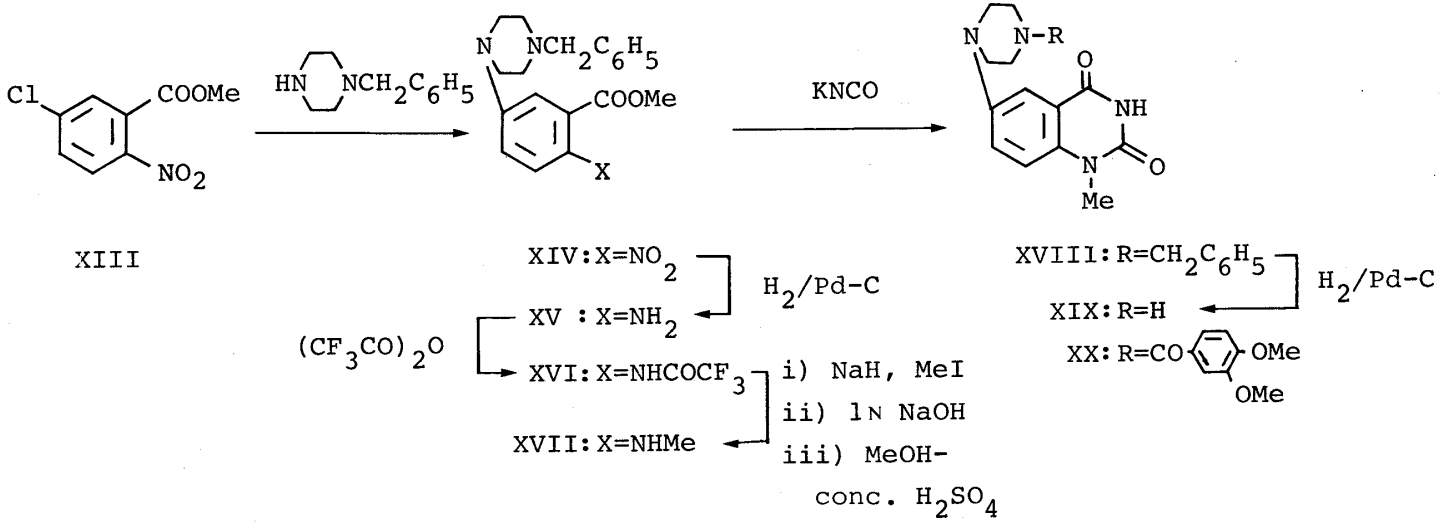



Chart 2

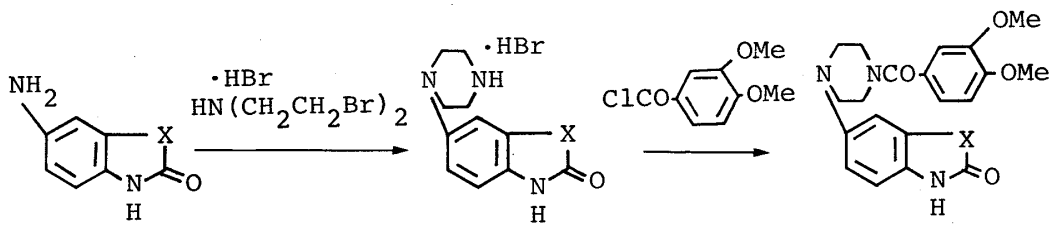
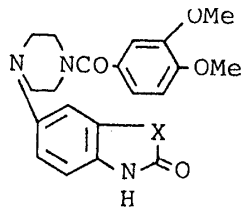



Chart 3

TABLE I. 1-Aromatic Ring Substituted 4-(3,4-Dimethoxybenzoyl)piperazines



XXIII

| Compd. No. | –X– | Yield (%) | mp (°C) (Recrystn. solv.) | Formula | Analysis (%) Calcd (Found) | | |
|---|---|---|---|---|---|---|---|
| | | | | | C | H | N |
| XXIIIa | $CH_2$ | 12 | 197—199 (dec.) (MeOH) | $C_{21}H_{23}N_3O_4$ | 66.12 (66.08 | 6.08 5.99 | 11.02 11.00) |
| XXIIIb | S | 18 | 200—202 (EtOH–$CHCl_3$) | $C_{20}H_{21}N_3O_4S$ | 60.14 (60.31 | 5.30 5.22 | 10.52 10.51) |

methylamine and $NaBH_4$. Catalytic hydrogenation of X using 5% palladium on charcoal (Pd–C) in EtOH afforded the diamine (XI). Condensation of XI with sulfuryl chloride in the presence of $Et_3N$ provided the benzothiazine-2,2-dioxide (XIIa).[8] Similarly, condensation of XI with phosgene gave the quinazolinone (XIIb). Reaction of XI with carbon disulfide gave the quinazoline-2-thione (XIIc) in 63% yield.

The 1-methyl quinazoline derivative (XX) was synthesized from the ester (XIII)[9] as outlined in Chart 2. Treatment of XIII with 1-benzylpiperazine in DMF gave compound XIV in 55% yield. The trifluoroacetylamino ester (XVI) was prepared from XIV *via* hydrogenation followed by treatment with trifluoroacetic anhydride in $CH_2Cl_2$. Methylation of XVI and hydrolysis with 1 N sodium hydroxide, followed by esterification of the carboxylic acid, provided the methylamino ester (XVII) in 41% yield. Compound XVII was transformed into the quinazoline (XVIII) by the ring-construction sequence as described for the synthesis of IXa. Conversion of XVIII to the desired XX was accomplished by hydrogenolysis over 10% Pd–C followed by acylation with 3,4-dimethoxybenzoyl chloride as described for the synthesis of IV.

Two additional analogues of I were also prepared (Chart 3). Treatment of the amine (XXIa, b)[10] with bis(2-bromoethyl)amine hydrobromide[11] in refluxing EtOH, followed by the addition of sodium carbonate and further heating, gave piperazines[12] (XXIIa, b). Derivatives of 4-(3,4-dimethoxybenzoyl)piperazines (XXIIIa, b) were obtained from XXIIa, b in the usual manner by using 3,4-dimethoxybenzoyl chloride (Table I).

**Biological Activity**

The results of the *in vitro* screening tests for activity on the myocardial contractility and heart rate are shown in Table II. The inotropic and chronotropic effects of the 1-aromatic ring substituted 4-(3,4-dimethoxybenzoyl)piperazine derivatives were compared with those of amrinone (5-amino-[3,4′-bipyridin]-6(1*H*)-one).[13]

Examination of the biological data reveals the structural requirements for activity within this series. As regards the myocardial contractility, the five-membered lactam analogues (XXIIIa, b) were substantially less potent. Among the six-membered lactam analogues, quinazolines (IXb, c, XIIb, c) were much more potent than the parent compound I,[2] whereas the oxazines (VIb, c) and the thiazine (VIa) were less potent. The effects of the methyl substituent on quinazoline-2,4-diones were examined. The 1,3-dimethyl analogue IXc and the 1-methyl analogue (XX) were less potent than the 3-methyl analogue (IXb), and XX was more potent than IXa. In general, however, alkylation of the amide nitrogen at the 1-position tends

TABLE II. Biological Activity of Aroyl Piperazine Derivatives on the Canine Heart

| Compd. No. | Inotropic effect[a)] | Chronotropic effect[a)] |
|---|---|---|
| VIa | 0.4 | 0.5 |
| VIb | 0.6 | LE |
| VIc | 0.7 | 0.5 |
| IXa | 0.8 | 0.2 |
| IXb | 7.9 | 0.8 |
| IXc | 2.3 | 0.3 |
| XIIa | LE | LE |
| XIIb | 2.9 | 3.1 |
| XIIc | 3.6 | 0.8 |
| XX | 1.5 | 0.2 |
| XXIIIa | 0.2 | LE |
| XXIIIb | 0.3 | LE |

*a*) The potency of inotropic and chronotropic effects of the test compounds was evaluated at doses (ED 50%) producing the half-maximal response to amrinone as follows. Activity ratio of test compound = ED 50% of amrinone/dose of test compound producing the same response as ED 50% of amrinone. The larger the activity ratio, the more potent is the test drug. The highest dose (1 $\mu$mol) of amrinone used in these experiments increased developed tension by about 50% of the basal tension, and increased sinus rate by about 15 beats/min. LE means lower than 0.1 activity ratio.

to decrease activity. The presence of an acidic hydrogen in the heteroaromatic ring is required for maximum potency.[2,14] The thiones (VIb, XIIc) retained most of the activity of the corresponding carbonyl compounds VIc and XIIb respectively, whereas the sulfone (XIIa) was practically inactive.

Among the compounds synthesized, IXa was found to have the most potent positive inotropic activity with a relatively minor increase in heart rate.

## Experimental

All melting points are uncorrected. Infrared (IR) spectra were recorded on a JASCO IRA-2 spectrometer. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian EM-390, Bruker WH-400 or Bruker AC-200 NMR spectrometer using tetramethylsilane or 3-(trimethylsilyl)propionic acid-$d_5$ as an internal standard. Mass spectra (MS) were obtained on a Shimadzu QP-1000 instrument.

**1-(3-Formyl-4-nitrophenyl)piperazine Hydrochloride (III)**——A mixture of 5-chloro-2-nitrobenzaldehyde dimethyl acetal (II, 41 g, 0.18 mol), anhydrous piperazine (83 g, 0.96 mol), and DMF (250 ml) was stirred at 80 °C for 4 h. After concentration, the residue was poured into 0.5 N NaOH solution, and extracted with $CH_2Cl_2$. The $CH_2Cl_2$ layer was washed with water, dried ($Na_2SO_4$) and concentrated *in vacuo*. A mixture of concentrated HCl (22 ml) and isopropyl alcohol (280 ml) was added to the residue, and the mixture was refluxed for 1 h, then allowed to cool. The precipitates were collected by filtration. Recrystallization from MeOH–$H_2O$ gave III (31 g, 63%) as yellow needles, mp 205—208 °C (dec.). IR (KBr): 1700, 1585, 1325 $cm^{-1}$. NMR (DMSO-$d_6$) $\delta$: 3.06—3.35, 3.57—3.90 (total 8H, m), 7.15 (1H, d, $J$=2.8 Hz), 7.28 (1H, dd, $J$=2.8, 9.4 Hz), 8.12 (1H, d, $J$=9.4 Hz), 9.26 (2H, br s), 10.33 (1H, s). *Anal.* Calcd for $C_{11}H_{13}N_3O_3 \cdot HCl$: C, 48.62; H, 5.19; N, 15.47. Found: C, 48.37; H, 5.20; N, 15.32.

**Preparation of IV, XX and XXIIIa, b. 1-(3,4-Dimethoxybenzoyl)-4-(3-formyl-4-nitrophenyl)piperazine (IV)**——A solution of 3,4-dimethoxybenzoyl chloride (4.4 g, 20 mmol) in DMF (20 ml) was added dropwise to a mixture of III (5 g, 18 mmol), $Et_3N$ (6 ml, 43 mmol) and DMF (50 ml) with stirring at 0—5 °C. The mixture was stirred at room temperature for 2 h, and then poured into saline and $CH_2Cl_2$. The organic layer was washed with water, dried ($Na_2SO_4$) and evaporated. The residue was recrystallized from $CHCl_3$–$Et_2O$ to give IV (5.4 g, 73%) as yellow prisms, mp 196—198 °C. IR (KBr): 1700, 1625, 1250 $cm^{-1}$. NMR ($CDCl_3$) $\delta$: 3.32—4.11 (8H, m), 3.92, 3.93 (each 3H, s), 6.89 (1H, d, $J$=8.8 Hz), 6.91—7.11 (3H, m), 7.16 (1H, d, $J$=2.8 Hz), 8.14 (1H, d, $J$=9.2 Hz), 10.52 (1H, s). *Anal.* Calcd for $C_{20}H_{21}N_3O_6$: C, 60.14; H, 5.30; N, 10.52. Found: C, 59.88; H, 5.35; N, 10.44.

Compounds XX and XXIIIa, b were prepared in the same manner as described for IV. The yields, melting points, and elemental analysis data of compounds XXIIIa, b are shown in Table I.

Compound XX was obtained in 60% yield as colorless needles, mp 230—233 °C (dec.) MeOH–$CHCl_3$). *Anal.* Calcd for $C_{22}H_{24}N_4O_5 \cdot 1/2H_2O$: C, 60.96; H, 5.81; N, 12.92. Found: C, 60.67; H, 5.43; N, 12.84.

**4-(4-Amino-3-hydroxymethylphenyl)-1-(3,4-dimethoxybenzoyl)piperazine (V)**——$NaBH_4$ (1.7 g, 0.045 mol) was added portionwise to a solution of IV (15 g, 0.038 mol) in a mixed solvent of MeOH (150 ml) and $CHCl_3$ (150 ml) with stirring at 0—5 °C. The reaction mixture was stirred for 1 h at 0—5 °C, and concentrated *in vacuo*. The residue was poured into water, and the resulting precipitates were collected by filtration and washed with ether. A suspension of the residue in MeOH (100 ml) was added dropwise to a mixture of $N_2H_4 \cdot H_2O$ (9.5 g, 0.17 mol) and Raney nickel (3 g) in MeOH (100 ml) with stirring at room temperature. After 30 min, the Raney nickel was removed by filtration through a celite layer, and the filtrate was concentrated *in vacuo*. The residue was chromatographed on silica gel ($CH_2Cl_2$ : MeOH = 70 : 1) to give V (11.2 g, 79%) as a colorless viscous oil. IR (KBr): 3350, 1605, 1505 $cm^{-1}$. NMR ($CDCl_3$) $\delta$: 2.81—3.26, 3.57—4.39 (total 11H, m), 3.89, 3.90 (each 3H, s), 4.66 (2H, s), 6.54—7.13 (6H, m). *Anal.* Calcd for $C_{20}H_{25}N_3O_4$: C, 64.67; H, 6.78; N, 11.31. Found: C, 64.39; H, 6.75; N, 11.28.

**6-[4-(3,4-Dimethoxybenzoyl)-1-piperazinyl]-1,4-dihydro-2*H*-3,1-benzothiazine-2-thione (VIa) and 6-[4-(3,4-Dimethoxybenzoyl)-1-piperazinyl]-1,4-dihydro-2*H*-3,1-benzoxazine-2-thione (VIb)**——A solution of V (1.7 g, 4.6 mmol) and potassium ethyl xanthate (1.1 g, 6.9 mmol) in 90% EtOH (150 ml) was refluxed for 4 h. AcOH (0.6 ml) was added to the reaction mixture, and the whole was concentrated *in vacuo*. The residue was poured into water and extracted with $CHCl_3$. The extract was washed with water, dried ($Na_2SO_4$) and concentrated *in vacuo*, affording a mixture of VIa and VIb as a yellow oil, which was separated by column chromatography on silica gel ($CH_2Cl_2$ : MeOH = 300 : 1). The first eluted compound was recrystallized from EtOH–$CHCl_3$ to give VIa (0.4 g, 20%) as yellow needles, mp 244—247 °C. IR (KBr): 1630, 1600, 1505 $cm^{-1}$. NMR ($CDCl_3$) $\delta$: 3.02—3.37, 3.66—4.12 (total 8H, m), 3.91, 3.92 (each 3H, s), 3.97 (2H, s), 6.64—7.10 (6H, m), 9.64 (1H, br s). MS *m/z*: 429 ($M^+$), 265, 165. *Anal.* Calcd for $C_{21}H_{23}N_3O_3S_2$: C, 58.72; H, 5.40; N, 9.78. Found: C, 58.45; H, 5.51; N, 9.57. The second eluted compound was recrystallized from EtOH–$CHCl_3$ to give VIb (1.1 g, 58%) as colorless needles, mp 193—195 °C. IR (KBr): 1605, 1510, 1245 $cm^{-1}$. NMR ($CDCl_3$) $\delta$: 2.98—3.35, 3.60—4.09 (total 8H), 3.91, 3.92 (each 3H, s), 5.30 (2H, s), 6.61—7.12 (6H, m), 9.65 (1H, br s). MS *m/z*: 413 ($M^+$), 219, 165. *Anal.* Calcd for $C_{21}H_{23}N_3O_4S$: C, 61.00; H, 5.61; N, 10.16. Found: C, 60.86; H, 5.67; N, 9.93.

**6-[4-(3,4-Dimethoxybenzoyl)-1-piperazinyl]-1,4-dihydro-2*H*-3,1-benzoxazin-2-one Hydrochloride (VIc)**——A solution of trichloroacetyl chloride (1.4 g, 7.7 mmol) in $CH_2Cl_2$ (10 ml) was added dropwise to a solution of V (2 g, 5.4 mmol) and $K_2CO_3$ (3.8 g, 27 mmol) in a mixed solvent of $CH_2Cl_2$ (50 ml) and $H_2O$ (20 ml) with stirring at −5 °C. The mixture was stirred at −5 °C for 3 h, and stirred for 18 h at room temperature. The organic layer was separated, washed with water, dried ($Na_2SO_4$) and concentrated *in vacuo*. A solution of 0.1 N KOH in absolute EtOH (50 ml) was added to the residue, and the resulting solution was heated at 80 °C for 1 h. After cooling, water (100 ml) and $CHCl_3$ were added. The $CHCl_3$ layer was washed with water, dried ($Na_2SO_4$) and concentrated *in vacuo*. The residue was treated with methanolic hydrogen chloride and evaporated. The residue was recrystallized from MeOH–$H_2O$ to give VIc (1.0 g, 41%) as colorless needles, mp 173—175 °C. IR (KBr): 1720, 1630, 1265 $cm^{-1}$. NMR (DMSO-$d_6$) $\delta$: 3.17—3.50, 3.63—4.01 (total 8H, m), 3.79, 3.80 (each 3H, s), 5.27 (2H, s), 6.82—7.14, 7.25—7.49 (total 6H, m), 10.21 (1H, br s). *Anal.* Calcd for $C_{21}H_{23}N_3O_5 \cdot HCl \cdot H_2O$: C, 55.82; H, 5.79; N, 9.30. Found: C, 55.71; H, 6.03; N, 9.37.

**5-[4-(3,4-Dimethoxybenzoyl)-1-piperazinyl]-2-nitrobenzoic Acid (VII)**——A solution of $KMnO_4$ (8 g, 0.051 mol) in $H_2O$ (100 ml) was added dropwise to a solution of IV (10 g, 0.025 mol) in acetone (500 ml) with stirring at 60 °C. After 1 h, the reaction mixture was filtered through celite, and the filtrate was concentrated *in vacuo*. The residue was acidified with 1 N HCl and the resulting precipitates were collected by filtration. Recrystallization from MeOH gave VII (6.5 g, 63%) as orange prisms, mp 237—241 °C. IR (KBr): 1710, 1565, 1330 $cm^{-1}$. NMR (DMSO-$d_6$) $\delta$: 3.05—3.98 (8H, m), 3.80 (6H, s), 6.50—7.27, 7.53—7.91 (total 6H, m), 8.15 (1H, br s). *Anal.* Calcd for $C_{20}H_{21}N_3O_7$: C, 57.83; H, 5.10; N, 10.12. Found: C, 57.85; H, 5.21; N, 10.24.

**Methyl 2-Amino-5-[4-(3,4-dimethoxybenzoyl)-1-piperazinyl]benzoate (VIII)**——A solution of VII (6 g, 0.014 mol) in MeOH (60 ml) was added dropwise to a mixture of $N_2H_4 \cdot H_2O$ (6 g, 0.12 mol), Raney nickel (1 g) and MeOH (300 ml) with stirring at room temperature. After 30 min, the Raney nickel was removed by filtration through a celite layer and the filtrate was concentrated *in vacuo*. The residue was neutralized with dilute HCl, and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water, dried ($Na_2SO_4$) and concentrated *in vacuo*. The residue was dissolved in $CHCl_3$ at 0—5°C and dry ethereal diazomethane was added until a yellow color persisted. After 30 min the solvent was evaporated off, and the residue was chromatographed on silica gel ($CH_2Cl_2$ : MeOH = 50 : 1) to give VIII (3 g, 54%) as a pale yellow viscous oil. IR (neat): 3470, 3370, 1690 $cm^{-1}$. NMR ($CDCl_3$) $\delta$: 2.82—3.26, 3.95—4.26 (total 8H, m), 3.87 (3H, s), 3.91, 3.92 (each 3H, s), 5.48 (2H, br s), 6.65 (1H, d, $J$ = 8.8 Hz), 6.87 (1H, d, $J$ = 8.7 Hz), 6.89—7.14 (3H, m), 7.42 (1H, d, $J$ = 2.8 Hz). *Anal.* Calcd for $C_{21}H_{25}N_3O_5$: C, 63.15; H, 6.31; N, 10.52. Found: C, 62.87; H, 6.30; N, 10.43.

**Preparation of IXa and XVIII. 6-[4-(3,4-Dimethoxybenzoyl)-1-piperazinyl]-1*H*,3*H*-quinazoline-2,4-dione Hydrochloride (IXa)**——A solution of KNCO (0.16 g, 2.0 mmol) in water (2 ml) was added dropwise to a solution of VIII (0.8 g, 2.0 mmol) in AcOH (5 ml) with stirring at room temperature. Stirring was continued for 2 h at 60 °C, then the reaction mixture was concentrated *in vacuo*. The residue was dissolved in dry MeOH (8 ml), and NaOMe (0.11 g, 2.0 mmol) was added. The solution was stirred for 1 h at room temperature, acidified with 1 N HCl, and concentrated *in vacuo*. The residue was recrystallized from DMF to give IXa (0.16 g, 20%) as colorless needles, mp 289—293 °C. IR (KBr): 1730, 1690, 1630 $cm^{-1}$. NMR (DMSO-$d_6$) $\delta$: 2.89—3.30, 3.33—3.97 (total 8H, m), 3.78, 3.80 (each 3H, s),

6.79—7.20 (3H, m), 7.09 (1H, d, $J=9$ Hz), 7.32 (1H, d, $J=5.2$ Hz), 7.42 (1H, dd, $J=2.5$, 9 Hz), 11.06 (2H, br s). *Anal.* Calcd for $C_{21}H_{22}N_4O_5$: C, 61.45; H, 5.40; N, 13.65. Found: C, 61.26; H, 5.37; N, 13.51.

Compound XVIII was prepared in the same manner as described for IXa in 77% yield as colorless needles, mp 223—226 °C (dec.) (MeOH–$CHCl_3$). *Anal.* Calcd for $C_{20}H_{22}N_4O_2$: C, 68.55; H, 6.33; N, 15.99. Found; C, 68.68; H, 6.26; N, 15.99.

**6-[4-(3,4-Dimethoxybenzoyl)-1-piperazinyl]-3-methyl-1*H*,3*H*-quinazoline-2,4-dione (IXb)**——A solution of VIII (0.4 g, 1.0 mmol) and methyl isocyanate (0.12 g, 2.1 mmol) in acetone (20 ml) was heated at 50 °C in an autoclave for 4.5 h, and concentrated *in vacuo*. A solution of NaOEt (68 mg, 1.0 mmol) in absolute EtOH (20 ml) was added to the residue, and the mixture was stirred at 60 °C for 30 min. The reaction mixture was neutralized with 1 N HCl, and poured into ice-water. The whole was extracted with $CHCl_3$. The organic layer was washed with water, dried ($Na_2SO_4$) and evaporated. The residue was recrystallized from DMF–EtOH to give IXb (0.26 g, 60%) as colorless needles, mp 215—217 °C. IR (KBr): 1715, 1640, 1515 $cm^{-1}$. NMR (DMSO-$d_6$) $\delta$: 2.98—3.40, 3.49—3.92 (total 8H, m), 3.25 (3H, s), 3.78, 3.80 (each 3H, s), 6.91—7.25 (3H, m), 7.11 (1H, d, $J=8.9$ Hz), 7.35 (1H, d, $J=2.6$ Hz), 7.44 (1H, dd, $J=2.6$, 8.9 Hz), 11.26 (1H, s). *Anal.* Calcd for $C_{22}H_{24}N_4O_5 \cdot 1/2H_2O$: C, 60.95; H, 5.81; N, 12.93. Found: C, 60.68; H, 5.64; N, 12.75.

**6-[4-(3,4-Dimethoxybenzoyl)-1-piperazinyl]-1,3-dimethyl-1*H*,3*H*-quinazoline-2,4-dione (IXc)**——A solution of IXb (0.28 g, 0.68 mmol) in DMF (5 ml) was treated with NaH (60% dispersion in oil, 31 mg) with stirring at room temperature. After 1 h, a solution of MeI (0.1 g, 0.7 mmol) in DMF (1 ml) was added dropwise to the suspension, and the mixture was stirred at room temperature for 1.5 h, poured into ice-water and extracted with $CHCl_3$. The organic layer was washed with water, dried ($K_2CO_3$) and evaporated. The residue was recrystallized from MeCN to give IXc (0.27 g, 88%) as colorless needles, mp 240—245 °C. IR (KBr): 1695, 1650, 1515 $cm^{-1}$. NMR ($CDCl_3$) $\delta$: 3.02—3.40, 3.60—4.17 (total 8H, m), 3.47, 3.58 (each 3H, s), 3.90, 3.91 (each 3H, s), 6.87 (1H, d, $J=8.7$ Hz), 6.90—7.11 (2H, m), 7.14 (1H, d, $J=9.1$ Hz), 7.32 (1H, dd, $J=2.8$, 9.1 Hz), 7.68 (1H, d, $J=2.8$ Hz). *Anal.* Calcd for $C_{23}H_{26}N_4O_5$: C, 63.00; H, 5.98; N, 12.78. Found: C, 63.03; H, 5.90; N, 12.80.

**1-(3,4-Dimethoxybenzoyl)-4-[3-(*N*-methylaminomethyl)-4-nitrophenyl]piperazine (X)**——A solution of IV (20 g, 0.057 mol) and $MeNH_2$ (60 ml, 40% in MeOH) in $CHCl_3$ (60 ml) was stirred at room temperature for 6 h. $NaBH_4$ (3.8 g, 0.1 mol) was added portionwise to the reaction mixture, and the whole was stirred at room temperature for 3 h. After removal of the solvent, $H_2O$ and $CHCl_3$ were added to the residue. The organic layer was washed with water, dried ($K_2CO_3$) and evaporated. The residue was recrystallized from EtOH to afford X (16 g, 77%) as yellow needles, mp 101—102 °C. IR (KBr): 1620, 1600, 1250 $cm^{-1}$. NMR ($CDCl_3$) $\delta$: 1.76 (1H, s), 2.46 (3H, s), 3.27—4.10 (8H, m), 3.90 (6H, s), 4.01 (2H, s), 6.57—7.20 (5H, m), 8.10 (1H, d, $J=7.5$ Hz). *Anal.* Calcd for $C_{21}H_{26}N_4O_5$: C, 60.85; H, 6.32; N, 13.52. Found: C, 60.64, H, 6.30; N, 13.48.

**4-[4-Amino-3-(*N*-methylaminomethyl)phenyl]-1-(3,4-dimethoxybenzoyl)piperazine (XI)**——A mixture of X (10 g, 0.024 mol), 5% Pd–C (1 g), and EtOH (300 ml) was stirred at room temperature under atmospheric pressure of hydrogen until the absorption of hydrogen ceased. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to give XI (8.3 g, 90%) as a pale yellow viscous oil. The crude XI was used immediately without further purification because of its instability. IR (KBr): 3400, 3330, 1625 $cm^{-1}$. NMR ($CDCl_3$) $\delta$: 2.42 (3H, s), 2.86—3.27, 3.53—4.19 (total 8H, m), 3.48 (3H, br s), 3.71 (2H, s), 3.89, 3.90 (each 3H, s), 6.50—7.13 (6H, m). MS *m/z*: 384 ($M^+$), 353, 165.

**Preparation of XIIa, b. 6-[4-(3,4-Dimethoxybenzoyl)-1-piperazinyl]-3,4-dihydro-1*H*-2,1,3-benzothiadiazine-2,2-dioxide (XIIa)**——A solution of $SO_2Cl_2$ (0.45 ml, 5.6 mmol) in $CH_2Cl_2$ (10 ml) was added dropwise to a solution of XI (1.7 g, 4.4 mmol) and $Et_3N$ (1.6 ml, 11 mmol) in $CH_2Cl_2$ (100 ml) with stirring at 0—5 °C. Stirring was continued for 2 h at 0—5 °C, then the reaction mixture was poured into 1 N HCl, and neutralized with saturated $NaHCO_3$ solution. The whole was extracted with $CHCl_3$. The organic layer was washed with water, dried ($Na_2SO_4$) and evaporated. The residue was recrystallized from EtOH to give XIIa (0.2 g, 10%) as colorless needles, mp 235—239 °C. IR (KBr): 1615, 1510, 1435 $cm^{-1}$. NMR (DMSO-$d_6$) $\delta$: 2.37 (3H, s), 2.58—4.14 (8H, m), 3.76, 3.77 (each 3H, s), 3.78 (2H, s), 6.37—7.07 (6H, m), 7.70 (1H, br s). *Anal.* Calcd for $C_{21}H_{26}N_4O_5S$: C, 56.49; H, 5.87; N, 12.55. Found: C, 56.21; H, 5.90; N, 12.48.

Compound XIIb was prepared in the same manner as described for XIIa in 12% yield as colorless needles, mp 144.5—146 °C (EtOH). *Anal.* Calcd for $C_{22}H_{26}N_4O_4$: C, 64.37; H, 6.39; N, 13.65. Found: C, 64.17; H, 6.32; N, 13.49.

**6-[4-(3,4-Dimethoxybenzoyl)-1-piperazinyl]-3,4-dihydro-3-methyl-1*H*-quinazoline-2-thione (XIIc)**——A mixture of XI (1.0 g, 2.6 mmol), $CS_2$ (7 ml) and EtOH (20 ml) was refluxed for 5 h, then allowed to cool. The precipitates were collected by filtration. Recrystallization from MeOH gave XIIc (0.7 g, 63%) as colorless needles, mp 168—170 °C. NMR ($CDCl_3$) $\delta$: 2.88—3.16, 3.53—3.97 (total 8H, m), 3.44 (3H, s), 3.89, 3.90 (each 3H, s), 4.51 (2H, s), 6.55 (1H, d, $J=2.1$ Hz), 6.68 (1H, d, $J=8.6$ Hz), 6.76 (1H, dd, $J=2.1$, 8.6 Hz), 6.86 (1H, d, $J=8.7$ Hz), 6.90—7.08 (2H, m), 8.47 (1H, br s). *Anal.* Calcd for $C_{22}H_{26}N_4O_3S$: C, 61.95; H, 6.14; N, 13.14. Found: C, 61.99; H, 6.14; N, 12.91.

**Methyl 5-(4-Benzyl-1-piperazinyl)-2-nitrobenzoate (XIV)**——A solution of methyl 5-chloro-2-nitrobenzoate (XIII) (24.5 g, 0.11 mol) and 1-benzylpiperazine (35 ml, 0.19 mol) in DMF (250 ml) was stirred at 90 °C for 6 h. The solution was poured into ice-water and extracted with ethyl acetate (AcOEt). The organic layer was washed with water, dried ($Na_2SO_4$) and evaporated. The residue was recrystallized from MeOH to give XIV (21.7 g, 55%) as yellow

needles, mp 89—92 °C. IR (KBr): 1740, 1600, 1580 $cm^{-1}$. NMR ($CDCl_3$) $\delta$: 2.50—2.65, 3.35—3.50 (total 8H, m), 3.56 (2H, s), 3.92 (3H, s), 6.75—6.70 (2H, m), 7.30—7.40 (5H, m), 7.95—8.05 (1H, m). *Anal.* Calcd for $C_{19}H_{21}N_3O_4 \cdot 1/4H_2O$: C, 63.23; H, 6.00; N, 11.64. Found: C, 63.55; H, 5.93; N, 11.61.

**Methyl 2-Amino-5-(4-benzyl-1-piperazinyl)benzoate Dihydrochloride (XV)**——A mixture of XIV (21.0 g, 59 mmol) and 10% Pd–C (1.0 g) in EtOH (300 ml) was stirred at room temperature under atmospheric pressure of hydrogen until the absorption of hydrogen ceased. The catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue was dissolved in EtOH saturated with hydrogen chloride and concentrated *in vacuo*. The residue was recrystallized from EtOH–$H_2O$ to give XV (17.5 g, 75%) as colorless prisms, mp 233—236 °C (dec.). IR (KBr): 2835, 2600, 1735 $cm^{-1}$. NMR (DMSO-$d_6$) $\delta$: 2.90—3.90 (10H, m), 4.37 (3H, s), 6.36 (3H, br s), 6.90—7.70 (8H, m), 11.50 (1H, br s). *Anal.* Calcd for $C_{19}H_{23}N_3O_2 \cdot 2HCl$: C, 57.29; H, 6.33; N, 10.55. Found: C, 57.17; H, 6.23; N, 10.46.

**Methyl 5-(4-Benzyl-1-piperazinyl)-2-trifluoroacetylaminobenzoate (XVI)**——A solution of $(CF_3CO)_2O$ (1.7 g, 12 mmol) in $CH_2Cl_2$ (5 ml) was added dropwise to a stirred solution of XV (3.1 g, 7.8 mmol) and $Et_3N$ (3.6 ml, 26 mmol) in $CH_2Cl_2$ (20 ml) with ice-cooling, and the mixture was stirred at room temperature for 30 min. The reaction mixture was poured into saturated $NaHCO_3$ solution, and extracted with $CHCl_3$. The organic layer was washed with water, dried ($Na_2SO_4$) and evaporated. The residue was recrystallized from MeOH to give XVI (2.8 g, 85%) as pale yellow needles, mp 116—118 °C. IR (KBr): 1720, 1685, 1540 $cm^{-1}$. NMR ($CDCl_3$) $\delta$: 2.55—2.70, 3.15—3.30 (total 8H, m), 3.58 (2H, s), 3.95 (3H, s), 7.16 (1H, dd, $J$=3.0, 9.2 Hz), 7.20—7.40 (5H, m), 7.57 (1H, d, $J$=3.0 Hz), 8.52 (1H, d, $J$=9.2 Hz), 11.96 (1H, br s). *Anal.* Calcd for $C_{21}H_{22}F_3N_3O_3$: C, 59.85; H, 5.26; N, 9.97. Found: C, 59.63; H, 5.22; N, 10.00.

**Methyl 5-(4-Benzyl-1-piperazinyl)-2-(*N*-methylamino)benzoate (XVII)**——Compound XVI (6.5 g, 15 mmol) was added portionwise to a suspension of NaH (60% dispersion in oil, 0.74 g, 19 mmol) in DMF (50 ml) with stirring at 0—5 °C, and the mixture was stirred at room temperature for 1 h. Then, a solution of MeI (1.9 ml, 31 mmol) in DMF (10 ml) was added dropwise at 0—5 °C. The reaction mixture was stirred at room temperature for 1.5 h, and poured into ice-water. The whole was extracted with AcOEt, and the extracts were washed with water, dried ($Na_2SO_4$) and concentrated *in vacuo*. The residue was added to a solution of NaOH (1.6 g, 40 mmol) in MeOH (40 ml), and the mixture was refluxed for 4 h. After cooling, the reaction mixture was acidified with concentrated $H_2SO_4$, and further refluxed for 3 h. The mixture was poured into saturated $NaHCO_3$ solution and extracted with AcOEt. The organic layer was washed with water, dried ($Na_2SO_4$) and evaporated. The residue was recrystallized from AcOEt–hexane to give XVII (2.1 g, 41%) as pale yellow needles, mp 92—94 °C. IR (KBr): 1680, 1515, 1225 $cm^{-1}$. NMR ($CDCl_3$) $\delta$: 2.55—2.68, 2.98—3.11 (total 8H, m), 2.88 (3H, d, $J$=5.0 Hz), 3,57 (2H, s), 3.83 (3H, s), 6.64 (1H, d, $J$=9.1 Hz), 7.16 (1H, dd, $J$=2.9, 9.1 Hz), 7.20—7.40 (6H, m), 7.50 (1H, d, $J$=2.9 Hz). *Anal.* Calcd for $C_{20}H_{25}N_3O_2$: C, 70.77; H, 7.42; N, 12.38. Found: C, 70.53; H, 7.30; N, 12.45.

**1-Methyl-6-(1-piperazinyl)-2,4(1*H*,3*H*)-quinazolinedione Hydrochloride (XIX)**——A mixture of XVIII (1.8 g, 5.1 mmol), 10% Pd–C (0.18 g), 1 N HCl (15 ml), $H_2O$ (10 ml) and EtOH (35 ml) was stirred at 50 °C under atmospheric pressure of hydrogen until the absorption of hydrogen ceased. The catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue was recrystallized from $H_2O$–MeOH to give XIX (1.4 g, 86%) as colorless needles, mp > 300 °C. IR (KBr): 1695, 1655, 1485 $cm^{-1}$. NMR (DMSO-$d_6$) $\delta$: 3.20—3.45 (8H, m), 3.42 (3H, s), 7.32—7.55 (3H, m), 9.12 (2H, br s), 11.47 (1H, s). *Anal.* Calcd for $C_{13}H_{16}N_4O_2 \cdot HCl \cdot H_2O$: C, 49.61; H, 6.08; N, 17.80. Found: C, 49.42; H, 5.86; N, 17.90.

**Preparation of XXIIa, b. 5-(1-Piperazinyl)benzothiazolone Hydrobromide (XXIIb)**——A mixture of 5-aminobenzothiazolone (XXIb) (15.8 g, 0.095 mol) and bis(2-bromoethyl)amine hydrobromide (32.5 g 0.1 mol) in EtOH (150 ml) was heated under reflux with stirring for 8 h, then cooled. $Na_2CO_3$ (14.4 g, 0.1 mol) was added to the mixture, and the whole was heated under reflux with stirring for 8 h, then allowed to cool. The precipitates were collected by filtration and washed with EtOH. Recrystallization from EtOH–$H_2O$ gave XXIIb (10.3 g, 34%) as colorless flakes, mp 286—289 °C (dec.). IR (KBr): 1690, 1500 $cm^{-1}$. NMR (DMSO-$d_6$) $\delta$: 2.64—3.75 (8H, m), 6.72—7.28 (3H, m), 9.15 (2H, br s), 13.20 (1H, br s). *Anal.* Calcd for $C_{11}H_{13}N_3OS \cdot HBr$: C, 41.78; H, 4.46; N, 13.29. Found: C, 41.69; H, 4.44; N, 13.09.

Compound XXIIa was prepared in the same manner as described for XXIIb, and XXIIa was obtained in 13% yield as colorless needles, mp 286—289 (dec.) ($H_2O$–MeOH). *Anal.* Calcd for $C_{12}H_{15}N_3O \cdot HBr$: C, 48.33; H, 5.41; N, 14.09. Found: C, 48.07; H, 5.50; N, 14.01.

**Method of Pharmacological Testing**——Inotropic and chronotropic effects of test compounds were examined by the use of isolated, blood-perfused dog heart preparations. The hearts were excised from mongrel dogs of either sex weighing 8—14 kg. The isolated, blood-perfused papillary muscle and sino-atrial node preparations were prepared according to the methods of Endoh and Hashimoto[15a] and Kubota and Hashimoto,[15b] respectively. The preparations were cross-circulated through the cannulated arteries with blood from a donor dog anesthetized with sodium pentobarbital and receiving heparin. The perfusion pressure was kept constant at 100 mmHg. The papillary muscle was stimulated at a frequency of 2 Hz and tension developed by the muscle was measured with a force displacement transducer (Shinkoh, UL-20-240). Sinus rate was measured by the use of a cardiotachometer (Data Graph, T-149) triggered by developed tension of the right atrium. Recording of these parameters was done on an ink-writing rectigraph (Sanei Instrument, 8S). The compounds were injected intraarterially with microsyringes.

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