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Novel Phenoxyalkylamine Derivatives. I. Synthesis and Pharmacological Activities of α-Isopropyl-α-[(phenoxyalkylamino)alkyl]-benzeneacetonitrile Derivatives

KAZUYA MITANI,* TOSHIHIKO YOSHIDA, KOJI MORIKAWA, YUJI IWANAGA, EIICHI KOSHINAKA, HIDEO KATO, and YASUO ITO

Central Research Laboratory, Hokuriku Seiyaku Co., Ltd., Inokuchi, Katsuyama, Fukui 911, Japan

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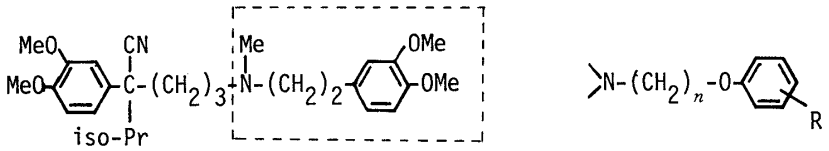
Novel α-isopropyl-α-[(phenoxyalkylamino)alkyl]benzeneacetonitrile derivatives, the phenoxyalkylamino moiety of which was introduced in place of the phenethylamino moiety of verapamil (known to be an excellent Ca^{2+}-antagonist), were synthesized and their pharmacological activities were evaluated. These compounds exhibited α-blocking activity along with Ca^{2+}-antagonistic activity, and their activities were influenced by the substituent on the amino nitrogen atom and by the number of carbons between the nitrogen atom and the benzeneacetonitrile moiety (*m*) as well as that between it and the phenoxy moiety (*n*). Among these compounds, the *N*-methyl derivative (**2h**) where $m=n=3$, was found to possess a high Ca^{2+}-antagonistic activity and the *N*-H derivative (**2c**) in which $m=3$ and $n=2$ possessed a high α-blocking activity.

Keywords——calcium ion-antagonistic activity; α-blocking activity; phenoxyalkylamine; structure–activity relationship; α-isopropyl-α-[(phenoxyalkylamino)alkyl]benzeneacetonitrile

We have been interested in variations of each activity of compounds exhibiting several types of pharmacological actions as a result of structural modifications. As a part of our studies on cardiovascular agents, we have focused our attention on verapamil,[1] which is a Ca^{2+}-antagonist widely used in clinical practice, and planned a number of structural modifications starting from verapamil. We designed some novel phenoxyalkylamine derivatives (**1**) having the phenoxyalkylamino moiety, which is known to be a mother structure of α-blockers,[2] instead of the phenethylamino moiety present in verapamil, with the aim of investigating their Ca^{2+}-antagonistic and/or α-blocking activities.

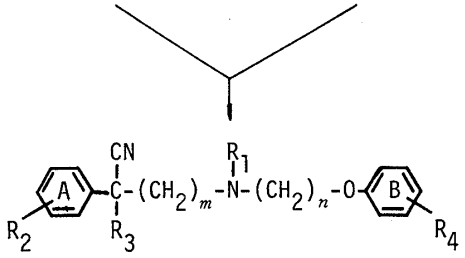
The α,β-blockers such as labetalol[3] or amosulalol[4] are regarded as being representative of compounds having dual types of pharmacological activity in one type of structure. However, hardly any investigations of paired Ca^{2+}-antagonistic and α-blocking activity have been carried out up to the present.

Our designed compound (**1**) possesses several substructures which can be modified, namely, the carbon chains (*m*, *n*), the substituents on the nitrogen atom (R_1), the A ring of the benzeneacetonitrile moiety (R_2), the quaternary carbon atom (R_3), the B ring of the phenoxy moiety (R_4) and the CN group. First, we investigated the effects of changing the carbon chains (*m*, *n*) and *N*-substituent (R_1) of **1** on its Ca^{2+}-antagonistic and α-blocking activities. We fixed the other positions in the molecule as follows. The A ring structure was kept as 3,4,5-trimethoxyphenyl, which showed a more potent action in a Ca^{2+}-antagonist than the 3,4-dimethoxyphenyl moiety.[5] The R_3 substituent on the quaternary C and the CN group were held as iso-Pr and CN groups, as in verapamil. The R_4 substituent on the phenoxy benzene ring (B ring) was the *o*-OMe group, which is one of the substituents expected to show potent



verapamil (Ca^{2+}-antagonist)

phenoxyalkylamine (α-blocker)



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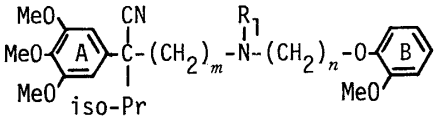

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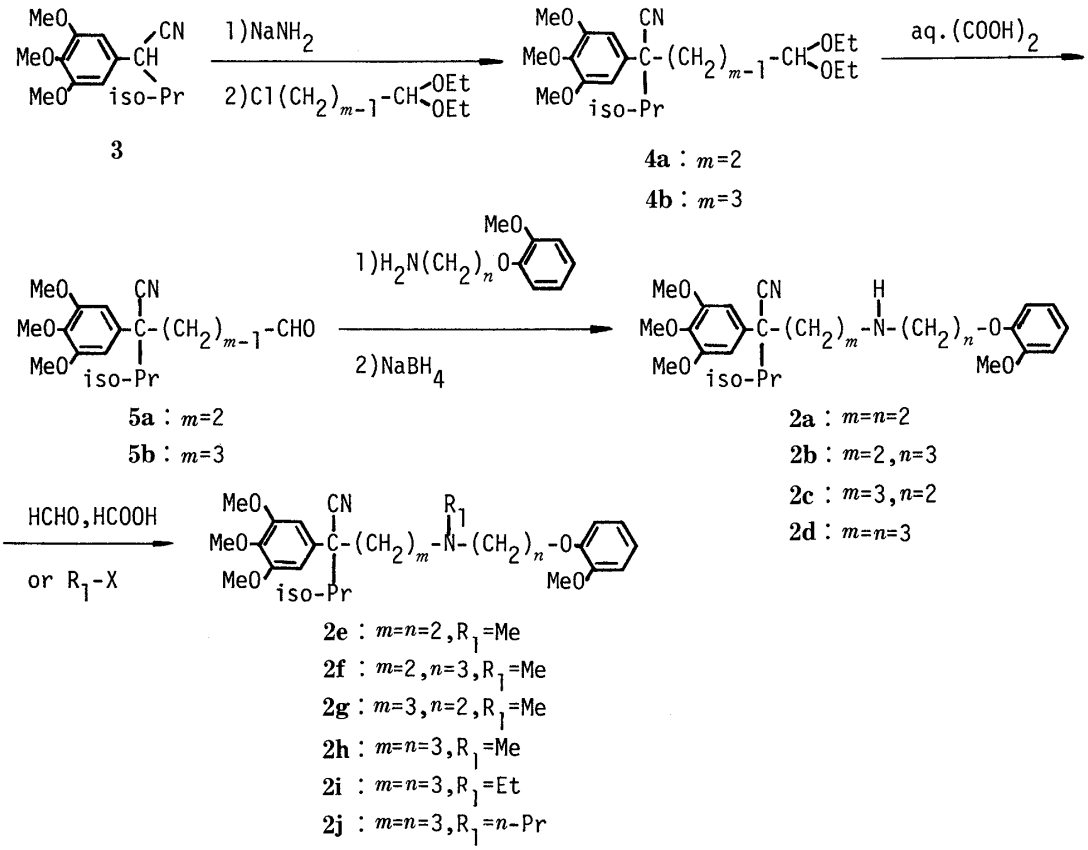
Chart 1



3

4a : m=2
4b : m=3

5a : m=2
5b : m=3

2a : m=n=2
2b : m=2, n=3
2c : m=3, n=2
2d : m=n=3

2e : m=n=2, R_1=Me
2f : m=2, n=3, R_1=Me
2g : m=3, n=2, R_1=Me
2h : m=n=3, R_1=Me
2i : m=n=3, R_1=Et
2j : m=n=3, R_1=n-Pr

Chart 2

α-blocking activity.[2a] We report here the synthesis and the pharmacological activities of these novel α-isopropyl-α-[(phenoxyalkylamino)alkyl]benzeneacetonitrile derivatives (**2**).

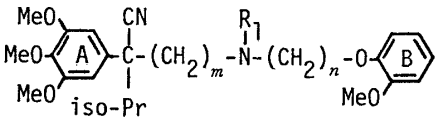
Synthesis

α-Isopropyl-α-[(phenoxyalkylamino)alkyl]benzeneacetonitrile derivatives (**2a—j**) were prepared as shown in Chart 2.

Of the two key intermediate aldehydes (**5a**, **b**), **5b** was obtained by the method of Ferdinand,[6] that is, α-isopropyl-3,4,5-trimethoxybenzeneacetonitrile (**3**) was alkylated with 3-chloropropionaldehyde diethylacetal to give the acetal (**4b**), which was subsequently hydrolyzed with aqueous oxalic acid to yield the aldehyde (**5b**). The novel aldehyde (**5a**) was also obtained in the same manner from **3** in an almost equivalent yield. The reaction of **5a** or **5b** with *o*-methoxyphenoxyalkylamines[7] gave the desired *N*-H derivatives (**2a—d**), which were reacted with formalin and formic acid or alkyl halide to give the *N*-alkyl derivatives (**2e—j**).

The physicochemical properties of the obtained compounds (**2a—j**) are summarized in Table I.

TABLE I. Physicochemical and Pharmacological Data for α-Isopropyl-α-[(phenoxyalkylamino)alkyl]-benzeneacetonitriles



Compd. No.	*m*	*n*	R_1	Yield[a] (%)	Salt	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found) C H N	Ca^{2+} [b] pA_2	α[c] pA_2
2a	2	2	H	46	Free	Oil	—	$C_{25}H_{34}N_2O_5$	442.2468[d] (442.2475)	5.79	7.09
2b	2	3	H	36	HCl	174—175	EtOH	$C_{26}H_{36}N_2O_5 \cdot HCl$	63.34 7.56 5.68 (63.26 7.55 5.57)	6.59	6.65
2c	3	2	H	32	Fumarate	149—150	EtOH–iso-Pr_2O	$C_{26}H_{36}N_2O_5 \cdot C_4H_4O_4$	62.92 7.04 4.89 (62.62 7.30 4.76)	6.59	8.42
2d	3	3	H	88	Fumarate	112—113	EtOH–Et_2O	$C_{27}H_{38}N_2O_5 \cdot C_4H_4O_4$	63.47 7.22 4.77 (63.07 7.30 4.70)	6.24	6.61
2e	2	2	Me	84	Oxalate	147—148	EtOH–iso-Pr_2O	$C_{26}H_{36}N_2O_5 \cdot C_2H_2O_4$	61.53 7.01 5.12 (61.43 7.22 5.01)	6.76	6.15
2f	2	3	Me	57	Free	Oil	—	$C_{27}H_{38}N_2O_5$	470.2781[d] (470.2779)	6.36	6.19
2g	3	2	Me	36	HCl	146—148	EtOH–iso-Pr_2O	$C_{27}H_{38}N_2O_5 \cdot HCl$	63.96 7.75 5.52 (63.75 8.01 5.42)	7.20	7.04
2h	3	3	Me	90	Free	Oil	—	$C_{28}H_{40}N_2O_5$	484.2937[d] (484.2935)	8.05	6.73
2i	3	3	Et	74	Free	Oil	—	$C_{29}H_{42}N_2O_5$	498.3094[d] (498.3081)	7.36	6.72
2j	3	3	*n*-Pr	78	Free	Oil	—	$C_{30}H_{44}N_2O_5$	512.3250[d] (512.3238)	6.33	6.60
	Verapamil									7.88	5.79
	Prazosin[e]									<5	8.63

a) Yield of free base. *b*) pA_2 values in the KCl-depolarized guinea-pig taenia coli. *c*) pA_2 values in the rabbit thoracic aorta. *d*) High mass data. The upper values are calculated and the lower ones are those found. *e*) A representative α-blocker.[8]

Results and Discussion

The Ca^{2+}-antagonistic activity was tested by using KCl-depolarized guinea-pig taenia coli and is expressed as the pA_2 value. The α-blocking activity was tested using rabbit thoracic aorta and is also shown as the pA_2 value. The data obtained are listed in Table I.

First, our attention was drawn to the resulting Ca^{2+}-antagonistic activities. The $R_1=H$ derivatives (**2a**—**d**) were less potent than verapamil, the pA_2 values being 5.8—6.6, but *N*-methylation of these compounds increased these activities, except for **2b** with $m=2$, $n=3$. Among these compounds with the $R_1=Me$ group, the most potent compound was **2h** with $m=3$, $n=3$, the pA_2 value of which was 8.05 (higher than that of verapamil), followed by **2g** with $m=3$, $n=2$, and then by **2e** with $m=2$, $n=2$. The extension of the $R_1=Me$ group of **2h** to an Et (**2i**) or *n*-Pr group (**2j**) somewhat decreased the activity. This result indicates that the $R_1=Me$ derivative with $m=3$ and $n=3$ in the carbon chains is the most favorable in terms of Ca^{2+}-antagonistic activity.

Next, our attention was focused on the α-blocking activities. The $R_1=H$ derivatives (**2a**—**d**) were more potent than verapamil, and **2c** with $m=3$, $n=2$ was the most effective, with a pA_2 value of 8.42. The order of activity was **2c** ($m=3$, $n=2$), **2a** ($m=2$, $n=2$), **2b** ($m=2$, $n=3$) and **2d** ($m=3$, $n=3$). *N*-Methylation of these compounds decreased the activity, except in the case of **2d** with $m=3$, $n=3$. This shows that the most favorable substructure for α-blocking activity is the $R_1=H$ one with $m=3$ and $n=2$ in the carbon chains.

In summary, the replacement of the phenethylamino moiety of verapamil by the phenoxyalkylamino moiety was shown to introduce α-blocking activity as well as the Ca^{2+}-antagonistic activity into the molecule, and these activities were influenced by changes in the carbon chain lengths (m, n) and the *N*-substituent (R_1).

In subsequent papers, we will report on the qualitative and quantitative structure–activity relationships for Ca^{2+}-antagonistic activity in this series of compounds with the highly favorable $m=3$ and $n=3$ carbon chains and with $R_1=H$ or Me as the *N*-substituent, where the substituents on the A ring (R_2), the quaternary carbon atom (R_3) and the B ring (R_4) are variously changed.

Experimental

Melting points were measured with a Yanagimoto melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded using a JASCO A-202 or Hitachi 270-30 spectrophotometer. Mass spectra (MS) were obtained on a Hitachi RMU-6M or JEOL DX-300 mass spectrometer. High-resolution MS were measured using a JEOL DX-300 mass spectrometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were measured with a JEOL FX-90Q spectrometer using tetramethylsilane as an internal standard.

α-Isopropyl-3,4,5-trimethoxy-α-[2-[[2-(2-methoxyphenoxy)ethyl]amino]ethyl]benzeneacetonitrile (2a)——A solution of α-(formylmethyl)-α-isopropyl-3,4,5-trimethoxybenzeneacetonitrile (**5a**, 6.00 g) and 2-(2-methoxyphenoxy)ethylamine (2.75 g) in MeOH (50 ml) was refluxed for 1 h, then cooled with ice water, and $NaBH_4$ (0.76 g) was added. The mixture was stirred at room temperature for 1 h, and then concentrated. The residue was acidified with 10% HCl and washed with Et_2O. The aqueous layer was made alkaline with K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified on a column of silica gel using $CHCl_3$ as the eluent to give **2a** (3.34 g, 46%) as a pale yellow oil. IR ν_{max}^{liq} cm^{-1}: 2230 (CN). ^{1}H-NMR ($CDCl_3$) δ: 0.81, 1.21 (each 3H, d, $J=6.5$ Hz, $CH(C\underline{H}_3)_2$), 2.93 (2H, t, $J=5.0$ Hz, $NC\underline{H}_2CH_2O$), 3.84, 3.85 (each 3H, s, $2\times OCH_3$), 3.87 (6H, s, $2\times OCH_3$), 4.05 (2H, t, $J=5.0$ Hz, $NCH_2C\underline{H}_2O$), 6.59 (2H, s, aromatic protons), 6.89 (4H, s, aromatic protons). High MS m/z: 442.2475 (M^+) (Calcd for $C_{25}H_{34}N_2O_5$ 442.2468).

Compounds **2b**—**d** were also prepared in the same manner as described above. The yields and characteristics of the products are listed in Table I.

α-Isopropyl-3,4,5-trimethoxy-α-[2-[*N*-[2-(2-methoxyphenoxy)ethyl]-*N*-methylamino]ethyl]benzeneacetonitrile (2e)——A mixture of **2a** (2.34 g), 37% formalin (7 ml) and HCOOH (14 ml) was stirred at 90 °C for 1 h. After cooling, the mixture was made alkaline with aqueous K_2CO_3 and extracted with AcOEt. The AcOEt layer was washed with

water, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified on a column of silica gel using $CHCl_3$ as the eluent to give **2e** (2.03 g, 84%) as a pale yellow oil. IR ν_{max}^{liq} cm^{-1}: 2240 (CN). ^{1}H-NMR ($CDCl_3$) δ: 0.81, 1.21 (each 3H, d, J=6.5 Hz, $CH(C\underline{H}_3)_2$), 2.33 (3H, s, NCH_3), 2.80 (2H, t, J=6.0 Hz, $NC\underline{H}_2CH_2O$), 3.84 (3H, s, OCH_3), 3.85 (9H, s, 3×OCH_3), 4.03 (2H, t, J=6.0 Hz, $NCH_2C\underline{H}_2O$), 6.58 (2H, s, aromatic protons), 6.88 (4H, s, aromatic protons).

The obtained free base was converted into the oxalate in a usual manner, and the resulting salt was recrystallized from EtOH–iso-Pr_2O to give colorless needles, mp 147—148 °C. *Anal.* Calcd for $C_{26}H_{36}N_2O_5 \cdot C_2H_2O_4$: C, 61.53; H, 7.01; N, 5.12. Found: C, 61.43; H, 7.22; N, 5.01.

Compounds **2f**—**h** were also prepared in the same manner as described above. The yields and characteristics of the products are listed in Table I.

α-Isopropyl-3,4,5-trimethoxy-α-[3-[*N*-[3-(2-methoxyphenoxy)propyl]-*N*-ethylamino]propyl]benzeneacetonitrile (2i)——A suspension of α-isopropyl-3,4,5-trimethoxy-α-[3-[[3-(2-methoxyphenoxy)propyl]amino]propyl]-benzeneacetonitrile (**2d**, 2.00 g), K_2CO_3 (0.39 g) and EtI (0.72 g) in EtOH (25 ml) was refluxed for 4 h and then concentrated. Water was added to the residue and the mixture was extracted with AcOEt. The AcOEt layer was washed with water, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified on a column of silica gel using $CHCl_3$ and $CHCl_3$–MeOH (98 : 2) as eluents to give **2i** (1.56 g, 74%) as a pale yellow oil. IR ν_{max}^{liq} cm^{-1}: 2220 (CN). ^{1}H-NMR ($CDCl_3$) δ: 0.80, 1.18 (each 3H, d, J=6.5 Hz, $CH(C\underline{H}_3)_2$), 0.95 (3H, t, J=7.0 Hz, $NCH_2C\underline{H}_3$), 2.44 (2H, q, J=7.0 Hz, $NC\underline{H}_2CH_3$), 3.84 (6H, s, 2×OCH_3), 3.85 (6H, s, 2×OCH_3), 4.03 (2H, t, J=6.5 Hz, $NCH_2CH_2C\underline{H}_2O$), 6.57 (2H, s, aromatic protons), 6.89 (4H, s, aromatic protons). High MS *m/z*: 498.3081 (M^+) (Calcd for $C_{29}H_{42}N_2O_5$ 498.3094).

α-Isopropyl-3,4,5-trimethoxy-α-[3-[*N*-[3-(2-methoxyphenoxy)propyl]-*N*-propylamino]propyl]benzeneacetonitrile (2j)——A suspension of **2d** (2.04 g), K_2CO_3 (0.40 g) and *n*-PrBr (0.64 g) in EtOH (25 ml) was refluxed for 11.5 h, and then treated by the same procedure as **2i** to give **2j** (1.73 g, 78%) as a pale yellow oil. IR ν_{max}^{liq} cm^{-1}: 2225 (CN). ^{1}H-NMR ($CDCl_3$) δ: 0.80, 1.18 (each 3H, d, J=6.5 Hz, $CH(C\underline{H}_3)_2$), 0.82 (3H, t, J=7.0 Hz, $NCH_2CH_2C\underline{H}_3$), 3.85 (6H, s, 2×$OCH_3$), 3.86 (6H, s, 2×$OCH_3$), 4.03 (2H, t, J=6.5 Hz, $NCH_2CH_2C\underline{H}_2O$), 6.57 (2H, s, aromatic protons), 6.89 (4H, s, aromatic protons). High MS *m/z*: 512.3238 (M^+) (Calcd for $C_{30}H_{44}N_2O_5$ 512.3250).

α-(2-Formylethyl)-α-isopropyl-3,4,5-trimethoxybenzeneacetonitrile (5b)——**5b** was prepared by the method of Ferdinand.[6] $NaNH_2$ (44.90 g) and then 3-chloropropionaldehyde diethylacetal (95.30 g) were added to a solution of α-isopropyl-3,4,5-trimethoxybenzeneacetonitrile (**3**, 118.60 g) in anhydrous tetrahydrofuran (THF, 1000 ml) at room temperature with stirring. The mixture was refluxed for 3.5 h, then poured into ice water and extracted with Et_2O. The Et_2O layer was washed with water, dried over Na_2SO_4 and evaporated under reduced pressure to give α-(3,3-diethoxypropyl)-α-isopropyl-3,4,5-trimethoxybenzeneacetonitrile (**4b**, 180.45 g) as a brown oil.

The obtained **4b** was dissolved in acetone (1200 ml) and $(COOH)_2 \cdot 2H_2O$ (72.00 g) in water (510 ml) was added to the solution. The mixture was refluxed for 1.5 h, then neutralized with aqueous K_2CO_3 and concentrated. The residue was diluted with water and extracted with Et_2O. The Et_2O layer was washed with water, dried over Na_2SO_4 and evaporated under reduced pressure to give **5b** (132.16 g, 91%) as a brown oil. IR ν_{max}^{liq} cm^{-1}: 2240 (CN), 1726 (CO). ^{1}H-NMR ($CDCl_3$) δ: 0.83, 1.23 (each 3H, d, J=6.5 Hz, $CH(C\underline{H}_3)_2$), 3.85 (3H, s, OCH_3), 3.86 (6H, s, 2×OCH_3), 6.55 (2H, s, aromatic protons), 9.68 (1H, s, CHO). High MS *m/z*: 305.1605 (M^+) (Calcd for $C_{17}H_{23}NO_4$ 305.1627).

α-(Formylmethyl)-α-isopropyl-3,4,5-trimethoxybenzeneacetonitrile (5a)——$NaNH_2$ (16.80 g) and then α-chloroacetaldehyde diethylacetal (39.80 g) were added to a solution of **3** (53.40 g) in anhydrous THF (500 ml) at room temperature with stirring. The mixture was refluxed for 4 h, and then treated by the same procedure as **4b** to give α-(2,2-diethoxyethyl)-α-isopropyl-3,4,5-trimethoxybenzeneacetonitrile (**4a**, 78.00 g) as a brown oil.

The obtained **4a** was dissolved in acetone (580 ml) and aqueous 10% $(COOH)_2$ (240 ml) was added to the solution. The mixture was refluxed for 6 h, and then treated by the same procedure as **5b** to give **5a** (62.20 g, quant.) as a brownish yellow oil. IR ν_{max}^{liq} cm^{-1}: 2230 (CN), 1730 (CO). ^{1}H-NMR ($CDCl_3$) δ: 0.89, 1.20 (each 3H, d, J=6.5 Hz, $CH(C\underline{H}_3)_2$), 2.97 (2H, d, J=2.0 Hz, $C\underline{H}_2CHO$), 3.85 (3H, s, OCH_3), 3.87 (6H, s, 2×OCH_3), 6.60 (2H, s, aromatic protons), 9.55 (1H, br s, CHO). High MS *m/z*: 291.1454 (M^+) (Calcd for $C_{16}H_{21}NO_4$ 291.1471).

Pharmacology

Ca^{2+}-Antagonistic Activity in Isolated Taenia Coli——The taenia coli was isolated from Hartley guinea-pig and suspended under a resting tension of 0.5 g in an organ bath maintained at 38±1 °C. The preparation was depolarized by Ca^{2+}-free, high-K^+ solution aerated with 95% O_2 and 5% CO_2. Ca^{2+}-free, high-K^+ solution was prepared by removing $CaCl_2$ from Locke Ringer solution and increasing the concentration of KCl to 100 mM. After an equilibration period, the contractions induced by cumulative applications of $CaCl_2$ were recorded isotonically. Compounds were applied 30 min before $CaCl_2$ application and their pA_2 values (pA_2 is the negative log of the antagonist concentration required to maintain a constant response when the concentration of the agonist is doubled) were calculated from dose ratios estimated graphically from the parallel shifts of concentration-response curves to $CaCl_2$.

α-Adrenoceptor-Blocking Activity in Isolated Aorta——The thoracic aorta was isolated from rabbit and suspended under a resting tension of 2.0 g in an organ bath maintained at 37±1 °C. After equilibration in Krebs–Henseleit solution aerated with 95% O_2 and 5% CO_2, the contraction induced by cumulative application of

noradrenaline was recorded isometrically. Compounds were applied 30 min before noradrenaline application and their pA_2 values were calculated from dose ratios estimated graphically from the parallel shifts of concentration-response curves to noradrenaline.

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