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Synthesis and Structure–Activity Relationship of Trimebutine Derivatives

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Trimebutine derivatives were synthesized by utilizing alkylation or acylation of isonitriles and nitrile as a key step. The colonic contractile effects of these compounds were examined, and T-1815 was found to have strong colonic propulsive activity.

Key words trimebutine; 2-aryl-2-dimethylaminobutane; colonic contractile effect; colonic propulsion

Trimebutine maleate is used in the treatment of gastrointestinal disorders such as chronic gastritis and irritable bowel syndrome.[1] To search for a compound having stronger activity on gastrointestinal tract, a series of derivatives was synthesized. The chemical structure of trimebutine is characterized by a quaternary carbon and two aryl groups. We assumed that the properties of the two aryl groups and their distance of separation are important determinants of the pharmacological activity. Thus, we synthesized derivatives possessing various aryl groups, including hetero aromatics. For construction of the quaternary carbon, we used alkylation or acylation of isonitrile and nitrile intermediates as a key step. Moreover, the ester bond in the structure was transformed into other linkages, such as ether bond, thioether bond, amide bond, carbon–carbon bond and carbon–nitrogen bond, without changing the number of atoms between the two aryl groups. The prepared compounds were examined for colonic contractile activity. The results are reported herein.

Chemistry

Ester derivatives (**1a—g**) and ether derivatives (**2a—h**) were prepared from 1-aryl-1-isocyanopropane (**7**), which is easily prepared from aryl ethyl ketone,[2] as shown in Chart 1. The isonitrile (**7**) was acylated with methyl chloroformate in the presence of lithium diisopropylamide (LDA)[3] to give methyl 2-aryl-2-isocyanobutyrate (**8**) in good yields. The reduction of the isocyanobutyrate (**8**) with $LiAlH_4$ followed by reductive methylation with formalin–$NaBH_3CN$[4] afforded the common intermediates, 2-aryl-2-dimethylaminobutanol (**9**) in good yields. The intermediates (**9**) were acylated with benzoyl chlorides to give the ester derivatives (**1a—g**) in high yields. Compound **9a** was alkylated with benzyl chlorides to give the ether derivatives (**2a—h**) in high yields.

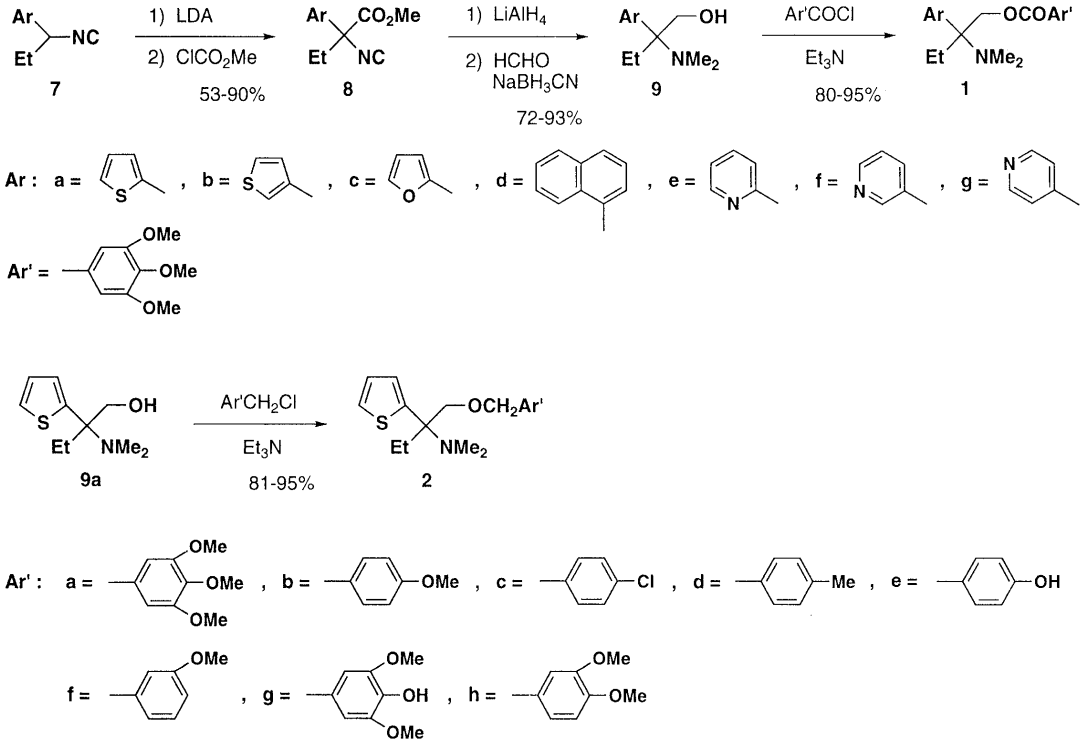

Chart 1

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Thioether derivatives (**3**) and alkyl derivative (**4**) were obtained as shown in Chart 2. Alkylation of 1-thienyl-1-isocyanopropane (**7a**) with alkyl halides in the presence of LDA gave the quaternary isocyano intermediates (**10**) and (**11**). These intermediates were reduced with $LiAlH_4$, followed by reductive methylation with formalin–$NaBH_3CN$ to afford the required compounds, **3** and **4**, respectively.

The amide derivative (**5**) was synthesized from methyl 2-thienyl-2-isocyanobutyrate (**8a**), as shown in Chart 3. The isocyanobutyrate (**8a**) was treated successively with dilute HCl, formic acid-formalin and $Ba(OH)_2$ to afford the dimethylamino acid (**12**) in a good yield. This product (**12**) was condensed with trimethoxybenzylamine by use of dicyclohexylcarbodiimide (DCC) to afford **5**.

Amine derivatives (**6a—c**) were synthesized by alkylation of the amino-nitrile (**14**) as a key step, as shown in Chart 4. The intermediate dimethylamino-nitrile (**14**) was obtained in a good yield by the treatment of 2-thiophenecarboxaldehyde (**13**) with sodium hydrogen sulfate, dimethylamine and sodium cyanide.[5] The amino-nitrile (**14**) was alkylated with ethyl iodide in the presence of LDA[6] to give the butyronitrile derivative (**15**) in a high yield. Reduction of **15** with $LiAlH_4$ afforded the butylamine derivative (**16**), which was reductively alkylated with benzaldehydes in the presence of $NaBH_3CN$[7] to give the required compounds (**6a—c**).

Structure–Activity Relationship The synthesized compounds were tested for colonic contractile activity in anesthetized rats, and the maximum tolerated dose (MTD) was determined in mice.

First, the ester derivatives having a variety of aryl groups at the 2-position of trimebutine were evaluated for colonic contractile activity. As shown in Table 1, the 3-thienyl derivative (**1b**) was the most effective, but it was rather toxic. From the viewpoint of both activity and toxicity, the 2-thienyl derivative (**1a**) seemed to be better than the other derivatives and was chosen as the lead compound for further examination.

Next, the ester bond in **1a** was changed to other bonds without changing the number of atoms between the two aryl groups. The ether (**2a**), thioether (**3**), alkyl (**4**), amide (**5**) and amine (**6a**) derivatives were tested. The results are summarized in Table 2. The ether derivative (**2a**), alkyl derivative (**4**) and amine derivative (**6a**) showed strong activity. But, the alkyl derivative (**4**) was inactive

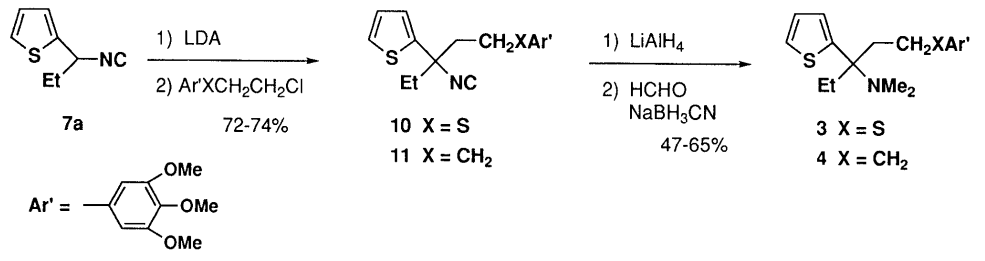


Chart 2

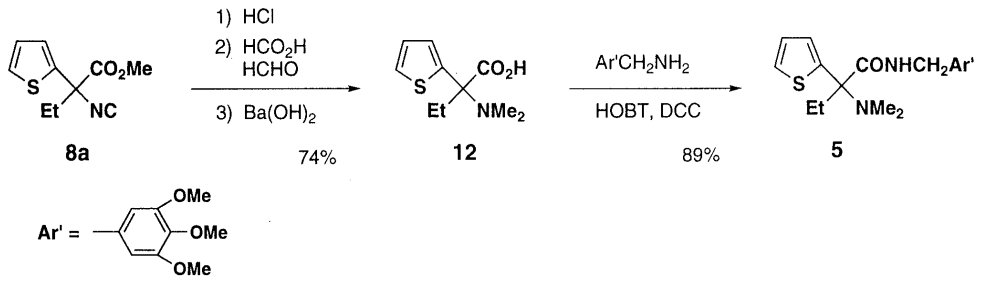


Chart 3

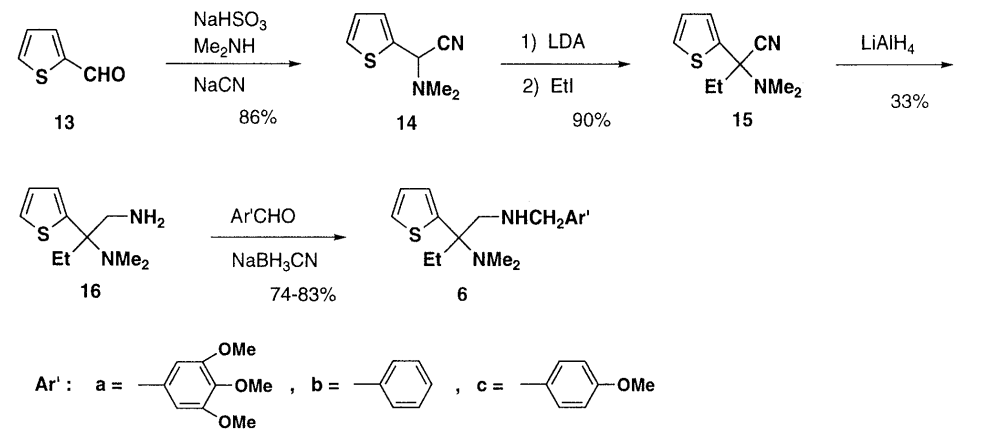
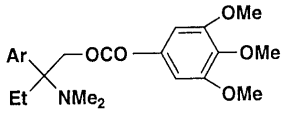


Chart 4

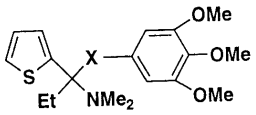
Table 1. Effect of Trimebutine Derivatives on Colonic Motility in Anesthetized Rats and Maximum Tolerated Dose (MTD) in Mice



Compound	Ar	Colon[a] (1 mg/kg i.v.)	MTD (mg/kg *p.o.*)
Trimebutine	Phenyl	++	1000
1a	2-Thienyl	++	≥3000
1b	3-Thienyl	+++	≥1000
1c	2-Furyl	++	≥300
1d	1-Naphthyl	++	≥1000
1e	2-Pyridyl	++	300
1f	3-Pyridyl	++	300
1g	4-Pyridyl	++	≥1000

a) See Experimental.

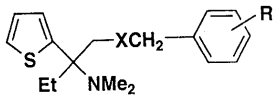
Table 2. Effect of Trimebutine Derivatives on Colonic Motility in Anesthetized Rats and Maximum Tolerated Dose (MTD) in Mice



Compound	X	Colon[a] (1 mg/kg i.v.)	MTD (mg/kg *p.o.*)
1a	CH_2OCO	++	≥3000
2a	CH_2OCH_2	+++	≤300
3	CH_2CH_2S	++	≥1000
4	$CH_2CH_2CH_2$	+++	≥1000
5	$CONHCH_2$	−	≥1000
6a	CH_2NHCH_2	+++	≤300

a) See Experimental.

Table 3. Effect of Trimebutine Derivatives on Colonic Motility in Anesthetized Rats and Maximum Tolerated Dose (MTD) in Mice



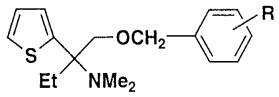
Compound	X	R	Colon[a] (1 mg/kg i.v.)	MTD (mg/kg *p.o.*)
2b	O	4-OMe	+	≥1000
2c	O	4-Cl	++	≥1000
2d	O	4-Me	++	≥1000
2e	O	4-OH	+	≥1000
2f	O	3-OMe	++	≥1000
2g	O	3,5-$(OMe)_2$, 4-OH	+++	≥1000
2h (T-1815)	O	3,4-$(OMe)_2$	+++	≥1000
6b	NH	H	−	≤300
6c	NH	4-OMe	+	≤300

a) See Experimental.

after i.d. administration. Though the ether derivative (**2a**) and amine derivative (**6a**) were effective, they showed fairly high toxicity.

For reduction of the toxicity, the substituents on the phenyl group in the ether derivative (**2a**) and amine derivative (**6a**) were changed to substituents other than the 3,4,5-trimethoxy group. Table 3 shows the colonic motility and MTD of these compounds. The 3,4-dimethoxy derivative (**2h**, T-1815) and 3,5-dimethoxy-4-hydroxy derivative (**2g**) showed strong activity and low toxicity.

Table 4. Effect of Trimebutine Derivatives on Clonidine-Induced Delay of Colonic Propulsion in Mice



Compound	R	Ameliorating effect[a] (10 mg/kg *p.o.*)	Ameliorating effect[a] (1 mg/kg *p.o.*)
2c	4-Cl	+++	−
2d	4-Me	+++	±
2g	3,5-$(OMe)_2$, 4-OH	±	
2h (T-1815)	3,4-$(OMe)_2$	+++	++

a) See Experimental.

The ameliorating effect of **2g** and **2h** on delayed colonic propulsion was examined (Table 4), and T-1815 (**2h**) was found to be superior to **2g**.

Conclusion

Starting from trimebutine, we prepared various derivatives to obtain a compound having strong colonic activity. Of these compounds, T-1815 (**2h**) shows strong colonic prokinetic activity and low toxicity. The pharmacological profile of T-1815 (**2h**) has been reported.[8]

Experimental

All melting points were measured using a Yamato MP-21 melting-point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1640 infrared spectrophotometer. NMR spectra were recorded on a Bruker AC-200 spectrometer with Me_4Si as an internal standard. Mass spectra (MS) were recorded on a Hitachi M-2000A spectrometer at 70 eV, and high-resolution mass spectra (HRMS) on a JEOL JMS HX-100 spectrometer. Column chromatography was carried out on silica gel (Kieselgel 60, 70—230 mesh, E. Merck).

Methyl 2-Isocyano-2-(2-thienyl)butyrate (8a) A solution of 1-isocyano-1-(2-thienyl)propane (**7a**) (20.0 g, 0.13 mol) in tetrahydrofuran (THF) (60 ml) was added to an LDA solution, which was prepared from diisopropylamine (23.0 ml, 0.16 mol), *n*-butyllithium (1.6 M in hexane) (100 ml, 0.16 mol) and THF (100 ml), at −78 °C under nitrogen. The mixture was stirred at the same temperature for 0.5 h. Then methyl chloroformate (14.0 ml, 0.17 mol) was added at −78 °C and the resulting mixture was stirred at the same temperature for 0.5 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl and the reaction mixture was extracted with ether. The organic layer was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane : AcOEt = 10 : 1) to give **8a** (22.2 g, 80%) as an oil. IR (film): 2900, 2150, 1750 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.05 (t, 3H, J = 7.0 Hz), 2.00—2.60 (m, 2H), 6.80—7.25 (m, 3H). MS *m/z*: 209 (M^+). HRMS Calcd for $C_{10}H_{11}NO_2S$ (M^+): 209.0510. Found: 209.0508.

2-Dimethylamino-2-(2-thienyl)butanol (9a) A solution of **8a** (6.0 g, 32 mmol) in THF (50 ml) was added to a suspension of $LiAlH_4$ (2.5 g, 66 mmol) in THF (20 ml) below 10 °C and the mixture was stirred at room temperature for 0.5 h. The reaction was quenched by the addition of 15% aqueous NaOH, then insoluble materials were filtered off and the filtrate was concentrated *in vacuo*. The residue (5.3 g) was dissolved in MeOH (50 ml). To this solution were added 35% HCHO (4.5 ml, 57 mmol), $NaBH_3CN$ (5.7 g, 86 mmol) and HCl–MeOH (4.6 mol/l,

Table 5. IR, ^{1}H-NMR and MS Data for **1a—g**

Compd.	Yield (%)	IR (film) cm^{-1}	^{1}H-NMR ($CDCl_3$) δ (ppm)	MS *m/z*
1a	82	2900, 1710	0.90 (t, 3H, J=7.0 Hz), 1.85—2.30 (m, 2H), 2.43 (s, 6H), 3.91 (s, 3H), 3.94 (s, 3H), 4.80 (s, 2H), 7.00—7.50 (m, 3H), 7.38 (s, 2H)	364 (M^+-Et)
1b	84	2900, 1710	0.79 (t, 3H, J=7.0 Hz), 1.78—2.13 (m, 2H), 2.33 (s, 6H), 3.80 (s, 6H), 3.83 (s, 3H), 4.68 (s, 2H), 6.98—7.28 (m, 5H)	364 (M^+-Et)
1c	83	2900, 1710	0.90 (t, 3H, J=7.0 Hz), 2.05 (q, 2H, J=7.0 Hz), 2.32 (s, 6H), 3.85 (s, 6H), 3.87 (s, 3H), 4.70 (s, 2H), 6.20—6.45 (m, 2H), 7.23 (s, 2H), 7.40 (m, 1H)	332 (M^+-Et)
1d	95	2900, 1710	0.46 (t, 3H, J=7.0 Hz), 2.02—2.38 (m, 2H), 2.48 (s, 6H), 3.74 (s, 6H), 3.82 (s, 3H), 4.90 (s, 2H), 7.13 (s, 2H), 7.20—7.38 (m, 2H), 7.50—7.80 (m, 3H), 9.10—9.20 (m, 2H)	437 (M^+)
1e	92	2900, 1720	0.78 (t, 3H, J=7.0 Hz), 1.80—2.10 (m, 2H), 2.25 (s, 6H), 3.73 (s, 3H), 3.77 (s, 6H), 4.50 (ABq, 2H), 6.90 (s, 2H), 6.90—7.05 (m, 1H), 7.38—7.65 (m, 2H), 8.35—8.50 (m, 1H)	374 (M^+)
1f	90	2900, 1720	0.77 (t, 3H, J=7.0 Hz), 1.75—2.05 (m, 2H), 2.27 (s, 6H), 3.79 (s, 3H), 3.82 (s, 6H), 4.40 (s, 2H), 6.98 (s, 2H), 7.07—7.22 (m, 1H), 7.74—7.87 (m, 1H), 8.32—8.40 (m, 1H), 8.69—8.72 (m, 1H)	374 (M^+)
1g	80	2900, 1730	0.79 (t, 3H, J=7.0 Hz), 1.80—2.10 (m, 2H), 2.25 (s, 6H), 3.72 (s, 3H), 3.76 (s, 6H), 4.48 (ABq, 2H), 6.94 (s, 2H), 7.55—7.63 (m, 2H), 8.50—8.58 (m, 2H)	374 (M^+)

Table 6. ^{1}H-NMR and MS Data for **2a—h**

Compd.	Yield (%)	^{1}H-NMR ($CDCl_3$) δ (ppm)	MS *m/z*
2a	85	0.80 (t, 3H, J=7.0 Hz), 1.80—2.20 (m, 2H), 2.26 (s, 6H), 3.75 (ABq, 2H), 3.78 (s, 9H), 4.46 (s, 2H), 6.50 (s, 2H), 6.70—7.20 (m, 3H)	379 (M^+)
2b	90	0.75 (t, 3H, J=7.0 Hz), 1.95 (m, 2H), 2.23 (s, 6H), 3.68 (ABq, 2H), 3.73 (s, 3H), 4.40 (s, 2H), 6.72 (d, 2H, J=8.0 Hz), 6.62—7.08 (m, 3H), 7.12 (d, 2H, J=8.0 Hz)	319 (M^+)
2c	92	0.79 (t, 3H, J=7.0 Hz), 1.99 (m, 2H), 2.27 (s, 6H), 3.79 (ABq, 2H), 4.52 (s, 2H), 6.75—7.30 (m, 7H)	323 (M^+)
2d	89	0.77 (t, 3H, J=7.0 Hz), 2.00 (m, 2H), 2.17 (s, 6H), 2.32 (s, 3H), 3.71 (ABq, 2H), 4.50 (s, 2H), 6.70—7.30 (m, 7H)	303 (M^+)
2e	85	0.75 (t, 3H, J=7.0 Hz), 2.03 (m, 2H), 2.20 (s, 6H), 3.70 (ABq, 2H), 4.35 (s, 2H), 5.40 (br s, 1H), 6.61 (d, 2H, J=9.0 Hz), 6.62—7.08 (m, 3H), 7.00 (d, 2H, J=9.0 Hz)	305 (M^+)
2f	94	0.78 (t, 3H, J=7.0 Hz), 2.04 (m, 2H), 2.28 (s, 6H), 3.78 (s, 3H), 3.80 (ABq, 2H), 4.54 (s, 7H), 6.70—7.30 (m, 2H)	319 (M^+)
2g	81	0.78 (t, 3H, J=7.0 Hz), 2.00 (m, 2H), 2.22 (s, 6H), 3.68 (ABq, 2H), 3.80 (s, 6H), 4.40 (s, 2H), 6.45 (s, 2H), 6.60—7.10 (m, 3H)	365 (M^+)
2h	95	0.78 (t, 3H, J=7.0 Hz), 2.03 (m, 2H), 2.26 (s, 6H), 3.75 (ABq, 2H), 3.86 (s, 6H), 4.50 (s, 2H), 6.70—7.30 (m, 6H)	349 (M^+)

Table 7. Physical Data for **1a—g** and **2a—h**

Compd.	mp (°C) (Recryst. solvent)	Formula	*Anal.* Calcd					Found				
			C	H	N	S	Cl	C	H	N	S	Cl
1a	163—164 (EtOH–Et_2O)	$C_{20}H_{27}NO_5S\cdot HCl$	55.87	6.56	3.26	7.46	8.25	55.98	6.43	3.25	7.52	8.26
1b	134—135 (EtOH–Et_2O)	$C_{20}H_{27}NO_5S\cdot HCl$	55.87	6.56	3.26	7.46	8.25	56.01	6.45	3.22	7.53	8.28
1c	138—140 (EtOH–Et_2O)	$C_{20}H_{27}NO_6\cdot HCl$	58.04	6.82	3.38		8.57	58.22	6.80	3.35		8.01
1d	140—142 (EtOH–Et_2O)	$C_{26}H_{31}NO_5\cdot HCl$	65.88	6.80	3.00		7.48	65.96	6.78	3.05		7.42
1e	104—105 (EtOH–Et_2O)	$C_{21}H_{28}N_2O_5\cdot 2HCl$	54.67	6.55	6.07		15.37	54.52	6.60	6.15		15.22
1f	95— 97 (AcOEt)	$C_{21}H_{28}N_2O_5\cdot C_4H_4O_4$[a]	59.52	6.39	5.55			59.65	6.36	5.50		
1g	138—141 (AcOEt)	$C_{21}H_{28}N_2O_5\cdot 2C_4H_4O_4$[a]	56.13	5.85	4.51			56.07	5.80	4.48		
2a	110—112 (AcOEt)	$C_{20}H_{29}NO_4S\cdot C_4H_4O_4$[a]	58.17	6.71	2.83	7.64		58.10	6.75	2.90	7.59	
2b	146—147 (EtOH)	$C_{18}H_{25}NO_2S\cdot C_{14}H_{10}O_4$[b]	68.43	6.28	2.49	5.71		68.24	6.31	2.53	5.81	
2c	134—136 (AcOEt)	$C_{17}H_{22}NO_2SCl\cdot C_4H_4O_4$[a]	57.33	5.96	3.18	7.29	8.06	57.24	6.02	3.11	7.15	8.00
2d	123—126 (AcOEt)	$C_{18}H_{25}NOS\cdot C_4H_4O_4$[a]	62.98	6.97	3.34	7.64		62.82	6.96	3.40	7.55	
2e	170—172 (EtOH)	$C_{17}H_{23}NO_2S\cdot C_{14}H_{10}O_4$[b]	67.99	6.07	2.56	5.85		67.93	6.10	2.62	6.01	
2f	86— 87 (AcOEt)	$C_{18}H_{25}NO_2S\cdot C_4H_4O_4$[a]	60.67	6.71	3.22	7.36		60.58	6.76	3.17	7.39	
2g	126—127 (AcOEt–hexane)	$C_{19}H_{27}NO_4S$	62.44	7.45	3.83	8.77		62.67	7.64	3.97	8.88	
2h	106—108 (EtOH)	$C_{19}H_{27}NO_3S\cdot C_{14}H_{10}O_4$[b]	66.99	6.30	2.37	5.42		66.83	6.49	2.23	5.25	

a) Maleic acid. *b*) 2-(4-Hydroxybenzoyl)benzoic acid.

18.7 ml), and the mixture was stirred at room temperature for 2 h. After the removal of MeOH, the mixture was basified with aqueous K_2CO_3 and extracted with AcOEt. The organic layer was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on silica gel ($CHCl_3$: MeOH = 10 : 1) to give **9a** (4.8 g, 82%) as an oil. IR (film): 3400, 2900, 2800 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.82 (t, 3H, J = 7.0 Hz), 1.93 (q, 2H, J = 7.0 Hz), 2.15 (s, 6H), 2.70 (br s, 1H), 3.78 (ABq, 2H), 6.60—7.20 (m, 3H). MS *m/z*: 170 ($M^+ - Et$). HRMS Calcd for $C_8H_{12}NOS$ ($M^+ - Et$): 170.0640. Found: 170.0647.

General Procedure for Synthesis of 2-Dimethylamino-2-(2-aryl)butyl 3,4,5-Trimethoxybenzoate (1) 3,4,5-Trimethoxybenzoyl chloride (20 mmol), Et_3N (20 mmol) and dimethylaminopyridine (0.1 g) were added to a solution of **9** (18.5 mmol) in THF (100 ml), and the mixture was stirred at room temperature for 16 h. Water was added and the mixture was extracted with AcOEt. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on silica gel to give **1** as an oil. Yields and spectral data of compounds **1a**—**g** are summarized in Table 5, and melting points and elementary analytical data of their salts are given in Table 7.

General Procedure for Synthesis of 2-Dimethylamino-2-(2-thienyl)butyl Substituted Benzyl Ether (2) A substituted benzyl chloride (16 mmol) was added in four portions to a suspension of **9a** (16 mmol) and KOH (80 mmol) in *N*,*N*-dimethylformamide (DMF) (4 ml), and the mixture was stirred at room temperature for 1 h, then acidified with 10% aqueous HCl and washed with ether. The aqueous layer was basified with K_2CO_3 and extracted with ether. The organic layer was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on silica gel to give **2** as an oil (except **2g**). Yields and spectral data of compounds **2a**—**h** are summarized in Table 6, and melting points and elementary analytical data of their salts are given in Table 7.

3-Isocyano-3-(2-thienyl)pentyl 3,4,5-Trimethoxyphenyl Thioether (10) An LDA solution was prepared from diisopropylamine (3.2 ml, 23 mmol), *n*-butyllithium (1.6 mol in hexane) (14 ml, 23 mmol) and THF (15 ml), and to this was added a solution of **8a** (2.8 g, 19 mmol) in THF (15 ml) at −78 °C under nitrogen. The mixture was stirred at the same temperature for 0.5 h. Then 2-(3,4,5-trimethoxyphenylthio)ethyl chloride (5.9 g, 23 mmol) in THF (7 ml) was added at −78 °C and the resulting mixture was stirred at the same temperature for 0.5 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl and the reaction mixture was extracted with ether. The organic layer was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane : AcOEt = 10 : 1) to give **10** (5.2 g, 74%) as an oil. IR (film): 2900, 2130 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.79 (t, 3H, J = 7.0 Hz), 1.50—2.15 (m, 2H), 2.60—3.00 (m, 4H), 3.72 (s, 9H), 6.39 (s, 2H), 6.60—6.90 (m, 2H), 7.00—7.10 (m, 1H). MS *m/z*: 377 (M^+). HRMS Calcd for $C_{19}H_{23}NO_3S_2$ (M^+): 377.1119. Found: 377.1121.

3-Dimethylamino-3-(2-thienyl)pentyl 3,4,5-Trimethoxyphenyl Thioether (3) Compound **3** was obtained from **10** (4.6 g, 12 mmol) by a procedure similar to that described for **9a**. The residue was chromatographed on silica gel (hexane : AcOEt = 3 : 1) to give **3** (3.2 g, 65%) as an oil. IR (film): 2900, 1590 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.83 (t, 3H, J = 7.0 Hz), 1.76—2.32 (m, 4H), 2.09 (s, 6H), 2.55—3.05 (m, 2H), 3.75 (s, 3H), 3.77 (s, 6H), 6.50 (s, 2H), 6.60—6.75 (m, 1H), 6.80—6.90 (m, 1H), 7.00—7.20 (m, 1H). MS *m/z*: 395 (M^+). mp (Maleate) 118—120 °C (AcOEt). *Anal.* Calcd for $C_{20}H_{29}NO_3S_2 \cdot C_4H_4O_4$: C, 56.34; H, 6.50; N, 2.74; S,12.53. Found: C, 56.22; H, 6.45; N, 2.83; S, 12.44.

4-Isocyano-4-(2-thienyl)-1-(3,4,5-trimethoxyphenyl)hexane (11) An LDA solution was prepared from diisopropylamine (2.2 ml, 16 mmol), *n*-butyllithium (1.6 mol in hexane) (10 ml, 16 mmol) and THF (10 ml), and to this was added a solution of **8** (2.0 g, 13 mmol) in THF (10 ml) at −78 °C under nitrogen. The mixture was stirred at the same temperature for 0.5 h. Then 3-(3,4,5-trimethoxyphenyl)propyl chloride (3.8 g, 16 mmol) in THF (5 ml) was added at −78 °C and the resulting mixture was stirred at the same temperature for 0.5 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl and the reaction mixture was extracted with ether. The organic layer was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane : AcOEt = 4 : 1) to give **11** (3.4 g, 72%) as an oil. IR (film): 2900, 2140 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.92 (t, 3H, J = 7.0 Hz), 1.40—2.15 (m, 6H), 2.40—2.70 (m, 2H), 3.76 (s, 9H), 6.21 (s, 2H), 6.75—6.95 (m, 2H), 7.05—7.20 (m, 1H). MS *m/z*: 359 (M^+). HRMS Calcd for $C_{20}H_{25}NO_3S$ (M^+): 359.1555. Found: 359.1552.

4-Dimethylamino-4-(2-thienyl)-1-(3,4,5-trimethoxyphenyl)hexane (4) Compound **4** was obtained from **11** (2.8 g, 7.8 mmol) by a procedure similar to that described for **9a**. The residue was chromatographed on silica gel ($CHCl_3$: MeOH = 30 : 1) to give **4** (1.4 g, 47%) as an oil. IR (film): 2900 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.82 (t, 3H, J = 7.0 Hz), 1.25—2.23 (m, 6H), 2.06 (s, 6H), 2.52 (t, 2H, J = 8.0 Hz), 3.72 (s, 3H), 3.75 (s, 6H), 6.24 (s, 2H), 6.60—7.10 (m, 3H). MS *m/z*: 348 ($M^+ - Et$). mp [2-(4-Hydroxybenzoyl)benzoic acid salt] 116—118 °C (EtOH). *Anal.* Calcd for $C_{21}H_{31}NO_3S \cdot C_{14}H_{10}O_4$: C, 67.83; H, 6.67; N, 2.26; S,5.17. Found: C, 67.90; H, 6.61; N, 2.23; S, 5.11.

2-Dimethylamino-2-(2-thienyl)butyric Acid (12) A mixture of **8a** (6.0 g, 32 mmol) and 17% HCl–MeOH (40 ml) was stirred at room temperature for 3 h. After the removal of MeOH, the residue was basified with aqueous K_2CO_3 and extracted with ether. The organic layer was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. A mixture of the residue (5.5 g), HCO_2H (3.5 ml, 96 mmol) and 35% HCHO (3.8 ml, 0.48 mol) was stirred at 105 °C for 1 h. The reaction mixture was basified with aqueous K_2CO_3 and extracted with AcOEt. The organic layer was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue (5.0 g) was dissolved in EtOH (10 ml). To this solution, $Ba(OH)_2 \cdot 8H_2O$ (26.2 g, 83 mmol) in H_2O (150 ml) was added and the mixture was refluxed for 72 h. Neutralization with dry ice afforded a precipitate, which was filtered off. The filtrate was concentrated *in vacuo* to give **5** (4.5 g, 74%). IR (nujol): 3400, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$ + DMSO-d_6) δ: 1.01 (t, 3H, J = 7.0 Hz), 2.26 (m, 2H), 2.59 (s, 6H), 6.80—7.30 (m, 3H). MS *m/z*: 213 (M^+). HRMS Calcd for $C_{10}H_{15}NO_2S$ (M^+): 213.0823. Found: 213.0820.

***N*-(3,4,5-Trimethoxybenzyl)-2-dimethylamino-2-(2-thienyl)butyroamide (5)** 1-Hydroxybenzotriazole (HOBT) (1.6 g, 12 mmol), 3,4,5-trimethoxybenzylamine (2.7 g, 14 mmol) and DCC (2.8 g, 14 mmol) were added to a solution of **12** (2.5 g, 12 mmol) in DMF (25 ml), and the mixture was stirred at room temperature for 16 h. After the removal of DMF, the mixture was diluted with AcOEt and the resulting precipitates were filtered off. The filtrate was washed with aqueous $NaHCO_3$ and extracted with 10% aqueous HCl. The aqueous layer was basified with $NaHCO_3$ and extracted with AcOEt. The organic layer was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on silica gel ($CHCl_3$: MeOH = 50 : 1) to give **5** (4.0 g, 89%) as an oil. IR (film): 3350, 2900, 1670, 1590 cm^{-1}. ^{1}H-NMR ($CDCl_3$ + DMSO-d_6) δ: 0.89 (t, 3H, J = 7.0 Hz), 2.80—3.30 (m, 2H), 2.07 (s, 6H), 3.75 (s, 9H), 4.36 (d, 2H, J = 6.0 Hz), 6.41 (s, 2H), 6.80—7.20 (m, 3H), 7.65 (m, 1H). MS *m/z*: 363 ($M^+ - Et$). mp (Hydrochloride) 168—169 °C (EtOH–Et_2O). *Anal.* Calcd for $C_{20}H_{28}N_2O_4S \cdot HCl$: C, 56.00; H, 6.81; N, 6.53; S,7.47; Cl, 8.26. Found: C, 56.02; H, 6.92; N, 6.66; S, 7.52; Cl, 8.38.

2-Dimethylamino-2-(2-thienyl)acetonitrile (14) A solution of $NaHSO_3$ (5.6 g, 54 mmol) and thiophen-2-aldehyde (**13**) (5.0 ml, 54 mmol) in H_2O (15 ml) was treated with 50% aqueous Me_2NH (5.4 ml, 54 mmol) and the mixture was stirred at room temperature for 1 h. Then NaCN (2.8 g, 54 mmol) was added and the whole was stirred at room temperature for 16 h. The reaction mixture was extracted with ether, and the organic layer was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled under reduced pressure (80 °C/3 mmHg) to give **14** (7.6 g, 86%). IR (film): 2900, 2200 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.31 (s, 6H), 4.87 (s, 1H), 6.80—7.30 (m, 3H). MS *m/z*: 166 (M^+). HRMS Calcd for $C_8H_{11}N_2S$ (M^+): 166.0565. Found: 166.0564.

2-Dimethylamino-2-(2-thienyl)butyronitrile (15) An LDA solution was prepared from diisopropylamine (7.7 ml, 55 mmol), *n*-butyllithium (1.6 mol in hexane) (34 ml, 55 mmol) and THF (40 ml), and to this was added a solution of **14** (7.6 g, 46 mmol) in THF (20 ml) at −78 °C under nitrogen. The mixture was stirred at the same temperature for 0.5 h, then iodoethane (5.3 ml, 66 mmol) was added at −78 °C and the resulting mixture was stirred at room temperature for 0.5 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl and the reaction mixture was extracted with ether. The organic layer was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled under reduced pressure (90 °C/5 mmHg) to give **15** (7.1 g, 90%). IR (film): 2900, 2200 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.80 (t, 3H, J = 7.0 Hz), 1.60—2.50 (m, 2H), 2.28 (s, 6H), 4.87 (s, 1H), 6.70—7.20 (m, 3H). MS *m/z* 194 (M^+). HRMS Calcd for $C_{10}H_{14}N_2S$ (M^+): 194.0878. Found: 194.0876.

2-Dimethylamino-2-(2-thienyl)butylamine (16) A solution of **15** (7.1 g, 37 mmol) in THF (50 ml) was added to a suspension of $LiAlH_4$ (2.8 g, 74 mmol) in THF (20 ml) below 10 °C, and the mixture was stirred at room temperature for 1 h. The reaction was quenched by the addition

of 15% aqueous NaOH, the insoluble materials were filtered off and the filtrate was concentrated *in vacuo*. The residue was distilled under reduced pressure (90 °C/4 mmHg) to give **16** (2.4 g, 33%). IR (film): 3400—3100 (br), 2900 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.85 (t, 3H, J=7.0 Hz), 1.60 (m, 2H), 1.70—2.10 (m, 2H), 2.13 (s, 6H), 3.00 (dd, 2H, J=12.0, 18.0 Hz), 6.60—7.20 (m, 3H). MS m/z: 168 ($M^+ - CH_2NH_2$). HRMS Calcd for $C_9H_{14}NS$ ($M^+ - CH_2NH_2$): 168.0868. Found: 168.0864.

***N*-(3,4,5-Trimethoxybenzyl)-2-dimethylamino-2-(2-thienyl)butylamine (6a)** 3,4,5-Trimethoxybenzaldehyde (2.1 g, 11 mmol), $NaBH_3CN$ (0.7 g, 11 mmol) and HCl–MeOH (4.6 mol/l, 2.4 ml) were added to a solution of **16** (1.4 g, 7.1 mmol) in MeOH (15 ml), and the mixture was stirred at room temperature for 16 h. After the removal of MeOH, the mixture was basified with aqueous K_2CO_3 and extracted with ether. The organic layer was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on silica gel ($CHCl_3$: MeOH = 20 : 1) to give **6a** (2.1 g, 79%) as an oil. IR (film): 3300, 2900, 1590 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.83 (t, 3H, J=7.0 Hz), 1.77 (s, 1H), 2.03 (q, 2H, J=7.0 Hz), 2.12 (s, 6H), 2.90 (ABq, 2H), 3.71 (s, 2H), 3.76 (s, 3H), 3.79 (s, 6H), 6.47 (s, 2H), 6.65—7.15 (m, 3H), 7.65 (m, 1H). MS m/z: 197 (M^+ − 3,4,5-trimethoxybenzyl). mp (Dihydrochloride) 137—139 °C (EtOH–Et_2O). *Anal.* Calcd for $C_{20}H_{30}N_2O_3S \cdot 2HCl$: C, 53.21; H, 7.14; N, 6.21; S,7.10; Cl, 15.71. Found: C, 53.10; H, 7.18; N, 6.15; S, 7.01; Cl, 15.58.

***N*-Benzyl-2-dimethylamino-2-(2-thienyl)butylamine (6b)** Compound **6b** was obtained from **16** (2.0 g, 10 mmol) by a procedure similar to that described for **6a**. The residue was chromatographed on silica gel ($CHCl_3$: MeOH = 20 : 1) to give **6b** (2.4 g, 83%) as an oil. IR (film): 3300, 2900, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.82 (t, 3H, J=7.0 Hz), 1.70 (s, 1H), 2.04 (q, 2H, J=7.0 Hz), 2.13 (s, 6H), 2.95 (ABq, 2H), 3.82 (s, 2H), 6.70—7.20 (m, 3H), 7.29 (s, 5H). MS m/z: 243 ($M^+ - NMe_2$). mp (Dihydrochloride) 155—157 °C (EtOH–Et_2O). *Anal.* Calcd for $C_{17}H_{24}N_2S \cdot 2HCl$: C, 56.50; H, 7.25; N, 7.75; S, 8.87; Cl, 19.62. Found: C, 56.21; H, 7.37; N, 7.98; S, 9.02; Cl, 19.35.

***N*-(4-Methoxybenzyl)-2-dimethylamino-2-(2-thienyl)butylamine (6c)** Compound **6c** was obtained from **16** (2.0 g, 10 mmol) by a procedure similar to that described for **6a**. The residue was chromatographed on silica gel ($CHCl_3$: MeOH = 20 : 1) to give **6a** (2.4 g, 74%) as an oil. IR (film): 3300, 2900, 1610 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.80 (t, 3H, J=7.0 Hz), 1.67 (s, 1H), 2.01 (q, 2H, J=7.0 Hz), 2.10 (s, 6H), 2.92 (ABq, 2H), 3.73 (s, 2H), 3.76 (s, 3H), 6.70—7.20 (m, 3H), 6.80 (d, 2H, J=8.0 Hz), 7.22 (d, 2H, J=8.0 Hz). MS m/z: 273 ($M^+ - NMe_2$). mp (Dihydrochloride) 147—151 °C (EtOH–Et_2O). *Anal.* Calcd for $C_{18}H_{26}N_2OS \cdot 2HCl$: C, 55.24; H, 7.21; N, 7.16; S, 8.19; Cl, 18.12. Found: C, 55.06; H, 7.32; N, 6.90; S, 7.99; Cl, 17.90.

Pharmacological Methods The colonic contractile activity was examined in anesthetized rats. Male Sprague-Dawley rats, weighing 270—320 g, were fasted overnight and anesthetized with subcutaneous injection of urethane (1.2 g/kg). The abdomen was exposed through a midline incision and a strain gauge force transducer (F-08IS, Star Medical Inc.) was sutured on the serosal surface of the proximal colon (3—5 cm distal to the ileo-cecal junction). Contractile activity of the circular muscle was recorded on a Linearcorder (WR-3101, Graphtec) *via* strain amplifiers (8M-52, NEC-San'ei). In each animal, intravenous administration of bethanechol at 30 μg/kg was repeated twice or three times to confirm approximately constant responses, and then the test compounds were administered intravenously. Contractile effect (E) of the test compounds was expressed as follows; $+++ : E \geq 0.70$, $++ : 0.70 > E \geq 0.40$, $+ : 0.40 > E \geq 0.10$, $- : 0.10 > E$, where E is a response relative to that induced by bethanechol (30 μg/kg, i.v.), which was taken as 1.0.

The colonic propulsive activity was studied basically according to the method of Pendleton *et al.*[9] Male Slc-ddy mice, weighing 22—28 g, were fasted for 4 h and a glass bead (3 mm in diameter) was inserted into the distal colon 3 cm above the anus 20 min after subcutaneous injection of an adrenergic α_2 agonist, clonidine (10 μg/kg). The time required to evacuate the bead was measured and used as an index of colonic propulsive activity. Each test compound was administered orally 30 min before bead insertion. The ameliorating effect (AE) of the test compounds on the delay time of glass bead evacuation induced by clonidine (10 μg/kg, s.c.) was expressed as follows; $+++ : AE \geq 70$, $++ : 70 > AE \geq 50$, $+ : 50 > AE > 30$, $\pm : 30 > AE \geq 10$, $- : 10 > AE$. AE was calculated by use of the following equation; $AE = (C - T)/C \times 100$, where C is the time required to evacuate the bead in animals given distilled water and clonidine, and T is the time required to evacuate the bead in animals given the test compound and clonidine.

The acute toxicities (maximum tolerance dose) of test compounds were determined by oral administration to groups of five male Slc-ddy mice (weighing 22—26 g).

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