Change of Mechanical Activity to Contraction from the Relaxation Induced by the Intracellular Ca^{2+} Antagonist KT-362; Effects of Alkylation of Side Chain, and Substitution of 2,3,4,5-Tetrahydro-1,5-Benzothiazepine Derivatives

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KT-362 (5-[3-[2-(3,4-Dimethoxyphenyl)ethyl]aminopropionyl]-2,3,4,5-tetrahydro-1,5-benzothiazepine fumarate) is an intracellular Ca^{2+} antagonist. The compound obtained by introducing methyl groups onto the nitrogen (R_2) of the side chain of KT-362 showed vasoconstrictive activity. Therefore we synthesized various derivatives, and examined their activities. Substitution at position R_2 of the side chain resulted in potent contractile activity, and the optimal alkyl length was two or three carbons. The potency was further increased by the introduction of a chloro group at the R_1 position of 2,3,4,5-tetrahydro-1,5-benzothiazepines. One of the synthesized compounds, 8-chloro-5-{*N*-ethyl-*N*-[2-(3,4-dimethoxyphenyl)ethyl]aminopropionyl}-2,3,4,5-tetrahydro-1,5-benzothiazepine fumarate (9b), showed an EC_{50} value of 3.47×10^{-8} M for contraction of rabbit iliac artery. The action of compound 9b was antagonized competitively by an H_1-histamine receptor antagonist, diphenhydramine, and the pA_2 value was 7.82. The maximum constriction was inhibited by a Ca^{2+} entry blocker, nicardipine, but not by an α_1-adrenoreceptor antagonist, prazosin. In a Ca^{2+}-free medium, tonic constriction induced by 9b disappeared, and only a phasic constriction was observed. Though this phasic constriction was inhibited by diphenhydramine, it was not inhibited by prazosin or nicardipine.

Key words 2,3,4,5-tetrahydro-1,5-benzothiazepine; KT-362; contractile activity; histamine agonist; structure–activity relationship

Previously, we have shown that KT-362 (5-[3-[2-(3,4-dimethoxyphenyl)ethyl]aminopropionyl]-2,3,4,5-tetrahydro-1,5-benzothiazepine fumarate) (Fig. 1) interferes with the mobilization of intracellular Ca^{2+} in vascular smooth muscles.[1-4] Intracellular Ca^{2+} antagonists have not been developed as yet, and KT-362 is expected to be clinically useful in diseases in which pathological changes of intracellular calcium are involved.

We tried to introduce an acetyl group on the nitrogen of the side chain of KT-362, in an attempt to increase the activity. However, the intracellular Ca^{2+}-inhibitory effect disappeared.[4] Next, we introduced a methyl group on this nitrogen, and obtained a compound with contractile activity. Therefore, we synthesized compounds with various alkyl groups, and examined their pharmacological activities.

Chemistry

The compounds employed in this study were synthesized according to published procedures (Charts 1, 2).[4,5] The 2,3,4,5-tetrahydro-1,5-benzothiazepine derivative **7** was synthesized as shown in Chart 2. Treatment of 2-aminothiophenols **3** with 1-bromo-3-chloropropane and isopropylamine gave the thioethers **4**, and ring closure with tripropylamine in toluene gave 2,3,4,5-tetrahydro-1,5-benzothiazepines **5**. 5-(3-Chloro-propionyl)-2,3,4,5-tetrahydro-1,5-benzothiazepine **6** was prepared by the reaction of **5** and 3-chloropropionyl chloride. The amino derivatives **7** were prepared by the reaction of **6** and phenethylamines or phenoxyethylamines in toluene at 110 °C.

Introduction of alkyl groups into the nitrogen of the side chain of **7** was carried out as shown in Chart 1. When R_2 was methyl, ethyl, isopropyl, cyclopentyl or cyclohexyl, method A (reductive amination) was employed. Treatment of **7** with aldehyde or ketone derivatives and $NaBH_3CN$ in methanol gave alkylated products (**8a**, **b**, **8d**, **8f**, **8g**, **9a**, **b** and **10a**—**f**). When R_2 was butyl or propyl, method B was employed. Compound **7** was alkylated with alkyl halides to provide alkylated products (**8c**, **8e**, **9c**, **9d**).

Results and Discussion

The contractile activities of prepared compounds were estimated with isolated rabbit iliac arteries, and the values of the concentration which induces a 50% contraction (40 mM KCl = 100%) and the maximal contractile percent

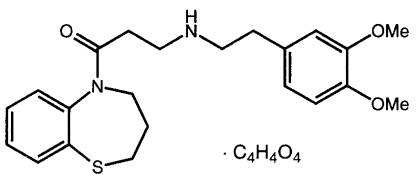

Fig. 1. KT-362 (Intracellular Ca^{2+} Antagonist)

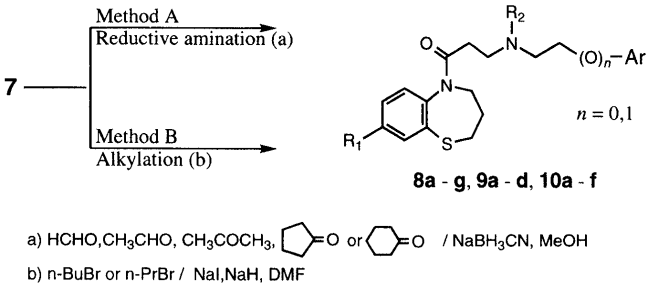

Chart 1

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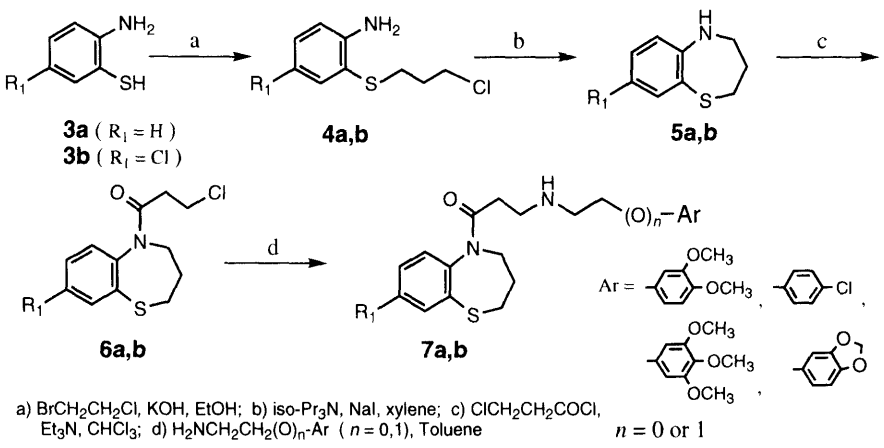
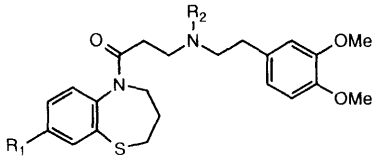


Chart 2

Table 1. Physical and Biological Data for 2,3,4,5-Tetrahydro-1,5-benzothiazepines



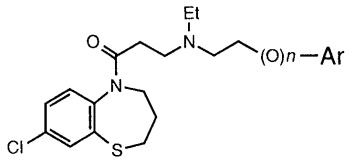
Compd. No.	R_1	R_2	mp (°C)	Formula	Analysis (%) Calcd (Found)			Contractile activity	
					C	H	N	EC_{50} (M)[a]	Max (%)[b]
8a	H	Me	106—107	$C_{23}H_{30}N_2O_3S \cdot C_4H_4O_4$	61.14 (61.23	6.46 6.59	5.28 5.41)	6.76×10^{-6}	65.6
8b	H	Et	76—77	$C_{24}H_{32}N_2O_3S \cdot C_4H_4O_4$	61.77 (61.57	6.67 6.87	5.15 5.30)	1.17×10^{-6}	101.9
8c	H	*n*-Pr	Oil	$C_{25}H_{34}N_2O_3S \cdot C_4H_4O_4$	62.37 (62.47	6.86 7.01	5.02 5.30)	6.75×10^{-7}	102.3
8d	H	iso-Pr	Oil	$C_{25}H_{34}N_2O_3S \cdot C_4H_4O_4$	62.37 (32.13	6.86 7.06	5.02 5.12)	6.17×10^{-7}	106.8
8e	H	*n*-Bu	98—99	$C_{26}H_{36}N_2O_3S \cdot C_4H_4O_4$	62.95 (63.01	6.99 7.11	4.89 4.73)	(—)	21.7
8f	H	cyclo-Pentyl	Oil	$C_{27}H_{36}N_2O_3S \cdot C_4H_4O_4$	63.71 (63.67	6.87 7.01	4.79 4.54)	(—)	12.9
8g	H	cyclo-Hexyl	Oil	$C_{28}H_{38}N_2O_3S \cdot C_4H_4O_4$	64.22 (63.98	7.02 7.16	4.68 4.87)	(—)	0
7c	Cl	H	116—118	$C_{22}H_{27}ClN_2O_3S \cdot C_4H_4O_4$	56.61 (56.72	5.44 5.63	5.08 5.09)	(—)	0
9a	Cl	Me	149—151	$C_{23}H_{29}ClN_2O_3S \cdot C_4H_4O_4$	57.39 (57.30	5.89 5.77	4.96 4.91)	2.29×10^{-7}	71.4
9b	Cl	Et	123—124	$C_{24}H_{31}ClN_2O_3S \cdot C_4H_4O_4$	58.07 (57.92	6.04 6.16	4.84 4.61)	3.47×10^{-8}	121.8
9c	Cl	*n*-Pr	Oil	$C_{25}H_{33}ClN_2O_3S \cdot C_4H_4O_4$	58.72 (58.85	6.24 6.47	4.72 4.53)	(—)	108.3
9d	Cl	*n*-Bu	Oil	$C_{26}H_{35}ClN_2O_3S \cdot C_4H_4O_4$	59.37 (59.35	6.43 6.52	4.62 4.71)	(—)	77.6
KT-362	H	H	164—165	$C_{22}H_{28}N_2O_3S \cdot C_4H_4O_4$	60.34 (60.46	6.01 6.24	5.21 5.42)	(—)	0

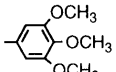
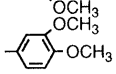
a) EC_{50} (M): Concentration which induces 50% contraction of rabbit iliac artery as compared with 40 mM KCl. *b*) Max (%): Maximal contractile force obtained (40 mM KCl = 100%).

(max%) are shown in Table 1.

In the *N*-alkyl analogues **8a**—**g**, elongation of the alkyl group at R_2 from CH_3 (**8a**) to *n*-C_3H_7 (**8c**) increased the contractile response activity, but *n*-C_4H_9 (**8e**) and C_6H_{11} (**8g**) showed diminished activity. The optimal alkyl length at the R_2 position was *n*-C_3H_7 (**8c**), giving an EC_{50} value of 6.75×10^{-7} M. When a halogen group was introduced at the R_1 position of 2,3,4,5-tetrahydro-1,5-benzothiazepine, the 8-chloro derivatives **9a** and **9b** showed an increase of contractile response activity as compared to **8a** and **8b**, from EC_{50} values of 6.76×10^{-6} and 1.17×10^{-6} to 2.29×10^{-7} and 3.47×10^{-8} M, (**8a**, **8b** *vs.* **9a**, **9b**). In the 8-chloro analogues **9a**—**d**, the optimal alkyl length at the R_2 position was C_2H_5 (**9b**), giving an EC_{50} value

Table 2. Physical and Biological Data for 8-Chloro-2,3,4,5-tetrahydro-1,5-benzothiazepines



Compd. No.	Ar	n	mp (°C)	Formula	Analysis (%) Calcd (Found)			Contractile activity	
					C	H	N	EC_{50} (M)[a]	Max (%)[b]
10a		0	82—83	$C_{22}H_{27}ClN_2OS \cdot HCl$	60.13 (60.32)	6.42 6.64	6.37 6.20)	1.05×10^{-7}	104.8
10b		0	123—125	$C_{22}H_{26}Cl_2N_2OS \cdot HCl$	55.76 (55.95	5.74 5.64	5.91 5.78)	8.56×10^{-8}	100.0
10c		0	86—88	$C_{23}H_{27}ClN_2O_3S \cdot HCl$	57.14 (56.98	5.79 8.91	5.79 5.69)	7.24×10^{-8}	90.9
10d		1	123—124	$C_{23}H_{27}ClN_2O_4S \cdot HCl$	55.33 (55.51	5.65 5.83	5.61 5.57)	(—)	7.6
10e		0	64—65	$C_{25}H_{33}ClN_2O_4S \cdot HCl$	56.70 (56.77	6.48 6.60	5.29 5.16)	(—)	46.2
10f		1	144—146	$C_{24}H_{31}ClN_2O_4S \cdot HCl$	55.81 (55.73	6.27 6.41	5.44 5.24)	3.02×10^{-6}	57.4

a) EC50 (M): Concentration which induces 50% contraction of rabbit iliac artery as compared with 40 mM KCl. *b*) Max (%): Maximal contractile force obtained (40 mM KCl = 100%).

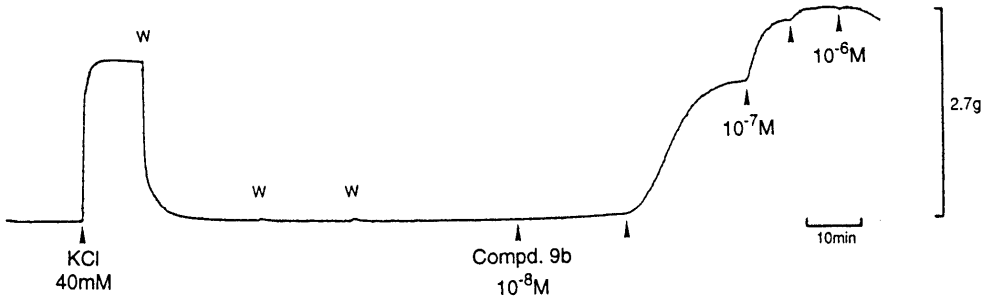


Fig. 2. A Typical Tracing of **9b**-Induced Contraction of Rabbit Iliac Artery in a Normal Medium

of 3.47×10^{-8} M. These results suggest that the introduction of an alkyl group at the nitrogen position of the side chain of compound **7c** enhances the contractile activity. Modification of the dimethoxy group of compound **9b**, such as conversion to the hydrogen derivative **10a** ($EC_{50} = 1.05 \times 10^{-7}$ M), chloro derivative **10b** ($EC_{50} = 8.56 \times 10^{-8}$ M), 1,3-dioxole derivative **10c** ($EC_{50} = 7.24 \times 10^{-8}$ M), trimethoxy derivative **10e** (inactive) decreased the contractile activity (Table 2).

As for the phenoxyethyl derivatives, **10d** (inactive) and **10f** ($EC_{50} = 3.02 \times 10^{-6}$ M) with an introduced oxygen atom, their activity was decreased (**10c**, **9b** *vs.* **10d**, **10f**). Representative data for the most potent compound **9b** are shown in Fig. 2. Compound **9b** caused a concentration–dependent contraction (10^{-8}—10^{-6} M) and the maximal contraction was 125% (40 mM KCl = 100%) at 10^{-6} M.

Then, we examined the effect of histamine H_1-blockers, diphenhydramine and pyrilamine, on the **9b** induced contraction. The concentration–response curve of compound **9b** was shifted in parallel to the right by treatment with diphenhydramine (pA_2; 7.82, slope = 0.96) and pyrilamine (not shown). Furthermore, the maximal contractile response was inhibited by a Ca^{2+}-channel blocker, nicardipine. On the other hand, the contractile response to compound **9b** was not affected by an α-blocker, prazosin. These results suggested that contraction induced by **9b** may be due to the activation of histamine H_1 receptors (Fig. 3).

Further, we examined the contractile activity of **9b** in a Ca^{2+}-free medium (Fig. 4). Compound **9b** showed a phasic contractile response in a Ca^{2+}-free solution. The contractile response was inhibited by diphenhydramine (10^{-7} M), but not by prazosin (10^{-6} M) or nicardipine (10^{-6} M). These results also imply that the phasic contractile response to **9b** in a Ca^{2+}-free solution is mediated by the histamine H_1-receptor.

On the other hand, compound **9b** did not show a contractile effect in isolated guinea pig ileum and trachea, suggesting that its action can not be explained only in

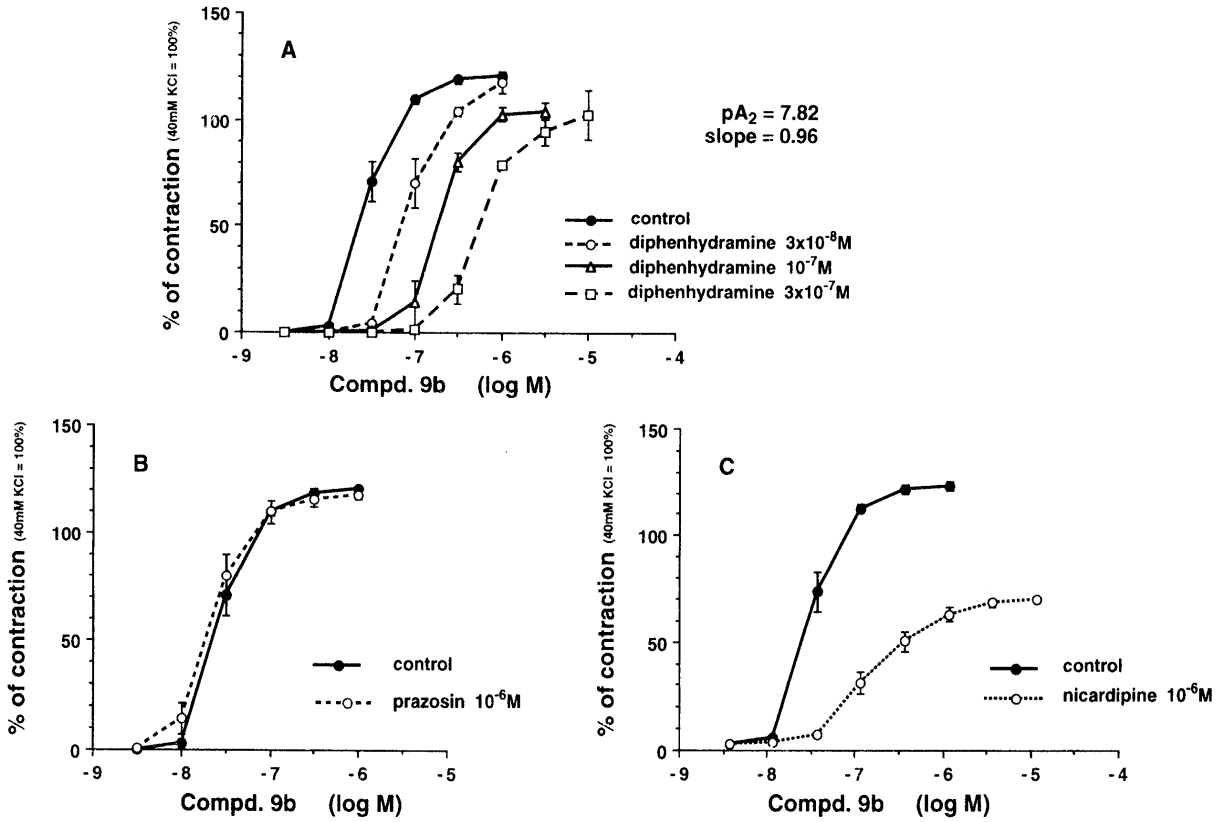


Fig. 3. Effects of Diphenhydramine (Panel A), Prazosin (Panel B) and Nicardipine (Panel C) on the **9b**-Induced Concentration–Response Curves of the Rabbit Iliac Artery

The maximal contraction induced by **9b** in a control preparation was 2.7 ± 0.3 g. Each point represents the mean $\pm$ S.E. of 5 preparations.

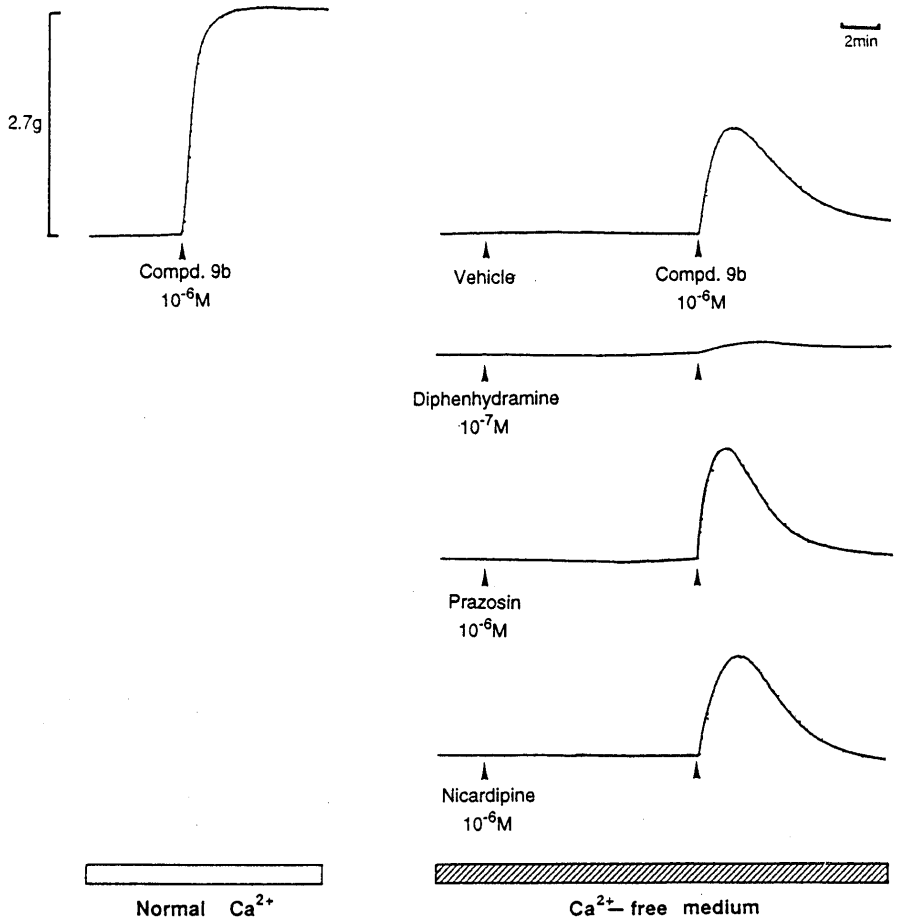


Fig. 4. The Effects of Diphenhydramine, Prazosin and Nicardipine on the Response to **9b** (10^{-6} M) in Rabbit Iliac Artery

Tissues were incubated in Ca^{2+}-free medium with 0.2 mM EGTA for 20 min. Compound **9** was added to the medium 10 min after treatment with other compounds.

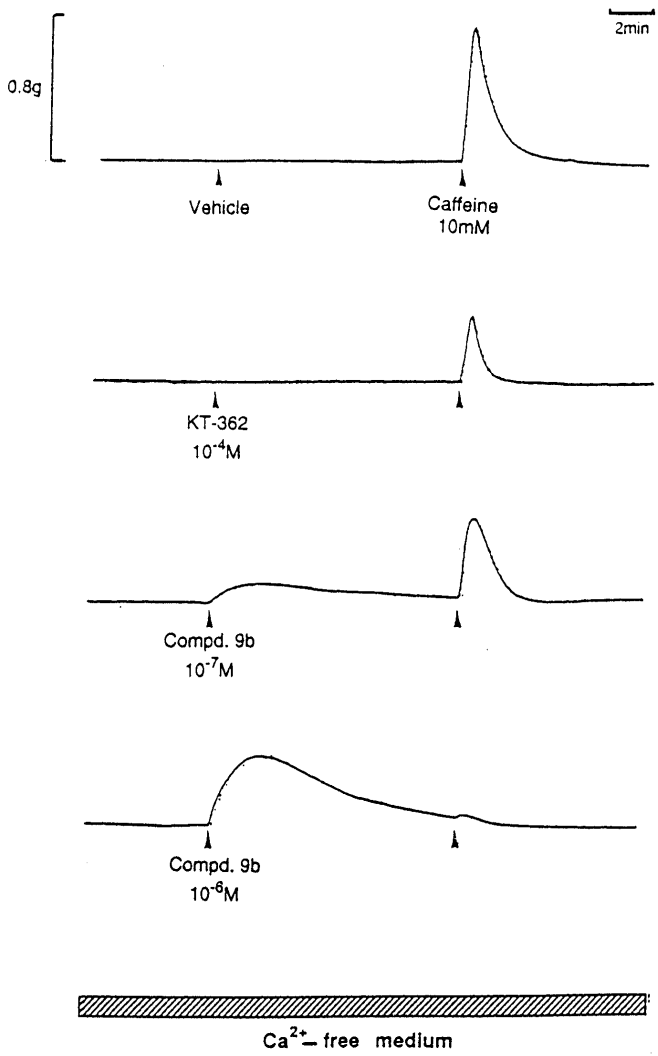


Fig. 5. The Effects of KT-362 and **9b** on the Response to Caffeine (10 mM) in Rabbit Iliac Artery

Tissues were incubated in Ca^{2+}-free medium for 20 min. Caffeine was added to the medium 10 min after treatment with other compounds.

terms of histamine H_1 agonist action, because H_1 agonists cause a strong contraction in both tissues. It is now generally accepted that caffeine releases intracellular Ca^{2+} in vascular smooth muscle, and KT-362 inhibited the residual caffeine-induced contractions of rabbit iliac artery in a Ca^{2+}-free medium (Fig. 5). Pretreatment with **9b** (10^{-7} M) also inhibited the residual caffeine-induced contraction, though compound **9b** itself caused a small contraction. A higher concentration of compound **9b** (10^{-6} M) caused a much greater slow phasic contraction in a Ca^{2+}-free medium and the contraction following application of caffeine was almost abolished. Therefore, the inhibition is considered to be mediated by the Ca^{2+}-releasing effect of compound **9b** on the caffeine-sensitive intracellular Ca^{2+} storage site.

In conclusion, we obtained active compounds by the introduction of small alkyl group into KT-362. The present results suggest that compound **9b** has a potent contractile activity in vascular smooth muscle. The contractile effect is assumed to be mediated by a promoting action on extracellular Ca^{2+} influx and Ca^{2+} release from the caffeine-sensitive intracellular Ca^{2+} storage site. The mechanism can not be explained only in terms of histamine H_1 agonistic action, because of no contracting activity was seen in ileum and trachea. Therefore we consider that the contracting effect of compound **9b** is mediated by Ca^{2+}- agonistic action. Further study is necessary to clarify the precise mechanism involved.

Experimental

Melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Hitachi 270-30. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were measured at 90 MHz on a Hitachi R-90H Fourier-transform NMR spectrometer. Chemical shifts are quoted in parts per million (ppm) with tetramethylsilane as an internal standard. Coupling constants (J) are given in Hz. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; br s, broad singlet; sept, septet; m, multiplet. Mass spectra (MS) were taken on a Hitachi M-80B spectrometer. Elemental analyses, determined by a Hitachi 026 CHN analyzer, were with in $\pm$0.4% of theoretical values. For column chromatography, silica gel (Merck, Kieselgel 60, 70—230 mesh) was used.

***β*-(2-Chloropropylthio)-1,4-chloroaniline (4b)** A solution of **3b** (2.36 g, 10.2 mmol), 1-bromo-3-chloropropane (1.93 g, 12.2 mmol) and KOH (0.74 g, 11.2 mmol) in 30 ml of EtOH was stirred at 25 °C for 3.0 h. The solvent was evaporated *in vacuo*, and the mixture was diluted with water and extracted with Et_2O. The combined organic phase was washed with water and brine, dried (Na_2SO_4), filtered and evaporated *in vacuo*. The resulting product was purified by silica gel column chromatography (Et_2O : Hexene = 1 : 1) to give 1.21 g (50.3%) of **4b** as a yellow oil. Mass (*m/z*): 235 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.84 (2H, m), 2.94 (2H, t, J = 3.7 Hz), 3.64 (2H, t, J = 6.2 Hz), 4.14 (2H, br s), 6.64 (1H, d, J = 8.5 Hz, aromatic), 7.00—7.34 (2H, m, aromatic).

8-Chloro-2,3,4,5-tetrahydro-1,5-benzothiazepine (5b) A solution of **4b** (1.2 g, 5.1 mmol), $isoPr_3N$ (0.8 g, 5.6 mmol) and NaI (80.0 mg, 0.51 mmol) in 25 ml of xylene was stirred at 140 °C for 20 h. The reaction mixture was cooled to room temperature, and the solvents were evaporated *in vacuo*. The residue was dissolved in ethyl acetate (AcOEt), and the solution was washed with water and brine, dried (Na_2SO_4), filtered and evaporated *in vacuo*. The resulting product was purified by silica gel column chromatography ($CHCl_3$) to give 0.8 g (78.8%) of **5b** as a yellow solid, mp 82—84 °C Mass (*m/z*): 199 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.95 (2H, m), 2.83 (2H, dd, J = 3.6, 5.6 Hz), 4.01 (1H, br s), 6.60 (1H, d, J = 8.4 Hz), 6.98 (1H, dd, J = 2.4, 8.4 Hz, aromatic), 7.32 (1H, d, J = 2.4 Hz, aromatic)

5-(3-Chloropropionyl)-8-chloro-2,3,4,5-tetrahydro-1,5-benzothiazepine (6b) *β*-Chloro-propionyl choride (0.56 g, 4.4 mmol) was added dropwise at 0 °C to a solution of **5b** (0.8 g, 4.00 mmol) and triethylamine (0.48 g, 4.40 mmol) in 40 ml of $CHCl_3$. The resulting mixture was stirred at 0 °C for 0.5 h. The solvent was evaporated *in vacuo*, and the residue was dissolved in AcOEt. This solution was washed with water and brine, dried (Na_2SO_4), filtered and evaporated *in vacuo*. The resulting product was purified by silica gel column chromatography (AcOEt : Hexane = 1 : 4) to give 0.69 g (59.3%) of **6b** as a colorless solid, mp 117—119 °C. Mass (*m/z*): 288 (M^+), ^{1}H-NMR ($CDCl_3$) δ: 1.85—3.10 (6H, m), 3.42—3.98 (2H, m), 4.70—4.98 (1H, m), 7.20—7.80 (3H, m, aromatic).

5-{3-[2-(3,4-Dimethoxyphenyl)ethyl]aminopropionyl}-8-chloro-2,3,4,5-tetrahydro-1,5-benzothiazepine (7c) A solution of **6b** (0.68 g, 2.34 mmol) and 3,4-dimethoxyphenethylamine (0.89 g, 4.91 mmol) in 25 ml of xylene was stirred at 140 °C for 12 h. The reaction mixture was cooled to room temperature, washed with water and brine, dried (Na_2SO_4), filtered and evaporated *in vacuo*. The resulting product was purified by silica gel column chromatography ($CHCl_3$: MeOH = 4 : 1) to give 0.51 g (50.1%) of **7c′** as a colorless oil. A solution of **7c′** (0.51 g, 1.18 mmol) and fumaric acid (0.14 mg, 1.18 mmol) in 15 ml of MeOH was stirred at room temperature for 30 min, and the solvent was removed *in vacuo*. The residue was recrystallized from MeOH–E_2O gave a pure sample of **7c** (0.57 g, 88.0%) as a white solid. IR (neat) cm^{-1}: 2944, 1692, 1656, 1515. Mass (*m/z*): 434 (M − fumaric acid)$^+$. ^{1}H-NMR ($CDCl_3$) δ: 1.98—3.50 (13H, m), 3.79 (3H, s, OCH_3), 3.85 (3H, s, OCH3), 4.75—4.90 (1H, m), 6.67—6.90 (3H, m, aromatic), 7.10—7.41 (2H, m, aromatic), 7.63 (1H, d, J = 2.2 Hz, aromatic).

Method A. 8-Chloro-5-{*N*-ethyl-*N*-[2-(3,4-dimethoxyphenyl)ethyl]-aminopropionyl}-2,3,4,5-tetrahydro-1,5-benzothiazepine Fumarate (9b)

Table 3. Spectral Data of 2,3,4,5-Tetrahydro-1,5-benzothiazepines

Compd. No.	Yield[a] (%)	MS, M^+ (*m/z*)	IR ν_{max} (cm^{-1})	^{1}H-NMR δ (ppm)
8a	44.0	414 (M–fumaric acid)$^+$	2926, 1653, 1268, 1158	0.98 (3H, t, J=6.8 Hz), 1.52—3.01 (15H, m), 3.81 (3H, s), 3.88 (3H, s), 4.72 (1H, m), 6.50—6.85 (3H, m), 7.10—7.35 (3H, m), 7.60 (1H, m)
8b	39.6	428 (M−fumaric acid)$^+$	2956, 1655, 1260	0.80 (3H, t, J=6.8 Hz), 1.20—1.60 (2H, m), 2.00—3.10 (15H, m), 3.81 (3H, s), 3.85 (3H, s), 4.75 (1H, m), 6.50—6.80 (3H, m), 7.10—7.35 (2H, m), 7.60 (1H, m)
8c	69.3	442 (M−fumaric acid)$^+$	3448, 2944, 1641, 1260	0.80 (3H, t, J=6.8 Hz), 1.01—1.50 (4H, m), 1.56—1.80 (2H, m), 2.00—3.10 (15H, m), 3.80 (3H, s), 3.84 (3H, s), 4.75 (1H, m), 6.50—6.85 (3H, m), 7.10—7.40 (2H, m), 7.60 (1H, m).
8d	17.1	442 (M−fumaric acid)$^+$	2950, 1650, 1260, 1157	0.85 (6H, m), 1.90—3.00 (14H, m), 3.79 (3H, s), 3.83 (3H, s), 4.76 (1H, m), 6.40—6.89 (3H, m), 7.00—7.25 (3H, m), 7.40—7.61 (1H, m)
8f	36.5	468 (M−fumaric acid)$^+$	2926, 1641, 1263	1.00—1.98 (8H, m), 2.20 (2H, m), 2.40—3.20 (12H, m), 3.84 (3H, m), 3.85 (3H, m), 7.20—7.70 (4H, m)
8g	42.2	482 (M−fumaric acid)$^+$	2938, 1653, 1263, 1158	0.98—1.95 (6H, m), 2.00—2.93 (14H, m), 3.81 (3H, s), 3.83 (3H, s), 4.75 (1H, m), 6.50—6.81 (3H, m), 7.15—7.40 (3H, m), 7.56 (1H, m)
9a	66.5	448 (M−fumaric acid)$^+$	2956, 1656, 1410, 1260	2.20 (1H, m), 2.28 (3H, s), 2.70—2.92 (12H, m), 3.83 (3H, s), 3.8 (3H, s), 6.72 (1H, m), 6.58—6.89 (3H, m), 7.10—7.35 (2H, m), 7.60 (1H, d, J=2.2 Hz)
9c	58.5	476 (M−fumaric acid)$^+$	2998, 1656, 1260	0.81 (3H, t, J=7.0 Hz), 1.32 (2H, m), 1.70—3.05 (15H, m), 3.70 (3H, s), 3.84 (3H, m), 4.68 (1H, m), 6.48—6.90 (3H, m), 6.95—7.38 (2H, m), 7.62 (1H, d, J=2.2 Hz)
9d	19.4	490 (M−fumaric acid)$^+$	2368, 1662, 1476, 1404	0.90 (3H, t, J=6.8 Hz), 1.30 (2H, m), 1.99—3.05 (15H, m), 3.77 (3H, s), 3.85 (3H, s), 4.77 (1H, m), 6.55—6.89 (3H, m), 7.00—7.40 (2H, m), 7.62 (1H, d, J=2.2 Hz)
10a	75.7	402 (M−HCl)$^+$	2296, 1659, 1476	0.92 (3H, t, J=7.0 Hz), 1.50—3.05 (15H, m), 4.71 (1H, m), 6.85—7.44 (7H, m), 7.60 (1H, d, J=2.2 Hz)
10b	80.5	436 (M−HCl)$^+$	2950, 1656, 1248	0.95 (3H, t, J=7.0 Hz), 1.80—3.10 (15H, m), 4.80 (1H, m), 6.89—7.40 (6H, m), 7.62 (1H, d, J=2.2 Hz)
10c	93.1	446 (M−HCl)$^+$	2938, 1659, 1485, 1191	0.96 (3H, t, J=7.2 Hz), 1.82—3.01 (15H, m), 4.72 (1H, m), 5.90 (2H, s), 6.40—6.80 (3H, m), 7.00—7.42 (2H, m), 7.61 (1H, d, J=2.2 Hz)
10d	77.4	462 (M−HCl)$^+$	2932, 1656, 1464	0.98 (3H, t, J=7.0 Hz), 1.80—3.00 (13H, m), 3.85 (2H, t, J=2.7 Hz), 4.70 (1H, m), 5.99 (2H, s), 6.25—7.30 (2H, m), 7.59 (1H, d, J=2.2 Hz)
10e	74.5	492 (M−HCl)$^+$	2926, 1656, 1512	0.97 (3H, t, J=7.2 Hz), 1.98—3.21 (15H, m), 3.81 (3H, s), 3.85 (3H, s), 4.81 (1H, m), 6.35 (2H, s), 7.01—7.35 (2H, m), 7.64 (1H, d, J=2.2 Hz)
10f	64.0	478 (M−HCl)$^+$	2938, 1656, 1475	0.99 (3H, t, J=7.2 Hz), 1.62—3.01 (13H, m), 3.90 (2H, t, J=3.3 Hz), 3.81 (3H, s), 3.82 (3H, s), 6.20—6.85 (3H, m), 7.20 (2H, m), 7.60 (1H, d, J=2.2 Hz)

a) Yield, based on comp. **7**.

Compound **7c′** (0.39 g, 0.90 mmol) was dissolved in 20 ml of absolute MeOH, then 0.20 g (3.60 mmol) of 80% acetaldehyde and 0.12 g (1.8 mmol) of $NaBH_3CN$ were added. The reaction mixture was stirred at room temperature for 18 h, then filtered, and the filtrate was evaporated *in vacuo*. The residue was extracted with AcOEt and the organic solution was washed with brine, dried (Na_2SO_4) and evaporated *in vacuo*. The resulting product was purified by silica gel column chromatography ($CHCl_3$) to give 0.32 g (77.0%) of **9b′** as a colorless oil. A solution of **9b′** (0.32 g, 0.69 mmol) and fumaric acid (0.08 mg, 0.69 mmol) in 10 ml of MeOH was stirred at room temperature for 30 min, and the solvent was removed *in vacuo*. The residue was recrystallized from isopropyl alcohol (IPA) gave a pure sample of **9b** (0.35 g, 87.0%) as a white solid. IR (cm^{-1}): 2938, 1656, 1260. Mass (*m/z*): 463 (M−fumaric acid)$^+$. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, t, J=7.2 Hz), 1.80—3.10 (15H, m), 3.77 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 4.65—4.80 (1H, m), 6.50—6.88 (3H, m, aromatic), 7.07—7.33 (2H, m, aromatic), 7.62 (1H, d, J=2.2 Hz, aromatic). Compounds (**8a**, **b**, **d**, **f**, **g**, **9a**, **10a**—**f**) were obtained similarly. The chemical data for these compounds (**8a**, **b**, **d**, **f**, **g**, **9a**, **10a**—**f**) are summarized in Table 3.

Method B. 5-{*N*-Butyl-*N*-[2-(3,4-dimethoxyphenyl)ethyl]aminopropionyl}-2,3,4,5-tetrahydro-1,5-benzothiazepine Fumarate (8e) Sodium hydride (0.11 g, 2.5 mmol) was added to a solution of KT-362 (free) (1.0 g, 2.5 mmol) in 20 ml of *N*,*N*-dimethylformamide (DMF) at 0 °C. After 15 min, 1-bromobutane (0.27 ml, 2.5 mmol) was added to the suspension and the mixture was heated to 80 °C for 8 h. After cooling to room temperature, the residue was dissolved in water, and extracted with AcOEt. The combined organic extract was washed with brine, dried (Na_2SO_4) and evaporated *in vacuo*. The resulting product was purified by silica gel column chromatography ($CHCl_3$: MeOH = 50 : 1) to give 0.88 g (77.2%) of **8e′** as a yellow oil. A solution of **8e′** (0.86 g, 1.88 mmol) and fumaric acid (0.22 g, 1.88 mmol) in 10 ml of MeOH was stirred at room temperature for 30 min, and the solvent was removed *in vacuo*. The residue was recrystallized from IPA to afford a pure sample of **8e** (1.01 g, 81.1%) as a white solid. IR (KBr) cm^{-1}: 2950, 1656, 1260. Mass (*m/z*): 455 (M−fumaric acid)$^+$. ^{1}H-NMR ($CDCl_3$) δ: 0.91 (3H, t, J=7.2 Hz), 1.30 (2H, m), 1.95—3.10 (15H, m), 3.77 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 4.63—4.77 (1H, m), 6.56—6.83 (3H, m, aromatic), 7.07—7.33 (2H, m, aromatic), 7.62 (1H, d, J=2.2 Hz, aromatic). Compounds **8c**, **9c**, **d** were obtained similarly. The chemical data for these compounds (**8c**, **9c**, **d**) are summarized in Table 3.

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