# Agents for the Treatment of Overactive Detrusor. IX.[1] Synthesis and Pharmacological Properties of Metabolites of *N-tert*-Butyl-4,4-diphenyl-2-cyclopentenylamine (FK584) in Human Urine

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**We synthesized the racemates of five presumed metabolites (1b—f) of (*S*)-(−)-*N-tert*-butyl-4,4-diphenyl-2-cyclopentenylamine hydrochloride (FK584, *S*(−)-1a), a novel agent for the treatment of overactive detrusor syndrome, in order to confirm the structures of the metabolites and also to evaluate their inhibitory activity against detrusor contraction. (±)-*N-tert*-Butyl-4-(4-hydroxyphenyl)- and 4-(4-hydroxy-3-methoxyphenyl)-4-phenyl-2-cyclopentenylamines (1b—e) were synthesized *via* 5-(4-methoxyphenyl)- and 5-(4-benzyloxy-3-methoxyphenyl)-5-phenyl-2-cyclopenten-1-one (9g, h), respectively. Compounds 1b—f prepared in this study were identical with the metabolites in human urine in gas chromatography–mass spectrometry and analytical HPLC. The inhibitory activity of compounds 1b—f against detrusor contraction *in vitro* induced by electrical field stimulation in guinea-pigs was less potent than that of FK584.**

**Key words** FK584; metabolite; detrusor contraction inhibition; (±)-*N-tert*-butyl-4-(4-hydroxyphenyl)-4-phenyl-2-cyclopentenylamine; (±)-*N*-(2-hydroxy-1,1-dimethylethyl)-4,4-diphenyl-2-cyclopentenylamine; (±)-*N-tert*-butyl-4-(4-hydroxy-3-methoxyphenyl)-4-phenyl-2-cyclopentenylamine

In the previous papers, we described the synthesis and pharmacological properties of (*S*)-(−)-*N-tert*-butyl-4,4-diphenyl-2-cyclopentenylamine hydrochloride (FK584, *S*(−)-**1a**), a novel agent for the treatment of overactive detrusor syndrome, which is now under clinical study.[1] Although FK584 was designed by modification of terodiline hydrochloride (HCl), an agent for the treatment of overactive detrusor syndrome, it exhibited different pharmacological profiles from those of terodiline HCl (Fig. 1).[1] Namely, its inhibitory activities against detrusor contractions *in vitro* induced by electrical field stimulation and carbachol in guinea-pigs were more potent than those of terodiline HCl, but its inhibitory activity against detrusor contraction induced with KCl was less potent than that of terodiline HCl. As a result, its inhibitory activity (i.v.) against distension-induced rhythmic bladder contraction in rats was more potent than that of terodiline HCl.

In a study on the pharmacokinetics of FK584 in humans, it was elucidated that most of FK584 was excreted after being metabolized. (1*S*)-4-(4-Hydroxyphenyl)- and (1*S*)-4-(4-hydroxy-3-methoxyphenyl)-4-phenyl-*N-tert*-butyl-2-cyclopentenylamines ((1*S*)-**1b**—**e**), and (*S*)-*N*-(1,1-dimethyl-2-hydroxyethyl)-4,4-diphenyl-2-cyclopentenylamine ((*S*)-**1f**) were proposed as the major metabolites in human urine on the basis of gas chromatography–mass spectrometry (Fig. 1).[2] These metabolites exist as glucuronic acid or sulfate conjugates. Among them, the (1*S*)-*cis*-(4-hydroxyphenyl) derivative (1*S*)-**1b** was found to be predominant.

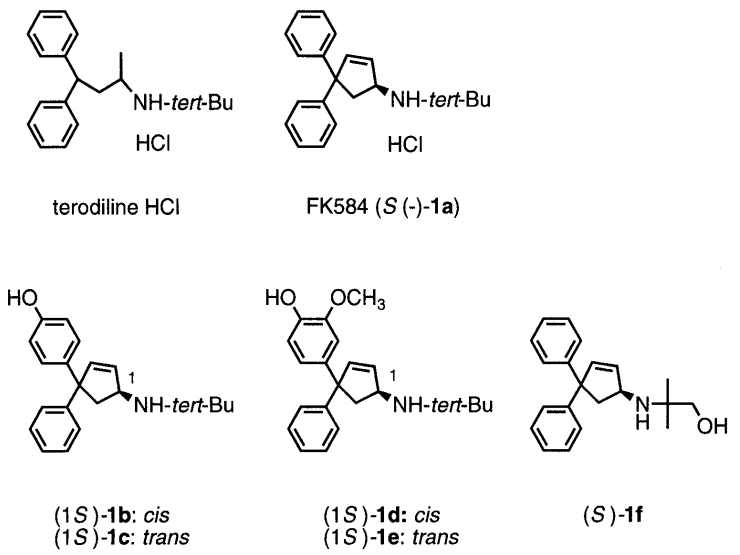


Fig. 1

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It was necessary to confirm the chemical structures of these metabolites by comparison with synthesized authentic samples, and to examine their pharmacological properties. This paper describes the synthesis of the racemates of the proposed metabolites **1b**—**f** (Charts 1—3) and their inhibitory activity against detrusor contraction.

## Synthesis

*cis*- and *trans*-*N*-*tert*-Butyl-4-(4-hydroxyphenyl)-4-phenyl-2-cyclopentenylamines **1b** and **1c** were synthesized *via* 5-(4-methoxyphenyl)-5-phenyl-2-cyclopenten-1-one (**9g**) as depicted in Chart 1. Halterman and McEvoy synthesized **9g** by Friedel–Crafts acylation of 2-(4-methoxyphenyl)-2-phenyl-4-pentenoic acid (**8g**) using $AlCl_3$ as a Lewis acid.[3] We found that the use of $EtAlCl_2$ instead of $AlCl_3$ increased the yield of **9g** from 38.3% to 49.8%. Compound **9g** was reduced to the corresponding 2-cyclopenten-1-ol (**10g**) by 1,2-reduction with diisobutylaluminum hydride (DIBAL). Compound **10g** was converted to the corresponding 2-cyclopentenylamine **1g** by method A or B. Method A was methanesulfonylation of **10g** with $MeSO_2Cl$ in the presence of $NEt_3$ in acetone and subsequent *S*N1′-type substitution reaction with *tert*-butylamine in the presence of NaI. Method B was the conversion of **10g** to the corresponding 2-cyclopentenyl chloride with $SOCl_2$ in *N*,*N*-dimethylformamide (DMF) and subsequent *S*N1′-type substitution reaction with *tert*-butylamine in the presence of KI.

The synthesis of **1b**, **c** was accomplished by demethylation of compound **1g** with $BBr_3 \cdot SMe_2$ and subsequent separation by preparative HPLC. The relative configurations of compounds **1b**, **c** were determined by analysis of the nuclear Overhauser effect (NOE) two-dimensional (2D)-NMR (NOESY) spectrum. In one isomer **1b**, NOEs were observed between the signal of the H-1 proton on the cyclopentene ring ($\delta$ 3.86) and those of the protons on the unsubstituted phenyl group ($\delta$ 7.09—7.29), indicating that the *tert*-butylamino group and the 4-hydroxyphenyl group are in a *cis* relationship to each other. In the other isomer **1c**, NOEs were observed between the signal of the H-1 proton on the cyclopentene ring ($\delta$ 3.87) and those of the H-2 and H-6 protons on the 4-hydroxyphenyl group ($\delta$ 6.98), indicating that the *tert*-butylamino group and the 4-hydroxyphenyl group were in a *trans* relationship to each other.

*cis*- and *trans*-*N*-*tert*-Butyl-4-(4-hydroxy-3-methoxyphenyl)-4-phenyl-2-cyclopentenylamines **1d**, **e** were synthesized *via* two key intermediates, 2-(4-benzyloxy-3-methoxyphenyl)-2-phenylacetic acid (**6h**) and 5-(4-benzyloxy-3-methoxyphenyl)-5-phenyl-2-cyclopenten-1-one (**9h**), as depicted in Chart 2. The starting material, 4-benzyloxy-3-methoxybenzonitrile (**2h**),[4] reacted with PhMgCl in tetrahydrofuran (THF) to produce 4-benzyloxy-3-methoxydiphenylmethanimine, which was hydrolyzed in one pot in refluxing concentrated HCl–MeOH–THF to afford 4-benzyloxy-3-methoxybenzophenone (**3h**). The reaction of the benzophenone **3h** with the *tert*-BuOK-generated ylide of $Me_3S^+I^-$ afforded the corresponding oxirane (**4h**), which was converted to the corresponding acetaldehyde (**5h**) by the action of $BF_3 \cdot Et_2O$. The aldehyde **5h** was oxidized to the key intermediate **6h** with $NaClO_2$.

For ring formation to obtain the desired 5,5-diphenyl-2-cyclopenten-1-one, Friedel–Crafts acylation was first attempted as follows: The treatment of **6h** with $SOCl_2$ afforded the corresponding acid chloride, which was reacted with allyl alcohol to produce the corresponding allyl ester (**7h**). The Claisen-type rearrangement of **7h** by use of NaH produced 2,2-diphenyl-4-pentenoic acid (**8h**), which was converted to the acid chloride by treatment with $SOCl_2$. When the Friedel–Crafts acylation of the acid chloride was carried out by use of $EtAlCl_2$ as a Lewis acid, the obtained cyclized product was the debenzylated compound **9d** and its yield was low (*ca.* 20%).

Thus, in order to prevent debenzylation, the ring formation was tried under neutral or basic conditions and accomplished by the intramolecular acylation of the α-sulfinylcarbanion[5] as shown in Chart 2. The key intermediate **6h** was converted to the corresponding methyl ester (**11h**) with HCl–MeOH. The enolate anion of **11h** was generated with lithium diisopropylamide (LDA) and alkylated with 3-(phenylthio)propyl bromide to afford 2,2-diphenyl-5-(phenylthio)pentanoic acid ester (**12h**),

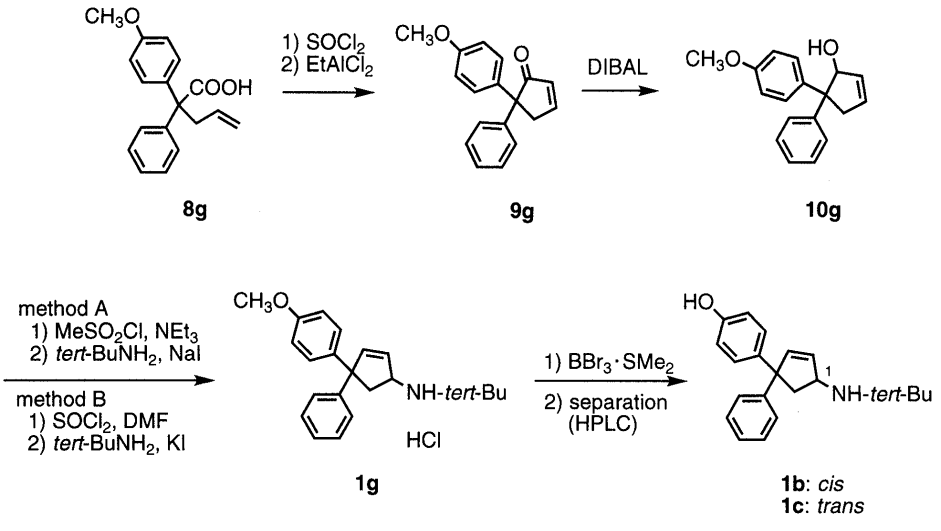


Chart 1

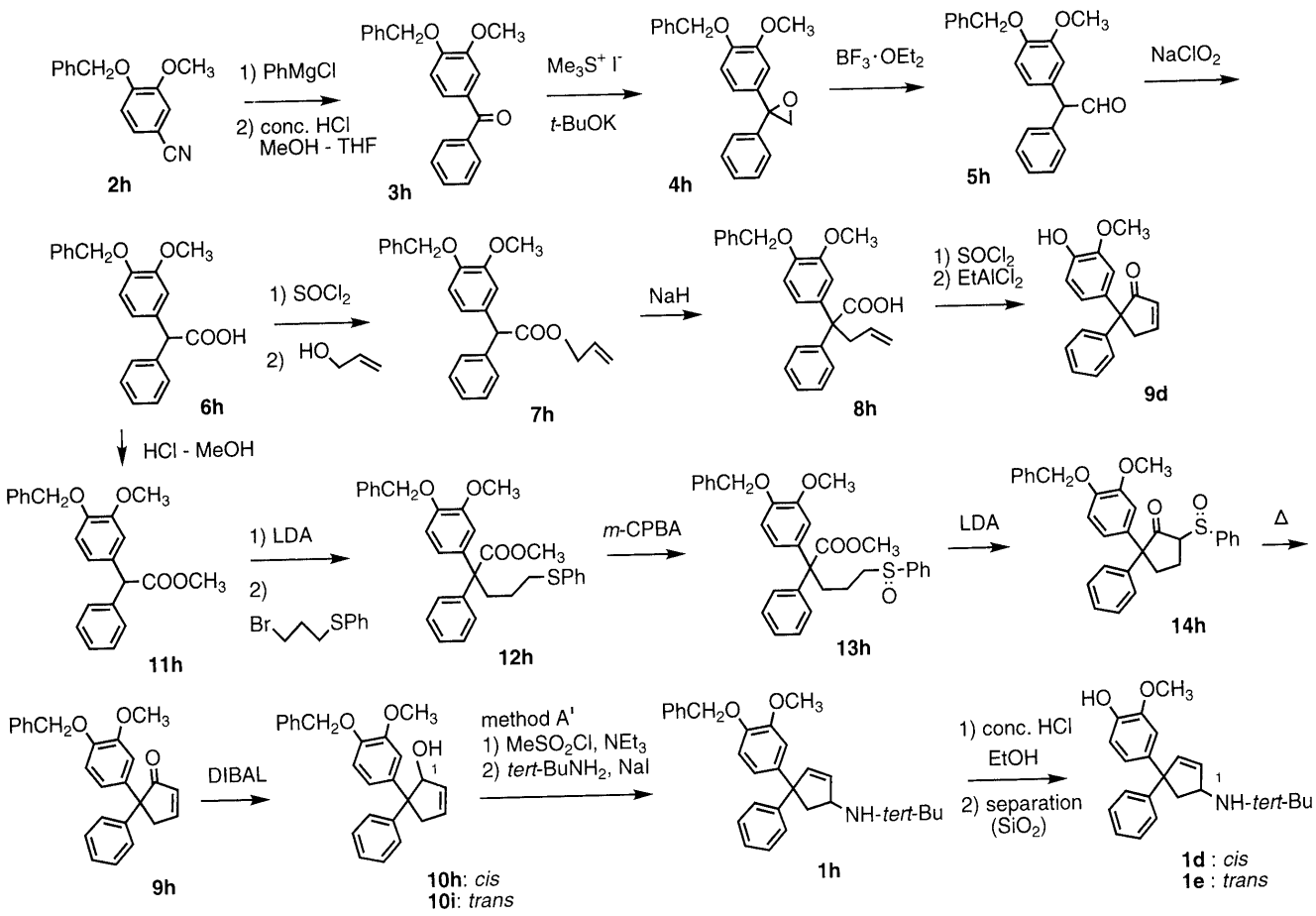


Chart 2

which was oxidized to the corresponding sulfoxide (**13h**) with *m*-chloroperbenzoic acid (*m*-CPBA). On generation of the α-sulfinylcarbanion of **13h** with LDA in THF, intramolecular acylation occurred to provide 2-phenylsulfinyl-5,5-diphenylcyclopentanone (**14h**), the pyrolysis of which in refluxing $CCl_4$ produced the desired key intermediate, 5,5-diphenyl-2-cyclopenten-1-one (**9h**) in a good yield (79.6% based on **13h**).

1,2-Reduction of **9h** with DIBAL and subsequent separation by silica gel column chromatography afforded the corresponding *cis* and *trans* 2-cyclopenten-1-ols (**10h, i**) in 34.4% and 25.6% yields, respectively. The relative configurations of **10h, i** were determined by analysis of the 2D-NOESY spectrum. Namely, NOEs were observed between the signal of the H-1 proton on the cyclopentene ring (δ 5.41 ppm) and those of the protons on the unsubstituted phenyl group (δ 7.19—7.43 ppm) or of the H-2, H-5, and H-6 protons on the 4-benzyloxy-3-methoxyphenyl group (δ 6.83—6.85 ppm). Compounds **10h, i** were converted to 4-(4-benzyloxy-3-methoxyphenyl)-*N*-*tert*-butyl-4-phenyl-2-cyclopentenylamine (**1h**) by method A′, which was the same as method A with the exception that methanesulfonylation was carried out in $CH_2Cl_2$ instead of acetone, since $CH_2Cl_2$ gave a superior yield. Both the *cis* isomer **10h** and the *trans* isomer **10i** afforded a *cis–trans* isomeric mixture of **1h** (*ca.* 37 : 63, respectively, on the basis of $^1$H-NMR), disclosing that this nucleophilic substitution reaction with *tert*-$BuNH_2$ was of *SN*1′-type. The debenzylation of **1h** was accomplished by heating it in concentrated HCl–EtOH (1 : 1) for 10 min,

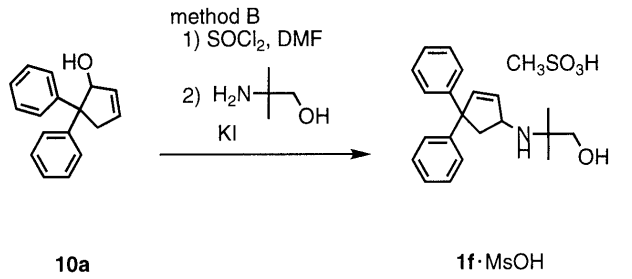


Chart 3

and the obtained *cis–trans* isomeric mixtures (**1d, e**) were separated by silica gel column chromatography to afford **1d, e** in 21.0% and 41.3% yields, respectively. The relative configurations of compounds **1d, e** were determined by analysis of the 2D-NOESY spectrum. Namely, NOEs were observed between the signal of the H-1 proton on the cyclopentene ring (δ 3.93 or 3.96 ppm) and those of the protons on the unsubstituted phenyl group (δ 7.10—7.30 ppm) or of the H-2, H-5, and H-6 protons on the 4-hydroxy-3-methoxyphenyl group (δ 6.59—6.70 ppm).

*N*-(2-Hydroxy-1,1-dimethylethyl)-4,4-diphenyl-2-cyclopentenylamine (**1f**) was synthesized by the reaction of 4,4-diphenyl-2-cyclopenten-1-ol (**10a**)[1] with 2-hydroxy-1,1-dimethylethylamine by method B as depicted in Chart 3.

Compounds **1b—f** prepared in this study were found to be identical with the metabolites in human urine in terms of behavior in gas chromatography–mass spectrometry

and analytical HPLC.

## Pharmacological Results and Discussion

Compounds **1b**—**f** prepared in this study were evaluated for inhibitory activity against detrusor contraction *in vitro* induced by electrical field stimulation in guinea-pigs. These results are listed in Table 1 in comparison with the data of FK584 (*S*(−)-**1a**). Compounds **1b**—**f** were found to be inferior to FK584 as regards inhibitory activities against detrusor contraction.

Table 1. Effect of FK584 (*S*(−)-**1a**) and Racemates of Its Metabolites in Human Urine (**1b**—**f**) on Detrusor Contraction *in Vitro* Induced by Electrical Field Stimulation in Guinea-Pigs

| No. | Inhibitory activity against detrusor contraction by electrical field stimulation $IC_{50}$ g/ml *in vitro* |
|---|---|
| FK584 (*S*(−)-**1a**) | $3.4 \times 10^{-7}$ |
| **1a** (racemate of FK584) | $4.6 \times 10^{-7}$ |
| **1b**·HCl (*cis*) | $2.3 \times 10^{-5}$ |
| **1c**·HCl (*trans*) | $2.1 \times 10^{-5}$ |
| **1d**·HCl (*cis*) | $1.6 \times 10^{-5}$ |
| **1e**·HCl (*trans*) | $1.3 \times 10^{-5}$ |
| **1f**·MsOH | $2.6 \times 10^{-6}$ |

Main metabolic pathways for terodiline HCl in human had been proposed on the basis of metabolites identified in human urine (Chart 4).[6a] The predominant metabolite in human urine was *N*-*tert*-butyl-4-(4-hydroxyphenyl)-4-phenyl-2-butylamine (M-1 (**15**)), the inhibitory activity of which against isolated man detrusor contraction induced electrically is weak in comparison with that of terodiline HCl.[6b] From the results obtained in this study, it was concluded that FK584 is similar to terodiline HCl with respect to the main metabolic pathways (Charts 4, 5), and the change of inhibitory activity against detrusor contraction after metabolism.

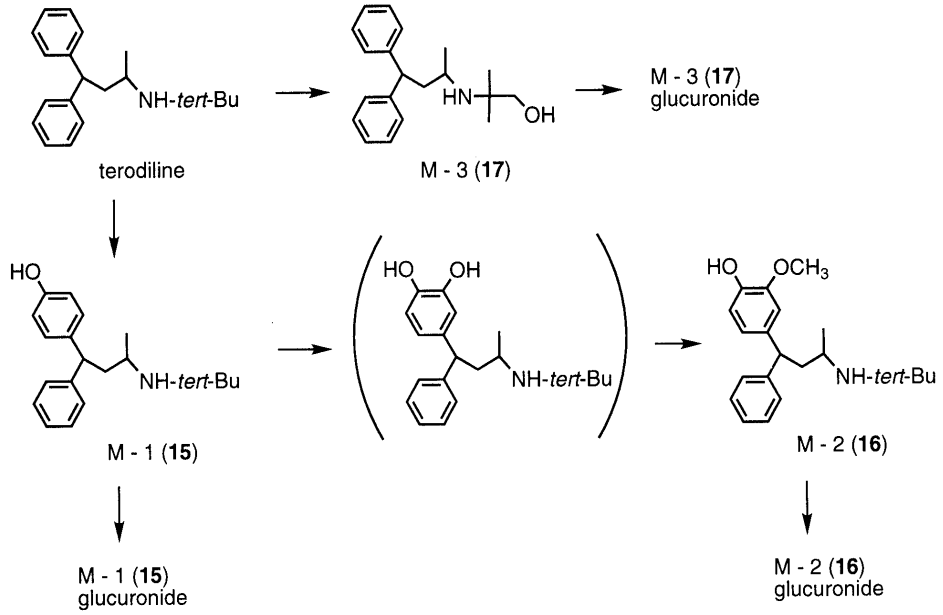


Chart 4. Main Metabolic Pathways for Terodiline in Humans[6a]

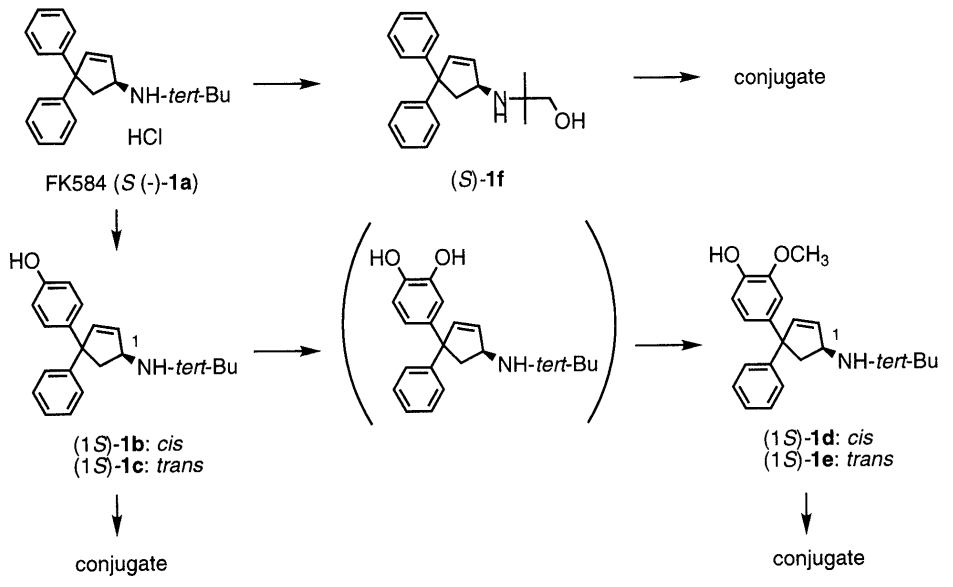


Chart 5. Proposed Main Metabolic Pathways for FK584 in Humans

In conclusion, compounds **1b—f** prepared in this study were identical with the metabolites in human urine in terms of behavior in gas chromatography–mass spectrometry and analytical HPLC. Their inhibitory activities against detrusor contraction were less potent than those of FK584.

## Experimental

The melting points were determined on a capillary melting point apparatus (Electrothermal) and are uncorrected. The infrared (IR) spectra were measured on a Hitachi 260-10 spectrometer. The $^1$H-NMR spectra were recorded on Bruker AC200P spectrometer using tetramethylsilane as an internal standard. The atmospheric pressure chemical ionization mass (APCI-MS) spectra were recorded on a Hitachi M1000H mass spectrometer. Preparative HPLC was carried out on Shimadzu SCL-8A.

**5-(4-Methoxyphenyl)-5-phenyl-2-cyclopenten-1-one[3] (9g)** A solution of 2-(4-methoxyphenyl)-2-phenyl-4-pentenoic acid[3] (**8g**, 640 mg, 2.27 mmol) and $SOCl_2$ (1.35 g, 11.35 mmol) in $CH_2Cl_2$ (4.5 ml) was stirred at room temperature for 1.5 d and under reflux for 7 h. The solvent was evaporated *in vacuo* to afford the acid chloride of **8g** as an oil. A solution of the acid chloride in $CH_2Cl_2$ (3.2 ml) was added dropwise to a stirred mixture of a 0.93 M solution of $EtAlCl_2$ in *n*-hexane (2.92 ml, 2.72 mmol) and $CH_2Cl_2$ (3.2 ml) under $N_2$ at −20—−30 °C over 10 min. The resulting mixture was stirred under the same conditions for 2 h, then MeOH (0.46 ml) was added dropwise and the mixture was stirred at the same temperature for 30 min. It was poured into ice-water and extracted with $CH_2Cl_2$. The extract was washed with brine, dried, and mixed with $NEt_3$ (0.63 ml, 4.54 mmol) under ice cooling. The resulting mixture was stirred at the same temperature for 1.5 h, washed successively with 1 N HCl, brine, aqueous $NaHCO_3$, and brine, dried, and evaporated *in vacuo*. The residue was chromatographed (toluene) over silica gel to afford **9g** (299 mg, 49.8%) as a pale yellow powder: mp 91.5—93.5 °C (from diisopropyl ether). *Anal.* Calcd for $C_{18}H_{16}O_2$: C, 81.79; H, 6.10. Found: C, 81.72; H, 6.07. IR (Nujol): 1685, 1605, 1585, 1250 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 3.48 (2H, m, $CH_2$), 3.78 (3H, s, $OCH_3$), 6.23—6.29 (1H, m, CH=C<u>H</u>CO), 6.79—6.88 (2H, m, aromatic H), 7.10—7.34 (7H, m, aromatic H), 7.80—7.86 (1H, m, C<u>H</u>=CHCO). (+)APCI-MS *m/z*: 265 ($M^+ + 1$).

**5-(4-Methoxyphenyl)-5-phenyl-2-cyclopenten-1-ol (10g)** A 0.93 M solution of DIBAL in *n*-hexane (20.9 ml, 19.4 mmol) was added dropwise to a stirred solution of **9g** (4.89 g, 18.5 mmol) in toluene (54 ml) under $N_2$ with ice cooling. The resulting mixture was stirred at room temperature for 3 h, and then treated successively with AcOEt (28 ml), ice-water (8 ml), and 1 N HCl (31 ml) under ice cooling. The AcOEt layer was separated, washed with 1 N HCl and brine (twice), dried, and evaporated *in vacuo*. The residue was chromatographed (toluene–AcOEt (gradient elution, 100:0—97:3)) over silica gel to afford **10g** (4.12 g, 83.6%) as a pale yellow oil. *Anal.* Calcd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 80.85; H, 7.03. IR (film): 3550, 3420, 1605, 1250 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.75 (1H, s, OH), 2.81—2.95, 3.36—3.47 (each 1H, d of m, $CH_2$), 3.76, 3.79 (3H, each s, $OCH_3$), 5.41 (1H, m, C<u>H</u>OH), 5.91, 6.12 (each 1H, m, olefinic H), 6.80, 6.83 (2H, d, $J$=8.8 Hz, aromatic H), 7.09 (2H of one diastereomer, d, $J$=8.8 Hz, aromatic H), 7.17—7.33 (2H of the other diastereomer +5H, m, aromatic H). The ratio of the *cis–trans* isomers was 58:42 on the basis of the $^1$H-NMR spectrum. (+)APCI-MS *m/z*: 249 ($M^+ - OH$).

***N-tert*-Butyl-4-(4-methoxyphenyl)-4-phenyl-2-cyclopentenylamine Hydrochloride (1g). Method A** $CH_3SO_2Cl$ (230 mg, 2.01 mmol) was added to a stirred solution of **10g** (447 mg, 1.68 mmol) in acetone (4.5 ml) under ice cooling, and then $NEt_3$ (203 mg, 2.01 mmol) was added. The mixture was stirred at the same temperature for 1 h 20 min. NaI (301 mg, 2.01 mmol) was added, and then *tert*-$BuNH_2$ (2.46 g, 33.6 mmol) was added dropwise thereto. The resulting mixture was stirred at the same temperature for 20 min and at room temperature for 3 h, then allowed to stand at room temperature overnight. It was diluted with water (10 ml) and 5% NaOH (5 ml) and extracted with AcOEt. The extract was washed twice with brine, dried, and evaporated *in vacuo*. The residue was chromatographed ($CH_2Cl_2$–MeOH (gradient elution, 100:0—3)) over silica gel, and treated with 4 N HCl in AcOEt to afford **1g** (192 mg, 31.9%) as a powder: mp 195—200 °C (dec.) (from $Et_2O$). *Anal.* Calcd for $C_{22}H_{27}NO \cdot HCl$: C, 73.83; H, 7.88; N, 3.91. Found: C, 74.15; H, 8.06; N, 3.85. IR (Nujol): 2750, 2680, 2620, 2480, 2430 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.48 (9H, s, $3CH_3$), 2.97—3.21 (2H, m, $CH_2$), 3.74, 3.80 (3H, s, $OCH_3$), 4.22 (1H, br s, CH–N), 6.05—6.12, 6.30—6.35 (each 1H, m, olefinic H), 6.77, 6.83 (2H, d, $J$=8.8 Hz, aromatic H), 7.04—7.31 (7H, m, aromatic H), 9.66 (2H, br s, NH·HCl). The ratio of the *cis–trans* isomers was 52:48 on the basis of the $^1$H-NMR spectrum. (+)APCI-MS *m/z*: 322 ($M^+ + 1$).

**Method B** $SOCl_2$ (1.75 g, 14.7 mmol) was added dropwise to a stirred solution of **10g** (3.72 g, 14.0 mmol) in DMF (15 ml) under ice cooling over 10 min and the mixture was stirred at the same temperature for 30 min. *tert*-$BuNH_2$ (5.63 g, 77.0 mmol) was added dropwise over 20 min and then KI (2.56 g, 15.4 mmol) was added. The resulting mixture was stirred at the same temperature for 30 min and at room temperature for 15 h, and then partitioned between 5% NaOH and AcOEt. The AcOEt layer was separated, washed with water and brine, dried, and evaporated *in vacuo*. The residue was chromatographed ($CH_2Cl_2$–MeOH (gradient elution, 100:0—4)) over silica gel to afford an oil, which was chromatographed (toluene–AcOEt (gradient elution, 100:0—7.5)) over basic alumina and treated with 4 N HCl in AcOEt to afford **1g** (2.72 g, 54.3%) as a powder. The ratio of the *cis–trans* isomers was 53:47 on the basis of the $^1$H-NMR spectrum.

***cis-N-tert*-Butyl-4-(4-hydroxyphenyl)-4-phenyl-2-cyclopentenylamine (1b) and *trans-N-tert*-Butyl-4-(4-hydroxyphenyl)-4-phenyl-2-cyclopentenylamine (1c)** A mixture of **1g** (2.24 g, 6.26 mmol) and $BBr_3 \cdot SMe_2$ (4.81 g, 15.4 mmol) in $CH_2Cl_2$ (45 ml) was stirred at room temperature for 3 d and under reflux for 7 h. The reaction mixture was poured into aqueous $NaHCO_3$ and extracted twice with AcOEt. The extracts were combined, washed with water and brine, dried, and evaporated *in vacuo*. The residue was chromatographed ($CH_2Cl_2$–MeOH (gradient elution, 10:0—1)) over silica gel. The eluate was evaporated *in vacuo* and the residue was triturated in $Et_2O$ to afford a pale brown powder (802 mg). The powder (770 mg) was subjected to preparative HPLC [column, YMC Pack D-ODS-15-C 120A (50 mm i.d. × 250 mm); solvent, $CH_3CN$:1% $NEt_3$ in 0.02 M $NaH_2PO_4$ (pH 6.5)=28:72; flow rate, 118 ml/min; detection, 215 nm; temperature, ambient]. The first eluate was concentrated *in vacuo*, basified with aqueous $NaHCO_3$, and extracted three times with AcOEt. The extracts were combined, dried, and evaporated *in vacuo*, and then the residue was washed with *n*-hexane to afford **1c** (142 mg, 7.7%) as a colorless powder. The second eluate afforded **1b** (200 mg, 10.8%) as a colorless powder in a similar manner.

**1b**: mp 170.5—172.5 °C. *Anal.* Calcd for $C_{21}H_{25}NO \cdot 1/10H_2O$: C, 81.56; H, 8.21; N, 4.53. Found: C, 81.54; H, 8.45; N, 4.61. IR (Nujol): 3240, 2780—2300, 1600, 1580, 1245 cm$^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.03 (9H, s, $3CH_3$), 1.91 (1H, dd, $J$=12.9, 7.5 Hz, C(<u>H</u>)H), 2.94 (1H, dd, $J$=12.9, 6.7 Hz, C(H)<u>H</u>), 3.86 (1H, br t, CH–N), 5.74 (1H, dd, $J$=5.5, 1.5 Hz, olefinic H), 6.22 (1H, dd, $J$=5.5, 1.9 Hz, olefinic H), 6.65, 6.97 (each 2H, d, $J$=8.6 Hz, aromatic H), 7.09—7.29 (5H, m, aromatic H), 9.20 (1H, br s, OH). In 2D-NOESY, NOEs were observed between the signal at $\delta$ 3.86 and the signals at $\delta$ 7.09—7.29. (+)APCI-MS *m/z*: 308 ($M^+ + 1$).

**1c**: mp 155—158 °C. *Anal.* Calcd for $C_{21}H_{25}NO \cdot 1/10H_2O$: C, 81.56; H, 8.21; N, 4.53. Found: C, 81.58; H, 8.42; N, 4.61. IR (Nujol): 3260, 2780—2300, 1600, 1580, 1260 cm$^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.04 (9H, s, $3CH_3$), 1.89 (1H, dd, $J$=12.8, 7.6 Hz, C(<u>H</u>)H), 2.95 (1H, dd, $J$=12.8, 6.7 Hz, C(H)<u>H</u>), 3.87 (1H, br t, CH–N), 5.73 (1H, dd, $J$=5.5, 1.6 Hz, olefinic H), 6.24 (1H, dd, $J$=5.5, 2.0 Hz, olefinic H), 6.64, 6.98 (each 2H, d, $J$=8.7 Hz, aromatic H), 7.09—7.30 (5H, m, aromatic H), 9.22 (1H, br s, OH). In 2D-NOESY, NOEs were observed between the signal at $\delta$ 3.87 and the signals at $\delta$ 6.98. (+)APCI-MS *m/z*: 308 ($M^+ + 1$).

The two obtained free bases **1b, c** were converted to the corresponding hydrochlorides (**1b**·HCl, **1c**·HCl) in a usual manner.

**1b**·HCl: mp 282—284 °C (dec.) (from $Et_2O$). *Anal.* Calcd for $C_{21}H_{25}NO \cdot HCl$: C, 73.35; H, 7.62; N, 4.07. Found: C, 73.05; H, 7.82; N, 4.13. IR (Nujol): 3260, 2760—2430, 1210 cm$^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.36 (9H, s, $3CH_3$), 2.45 (1H, dd, $J$=13.3, 8.0 Hz, C(<u>H</u>)H), 3.27 (1H, dd, $J$=13.3, 7.2 Hz, C(H)<u>H</u>), 4.44 (1H, br s, CH–N), 6.07 (1H, d, $J$=5.5 Hz, olefinic H), 6.66 (1H, br d, $J$=5.5 Hz, olefinic H), 6.72, 7.02 (each 2H, d, $J$=8.6 Hz, aromatic H), 7.18—7.33 (5H, m, aromatic H), 8.8 (1H, br, $NH_2^+$, 9.25 (1H, br d, $NH_2^+$), 9.37 (1H, s, OH).

**1c**·HCl: mp 295—297 °C (dec.) (from $Et_2O$). *Anal.* Calcd for $C_{21}H_{25}NO \cdot HCl$: C, 73.35; H, 7.62; N, 4.07. Found: C, 73.09; H, 7.89; N, 4.15. IR (Nujol): 3220, 2630—2480, 2430, 1210 cm$^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.36 (9H, s, $3CH_3$), 2.42 (1H, dd, $J$=13.3, 8.0 Hz, C(<u>H</u>)H), 3.27 (1H, dd, $J$=13.3, 7.2 Hz, C(H)<u>H</u>), 4.44 (1H, br s, CH–N), 6.04 (1H, d, $J$=5.6 Hz, olefinic H), 6.68 (1H, br d, $J$=5.6 Hz, olefinic H), 6.68, 7.00 (each 2H, d, $J$=8.6 Hz, aromatic H), 7.20—7.35 (5H, m, aromatic

H), 8.68 (1H, br, $NH^+$), 9.19 (1H, br d, $NH^+$), 9.34 (1H, s, OH).

**4-Benzyloxy-3-methoxybenzophenone (3h)** A 2 M solution of PhMgCl in THF (296 ml, 592 mmol) was added dropwise to a stirred solution of 4-benzyloxy-3-methoxybenzonitrile[4] (**2h**, 88.62 g, 370 mmol) in benzene (226 ml) under $N_2$ at room temperature, then the mixture was stirred at the same temperature for 50 min and at 70 °C for 7 h. Concentrated HCl (197 ml) was added dropwise to the stirred reaction mixture under ice cooling and then MeOH (1.00 l) was added thereto. The resulting mixture was stirred under reflux for 7 h, cooled to room temperature, and concentrated *in vacuo*. The residue was partitioned between AcOEt and water. The AcOEt layer was separated, washed with brine, dried, and evaporated *in vacuo*. The powdery residue was washed with *n*-hexane to afford 3 h (110.90 g, 94.1%) as a pale yellow powder: mp 85—89 °C (lit.[7] mp 88—89 °C). *Anal.* Calcd for $C_{21}H_{18}O_3$: C, 79.23; H, 5.70. Found: C, 79.18; H, 5.85. IR (Nujol): 1650, 1590, 1270, 1210 $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 3.95 (3H, s, $OCH_3$), 5.25 (2H, s, $CH_2$), 6.90 (1H, d, $J$=8.4 Hz, aromatic H), 7.25—7.61 (10H, m, aromatic H), 7.72—7.77 (2H, m, aromatic H). (+)APCI-MS *m/z*: 319 ($M^+$+1).

**2-(4-Benzyloxy-3-methoxyphenyl)-2-phenyloxirane (4h)** A solution of *tert*-BuOK (5.69 g, 50.7 mmol) in dimethylsulfoxide (DMSO, 26 ml) was added dropwise to a stirred suspension of **3h** (13.44 g, 42.2 mmol) and $Me_3S^+I^-$ (10.34 g, 50.7 mmol) in DMSO (76 ml) under $N_2$ at room temperature and the resulting mixture was stirred under the same conditions for 18 h. It was poured into ice-water and the resulting aqueous mixture was extracted with a mixture of AcOEt and $Et_2O$. The extract was washed with water (three times) and brine, dried, and evaporated *in vacuo*. The powdery residue was washed with *n*-hexane to afford **4h** (12.62 g, 90.0%) as a colorless powder: mp 66—73 °C. *Anal.* Calcd for $C_{22}H_{20}O_3$: C, 79.50; H, 6.06. Found: C, 79.91; H, 6.20. IR (Nujol): 1245, 1220 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 3.24, 3.29 (each 1H, d, $J$=5.6 Hz, $CH_2$ of oxirane), 3.85 (3H, s, $OCH_3$), 5.15 (2H, s, $PhCH_2O$), 6.78, 6.84 (each 1H, d, $J$=8.4 Hz, aromatic H), 6.91 (1H, d, $J$=1.3 Hz, aromatic H), 7.25—7.45 (10H, m, aromatic H). (+)APCI-MS *m/z*: 333 ($M^+$+1).

**2-(4-Benzyloxy-3-methoxyphenyl)-2-phenylacetaldehyde (5h)** $BF_3 \cdot Et_2O$ (17.4 ml, 141 mmol) was added dropwise to a stirred solution of **4h** (12.38 g, 37.2 mmol) in $Et_2O$ (465 ml) at room temperature and the resulting mixture was stirred at the same temperature for 40 min. Water (120 ml) was added dropwise to the stirred reaction mixture under ice cooling. The $Et_2O$ layer was separated, washed with water (three times) and brine, dried, and evaporated *in vacuo*. The powdery residue was washed with *n*-hexane to afford **5h** (11.53 g, 93.2%) as a colorless powder: mp 78—83 °C. *Anal.* Calcd for $C_{22}H_{20}O_3$: C, 79.50; H, 6.06. Found: C, 79.73; H, 6.18. IR (Nujol): 1720, 1260, 1225 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 3.84 (3H, s, $OCH_3$), 4.82 (1H, d, $J$=2.5 Hz, CH), 5.15 (2H, s, $PhCH_2O$), 6.69 (1H, dd, $J$=8.2, 2.0 Hz, aromatic H), 6.74 (1H, d, $J$=2.0 Hz, aromatic H), 6.88 (1H, d, $J$=8.2 Hz, aromatic H), 7.19—7.45 (10H, m, aromatic H), 9.91 (1H, d, $J$=2.5 Hz, CHO). (+)APCI-MS *m/z*: 333 ($M^+$+1).

**2-(4-Benzyloxy-3-methoxyphenyl)-2-phenylacetic Acid (6h)** A solution of $NaClO_2$ (26.20 g, 246 mmol) in 26% aqueous $NaH_2PO_4$ (246 ml) was added dropwise to a stirred solution of **5h** (65.48 g, 197 mmol) and 2-methyl-2-butene (355 ml) in *tert*-BuOH (709 ml) at room temperature over 30 min. The resulting mixture was stirred at the same temperature for 3 h and extracted with AcOEt. The extract was washed twice with brine, dried, and evaporated *in vacuo*. The residue was triturated in toluene and the precipitated powder was collected by filtration to afford **6h** (34.48 g, 50.2%) as a colorless powder. The filtrate was chromatographed (toluene–$CH_2Cl_2$ (gradient elution, 10 : 0—8 : 2)) over silica gel to afford **6h** (17.74 g, 25.8%). mp 138.5—141.5 °C. *Anal.* Calcd for $C_{22}H_{20}O_4$: C, 75.84; H, 5.79. Found: C, 75.95; H, 5.92. IR (Nujol): 2700, 2600, 1680, 1260, 1240 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 3.83 (3H, s, $OCH_3$), 4.97 (1H, s, CHCOO), 5.13 (2H, s, $PhCH_2O$), 6.81 (2H, s, aromatic H), 6.87 (1H, s, aromatic H), 7.18—7.44 (10H, m, aromatic H). (+)APCI-MS *m/z*: 303 ($M^+$−COOH).

**Allyl 2-(4-Benzyloxy-3-methoxyphenyl)-2-phenylacetate (7h)** A solution of **6h** (871 mg, 2.50 mmol), $SOCl_2$ (1.49 g, 12.5 mmol), and DMF (15 mg) in $CH_2Cl_2$ (4 ml) was stirred at room temperature overnight and under reflux for 3.5 h, then cooled to room temperature, and evaporated *in vacuo*. The residue was dissolved in $CH_2Cl_2$ (2 ml) and allyl alcohol (218 mg, 3.75 mmol) was added thereto at room temperature. The resulting mixture was stirred at the same temperature for 3 h and partitioned between toluene–water. The organic layer was separated, washed with aqueous $NaHCO_3$ and brine, dried, and evaporated *in vacuo*. The residue was chromatographed (toluene–AcOEt (gradient elution, 99.5 : 0.5—97 : 3)) over silica gel to afford **7h** (591 mg, 60.9%) as an oil. *Anal.* Calcd for $C_{25}H_{24}O_4$: C, 77.30; H, 6.23. Found: C, 77.02; H, 6.16. IR (film): 1725, 1260, 1220 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 3.84 (3H, s, $OCH_3$), 4.65 (2H, dd, $J$=5.7, 1.2 Hz, $COOCH_2$), 4.98 (1H, s, CHCOO), 5.13 (2H, s, $PhCH_2O$), 5.17—5.30 (2H, m, CH=C<u>H</u>$_2$), 5.80—6.00 (1H, m, C<u>H</u>=$CH_2$), 6.75—6.86 (2H, m, aromatic H), 6.89 (1H, d, $J$=1.5 Hz, aromatic H), 7.25—7.44 (10H, m, aromatic H). (+)APCI-MS *m/z*: 389 ($M^+$+1), 303, 213.

**2-(4-Benzyloxy-3-methoxyphenyl)-2-phenyl-4-pentenoic Acid (8h)** A solution of **7h** (780 mg, 2.01 mmol) in toluene (5 ml) was added dropwise to a stirred suspension of 60% NaH (113 mg, 2.81 mmol) in toluene (5 ml) at 120 °C and the resulting mixture was stirred at the same temperature for 40 min. The reaction mixture was cooled to room temperature and poured into concentrated HCl–ice-water. The toluene layer was separated, washed with brine, dried, and evaporated *in vacuo*. The oily residue was chromatographed ($CH_2Cl_2$–MeOH (gradient elution, 100 : 1—2)) over silica gel to afford **8h** (605 mg, 77.5%) as an oil. *Anal.* Calcd for $C_{25}H_{24}O_4$: C, 77.30; H, 6.23. Found: C, 77.46; H, 6.56. IR (film): 3300, 2600, 2520, 1690, 1250, 1225 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 3.13 (2H, m, $CH_2$), 3.76 (3H, s, $OCH_3$), 4.90—4.98 (2H, br s, CH=C<u>H</u>$_2$), 5.14 (2H, s, $PhCH_2O$), 5.48—5.66 (1H, m, C<u>H</u>=$CH_2$), 6.83—6.86 (3H, m, aromatic H), 7.15—7.46 (10H, m, aromatic H). (+)APCI-MS *m/z*: 389 ($M^+$+1), 343.

**Friedel–Crafts Acylation of 8h** A solution of **8h** (470 mg, 1.21 mmol) and $SOCl_2$ (720 mg, 6.05 mmol) in $CH_2Cl_2$ (2.4 ml) was stirred at room temperature for 3.5 h and under reflux for 2 h, then DMF (7 mg) was added thereto and the mixture was refluxed for 2.5 h. It was evaporated *in vacuo* to afford the acid chloride of **8h** as an oil. A 0.93 M solution of $EtAlCl_2$ in *n*-hexane (1.43 ml, 1.33 mmol) was added dropwise to a stirred solution of the obtained acid chloride in $CH_2Cl_2$ (1.4 ml) at −70 °C over 10 min. The resulting mixture was stirred at the same temperature for 1.5 h, then MeOH (0.23 ml) was added dropwise thereto and the mixture was stirred at the same temperature for 30 min. It was poured into ice-water and extracted with $CH_2Cl_2$. The extract was washed with brine and dried, then mixed with $NEt_3$ (0.34 ml, 2.42 mmol) under ice cooling. The resulting mixture was stirred at the same temperature for 1 h and at room temperature for 3.5 h, washed successively with 1 N HCl, brine, aqueous $NaHCO_3$, and brine, dried, and evaporated *in vacuo*. The residue was chromatographed (toluene–AcOEt (gradient elution, 20 : 0—1)) over silica gel to afford 5-(4-hydroxy-3-methoxyphenyl)-5-phenyl-2-cyclopenten-1-one (**9d**, 73 mg, 21.5%) as an oil. *Anal.* Calcd for $C_{18}H_{16}O_3$: C, 77.13; H, 5.75. Found: C, 77.34; H, 5.66. IR (Nujol): 3400, 1690, 1260, 1200 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 3.49 (2H, m, $CH_2$), 3.78 (3H, s, $CH_3$), 5.56 (1H, br s, OH), 6.27 (1H, m, CH=C<u>H</u>CO–), 6.74 (1H, dd, $J$=8.2, 2.1 Hz, aromatic H), 6.80 (1H, d, $J$=2.1 Hz, aromatic H), 6.86 (1H, d, $J$=8.2 Hz, aromatic H), 7.15—7.33 (5H, m, aromatic H), 7.84 (1H, m, C<u>H</u>=CHCO–). (+)APCI-MS *m/z*: 281 ($M^+$+1).

**Methyl 2-(4-Benzyloxy-3-methoxyphenyl)-2-phenylacetate (11h)** A suspension of **6h** (10.0 g, 28.7 mmol) in 10% methanolic HCl (100 ml) was stirred at room temperature for 15 h and evaporated *in vacuo*. The residue was purified by column chromatography over silica gel (toluene–ethyl acetate (gradient elution, 100 : 0—5) to afford a powder, which was washed with *n*-hexane to afford **11h** (8.58 g, 82.5%) as a colorless powder: mp 61—65 °C. *Anal.* Calcd for $C_{23}H_{22}O_4$: C, 76.22; H, 6.12. Found: C, 76.41; H, 5.92. IR (Nujol): 1720, 1235, 1220 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 3.74, 3.84 (each 3H, s, $2CH_3$), 4.96 (1H, s, CHCOO), 5.13 (2H, s, $PhCH_2O$), 6.74—6.89 (3H, m, aromatic H), 7.22—7.45 (10H, m, aromatic H). (+)APCI-MS *m/z*: 363 ($M^+$+1), 303 ($M^+$−$COOCH_3$).

**Methyl 2-(4-Benzyloxy-3-methoxyphenyl)-2-phenyl-5-(phenylthio)pentanoate (12h)** A 1.5 M solution of LDA·THF in cyclohexane (19.4 ml, 29.1 mmol) was added dropwise over 15 min to a stirred solution of **11h** (8.45 g, 23.3 mmol) in THF (59 ml) under $N_2$ at −7—0 °C, and the resulting mixture was stirred under the same conditions for 45 min. A solution of 3-bromopropyl phenyl sulfide[8] (8.08 g, 35.0 mmol) in THF (40 ml)–hexamethylphosphoric triamide (HMPA, 16 ml) was added dropwise thereto at −65—−60 °C over 15 min and the mixture was stirred while the temperature was gradually allowed to rise to −35 °C over 3 h. The reaction mixture was poured into AcOEt–ice-water. The organic layer was separated, washed three times with brine, dried, and evaporated *in vacuo*. The residue was chromatographed (toluene–AcOEt (gradient elution, 100 : 0—5)) over silica gel to afford **12h** (11.25 g, 94.2%) as a yellow oil, which was used for the next step without further

purification. IR (film): 1720, 1250, 1220 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.38—1.51, 2.43—2.52 (each 2H, m, $CH_2CH_2$), 2.85 (2H, t, $J$=7.0 Hz, $CH_2S$), 3.64, 3.74 (each 3H, s, $2CH_3$), 5.13 (2H, s, $PhCH_2O$), 6.76—6.79 (3H, m, aromatic H), 7.12—7.46 (15H, m, aromatic H). (+)APCI-MS $m/z$: 513 ($M^+$+1), 453 ($M^+$−$COOCH_3$).

**Methyl 2-(4-Benzyloxy-3-methoxyphenyl)-2-phenyl-5-(phenylsulfinyl)-pentanoate (13h)** 80% *m*-CPBA (9.98 g, 46.3 mmol) was added portionwise to a stirred solution of **12h** (26.34 g, 51.4 mmol) in $CH_2Cl_2$ (263 ml) under $N_2$ at −66——64 °C and the resulting mixture was stirred under the same conditions for 2 h 45 min. The reaction mixture was washed successively with aqueous $NaHSO_3$, aqueous $NaHCO_3$, and brine, dried, and evaporated *in vacuo*. The residue was chromatographed (toluene–AcOEt (gradient elution, 20 : 1—1 : 1)) over silica gel to afford **13h** (23.76 g, 87.4%) as a pale yellow oil, which was used for the next step without further purification. IR (film): 1725, 1255, 1230, 1035 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.5, 2.44, 2.64—2.75 (each 2H, m, $CH_2CH_2$-$CH_2SO$–), 3.66 (3H, s, $CH_3$), 3.75, 3.76 (3H, each s, $CH_3$), 5.14 (2H, s, $PhCH_2O$), 6.70—6.83 (3H, m, aromatic H), 7.15—7.47 (15H, m, aromatic H). (+)APCI-MS $m/z$: 529 ($M^+$+1).

**2-(4-Benzyloxy-3-methoxyphenyl)-2-phenyl-5-(phenylsulfinyl)cyclopentanone (14h)** A 1.5 M solution of LDA·THF in cyclohexane (14.7 ml, 22.0 mmol) was added dropwise to a stirred solution of **13h** (5.29 g, 10.0 mmol) in THF (100 ml) under $N_2$ at −65——58 °C over 40 min, then the resulting mixture was stirred at the same temperature for 40 min and at 0 °C for 40 min. Aqueous $NH_4Cl$ (11.8 g, 220 mmol) was added dropwise thereto and the mixture was extracted with AcOEt. The extract was washed with brine, dried, and evaporated *in vacuo*. The residue was chromatographed (toluene–AcOEt (gradient elution, 100 : 0—85 : 15)) over silica gel to afford **14h** (4.37 g, 88.0%) as a yellow oil, which was used for the next step without further purification. IR (film): 1725, 1255, 1225, 1035 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.80—1.96, 2.42—2.53 (2H, each m, $CH_2$), 2.62—2.81 (2H, m, $CH_2$), 3.42—3.50 (1H, m, CHSO), 3.75, 3.77, 3.79, 3.80 (3H, each s, $OCH_3$), 5.12, 5.13 (2H, each s, $PhCH_2O$), 6.32—6.82 (3H, m, aromatic H), 7.05—7.60 (15H, m, aromatic H). (+)APCI-MS $m/z$: 497 ($M^+$+1), 371 ($M^+$−SOPh).

**5-(4-Benzyloxy-3-methoxyphenyl)-5-phenyl-2-cyclopenten-1-one (9h)** A solution of **14h** (4.18 g, 8.42 mmol) in $CCl_4$ (209 ml) was refluxed for 16 h, cooled to room temperature, washed with aqueous $NaHCO_3$ and brine, dried, and chromatographed (toluene–AcOEt (gradient elution, 20 : 0—19 : 1)) over silica gel to afford **9h** (2.82 g, 90.4%) as a pale yellow solid: mp 58—63 °C. *Anal.* Calcd for $C_{25}H_{22}O_3$: C, 81.06; H, 5.99. Found: C, 81.20; H, 5.97. IR (film): 1700, 1255, 1235 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 3.48 (2H, m, $CH_2$), 3.78 (3H, s, $OCH_3$), 5.13 (2H, s, $PhCH_2O$), 6.23—6.28 (1H, m, –CH=CHCO), 6.67—6.73 (1H, m, aromatic H), 6.78—6.83 (2H, m, aromatic H), 7.15—7.45 (10H, m, aromatic H), 7.80—7.86 (1H, m, $-CH_2CH$=CHCO). (+)APCI-MS $m/z$: 371 ($M^+$+1).

***cis*-5-(4-Benzyloxy-3-methoxyphenyl)-5-phenyl-2-cyclopenten-1-ol (10h) and *trans*-5-(4-Benzyloxy-3-methoxyphenyl)-5-phenyl-2-cyclopenten-1-ol (10i)** A solution of **9h** (1.11 g, 3.00 mmol) in toluene (5 ml) was added to a stirred 1.02 M solution of DIBAL in toluene (3.2 ml, 3.30 mmol) under $N_2$ at −15——12 °C, then the resulting mixture was stirred under the same conditions for 1 h and under ice cooling for 1 h. It was added dropwise to stirred 1 N HCl (30 ml) under ice cooling, then the resulting mixture was stirred at the same temperature for 15 min and at room temperature for 1.5 h. The toluene layer was separated, washed with 20% aqueous potassium sodium tartrate (50 ml) and brine, dried, and evaporated *in vacuo*. The residue was chromatographed (toluene–AcOEt (gradient elution, 99 : 1—95 : 5)) over silica gel. The first eluate afforded **10i** (286 mg, 25.6%) as a colorless oil and the second eluate afforded **10h** (384 mg, 34.4%) as a colorless powder.

**10h**: mp 120—127 °C. *Anal.* Calcd for $C_{25}H_{24}O_3$: C, 80.62; H, 6.49. Found: C, 80.22; H, 6.57. IR (Nujol): 3530, 1585, 1260, 1230 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.48 (1H, br s, OH), 2.85—2.95, 3.37—3.46 (each 1H, m, $CH_2$), 3.75 (3H, s, $OCH_3$), 5.11 (2H, s, $PhCH_2O$), 5.41 (1H, m, CHOH), 5.89—5.93, 6.07—6.11 (each 1H, m, olefinic H), 6.60—6.84 (3H, m, aromatic H), 7.19—7.43 (10H, m, aromatic H). In 2D-NOESY, NOEs were observed between the signal at $\delta$ 5.41 and the signals at $\delta$ 7.19—7.43. (+)APCI-MS $m/z$: 355 ($M^+$−OH).

**10i**: *Anal.* Calcd for $C_{25}H_{24}O_3$: C, 80.62; H, 6.49. Found: C, 80.78; H, 6.60. IR (Nujol): 3520, 3410, 1595, 1585, 1255, 1235 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.46 (1H, br s, OH), 2.86—2.96, 3.36—3.46 (each 1H, m, $CH_2$), 3.82 (3H, s, $OCH_3$), 5.14 (2H, s, $PhCH_2O$), 5.41 (1H, m, CHOH), 5.87—5.91, 6.10—6.14 (each 1H, m, olefinic H), 6.83—6.85 (3H, m, aromatic H), 7.17—7.47 (10H, m, aromatic H). In 2D-NOESY, NOEs were observed between the signal at $\delta$ 5.41 and the signals at $\delta$ 6.83—6.85. (+)APCI-MS $m/z$: 355 ($M^+$−OH).

**4-(4-Benzyloxy-3-methoxyphenyl)-*N*-*tert*-butyl-4-phenyl-2-cyclopentenylamine (1h)** Compound **10h** afforded **1h** (*cis–trans* isomeric mixture; the ratio was 38/62, respectively, on the basis of $^1$H-NMR) in 33.4% yield by method A. Compound **10i** afforded **1h** (*cis–trans* isomeric mixture; the ratio was 37/63, respectively, on the basis of $^1$H-NMR) in 39.6% yield by method A.

**Method A′** $CH_3SO_2Cl$ (945 mg, 8.25 mmol) was added to a stirred solution of a mixture of **10h** and **10i** (2.56 g, 6.87 mmol) in $CH_2Cl_2$ (31 ml) under ice cooling, then $NEt_3$ (835 mg, 8.25 mmol) was added dropwise thereto and the resulting mixture was stirred at the same temperature for 45 min. After dropwise addition of *tert*-$BuNH_2$ (10.05 g, 137 mmol) at the same temperature, NaI (1.24 g, 8.25 mmol) and acetone (31 ml) were added successively and the mixture was stirred at the same temperature for 45 min and at room temperature overnight. It was poured into 1 N NaOH (20 ml) and extracted with $CH_2Cl_2$. The extract was washed with brine, dried, and evaporated *in vacuo*. The residue was chromatographed ($CH_2Cl_2$–MeOH (gradient elution, 20 : 0—1)) over silica gel to afford **1h** (1.44 g, 49.0%) as a pale brown oil. *Anal.* Calcd for $C_{29}H_{33}NO_2 \cdot H_2O$: C, 78.17; H, 7.92; N, 3.14. Found: C, 78.56; H, 7.86; N, 3.18. IR (Nujol): 3300, 1595, 1255, 1220 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.16, 1.17 (9H, each s, $3CH_3$), 2.05 (1H, br, NH), 2.07—2.18, 2.99—3.10 (each 1H, m, $CH_2$), 3.78, 3.81 (3H, each s, $OCH_3$), 4.06 (1H, m, CH–N), 5.11, 5.12 (2H, s, $PhCH_2O$), 5.88—5.92, 6.16—6.21 (each 1H, m, olefinic H), 6.58—6.82 (3H, m, aromatic H), 7.12—7.46 (10H, m, aromatic H). The ratio of *cis* and *trans* isomers in the mixture **1h** was 34/66, respectively, on the basis of $^1$H-NMR. (+)APCI-MS $m/z$: 428 ($M^+$+1).

***cis*-*N*-*tert*-Butyl-4-(4-hydroxy-3-methoxyphenyl)-4-phenyl-2-cyclopentenylamine (1d) and *trans*-*N*-*tert*-Butyl-4-(4-hydroxy-3-methoxyphenyl)-4-phenyl-2-cyclopentenylamine (1e)** A solution of **1h** (3.57 g, 8.35 mmol) in EtOH (56 ml)–concentrated HCl (56 ml) was refluxed for 10 min, cooled to room temperature, and concentrated *in vacuo*. The residue was basified with aqueous $NaHCO_3$ and extracted twice with AcOEt. The extracts were combined, dried, and evaporated *in vacuo*. The residue was chromatographed ($CH_2Cl_2$–MeOH (gradient elution, 99 : 1—93 : 7)) over silica gel. The first eluate afforded **1e** (1.33 g, 41.3%) as a colorless powder and the second eluate afforded **1d** (0.591 g, 21.0%) as a colorless powder.

**1d**: mp 138—141 °C. *Anal.* Calcd for $C_{22}H_{27}NO_2$: C, 78.30; H, 8.06; N, 4.15. Found: C, 78.17; H, 7.95; N, 4.13. IR (Nujol): 3500—2300, 1590, 1265, 1220, 1200 $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.07 (9H, s, $3CH_3$), 2.06, 2.96 (each 1H, m, $CH_2$), 3.69 (3H, s, $OCH_3$), 3.93 (1H, m, CH–N), 5.74—5.78, 6.29 (each 1H, m, olefinic H), 6.52 (1H, dd, $J$=8.2, 2.0 Hz, aromatic H), 6.66 (1H, d, $J$=8.2 Hz, aromatic H), 6.80 (1H, d, $J$=2.0 Hz, aromatic H), 7.10—7.30 (5H, m, aromatic H), 8.77 (1H, br s, OH). In 2D-NOESY, NOEs were observed between the signal at $\delta$ 3.93 and the signals at $\delta$ 7.10—7.30. (+)APCI-MS $m/z$: 338 ($M^+$+1).

**1e**: mp 161—166 °C. *Anal.* Calcd for $C_{22}H_{27}NO_2 \cdot 1/10H_2O$: C, 77.89; H, 8.08; N, 4.13. Found: C, 77.70; H, 8.28; N, 4.09. IR (Nujol): 3200—2150, 1600, 1585, 1265, 1230, 1200 $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.08 (9H, s, $3CH_3$), 1.97, 3.00 (each 1H, m, $CH_2$), 3.66 (3H, s, $OCH_3$), 3.96 (1H, m, CH–N), 5.75—5.80, 6.32 (each 1H, m, olefinic H), 6.59—6.70 (3H, m, aromatic H), 7.10—7.32 (5H, m, aromatic H), 8.81 (1H, br s, OH). In 2D-NOESY, NOEs were observed between the signal at $\delta$ 3.96 and the signals at $\delta$ 6.59—6.70. (+)APCI-MS $m/z$: 338 ($M^+$+1).

The two obtained free bases **1d, e** were converted to the corresponding hydrochlorides (**1d**·HCl, **1e**·HCl) in a usual manner.

**1d**·HCl: mp 200—204 °C (from AcOEt). *Anal.* Calcd for $C_{22}H_{27}NO_2 \cdot$ HCl: C, 70.67; H, 7.55; N, 3.75. Found: C, 70.49; H, 7.85; N, 3.69. IR (Nujol): 3320, 2750—2450, 1265, 1235, 1195 $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.37 (9H, s, $3CH_3$), 2.44—2.5, 3.21—3.33 (each 1H, m, $CH_2$), 3.72 (3H, s, $OCH_3$), 4.42 (1H, m, CH–N), 6.07 (1H, br d, $J$=5.7 Hz, olefinic H), 6.58 (1H, dd, $J$=8.2, 2.0 Hz, aromatic H), 6.67—6.71 (1H, m, olefinic H), 6.73 (1H, d, $J$=8.2 Hz, aromatic H), 6.78 (1H, d, $J$=2.0 Hz, aromatic H), 7.14—7.33 (5H, m, aromatic H), 8.80 (1H, br, $NH^+$), 8.90 (1H, s, OH), 9.25 (1H, br d, $NH^+$).

**1e**·HCl: mp 172—175 °C (from AcOEt). *Anal.* Calcd for $C_{22}H_{27}NO_2 \cdot HCl \cdot 1/10H_2O$: C, 70.33; H, 7.56; N, 3.73. Found: C, 70.18; H, 7.38; N, 3.60. IR (Nujol): 3500—2300, 1260, 1195 $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.36 (9H, s, $3CH_3$), 2.39—2.51, 3.22—3.33 (each 1H, m, $CH_2$), 3.67 (3H, s, $OCH_3$), 4.39 (1H, m, CH–N), 6.09 (1H, br d, $J$=5.5 Hz,

olefinic H), 6.64—6.73 (4H, m, olefinic H, aromatic H), 7.16—7.37 (5H, m, aromatic H), 8.77 (1H, br, $NH^+$), 8.91 (1H, s, OH), 9.27 (1H, br d, $NH^+$).

***N*-(2-Hydroxy-1,1-dimethylethyl)-4,4-diphenyl-2-cyclopentenylamine Methanesulfonate (1f·MsOH) 1f**·MsOH was synthesized by the reaction of **10a** with 2-hydroxy-1,1-dimethylethylamine according to method B. Yield: 37.4%. Colorless crystals: mp 178—181 °C (from AcOEt–EtOH). *Anal.* Calcd for $C_{21}H_{25}NO \cdot CH_3SO_3H$: C, 65.48; H, 7.24; N, 3.47. Found: C, 65.42; H, 7.39; N, 3.46. IR (Nujol): 3400, 2730—2450, 1595, 1225, 1195, 1040 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.38 (6H, s, $2CH_3$), 2.60 (3H, s, $CH_3SO_3$), 2.77 (1H, dd, $J$=13.3, 8.5 Hz, C(H)H), 3.23 (1H, dd, $J$=13.3, 6.8 Hz, C(H)H), 3.61 (2H, s, $OCH_2$), 3.64 (1H, s, OH), 4.35 (1H, m, CH–N), 6.16—6.21, 6.40—6.44 (each 1H, m, olefinic H), 7.12—7.35 (10H, m, aromatic H), 8.31, 8.41 (2H, br, NH, $SO_3H$). (+)APCI-MS $m/z$: 308 ($M^+ + 1$).

**Biological Tests** Inhibitory activity against detrusor contraction *in vitro* induced by electrical field stimulation in guinea-pigs was examined in a similar manner to that described previously.[1)]

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