Agents for the Treatment of Overactive Detrusor. VIII.[1a] Synthesis and Pharmacological Properties of 4,4-Diphenyl-2-cycloalkenylamines Including FK584 and 3,3- or 4,4-Diphenylcycloalkylamines

Kiyoshi TANIGUCHI,*[,a] Kazuo OKUMURA,[a] Kazuhiko TAKE,[a] Kazunori TSUBAKI,[a] Takao TERAI,[a] Isao NAKANISHI,[b] and Youichi SHIOKAWA[a]

New Drug Research Laboratories,[a] and Molecular Design Group,[b] Fujisawa Pharmaceutical Co., Ltd., 1–6, 2-chome, Kashima, Yodogawa-ku, Osaka 532, Japan. Received June 15, 1994; accepted August 17, 1994

This article describes the synthesis of 4,4-diphenyl-2-cycloalkenylamines (3, 5a) including FK584 (*S*(−)-3a) and 3,3- or 4,4-diphenylcycloalkylamines (2, 4, 5b), and their inhibitory activities against detrusor contraction. The order of inhibitory activity (i.v.) of the *N*-*tert*-butylamine derivatives against urinary bladder rhythmic contraction in rats was as follows: *S*(−)-4,4-diphenyl-2-cyclopentenylamine (FK584, *S*(−)-3a) > 4,4-diphenylcyclohexylamine (5b) = *R*(−)-3,3-diphenylcyclopentylamine (*R*(−)-4) ≧ 3,3-diphenylcyclobutylamine (2) ≧ terodiline hydrochloride (HCl) (1) = *RS*(±)-4,4-diphenyl-2-cyclohexenylamine (5a) > *R*(+)-4,4-diphenyl-2-cyclopentenylamine (*R*(+)-3a) ≧ *S*(+)-3,3-diphenylcyclopentylamine (*S*(+)-4). Although the inhibitory activity of FK584 and compounds *R*(−)-4 and 5b against detrusor contraction *in vitro* induced with KCl in guinea-pigs was less potent than that of terodiline HCl, their inhibitory activities against detrusor contractions *in vitro* induced by electrical field stimulation and carbachol were more potent than those of terodiline HCl.

Keywords FK584; 4,4-diphenyl-2-cyclopentenylamine; bladder contraction inhibition; detrusor contraction inhibition; antimuscarinic activity; diphenylcycloalkylamine

As described in the previous papers, we are continuing to seek new agents for the treatment of overactive detrusor.[1] As lead compounds, we have selected oxybutynin hydrochloride (HCl) and terodiline hydrochloride (HCl) (**1**). By the structural modification of terodiline HCl, we generated *S*(−)-*N*-*tert*-butyl-4,4-diphenyl-2-cyclopentenylamine hydrochloride (FK584, *S*(−)-**3a**), which is now under clinical study.[1b] This article describes the synthesis, pharmacological properties, and structure–activity relationships of 4,4-diphenyl-2-cycloalkenylamines (**3**, **5a**) including FK584 and 3,3- or 4,4-diphenylcycloalkylamines (**2**, **4**, **5b**) (Chart 1).

In clinical studies, terodiline HCl showed longer duration of action and fewer side effects (mydriasis and dry mouth) due to antimuscarinic activity than oxybutynin HCl. However its clinical effect on the bladder was weaker than that of oxybutynin HCl.[2,3] For the purpose of enhancing the potency of terodiline HCl, we have adopted the cyclization of terodiline HCl as an approach for generation of new agents. Although terodiline HCl is characterized by several pharmacological actions such as antimuscarinic, calcium channel antagonistic, local anesthetic, and spasmolytic actions on the detrusor smooth muscle,[2] each of its actions may occur by interaction of a different conformation with muscarinic receptor, calcium channel, or detrusor smooth muscle. Therefore, the constraint of its conformation by cyclization was expected to change the balance of pharmacological actions. We hoped that one or more of the several pharmacological actions might be enhanced.

N-*tert*-Butyl-3,3 or 4,4-diphenylcyclobutyl, -2-cyclopentenyl, cyclopentyl, -2-cyclohexenyl, and cylohexyl-

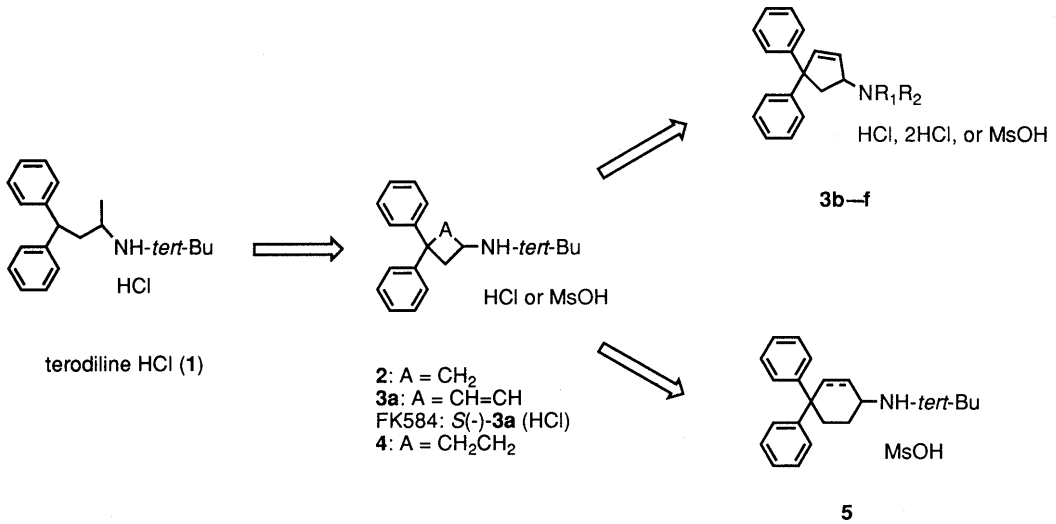


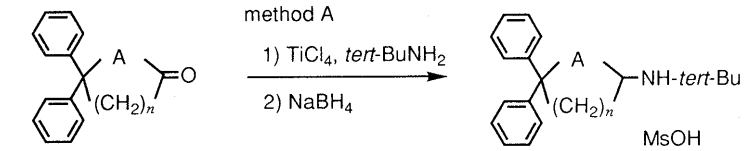
Chart 1

amines (**2**, **3a**, **4**, **5**) were initially synthesized as shown in Chart 1 and evaluated in comparison with terodiline HCl. Compounds **2**—**5** synthesized in this study are listed in Table I.

Synthesis

Cyclobutyl-, 2-cyclohexenyl-, and cyclohexylamines (**2**, **5a**, **5b**) were synthesized by condensation of cyclobutanone (**6**), 2-cylohexen-1-one (**7a**), and cyclohexanone (**7b**), respectively, with *tert*-butylamine in the presence of $TiCl_4$ in CH_2Cl_2 and subsequent reduction with $NaBH_4$ in the presence of MeOH in one pot, as depicted in Chart 2 (method A).

The objective 2-cyclopentenylamines (**3**) were synthesized *via* 2-cyclopenten-1-ol (**9**) as depicted in Chart 3. The starting material, 2-cyclopenten-1-one (**8**) was reduced to the 2-cyclopenten-1-ol **9** with diisobutylaluminum hydride (DIBAL) in toluene. Among compounds **3**, **3a** and **3c**—**e** were synthesized by methanesulfonylation of the 2-cyclopenten-1-ol **9** with $MeSO_2Cl$ in the presence of NEt_3 in acetone and subsequent substitution reaction with the corresponding amines (**12**) in the presence of NaI in one



6: A = CH_2, n = 1
7a: A = CH=CH, n = 2
7b: A = CH_2CH_2, n = 2

2: A = CH_2, n = 1
5a: A = CH=CH, n = 2
5b: A = CH_2CH_2, n = 2

Chart 2

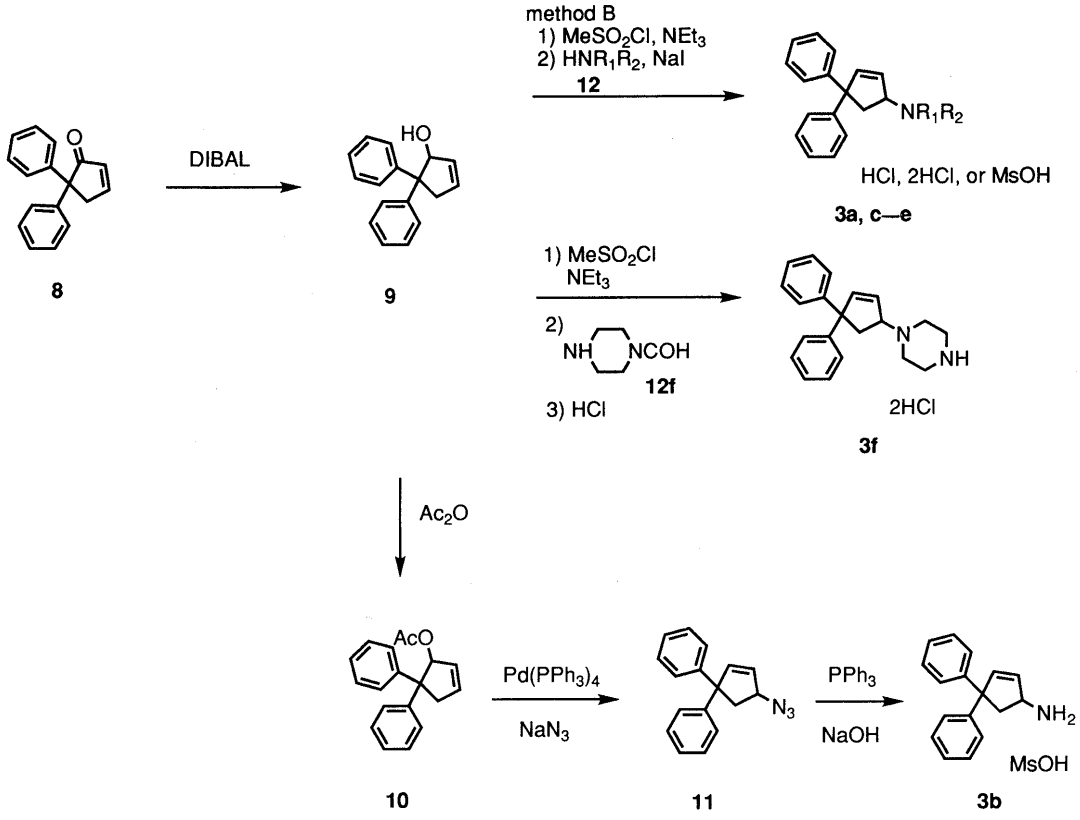


Chart 3

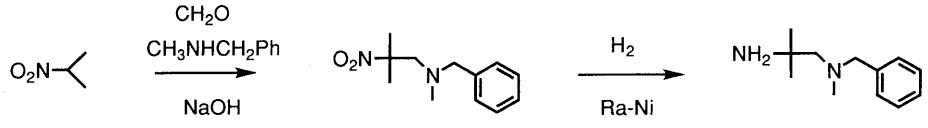
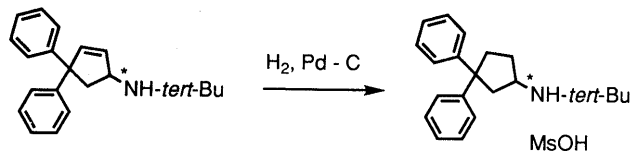


Chart 4

pot (method B).

The 1-(2-cyclopentenyl)piperazine derivative (**3f**) was obtained by methanesulfonylation of the 2-cyclopenten-1-ol **9** with $MeSO_2Cl$ in the presence of NEt_3 in *N*,*N*-dimethylformamide (DMF) and subsequent substitution reaction with 1-formylpiperazine (**12f**) in one pot followed by the treatment with methanolic HCl.

N-Unsubstituted-4,4-diphenyl-2-cyclopentenylamine (**3b**) was synthesized by decomposing 4,4-diphenyl-2-cyclopentenylazide (**11**) by successive use of PPh_3 and aqueous NaOH in tetrahydrofuran (THF). The azide **11** was synthesized by regioselective substitution reaction of 2-cyclopentenyl acetate (**10**), which was prepared by acetylation of the 2-cyclopenten-1-ol **9**, with NaN_3 in the presence of $Pd(PPh_3)_4$ (catalytic amount).[1b]



S(-)-**3a**(free base)
R(+)-**3a**(free base)

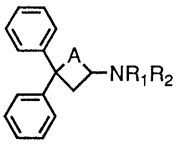
R(-)-**4**
S(+)-**4**

Chart 5

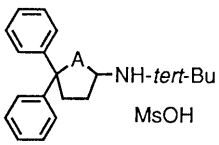
Most of the amines **12** used for the synthesis of the objective 2-cyclopentenylamines **3** are commercially available. *N*-Benzyl-*N*,2,2-trimethylethylenediamine (**12d**) was synthesized as depicted in Chart 4. The aminomethylation of 2-nitropropane (**13**) with formaldehyde and *N*-methylbenzylamine in the presence of 2% NaOH produced *N*-methyl-*N*-(2-methyl-2-nitropropyl)benzylamine (**14**), which was reduced to the amine **12d** with H_2 on Raney Ni in EtOH.

Optically active 3,3-diphenylcyclopentylamines (*R*(−)-**4**, *S*(+)-**4**) were prepared by catalytic hydrogenation of the corresponding optically active 4,4-diphenyl-2-cyclopentenylamines (*S*(−)-**3a**, *R*(+)-**3a**, respectively) obtained by optical resolution[1b] of the racemate **3a** over Pd on carbon in AcOEt (Chart 5).

TABLE I. Physical Properties of 3,3- or 4,4-Diphenylcycloalkylamines (**2**, **4**, **5b**) and 4,4-Diphenyl-2-cycloalkenylamines (**3**, **5a**) and Their Effect on Urinary Bladder Rhythmic Contraction in Rats



2, **3**, **4**



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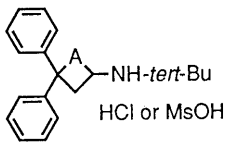
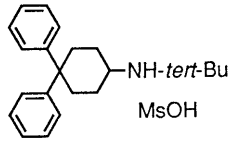
No.	A	NR_1R_2	Form	Method	Yield (%)	mp (°C) (Recryst. solvent)[a]	Formula	Analysis (%) Calcd (Found) C	H	N	Inhibitory activity against bladder contraction Maximum inhibition (%)[b] 1 mg/kg i.v.
2	CH_2	NH-*tert*-Bu	MsOH	A	85.3	197—198 (EA–IE)	$C_{20}H_{25}N \cdot CH_3SO_3H$	67.17 (67.56)	7.78 (7.93)	3.73 (3.75)	26.4
3a[c]	CH=CH	NH-*tert*-Bu	MsOH	B	63.8	204—206 (EA)	$C_{21}H_{25}N \cdot CH_3SO_3H$	68.19 (68.14)	7.54 (7.57)	3.61 (3.62)	40.0
S(−)-**3a** (FK584)	CH=CH	NH-*tert*-Bu	HCl	c)		259—261 (dec.) (EE–W)	$C_{21}H_{25}N \cdot HCl$	76.92 (76.80)	7.99 (7.90)	4.27 (4.29)	55.0
R(+)-**3a**	CH=CH	NH-*tert*-Bu	HCl	c)		259—260 (dec.) (EE–W)	$C_{21}H_{25}N \cdot HCl$	76.92 (77.13)	7.99 (8.11)	4.27 (4.36)	7.5
3b	CH=CH	NH_2	MsOH	d)	63.5	187 (EE)	$C_{17}H_{17}N \cdot CH_3SO_3H$	65.23 (64.84)	6.39 (6.45)	4.23 (4.12)	I.A.
3c	CH=CH	NHEt	HCl	B	18.1	209—210 (EA–IA)	$C_{19}H_{21}N \cdot HCl$	76.11 (75.87)	7.40 (7.25)	4.67 (4.66)	49.6
3d	CH=CH	$NHCMe_2CH_2NMeCH_2Ph$	2HCl	B	11.6	196—197 (dec.) (E–EA)	$C_{29}H_{34}N_2 \cdot 2HCl$	72.04 (71.98)	7.50 (7.40)	5.79 (5.67)	40.0
3e	CH=CH	NMe_2	HCl	B	75.2	189—190 (A–IA)	$C_{19}H_{21}N \cdot HCl$	76.11 (76.44)	7.40 (7.43)	4.67 (4.44)	62.2
3f	CH=CH	1-Piperazyl	2HCl	d)	29.5	244 (dec.) (M)	$C_{22}H_{24}N_2O \cdot 2HCl \cdot H_2O$	63.80 (63.32)	7.14 (7.20)	7.09 (6.84)	45.9
4	CH_2CH_2	NH-*tert*-Bu	MsOH	c)	29.8	243—244 (EA)	$C_{21}H_{27}N \cdot CH_3SO_3H$	67.83 (67.46)	8.02 (7.88)	3.60 (3.53)	37.3
R(−)-**4**	CH_2CH_2	NH-*tert*-Bu	MsOH	e)	90.6	178 (EA–EE)	$C_{21}H_{27}N \cdot CH_3SO_3H$	67.83 (67.72)	8.02 (8.11)	3.60 (3.54)	32.8
S(+)-**4**	CH_2CH_2	NH-*tert*-Bu	MsOH	e)	93.6	178 (EA–EE)	$C_{21}H_{27}N \cdot CH_3SO_3H$	67.83 (67.69)	8.02 (8.01)	3.60 (3.51)	I.A.
5a	CH=CH	—	MsOH	A	37.0	227—229 (E–EE)	$C_{22}H_{27}N \cdot CH_3SO_3H$	68.79 (68.50)	7.78 (7.36)	3.49 (3.55)	16.9
5b	CH_2CH_2	—	MsOH	A	64.9	253—255 (EA–M)	$C_{22}H_{29}N \cdot CH_3SO_3H$	68.45 (67.95)	8.24 (7.90)	3.47 (3.44)	36.6
Terodiline HCl (**1**)											18.5

a) A=acetone, E=ethanol, EA=ethyl acetate, EE=diethyl ether, IA=isopropanol, IE=diisopropyl ether, M=methanol, W=water. *b*) I.A.=inactive. *c*) The reaction of 4,4-diphenyl-2-cyclopenten-1-one and *tert*-butylamine by a procedure similar to method A (Chart 2) simultaneously afforded compound **4** in 29.8% yield and compound **3a** in 22.6% yield.[1b] Compounds *S*(−)- and *R*(+)-**3a** were prepared by optical resolution of the racemate **3a** by means of (−)-di-*p*-toluoyl-L-tartaric acid and (+)-di-*p*-toluoyl-D-tartaric acid, respectively. *S*(−)-**3a**: $[\alpha]_D^{26}$ −189.4° (*c*=1.073, MeOH). *R*(+)-**3a**: $[\alpha]_D^{26}$ +189.2° (*c*=0.60, MeOH). *d*) Synthesized as shown in Chart 3. *e*) Synthesized as shown in Chart 5.

TABLE II. Effect of Selected Compounds (FK584 (*S*(−)-**3a**), *R*(−)-**4**, **5b**) on Urinary Bladder Rhythmic Contraction and Mydriasis in Rats and on Detrusor Contractions *in Vitro* Induced by Electrical Field Stimulation, KCl, and Carbacol in Guinea-Pigs



3a, 4



5b

No.	A	Inhibitory activity against bladder contraction ED_{30} mg/kg i.v.	Mydriatic activity [selectivity] MED[a] mg/kg i.v. [MED/ED_{30}]	Inhibitory activity against detrusor contraction IC_{50} g/ml *in vitro*		
				Electrical field stimulation	KCl	Carbachol
S(−)-**3a** (FK584)	CH=CH	0.18	1.0 [5.6]	3.4×10^{-7} [b]	1.8×10^{-5}	4.6×10^{-7}
R(−)-**4**	CH_2CH_2	0.84	3.2 [3.8]	6.4×10^{-7} [b]	3.0×10^{-5}	2.5×10^{-6}
5b	—	0.68	3.2 [4.7]	2.9×10^{-7} [b]	5.8×10^{-5}	1.5×10^{-6}
Terodiline HCl (**1**)		1.9	10 [5.2]	1.4×10^{-5} [b]	7.9×10^{-6}	9.8×10^{-6}
Atropine		0.035	0.01 [0.28]	2.2×10^{-8} [c]	$>1.0\times10^{-4}$	5.2×10^{-8}

a) MED = minimum effective dose. *b*) Complete inhibition. *c*) Partial inhibition.

Pharmacological Results and Discussion

FK584 (*S*(−)-**3a**) and related 2-cyclopentenyl, cycloalkyl, and 2-cyclohexenylamines **2**—**5** prepared in this study were evaluated for inhibitory activity (i.v.) against urinary bladder rhythmic contraction in rat cystometry. The results are listed in Tables I and II in comparison with the data for terodiline HCl **1**.

In this study, *N*-*tert*-butyl-3,3 or 4,4-diphenylcyclobutyl, -2-cyclopentenyl, cyclopentyl, -2-cyclohexenyl, and cylohexylamines (**2**, **3a**, **4**, **5a**, **5b**) were initially evaluated in comparison with terodiline HCl. The order of inhibitory activity against bladder contraction was as follows: *S*(−)-4,4-diphenyl-2-cyclopentenylamine (FK584, *S*(−)-**3a**) > *RS*(±)-4,4-diphenyl-2-cyclopentenylamine (**3a**) = 4,4-diphenylcyclohexylamine (**5b**) = *RS*(±)-3,3-diphenylcyclopentylamine (**4**) = *R*(−)-3,3-diphenylcyclopentylamine (*R*(−)-**4**) ≧ 3,3-diphenylcyclobutylamine (**2**) ≧ terodiline HCl = *RS*(±)-4,4-diphenyl-2-cyclohexenylamine (**5a**) > *R*(+)-4,4-diphenyl-2-cyclopentenylamine (*R*(+)-**3a**) ≧ *S*(+)-3,3-diphenylcyclopentylamine (*S*(+)-**4**). The inhibitory activity of compounds *R*(+)-**3a** and *S*(+)-**4** against bladder contraction was markedly less potent than that of FK584 (*S*(−)-**3a**) or compound *R*(−)-**4**, the corresponding optical isomers, respectively, suggesting that the absolute configuration of the two phenyl groups and the *tert*-butylamino group might be important for the expression of inhibitory activity against bladder contraction.

Next, modifications of the *tert*-butyl group of compound **3a** were carried out. The removal of the *tert*-butyl group (**3b**) resulted in complete loss of the inhibitory activity against bladder contraction, suggesting that the *tert*-butyl group might play an important role in interaction with muscarinic receptor or tissue in detrusor smooth muscle. The inhibitory activity of NHEt and NMe_2 derivatives (**3c**, **3e**) against bladder contraction was more potent than that of terodiline HCl and compound **3a**, but their duration of action was shorter than that of compound **3a**. So it seemed to be necessary that the *N*-substituents possess suitable bulkiness and/or lipophilicity. Although the duration of action of $NHCMe_2CH_2NHMeCH_2Ph$ and 1-piperazyl derivatives (**3d**, **3f**) possessing an N atom in the *N*-alkyl group was also shorter than that of compound **3a**, their inhibitory activity against bladder contraction was more potent than that of terodiline HCl, indicating that investigation of alternative *N*-substituent groups to the *tert*-butyl group could be an effective approach.

Among the cyclic compounds **2**—**5** prepared in this study, the three most potent compounds, FK584 (*S*(−)-**3a**), *R*(−)-**4**, and **5b**, were further evaluated for mydriatic activity in rats (i.v.),[4] an index of side effects due to antimuscarinic activity, and for inhibitory activity against detrusor contractions *in vitro* induced by electrical field stimulation, KCl, and carbachol in guinea-pigs. These results are listed in Table II. The antimuscarinic activity of FK584, a representative of these three compounds, was also confirmed by its binding affinity to bladder muscarinic receptor as follows.[5a] The specific binding of [^{3}H]*N*-methylscopolamine ([^{3}H]NMS) to membrane preparations of the urinary bladder (detrusor muscle) of dogs was inhibited concentration-dependently by the addition of unlabeled FK584 (10^{-8}—10^{-5} M). The pharmacological profiles of these three compounds were found to be similar to one another. Namely, these compounds were found to possess good selectivity between inhibitory activity against bladder contraction and mydriatic activity, to a degree comparable to that of terodiline HCl. Although the inhibitory activity of these compounds against detrusor contraction *in vitro* induced with KCl was less potent than that of terodiline HCl, their inhibitory activities against detrusor contractions induced by electrical field stimulation and carbachol were more potent than those of terodiline HCl. These compounds also completely inhibited the contraction induced by electrical field stimulation, unlike atropine, a typical pure antimuscarinic agent.[5b] Therefore, the effect of these compounds on detrusor muscle was supposed to be attributed to not only antimuscarinic action but also other pharmacological

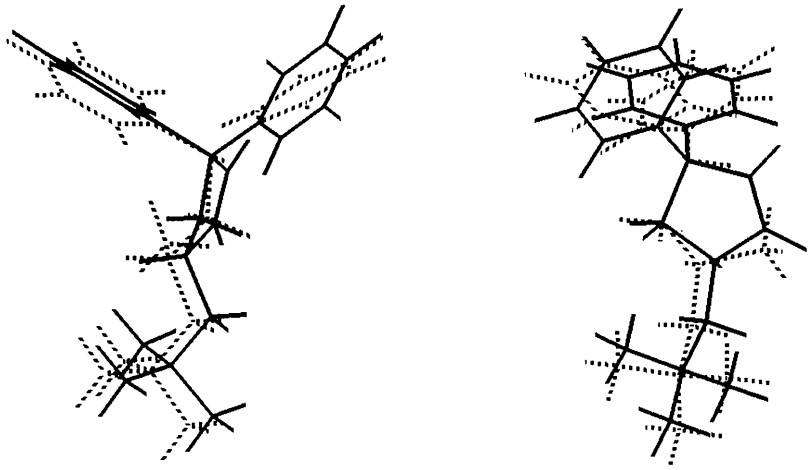


Fig. 1. Superimposition of FK584 (*S*(−)-**3a**) (Solid Line) and *R*(+)-Terodiline HCl (Dotted Line)
The right-hand figure is the right side view of the left-hand figure.

actions.

We wanted to understand why terodiline HCl was inferior to FK584 (*S*(−)-**3a**) in antimuscarinic activity, which affected inhibitory activities against bladder contraction *in vivo* and detrusor contraction *in vitro* induced by electrical field stimulation.

Hence, using computer-assisted molecular modeling, we compared the chemical structures of FK584 and terodiline HCl. Based on the report of Ariëns and Simonis,[6] we speculated that the amines (positive charge center) and the two phenyl groups (lipophilic center) of FK584 and terodiline HCl interacted with the muscarinic receptor and accessory areas close to the muscarinic receptor, respectively. So we carried out a superimposition procedure focusing on the positions of the *tert*-butylamino groups and two phenyl groups of each compound. We used the *R*(+)-isomer of terodiline HCl for the molecular modeling because the antimuscarinic action of the *R*(+)-isomer on isolated detrusor was more potent than that of the *S*(−)-isomer.[7] The low-energy conformations of FK584 and *R*(+)-terodiline HCl were obtained by molecular orbital calculations on the basis of the X-ray crystallography analyses of the *S*(+)-mandelic acid salt of FK584[1c] and terodiline HCl,[8] respectively. Superimposition of one of the low-energy conformations of *R*(+)-terodiline HCl on that of FK584 showed that the *tert*-butylamino groups and two phenyl groups of each compound could exist close to each other (Fig. 1). Therefore, the conformation of *R*(+)-terodiline HCl shown in Fig. 1 may be an active conformation for antimuscarinic activity. However, the magnitude of energy rise from the conformations shown in X-ray crystallographic analyses to those shown in Fig. 1 was somewhat different between FK584 and *R*(+)-terolidine HCl: 0.5 kcal/mol for FK584, and 7.6 kcal/mol for *R*(+)-terodiline HCl. This difference could account for the difference (21-fold) of antimuscarinic activity between terodiline HCl and FK584. The difference in the magnitude of the energy rise was supposed to depend on the conformations of the carbons chains between the N atoms and the phenyl groups. Namely, although FK584, possessing a remarkably rigid chemical structure, originally adopted an almost eclipsed conformation, terodiline HCl, possessing a flexible one in contrast with FK584, could not readily adopt the unstable eclipsed conformation.

The above findings appear to explain why the conversion of the flexible methylene chain of terodiline HCl into a rigid cyclopentene ring led to enhancement of the antimuscarinic activity, affecting the inhibitory activity against detrusor contraction.

For superimposition of the *tert*-butylamino group and two phenyl groups of *R*(+)-**3a** on those of FK584 (*S*(−)-**3a**) shown in Fig. 1, *R*(+)-**3a** was required to adopt a conformation higher in energy by 35.0 kcal/mol than its low-energy conformation. This result may be related to the markedly weaker inhibitory activity of *R*(+)-**3a** against bladder contraction in comparison with FK584.

In conclusion, FK584 (*S*(−)-**3a**) and compounds *R*(−)-**4** and **5b**, which were obtained through cyclization of terodiline HCl, exhibited similar pharmacological profiles to one another. Namely, their inhibitory activities against detrusor contractions *in vitro* induced by electrical field stimulation and carbachol were more potent than those of terodiline HCl, but their inhibitory activity against detrusor contractions induced with KCl was less potent than that of terodiline HCl. As a result, their inhibitory activity (i.v.) against urinary bladder contraction was more potent than that of terodiline HCl.

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 a Bruker AC200P spectrometer using tetramethylsilane as an internal standard. The following abbreviations are used: s = singlet, br = broad, d = doublet, dd = double doublet, t = triplet, q = quartet, quin = quintet, m = multiplet. The MS were recorded on Hitachi M-80 and M1000H mass spectrometers.

***N-tert*-Butyl-4,4-diphenylcyclohexylamine Methanesulfonate (5b). Method A** A solution of $TiCl_4$ (0.66 g) in CH_2Cl_2 (6 ml) was added dropwise to a stirred solution of 4,4-diphenylcyclohexanone[9] (**7b**, 1.15 g) and *tert*-butylamine (2.01 g) in CH_2Cl_2 (20 ml) at −70 °C—−50 °C. The mixture was stirred at the same temperature for 30 min, and then $NaBH_4$ (0.34 g) and MeOH (20 ml) were added successively thereto. The resulting mixture was stirred at the same temperature for 30 min, diluted with water (5 ml), and filtered. The filtrate was concentrated *in vacuo* and

extracted with AcOEt. The extract was washed with brine, dried, and evaporated *in vacuo*. A solution of the residue in AcOEt and a solution of $MeSO_3H$ (441 mg) in MeOH (3 ml) were mixed and the resulting precipitate was collected by filtration to afford **5b** (1.20 g). Its physical data are listed in Tables I and III.

N-tert-Butyl-3,3-diphenylcyclobutylamine methanesulfonate (**2**) and *N-tert*-butyl-4,4-diphenyl-2-cyclohexenylamine methanesulfonate (**5a**) were prepared from 3,3-diphenylcyclobutanone[10] (**6**) and 4,4-diphenyl-2-cyclohexen-1-one[9] (**7a**), respectively, in a similar manner to that used for **5b** and their physical data are listed in Tables I and III.

***N*-Methyl-*N*-(2-methyl-2-nitropropyl)benzylamine (14)** A 36% formalin solution (21.0 ml) was added dropwise to a stirred solution of 2-nitropropane (18.38 g) and 2% NaOH (8.4 ml) in 1,4-dioxane (100 ml) under ice cooling over 20 min and the resulting mixture was stirred at 100 °C for 24 h. The reaction mixture was cooled and partitioned between AcOEt and aqueous NaOH. The organic layer was dried and evaporated *in vacuo*. The residue was distilled under a reduced pressure to afford **14** (36.79 g, 78.8%) as an oil, bp 96—99 °C (0.01 mmHg). *Anal.* Calcd for $C_{12}H_{18}N_2O_2$: C, 64.84; H, 8.16; N, 12.60. Found: C, 65.09; H, 7.98; N, 12.49. IR (film): 1535, 1340 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.55 (6H, s, $2CH_3$), 2.19 (3H, s, NCH_3), 2.94 (2H, s, CH_2), 3.57 (2H, s, CH_2), 7.30 (5H, m, aromatic H). EI-MS *m/z*: 222 (M^+), 176, 131, 91.

***N*-Benzyl-*N*,2,2-trimethylethylenediamine (12d)** Compound **14** (5.56 g) was hydrogenated at room temperature in the presence of Raney Ni (1.0 g) and H_2 at atmospheric pressure in EtOH (40 ml) for 6 h. After removal of the catalyst, the solution was evaporated *in vacuo* and the residue was distilled under a reduced pressure to afford **12d** (2.36 g, 49.1%) as an oil, bp 105 °C (7 mmHg). *Anal.* Calcd for $C_{12}H_{20}N_2$: C, 74.95; H, 10.48; N, 14.57. Found: C, 75.20; H, 10.39; N, 14.70. IR (film): 3350, 3270 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.07 (6H, s, $2CH_3$), 1.44 (2H, s, NH_2), 2.27 (3H, s, NCH_3), 2.34 (2H, s, CH_2), 3.63 (2H, s, CH_2), 7.35 (5H, m, aromatic H). EI-MS *m/z*: 167, 134, 120, 91, 58.

5,5-Diphenyl-2-cyclopenten-1-ol (9) A solution of 5,5-diphenyl-2-cyclopenten-1-one[1b] (**8**, 16.40 g) in toluene (125 ml) was added dropwise to a stirred 1.02 M solution of DIBAL in toluene (72.1 ml) under an N_2 atmosphere at −25—0 °C, and the resulting solution was stirred at the same temperature for 20 min and at 0 °C for 45 min. The reaction mixture was added to stirred 5% HCl (164 ml) under ice cooling and the resulting mixture was stirred at the same temperature for 1.5 h and at room temperature for 1 h. The toluene layer was separated, washed successively with 20% aqueous Na K tartrate·$4H_2O$ (100 g) and brine, dried, and evaporated *in vacuo*. The residue was chromatographed (toluene–AcOEt) over silica gel to afford an oil, which was crystallized from *n*-hexane to afford **9** (9.56 g, 57.8%) as a colorless powder: mp 50—55 °C (from *n*-hexane). *Anal.* Calcd for $C_{17}H_{16}O$: C, 86.41; H, 6.82. Found: C, 86.56; H, 7.11. IR (film): 3520, 3440, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.22 (1H, d, J=9.8 Hz, OH), 2.84—2.97 (1H, m, CH_2), 3.40—3.52 (1H, m, CH_2), 5.41—5.49 (1H, m, CHO), 5.88—5.95 (1H, m, =CH), 6.08—6.14 (1H, m, =CH), 7.15—7.33 (10H, m, aromatic H). (+)Atomospheric pressure chemical ionization ((+)APCI)-MS *m/z*: 219 ($M^+ - OH$).

Preparation of 4,4-Diphenyl-2-cyclopentenylamines (3a, 3c—e). Method B: *N,N*-Dimethyl-4,4-diphenyl-2-cyclopentenylamine Hydrochloride (3e) CH_3SO_2Cl (1.17 g) was added to a stirred solution of **9** (2.00 g) in acetone (20 ml) under ice cooling, and then NEt_3 (1.50 ml) and NaI (1.52 g) were successively added thereto. The mixture was stirred at the same temperature for 20 min, then Me_2NH (**12e**, 7.0 g) was bubbled into it. The resulting mixture was stirred at the same temperature for 4 h, allowed to stand at room temperature overnight, then diluted with brine and extracted with AcOEt. The extract was washed with water and brine, dried, and evaporated *in vacuo*. The residue was chromatographed ($CHCl_3$–MeOH) over silica gel and treated with ethanolic HCl to afford a powder, which was recrystallized from acetone–iso-PrOH to afford **3e** (1.91 g) as a powder. Its physical data are listed in Tables I and III.

The other compounds **3** prepared by method B are listed in Table I and their spectral data are listed in Table III.

1-(4,4-Diphenyl-2-cyclopentenyl)piperazine Dihydrochloride (3f) A solution of CH_3SO_2Cl (1.31 ml) in DMF (3 ml) was added dropwise to a stirred solution of **9** (1.00 g) and NEt_3 (2.36 ml) in DMF (7 ml) under ice cooling over 5 min and the mixture was stirred at the same temperature for 2.5 h. 1-Formylpiperazine (4.36 ml) was added dropwise to the reaction mixture at the same temperature and the resulting mixture was stirred at room temperature overnight. The reaction mixture was partitioned between AcOEt and water. The AcOEt layer was separated, washed with water and brine, dried, and evaporated *in vacuo*. The residue was purified by column chromatography (CH_2Cl_2–MeOH) over silica gel, treated with 3.2 N HCl in MeOH, and recrystallized from MeOH to afford **3f** (0.46 g). Its physical data are listed in Tables I and III.

4,4-Diphenyl-2-cyclopentenylazide (**11**) was prepared by the reaction of 5,5-diphenyl-2-cyclopentenyl acetate (**10**) with NaN_3 in the presence of $Pd(PPh_3)_4$ (catalytic amount) in THF–water at room temperature under an Ar atmosphere.[1b] Compound **10** was prepared by acetylation of compound **9** with Ac_2O in the presence of a catalytic amount of 4-dimethylaminopyridine in pyridine at room temperature.[1b]

4,4-Diphenyl-2-cyclopentenylamine Methanesulfonate (3b) PPh_3 (1.10 g) was added to a solution of 4,4-diphenyl-2-cyclopentenylazide[1b] (**11**, 1.00 g) in THF (15 ml) at room temperature and the mixture was

TABLE III. IR, ^{1}H-NMR, and MS Spectral Data for Compounds **2**, **3**, **4**, and **5**

No.	IR (Nujol) cm^{-1}	^{1}H-NMR (solvent) δ ppm (J in Hz)	EI-MS *m/z*
2	2650, 2470, 1220, 1165, 1035	($CDCl_3$) 1.37 (9H, s), 2.33 (3H, s), 3.22 (4H, d, 8.3), 3.67 (1H, quin, 8.3), 7.06—7.43 (10H, m), 8.71 (2H, s)	279 (M^+), 99, 84
3b	2750—2500, 1200, 1040	($CDCl_3$) 2.42 (1H, dd, 13.6, 8.0), 2.47 (3H, s), 3.17 (1H, dd, 13.6, 7.1), 4.32—4.50 (1H, m), 5.96 (1H, dd, 5.6, 1.5), 6.32 (1H, dd, 5.6, 1.9), 7.00—7.40 (10H, m), 7.86 (3H, br s)	
3c	2680, 2450, 1595	(DMSO-d_6) 1.22 (3H, t, 7.2), 2.33 (1H, dd, 13.3, 8.3), 3.00 (2H, q of d, 7.2, 1.8), 3.25 (1H, dd, 13.3, 7.0), 4.25—4.35 (1H, m), 6.07 (1H, dd, 5.7, 1.4), 6.76 (1H, dd, 5.7, 1.9), 7.12—7.46 (10H, m), 9.25 (2H, br s)	263 (M^+), 234, 186
3d	2750, 2600, 2500, 1600, 1580	(DMSO-d_6) 1.40 (3H, s), 1.59 (3H, s), 2.45—2.70 (1H, m), 2.89 (3H, s), 2.82 (1H, dd, 13.2, 6.9), 3.35—3.90 (2H, m), 4.35 (1H, m), 4.45 (2H, s), 6.11 (1H, d, 5.4), 6.74 (1H, d, 5.4), 6.95—7.85 (15H, m), 9.64 (1H, br s), 10.23 (1H, s), 11.03 (1H, br s)	276, 219, 91
3e	2550, 2430, 1590	(DMSO-d_6) 2.44 (1H, dd, 13.6, 8.1), 2.74 (6H, s), 3.20 (1H, dd, 13.6, 7.1), 4.40—4.55 (1H, m), 6.14 (1H, dd, 5.8, 1.6), 6.85 (1H, dd, 5.8, 2.0), 7.20—7.40 (10H, m), 10.73 (1H, br s)	263 (M^+), 248, 219, 186
3f	3450, 2750—2100, 1620, 1600	(CD_3OD) 2.58 (1H, dd, 13.9, 7.7), 3.39 (1H, dd, 13.9, 7.5), 3.63 (8H, br s), 4.76 (1H, m), 6.17 (1H, dd, 5.7, 1.6), 6.87 (1H, dd, 5.7, 1.9), 7.10—7.40 (10H, m)	304 (M^+)
R(−)-**4**	2720—2480, 1220, 1160, 1040	($CDCl_3$) 1.37 (9H, s), 2.00—2.70 (5H, m), 2.65 (3H, s), 3.10—3.28 (1H, m), 3.38—3.58 (1H, m), 7.05—7.30 (10H, m), 8.43 (2H, br s)	
S(+)-**4**	2720—2480, 1220, 1160, 1040	($CDCl_3$) 1.37 (9H, s), 2.00—2.70 (5H, m), 2.65 (3H, s), 3.10—3.28 (1H, m), 3.38—3.58 (1H, m), 7.05—7.30 (10H, m), 8.43 (2H, br s)	
5a	2750—2300, 1220, 1160, 1040	($CDCl_3$) 1.43 (9H, s), 1.75—2.33 (4H, m), 2.50 (3H, s), 3.60—3.90 (1H, m), 6.09 (1H, dd, 10.0, 2.0), 6.36 (1H, d, 10.0), 7.00—7.30 (10H, m), 8.30 (2H, br s)	
5b	2720—2470, 1220, 1160, 1040	($CDCl_3$) 1.36 (9H, s), 1.60—2.95 (9H, m), 2.35 (3H, s), 6.96—7.35 (10H, m), 7.90 (2H, br s)	

stirred at the same temperature for 2 h. Then 1 N NaOH (10 ml) was added, and the resulting mixture was stirred at the same temperature for 2 h and extracted with AcOEt. The extract was washed with brine, dried, and evaporated *in vacuo*. The residue was chromatographed ($CHCl_3$–MeOH) over silica gel to afford the free base of **3b** (0.73 g), which was converted to the methanesulfonate in a usual manner to afford **3b**[11] (0.81 g). Its physical data are listed in Tables I and III.

***R*(−)-*N*-*tert*-Butyl-3,3-diphenylcyclopentylamine Methanesulfonate (*R*(−)-4)** The methanesulfonate of *S*(−)-**3a** (0.50 g) was converted to the free base (0.39 g) in a usual manner. The free base was hydrogenated at room temperature in the presence of 10% Pd on carbon (0.04 g) and H_2 at atmospheric pressure in AcOEt (10 ml) for 10 h. After removal of the catalyst, the solution was evaporated *in vacuo* and the oily residue was converted to the methanesulfonate in a usual manner. The methanesulfonate was crystallized from Et_2O and recrystallized from AcOEt–Et_2O to afford *R*(−)-**4** (0.37 g): $[\alpha]_D^{23}$ −4.75° (*c*=0.40, MeOH).

S(+)-*N*-*tert*-Butyl-3,3-diphenylcyclopentylamine methanesulfonate (S(+)-**4**) was prepared from *R*(+)-**3a** in a similar manner to that used for *R*(−)-**4**. $[\alpha]_D^{23}$ +4.60° (*c*=1.00, MeOH).

Their other physical data are listed in Tables I and III.

Biological Tests Inhibitory Activity against Urinary Bladder Rhythmic Contraction in Rats: Sprague Dawley rats, weighing 220—320 g, were anesthetized with a subcutaneous dose of 1.0 g/kg of urethane and fixed in a supine position. The lower abdomen was opened along the midline to expose fully the urinary bladder. A rubber balloon was inserted into the bladder through a small incision in the wall around the apex, and was connected with a pressure transducer through a polyethylene tube. The bladder was carefully packed with a cotton-wool pad soaked in warm saline and kept warm. The balloon was filled with approximately 1 ml of water, and then pressured. Rhythmic contractions of the urinary bladder became constant at a threshold intravesical pressure between 5 and 15 mmHg, and reached a maximum contraction at 50 to 70 mmHg with an amplitude of contraction of 40 to 60 mmHg. After this control period, the drugs were administered intravenously, and the inhibitory effects were estimated in terms of the reduction in amplitude of the bladder contractions.

Inhibitory Activities against Detrusor Contractions *in Vitro* Induced by Electrical Field Stimulation, KCl, and Carbachol: Guinea-pigs weighing 320—650 g were killed by exsanguination. The lower abdomen was opened and longitudinally oriented strips of the urinary bladder, 15—20 mm long and 5 mm wide, were excised. The strips were suspended in tissue baths containing 25 ml of Krebs solution. Throughout the experiment, the bathing solution was maintained at 37 °C and continuously aerated with a 95% O_2 and 5% CO_2 gas mixture. Bladder strip contractions were recorded isometrically with an electromechanical displacement transducer and a polygraph. All muscle strips were stretched initially to 1 g of tension and allowed to accommodate to this length, and to the bath milieu, for at least 30 min before any drug additions were made. In each instance 15 min intervals were allowed between drug additions. Single strips were exposed only to electrical stimulation or a single agonist and a drug.

To stimulate the bladder strips electrically, two platinum electrodes were placed parallel to each other and 15 mm apart both side of the tissue preparation. The intensity of square wave stimuli was adjusted to obtain submaximal contractions at a constant frequency of 10 Hz and duration of 1 ms. Usually the electrical intensity was around 10 V, and stimulation was applied to the detrusor strips for 5 s every 5 min. Fixed doses of KCl (30 mM) and carbachol (10 μM) were used as agonists. The effects of agents upon the action of the electrical stimuli or the agonists were examined by adding various concentrations of the drugs to the bath 10 min prior to the administration of electrical stimuli or the agonists.

Mydriatic activity in rats was examined by the methods of Parry and Heathcote.[4]

Molecular Modeling The energy-optimized structures of FK584 (*S*(−)-**3a**), *R*(+)-terodiline HCl, and compound *R*(+)-**3a** were obtained by STO-3G (Gaussian 92[12]) *ab initio* calculation. The superimposition of the compounds was done by the in-house program FIT. All the calculations were performed on an IRIS Indigo graphic workstation. MOL-GRAPH (Daikin Kogyo, Ltd., Japan) was used as a graphic tool.

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