New 2-Aryliminoimidazolidines. II.[1a] Synthesis and Antihypertensive Activity of 2-(Biphenylimino)-imidazolidines

Kiyoshi TANIGUCHI, Yousuke KATSURA, Ikuo UEDA,[2] and Masaaki MATSUO*

New Drug Research Laboratories, Fujisawa Pharmaceutical Co., Ltd., 1–6, 2-chome, Kashima, Yodogawa-ku, Osaka 532, Japan. *Received May 2, 1991*

For improvement of the duration of action of FR35447 (I), 2-(biphenylimino)imidazolidines (III) were synthesized and their hypotensive activity was tested against conscious normotensive rats. 2-(4′-Fluoro-[1,1′-biphenyl]-2-ylimino)imidazolidine (III l) exhibited superior hypotensive potency and was comparable to clonidine (II) in its duration of action.

The structure–activity relationships of III are also described.

Keywords hypotensive activity; 2-aryliminoimidazolidine; 2-(biphenylimino)imidazolidine; clonidine; structure–activity relationship; action duration

In the previous papers,[1] we described the synthesis and hypotensive properties of the novel antagonist to peripheral α-adrenergic receptors, 2-(5-chloro-2-phenoxyphenylimino)imidazolidine (I, FR35447). It has now been found that FR35447 is superior to clonidine (II) in terms of the potency of hypotensive effect, although its duration of action is not sufficient. Therefore, we planned to generate new hypotensive imidazolidines which possess more potent and long lasting hypotensive activity in comparison to clonidine or FR35447 (Fig. 1).

We speculated that the phenoxy group in FR35447 played an important role in binding to peripheral α-adrenergic receptors and consequently FR35447 exhibited potent hypotensive activity. However, the phenoxy group seemed to be unusable for improvement of the duration of action. Thus we focused our attention on a phenyl group as an alternative structural improvement for the design of new hypotensive imidazolidines.

This article describes the chemistry and the pharmacology of novel 2-(biphenylimino)imidazolidines (III) (Chart 1).

Chemistry The objective 2-(biphenylimino)imidazolidines (III) were synthesized *via* the corresponding thioureas (VII) as shown in Chart 1.

The known starting materials, aminobiphenyls (V) were prepared according to literature methods.[3] Unknown 6-chloro, 2′,4′-difluoro, and 2′,6′-difluoro-2-amino-1,1′-biphenyl (Va—c) were prepared by reduction of the corresponding nitrobiphenyls (IV) with iron powder in the presence of ammonium chloride. The 2-chloro-6-nitro-1,1′-biphenyl (IVa), a precursor of Va, was prepared by the Sandmeyer reaction from 2-amino-6-nitro-1,1′-biphenyl. The 2,4-difluoro and 2,6-difluoro-2′-nitro-1,1′-biphenyl (IVb and c) were prepared by Ullmann condensations[3a] from the corresponding difluoroiodobenzenes and 1-bromo-2-nitrobenzene.

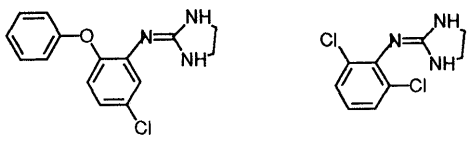


Fig. 1

The aminobiphenyls (V) were successively allowed to react with *N*-benzoylisothiocyanate to give *N*-benzoylthioureas (VI), which were hydrolyzed to the corresponding thioureas (VII). The objective 2-(biphenylimino)-imidazolidines (III) were synthesized by the reaction of the *S*-methylisothiouronium salts, which were prepared by methylation of VII, with ethylenediamine. The imidazolidines (III) synthesized in this study are listed in Table I.

Pharmacological Results The imidazolidines (III) prepared were tested for hypotensive activity. Each compound was given orally to conscious normotensive rats of the Wistar strain at a dose of 10 mg/kg. Mean arterial blood pressure was measured with a pressure transducer through a polyethylene cannula inserted into a femoral artery, and recorded on a polygraph. The experiments were conducted on groups of five animals. The test results are summarized in Table I.

We compared *ortho* phenyl (IIIa) and *meta* phenyl (IIIt) derivatives in order to estimate the suitable position of the phenyl group. As a result, IIIa was found to be a suitable prototype having an appropriate duration of action. Thus we introduced several substituents on both phenyl rings of IIIa to investigate the effects of the substituents on potency and duration of action.

Compounds (IIIb—e) containing a chlorine atom on the benzene ring of the phenyliminoimidazolidine moiety were inactive or less active than the prototype IIIa. The lack of activity of 3-chloro (IIIb) and 6-chloro (IIIe) derivatives

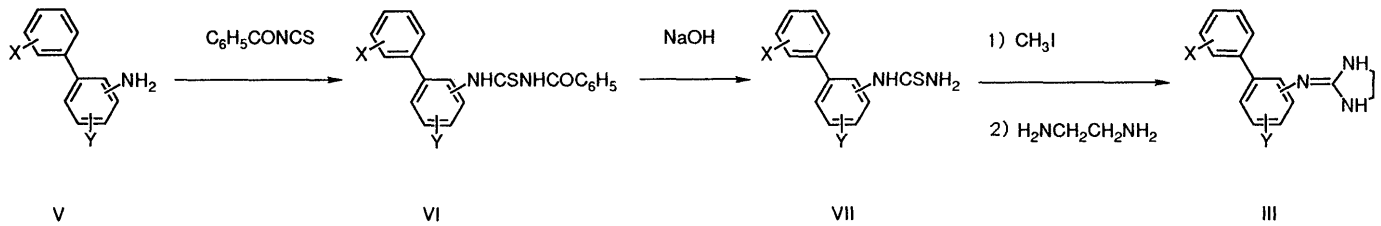
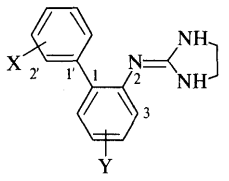
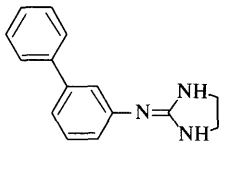


Chart 1

TABLE I. Physical Properties and Hypotensive Activities of 2-(Biphenylimino)imidazolidines (III)



IIIa—s



IIIt

No.	X	Y	Yield (%)	mp (°C) (Recryst. solvent[a])	Formula	Analysis (%) Calcd (Found) C	H	N	Hypotensive activity[b] 10 mg/kg *p.o.* Potency[c] Δ_{max} (%)	Duration[d] $t_{1/2}$(h)	Rank
IIIa	H	H	63.1	170—171 (EA–E)	$C_{15}H_{15}N_3$	75.92 (76.56	6.37 6.37	17.71 17.80)	14.8	>6	(+++)
IIIb	H	3-Cl	23.2	152—153 (EA)	$C_{15}H_{14}ClN_3 \cdot 1/3H_2O$	64.87 (65.10	5.32 5.24	15.13 15.09)	[e]		
IIIc	H	4-Cl	33.9	160—162 (EA)	$C_{15}H_{14}ClN_3$	66.30 (66.49	5.19 4.91	15.46 15.39)	14.6	>6	(++)
IIId	H	5-Cl	48.9	173—174 (EA)	$C_{15}H_{14}ClN_3$	66.30 (66.42	5.19 4.87	15.46 15.38)	11.4	>6	(+)
IIIe	H	6-Cl	51.5	165—167 (EA)	$C_{15}H_{14}ClN_3$	66.30 (66.73	5.19 5.00	15.46 15.58)	I.A.[f]		
IIIf	H	4-CH_3	25.5	178—180 (EA–E)	$C_{16}H_{17}N_3$	76.46 (76.73	6.82 6.81	16.72 16.72)	20.7	>6	(+++)
IIIg	2′-CH_3	H	33.0	145—147 (EA)	$C_{16}H_{17}N_3$	76.46 (76.23	6.82 6.70	16.72 16.73)	9.2	>6	(++)
IIIh	3′-CH_3	H	37.0	150—152 (EA)	$C_{16}H_{17}N_3$	76.46 (76.88	6.82 6.86	16.72 16.71)	38.1	1.5	
IIIi	4′-CH_3	H	60.4	175—178 (EA)	$C_{16}H_{17}N_3$	76.46 (76.17	6.82 6.84	16.72 16.48)	30.9	1.5	
IIIj	2′-F	H	45.3	122—124 (H–EA)	$C_{15}H_{14}FN_3$	70.57 (70.79	5.53 5.44	16.46 16.54)	41.1	>6	(++)
IIIk	3′-F	H	52.9	143—145 (EA)	$C_{15}H_{14}FN_3$	70.57 (70.50	5.53 5.20	16.46 16.39)	28.9	>6	(+++)
IIIl	4′-F	H	39.7	174—176 (EA)	$C_{15}H_{14}FN_3$	70.57 (70.27	5.53 5.22	16.46 16.28)	32.0	>6	(+++)
IIIm	2′-Cl	H	49.8	150—152 (EA)	$C_{15}H_{14}ClN_3$	66.30 (66.41	5.19 5.03	15.46 15.35)	34.5	>6	(++)
IIIn	4′-Cl	H	63.0	148—150 (H–EA)	$C_{15}H_{14}ClN_3$	66.30 (66.32	5.19 4.98	15.46 15.38)	28.0	>6	(+)
IIIo	2′,4′-F_2	H	28.3	131—132 (H–EA)	$C_{15}H_{13}F_2N_3$	65.92 (66.01	4.79 4.62	15.38 15.40)	19.7	3	
IIIp	2′,6′-F_2	H	63.4	154—156 (EA)	$C_{15}H_{13}F_2N_3$	65.92 (66.20	4.79 4.53	15.38 15.43)	25.7	3	
IIIq	2′-CF_3	H	52.1	176—180 (EA)	$C_{16}H_{14}F_3N_3$	62.94 (63.10	4.62 4.66	13.76 13.85)	15.5	6	
IIIr	2′-NO_2	H	27.6	185—188 ($CHCl_3$)	$C_{15}H_{14}N_4O_2$	63.82 (63.73	5.00 4.85	19.85 19.88)	I.A.[f]		
IIIs	2′-OCH_3	H	19.8	150—153 (H–EA)	$C_{16}H_{17}N_3O$	71.88 (71.96	6.41 6.10	15.71 15.74)	15.0	>6	(+++)
IIIt	—	—	21.1	165—167 (EA)	$C_{15}H_{15}N_3$	75.92 (75.85	6.37 6.25	17.71 17.68)	17.1	3	
I	FR35447								57.4	>6	(++)
									36.4[g]	2[g]	
II	Clonidine								23.5	>6	(+++)

a) EA = ethyl acetate, E = ethanol, H = *n*-hexane. *b*) Mean arterial blood pressure was measured for 6 h after administration. *c*) Δ_{max} means maximum decrease in blood pressure (% of initial value). *d*) $t_{1/2}$ means hours that after administration the decrease in blood pressure becomes one-half of maximum decrease (Δ_{max}). (+++), (++), and (+) mean that decreases in blood pressure at 6 h after administration are 100—85%, 85—65%, and 65—50% of Δ_{max}, respectively (The decrease in FR35447 was 74% of Δ_{max}.). *e*) Increase in blood pressure was observed. Maximum increase was 11.6%. *f*) Inactive. *g*) 1 mg/kg *p.o.*

may be due to steric hindrance between the chlorine atom and the phenyl group or the imidazolidine moiety. On the contrary, compound (IIIf) bearing a methyl group at the 4-position of the benzene ring exhibited potent hypotensive activity and sufficient duration of action.

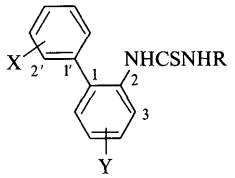
The introduction of various substituents on the *ortho* phenyl group of IIIa enhanced the potency in some compounds. Except for the 2′-methyl derivative (IIIg), compounds (IIIh and i) substituted with a methyl group on the phenyl group exhibited superior potency to clonidine, but their duration of action was inferior to that of clonidine. Compounds (IIIj—n) substituted with a fluorine or a chlorine atom on the phenyl group exhibited superior potency and also long lasting action comparable to

clonidine. Compounds having other substituents such as trifluoromethyl (IIIq), nitro (IIIr), and methoxy (IIIs) at the 2'-position on the phenyl group exhibited weak or no activity.

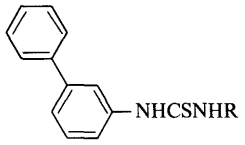
In the FR35447 series, the introduction of appropriate substituents on the benzene ring of the phenyliminoimidazolidine moiety of FR35447, rather than on the phenoxy group, resulted in the enhancement of hypotensive activity.[1a] It is of interest that in the present study on these biphenyl derivatives (III) the contrary relationships were observed. Namely, the introduction of appropriate substituents on the *ortho* phenyl group of III, rather than on the benzene ring of the phenyliminoimidazolidine moiety, contributed to enhancement of the activity.

In conclusion, the introduction of an *ortho* phenyl group into the phenyliminoimidazolidine improved the duration of action in hypotensive imidazolidines. Compound IIIl, which exhibited superior hypotensive potency and was comparable to clonidine in its duration of action, was selected as a candidate for further study.

TABLE II. Physical Properties of Benzoylthioureas (VI) and Thioureas (VII)



VIa—s: R=COC_6H_5
VIIa—s: R=H



VIt: R=COC_6H_5
VIIt: R=H

No.	X	Y	VI Yield (%)	VI mp (°C) (Recryst. solvent[a])	VI Formula	VI Analysis (%) Calcd (Found) C	H	N	VII Yield (%)	VII mp (°C) (Recryst. solvent[a])	VII Formula	VII Analysis (%) Calcd (Found) C	H	N
a	H	H	56.3	125—126 (A)	$C_{20}H_{16}N_2OS$	72.26 (72.47	4.85 4.76	8.43 8.47)	99.4	184—185 (W)	$C_{13}H_{12}N_2S$	68.39 (68.37	5.30 5.30	12.27 12.23)
b	H	3-Cl	73.3	197—200 (A)	$C_{20}H_{15}ClN_2OS$	65.48 (65.26	4.12 3.94	7.64 7.55)	87.9	171—176 (EE)	$C_{13}H_{11}ClN_2S$	59.42 (59.41	4.22 4.14	10.66 10.62)
c	H	4-Cl	66.2	138—140 (A)	$C_{20}H_{15}ClN_2OS$	65.48 (65.57	4.12 3.97	7.64 7.65)	98.5	187—189 (EE)	$C_{13}H_{11}ClN_2S$	59.42 (59.45	4.22 3.98	10.66 10.65)
d	H	5-Cl	60.9	190—191 (A)	$C_{20}H_{15}ClN_2OS$	65.48 (65.19	4.12 3.89	7.64 7.56)	94.6	205—206 (EE)	$C_{13}H_{11}ClN_2S$	59.42 (59.55	4.22 4.12	10.66 10.66)
e	H	6-Cl		[b]					53.5[c]	186—188 (EE)	$C_{13}H_{11}ClN_2S$	59.42 (59.61	4.22 4.13	10.66 10.45)
f	H	4-CH_3	100	134—137 (W)	$C_{21}H_{18}N_2OS$	72.80 (72.51	5.24 5.33	8.09 8.15)	90.3	187—192 (EE)	$C_{14}H_{14}N_2S$	69.39 (69.08	5.82 5.93	11.56 11.49)
g	2'-CH_3	H	99.3	141—146 (W)	$C_{21}H_{18}N_2OS \cdot 1/4H_2O$	71.87 (71.84	5.31 5.23	7.98 8.32)	64.5	142—144 (EA–H)	$C_{14}H_{14}N_2S$	69.39 (69.25	5.82 5.93	11.56 11.66)
h	3'-CH_3	H	73.6	102—106 (EE)	$C_{21}H_{18}N_2OS \cdot 1/4H_2O$	71.87 (71.81	5.31 5.21	7.98 8.22)	77.4	128—136 (EE)	$C_{14}H_{14}N_2S \cdot 1/3H_2O$	67.71 (67.70	5.95 5.94	11.28 11.33)
i	4'-CH_3	H	93.6	118—121 (EE)	$C_{21}H_{18}N_2OS$	72.80 (72.41	5.24 5.24	8.09 8.12)	77.1	193—195 (EE)	$C_{14}H_{14}N_2S$	69.39 (69.36	5.82 5.94	11.56 11.60)
j	2'-F	H	93.9	124—126 (B–H)	$C_{20}H_{15}FN_2OS$	68.55 (68.32	4.31 4.19	7.99 7.97)	96.6	195—197 (A–IE)	$C_{13}H_{11}FN_2S$	63.40 (63.50	4.50 4.40	11.37 11.37)
k	3'-F	H	69.2	118—119 (A–IE)	$C_{20}H_{15}FN_2OS$	68.55 (68.41	4.31 4.41	7.99 7.61)	58.2	159—162 (EE)	$C_{13}H_{11}FN_2S$	63.40 (63.41	4.50 4.54	11.37 11.34)
l	4'-F	H	49.5	115—117.5 (A–IE)	$C_{20}H_{15}FN_2OS$	68.55 (68.68	4.31 4.16	7.99 7.89)	61.9	158—161 (A–IE)	$C_{13}H_{11}FN_2S$	63.40 (63.73	4.50 4.45	11.37 11.36)
m	2'-Cl	H	69.3	163—165 (A–C)	$C_{20}H_{15}ClN_2OS$	65.48 (65.48	4.12 4.00	7.64 7.60)	95.8	190—192 (W)	$C_{13}H_{11}ClN_2S$	59.42 (59.43	4.22 4.16	10.66 10.56)
n	4'-Cl	H	76.4	120—122 (A)	$C_{20}H_{15}ClN_2OS$	65.48 (65.11	4.12 4.18	7.64 7.65)	90.1	199—201 (EE)	$C_{13}H_{11}ClN_2S$	59.42 (59.07	4.22 4.08	10.66 10.55)
o	2',4'-F_2	H		[b]					67.0[c]	153—157 (EE)	$C_{13}H_{10}F_2N_2S$	59.08 (58.88	3.81 3.73	10.60 10.61)
p	2',6'-F_2	H	31.6	150—158 (A)	$C_{20}H_{14}F_2N_2OS$	65.21 (65.37	3.83 3.75	7.60 7.62)	88.5	232—234 (W)	$C_{13}H_{10}F_2N_2S$	59.08 (59.18	3.81 3.63	10.60 10.48)
q	2'-CF_3	H	66.0	139—145 (EE)	$C_{21}H_{15}F_3N_2OS$	62.99 (62.81	3.78 3.61	7.00 7.03)	81.8	186—187 (EE)	$C_{14}H_{11}F_3N_2S$	56.75 (56.85	3.74 3.68	9.45 9.40)
r	2'-NO_2	H		[b]					79.8[c]	186—194 (EE)	$C_{13}H_{11}N_3O_2S$	57.13 (57.22	4.06 3.89	15.37 15.06)
s	2'-OCH_3	H	83.7	139—144 (H)	$C_{21}H_{18}N_2O_2S$	69.59 (68.98	5.01 4.92	7.73 7.85)	83.9	154—158 (EE)	$C_{14}H_{14}N_2OS$	65.09 (64.91	5.46 5.41	10.84 10.85)
t	—	—	70.3	157—158 (A)	$C_{20}H_{16}N_2OS$	72.26 (71.88	4.85 4.69	8.43 8.36)	94.7	183—185 (EE)	$C_{13}H_{12}N_2S$	68.39 (68.67	5.30 5.36	12.27 12.18)

a) A = acetone, B = benzene, C = chloroform, EA = ethyl acetate, EE = diethyl ether, H = *n*-hexane, IE = diisopropyl ether, W = purified by washing with water. *b*) Crude product was used for the next step without further purification. *c*) Yield based on the aniline derivatives used.

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 proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded with Varian EM-60 and JEOL MH-60 spectrometers using tetramethylsilane as an internal standard. The following abbreviations are used; s = singlet, br s = broad singlet, m = multiplet.

2-Chloro-6-nitro-1,1′-biphenyl (IVa) A solution of 2-amino-6-nitro-1,1′-biphenyl[3a] (7.00 g) in CH_3CN (30 ml) was added dropwise to a stirred mixture of *tert*-butyl nitrite (5.83 ml) and $CuCl_2$ (5.28 g) in CH_3CN (150 ml) at room temperature over 45 min. The resulting mixture was stirred for 1 h, evaporated *in vacuo*, and partitioned between Et_2O and dil. HCl. The Et_2O layer was washed with aqueous Na_2CO_3 and brine, dried, and evaporated *in vacuo* to afford IVa (5.20 g, 68.1%) as a yellow powder: mp 102—108 °C (from *n*-hexane–benzene). *Anal.* Calcd for $C_{12}H_8ClNO_2$: C, 61.69; H, 3.45; N, 5.99. Found: C, 61.73; H, 3.35; N, 6.33. IR (Nujol): 1525, 1370 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.15—7.95 (8H, m, aromatic H).

2,4-Difluoro-2′-nitro-1,1′-biphenyl (IVb) A mixture of 2,4-difluoro-1-iodobenzene[4] (49.1 g), 1-bromo-2-nitrobenzene (63.1 g), and copper powder (59.5 g) was stirred at 120 °C for 18 h, cooled, and extracted with CH_2Cl_2. The extract was evaporated *in vacuo* and chromatographed (*n*-hexane–benzene) over silica gel to afford IVb (28.0 g, 47.6%) as a pale yellow powder: mp 58—65 °C (from *n*-hexane). *Anal.* Calcd for $C_{12}H_7F_2NO_2$: C, 61.28; H, 3.00; N, 5.96. Found: C, 61.25; H, 2.79; N, 5.96. IR (Nujol): 1520, 1360 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 6.7—8.15 (7H, m, aromatic H).

2,6-Difluoro-2′-nitro-1,1′-biphenyl (IVc) IVc was prepared in a manner similar to that used for IVb, 56.6%, yellow crystals: mp 105—110 °C (from *n*-hexane). *Anal.* Calcd for $C_{12}H_7F_2NO_2$: C, 61.28; H, 3.00; N, 5.96. Found: C, 61.20; H, 2.83; N, 5.97. IR (Nujol): 1520, 1360 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 6.8—8.3 (7H, m, aromatic H).

2-Amino-6-chloro-1,1′-biphenyl (Va) A solution of IVa (5.10 g) in EtOH (20 ml) was added dropwise to a stirred mixture of iron powder (5.36 g) and NH_4Cl (0.65 g) in refluxing EtOH (80 ml) and water (10 ml). The mixture was stirred under reflux for 30 min. After filtration, the filtrate was evaporated *in vacuo* and partitioned between Et_2O and aqueous $NaHCO_3$. The Et_2O layer was washed with brine, dried, evaporated *in vacuo*, and chromatographed (toluene) over silica gel to afford Va (4.41 g, 99.3%) as a pale yellow oil. *Anal.* Calcd for $C_{12}H_{10}ClN$: C, 70.77; H, 4.95; N, 6.88. Found: C, 70.42; H, 5.05; N, 6.85. IR (film): 3480, 3380 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.50 (2H, br s, NH_2), 6.45—7.7 (8H, m, aromatic H).

The following compounds (Vb and c) were prepared from IVb and c, respectively, in a manner similar to that used for Va.

2-Amino-2′,4′-difluoro-1,1′-biphenyl (Vb) Vb: 91.5%, pale brown needles: mp 76—77 °C (from *n*-hexane). *Anal.* Calcd for $C_{12}H_9F_2N$: C, 70.24; H, 4.42; N, 6.83. Found: C, 70.18; H, 4.28; N, 6.81. IR (Nujol): 3480, 3400 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.6 (2H, br s, NH_2), 6.65—7.6 (7H, m, aromatic H).

2-Amino-2′,6′-difluoro-1,1′-biphenyl (Vc) Vc: 96.7%, a colorless powder: mp 84—88 °C (from *n*-hexane–diisopropyl ether). *Anal.* Calcd for $C_{12}H_9F_2N$: C, 70.24; H, 4.42; N, 6.83. Found: C, 69.99; H, 4.15; N, 6.78. IR (Nujol): 3480, 3400 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.6 (2H, br s, NH_2), 6.7—7.65 (7H, m, aromatic H).

2-Amino-1,1′-biphenyl was commercially available. The other known compounds (V) used in this report were prepared according to the literature.[3]

1-Benzoyl-3-(4′-fluoro-[1,1′-biphenyl]-2-yl)thiourea (VII) Benzoyl chloride (5.03 ml) was added dropwise under reflux to a stirred solution of NH_4SCN (3.60 g) in acetone (200 ml). The mixture was stirred under reflux for 1.5 h, and then 2-amino-4′-fluoro-1,1′-biphenyl[3a] (7.70 g) in acetone (50 ml) was added dropwise. The resulting mixture was stirred under reflux for 1 h, concentrated *in vacuo*, and diluted with water. The precipitated powder was collected by filtration, and washed with water to afford VII (7.14 g) as colorless needles. IR (Nujol): 3240, 3190, 1660 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.0—8.05 (13H, m, aromatic H), 9.23 (1H, br s, NH), 12.32 (1H, br s, NH). The other physical data are listed in Table II.

The other compounds (VI) were prepared in a manner similar to that used for VII (Table II).

4′-Fluoro-[1,1′-biphenyl]-2-ylthiourea (VIII) A mixture of VII (14.9 g) and NaOH (1.71 g) in MeOH (200 ml) was refluxed for 10 min, concentrated *in vacuo*, and diluted with water. The precipitated powder was collected by filtration and washed with water and Et_2O to afford VIII (6.50 g) as colorless crystals. IR (Nujol): 3410, 3360, 3230, 3160 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 7.15—7.6 (10H, m, aromatic H and NH_2), 9.20 (1H, br s, NH). The other physical data are listed in Table II.

The other compounds (VII) were prepared in a manner similar to that used for VIII (Table II).

2-(4′-Fluoro-[1,1′-biphenyl]-2-ylimino)imidazolidine (III) A mixture of VIII (6.20 g) and CH_3I (1.89 ml) in MeOH (150 ml) was stirred under reflux for 3 h and concentrated *in vacuo* to afford *N*-(4′-fluoro-[1,1′-biphenyl]-2-yl)-*S*-methylisothiourea hydroiodide, which was used without purification for the following reaction. A mixture of the *S*-methylisothiourea hydroiodide and ethylenediamine (5.05 ml) in EtOH (50 ml) was stirred under reflux for 8 h, evaporated *in vacuo*, diluted with aqueous Na_2CO_3, and extracted with CH_2Cl_2. The extract was washed with brine, dried, and evaporated *in vacuo*. The residue was recrystallized from AcOEt to afford III (2.55 g) as colorless crystals. ^{1}H-NMR ($CDCl_3$) δ: 3 20 (4H, s, $CH_2 \times 2$), 4.67 (2H, br s, NH × 2), 7.05—7.4 (8H, m, aromatic H). The other physical data are listed in Tables I and III.

The other compound (III) were prepared in a manner similar to that used for III (Tables I and III).

TABLE III. IR and ^{1}H-NMR Spectral Data for the Compounds in Table I

No.	IR (Nujol) cm^{-1}	^{1}H-NMR ($CDCl_3$) δ
IIIa	3480 3210 1670	3.13 (4H, s), 5.93 (2H, br s), 6.8—7.5 (9H, m)[a]
IIIb	3475 3150 1660	3.16 (4H, s), 5.84 (2H, s), 6.8—7.35 (8H, m)[a]
IIIc	3460 1680	3.03 (4H, s), 5.18 (2H, br s), 6.85—7.35 (8H, m)
IIId	3425 3210 3140 1680	3.10 (4H, s), 4.93 (2H, br s), 6.85—7.4 (8H, m)
IIIe	3425 3150 1640	3.10 (4H, s), 4.38 (2H, br s), 6.8—7.3 (8H, m)
IIIf	3405 1670	2.33 (3H, s), 3.07 (4H, s), 4.98 (2H, br s), 6.8—7.6 (8H, m)
IIIg	3050 1675	2.17 (3H, s), 3.23 (4H, s), 4.23 (2H, s), 7.1—7.3 (8H, m)
IIIh	3375 3100 1650[b]	2.37 (3H, s), 3.20 (4H, s), 4.72 (2H, br s), 7.0—7.45 (8H, m)
IIIi	3375 3150 1650[b]	2.37 (3H, s), 3.15 (4H, s), 5.05 (2H, s), 7.0—7.5 (8H, m)
IIIj	3460 1670	3.23 (3H, s), 4.67 (2H, br s), 7.05—7.4 (8H, m)
IIIk	3460 3405 3225 1675	3.13 (4H, s), 5.18 (2H, br s), 6.85—7.4 (8H, m)
IIIl	3420 3380 1670	[c]
IIIm	3475 3200 1655	3.20 (4H, s), 4.68 (2H, br s), 7.0—7.45 (8H, m)
IIIn	3490 3405 3120 1665	3.13 (4H, s), 4.85 (2H, br s), 6.95—7.35 (8H, m)
IIIo	3405 1670	3.22 (4H, s), 4.73 (2H, br s), 6.7—7.35 (7H, m)
IIIp	3430 3160 1665	3.17 (4H, s), 5.00 (2H, br s), 6.65—7.5 (7H, m)
IIIq	3450 1655	3.27 (4H, s), 4.70 (2H, s), 6.95—7.8 (8H, m)
IIIr	3450 1655 1520 1355	3.37 (4H, s), 4.45 (2H, br s), 6.95—7.9 (8H, m)
IIIs	3440 1665	3.13 (4H, s), 3.73 (3H, s), 4.73 (2H, br s), 6.9—7.35 (8H, m)
IIIt	3340 1655	3.38 (4H, s), 5.87 (2H, br s), 6.95—7.85 (9H, m)[a]

a) In DMSO-d_6. *b*) Measured by KBr method. *c*) See Experimental.

Acknowledgements We wish to thank Dr. T. Kamitani[5] and the staff of the pharmacological division of Fujisawa Pharmaceutical Co., Ltd. for the testing of the compounds. We are also indebted to the staff of Analytical Research Laboratories, Fujisawa Pharmaceutical Co., Ltd. for elemental analyses.

References and Notes

1) *a*) M. Matsuo, K. Taniguchi, Y. Katsura, T. Kamitani, and I. Ueda, *Chem. Pharm. Bull.*, **33**, 4409 (1985); *b*) T. Kamitani, M. Katamoto, K. Tsujioka, T. Terai, M. Ohtsuka, T. Ono, H. Kikuchi, and S. Kumada, *Jpn. J. Pharmacol.*, **39**, 251 (1985).
2) Present address: *The Institute of Scientific and Industrial Research, Osaka University, Ibaraki, Osaka 567, Japan.*
3) *a*) M. J. S. Dewar and P. J. Grisdale, *J. Org. Chem.*, **28**, 1759 (1963); *b*) Th de Crauw, *Recl. Trav. Chim. Pays-Bas*, **50**, 753 (1931) [*Chem. Abstr.*, **25**, 4859 (1931)]; K. Hoegerle and P. L'Écuyer, *Can. J. Chem.*, **37**, 2068 (1959); P. A. S. Smith, J. M. Clegg, and J. H. Hall, *J. Org. Chem.*, **23**, 524 (1958); V. A. Petrow, *J. Chem. Soc.*, **1945**, 18; E. Hammerschmidt and F. Voegtle, *Chem. Ber.*, **112**, 1785 (1979); *idem, ibid.*, **113**, 1125 (1980); L. Mascarelli and D. Gatta, *Atti Accad. Lincei*, **13**, 887 (1931) [*Chem. Abstr.*, **26**, 1272 (1932)]; C. K. Bradsher and L. J. Wissow, *J. Am. Chem. Soc.*, **68**, 404

(1946); E. J. Forbes, J. C. Tatlow, and R. T. Wragg, *Tetrahedron*, **8**, 73 (1960); D. Purdie, *J. Am. Chem. Soc.*, **63**, 2276 (1941); G. Smolinsky, *ibid.*, **83**, 2489 (1961); I. G. M. Campbell and A. W. White, *J. Chem. Soc.*, **1958**, 1184.

4) M. M. Nad, T. V. Talalaeva, G. V. Kazennikova, and K. A. Kocheshkov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, **1959**, 65 [*Chem. Abstr.*, **53**, 14976*f* (1959)].

5) Present address: *Technical R and D Division, Terumo Corporation, 1500, Inokuchi, Nakai-machi, Ashigarakami-gun, Kanagawa 259–01, Japan.*