Studies on Aromatase Inhibitors. II.[1] Synthesis and Biological Evaluation of 1-Amino-1*H*-1,2,4-triazole Derivatives

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1-*N*,*N*-Disubstituted amino-1*H*-1,2,4-triazole derivatives were prepared and evaluated for aromatase-inhibitory activity (*in vitro*) and for the inhibitory activity on pregnant mare serum gonadotropin (PMSG)-induced estrogen synthesis (*in vivo*). 1-*N*-*para*-Substituted benzylamino derivatives, having an electron-withdrawing group on the phenyl moiety, exhibited aromatase-inhibitory activity *in vitro* and *in vivo*. Among them, 1-[(4-nitrobenzyl)(4-nitrophenyl)amino]-1*H*-1,2,4-triazole (5b) was the most potent aromatase inhibitor. These 1-*N*-benzylamino derivatives also showed relatively strong inhibitory activity on aldosterone synthesis, indicating that the selectivity of these derivatives for aromatase inhibition was not sufficient in comparison with that of the 4-amino-4*H*-1,2,4-triazole derivatives.

Key words aromatase; estrogen; 1-amino-1*H*-1,2,4-triazole; aldosterone

Aromatase plays an important role in the biosynthesis of estrogens from androgens. Estrogen depletion by the use of aromatase inhibitors may be of therapeutic value for treating estrogen-dependent diseases, such as breast cancer.[2-7] Aromatase belongs to the microsomal cytochrome P-450 family of enzymes.[8] A number of non-steroidal aromatase inhibitors are being developed.[9-12] These inhibitors have an aza-hetero ring containing an sp^2 nitrogen atom which binds to the heme iron atom of aromatase to show inhibitory activity. As part of our search for new aza-heterocyclic derivatives as aromatase inhibitors, we previously reported[1] that a series of 4*H*-1,2,4-triazol-4-ylamino derivatives (4-ylamino type) showed aromatase-inhibitory activity. 4-[(4-Bromobenzyl)(4-cyanopheny)amino]-4*H*-1,2,4-triazole (YM511) was a highly potent aromatase inhibitor with IC_{50} values of 0.4 and 0.12 nM in *in vitro* experiments using rat ovary and human placenta, respectively, and was a weak inhibitor of other enzymes involved in steroid hormone synthesis. Most known aromatase inhibitors of the triazole type, such as CGS20267[13] and D1033,[10] are 1*H*-1,2,4-triazol-1-yl type derivatives. These facts prompted us to synthesize and evaluate a series of 1*H*-1,2,4-triazol-1-ylamino type derivatives in order to study their potency and selectivity as aromatase inhibitors (Fig. 1). In this study, we found that the aromatase-inhibitory effect of 1*H*-1,2,4-triazol-1-ylamino derivatives was also potent, but many compounds of this series also exhibited higher inhibitory activities for aldosterone synthesis than did the 4-amino-4*H*-1,2,4-triazol-4-ylamino-type derivatives.

Chemistry

The synthesis of *N*,*N*-disubstituted aminotriazole derivatives (**4** and **5**) is outlined in Chart 1. Desired compounds were prepared in two steps from 1-amino-1*H*-1,2,4-triazole using a similar procedure to that which we described previously.[1] 1-Amino-1*H*-1,2,4-triazole (**1**)[14] was treated with 4-fluorobenzonitrile and 4-fluoronitrobenzene in the presence of potassium *tert*-butoxide in dimethylsulfoxide (DMSO) to afford the *para*-cyanophenylamino (**2**) and *para*-nitrophenylamino (**3**) derivatives, respectively. Compound **2** was reacted again with 4-fluorobenzonitrile in *N*,*N*-dimethylformamide (DMF) using sodium hydride as a base to give the *N*,*N*-bisaryl derivative (**4a**) (method A). Compounds **4b** and **5a** were similarly prepared by the reaction of **2** and **3** with 4-fluoronitrobenzene. *N*-Benzyl derivatives (**4c—l** and **5b—d**) were obtained by the reaction of **2** and **3** with benzyl halide in the presence of potassium carbonate in acetonitrile (method B).

Results and Discussion

Inhibitory activities of the series of triazole derivatives on aromatase (*in vitro*), aldosterone synthesis (*in vitro*) and pregnant mare serum gonadotropin (PMSG)-induced estrogen synthesis (*in vivo*) were evaluated. In the *in vitro* rat ovarian microsome assay, aromatase-inhibitory activity of the compounds at concentrations of 1 and 10 nM was expressed as percent inhibition of the aromatization of androstenedione. In the rat *in vivo* assay, the estrogen synthesis-inhibitory activity of the compounds at the dosages of 0.03 and 0.3 mg *p.o.* was expressed as percent

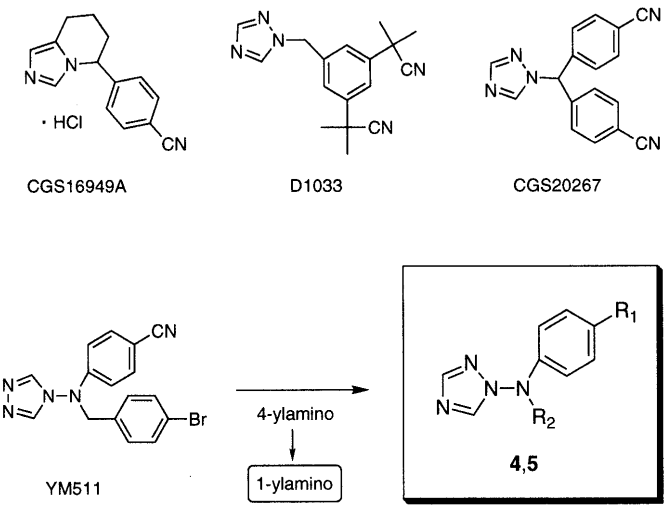

Fig. 1

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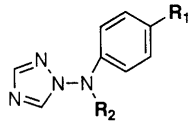
Table 1. Physical and Biological Data for 1-[(4-Cyano or Nitrophenyl)amino]-1*H*-1,2,4-triazole Derivatives



Compd.	R_1	R_2	Method[a]	Yield (%)	mp (°C)	Recryst. solvent	% inhibition of aromatase[b] (*in vitro*, nM)		% inhibition of PMSG-induced estrogen synthesis[c] (*in vivo*, mg/kg *p.o.*)	
							1	10	0.03	0.3
4a	CN	4-CN–Ph	A	70	186—187	AcOEt–Et_2O	58.1	84.5	21.3	84.9
4b	CN	4-NO_2–Ph	A	67	178—179	AcOEt–Et_2O	49.9	86.4	28.6	84.2
4c	CN	$PhCH_2$	B	65	89—90	AcOEt–*n*-hexane	35.0	80.8	36.6	74.4
4d	CN	4-CN–$PhCH_2$	B	50	169—171	AcOEt–*n*-hexane	39.8	81.1	75.4	92.5
4e	CN	4-NO_2–$PhCH_2$	B	41	136—137	AcOEt	30.3	63.1	78.1	95.6
4f	CN	4-F–$PhCH_2$	B	75	133—134	AcOEt–*n*-hexane	43.2	85.5	63.4	88.6
4g	CN	4-Cl–$PhCH_2$	B	60	134—135	AcOEt–*n*-hexane	78.9	91.0	75.1	92.5
4h	CN	4-Br–Ph–CH_2	B	65	124—125	AcOEt–Et_2O	36.5	79.6	67.2	80.9
4i	CN	4-I–$PhCH_2$	B	62	140—141	AcOEt–*n*-hexane	82.5	94.8	44.6	87.2
4j	CN	4-Me–$PhCH_2$	B	74	133—134	AcOEt–*n*-hexane	56.1	90.8	−18.2	−13.6
4k	CN	4-MeO–$PhCH_2$	B	67	113—114	AcOEt–*n*-hexane	45.9	74.2	−3.3	20.7
4l	CN	5-Benzofurazanylmethyl[d]	B	70	169—170	AcOEt–*n*-hexane	64.1	86.3	84.9	94.8
5a	NO_2	4-NO_2–Ph	A	72	153—154	EtOH–iso-Pr_2O	31.0	66.4	46.9	73.1
5b	NO_2	4-NO_2–$PhCH_2$	B	57	128—129	EtOH	67.8	88.4	90.7	92.6
5c	NO_2	4-Br–$PhCH_2$	B	70	129—130	EtOH	45.5	69.7	72.1	93.6
5d	NO_2	5-Benzofurazanylmethyl	B	76	152—153	EtOH	61.7	87.4	80.8	83.7
YM511							68.2	92.0	90.0	97.8
CGS20267							37.5	81.3	95.1	NT[e]

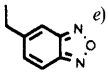
a) A: NaH, DMF B: K_2CO_3, CH_3CN. *b*) % inhibition of aromatization of androstenedione in the *in vitro* rat ovarian microsome assay. Values were determined in a single experiment. Each assay was performed in triplicate. *c*) % inhibition of estrogen synthesis in the *in vivo* rat PMSG-induced estrogen synthesis assay. Each compound was tested in groups of five rats and data represent mean values of peak inhibition. *d*) 5-Benzofurazanylmethyl:  *e*) NT: not tested.

Table 2. Inhibitory Activities of Compounds **4**, **5**, YM511 and CGS20267 against Aldosterone Synthesis

Compound	% inhibition of aldosterone synthesis[a] (*in vitro*, μM)	
	0.3	1
4a	3	0
4e	102	102
4h	82	101
4l	23	30
5a	0	0
5b	75	93
5c	103	104
5d	9	19
YM511	24	35
CGS20267	22	33

a) % inhibition of aldosterone synthesis in the *in vitro* rat adrenal cell assay. Values were determined in a single experiment. Each assay was performed in triplicate.

inhibition of PMSG-induced estrogen synthesis.

The pharmacological data for the synthesized compounds are summarized in Tables 1 and 2.

The bis *para*-cyanophenylamino derivative (**4a**), an aza-analog of CGS20267, showed potent aromatase-inhibitory activity *in vitro*. Other *N*,*N*-diaryl derivatives (**4b** and **5a**) exhibited inhibitory activity similar to that of CGS20267 *in vitro*. As for estrogen synthesis (*in vivo*), however, the inhibitory activities of these compounds were less potent than that of CGS20267. In the case of the 4-amino-4*H*-1,2,4-triazol-4-ylamino series, introduction of a *para*-substituted benzyl group onto the R_2 moiety resulted in increased activity.[1] Therefore, we investigated various benzyl substituents in the 1-ylamino series. In both the *para*-cyanophenylamino (**4**) and *para*-nitrophenylamino (**5**) derivative series, introduction of a benzyl group having a cyano (**4d**), nitro (**4e** and **5b**) or halogen (**4f—i** and **5c**) substituent on the phenyl ring increased the inhibitory activity, especially *in vivo*. Compounds **4l** and **5d**, with a bicyclic benzofurazanyl group, also had potent *in vivo* activities. On the other hand, compounds **4j** and **4k**, having a methyl and a methoxyl group, respectively, which have an electron-donating effect, showed no inhibitory activities *in vivo*, although their *in vitro* activities were marked. These results suggested that the electron-withdrawing substituent on the phenyl ring of the benzyl moiety is indispensable for high *in vivo* activity. Among them, compound **5b** with the *para*-nitrobenzyl group was the most potent aromatase inhibitor (90.7% inhibition at 0.03 mg/kg *p.o.* in *in vivo*) with a potency equal to that of YM511.

Next, we studied the inhibitory effect of typical compounds in this series on aldosterone synthesis (Table 2). Interestingly, there were great differences between the inhibitory activities of *N*-phenyl derivatives and *N*-benzyl derivatives. For example, the *para*-nitrobenzyl derivative

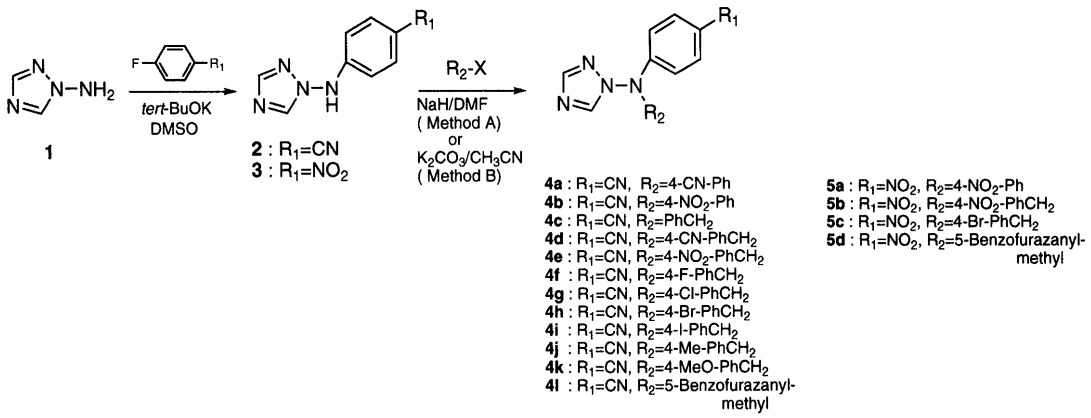


Chart 1

Table 3. Physical and Spectral Data for Compounds **4a—l** and **5a—d**

Compd.	Formula	Analysis (%) Calcd (Found)				^{1}H-NMR (DMSO-d_6) δ[a]	MS m/z
		C	H	N	X		
4a	$C_{16}H_{10}N_6$	67.12 (67.15)	3.52 3.65	29.35 29.31)		7.05 (4H, d, J=9), 7.66 (4H, d, J=9), 8.12 (1H, s), 8.37 (1H, s)[b]	286 (M^+)
4b	$C_{15}H_{10}N_6O_2$	58.82 (58.66	3.29 3.34	27.44 27.44)		7.02 (2H, d, J=9), 7.15 (2H, d, J=9), 7.69 (2H, d, J=9), 8.23 (2H, d, J=9), 8.28 (1H, s), 8.40 (1H, s)[b]	306 (M^+)
4c	$C_{16}H_{13}N_5$	69.80 (69.72	4.76 4.81	25.44 25.41)		5.03 (2H, s), 6.75 (2H, d, J=9), 7.28—7.36 (5H, m), 7.75 (2H, d, J=9), 8.16 (1H, s), 8.62 (1H, s)	275 (M^+)
4d	$C_{17}H_{12}N_6$	67.99 (67.94	4.03 4.17	27.98 27.99)		5.18 (2H, s), 6.70 (2H, d, J=9), 7.61 (2H, d, J=9), 7.75 (2H, d, J=9), 7.82 (2H, d, J=9), 8.19 (1H, s), 8.77 (1H, s)	300 (M^+)
4e	$C_{16}H_{12}N_6O_2$	60.00 (60.02	3.78 3.91	26.24 26.21)		5.04 (2H, s), 6.67 (2H, d, J=9), 7.54 (2H, d, J=9), 7.58 (2H, d, J=9), 7.96 (1H, s), 8.05 (1H, s), 8.21 (2H, d, J=9)[b]	320 (M^+)
4f	$C_{16}H_{12}FN_5$	65.52 (65.60	4.12 4.23	23.88 23.83	6.48 (X=F) 6.47)	5.02 (2H, s), 6.76 (2H, d, J=9), 7.03—7.47 (4H, m), 7.75 (2H, d, J=9), 8.15 (1H, s), 8.60 (1H, s)	293 (M^+)
4g	$C_{16}H_{12}ClN_5$	62.04 (61.85	3.90 3.94	22.61 22.64	11.45 (X=Cl) 11.35)	5.05 (2H, s), 6.74 (2H, d, J=9), 7.04—7.44 (4H, m), 7.75 (2H, d, J=9), 8.17 (1H, s), 8.66 (1H, s)	309 (M^+)
4h	$C_{16}H_{12}BrN_5$	54.26 (54.30	3.41 3.43	19.77 19.84	22.56 (X=Br) 22.75)	4.87 (2H, s), 6.69 (2H, d, J=9), 7.14 (2H, d, J=9), 7.47 (2H, d, J=9), 7.57 (2H, d, J=9), 7.87 (1H, s), 8.03 (1H, s)[b]	353 (M^+)
4i	$C_{16}H_{12}IN_5$	47.97 (47.62	3.01 3.00	17.46 17.50	31.63 (X=I) 31.71)	4.85 (2H, s), 6.69 (2H, d, J=8), 7.01 (2H, d, J=8), 7.52—7.71 (3H, m), 7.87 (1H, s), 8.02 (1H, s)[b]	401 (M^+)
4j	$C_{17}H_{15}N_5$	70.57 (70.46	5.23 5.28	24.20 24.12)		2.32 (3H, s), 4.85 (2H, s), 6.71 (2H, d, J=8), 7.11 (4H, s), 7.56 (2H, d, J=8 Hz), 7.80 (1H, s), 8.01 (1H, s)[b]	289 (M^+)
4k	$C_{17}H_{15}N_5O$	66.87 (66.88	4.95 5.09	22.94 22.92)		3.72 (3H, s), 4.93 (2H, s), 6.77 (2H, d, J=9), 6.85 (2H, d, J=9), 7.23 (2H, d, J=9), 7.74 (2H, d, J=9), 8.15 (1H, s), 8.53 (1H, s)	305 (M^+)
4l	$C_{16}H_{11}N_7O$	60.56 (60.51	3.49 3.53	30.90 30.88)		5.26 (2H, s), 6.75 (2H, d, J=9), 7.68 (1H, d, J=9), 7.77 (2H, d, J=9), 8.03 (1H, s), 8.08 (1H, d, J=9), 8.22 (1H, s), 8.89 (1H, s)	317 (M^+)
5a	$C_{14}H_{10}N_6O_4$	51.54 (51.39	3.09 3.43	25.76 25.36)		7.22 (4H, d, J=9), 8.28 (4H, d, J=9), 8.37 (1H, s), 9.24 (1H, s)	326 (M^+)
5b	$C_{15}H_{12}N_6O_4$	52.94 (52.66	3.55 3.74	24.70 24.62)		5.33 (2H, s), 6.75 (2H, d, J=9), 7.72 (2H, d, J=9), 8.10—8.27 (5H, m), 8.84 (1H, s)	340 (M^+)
5c	$C_{15}H_{12}BrN_5O_2$	48.16 (48.00	3.23 3.31	18.72 18.72	21.35 (X=Br) 21.42)	5.10 (2H, s), 6.76 (2H, d, J=9), 7.33 (2H, d, J=9), 7.54 (2H, d, J=9), 8.17 (2H, d, J=9), 8.20 (1H, s), 8.72 (1H, s)	374 (M^+)
5d	$C_{15}H_{11}N_7O_3$	53.41 (53.29	3.29 3.32	29.07 29.16)		5.33 (2H, s), 6.78 (2H, d, J=9), 7.70 (1H, q, J=9), 8.07 (1H, s), 8.10 (1H, d, J=9), 8.20 (2H, d, J=9), 8.26 (1H, s), 8.95 (1H, s)	337 (M^+)

a) J=Hz. *b*) Measured in $CDCl_3$.

(**5b**) inhibited aldosterone synthesis strongly, while the *para*-nitro phenyl derivative (**5a**) showed no inhibitory activity. *para*-Bromobenzyl derivatives (**4h** and **5c**) also showed potent activities. Compounds **4l** and **5d** having the benzofurazanyl ring, which is well known as a bioisostere of the nitrophenyl moiety, exhibited weak activities, although these compounds, as well as the parent compounds **4e** and **5b**, showed potent aromatase inhibition, indicating that the benzofurazanyl substituent is not a bioisostere of the nitrophenyl moiety for inhibition

of aldosterone synthesis. As we have previously reported, there was high selectivity toward aromatase inhibition in the case of a series of 4*H*-1,2,4-triazol-4-ylamino derivatives, even though the substituent R_2 was the benzyl moiety. It is of great interest that the enzyme selectivity for aromatase can be varied by changing the position of only one nitrogen atom in the triazole ring. From these results, we considered that the selectivity of inhibition of the enzymes involved in aromatase and aldosterone synthesis depends more on an electronic effect rather than on a steric effect.

In conclusion, we evaluated a series of 1*H*-1,2,4-triazol-1-ylamino derivatives for aromatase-inhibitory activity. *para*-Substituted benzyl derivatives (**4d**—**k** and **5b**, **c**) and benzofurazanylmethyl derivatives (**4l** and **5d**) showed high activities *in vitro* and *in vivo*. Among them, the *para*-nitrobenzyl derivative (**5b**) was the most potent aromatase inhibitor, but this compound also exhibited relatively strong inhibitory activity against aldosterone synthesis.

Experimental

Melting points were determined on a Yanaco MP-500D micro melting point apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a JEOL EX-90, a JEOL FX-100, a JNM-EX 400 or a JNM-GX 500 spectrometer using tetramethylsilane as an internal standard. Mass spectra (MS) were recorded on a Hitachi M-80 (EI) or a JEOL JMS DX-300 (FAB) mass spectrometer. Elemental analysis was performed with a Yanaco MT-5 analyzer. Column chromatography was performed on silica gel (Wakogel C-200 or Merck Kieselgel 60, 70—230 mesh).

1-[(4-Cyanophenyl)amino]-1*H*-1,2,4-triazole (2) 1-Amino-1*H*-1,2,4-triazole (**1**,[14] 4.00 g, 47.6 mmol) was added portionwise to a suspension of potassium *tert*-butoxide (5.33 g, 47.6 mmol) in DMSO (20 ml) at 10—15 °C with stirring. The reaction mixture was stirred for 30 min at room temperature, and then 4-fluorobenzonitrile (2.88 g, 23.8 mmol) in DMSO (5 ml) was added dropwise at below 30 °C. After having been stirred for 30 min at room temperature, the mixture was poured into water and neutralized with 1 N HCl. The precipitate was collected by filtration and purified by silica gel column chromatography. The $CHCl_3$–MeOH (100 : 1) eluate gave a crystalline product, which was recrystallized from acetone to give **2** (6.43 g, 73%). mp 197—199 °C. ^{1}H-NMR (DMSO-d_6) δ: 6.56 (2H, d, J=9 Hz), 7.70 (2H, d, J=9 Hz), 8.18 (1H, s), 8.82 (1H, s), 10.51 (1H, s). EI-MS m/z: 185 (M^+).

1-[(4-Nitrophenyl)amino]-1*H*-1,2,4-triazole (3) Compound **3** was prepared from **1** with 4-fluoronitrobenzene in a similar manner to that described for compound **2**. Yield 84%. mp 182—184 °C. ^{1}H-NMR (DMSO-d_6) δ: 6.59 (2H, d, J=9 Hz), 8.16 (2H, d, J=9 Hz), 8.20 (1H, s), 8.85 (1H, s), 10.80 (1H, s). EI-MS m/z: 205 (M^+).

1-[Bis(4-cyanophenyl)amino]-1*H*-1,2,4-triazole (4a) Method A: Compound **2** (0.20 g, 1.1 mmol) was added to a suspension of sodium hydride (60% in mineral oil, 43 mg, 1.1 mmol) in DMF (5 ml) with ice-cooling. The mixture was stirred for 30 min at 40—50 °C, and cooled to room temperature. 4-Fluorobenzonitrile (0.13 g, 1.1 mmol) was added to this mixture and the whole was stirred for 2 h at 100 °C, then concentrated under reduced pressure. Water was added to the resultant residue and products were extracted with $CHCl_3$. The organic layer was washed with water, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was subjected to silica gel column chromatography with $CHCl_3$–MeOH (100 : 1) to give a crystalline product, which was recrystallized from AcOEt–Et_2O to afford **4a** (0.21 g, 68%). Compounds **4b** and **5a** in Table 1 were similarly synthesized.

1-[Benzyl(4-cyanophenyl)amino]-1*H*-1,2,4-triazole (4c) Method B: A mixture of compound **2** (0.20 g, 1.1 mmol), benzyl bromide (0.20 g, 1.2 mmol) and K_2CO_3 (0.18 g, 1.3 mmol) in CH_3CN (10 ml) was stirred for 2.5 h at room temperature. The reaction mixture was diluted with water and extracted with $CHCl_3$. The organic layer was washed with water, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography. Elution with $CHCl_3$–MeOH (100 : 1) gave a crystalline product, which was recrystallized from AcOEt–*n*-hexane to afford **4c** (0.19 g, 65%). Compounds **4d**—**l**, and **5b**—**d** in Table 1 were similarly synthesized.

Aromatase-Inhibitory Activity [1β,2β-^{3}H]Androstenedione (0.1 μmol) (44.2 Ci/mmol, Du Pont New England Nuclear, Boston, MA, U.S.A.) was incubated with rat (Wistar, about 3 weeks old) ovarian microsomes (160 μg/ml, specific activity 0.021 pmol/min/mg of protein) in potassium phosphate buffer[15] (pH 7.4). The incubation medium also contained various concentrations of test compounds dissolved in DMF (final concentration 0.5%) in the presence of an NADPH regenerating system[16] or 5 mM NADPH.[17] The reaction mixture was treated with $CHCl_3$ and activated charcoal to remove residual steroids. The radioactivity in an aliquot of the supernatant was determined with a Packard liquid scintillation spectrometer (model 2500TR). The inhibitory activity of test compounds was obtained as the percentage inhibition of aromatization in the solvent control.

Inhibitory Activity of Aldosterone Synthesis Aldosterone synthesis activity was measured according to the method described by De Coster *et al.*[18] Rat (Wistar, about 20 weeks old) adrenal cells suspended (3×10^5 cells/ml) in 199 medium containing 0.2% bovine serum albumin were preincubated at 37 °C for 30 min with various concentrations of test compounds dissolved in DMSO. This was followed by 2 h incubation with 1 ng/ml adrenocorticotropic hormone (ACTH) to stimulate aldosterone synthesis. The amount of aldosterone released from the cells in the presence or absence of the test compound was measured by radioimmunoassay. The inhibitory activity of test compounds was obtained as the percentage inhibition with respect to the solvent control.

Inhibitory Activity on PMSG-Induced Estrogen Synthesis (*In Vivo*) The *in vivo* inhibition of aromatase activity by the test compounds was evaluated according to the literature.[15,19] Briefly, female rats (Wistar, about 3 weeks-old, n=5) were injected subcutaneously with 100 IU/rat of PMSG. After 72 h, the rats were given 20% polyethylene glycol or various doses of the test compound orally. At 3 h after administration, the rats were killed, their ovaries were removed, and the estrogen content of the ovaries was measured by radioimmunoassay. The inhibitory activity of the test compound was expressed as the percentage inhibition with respect to the control.

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