Studies on Aromatase Inhibitors. III.[1] Synthesis and Biological Evaluation of [(4-Bromobenzyl)(4-cyanophenyl)amino]azoles and Their Azine Analogs

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A series of [(4-bromobenzyl)(4-cyanophenyl)amino]azoles and their azine analogs, which have the side chain of the selective aromatase inhibitor YM511, were synthesized and evaluated for aromatase-inhibitory activity (*in vitro*) and for pregnant mare serum gonadotropin (PMSG)-induced estrogen synthesis inhibitory activity (*in vivo*). Among these aza-heterocycles, the pyrimidin-5-yl derivative (6a) was the most potent aromatase inhibitor and its *in vitro* inhibitory activity was comparable to that of YM511. Compound 6a also showed weak inhibitory activity on aldosterone synthesis. These data indicated that the pyrimidin-5-yl moiety is useful as a new azole fragment in place of the 4*H*-1,2,4-triazol-4-yl moiety of the aromatase inhibitor YM511.

Key words aromatase; estrogen; aminopyrimidine; aldosterone

In our preceding papers,[1] we reported that two series of novel amino triazole derivatives showed aromatase-inhibitory activity. Among these derivatives, 4-[(4-bromobenzyl)(4-cyanophenyl)amino]-4*H*-1,2,4-triazole (YM511), which is a 4-ylaminotriazole type compound, was the most potent and selective inhibitor, and is expected to be a useful agent for the treatment of estrogen-dependent diseases, such as breast cancer. In our continuing studies to obtain more potent aromatase inhibitors, our attention was next focused on the triazole ring of these *N*,*N*-disubstituted aminotriazole derivatives. The structure of common non-steroidal aromatase inhibitors can be regarded as consisting of two parts,[2-9] one being the azole part with an sp^2 nitrogen atom, which binds to the heme iron atom of aromatase, and the other, the bulky aryl part which mimics the steroid ring of the substrate. Based on the above concept, we have replaced the azole moiety of YM511 with other aza-heterocycles to find a new heterocyclic moiety (Fig. 1).

Chemistry

The synthetic routes to the (4-bromobenzyl)(4-cyanophenyl)amino-azoles and their azine analogs (**6a—f**) are shown in Chart 1. Aminoazine derivatives (**1a—c**) and aminothiadiazole (**1d**) were reacted with *para*-fluorobenzonitrile in the presence of potassium *tert*-butoxide in dimethylsulfoxide (DMSO) to afford the *N*-monosubstituted amino derivatives (**2a—d**). Pyrazine (**2e**) and pyridine *N*-oxide (**5**) derivatives were obtained by the reaction of *para*-aminobenzonitrile with chloropyrazine (**3**) and 3-fluoropyridine *N*-oxide (**4**)[10] in the presence of potassium *tert*-butoxide in DMSO, respectively. Reduction of the *N*-oxide of **5** with phosphorus trichloride gave the pyridine derivative **2f**. Compounds **2a—f** were benzylated with *para*-bromobenzyl bromide using sodium hydride as a base to give **6a—f**. In these cases, the arylation or alkylation reactions of **1b—d** and **2b—e** predominantly proceeded on their *exo*-amino substituents. The structures of **6b—e** were confirmed by heteronuclear multiple bond correlation (HMBC) and nuclear Overhauser effect (NOE) experiments; the results are shown by arrows in Fig. 2.

Results and Discussion

Inhibitory activities of the series of azole and azine 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 dose of 0.03 and 0.3 mg/kg *p.o.* was expressed as percent inhibition of PMSG-induced estrogen synthesis.

The pharmacological results are summarized in Table 1. Among these aza-heterocycles, the pyrimidine (**6a**),

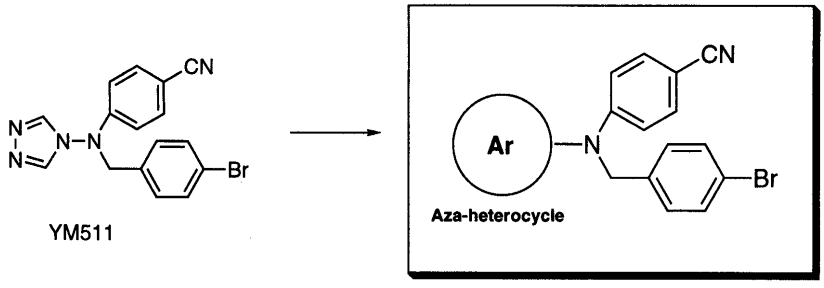

Fig. 1

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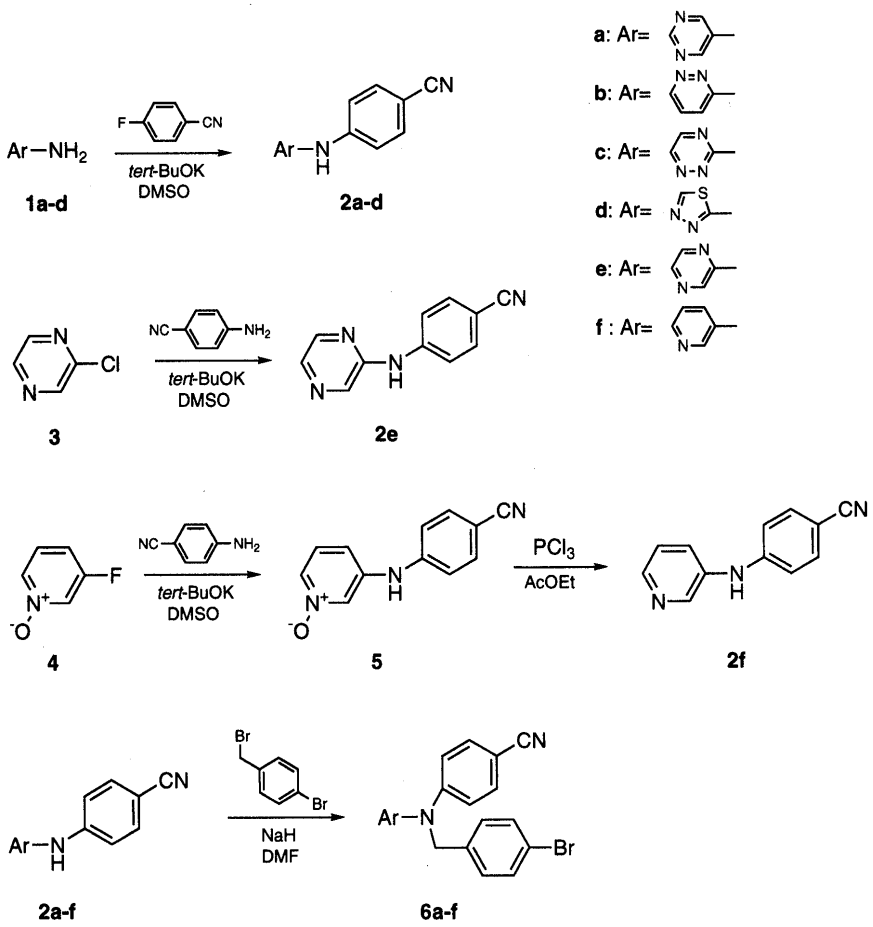


Chart 1

thiadiazole (**6d**), pyrazine (**6e**) and pyridine (**6f**) derivatives showed aromatase-inhibitory activity *in vitro*. The pyrimidine (**6a**) and pyridine (**6f**) derivatives were more potent than YM511. Compounds **6a** and **6f** also inhibited estrogen synthesis (*in vivo*). The *in vivo* efficacy of compound **6a** was about ten times greater than that of compound **6f**, but less than that of YM511. We also evaluated the enzyme selectivity of these compounds with respect to synthesis of other steroid hormones, in particular, their inhibitory activities on aldosterone synthesis, because it has been reported that CGS16949A, a non-steroidal aromatase inhibitor, significantly suppresses the serum aldosterone level.[11-13] Inhibitory activities of compounds **6a** and **6f** on aldosterone synthesis at 1 μM were 27% and 76%, respectively, indicating that the derivative with the pyrimidin-5-yl moiety as the azole part was a weak inhibitor of aldosterone synthesis and that its selectivity for aromatase was comparable to that of the 4*H*-1,2,4-triazole-4-yl molecule (YM511).

In this study, we have found that the pyrimidine derivative **6a** is a potent aromatase inhibitor among various aza-heterocycles, and the pyrimidin-5-yl moiety can replace the 4*H*-1,2,4-triazol-4-yl moiety as the azole fragment of an aromatase inhibitor. Further structure–activity relationship studies of the pyrimidine derivatives are in progress.

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, and ^{13}C-NMR spectra were recorded on a JNM-A 500 spectrometer using tetramethylsilane as an internal standard. Mass spectra (MS) were recorded on a Hitachi M-80 (EI). 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).

5-(4-Cyanophenyl)aminopyrimidine (2a) 5-Aminopyrimidine (**1a**,[14] 1.90 g, 20 mmol) was added portionwise to a suspension of potassium *tert*-butoxide (2.80 g, 25 mmol) in DMSO (10 ml) at 10—15 °C with stirring. The mixture was stirred for 1 h at room temperature, and then 4-fluorobenzonitrile (1.21 g, 10 mmol) in DMSO (3 ml) was added dropwise. The mixture was stirred for 30 min at 50 °C, then poured into water and neutralized with 1 N HCl. The resultant precipitate was collected by filtration and purified by silica gel column chromatography. Elution with $CHCl_3$–MeOH (50 : 1) gave a crystalline product, which was washed with ether to give **5** (1.04 g, 53%), mp 241—242 °C. ^{1}H-NMR (DMSO-d_6) δ: 7.19 (2H, d, J=9 Hz), 7.68 (2H, d, J=9 Hz), 8.70 (2H, s), 8.82 (1H, s), 9.16 (1H, br s). EI-MS m/z: 196 (M^+).

3-(4-Cyanophenyl)aminopyridazine (2b), 3-(4-Cyanophenyl)amino-1,2,4-triazine (2c) and 2-(4-Cyanophenyl)amino-1,3,4-thiadiazole (2d) Compounds **2b**—**d** were prepared from 3-aminopyridazine,[15] 3-amino-1,2,4-triazine and 2-amino-1,3,4-thiadiazole with 4-fluorobenzonitrile, respectively, in a similar manner to that described for compound **2a**.

Compound **2b**: Yield 62%, mp 292—295 °C. ^{1}H-NMR (DMSO-d_6) δ: 7.23 (1H, dd, J=9, 1 Hz), 7.55 (1H, dd, J=9, 5 Hz), 7.75 (2H, d, J=9 Hz), 7.98 (2H, d, J=9 Hz), 8.78 (1H, dd, J=5, 1 Hz), 9.86 (1H, br). EI-MS m/z: 195 $(M-H)^+$.

Compound **2c**: Yield 40%, mp 233—235 °C. ^{1}H-NMR (DMSO-d_6) δ: 7.78 (2H, d, J=9 Hz), 8.00 (2H, d, J=9 Hz), 8.58 (1H, d, J=2 Hz), 8.96 (1H, d, J=2 Hz). EI-MS m/z: 197 (M^+).

Compound **2d**: Yield 20%, mp 280—282 °C. ^{1}H-NMR (DMSO-d_6) δ: 7.81 (4H, s), 9.03 (1H, s). EI-MS m/z: 202 (M^+).

2-(4-Cyanophenyl)aminopyrazine (2e) 4-Aminobenzonitrile (2.36 g,

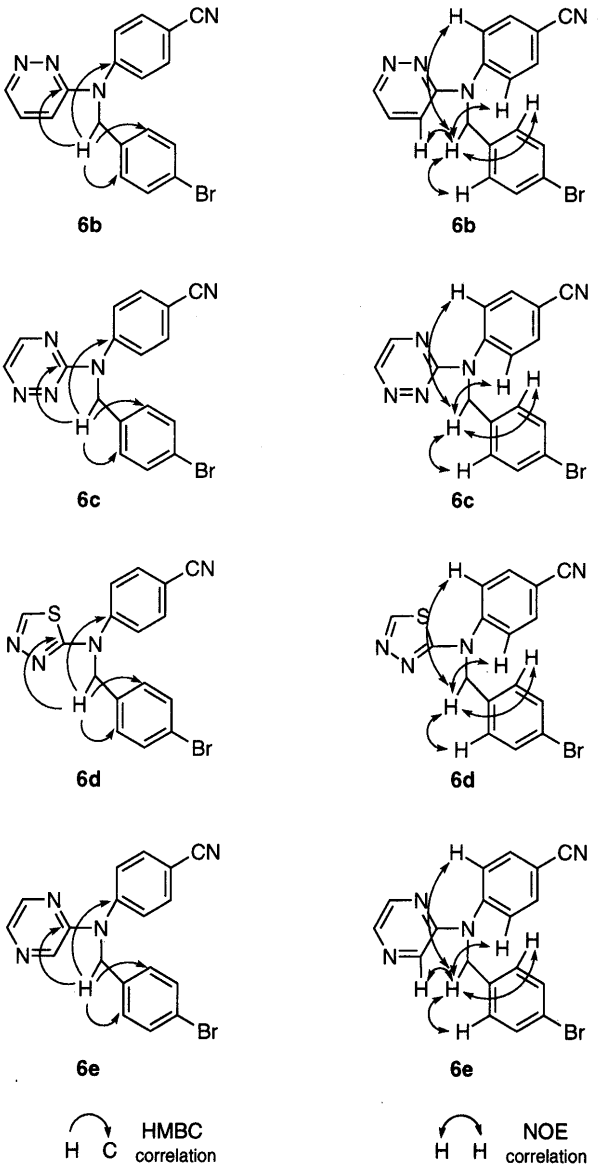


Fig. 2. HMBC and NOE Observations for Compounds **6b—e**

20 mmol) was added portionwise to a suspension of potassium *tert*-butoxide (3.36 g, 30 mmol) in DMSO (30 ml) at 10—15 °C with stirring. The mixture was stirred for 30 min at room temperature, and then chloropyrazine (**3**, 2.29 g, 20 mmol) in DMSO (5 ml) was added dropwise. The mixture was stirred for 30 min at 60 °C, then poured into water. The resultant precipitate was collected by filtration and purified by silica gel column chromatography. Elution with $CHCl_3$ gave a crystalline product, which was washed with ether to give **2e** (1.32 g, 34%), mp 196—197 °C. ^{1}H-NMR (DMSO-d_6) δ: 7.74 (2H, d, J=9 Hz), 7.89 (2H, d, J=9 Hz), 8.08 (1H, d, J=3 Hz), 8.23 (1H, d, J=3 Hz), 8.32 (1H, s), 10.03 (1H, s). EI-MS m/z: 196 (M^+).

3-(4-Cyanophenyl)aminopyridine *N*-Oxide (5) Compound **5** was prepared from 3-fluoropyridine *N*-oxide (**4**)[10] with 4-aminobenzonitrile in a similar manner to that described for compound **2e**.

Compound **5**: Yield 64%, mp 249—251 °C. ^{1}H-NMR (DMSO-d_6) δ: 7.18 (2H, d, J=9 Hz), 7.24—7.33 (2H, m), 7.69 (2H, d, J=9 Hz), 7.81—7.91 (1H, m), 8.01—8.05 (1H, m), 9.17 (1H, br). EI-MS m/z: 211 (M^+).

3-(4-Cyanophenyl)aminopyridine (2f) Phosphorus trichloride (1.0 ml, 11 mmol) was added to a suspension of compound **5** (1.02 g, 4.8 mmol) in AcOEt (50 ml). The reaction mixture was refluxed for 10 min and cooled. The mixture was basified with 1 N NaOH and extracted with AcOEt. The organic layer was washed with water, dried over $MgSO_4$ and evaporated *in vacuo* to give a crystalline product, which was washed with ether to give **2f** (0.90 g, 95%), mp 151—152 °C. ^{1}H-NMR (DMSO-d_6) δ: 7.10 (2H, d, J=9 Hz), 7.27—7.41 (2H, m), 7.63 (2H, d, J=9 Hz), 8.23 (1H, dd, J=5, 1 Hz), 8.44 (1H, d, J=2 Hz), 9.03 (1H, br). EI-MS m/z: 195 (M^+).

5-[(4-Bromobenzyl)(4-cyanophenyl)amino]pyrimidine (6a) Compound **2a** (0.2 g, 1.0 mmol) was added to a suspension of sodium hydride (60% in mineral oil, 44 mg, 1.1 mmol) in *N*,*N*-dimethylformamide (DMF, 5 ml) with ice-cooling. The mixture was stirred for 30 min at 40—50 °C, and cooled to room temperature. 4-Bromobenzyl bromide (0.25 g, 1.0 mmol) was added and the reaction mixture was stirred for 2 h at room temperature. The mixture was concentrated under reduced pressure. Water was added to the resultant residue and the mixture was 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. The $CHCl_3$ eluate gave a crystalline product, which was recrystallized from AcOEt–Et_2O to give **6a** (0.13 g, 36%), mp 134—135 °C. ^{1}H-NMR (DMSO-d_6) δ: 7.19 (2H, d, J=9 Hz), 7.68 (2H, d, J=9 Hz), 8.70 (2H, s), 8.82 (1H, s), 9.16 (1H, br s). EI-MS m/z: 196 (M^+). *Anal.* Calcd for $C_{18}H_{13}BrN_4$: C, 59.19; H, 3.59; Br, 21.88; N, 15.34. Found: C, 59.18; H, 3.61; Br, 21.70; N, 15.38.

3-[(4-Bromobenzyl)(4-cyanophenyl)amino]pyridazine (6b), 3-[(4-Bromobenzyl)(4-cyanophenyl)amino]-1,2,4-triazine (6c), 2-[4-(Bromobenzyl)-(4-cyanophenyl)amino]-1,3,4-thiadiazole (6d), 2-[(4-Bromobenzyl)(4-cyanophenyl)amino]pyrazine (6e) and 3-[(4-Bromobenzyl)(4-cyanophenyl)-amino]pyridine (6f) Compounds **6b—f** were prepared from compounds **2b—f** with 4-bromobenzyl bromide, respectively, in a similar manner to that described for compound **6a**.

Compound **6b**: Yield 28%, mp 116—117 °C. ^{1}H-NMR ($CDCl_3$) δ: 5.37 (2H, s), 7.03 (1H, d, J=9 Hz), 7.17 (2H, d, J=8 Hz), 7.28 (2H, d, J=8 Hz), 7.32 (1H, br), 7.40 (2H, d, J=8 Hz), 7.66 (2H, d, J=8 Hz), 8.78 (1H, br). ^{13}C-NMR ($CDCl_3$) δ: 53.1, 108.6, 116.1, 118.4, 121.4, 124.8, 127.2, 129.3, 131.8, 134.0, 136.4, 145.8, 148.3, 158.8. EI-MS m/z: 365 (M^+). *Anal.* Calcd for $C_{18}H_{13}BrN_4$: C, 59.19; H, 3.59; Br, 21.88; N, 15.34. Found: C, 59.16; H, 3.63; Br, 21.70, N, 15.28.

Compound **6c**: Yield 51%, mp 106—107 °C. ^{1}H-NMR ($CDCl_3$) δ: 5.32 (2H, s), 7.13 (2H, d, J=9 Hz), 7.39 (2H, d, J=4 Hz), 7.45 (2H, d, J=4 Hz), 7.68 (2H, d, J=9 Hz), 8.20 (1H, d, J=2 Hz), 8.74 (1H, d, J=2 Hz). ^{13}C-NMR ($CDCl_3$) δ: 53.2, 110.1, 118.4, 121.7, 127.1, 129.3, 131.9, 133.4, 135.8, 142.5, 146.8, 148.8, 161.4. EI-MS m/z: 366 (M^+). *Anal.* Calcd for $C_{17}H_{12}BrN_5$: C, 55.76; H, 3.30; Br, 21.82; N, 19.12. Found: C, 55.63; H, 3.37; Br, 21.97; N, 19.21.

Compound **6d**: Yield 27%, mp 101—103 °C. ^{1}H-NMR ($CDCl_3$) δ: 5.26 (2H, s), 7.17 (2H, d, J=9 Hz), 7.44 (2H, d, J=9 Hz), 7.45 (2H, d, J=9 Hz), 7.67 (2H, d, J=9 Hz), 8.54 (1H, s). ^{13}C-NMR ($CDCl_3$) δ: 56.9, 109.8, 118.1, 122.1, 124.1, 129.3, 132.1, 134.0, 134.7, 144.0, 148.8, 169.2. EI-MS m/z: 371 (M^+). *Anal.* Calcd for $C_{16}H_{11}BrN_4S$: C, 51.76; H, 2.99; Br, 21.52; N, 15.09; S, 8.64. Found: C, 51.68; H, 2.86; Br, 21.37; N, 15.05; S, 8.74.

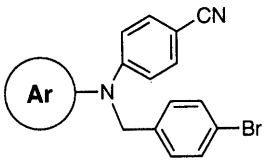
Compound **6e**: Yield 57%, mp 108—109 °C. ^{1}H-NMR ($CDCl_3$) δ: 5.22 (2H, s), 7.13 (2H, d, J=9 Hz), 7.31 (2H, d, J=9 Hz), 7.41 (2H, d, J=9 Hz), 7.63 (2H, d, J=9 Hz), 8.06 (1H, d, J=4 Hz), 8.18—8.19 (1H, m), 8.25 (1H, s). ^{13}C-NMR ($CDCl_3$) δ: 52.7, 108.2, 118.5, 121.4, 124.1, 128.9, 131.9, 133.9, 134.7, 136.1, 136.3, 142.1, 148.2, 153.3. EI-MS m/z: 365 (M^+). *Anal.* Calcd for $C_{18}H_{13}BrN_4$: C, 59.19; H, 3.59; Br, 21.88; N, 15.34. Found: C, 59.17; H, 3.57; Br, 21.84; N, 15.25.

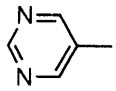
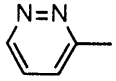
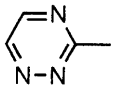
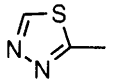
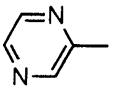
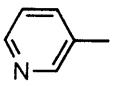
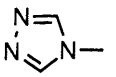
Compound **6f**: Yield 64%, mp 107—108 °C. ^{1}H-NMR ($CDCl_3$) δ: 4.97 (2H, s), 6.82 (2H, d, J=9 Hz), 7.15 (2H, d, J=9 Hz), 7.37—7.63 (6H, m), 8.25—8.85 (2H, br). EI-MS m/z: 364 (M^+). *Anal.* Calcd for $C_{19}H_{14}BrN_3$: C, 62.65; H, 3.87; Br, 21.94; N, 11.54. Found: C, 62.60; H, 3.79; Br, 21.71; N, 11.53.

Aromatase-Inhibitory Activity [1β,2β-^{3}H]Androstendione (0.1 μmol) (44.2 Ci/mmol, Du Pont New England Nuclear, Boston, MA, U.S.A.) was incubated with rat (Wistar strain, about 3 weeks old) ovarian microsomes (160 μg/ml, specific activity 0.021 pmol/min/mg of protein) in potassium phosphate buffer[16] (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[17] or 5 mM NADPH.[18] 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 the aromatization with respect to the solvent control.

Inhibitory Activity of Aldosterone Synthesis Aldosterone synthesis activity was measured according to the method described by De Coster *et al.*[19] Rat (Wistar strain, about 20 weeks old) adrenal cells suspended

Table 1. Biological Data for [(4-Bromobenzyl)(4-cyanophenyl)amino]azoles and Their Azine Analogs



Compound	Ar	% inhibition of aromatase[a] (*in vitro*, nM) 1	10	% inhibition of PMSG-induced estrogen synthesis[b] (*in vivo*, mg/kg *p.o.*) 0.03	0.3	% inhibition of aldosterone synthesis[c,d] (*in vitro*, μM) 0.3	1
6a		85.4	96.4	65.7	84.9	21	27
6b		−8.1	3.6	−13.0	12.5	—	—
6c		−5.7	1.7	−2.5	9.7	—	—
6d		12.7	47.7	−8.2	−18.1	—	—
6e		44.5	86.8	0.0	27.3	—	—
6f		84.0	93.9	7.7	84.2	42	76
YM511		68.2	92.0	90.0	97.8	24	35

a) % 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. *b*) % 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. *c*) % 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. *d*) —: not tested.

(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 of PMSG-Induced Estrogen Synthesis (*in Vivo*) The *in vivo* inhibition of aromatase activity by the test compounds was evaluated according to the literature methods.[20] Briefly, female rats (Wistar strain, about 3 weeks old, $n=5$) were injected subcutaneously with 100 IU/rat of PMSG. After 72 h, rats were administered 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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