Studies on Disease-Modifying Antirheumatic Drugs. III.¹
Bone Resorption Inhibitory Effects of Ethyl 4-(3,4-Dimethoxyphenyl)-
6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate
(TAK-603) and Related Compounds

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In the course of our studies aimed at obtaining new drugs for treatment of bone and joint diseases, chemical
modification of the potent bone resorption inhibitors justicidins, was performed and various naphthalene lac-
tones, quinoline lactones and quinoline derivatives bearing an azole moiety at the side chain were prepared.
Their inhibitory effects on bone resorption were evaluated by Raisz’s method, and several compounds, including
ethyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate (6c, TAK-603),
were found to have activities comparable with or superior to the justicidins. The 4-(3-isopropoxy-4-methoxy)-
phenyl derivative (6d), in particular, displayed a marked increase in potency. TAK-603 and compound 6d were
very effective in preventing osteoclast formation and bone resorption by mature osteoclasts. Further, TAK-603
was shown to be effective in preventing bone loss in ovariectomized mice.

Key word TAK-603; justicidin; bone and joint disease; antiresorptive activity; bone resorption

Rheumatoid arthritis (RA) is a serious, chronic, and sys-
temic disease characterized by inflammation and progressive
joint destruction. Since RA is an autoimmune disease, dis-
ese-modifying antirheumatic drugs (DMARDs), which have
selective and direct effects on the abnormal immune system,
have attracted a great deal of attention as potentially effective
treatments for RA.² Development of osteopenia in the region
of inflamed joints is a common clinical feature of RA. Previ-
ous histological studies of bone specimens obtained from pa-
tients with chronic RA have demonstrated an increase in
bone resorption, suggesting increased bone turnover.³ There-
fore, DMARDs possessing antiresorptive activity as well as
immune system modulating effects are expected to be useful
in the treatment of RA.

Our search for a new type of DMARD with antiresorptive
activity began with chemical modification of the potent bone
resorption inhibitors justicidins (1, Fig. 1),⁴, which were iso-
lated from Justicia Procumbens, since factors such as inter-
leukin (IL)-1β and prostaglandin (PG) E₂ play important
roles in both RA and bone metabolism.⁵ Although justi-
cidins possess only weak anti-inflammatory activity⁶, these
compounds with antiresorptive activity are very attractive
lead compounds for the development a new type of DMARD.
Thus, the justicidin structure was modified to obtain com-
ounds with better pharmacological properties. Naphthalene
lactones (2), quinoline lactones (3), and quinoline derivatives
(4—6), bearing a heteroaryl moiety at the side chain of the 2-
position, were prepared to evaluate their antiresorptive and
anti-inflammatory activities. We previously reported structure–activity relationships (SAR) with respect to the anti-in-
flammatory effect of these derivatives, leading to the finding
of a new type of DMARD, TAK-603 (6c).⁷ This report de-
tails some SAR information concerning the bone resorption
inhibitory effects of this series of compounds.⁸

Chemistry

The naphthalene lactone derivatives (2, Table 1) were pre-
pared using the method of Stevenson and co-workers,⁹,10 as
shown in Chart 1. Condensation of carboxylic acids (7) with
alcohols (8) gave the esters (9), which were converted to the
dihyronaphthalene lactones (10) by heating in acetic anhy-
dride. Aromatization of 10 yielded 2.

Friedländer reaction¹¹ of 2-aminobenzophenones (11) with
tetronic acid afforded quinoline lactones (3) (Chart 2).¹²

The syntheses of 2-(heteroarylthiomethyl)-(4), 2-(1-methyl-
imidazol-2-ylthethyl)-(5) and 2-(azolylmethyl)quinolines (6),
the structures of which are shown in Table 2, were detailed in
our previous reports.¹³ Compounds 4c, g, i and m were
newly prepared for this study by the same methods, and their
physical and spectral data are shown in Table 3.

Results and Discussion

The structures and physical data for the naphthalene and
quinoline derivatives prepared are shown in Tables 1—3.
Since we selected the potent bone resorption inhibitors, the
justicidins, as lead compounds aiming at a new type of
DMARD, these compounds were first evaluated for their in-
hibition of ⁴⁵Ca release from a fetal long-bone culture system
(Raisz’s assay).¹³ The results are summarized in Table 4.

Modification was begun by changing the alkoxy sub-
stituents on the naphthalene skeleton and the pendant phenyl
moiety. In general, these justicidin analogues (2a—c) were
fully active. Replacement of the naphthalene ring by a quinoline ring

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was tried next in an attempt to improve the pharmacological properties, and it was found that activity was retained in the quinoline lactone derivatives (3a—c vs. 2a—c). This finding suggested that the quinoline ring was an effective core structure, encouraging us to introduce various heteroaryl moieties to the 2-methyl position, generated by ring opening of the lactone. The 2-(1-methylimidazol-2-ylthiomethyl)quinoline derivative (4a) was the first compound found with the desired biological activity in this series of compounds. Thus, further modification of 4a was performed.

Firstly, the effect of changing a heteroaryl moiety on the side chain at the 2-position of the quinoline skeleton was evaluated for compounds with a 1-methylimidazolyl (4a), a 4-methyltriazolyl (4b) or a thiazolyl (4c) moiety. These 2-azolylthio derivatives exhibited potent activity comparable with that of 4a. Compounds 4d—g represent variations of the 6,7-dimethoxy moiety on the quinoline ring possessing the 2-(1-methylimidazol-2-ylthio)methyl substituent. Among these derivatives, compounds bearing a 6,7-dialkoxy moiety (4a, 4d, 4e) had potent activity. This result is similar to that for the lactone derivatives. Concerning the substituents on the pendent phenyl ring at the 4-position, potent activity was observed for compounds with 4-methoxy (4h) and 4-methyl (4j) substituents, despite the reduction in activity with the unsubstituted compound (4l).

Although more data need to be accumulated for further discussion, we proceeded to explore the SAR around 4a. The activities of compounds 5 and 6a—c illustrate the influence of the linker between the quinoline and the heteroaryl rings. The sulphone moiety of 4a can be substituted with a methylene (5) or can be removed (6b, c). An abrupt increase in potency was achieved through replacement of the 3,4-dimethoxyphenyl group of 6c by a 3-isopropoxy-4-methoxyphenyl group (6d).

Compounds 2—6, which were derived from justicidins as lead compounds and found to possess antiresorptive activity, were evaluated for anti-inflammatory activity using an adjuvant arthritis model in the rat. Compounds 4, 5 and 6 had...
potent anti-inflammatory activity.7) Among compounds possessing both antiresorptive and anti-inflammatory activities, 6c (TAK-603) was selected for clinical studies based on its pharmacological profile.19) Compound 6d, which was synthesized during study of the metabolites of 6c,10) exhibited reduced anti-inflammatory activity,15) suggesting that some factors other than bone-resorbing function participate in adjuvant-induced inflammation.

Considering the biological results described above, two compounds, 6c (TAK-603) and 6d, were selected for detailed evaluation of antiresorptive activity. Ca release from bone induced by bone-resorbing factors,16) human IL-1β, human parathyroid hormone (hPTH) and fetal bovine serum (FBS), was reduced by 6c and 6d (Table 5). Both compounds inhibited pit formation caused by pre-existing tartrate-resistant acid phosphatase (TRAP)-positive multinucleated cells (MNCs) on dentin slices.17) Furthermore, new TRAP-positive MNC formation in culture dishes, without dentin slices, was also inhibited (Table 6). These results indicate that 6c and 6d inhibited both the activation of mature osteoclasts and the formation of new ones.

As shown in Table 7, 6c was effective in an in vivo model, ovarioctomized mice. In this model, 6c (TAK-603) had a preventive effect at an oral dose of 10 mg/kg/day.18) Since the final stage of RA is bone destruction, the antiresorptive activity of 6c (TAK-603) may be useful in controlling cartilage destruction. Concerning 6d, in vivo studies using this model are presently under way.

In conclusion, we have found that quinoline derivatives bearing an azole moiety at the side chain of the 2-position have effects on bone metabolism as well as anti-inflammatory activity. Ethyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate (TAK-603), which had the most promising profile19) in this series of compounds, is expected to be useful as a new type of DMARD. Although several approaches to elucidate the detailed mechanism of TAK-603 are now in progress, we are convinced that the antiresorptive activity of this compound will be one of its most characteristic features as an anti-inflammatory drug.

### Table 3. Physical and Spectral Data for Compounds 4c, g, i and m

<table>
<thead>
<tr>
<th>Compd.</th>
<th>mp (°C)</th>
<th>Solvent</th>
<th>1H-NMR (ppm, in CDCl3, J in Hz)</th>
<th>IR (KBr, cm−1)</th>
<th>Formula</th>
<th>Anal. Calcd (Found)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4c</td>
<td>145—146</td>
<td>EA-H</td>
<td>0.98 (3H, t, J = 7.2), 3.80 (3H, s), 3.88 (3H, s), 3.97 (3H, s), 4.05 (2H, q, J = 7.2), 4.06 (3H, s), 4.89 (2H, s), 6.91—7.02 (4H, m), 7.22 (1H, d, J = 3.4), 7.45 (1H, s), 7.69 (1H, d, J = 3.4)</td>
<td>1710 C26H27N3O6S</td>
<td>59.30 4.98 5.32</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>4g</td>
<td>119—120</td>
<td>EA-H</td>
<td>0.99 (3H, t, J = 7.2), 3.51 (3H, s), 3.88 (3H, s), 3.98 (3H, s), 4.08 (2H, q, J = 7.2), 4.65 (2H, s), 6.85—7.03 (4H, m), 7.10 (1H, s), 7.64—7.69 (2H, m), 7.96 (1H, d, J = 9.6)</td>
<td>1716 C26H27N3O6S</td>
<td>59.30 4.98 5.32</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>4i</td>
<td>117—118</td>
<td>EA-H</td>
<td>0.96 (3H, t, J = 7.2), 1.47 (3H, s), 3.43 (3H, s), 3.78 (3H, s), 4.02 (2H, q, J = 7.2), 4.04 (3H, s), 4.11 (2H, q, J = 7.2), 4.61 (2H, s), 4.86 (2H, s), 6.88 (1H, s), 6.88 (1H, d, J = 1.2), 7.00 (2H, d, J = 8.8), 7.09 (1H, d, J = 1.2), 7.26 (2H, d, J = 8.8), 7.37 (1H, s)</td>
<td>1714 C26H27N3O6S</td>
<td>59.30 4.98 5.32</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>4m</td>
<td>137—138</td>
<td>A-E</td>
<td>0.93 (3H, t, J = 7.2), 3.32 (3H, s), 4.04 (2H, q, J = 7.2), 4.59 (1H, d, J = 13.6), 4.70 (1H, d, J = 13.6), 6.85 (1H, d, J = 1.2), 7.10 (1H, d, J = 1.2), 7.20—7.30 (2H, m), 7.36—7.60 (3H, m), 7.66 (1H, dd, J = 9.0, 2.0), 7.97 (1H, d, J = 9.0)</td>
<td>1739 C26H27N3O6S</td>
<td>59.30 4.98 5.32</td>
<td>81</td>
<td></td>
</tr>
</tbody>
</table>

### Table 4. Bone Resorption Inhibitory Effect of the Compounds Prepared**

<table>
<thead>
<tr>
<th>Compd.</th>
<th>Conc. (μM)</th>
<th>4Ca release (% vs. control)</th>
<th>Compd.</th>
<th>Conc. (μM)</th>
<th>4Ca release (% vs. control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>10</td>
<td>50***</td>
<td>4h</td>
<td>10</td>
<td>63**</td>
</tr>
<tr>
<td>2b</td>
<td>10</td>
<td>57**</td>
<td>4i</td>
<td>10</td>
<td>70**</td>
</tr>
<tr>
<td>2c</td>
<td>10</td>
<td>48**</td>
<td>4j</td>
<td>10</td>
<td>67**</td>
</tr>
<tr>
<td>3a</td>
<td>27**</td>
<td>74*</td>
<td>4k</td>
<td>10</td>
<td>80**</td>
</tr>
<tr>
<td>3b</td>
<td>26**</td>
<td>&gt;80</td>
<td>4l</td>
<td>10</td>
<td>80**</td>
</tr>
<tr>
<td>3c</td>
<td>31**</td>
<td>59**</td>
<td>4m</td>
<td>10</td>
<td>80**</td>
</tr>
<tr>
<td>4a</td>
<td>30</td>
<td>57***</td>
<td>5</td>
<td>10</td>
<td>79**</td>
</tr>
<tr>
<td>4b</td>
<td>10</td>
<td>76**</td>
<td>6a</td>
<td>10</td>
<td>80**</td>
</tr>
<tr>
<td>4c</td>
<td>10</td>
<td>59***</td>
<td>6b</td>
<td>10</td>
<td>76**</td>
</tr>
<tr>
<td>4d</td>
<td>10</td>
<td>72**</td>
<td>6c</td>
<td>30</td>
<td>59**</td>
</tr>
<tr>
<td>4e</td>
<td>10</td>
<td>66**</td>
<td>6d</td>
<td>3</td>
<td>44**</td>
</tr>
<tr>
<td>4f</td>
<td>10</td>
<td>&gt;80</td>
<td>1a</td>
<td>25</td>
<td>48**</td>
</tr>
<tr>
<td>4g</td>
<td>10</td>
<td>70**</td>
<td>(Justicidin A)</td>
<td>1b</td>
<td>25</td>
</tr>
</tbody>
</table>

### Table 5. Inhibitory Effect of 6c and 6d on FBS, hPTH and IL-1β Stimulated Release of 4Ca from Fetal Rat Long Bones in Organ Culture

<table>
<thead>
<tr>
<th>Stimulator</th>
<th>Compd.</th>
<th>Conc. (μM)</th>
<th>4Ca release (%)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBS</td>
<td>6d</td>
<td>0</td>
<td>28.9±2.0 (100.0)</td>
</tr>
<tr>
<td>hPTH</td>
<td>6d</td>
<td>0.3</td>
<td>23.1±2.3 (79.9)**</td>
</tr>
<tr>
<td>IL-1β</td>
<td>6d</td>
<td>0.5</td>
<td>23.6±1.3 (68.8)**</td>
</tr>
<tr>
<td></td>
<td>6c (TAK-603)</td>
<td>30</td>
<td>17.4±1.6 (62.0)**</td>
</tr>
</tbody>
</table>

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a) Bone resorption inhibitory effects were evaluated by Raisz’s method (see Biological Procedures). b) Actual assay was performed at a concentration of 10 μg/ml, which is equivalent to this μM value. Statistically significant at *p < 0.05, **p < 0.01 and ***p < 0.001 by Student’s t-test. c) Recrystallization solvent, EA = ethyl acetate, H = hexane, A = acetone, E = Et2O. d) Yield from the corresponding 2-chloromethyl quinoline derivative (see ref.7).
Table 6. Effect of 6c (TAK-603) and 6d on Pit Formation and New Osteoclast Formation by Mature Osteoclasts

<table>
<thead>
<tr>
<th>Concentration (μM)</th>
<th>No. of pits/dentin slice</th>
<th>No. of TRAP(+)-MNCs/dentin slice</th>
<th>No. of TRAP(+)-MNCs/culture dish</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>70.5±4.7</td>
<td>57.5±2.4</td>
<td>66.3±3.0</td>
</tr>
<tr>
<td>6c (TAK-603)</td>
<td>10−7</td>
<td>71.3±6.7</td>
<td>62.3±7.0</td>
</tr>
<tr>
<td></td>
<td>10−6</td>
<td>47.0±7.0*</td>
<td>46.8±3.2**</td>
</tr>
<tr>
<td></td>
<td>10−5</td>
<td>31.8±5.0**</td>
<td>23.0±3.4**</td>
</tr>
<tr>
<td>6d</td>
<td>10−9</td>
<td>69.0±6.0</td>
<td>67.8±3.2</td>
</tr>
<tr>
<td></td>
<td>10−7</td>
<td>34.0±6.7**</td>
<td>63.8±3.4</td>
</tr>
<tr>
<td></td>
<td>10−5</td>
<td>2.5±1.0**</td>
<td>13.0±2.9**</td>
</tr>
</tbody>
</table>

a) Effect on the number of resorption pits in mouse unfractionated bone cell cultures. b) Effect on the number of pre-existing TRAP-positive MNCs in mouse unfractionated bone cell cultures. c) Effect on the formation of new TRAP-positive MNCs in culture dishes without dentin slices. Data are the mean±S.E. (n=4). Statistically significant at *p<0.05, **p<0.01 by Student’s t-test.

Experimental

Chemistry Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Elemental analyses (C, H, N) were performed by the Analytical Department of Takeda Chemical Industries, Ltd. 1H-NMR spectra of deuterochloroform (CDCl3) or dimethyl sulfoxide (DMSO-d6) solutions (internal standard tetramethylsilane (TMS), δ 0) were recorded on a Varian EM-390 (CW–60 MHz) or a Gemini-200 (FT-200 MHz) spectrometer. Infrared (IR) spectra were recorded on a Hitachi IR-215 spectrometer. All compounds exhibited 1H-NMR, IR, and analytical data consistent with the proposed structures. Column chromatography was performed with E. Merck Silica gel 60 (0.063—0.200 mm).

General Procedure for Quinoline Lactones 3. 4-(3,4-Methylenedioxy)-2-hydroxymethyl-6,7-dimethoxyquinoline-3-carboxylic Acid Lactone (3a) A mixture of 2-amino-3,4-dimethoxy-4,5-methylenedioxybenzophenone (200 mg, 0.66 mmol), tetronic acid (80 mg, 0.79 mmol), concentrated H2SO4 (1 drop) and AcOH (3 ml) was stirred at 100 °C for 1 h, and then concentrated in vacuo. The residue was neutralized with saturated aqueous NaHCO3, and extracted with CH2Cl2. The extract was washed successively with H2O and brine, dried over MgSO4, and concentrated in vacuo.

3,4-Dihydro-3-hydroxymethyl-1-(4-methoxyphenyl)-6,7-dimethoxy-1-(3,4-methylenedioxyphenyl)-3-carboxylic Acid Lactone (3b): Colorless prisms. 1H-NMR (CDCl3) δ: 3.90 (3H, s), 3.99 (3H, s), 5.18 (2H, s), 5.37 (2H, s), 6.95 (1H, d, J=2.0 Hz), 6.98 (1H, dd, J=8.0, 2.0 Hz), 7.06 (1H, d, J=8.0 Hz), 7.22 (1H, s), 7.46 (1H, s) (IR (KBr) ν: 1768 cm−1). Anal. Calc’d for C15H12NO5: C, 56.75; H, 3.48. Found: C, 56.5; H, 3.4.

Table 7. Effect of 6c (TAK-603) on Changes in Femoral Bone Dry Weight in Ovariectomized Mice

<table>
<thead>
<tr>
<th>Ovx Control</th>
<th>Dose (mg/kg)</th>
<th>Femur dis. 1/3 (mg)</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham-operated</td>
<td>—</td>
<td>13.0±0.2**</td>
<td>100.0**</td>
</tr>
<tr>
<td>Ovx Control</td>
<td>+</td>
<td>11.7±0.2</td>
<td>0.0</td>
</tr>
<tr>
<td>6c (TAK-603)</td>
<td>+</td>
<td>12.8±0.3*</td>
<td>86.7*</td>
</tr>
</tbody>
</table>

Data are the mean±S.E. (n=6—7). Statistically significant at *p<0.05, **p<0.01 by Student’s t-test.
3.4.5.6.7.8-Heptaenoxy-4Hbenzopyran-3-ol (2H, s), 6.79 (1H, dd, 8 Hz), 7.12 (1H, s), 7.20 (1H, s), 7.70 (1H, s). IR (KBr) v: 1750 cm⁻¹. Anal. Calc for C₂₀H₁₂O₆: C, 69.10; H, 4.40. Found: C, 69.10; H, 4.40.

General Procedure for Naphthalene Lactones 2. 3-Hydroxymethyl-6,7-methylenedioxy-1-(3,4-methylenedioxyphenyl)naphthalene-2-carboxylic Acid Lactone (2a) A mixture of 10a (840 mg, 2.44 mmol), N-bromosuccinimide (NBS) (510 mg, 2.9 mmol), benzoyl peroxide (70 mg, 0.29 mmol) and CCl₄ (120 ml) was refluxed for 3 h, and the solvent was evaporated. The residue was chromatographed on SiO₂ with AcOEt–hexane (1:1) to give crystals. Recrystallization from AcOEt–acetone afforded 2a as pale yellow prisms. ¹H-NMR (CDCl₃): δ: 3.85 (3H, s), 3.98 (3H, s), 5.37 (2H, s), 6.07 (2H, s), 6.09 (2H, s), 6.79 (1H, dd, J=8, 2 Hz), 6.81 (1H, d, J=21 Hz), 6.97 (1H, d, J=7, 2 Hz), 7.12 (1H, s), 7.20 (1H, s), 7.70 (1H, s). IR (KBr) v: 1760 cm⁻¹. Anal. Calc for C₂₁H₁₈O₅: C, 71.42; H, 4.79. Found: C, 71.60; H, 4.67.

Biological Procedures. Bone Resorption Inhibitory Effect The bone resorption inhibitory effect was determined by Raisz’ method 13): ⁴⁵Ca (radioisotope of calcium in ⁴⁵CaCl₂ solution) (50 μg/ml) was administered subcutaneously into a Sprague–Dawley rat on the 18th day of pregnancy. On the next day, the femur and tibia of the rat were cut one-third from the distal end, was determined after heating at 110°C for 3 h in an oven. ⁶⁰Co was administered orally once a day for three weeks after the ovariectomy.

References and Notes
3) Suzuki Y., Mizushima Y., Osteoporosis Int., 7 (Suppl. 3), S217—S222 (1997).
6) Anti-inflammatory activity of justicidin A (1a) in an adjuvant arthritic rat model: 10% inhibition of paw edema (50 mg/kg, p.o., 14 d) (see ref. 7).
12) a) Sohda T., Taketomi S., Baba A., Eur. Pat. Appl., EP364169; b) Histoinsu(4z)-2z-dehydroxy-2z-25z-dihydroxvita- mine D₁ (1z,25z(OH)₂D₃). Experiments were completed by removing the culture medium and adding 0.1 M cacyclate buffer solution (pH 7.4) containing 2% paraformaldehyde. The total number of TRAP-positive MNCs on each dentin slice was counted after TRAP staining of the cells. Cells were then removed from the dentin slices by ultrasonication for 30 s in distilled water, and air-dried. The slices were stained with hematoxylin and the number of densely stained pits was counted under light microscope.

Osteoclast-Formation Assay The unfractionated bone cell suspension (2x10⁶ cells/well) with a TRAP-positive MNC density of 100 cells/well was cultured in a 96-well plate without dentin slices in the absence of 1α,25(OH)₂D₃ for 4 d. After depletion of TRAP-positive MNCs was confirmed, the cells were further incubated for 6 d in culture medium containing test compound in the presence of 10⁻¹⁰ M 1α,25(OH)₂D₃. The number of newly formed TRAP-positive MNCs in the culture medium was then counted after TRAP staining of the cells. Our previous study demonstrated that pre-existing TRAP-positive MNCs were depleted by culturing in the absence of 1α,25(OH)₂D₃, but new TRAP-positive MNC formation is induced by the addition of 1α, 25(OH)₂D₃ in culture dishes even after complete depletion of TRAP-positive MNCs.

Effect on Changes in Femoral Bone Weight in Ovariectomized Mice Thirteen-week-old female C3H mice were ovariectomized by a dorsal approach under ether anesthesia. Three weeks later, the right femur of each mouse was removed and cleaned of soft tissue. The dry weight of the femur, which was cut one-third from the distal end, was determined after heating at 110°C for 3 h in an oven. ⁶⁰Co was administered orally once a day for three weeks after the ovariectomy.


19) Anti-inflammatory activity of 6e in an adjuvant arthritic rat model: 65% inhibition of paw edema (12.5 mg/kg, p.o., 14 d). ED50: 2.6 mg/kg (see ref. 7).

