Studies on Antiatherosclerotic Agents.¹ Synthesis and Inhibitory Activities on Platelet Aggregation of 4-Aryl Derivatives of 7-Ethoxycarbonyl-6,8-dimethyl-1(2H)-phthalazinone

Yukuo EGUCHI,* Yuko SATO, Satomi SEKIZAKI, and Masayuki ISHIKAWA

Institute for Medical and Dental Engineering, Tokyo Medical and Dental University, 2-3-10, Sarugakoi, Kanda, Chiyoda-ku, Tokyo 101, Japan.
Received February 21, 1991

4-Aryl derivatives of 7-ethoxycarbonyl-6,8-dimethyl-1(2H)-phthalazinone and related derivatives were newly synthesized in order to test for their inhibitory activities on platelet aggregation. 4-(2-Anisy1) compound and the corresponding 1-chloro derivative demonstrated significant activity.

Keywords synthesis; arylcadmium reagent; coupling reaction; 4-(2-anisy1)-7-ethoxycarbonyl-6,8-dimethyl-1(2H)-phthalazinone; inhibitory effect; platelet aggregation

In the course of studies on the search for antiatherosclerotic agents, we have found that 7-ethoxycarbonyl-6,8-dimethyl-4-hydroxymethyl-1(2H)-phthalazinone¹⁰ (I) showed potent inhibitory activity on platelet aggregation and cyclic-adenosine monophosphate (AMP) phosphodiesterase. In subsequent studies, compound I was examined for its bioavailability in animals as a potential agent. The examination revealed rapid metabolism of the 4-hydroxymethyl group to the 4-carboxylic acid, which was devoid of the biological activity. It was considered difficult to maintain the activity as an effective plasma level in animals due to low solubility of compound I in water and lipid. Compound I was therefore modified¹¹,¹²,¹³ in part or the 4-hydroxymethyl group was replaced with other alkyl moieties¹¹,¹² to improve bioavailability without loss of the activity. Some of the other compounds exhibited fairly potent inhibitory activity on platelet aggregation, however they did not show good balance as a potential agent.

According to the literature, the phthalazines with substituents on their a (1 and/or 4) position such as azelastine³³ with a benzyl, carbazanè with a cyclic amino, and MY-5445³⁰ with a phenyl, and also aromatic amino moieties have been reported to possess anti-allergic, phosphodiesterase inhibitory, and anti-platelet aggregatory effects, respectively. Considering the structure–activity requirements of the phthalazines, the activities might be primarily attributable to the ring system, but the substituents are also considered to have a role in providing adequate bioavailability.

Based on the structure–activity requirements of the phthalazines, compound I was subjected to construction of an aryl moiety in place of the 4-hydroxymethyl group, and a series of derivatives was synthesized.

This paper deals with the synthesis and inhibitory activities on platelet aggregation of 4-aryl derivatives of 7-ethoxycarbonyl-6,8-dimethyl-1(2H)-phthalazinone and the related a substituted phthalazines.

Chemistry The synthesis of 4-aryl compounds (3a–k) and the analogous 4-(2-thienyl) compound (4) were attainable as outlined in Chart 1 by the reactions of 4-ethoxycarbonyl-3,5-dimethylphthalic anhydride (1)¹³ with the corresponding arylcadmium reagents to afford the aryl benzoic acid intermediates (2), which, in turn, were condensed by treatment with hydrazine hydrate in ethanol (EtOH). Since the reactions were accompanied by an amount of 1,1-diarylethaldials (2), which arose from subsidiary reaction between the initially formed intermediate 2 and cadmium reagents, column chromatographical purification of the compounds was necessary, and the yields were rather low: 23–60%. Compounds 3k, 3i, and 3e were further modified as shown in Chart 2; oxidation of 4-(2-thioanisyl) compound 3k using an equimolar amount of m-chloroperbenzoic acid (m-CPBA) afforded 4-(2-methylsulfinylphenyl) derivative (3l) in 75% yield,

![Chart 1](image-url)

© 1991 Pharmaceutical Society of Japan
while the treatment of an excess \( m \)-CPBA gave 4-(2-methylene sulfonylphenyl) derivative (3m) in good yield. Catalytic debenzylation of 3i over palladium on carbon (Pd–C) under atmospheric pressure led smoothly to the corresponding 4-(2-hydroxyphenyl) derivative (3h). Meanwhile, compound 3e was reacted with methyl iodide and dimethylamine and chlorin in 5% potassium hydroxide (KOH) in EtOH, and the N\(^2\)-alkylated derivatives (3o, p) were obtained in 62 and 40% yields, respectively.

Additionally, the other 4-benzyl analogues (6a, b) were prepared by coupling reactions of a related 4-bromomethyl compound (5)\(^{18} \) with aryl magnesium reagents catalyzed by bis(triphenylphosphine)palladium(II) chloride in the described manner.\(^{6,7} \)

Conversion of the phthalazinone to phthalazine was readily accomplished by heating 3e with POC\(_3\) for half an hour to afford an \( \alpha \) chlorinated derivative (7a) in 80% yield. The resulting compound 7a was transformed into the requisite \( \alpha \) substituted phthalazines by the following procedures (a–d): (a) The chlorine atom of 7a was substituted with methoxy and ethylthio moieties by the conventional synthetic procedures\(^{18} \) to afford 7b and 7c, respectively. (b) Several amino derivatives (7d–i) were derivatized from 7a by treatment of the corresponding amines without solvents, with moderate yields. Since dimethylamino and \( \alpha \)-chloroaminod derivatives (7d, b) were obtained as an oil, they led to oxalate and HCl salt, respectively. (c) Dechlorination of 7a by hydrogen in the presence of Pd–C afforded a naked phthalazine (7k). The compound was converted into HCl salt with high solubility in water. (d) Phenylacetylmoiety was also introduced.

<table>
<thead>
<tr>
<th>method</th>
<th>agent</th>
<th>temp. (°C)</th>
<th>time (h)</th>
<th>X</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7b</td>
<td>NaOEt</td>
<td>60</td>
<td>0.5</td>
<td>OEt</td>
<td>68</td>
</tr>
<tr>
<td>7c</td>
<td>NaSEt</td>
<td>80</td>
<td>0.5</td>
<td>Et</td>
<td>63</td>
</tr>
<tr>
<td>7d</td>
<td>4%dmethylamine</td>
<td>r.r.</td>
<td>12</td>
<td>N(Me)(_2)</td>
<td>C(_2)OH</td>
</tr>
<tr>
<td>7e</td>
<td>piperidine</td>
<td>80</td>
<td>3</td>
<td>N(_2)H(_2)</td>
<td>58</td>
</tr>
<tr>
<td>7f</td>
<td>N-benzylpiperazine</td>
<td>100</td>
<td>2</td>
<td>N(_2)H(_2)</td>
<td>C(_2)Ph</td>
</tr>
<tr>
<td>7g</td>
<td>m-chloroaniline</td>
<td>80</td>
<td>3</td>
<td>NH(_2)CH(_2)</td>
<td>m-Cl</td>
</tr>
<tr>
<td>7h</td>
<td>m-chloroaniline</td>
<td>80</td>
<td>3</td>
<td>NH(_2)CH(_2)</td>
<td>m-Cl</td>
</tr>
<tr>
<td>7i</td>
<td>m-nitrobenzylamine</td>
<td>80</td>
<td>3</td>
<td>NH(_2)CH(_2)N(_2)H(_2)</td>
<td>p-OMe</td>
</tr>
<tr>
<td>7j</td>
<td>benzylicanine</td>
<td>90</td>
<td>2</td>
<td>NH(_2)CH(_2)Ph</td>
<td>81</td>
</tr>
<tr>
<td>7k</td>
<td>H(_2), Pd–C</td>
<td>r.r.</td>
<td>8</td>
<td>H(_2)-HCl</td>
<td>44</td>
</tr>
<tr>
<td>7l</td>
<td>PhC(_2)-CH(_2)_3(PbPb)-PbCl(_2)</td>
<td>90</td>
<td>4</td>
<td>C(_2)-Ph</td>
<td>71</td>
</tr>
<tr>
<td>7m</td>
<td>H(_2), Pd–C</td>
<td>r.r.</td>
<td>6</td>
<td>CH(_2)_3CH(_2)-Ph</td>
<td>88</td>
</tr>
</tbody>
</table>

Chart 3
to afford 71 by the manner described using phenylacetylene with a catalyst of palladium complex. This 71 was then reduced in hydrogen over Pd–C, affording an α phenethyl derivative (7m) in good yield.

Since compound 7a was considerably susceptible to hydrolysis to regenerate 3e under conditions of even a weak hydrolytic medium, such as hot EtOH–water, it was possible that if 7a were N2-oxidized, it would not undergo hydrolytic change to generate 3e. Compound 7a was then subjected to N-oxidation reaction by means of hydrogen peroxide in glacial acetic acid; fortunately, an oxygen atom was directed to the N2 position near the chlorine atom of 7a, despite there being a result obtained that an oxygen atom was introduced to the N3 position, when N-oxidation reaction was carried out on related 1-chloro-4-methylphthalazinone under a similar reaction condition. Location of the oxygen atom introduced was confirmed by the fact that compound 8 remained intact with prolonged heating in 5% KOH–EtOH. Presumably, an electronic repulsion of the 4-(2-ansilyl) moiety near the N3 atom resulted in a settlement of the oxygen atom on the N2 position in the N-oxidation reaction.

When 3e was reacted with N-bromosuccinimide in CCl4, the 8-methyl hydrogen of 3e was selectively brominated to give 9 with a minor quantity of dibrominated compound (10). The structure of 9 was determined by comparison of proton nuclear magnetic resonance (1H-NMR) spectra of 3e and 9. 6-Methyl protons of 3e appeared at 2.32 ppm, while the 8-methyl protons at 2.94 ppm. The latter signals demonstrated a lower value under influence of both carbonyls on adjacent sides of the 8-methyl protons. On the other hand, methyl signals of 9 exhibited at 2.37 ppm. The value approximates the 2.32 ppm observed in 6-methyl protons of 3e. Compound 10 was consistent with an analysis of spectra taken by high frequency 1H-NMR spectroscopy. Checking on the signals appearing at 6.93 ppm in a doublet pattern with a coupling constant of 8.8 Hz suggests the existence of a methoxy group as well as a proton at the ortho position; the signals thus correspond to H3 of the 4-(2-anisyl) moiety. Signals appearing at 7.61 ppm in a doublet-doublet with 8.8 and 2.5 Hz correspond to H2 of the moiety due to a downfield shift by bromine effect with couplings between the ortho H3 and the meta H2. The 6-proton designated at 7.43 ppm was in a doublet pattern with 2.5 Hz.

Finally, compound 9 was converted to an acetoxymethyl derivative (11) by reaction with acetyl acid which, in turn, was reacted with 5% KOH in EtOH to provide the lactone derivative (12a). When 9 was reacted with ammonia in EtOH, the lactam derivative (12b) was obtained in good yield.

Results and Discussion

Compounds listed in Tables I and II were tested for their inhibitory activities on platelet aggregation induced by both arachidonic acid (AA, 100 μM) and adenosine diphosphate (ADP, 30 μM). The optical density method of Born was used to assess the ability of test compounds. The inhibitory activities were expressed by the term IC50 as the concentration that inhibited the induced aggregation by 50%. The data obtained at several concentrations were presented as means of three runs.

### Table I. Biological Activities of Compounds

<table>
<thead>
<tr>
<th>Compd.</th>
<th>Inhibition of AA and ADP-induced platelet aggregation (IC50, μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AA (100 μM)</td>
</tr>
<tr>
<td>3a</td>
<td>3—7</td>
</tr>
<tr>
<td>3b</td>
<td>20</td>
</tr>
<tr>
<td>3c</td>
<td>100</td>
</tr>
<tr>
<td>3d</td>
<td>50—70</td>
</tr>
<tr>
<td>3e</td>
<td>1—3</td>
</tr>
<tr>
<td>3f</td>
<td>50—70</td>
</tr>
<tr>
<td>3g</td>
<td>5—10</td>
</tr>
<tr>
<td>3h</td>
<td>30—50</td>
</tr>
<tr>
<td>3i</td>
<td>100</td>
</tr>
<tr>
<td>3j</td>
<td>100</td>
</tr>
<tr>
<td>3k</td>
<td>5—7</td>
</tr>
<tr>
<td>3l</td>
<td>50—70</td>
</tr>
<tr>
<td>3m</td>
<td>50—70</td>
</tr>
<tr>
<td>3n</td>
<td>20</td>
</tr>
<tr>
<td>3o</td>
<td>30—50</td>
</tr>
<tr>
<td>3p</td>
<td>100</td>
</tr>
<tr>
<td>4a</td>
<td>100</td>
</tr>
<tr>
<td>6a</td>
<td>70</td>
</tr>
</tbody>
</table>

### Table II. Biological Activities of Compounds

<table>
<thead>
<tr>
<th>Compd.</th>
<th>Inhibition of AA and ADP-induced platelet aggregation (IC50, μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AA (100 μM)</td>
</tr>
<tr>
<td>7a</td>
<td>1—2</td>
</tr>
<tr>
<td>7b</td>
<td>50—100</td>
</tr>
<tr>
<td>7c</td>
<td>100</td>
</tr>
<tr>
<td>7d</td>
<td>30—50</td>
</tr>
<tr>
<td>7e</td>
<td>50—70</td>
</tr>
<tr>
<td>7f</td>
<td>70</td>
</tr>
<tr>
<td>7g</td>
<td>100</td>
</tr>
<tr>
<td>7h</td>
<td>100</td>
</tr>
<tr>
<td>7i</td>
<td>70</td>
</tr>
<tr>
<td>7j</td>
<td>70</td>
</tr>
<tr>
<td>7k</td>
<td>3—7</td>
</tr>
<tr>
<td>7l</td>
<td>100</td>
</tr>
<tr>
<td>7m</td>
<td>100</td>
</tr>
<tr>
<td>8</td>
<td>20—50</td>
</tr>
<tr>
<td>12a</td>
<td>100</td>
</tr>
<tr>
<td>12b</td>
<td>100</td>
</tr>
</tbody>
</table>

In a preliminary test, the reference phthalazine 1 marked the IC50 1—5 μM on AA, and 10—20 μM on ADP, respectively.

As can be seen, the results showed no effective compounds marked on ADP, except 4-benzyl compounds 6a, b which exhibited activity to some extent. On the contrary, some compounds demonstrated considerable inhibitory activity on AA when compared to the referenced phthalazine 1. Among them, the 4-phenyl 3a, o-anisyl 3e, o-chlorophenyl 3g, N2-methylated o-anisyl compounds 3o in Table I, an α chloro 7a and its dechlorinated compound 7k in Table II showed fairly potent activity, and o-anisyl and its α chlorinated compounds 3e, 7a demonstrated particularly significant activities. The potencies of the activities on AA of both compounds were comparable to the referenced phthalazine 1.

From the results of this test, the structure–activity relation of 3e and 7a, together with the tested compounds may be explained as follows.
In comparing the 4-tolyl compounds $3b$, $c$, $d$, the activities decreased in ortho-, para-, and meta-order. This tendency was also observed in the anisyl $3e$, $f$, chlorophenyl $3g$, $h$, and benzlyoxphenyl $3i$, $j$ compounds. With regard to the ortho-substituents on the 4-aril moieties, the unsubstituted and methoxy moieties seemed to be effective. Replacing the methoxy oxygen with sulfur decreased the activity. The aryl moiety had to be connected directly to the phthalazinone for the activity in this test.

In the derivatives of $3e$ in Table II, the potencies of the activities were generally decreased only when the $z$ carbonyl moiety was substituted for the other moieties. However, it was clear that the chlorine moiety $7a$ significantly enhanced the activity of $3e$. Meanwhile, hydrolytic change of the chlorine moiety from $7a$ to $3e$ was definitely observed in a diluted hydrolytic media. The $N^2$-oxide $8$ gained considerable durability from the change, while the activity was greatly decreased. Compound $7a$ thus appeared to act as a precursor for $3e$.

The modified compound $3e$, and both $12a$ and $12b$ lost their activity. It was found that the 7-ethyl ester might have a role in the platelet aggregation inhibitory activity.

As described, although compounds $3e$, $7a$ did not show the activity on ADP, these compounds were selected as candidates for further pharmacological evaluations from this experiment. Concerning the solubility in lipid, both compounds increased their ability in organic solvents. The 4-(o-anisyl) moiety might provide an adequate bioavailability, and hopefully protect from the rapid metabolic degradation which was seen in the referenced phthalazinone $I$.

**Experimental**

All melting points were determined in a capillary tube and are uncorrected. Mass spectra (MS) were recorded by a Hitachi RMU-7L spectrometer, ultraviolet (UV) spectra with a Hitachi model 323 and U-3200 spectrometers, infrared (IR) spectra were determined with a Hitachi model 285 spectrometer, and $^1$H-NMR spectra with a JEOL JUM-C-60 H1 machine. $^1$H-NMR spectra of compound $10$ were taken by a JEOL JNM-FX 270 spectrometer. Merck Silica gel 60 was used for column chromatography.

<table>
<thead>
<tr>
<th>Compd.</th>
<th>mp (°C)</th>
<th>Formula</th>
<th>Analysis (%)</th>
<th>UV (EEOH, nm)</th>
<th>$^1$H-NMR (CDCl$_3$, $J$=Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$3a$</td>
<td>207–209</td>
<td>C$<em>{14}$H$</em>{11}$N$_2$O$_5$</td>
<td>70.79 5.63 8.69</td>
<td>277, 293, 322</td>
<td>1.43 (H, t, 7), 2.38 (H, s), 2.96 (H, s), 4.48 (2H, q, 7), 7.36 (1H, s), 7.51 (1H, s), 10.37 (1H, s)</td>
</tr>
<tr>
<td>$3b$</td>
<td>223–224</td>
<td>C$<em>{14}$H$</em>{11}$N$_2$O$_5$</td>
<td>71.48 5.99 8.33</td>
<td>219, 298, 311,</td>
<td>1.42 (H, t, 7), 2.14 (H, s), 2.31 (H, s), 2.95 (3H, s), 4.42</td>
</tr>
<tr>
<td>$3c$</td>
<td>175–176</td>
<td>C$<em>{14}$H$</em>{11}$N$_2$O$_5$</td>
<td>(71.31 6.00 8.46)</td>
<td>324</td>
<td>(2H, q, 7), 6.93 (1H, s), 7.34 (4H, s), 10.79 (1H, s)</td>
</tr>
<tr>
<td>$3d$</td>
<td>205–207</td>
<td>C$<em>{14}$H$</em>{11}$N$_2$O$_5$</td>
<td>(71.31 6.04 8.38)</td>
<td>215, 225, 300,</td>
<td>1.42 (H, t, 7), 2.37 (H, s), 2.45 (3H, s), 2.93 (Hz, s), 4.46</td>
</tr>
<tr>
<td>$3e$</td>
<td>185–187</td>
<td>C$<em>{14}$H$</em>{11}$N$_2$O$_5$</td>
<td>(71.31 6.04 8.38)</td>
<td>325</td>
<td>(2H, q, 7), 7.54 (1H, s), 10.44 (1H, s)</td>
</tr>
<tr>
<td>$3f$</td>
<td>210–211</td>
<td>C$<em>{14}$H$</em>{11}$N$_2$O$_5$</td>
<td>(71.31 6.04 8.38)</td>
<td>277, 301, 311,</td>
<td>1.42 (H, t, 7), 2.36 (H, s), 2.46 (3H, s), 2.93 (3H, s), 4.48</td>
</tr>
<tr>
<td>$3g$</td>
<td>224–225</td>
<td>C$<em>{14}$H$</em>{11}$N$_2$O$_5$</td>
<td>(71.31 6.04 8.38)</td>
<td>325</td>
<td>(2H, q, 7), 7.73 (1H, s), 10.44 (1H, s)</td>
</tr>
<tr>
<td>$3h$</td>
<td>245–247</td>
<td>C$<em>{14}$H$</em>{11}$N$_2$O$_5$</td>
<td>(71.31 6.04 8.38)</td>
<td>217, 282, 295,</td>
<td>1.41 (H, t, 7), 2.32 (H, s), 2.94 (3H, s), 3.72 (2H, s), 4.45</td>
</tr>
<tr>
<td>$3i$</td>
<td>186–188</td>
<td>C$<em>{14}$H$</em>{11}$N$_2$O$_5$</td>
<td>(71.31 6.04 8.38)</td>
<td>310</td>
<td>(2H, q, 7), 6.96–7.50 (1H, s), 10.46 (1H, s)</td>
</tr>
<tr>
<td>$3j$</td>
<td>245–247</td>
<td>C$<em>{14}$H$</em>{11}$N$_2$O$_5$</td>
<td>(71.31 6.04 8.38)</td>
<td>229, 262, 303,</td>
<td>1.42 (H, t, 7), 2.37 (H, s), 2.95 (3H, s), 3.89 (3H, s), 4.46</td>
</tr>
<tr>
<td>$3k$</td>
<td>182–184</td>
<td>C$<em>{14}$H$</em>{11}$N$_2$O$_5$</td>
<td>(71.31 6.04 8.38)</td>
<td>310</td>
<td>(2H, q, 7), 7.22 (4H, d, 9), 7.38 (1H, s), 10.66 (1H, s)</td>
</tr>
<tr>
<td>$3l$</td>
<td>210–212</td>
<td>C$<em>{14}$H$</em>{11}$N$_2$O$_5$</td>
<td>(71.31 6.04 8.38)</td>
<td>277, 260, 297,</td>
<td>1.41 (H, t, 7), 2.34 (H, s), 2.95 (3H, s), 4.48 (2H, q, 7),</td>
</tr>
<tr>
<td>$3m$</td>
<td>252–254</td>
<td>C$<em>{14}$H$</em>{11}$N$_2$O$_5$</td>
<td>(71.31 6.04 8.38)</td>
<td>310, 323</td>
<td>6.92 (1H, s), 7.45 (4H, m), 10.62 (1H, s)</td>
</tr>
<tr>
<td>$3n$</td>
<td>222–223</td>
<td>C$<em>{14}$H$</em>{11}$N$_2$O$_5$</td>
<td>(71.31 6.04 8.38)</td>
<td>218, 282, 296,</td>
<td>1.42 (H, t, 7), 2.31 (H, s), 2.95 (3H, s), 3.89 (3H, s), 4.46</td>
</tr>
<tr>
<td>$3o$</td>
<td>113–115</td>
<td>C$<em>{14}$H$</em>{11}$N$_2$O$_5$</td>
<td>(71.31 6.04 8.38)</td>
<td>320</td>
<td>(2H, q, 7), 7.19 (10H, m), 10.54 (1H, s)</td>
</tr>
<tr>
<td>$3p$</td>
<td>106–108</td>
<td>C$<em>{14}$H$</em>{11}$N$_2$O$_5$</td>
<td>(71.31 6.04 8.38)</td>
<td>209, 227, 303</td>
<td>1.42 (H, t, 7), 2.38 (H, s), 2.95 (3H, s), 4.48 (2H, q, 7),</td>
</tr>
<tr>
<td>$3q$</td>
<td>186–188</td>
<td>C$<em>{14}$H$</em>{11}$N$_2$O$_5$</td>
<td>(71.31 6.04 8.38)</td>
<td>320</td>
<td>5.16 (2H, s), 7.00–7.50 (10H, m), 10.19 (1H, s)</td>
</tr>
<tr>
<td>$3r$</td>
<td>140–141</td>
<td>C$<em>{14}$H$</em>{11}$N$_2$O$_5$</td>
<td>(71.31 6.04 8.38)</td>
<td>219, 297</td>
<td>1.41 (H, t, 7), 2.32 (H, s), 2.78 (3H, s), 4.26 (4H, m), 10.77 (1H, s)</td>
</tr>
<tr>
<td>$3s$</td>
<td>166–168</td>
<td>C$<em>{14}$H$</em>{11}$N$_2$O$_5$</td>
<td>(71.31 6.04 8.38)</td>
<td>320</td>
<td>1.41 (H, t, 7), 2.32 (H, s), 2.78 (3H, s), 4.26 (4H, m), 10.77 (1H, s)</td>
</tr>
</tbody>
</table>

a) Recrystallization solvent. b) NMR spectra were taken in CDCl$_3$-$d_6$.
<table>
<thead>
<tr>
<th>Compd.</th>
<th>mp (°C) (Solvent)*</th>
<th>Formula</th>
<th>Analysis (Found)</th>
<th>H-NMR (CDCl₃, J=Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7a</td>
<td>125–126 (Ether)</td>
<td>C₉H₁₅NO₂₃</td>
<td>64.70</td>
<td>5.12</td>
</tr>
<tr>
<td>7b</td>
<td>113–115 (Ether)</td>
<td>C₈H₁₅NO₃</td>
<td>69.45</td>
<td>6.36</td>
</tr>
<tr>
<td>7c</td>
<td>119–121 (Ether)</td>
<td>C₈H₁₅NO₃S</td>
<td>66.65</td>
<td>6.10</td>
</tr>
<tr>
<td>7d</td>
<td>170–172 (Acetone-ether)</td>
<td>C₈H₁₅NO₃</td>
<td>61.40</td>
<td>5.80</td>
</tr>
<tr>
<td>7e</td>
<td>140–142 (Ether)</td>
<td>C₈H₁₅NO₃</td>
<td>71.57</td>
<td>6.97</td>
</tr>
<tr>
<td>7f</td>
<td>196–198 (MeOH)</td>
<td>C₈H₁₅NO₃</td>
<td>72.91</td>
<td>6.71</td>
</tr>
<tr>
<td>7g</td>
<td>151–153 (Ether)</td>
<td>C₈H₁₅NO₃</td>
<td>67.60</td>
<td>5.41</td>
</tr>
<tr>
<td>7h</td>
<td>117–120 (Ether)</td>
<td>C₈H₁₅Cl₂</td>
<td>52.20</td>
<td>5.22</td>
</tr>
<tr>
<td>7i</td>
<td>120–121 (MeOH)</td>
<td>C₈H₁₅Cl₂</td>
<td>71.32</td>
<td>6.20</td>
</tr>
<tr>
<td>7j</td>
<td>136–138 (Benzene-ether)</td>
<td>C₈H₁₅Cl₂</td>
<td>71.45</td>
<td>6.16</td>
</tr>
<tr>
<td>7k</td>
<td>110–112 (Ether)</td>
<td>C₈H₁₅Cl₂</td>
<td>71.41</td>
<td>5.99</td>
</tr>
<tr>
<td>7l</td>
<td>185–187 (EtOAcether)</td>
<td>C₈H₁₅Cl₂</td>
<td>77.04</td>
<td>5.54</td>
</tr>
<tr>
<td>7m</td>
<td>123–125 (EtOAc)</td>
<td>C₆H₁₂NO₂</td>
<td>67.34</td>
<td>6.41</td>
</tr>
<tr>
<td>7n</td>
<td>217–219 (MeOH)</td>
<td>C₆H₁₂NO₂</td>
<td>62.03</td>
<td>4.91</td>
</tr>
<tr>
<td>7o</td>
<td>100–105 (MeOH)</td>
<td>C₆H₁₂NO₂</td>
<td>66.07</td>
<td>4.38</td>
</tr>
<tr>
<td>7p</td>
<td>285–287 (MeOH)</td>
<td>C₆H₁₂NO₂</td>
<td>67.28</td>
<td>4.73</td>
</tr>
</tbody>
</table>

Preparation of 3a–k, and d. 4-(2-Anisyl)-7-ethoxy carbonyl-6,8-dimethyl-1(2H)-phthalazinone (3e). To the Grignard reagent [prepared from octo broma anisole (9.35 g, 0.05 mol), Mg turning (1.94 g, 0.08 mol) in anhydro ethanol (120 mL)] was added portionwise anhydrous CDCl₃ (9.2 g, 0.05 mol). The mixture was stirred for 30 min at room temperature, then was added dropwise a solution of I (8.68 g, 0.035 mol) in tetrahydrofuran (THF) (50 mL). The mixture was heated to reflux for 1 h. The reaction mixture was decomposed by addition of 5% H₂SO₄. The organic layer (A) was extracted with 10% K₂CO₃. The alkaline extract was acidified with 1 N HCl, and it was re-extracted with EtOAc. Working-up afforded an oil, which was dissolved in EtOH (100 mL) and treated with hydrazine hydrate (4 mL). The new mixture was heated to 80°C for 2 h. Evaporation of the solvent and purification by the column chromatography with benzene-EtOAc (100:3) afforded 6.8 g (51%) of 3e, melted at 205–210°C (EtOAc-ether). Anal. Caled. for C₆H₁₂NO₂: C, 68.17; H, 5.72; N, 7.95. Found: 68.20; H, 5.68; N, 7.89. MS m/z: 352 (M⁺), 322 (M⁺–H), 319 (M⁺–OMe), 293 (M⁺–OH), 233 (M⁺–OEt), 215 (M⁺–OEt₂), 197 (M⁺–OEt₃). 1H-NMR (CDCl₃): δ 1.41 (3H, t, J=7 Hz), 2.32 (3H, s), 2.94 (3H, s), 3.72 (3H, s), 4.45 (2H, q, J=7 Hz), 6.96–7.50 (5H, m), 10.46 (1H, s).

hydrous THF (120mL) was added 5 (4.0g, 0.01 mol), and then bis-(triphenylphosphine)palladium(II) chloride (50 mg, 0.07mmol). The reaction mixture was refluxed at room temperature for 20h and was decomposed by addition of 5% H2SO4. The organic layer was separated and washed with water, then evaporated to afford crude oil. The oil was purified by column chromatography with benzene-EtOAc (10:1) to afford 2.5g (58%) of 6b, melted at 166-168°C (EtOAc-ethyl ether). Anal. Calcd for C21H17NO2 (594.4): C, 72.86; H, 5.33. Found: C, 72.86; H, 5.30. 7-Methyl-7-ethoxycarbonyl-2-methyl-4-(2-furyl)-phthalazinone (7a) A mixture of 3e (3.0g, 0.08 mol) and POCl3 (10mL) was refluxed for 30min. The mixture was concentrated under reduced pressure. The mixture was poured into ice-water with vigorous stirring. The aqueous phase was neutralized with 5% K2CO3, then extracted with chloroform. The extract was washed with water and evaporated to afford crude 7a. Recrystallization from ether gave 2.7g (95.7%) of pale yellow crystals. mp 125-126°C (ether). Anal. Calcd for C26H23NO3 (408.4): C, 74.92; H, 5.65; N, 6.38. Found: C, 74.92; H, 5.65; N, 6.38. 5-Methyl-5-phenyl-1,3-dimethyl-1H-pyrazol-2-one (7b) Compound 7b were prepared by condensation of 2.7g with each of the conventional proplacids.

6-Acetoxy-6-ethoxycarbonyl-5,7-dimethylphthalazine (7k) A suspension of 7a (500mg, 1.3mmol) in EtOAc (30mL) containing a few drops of conc. HCl was shaken in H2O under 5% Pd-C (70mg) under atmospheric pressure. Completion of the reaction took about 8h at room temperature. Purification by column chromatography with chloroform-MeOH (90:1) afforded 7k, mp 110°C (ether). Anal. Calcd for C26H23NO3 (408.4): C, 74.92; H, 5.65; N, 6.38. Found: C, 74.92; H, 5.65; N, 6.38.

8-Acetoxy-6-ethoxycarbonyl-5,7-dimethylphthalazine (7l) A mixture of 7a (175mg, 0.5mmol) in acetic acid (30mL) containing 30% H2O (0.5mL) was heated at 80°C for 2h. The mixture was concentrated to a volume of 2mL and was left at room temperature. Precipitated crystals were filtered. Recrystallization from aceton-ether afforded 154mg (54.8%) of 7l, mp 219°C (ether). Anal. Calcd for C26H23NO3 (408.4): C, 74.92; H, 5.65; N, 6.38. Found: C, 74.92; H, 5.65; N, 6.38.

8-Acetoxy-6-ethoxycarbonyl-5,7-dimethylphthalazine (7m) A mixture of 7a (175mg, 0.5mmol) in acetic acid (30mL) containing 30% H2O (0.5mL) was heated at 80°C for 2h. The mixture was concentrated to a volume of 2mL and was left at room temperature. Precipitated crystals were filtered. Recrystallization from aceton-ether afforded 154mg (54.8%) of 7l, mp 219°C (ether). Anal. Calcd for C26H23NO3 (408.4): C, 74.92; H, 5.65; N, 6.38. Found: C, 74.92; H, 5.65; N, 6.38.

References
7) T. Hayashi, M. Konishi, and M. Kumada, Tetrahedron Lett., 21,