VASORELAXANT ACTIVITY OF A NEW PHTHALAZINONE. SYNTHESIS AND STUDIES ON THE MECHANISM OF ACTION

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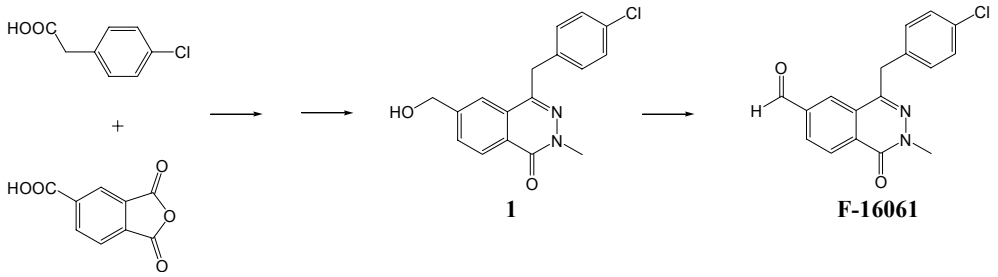
Hypertension is one of the most common cardiovascular diseases, leading to the development of stroke, coronary heart disease, cardiac failure or renal insufficiency [1]. Consequently, much work is ongoing with the aim of developing novel and more efficacious antihypertensive drugs. Drugs which increase vascular relaxation through different mechanisms are a major focus of such work.

Many studies have shown that phthalazinone derivatives can display important antihypertensive and anti-asthmatic effects, and such drugs have also been demonstrated to exert inhibitory activity on phosphodiesterases and on platelet aggregation [2].

We have synthesized a new family of phthalazinones displaying vasorelaxant activity. Among them, compound **F-16061** exerted the greatest vasorelaxant effect on rat aortic rings previously stimulated with phenylephrine (PE). Additionally, when pre-incubated with rat aorta, this compound reduced the subsequent vasoconstrictive effect of PE. The phthalazinone was prepared, as shown in the scheme below, through condensation of trimellitic anhydride with *p*-chlorophenylacetic acid to give an intermediate benzalphthalide, which was properly reduced to the corresponding alcohol, further treated with methylhydrazine to provide phthalazinone **1**, whose Swern oxidation led to the corresponding aldehyde, **F-16061**.



We have performed further experiments in order to establish the mechanism of action of **F-16061**. We examined its inhibitory effects on aggregation of human platelets, as well as intracellular calcium changes in platelets loaded with the calcium-sensitive dye Fura-2-AM, and $^{45}Ca^{2+}$ uptake / release in saponin-permeabilized human platelets. Results suggest that **F-16061** inhibits platelet aggregation, and that its effects are mediated through inhibition of calcium release from intracellular stores by blocking IP_3 receptors. In conclusion, this compound has important vasorelaxant and platelet inhibitory actions, which appear to be mediated through IP_3 receptor blockade resulting in a decrease in intracellular calcium release. Whether this compound will have therapeutic usefulness remains to be determined.

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[1] J.A. Oates, Antihypertensive Agents and the Drug Therapy of Hypertension, (Section V.33 in Goodman &Gilman's The Pharmacological Basis of Therapeutics), 9th ed., pp. 780-808. Pergamon Press, New York, **1996**

[2] S. Demirayak, A.C. Karaburun, R. Beis, *Eur. J. Med. Chem.* **2004**, *39*, 1089-1095.