IMPROVEMENT OF THE PHARMACOLOGICAL PROFILE OF COX-II ACTIVE RESVERATROL-ANALOGUES

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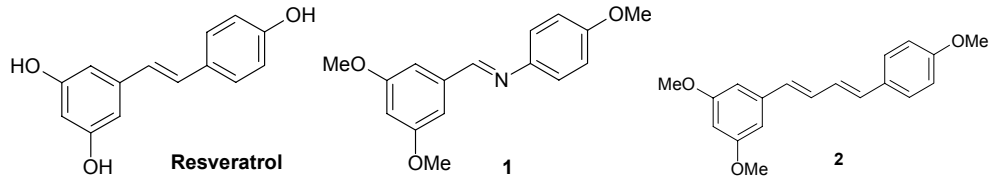
Resveratrol shows a variaty of pharmacological effects like a moderate inhibition of both COX-I and COX-II with a selectivity index of about 1. In our work the effect of resveratrol was studied in isolated smooth muscle preparations (terminal ilea, aortic- and arteria pulmonalis-rings) and compared to the effect of two newly synthesized derivatives **1** and **2** (Fig. 1).

Fig.1:



The relaxing effect of the compounds was measured using the method described by Reiter [1]. Aortic- and arteria pulmonalis-rings were precontracted by 90 mmol/l KCl, terminal ilea by 60 mmol KCl. Resveratrol concentration-dependently reduced contractility of vascular smooth muscle (aorta, n = 5, EC_{50} = 145 µmol/l; arteria pulmonalis, n = 6, EC_{50} = 126 µmol/l). The most potent effect was seen in terminal ilea (n = 5, EC_{50} = 46.4 µmol/l). Compound **1**, a methoxy derivative of resveratrol with nitrogen in the molecule building an imine, lacked of any effects on the preparations studied. Only in terminal ilea it exerted a weak relaxing effect. Compound **2**, a methoxy derivative with an additional ethenyl group in the stilbene scaffold, did not cause any effect in smooth muscle preparations.
Former studies showed that molecules **1** and **2** had an selective inibitory effect on COX-II in µmolar concentration. Therefore we conclude that changes in the molecular structure lead to compounds with an improved COX-II-inhibition and a complete loss of the vasodilatory effect.

[1] Reiter M (1967) Bioassay of inotropic agents on the isolated papillary muscle. Drug Res 17:1249-1253.