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6-phenylamino-5,8-quinolinedione (LY83583) as a quinone inhibits nitric oxide synthase (NOS). LY83583 is an inhibitor of endothelial NO-dependent vasorelaxation and lowers intracellular cGMP in several tissues and inhibits NOS activity. 6-(Substituted-phenyl)amino-5,8-quinolinediones inhibited the ACh-induced vasorelaxation of PE-precontracted rat aorta with the intact endothelium. The presence of nitrogen on the quinones was important for the inhibitory activities and the 5,8-quinolinediones with a 6-(fluorinated-phenyl)amino group, inhibited strongly the vasorelaxation. From this information, 6/7-arylamino-5,8-quinazolinediones as bioisosteres of 5,8-quinolinediones were prepared and evaluated their biological activities. The most of 5,8-quinolinediones tested inhibited the vasorelaxation of rat aorta with the endothelium

[PD1-17] [10/20/2000 (Fri) 11:30 - 12:30 / [Hall B]]

Synthesis of Novel D- and L-3'-Deoxy-3'-C-hydroxymethyl Nucleosides with exocyclic methylene as potential Ribonucleotide Reductase Inhibitor

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Ribonucleotide reductase catalyzes the conversion of ribonucleotides to the 2'-deoxyribonucleotides and has been regarded as attractive target for the development of antitumor agents. Among compounds reported, 2'-deoxy-2'-vinyl-substituted nucleoside has been known to act as ribonucleotide reductase inhibitor and its cyclopropyl analogue also appear to act as the same mechanism. Since for the structure-Activity relationship study we were interested in designing and synthesizing the corresponding 3'-homologated derivative of the above nucleoside. And L-nucleosides sometimes show better biological activity profile than the corresponding D-isomer, we synthesized D- and L-3'-deoxy-3'-C-hydroxymethyl nucleosides with exocyclic methylene at 2'-position of the sugar ring. The final D- and L-nucleosides were synthesized from D- and L-xylose via 3-homologated ribosyl acetate as the key intermediate, respectively. Synthesis and antiviral activities will be in detail presented in the meeting.

[PD1-18] [10/20/2000 (Fri) 11:30 - 12:30 / [Hall B]]

Syntheses and Inhibition Activity of Nitric Oxide Synthase by Yakuchinone Derivatives

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L-Arginine-derived nitric oxide (NO) is an intracellular mediator produced in mammalian cells by two types of nitric oxide synthase, constitutive-NOS(c-NOS) and inducible NOS(i-NOS). I-NOS is Ca2+-independent and is induced by lipopolysaccharides (LPS) or proinflammatory cytokines such as TNF- , IL-1 and IFN-ɣ. The NO produced in large amounts by the i-NOS is responsible for vasodilation and hypotension observed in septic shock and inflammation. In order to prepare i-NOS inhibitor, several yakuchinone derivatives were synthetized and their inhibitory activity of NO production in LPS-activated macrophages were evaluated. The amounts of NO produced by i-NOS was determined by using Griess reagent in the form of NO2-,and the IC50 values were determined as the concentations required for inhibiting the production of NO by 50%.