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MOLECULAR MODELLING OF AN ARTIFICIAL SELF-PAIRING PEPTIDE NUCLEIC ACID (PNA)

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Peptide nucleic acid (PNA) analogues of DNA have attracted interest as potential regulators of gene expression. Besides the synthesis of potentially self-pairing systems also computer based simulations of their properties are part of our current investigations.

Molecular modelling studies on two similar systems proposed by A. Eschenmoser, based on a dipeptide structural repeating unit comprising aspartic acid, in which a 1,3,5-triazine base is acylated to the aspartic acid side-chain and glycine as a second amino acid aimed at providing information about the abiltity of the compounds to build up self-pairing systems.

Conformational analysis of the different tautomers of the triazine base was performed semiempirically with the program VAMP 6.1. Molecular mechanics and molecular dynamics calculations (AMBER forcefield) for single and double stranded oligomers, consisting of the preferred tautomers, were performed using INSIGHT II (MSI/Biosym).

The results of the calculations indicate that these systems (tetramer, octamer) favour self-pairing double strands, in which the stability of the assemblies is achieved by three hydrogen bonds between each pair of the triazine bases and additionally by base stacking between the strands.

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SYNTHESIS AND PHARMACOCHEMICAL INVESTIGATION OF NOVEL DERIVATIVES OF TWO NON-STEROIDAL ANTI-INFLAMMATORIES WITH IMPROVED THERAPEUTIC INDEX

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Oxidative stress is implicated in the pathology of inflammation. Antioxidant treatment reduces inflammation, by scavenging reactive oxygen species and inhibiting prostaglandin synthesis. Thus, we designed two novel amides of the antiinflammatories indomethacin and ibuprophen, with cysteamine, an antioxidant.

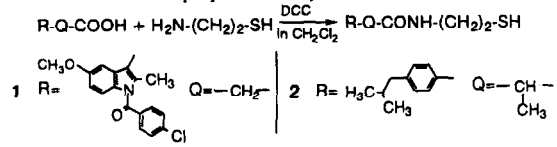

Figure: Synthesis of the new compounds

The synthesis, giving good yields, is shown in the figure. Structures were confirmed spectroscopically and by elemental analyses. The compounds were evaluated as antioxidants by their effect on *in vitro* lipid peroxidation of rat hepatic microsomal membranes, induced by Fe(II)/ascorbate, assessed as the thiobarbituric acid reactive material and their interaction with 1,1-diphenyl-2-picryl hydrazyl stable radical (DPPH). The antiinflammatory activity (the carrageenan induced rat paw oedema test) and toxicity (mortality, perforating ulcers and body weight loss) were assessed. We found that the new derivatives inhibited lipid peroxidation and interacted with DPPH effectively, greater than the parent compounds. They reduced inflammation and were less toxic than the starting drugs. Therefore, combining antiinflammatory and antioxidant activities, and hiding the carboxylic group simultaneously, we produced potentially very useful structures.

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SYNTHESIS OF NITROOXYLATED 4-PHENYL-1,4-DIHYDROPYRIDINES AS POTENTIAL VASO-NEUTRAL CALCIUM CHANNEL ACTIVATORS

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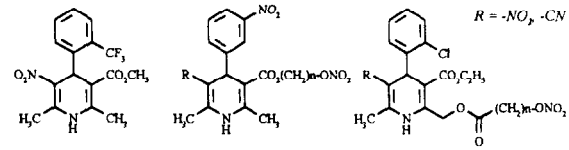
Some 5-cyano and 5-nitro-4-aryl-1,4-dihydropyridines such as BAY K 8644 are calcium channel activators, displaying a positive inotropic effect due to an increase of the transmembranic Ca-input. However, treatment of coronary insufficiency is opposed by their vasoconstrictive, hypertension effecting activity. The idea of the new hybrid structures **1** and **2** is to overcome the vasoconstrictive effect of positive inotropic calcium channel activators by the vasorelaxing activity of the organic nitrate und thus step on to a way which might lead to positive inotropic, but not vasoconstrictive dihydropyridines. The corresponding β-cyanoethylesters of **1** were obtained via Hantzsch reaction from 3-nitrobenzaldehyd, β-cyanoethylaceto-acetate and the enamines of nitro- resp. cyano-acetone. Hydrolysis and reesterification with nitratoalkylhalides gave **1**. Compounds **2** were prepared from the 2-hydroxymethyl precursors by CDI-catalized acylation with nitratoacids.



BAY K 8644 **1** **2**

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PREPARATIVE RESOLUTION OF RACEMIC PIRLINDOLE: CHROMATROGRAPHIC METHODS AND DETERMINATION OF THE ABSOLUTE CONFIGURATION

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Pirlindole,8-methyl-2,3,3,3a,4,5,6-hexahydro-1*H*-pyrazino [3,2,1-*j*,*k*]carbazole hydrochloride, is an antidepressant drug identified as a selective and reversible inhibitor of monoamine oxidase-A (RIMA). This compound presents a stereogenic center and was evaluated until now as the racemic mixture. The present work describes the preparative resolution of the enantiomers of pirlindole using a derivatization method (with amino acid derivatives as chiral derivatizing agents) followed by a chromatographic treatment (MPLC). Several grams of each stereoisomers were isolated, their chemical and optical purities were determined respectively using classical HPLC and chiral HPLC methods. The specific rotation of each antipode was measured in methanol and the determination of the absolute configuration of the enantiomers was performed by crystallography. The optically pure isomers of pirlindole was used to evaluate the effect of stereochemistry on the antidepressant activity.