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Calcium channel blockers have been proven to be clinically useful agents in treating various cardiovascular disorders. The chemical structures of the major blockes are classified into three groups, dihydropyridines, phenylalkylamines and 1,5-benzothiazepines, which are represented by nifedipine, verapamil and diltiazem, respectively. Because of their highly clinical usefulness a number of modifications have been done on dihydropyridines and phenylalkylamines for the purpose improving their bioavailability and duration of action. However, there have been only a few reports concerning modifications of benzothiazepines. Diltiazem is usually administered twice or three times a day and its antihypertensive potency is far less than that of dihydropyridines. In order to synthesize a potent and long-lasting diltiazem congener, we intended to synthesize the hybrid structure of nifedipine and 8-chlorodiltiazem. 4-(1-pyrrolyl)amino-3-mercaptopyridine was synthesize from 4-amino-3-mercaptopyridine and 2,5-dimethoxytetrahydrofuran, and it was reacted with ethyl 2-(4-methoxyphenyl)-2-bromoacetate to give 2-(4-methoxy phenyl)-pyrrolo[2,1-d]-pyrido[3,4-b][1,5]thiazepine derivatives.

[PD1-22] [10/20/2000 (Fri) 11:30 - 12:30 / [Hall B]]

Asymmetric synthesis of (R)-(+)-etomoxir via enzymatic resolution

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An asymmetric synthesis of (R)-(+)-etomoxir 1, employing enzymatic resolution of ethyl 2-alkyl-2,3-dihydroxypropionate using Amano AK via transacylation is reported. Highly enantioselective enzymatic resolution of ethyl 2-alkyl-2,3-dihydroxypropionate was developed by using Amano AK in MTBE. By this process, (R)-(+)-etomoxir could be prepared in 30% yield and 98% ee over five steps from triehyl phosphonoacetate.

[PD1-23] [10/20/2000 (Fri) 11:30 - 12:30 / [Hall B]]

Comparative Molecular Field Analysis (CoMFA) Study of Antitumor 3 - Arylisoquinolines

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A three-dimensional quantitative structure-activity relationship (3D-QSAR) was performed for antitumor 3-arylisoquinoline derivatives by using comparative molecular field analysis (CoMFA) against four tumor cell-lines (A549, SK-OV-3, SK-MEL-2, and HCT15). CoMFA procedure was progressed with a set of 83 3-arylisoquinolines and x-ray crystal structure of 7,8-dimethoxy-3-(2-methylphenyl)isoquinolinone was used to determine molecular conformations. As a result we could get good Cross-Validated R^2 (Q^2) values and pharmacophore models. The synthesis and CoMFA of antitumor 3-arylisoquinoline will be discussed.

[PD1-24] [10/20/2000 (Fri) 11:30 - 12:30 / [Hall B]]