ABSTRACTS OF PAPERS

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79. XU 62-320, AN HMG-CoA REDUCTASE INHIBITOR, MORE POTENT THAN COMPACTIN

F. G. Kathawala[1], T. Scallen[2], R. G. Engstrom[1], D. B. Weinstein[1], H. Schuster[1], R. Stabler[1], J. Kratunis[1], J. R. Wareing[1], C. F. Jewell[1], L. Widler[1], S. Wattanasin[1]
[1]Sandoz Research Institute, East Hanover, New Jersey 07936, U.S.A.
[2]Department of Biochemistry, School of Medicine, University of New Mexico, Albuquerque, New Mexico, U.S.A.

Currently there exists a high level of interest in the development of safe and effective HMG-CoA reductase inhibitors. Efforts at Sandoz Research Institute in the design and synthesis of novel HMG-CoA reductase inhibitors have led to XU 62-320: [R*,S*-(E)]-(±)-Sodium-3,5-dihydroxy-7-[3-(4-fluorophenyl)-1(1-methylethyl)-1H-indol-2-yl]-hept-6-enoate, which is more potent than compactin in inhibiting HMG-CoA reductase in vitro and cholesterol biosynthesis in vivo. Design, synthesis and structure activity relationships with the series of compounds related to XU-62-320, currently in clinical trials, will be presented.

80. SYNTHESIS OF THE 3R, 5S ENANTIOMER OF XU 62-320 AND ITS ANALOGS

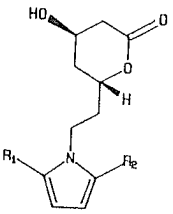
Charles F. Jewell, Jr.[1], James R. Wareing[1], Leo Widler[1], Russell Stabler[1], Faizulla G. Kathawala[1], and Terry Scallen[2].
[1]Sandoz Research Institute, East Hanover, NJ 07936
[2]University of New Mexico, School of Medicine, Dept. of Biochemistry, Albuquerque, NM 87131.

On-going efforts at the Sandoz Research Institute to develop safe and effective HMG-CoA reductase inhibitors have led to XU 62-320, [R*,S*-(E)](±)-Sodium-3,5-dihydroxy-7-[3-(4-fluorophenyl)-1(-methylethyl)-1H-indol-2-yl]-hept-6-enoate, which is more potent than compactin in inhibiting HMG-CoA reductase in vitro and cholesterol biosynthesis in vivo. This presentation describes the synthesis of the single enantiomer of XU 62-320 which has the same absolute configuration as compactin.

81. TRANS-6-[2-(SUBSTITUTED-PYRROL-1-YL)ETHYL]-4-HYDROXY-PYRAN-2-ONES, A NEW CLASS OF HMG-COA REDUCTASE INHIBITORS.

B. D. Roth, M. L. Hoefle, D. R. Sliskovic, C. D. Stratton, M. W. Wilson, and R. S. Newton, Departments of Chemistry and Pharmacology, Warner-Lambert/Parke-Davis Pharmaceutical Research, Ann Arbor, Michigan 48105. 2800 Plymouth Road.

Inhibition of HMG-CoA Reductase, the rate limiting enzyme in cholesterol biosynthesis, has proved to be an effective method for reducing serum cholesterol levels in both animals and man. The in vitro testing of a novel series of 6-[2-(substituted-pyrrol-1-yl)ethyl]pyran-2-ones has shown them to be a new series of potent inhibitors. The synthesis and structure/activity relationships of these novel inhibitors will be discussed.



82. ANTIHYPERTENSIVE 3-(1-SUBSTITUTED-4-PIPERIDINYL)-1,2-BENZISOTHIAZOLES.

J. T. Strupczewski, B. L. Schmid, E. W. Long, J. Kitzen, and R. Ress, Chemical Research and Pharmacology Departments, Hoechst-Roussel Pharmaceuticals Inc., Somerville, New Jersey 08876. Route 202-206 North.

The unexpected discovery of the potent antihypertensive activity of the carboximidic acid ester 4a provided the impetus to investigate other carboximidic acid esters, as well as a limited number of related 3-(1-substituted-4-piperidinyl)-1,2-benzisothiazoles.