ABSTRACTS OF PAPERS

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pyrazines have been demostrated to bind with nM potency to muscarinic receptors without producing the side effects of salivation and tremor in mice usually associated with the m3 receptors. Derivatives linking the 3.2.1 azacycle with 1,2,5-thiadiazoles incorporating an oxygen link also have excellent binding affinity to the muscarinic receptors but are non selective as indicated by the production of salivation and tremor in mice. The most potent analogs were those substituted in the 3 position of the pyrazine by alkylthiols with 2-5 carbons.

046.

1,2,3,4-TETRAHYDRO-2-ISOQUINOLINECARBOXYLATE DERIVATIVES:A NOVEL CLASS OF SELECTIVE MUSCARINIC ANTAGONISTS. III. M. Takeuchi , R. Naito, Y. Yonetoku, K. Ikeda, Y. Isomura , Institute for Drug Discovery Research, Yamanouchi Pharmaceutical Co., Ltd. 21 Miyukigaoka, Tsukuba City, Ibaraki 305, Japan

As a part of searching for novel bladder selective muscarinic M3 antagonists as potential therapeutic agents for urinary incontinence, we have already reported two series of carbamate derivatives. In order to develop more bladder selective M3 antagonists, a series of 1,2,3,4-tetrahydro-2-isoquinolinecarboxylate derivatives was prepared and evaluated for the binding affinities for the muscarinic receptors and for in vivo effects on reflexly- evoked rhythmic contraction of bladder and oxotremorine-induced salivary secretion in rats. Among these compounds, (+)-(1S,3'R)-3'-quinuclidinyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate hydrochloride(YM-53705) showed high affinity for M3 receptor with a Ki value of 12nM and 10-fold selectivity between rhythmic contraction (ID30=0.21mg/kg,i.v.) and salivary secretion (ID50=2.1mg/kg,i.v.). YM-53705 will be expected as a drug for the treatment of urinary incontinence without side-effect such as dry mouth.

047. PHARMACOPHORE IMPROVEMENT OF ALLOSTERIC MODULATORS OF MUSCARINIC RECEPTORS. U. Holzgrabe, H.M. Botero Cid, E. Kostenis, E. Mies-Klomfaß, and K. Mohr, Pharmaceutical Institute, University of Bonn, Kreuzbergweg 26, D-53115 Bonn, Germany

A variety of drugs has been described to retard the dissociation of antagonists, e. g. N-methylscopolamine, from the M_2-acetylcholine receptor. This effect is attributed to an allosteric modulation of the receptor protein which might be exploited in case of organophosphorus poisonings. Recently we developed a pharmacophore model using neuromuscular blockers as well as compounds consisting of a bisquaternary middle chain and aromatic heterocycles, such as phthalimido groups, at both lateral ends. Two positive charges in the middle chain as well as two aromatic areas at both ends arranged in an S-shape conformation were found to be essential for a high allosteric potency. Herein, substituents of increasing size, e. g. alkoxy groups and aryl rings, were added to the phthalimido skeletons, in order to improve the potency and to elucidate whether there is any sterical restriction at the allosteric binding site. In this series a positive correlation was found between the allosteric potency and the lipophilicity of the introduced substituents. Accordingly, an additional hydrophobic interaction is probably the explanation to the high potency of benzylidene substituted phthalimido derivatives.

048. SYNTHESIS AND EVALUATION OF 5-AMINOMETHYL DERIVATIVES OF 3,3-DIETHYL-2(3H)-FURANONE AS SUBTYPE-SPECIFIC MUSCARINIC LIGANDS.

Alemayyehu Ahungena, Daniel J. Canney, Department of Pharmaceutical Sciences, School of Pharmacy, Temple University, Philadelphia, PA 19140.

Structurally rigid lactone derivatives of the nonselective muscarinic antagonist benactyzine (**1**) exhibit subtype-specific properties. A series of 5-aminomethyl lactones (**2b**) were prepared and evaluated based on this report. 3,3-diethyl-5-imidazolylmethyl-2(3*H*)-furanone (**3a**), showed a three-fold selectivity for the M_2 receptor subtype over either M_1 or M_3. To investigate the effect of alkyl-substitution on subtype selectivity, a series of 2'-alkyl derivatives of **3a** were synthesized. The binding properties of the novel lactone derivatives (**3b**) of **3a**, and their thio analogs (**3c**), are described here.