Synthesis of 2-Phenylisothiazol-3(2*H*)-one 1,1-Dioxides: Inhibitors of Human Leukocyte Elastase

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Professor Dr. P. Welzel on the occasion of his 65th birthday

A series of 2-phenylisothiazol-3(2*H*)-one 1,1-dioxides **14a – q** were synthesized by oxidation of isothiazolium perchlorates **12**. The inhibition of the serine proteases cathepsin G, chymotrypsin and human leukocyte elastase (HLE) by **14** was investigated. Some 4,5-diphenyl substituted derivatives (**14i – k**) were found to inhibit HLE in a time-dependent manner and exhibited k_{obs}/[I] values > 500 $M^{-1}s^{-1}$. **14k** (k_{obs}/[I] = 2400 $M^{-1}s^{-1}$), was the most potent HLE inhibitor of this series. Kinetic investigations led to the conclusion that 2-phenylisothiazol-3(2*H*)-one 1,1-dioxides interact with HLE at the active site as well as at another binding site, resulting in a complex type of inhibition.

Key words: Sultams, Human Leukocyte Elastase, Enzyme Inhibition