PP-02

Anthranilic acid-Based Inhibitors of Phosphodiesterase: Design, Synthesis, and Bioactive Evaluation

Han-Hsiang Wang[1], Tsong-Long Hwang[1], Yih-Dih Cheng[1,2], Wen-Yi Chang[1], Yi-Ting Liu[1], Pei-Wen Hsieh (謝珮文)[1,*]

[1]*Graduate Institute of Natural Products, Chang Gung University, Taoyuan 333, Taiwan.*

[2]*Chang Gung Memorial Hospital, Chia-Yi 613, Taiwan.*

The inflammatory lung diseases, including asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis, and lung injury, were caused via activated neutrophil recruiting and releasing chemoattractants into the airway. Superoxide anion ($O_2^{\cdot-}$), a precursor of other ROS, was generated by NADPH oxidase. It was not only linked to the killing of invade microorganisms; but it also was able to elicit tissue damage. Therefore, it is crucial to control superoxide generation in physiological conditions. To our knowledge, many cellular signaling mechanisms, such as PI3K and cAMP/PKC-dependent pathways, involve in negative regulation of neutrophil oxidant production. Of these, the cyclic nucleotides, cAMP or cGMP, were an important second messenger to restrain FMLP-induce generation, and they were hydrolyzed by phosphodiesterases (PDEs). Our previous studies identified **1** and **2**, potently inhibited superoxide generation induced by formyl-L-methionyl-L-leucyl-L-phenylalanine (FMLP) in human neutrophil. Furthermore, **1** was able to elevate of cAMP levels and PKA activity via inhibiting phosphodiesterase. Accordingly, two lead agents of phosphodiesterase inhibitors, **1** and **2**, were modified in an attempt to improve anti-inflammatory activity. In this study, a series of anthranilic acid derivatives were synthesized and subjected to neutrophil functional assay. Of these, **46** exhibited the most potent and selectively inhibitory effects on PDE4 with IC_{50} values of 4.2 μM.