Identification of Leads against Chronic Obstructive Pulmonary Disease from natural and synthetic sources

Thesis submitted by

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2022

Abstract

Chronic obstructive pulmonary disease (COPD) is a major and rapidly growing worldwide health concern. Smoking is responsible for approximately 80-90% of all COPD cases globally. In COPD, neutrophil elastase causes emphysema, which results in the loss of lung tissue and the closing of small airways. When it comes to the progression of COPD in patients, neutrophil elastase has emerged as a critical focus for therapeutic development. A range of mangrove plants, including Sonneratia apetala Buch.-Ham, can be found in the Indian Sundarban regions. Fruit and leaf extracts have been demonstrated to alleviate the symptoms of cough and asthma. This study aims to determine if fruit extracts of Sonneretia apetala inhibit neutrophil elastase and so stop the advancement of lung emphysema caused by neutrophil elastase. The IC_{50} of the hydroalcoholic extract of the fresh fruits of *Sonneratia apetala* Buch.-Ham. (SAM) was calculated using the neutrophil elastase enzyme kinetic test. The extract underwent additional LC-MS2 profiling to determine the main phytochemicals and ten such compounds were identified. Human epithelial cells' in vitro morphological change caused by elastase was likewise reversed by SAM, and the vitality was determined by an MTT experiment which showed no toxicity of the herbal extracts. Furthermore, in the mice model, neutrophil elastase-induced alveolar collapse was lessened by SAM. Thus, we discovered for the first time in this work that *Sonneretia apetala* fruit extract (SAM) has the ability to both *in vitro* and *in vivo* block human neutrophil elastase. In a quest for novel synthetic neutrophil elastase inhibitors, we synthesised and tested seven brand-new benzoxazinone derivatives. By using an enzyme substrate kinetic assay and discovered that they were inhibitors of human neutrophil elastase. One of these substances, PD05, became the most effective inhibitor with a lower IC_{50} compared to the control drug sivelestat.However, PD05 demonstrated a high binding affinity for human neutrophil elastase (Kd=1.63nM) and a

faster association and dissociation rate, and its interaction with human neutrophil elastase was totally reversible. In vitro preclinical pharmacokinetic investigations revealed a favourable protein binding aqueous solubility and low permeability. The chemical successfully inhibited elastase-induced rounding and retracted cell morphology and cell cytotoxicity. In a mouse model, neutrophil elastase-induced alveolar collapse can be decreased by PD05. In conclusion, we show that the newly synthesised benzoxazinone derivative PD05 has anti-elastase capability *in situ*, *in vitro*, and *in vivo*, making it a suitable option for additional research as a COPD treatment.