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Digest paper

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Into clinical testing with pre-adaptive pharmacophores

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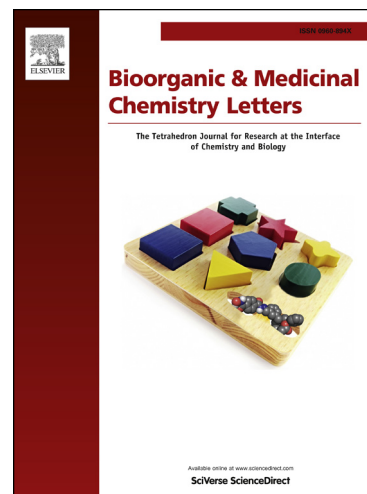
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Neutrophil elastase inhibitors for the treatment of (cardio)pulmonary diseases: Into clinical testing with pre-adaptive pharmacophores

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Abbreviations: AAT, alpha-1 antitrypsin (alpha-1 proteinase inhibitor, α -1 PI); AATD, alpha-1 antitrypsin deficiency; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; BE, bronchiectasis; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; HNE, human neutrophil elastase; NCF, non-cystic fibrosis; NE neutrophil elastase; NSCLC, non-small cell lung carcinoma; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; SIRS, systemic inflammatory response syndrome

ABSTRACT

Alpha-1 antitrypsin deficiency is linked with an increased risk of suffering from lung emphysema. This discovery from the 1960s led to the development of the protease–antiprotease (im)balance hypothesis: Overshooting protease concentrations, especially high levels of elastase were deemed to have a destructive effect on lung tissue. Consequently, it was postulated that efficient elastase inhibitors could alleviate the situation in patients. However, despite intensive drug discovery efforts, even five decades later, no neutrophil elastase inhibitors are available for a disease-modifying treatment of (cardio)pulmonary diseases such as chronic obstructive pulmonary disease. Here, we critically review the attempts to develop effective human neutrophil elastase inhibitors while strongly focussing on recent developments with. On purpose and with perspective distortion we will

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