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PATENT HIGHLIGHT

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Neutrophil Elastase Inhibitors as Potential Anti-Inflammatory Therapies

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Title:	Substituted Bicyclic Dihydropyrimidinones and Their Use as Inhibitors of Neutrophil Elastase Activity		
Patent Application Number:	WO 2014/122160 A1	**Publication Date:**	14 August 2014
Priority Application:	EP 13154256.5	**Priority Date:**	6 February 2013
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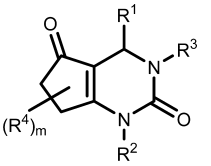
Disease Area:	Pulmonary, gastrointestinal and genitourinary inflammatory diseases, chronic obstructive pulmonary disease, autoimmune and allergic disorders, allograft rejection, and oncological diseases	**Biological Target:**	Neutrophil Elastase (NE)

Summary: The invention in this patent application relates to bicyclic dihydropyrimidinone derivatives represented generally by formula (I) that are inhibitors of neutrophil elastase. These compounds may potentially provide treatments for pulmonary and gastrointestinal inflammatory diseases, chronic obstructive pulmonary disease, and other autoimmune and allergic disorders.

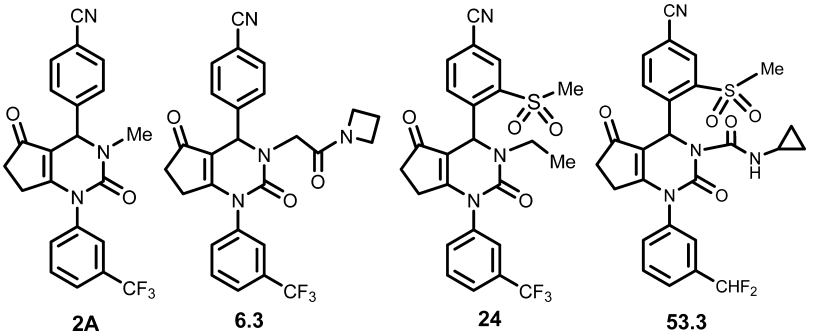
Elastases are serine proteases that hydrolyze elastin and other proteins. Neutrophil elastase (NE) is expressed in the bone marrow precursor cells and stored at high concentrations in the granula of peripheral blood granulocytes until released upon cellular activation. NE plays important roles in the degradation of extracellular matrix (ECM) and in promoting migration and chemotaxis of monocytes and vascular smooth muscle cells. It also affects the components of the coagulation and fibrinolytic pathways. However, the over activity of NE has been linked to the pathologies of several inflammatory diseases including idiopathic pulmonary fibrosis, rheumatoid arthritis, adult respiratory distress syndrome, chronic obstructive pulmonary disease (COPD), and cystic fibrosis. Consequently, the inhibition of NE activities has been a therapeutic target for the treatment of these diseases. Neutrophil elastase inhibitors such as the compounds described in this patent application may potentially treat diseases like COPD, idiopathic pulmonary fibrosis and other fibrotic diseases, cancer, acute lung injury, acute respiratory distress syndrome, bronchiectasis, cystic fibrosis, alpha1-antitrypsin deficiency, and others.

Important Compound Classes:



Formula (I)

Key Structures: The inventors described the structures of >270 compounds of formula (I) including the four compounds below:



2A **6.3** **24** **53.3**

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Biological Assay: The following assays were used to test all or some of the formula (I) compounds:

1. Human Neutrophil Elastase Assay
2. Assay for the Determination of Neutrophil Elastase Inhibitory Activity in Human Plasma
3. Assay for the Determination of Metabolic Stability with Human Liver Microsomes
4. Assay for the Determination of Metabolic Stability with Human Hepatocytes
5. Assay for Determination of Drug Transport Across Human Caco-2 Cells
6. Assay for Determination of Cytochrome P450 2c9 Inhibition
7. Assay for Determination of Cytochrome P450 2c19 Inhibition
8. Assay for Determination of Cytochrome P450 2c8 Inhibition

Biological Data: The results of the biological assays 1 and 2 obtained from the representative examples highlighted above are listed in the following table:

Human Neutrophil Elastase Assay		Neutrophil Elastase Inhibitory Activity in Human Plasma	
Compound	IC_{50} (nM)	Compound	EC_{50} (μM)
2A	2.4	**2A**	0.003
6.3	3.7	**6.3**	0.004
24	1.6	**24**	0.002
53.3	<1	**53.3**	< 0.001

Recent Review Articles:

1. Henriksen, P. A. *Curr. Opin. Hematol.* **2014**, *21* (1), 23−28.
2. Lucas, S. D.; Costa, E.; Guedes, R. C.; Moreira, R. *Med. Res. Rev.* **2013**, *33* (S1), E73−E101.
3. Sjoe, P. *Future Med. Chem.* **2012**, *4* (5), 651−660.
4. Fitzgerald, M. F. *Prog. Respir. Res.* **2010**, *39*, 225−230.

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Notes

The authors declare no competing financial interest.