New molecules (pyridazinones fluorinated) for the treatment of respiratory diseases

Type 4 Phosphodiesterases (PDE-4) are a major subfamilies of PDE enzymes present in inflammatory and immune cells, bronchial smooth muscle and brain. Inhibition of PDE4 activity results in the bronch by anti-inflammatory effects in combination with a relaxation of bronchial smooth muscle. A new family of pyridazinone-type molecules were synthesized, for selective inhibition of PDE4 compared to other isoforms.

**BENEFITS:**
- Obtained by synthesis of new fluorinated pyridazinones
- The methodology allows, according to a general formula, large number of pharmaco-modulations: structure-activity-selectivity developments
- The nature of the fluorinated pattern allows the modulation of the selectivity of molecules and limits the known side-effects
- Activity equal or greater than marketed molecule Roflumilast
- Selectivity for PDE-4B (bronchi) relative to isoforms (PDE-4D) and subtypes (PDE-1, PDE-7A, PDE-10A).
- Specific inhibition of subtype PDE-4B reduces the known side-effects related to a non specific inhibition such as headache, nausea, weight loss, depression, etc.

**APPLICATIONS:**
- Treatment of inflammatory lung diseases
- COPD (chronic obstructive pulmonary disease) - Asthma
- Applications to be considered in cystic fibrosis
- Possible veterinary applications (Asthma)

**DEVELOPMENT STATUS:**
- In vitro validation of the biological activity on isolated enzymes
- Comparison with reference substances (Zardaverine, Roflumilast and IBMX)
- Leads Optimisation ongoing
- Ex vivo and in vivo tests in a mouse model ongoing

**INTELLECTUAL PROPERTY:**
- Patent Application No. FR14/60501 on October 31, 2014

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**Keywords:**
- COPD
- Asthma
- Phosphodiesterases
- PDE-4 inhibitors