# FIRST DUAL $M_3$ ANTAGONISTS / PDE4 INHIBITORS FOR THE TREATMENT OF COPD

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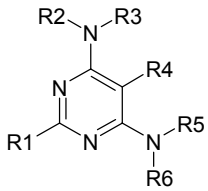
COPD is a chronic, progressive and poorly reversible condition characterized by impaired expiratory outflow and abnormal inflammatory response of the lungs to noxious particles and gases. COPD is one of the most common chronic diseases worldwide, it affects 4-6 % of people older than 45 and is predicted to be the third leading cause of death by 2020. Cigarette smoking is by far the most important risk factor for the development and progression of the condition.[1] There are currently no drug therapies able to slow down the progression of the disease. Patients are commonly treated with drugs developed for asthma but it proves to be quite inefficient as both inflammatory processes differ markedly.[1, 2] Bronchodilator drugs are the current mainstay of treatment for symptoms relief. Anticholinergic bronchodilators, particularly selective muscarinic $M_3$ antagonists, are currently the preferred choice for the symptomatic management of COPD. However, although bronchodilators are quite effective to improve symptoms, they do not address the underlying chronic inflammation or the changes in airway structure. Among the new anti-inflammatory agents currently being developed, PDE4 inhibitors proved to be very efficient in attenuating the responses of various inflammatory cells through their ability to elevate cAMP levels. Although new generation's compounds, currently in Phase III for the treatment of COPD, have been shown to significantly improve lung function of patients, their bronchodilating effect remains rather limited. Therefore, the combination of selective muscarinic $M_3$ antagonism with selective PDE4 inhibition may lead to a new class of drugs combining both bronchodilating and anti-inflammatory properties.
We present here the discovery and optimization of the first family of dual $M_3$ antagonists and PDE4 inhibitors as potential new drugs for COPD treatment.[3] Full details of synthesis and SAR around 4,6-diaminopyrimidine derivatives are given together with some interesting pharmacological properties of selected leads. We show that an optimal balance between activities, physicochemical properties and selectivity profile can be reached by the proper choice of substituants.




[1] Rand Sutherland, E. ; Martin, R.J. *J. Allergy Clin. Immunol*. **2003**, *112*, 819-827.
[2] Barnes, P.J.; Hansel, T.T. *Lancet* **2004**, *364*, 985-996.
[3] Provins, L. *et al* WO03/087064.