SYNTHESIS OF ROFLUMILAST IMPURITIES

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ABSTRACT
Roflumilast is a PDE-4 inhibitor with anti-inflammatory effect. Impurities observed during the synthesis and the other possible by-products are identified. All the identified impurities are synthesized to have a better control over the synthesis of the Roflumilast.

KEYWORDS: Roflumilast, impurities.

INTRODUCTION
Phosphodiesterase-4 (PDE-4) inhibitors are known to be widely used for treatment of respiratory diseases such as chronic obstructive pulmonary disease (COPD) and asthma. COPD is the fourth leading cause of death in the world, which is generally associated with people habituated to tobacco smoking. It is a complex lung disease with pathophysiological features such as inflammation, airway obstruction, respiratory bronchiolar–alveolar–vasculature remodeling, pulmonary hyperinflation, gas-exchange abnormalities, and pulmonary hypertension. Depending on the severity of damage to lung function, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) has classified the disease into four stages (I-IV). The drugs designed to fight with COPD act upon Phosphodiesterases (PDEs), a family of enzymes that catalyse the metabolism of the intracellular cyclic nucleotides, c-AMP and c-GMP. PDE4 inhibitors are one among such type which benefit patients with asthma or chronic obstructive pulmonary disease. Cilomilast 1, Rolipram 2, Roflumilast 3, etc., are few recently developed PDE4 inhibitors with anti-inflammatory effects, used for the treatment of COPD disorders (figure 1).
Roflumilast 3, a synthetic pyridine derivative, is a selective phosphodiesterase type 4 (PDE4) inhibitor and an important regulator of cyclic adenosine monophosphate (cAMP) in most cell types involved in inflammatory processes. Roflumilast is rapidly metabolised to an active metabolite roflumilast N-oxide, which also inhibited PDE4, with about 2 to 3 times lower potency than roflumilast. The orally active PDE4 inhibitor Roflumilast-N-oxide has been approved for treatment of severe exacerbations of COPD as add-on therapy to standard drugs. Roflumilast bearing a trade name Daxas®/ Daliresp™ which has been approved by FDA in March 2011 is marketed jointly by Nycomed and MSD.

A literature review on Roflumilast revealed presence of various impurities such as 4 - 8.\(^5\) The stringent regulations required for the manufacture of API, intrigued us to explore the synthesis of impurity standards related to Roflumilast. As per our knowledge no single report for the preparation of Roflumilast impurities is found in literature till date. Herein we report a facile method for the synthesis of Roflumilast along with its impurities 4 - 8 (figure 2) starting from commercially available starting material 3,4-dihydroxy benzaldehyde 10.
MATERIALS AND METHODS
All the materials used are laboratory grade, water used is milliQ water.

RESULTS AND DISCUSSION
The possible starting material envisaged for the preparation of Roflumilast 3 in minimum steps is 3, 4-dihydroxybenzaldehyde 10. The synthesis requires introduction of a difluoromethyl group, a cyclopropylmethyl group and a dichloroamino pyridine moiety to the key starting material. A literature search indicated chlorodifluoroacetic acid 9 as a possible precursor for the introduction of difluoromethyl group.

Scheme 1: Preparation of Roflumilast 3 along with its impurities 4, 5 and 6. reagents and conditions: a) K2CO3, DMF, benzyltrimethyl ammonium chloride, b) K2CO3, DMF, cyclopropylmethyl bromide 13 c) CrO3, H2SO4, acetone. d) (i) SOCl2, toluene (ii) 4-amino-3,5-dichloropyridine 17, NaH, THF over two steps.
Potassium salt of chlorodifluoroacetic acid 9 in DMF in presence of catalytic amount of benzyltrimethyl ammonium chloride alkylated the 4\textsuperscript{th} position of 3,4-dihydroxy benzaldehyde which resulted in compound 10, along with compounds 4 and 12 as impurities. Compound 10 was further alkylated to 14 using cyclopropylmethyl bromide 13 and K\textsubscript{2}CO\textsubscript{3} as base in DMF. Compound 15 was identified as an impurity associated with 14 during the synthesis. Jones oxidation of compound 14 resulted in acid 16. An acyl chloride was prepared from compound 16, which was then coupled with 4-amino-3,5-dichloro pyridine to get the target molecule 3. A similar approach was followed for the preparation of impurities 5 and 6 from intermediates 15 and 12 respectively (scheme 1).

Compound 15 on Jones oxidation yielded acid 18 which on treatment with thionyl chloride followed by coupling with compound 17 resulted in the formation of impurity 5. Similarly preparation of impurity 6, a regio-isomer of Roflumilast 3, was initiated using compound 12 formed in first step of Roflumilast synthesis. Compound 12 upon alkylation using cyclopropyl methyl bromide 13 formed compound 19 which upon Jones oxidation resulted in acid 20. Compound 20 was converted to corresponding acid chloride by treating with thionyl chloride, which when coupled with compound 17 resulted in the regio-isomer 6 (scheme 1).

Scheme 2: Preparation of impurity 7. reagents and conditions: a) mCPBA, DCM.

The N-oxide impurity 7, which was isolated and characterised was observed as a degradation product of compound 6. Apart from that reaction of Roflumilast 3 with mCPBA also gave the N-oxide impurity 7, whose analytical data eclipsed with that of the isolated sample (scheme 2). The impurity 4 obtained in stage 1 of Roflumilast synthesis was used for the preparation of impurity 8, following the procedure used for impurities 5 and 6 (scheme 3).
Scheme 3: Preparation of impurity 8. reagents and conditions: a) CrO3, H2SO4, acetone. b) (i) SOCl2, toluene (ii) 4-amino-3,5-dichloropyridine 17, NaH, THF over two steps.

CONCLUSION
In conclusion we completed the synthesis of Roflumilast 3 and exploited the formation of corresponding compounds 3,4-Bis(cyclopropylmethoxy)- benzaldehyde 15, 3-(Difluoromethoxy)-4-Hydroxy benzaldehyde12 and 3,4-bis (difluoromethoxy) benzaldehyde 4 for the synthesis of impurities 3,4-Bis(cyclopropylmethoxy)-N-(3,5-dichloropyridin-4yl)benzimide 5, 4-(cyclopropylmethoxy)-N-(3,5-dichloro-4-pyridinyl)-3-(difluoromethoxy) benzimide 6, 3-(cyclopropylmethoxy)-N-(3,5-dichloro-4-pyridinyl-1-oxide)-4-difluoromethoxy) benzimide7 and N-(3,5-Dichloropyridin-4-yl)-3,4-bis (difluoromethoxy) benzamide 8 respectively. The synthetically prepared impurities were characterized by conventional spectroscopic studies.

REFERENCES