International Journal of Advance Research in Science and Engineering
Volume No.06, Issue No. 11, November 2017
www.ijarse.com
IJARSE
ISSN: 2319-8354

Discovery of Novel PDE4 inhibitor 33-SDS-LR and Its role in Inflammation

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PDE4 is the main cAMP degrading enzyme present in immune cells like basophils, eosinophils, macrophages, dendritic cells and T cells. PDE4 is associated with the pathogenesis of various diseases like asthma, psoriasis, atopic dermatitis, COPD, systemic lupus erythematosis, rheumatoid arthritis and ankylosing spondylitis. Roflumilast, apremilast and crisbarole are the FDA approved PDE4 inhibitors used in the treatment of some inflammatory and autoimmune diseases. Unfortunately, the use of PDE4 inhibitors have been compromised by side effects such as nausea and emesis and so clinical use of PDE4 inhibitors is still limited. In search of new PDE4 inhibitors our lab discovered novel PDE4 inhibitor 33-SDS-LR showing PDE4 inhibition with an enzymatic IC_{50} value of 200 nM. Next we explored 33-SDS-LR for further studies in cell based assays were it increased the cellular cAMP levels in MCF 7 cells with a maximum increase at 30 µM. Furthermore 33-SDS-LR was explored for anti-inflammatory studies in RAW 264.7 macrophages. 33-SDS-LR inhibited the lipopolysacharide (1µg/mL) and interferon gamma (20ng/mL) induced production of TNFα, IL1β, NO and iNOS expression in RAW264.7 macrophages. Next 33-SDS-LR was explored for its role in T cell mediated immune response. 33-SDS-LR inhibited the Concanavalin A (5µg/mL) induced T cell proliferation with a maximum inhibition at 30 µM. Stastical analyses were done by using Graphpad prism software and by using one way ANOVA. P value less than 0.05 were considered.

Key words: *PDE4, Lipopolysacharide, Interferon gamma, interleukin1 beta, tumor necrosis factor alpha, nitric oxide and concanavalin A.*