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Discovery of potent and selective Spleen Tyrosine Kinase inhibitors for the topical treatment of inflammatory skin disease

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ABSTRACT

The discovery and lead optimisation of a novel series of SYK inhibitors is described. These were optimised for SYK potency and selectivity against Aurora B. Compounds were profiled in a human skin penetration study to identify a suitable candidate molecule for pre-clinical development. Compound **44** (GSK2646264) was selected for progression and is currently in Phase I clinical trials.

Spleen Tyrosine Kinase (SYK) is a 72 kDa cytosolic non-receptor tyrosine kinase that is involved in signal transduction in a variety of cell types, including B lymphocytes, mast cells and macrophages.[1] SYK and Zeta-chain-associated protein kinase 70 (ZAP-70) are the only members of the SYK family of protein tyrosine kinases and share a similar domain organisation with two N-terminal SH2 domains and a C-terminal kinase domain. ZAP-70 has much lower intrinsic enzyme activity and its expression is mainly restricted to T-cells and NK cells.[2] SYK plays a key role in coupling activated immunoreceptors to downstream events that mediate diverse cellular responses, including proliferation, differentiation and phagocytosis. Inhibition of SYK mediated immunoreceptor (Ig Fcε, Ig Fcγ and B-cell receptors) signalling leads to the inhibition of mast cell, macrophage and B-cell activation and subsequent release of inflammatory modulators.[3] Therefore, the discovery of safe small molecule SYK inhibitors has attracted much attention in a number of therapeutic areas, including the treatment of rheumatoid arthritis, B-cell lymphoma and asthma / rhinitis.[4-10]

The treatment of several skin diseases such as chronic urticaria, atopic dermatitis and rosacea are inadequately treated by topically applied medication and the development of a SYK inhibitor which should reduce the overall inflammatory response could be beneficial if topically applied. Topical administration was preferred over an oral treatment as drug is applied locally to disease tissue, leading to higher drug levels in the skin whilst minimising the systemic exposure of drug and hence reducing any potential safety risks.

GSK has investigated several chemical series previously, including the pyrimidine carboxamides[11] and the azanaphthyridines.[12] Both templates had developability issues, with several analogues from each series being positive