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ABSTRACT

Design and optimization of a novel series of imidazo[1,2-b]pyridazine PDE10a inhibitors are described. Compound **31** displays excellent pharmacokinetic properties and was also evaluated as an insulin secretagogue in vitro and in vivo.

Phosphodiesterases (PDEs) are a family of enzymes encoded by 21 genes subdivided into 11 distinct families according to structural and functional properties. These enzymes are hydrolases that metabolically inactivate widely occurring intracellular second messengers, 3′,5′-cyclic adenosine monophosphate (cAMP) and 3′,5′-cyclic guanosine monophosphate (cGMP), by catalytic hydrolysis of the 3′-ester bond, while forming the inactive 5′-monophosphate. On the basis of substrate specificity, the PDE families can be divided into three groups: i) the cAMP-specific PDEs, which include PDE4, 7 and 8; ii) the cGMP-specific enzymes PDE5, 6 and 9; and iii) the dual-substrate PDEs, PDE1, 2 and 3, as well as PDE10 and 11.[1] Although PDE10a is predominantly expressed in the brain, it is also expressed in neuroendocrine tissues such as pancreatic islets, adrenal gland, pituitary gland, and in neuronal ganglia throughout the intestine.[1, 2]

In pancreatic islet β-cells, incretins activate the GLP-1 receptor, an adenylate cyclase (AC)-coupled GPCR (G-protein coupled receptor), which elevates intracellular cyclic adenosine mono-phosphate (cAMP) levels. Because cAMP is a major regulator of glucose-stimulated insulin secretion (GSIS) from pancreatic islet β-cells, inhibition of the PDE10a activity may results in the enhancement of cAMP levels with concomitant insulin secretion.[3]

A peripherally-restricted PDE10a inhibitor has been shown to enhance insulin secretion and reduce glucose excursion in lean Wistar rats.[2] Further validation that PDE10a inhibition may have beneficial effects on controlling obesity comprises the phenotype of the PDE10a knockout mice which were resistant to weight gain on a high fat diet, without an appreciable change in food consumption.[5] The differences in weight between the PDE10a knockout and wild type mice were predominantly due to differences in adiposity, and not lean mass. When compared to wild type mice, the PDE10a knockout mice had lower plasma insulin, triglycerides, non-esterified free fatty acids and leptin.[3]

These data suggest that PDE10a inhibitors may be beneficial for the treatment of Type 2 diabetes and obesity, while potentiating GSIS with the potential for weight loss. Since compounds that cross the blood brain barrier may exhibit potential CNS side effects due to the high expression levels of PDE10a in the brain, identifying peripherally restricted PDE10a inhibitors with excellent sub-type selectivity and the desired efficacy was the major focus of project. Herein is reported an account of the our efforts on the investigation of peripherally restricted PDE10A inhibitors.

An internally identified imidazo[1,2-b]pyridazine PDE10a chemotype[4] (Fig. 1), first investigated for CNS disorders, was chosen as the lead structure in our investigation. The imidazo[1,2-b]pyridazine **1** occupies the hydrophobic clamp of the PDE10a catalytic site that recognizes the adenosine or guanosine ring structures of cAMP or cGMP while interacting with the conserved Gln-716. The N-linked morpholine acts as a hydrogen bond acceptor from the tightly-bound buried water molecules that are an integral part of the structure of the enzyme. The alkyl ether side chain-attached pyridine can exert hydrophobic interactions with protein outside the catalytic site.[1] The presence of the C-3 aryl substituent increases the potency of the compounds. The substituent on the aryl group on the other

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