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In This Issue

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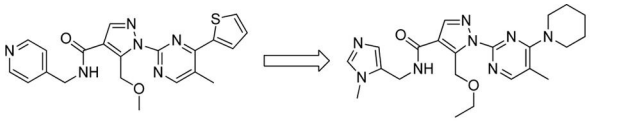
NOVEL GPR142 AGONIST FOR TYPE 2 DIABETES

Type 2 diabetes is the most common form of diabetes, wherein the body develops insulin resistance or reduced insulin production, resulting in high blood glucose. Insulin secretagogues are used for effective control of insulin production in patients. However, some agents are associated with the risk of hypoglycemia as they trigger insulin release independently of the level of blood glucose. Therefore, novel glucose-dependent insulin secretagogues are highly desired for the treatment of diabetes.

Here, Toda et al. (DOI: 10.1021/ml400186z) describe the discovery of a potent and orally bioavailable GPR142 agonist. GPR142 is a novel G protein coupled receptor that is expressed predominantly in pancreatic beta-cells and mediates enhancement of glucose-stimulated insulin secretion. The authors report that the GPR agonist shows dose-dependent glucose lowering effects in an oral glucose tolerance test in mice and monkeys. This is the first example that GPR142 agonist demonstrates in vivo efficacy in monkeys.



HTS hit 1
GPR142 EC_{50} = 1.5 μM
F = 3.9% in cynomolgus monkeys

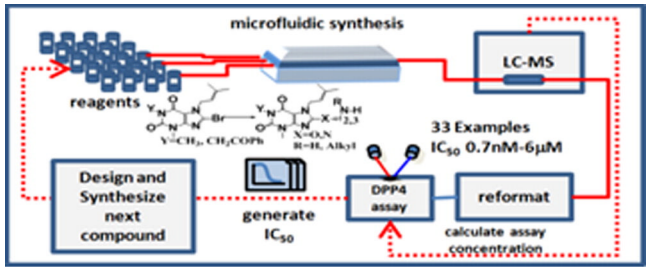
33
GPR142 EC_{50} = 0.022 μM
F = 26% in cynomolgus monkeys

Glucose lowering effect in mice and monkeys

CLOSED LOOP DRUG DESIGN

Medicinal chemistry involves the design, synthesis, and development of bioactive molecules. As such, the process often requires screening, isolation or synthesis of novel molecules, which is then optimized to yield a candidate molecule for the clinic.

In this issue, Czechtizky et al. (DOI: 10.1021/ml400171b) describe the use of an innovative automated discovery platform for rapid structure−activity relationship generation. In this approach, molecules are designed for synthesis and screening based upon the emerging structure−activity relationship in a true serial iterative manner. The authors demonstrate the correlation between the results obtained on their system against ones generated in a more traditional way, validating the new approach using a blinded set of xanthine-derived dipeptidyl peptidase 4 antagonists.



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