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Abstracts

3-SUBSTITUTED 2-OXINDOLE DERIVATIVES AS POTENTIAL ANTI-DIABETIC AND ANTITUMOR AGENTS

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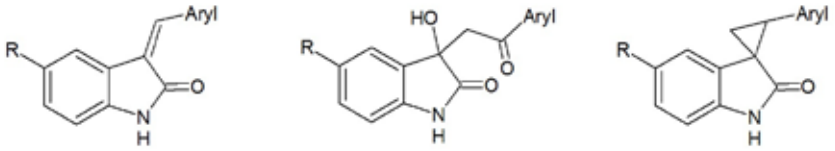
Inhibition of glycogen synthase kinase 3β *(*GSK-3β*)* is a new and widely investigated approach to the treatment of diabetes mellitus [a], cancer and Alzheimer's disease. We report the synthesis of novel GSK-3β inhibitors with pronounced antioxidant, anti-inflammatory and antitumor activity [b]. Over 50 3-substituted 2-oxindole derivatives were synthesized and tested *in vitro* against GSK-3β and α-glucosidase, another molecular targets linked with diabetes [c].



The convenient choice of 2-oxindole scaffold allowed for the wide range of substituent variation which resulted in the possibility of effective and selective binding to both molecular targets. Lead compounds were shown to inhibit GSK-3β and α-glucosidase in a cell-based assay with IC_{50} 4.19 nM and 6.78 μM respectively with low cytotoxicity.

Oral glucose tolerance test in rat model of type 2 diabetes mellitus demonstrated prominent antihyperglycemic activity of 3-substituted 2-oxindole derivatives.

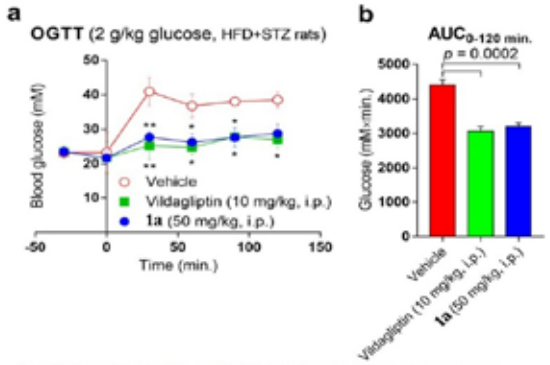


Fig. 1. Effect of compound **1a** and DPP-4 inhibitor vildagliptin on glucose response during an oral glucose tolerance test in HFD+STZ diabetic rats.

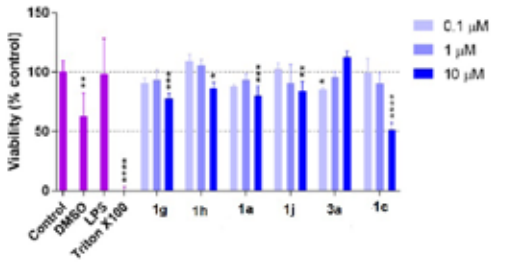


Fig. 2. Assessment of cytotoxicity in human PBMCs

GSK-3β inhibitors are proven to successfully combat systemic inflammatory process and oxidative stress, factors crucial in the development of type-2 diabetes **[d]** Obtained substances were able to significantly reduce iNOS activity in LPS-induced macrophages, showcasing their anti-inflammatory properties. Novel 3-arylidene 2-oxindole derivatives were tested *in vitro* on lung adenocarcinoma (A549) and colon cancer (HCT116) cell lines and displayed cytotoxicity in the low micromolar range. Key substitutes were found both for compounds exhibiting cytotoxicity in the low micromolar range and compounds with antidiabetic properties.

References

a) Biochemical Pharmacology, 2013, Vol. 86, no 2, P. 191-199.
b) Bioorganic & Medicinal Chemistry, 2019, Vol. 27, no 9, P. 1804-1817
c) Clinical and Investigative medicine, 1995, Vol. 18, no 4, P. 303-311
d) Journal of Diabetes Investigation, 2010, Vol. 1, no 3, P. 90-96
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