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Early drug discovery for type 2 diabetes mellitus: An academia perspective

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Type 2 diabetes mellitus and related metabolic disorders represent a major health concern and growing burden worldwide and in Russia. Underlying molecular mechanisms are also largely involved in other pathologies, including obesity, cancer, aging, neurodegeneration, and cardiovascular diseases. Therefore, identification of new compounds with antidiabetic potential is of great interest in the metabolic disease area.

The majority of drugs today come from commercial pharmaceutical and biotech companies [1] which heavily rely on high-throughput screening campaigns to identify novel biologically active entities. Hit identification rates are way below 1% [2] while R&D costs are high. Drug development in academia is hampered by limited resources, lack of know-how, and lack of a regional ecosystem. At the same time, academic expertise empowered with modern approaches and collaborative networking may provide a cost-effective venue for valuable early-stage drug discovery.

In our current project, we pursue potential antidiabetic agents. Collection of ca. 2500 drug-like compounds was obtained through collaboration with 9 academic institutions. ChEMBL mining afforded published active compounds against therapeutically relevant targets. Pharmacophore fingerprint calculation coupled with expert examination was used to build focused libraries of previously untested ca. 500 compounds. Biochemical screening with subsequent disqualification of apparent hits (poorly soluble, aggregators, redox-active) identified 49 true hits against 7 target proteins. Follow-up cellular and animal assays provided validated leads for further development of first-in-class antidiabetic agents: micromolar MST1 and PTP1B inhibitors, glucokinase activator, and submicromolar AMPK activator and GSK3B inhibitor.

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