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# Pyrimidine-based thiazolidinedione hybrids: Design, synthesis, and antidiabetic evaluation

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**ABSTRACT** A series of new pyrimidine-based thiazolidinedione analogs **(6a-m)** was synthesized and evaluated for their antidiabetic evaluation. Compounds **5a-d** were prepared and then reacted with **3a-d** to give title compounds **6a-m**. During *in vitro* α-amylase inhibitory activity, compounds **6a**, **6d**, **6e**, **6f**, **6g**, **6h**, **6i,** and **6k** showed promising results with half-maximal inhibitory concentration ($IC_{50}$) values between 19.54 and 25.66 µg/mL. Among them, compound **6a** was the most potent ($IC_{50}$ = 19.54 µg/mL, outperforming the reference drug acarbose ($IC_{50}$ = 26.22 µg/mL). These eight candidates were subsequently evaluated through *in vivo* screening using a streptozotocin -induced diabetic rat model at dose levels 50 and 100 mg/kg, with pioglitazone (30 mg/kg) as the standard. Among them, compounds **6a** and **6d** exhibited significant glucose lowering effects at the higher dose, with **6d** surpassing the efficacy of pioglitazone (126.42 ± 1.23 vs. 133.4 ± 1.44 mg/dL) and **6a** showing comparable activity (134.5 ± 3.32 vs. 133.4 ± 1.44 mg/dL). Body weight analysis over a 21-day treatment period also reflected these findings, with **6a** and **6d** restoring weight close to normal levels. Further biochemical assessments revealed that both compounds improve lipid profiles and significantly normalized elevated liver enzyme levels suggesting minimal hepatotoxicity. Overall, the results highlight compound **6d** as promising antidiabetic agents with potential for further preclinical development due to their effective glycemic control, favorable metabolic effects, and safety profile.

**KEY WORDS** Anti-diabetic agents, Insulin sensitizers, Pyrimidine, Thiazolidinedione.

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