# Development of diarylpentadienone analogues as alpha-glucosidase inhibitor: synthesis, *in vitro* biological and *in vivo* toxicity evaluations, and molecular docking analysis

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**ABSTRACT**

A series of aminated- (**1**–**9**) and sulfonamide-containing diarylpentadienones (**10**–**18**) were synthesized, structurally characterized, and evaluated for their *in vitro* anti-diabetic potential on α-glucosidase and DPP-4 enzymes. It was found that all the new molecules were non-associated PAINS compounds. The sulfonamide-containing series (compounds **10**–**18)** selectively inhibited α-glucosidase over DPP-4, in which compound **18** demonstrated the highest activity with an $IC_{50}$ value of 5.69 ± 0.5 μM through a competitive inhibition mechanism. Structure-activity relationship (SAR) studies concluded that the introduction of the trifluoromethylbenzene sulfonamide moiety was essential for the suppression of α-glucosidase. The most active compound **18**, was then further tested for *in vivo* toxicities using the zebrafish animal model, with no toxic effects detected in the normal embryonic development, blood vessel formation, and apoptosis of zebrafish. Docking simulation studies were also carried out to better understand the binding interactions of compound **18** towards the homology modeled α -glucosidase and the human lysosomal α -glucosidase enzymes. The overall results suggest that the new sulfonamide-containing diarylpentadienones, compound **18**, could be a promising candidate in the search for a new α-glucosidase inhibitor, and can serve as a basis for further studies involving hit-to-lead optimization, *in vivo* efficacy and safety assessment in an animal model and mechanism of action for the treatment of T2DM patients.

**KEYWORDS**

Diarylpentadienones; Sulfonamide; α-glucosidase inhibitor; Zebrafish; Molecular docking

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