HYBRID SULFONYLUREA-LINKED CHALCONOIDS AS ANTIDIABETIC AGENTS: EVALUATION OF ANTIHYPERGLYCEMIC EFFECTS IN STREPTOZOTOCIN-INDUCED TYPE 2 DIABETIC RATS

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ABSTRACT

The proposed investigation was carried out to evaluate the antihyperglycemic potential and to explore the structure-activity relationship (SAR) of a series of 28 hybrid sulfonylurea-linked chalconoids using streptozotocin-induced type 2 diabetic rats. Among all the compounds tested, compound SC 21 exhibited remarkable antidiabetic activity.

Keywords: Hybrid sulfonylurea-linked chalconoid; the antihyperglycemic effect, type 2 diabetes.

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INTRODUCTION

Drug discovery is a continuous process which, depending on the strategy used, typically comprises several discrete stages: target identification and validation; assay development; screening (whole cell or molecular target-based) to identify hits; procurement/synthesis and assessment of analogues to develop structure-activity relationships (SAR) and identify leads; iterative medicinal chemistry to optimize leads; and preclinical development prior to clinical evaluation¹. Diabetes defines a group of metabolic diseases categorized by hyperglycemia and pancreatic β -cell dysfunction. Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease characterized by high blood sugar levels resulting from the reduction of insulin secretion and/or insulin resistance². It is widely known that elevation of blood glucose caused by disruption of carbohydrate, protein and fat metabolism can lead to diabetic complications in several organs and tissues, including eyes, kidneys, nerves and blood vessels³. Although various clinically used antidiabetic drugs are available, it has been shown that current clinical management is not adequately addressed by existing therapies, and therefore an exploration of the novel scaffolds as antidiabetic agents are still in demand⁴.

The search for new drugs with antidiabetic activity remains a focused area of worldwide research. Chalcones are naturally occurring bichromophoric compounds captivated significant attention due to its diverse range of pharmacological properties such as heat shock protein-inducer⁵, antimetabolic⁶, antiproliferative⁷, antibacterial⁸, pro-angiogenic⁹, antiviral¹⁰, antioxidant¹¹, leishmanicidal¹², anti-inflammatory¹³, anti-Alzheimer's¹⁴, β -secretase inhibitors¹⁵, spasmolytic¹⁶, antimicrobial¹⁷, acetylcholinesterase inhibitors¹⁸, antimycobacterial¹⁹, suppressor of COX-2 expression²⁰, antimalarial²¹, anti-apoptotic²², cytotoxic²³, anticancer²⁴, and anti-prostatic²⁵. Similarly sulfonylurea moiety has also gained privileged status due to its biological activity profiles which includes hypoglycemic²⁶, peroxisome proliferator-activated receptor γ agonistic²⁷, antimicrobial²⁸, herbicidal²⁹, selective EP4 receptor antagonists³⁰, selective bombesin receptor subtype-3 (SCS-3) agonist³¹, antagonists of the CXCR2 receptor³², antimalarial³³, *Vibrio fischeri* quorum sensing regulator³⁴, selective antagonists of the TP α and

TP β isoforms of the human thromboxane A2 receptor³⁵, reversible inhibitors of human steroid sulfatase³⁶, K_{ATP}-channel openers³⁷, antagonists of the ANG II AT1 receptors³⁸, inhibitors of Acyl-CoA: cholesterol O-Acyltransferase³⁹, inhibitors of aldehyde dehydrogenase⁴⁰, non-competitive Inhibitor of acetohydroxyacid synthase from *Mycobacterium tuberculosis*⁴¹, cancer chemotherapeutic⁴², antitumor⁴³, oncolytic⁴⁴, diuretic⁴⁵, selective β 3 adrenergic receptor agonist⁴⁶, and vasodilator⁴⁷. Therefore, a series of novel hybrid sulfonylurea-linked chalconoids (SC1-28) were designed, synthesized, characterized and earlier reported from our laboratories as potential cytotoxic and antimicrobial agents⁴⁸. It is proved from the literature that the compounds containing neither sulfonylurea nor chalcone moieties often shows significant antidiabetic activity profiles.

EXPERIMENTAL

In the present investigation, a series of novel hybrid sulfonylurea-linked chalconoids (SC1-28)⁴⁸ shown in (Fig.-1) were evaluated them for *in vivo* antihyperglycemic potential using streptozotocin-induced type 2 diabetic rats⁴⁹. The experimental protocol has been approved by the Institutional Animal Ethics Committee (IAEC) and by the Animal Regulatory Body of the Government. (Regd. No. 516/01/A/CPCSEA). The direct comparison of the antihyperglycemic effect of the sulfonylurea-linked chalcones SC1-28 is made rather difficult by the fact that not only the maximal decrease of the blood glucose level produced by the standard doses of the compound but also the dose-response curves vary from compound to compound.

Compound	Ar	Compound	Ar
SC1	C ₆ H ₅	SC15	3-NO ₂ C ₆ H ₄
SC2	4-MeC ₆ H ₄	SC16	5-OH,2-NO ₂ C ₆ H ₃
SC3	4-NMe ₂ C ₆ H ₄	SC17	3-FC ₆ H ₄
SC4	3-OMeC ₆ H ₄	SC18	4-FC ₆ H ₄
SC5	4-OMeC ₆ H ₄	SC19	2-ClC ₆ H ₄
SC6	3,4-diOMeC ₆ H ₃	SC20	4-ClC ₆ H ₄
SC7	2,4-diOMeC ₆ H ₃	SC21	2,4-diClC ₆ H ₃
SC8	3,4, 5-triOMeC ₆ H ₂	SC22	3-BrC ₆ H ₄
SC9	2-OHC ₆ H ₄	SC23	4-Allyl-OC ₆ H ₄
SC10	3-OHC ₆ H ₄	SC24	Phenylethene-yl
SC11	4-OHC ₆ H ₄	SC25	Pyrrol-2-yl
SC12	3-OEt,4-OHC ₆ H ₃	SC26	Pyridin-3-yl
SC13	3-OMe,4-OHC ₆ H ₃	SC27	Pyridin-4-yl
SC14	2-NO ₂ C ₆ H ₄	SC28	Anthracen-9-yl

Fig.-1: Chemical Structures of the Sulfonylurea-linked Chalconoid (SC1-28)⁴⁸

RESULTS AND DISCUSSION

The results of *in vivo* antihyperglycemic activity of the synthesized sulfonylurea-linked chalcones (SC1-28) showed that all the compounds were found to possess moderate to potential ability to reduce blood glucose levels in streptozotocin-induced type 2 diabetic rats. We consequently found that the blood glucose reduction ability of the titled compounds (SC1-28) was followed a dose-dependent manner in their antihyperglycemic activity. Among all the tested compounds, compound SC21 (Fig.-2) showed

significant antihyperglycemic activity at various doses such as 10, 30 and 50 mg/kg b.w with percentage blood glucose reduction values $14.66 \pm 0.27\%$, $20.18 \pm 1.34\%$ and $21.78 \pm 2.61\%$, respectively at 4 h. Similarly, compound SC5 also showed promising antihyperglycemic activity. In the same way, compounds such as SC13, SC19, SC4, SC3, SC11, SC27, SC1, SC22, SC9, SC10, SC10, SC26, SC20, SC23 and SC8 exhibited a moderate range of antihyperglycemic activity at all the doses. The other compounds such as SC12, SC24, SC7, SC6, SC15, SC2, SC25, SC16, SC14, SC17, SC28 and SC18 showed lower level of antihyperglycemic activity when compared to that of the reference drug gliclazide with percentage blood glucose reduction values $40.51 \pm 1.46\%$ and $45.34 \pm 3.02\%$ at dose 2 mg/kg b.w.

Fig.-2: Chemical Structure of the Sulfonylurea-linked Chalconoid (SC21).

It is noteworthy to establish the structure-activity relationships (SARs) for the observed antihyperglycemic activity of sulfonylurea-linked chalcones SC1-28. It is clear from the results of antihyperglycemic activity that the structural requirements for retaining (or enhancing) antihyperglycemic property in sulfonylurea-linked chalcones SC1-28 are not inflexible. As such, the following are the conventional SARs. The α,β -unsaturated ketone and sulfonylurea-linker moieties are the vital structural pharmacophores for maintaining the antihyperglycemic activity. It is remarkable that an enhanced level of activity was observed when the phenyl ring of α,β -unsaturated carbonyl system is substituted with different functional groups and decreased by some other substituents. The order of activity was SC5 (4-OCH₃) > SC13 (3-OCH₃,4-OH) > SC19 (2-Cl) > SC4 (3-OCH₃) > SC3 (N(CH₃)₂) > SC11 (4-OH) > SC22 (3-Br) > SC9 (2-OH) > SC10 (3-OH) > SC20 (4-Cl) > SC23 (4-Allyloxy) > SC8 (3,4,5-triOCH₃) > SC12 (3-C₂H₅,4-OH) > SC24 (phenylethenyl) > SC7 (2,4-diOCH₃) > SC6 (3,4-diOCH₃) > SC15 (3-NO₂) > SC2 (4-CH₃) > SC16 (5-OH,2-NO₂) > SC14 (2-NO₂) > SC17 (3-F) > SC18 (4-F), respectively. An *ortho* and *para* substitution on the phenyl ring of α,β -unsaturated carbonyl system with less electronegative halogens compared to fluorine, such as chloro may significantly enhance the activity as seen in the case of compound SC21. A *para*-substitution on the phenyl ring of α,β -unsaturated carbonyl system with electron-donating groups possibly will increase the activity. A *para*-substitution on the phenyl ring of α,β -unsaturated carbonyl system with hydroxyl group relevant for maintaining activity. The replacement of phenyl ring with a pyridine-4-yl ring as in compound SC27 exhibited a significant increase in activity compared to the compounds possessing other aromatic or heteroaromatic ring systems, the order of activity was SC26 (pyridin-3-yl) > SC25 (pyrrole) > SC28 (anthracen-9-yl), respectively.

CONCLUSION

In summary, we have evaluated a series of sulfonylurea-linked chalconoids and among the compounds tested α,β -unsaturated carbonyl system and sulfonylurea moieties were appeared to be pivotal to retain the antihyperglycemic potential of this chemotype. This study would be the remarkable implications to develop new hybrid scaffolds consisting of either chalcone or sulfonylurea chemical pharmacophores in their basic nucleus.

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