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Antidiabetic and antioxidant activities of synthetic 2-styrylchromones

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Abstract: 2-Styrylchromones are very potent bioactive substances showing innumerable activities like antioxidant, antidiabetic, antiviral, antiinflammatory, anticancer, anti-microbial etc. All these activities are due to their core structure (benz-γ-pyrone) containing styryl group at 2nd position. Substituents especially hydroxyl groups are responsible for anti-diabetic and antioxidant activities. 2-Styrylchromones with a greater number of –OH substituents showed high activity than the remaining compounds. Compounds 5, 6, 7 and 9 having significant activity where the nature and position of substituents play a vital role. The synthetic compound with –OH groups at 4', 6 and 7 positions competed with standard drugs in respective activities.

Keywords: 2-styrylchromones; antidiabetic activity; antioxidant activity, streptozotocin induced diabetic; glibenclamide; superoxide radical scavenging.

1. Introduction

2-Styrylchromones are rare class of naturally occurring chromone derivatives,[1,2] possessing wide range of biological activities[3-5] comprising medicinal and disinfectant properties.[6-9] The core structure with appropriate substituents at various positions is responsible for their effective biological activities which attracted the researcher into biological activity studies of chomone derivatives and their synthesis. Although several attempts have been made to synthesize[10-17] 2-styrylchromones; there remains significant scope for developing the efficient and eco-friendly methods to produce novel and potent bioactive analogues.

This interest has motivated many researchers, leading to the development of a wide range of 2-styrylchromone derivatives[12,18-21] which have been reported as potential therapeutic agents. Chromone moiety bearing styryl group at 2nd position (Figure-1) has garnered significant attention due to their notable antioxidant,[22] anti-cancer,[23] anti-proliferal,[24] anti-tumour[25] and anti-viral[26] activities. Additionally, some studies have highlighted the potential of chromone derivatives as antidiabetic agents.[27, 28]

Anti-diabetic agents constitute a diverse group of drugs, both chemically and pharmacologically, used to manage diabetes - a common endocrine disorder characterized by persistently high blood sugar levels.[29,30] The primary goal of diabetes treatment is to regulate blood glucose levels

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consistently over 24 hours while avoiding clinical hypoglycemia.[31] This is accomplished through medications that stimulate insulin secretion, enhance insulin sensitivity, or limit carbohydrate absorption. Research has established that maintaining optimal blood glucose control significantly reduces the risk of micro-vascular complications, such as retinopathy and nephropathy, such as retinopathy and nephropathy, as well as long-term neuropathic complications in both type-1[32] and type-2[33] diabetes.

Antioxidants are compounds that inhibit the formation of free radicals involved in oxidation processes, which can lead to the degradation of organic materials, including biological tissues. To enhance the longevity of various products, antioxidants are frequently incorporated into industrial materials such as polymers, fuels, and lubricants.[34] In living organisms, natural antioxidants like glutathione, mycothiol, and bacillithiol, along with enzymatic systems such as superoxide dismutase, play a crucial role in protecting cells from oxidative stress.[35] Although certain dietary antioxidants demonstrate antioxidant activity in vitro, there is limited evidence supporting their effectiveness in vivo.[36] Moreover, dietary supplements marketed as antioxidants have not been conclusively shown to improve health or prevent disease in humans,[36,37] leading researchers to increasingly explore synthetic antioxidants as alternative solutions.

Diabetes mellitus is a chronic metabolic disorder marked by sustained high blood glucose levels resulting from impaired insulin secretion, insulin action, or a combination of both. It has emerged as a significant global health challenge, leading to various health issues as mentioned above. The rising prevalence of diabetes has driven extensive research into discovery of promising anti-diabetic agents that can help regulate blood glucose levels effectively and safely. Anti-diabetic activity studies remain a crucial field in pharmaceutical and biomedical research, aiming to develop safer and more efficient treatments to combat diabetes and its complications.

Antioxidant activity studies have gained significant attention due to the critical role of oxidative stress in the development of various diseases, including cardiovascular diseases, neurodegenerative disorders, diabetes, cancer, and aging-related conditions. These studies focus on identifying, characterizing, and evaluating compounds that can neutralize free radicals and reduce oxidative damage in biological systems. Antioxidant activity studies continue to be a vital area of research, contributing to advancements in synthesis of potential antioxidants with the goal of improving health and longevity.

In the view of above biological activities, we have synthesized 2-styrylchromones in solvent free conditions [38-44] with mild oxidative cyclization agents.[45, 46]

2. Experimental

2.1. Chemical Materials and Apparatus

All AR grade (qualigens, Aldrich, Sd fine etc) chemicals required for our research work were purchased from National Scientific products, Guntur, and used directly without further purification. After recrystallization, melting point of each compound was found by using melting point apparatus in open capillary tubes. The structures of all synthetic compounds were finalized with IR, NMR (Bruker, 400 MHz), LC Mass spectra and elemental analysis was done by Vario El-III instrument.

2.2. Biological Materials and Apparatus

The synthetic compounds were tested for antidiabetic activity using streptozotocin induced method with Accu-Chek glucometer, 1 ml syringe, oral needle using Glibenclamide as reference compound. And antioxidant activity was studied by NBT method with Universal MB Tech Incubator, Spectrophotometer (560 nm) using Vit-C, Vit-E, BHA and BHT as reference compounds.

2.3. Chemistry

All the compounds (**1-12**) tested for their anti-diabetic and antioxidant activities were synthesized[47] from substituted acetophenones and cinnamaldehydes in 1:1 molar ratio using PEG-400 and piperidine at 40-50 °C with stirring for about half an hour, followed by oxidative cyclization of the resulting yellow colored dienone intermediate in the presence of catalytic amount of powdered iodine

at ≈140 °C in the same reaction vessel for about 3-4 hours refluxing as per the scheme-1. The physical data of synthetic compounds was depicted in the table-1.

2.4. Anti-diabetic Activity

Prior to the experimentation ethical approval was taken by the IAEC committee with the approval number IAEC/XIV/03/BCOP/2021. For the anti-diabetic screening, rats were selected and overnight fasted before the experimentation. The diabetes was induced by using the streptozotocin (STZ) of 60 mg/kg administered through the intra peritoneal route. On the fourth day the blood glucose levels are assessed for the individual animal to know the elevated fasting blood glucose. On obtaining the blood glucose level of above 200 mg/dl considered as diabetic. The animals are categorized into respective groups i.e. control, standard (Glibenclamide 2.5 mg/kg) and respective groups receives the test compounds. After administration the blood glucose was estimated by using glucometer for the following timings 0, 30, 60, 90, and 120 min.

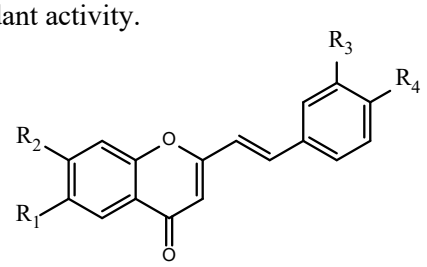
2.5. Antioxidant Activity

Generally, two different mechanisms were used to study the antioxidant activity of the compounds, namely, superoxide scavenging and 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging activities. But superoxide radical scavenging (NBT) method was used in the present research. In this, superoxide radicals are generated *in vitro* by non-enzymatic system and determined spectrophotometrically (560 nm) by following the Nitro Blue Tetrazolium (NBT) photo reduction method of McCord and Fridovich.[48,49] The antioxidant potential of the compounds was evaluated by calculating their IC_{50} values, determined from dose–response curves plotting compound concentration (μM) against the corresponding percentage of radical inhibition.

3. Results and Discussion

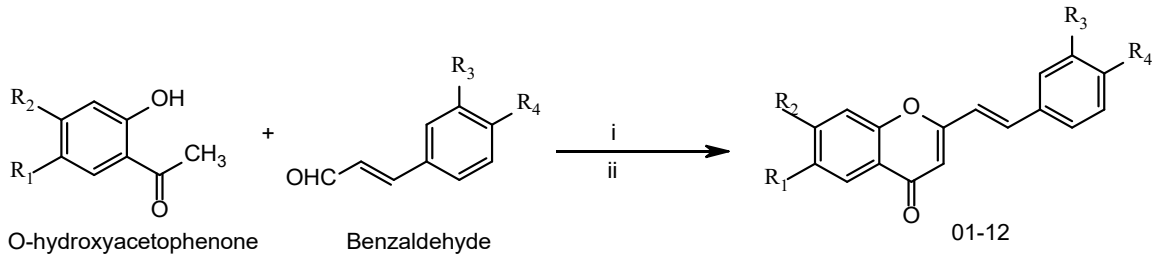
3.1. Chemistry

Our research group have synthesized[47] totally twelve compounds by following above general procedure in good yield and structural determination was completed with common spectroscopic techniques[47]. All synthesized compounds were tested to evaluate their pharmacological *in-vivo* anti-diabetic activity and *in-vitro* antioxidant activity.



1	3',4'-dimethoxy-6-hydroxy-2-styrylchromone	**7**	4',6-diydroxy-3'-methoxy-2-styrylchromone
2	3', 4',6-trimethoxy-2-styrylchromone	**8**	3',6-dimethoxy-4'-hydroxy-2-styrylchromone
3	3', 4'-dimethoxy-7-hydroxy-2-styrylchromone	**9**	7-hydroxy- 4'-methoxy-2-styrylchromone
4	3', 4',7-trimethoxy-2-styrylchromone	**10**	4',7-dimethoxy-2-styryl-chromone
5	4',7-dihydroxy3'-methoxy-2-styrylchromone	**11**	6-hydroxy-4'-methoxy-2-styryl-chromone
6	3',7-dimethoxy-4'-hydroxy-2-styrylchromone	**12**	4',6-dimethoxy-2styryl-chromone

Figure 1. Synthetic 2-Styrylchromones structure



Scheme 1. (i) PEG-400, $C_5H_{11}N$, 45-50 °C, 1/2 hr. (ii) I_2, at 130-40 °C, 4 hrs

Table 1. Physical data of synthetic 2-styrylchromones

S.No.	Substitution				Formula	Colour	Yield	M.P.(°C)
	R_1	R_2	R_3	R_4				
1	OH	H	OMe	OMe	$C_{19}H_{16}O_5$	Light Brown	82.3%	208-210
2	OMe	H	OMe	OMe	$C_{20}H_{18}O_5$	Snuff	84.9%	186-187
3	H	OH	OMe	OMe	$C_{19}H_{16}O_5$	Brick Red	81.7%	223-225
4	H	OMe	OMe	OMe	$C_{20}H_{18}O_5$	Yellowish	84.3%	179-181
5	H	OH	OMe	OH	$C_{18}H_{14}O_5$	Brick Red	80.7%	258-260
6	H	OMe	OMe	OH	$C_{19}H_{16}O_5$	Brown	83.3%	227-229
7	OH	H	OMe	OH	$C_{18}H_{14}O_5$	Pale Yellow	82.2%	265-267
8	OMe	H	OMe	OH	$C_{19}H_{16}O_5$	Greenish	83.9%	231-233
9	H	OH	H	OMe	$C_{18}H_{14}O_4$	Orange	81.6%	250-253
10	H	OMe	H	OMe	$C_{19}H_{16}O_4$	Yellowish	82.8%	172-175
11	OH	H	H	OMe	$C_{18}H_{14}O_4$	Brown	81.6%	256-257
12	OMe	H	H	OMe	$C_{19}H_{16}O_4$	Pale Yellow	83.7%	167-169

3.2. Anti-diabetic Activity Studies

M.N. Sarian et.al[50] have conducted a study to examine the anti-diabetic potential of various structurally similar flavonoids, focusing on how specific molecular features, including methylation and acetylation, influence this activity. Using α-glucosidase and DPP-4 enzyme assays, they discovered that both the number and arrangement of hydroxyl groups significantly impacted the compounds' ability to exhibit anti-diabetic effects, such as $ABTS^+$ radical scavenging and enhanced α-glucosidase activity. The presence of a double bond between carbon atoms C_2 and C_3, along with a ketone group at the C_4 position, were identified as critical structural components for this bioactivity. However, modifying the hydroxyl groups through methylation or acetylation was shown to reduce the in vitro anti-diabetic efficacy of the flavonoids.

Literature reports[51,52] indicate that certain flavonoids exhibit notable anti-diabetic effects. Among them, C-alkylated flavonoids—a relatively uncommon subgroup—stand out due to their rapid absorption when taken orally, which contrasts sharply with the typically low oral bioavailability seen in most flavonoids.[53,54] These compounds may help to reduce blood glucose levels, possibly by promoting the regeneration of pancreatic islet cells and enhancing insulin secretion in diabetic rats treated with streptozotocin.[55, 56]

The chemical compound which can prevent or alleviate diabetes is an anti-diabetic. Anti-diabetics control the blood glucose and are used to treat diabetes mellitus. Anti-diabetics stabilize blood glucose levels in people with diabetes. The anti-diabetic activity study was conducted by using streptozotocin induced diabetic rats. It was found that these compounds showed low to good blood glucose lowering effect compared to standard glibenclamide (Figure 2).

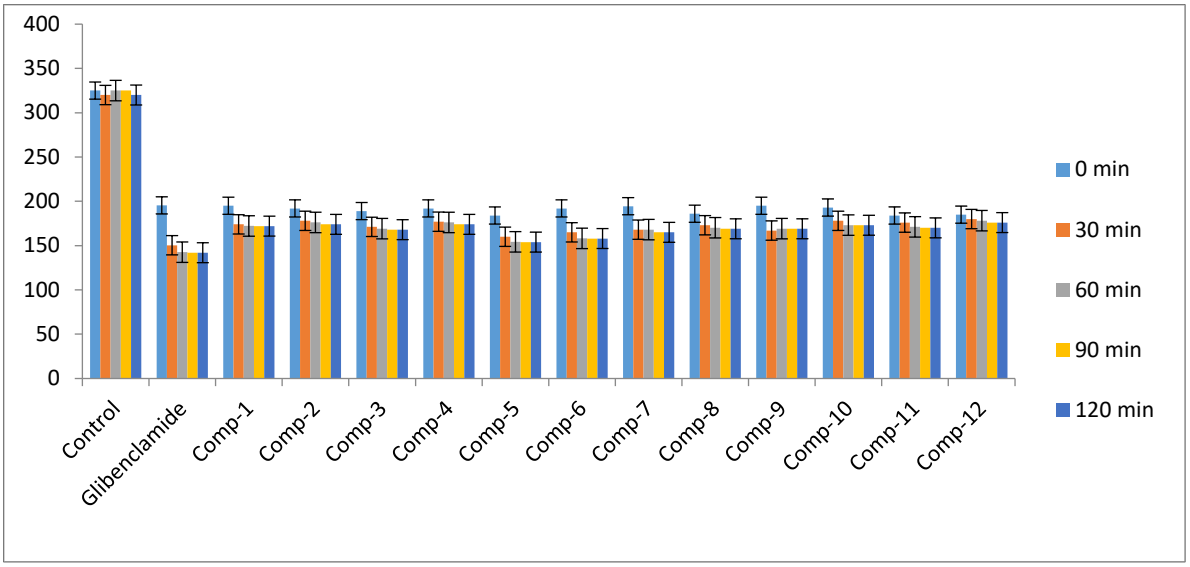


Figure 2. Anti-diabetic activity of synthesized 2-Styrylchromones

All the synthesized 2-styrylchromones were subjected for the elucidation of anti-diabetic activity. Hydroxylated 2-styrylchromones have demonstrated significant antidiabetic potential, particularly through the inhibition of key carbohydrate-hydrolyzing enzymes such as α-amylase and α-glucosidase. As per the study, compounds 5, 6, 7 and 9 are significant among all which shown in the figure-2. The anti-diabetic activity was attained because of presence functional groups like phenolic hydroxyl groups. The most effective compounds are 5, 6 when compared with the other test compounds. These are highly significant having percentage of inhibition >50. The obtained results were statistically analysed for the significance using student t-test through minitab software. All the compounds exhibits $p>0.05$ states that 12 compounds exhibit anti-diabetic acitivty when compared with the control.

The synthetic compounds those which contain more hydroxyl groups at particular orientation exhibited good anti-diabetic activity. The same has been revealed by molecular docking studies with the compounds those which are having good binding energy with α-amylase enzyme. Hydrogen bonding interactions between the compounds and their target enzymes play a critical role in modulating biological activity, with the spatial orientation of hydrogen bond donating or accepting groups markedly influencing inhibitory potency. So, the compounds with phenolic hydroxyl groups at 4' and 7 positions gave better anti-diabetic activity than the compounds with same functional groups at 3' and 6 positions. But, when these hydroxyl groups were replaced by methoxyl substituents, the slackening of anti-diabetic activity was observed.

The activity Studies have revealed that both the presence and positional orientation of hydroxyl groups on the core structure of chromone significantly influence the enzyme inhibitory profile, with OH-substituted derivatives exhibiting potent dual inhibition of enzymes. This will conclude that the above mentioned compounds are useful in treating diabetes.

3.3. Antioxidant Activity Studies

Oxidative stress occurs when reactive species cause damage to biological molecules, and antioxidants are agents that counteract this by either slowing or preventing oxidative reactions. These reactive species, which include both radicals and non-radicals like reactive oxygen species (ROS) and reactive nitrogen species (RNS), are naturally formed during various metabolic activities and serve vital roles in normal cellular function.[57,58] In an in vitro study, Filipe et al. developed a series of 2-styrylchromone compounds and assessed their antioxidant capacity by examining how effectively they inhibited copper ion (Cu^{2+})-mediated oxidation of human serum low-density lipoproteins (LDL), a model commonly used to simulate lipid oxidation processes.

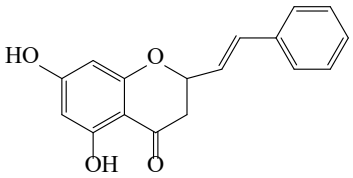


Figure 3. Structure of 5,7-dihydroxy-2-styrylchromone

All synthetic 2-styrylchromones were screened for their antioxidant activity by in vitro superoxide radical scavenging (NBT) method. As expected majority of compounds produced better activity than the reference compounds. The test results are depicted in the Figure-4.

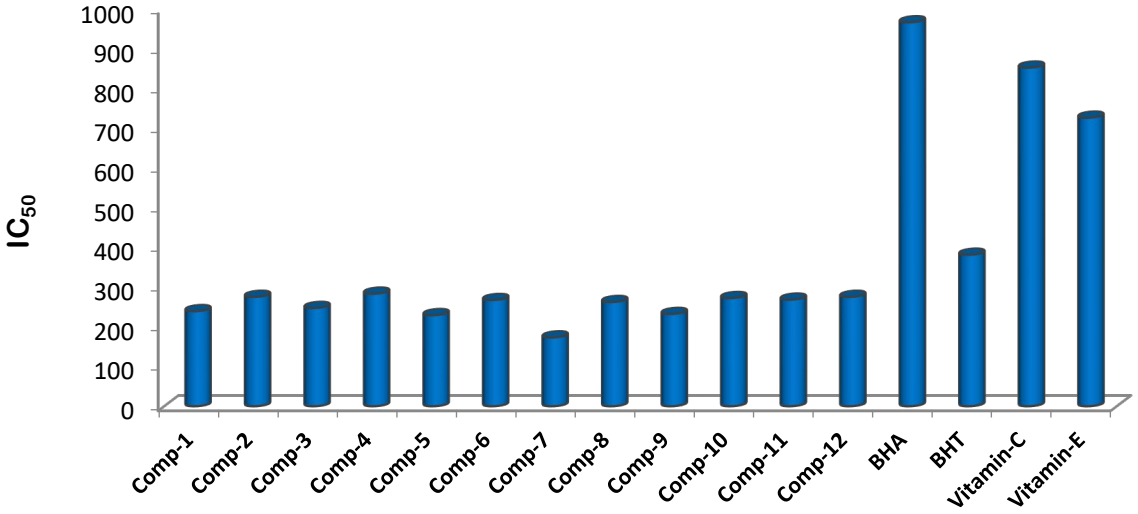


Figure 4. Antioxidant activity of 2-styrylchromones

Analysis of the results, supported by literature, demonstrates that 2-styrylchromones bearing phenolic hydroxyl groups possess superior antioxidant properties compared to standard commercial antioxidants. The findings suggest that the presence of multiple phenolic –OH groups significantly enhances antioxidant potential. For example, compounds such as 5, 7, and 9, which have a higher number of these hydroxyl groups, showed greater efficacy than those with fewer or none. This improved activity is likely due to the enhanced stability of the resulting aroxyl radicals through π-electron delocalization, allowing certain hydroxyl groups, depending on their position in the molecule to more readily donate protons and effectively neutralize reactive species.[59]

Interestingly, even compounds with the same number of hydroxyl and methoxy groups displayed differences in antioxidant activity, which can be attributed to the spatial arrangement of these substituents. The specific position of the hydroxyl groups has a profound influence on the compound's effectiveness. For instance, 2-styrylchromone 7, featuring hydroxyl groups at the 4' and 6 positions and a methoxy group at the 3' position, demonstrated greater antioxidant activity than compound 5, which contains hydroxyl groups at the 4' and 7 positions along with the same methoxy substitution. The presence of methoxy groups alone appeared to have little impact on activity.

Structure–activity relationship (SAR) studies offer valuable insights into the electronic properties of molecules and their interactions with free radicals, thereby elucidating the underlying mechanisms of their antioxidant activity. The presence of hydrogen donating (-OH) groups, electron releasing groups (-OMe) on both B and A rings and styryl group have been shown to markedly enhance antioxidant activity. Therefore, both the quantity and exact positioning of the substituents are critical determinants of the antioxidant potential of 2-styrylchromones.

4. Conclusion

We have screened the anti-diabetic activity and antioxidant activities of synthetic 2-styrylchromones by streptozotocin induced method and superoxide radical scavenging (NBT) method respectively. The compounds with more hydroxyl groups on benzene nuclei gave better activity than the compound having least or no phenolic hydroxyl groups. When the –OH group is replaced by –OMe, the activity of corresponding product became low. The activity was also influenced by orientation (position) of groups. The –OH groups at 4'and6 positions causes' enhanced activity than the positions at 3'and7. So, the biological activity of synthesized compounds depended not only on the number and nature of substituents but also on the orientations.

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