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Novel Chalcone Derivatives as Potential Antihyperglycemic Agents: Synthesis and Biological Evaluation

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ABSTRACT:
In this study, a series of chalcone derivatives (compounds 1-18) were synthesized using 4-fluoroacetophenone and various substituted benzaldehydes. The synthesis involved treating the mixture of 4-fluoroacetophenone and benzaldehyde derivatives in methanol with aqueous NaOH, resulting in the formation of the desired chalcones. These compounds were evaluated for their antihyperglycemic activity using two models: the sucrose-loaded model (SLM) and the streptozotocin (STZ)-induced β-cell damaged diabetic model in male Sprague-Dawley albino rats. The results indicated that several compounds exhibited significant antihyperglycemic activity. Compounds 3, 4, and 10 notably showed substantial activity in both models. Metformin and glibenclamide were benchmarks, with glibenclamide showing the highest activity. This study highlights the potential of certain chalcone derivatives as effective antihyperglycemic agents, providing a foundation for further research and optimization.

Keywords: Chalcones, Antihyperglycemic activity, Sucrose-loaded model, Streptozotocin-induced diabetes, 4-Fluoroacetophenone, Benzaldehyde derivatives.

INTRODUCTION-

Chalcones, a class of organic compounds characterized by an α,β-unsaturated carbonyl system, have garnered significant attention in synthetic drug discovery and development.[1,2,3] Their structural framework, consisting of two aromatic rings linked by a three-carbon α,β-unsaturated carbonyl system,[4,5] serves as a versatile scaffold for synthesizing a myriad of bioactive molecules.[6] This unique structural motif endows chalcones[7,8,9] and their derivatives[10] with a wide spectrum of biological activities[11], including anti-inflammatory,[12] anticancer[13],[17]antimicrobial[14], and antidiabetic properties.[15,16]

Despite the extensive pharmacological potential of chalcones, the search for effective therapeutic agents to combat Diabetes mellitus remains a formidable challenge.[18] Diabetes mellitus, a chronic metabolic disorder characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both, affects millions worldwide and poses significant

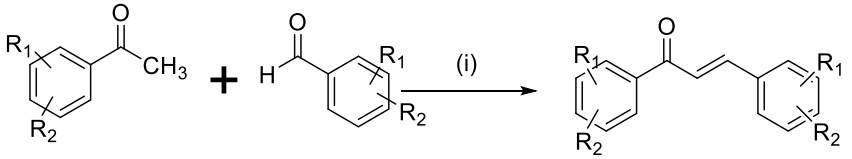
health risks.[19] The current therapeutic options for diabetes management, such as insulin therapy and oral hypoglycemic agents, often come with limitations and side effects, necessitating the continuous pursuit of novel and more effective antidiabetic agents.[20]
This study aimed to design and synthesize novel chalcone derivatives with the potential to exhibit promising antidiabetic activities. By leveraging the structural diversity of chalcones, we sought to create a library of compounds that could be evaluated for their efficacy as therapeutic agents in the management of diabetes. Specifically, chalcones were prepared from 4-fluoroacetophenone and various aldehydes, including salicylaldehyde, 4-hydroxybenzaldehyde, 4-chlorobenzaldehyde, 4-nitrobenzaldehyde, 3-nitrobenzaldehyde, and veratraldehyde. Through rigorous synthetic chemistry techniques and comprehensive biological evaluations, this research endeavored to identify chalcone-based molecules that could contribute significantly to the treatment of Diabetes mellitus.[21]

MATERIALS AND METHODS

Synthesis

The chalcones were synthesized using 4-fluoroacetophenone and various substituted benzaldehydes through a well-defined synthetic route. Initially, 0.256 g (0.02 mol) of 4-fluoroacetophenone was mixed with the appropriate benzaldehyde derivative in 10 mL of methanol. The benzaldehyde derivatives included salicylaldehyde, 4-hydroxybenzaldehyde, 4-chlorobenzaldehyde, 4-nitrobenzaldehyde, 3-nitrobenzaldehyde, and veratraldehyde. This mixture was treated with 5 g of aqueous NaOH and stirred at room temperature for 1.5 hours using a magnetic stirrer, resulting in a deep orange, thick liquid. The reaction mixture was then left overnight to ensure the reaction proceeded to completion.
The next day, the resulting residue was neutralized with 4N HCl, yielding a yellow precipitate. This precipitate was separated by filtration and dried in a desiccator over KOH. The dried chalcone powder was triturated with benzene in a mortar and pestle and subsequently filtered. The product was dissolved in hot methanol, and the resulting clear solution was diluted with an excess of water, leading to the precipitation of cream-yellow voluminous material. This precipitate was filtered, washed with water, and dried in desiccators. To obtain pure chalcone crystals, the dried product underwent purification by column chromatography.

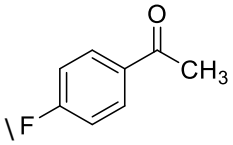
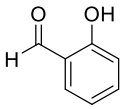
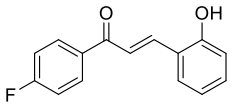
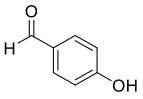
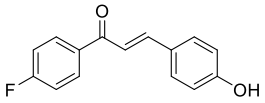
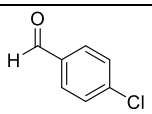
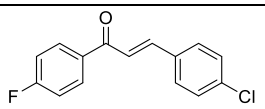
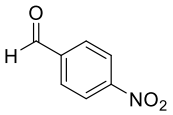
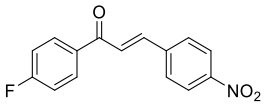
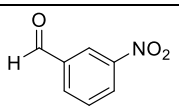
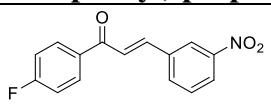
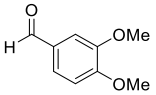
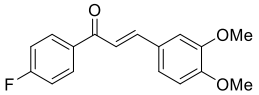
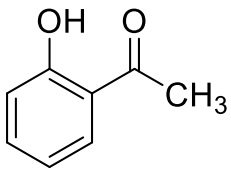
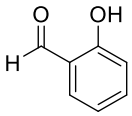
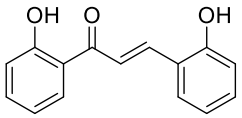
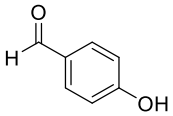
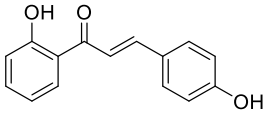
The structures of the synthesized chalcones were confirmed using various spectral data. Nuclear Magnetic Resonance (NMR) spectroscopy was employed to determine the chemical structure and purity of the compounds. Mass Spectrometry (MS) was used to identify the molecular weights and fragmentation patterns. Infrared (IR) spectroscopy provided information on the functional groups present in the chalcones.

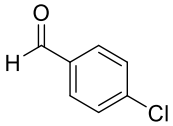
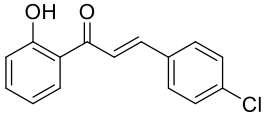
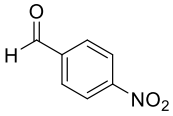
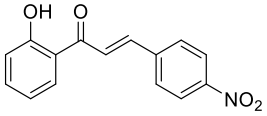
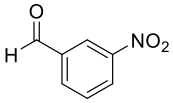
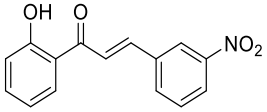
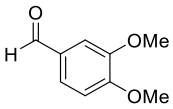
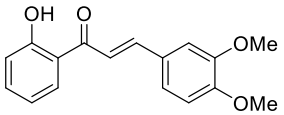
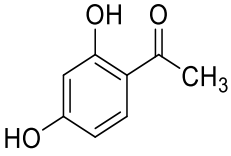
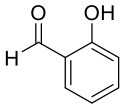
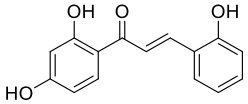
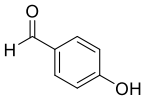
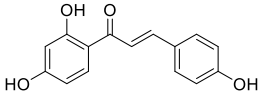
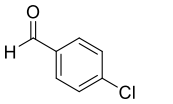
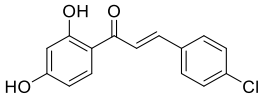
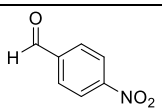
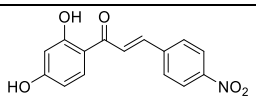
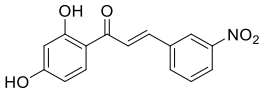


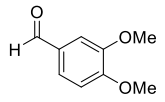
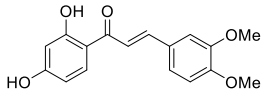
Reagents: (i) aqus.NaOH/KOH, Methanol, (ii)Methanol, Metal salts,

Fig-1 Synthetic Scheme

Table-1-Structure of Different Substrates, Reagent, and Product

S L No	Substrate	Reagent	Product
1	 4-fluroacetophenone	 2-hydroxy benzaldehyde	 **(E)-1-(4-fluorophenyl)-3-(2-hydroxyphenyl) prop-2-en-1-one**
2		 **4-hydroxy benzaldehyde**	 **(E)-1-(4-fluorophenyl)-3-(4-hydroxyphenyl) prop-2-en-1-one**
3		 **4-chloro benzaldehyde**	 **(E)-3-(4-chlorophenyl)-1-(4-fluorohenyl) prop-2-en-1-one**
4		 **4-nitro benzaldehyde**	 **(E)-1-(4-fluorophenyl)-3-(4-nitrophenyl) prop-2-en-1-one**
5		 3-nitrobenzaldehyde	 (E)-1-(4-fluorophenyl)-3-(3-nitrophenyl) prop-2-en-1-one
6		 **3,4 dimethoxy-benzaldehyde**	 **(E)-3-(3,4-dimethoxyphenyl)-1-(4-fluorophenyl)prop-2-en-1-one**
7	 2-hydroxy acetophenone	 2-hydroxy benzaldehyde	 **(E)-1, 3-bis(2-hydroxyphenyl) prop-2-en-1-one**
8		 **4-hydroxy benzaldehyde**	 **(E)-1-(2-hydroxyphenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one**

9		 **4-chloro benzaldehyde**	 **(E)-3-(4-chloroyphenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one**
10		 **4-nitro benzaldehyde**	 **(E)-1-(2-hydroxyphenyl)-3-(4-nitrophenyl)prop-2-en-1-one.**
11		 3-nitrobenzaldehyde	 **(E)-1-(2-hydroxyphenyl)-3-(3-nitrophenyl)prop-2-en-1-one**
12		 **3,4 dimethoxy-benzaldehyde**	 **(E)-3-(3,4-dimethoxyphenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one**
13		 2-hydroxy benzaldehyde	 **(E)-1-(2,4-dihydroxyphenyl)-3-(2-hydroxyphenyl)prop-2-en-1-one**
14		 **4-hydroxy benzaldehyde**	 **(E)-1-(2,4-dihydroxyphenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one**
15		 **4-chloro benzaldehyde**	 **(E)-3-(4-chlorophenyl)-1-(2,4-dihydroxyphenyl)prop-2-en-1-one**
16		 **4-nitro benzaldehyde**	 **(E)-1-(2,4-dihydroxyphenyl)-3-(4-nitrophenyl)prop-2-en-1-one**
17		 3-nitrobenzaldehyde	 **(E)-1-(2,4-dihydroxyphenyl)-3-(3-nitrophenyl)prop-2-en-1-**

			one
18		 **3,4 dimethoxy-benzaldehyde**	 **(E)-1-(2,4-dihydroxyphenyl)-3-(3,4-dimethoxyphenyl)prop-2-en-1-one**

Pharmacological Evaluation-

All synthesized compounds (1-18) were evaluated for antihyperglycemic activity using two models: the sucrose-loaded model[22] (SLM) and the streptozotocin (STZ)-induced β-cell damaged diabetic model[23] in male Sprague-Dawley albino rats.

Sucrose-Loaded Rat Model (SLM)

In the sucrose-loaded rat model (SLM), the compounds were tested for their effect on the glucose tolerance curve in rats with an average body weight of 160 ± 20 g. This model indirectly measures antihyperglycemic activity. After 16 hours of fasting, the blood glucose levels of all animals were checked using Glucostrips (Dr.Trust, Amazon, India). Animals with blood glucose levels between 60–80 mg/dl (3.33–4.44 mM) were divided into groups of five to six animals each. The experimental groups received an oral suspension of the synthetic compounds (prepared in 1.0% gum acacia) at a dosage of 100 mg/kg body weight, while the control group received an equal amount of 1.0% gum acacia. A sucrose load (10.0 g/kg) was administered orally to each animal 30 minutes after the test sample or vehicle administration. Blood glucose levels were measured at 30, 60, 90, and 120 minutes post-sucrose administration. During the experiment, food was removed from the cages, but water was allowed. The glucose tolerance of each animal was quantified using the Area Under Curve (AUC) method. The percentage of antihyperglycemic effect was determined by comparing the AUC of the experimental and control groups. Samples that showed significant inhibition of postprandial hyperglycemia (AUC) were considered active.

Streptozotocin-Induced Diabetic Rats (STZ)

Male Sprague-Dawley albino rats with an average body weight of 140 ± 20 g, and blood glucose levels between 60–80 mg/dl, were selected for the STZ-induced diabetic model. Streptozotocin (Sigma Aldrich) was dissolved in 100 mM citrate buffer (pH 4.5) and freshly prepared solution was injected intraperitoneally at a dose of 60 mg/kg body weight into overnight fasted animals. Blood glucose levels were checked after 48 hours using Glucostrips (Dr.Trust, Amazon, India), and animals with blood glucose levels between 180–270 mg/dl were considered suitable for the experiment. These diabetic animals were divided into groups, and their blood glucose levels were checked again on the day of the experiment (Day 3). Animals with similar blood glucose profiles were divided into groups of five to six animals each. The experimental groups received an oral suspension of the test sample (prepared in 1% gum acacia) at 100 mg/kg body weight, while the control group received an equal amount of 1% gum acacia. A sucrose load (2.5 g/kg) was administered orally to each animal 30 minutes after the test sample or vehicle administration. Blood glucose levels were measured at 30, 60, 90, 120, 180, 240, 300 minutes, and 24 hours post-sucrose administration. During the experiment, food was removed from the cages, but water was allowed. The percentage fall in blood glucose levels due to the test sample was calculated using the AUC method. The average reduction in AUC in the experimental group compared

to the control group indicated the percentage of antihyperglycemic activity. Metformin and glybenclamide, which act through different mechanisms, were used as standard drugs to compare the activity of the compounds.

RESULT AND DISCUSSION-

In this study, we synthesized and characterized a series of eighteen compounds, and their properties were evaluated through various analytical techniques and results are given in **Table2**. The compounds exhibited solid crystalline or powder forms, with yields consistently around 80-90%. The melting points ranged from 411.55 K to 691.16 K, indicating thermal stability. Mass spectrometry revealed the molecular weights of the compounds, with [M+1] peaks varying from 242 to 337, confirming the expected molecular structures.

The IR spectra for these compounds showed characteristic absorption bands, including peaks around 3200 cm^{-1}, indicating the presence of hydroxyl groups. Other notable peaks included 1039 cm^{-1}, 1500 cm^{-1}, 1600 cm^{-1}, and 1690 cm^{-1}, corresponding to various functional groups within the molecules. These consistent IR peaks across different compounds suggest similar structural motifs and functional groups, reinforcing the successful synthesis of the intended compounds.

The ^{1}H NMR spectra provided further insight into the chemical environment of the protons within the molecules. The spectra consistently displayed signals corresponding to aromatic protons, with multiplet patterns indicating the presence of substituted aromatic rings. For instance, compound 1 showed signals at δ 9.90, 8.96, and 7.89, corresponding to hydroxyl, β-H, and α-H protons, respectively. These peaks were similarly observed in other compounds, although slight shifts in chemical shifts and coupling constants were noted, reflecting the differences in substitution patterns on the aromatic rings. Compounds 5 and 6 exhibited additional methoxy (OMe) signals at δ 3.85, further distinguishing them from the other compounds.

The variation in the NMR spectra highlights the subtle structural differences among the compounds, which can significantly impact their biological activity. Compounds with different substitution patterns on the aromatic rings, such as methoxy or hydroxyl groups, may interact differently with biological targets, potentially influencing their pharmacological properties.

Table 2 Characterization and Spectral Analysis of Compounds (1 to 18)

1	Solid crystal, Yield: 80%, MS: 243(M+1). m.p,: 480.83K IR(KBr) 1039, 1500, 1600, 1690, 3200, ^{1}H NMR (500 MHz,) δ 9.90 (s, 1H, OH), 8.96 (d, *J* = 16.61 Hz, 1H, *β*H), 7.89 (d, *J* = 15.49 Hz, 1H, *α*H), 7.83 (d, *J*=8.5 1H, 6-H), 7.40 (d, *J* = 8.9 Hz, 1H, 5-H), 7.42 (d, *J* = 8.9 Hz, 1H, 3-H), 7.82 (d, *J*=8.5 1H, 2-H), 7.04 (m, 1H 4'-H), 7.49 (d, J=8.4 1H, 6'-H),6.98 (m, 2H, 4', 5'- H), 6.70 (d, *J*=8.4 1H, 3'-H)
2	Solid, Yield: 80%, MS: 243(M+1). m.p, 480.83K. IR(KBr) 700, 1039, 1500, 1600, 1690, 3200, ^{1}H NMR (500 MHz,) δ 9.24 (s, 1H, OH), 8.06 (d, *J* = 21.8 Hz, 1H, *β*H), 7.9 (d, *J* = 7.9 Hz, 1H, *α*H), 7.83 (dd, *J*=8.5, 2H, 2-6 H), 7.49 (dd, *J* = 8.9, Hz, 2H, 3'- 5' H), 7.42 (dd, *J* = 8.9, Hz, 2H, 2'-6' H), 6.58 (d, *J*=8.5, 2H, 3'- 5' H),
3	Solid, Yield: 80%, MS: 260(M+1). m.p, 411.55K. FT-IR (KBr)(cm^{-1}) 700, 745, 1039, 1500, 1600, 1690, ^{1}H NMR (500 MHz,) δ 9.24 (s, 1H, OH), 8.06 (d, *J* = 21.8 Hz, 1H, *β*H), 7.9 (d, *J* = 7.9 Hz, 1H, *α*H), 7.83 (dd, *J*=8.5, 2H, 2'-6' H), 7.49 (dd, *J* = 8.9, Hz, 2H, 3- 5H), 7.42 (dd, *J* = 8.9, Hz, 2H, 2'-6' H), 6.58 (d, *J*=8.5, 2H, 3'- 5' H).
4	Solid, Yield: 80%, MS: 271(M+1). m.p, 411.55K. IR(KBr) 700, 1039, 1339, 1500, 1600, 1690, ^{1}H NMR (500 MHz,), δ 8.06 (d, *J* = 21.8 Hz, 1H, *β*H), 7.9 (d, *J* = 7.9 Hz, 1H, *α*H), 7.83 (dd, *J* =8.5, 2H, 2-6, H), 7.49 (dd, *J* = 8.9, Hz, 2H, 3-

	5,H), 7.42 (dd, *J* = 8.9, Hz, 2H, 2'-6' H), 6.58 (d, *J*=8.5, 2H, 3'- 5'H),
5	Solid, Yield: 80%, MS: 271(M+1). m.p, 411.55K. IR(KBr) 700, 1039, 1339, 1500, 1600, 1690, ^{1}H NMR (500 MHz,) δ 8.31(s,1H, 2'- H), 8.14(d, *J* = 8.9, Hz, 1H, 4'- H,) 8.06 (d, *J* = 21.8 Hz, 1H, *β*H), 7.9 (d, *J* = 7.9 Hz, 1H, *α*H), 7.83 (dd, *J*=8.5, 2H, 2-6, H), 7.49 (dd, *J* = 8.9, Hz, 2H, 3- 5,H), 7.92 (d, *J* = 8.9, Hz, 1H, 6'- H), 7.69(m, 1H,5'-H).
6	Solid, Yield: 80%, MS: 271(M+1). m.p, 411.55K. IR(KBr) 700, 1039, 1339, 1500, 1600, 1690, 2800, ^{1}H NMR (500 MHz,) δ 8.96 (d, *J* = 17.8 Hz, 1H, *β*H), 7.89 (d, *J* = 17.9 Hz, 1H, *α*H), 7.83 (dd, *J*=8.5 2H, 2- 6,H), 7.48 (dd, *J* = 8.9 Hz, 2H, 3- 5,H), 7.23(s,1H, 2'H), 7.16(d, *J* = 8.9 Hz, 1H, 5'- H), 7.06 (d, *J* =8.5 1H, 6' H),3.85,(s, 6H, OMe).
7	Solid crystal, Yield: 90%, MS: 242(M+1). mp,579.44K. IR(K Br): 243(M+1). m.p,: 480.83K IR(KBr) 600-700, 1500, 1600, 3200, ^{1}H NMR (500 MHz,) δ 12.50 (s, 1H, OH), 10.29 (s, 1H, OH), 7.87 (d, *J* = 16.61 Hz, 1H, *β*H), 7.84 (d, *J* = 15.49 Hz, 1H, *α*H), 8.05 (dd, *J* = 11.9, 3.8 Hz, 4H, 4-5, 4'-5'H), 7.78 (dd, *J* = 7.7 Hz, 2H, 3-6H), 6.89 (dd, *J* = 5.4 Hz, 2H, 3'-6'H).
8	Solid crystal, Yield: 90%, MS: 242 (M+1). m.p,579.44K. IR(KBr) 600-700, 1500, 1600, 3200, ^{1}H NMR (500 MHz,) δ 12.50 (s, 1H, OH), 9.29 (s, 1H, OH), 7.87 (d, *J* = 16.61 Hz, 1H, *β*H), 7.84 (d, *J* = 15.49 Hz, 1H, *α*H), 8.05 (dd, *J*= 11.9, 3.8 Hz, 2H), 7.78 (d, *J* = 7.7 Hz, 1H), 6.89 (d, *J* = 5.4 Hz, 1H), 7.78 (d, *J* = 7.7 Hz, 2H), 6.98 (d, *J* = 7.7 Hz, 2H)
9	Solid crystal, Yield: 90%, MS: 260 (M+1). m.p,510.55K. IR(KBr) 600-700, 745, 1500, 1690, 3200, ^{1}H NMR (500 MHz,) δ 12.50 (s, 1H, OH), 7.87 (d, *J* = 16.61 Hz, 1H, *β*H), 7.84 (d, *J* = 15.49 Hz, 1H, *α*H), 8.05 (dd, *J* = 11.9, 3.8 Hz, 2H), 7.78 (d, *J* = 7.7 Hz, 1H), 6.89 (d, *J* = 5.4 Hz, 1H). 7.78 (d, *J* = 7.7 Hz, 2H), 7.68 (d, *J* = 7.7 Hz, 2H).
10	Solid crystal, Yield: 90%, MS: 271(M+1). m.p,411.55K. IR(KBr) 700, 1339, 1500, 1600, 1690, 3200. ^{1}H NMR (500 MHz,) δ 12.50 (s, 1H, OH), 7.87 (d, *J* = 16.61 Hz, 1H, *β*H), 7.84 (d, *J* = 15.49 Hz, 1H, *α*H), 8.05 (dd, *J* = 11.9, 3.8 Hz, 2H), 7.78 (d, *J* = 7.7 Hz, 1H), 6.89 (d, *J* = 5.4 Hz, 1H). 8.08 (d, *J* = 7.7 Hz, 2H), 8.48 (d, *J* = 7.7 Hz, 2H).
11	Solid crystal, Yield: 90%, MS: 271(M+1). m.p,411.55K. IR(KBr) 600-700, 1339, 1500, 1600, 1690, 3200. ^{1}H NMR (500 MHz,) δ 12.50 (s, 1H, OH), 7.87 (d, *J* = 16.61 Hz, 1H, *β*H), 7.84 (d, *J* = 15.49 Hz, 1H, *α*H), 8.05 (d, *J* = 11.9, 3.8 Hz, 1H), 7.78 (dd, *J* = 7.7 Hz, 2H), 6.89 (d, *J* = 5.4 Hz, 1H). 8.31 (S,1 H,), 8.15 (d, *J* = 7.7 Hz, H), 7.68 (d, *J* = 7.7 Hz, 1H), 7.60 (d, *J* = 7.7 Hz, 1H).
12	Solid crystal, Yield: 80%, MS: 337 (M+1). m.p, 559.76K. IR(KBr) 600-700, 1339, 1500, 1600, 1690, 2800, 3200 ^{1}H NMR (500 MHz,) δ 12.50 (s, 1H, OH), 7.87 (d, *J* = 16.61 Hz, 1H, *β*H), 7.84 (d, *J* = 15.49 Hz, 1H, *α*H), 8.05 (dd, *J* = 11.9, 3.8 Hz, 1H), 7.78 (d, *J* = 7.7 Hz, 2H), 6.89 (d, *J* = 5.4 Hz, 1H). 7.23(s, 1H), 7.16(d, *J* = 8.9 Hz, 1H, B5 H), 7.06 (d, *J* =8.5 1H, 6'- H), 3.85,(s, 6H, OMe).
13	Powder, Yield: 80%, MS: 256 (M+1). m.p,691.16K. IR(KBr) 600-700, 1500, 1600, 3200, ^{1}H NMR (500 MHz,) δ 12.50 (s, 1H, OH), 10.29 (s,1H, OH), 10.08 (s, 1H, OH), 7.87 (d, *J* = 16.61 Hz, 1H, *β*H), 7.84 (d, *J* = 15.49 Hz, 1H, *α*H), 7.12(d, *J*=8.15H_Z 6-H), 6.98(s, 1H, 2-H), 6.68 (d, *J*=8,10H_Z 5-H), 7.04 (m, 1H 4-'H), 7.49 (d, *J*=8.4 1H, 6'-H), 6.98 (m, 1H, 5'- H), 6.70 (d, *J*=8.4 1H, 3'-H),

14	Yield: 80%, MS: 256 (M+1). m.p,691.16K. IR(KBr) 600-700, 1500, 1600, 3200. ^{1}H NMR (500 MHz,) δ 12.50 (s, 1H, OH), 10.29 (s, 1H, OH), 10.08 (s, 1H, OH), 7.87 (d, *J* = 16.61 Hz, 1H, *β*H), 7.84 (d, *J* = 15.49 Hz, 1H, *α*H), 7.12(d, *J* =8.15H$_Z$ 1H, 6-H), 6.98(s, 1H, 3-H), 6.68 (d, *J* =8,10H$_{Z,,}$ 1H, 5-H), 7.78 (d, *J* = 7.7 Hz, 2H, 2'-6'H), 6.98 (d, *J* = 7.7 Hz, 2H, 3'-5'H).
15	Yield: 80%, MS: 256 (M+1). m.p,691.16K. IR(KBr) 600-700, 745, 1500, 1600, 3200, ^{1}H NMR (500 MHz,) δ 12.50 (s, 1H, OH), 10.90 (s, 1H, OH), 7.87 (d, *J* = 16.61 Hz, 1H, *β*H), 7.84 (d, *J* = 15.49 Hz, 1H, *α*H), 7.12(d, *J* =8.15H$_Z$ 1H, 6-H), 6.98(s, 1H, 3-H), 6.68 (d, *J* =8,10H$_{Z,}$ 1H , 5-H), 7.78 (d, *J* = 7.7 Hz, 2H, 2'-6' H), 7.68 (d, *J* = 7.7 Hz , 2H, 3'-5'H).
16	Yield: 80%, MS: 256 (M+1). m.p,691.16K. IR(KBr) 600-700,1339,1500, 1600, 3200, ^{1}H NMR (500 MHz,) δ 12.50 (s, 1H, OH), 10.90 (s, 1H, OH), 7.87 (d, *J* = 16.61 Hz, 1H, *β*H), 7.84 (d, *J* = 15.49 Hz, 1H, *α*H), 7.12(dd, *J*=8.15H$_Z$, 2H, 2'-6'-H), 6.98(S, 1H, 2-H, 3'-5' H), 6.68 (d, *J* =8,10H$_{Z,}$, 1H,5-H), 8.08 (d, *J* = 7.7 Hz, 1H, 6-H), 6.48 (s, 1H, 2-H).
17	Powder, Yield: 75%, MS: 256 (M+1). m.p,691.16K. IR(KBr) 600-700,1339,1500, 1600, 3200, ^{1}H NMR (500 MHz,) δ 12.50 (s, 1H, OH), 10.90 (s, 1H, OH), 7.87 (d, *J* = 16.61 Hz, 1H, *β*H), 7.84 (d, *J* = 15.49 Hz, 1H, *α*H), 7.12(d, *J*=8.15H$_Z$, 1H 6-H), 6.98(s, 1H, 3-H), 6.68 (d, *J*=8,10H$_{Z,}$ 5-H), 8.31 (s, 1H, 2'-H), 8.15 (d, *J* = 7.7 Hz,1H, 4-'H), 7.68 (d, *J* = 7.7 Hz, 1H,5-'H), 7.60 (d, *J* = 7.7 Hz, 1H, 6-'H).
18	. Powder, Yield: 80%, MS: 256 (M+1). m.p, 691.16K. IR(KBr) 600-700,1500, 1600, 2800, 3200, ^{1}H NMR (500 MHz,) δ 12.50 (s, 1H, OH), 10.90 (s, 1H, OH), 7.87 (d, *J* = 16.61 Hz, 1H, *β*H), 7.84 (d, *J* = 15.49 Hz, 1H, *α*H), 7.12(d, *J*=8.15H$_Z$ 6-H), 6.98 (s, 1H, 3-H), 6.68 (d, *J*=8,10H$_{Z,}$ 5-H), 7.23(s, 1H, 2'-H), 7.16(d, *J* = 8.9 Hz, 1H, 5'- H), 7.06 (d, *J*=8.5 1H, 6'- H), 3.85,(s, 6H, OMe).

The antihyperglycemic activity of the synthesized compounds (1-18) was evaluated using two different models: the STZ-induced diabetic model and the SLM. The results are presented in the provided **Table-3** and indicate varying levels of activity across the different compounds.Compound 3 demonstrated significant antihyperglycemic activity in both models, with 23% in the STZ model and 21.1% in the SLM. Similarly, compound 4 showed high activity, with 20% in the STZ model and an impressive 32% in the SLM. These results suggest that compounds 3 and 4 are potent candidates for further investigation due to their consistent performance across both models.

On the other hand, compound 10 also showed substantial activity, with 21.3% in the STZ model and 24.5% in the SLM, indicating its potential as an effective antihyperglycemic agent. Compound 11 followed with notable activity, showing 13.5% in the STZ model and 20.4% in the SLM.Metformin, a standard antihyperglycemic drug, displayed 19.1% activity in the STZ model and 12.9% in the SLM, serving as a benchmark for comparing the efficacy of the synthesized compounds. Glibenclamide, another standard drug, showed the highest activity among all tested compounds, with 29% in the STZ model and 33.7% in the SLM.

Some compounds exhibited significant activity in one model but not the other. For instance, compound 7 showed no activity (NIL) in the STZ model but had a high activity of 38% in the SLM. Conversely, compound 12 was inactive (NIL) in the STZ model but showed 19.5% activity in the SLM.Several compounds, such as 1, 2, and 14, displayed moderate activity in both models, indicating their potential but suggesting the need for further optimization. Compound 5 was not determined (ND) in the STZ model but showed low activity in the SLM (6.68%).Compounds with insignificant activity (NIL) in both models include 6, 7, and 18, indicating they may not be promising candidates for antihyperglycemic treatment.

Overall, the comparative analysis of the antihyperglycemic activity of the synthesized compounds highlights compounds 3, 4, and 10 as the most promising candidates, showing significant activity in both models. Further studies and optimizations are needed to fully understand the potential of these compounds as effective antihyperglycemic agents.

Table-3-*In vivo* antihyperglycemic activity of chalcones derivatives (1-18) in STZ and SLM rat models

Compounds	**% Antihyperglycemic activity**	
	STZ	SLM
1	18.2	14.5
2	6.18	10.8
3	23	21.1
4	20	32
5	ND	6.68
6	NIL	11.8
7	NIl	38
8	11.3	20
9	ND	5.03
10	21.3	24.5
11	13.5	20.4
12	NIL	19.5
13	3.4	18.4
14	11.2	14.5
15	2.35	3.54
16	6.5	7.54
17	4.5	2.54
18	NIL	4.56
Metformin	19.1	12.9
Glybenclamide	29	33.7

ND, Not Determined; NIL, Insignificant activity

Conclusion

In this study, a series of chalcone derivatives (compounds 1-18) were synthesized using 4-fluoroacetophenone and various substituted benzaldehydes through a well-defined synthetic route. The synthesis involved mixing 4-fluoroacetophenone with different benzaldehyde

derivatives in methanol, followed by treatment with aqueous NaOH and stirring at room temperature to yield the desired chalcones.The synthesized compounds were then evaluated for their antihyperglycemic activity using two models: the sucrose-loaded model (SLM) and the streptozotocin (STZ)-induced β-cell damaged diabetic model in male Sprague-Dawley albino rats. The results revealed that several compounds exhibited significant antihyperglycemic activity.

Among the tested compounds, compounds 3 and 4 emerged as the most promising candidates, demonstrating substantial antihyperglycemic activity in both models, with 23% and 20% in the STZ model, and 21.1% and 32% in the SLM, respectively. Compound 10 also showed notable activity, with 21.3% in the STZ model and 24.5% in the SLM, indicating its potential as an effective antihyperglycemic agent.Other compounds, such as 11, 12, and 14, displayed moderate activity, suggesting the need for further optimization. The standard drugs metformin and glybenclamide were used as benchmarks, with glybenclamide showing the highest activity among all tested compounds.The comparative analysis of the antihyperglycemic activity highlighted the potential of certain chalcone derivatives, particularly compounds 3, 4, and 10, as effective antihyperglycemic agents. The study's findings provide a strong foundation for further investigation and optimization of these compounds to develop new treatments for hyperglycemia and diabetes.

In conclusion, the synthesis and evaluation of these chalcone derivatives offer promising insights into the development of novel antihyperglycemic agents, with several compounds showing significant potential for further research and development.

ABBREVIATION:

SLM: Sucrose-Loaded Model
STZ: Streptozotocin
NaOH: Sodium Hydroxide
AUC: Area Under Curve
4-FAP: 4-Fluoroacetophenone
GLU: Glucose
MeOH: Methanol
GUM: Gum Acacia
ND: Not Determined
NIL: Insignificant Activity

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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