ISSN: 2754-5008

Journal of Pharmaceutical Research and Reports

SCIENTIFIC Research and Community

Research Article

Open Access

Solvent-Free Synthesis of Five Membered Heterocycles from Chalcones and their Biological Evaluation for Anti-Hyperglycaemic Activity

Anil Kumar*, Mukesh Kumar, Vikas Yadav, Manoj Kumar and Anuraj

Research Division, Department of Chemistry, Sahu Jain College, Najibabad, UP, India

ABSTRACT

The development of environmentally friendly and efficient protocol for the synthesis of heterocyclic compounds is the current demand of synthetic community. Solvent-free synthesis has emerged as a sustainable approach reducing waste generation, and minimizing environmental impact. In this connection, we have developed a solvent-free method for the construction of five membered heterocycles i.e. isoxazoline and pyrazoline from α, β-unsaturated carbonyl compounds and Hydrazine/hydroxylamine hydrochloride. This protocol involves the [3+2] cycloaddition reaction between α, β-unsaturated carbonyl compounds and hydrazine hydrochloride/hydroxylamine hydrochloride under solvent free conditions to provide the substituted isoxazoline and pyrazoline in excellent yields. The synthesized compounds were characterized through 1H NMR, 13C NMR, Mass spectral data and IR. These newly synthesized compounds were screened for their antihyperglycemic activity using sucrose loaded diabetic model. Isoxazoline derivatives offered potent antihyperglycemic response than correspondence pyrazoline derivatives. Compounds bearing isoxazoline ring II A and II E showed maximum % fall of blood glucose level than control group which was comparable to the standard drug metformin. The newer compounds VIA, VIB, and VIC also evaluated for their anti-hyperglycemic activities, compound VIC showed appreciable response (62.5% antihyperglycemic activity).

***Corresponding author**

Anil Kumar, Research Division, Department of Chemistry, Sahu Jain College, Najibabad, UP, India.

Received: December 28, 2025; **Accepted:** January 03, 2025; **Published:** January 10, 2025

Keywords: Anti-hyperglycemic, Chalcone, Heterocyclic, Isoxazoline, Pyrazoline

Introduction

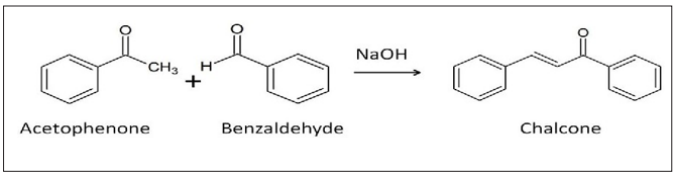
Diabetes Mellitus (DM), commonly called diabetes, is a group of metabolic disorders and diseases characterized by high blood sugar levels over prolonged period. The symptoms of high blood glucose (sugar) levels include increased thirst, increased hunger, and frequent urination [1]. Diabetes can cause many complications if not carefully treated and controlled. So far, there is no known cure for diabetes. Acute complications can include hyperosmolar hyperglycemic state, diabetic ketoacidosis, or death [2]. Serious long-term complications are cardiovascular disease, stroke, foot ulcers, damage to the eyes, and chronic kidney disease. Diabetes is as a result of either pancreas not making enough insulin, or cells of the body improperly responding to the insulin produced [3]. There are three main types of diabetes, and a collection of "other specific types". Diabetes type 1 results from failure of pancreas to produce enough insulin caused by loss of beta cells. Diabetes type 1 was earlier referred to as the juvenile diabetes or Insulin-Dependent Diabetes Mellitus (IDDM). The loss of beta cells is as a result of an autoimmune response [4]. The cause of the autoimmune response is unknown [1]. Type 2 diabetes condition where cells fail to properly respond to insulin. As the disease progresses, lack of insulin may develop. This form was previously known as "adult-onset diabetes" or "Non-Insulin- Dependent Diabetes Mellitus" (NIDDM). The most common cause is combination of excessive body weight (obesity) and insufficient exercise [1]. Gestational diabetes is the third most common form, and occurs when a pregnant woman without previous history of diabetes mellitus develops high blood sugar levels [1]. Prevention and treatment of diabetes involve maintaining healthy diet, regular physical exercise, normal body weight, and also avoiding tobacco use. Control of blood pressure, eye care, and maintaining proper foot care are important for individuals with the disease [1]. Type 1 diabetes must be properly managed with insulin injections. The type 2 diabetes may be treated with medication with or without insulin. The Insulin and some oral medication can cause low blood sugar [5]. Weight loss surgery in individuals with obesity is sometimes very effective measure in people with type 2 diabetes. Gestational diabetes often resolves after birth of the baby [6]. Diabetic patients are advised to avoid sugars and sugary soft drinks. They may instead opt for diet soft drinks sweetened with sugar substitutes such as sugar alcohols which contribute little or no-calorie. In 2017, an estimated 425 million individuals had diabetes worldwide, with type 2 diabetes making up around 90% of the cases [7-9]. This represents 8.8% of adult population, with equal rates in both men and women. Trends suggest that the rates will continue to rise [2]. Diabetes at least doubles an individual's risk of early death. In 2017 alone, diabetes resulted in about 3.2 to 5.0 million deaths [2]. The global economic costs of diabetes-related health expenditures in 2017 were estimated at US$727 billion [2]. Average medical expenditures among individuals with diabetes are around 2.3 times higher [10].

Protein tyrosine phosphatase 1B (PTP1B) has a key role in the pathogenesis and development of a variety of diseases.Protein tyrosine phosphatase 1B (PTP1B), a non-transmembrane

phosphatase, has a major role in a variety of signalling pathways, including direct negative regulation of classic insulin and leptin signalling pathways, and is implicated in the pathogenesis of several cardiometabolic diseases and cancers. As such, PTP1B has been a therapeutic target for over two decades, with PTP1B inhibitors identified either from natural sources or developed throughout the years. Some of these inhibitors have reached phase I and/or II clinical trials in humans for the treatment of type 2 diabetes mellitus, obesity and/or metastatic breast cancer [11].

Enzyme protein tyrosine phosphatase 1B (PTP1B) play a major role in insulin signaling pathway, PTP1B modify insulin sensitivity and de phosphorylation of insulin receptor resulting initiation of pathogenesis of Type II diabetes [12]. A literature study also revealed that PTPB1 a class I phosphatase which is a widely expressed nonreceptor PTP capable of inhibiting several membrane receptor tyrosine kinases, such as the epidermal growth factor receptor (EGFR), the macrophage colony stimulating factor receptor (MCSFR), the platelet-derived growth factor receptor, the insulin receptor (IR) and the insulin-like growth factor receptor-1 [13-19].

Chalcone is a unique, α, β-unsaturated carbonyl with biologically active properties and is a precursor of various heterocyclic compounds. Chalcones are considered as mediators for various synthesis of therapeutic compounds. For decades, chalcones have attracted special attentions among researchers due to their pharmaceutical properties and easy preparation [20]. Chalcones are generally prepared by condensation reactions via base or acid catalysis. Although chalcones are a type of easily synthesized α,β-unsaturated ketone, an increasing number of new techniques and procedures have recently been reported due to their interesting biological activities and the development of various catalysts or reaction conditions [21]. Among different methods, we have: Cross Aldol Condensation (Claisen-Schmidt), Meyer-Schuster Rearrangement, Deamination of Aziridine, Debromination of Vicinal Dibromides, Oxidation of Benzylic Alcohols, Wittig Reaction, Coupling Reactions, Dehydrogenation and Deoxygenation. However, the Claisen-Schmidt condensation remains the best known as it offers preparations of chalcones by reaction of acetophenone and benzaldehyde [20,21].



Biological Activity of Chalcones and their Derivatives

Chalcones and their derivatives possess diversified biological activities; therefore, researchers paid great attention towards this molecule for searching potent therapeutic agents against various diseases [22,23]. Literature reported several chalcones and their derivative that have shown promise to inhibit cyclooxygenase (COX) [24-30]. In a study to assess the anti-inflammatory effect, new chalcone derivatives using carrageenan-induced hind paw edema model, the results showed that 5′- chloro-2′-hydroxy-4′6′-dimethyl-3, 4, 5- trimethoxychalcone (1) exhibited the most potent anti- inflammatory activity with a 90% inhibition of edema [25].

Several synthetic chalcones have been reported in vitro to have potential inhibitory activity against α-glucosidase or α-amylase [31-33]. In Vivo, several authors have evaluated the anti-hyperglycemic activity of synthetic chalcones in streptozotocin-induced diabetic rats [34-44]. It was found that these compounds have a moderate to potential ability to reduce blood sugar.

Considering these all facts in present work it was planned to synthesize novel heterocyclic derivatives of chalcones as PTP1B inhibitors and antihyperglycemic agents.

Experimental

Material

All the required and reference compounds were purchased from Aldrich chemical. Ethanol, glacial acetic acid and all other regents were purchased from S.D. Fine chem. Analytical TLC was performed on pre coated plastic sheet of selical gel. G/UV 254 of 0.2 mm thickness (Macherey-Nagel, Germany).

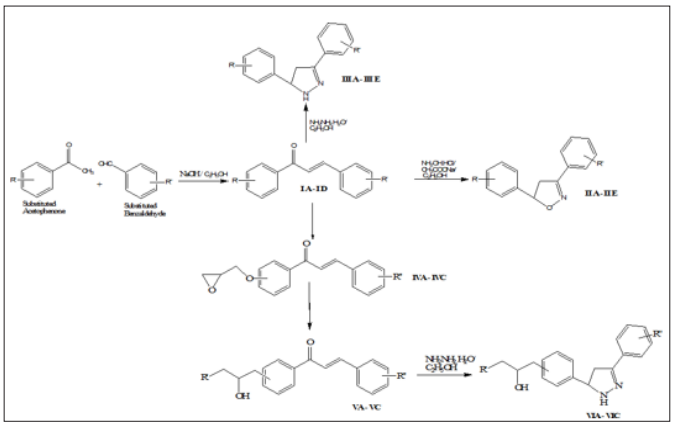
General

The melting point of the compounds was determined by using stuart melting point apparatus and were uncorrected. The IR spectra of the synthesized compounds were recorded on Shimadzu FT. IR- 8300 using KBr pellets. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker 400 MHz operating at 300MHz . ^{1}H NMR spectrometer using TMS as internal standard. The mass spectra were recorded on GCMS-TQ8050 NX spectrometer.

Methods of Preparation

Synthesis of Chalcones Derivatives (IA-IE)

A solution of sodium hydroxide (30%) in water and rectified spirit was placed in a flask provided with a mechanical stirrer. The flask was immersed in a bath of crushed ice. Substituted acetophenone was poured with constant stirring, substituted benzaldehydes were added to the solution. The temperature of the mixture was kept at about 25 °C and stirred vigorously until the mixture was thick enough to retard the stirring (approx. 6 h). The reaction mixture was kept at 8 °C overnight and product was filtered with suction using buchner funnel, washed with cold water until the washings were neutral to litmus. The crude product was recrystallized finally using ethanol.



Scheme of Work

Synthesis of Isoxazoline Derivatives (IIA-IIE)

A mixture of substituted chalcones (IA-IE) and hydroxylamine hydrochloride in ethanol was taken in a round bottom flask. The reaction mixture was refluxed for 6 h on a water bath then kept overnight at 8 °C. The precipitates were filtered, washed with distilled water and dried. The product was recrystallized with ethanol to obtain pure products (IIA-IIE).

- **4-(3-(4-Methoxyphenyl) Isoxazol-5-Yl) Phenol (II A):** Yield = 63%, IR(KBr) in cm^{-1}: 3230 (-OH str,), 3227 (C-H str. aliphatic), 1525 (C=N str. aromatic), 1485 (C=C str. aromatic),

815 (C-H def aromatic). ^{1}H NMR(CdCl3) in ppm : 7.62 -8.55 (r, 4H, aromatic ring), 6.81-7.53 (m,6 C-H, aromatic ring), 5.0 (d, C- OH aromatic), 5.6 (m, 1H, C-H), 2.85-3.73 (s, -OCH3). Mass spectra: m/z 269.04.

- **3-(3-(4-Methoxyphenyl) Isoxazol-5-Yl) Phenol (II B):** Yield = 54%, IR(KBr) in cm^{-1}: 3085 (-OH str.), 3227 (C-H str. aliphatic), 1525 (C=N str. aromatic), 1485 (C=C str. aromatic), 1315 (C-O-N str. aromatic). ^{1}H NMR(CdCl3) in ppm : 7.60-8.55 (r, 4H, aromatic ring), 6.95 - 7.55 (m, 6 C-H, aromatic ring), 5.5 (d, C-OH aromatic), 5.7 (m, 1H, C-H), 2.87-3.73 (s, -OCH3). Mass spectra: m/z 268.09.
- **2-(3-(4-Methoxyphenyl) Isoxazol-5-Yl) Phenol (II C):** Yield 60% (ethanol), IR: 3082 (-OH str.), 3225 (C-H str. aliphatic), 1520 (C=N str. aromatic), 1483 (C=C str. aromatic), 1319 (C-O-N str. aromatic). ^{1}H-NMR: 7.61-8.51 (r, 4H, aromatic ring), 6.88-7.37 (m, 6 C-H, aromatic ring), 5.0 (d, C- OH aromatic), 5.3 (m, 1H, -CH), 2.87- 3.73 (s, -OCH3). Mass spectra: m/z 268.
- **4- (3- (3,4-Dimethoxy phenyl) Isoxazol-5-Yl) Phenol (II D):** Yield 61% (ethanol), IR: 2920 (-OH str.), 1682 (aromatic C=C str.), 1612 (aromatic C=N str.), 1058 (C-O-C str. asymmetric), 866 (C-H def. aromatic), 746 (C-H bend). ^{1}H-NMR: 7.61 8.51 (r, 4H, aromatic ring), 6.88-7.31 (m, 6 C-H, aromatic ring), 5.0 (d, C-OH aromatic), 5.3 (m, 1H, C-H), 2.18-3.73 (s, 2 -OCH3). Mass spectra: m/z 298.08
- **4-(3-(Benzo [D][1,3]Dioxol-5-Yl) Isoxazol-5 Yl) Phenol (II E):** Yield 59% (ethanol), IR: 2920 (- OH str.), 1682 (aromatic C=C str.), 1612 (aromatic C=N str.), 1348 (C-O-N str. aromatic), 765 (C-H bend). ^{1}H-NMR: 7.61-8.51 (r, 4H, aromatic ring), 6.7-7.31 (m, 6 C-H, aromatic ring), 5.0 (d, C-OH 2320-5148 aromatic), 5.3 (m, 1H, C-H), 5.9 (d, -CH2). Mass spectra: m/z 283.11

Synthesis of Pyrazoline Derivatives (IIIA-IIIE)

In a mixture of substituted chalcones (IA-IE) in ethanol, hydrazine hydrate was added drop by drop in a round bottom flask. The reaction mixture was heated under reflux condition for 6 h on a water bath followed with addition of ice-cold water. The mixture was kept overnight at 8 °C. The precipitates were filtered, washed with distilled water and dried. The product was recrystallized with ethanol to obtain pyrazoline derivatives (III A III E).

- **4-(3-(4-Methoxy phenyl) -1H-Pyrazol-5-Yl) Phenol (III A):** Yield 60% (ethanol), IR: 3246 (-OH str.), 3236 (aromatic -NH- str.), 3229 (C-H str.), 3022 (C-H str. aliphatic), 1522 (C=C str.), 1420 (C=N str. aromatic), 820 (C-H bend, aromatic). 1H NMR: 7.5 (r, 4H, aromatic ring), 6.7-7.37 (m, 4 C-H, aromatic ring), 5.0 (d, C-OH aromatic), 2.87-3.7 (s, -OCH3), 13.7 (r, -NH-). Mass spectra: m/z 268.
- **3-(3-(4-Methoxy phenyl) -1H-Pyrazol-5-Yl) Phenol (III B):** Yield 55% (ethanol), IR: 3246 (-OH str.), 3236 (aromatic -NH- str.), 3229 (C-H str.), 3025 (C-H str. aliphatic), 1690 (C=C str.), 1425 (C=N str. aromatic), 901 (C-H bend). 1H-NMR: 7.6 (r, 4H, aromatic ring), 6.8-7.37 (m, 4 C-H, aromatic ring), 5.0 (d, C-OH aromatic), 2.87-3.7 (s, -OCH3), 13.7 (r, -NH-). Mass spectra: m/z 268.
- **2-(3-(4- Methoxy phenyl) -1H-Pyrazol-5-Yl) Phenol (III C):** Yield 53% (ethanol), IR: 3246 (-OH str.), 3236 (aromatic -NH- str.), 3229 (C-H str.), 3025 (C-H str. aromatic), 1416 (C=N str. aromatic), 1352 (C=C str.), 910 (C-H bend). 1H-NMR: 7.6 (r, 4H, aromatic ring), 6.79-7.37(m, 4 C-H, aromatic ring), 5.0 (d, C-OH aromatic), 2.87- 3.7(s, OCH3), 13.7 (r, -NH-). Mass spectra: m/z 267.80.
- **4-(3-(3, 4-Dimethoxy phenyl) -1H-Pyrazol-5-Yl) Phenol (III D): Yield 58% (ethanol), IR:** 3082 (- OH str.), 3232 (aromatic C-H str.), 1609 (N-H bend), 1520 (C=C str.), 1120 (C-O-C str. asymmetric), 910 (C-H bend), 876 (C-H bend). ^{1}H-NMR: 7.6 (r, 4H, aromatic ring), 6.79-7.31 (m, 4 C-H, aromatic ring), 5.0 (d, C-OH aromatic), 2.87-3.7 (s, 2 -OCH3), 13.7 (r, -NH-). Mass spectra: m/z 294.12.
- **4-(3-(Benzo [D][1, 3] Dioxol – 5 - Yl) -1H Pyrazol -5-Yl) Phenol (III E):** Yield 57% (ethanol), IR: 3082 (-OH str.), 3232 (aromatic C-H str.), 1609 (N-H bend), 1520 (C=C str.), 1495 (C O-C str. asymmetric), 947(C-H bend), 875 (C-H bend). ^{1}H-NMR: 7.6 (r, 4H, aromatic ring), 6.79 7.31 (m, 4 C-H, aromatic ring), 5.0 (d, C-OH aromatic), 5.9 (d, CH2 in ring), 13.7 (r, -NH-). Mass spectra: m/z 282.11.

Synthesis of Novel Pyrazoline Derivatives (VI A - VI C)

Substituted chalcones (IA-IC) treated with Epichlorhydrine and Sodium hydride to yield intermediates (IV A-IV C) which on reacting with a substituted amine in methanol offers another intermediate compounds (VA-VC). Finally, hydrazine hydrate was added drop by drop in a mixture of intermediates (VA-VC) in ethanol. The reaction mixture was heated under reflux for 6 h on a water bath followed with addition of ice-cold water. The mixture was kept overnight at 8 °C. The precipitates were filtered, washed with distilled water and dried. The product was recrystallized with ethanol to obtain newer pyrazoline derivatives (VI A-VI C).

- **1-(tert - Butylamino) – 3 - (4 - (3 - (4 - Methoxy phenyl)-4, 5-Dihydro-1H-Pyrazol-5-Yl) Phenyl) Propan-2-Ol (VI A):** Yield 58% (ethanol), IR: 3247 (-OH str.), 3228 (C-H str.), 3022 (C-H str. aliphatic), 1522 (C=C str.), 1420 (C=N str. aromatic), 823 (C-H bend, aromatic). ^{1}H NMR: δ 1.69 (2H, dtt, J = 13.2, 6.9, 1.7 Hz), 2.29 (4H, ddt, J = 9.9, 6.7, 1.7 Hz), 5.79 (2H, ddd, J = 6.2, 1.8, 1.7Hz). Mass spectra: m/z 381.
- **1-(Butylamino)-3-(4-(3-(4-Methoxy phenyl)-4,5 Dihydro-1H-Pyrazol-5-Yl) Phenyl) Propan-2- Ol (VI B):** Yield 53% (ethanol), IR: 3244 (-OH str.), 3227 (C-H str.), 3023 (C-H str. aliphatic), 1520 (C=C str.), 1423 (C=N str.), 824 (C-H bend, aromatic). 1H NMR: δ 0.85-0.90 (6H, 0.88 (d, J = 6.7 Hz), 0.88 (d, J = 6.7 Hz)), 1.74 (1H, septt, J = 6.7, 5.5 Hz), 2.57-2.61 (2H, 2.59 (d, J = 5.5 Hz), 2.59 (d, J = 5.5 Hz)), 2.84-2.88 (2H, 2.86 (d, J = 5.9 Hz), 2.86 (d, J = 5.9 Hz)), 2.88-2.97 (3H, 2.92 (dd, J = 8.1, 6.3 Hz), 2.95 (d, J = 7.2 Hz), 2.95 (d, J = 7.2 Hz)), 3.04 (1H, dd, J = 6.3, 4.3 Hz), 3.80 (3H, s), 3.96 (1H, tt, J = 7.2, 5.9 Hz). Mass spectra: m/z 382.
- **1-(tert-Butylamino)-3-(3-(3-(4-Methoxy phenyl)-4,5-Dihydro-1H-Pyrazol-5-Yl) Phenyl)Propan 2-Ol (VI C):** Yield 59% (ethanol), IR: 3244 (-OH str.), 3227 (C-H str.), 3023 (C-H str.), 1520 (C=C str.), 1423 (C=N str.), 824 (C-H bend). 1H NMR: 2.95 (d, J = 7.2 Hz), 2.95 (d, J =7.2 Hz), 3.04 (1H, dd, J = 6.3, 4.3 Hz), 3.80 (3H, s), 3.96 (1H, tt, J = 7.2, 5.9 Hz), 7.12-7.24 (4H, 7.21 (ddd, J = 8.2, 1.4, 0.6 Hz), 7.15 (ddd, J = 8.2, 1.3, 0.6 Hz)). Mass spectra: m/z 381.

Anti-Hyperglycemic Activity of Newly Synthesised Compounds

Compounds were evaluated for their impact on the percentage decrease in blood glucose levels in mice weighing 40–50 grams on average. The biochemical analyzer (ANOVA 2021) was used to measure the blood glucose levels of every animal following a 16-hour fast. Animals with blood glucose levels between 60 and 80 mg/dl were split up into three-person groups. The synthetic chemical suspension (prepared in 0.1% CMC) was given orally to animals in experimental groups at a dose of 100 mg/kg. Equal amounts of 0.1% CMC were administered to the control animals. Animals of standard group were given metformin and % anti-hyperglycemic activity was calculated by comparing blood glucose level of experimental and control group.

Results and Discussion

The synthesis of the target derivatives was carried out as described in Scheme 1; chalcones were first created using the Claisen Schmidt reaction. In the following step, chalcone intermediates were cyclized to create the diaryl isooxazoline and pyrazoline derivatives. The production of para substituted derivatives took less time than that of ortho and meta substituted chalcones, indicating that the position of the substituents significantly influences the rate of reaction. Reaction kinetics showed that the ortho and para directing effect of the phenolic group offers faster reaction completion for compounds II A, II D, III A, and III D. Compounds having hydroxyl groups on both rings at the para position were synthesized with excellent yield. The synthesis of aryl hydrazones during the refluxing process has a significant impact on nucleophilic assault on the carbon-carbon double bond at the β site. Because of their differing electron withdrawing capacities, which alter the electropositive character of the β carbon, the various substituents on the aryl ring have an impact on the rate of reaction. For compounds II A, II D, III A, and III D, increasing the positive character of the β carbon through electron withdrawing substituents on the aryl ring led to a quicker completion of reaction 16, 17.

Table 1: Physicochemical Characteristics of Synthesized Derivatives

S. No	Compound Code	R'	R"	Mol. Formula	Melting point(°C) approx.	Rf * value
1	II A	4' - OH	4- OCH_3	$C_{16}H_{13}NO_3$	93	0.72
2	II B	3' - OH	4- OCH_3	$C_{16}H_{13}NO_3$	96	0.61
3	II C	2' - OH	4- OCH_3	$C_{16}H_{13}NO_3$	99	0.71
4	II D	4' - OH	3,4 - OMe	$C_{17}H_{15}NO_4$	103	0.71
5	II E	4' - OH	3,4-Methylenedioxy	$C_{16}H_{11}NO_4$	165	0.67
6	III A	4' - OH	4- OCH_3	$C_{16}H_{14}N_2O_2$	174	0.71
7	III B	3' - OH	4- OCH_3	$C_{16}H_{14}N_2O_2$	164	0.49
8	III C	2' - OH	4- OCH_3	$C_{16}H_{14}N_2O_2$	166	0.69
9	III D	4' - OH	3,4 - OMe	$C_{17}H_{16}N_2O_3$	183	0.85
10	III E	4' - OH	3,4-Methylenedioxy	$C_{16}H_{12}N_2O_3$	164	0.62
11	VIA	4'-$NHC(CH_3)_3$	4- OCH_3	$C_{23}H_{31}N_3O_2$	153	0.63
12	VIB	4'-$NH(CH_2)_3CH_3$	4- OCH_3	$C_{23}H_{31}N_3O_2$	164	0.61
13	VIC	3'-$NHC(CH_3)_3$	4- OCH_3	$C_{23}H_{31}N_3O_2$	144	0.72

Rf * value in solvent system: chloroform: ethylacetate

Testing of Anti-Hyperglycemic Activity of Compounds (IIA-IIE, IIIA-IIIE, IVA-IVE and VIA- VIC)

All the compounds were evaluated for their in-vivo ant hyperglycemic activity using sucrose loaded diabetic model and fall in blood glucose level was measured as ant hyperglycemic activity of synthesized derivatives. Most of the synthesized derivatives revealed appreciable antihyperglycemic activity however isoxazoline derivatives showed more potent efficacy than pyrazoline derivatives.

Compounds IIA, IIB, IIC, IID, and IIE shows 71.2%,51.5%, 52.0 %, 68.0%, and 73.1% antihyperglycemic activity respectively. In the same manner compounds III A shows 62.5%, III B shows 49.5%, III C shows 53.0% III D shows 48.8% and III E shows 65.4% antihyperglycemic activity. The novel compounds VIA, VIB and VIC were also investigated for their antihyperglycemic activities The newly synthesized compounds VIA shows 56.5%, VIB shows 47.0% and VIC shows 62.5% antihyperglycemic activity by using Metformin (standard) 69.3% and Gum acacia (control). The result reveals that compound IIA and IIE possess potent response with 71% and 73.1% anti- hyperglycemic effect respectively while the novel compounds VIA, VIB and VIC were also investigated for their antihyperglycemic activities, compound VIC showed prompt anti hyperglycemic activity than compounds VIA and VIB. The antihyperglycemic activities of the synthesized derivatives may be attributed to the presence of a central heterocyclic ring, which provides optimal binding configurations with the enzyme PTP1B. The hydroxy substitution in compound IIA facilitates polar interactions with the enzyme's binding sites, thereby enhancing its activity. Likewise, the compound featuring a bulky methoxy group creates a constrained and rigid environment that improves interactions with the drug receptor, resulting in compound IIE demonstrating a significant antihyperglycemic effect comparable to that of the standard medication metformin.

Conclusion

Upon reviewing the newly synthesized compounds within this series, it can be concluded that compound II E exhibited the highest potency in terms of anti-hyperglycemic activity. The findings of the current study indicate that isoxazoline and pyrazoline derivatives of chalcone hold significant potential for the further development of antihyperglycemic agents.

Acknowledgement

The authors wish to express their sincere thanks to Principal, Sahu Jain College, Najibabad for providing necessary lab facilities. We wish to express our thanks to Prof. R. N . Goyal (Former Head), Department of Chemistry, Indian Institute of Technology, Roorkee and Director, CDRI Lucknow for providing us the instrumental facility for helping the testing of compounds.

References

1. WHO (2013) Diabetes Fact sheet N°312.
2. International Diabetes Federation (2017) IDF Diabetes Atlas, 8th edn. Brussels Belgium: International Diabetes Federation. https://www.scirp.org/reference/referencespapers?referenceid=2187493.
3. Shoback DG, Gardner D (2011) Chapter 17 Greenspan's basic

& clinical endocrinology (9th ed.). New York: McGraw-Hill Medical. https://www.scirp.org/reference/referencespapers?referenceid=1278008.

4. Norman A, Henry H (2015) Hormones. Elsevier 136 137. https://shop.elsevier.com/books/hormones/norman/978-0-08-091906-5.
5. Rippe RS, Irwin JM (2010) Manual of intensive care medicine (5th ed.). Wolters Kluwer Health/Lippincott Williams & Wilkins 549.
6. Cash J (2014) Family Practice Guidelines (3rd ed.). Springer 396. https://www.springerpub.com/media/springer-downloads/Cash_Glass-editable%20forms_3-23-15.pdf?srsltid=AfmBOorgadiDvhoYZzt38ZuoT5dtwG5zaD8weNnOen2BJpgzRp_VpzQr.
7. Awuchi CG (2017) Sugar Alcohols: Chemistry, Production, Health Concerns and Nutritional Importance of Mannitol, Sorbitol, Xylitol, and Erythritol. International Journal of Advanced Academic Research 3: 31-66.
8. Awuchi, Chinaza Godswill, Echeta, Kate Chinelo (2019) Current Developments in Sugar Alcohols: Chemistry, Nutrition, and Health Concerns of Sorbitol, Xylitol, Glycerol, Arabitol, Inositol, Maltitol, and Lactitol. International Journal of Advanced Academic Research 5: 1-33.
9. Shi Y, Hu FB (2014) The global implications of diabetes and cancer. Lancet 383: 1947-1948.
10. CDC (2019) Deaths and Cost-Data & Statistics-Diabetes-CDC. Available at: www.cdc.gov.
11. Mirela Delibegović, Sergio Dall'Angelo, Ruta Dekeryte (2024) Protein tyrosine phosphatase 1B in metabolic diseases and drug development. Nature Reviews Endocrinology 20: 366-378.
12. Jain, Jain DK (2019) Synthesis, Characterization and Biological Evaluation of Some New Heterocyclic Derivatives of Chalcone as Antihyperglycemic Agents. IJPSR 10: 5700-5706.
13. J Flint, TTiganis D, Barford, NK Tonks (1997) Development of substrate-trapping mutants to identify physiological substrates of protein tyrosine phosphatases. Proc Natl Acad Sci USA 94: 1680-1685
14. G Fan, S Aleem, M Yang, W Todd Miller, Nicholas K Tonks (2015) Protein-tyrosine phosphatase and kinase specificity in regulation of SRC and breast tumor kinase. J Biol Chem 290: 15934-15947.
15. Tonks NK (2013) Protein tyrosine phosphatases--from housekeeping enzymes to master regulators of signal transduction. FEBS J 280: 346-378.
16. W Zhu, BL Zhou, LJ Rong (2020) Roles of PTBP1 in alternative splicing, glycolysis, and oncogensis 21: 122-136.
17. J Zhu W, Zhou BL, Rong LJ, Ye L, Xu HJ (2020) Roles of PTBP1 in alternative splicing, glycolysis, and oncogensis. J Zhejiang Univ Sci B 21: 122-136.
18. WJ Lennarz, MD Lane (2004) Encyclopedia of Biological Chemistry, Elsevier, New York 536-542.
19. M Streuli, NX Krueger, T Thai (1990) Distinct functional roles of the two intracellular phosphatase like domains of the receptor-linked protein tyrosine phosphatases LCA and LAREMBO J 9: 2399-2407
20. Farooq S, Ngaini Z (2019) Recent synthetic methodologies for chalcone synthesis (2013-2018). Current Organocatalysis 6: 184-192.
21. Zhuang C, Zhang W, Sheng C, Zhang W, Xing C, et al. (201 Chalcone: a privileged structure in medicinal chemistry. Chemical Reviews 117: 7762-7810.
22. Nowakowska Z (2007) A review of anti-infective and anti-inflammatory chalcones. Eur J Med Chem 42: 125-137.
23. Jin C, Liang Y, He H, Fu L (2011) Synthesis and antitumor activity of novel chalcone derivatives. Biomed Pharmacother 10: 1-3.
24. Araico A, Terencio MC, Alcaraz MJ, Dominguez JN, Leon C, et al. (2006) Phenylsulphonyl urenyl chalcone derivatives as dual inhibitors of cyclo oxygenase-2 and 5- lipoxygenase. Life sciences 78: 2911-2918.
25. Bano S, Javed K, Ahmad S, Rathish IG, Singh S, et al. (2013) Synthesis of some novel chalcones, flavanones and flavones and evaluation of their anti- nflammatory activity. European Journal of Medicinal Chemistry 65: 51-59.
26. Farzaneh S, Zeinalzadeh E, Daraei B, Shahhosseini S, Zarghi A (2018) New ferrocene compounds as selective cyclooxygenase (COX-2) inhibitors: design, synthesis, cytotoxicity and enzyme-inhibitory activity. Anti-Cancer Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Cancer Agents 18: 295-301.
27. Jantan I, Bukhari SNA, Adekoya OA, Sylte I (2014) Studies of synthetic chalcone derivatives as potential inhibitors of secretory phospholipase A2, cyclooxygenases, lipoxygenase and pro-inflammatory cytokines. Drug Design, Development and Terapy 8: 1405-1418.
28. Naidu MA (2018) Evaluation of Antidiabetic Activity of Novel Diarylsulfonylurea- Chalcone Hybrids in Streptozotocin-Induced Diabetic Models in Rats. Asian Journal of Pharmaceutics (AJP) 12: 382-405.
29. OkudaTanino A, Sugawara D, Tashiro T, Iwashita M, Obara Y, et al. (2017) Licochalcones extracted from Glycyrrhiza inflata inhibit platelet aggregation accompanied by inhibition of COX-1 activity. PLoS One 12: e0173628.
30. Özdemir A, Altıntop MD, Turan Zitouni G, Çiftçi GA, Ertorun I, et al. (2015) Synthesis and evaluation of new indole-based chalcones as potential antiinflammatory agents. European journal of medicinal chemistry 89: 304-309.
31. Ansari FL, Umbreen S, Hussain L, Makhmoor T, Nawaz SA, Lodhi MA, et al. (2005) Syntheses and Biological Activities of Chalcone and 1, 5 Benzothiazepine Derivatives: Promising New Free-Radical Scavengers, and Esterase, Urease, and α-Glucosidase Inhibitors. Chemistry & Biodiversity 2: 487-496.
32. Bak EJ, Park HG, Lee CH, Lee TI, Woo GH, et al. (2011) Effects of novel chalcone derivatives on α-glucosidase, dipeptidyl peptidase-4, and adipocyte differentiation in vitro. BMB reports 44: 410-414.
33. Cai CY, Rao L, Rao Y, Guo JX, Xiao ZZ, et al. (2017) Analogues of xanthones - Chalcones and bis-chalcones as α-glucosidase inhibitors and anti- diabetes candidates. European Journal of Medicinal Chemistry 130: 51-59.
34. Acharjee S, Maity TK, Samanta S, Mana S, Chakraborty T, et al. (2018) Antihyperglycemic activity of chalcone based novel 1-{3-[3-(substituted phenyl) prop-2- enoyl] phenyl} thioureas. Synthetic Communications 48: 3015-3024.
35. Mahapatra DK, Bharti SK, Asati V (2017) Chalcone derivatives: anti-inflammatory potential and molecular targets perspectives. Current Topics in Medicinal Chemistry 17: 3146-3169.
36. Najafian M, Ebrahim Habibi A, Yaghmaei P, Parivar K, Larijani B (2010) Core structure of flavonoids precursor as an antihyperglycemic and antihyperlipidemic agent: an in vivo study in rats. Acta biochimica polonica 57: 553-560.
37. Raju DB, Rao AV, Prasad YR (2018) Hybrid sulfonylurea-linked chalconoids as antidiabetic agents: evaluation of antihyperglycemic effects in streptozotocin-induced type 2

diabetic rats. Rasayan J Chem 11: 1334-1338.

38. Rawat P, Kumar M, Rahuja N, Srivastava DSL, Srivastava AK, et al. (2011) Synthesis and antihyperglycemic activity of phenolic C-glycosides. Bioorganic & medicinal chemistry letters 21: 228-233.
39. Satyanarayana M, Tiwari P, Tripathi BK, Srivastava AK, Pratap R (2004) Synthesis and antihyperglycemic activity of chalcone based aryloxypropanolamines. Bioorganic & medicinal chemistry 12: 883-889.
40. Sengupta SA, Maity TK, Samanta S (2017) Synthesis, biological screening and in silico studies of chalcone based novel phenyl urea derivatives as potential antihyperglycemics. Journal of Pharmaceutical Research 16: 237-246.
41. Shukla P, Satyanarayana M, Verma PC, Tiwari J, Dwivedi AP, et al. (2017) Chalcone-based aryloxypropanolamine as a potential antidiabetic and antidyslipidaemic agent. Current Science 112: 1675-1689.
42. Shukla P, Singh AB, Srivastava AK, Pratap R (2007) Chalcone based aryloxypropanolamines as potential antihyperglycemic agents. Bioorganic & Medicinal Chemistry Letters 17: 799-802.
43. Tajammal A, Batool M, Ramzan A, Samra MM, Mahnoor I, et al. (2017) Synthesis, antihyperglycemic activity and computational studies of antioxidant chalcones and flavanones derived from 2, 5 dihydroxyacetophenone. Journal of Molecular Structure 1148: 512-520.