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RECENT PERSPECTIVES OF CHALCONE BASED MOLECULES AS PROTEIN TYROSINE PHOSPHATASE 1B (PTP1B) INHIBITORS

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ABSTRACT:
Type 2 diabetes, also known as diabetes mellitus (DM), is a complex illness defined by high blood sugar, abnormal lipid, carbohydrate, and protein metabolism, and an elevated risk of vascular disease consequences. Type 2 diabetes (t2D) and obesity, in which Protein Tyrosine Phosphatase 1B (PTP1B) acts as a negative regulator of the insulin and leptin-signaling pathway, have received sufficient attention. Insulin signaling is downregulated by PTP-1B, which is responsible for dephosphorylating the insulin receptor. Inhibitors of protein tyrosine phosphatase 1B (PTP1B) are the most recent potential treatment for diabetes because they boost insulin production by blocking the dephosphorylation of the insulin receptor. Some natural items have shown promise as potential diabetes treatments. PTP1B is strongly inhibited by chalcones, also known as 1,3-diphenyl-2E-propen-1-one, an open chain intermediate in the synthesis of aurones from flavones with a benzylideneacetophenone scaffold in which two aromatic nuclei are connected by a three-carbon, unsaturated carbonyl bridge. The pharmacology, mode of action, structural features, and substituents necessary for PTP1B modulation have all been examined in detail in this chapter. To become effective therapeutic drugs or formulations for the control of diabetes, however, all of these inhibitors will need to be extensively researched and tested for their effectiveness and toxicity.

Keywords: Anti-diabetic, Chalcone, Diabetes, Inhibitors, PTP1B, Protein Tyrosine Phosphatase

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1. INTRODUCTION

Increased blood sugar levels, abnormalities in the metabolism of lipids, carbohydrates, and proteins, and an elevated risk of vascular disease consequences define the Diabetes Mellitus (DM) spectrum of diseases. Major organs, including the heart, eyes, nerves, blood arteries, and kidneys, may get damaged or fail entirely in the presence of persistent hyperglycemic conditions [2]. Polyuria, polydipsia, polyphagia, glycosuria, unexplained weight loss, random plasma glucose concentration of more than 200 mg/dL, and fasting plasma glucose concentration of more than 126 mL/dL are all symptoms of diabetes mellitus, according to the American Diabetes Association (ADA) [3]. Multiple mechanisms, including altered insulin secretion, hepatic gluconeogenesis, and decreased absorption of glucose by skeletal muscle, adipose tissues, and the liver, contribute to deviations in normal glucose homeostasis [4]. Type I diabetes occurs when the body does not create enough insulin to properly metabolize carbohydrates like sugar and starch. When cells become "resistant" to insulin, a condition known as type II diabetes (t2D) sets in [5]. Type II diabetes is characterized by muscle and fat cells that are less responsive to insulin than normal. Insulin and the sulfonylureas are useful in treating T2D, but they might cause side effects including hypoglycemia if patients do not take their medication as prescribed. Because not all type 2 diabetes patients benefit from glitazone administration, there is a pressing need for alternative, more effective oral medications, especially those that may stabilize glucose and insulin levels [6]. Fasting and postprandial blood glucose concentrations are affected by insulin, which is released by pancreatic -cells in two distinct periods. After eating, the body releases insulin quickly in response to the rising glucose concentration, and then insulin levels rise steadily over the course of the following hours [7].

Successful treatment of DM often involves the use of drugs that improve muscle and adipose tissue's sensitivity to insulin (insulin sensitizers). Dipeptidyl peptidase-4 (DPP-4) and phosphotransferase 1B (PTP1B) inhibitors are two of the most important enzyme inhibitors discovered so far for use in diabetotherapy. By preventing insulin from being degraded or

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rendered ineffective, these chemicals increase its shelf life [8]. Inhibitors of PTP1B are the most recent potential treatment for diabetes. Phosphonates, malonates, carboxylates, and cinnamates are only some of the many negatively charged moiety-functionalized tyrosine mimetic PTP1B inhibitors that have been produced [9]. Ertiprotafib and trodusquemine, two inhibitors, have recently progressed into clinical studies for the treatment of diabetes and obesity. Despite this, ertiprotafib's second-stage clinical study was halted owing to lack of effectiveness [10]. Significant anti-diabetic ability has been shown by natural and semi (synthetic) chalcones via inhibition of the PTP1B enzyme without the manifestation of serious diabetic consequences. Additional research into the effectiveness and toxicity characteristics of these inhibitors is required before they can be developed into formulations.

2. PTP1B: ROLE IN DIABETES MELLITUS

Using their phosphorylation and de-phosphorylation events, protein kinases and phosphatases mediate a wide range of cellular functions, including insulin's metabolic and cellular effects [11]. PTP1B is an intercellular, non-receptor Protein tyrosine phosphatase that is expressed ubiquitously, including in the conventional insulin-targeted tissues of liver, muscle, and fat [12]. PTP1B's critical function in t2D and obesity as a negative regulator of the insulin and leptin-signaling pathway [13] has brought it much attention. The insulin receptor (IR) is activated by autophosphorylation of tyrosine (Tyr) residues in the IR activation loop, resulting in metabolic insulin signal transduction. The IR is dephosphorylated by a number of protein tyrosine phosphatases (PTPs), including receptor protein tyrosine phosphatase alpha (rPTP-a), leukocyte antigen-related tyrosine phosphatase (LAR), SH2-domain-containing phosphotyrosine phosphatase 2 (SHP2), and protein tyrosine phosphatase 1B (PTP1B). Dephosphorylation of the insulin receptor (IR), insulin receptor substrate-1 (IRS-1), and insulin receptor substrate-2 (IRS-2) by PTP1B inhibits insulin signaling [14]. When it comes to metabolic signaling at the end of the insulin pathway, PI3K is the enzyme of choice. PDK1 is activated by PIP2, which is generated by the selective phosphorylation of PI substrates by PI3K. In turn, this stimulates

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glucose absorption by activating protein kinase AKT, a crucial step in the translocation of insulin-stimulated GLUT4 to the plasma membrane. When PTP1B is inhibited, insulin production, cellular sensitivity, and glucose absorption are all improved. Treatment of diabetic mice with PTP1B antisense oligonucleotides reduced the expression level of the enzyme, which resulted in normalized blood glucose and improved insulin sensitivity [15]. Several studies have shown that PTP1B-knockout mice have improved insulin sensitivity, improved glucose tolerance, and resistance to diet-induced obesity. Clinical research has also shown that PTP-1B is the primary mediator of insulin receptor dephosphorylation and the subsequent downregulation of insulin signaling [16]. Together, these biochemical, genetic, and pharmacological investigations offer robust proof of concept, confirming the premise that inhibition of PTP1B might treat both diabetes and obesity and making PTP1B an interesting target for drug development [17]. Therefore, finding effective small molecule inhibitors of protein tyrosine phosphatase 1B is a primary focus in the treatment of type 2 diabetes mellitus.

In the first step of PTP-mediated catalysis, the sulfur atom of the thiolate side chain of the Cys attacks the substrate phosphate as a nucleophile, and in the second step, the side chain of a conserved acidic residue (Asp181 in PTP1B) acts as a general acid to protonate the tyrosyl-leaving group of the substrate. A cysteinyl-phosphate catalytic intermediate is produced as a result. Later, the catalytic intermediate is hydrolyzed, resulting in the liberation of phosphate [18]. This process is mediated by Gln 262, which coordinates a water molecule, and Asp181, which acts as a general base. Despite the fact that multiple PTP1B inhibitors have been discovered, novel PTP1B inhibitors with superior pharmacological characteristics are still being sought due to the limited selectivity and poor pharmacokinetic qualities of the currently available compounds. Better selectivity and enhanced pharmacokinetic qualities may make chalcones a useful tool for the management of diabetes and its consequences.

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3. CHALCONES

Some natural items have shown promise as potential diabetes treatments. The flavonoids class has been the most consistent performer in several biological roles [19]. Flavonoids are a class of polyphenols that are heat stable and have several health advantages. The nearly 4000 polyphenolic chemicals found in plants today are likely over a billion years old [20]. They are ubiquitously found in fruits, vegetables, tea, wine, and are usually subdivided into six classes including flavonols (e.g., quercetin, kaempferol), flavones (e.g., apigenin, luteolin), flavanones (e.g., hesperidin, naringenin), flavan-3-ols (e.g., catechin, theaflavin, and gallic esters of catechin and theaflavins), anthocyanidins (e.g., pelargonidin, cyanidin) and isoflavones (e.g., genistein, daidzein) [21]. Consuming foods rich in natural flavonoids has been linked to a variety of health benefits, including a lower chance of developing cancer, better regulation of blood sugar levels, and other metabolic benefits. Natural chalcones, also known as 1,3-diphenyl-2*E*-propene-1-one, are an open chain intermediate in the synthesis of flavones from aurones. They are what flavonoids and isoflavonoids are derived from. The two aromatic nuclei are connected by a three-carbon, unsaturated carbonyl bridge inside a benzylideneacetophenone scaffold [22]. Natural chromophoric compounds with a, unsaturated carbonyl bridge were originally synthesized by Kostanecki and Tambor, who gave them the name "chalcone" [23]. The pharmacological potentials of chalcones, including their anti-hypertensive [24], anti-arrhythmic [25], anti-platelet [26], anti-diabetic [27], anti-neoplastic [28], anti-angiogenic [29], anti-retroviral [30], anti-inflammatory [31], anti-gout [32], anti-histaminic [33], and anti-oxidant [34] effects, have made them increasingly

4. CHALCONES AS PTP1B INHIBITORS

Many chalcones with putative PTP1B inhibitory action were isolated from their natural environments. Three chalcones with methylcyclohexene substitutes, all deriving from the Diels-Alder reaction, were identified by Hoang et al. from the *Morus bombycis* plant. These

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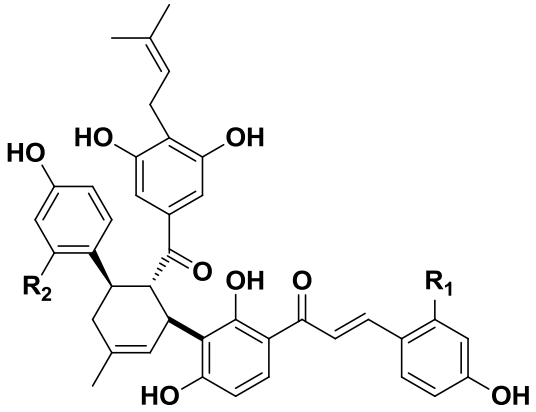
compounds are designated as kuwanon J (1), kuwanon R (2), and kuwanon V (3). All of these compounds exhibited potent mixed-type inhibition of PTP1B, with IC_{50} values ranging from 2.7 to 13.8 μM. The quantity of hydroxyl groups has a crucial impact in determining effectiveness. It is anticipated that the hydroxyl groups will form an efficient hydrogen bonding connection with the amide backbone of the active-site loop, providing the necessary penetration into the active site. Based on these data, it seems that the potential inhibitory effects against PTP1B greatly increase with the quantity of OH groups in chalcone-derived Diels-Alder-type compounds. When compared to compound (3), which includes just six OH groups, compound (2)'s potent dose-independent inhibition is clear. The inclusion of the hydroxyl (OH) group at carbon-2 in compound (1) boosts its activity up to thrice with regard to compound (3). There is a clear 1>2>3 pattern in the inhibitory action of Diels-Alder-type compounds generated from chalcones [52].



(1) R_1 = OH, R_2 = OH ; **(2)** R_1 = H, R_2 = OH ; **(3)** R_1 = H, R_2 = H

It has been reported that broussochalcone (4), which was isolated from Broussonetia papyrifa, inhibits PTP1B efficiently with an IC_{50} of 21.5 μM. It is hypothesized that the two hydroxyl groups at each rings contribute to the potent inhibition. The inhibitory action rises in tandem with the quantity of hydroxyl groups [53].

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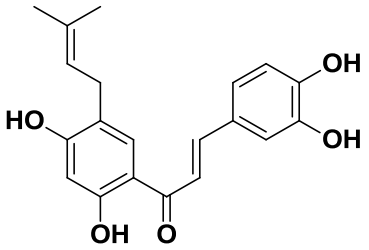
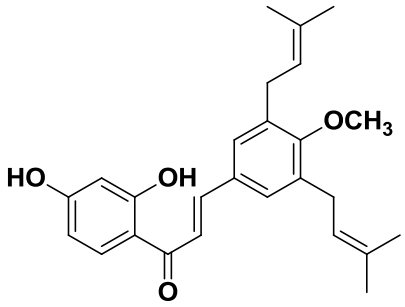


(4)

The ethyl acetate-soluble extract of *Erythrina mildbraedii*'s root bark yielded a new chalcone, abyssinone-VI-4-O-methyl ether (5), which displayed PTP1B inhibitory action *in vitro* with an IC_{50} value of 14.8 μM [54].



(5)

PTP1B has been shown to be inhibited by licochalcone A, which has been isolated from Glycyrrhiza inflata, and its semi-synthetic derivatives. Isoleucine (6), echinatin (7), licochalcone A (8), licochalcone C (9), licochalcone E (10), licochalcone B (11) and licochalcone D (12) are the chalcones that were extracted. Methylation was used to create the semi-synthetic derivatives (13) and (14), whereas acetylation of licochalcone A yielded molecules (15) and (16). THP-protection of the 4-hydroxy group in the A ring was followed by methylation or acetylation of the 4'-hydroxyl group in the B ring, and then the THP-ether was cleaved under acidic conditions to provide compounds 17 and 18. Compounds (19) and (20) are produced when compound (13) and compound (17) are acetylated, respectively. The most potent action was shown by the semi-

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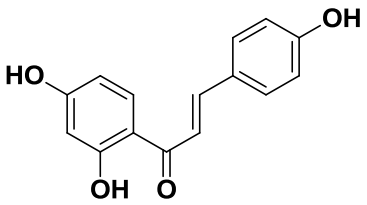
synthetic derivative (13), which was found in [55, 56]. By blocking PTP1B oxidation and IR/PI3K/AKT phosphorylation, isoliquiritigenin (ISL) helps restore PTP1B activity in the early phases of insulin-induced adipogenesis. Inhibition of PTP1B oxidation by ISL's antioxidant activity reduced insulin receptor (IR)/PI3K/AKT signaling and, in turn, insulin's ability to drive 3T3-L1 cells to differentiate into adipocytes [57, 58].



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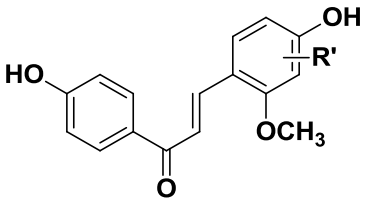
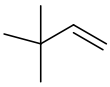
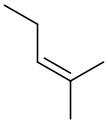
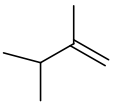
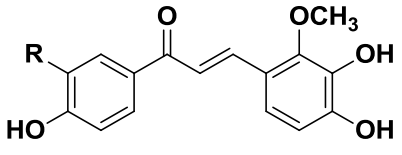
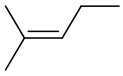


(7) R’ = H ; **(8)** R’ = 5’-  ; **(9)** R’ = 3’-  ; **(10)** R’ = 5’- 



(11) R = H ; **(12)** R = 

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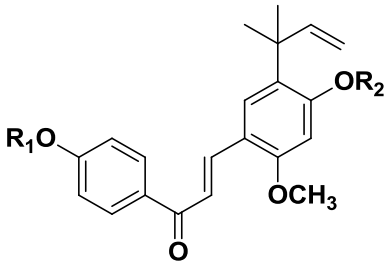
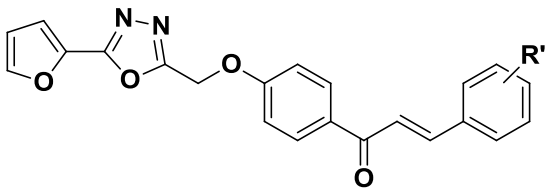


(13) $R_1 = CH_3$, $R_2 = H$; **(14)** $R_1 = CH_3$, $R_2 = CH_3$; **(15)** $R_1 = COCH_3$, $R_2 = H$; **(16)** $R_1 = COCH_3$, $R_2 = COCH_3$; **(17)** $R_1 = H$, $R_2 = CH_3$; **(18)** $R_1 = H$, $R_2 = COCH_3$; **(19)** $R_1 = CH_3$, $R_2 = COCH_3$; **(20)** $R_1 = COCH_3$, $R_2 = CH_3$

Recent rational synthesis has produced a wealth of chalcone derivatives with putative PTP1B inhibitory properties, making the chalcone scaffold one of the most popular in all of medicinal chemistry. The Claisen-Schmidt condensation of benzaldehyde and acetophenone using 40% sodium hydroxide as a catalyst [59] is the standard method for producing chalcones and related chemicals. More and more people are turning to microwave irradiation of the aforementioned chemicals to produce chalcone [60]. A limited number of novel heterocyclic ring-substituted chalcone derivatives (21-29) were synthesized by Chen et al. using the structure of PTP1B as a starting point, and the most potent of these compounds inhibited PTP1B. Compared to compounds with electron-donating groups on ring B, compounds with electron-drawing groups showed more potential for inhibiting PTP1B activity in a SAR study. Compound 28 was the most effective; it had an IC_{50} of 3.12 μM and a 99.17% inhibitory effectiveness [61].



(21) R' = H ; **(22)** R' = 4-F ; **(23)** R' = 2-Cl ; **(24)** R' = 4-Cl ; **(25)** R' = 2,6-$(Cl)_2$; **(26)** R' = 2-Br ; **(27)** R' = 4-Br ; **(28)** R' = 2-F ; **(29)** R' = 3-Cl

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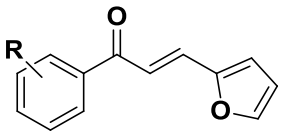
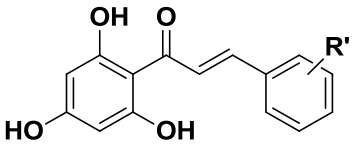
Among a group of furan chalcone derivatives found to have comparable action, compounds 30 and 31 stood out in experiments as having the lowest IC_{50} values for competitive inhibition of PTP1B. The 2,4-OH (30), 2-OH (32), and 3-OH (33) hydroxylated derivatives were likewise superior inhibitors [62].



(30) R = 2, 4-OH ; **(31)** R = 3-Cl ; **(32)** R = 2-OH ; **(33)** R = 3-OH

Similar to the reference medications Na3VO4 and oleanolic acid, many 2',4',6'-trihydroxy chalcone derivatives (34-42) have been reported as interesting pharmacological candidates for in vitro PTP1B inhibition. Researchers have found that the presence of electron-donating groups on ring B is crucial for displaying considerable inhibitory action [63, 64].



(34) R' = 3-OCH_3, 4-OH ; **(35)** R' = 3-OCH_3, 4-$OCH_2CH{=}CH_2$; **(36)** R' = 4-OCH_3 ; **(37)** R' = 3, 4-$(OCH_3)_2$; **(38)** R' = 4-CH_3 ; **(39)** R' = H ; **(40)** R' = 2-F ; **(41)** R' = 3-Cl ; **(42)** R' = 2,4-Cl

Isolated from the *Macaranga denticulata* plant were the polycyclic dimeric chalcone macdentichalcone (43) and the monomeric chalcone 1-(5,7-dihydroxy-2,2,6-trimethyl-2*H*-1-benzopyran-8-yl)-3-phenyl-2-propen-1-one (44) that has been proposed as a biosynthetic precursor of (43). The IC_{50} values for these two drugs against PTP1B in vitro were 21 μM and 22 μM, respectively [65].

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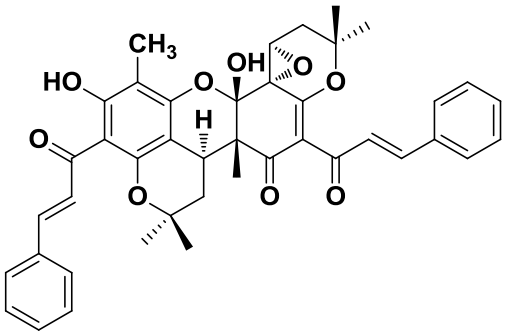

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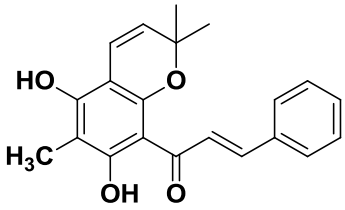
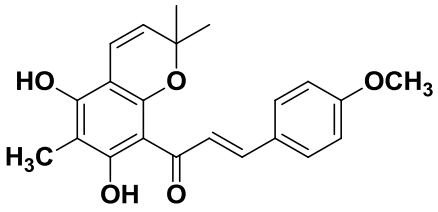


(44)

Common chalcone compounds based on coumarin, such as (2*E*),-1-(5,7-dihydroxy-2,2,6-trimethyl-2*H*-benzopyran-8-yl)-3-(4-methoxyphenyl)(2*E*)-2-propen-1-one (45). IC_{50} values of were found for the inhibitory actions of 1-(5,7-dihydroxy-2,2-dimethyl-2*H*-benzopyran-8-yl)-3-phenyl-2-propen-1-one (46) and laxichalcone (47) [66].



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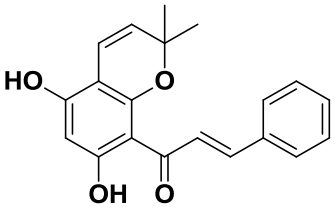

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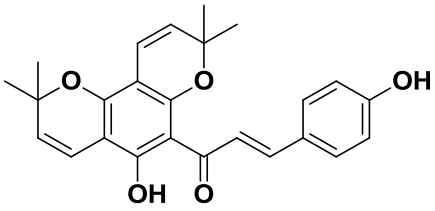

(47)

Six of these chalcones, xanthoangelol K (48), xanthoangelol (49), xanthoangelol F (50), 4-hydroxyderricin (51), xanthoangelol D (52) and xanthoangelol E (53), had a significant impact in inhibiting PTP1B, with IC_{50} values of 0.82, 1.97, 1.67, 2.47, 3.97, 1.43, and 2.53 µg/ml.

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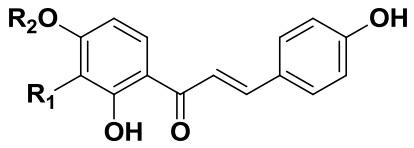
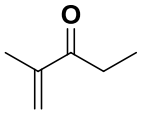
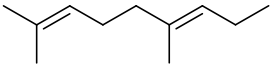
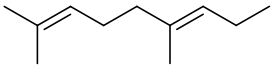
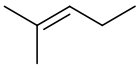
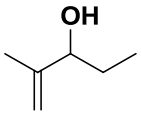
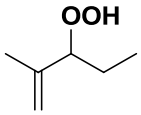
Compound (48) inhibited PTP1B with the kinetics of a competitive inhibitor, according to a kinetic analysis. Hydrogen bonds with Arg47, Asp48, and a p-p contact with Phe182 of PTP1B help keep the molecule in place, and molecular docking simulations have shown that ring B of 1 may anchor in a pocket of PTP1B [67].



(48) R_1 =  , $R_2 = CH_3$; **(49)** R_1 =  , $R_2 = H$;

(50) R_1 =  , $R_2 = CH_3$; **(51)** R_1 =  , $R_2 = CH_3$;

(52) R_1 =  , $R_2 = CH_3$; **(53)** R_1 =  , $R_2 = CH_3$

CONCLUSION

In this study, we looked at the structural characteristics of anti-diabetic chalcones that inhibit protein tyrosine phosphatase 1B (PTP-1B), one of the most promising hypoglycemic targets. Structure-activity relationships (SARs) of the 1,3-diphenyl-2E-propene-1-one based inhibitors where the profound role of electron withdrawing/donating groups along with the importance of the heteroaryl ring are discussed in detail, as well as the molecular pathway involved in the insulin-glucose interphase and the likely mechanism of chalcone modulators. None of them have been given serious attention in medicinal chemistry for hypoglycemia management as a modulator so far. This will undoubtedly lead to exciting new developments in the next decade(s),

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as their simple chemistry, wide variety of modulation potentials, etc. make them promising candidates for anti-hyperglycemic action.

CONFLICT OF INTEREST

No conflict of interest is declared.

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