CHAPTER 6

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

DEBARSHI KAR MAHAPATRA, SANJAY KUMAR BHARTI, and VIVEK ASATI

Department of Pharmaceutical Chemistry, Dadasaheb Balpande College of Pharmacy, Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur, Maharashtra, India

Institute of Pharmaceutical Sciences, Guru Ghasidas Vishwavidyalaya (A Central University), Bilaspur – 495009, Chhattisgarh, India, E-mail: skbharti.ggu@gmail.com

ABSTRACT

Diabetes mellitus (DM) is a heterogeneous group of disorders which is characterized by increased blood sugar level, altered metabolism of lipids, carbohydrates, and proteins and increased risk of complications from vascular disease. Protein Tyrosine Phosphatase 1B (PTP1B) has gained adequate notice due to its crucial role in type 2 diabetes (t2D) and obesity as a negative regulator of the insulin and leptin-signaling pathway. PTP-1B is primarily responsible for dephosphorylation of the insulin receptor and thus down regulates insulin signaling. PTP1B inhibitors are the latest candidate for the management of diabetes, where they prevent dephosphorylation of the insulin receptor and consequently increase insulin level. Natural products have been reported to exhibit promising anti-diabetic activity. Chalcones or 1,3-diphenyl-2*E*-propene-1-one, the open chain intermediate in aurones synthesis of flavones containing benzylideneacetophenone scaffold, where the two aromatic nuclei are joined by a three-carbon α, β

unsaturated carbonyl bridge have shown tremendous PTP1B inhibition. In this chapter, a concrete focus on pharmacology, mechanism of action, and structural aspects along with substituents required for modulating PTP1B has been discussed. Still, none of these inhibitors have gained adequate attention at present and need to be explored and evaluated properly in terms of efficacy and toxicity to develop as therapeutic agents/formulations for the management of diabetes in future.

6.1 INTRODUCTION

Diabetes Mellitus (DM) is a heterogeneous group of disorders which is characterized by increased blood sugar level, altered metabolism of lipids, carbohydrates, and proteins and increased risk of complications from vascular disease [1]. The chronic hyperglycemic conditions are associated with dysfunction and failure of major organs like heart, eyes, nerves, blood vessels and kidneys [2]. The American Diabetes Association (ADA) defines that DM is characterized by polyuria, polydipsia, polyphagia, glycosuria, unexplained weight loss and random plasma glucose concentration of greater than 200 mg/dL along with fasting plasma glucose concentration of greater than 126 mL/dL [3]. Variations in normal glucose homeostasis occur by numerous factors like impaired insulin secretion, hepatic gluconeogenesis and reduced uptake of glucose by skeletal muscle, adipose tissues and liver [4]. In the case of type I diabetes, the body does not produce enough insulin that is required to convert sugar, starches, etc. into energy. Type II diabetes (t2D) is a condition characterized by situation where cells do not properly use insulin as a result of "resistance" [5]. The most prominent features of type II diabetes is decreased sensitivity of muscle and adipose cells to insulin. T2D is often characterized by intrinsic problems like compliance, ineffectiveness and hypoglycemic episodes with insulin and the sulfonylureas. Administration of glitazones are not effective in all t2D patients, therefore, the great need for more effective orally administered agents particularly ones that normalize both glucose and insulin levels still remains a challenge [6]. Insulin is secreted in two discrete phases from pancreatic β-cells which influence the magnitude of both fasting and postprandial blood glucose concentrations. In the beginning, a rapid release of insulin occurs, when the glucose concentration

increases concurrently after a meal, which is followed by a phase of sustained increase in circulating insulin concentrations [7].

Generally, those compounds which increase the sensitivity of muscle and adipose to insulin (insulin sensitizers) are foremost choice for successful treatment of DM. For diabetotherapy, several enzyme inhibitors had been developed so far, of them Dipeptidyl Peptidase-4 (DPP-4) and PTP1B inhibitors are of foremost importance. These compounds prolong the duration of insulin by preventing its degradation/inactivation [8]. Protein Tyrosine Phosphatase 1B (PTP1B) inhibitors are the latest candidate for the management of diabetes. A large number of PTP1B inhibitors having tyrosine mimetic structures, functionalized with negatively charged moieties such as phosphonates, malonates, carboxylates, or cinnamates have been developed [9]. Recently, two inhibitors ertiprotafib and trodusquemine have advanced into clinical trials for the treatment of diabetes and obesity. Although, the second phase clinical trial for ertiprotafib was discontinued due to lack of efficacy [10]. Natural and semi (synthetic) chalcones have shown significant anti-diabetic property by inhibiting PTP1B enzyme without showing major associated diabetic complications. At present, these inhibitors have not received adequate attention and need further exploration regarding efficacy and toxicological profiles to develop as formulations.

6.2 PTP1B: ROLE IN DIABETES MELLITUS

Protein kinases and phosphatases are groups of enzymes responsible for mediating various intra-cellular functions such as mediation of metabolic and cellular actions of insulin, etc. using their phosphorylation and de-phosphorylation reactions [11]. Among them, Protein Tyrosine Phosphatase 1B (PTP1B), an intercellular non-receptor Protein Tyrosine Phosphatase is localized to the cytoplasmic face of the endoplasmic reticulum and is expressed ubiquitously, including in the classical insulin-targeted tissues such as liver, muscle and fat [12]. PTP1B has gained adequate notice due to its crucial role in type 2 diabetes (t2D) and obesity as a negative regulator of the insulin and leptin-signaling pathway [13]. Metabolic insulin signal transduction occurs through activation of the insulin receptor (IR), including autophosphorylation of tyrosine (Tyr) residues in the insulin receptor activation loop. Several protein tyrosine phosphatases

(PTPs), such as receptor protein tyrosine phosphatase (rPTP-a), leukocyte antigen-related tyrosine phosphatase (LAR), SH2-domain-containing phosphotyrosine phosphatase (SHP2), and protein tyrosine phosphatase 1B (PTP1B) have been implicated in the dephosphorylation of the IR. PTP1B downregulates insulin signaling by dephosphorylating the insulin receptor (IR), insulin receptor substrate-1 (IRS-1) and insulin receptor substrate-2 (IRS-2) [14]. In insulin pathway, PI3K is the key enzyme that downstream metabolic signaling. PI3K specifically phosphorylates PI substrates to produce PIP2 which activates PDK1. This process, in turn, activates protein kinase AKT, an essential component for insulin-stimulated GLUT4 translocation to plasma membrane, which increases uptake of glucose (Figure 6.1). Inhibition of PTP1B leads to increased insulin level, cellular sensitivity and uptake of glucose. Various studies have shown that PTP1B-knockout mice exhibit enhanced insulin sensitivity, improved glucose tolerance and resistance to diet-induced obesity treatment of diabetic mice with PTP1B antisense oligonucleotides reduced the expression level of the enzyme and subsequently normalized the blood glucose and improved insulin sensitivity [15]. Clinical studies have also demonstrated that PTP-1B is primarily responsible for dephosphorylation of the insulin receptor and thus down regulates insulin signaling [16]. Collectively, these biochemical, genetic and pharmacological studies provide strong proof-of-concept, validating the notion that inhibition of PTP1B could address both diabetes and obesity and making PTP1B an exciting target for drug development [17]. Therefore, the search for potent small molecule protein tyrosine phosphatase 1B inhibitors is a major thrust area in the management of type 2 diabetes mellitus.

PTP-mediated catalysis proceeds via two-step mechanism wherein the initial step, a nucleophilic attack by the sulfur atom of the thiolate side chain of the Cys on the substrate phosphate, coupled with protonation of the tyrosyl-leaving group of the substrate by the side chain of a conserved acidic residue (Asp181 in PTP1B) acting as a general acid. This leads to formation of a cysteinyl-phosphate catalytic intermediate. In the later step, mediated by Gln 262, which coordinates a water molecule, and Asp181, which functions as a general base, there is hydrolysis of the catalytic intermediate and release of phosphate (Figure 6.2) [18]. Although several types of PTP1B inhibitors have been reported, because of the low selectivity and poor pharmacokinetic properties, new types of PTP1B inhibitors with

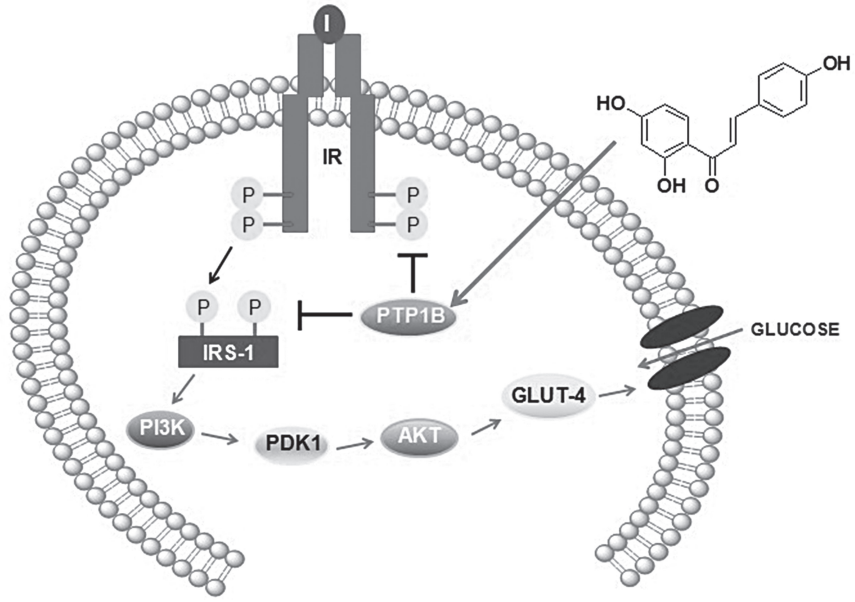


FIGURE 6.1 **(See color insert.)** The physiological role of PTP-1B in glucose metabolism.

improved pharmacological properties are still being sought. Chalcones may be believed to play a major role in the inhibition of PTP1B and can be used to manage diabetes and associated complications with better selectivity and improved pharmacokinetic properties.

6.3 CHALCONES

Natural products have been reported to exhibit promising anti-diabetic activity. They have been the mainstay of various biological activities, of them flavonoids class remained the principle candidate [19]. Flavonoids are a group of heterogeneous heat stable polyphenols with various health benefits. There are more than 4000 polyphenolic compounds have probably existed in the plant kingdom for over 1 billion years [20]. They are ubiquitously found in fruits, vegetables, tea, wine, and are usually subdivided into six classes including flavonols (e.g., quercetin, kaempferol),

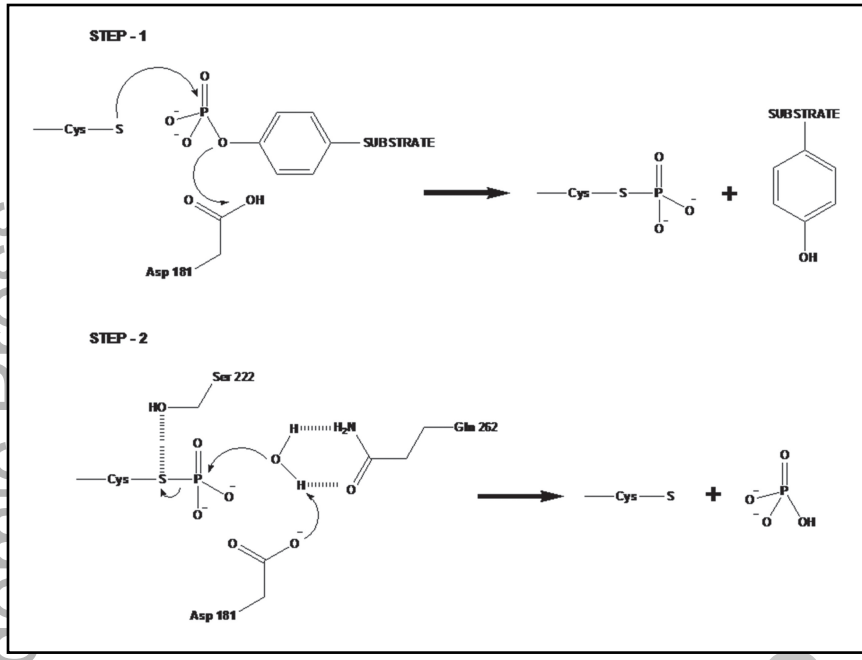


FIGURE 6.2 The process and biochemical pathway of PTP-mediated catalysis in human body.

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]. Various studies have suggested that dietary intake of natural flavonoids displayed protective, modulatory, and mimetic properties that reduce the risk of tumors formation, provide effective hypoglycemic control, etc. Chalcones or 1,3-diphenyl-2E-propene-1-one is an open chain intermediate in aurones synthesis of flavones that exists in many conjugated forms in nature. They are the precursors of flavonoids and isoflavonoids. It contains a benzylideneacetophenone scaffold where the two aromatic nuclei are joined by a three-carbon α, β unsaturated carbonyl bridge [22]. Kostanecki and Tambor, first synthesized a series of natural chromophoric products comprising of α, β unsaturated carbonyl bridge and termed them "chalcone" [23]. Chalcones gained popularity among researchers in this century as compared to other scaffolds due

to its uncomplicated chemistry, simplicity in chemical synthesis, multiplicity of substitutions and multifarious pharmacological potentials such as 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], anti-oxidant [34], anti-obesity [35], hypolipidemic [36], anti-tubercular [37], anti-filarial [38], anti-invasive [39], anti-malarial [40], anti-protozoal [41], anti-bacterial [42], anti-fungal [43], anti-ulcer [44], anti-steroidal [45], immunosuppressant [46], hypnotic [47], anxiolytic [48], anti-spasmodic [49], anti-nociceptive [50], osteogenic [51], etc.

6.4 CHALCONES AS PTP1B INHIBITORS

A large number of chalcones were isolated from nature which has been reported to exhibit potential PTP1B inhibition activity (Figure 6.3). Hoang et al. isolated three methylcyclohexene substituted chalcones derived Diels-Alder type compounds from *Morus bombycis* namely, kuwanon J **(1)**, kuwanon R **(2)**, and kuwanon V **(3)**. All these derivatives showed remarkable inhibition of PTP1B with IC_{50} in range of 2.7–13.8 μM in mixed–type manner. The number of hydroxyl moieties play essential role on activity. The hydroxyl groups not only provided the needed penetration into the active site but also likely to produce an effective hydrogen bonding interaction with the amide backbone of the active-site loop. These facts suggest that with an increase in number of OH groups in chalcone-derived Diels–Alder-type compounds, the potential inhibitory effects against PTP1B increases tremendously. The compound **(2)**, having seven OH groups demonstrate strong dose-independent inhibition, compared to **(3)**, which contains six OH groups. Compound **(1)** has an additional OH group at C-2, which increases the potency of **(1)** upto 3 times with respect to **(3)**. The order of inhibitory activity of chalcone-derived Diels–Alder-type compounds can be summarize as 1>2>3. [52]. Broussochalcone **(4)**, isolated from *Broussonetia papyrifa* was reported to effectively inhibit PTP1B with IC_{50} of 21.5 μM. The two-hydroxyl groups at both the rings are assumed to be responsible for effective inhibition. As the number of hydroxyl groups increases, the inhibitory activity increases concurrently [53]. A novel chalcone, abyssinone-VI-4-O-methyl ether **(5)** was isolated from ethyl acetate-soluble extract of the root bark of *Erythrina mildbraedii*

exhibited *in vitro* PTP1B inhibitory activity with IC_{50} value 14.8 μM [54]. Licochalcone A, isolated from *Glycyrrhiza inflata* and its semi-synthetic derivatives have been reported to be inhibitor of PTP1B. The isolated chalcones isoliquiritigenin **(6)**, echinatin **(7)**, licochalcone A **(8)**, licochalcone C **(9)**, licochalcone E **(10)**, licochalcone B **(11)**, and licochalcone D **(12)**. The semi-synthetic derivatives **(13)** and **(14)** were fabricated by methylation and compounds **(15)** and **(16)** were formed by acetylating the licochalcone A. Compounds **(17)** and **(18)** were prepared by THP-protection of the 4-hydroxy group in the A ring followed by methylation or acetylation of the 4′-hydroxyl group in the B ring and subsequent cleavage of the THP-ether under acidic conditions. Acetylation of compound **(13)** and compound **(17)** affords compounds **(19)** and **(20)**. The semi-synthetic derivative **(13)** presented the highest activity [55–56]. Isoliquiritigenin (ISL) restores PTP1B activity by inhibiting PTP1B oxidation and IR/PI3K/AKT phosphorylation during the early stages of insulin-induced adipogenesis. The antioxidant capacity of ISL attenuated insulin IR/PI3K/AKT signaling through inhibition of PTP1B oxidation, and ultimately attenuated insulin-induced adipocyte differentiation of 3T3-L1 cells [58].

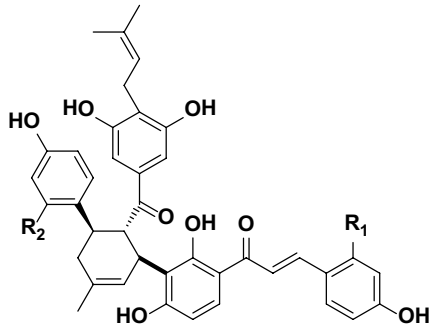
Chalcone scaffold is one of the privileged scaffolds across medicinal chemistry due to ease of synthesis, a large number of chalcone derivatives having potential PTP1B inhibition activity have been recently synthesized rationally. Chalcones and their derivatives are synthesized classically by Claisen-Schmidt condensation between benzaldehyde and acetophenone employing a solution of sodium hydroxide (40%) as catalyst [59]. Recently, microwave assisted synthesis of chalcone gained popularity where irradiation of above chemicals with domestic microwave is often employed [60]. Based on the natural structural template, Chen *et al*. synthesized few novel heterocyclic ring-substituted chalcone derivatives as potent inhibitor of PTP1B where derivatives **(21–29)** showed best inhibitory activity. SAR studies revealed that electron-withdrawing groups on ring B showed better PTP1B inhibitory activity than the compounds containing electron-donating groups. Compound **(28)** showed best result with 99.17% inhibition with IC_{50} value 3.12±0.18 μM [61]. A series of furan chalcone derivatives were reported to exhibit similar activity where two compounds **(30)** and **(31)** showed most effective PTP1B inhibition in competitive manner as experimentally displayed by IC_{50} values of 2.49 and 2.9, respectively. The hydroxylated derivatives containing 2,4-OH

(30), 2-OH **(32)**, and 3-OH **(33)** also showed better inhibitory activity [62]. A number of 2,'4,'6′-trihydroxy chalcone derivatives **(34–42)** have been represented as promising pharmacological candidates for *in vitro* PTP1B inhibition which was similar to reference drugs Na_3VO_4 and oleanolic acid, respectively. From above studies, authors concluded that electron-donating groups on ring B are the key factor in exhibiting significant inhibitory activity [63–64].

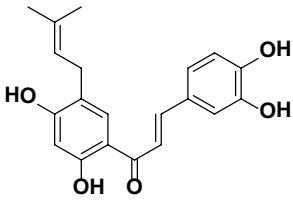
Macdentichalcone **(43)**, an unprecedented polycyclic dimeric chalcone featuring a unique quinonoid moiety, was isolated from *Macaranga denticulata*, together with 1-(5,7-dihydroxy-2,2,6-trimethyl-2H-1-benzopyran-8-yl)-3-phenyl-2-propen-1-one **(44)**, a known monomeric chalcone proposed as a biosynthetic precursor of **(43)**. Both compounds presented noteworthy inhibitory activity against PTP1B *in vitro* with IC_{50} values of 21.0 ± 3.4 μM and 22.0 ± 3.9 μM, respectively [65]. The well-known coumarin based chalcone compounds, (2*E*)-1-(5,7-dihydroxy-2,2,6-trimethyl-2H-benzopyran-8-yl)-3-(4-methoxyphenyl)-2-propen-1-one **(45)**, (2*E*)-1-(5,7-dihydroxy-2,2-dimethyl-2H-benzopyran-8-yl)-3-phenyl-2-propen-1-one **(46)**, and laxichalcone **(47)** showed inhibitory activities against protein tyrosine phosphatase 1B (PTP1B) *in vitro* with IC_{50} values of [66]. Among them, six chalcones, xanthoangelol K **(48)**, xanthoangelol **(49)**, xanthoangelol F **(50)**, 4-hydroxyderricin **(51)**, xanthoangelol D **(52)**, and xanthoangelol E **(53)** showed strong PTP1B inhibitory effect with IC_{50} values of 0.82, 1.97, 1.67, 2.47, 3.97, 1.43, and 2.53 μg/mL, respectively. A kinetic study revealed that compound **(48)** inhibited PTP1B with characteristics typical of a competitive inhibitor. Molecular docking simulations elucidated that ring B of 1 may anchor in a pocket of PTP1B and the molecule is stabilized by hydrogen bonds with Arg47, Asp48, and p–p interaction with Phe182 of PTP1B [67].

6.5 CONCLUSION

The structural features of anti-diabetic chalcones inhibiting protein tyrosine phosphatase 1B **(**PTP-1B), one of the most promising hypoglycemic target have been highlighted in this chapter. A sufficient stress have been given to the molecular pathway involved in insulin-glucose interphase with probable mechanism of chalcone modulators; and structure-activity relationships (SARs) of the 1,3-diphenyl-2E-propene-1-one based



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



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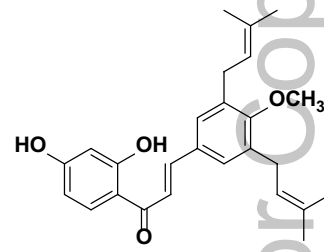

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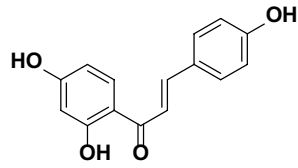

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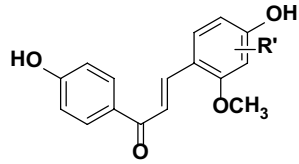


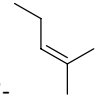
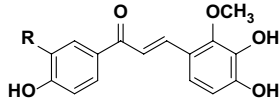
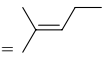
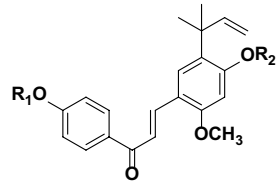
(7) R' = H ; **(8)** R' = 5'-  ; **(9)** R' = 3'-  ; **(10)** R' = 5'- 

FIGURE 6.3 List of reported PTP-1B inhibitors of chalcone scaffolds.

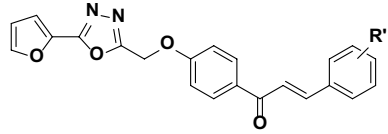




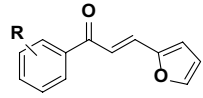
(11) R = H ; **(12)** R =



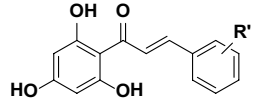
(13) $R_1 = CH_3$, R_2 = H ; **(14)** $R_1 = CH_3$, $R_2 = CH_3$; **(15)** $R_1 = COCH_3$, R_2 = H ; **(16)** $R_1 = COCH_3$, $R_2 = COCH_3$; **(17)** R_1 = H, $R_2 = CH_3$; **(18)** R_1 = H, $R_2 = COCH_3$; **(19)** $R_1 = CH_3$, $R_2 = COCH_3$; **(20)** $R_1 = COCH_3$, $R_2 = CH_3$



(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

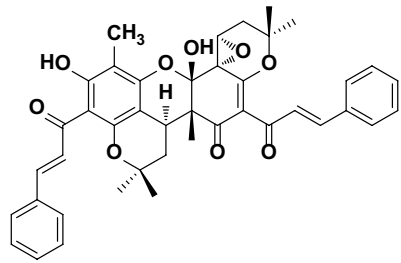


(30) R = 2, 4-OH ; **(31)** R = 3-Cl ; **(32)** R = 2-OH ; **(33)** R = 3-OH



(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

FIGURE 6.3 *(Continued)*



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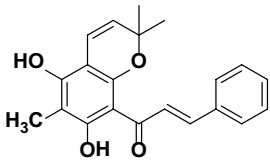

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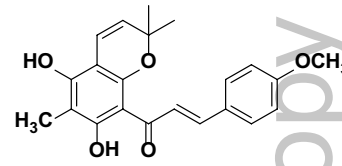

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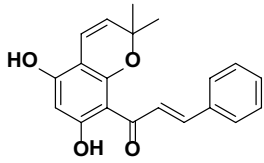

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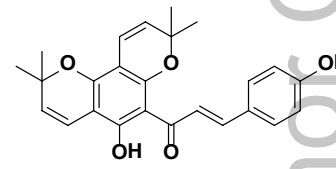

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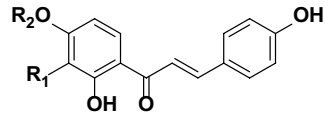
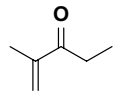
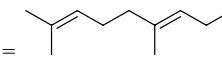
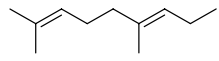
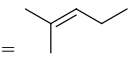


(48) R_1 =  , $R_2 = CH_3$; **(49)** R_1 =  , $R_2 = H$;

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

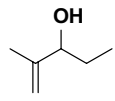
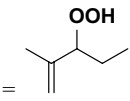
(52) R_1 =  , $R_2 = CH_3$; **(53)** R_1 =  , $R_2 = CH_3$

FIGURE 6.3 *(Continued)*

inhibitors where the profound role of electron withdrawing/donating groups along with importance of heteroaryl ring are comprehensively discussed. As a modulator, at present, none of them have gained proper consideration in medicinal chemistry for hypoglycemic control. Although, they have a huge future prospective to be regarded as potential players for anti-hyperglycemic activity owing to their simple chemistry, multifarious modulation potentials, etc. which will certainly open new avenues in the upcoming decade(s).

KEYWORDS

- **chalcone**
- **diabetes**
- **inhibitors**
- **protein tyrosine phosphatase**
- **PTP1B**
- **structure-activity relationships**

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