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Natural and synthetic glycosylated chalcones as promising bioactive compounds†

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The glycosylated chalcones are being revisited as promising chemical scaffolds in medicinal chemistry because of their improved bioavailability compared to aglycone chalcones. This article briefly highlights the natural *O*- and *C*-glycosylated chalcones present in literature and presents the summary of our recent synthesis of *C*-glucosylated isoliquiritigenin, a *C*-glucosylated chalcone with promising aldose reductase inhibition properties.

Keywords: Glycosylated chalcones, natural glycosides, dihydro chalcones, Aldose reductase inhibition.

1. Introduction

Small organic molecules have been explored as attractive scaffolds to address the problems in medicinal chemistry, which leads to the development of potential therapeutic drugs for various disease[1]. Natural as well as synthetic chalcones have emerged as privileged structures in medicinal chemistry due to diverse biological activities including antimalarial, anti-inflammatory, anticancer and antidiabetic activities associated with simple structural units embedded therein[2a]. Chalcone compounds have a common chemical structure of 1,3-diaryl-2-propen-1-one, also known as chalconoid, that exists as *trans* and *cis* isomers, with the *trans* isomer being thermodynamically more stable. In general, the phenyl ring attached to the carbonyl group is defined to be the A ring and the other benzene ring is named as the B ring (Fig. 1).

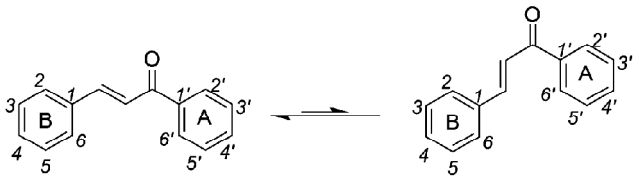


Fig. 1. General structure of chalcone.

Although several mini reviews, describing varied aspects of chalcones were there in the literature prior to 2017[3], Xing *et al.* in 2017, have revisited and summarized several aspects of chalcones, in terms of biosynthesis, synthetic methodologies and target exploration[2a]. Use of chalcones for their antineoplastic properties operating through action on mitochondria present in cancer cells is surfacing as a new strategy towards search of anti-cancer lead molecules[2b]. The inadequate water solubility and poor bioavailability of chalcones appear to be a prominent limitation to their further exploration in medicinal chemistry. Improvement of aqueous solubility and thereby its oral bioavailability remains one of the most challenging aspects of drug development process especially for drug delivery systems. There are numerous approaches available and reported in literature to enhance the solubility of poorly water-soluble drugs[4]. It is envisioned that presence of a carbohydrate moiety could improve the bioavailability of natural products by improving its solubility in aqueous medium. Glycosylation in general is an important tool in medicinal chemistry for the structural and functional diversification of natural products and the attachment of a sugar residue core increases the aqueous solubility and bioavailability of the compound. Glycosylation also renders beneficial physiological and pharmacological properties to the glycosylated compound. Synthesis and diversified applications of *C*-glycosides of natural products in general are comprehensively covered in recent reviews[5].

†**Review.**

Natural glycosylated chalcones

Although, glycosylated chalcones considered as obligate intermediates in flavonoid biosynthesis do not accumulate in appreciable quantities in most plants, several plants containing varied un-glycosylated chalcones have been used in traditional medicine with many beneficial biological effects. The glycosylated chalcones in nature are mostly *O*-glycosylated. Illustrative examples are presented in Fig. 2. Zhu *et al*. in 2011, isolated two new glycosylated chalcones **1** and **2** along with one known **3** from the stems of Entada phaseoloides, often used as part of Chinese herbal medicines[6]. In 2010, Koketsu *et al*. isolated three other bioactive glycosylated chalcones compound **4**, **5** and **6** from the aerial parts of *Brassica rapa* L. '*hidabeni*' and examined the effects of these compounds on the antigen-stimulated degranulation in rat basophilic leukemia RBL-2H3 cells[7]. Treatment with **4** and **5** markedly inhibited antigen (Ag)-stimulated degranulation. Ishimaru *et al*. in 2006, isolated two new chalcone glycosides **7** and **8** from *Sapium sebiferum*. Interestingly chalcone **8** has an allenic ester moiety at C6 position of glucose ring[8]. All these examples illustrate that glycosyl residues are attached through phenolic oxygen in ring A. Shufen *et al*. isolated a *O*-glucosylated chalcone, isoliquiritin **9**[9], form licorice after multistep chromatographic fractionation. This represents an example wherein the glucosyl residue is carried by ring B.

In contrast to *O*-glycosylated chalcones, there are very few examples of *C*-glycosylated chalcones (Fig. 3). The *C*-glycoside chalcone **10** and dihydro chalcone **11** have been isolated from the aqueous extract of heartwood of *Pterocarpus marsupium* (Leguminaceae). Inspired from the bioactivity of these *C*-glycosides, Maurya's group has synthesized several phenolic *C*-glycosides and evaluated their anti-hyperglycemic activity[10]. Chalcone *C*-glucoside **10** and dihydrochalcone *C*-glucoside **11** lowered the blood glucose levels to 33.6% and 26.5% respectively after 24 h on STZ model, which was comparable to the standard clinically used drug metformin. Aspalathin **12**, another dihydrochalcone *C*-glucopyranoside, first characterized by Koeppen and coworkers in 1965[11], is showing renewed activity as a nutraceutical ingredient in foods and beverages[12] due to its beneficial effects on glucose homeostasis in type 2 diabetes by stimulating glucose-uptake in muscle cells and insulin secretion. Limited supply of the same from natural sources

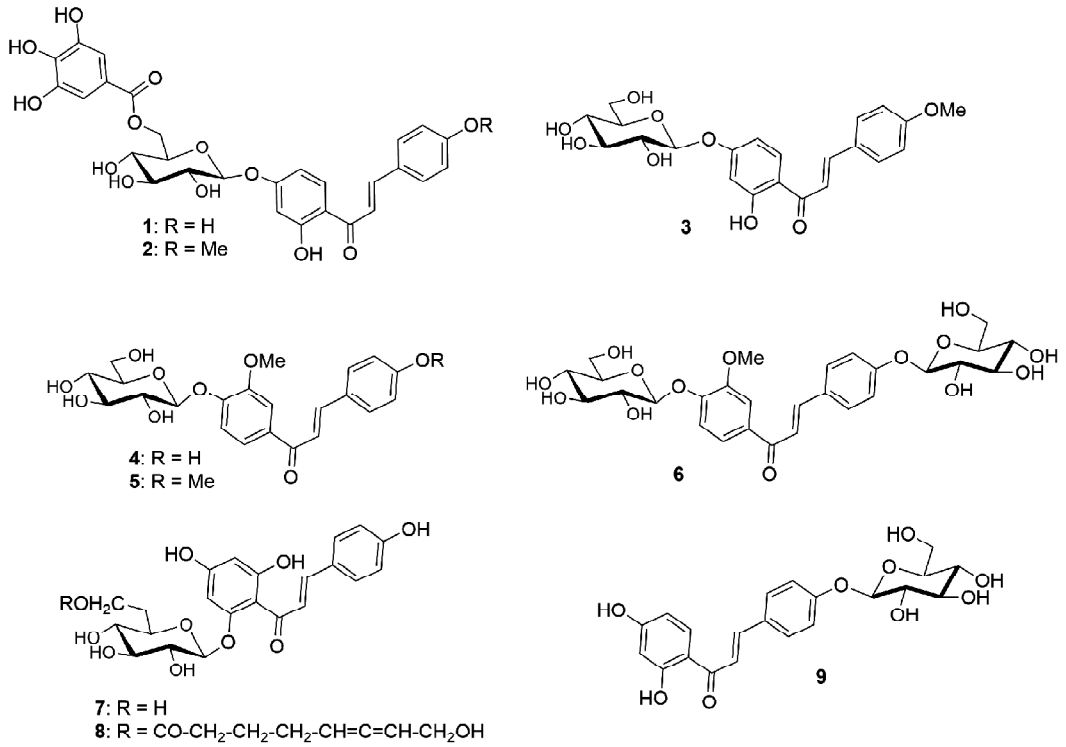


Fig. 2. Representative natural glycosylated chalcones **1-9.**

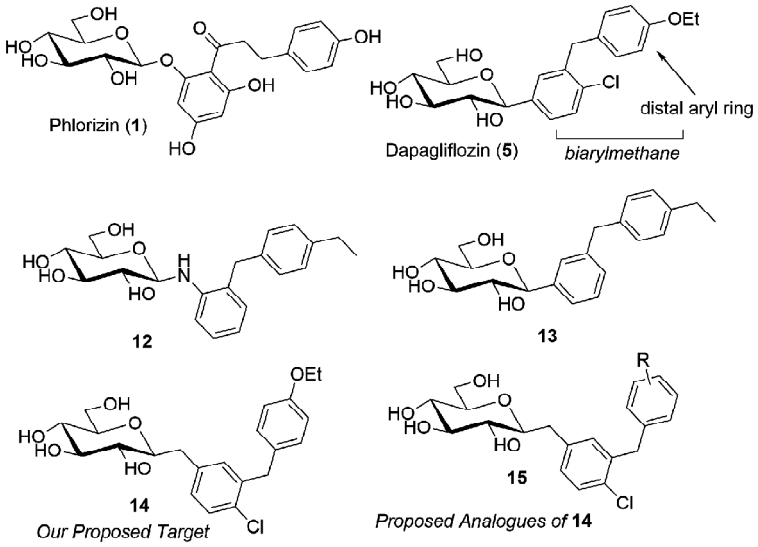


Fig. 3. Natural glucosylated chalcones and dihydrochalcones.

has prompted convenient synthetic routes from several groups[13,14].

Phlorizin **14a**, a natural *O*-glucosylated dihydrochalcone found in dietary constituent of number of fruits and trees has been used as a pharmaceutical and tool for physiology research for over 150 years. Phlorizin's principal pharmacological action is to produce renal glycosuria and block intestinal glucose absorption. It is the first SGLT2 inhibitor of *O*-glycoside class[15a-b] and led to the discovery of the first antidiabetic drug, dapagliflozin[15c], functioning through inhibition of SGLT2. Trilobatin **14b** (Fig. 3), glucosylated at 4′-*O* and isomeric to phlorizin, also exists in nature in various plants[16].

Synthetic *O*- and *C*-glucosylated chalcones

Based on a new concept of direct conjugation of hydrophobic drugs with hydrophilic small molecules, Sudipta *et al*. in 2018[17], synthesized the glucosylated chalcone-boronic acid hybrids, compound **15** (Fig. 4). This was to alleviate major limitations associated with bioactive aglycone chalcone **16**, such as poor water solubility and erratic biodistribution. Interestingly **15** and several other similar compounds self-assembled in water into nanoscale spherical particles and could encapsulate the anticancer drug doxorubicin for breast cancer. The nanoparticle encapsulated drug showed improved efficacy against breast cancer cells.

A series of glycosylated 1,4-substituted triazolyl chalcone derivatives **17** have been synthesized by Misra *et al*. in 2019, in high yield, using 1,3-cycloaddition (click chemistry) of D-glucosyl azides with a variety of propargylated chalcone derivatives followed by de-*O*-acetylation[18]. The synthesized compounds were evaluated for their cytotoxic potential against the human breast carcinoma cell lines and non-cancerous cells. The MTT assay identified three promising cytotoxic compounds among this class for further biochemical studies.

The protected chalcone *C*-glucoside **18** was used by Suzuki *et al*. in 2016 for the synthesis of quinol *C*-glycoside, a novel synthetic analog of carthamin, a natural red pigment[19]. Attempts at the construction of the key quinol *C*-glycoside structure by oxidative de-aromatization of *C*-glycosyl chalcone was generalized with bis(trifluoroacetoxy)iodobenzene in wet acetonitrile in the presence of $NaHCO_3$. An interesting photochemical stability/instability of the chalcone geometry in the synthesized compounds was observed. The chalcone **19** is a key precursor for the synthesis of isoflavonoid natural products genistein and orobol[20]. Oxidative rearrangement of **18** with diacetoxyiodosobenzene followed by acid-catalyzed cyclization with aqueous 6 *M* hydrochloric acid afforded the desired natural products. Similarly, chalcone **20** was used for the synthesis 6,8-di-*C*-glycosylflavanones[21].

C-Glucosylated isoliquiritigenin: A novel chalcone for aldose reductase inhibition

Aldose reductase (ALR) is an NADPH-dependent aldoketoreductase (EC 1.1.1.21). It catalyzes reduction of avariety of hydrophobic as well as hydrophilic aldehydes and is the first enzyme involved in the so-called polyol pathway, wherein

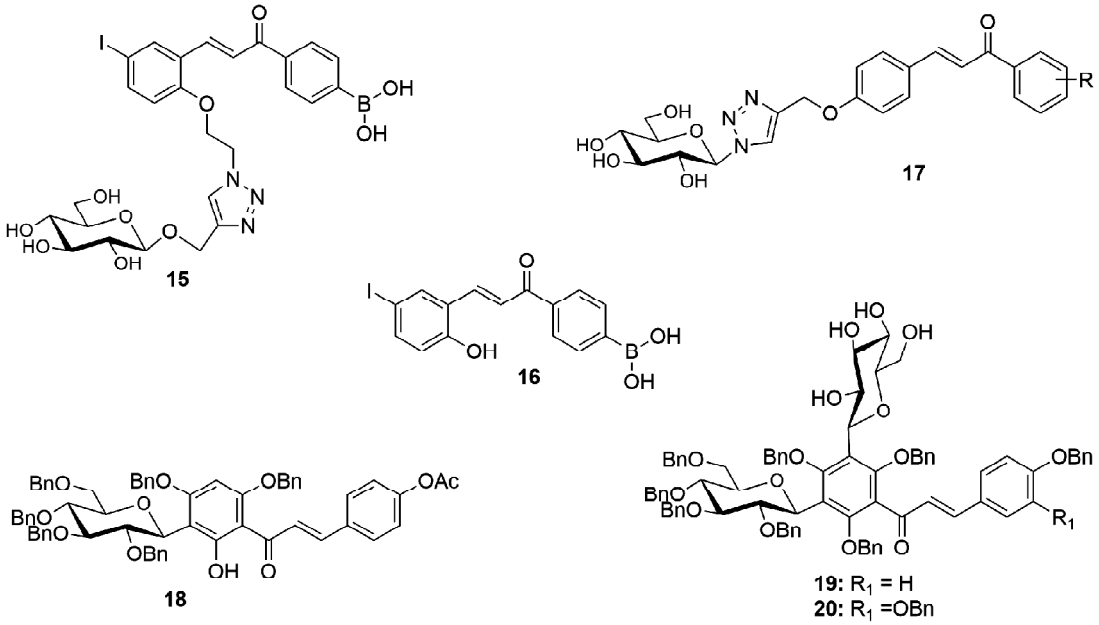


Fig. 4. Synthetic glycosylated chalcones for varied applications.

glucose is reduced by ALR to sorbitol. Increased level of glucose during hyperglycemic conditions has been considered to be the main cause of tissue damage through different mechanisms, including an osmotic imbalance due to sorbitol accumulation[22]. In this context, ALR has surfaced as a target enzyme to develop drugs that actas ALR inhibitors (ALRIs) for prevention of the onset of diabetic complications.

The chalcone, isoliquiritigenin (ISL) **21** and its dihydrochalcone analogue, davidigenin **22** are natural products showing ALR2 inhibition similar to quercetin **23** a well-known ALR2 inhibitor. The former has been isolated from glycyrrhizae radix (licorice)[23] and the later from artemesia plant[24]. Inadequate water solubility and bioavailability are the limitations associated with these chalcones as ALRIs. With the view to increase water solubility and bioavailability, while retaining the innate activity, we had envisaged 4-*C*-glucosylated targets **22** and **23** as potential targets for synthesis and evaluation as ALRIs (Fig. 5).

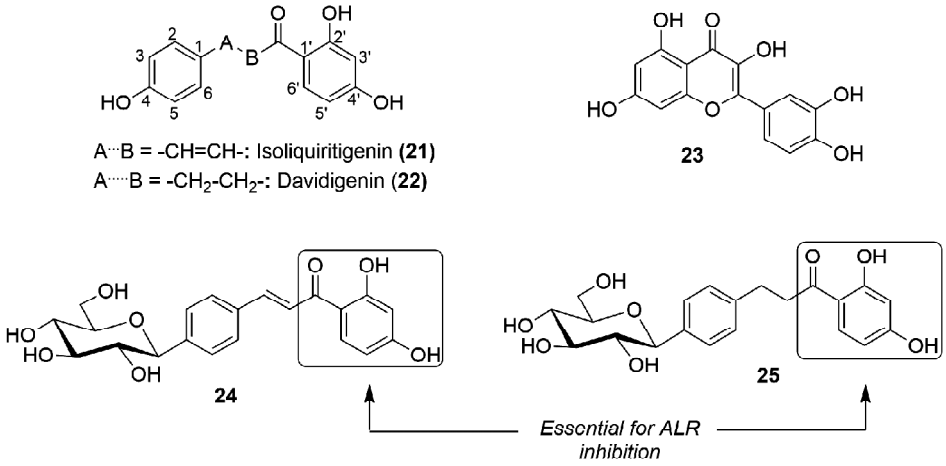
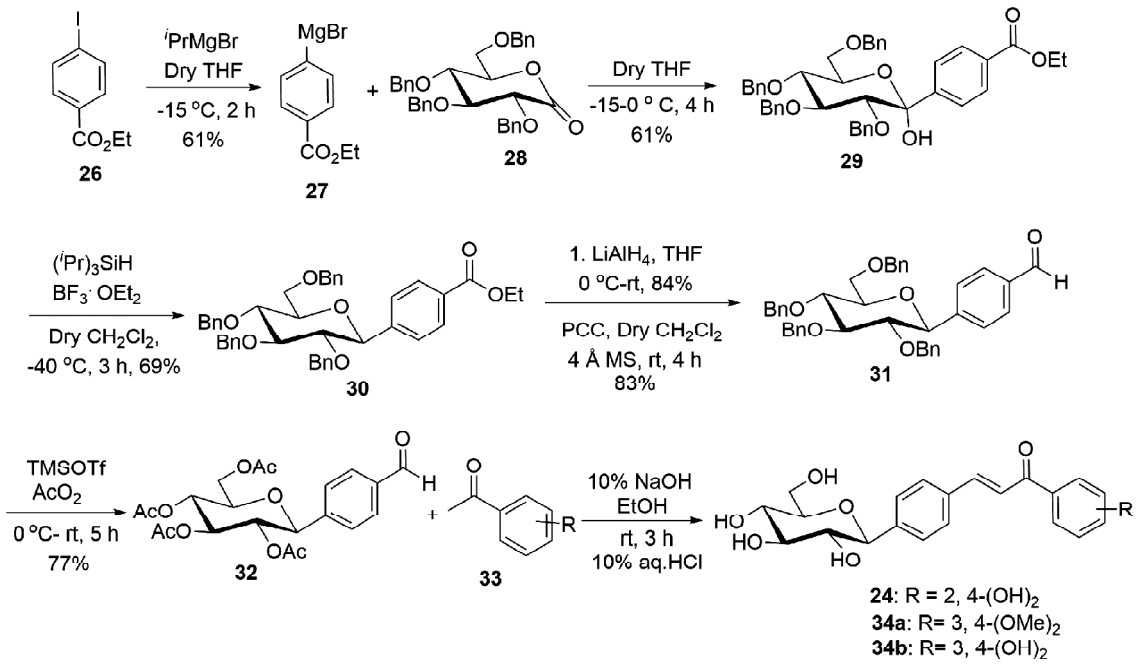


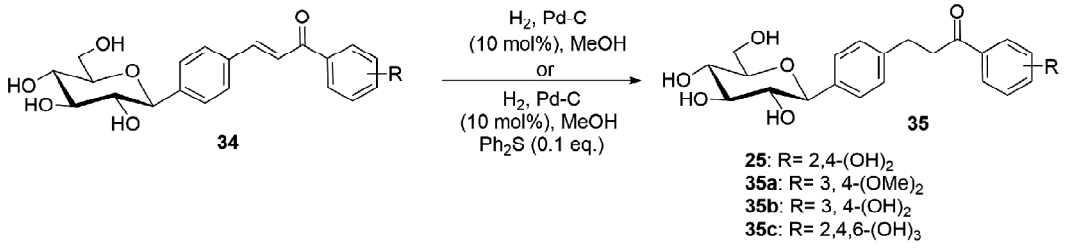
Fig. 5. Proposed *C*-glycosylated chalcone **24** and dihydrochalcone **25**.

Synthesis of targeted compound **24**, **25** and analogues essentially banked on classical Claisen-Schmidt condensation reaction between suitably protected *C*-4-glucosylated benzaldehyde **31** and acetophenones **32** and subsequent deprotections. The synthesis of hitherto unknown building block **31** was readily achieved as described in synthetic Scheme 1[25]. It involved the formation of functionalized aryl magnesium bromide from ethyl-4-iodobenzoate **26** using well known and elegant procedure developed by Knochel's group[26] and the addition of arylmagnesium bromide **27** onto protected D-gluconolactone **28** for the desired C-C bond formation. Reductive anomeric deoxygenation in lactol **29** was carried out using triisopropylsilane and $BF_3.OEt_2$ to afford **30**. Subsequent functional group interconversions on **30** afforded the envisaged benzyl-ether protected building block **31**. Although Claisen-Schmidt reaction with acetophenones could be effected on **31**, threat to the double bond reduction and carbonyl, during debenzylation under hydrogenolytic conditions on chalcones, merited change in the nature of protection on the glucosyl residue in **31**. This was effected, using TMSOTf assisted debenzylation in the presence of acetic anhydride, which afforded building block **32** with acetyl-ester protection. The aldehyde **32** underwent trouble free Claisen-Schmidt reaction with known acetophenones to furnishing the corresponding chalcones, **24**, **34a** and **34b** in good yields.

Although direct hydrogenation using Pd-C (10 mol%) under H_2 balloon pressure (1 atm) was successful for the formation of dihydrochalcone **25** and **35c**, addition of 0.1 equivalent of Ph_2S[27] was mandatory in order to avoid the additional reduction of carbonyl group during the formation of dihydrochalcones, **35a** and **35b** (Scheme 2).



Scheme 1. Synthesis of *C*-glucosylated chalcone **24**.



Scheme 2. Formation of dihydrochalcones from corresponding chalcones.

To our delight, both *C*-glucosylated ISL **24** and *C*-glucosylated davidigenin **25** have exhibited the promising ALR inhibitory activity. The natural product, ISL (**21**), showed 91% inhibition at 100 μM concentration, whereas *C*-glucosylated ISL, **24**, exhibited 100% inhibition at 120 μM concentration. Methyl ether derivatization of phenolic hydroxyl in **24** significantly reduced the activity, thereby corroborating the importance of phenolic hydroxyls. Chalcones containing tri-oxygenated aromatic ring A with oxygenation pattern being 2, 4, 6 essentially showed no activity. Chalcone **34b**, di-oxygenated and positional isomer of *C*-glucosylated ISL **24**, had 61% inhibition at 120 μM and the corresponding methyl ether derivative, exhibited 100% inhibition at 200 μM, whereas the chalcone with mono-oxygenated ring A, had no activity, even at 250 μM. The oxygenation pattern and the number of phenolic hydroxyls in aromatic ring A seems to be crucial for activity. *C*-Glucosylated davidigenin **25**, exhibited AR inhibitory activity of 73% at 120 μM while all other dihydrochalcones were relatively less active compared to the corresponding chalcones. The most promising *C*-glucosylated chalcones and dihydrochalcones for aldose reductase inhibition are presented in Table 1.

Table 1. IC_{50} values for **24**, **25**, **34a-b**, **35a** and **35c** comparing with ISL

Entry	Compd.	IC_{50} (μM)	Entry	Compd.	IC_{50} (μM)
1	ISL	19.00	5	**34a**	145.0
2	**24**	21.00	6	**35b**	245.0
3	**34b**	55.00	7	**35c**	336.0
4	**25**	72.00			

Conclusion

Brief overview of natural and synthetic glycosylated chalcones available in the literature has been presented. *C*-Glucosylated chalcones being more stable analogues, compared to *O*-glycosylated chalcones, are likely to emerge as promising compounds for therapeutic applications. The *O*-glucoside of isoliquiritigenin, known as isoliquiritine, is hydrolytically unstable and in this context synthesis of *C*-glycosylated isoliquiritigenin gains significance. First synthesis of the same has been achieved and evaluated for aldose reductase inhibition. Promising activity should open further avenues for exploration.

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