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Synthesis, biopharmaceutical characterization, antimicrobial and antioxidant activities of 1-(4′-*O*-β-D-glucopyranosyloxy-2′-hydroxyphenyl)-3-aryl-propane-1,3-diones

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ABSTRACT

This research communication is toward the investigation of the antibacterial, antifungal and antioxidant activities of the synthesized compounds 1-(4′-*O*-β-D-glucopyranosyloxy-2′-hydroxyphenyl)-3-aryl-propane-1,3-diones (**5a**)–(**5h**). These compounds have been obtained by the interaction of α-aceto-bromoglucose with 1-(2′,4′-dihydroxyphenyl)-3-aryl-propane-1,3-diones (**3a**)–(**3h**) under anhydrous condition and at lower temperature. The structures of these newly synthesized *O*-β-D-glucopyranosides were established on the basis of chemical, elemental, and spectral analyses. Further, the compounds (**5b**), (**5c**), (**5d**) and (**5g**) showed potent antibacterial and antifungal activity. A good correlation was obtained between the theoretical predictions of bioavailability using Lipinski's rule-of-five and experimental verification.

1. Introduction

The clinical relevance of bacterial and fungal diseases has increased over the past 30 years due to an increasing population of immunocompromised patients who have cancer, AIDS or have received transplants. Actually the problems of multi-drug resistant microorganism have reached on alarming level in many countries around the world. A numbers of recent clinical reports describe the increasing occurrence of penicillin-resistant *Staphylococcus aureus* and other antibiotic-resistant human pathogenic microorganisms in United States of America and European countries. Infections caused by those microorganisms pose a serious challenge to the medical community and need for an effective therapy has led to a search for novel more selective and efficient antimicrobial agents.

In this work, we report the synthesis, antimicrobial and antioxidant activity of *O*-β-D-glucoside derivatives of β-diketones. The β-diketones and carbohydrate have broad spectrum of medicinal values. β-diketones shown to have anecdotal extent of pharmacological activities like antibacterial [1], antiviral [2], insecticidal [3], antioxidant [4] and potential prophylactic antitumor activity [5,6]. It has also been used as an anti-sunscreen agent [7]. In liquid solutions [8] as well as in the solid state [9] beta-diketones exists almost exclusively as the enol tautomer, which is stabilized by the intramolecular hydrogen bonding. Recently it is reported that β-ketoenols are important pharmacophores of HIV-1 integrase (IN) inhibitors [10].

The rational design of new HIV-1 Integrase (H-I) inhibitors, one validated target for chemotherapeutic intervention [11], is fundamentally based on intermolecular coordination between H-I/chemical inhibitor/metals (Mg^{2+} and Mn^{2+}, co-factors of the enzyme), leading in the formation of bimetallic complexes [12,13]. Thereby, several bimetallic metal complexes, in many cases exploring the well-known polydentate ligands, appear in this scenario as the most promising concept to employ in either enzyme/drug interaction or electron transfer process, in the last case involving the biological oxygen transfer [14–16]. Another exciting

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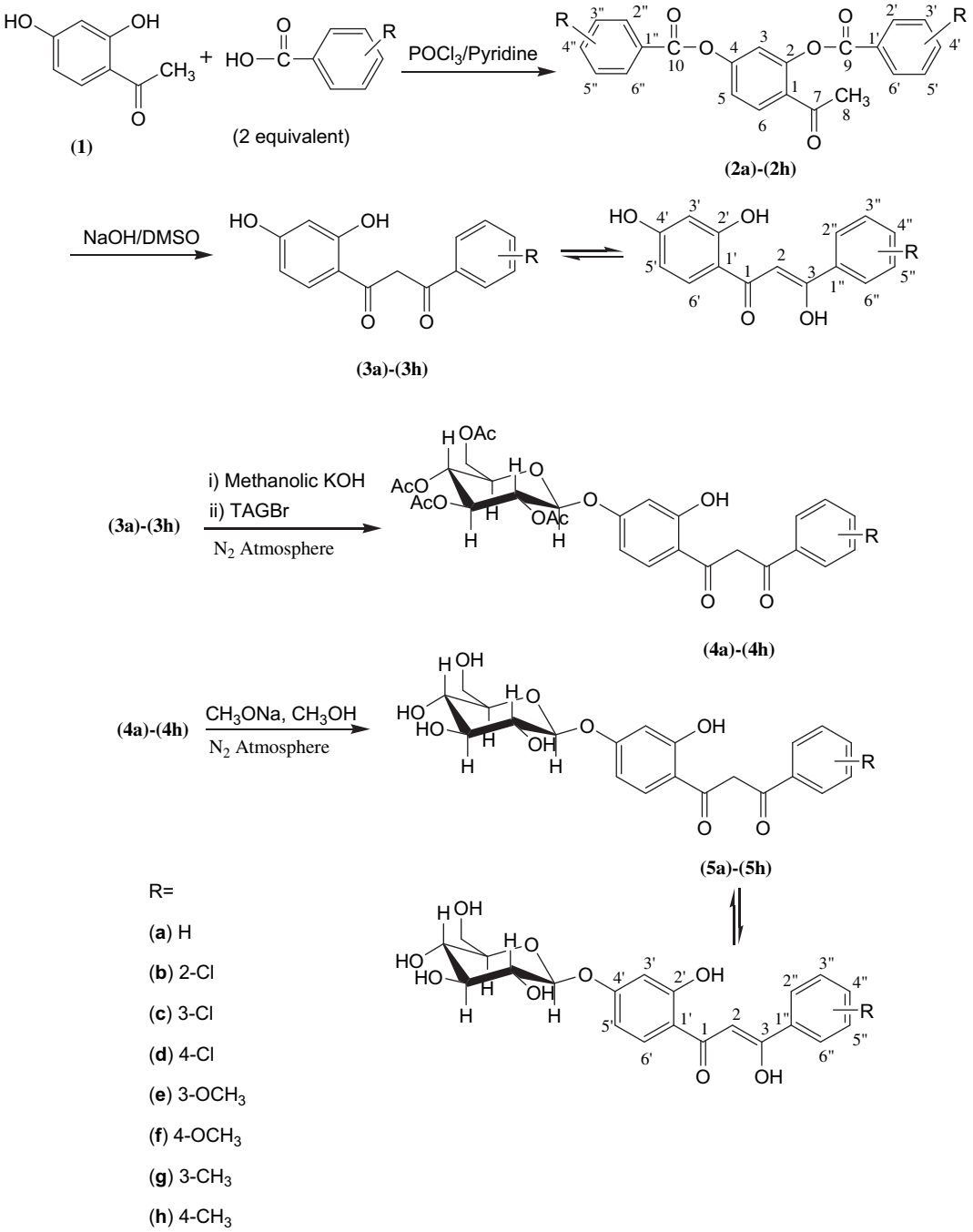
example of application for such polydentate ligand involves the synergic water activation, which occurs via the so-called "remote metallic atoms". Such organometallic compounds are structurally deemed to promote or block the H-I activity [17]. These explanations above detailed clearly demonstrate that polydentate ligands are of special interest in the bioorganometallic chemistry field [18]. Looking for the design of new bimetallic coordinating ligands to further explore in the building of intermolecular system involving H-I/inhibitor/metal complexation, we have targeted to study the synthesis and structural biology of diketo O,O,O-ligands (**5a**)–(**5h**).

Correspondingly, carbohydrates play important structural and functional roles in numerous physiological processes, including various disease states [19,20]. The relatively recent recognition of carbohydrates as a medicinally relevant class of biomolecules has led to the investigation of therapeutic agents based on either glycan structure or mimics thereof [21]. For example, cancer cell metastasis [22] and cell–cell adhesion in the inflammatory response [23] are dependent on cell surface presentation of specific glycans. Synthetic carbohydrates-based cancer vaccines [24] and small molecules selective inhibitors [25] are thereof being pursued as potential medicinal agents, respectively. Likewise, the initial stages of bacterial or viral infection often rely on the recognition of host cell glycoconjugates by the invading organism [26].

The enormous significance of β-diketones and carbohydrate-based drugs caught our attention for the synthesis of *O*-β-D-glucosyl derivatives of β-diketones and to study their pharmacological



Scheme 1. Synthesis of 1-(4′-*O*-β-D-glucopyranosyloxy-2′-hydroxyphenyl)-3-arylpropane-1,3-diones (**5a**)–(**5h**).

activities viz., antibacterial, antifungal and antioxidant in first stage and then against HIV and various virus.

2. Chemistry

In this study eight new *O*-β-D-glucosides of 1-(2′,4′-dihydroxyphenyl)-3-aryl-propane-1,3-diones have been synthesized and their antibacterial, antifungal and antioxidant activities were evaluated.

At the first stage, 1-(2′,4′-dihydroxyphenyl)-3-aryl-propane-1,3-diones (**3a**)–(**3h**) were prepared from 2,4-diaroyloxyacetophenones (**2a**)–(**2h**) employing Baker-Venkataraman transformation. The functionalized β-diketones (**3a**)–(**3h**) in 2.5% methanolic KOH solution were then coupled with α-acetobromoglucose (glucosyl donor used for glucosylation) under nitrogen atmosphere to give 1-[2′-hydroxy-4′-(2‴,3‴,4‴,6‴-tetra-*O*-acetyl-*O*-β-D-glucopyranosyloxy) phenyl]-3-aryl-propane-1,3-diones (**4a**)–(**4h**). In the final stage, tetra-*O*-acetyl-*O*-β-D-glucosides (**4a**)–(**4h**) were deacetylated in dry methanol with sodium methoxide solution under nitrogen atmosphere to afford 1-(4′-*O*-β-D-glucopyranosyloxy-2′-hydroxyphenyl)-3-aryl-propane-1,3-diones (**5a**)–(**5h**). The structures of the synthesized compounds were confirmed by spectral methods (FT IR, ^{1}H NMR, ^{13}C NMR, Mass) and elemental analysis. The detailed synthetic strategy is outlined in the Scheme 1.

3. In vitro antimicrobial and antioxidant activity

The present paper is focused on the synthesis of novel *O*-β-D-glucosides of 1-(2′,4′-dihydroxyphenyl)-3-aryl-propane-1,3-diones as possible antibacterial, antifungal and antioxidant agent. The minimal inhibitory concentrations (MICs, mg mL^{-1}) of tested compounds against certain bacteria and fungi are shown in Tables 1 and 2. A series of novel compounds (**5a**)–(**5h**) were prepared and tested for their in vitro antimicrobial activity against the four strains of bacteria (gram +ve, gram −ve), and two strains of fungi (*Candida albicans* and *Candida glabrata*). Four compounds of the obtained series showed high in vitro antimicrobial activity. 1-(4′-*O*-β-D-Glucopyranosyloxy-2′-hydroxyphenyl)-3-(2″-chlorophenyl)-propane-1,3-dione (**5b**) showed excellent activity against *Escherichia coli* and *Pseudomonas aeruginosa*, 1-(4′-*O*-β-D-glucopyranosyloxy-2′-hydroxyphenyl)-3-(3″-chlorophenyl)-propane-1,3-dione (**5c**) showed excellent activity against *E. coli* indicated in vitro antibacterial activity comparable to slightly lower than the Ampicillin. 1-(4′-*O*-β-D-Glucopyranosyloxy-2′-hydroxyphenyl)-3-(4″-chlorophenyl)-propane-1,3-dione (**5d**) and 1-(4′-*O*-β-D-glucopyranosyloxy-2′-hydroxyphenyl)-3-(3″-methylphenyl)-propane-1,3-dione (**5g**) showed excellent activity against *C. albicans* in vitro antifungal activity comparable to slightly lower than the Fluconazole and against *S. aureus* indicated in vitro antibacterial activity comparable to slightly lower than the Ampicillin respectively. The presence of electron-withdrawing group on the aromatic ring in general increases the antimicrobial activities of the tested compounds compared to compounds having electron-donating groups. Based upon the results it will also be necessary to optimize the lead compound by substitution in the C_2, C_3 and C_4 position in both the phenyl ring by chloro and polar group seems to be very important for antibacterial effect, as well as the presence of glucosidic moiety in the aromatic ring seems to be very important for antibacterial effect and cell–cell recognition.

These results suggested that *O*-β-D-glucosides had effective improvement of bioavailability and the electro-acceptor or electro-donor nature of substituent (R) had effective and direct impact on selective antimicrobial activities against both bacteria and fungi. Table 2 also summarizes free radical scavenging activity (antioxidant activity) using the DPPH assay method. According to these results, the newly synthesized *O*-β-D-glucosides had more promising antioxidant activity.

4. Results and discussion

4.1. Spectroscopic characterizations of compounds

4.1.1. IR spectra

The IR spectra of (**3a**) showed a stretching frequency at 3420 cm^{-1} and 1743 cm^{-1} corresponds to OH and C=O respectively. The *O*-β-D-glucoside 1-(4′-*O*-β-D-glucopyranosyloxy-2′-hydroxyphenyl)-3-phenyl-propane-1,3-dione (**5a**) posses the characteristic bands at 3400 cm^{-1} (OH peak of carbohydrate residue) and 2854 cm^{-1} (glucosidic CH) indicating the formation of *O*-β-D-glucoside. This was also confirmed by its ^{1}H NMR, ^{13}C NMR, and Mass spectral data.

4.1.2. ^{1}H and ^{13}C NMR spectra

The ^{1}H NMR spectrum of (**3a**) exhibited a singlet at δ 15.72 ppm due to enolic proton (since enol form in β-diketone is more stable), a singlet at δ 12.02 ppm due to phenolic proton adjacent to the carbonyl group and a singlet at δ 4.76 ppm corresponds to the phenolic proton away from carbonyl group. ^{13}C NMR spectra gives a singlet at δ 192.1 ppm due to ketonic carbon C-1 and at δ 178.4 ppm due to enolic carbon C-3 confirming the keto-enol tautomerism in β-diketone (**3a**). The presence of characteristic ^{1}H NMR peaks and ^{13}C NMR peaks are consistent with the structure of 1-(2′,4′-dihydroxyphenyl)-3-phenyl-propane-1,3-dione (**3a**). The

Table 1
Antibacterial activity of compounds (**5a**)–(**5h**). Minimum inhibitory concentrations (MICs, mg/mL).

Compound	R	Antibacterial Activity[a]			
		S. aureus ATCC 25923	*B. subtilis* ATCC 6633	*E. coli* ATCC 27853	*P. aeruginosa* ATCC 27853
5a	H	0.3	0.15	1.25	0.15
5b	2-Cl	0.15	1.25	0.02	0.02
5c	3-Cl	0.15	0.625	0.02	1.25
5d	4-Cl	0.15	0.3	0.07	0.02
5e	3-OCH_3	0.625	0.15	2.5	5.0
5f	4-OCH_3	2.5	2.5	5	0.03
5g	3-CH_3	0.02	2.5	5.0	10
5h	4-CH_3	0.625	2.5	5.0	5.0
Ampicillin	–	0.019	0.005	0.01	0.005

[a] Antibacterial activity: In present protocol 1.25 mg mL^{-1} is considered as moderate activity, 0.07 mg mL^{-1} is considered as good activity and 0.019 mg mL^{-1} is considered as excellent activity compared to the standard drug Ampicillin.

Table 2
Antifungal and antioxidant activity of compounds (**5a**)–(**5h**). Minimum inhibitory concentration (MICs, mg/mL).

Compound	R	Antifungal Activity[a]		Antioxidant Activity
		C. albicans ATCC 10231	*C. glabrata* ATCC 36583	DPPH % Inhibition antioxidant
5a	H	2.5	2.5	81.15
5b	2-Cl	5.0	5.0	89.11
5c	3-Cl	10	10	83.52
5d	4-Cl	0.15	5.0	84.34
5e	3-OCH_3	10	5.0	77.34
5f	4-OCH_3	1.25	2.5	73.45
5g	3-CH_3	2.5	10	79.49
5h	4-CH_3	5.0	5.0	81.98
Fluconazole	–	0.01	0.01	–
Ascorbic acid	–	–	–	98.03

[a] Antifungal activity: In present protocol 0.15 mg mL^{-1} is considered as excellent activity compared to the standard drug Fluconazole.

Mass spectrum showed a molecular ion peak at 256 (M^+), confirms the molecular formula $C_{15}H_{12}O_4$ of (**3a**). The ^1H and ^{13}C NMR data show the presence of carbohydrate moiety. The chemical shifts of the anomeric proton show β-linkage at δ 5.89 ($J_{1,\ 2}$ = 8.2 Hz), indicating the linkage of the carbohydrate unit to the C-4″ position of the aglycone moiety. Compound (**5a**) exhibited δ 7.43 (d, 2H, $J_{2''-6''}$ = 8.8 Hz, 2″-H, 6″-H), 6.54–7.73 (m, 5H, Ar–H), and the characteristic pyranosyl ring protons at δ 3.41–4.80, all are in agreement with the structure of 1-(4′-*O*-β-D-glucopyranosyloxy-2′-hydroxyphenyl)-3-phenyl-propane-1,3-dione (**5a**). Further the structure of **5a** was confirmed by its molecular ion peak at 418.

5. Virtual screenings and molecular properties calculations

5.1. Molinspiration calculations [27,33]

MiLog*P* (octanol/water partition coefficient) is calculated by the methodology developed by Molinspiration as a sum of fragment-based contributions and correction factors (Tables 3 and 4). The method is very robust and is able to process practically all organic and most organometallic molecules. Molecular Polar Surface Area TPSA is calculated based on the methodology published by Ertl et al. as a sum of fragment contributions [27,32]. O- and N- centered polar fragments are considered. PSA has been shown to be a very good descriptor characterizing drug absorption, including intestinal absorption, bioavailability, Caco-2 permeability and blood–brain barrier penetration. Prediction results of compounds (**5a**)–(**5h**) molecular properties (TPSA, GPCR ligand and ICM) are valued in Tables 3 and 4 (Supplementary information). Oral bioavailability is a desirable property of compounds under investigation in the drug discovery process. Lipinski's rule-of-five is a simple model to forecast the absorption and intestinal permeability of a compound. In the rule-of-five model, compounds are considered likely to be well absorbed when they possess these attributes-molecular weight < 500, cLog*P* < 5, number of H-bond donors < 5, number H-bond acceptors < 10, and number of rotatable bonds < 10. Lipophilicity (log *P* value) and polar surface area (PSA) values are two important properties for the prediction of oral bioavailability of drug molecules [28,29]. Therefore we have calculated log *P* and PSA values for compounds (**5a**)–(**5h**) using molinspiration software programs and compared them with the values obtained for standard drugs Ampicillin and Fluconazole. For all the compounds, without exception, the calculated clog*P* values were around 0.5–2.5 (<5), which is the upper limit for the drugs to be able to penetrate through biomembranes according to Lipinski's rules. So all of these compounds present good oral bioavailability.

The lowest degree of lipophilicity among all the compounds was exhibited by compounds (**5a**)–(**5h**), which are an indication for good water solubility. The polar surface area (PSA) is calculated from the surface areas that are occupied by oxygen and nitrogen atoms and by hydrogen atoms attached to them. Thus, the PSA is closely related to the hydrogen bonding potential of a compound [29]. Molecules with PSA values around of 160 Å or more are expected to exhibit poor intestinal absorption [29]. Table 4 shows that all the compounds are within this limit. It has to be kept in mind that log *P* and PSA values are only two important, although not sufficient criteria for predicting oral absorption of a drug [30]. To support this contention, note that all the compounds have only one violation of the Rule-of-five. Two or more violations of the rule-of-five suggest the probability of problems in bioavailability [31]. All B and C Tautomeric forms of the compounds (**5a**)–(**5h**) have only one violation of the rule-of-five with Tautomeric form A is having zero violation. Drug likeness of compounds (**5a**)–(**5h**) is tabulated in Table 4. Drug likeness may be defined as a complex balance of various molecular properties and structure features which determine whether particular molecule is similar to the known drugs. These properties, mainly hydrophobicity, electronic distribution, hydrogen bonding characteristics, molecule size and flexibility and presence of various pharmacophore features influence the behavior of molecule in a living organism, including bioavailability, transport properties, affinity to proteins, reactivity, toxicity, metabolic stability and many others. Activity of all eight compounds and standard drugs were rigorously analyzed under four criteria of known successful drug activity in the areas of GPCR ligand activity, ion channel modulation, kinase inhibition activity, and nuclear receptor ligand activity. Results are shown for all compounds in Table 4 by means of numerical assignment. Likewise all compounds have consistent negative values in all categories and numerical values conforming and comparable to that of standard drugs used for comparison. Therefore it is readily seen that all the compounds are expected to have near similar activity to standard drugs used based upon these four rigorous criteria (GPCR ligand, ion channel modulator, kinase inhibitor, and nuclear receptor ligand).

5.2. Osiris calculations [27,34]

Structure based design is now fairly routine but many potential drugs fail to reach the clinic because of ADME-Tox liabilities. One very important class of enzymes, responsible for many ADMET problems, is the cytochromes P450. Inhibition of these or production of unwanted metabolites can result in many adverse drug reactions. With our recent work on the drug design by combination of various pharmacophore sites by using heterocyclic structure, it is now possible to predict activity and/or inhibition with increasing success in two targets (bacteria and HIV) [27,35]. This was done using a combined electronic/structure docking procedure and an example will be given here. The remarkably well behaved mutagenicity of divers synthetic molecules classified in data base of CELERON Company of Swiss can be used to quantify the role played by various organic groups in promoting or interfering with the way a drug can associate with DNA. The Osiris calculations are tabulated in Tables 3 and 4 (Supplementary information). Toxicity risks (mutagenicity, tumorogenicity, irritation, reproduction) and physicochemical properties (miLog*P*, solubility, drug likeness and drug-score) of compounds (**5a**)–(**5h**) are calculated by the methodology developed by Osiris. The toxicity risk predictor locates fragments within a molecule, which indicate a potential toxicity risk. Toxicity risk alerts are an indication that the drawn structure may be harmful concerning the risk category specified. From the data evaluated in Table 4 indicates that, all structures are supposed to be non-mutagenic, non-irritating with no reproductive effects when run through the mutagenicity assessment system comparable with standard drugs used. The log *P* value of a compound, which is the logarithm of its partition coefficient between n-octanol and water, is a well-established measure of the compound's hydrophilicity. Low hydrophilicities and therefore high log *P* values may cause poor absorption or permeation. It has been shown for compounds to have a reasonable probability of being well absorb their log *P* value must not be greater than 5.0. On this basis, all the compounds (**5a**)–(**5h**) are having log *P* values in the acceptable criteria. Along with this, compound (**5g**), which have shown good antibacterial screening results against *S. aureus* ATCC 25923 (MIC = 0.019), is having same log *P* value as compared to other compounds in the series.

5.2.1. The aqueous solubility of compounds

The aqueous solubility of a compound significantly affects its absorption and distribution characteristics. Typically, a low solubility goes along with a bad absorption and therefore the general

aim is to avoid poorly soluble compounds. Our estimated log *S* value is a unit stripped logarithm (base 10) of a compound's solubility measured in mol/liter. There are more than 80% of the drugs on the market have an (estimated) log *S* value greater than −4. In case of compounds (**5a**)–(**5h**), values of log *S* are around −4. Further, Table 4 shows drug likeness of compounds (**5a**)–(**5h**) which is in the comparable zone with that of standard drugs used for comparison. We have calculated overall drug score (DS) for the compounds (**5a**)–(**5h**) and compared with that of standard drugs Ampicillin and Fluconazole used as shown in Table 4. The drug score combines drug likeness, miLog*P*, log *S*, molecular weight and toxicity risks in one handy value than may be used to judge the compound's overall potential to qualify for a drug. This value is calculated by multiplying contributions of the individual properties with the equation (1):

$$\mathrm{DS} = \prod\left(\frac{1}{2} + \frac{1}{2}Si\right)\prod ti \qquad (1)$$

where; $S = 1/1 + \mathrm{eap} + \mathrm{b}$.

DS is the drug score. *Si* is the contributions calculated directly from of miLog*P*; log *S*, molecular weight and drug likeness (*pi*) via the second equation, which describes a spline curve. Parameters *a* and *b* are (1, −5), (1, 5), (0.012, −6) and (1, 0) for miLog*P*, log *S*, molecular weight and drug likeness, respectively. *ti* is the contributions taken from the four toxicity risk types. The *ti* values are 1.0, 0.8 and 0.6 for no risk, medium risk and high risk, respectively. The reported compounds (**5a**)–(**5h**) showed moderate to good drug score as compared with standard drugs used.

5.3. Petra calculations [27,34]

PETRA is a program package comprising various empirical methods for the calculation of physicochemical properties in organic molecules. All methods are empirical in nature and have been developed over the last 20 years in the research group of Prof. J. Gasteiger.

The following chemical effects can be quantified: heats of formation, bond dissociation energies, sigma charge distribution, π-charge distribution, inductive effect, resonance effect, delocalization energies and polarizability effect. The series of compounds (**5a**)–(**5h**) have been subjected to delocalized-charge calculations using Petra method of the non-hydrogen common atoms, obtained from the partial *pi*-charge of the heteroatoms, have been used to model the bioactivity against bacteria. It is found that the negative charges of the oxygen atoms and the partial *pi* positive charges of oxygen atoms contribute positively in favor of an antibacterial activity, more, and this is in good agreement with the mode of antibacterial action of the compounds bearing ($X^{\delta-}\cdots Y^{\delta+}$) pharmacophore(s) site(s). It was hypothesized that difference in charges between two heteroatoms of the same pharmacophore site ($X^{\delta-}\cdots Y^{\delta+}$) may facilitate the inhibition of bacteria, more than viruses. This hypothesis was rationalized as follows [27,34].

The structure of synthesized beta-diketo-sugar derivatives (**5a**)–(**5h**) for ease of analysis can be divided into three parts, Viz., central diketo skeleton, substituted-phenyl ring and another phenyl ring as side chain attached to glucosyl moiety. We have fixed the former diketo skeleton part and varied the latter two by substituting with several functional groups such as 2-Cl, 3-Cl, 4-Cl, 3-OCH_3, 4-OCH_3, 3-CH_3, 4-CH_3 and substituting the H-2 of second phenyl ring by 2-hydroxyl one in case of all compound (**5a**)–(**5h**). Compound (**5f**) is among the least active substances to have been evaluated as antibacterial agents in this series having average zone of inhibition ranging from 5 mm to 10 mm (MICs = 0.03–5 mg/mL). In case of compound (**5a**), there is no substitution on the terminal phenyl ring. Accordingly, an effort was initiated to establish a pharmacophore hypothesis to delineate the requirements of the active site via a comprehensive program of analog synthesis and evaluation of the effects of structural modification(s) on antibacterial activity of (**5a**). We then set out to determine the resultant in vitro effects of chemical alterations in this region. The modulating antibacterial effect(s) of substituent having different electronegative properties, located at the ortho, meta and para-positions of phenyl ring sites were ascertained next. A combination of the intact diketo-2-hydroxyl-phenyl-sugar skeleton and substituted −Cl at position-2 on the phenyl ring (**5b**), at position-3 (in case of **5c**) and at position-4 (in case of **5d**) generated higher antibacterial activity with respect to remaining series in both the Gram-positive and Gram-negative inhibition tests. We postulate that the strong tendency to form a ($OH^{\delta+}\cdots O^{\delta-}$) dipolar pharmacophore site in the predominant form is likely to be responsible for the rise of biological activity observed with these semi π-conjugated derivatives. If this hypothesis is correct, by modifying parent molecule (**5a**), we may be able not only to modulate the degree of interaction of the compound with various bacteria but to orient the nature (antibacterial or antiviral) of bioactivity.

6. Conclusion

The O,O-functionalized beta-diketo-sugar [1-(4′-*O*-β-D-glucopyranosyloxy-2′-hydroxyphenyl)-3-aryl-propane-1,3-diones] molecules have been synthesized by glucosylation of 1-(2′,4′-dihydroxyphenyl)-3-aryl-propane-1,3-diones with glucosyl donor in good yield. All the synthesized *O*-β-D-glucosides (**5a**)–(**5h**) were characterized by spectral and elemental analyses. The synthesized compounds were studied theoretically for prediction of bioactivity and verified experimentally. All the compounds (**5a**)–(**5h**) were screened for the antimicrobial and antioxidant activity. The compounds (**5b**), (**5c**), (**5d**) and (**5g**) were found to be potent antibacterial and antifungal agents comparable with Ampicillin and Fluconazole. The newly synthesized (**5a**)–(**5h**) were also shown to have the promising antioxidant activity. Both, the theoretical predictions and experimental verification found to have a good correlation. Thus, it is concluded that the compounds were found to possess a broad range of hydrophilic and lipophilic character, revealed by their Log *S* and Log *P* values respectively. All the B and C tautomeric forms of the compounds (**5a**)–(**5h**) have only one violation of the rule-of-five whereas tautomeric form A is having zero violation, hence an indication of favorable bioavailability based on drug likeness. The presence of glucosyl moiety in the compounds increased its significant hydrophilic nature (supported by its Log *S* values around −4). The considerable number of hydrogen donor/acceptor atoms incurred significant hydrophilic character into the majority of these drugs (supported by Log *P* values less than 5). Comparing relative activity scores of Ampicillin and Fluconazole utilizing four drug classes (GPCR ligand, ion channel modulator, kinase inhibitor, and nuclear receptor ligand) showed all compounds are very highly correlated with expected similar bioactivity. On the basis of hypothesis based on Petra, it is found that, these compounds could form the highly interesting combined two or more pharmacophore sites in one molecule typically. It is predicted that most of these compounds could be used without great risk of toxicity in diverse antibacterial activity. Thus, the drug score combines drug likeness, miLog*P*, log *S*, molecular weight and toxicity risks in one handy value not only proves the compound's overall potential to qualify for a drug but also potentially interesting for further optimization.

7. Experimental protocols

7.1. Materials and methods

Melting points were determined in open glass capillaries and are uncorrected. Elemental analyses were determined using the Perkin Elmer 2400 CHN analyzer. FT-IR spectra were recorded using (KBr) disc on Perkin–Elmer spectrum Rx-I spectrometer. ^{1}H NMR and ^{13}C NMR were recorded on Bruker AC-300 F (300 MHz) NMR spectrometer by using DMSO-d_6 and $CDCl_3$ as solvent and tetramethylsilane as an internal standard. Mass spectra were recorded on 70-S Mass spectrometer using m-nitrobenzyl alcohol (NBA) matrix.

7.2. General procedure for the synthesis of compounds (**2**)–(**5**)

7.2.1. General procedure for the preparation of 2,4-diaroyloxyacetophenones (**2**)

Resacetophenone (**1**) (0.01 mol) and aromatic carboxylic acids (0.02 mol) were dissolved in 5 mL of redistilled pyridine and cooled, to that $POCl_3$ 1 mL was added drop wise with constant stirring maintaining the temperature below 20 °C. The reaction mixture was kept overnight at room temperature and poured with stirring on ice cold dil HCl (1 mol in 50 mL). A white granulated solid compound (**2**) separated out which was washed with cold water, dil $NaHCO_3$ solution and again with cold water. The product was filtered off, dried and recrystallized from alcohol. The completion of the reaction was monitor by TLC.

*7.2.1.1. 2,4-Dibenzoyloxyacetophenone (**2a**).* Yield 78%; mp 78 °C; FT-IR (KBr): 1765 (ester C=O), 1690 (C=O), 1601 (aromatic C=C), 1145 (C-O); ^{1}H NMR (DMSO-d_6, δ, 300 MHz) 2.53 (s, 3H, CH_3), 8.02 (d, 2H, $J_{2'-6'}$ = 7.8 Hz, 2′-H, 6′-H), 8.07 (d, 2H, $J_{2''-6''}$ = 7.8 Hz, 2″-H, 6″-H), 6.73–7.91 (m, 8H, Ar–H), 6.73 (s, 3-H, Ar–H); ^{13}C NMR (DMSO-d_6, δ, 300 MHz) 199.5 (s, C-7, C=O), 153.7 (s, C-2, C–O), 156.4 (s, C-4, C–O), 165.1 (s, C-9, C-10, C=O), 130.1 (s, C-1′), 129.7 (s, C-2′, C-6′), 128.2 (s, C-3′, C-5′), 133.1 (s, C-4′), 130.2 (s, C-1″), 129.5 (s, C-2″, C-6″), 128.3 (s, C-3″, C-5″), 133.3 (s, C-4″), 28.8 (s, CH_3 of C-8), 120.3 (s, C-1), 108.5 (s, C-3), 113.7 (s, C-5), 131 (s, C-6). Anal. Calcd. for $C_{22}H_{16}O_5$ (M^+): (360) C, 73.33; H, 4.48. Found: C, 73.35; H, 4.49.

*7.2.1.2. 2,4-Bis(2-chlorobenzoyloxy)acetophenone (**2b**).* Yield 69%; mp 99 °C; FT-IR (KBr): 1763 (ester C=O), 1685 (C=O), 1602 (aromatic C=C), 1131 (C–O); ^{1}H NMR (DMSO-d_6, δ, 300 MHz) 2.49 (s, 3H, CH_3), 6.74–8.40 (m, 10H, Ar–H), 6.69 (s, 3-H, Ar–H); ^{13}C NMR (DMSO-d_6, δ, 300 MHz) 199.1 (s, C-7, C=O), 155.7 (s, C-2, C–O), 156.6 (s, C-4, C–O), 165.1 (s, C-9, C-10, C=O), 130.5 (s, C-1′), 134.7 (s, C-2′), 128.6 (s, C-3′), 135.1 (s, C-4′), 127 (s, C-5′), 131.1 (s, C-6′), 130.4 (s, C-1″), 134.4 (s, C-2″), 128.8 (s, C-3″), 135.6 (s, C-4″), 127.3 (s, C-5″), 131.4 (s, C-6″), 29.2 (s, CH_3 of C-8), 119 (s, C-1), 108.9 (s, C-3), 113.2 (s, C-5), 130.9 (s, C-6). Anal. Calcd. for $C_{22}H_{14}Cl_2O_5$ (M^+): (429) C, 61.56; H, 3.29. Found: C, 61.60; 3.36.

*7.2.1.3. 2,4-Bis(3-chlorobenzoyloxy)acetophenone (**2c**).* Yield 76%; mp 101 °C, FT-IR (KBr): 1763 (ester C=O), 1680 (C=O), 1599 (aromatic C=C), 1140 (C–O); ^{1}H NMR (DMSO-d_6, δ, 300 MHz) 2.57 (s, 3H, CH_3), 6.73–8.19 (m, 10H, Ar–H), 6.68 (s, 3-H, Ar–H); ^{13}C NMR (DMSO-d_6, δ, 300 MHz) 199.7 (s, C-7, C=O), 154.9 (s, C-2, C–O), 153.4 (s, C-4, C–O), 166.3 (s, C-9, C-10, C=O), 130.9 (s, C-1′), 134.2 (s, C-2′), 130.6 (s, C-3′), 135.2 (s, C-4′), 128.0 (s, C-5′), 130.9 (s, C-6′), 130.7 (s, C-1″), 134.4 (s, C-2″), 130.7 (s, C-3″), 135.3 (s, C-4′), 128.2 (s, C-5″), 131.1 (s, C-6″), 28.8 (s, CH_3 of C-8), 118.3 (s, C-1), 109.2 (s, C-3), 113.7 (s, C-5), 131.2 (s, C-6). Anal. Calcd. for $C_{22}H_{14}Cl_2O_5$ (M^+): (429) C, 61.56; H, 3.29. Found: C, 61.62; 3.33.

*7.2.1.4. 2,4-Bis(4-chlorobenzoyloxy)acetophenone (**2d**).* Yield 68%; mp 105 °C; FT-IR (KBr): 1762 (ester C=O), 1689 (C=O), 1602 (aromatic C=C), 1139 (C-O); ^{1}H NMR (DMSO-d_6, δ, 300 MHz): 2.61 (s, 3H, CH_3), 8.06 (d, 2H, $J_{2'-6'}$ = 8.4 Hz, 2′-H, 6′-H), 7.47 (d, 2H, $J_{3'-5'}$ = 8.4 Hz, 3′-H, 5′-H), 8.08 (d, 2H, $J_{2''-6''}$ = 8.4 Hz, 2″-H, 6″-H), 7.49 (d, 2H, $J_{3''-5''}$ = 8.4 Hz, 3″-H, 5″-H), 6.69–7.74 (m, 2H, Ar–H), 6.71 (s, 3-H, Ar–H); ^{13}C NMR (DMSO-d_6, δ, 300 MHz) 199.5 (s, C-7, C=O), 154.7 (s, C-2, C–O), 154.5 (s, C-4, C–O), 165.4 (s, C-9, C-10, C=O), 129.4 (s, C-1′), 130.8 (s, C-2′, C-6′), 128.7 (s, C-3′, C-5′), 138.3 (s, C-4′), 129.5 (s, C-1″), 130.7 (s, C-2″, C-6″), 128.9 (s, C-3″, C-5″), 138.5 (s, C-4″), 29.8 (s, CH_3 of C-8), 120.1 (s, C-1), 109.5 (s, C-3), 112.7 (s, C-5), 130.2 (s, C-6). $C_{22}H_{14}Cl_2O_5$ (M^+): (429) C, 61.56; H, 3.29. Found: C, 61.61; 3.31.

*7.2.1.5. 2,4-Bis(3-methoxybenzoyloxy)acetophenone (**2e**).* Yield 75%; mp 90 °C; FT-IR (KBr): 1760 (ester C=O), 1681 (C=O), 1600 (aromatic C=C), 1143 (C–O); ^{1}H NMR (DMSO-d_6, δ, 300 MHz) 2.53 (s, 3H, CH_3), 7.02–8.05 (m, 10H, Ar–H), 6.63 (s, 3-H, Ar–H), 3.70 (s, 6H, 3′-OCH_3, 3″-OCH_3); ^{13}C NMR (DMSO-d_6, δ, 300 MHz) 199.0 (s, C-7, C=O), 155.9 (s, C-2, C-O), 156.0 (s, C-4, C–O), 166.8 (s, C-9, C-10, C=O), 131.1 (s, C-1′), 114.2 (s, C-2′), 160.6 (s, C-3′), 119.2 (s, C-4′), 129.7 (s, C-5′), 122.9 (s, C-6′), 131.2 (s, C-1″), 114.4 (s, C-2″), 160.7 (s, C-3″), 119.3 (s, C-4″), 129.9 (s, C-5″), 123.1 (s, C-6″), 29.4 (s, CH_3 of C-8), 119.3 (s, C-1), 109.8 (s, C-3), 112.7 (s, C-5), 130.2 (s, C-6), 56.2 (s, OCH_3 of C-7′ & OCH_3 of C-7″). Anal. Calcd. for $C_{24}H_{20}O_7$ (M^+): (420) C, 68.57; H, 4.80. Found: C, 68.59; H, 4.82.

*7.2.1.6. 2,4-Bis(4-methoxybenzoyloxy)acetophenone (**2f**).* Yield 71%; mp 102 °C; FT-IR (KBr): 1766 (ester C=O), 1685 (C=O), 1603 (aromatic C=C), 1144 (C–O); ^{1}H NMR (DMSO-d_6, δ, 300 MHz) 2.59 (s, 3H, CH_3), 8.03 (d, 2H, $J_{2'-4'}$ = 8.1 Hz, 2′-H, 4′-H), 6.99 (d, 2H, $J_{3'-5'}$ = 8.1 Hz, 3′-H, 5′-H), 8.04 (d, 2H, $J_{2''-4''}$ = 8.1 Hz, 2″-H, 4″-H), 6.98 (d, 2H, $J_{3''-5''}$ = 8.1 Hz, 3″-H, 5″-H), 6.68–7.76 (m, 2H, Ar–H), 6.79 (s, 3-H, Ar–H), 3.68 (s, 6H, 4′-OCH_3, 4″-OCH_3); ^{13}C NMR (DMSO-d_6, δ, 300 MHz) 199.7 (s, C-7, C=O), 155.7 (s, C-2, C–O), 155.9 (s, C-4, C–O), 164.4 (s, C-9, C-10, C=O), 122.4 (s, C-1′), 131.8 (s, C-2′, C-6′), 114.7 (s, C-3′, C-5′), 165.3 (s, C-4′), 122.5 (s, C-1′), 131.9 (s, C-2′, C-6′), 114.9 (s, C-3′, C-5′), 165.5 (s, C-4′), 29.1 (s, CH_3 of C-8), 120.4 (s, C-1), 108.7 (s, C-3), 112.1 (s, C-5), 130.9 (s, C-6), 56.1 (s, OCH_3 of C-7′ & OCH_3 of C-7″). Anal. Calcd. for $C_{24}H_{20}O_7$ (M^+): (420) C, 68.57; H, 4.80. Found: C, 68.56; H, 4.85.

*7.2.1.7. 2,4-Bis(3-methylbenzoyloxy)acetophenone (**2g**).* Yield 76%; mp 109 °C; FT-IR (KBr): 1767 (ester C=O), 1689 (C=O), 1603 (aromatic C=C), 1146 (C–O); ^{1}H NMR (DMSO-d_6, δ, 300 MHz) 2.58 (s, 3H, CH_3), 6.79–8.10 (m, 10H, Ar–H), 6.75 (s, 3-H, Ar–H), 2.39 (s, 6H, 3′-CH_3, 3″-CH_3); ^{13}C NMR (DMSO-d_6, δ, 300 MHz) 199.6 (s, C-7, C=O), 154.9 (s, C-2, C–O), 155.0 (s, C-4, C–O), 166.2 (s, C-9, C-10, C=O), 130.1 (s, C-1′), 130.2 (s, C-2′), 138.6 (s, C-3′), 134.2 (s, C-4′), 128.7 (s, C-5′), 127.9 (s, C-6′), 130.2 (s, C-1″), 130.4 (s, C-2″), 138.7 (s, C-3″), 134.3 (s, C-4″), 128.9 (s, C-5″), 128.0 (s, C-6″), 29.1 (s, CH_3 of C-8), 120.3 (s, C-1), 109.6 (s, C-3), 112.9 (s, C-5), 130.8 (s, C-6), 24.8 (s, CH_3 of C-7′ & CH_3 of C-7″). Anal. Calcd. for $C_{24}H_{20}O_5$ (M^+): (388) C, 74.21; H, 5.19. Found: C, 74.23; H, 5.22.

*7.2.1.8. 2,4-Bis(4-methylbenzoyloxy)acetophenone (**2h**).* Yield 72%; mp 116 °C; FT-IR (KBr): 1767 (ester C=O), 1680 (C=O), 1601 (aromatic C=C), 1141 (C–O); ^{1}H NMR (DMSO-d_6, δ, 300 MHz): 2.52 (s, 3H, CH_3), 8.01 (d, 2H, $J_{2'-4'}$ = 8.6 Hz, 2′-H, 4′-H), 7.19 (d, 2H, $J_{3'-5'}$ = 8.6 Hz, 3′-H, 5′-H), 8.03 (d, 2H, $J_{2''-4''}$ = 8.6 Hz, 2″-H, 4″-H), 7.20 (d, 2H, $J_{3''-5''}$ = 8.6 Hz, 3″-H, 5″-H), 6.79–7.73 (m, 2H, Ar–H), 6.71 (s, 3-H, Ar–H), 2.43 (s, 6H, 4′-CH_3, 4″-CH_3); ^{13}C NMR (DMSO-d_6, δ, 300 MHz) 199.1 (s, C-7, C=O), 155.2 (s, C-2, C–O), 155.4 (s, C-4, C–O), 166.4 (s, C-9, C-10, C=O), 122.3 (s, C-1′), 130.4 (s, C-2′, C-6′), 129.7 (s, C-3′, C-5′), 143.3 (s, C-4′), 122.4 (s, C-1″), 130.6 (s, C-2″, C-

6″), 129.9 (s, C-3″, C-5″), 143.4 (s, C-4″), 29.5 (s, CH_3 of C-8), 120.2 (s, C-1), 108.8 (s, C-3), 113.1 (s, C-5), 131.9 (s, C-6), 24.1 (s, CH_3 of C-7′ & CH_3 of C-7″). $C_{24}H_{20}O_5$ (M^+): (388) C, 74.21; H, 5.19. Found: C, 74.24; H, 5.20.

*7.2.2. General procedure for the preparation of 1-(2′,4′-dihydroxyphenyl)-3-aryl-propane-1,3-diones (**3**)*

The product (**2**) (0.005 mol) was dissolved in 4 mL of DMSO. To that solution powdered NaOH (1 g) was added with vigorous stirring for about 5 min. The stirring was continued for about 5 min further. The reaction mixture was then cooled and poured on cold water. The pale yellow solid product (**3**) obtained was washed with water and filtered off. It was crystallized from alcohol. The progress of the reaction was monitored by TLC.

*7.2.2.1. 1-(2′,4′-Dihydroxyphenyl)-3-phenyl-propane-1,3-dione (**3a**).* Yield 67%; mp 158 °C; FT-IR (KBr): 3420 (OH), 1743 (C=O), 1598 (aromatic C=C), 1142 (C–O); ^{1}H NMR (DMSO-d_6, δ, 300 MHz) 15.72 (s, 1H, enolic OH), 12.02 (s, 1H, 2′-OH), 4.76 (s, 1H, 4′-OH), 8.41 (s, 1H, –CH=), 7.39 (d, 2H, $J_{2''-6''}$ = 8.4 Hz, 2″-H, 6″-H), 6.48–7.47 (m, 5H, Ar–H), 6.39 (s, 3′-H, Ar–H); ^{13}C NMR (DMSO-d_6, δ, 300 MHz) 189.8 (s, C-1, C=O), 184.9 (s, C-3), 94 (s, C-2, –CH=), 115.4 (s, C-1′), 163.2 (s, C-2′), 104.5 (s, C-3′), 165.7 (s, C-4′), 109 (s, C-5′), 132.7 (s, C-6′), 130.4 (s, C-1″), 126.4 (s, C-2″, C-6″), 128.7 (s, C-3″, C-5″), 128 (s, C-4″). Anal. Calcd. for $C_{15}H_{12}O_4$ (M^+): (256) C, 70.31; H, 4.72. Found: C, 70.55; 4.91.

*7.2.2.2. 1-(2′,4′-Dihydroxyphenyl)-3-(2″-chlorophenyl)-propane-1,3-dione (**3b**).* Yield 70%; mp 151 °C; FT-IR (KBr): 3417 (OH), 1738 (C=O), 1599 (aromatic C=C), 1144 (C–O); ^{1}H NMR (DMSO-d_6, δ, 300 MHz) 15.79 (s, 1H, enolic OH), 12.00 (s, 1H, 2′-OH), 4.79 (s, 1H, 4′-OH), 8.49 (s, 1H, –CH=), 6.41–7.39 (m, 6H, Ar–H), 6.33 (s, 3′-H, Ar–H); ^{13}C NMR (DMSO-d_6, δ, 300 MHz) 189.7 (s, C-1, C=O), 185.9 (s, C-3), 93 (s, C-2, –CH=), 115.3 (s, C-1′), 163.4 (s, C-2′), 104.1 (s, C-3′), 165.2 (s, C-4′), 109.4 (s, C-5′), 133.1 (s, C-6′), 131.7 (s, C-1″), 131.2 (s, C-2″), 128.8 (s, C-3″), 129.4 (s, C-4″), 126.8 (s, C-5″), 130.2 (s, C-6″). Anal. Calcd. for $C_{15}H_{11}ClO_4$ (M^+): (290) C, 61.98; H, 3.81. Found: C, 62.09; 3.97.

*7.2.2.3. 1-(2′,4′-Dihydroxyphenyl)-3-(3″-chlorophenyl)-propane-1,3-dione (**3c**).* Yield 71%; mp 124 °C; FT-IR (KBr): 3423 (OH), 1739 (C=O), 1600 (aromatic C=C), 1143 (C–O); ^{1}H NMR (DMSO-d_6, δ, 300 MHz) 15.89 (s, 1H, enolic OH), 12.01 (s, 1H, 2′-OH), 4.86 (s, 1H, 4′-OH), 8.42 (s, 1H, –CH=), 6.47–7.23 (m, 6H, Ar–H), 6.33 (s, 3′-H, Ar–H); ^{13}C NMR (DMSO-d_6, δ, 300 MHz) 190.1 (s, C-1, C=O), 185.2 (s, C-3), 93.4 (s, C-2, –CH=), 115.9 (s, C-1′), 163.2 (s, C-2′), 104.3 (s, C-3′), 164.2 (s, C-4′), 109 (s, C-5′), 132.7 (s, C-6′), 131.8 (s, C-1″), 126.2 (s, C-2″), 134.4 (s, C-3″), 128.4 (s, C-4″), 130.8 (s, C-5″), 124.4 (s, C-6″). Anal. Calcd. for $C_{15}H_{11}ClO_4$ (M^+): (290) C, 61.98; H, 3.81. Found: C, 61.97; H, 3.92.

*7.2.2.4. 1-(2′,4′-Dihydroxyphenyl)-3-(4″-chlorophenyl)-propane-1,3-dione (**3d**).* Yield 69%; mp 210 °C; IR (KBr): 3422 (OH), 1733 (C=O), 1600 (aromatic C=C), 1143 (C–O); ^{1}H NMR (DMSO-d_6, δ, 300 MHz) 15.89 (s, 1H, enolic OH), 12.09 (s, 1H, 2′-OH), 4.72 (s, 1H, 4′-OH), 8.51 (s, 1H, –CH=), 7.30 (d, 2H, $J_{2''-4''}$ = 7.9 Hz, 2″-H, 4″-H), 7.12 (d, 2H, $J_{3''-5''}$ = 7.9 Hz, 3″-H, 5″-H), 6.46–7.40 (m, 2H, Ar–H), 6.37 (s, 3′-H, Ar–H); ^{13}C NMR (DMSO-d_6, δ, 300 MHz) 189.7 (s, C-1, C=O), 185.3 (s, C-3), 94.5 (s, C-2, –CH=), 116.4 (s, C-1′), 163.6 (s, C-2′), 104.5 (s, C-3′), 164.7 (s, C-4′), 109.5 (s, C-5′), 132.1 (s, C-6′), 128.4 (s, C-1″), 127.4 (s, C-2″, C-6″), 128.8 (s, C-3″, C-5″), 133.5 (s, C-4″). Anal. Calcd. for $C_{15}H_{11}ClO_4$ (M^+): (290) C, 61.98; H, 3.81. Found: C, 62.15; H, 4.01.

*7.2.2.5. 1-(2′,4′-Dihydroxyphenyl)-3-(3″-methoxyphenyl)-propane-1,3-dione (**3e**).* Yield 73%; mp 189 °C; IR (KBr): 3428 (OH), 1743 (C=O), 1601 (aromatic C=C), 1145 (C–O); ^{1}H NMR (DMSO-d_6, δ, 300 MHz) 16.01 (s, 1H, enolic OH), 12.05 (s, 1H, 2′-OH), 4.89 (s, 1H, 4′-OH), 8.42 (s, 1H, –CH=), 6.43–7.49 (m, 6H, Ar–H), 6.39 (s, 3′-H, Ar–H), 3.76 (s, 3H, 3″-OCH_3); ^{13}C NMR (DMSO-d_6, δ, 300 MHz): 189.7 (s, C-1, C=O), 184.9 (s, C-3), 93.4 (s, C-2, –CH=), 115.6 (s, C-1′), 163.7 (s, C-2′), 104.1 (s, C-3′), 164.2 (s, C-4′), 109.8 (s, C-5′), 132.7 (s, C-6′), 131.4 (s, C-1″), 110.2 (s, C-2″), 160.4 (s, C-3″), 113.4 (s, C-4″), 129.8 (s, C-5″), 118.4 (s, C-6″), 55.9 (s, OCH_3 of C-7″). Anal. Calcd. for $C_{16}H_{14}O_5$ (M^+): (286) C, 67.13; H, 4.93. Found: C, 67.11; H, 4.89.

*7.2.2.6. 1-(2′,4′-Dihydroxyphenyl)-3-(4″-methoxyphenyl)-propane-1,3-dione (**3f**).* Yield 64%; mp 164 °C; FT-IR (KBr): 3419 (OH), 1713 (C=O), 1600 (aromatic C=C), 1139 (C–O); ^{1}H NMR (DMSO-d_6, δ, 300 MHz): 15.99 (s, 1H, enolic OH), 12.29 (s, 1H, 2′-OH), 4.68 (s, 1H, 4′-OH), 8.41 (s, 1H, –CH=), 7.20 (d, 2H, $J_{2''-4''}$ = 8.1 Hz, 2″-H, 4″-H), 7.19 (d, 2H, $J_{3''-5''}$ = 8.1 Hz, 3″-H, 5″-H), 6.49–7.41 (m, 2H, Ar–H), 6.37 (s, 3′-H, Ar–H), 3.65 (s, 3H, 4″-OCH_3); ^{13}C NMR (DMSO-d_6, δ, 300 MHz) 189.3 (s, C-1, C=O), 184.9 (s, C-3), 94 (s, C-2, –CH=), 116.3 (s, C-1′), 163.9 (s, C-2′), 104.5 (s, C-3′), 165.7 (s, C-4′), 110.4 (s, C-5′), 131.2 (s, C-6′), 122.4 (s, C-1″), 127.8 (s, C-2″, C-6″), 114.8 (s, C-3″, C-5″), 159.5 (s, C-4″), 56 (s, OCH_3 of C-7″). Anal. Calcd. for $C_{16}H_{14}O_5$ (M^+): (286) C, 67.13; H, 4.93. Found: C, 67.21; H, 4.95.

*7.2.2.7. 1-(2′,4′-Dihydroxyphenyl)-3-(3″-methylphenyl)-propane-1,3-dione (**3g**).* Yield 74%; mp 136 °C; IR (KBr): 3439 (OH), 1744 (C=O), 1600 (aromatic C=C), 1148 (C–O); ^{1}H NMR (DMSO-d_6, δ, 300 MHz): 16.03 (s, 1H, enolic OH), 12.01 (s, 1H, 2′-OH), 4.78 (s, 1H, 4′-OH), 8.49 (s, 1H, –CH=), 6.46–7.47 (m, 6H, Ar–H), 6.39 (s, 3′-H, Ar–H), 2.46 (s, 3H, 3″-CH_3); ^{13}C NMR (DMSO-d_6, δ, 300 MHz) 189.9 (s, C-1, C=O), 184.7 (s, C-3), 93.8 (s, C-2, –CH=), 115.9 (s, C-1′), 164.7 (s, C-2′), 104.1 (s, C-3′), 164 (s, C-4′), 109.2 (s, C-5′), 131.9 (s, C-6′), 130.4 (s, C-1″), 126.2 (s, C-2″), 138.4 (s, C-3″), 128.4 (s, C-4″), 128.8 (s, C-5″), 123.4 (s, C-6″), 24.8 (s, CH_3 of C-7″). Anal. Calcd. for $C_{16}H_{14}O_4$ (M^+): (270) C, 71.10; H, 5.22. Found: C, 71.19; H, 5.32.

*7.2.2.8. 1-(2′,4′-Dihydroxyphenyl)-3-(4″-methylphenyl)-propane-1,3-dione (**3h**).* Yield 72%; mp: 170 °C; FT-IR (KBr): 3425 (OH), 1723 (C=O), 1602 (aromatic C=C), 1140 (C–O); ^{1}H NMR (DMSO-d_6, δ, 300 MHz) 15.97 (s, 1H, enolic OH), 12.12 (s, 1H, 2′-OH), 4.78 (s, 1H, 4′-OH), 8.43 (s, 1H, –CH=), 7.19 (d, 2H, $J_{2''-4''}$ = 8.6 Hz, 2″-H, 4″-H), 7.11(d, 2H, $J_{3''-5''}$ = 8.6 Hz, 3″-H, 5″-H), 6.42–7.39 (m, 2H, Ar–H), 6.41 (s, 3′-H, Ar–H); 2.45 (s, 3H, 4″-CH_3); ^{13}C NMR (DMSO-d_6, δ, 300 MHz) 189.6 (s, C-1, C=O), 184.5 (s, C-3), 94.2 (s, C-2, –CH=), 116.3 (s, C-1′), 164.3 (s, C-2′), 104.6 (s, C-3′), 165.7 (s, C-4′), 109.6 (s, C-5′), 131.6 (s, C-6′), 127.4 (s, C-1″), 126.8 (s, C-2″, C-6″), 129.2 (s, C-3″, C-5″), 137.5 (s, C-4″), 24.4 (s, CH_3 of C-7″). Anal. Calcd. for $C_{16}H_{14}O_4$ (M^+): (270) C, 71.10; H, 5.22. Found: C, 71.21; H, 5.33.

*7.2.3. General procedure for the synthesis of 1-[2′-hydroxy-4′-(2‴,3‴,4‴,6‴-tetra-O-acetyl-O-β-D-glucopyranosyloxy)phenyl]-3-aryl-propane-1,3-diones (**4**)*

To a solution of 1-(2′,4′-dihydroxyphenyl)-3-aryl-propane-1,3-diones (**3**) (0.01 mol in 25 mL of 2.5% methanolic KOH) under nitrogen atmosphere, was added drop wise TAGBr (4 g in 30 mL dry acetone). The resulting mixture was stirred at 0–3 °C for 8 h. The reaction mixture was stirred continuously for 10 h. The progress of the reaction was monitored by TLC. The solvent was removed under reduced pressure. The resulting brown syrup was dissolved in methanol: chloroform (5:15) and chromatographed on 60–120 mesh silica gel eluting with 10% methanol in chloroform to obtain the brown syrupy compound (**4**).

*7.2.3.1. 1-[2′-Hydroxy-4′-(2‴,3‴,4‴,6‴-tetra-O-acetyl-O-β-D-glucopyranosyloxy)phenyl]-3-phenyl-propane-1,3-dione (**4a**).* Yield 76%; $[\alpha]_D^{25} = -4.3$ (*c* 0.1, CH_3OH); IR (KBr): 3401 (–OH), 2842 (glucosidic

CH), 1766 (C=O of *O*-acetyl groups of glycone moiety), 1743 (C=O), 1598 (aromatic C=C), 1142 (C–O); ^{1}H NMR (DMSO-d$_6$, δ, 300 MHz): 15.49 (s, 1H, enolic OH), 11.87 (s, 1H, 2′-OH), 8.32 (s, 1H, –CH=), 7.42 (d, 2H, $J_{2''-6''}$ = 8.3 Hz, 2″-H, 6″-H), 6.38–7.26 (m, 5H, Ar–H), 6.39 (s, 3′-H, Ar–H), 2.06, 2.02, 1.99, 2.01 (s, 3H, OAc), 3.43–4.92 (m, 6H, β-D-glucopyranosyl ring), 4.79 (d, 1‴-H, anomeric proton, $J_{1,2}$ = 7.9 Hz); ^{13}C NMR (DMSO-d$_6$, δ, 300 MHz): 189.8 (s, C-1, C=O), 184.9 (s, C-3), 94 (s, C-2, –CH=), 115.4 (s, C-1′), 163.2 (s, C-2′), 104.5 (s, C-3′), 164.5 (s, C-4′), 109 (s, C-5′), 132.7 (s, C-6′), 130.4 (s, C-1″), 126.4 (s, C-2″, C-6″), 128.7 (s, C-3″, C-5″), 128 (s, C-4″), 21.1 (s, C-atom, CH$_3$ of acetyl group), 170.8 (s, C=O, acetyl group), 102.1 (s, C-1‴, anomeric C-atom), 72.6 (s, C-2‴), 71.2 (s, C-3‴), 71.6 (s, C-4‴), 74.9 (s, C-5‴), 65.8 (s, C-6‴). Anal. Calcd. for $C_{29}H_{30}O_{13}$ (M^+): (586): C, 59.38; H, 5.16. Found: C, 59.22; H, 5.10.

*7.2.3.2. 1-[2′-Hydroxy-4′-(2‴,3‴,4‴,6‴-tetra-O-acetyl-O-β-D-glucopyranosyloxy)phenyl]-3-(2″-chloro phenyl)-propane-1,3-dione (**4b**).* Yield 70%; $[\alpha]_D^{25}$ = –7.5 (*c* 0.1, CH$_3$OH); IR (KBr): 3400 (–OH), 2841 (glucosidic CH), 1763 (C=O of *O*-acetyl groups of glycone moiety), 1740 (C=O), 1599 (aromatic C=C), 1145 (C–O); ^{1}H NMR (DMSO-d$_6$, δ, 300 MHz) 15.70 (s, 1H, enolic OH), 12.10 (s, 1H, 2′-OH), 8.43 (s, 1H, –CH=), 6.23–7.45 (m, 6H, Ar–H), 6.30 (s, 3′-H, Ar–H), 2.03, 2.00, 1.95, 2.05 (s, 3H, OAc), 3.33–4.90 (m, 6H, β-D-glucopyranosyl ring), 4.85 (d, 1‴-H, anomeric proton, $J_{1,2}$ = 8.0 Hz); ^{13}C NMR (DMSO-d$_6$, δ, 300 MHz): 188.9 (s, C-1, C=O), 184.9 (s, C-3), 93.1 (s, C-2, –CH=), 114.5 (s, C-1′), 163.9 (s, C-2′), 102.6 (s, C-3′), 167.2 (s, C-4′), 108.4 (s, C-5′), 132.6 (s, C-6′), 131.3 (s, C-1″), 132.4 (s, C-2″), 128.8 (s, C-3″), 129.6 (s, C-4″), 126.8 (s, C-5″), 127.2 (s, C-6″), 21.2 (s, C-atom, CH$_3$ of acetyl group), 170.2 (s, C=O, acetyl group), 102.9 (s, C-1‴, anomeric C-atom), 73.2 (s, C-2‴), 71.4 (s, C-3‴), 70.1 (s, C-4‴), 74.6 (s, C-5‴), 66.4 (s, C-6‴). Anal. Calcd. for $C_{29}H_{29}ClO_{13}$ (M^+): (620) C, 56.09; H, 4.71. Found: C, 56.00; H, 4.81.

*7.2.3.3. 1-[2′-Hydroxy-4′-(2‴,3‴,4‴,6‴-tetra-O-acetyl-O-β-D-glucopyranosyloxy)phenyl]-3-(3″-chlorophenyl)-propane-1,3-dione (**4c**).* Yield 72%; $[\alpha]_D^{25}$ = –3.9 (*c* 0.1, CH$_3$OH); IR (KBr): 3410 (–OH), 2849 (glucosidic CH), 1769 (C=O of *O*-acetyl groups of glycone moiety), 1744 (C=O), 1601 (aromatic C=C), 1148 (C–O); ^{1}H NMR (DMSO-d$_6$, δ, 300 MHz) 15.80 (s, 1H, enolic OH), 12.05 (s, 1H, 2′-OH), 8.42 (s, 1H, –CH=), 6.53–7.65 (m, 6H, Ar–H), 6.39 (s, 3′-H, Ar–H), 2.05, 2.03, 1.99, 2.00 (s, 3H, OAc), 3.44–4.99 (m, 6H, β-D-glucopyranosyl ring), 4.89 (d, 1‴-H, anomeric proton, $J_{1,2}$ = 7.9 Hz); ^{13}C NMR (DMSO-d$_6$, δ, 300 MHz): 189.2 (s, C-1, C=O), 186.8 (s, C-3), 92.7 (s, C-2, –CH=), 114.6 (s, C-1′), 163.6 (s, C-2′), 102.9 (s, C-3′), 167.0 (s, C-4′), 109.5 (s, C-5′), 132.4 (s, C-6′), 131.6 (s, C-1″), 126.9 (s, C-2″), 132.4 (s, C-3″), 128.3 (s, C-4″), 130.1 (s, C-5″), 127.4 (s, C-6″), 21.3 (s, C-atom, CH$_3$ of acetyl group), 170.9 (s, C=O, acetyl group), 102.5 (s, C-1‴, anomeric C-atom), 71.2 (s, C-2‴), 71.5 (s, C-3‴), 71.1 (s, C-4‴), 73.6 (s, C-5‴), 66.9 (s, C-6‴). Anal. Calcd. for $C_{29}H_{29}ClO_{13}$ (M^+): (620) C, 56.09; H, 4.71. Found: C, 56.00; H, 4.81.

*7.2.4. General procedure for the synthesis of 1-(4′-O-β-D-glucopyranosyloxy-2′-hydroxyphenyl)-3-aryl-propane-1,3-diones (**5**)*

A freshly prepared sodium methoxide (3 mL, 0.1 mol) was added to a solution of 1-[2′-hydroxy-4′-(2‴,3‴,4‴,6‴-tetra-*O*-acetyl-*O*-β-D-glucopyranosyloxy)phenyl]-3-aryl-propane-1,3-dione (**4**) (0.005 mol) in dry methanol (20 mL) and stirred at room temperature under nitrogen atmosphere for 10 h. The reaction mixture was neutralized with ion-exchange resin (Amberlite IR-120, SD Fine H^+ form), filtered and concentrated in vaccuo to afford viscous 1-(4′-*O*-β-D-glucopyranosyloxy-2′-hydroxyphenyl)-3-aryl-propane-1,3-dione (**5**) as solid yield. The compounds were found to be optically active.

*7.2.4.1. 1-(4′-O-β-D-glucopyranosyloxy-2′-hydroxyphenyl)-3-phenyl-propane-1,3-dione (**5a**).* Yield 69%; $[\alpha]_D^{25}$ = –14.6 (*c* 0.1, CH$_3$OH); FT-IR (KBr): 3400 (br, OH peak of carbohydrate residue), 3420 (OH), 1738 (C=O), 2854 (glucosidic CH), 1597 (aromatic C=C), 1143 (C–O); ^{1}H NMR (DMSO-d$_6$, δ, 300 MHz) 15.85 (s, 1H, enolic OH), 12.56 (s, 1H, 2′-OH), 3.41–4.80 (m, 6H, β-D-glucopyranosyl ring), 5.89 (d, 1‴-H, anomeric proton, $J_{1,2}$ = 8.2 Hz), 2.3 (s, 4H, glucosidic OH), 8.49 (s, 1H, –CH=), 7.43 (d, 2H, $J_{2''-6''}$ = 8.8 Hz, 2″-H, 6″-H), 6.54–7.73 (m, 5H, Ar–H), 6.39 (s, 3′-H, Ar–H); ^{13}C NMR (DMSO-d$_6$, δ, 300 MHz) 190.1 (s, C-1, C=O), 184.3 (s, C-3), 93.6 (s, C-2, –CH=), 115.5 (s, C-1′), 164.0 (s, C-2′), 104.9 (s, C-3′), 162.1 (s, C-4′), 109.8 (s, C-5′), 132.3 (s, C-6′), 130.4 (s, C-1″), 127.6 (s, C-2″, C-6″), 128.5 (s, C-3″, C-5″), 128.9 (s, C-4″), 64.2 (s, C-6‴), 73.1 (s, C-4‴), 74.9 (s, C-2‴), 77.6 (s, C-3‴), 82.1 (s, C-5‴), 106.3 (s, C-1‴, anomeric C-atom); Anal. Calcd. for $C_{21}H_{22}O_9$ (M^+): (418) C, 60.28; H, 5.30. Found: C, 60.50; H, 5.42%.

*7.2.4.2. 1-(4′-O-β-D-glucopyranosyloxy-2′-hydroxyphenyl)-3-(2″-chlorophenyl)-propane-1,3-dione (**5b**).* Yield 73%; $[\alpha]_D^{25}$ = –16.1 (*c* 0.1, CH$_3$OH); FT-IR (KBr): 3404 (br, OH peak of carbohydrate residue), 3419 (OH), 1732 (C=O), 2850 (glucosidic CH), 1600 (aromatic C=C), 1149 (C–O); ^{1}H NMR (DMSO-d$_6$, δ, 300 MHz): 15.90 (s, 1H, enolic OH), 12.09 (s, 1H, 2′-OH), 3.49–4.92 (m, 6H, β-D-glucopyranosyl ring), 5.74 (d, 1‴-H, anomeric proton, $J_{1,2}$ = 8.0 Hz), 2.1 (s, 4H, glucosidic OH), 8.40 (s, 1H, –CH=), 6.49–7.40 (m, 6H, Ar–H), 6.39 (s, 3′-H, Ar–H); ^{13}C NMR (DMSO-d$_6$, δ, 300 MHz): 189.9 (s, C-1, C=O), 185.0 (s, C-3), 93.5 (s, C-2, –CH=), 116.3 (s, C-1′), 164.4 (s, C-2′), 104.5 (s, C-3′), 165.6 (s, C-4′), 109.1 (s, C-5′), 133.3 (s, C-6′), 131.0 (s, C-1″), 131.5 (s, C-2″), 128.9 (s, C-3″), 129.7 (s, C-4″), 125.8 (s, C-5″), 132.2 (s, C-6″), 64.9 (s, C-6‴), 73.6 (s, C-4‴), 75.6 (s, C-2‴), 78.3 (s, C-3‴), 83.4 (s, C-5‴), 106.5 (s, C-1‴, anomeric C-atom); Anal. Calcd. for $C_{21}H_{21}ClO_9$ (M^+): (452) C, 55.70; H, 4.67. Found: C, 55.69; H, 4.70%.

*7.2.4.3. 1-(4′-O-β-D-glucopyranosyloxy-2′-hydroxyphenyl)-3-(3″-chlorophenyl)-propane-1,3-dione (**5c**).* Yield 73%; $[\alpha]_D^{25}$ = –15.5 (*c* 0.1, CH$_3$OH); FT-IR (KBr): 3409 (br, OH peak of carbohydrate residue), 3429 (OH), 1742 (C=O), 2859 (glucosidic CH), 1605 (aromatic C=C), 1147 (C–O); ^{1}H NMR (DMSO-d$_6$, δ, 300 MHz): 15.99 (s, 1H, enolic OH), 12.08 (s, 1H, 2′-OH), 3.31–4.90 (m, 6H, β-D-glucopyranosyl ring), 5.70 (d, 1‴-H, anomeric proton, $J_{1,2}$ = 7.9 Hz), 2.4 (s, 4H, glucosidic OH), 8.49 (s, 1H, –CH=), 6.50–7.21 (m, 6H, Ar–H), 6.41 (s, 3′-H, Ar–H); ^{13}C NMR (DMSO-d$_6$, δ, 300 MHz): 190.9 (s, C-1, C=O), 184.9 (s, C-3), 93.9 (s, C-2, –CH=), 115.8 (s, C-1′), 163.1 (s, C-2′), 104.5 (s, C-3′), 164.5 (s, C-4′), 109.1 (s, C-5′), 132.2 (s, C-6′), 132.6 (s, C-1″), 126.6 (s, C-2″), 135.4 (s, C-3″), 128.7 (s, C-4″), 131.3 (s, C-5″), 125.6 (s, C-6″); 64.4 (s, C-6‴), 72.4 (s, C-4‴), 76.3 (s, C-2‴), 77.2 (s, C-3‴), 82.4 (s, C-5‴), 106.0 (s, C-1‴, anomeric C-atom); Anal. Calcd. for $C_{21}H_{21}ClO_9$ (M^+): (452) C, 55.70; H, 4.67. Found: C, 55.77; H, 4.81%.

*7.2.4.4. 1-(4′-O-β-D-glucopyranosyloxy-2′-hydroxyphenyl)-3-(4″-chlorophenyl)-propane-1,3-dione (**5d**).* Yield 68%; $[\alpha]_D^{25}$ = –18.1 (*c* 0.1, CH$_3$OH); IR (KBr): 3410 (br, OH peak of carbohydrate residue), 3431 (OH), 1731 (C=O), 2823 (glucosidic CH), 1604 (aromatic C=C), 1149 (C–O); ^{1}H NMR (DMSO-d$_6$, δ, 300 MHz): 15.99 (s, 1H, enolic OH), 12.12 (s, 1H, 2′-OH), 3.44–4.99 (m, 6H, β-D-glucopyranosyl ring), 5.79 (d, 1‴-H, anomeric proton, $J_{1,2}$ = 7.8 Hz), 2.2 (s, 4H, glucosidic OH), 8.52 (s, 1H, –CH=), 7.39 (d, 2H, $J_{2''-4''}$ = 7.9 Hz, 2″-H, 4″-H), 7.22 (d, 2H, $J_{3''-5''}$ = 7.9 Hz, 3″-H, 5″-H), 6.47–7.49 (m, 3H, Ar–H), 6.39 (s, 3′-H, Ar–H); ^{13}C NMR (DMSO-d$_6$, δ, 300 MHz): 191.1 (s, C-1, C=O), 184.3 (s, C-3), 94.9 (s, C-2, –CH=), 115.4 (s, C-1′), 164.9 (s, C-2′), 103.9 (s, C-3′), 164.8 (s, C-4′), 109.7 (s, C-5′), 132.9 (s, C-6′), 128.9 (s, C-1″), 127.8 (s, C-2″, C-6″), 128.9 (s, C-3″, C-5″), 133.5 (s, C-4″), 64.0 (s, C-6‴), 72.9 (s, C-4‴), 75.4 (s, C-2‴), 77.5 (s, C-3‴),

82.7 (s, C-5‴), 106.4 (s, C-1‴, anomeric C-atom); Anal. Calcd. for $C_{21}H_{21}ClO_9$ (M^+): (452) C, 55.70; H, 4.67. Found: C, 55.73; H, 4.71%.

*7.2.4.5. 1-(4′-O-β-D-glucopyranosyloxy-2′-hydroxyphenyl)-3-(3″-methoxyphenyl)-propane-1,3-dione (**5e**).* Yield 73%; $[\alpha]_D^{25} = -17.3$ (*c* 0.1, CH_3OH); IR (KBr): 3400 (br, OH peak of carbohydrate residue), 3422 (OH), 1733 (C=O), 2825 (glucosidic CH), 1600 (aromatic C=C), 1143 (C–O); ^{1}H NMR (DMSO-d_6, δ, 300 MHz): 16.00 (s, 1H, enolic OH), 12.01 (s, 1H, 2′-OH), 3.49–4.91 (m, 6H, β-D-glucopyranosyl ring), 5.73 (d, 1‴-H, anomeric proton, $J_{1,2} = 7.9$ Hz), 2.0 (s, 4H, glucosidic OH), 8.49 (s, 1H, –CH=), 6.39–7.40 (m, 6H, Ar–H), 6.32 (s, 3′-H, Ar–H), 3.79 (s, 3H, 3″-OCH_3); ^{13}C NMR (DMSO-d_6, δ, 300 MHz): 189.1 (s, C-1, C=O), 184.4 (s, C-3), 93.0 (s, C-2, –CH=), 116.6 (s, C-1′), 163.9 (s, C-2′), 105.1 (s, C-3′), 164.9 (s, C-4′), 108.9 (s, C-5′), 133.7 (s, C-6′), 132.4 (s, C-1″), 110.8 (s, C-2″), 160.7 (s, C-3″), 111.4 (s, C-4″), 129.7 (s, C-5″), 118.9 (s, C-6″), 56.0 (s, OCH_3 of C-7″), 64.4 (s, C-6‴), 72.5 (s, C-4‴), 75.2 (s, C-2‴), 77.3 (s, C-3‴), 81.7 (s, C-5‴), 105.3 (s, C-1‴, anomeric C-atom); MS (EI, 70 eV): *m*/*z* (%) 286 (M^+, 100), 224 (32), 105 (49), 51 (13). Anal. Calcd. for $C_{22}H_{24}O_{10}$ (M^+): (448) C, 58.93; H, 5.39. Found: C, 58.89; H, 5.45%.

*7.2.4.6. 1-(4′-O-β-D-glucopyranosyloxy-2′-hydroxyphenyl)-3-(4″-methoxyphenyl)-propane-1,3-dione (**5f**).* Yield 66%; $[\alpha]_D^{25} = -13.6$ (*c* 0.1, CH_3OH); FT-IR (KBr): 3405 (br, OH peak of carbohydrate residue), 3413 (OH), 1723 (C=O), 2828 (glucosidic CH), 1603 (aromatic C=C), 1142 (C–O); ^{1}H NMR (DMSO-d_6, δ, 300 MHz): 15.91 (s, 1H, enolic OH), 12.02 (s, 1H, 2′-OH), 3.53–4.79 (m, 6H, β-D-glucopyranosyl ring), 5.81 (d, 1‴-H, anomeric proton, $J_{1,2} = 8.0$ Hz), 2.5 (s, 4H, glucosidic OH), 8.49 (s, 1H, –CH=), 7.28 (d, 2H, $J_{2''-4''} = 8.1$ Hz, 2″-H, 4″-H), 7.11 (d, 2H, $J_{3''-5''} = 8.1$ Hz, 3″-H, 5″-H), 6.39–7.31 (m, 3H, Ar–H), 6.41 (s, 3′-H, Ar–H), 3.71 (s, 3H, 4″-OCH_3); ^{13}C NMR (300 MHz, DMSO-d_6): δ 190.3 (s, C-1, C=O), 185.9 (s, C-3), 93.8 (s, C-2, –CH=), 116.9 (s, C-1′), 164.9 (s, C-2′), 105.5 (s, C-3′), 165.3 (s, C-4′), 110.0 (s, C-5′), 133.2 (s, C-6′), 122.9 (s, C-1″), 128.8 (s, C-2″, C-6″), 117.8 (s, C-3″, C-5″), 160.5 (s, C-4″), 56.7 (s, OCH_3 of C-7″), 64.9 (s, C-6‴), 72.1 (s, C-4‴), 75.7 (s, C-2‴), 77.6 (s, C-3‴), 81.8 (s, C-5‴), 105.5 (s, C-1‴, anomeric C-atom); Anal. Calcd. for $C_{22}H_{24}O_{10}$ (M^+): (448) C, 58.93; H, 5.39. Found: C, 58.99; H, 5.41%.

*7.2.4.7. 1-(4′-O-β-D-glucopyranosyloxy-2′-hydroxyphenyl)-3-(3″-methylphenyl)-propane-1,3-dione (**5g**).* Yield 75%; $[\alpha]_D^{25} = -19.2$ (*c* 0.1, CH_3OH); IR (KBr): 3409 (br, OH peak of carbohydrate residue), 3430 (OH), 1749 (C=O), 2834 (glucosidic CH), 1605 (aromatic C=C), 1129 (C–O); ^{1}H NMR (DMSO-d_6, δ, 300 MHz): 16.09 (s, 1H, enolic OH), 11.88 (s, 1H, 2′-OH), 3.40–4.81 (m, 6H, β-D-glucopyranosyl ring), 5.65 (d, 1‴-H, anomeric proton, $J_{1,2} = 7.8$ Hz), 2.3 (s, 4H, glucosidic OH), 8.51 (s, 1H, –CH=), 6.43–7.43 (m, 6H, Ar–H), 6.41 (s, 3′-H, Ar–H), 2.51 (s, 3H, 3″-CH_3); ^{13}C NMR (DMSO-d_6, 300 MHz) δ: 191.2 (s, C-1, C=O), 183.7 (s, C-3), 92.8 (s, C-2, –CH=), 116.4 (s, C-1′), 164.6 (s, C-2′), 104.8 (s, C-3′), 164.7 (s, C-4′), 109.2 (s, C-5′), 132.9 (s, C-6′), 130.4 (s, C-1″), 126.9 (s, C-2″), 137.4 (s, C-3″), 128.4 (s, C-4″), 128.8 (s, C-5″), 123.4 (s, C-6″), 26.8 (s, CH_3 of C-7″), 65.0 (s, C-6‴), 72.9 (s, C-4‴), 75.9 (s, C-2‴), 77.9 (s, C-3‴), 81.4 (s, C-5‴), 105.8 (s, C-1‴, anomeric C-atom); Anal. Calcd. for $C_{22}H_{24}O_9$ (M^+): (432) C, 61.11; H, 5.59. Found: C, 61.13; H, 5.64%.

*7.2.4.8. 1-(4′-O-β-D-glucopyranosyloxy-2′-hydroxyphenyl)-3-(4″-methylphenyl)-propane-1,3-dione (**5h**).* Yield 70%; $[\alpha]_D^{25} = -16.6$ (*c* 0.1, CH_3OH); FT-IR (KBr): 3413 (br, OH peak of carbohydrate residue), 3435 (OH), 1733 (C=O), 2839 (glucosidic CH), 1600 (aromatic C=C), 1149 (C–O); ^{1}H NMR (DMSO-d_6, δ, 300 MHz): 15.94 (s, 1H, enolic OH), 12.19 (s, 1H, 2′-OH), 3.53–4.71 (m, 6H, β-D-glucopyranosyl ring), 5.74 (d, 1‴-H, anomeric proton, $J_{1,2} = 7.8$ Hz), 2.5 (s, 4H, glucosidic OH), 8.43 (s, 1H, –CH=), 7.23 (d, 2H, $J_{2''-4''} = 8.5$ Hz, 2″-H, 4″-H), 7.34 (d, 2H, $J_{3''-5''} = 8.4$ Hz, 3″-H, 5″-H), 6.50–7.24 (m, 3H, Ar–H), 6.43 (s, 3′-H, Ar–H); 2.67 (s, 3H, 4″-CH_3); ^{13}C NMR (DMSO-d_6, 300 MHz) δ: 189.9 (s, C-1, C=O), 184.6 (s, C-3), 94.7 (s, C-2, –CH=), 116.8 (s, C-1′), 164.5 (s, C-2′), 105.6 (s, C-3′), 164.7 (s, C-4′), 109.8 (s, C-5′), 133.6 (s, C-6′), 127.7 (s, C-1″), 127.8 (s, C-2″, C-6″), 129.8 (s, C-3″, C-5″), 138.5 (s, C-4″), 24.9 (s, CH_3 of C-7″), 65.4 (s, C-6‴), 72.0 (s, C-4‴), 75.1 (s, C-2‴), 76.9 (s, C-3‴), 82.4 (s, C-5‴), 105.6 (s, C-1‴, anomeric C-atom); Anal. Calcd. for $C_{22}H_{24}O_9$ (M^+): (432) C, 61.11; H, 5.59. Found: C, 61.13; H, 5.64%.

8. Biological properties

8.1. Antibacterial activity (in vitro)

Two Gram-positive (*S. aureus* ATCC 25923 and *Bacillus subtilis* ATCC 6633) and two Gram-negative (*E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853) bacteria were used as quality control strains. For determining anti-yeast activities of the compounds, the following reference strains were tested: *C. albicans* ATCC 10231 and *C. glabrata* ATCC 36583. Ampicillin trihydrate and Fluconazole were used as standard antibacterial and antifungal agents, respectively. Solutions of the test compounds and reference drugs were dissolved in DMSO at a concentration of 20 mg mL^{-1}. The twofold dilution of the compounds and reference drug were prepared (20, 10, 5.0, 2.5, 1.25, 0.625, 0.31, 0.15, 0.07, 0.03, 0.019, 0.01, 0.005>) mg mL^{-1}. Antibacterial activities of the bacterial strains were carried out in Muller–Hinton broth (Difco) medium, at pH 6.9, with an inoculum of (1–2) × 10^3 cells mL^{-1} by the spectrophotometric method and an aliquot of 100 μL was added to each tube of the serial dilution. The chemical compounds-broth medium serial tube dilutions inoculated with each bacterium were incubated on a rotary shaker at 37 °C for 24 h at 150 rpm.

8.2. Antifungal activity (in vitro)

All fungi were cultivated in Sabouraud Dextrose Agar (Merck). The fungi inoculums were prepared in Sabouraud liquid medium (Oxoid) which had been kept at 36 °C overnight and was diluted with RPMI-1640 medium with L-glutamine buffered with 3-[N-morpholino]-propanesulfonic acid (MOPS) at pH 7 to give a final concentration of 2.5 × 10^3 cfu/mL. The microplates were incubated at 36 °C and read visually after 24 h, except for *Candida* species when it was at 48 h. The incubation chamber was kept humid. At the end of the incubation period, MIC values were recorded as the lowest concentrations of the substances that gave no visible turbidity. The DMSO diluents at a maximum final concentration of 12.5% had no effect on the microorganism's growth.

8.3. Minimum inhibitory concentration (MIC)

The MICs of the chemical compounds assays were carried out as described by Clause [36] with minor modifications. The minimum inhibitory concentrations of the chemical compounds were recorded as the lowest concentration of each chemical compounds in the tubes with no growth (i.e. no turbidity) of inoculated bacteria.

8.4. Antioxidant assay

In vitro free radical scavenging activities of (**5a**)–(**5h**) were evaluated by DPPH assay method. This method is based on the reduction of a methanolic solution of the colored DPPH radical. To a set of test tubes containing 3 mL of methanol, 50 μL of DPPH reagent (2 mg/mL) was added. The initial absorbance was measured. To this test tube, methanolic solution of different test solutions (1 mg/mL) was added (10–50 μL). Ascorbic acid (0.5 mg/mL) was added in the range of 10–25 μL. After 20 min, absorbance

was recorded at 516 nm. The experiment was performed in triplicate. The percentage reduction in absorbance was calculated from the initial and final absorbance of each solution. Percentage scavenging of DPPH radical was calculated using the formula:

$$\%\ \text{Scavenging of DPPH} = [(\text{Control} - \text{Test})/(\text{Control})] \times 100$$

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Appendix. Supplementary material

Supplementary data related to this article can be found online at doi:10.1016/j.ejmech.2011.01.068.

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