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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Antibacterial, antifungal and antioxidant activity of some new water-soluble β-diketones

Javed Sheikh · Taibi Ben Hadda

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Abstract A new series of eight compounds 1-(4′-*O*-β-D-glucopyranosyloxy-2′-hydroxy-5′-substituted phenyl)-3-heteroaryl-propane-1,3-diones (DKG) were prepared by the interaction of α-acetobromoglucose with 1-(2′,4′-dihydroxy-5′-substituted phenyl)-3-heteroaryl-propane-1,3-diones under anhydrous condition at lower temperature. The structures of these *O*-β-D-glucopyranosides were established on the basis of chemical, elemental, and spectral analyses. Further, the compounds were tested for their antibacterial, antifungal, and antioxidant properties. A correlation of structure and activities relationship of these compounds with respect to molecular modeling, Lipinski rule of five, drug-likeness, toxicity profiles, and other physicochemical properties of drugs are described and verified experimentally.

Keywords β-Diketones glucosides (DKG) · Antibacterial · Antifungal · Antioxidant activity

Introduction

This research communication relates to novel pharmaceutical forms for antibiotics containing hydroxyl sugar and β-diketones bearing potential *O*,*O*,*O*-pharmacophore site, in which the known side effects are thought to be reduced and which can be used in a simple manner. The β-diketones and carbohydrates have broad spectrum medicinal values. β-Diketones exhibits number of pharmacological activities like antibacterial (Bennett *et al*., 1999; Sheikh *et al*., 2009a, 2011), antiviral (Diana *et al*., 1978), insecticidal (Crouse *et al*., 1989), antioxidant (Nishiyama *et al*., 2002), and potential prophylactic antitumor activity (Acton *et al*., 1980). It has also been used as an anti-sunscreen agent (Andrae *et al*., 1997). In liquid solutions (Tobita *et al*., 1995) as well as in the solid state (Kaitner and Mestrovic, 1993) β-diketones exists almost exclusively as the enol tautomer, which is stabilized by the intramolecular hydrogen bonding.

Similarly, carbohydrates play important structural and functional roles in numerous physiological processes, including various disease states (Dwek, 1996; Sears and Wong, 1998; Varki, 1993). 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 (Sears and Wong, 1999). For example, cancer cell metastasis (Hakomori and Zhang, 1997) and cell–cell adhesion in the inflammatory response (Kanas, 1996) are dependent on cell surface presentation of specific glycans. Synthetic carbohydrates-based cancer vaccines (Danishefsky and Allen, 2000) and small molecules selective inhibitors (Simanek *et al*., 1998) 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 (Karlsson, 1995).

In this study, we report the synthesis, antibacterial, antifungal, and antioxidant activity of *O*-β-D-glucosyl

J. Sheikh (✉)
National Environmental Engineering Research Institute,
Nehru Marg, Nagpur 440020, India
e-mail: sheikhchemie@gmail.com; javedchemie@gmail.com

J. Sheikh
Department of Chemistry, RTM Nagpur University,
Nagpur 440033, India

T. B. Hadda
Laboratoire Chimie des Matériaux, FSO,
Université Mohammed I, 60000 Oujda, Morocco

derivatives of β-diketones. In addition, we have performed molecular properties calculations of synthesized compounds by using Petra/Osiris/Molinspiration (POM) theory to understand the characteristic features responsible for their bioactivity.

Chemistry

The present communication is featured on the synthesis of 1-(4′-*O*-β-D-glucopyranosyloxy-2′-hydroxy-5′-substituted phenyl)-3-heteroaryl-propane-1,3-diones (**3a**–**h**). The compounds (**1a**–**h**) have been prepared by the Baker–Venkataraman transformation of a substituted aroyloxyacetophenones with base (Sheikh *et al*., 2009b).

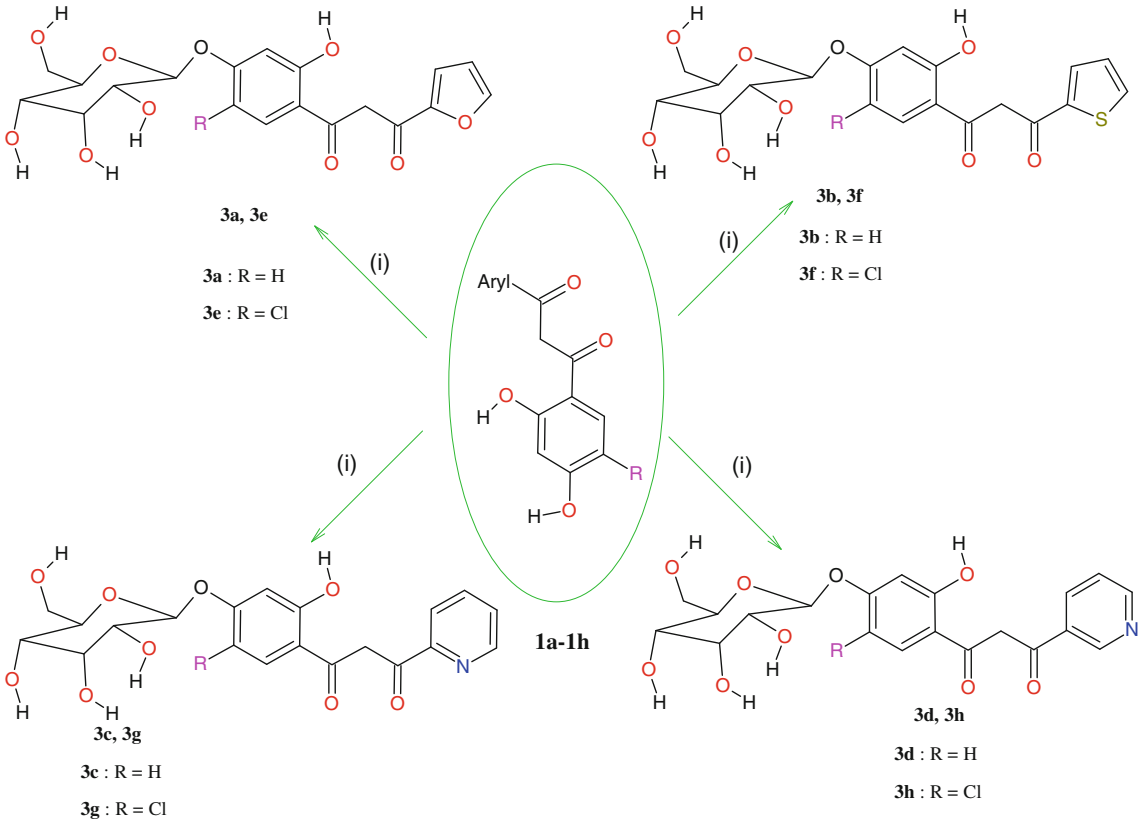
The 1-(2′,4′-dihydroxy-5′-substituted phenyl)-3-heteroaryl-propane-1,3-diones (**1a**–**h**) in 2.5 % methanolic KOH solution were coupled with α-acetobromoglucose (glucosyl donor used for glucosylation) under nitrogen atmosphere to give 1-[2′-hydroxy-4′-(2‴,3‴,4‴,6‴-tetra-*O*-acetyl-*O*-β-D-glucopyranosyloxy)-5′-substituted phenyl]-3-heteroaryl-propane-1,3-diones (**2a**–**h**). In final stage, tetra-*O*-acetyl-*O*-β-D-glucosides (**2a**–**h**) were deacetylated in dry methanol with sodium methoxide solution under nitrogen atmosphere to afford 1-(4′-*O*-β-D-glucopyranosyloxy-2′-hydroxy-5′-substituted phenyl)-3-heteroaryl-propane-1,3-diones (**3a**–**h**). The structures of synthesized compounds were confirmed by the spectral methods (FT-IR, ^{1}H NMR, ^{13}C NMR, mass) and elemental analyses. The detailed synthetic strategy is outlined in Scheme 1.

Results and discussion

Spectroscopic characterizations of compounds

IR spectra

The IR spectra of 1-(4′-*O*-β-D-glucopyranosyloxy-2′-hydroxyphenyl)-3-furyl-propane-1,3-dione (**3a**) shown a stretching frequency at 3,422 and 1,735 cm^{-1} corresponds to OH and C=O, respectively. Further, (**3a**) posses the characteristic bands at 3,401 cm^{-1} (OH peak of carbohydrate residue) and 2,857 cm^{-1} (glucosidic CH) indicating the presence of *O*-β-D-glucosyl moiety in the molecule (Fig. 1). It was also confirmed by its ^{1}H- and ^{13}C NMR, and mass spectral data (Table 1).



Scheme 1 Synthesis of 1-(4′-*O*-β-D-glucopyranosyloxy-2′-hydroxy-5′-substituted phenyl)-3-heteroaryl-propane-1,3-diones (**3a**–**h**). (*i*) glucosylation

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

The presence of characteristic ^{1}H and ^{13}C NMR peaks are consistent with the structure of 1-(4′-*O*-*β*-D-glucopyranosyloxy-2′-hydroxyphenyl)-3-furyl-propane-1,3-dione (**3a**). The (**3a**) exhibited ^{1}H NMR peaks at δ 3.44–4.86 (m, 6H, *β*-D-glucopyranosyl ring), 2.5 (s, 4H, glucosidic OH) and *β*-linkage at 5.91 (d, 1‴-H, anomeric proton, $J_{1,2} = 8.2$ Hz) ppm indicating the linkage of the carbohydrate unit to the C-4′' position of the aglycone moiety (Table 1).

The anomeric carbon in ^{13}C NMR is confirmed at δ 106.4 ppm (s, C-1‴, anomeric C-atom). Further, the mass spectrum shown a molecular ion peak at 408 (M^{+}), confirms the molecular formula $C_{19}H_{20}O_{10}$ of (**3a**).

In vitro antimicrobial and antioxidant activity

The water-soluble functionalized sugar based *β*-diketones (**3a–h**) are evaluated for the antibacterial, antifungal, and antioxidant activities. The minimal inhibitory concentrations (MICs, mg/mL) of tested compounds against certain bacteria and fungi are shown in Tables 2 and 3. The compounds (**3a–h**) were tested for their in vitro antimicrobial activity against four strains of bacteria (gram +ve and gram −ve), and two strains of fungi (*C. albicans* and *C. glabrata*). The four compounds of the series have shown relatively high in vitro antimicrobial activity. The compound 1-(5′-chloro-4′-*O*-*β*-D-glucopyranosyloxy-2′-hydroxyphenyl)-3-(2-pyridyl)-propane-1,3-dione (**3g**) shown excellent activity against *E. coli* and *P. aeruginosa*, and excellent activity against *C. albicans* indicated in vitro antifungal activity comparable to slightly lower than fluconazole. 1-(4′-*O*-*β*-D-glucopyranosyloxy-2′-hydroxyphenyl)-3-(2-pyridyl)-propane-1,3-dione (**3c**) and 1-(5′-chloro-4′-*O*-*β*-D-glucopyranosyloxy-2′-hydroxyphenyl)-3-furyl-propane-1,3-dione (**3e**) shown excellent activity against *P. aeruginosa* indicated in vitro antibacterial activity comparable to slightly lower than ampicillin. The compound (**3f**) shown excellent activity against *C. glabrata*

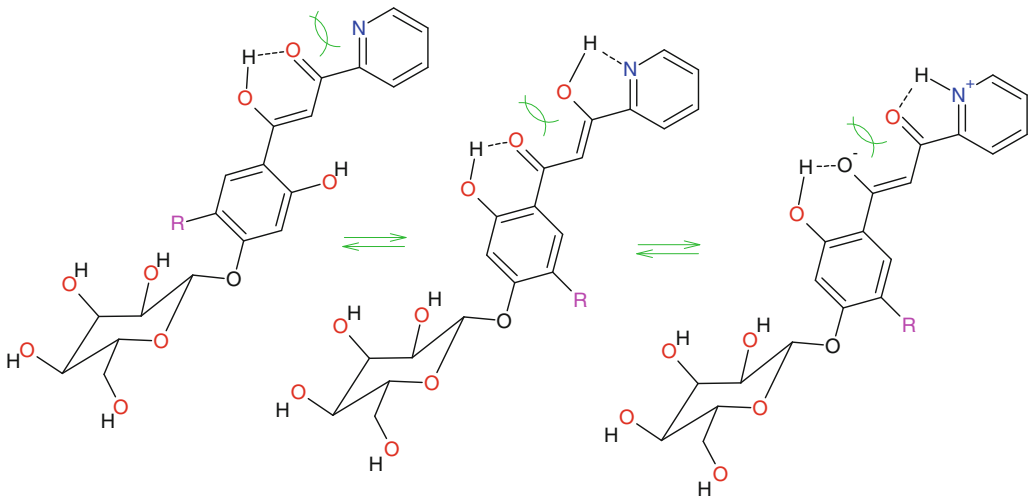


Fig. 1 Intervention of heterocyclic aryl in tautomerism

Table 1 IR and ^{1}H NMR data of compounds (**3a–h**)

Compounds	IR (KBr)				^{1}H NMR (DMSO d_6, δ, 300 MHz)			
	OH (carbohyd)	=C–OH (enol)	C=O (keto)	C–O (Moieties)	OH (Enolic)	2′-OH (phenol)	H (gluco)	OH (gluco)
3a	3,401	3,422	1,735	1,146	15.91	12.22	3.44–4.86	2.5
3b	3,408	3,426	1,735	1,146	16.01	12.20	3.45–4.88	2.8
3c	3,410	3,435	1,742	1,145	15.96	12.03	3.35–4.97	2.9
3d	3,413	3,429	1,734	1,151	15.98	12.13	3.43–4.97	2.2
3e	3,410	3,431	1,732	1,141	15.94	12.09	3.47–4.89	2.6
3f	3,404	3,429	1,735	1,144	16.11	12.07	3.51–4.98	2.7
3g	3,413	3,431	1,742	1,142	15.99	12.13	3.41–4.99	2.8
3h	3,417	3,437	1,734	1,155	16.11	12.10	3.51–4.98	2.5

Table 2 Antibacterial activity of compounds (**3a–h**)

Compounds	R	Aryl	Antibacterial activity[a]			
			S. aureus ATCC 25923	*B. subtilis* ATCC 6633	*E. coli* ATCC 27853	*P. aeruginosa* ATCC 27853
3a	H		0.625	0.15	2.5	5.0
3b	H		0.3	0.15	1.25	0.15
3c	H		0.15	0.3	0.07	0.019
3d	H		0.15	0.625	0.3	1.25
3e	Cl		0.15	0.3	0.07	0.019
3f	Cl		0.3	0.625	5	0.03
3g	Cl		0.15	1.25	0.019	0.019
3h	Cl		5.0	0.3	5.0	5.0
Ampicillin	–	–	0.019	0.005	0.01	0.005

Minimum inhibitory concentrations (MICs, mg/mL)

[a] Antibacterial activity: in present protocol 1.25 mg/mL is considered as moderate activity, 0.07 mg/mL is considered as good activity and 0.019 mg/mL is considered as excellent activity compared to the standard drug ampicillin

indicated in vitro antifungal activity comparable to slightly lower than fluconazole. The presence of electron-withdrawing group on the aromatic ring in general increases the antimicrobial activities of the tested compounds compared to compounds having no substitution/electron donating group.

Based upon the results it may also be necessary to optimize the lead compound by substitution at C-5 position of the phenyl ring by chloro and polar group, and heterocyclic substitution at C-3 carbon of β-diketones seems to be very important for the antibacterial effect; as well as the presence of glucosidic moiety on the aromatic ring seems to be very important for the antibacterial effect and cell–cell recognition. Moreover, the glucosidic moiety on the aromatic ring acts as a drug handle to guide the aglycon molecule through the drug metabolism.

These results (Table 2) suggested that *O*-β-D-glucosides have effective improvement of bioavailability and the electro-acceptor or electro-donor nature of substituent (R) have effective and direct impact on selective antimicrobial activities against both bacteria and fungi. Table 3 also summarizes free radical scavenging activity (antioxidant activity) using the DPPH assay method. According to these results, the newly synthesized *O*-β-D-glucosides have more promising antioxidant activity.

Table 3 Antifungal and antioxidant activity of compounds (**3a–h**)

Compounds	Antifungal activity[a]		Antioxidant activity
	C. albicans ATCC 10231	*C. glabrata* ATCC 36583	DPPH % Inhib. antioxidant
3a	5.0	5.0	84.34
3b	2.5	5.0	74.21
3c	2.5	5.0	79.02
3d	10	5.0	74.21
3e	2.5	5.0	77.01
3f	5.0	0.15	81.15
3g	0.15	2.5	85.53
3h	10.0	10.0	79.54
Fluconazole	0.01	0.01	–
Ascorbic acid	–	–	98.03

Minimum inhibitory concentration (MICs, mg/mL)

[a] Antifungal activity: in present protocol 0.15 mg/mL is considered as excellent activity compared to the standard drug fluconazole

Molecular properties calculations (Parvez *et al*., 2010; Sheikh *et al*., 2011)

For the compounds (**3a–h**), depending on the pH and position of the dissociated hydroxyl hydrogen atoms, many possible β-diketones glucosides (DKG) conformations can be described for the neutral (N) forms. These relevant structures are sketched in Figs. 2 and 3.

In past, for example, in structure of curcumin derivatives, attention was mainly devoted to the diketo form. However, from a chemical point of view, all other forms (tautomers and their conformers) are possible.

For the development of binding approaches for DKG environment, the identification of the active diketo structures present is important. Neither experimental nor theoretical data is available for the identification of water-solved DKG species. Theoretically, NMR spectroscopy could be useful for identifying chemical structures. Theoretical ab initio studies could supplement these measurements. In addition, calculations of energetics, atomic charges, minimum energy structures, geometry, and natural bond orbital (NBO) could indicate the electronic density distribution of each atom. Finally, by taking NBO results showing the presence of C–O single bonds in consideration, realistic Lewis structures can be determined. These systematic data, regarding the variation of molecular properties, are important for the chemical structure and could therefore provide first insights into the still poorly understood chemical bonding of DKG complexes.

In brief, the objective of this study is to investigate the potential pharmacophore sites of DKG species using antibacterial and antifungal screenings dependence on pH and comparison with the calculated molecular properties. To verify these structures, further POM analyses were carried out; for example calculation of net atomic charges, bond polarity, atomic valence, electron delocalization, and lipophilicity.

Finally, to investigate the combined antibacterial/antifungal bioactivity of the DKG species, tautomeric structures were performed. Current thinking in the generation of specific drug leads embodies the concept of achieving high molecular diversity within the boundaries of reasonable drug-like properties. Natural and semi-natural products, examples, penicillin, and synthetic fluconazole have high chemical

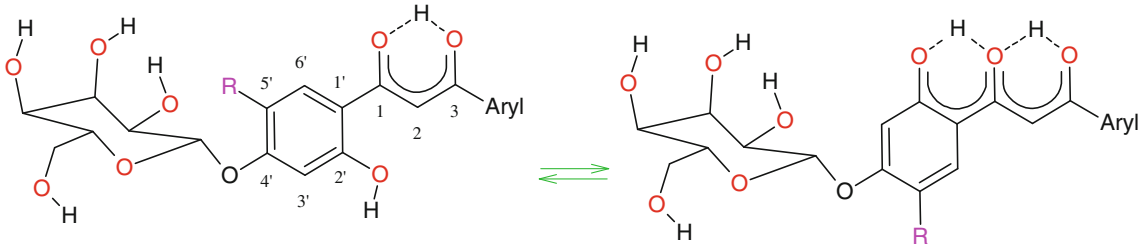


Fig. 2 General tautomerism process in series of compounds (**3a–h**)

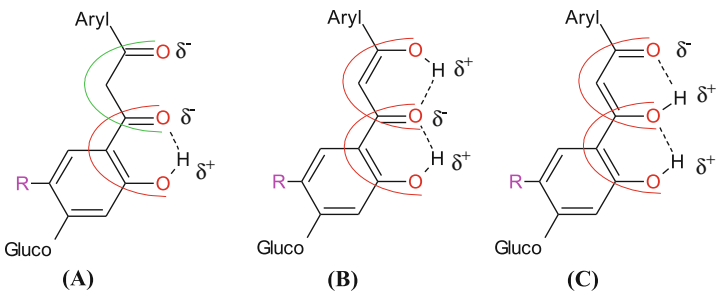


Fig. 3 Different ($O–H^{\delta+}–{}^{\delta-}O$) hexa-membered antibacterial pharmacophore sites (*red half circle*) present in **a**, **b**, and **c** tautomers. The opened ($O^{\delta-}–{}^{\delta-}O$) four-membered antifungal pharmacophore site (*green half circle*) present only in **a** tautomerm (Color figure online)

diversity, biochemical specificity, and other molecular properties that make them favorable as lead and standard reference (SR) structures for drug discovery, and which serve to differentiate them from libraries of synthetic and combinatorial compounds.

Various investigators have used computational methods to understand differences between natural products and other sources of drug leads. Modern drug discovery is based in large part on high throughput screening of small molecules against macromolecular disease targets requiring that molecular screening libraries contain drug-like or lead-like compounds. We have analyzed known SRs for drug-like and lead-like properties. With this information in hand, we have established a strategy to design specific drug-like or lead-like ampicillin and fluconazole (**3a**–**h**).

Conclusion

The water-soluble *O*,*O*,*O*-functionalized compounds 1-(4′-*O*-*β*-D-glucopyranosyloxy-2′-hydroxy-5′-substituted phenyl)-3-heteroaryl-propane-1,3-diones (**3a**–**h**) have been synthesized by glucosylation of 1-(2′,4′-dihydroxy-5′-substituted phenyl)-3-heteroaryl-propane-1,3-diones with glucosyl donor in good yield. All the compounds (**3a**–**h**) were screened for the antimicrobial and antioxidant activity. The compounds (**3c**), (**3e**), (**3f**), and (**3g**) were found to be potent antibacterial and antifungal agents but less active than ampicillin and fluconazole. The newly synthesized (**3a**–**h**) were also shown to posses promising antioxidant activity. In contrast to glucosyl moiety which increases aqueous solubility, the tautomerism decreases bioactivity of series. It is predicted that the most of these compounds could be used without great risk of toxicity in diverse antibacterial activity. Thus, the POM calculations and actual experimental verification in one handy value not only proves the compounds' overall potential to qualify for a drug but also potentially interesting for further optimization and exploration of *β*-diketo functionality.

Experimental

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) disk on Perkin Elmer spectrum Rx-I spectrometer. ^{1}H 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.

General procedure for the synthesis of *O*-*β*-D-glucosides of *β*-diketones (**3a**–**h**)

*General procedure for the synthesis of (**2a**–**h**)*

To a solution of 1-(2′,4′-dihydroxy-5′-substituted phenyl)-3-heteroaryl-propane-1,3-diones (**1a**–**h**) (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 (**2a**).

*1-[2′-Hydroxy-4′-(2‴,3‴,4‴,6‴-tetra-O-acetyl-O-β-D-glucopyranosyloxy)phenyl]-3-furyl-propane-1,3-dione (**2a**)* Yield 73 %; $[\alpha]_D^{25} = -5.1$ (*c* 0.1, CH_3OH); IR (KBr): 3403 (–OH), 2844 (glucosidic CH), 1763 (C=O of *O*-acetyl groups of glycone moiety), 1741 (C=O), 1599 (aromatic C=C), 1148 (C–O); ^{1}H NMR (DMSO-d_6, δ, 300 MHz): 15.89 (s, 1H, enolic OH), 11.81 (s, 1H, 2′-OH), 8.39 (s, 1H, –CH=), 6.41–7.49 (m, 6H, Ar–H), 2.03, 2.04, 1.98, 2.03 (s, 3H, OAc), 3.47–4.98 (m, 6H, *β*-D-glucopyranosyl ring), 4.81 (d, 1‴-H, anomeric proton, $J_{1,2} = 7.8$ Hz); ^{13}C NMR (DMSO-d_6, δ, 300 MHz): 189.9 (s, C-1, C=O), 185.1 (s, C-3), 94.2 (s, C-2, –CH=), 115.6 (s, C-1′), 163.7 (s, C-2′), 104.6 (s, C-3′), 164.8 (s, C-4′), 159.1 (s, C-5′), 131.7 (s, C-6′), 136.9 (s, C-1″), 125.6 (s, C-2″), 119.1 (s, C-3″), 148.1 (s, C-4″), 21.3 (s, C-atom, CH_3 of acetyl group), 170.9 (s, C=O, acetyl group), 102.4 (s, C-1‴, anomeric C-atom), 72.8 (s, C-2‴), 71.0 (s, C-3‴), 71.9 (s, C-4‴), 75.1 (s, C-5‴), 65.7 (s, C-6‴). Anal. Calcd. for $C_{27}H_{28}O_{14}$ (M^+): (576): C, 56.25; H, 4.90. Found: C, 56.27; H, 4.91.

*1-[2′-Hydroxy-4′-(2‴,3‴,4‴,6‴-tetra-O-acetyl-O-β-D-glucopyranosyloxy)phenyl]-3-thienyl-propane-1,3-dione (**2b**)* Yield 71 %; $[\alpha]_D^{25} = -8.1$ (*c* 0.1, CH_3OH); IR (KBr): 3400 (–OH), 2849 (glucosidic CH), 1765 (C=O of *O*-acetyl groups of glycone moiety), 1743 (C=O), 1601 (aromatic C=C), 1141 (C–O); ^{1}H NMR (DMSO-d_6, δ, 300 MHz): 15.92 (s, 1H, enolic OH), 11.89 (s, 1H, 2′-OH), 8.44 (s, 1H, –CH=), 6.46–7.39 (m, 6H, Ar–H), 2.06, 2.01, 1.91, 2.03 (s, 3H, OAc), 3.48–4.94 (m, 6H, *β*-D-glucopyranosyl ring), 4.86 (d, 1‴-H, anomeric proton, $J_{1,2} = 7.8$ Hz); ^{13}C NMR (DMSO-d_6, δ, 300 MHz): 189.5 (s, C-1, C=O), 184.8 (s, C-3), 93.9 (s, C-2, –CH=), 115.5 (s,

C-1′), 163.8 (s, C-2′), 104.3 (s, C-3′), 164.2 (s, C-4′), 159.5 (s, C-5′), 131.9 (s, C-6′), 137.1 (s, C-1″), 124.2 (s, C-2″), 118.8 (s, C-3″), 148.9 (s, C-4″), 21.9 (s, C-atom, CH_3 of acetyl group), 171.3 (s, C=O, acetyl group), 102.8 (s, C-1‴, anomeric C-atom), 72.9 (s, C-2‴), 71.6 (s, C-3‴), 72.4 (s, C-4‴), 75.3 (s, C-5‴), 65.5 (s, C-6‴). Anal. Calcd. for $C_{27}H_{28}O_{13}S$ (M^+): (592): C, 54.73; H, 4.76. Found: C, 54.75; H, 4.77.

1-[2′-Hydroxy-4′-(2‴,3‴,4‴,6‴-tetra-O-acetyl-O-β-D-gluco pyranosyloxy)phenyl]-3-(2-pyridyl)-propane-1,3-dione ***(2c)*** Yield 75 %; $[\alpha]_D^{25} = -4.1$ (*c* 0.1, CH_3OH); IR (KBr): 3409 (–OH), 2853 (glucosidic CH), 1761 (C=O of *O*-acetyl groups of glycone moiety), 1739 (C=O), 1598 (aromatic C=C), 1141 (C–O); ^{1}H NMR (DMSO-d_6, δ, 300 MHz) 15.91 (s, 1H, enolic OH), 12.04 (s, 1H, 2′-OH), 8.51 (s, 1H, –CH=), 6.55–7.71 (m, 7H, Ar–H), 2.04, 2.05, 1.97, 2.03 (s, 3H, OAc), 3.43–4.94 (m, 6H, β-D-glucopyranosyl ring), 4.83 (d, 1‴-H, anomeric proton, $J_{1,2} = 7.9$ Hz); ^{13}C NMR (DMSO-d_6, δ, 300 MHz): 189.4 (s, C-1, C=O), 186.6 (s, C-3), 92.2 (s, C-2, –CH=), 114.2 (s, C-1′), 163.9 (s, C-2′), 103.7 (s, C-3′), 164.1 (s, C-4′), 108.6 (s, C-5′), 132.6 (s, C-6′), 130.8 (s, C-1″), 121.5 (s, C-2″), 132.2 (s, C-3″), 128.1 (s, C-4″), 129.3 (s, C-5″), 21.5 (s, C-atom, CH_3 of acetyl group), 170.4 (s, C=O, acetyl group), 103.6 (s, C-1‴, anomeric C-atom), 71.4 (s, C-2‴), 71.2 (s, C-3‴), 71.6 (s, C-4‴), 73.5 (s, C-5‴), 67.0 (s, C-6‴). Anal. Calcd. for $C_{28}H_{29}NO_{13}$ (M^+): (587) C, 57.24; H, 4.98. Found: C, 57.26; H, 4.99.

General procedure for the synthesis of 1-(4′-O-β-D-gluco pyranosyloxy-2′-hydroxy-5′-substituted phenyl)-3-heteroaryl-propane-1,3-diones ***(3a–h)***

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)-5′-substituted phenyl]-3-heteroaryl-propane-1,3-dione (**2**) (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′-hydroxy-5′-substituted phenyl)-3-heteroaryl-propane-1,3-dione (**3**) as solid yield. The compounds were found to be optically active.

1-(4′-O-β-D-glucopyranosyloxy-2′-hydroxyphenyl)-3-furyl-propane-1,3-dione ***(3a)*** Yield 71 %; $[\alpha]_D^{25} = -13.8$ (*c* 0.1, CH_3OH); FT-IR (KBr): 3401 (br, OH peak of carbohydrate residue), 3422 (OH), 1735 (C=O), 2857 (glucosidic CH), 1599 (aromatic C=C), 1146 (C–O); ^{1}H NMR (DMSO- d_6, δ, 300 MHz) 15.91 (s, 1H, enolic OH), 12.22 (s, 1H, 2′-OH), 3.44–4.86 (m, 6H, β-D-glucopyranosyl ring), 5.91 (d, 1‴-H, anomeric proton, $J_{1,2} = 8.2$ Hz), 2.5 (s, 4H, glucosidic OH), 8.55 (s, 1H, –CH=), 6.55–7.71 (m, 6H, Ar–H); ^{13}C NMR (DMSO-d_6, δ, 300 MHz) 190.4 (s, C-1, C=O), 184.7 (s, C-3), 93.8 (s, C-2, –CH=), 115.4 (s, C-1′), 164.8 (s, C-2′), 105.1 (s, C-3′), 162.5 (s, C-4′), 109.3 (s, C-5′), 131.6 (s, C-6′), 130.7 (s, C-1″), 121.6 (s, C-2″), 122.5 (s, C-3″), 128.9 (s, C-4″), 64.4 (s, C-6‴), 73.5 (s, C-4‴), 75.2 (s, C-2‴), 77.7 (s, C-3‴), 82.4 (s, C-5‴), 106.4 (s, C-1‴, anomeric C-atom); Anal. Calcd. for $C_{19}H_{20}O_{10}$ (M^+): (408) C, 55.88; H, 4.94. Found: C, 55.87; H, 4.95 %.

1-(4′-O-β-D-glucopyranosyloxy-2′-hydroxyphenyl)-3-thienyl-propane-1,3-dione ***(3b)*** Yield 68 %; $[\alpha]_D^{25} = -11.2$ (*c* 0.1, CH_3OH); FT-IR (KBr): 3408 (br, OH peak of carbohydrate residue), 3426 (OH), 1735 (C=O), 2844 (glucosidic CH), 1591 (aromatic C=C), 1146 (C–O); ^{1}H NMR (DMSO-d_6, δ, 300 MHz) 16.01 (s, 1H, enolic OH), 12.20 (s, 1H, 2′-OH), 3.45–4.88 (m, 6H, β-D-glucopyranosyl ring), 5.97 (d, 1‴-H, anomeric proton, $J_{1,2} = 8.2$ Hz), 2.8 (s, 4H, glucosidic OH), 8.51 (s, 1H, –CH=), 6.45–7.69 (m, 6H, Ar–H); ^{13}C NMR (DMSO-d_6, δ, 300 MHz) 190.1 (s, C-1, C=O), 184.3 (s, C-3), 93.2 (s, C-2, –CH=), 115.5 (s, C-1′), 165.6 (s, C-2′), 105.3 (s, C-3′), 162.8 (s, C-4′), 109.1 (s, C-5′), 132.1 (s, C-6′), 130.2 (s, C-1″), 121.0 (s, C-2″), 122.7 (s, C-3″), 127.5 (s, C-4″), 65.6 (s, C-6‴), 73.7 (s, C-4‴), 75.5 (s, C-2‴), 77.8 (s, C-3‴), 82.5 (s, C-5‴), 106.8 (s, C-1‴, anomeric C-atom); Anal. Calcd. for $C_{19}H_{20}O_9S$ (M^+): (424) C, 53.77; H, 4.75. Found: C, 53.78; H, 4.76 %.

1-(4′-O-β-D-glucopyranosyloxy-2′-hydroxyphenyl)-3-(2-pyridyl)-propane-1,3-dione ***(3c)*** Yield 71 %; $[\alpha]_D^{25} = -14.3$ (*c* 0.1, CH_3OH); FT-IR (KBr): 3410 (br, OH peak of carbohydrate residue), 3435 (OH), 1742 (C=O), 2861 (glucosidic CH), 1603 (aromatic C=C), 1145 (C–O); ^{1}H NMR (DMSO-d_6, δ, 300 MHz): 15.96 (s, 1H, enolic OH), 12.03 (s, 1H, 2′-OH), 3.35–4.97 (m, 6H, β-D-glucopyranosyl ring), 5.78 (d, 1‴-H, anomeric proton, $J_{1,2} = 7.9$ Hz), 2.9 (s, 4H, glucosidic OH), 8.58 (s, 1H, –CH=), 6.57–7.41 (m, 7H, Ar–H); ^{13}C NMR (DMSO-d_6, δ, 300 MHz): 190.4 (s, C-1, C=O), 184.5 (s, C-3), 93.6 (s, C-2, –CH=), 115.7 (s, C-1′), 164.4 (s, C-2′), 104.9 (s, C-3′), 164.5 (s, C-4′), 109.6 (s, C-5′), 132.9 (s, C-6′), 131.5 (s, C-1″), 126.4 (s, C-2″), 123.4 (s, C-3″), 129.7 (s, C-4″), 131.3 (s, C-5″), 64.5 (s, C-6‴), 72.6 (s, C-4‴), 76.8 (s, C-2‴), 77.9 (s, C-3‴), 82.3 (s, C-5‴), 106.2 (s, C-1‴, anomeric C-atom); Anal. Calcd. for $C_{20}H_{21}NO_9$ (M^+): (419) C, 57.28; H, 5.05. Found: C, 57.30; H, 5.06 %.

1-(4′-O-β-D-glucopyranosyloxy-2′-hydroxyphenyl)-3-(3-pyridyl)-propane-1,3-dione ***(3d)*** Yield 69 %; $[\alpha]_D^{25} = -16.1$ (*c* 0.1, CH_3OH); IR (KBr): 3413 (br, OH peak of carbohydrate residue), 3429 (OH), 1734 (C=O), 2825 (glucosidic CH), 1603 (aromatic C=C), 1151 (C–O); ^{1}H NMR (DMSO-d_6, δ, 300 MHz): 15.98 (s, 1H, enolic OH),

12.13 (s, 1H, 2′-OH), 3.43–4.97 (m, 6H, β-D-glucopyranosyl ring), 5.72 (d, 1‴-H, anomeric proton, $J_{1,2} = 7.8$ Hz), 2.2 (s, 4H, glucosidic OH), 8.50 (s, 1H, –CH=), 6.47–7.49 (m, 7H, Ar–H), ^{13}C NMR (DMSO-d_6, δ, 300 MHz): 191.4 (s, C-1, C=O), 184.3 (s, C-3), 94.5 (s, C-2, –CH=), 115.4 (s, C-1′), 164.2 (s, C-2′), 111.9 (s, C-3′), 164.5 (s, C-4′), 109.7 (s, C-5′), 132.9 (s, C-6′), 125.9 (s, C-1″), 126.8 (s, C-2″), 128.9 (s, C-3″), 133.5 (s, C-4″), 132.5 (s, C-5″), 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 $C_{20}H_{21}NO_9$ (M^+): (419) C, 57.28; H, 5.05. Found: C, 57.29; H, 5.04 %.

*1-(5′-Chloro-4′-O-β-D-glucopyranosyloxy-2′-hydroxyphenyl)-3-furyl-propane-1,3-dione (**3e**)* Yield 73 %; $[\alpha]_D^{25} = -13.1$ (*c* 0.1, CH_3OH); FT-IR (KBr): 3410 (br, OH peak of carbohydrate residue), 3431 (OH), 1732 (C=O), 2851 (glucosidic CH), 1601 (aromatic C=C), 1141 (C–O); ^{1}H NMR (DMSO- d_6, δ, 300 MHz) 15.94 (s, 1H, enolic OH), 12.09 (s, 1H, 2′-OH), 3.47–4.89 (m, 6H, β-D-glucopyranosyl ring), 5.99 (d, 1‴-H, anomeric proton, $J_{1,2} = 8.2$ Hz), 2.6 (s, 4H, glucosidic OH), 8.59 (s, 1H, –CH=), 6.45–7.74 (m, 5H, Ar–H); ^{13}C NMR (DMSO-d_6, δ, 300 MHz) 190.0 (s, C-1, C=O), 184.1 (s, C-3), 93.6 (s, C-2, –CH=), 115.9 (s, C-1′), 164.1 (s, C-2′), 105.8 (s, C-3′), 162.7 (s, C-4′), 114.2 (s, C-5′), 131.1 (s, C-6′), 130.7 (s, C-1″), 120.9 (s, C-2″), 122.7 (s, C-3″), 129.6 (s, C-4″), 64.8 (s, C-6‴), 72.3 (s, C-4‴), 75.5 (s, C-2‴), 77.9 (s, C-3‴), 82.2 (s, C-5‴), 106.4 (s, C-1‴, anomeric C-atom); Anal. Calcd. for $C_{19}H_{19}ClO_{10}$ (M^+): (442) C, 51.54; H, 4.32. Found: C, 51.56; H, 4.34 %.

*1-(5′-Chloro-4′-O-β-D-glucopyranosyloxy-2′-hydroxyphenyl)-3-thienyl-propane-1,3-dione (**3f**)* Yield 65 %; $[\alpha]_D^{25} = -15.6$ (*c* 0.1, CH_3OH); FT-IR (KBr): 3404 (br, OH peak of carbohydrate residue), 3429 (OH), 17356 (C=O), 2859 (glucosidic CH), 1597 (aromatic C=C), 1144 (C–O); ^{1}H NMR (DMSO-d_6, δ, 300 MHz) 16.11 (s, 1H, enolic OH), 12.07 (s, 1H, 2′-OH), 3.51–4.98 (m, 6H, β-D-glucopyranosyl ring), 5.99 (d, 1‴-H, anomeric proton, $J_{1,2} = 8.2$ Hz), 2.7 (s, 4H, glucosidic OH), 8.61 (s, 1H, –CH=), 6.49–7.76 (m, 5H, Ar–H); ^{13}C NMR (DMSO-d_6, δ, 300 MHz) 190.5 (s, C-1, C=O), 184.8 (s, C-3), 93.7 (s, C-2, –CH=), 115.8 (s, C-1′), 164.6 (s, C-2′), 105.6 (s, C-3′), 161.4 (s, C-4′), 111.4 (s, C-5′), 133.1 (s, C-6′), 130.4 (s, C-1″), 121.5 (s, C-2″), 121.4 (s, C-3″), 126.6 (s, C-4″), 65.3 (s, C-6‴), 73.1 (s, C-4‴), 75.0 (s, C-2‴), 77.5 (s, C-3‴), 82.2 (s, C-5‴), 106.4 (s, C-1‴, anomeric C-atom); Anal. Calcd. for $C_{19}H_{19}ClO_9S$ (M^+): (458) C, 49.73; H, 4.17. Found: C, 49.72; H, 4.16 %.

*1-(5′-Chloro-4′-O-β-D-glucopyranosyloxy-2′-hydroxyphenyl)-3-(2-pyridyl)-propane-1,3-dione (**3g**)* Yield 75 %; $[\alpha]_D^{25} = -15.6$ (*c* 0.1, CH_3OH); FT-IR (KBr): 3413 (br, OH peak of carbohydrate residue), 3431 (OH), 1742 (C=O), 2860 (glucosidic CH), 1601 (aromatic C=C), 1142 (C–O); ^{1}H NMR (DMSO-d_6, δ, 300 MHz): 15.99 (s, 1H, enolic OH), 12.13 (s, 1H, 2′-OH), 3.41–4.99 (m, 6H, β-D-glucopyranosyl ring), 5.81 (d, 1‴-H, anomeric proton, $J_{1,2} = 7.9$ Hz), 2.8 (s, 4H, glucosidic OH), 8.54 (s, 1H, –CH=), 6.55–7.45 (m, 6H, Ar–H); ^{13}C NMR (DMSO-d_6, δ, 300 MHz): 190.3 (s, C-1, C=O), 184.9 (s, C-3), 94.9 (s, C-2, –CH=), 117.8 (s, C-1′), 164.6 (s, C-2′), 104.9 (s, C-3′), 164.5 (s, C-4′), 109.6 (s, C-5′), 131.6 (s, C-6′), 132.9 (s, C-1″), 126.7 (s, C-2″), 123.8 (s, C-3″), 128.6 (s, C-4″), 132.7 (s, C-5″), 65.2 (s, C-6‴), 72.8 (s, C-4‴), 76.5 (s, C-2‴), 77.8 (s, C-3‴), 82.8 (s, C-5‴), 106.7 (s, C-1‴, anomeric C-atom); Anal. Calcd. for $C_{20}H_{20}ClNO_9$ (M^+): (453) C, 52.93; H, 4.44. Found: C, 52.94; H, 4.46 %.

*1-(5′-Chloro-4′-O-β-D-glucopyranosyloxy-2′-hydroxyphenyl)-3-(3-pyridyl)-propane-1,3-dione (**3h**)* Yield 63 %; $[\alpha]_D^{25} = -15.6$ (*c* 0.1, CH_3OH); IR (KBr): 3417 (br, OH peak of carbohydrate residue), 3437 (OH), 1734 (C=O), 2831 (glucosidic CH), 1607 (aromatic C=C), 1155 (C–O); ^{1}H NMR (DMSO-d_6, δ, 300 MHz): 16.11 (s, 1H, enolic OH), 12.10 (s, 1H, 2′-OH), 3.51–4.98 (m, 6H, β-D-glucopyranosyl ring), 5.79 (d, 1‴-H, anomeric proton, $J_{1,2} = 7.8$ Hz), 2.5 (s, 4H, glucosidic OH), 8.54 (s, 1H, –CH=), 6.51–7.63 (m, 6H, Ar–H), ^{13}C NMR (DMSO-d_6, δ, 300 MHz): 192.1 (s, C-1, C=O), 185.3 (s, C-3), 94.0 (s, C-2, –CH=), 116.6 (s, C-1′), 164.7 (s, C-2′), 111.6 (s, C-3′), 164.6 (s, C-4′), 109.9 (s, C-5′), 131.8 (s, C-6′), 123.9 (s, C-1″), 122.7 (s, C-2″), 128.7 (s, C-3″), 133.9 (s, C-4″), 137.4 (s, C-5″), 64.6 (s, C-6‴), 72.7 (s, C-4‴), 75.5 (s, C-2‴), 77.8 (s, C-3‴), 82.1 (s, C-5‴), 105.5 (s, C-1‴, anomeric C-atom); Anal. Calcd. for $C_{20}H_{20}ClNO_9$ (M^+): (453) C, 52.93; H, 4.44. Found: C, 52.95; H, 4.42 %.

Antimicrobial screenings of compounds (**3a**–**h**)

Antibacterial activity (in vitro)

Two gram-positive (*Staphylococcus aureus* ATCC 25923 and *Bacillus subtilis* ATCC 6633) and two gram-negative (*Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853) bacteria were used as quality control strains. For determining anti-yeast activities of the compounds, the following reference strains were tested: *Candida albicans* ATCC 10231 and *Candida 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. 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. 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) $\times$ 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.

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 $\times$ 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.

Minimum inhibitory concentration

The MICs of the chemical compounds assays were carried out as described by Clause (1989) with minor modifications. The MICs 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.

Antioxidant assay

In vitro free radical scavenging activities of (**3a**–**h**) 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) were 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 521 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:

$$\% \text{ Scavenging of DPPH} = [(\text{control} - \text{test}/\text{control})] \times 100.$$

Molecular properties calculations

Molinspiration calculations (Parvez, et al., 2010; Sheikh et al., 2011)

clog P (octanol/water partition coefficient) is calculated by the methodology developed by molinspiration as a sum of fragment-based contributions and correction factors. The method is very robust and is able to process practically all organic and the most organometallic molecules. Molecular polar surface area (PSA) TPSA is calculated based on the methodology published by Ertl et al. as a sum of fragment contributions. 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. Predicted results of compounds and molecular properties (TPSA, GPCR ligand, and ICM) are valued (Tables 4, 5). Lipophilicity (log *P* value) and PSA values are two important predictors of per oral bioavailability of drug molecules (Chang *et al*., 2004; Clark, 1999). Therefore, we calculated log *P* and PSA values for compounds (**3a**–**h**) using molinspiration software programs and compared them to the values obtained for standard market available drugs. For all compounds the calculated log *P* values were lower than 5, which is the upper limit for drugs to be able to penetrate through biomembranes according to Lipinski's rules. The 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 (Clark, 1999). Molecules with PSAs of 140 Å or more are expected to exhibit poor intestinal absorption (Clark, 1999). Table 4 shows that all the compounds are not within this limit with all compounds is having minimum non comparable values of log *P* and PSA to reference drugs. This is also supported by the antibacterial screening data of compounds in terms of maximum zone of inhibitions. 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. To support this contention, note that all the compounds have zero violations of the rule of five. The rule of five is a set of parameters devised to aid the screening of potential drug hits identified through processes such as high throughput screening (Lipinski *et al*., 2001). The criteria of Lipinski et al. (2001) are as follows: (i) not more than five hydrogen bond donors; (ii) not more than ten hydrogen bond acceptors; (iii) formula weight <500; and (iv) log $P < 5$. Two or more violations of the rule of five suggest the probability of problems in bioavailability (Lipinski *et al*., 2001). All the compounds have zero–one violations of the rule of five. Drug-likeness of compounds (**3a**–**h**) is tabulated

Table 4 Molinspiration calculations of molecular properties and drug-likeness of compounds (**3a–h**)

Compounds	MW	Molinspiration calculations					Drug-likeness			
		cLog P	TPSA	OHNI	N viol.	Vol.	GPCRL	ICM	KI	NRL
3a										
Taut1-3a	408	−0.21	167	5	0	339	−0.81	−1.02	−1.02	−1.33
Taut2-3a	408	0.98	170	6	1	339	−0.82	−1.01	−1.07	−1.30
3b										
Taut1-3b	424	0.43	154	5	0	349	−0.90	−0.86	−0.99	−1.04
Taut2-3b	424	1.62	157	6	1	348	−0.91	−1.03	−1.04	−0.96
3c										
Taut1-3c	419	−0.64	167	5	0	354	−0.63	−0.79	−0.75	−0.78
Taut2-3c	419	0.55	170	6	1	353	−0.67	−0.80	−0.82	−0.76
3d										
Taut1-3d	419	−0.71	167	5	0	354	−0.62	−0.71	−0.67	−0.74
Taut2-3d	419	0.48	170	6	1	353	−0.76	−0.83	−0.84	−0.79
3e										
Taut1-3e	443	0.39	167	5	0	353	−0.81	−1.00	−0.97	−1.37
Taut2-3e	443	1.58	170	6	1	353	−0.83	−0.99	−1.01	−1.34
3f										
Taut1-3f	459	1.03	154	5	0	362	−0.90	−0.84	−0.94	−1.08
Taut2-3f	459	2.22	157	6	1	362	−0.91	−1.01	−0.98	−1.01
3g										
Taut1-3g	454	−0.04	167	5	0	367	−0.65	−0.78	−0.71	−0.83
Taut2-3g	454	1.15	170	6	1	367	−0.68	−0.79	−0.78	−0.82
3h										
Taut1-3h	454	−0.10	167	5	0	367	−0.63	−0.71	−0.64	−0.79
Taut2-3h	454	1.09	170	6	1	367	−0.77	−0.82	−0.81	−0.84

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 pharmacophores 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 Tables 4 and 5 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 analogs 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).

Osiris calculations (Parvez et al., 2010; Sheikh et al., 2011)

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. Of the most important program, Osiris is already available online. With our recent publication of the drug design 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 virus). This is done using a combined electronic/structure docking procedures and an example is given here. The remarkably well behaved mutagenicity of divers synthetic molecules classified in data base of Celeron Company of Switzerland 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. Toxicity risks (mutagenicity, tumorigenicity, irritation, and reproduction) and physico-chemical properties (clog P, solubility, drug-likeness, and drug score

Table 5 Osiris calculations of compounds (**3a–h**) (Color table online)

Compounds	Toxicity risks				Osiris calculations				
	MUT	TUMO	IRRI	REP	MW	cLogP	*S*	DL	D-S
3a									
Taut1-3a					408	−0.71	−2.86	−8.5	0.41
Taut2-3a					408	−0.82	−2.35	−2.62	0.22
3b									
Taut1-3b					424	0.03	−3.19	−7.94	0.4
Taut2-3b					424	−0.08	−2.68	−1.84	0.37
3c									
Taut1-3c					419	−0.79	−2.41	−7.38	0.42
Taut2-3c					419	−0.89	−1.9	−2.23	0.37
3d									
Taut1-3d					419	−0.89	−2.39	−7.33	0.33
Taut2-3d					419	−1.00	−1.87	−1.87	0.38
3e									
Taut1-3e					442	−0.10	−3.60	−9.88	0.37
Taut2-3e					442	−0.20	−3.09	−3.99	0.19
3f									
Taut1-3f					458	0.64	−3.93	−9.32	0.35
Taut2-3f					458	0.54	−3.41	−3.21	0.31
3g									
Taut1-3g					453	−0.17	−3.15	−8.75	0.38
Taut2-3g					453	−0.28	−2.63	−3.60	0.32
3h									
Taut1-3h					453	−0.28	−3.12	−8.7	0.31
Taut2-3h					453	−0.28	−2.63	−3.60	0.32

[DS]) of compounds (**3a–h**) are calculated by the methodology developed by Osiris as a sum of fragment-based contributions and correction factors (Tables 4, 5).

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. The data evaluated in Tables 4 and 5 indicate that all the structures are supposed to be mutagenic when run through the mutagenicity assessment system but as far as irritating and reproductive effects are concerned, all the compounds are at low risk 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 hydrophilicity 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 >5.0. On this basis, all the series is having log *P* values under the acceptable criteria. Along with this, compounds (**3e**) and (**3g**) which have shown good antibacterial screening results is having low log *P* values as compared to other compounds in the series. 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/L. There are more than 80 % of the drugs on the market have an (estimated) log $S > -4$. In case of compounds (**3e**) and (**3g**), values of log *S* are low as compared to others in the series. Further, the Table 4 shows drug-likeness of compounds (**3a–h**) which is in the comparable zone with that of standard drugs used. We have calculated overall DS for the compounds (**3a–h**) and compared with that of standard drugs ampicillin used as shown in Tables 4 and 5. The DS combines drug-likeness, clog P, log *S*, molecular weight and toxicity risks in one handy value may be used to judge the compound's overall potential to qualify for a drug. The reported compounds (**3a–h**) shown moderate to good DS as compared with standard drugs used.

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