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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

5-phenyl-1-benzofuran-2-yl derivatives: synthesis, antimicrobial, and antioxidant activity

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Abstract Previously unknown biphenyl containing 5-phenyl-1-benzofuran-2-yl derivatives; methanones (**2a–i**), tertiary alcohols (**3a–l**), and carbinols (**4a–f**) were synthesized and evaluated for their antimicrobial and antioxidant activities to study the effect of functionalization at the carbonyl carbon and substitution at biphenyl ring on these activities. The introduction of hydroxyl group at carbonyl carbon enhanced the antioxidant property (**3a**, **3g**, **3h**, **4a**, and **4b)**, while antimicrobial activity decreased; the carbinol and tertiary alcohols corresponding to methanone **2a** and **2b** showed no antimicrobial activity. Biphenyl methanones **1**, **2a**, **2f**, and **2g** exhibited antimicrobial activity with minimal inhibitory concentration ranging between 0.001 and 0.500 mg/mL, tertiary alcohols **3a**, **3g**, and **3h** and carbinols **4a** and **4b** exhibited the promising antioxidant property. The mode of action of these active compounds was carried out by docking of receptor GlcN6P synthase with newly synthesized candidate ligands **1**, **2a**, **2e**, **2f**, **2g**, **2h**, **3a**, **3g**, **3h**, **4c**, and **4d**.

Keywords Benzofuran · Antimicrobial · Antioxidant · Toxicity · Biphenylmethanone · Carbinols

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Introduction

Life threatening infectious disease caused by multi-drug-resistant pathogenic bacteria (Gram-positive/Gram-negative) increased an alarming level around the world. Owing to this increased microbial resistance, new classes of antimicrobial agents with novel mechanisms are today's need to fight against the multidrug-resistant infections. Heterocyclic compounds play an important role in an untiring effort aimed at developing new antimicrobial agents with new mechanism of action. These heterocyclic compounds are well known to possess diverse pharmacological properties, viz. anti-inflammatory, anticancer, anticonvulsant, antimalarial etc. Benzofurans are very interesting heterocycles, which are ubiquitous in nature and show a wide range of biological activities. Substituted phenyl-benzofuran in various positions have been shown to display different biological activity, 2-substituted benzofurans (Khan and co workers, 2005; Gundogdu and co workers, 2006) as antimicrobials; 3-amino-1-benzofurans and 3-methyl-1-benzofurans as analgesics (Radl and co workers, 2000); benzofurany-lacryloylpiperazines as antidepressants (Dauzonne *et al*., 1995); (4-hydroxy-3-methyl-6-phenyl-benzofuran-2-yl)phenylmethanone as potent anti-tumor agent (Hayakawa and co workers, 2004). Cloridarol, a 2-substituted benzofuran is used in for treatment of lipidemia and as an anticoagulant and racemates of 2-benzofuranyl

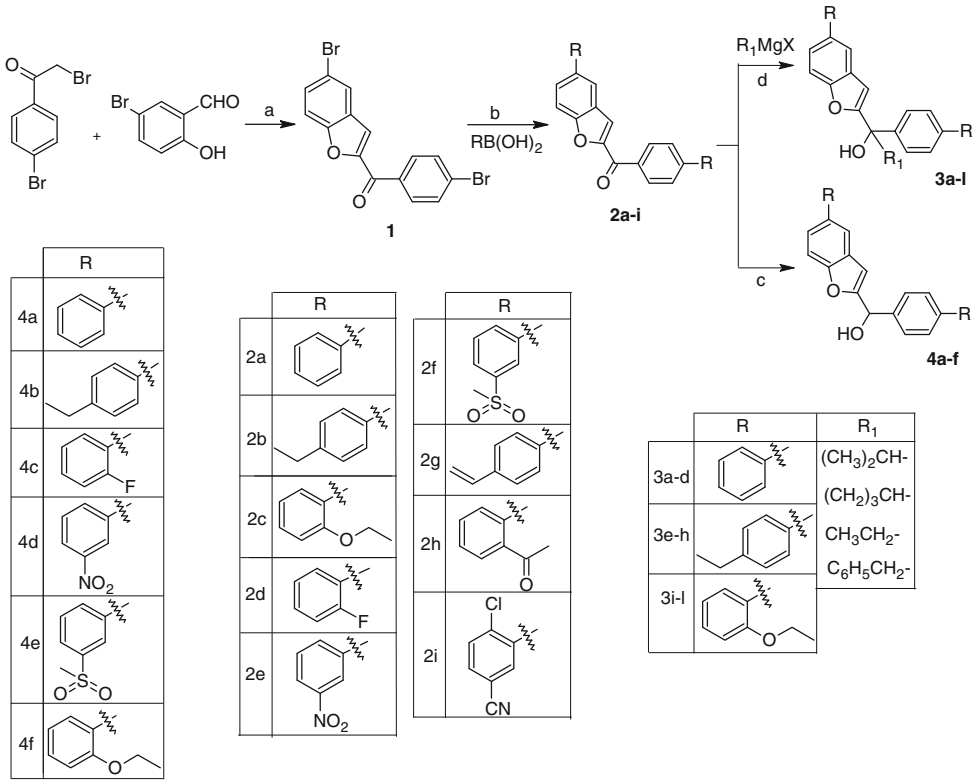
carbinols have been shown to display antifungal and aromatase inhibiting activities (Ghelardoni and co workers, 1981). Recently, synthesis of aryl 2-benzofuranyl derivatives with high enantiomeric purity has been reported (Messina and co workers, 1999). Amiodarone, a benzofuran derivative was shown to have antiarrhythmic property and belong to a new class of antiarrhythmic and anti-ischemia drugs (Singh and Vaughan 1970).

In this communication we report the synthesis and characterization of hitherto unknown 5-phenyl-1-benzofuran-2-yl derivatives containing benzofuran pharmacophore; methanones (**2a–i)**, carbinols (**3a–l)** and tertiary alcohols (**4a–f**), three different series of compounds containing different substitutions at biphenyl ring and functionalization at carbonyl carbon. Further, it comprises the investigation of in vitro antimicrobial activity against *Escherichia coli* (NCTC 12923), *Staphylococcus aureus* (NCTC 10788), *Bacillus subtilis* (NCTC 10400), and *Candida albicans* (NCPF 3179) and antioxidant activity by DPPH method. Based on the promising in vitro antimicrobial results and by considering GlcN6P synthase as the target receptor it was thought worthy to perform molecular docking studies and screening for supportive coordination between in silico studies with in vitro results. Comparative and automated docking studies with newly synthesized compounds were performed to determine the best in silico conformation. The present contribution also describes our efforts to understand the influence of structural variation at carbonyl compound and substitution at biphenyl ring on the antimicrobial and antioxidant property and to obtain the active compounds with enhanced activity.

Materials and methods

Chemistry

(5-bromo-1-benzofuran-2-yl)(4-bromophenyl)methanone **1** was synthesized from the reaction of 2-bromo-1-(4-bromophenyl)ethanone and 5-bromo-2-hydroxybenzaldehyde with aqueous Na_2CO_3 and 4-dimethylaminopyridine (DMAP) at 80 °C (Shang and co workers, 2010). The target compounds **2a–i** were obtained by Suzuki coupling reaction (Miyaura *et al.*, 1981) of dibromo compound **1** catalyzed by Tetrakis(triphenylphosphine)palladium $[Pd(PPh_3)_4]$ with suitable boronic acids. Compounds **2a–c** were reacted with suitable Grignard reagents to obtain corresponding tertiary alcohols, **3a–l**. Compounds **2a–f** were converted to their corresponding racemic carbinols **4a–f** using sodium borohydride (Scheme 1). All these compounds were characterized by using spectroscopic methods. ^1H and ^{13}C NMR spectra were recorded with a Brucker Avance DPX400 spectrometer operating at 400 MHz, with Me_4Si as internal standard. The chemical shifts are expressed as δ values in parts per million (ppm) and the coupling constants (J) are given in hertz (Hz). Mass spectra were



Scheme 1 Synthesis of substituted 5-phenyl-1-benzofuran-2-yl derivatives. Reagents and conditions **a** DMAP, Na_2CO_3, H_2O, 80 °C, 5 h **b** $Pd(PPh_3)_4$, EtOH, Na_2CO_3(aq), toluene, 110 °C, 5 h, then H_2O_2, RT, 1 h **c** $NaBH_4$, dioxane, 2–6 h **d** Grignard reagent, THF, RT, 5–6 h

determined with Agilent LC/MS instrument. Flash column chromatography was performed with silica gel (230–400 mesh) (Merck), TLC was carried out on precoated silica plates (kiesel gel 60 F_{254}, BDH). Melting points were determined in open capillaries on Buchi melting point apparatus and are uncorrected. All reagents involved in the experiments are commercially available and used without further purification. The yields are of purified compounds and are not optimized.

General

*Synthesis of (5-bromo-1-benzofuran-2-yl) (4-bromophenyl)methanone (**1**)*

To DMAP (10 % mmol) and Na_2CO_3 (1.5 mmol) in water, 2-bromo-1-(4-bromophenyl)ethanone (1 mmol) and 5-bromo-2-hydroxybenzaldehyde (1 mmol) were added. The resulting mixture was stirred at 80 °C for 5 h. The mixture was extracted with CH_2Cl_2 (30 mL), washed with water. The organic layers were combined washed with saturated sodium chloride solution, dried over anhydrous Na_2SO_4, and evaporated in vacuum. The residue was purified by column chromatography on silica gel (230–400 mesh) (ethyl acetate/petroleum ether = 20/80, v/v) to give the pure product **1** (89 %). ^{1}H NMR ($CDCl_3$, δ ppm): 8.1 (s, 1H), 7.9 (d, $J = 7.8$ Hz, 2H), 7.7 (d, $J = 7.7$ Hz, 2H), 7.65–7.68 (m, 1H), 7.6 (s, 1H), 7.5–7.58 (m, 2H). m.p.: 125.5–128.5 °C. MW: 380.06; [*m*/*z*]+: 381.0.

*General method for the preparation of the biphenyl methanones **2a**–**i***

Two molar aqueous Na_2CO_3 (11.65 mL) was added to a solution of (5-bromo-1-benzofuran-2-yl)(4-bromophenyl)methanone **1** (1.0 g, 3.32 mmol) in toluene (20 mL). The mixture was bubbled with nitrogen for one minute and then $Pd(PPh_3)_4$ (0.20 g, 0.166 mmol) was added to the mixture. Phenyl or substituted phenyl boronic acid (6.64 mmol) in ethanol (5 mL) was added to the above mixture and the reaction was refluxed at 110 °C for 5 h. After the reaction was complete, the residual borane was oxidized by the addition of H_2O_2 (30 %, 2.5 mL) at room temperature for 1 h. The solvent was removed under the vacuum. The crude product was extracted with CH_2Cl_2 (100 mL) and washed with water (2 × 100 mL) and saturated sodium chloride solution (100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under the vacuum to result light yellow oily residue. Purification by flash column chromatography (ethyl acetate/petroleum ether = 30/70, v/v) gave the corresponding biphenyl methanone **2a**–**i**.

*Biphenyl-4-yl(5-phenyl-1-benzofuran-2-yl)methanone (**2a**)*

Pale yellow solid (78 %), m.p.: 162–168 °C. ^{1}H NMR (DMSO-d_6, δ ppm); 7.89 (s, 1H), 7.26–7.34 (m, 5H), 7.13–7.22 (m, 6H), 6.97–7.06 (m, 5H), 6.97 (s, 1H); Anal. calcd. for $C_{27}H_{18}O_2$: C, 86.53; H, 4.80; O, 8.54 %; found: C, 86.50; H, 4.76; O, 8.50 %. MW: 374.43; [*m*/*z*]+: 375.33.

*(4′-Ethyl-biphenyl-4-yl)-[5-(4-ethyl-phenyl)-benzofuran-2-yl]methanone (**2b**)*

Pale yellow solid (69 %), m.p.: 136.5-139 °C. ^{1}H NMR (DMSO-d_6, δ ppm); 9.1 (s, 1H), 8.01 (d, $J = 8.2$ Hz, 2H), 7.67 (d, $J = 8.39$ Hz, 2H), 7.64 (dd, $J_1 = 1.74$ Hz, $J_2 = 10.4$ Hz, 4H), 7.22–7.44 (m, 3H), 6.9 (d, $J = 2.9$ Hz, 2H), 6.63 (d, $J = 2.8$ Hz, 2H), 2.60 (q, $J = 7.6$ Hz, 4H), 1.1 (t, $J = 7.1$ Hz, 6H); Anal. calcd. for $C_{31}H_{26}O_2$: C, 86.40; H, 6.03; O, 7.43 %; found: C, 86.37; H, 6.00; O, 7.41 %. MW: 430.53; [*m*/*z*]+: 431.41.

*(2′-Ethoxy-biphenyl-4-yl)-[5-(2-ethoxy-phenyl)-benzofuran-2-yl]methanone (**2c**)*

Pale yellow solid (84 %), m.p.: 125–128 °C. ^{1}H NMR (DMSO-d_6, δ ppm); 7.60–7.67 (m, 4H), 7.45 (d, $J = 8.2$ Hz, 1H), 7.38 (dd, $J_1 = 1.78$ Hz, $J_2 = 10$ Hz, 1H), 7.26–7.28 (m, 5H), 6.96–7.15 (m, 4H), 6.90 (s, 1H), 3.98 (q, $J = 6.76$ Hz, 4H), 1.26 (t, $J = 7.60$ Hz, 6H); Anal. calcd. for $C_{31}H_{26}O_4$: C, 80.50; H, 5.67; O, 13.84 %; found: C, 80.35; H, 5.65; O, 13.8 %. MW: 462.5; [*m*/*z*]+: 463.4.

*(2′-Fluoro-biphenyl-4-yl)-[5-(2-fluoro-phenyl)-benzofuran-2-yl]methanone (**2d**)*

Pale yellow solid (68 %), m.p.: 120–124 °C. ^{1}H NMR (DMSO-d_6, δ ppm); 8.01 (d, $J = 8$ Hz, 2H), 7.90 (s, 1H), 7.46–7.87 (m, 5H), 7.30–7.41 (m, 8H); Anal. calcd. for $C_{27}H_{16}F_2O_2$: C, 78.94; H, 3.89; O, 7.79 %; found: C, 78.9; H, 3.84; O, 7.75 %. MW: 410.4; [*m*/*z*] +: 411.43.

*(3′-Nitro-biphenyl-4-yl)-[5-(3-nitro-phenyl)-benzofuran-2-yl]methanone (**2e**)*

Pale yellow solid (80 %), m.p.: 165–169 °C. ^{1}H NMR (DMSO-d_6, δ ppm); 8.01 (d, $J = 8$ Hz, 2H), 7.92 (s, 1H), 7.43–7.85 (m, 5H), 7.28–7.39 (m, 8H); Anal. calcd. for $C_{27}H_{16}N_2O_6$: C, 69.76; H, 3.44; N, 6.02; O, 20.67 %; found: C, 69.72; H, 3.40; N, 5.98; O, 20.61 %; MW: 464.42; [*m*/*z*] +: 465.41.

*(3′-Methanesulfonyl-biphenyl-4-yl)-[5-(3-methanesulfonyl-phenyl)-benzofuran-2-yl]methanone (**2f**)*

Brown solid (69 %), m.p.: 123–135 °C. ^{1}H NMR (DMSO-d_6, δ ppm); 8.26 (s, 2H), 8.01–8.15 (m, 6H), 7.75–7.81 (m, 4H), 7.70 (t, $J = 8$ Hz, 2H), 7.12 (d, $J = 8.4$ Hz, 2H), 3.02 (s, 6H); Anal. calcd. for $C_{29}H_{22}O_6S_2$: C, 65.58; H, 4.14; O, 18.09; S, 12.09 %; found: C, 65.54; H, 4.12; O, 18.05; S, 12.07 %. MW: 530.6; [*m*/*z*]+: 531.5.

*(4′-Vinyl-biphenyl-4-yl)-[5-(4-vinyl-phenyl)-benzofuran-2-yl]methanone (**2g**)*

Yellow solid (72 %), m.p.: 126–129 °C. ^{1}H NMR (DMSO-d_6, δ ppm); 7.6–7.7 (m, 4H), 7.48 (d, $J = 8.4$ Hz, 1H), 7.44 (dd, $J_1 = 1.7$ Hz, $J_2 = 10.2$ Hz, 1H), 7.34–7.38 (m, 5H), 7.24–7.32 (m, 4H), 7.20 (s, 1H), 7.19 (t, $J = 1.82$ Hz, 2H), 5.99 (d, $J = 17.64$ Hz, 1H); Anal. calcd. for $C_{31}H_{22}O_2$: C, 87.22; H, 5.15; O, 7.5 %; found: C, 87.18; H, 5.11; O, 7.46 %. MW: 426.5; [*m*/*z*]+: 427.4.

*1-{3-[2-(3′-Acetyl-biphenyl-4-carbonyl)-benzofuran-5-yl]-phenyl}ethanone (**2h**)*

Yellow solid (63 %), m.p.: 109.5–114.0 °C. ^{1}H NMR (DMSO-d_6, δ ppm); 7.6–7.68 (m, 4H), 7.40 (d, $J = 8.16$ Hz, 1H), 7.35 (dd, $J_1 = 1.7$ Hz, $J_2 = 10.2$ Hz, 1H), 7.23–7.26 (m, 5H), 6.99–7.14 (m, 4H), 6.97 (s, 1H), 2.5 (s, 6H); Anal. calcd. for $C_{31}H_{22}O_4$ C, 81.21; H, 4.84; O, 13.96 %; found: C, 81.10; H, 4.82; O, 13.92 %. MW: 458.5; [*m*/*z*]+: 459.4.

*6-Chloro-4′-[5-(2-chloro-5-cyano-phenyl)benzofuran-2-carbonyl]biphenyl-3-carbonitrile (**2i**)*

Pale yellow solid (75 %), m.p.: 182–188 °C. ^{1}H NMR (DMSO-d_6, δ ppm); 7.54 (s, 1H), 7.50 (d, $J = 7.29$ Hz, 1H), 7.24–7.29 (m, 5H), 7.12–7.23 (m, 6H), 6.98 (s, 1H); Anal. calcd. for $C_{29}H_{14}C_{l2}N_2O_2$ C, 70.54; H, 2.83; N, 5.67; O, 6.48 %; found: C, 70.50; H, 2.79; N, 5.63; O, 6.44 %. MW: 493.33; [*m*/*z*]+: 494.31.

*General method for the preparation of the tertiary alcohols **3a–l***

To a cooled (0 °C) solution of biphenyl methanone (1 mmol) in anhydrous THF (25 mL) was added Grignard reagent (6 mmol) under nitrogen and then the mixture was allowed to stir at room temperature under nitrogen for 5–6 h. After the reaction was complete, the residual Grignard reagent was quenched by the addition of aqueous hydrochloric acid (1.5 N, 20 mL) and stirred at room temperature for 30 min. The solvent was concentrated under reduced pressure and water (10 mL) was added to the residue. The product was extracted with ethyl acetate (2 × 50 mL) and washed with saturated sodium chloride solution (25 mL), the organic layers were combined and dried over anhydrous Na_2SO_4 and the solvent concentrated under reduced pressure to obtain crude compounds. Purification by flash column chromatography (ethyl acetate/petroleum ether = 40/60, v/v) gave the corresponding tertiary alcohols **3a–l**.

*1-Biphenyl-4-yl-2-methyl-1-(5-phenyl-benzofuran-2-yl)propan-1-ol (**3a**)*

Brown syrup (53 %), ^{1}H NMR (DMSO-d_6, δ ppm); 7.79 (s, 1H), 7.26–7.33 (m, 5H), 7.12–7.20 (m, 6H), 6.98–7.07 (m, 5H), 6.90 (s, 1H), 5.87 (s, 1H), 4.08–4.21 (m, 1H), 1.25 (d, $J = 3.6$ Hz, 6H); Anal. calcd. for $C_{30}H_{26}O_2$ C, 86.01; H, 6.21; O, 7.64 %; found: C, 85.97; H, 6.18; O, 7.60 %. MW: 418.52; [*m*/*z*]+: 419.5.

*1-Biphenyl-4-yl-2,2-dimethyl-1-(5-phenyl-benzofuran-2-yl)propan-1-ol (**3b**)*

Yellow solid (65 %), m.p.: 105–108 °C. ^{1}H NMR (DMSO-d_6, δ ppm); 7.89 (s, 1H), 7.26–7.35 (m, 5H), 7.14–7.24 (m, 6H), 6.98–7.07 (m, 5H), 6.97 (s, 1H), 6.07 (s, 1H), 1.05 (s, 9H); Anal. calcd. for $C_{31}H_{28}O_2$ C, 86.08; H, 6.47; O, 7.39 %; found: C, 86.02; H, 6.42; O, 7.35 %. MW: 432.55; [*m*/*z*]+: 433.44.

*1-Biphenyl-4-yl-1-(5-phenyl-benzofuran-2-yl)propan-1-ol (**3c**)*

Yellow solid (58 %), m.p.: 132–137 °C. ^{1}H NMR (DMSO-d_6, δ ppm); 7.84 (s, 1H), 7.24–7.31 (m, 5H), 7.10–7.25 (m, 6H), 6.98–7.10 (m, 5H), 6.90 (s, 1H), 5.98 (s, 1H), 2.58 (q, $J = 7.6$ Hz, 2H), 1.10 (t, $J = 7.55$ Hz, 3H); Anal. calcd. for $C_{29}H_{24}O_2$ C, 86.03; H, 5.93; O, 7.91 %; found: C, 86.01; H, 5.89; O, 7.87 %. MW: 404.49; [*m*/*z*]+: 405.4.

*1-Biphenyl-4-yl-2-phenyl-1-(5-phenyl-benzofuran-2-yl)ethanol (**3d**)*

Brown syrup (76 %), ^{1}H NMR (DMSO-d_6, δ ppm); 7.82 (s, 1H), 7.40–7.81 (m, 7H), 7.28–7.33 (m, 3H), 7.14–7.23 (m, 6H), 6.98–7.06 (m, 5H), 6.82 (s, 1H), 6.15 (s, 1H), 5.10 (d, $J = 4$ Hz, 2H); Anal. calcd. for $C_{34}H_{26}O_2$ C, 87.44; H, 5.57; O, 6.85 %; found: C, 87.41; H, 5.52; O, 6.81 %. MW: 466.56; [*m*/*z*]+: 467.62.

*1-(4′-Ethyl-biphenyl-4-yl)-1-[5-(4-ethyl-phenyl)-benzofuran-2-yl]-2-methyl-propan-1-ol (**3e**)*

Brown syrup (60 %), ^{1}H NMR (DMSO-d_6, δ ppm); 7.78 (s, 1H), 7.45–7.60 (m, 7H), 7.25–7.35 (m, 5H), 6.95 (d, $J = 8.45$ Hz, 2H), 6.85 (s, 1H), 5.85 (s, 1H), 2.80 (m, 1H), 2.58 (q, $J = 7.79$ Hz, 4H), 1.25 (d, $J = 3.5$ Hz, 6H); 1.07 (t, $J = 7.45$ Hz), 6H); Anal. calcd. for $C_{34}H_{34}O_2$ C, 85.96; H, 7.16; O, 6.74 %; found: C, 85.92; H, 7.12; O, 6.70 %. MW: 474.63; [*m*/*z*]+: 475.52.

*1-(4′-Ethyl-biphenyl-4-yl)-1-[5-(4-ethyl-phenyl)-benzofuran-2-yl]-2,2-dimethyl-propan-1-ol (**3f**)*

Brown syrup (52 %), ^{1}H NMR (DMSO-d_6, δ ppm); 7.61–7.70 (m, 4H), 7.44 (d, $J = 8.41$ Hz, 1H), 7.34 (dd, $J_1 = 1.7$ Hz, $J_2 = 10.1$ Hz, 1H), 7.25–7.29 (m, 5H), 6.95–7.10 (m, 4H), 6.90 (s, 1H), 6.01 (s, 1H), 2.59 (q, $J = 7.55$ Hz, 4H), 1.09 (t, $J = 7.7$ Hz, 6H); 1.03 (s,9H); Anal. calcd. for $C_{35}H_{36}O_2$ C, 85.95; H, 7.36; O, 6.54 %; found: C, 85.91; H, 7.32; O, 6.51 %. MW: 488.65; [*m*/*z*]+: 489.6.

*1-(4′-Ethyl-biphenyl-4-yl)-1-[5-(4-ethyl-phenyl)-benzofuran-2-yl]propan-1-ol (**3g**)*

Brown solid (85 %), m.p.: 139-141 °C. ^{1}H NMR (DMSO-d_6, δ ppm); 7.80 (s, 1H), 7.45–7.59 (m, 7H), 7.24–7.30 (m, 5H), 6.95 (d, $J = 8.4$ Hz, 1H), 6.84 (s, 1H), 6.62 (d, $J = 8.4$ Hz, 1H), 5.95 (s, 1H), 2.58 (q, $J = 7.6$ Hz, 6H), 1.08 (t, $J = 7.6$ Hz, 9H); Anal. calcd. for $C_{33}H_{32}O_2$ C, 85.97; H, 6.94; O, 6.94 %; found: C, 85.91; H, 6.91; O, 6.92 %. MW: 460.6; [*m*/*z*]+: 461.57.

*1-(4′-Ethyl-biphenyl-4-yl)-1-[5-(4-ethyl-phenyl)-benzofuran-2-yl]-2-phenyl-ethanol (**3h**)*

Yellow solid (92 %), m.p.: 146–148 °C. ^{1}H NMR (DMSO-d_6, δ ppm); 7.78 (s, 1H), 7.27–7.54 (m, 4H), 7.19–7.24 (m, 5H), 6.98–7.09 (m, 10H), 6.80 (s, 1H), 6.20 (s, 1H), 4.46 (d, $J = 5.5$ Hz, 2H), 2.57 (q, $J = 7.76$ Hz, 4H), 1.07 (t, $J = 7.7$ Hz, 6H); Anal. calcd. for $C_{38}H_{34}O_2$ C, 87.24; H, 6.50; O, 6.12 %; found: C, 87.20; H, 6.46; O, 6.09 %. MW: 522.67; [*m*/*z*]+: 523.6.

*1-(2′-Ethoxy-biphenyl-4-yl)-1-[5-(2-ethoxy-phenyl)-benzofuran-2-yl]-2-methyl-propan-1-ol (**3i**)*

White solid (50 %), m.p.: 123–128 °C. ^{1}H NMR (DMSO-d_6, δ ppm); 7.61–7.68 (m, 4H), 7.5 (d, $J = 8.3$ Hz, 1H), 7.36 (dd, $J_1 = 1.7$ Hz, $J_2 = 10.5$ Hz, 1H), 7.27–7.29 (m, 5H), 6.96–7.10 (m, 4H), 6.90 (s, 1H), 5.81 (s, 1H), 4.08 (m, 1H), 3.99 (q, $J = 6.8$ Hz, 4H), 1.27 (t, $J = 7.6$ Hz, 6H), 1.25 (d, $J = 3.6$ Hz, 6H); Anal. calcd. for $C_{34}H_{34}O_4$ C, 80.53; H, 6.71; O, 12.63 %; found: C, 80.50; H, 6.65; O, 12.61 %. MW: 506.63; [*m*/*z*]+: 507.5.

*1-(2′-Ethoxy-biphenyl-4-yl)-1-[5-(2-ethoxy-phenyl)-benzofuran-2-yl]-2,2-dimethyl-propan-1-ol (**3j**)*

Yellow solid (60 %), m.p.: 105–109 °C. ^{1}H NMR (DMSO-d_6, δ ppm); 7.61–7.67 (m, 4H), 7.45 (d, $J = 8.4$ Hz, 1H), 7.35 (dd, $J_1 = 1.6$ Hz, $J_2 = 10$ Hz, 1H), 7.25–7.28 (m, 5H), 6.95–7.08 (m, 4H), 6.90 (s, 1H), 6.01 (s, 1H), 4.01 (q, $J = 1.6$ Hz, 4H), 1.22 (t, $J = 7.6$ Hz, 6H), 1.02 (s, 9H); Anal. calcd. for $C_{35}H_{36}O_4$ C, 80.66; H, 6.91; O, 12.29 %; found: C, 80.61; H, 6.86; O, 12.21 %. MW: 520.65; [*m*/*z*]+: 521.6.

*1-(2′-Ethoxy-biphenyl-4-yl)-1-[5-(2-ethoxy-phenyl)-benzofuran-2-yl]propan-1-ol (**3k**)*

Yellow solid (61 %), m.p.: 165–167 °C. ^{1}H NMR (DMSO-d_6, δ ppm); 7.66 (s, 1H), 7.45–7.49 (m, 5H), 7.26–7.34 (m, 5H), 7.06 (t, $J = 2.8$ Hz, 2H), 6.97 (q, $J = 7.2$ Hz, 2H), 6.83 (s, 1H), 5.92 (s, 1H), 4.01 (q, $J = 1.6$ Hz, 6H), 1.23 (t, $J = 7.6$ Hz, 9H); Anal. calcd. for $C_{33}H_{32}O_4$ C, 80.37; H, 6.49; O, 12.99 %; found: C, 80.32; H, 6.47; O, 12.91 %. MW: 492.6; [*m*/*z*]+: 493.5.

*1-(2′-Ethoxy-biphenyl-4-yl)-1-[5-(2-ethoxy-phenyl)-benzofuran-2-yl]-2-phenyl-ethanol (**3l**)*

Brown syrup (76 %), ^{1}H NMR (DMSO-d_6, δ ppm); 7.63 (s, 1H), 7.28–7.55 (m, 4H), 7.19–7.24 (m, 5H), 6.98–7.06 (m, 10H), 6.84 (s, 1H), 6.15 (s, 1H), 4.46 (d, $J = 5.6$ Hz, 2H), 4.02 (q, $J = 1.65$ Hz, 4H), 1.23 (t, $J = 7.6$ Hz, 6H); Anal. calcd. for $C_{38}H_{34}O_4$ C, 82.2; H, 6.12; O, 11.5 %; found: C, 82.01; H, 6.08; O, 11.3 %. MW: 554.67; [*m*/*z*]+: 555.6.

*General method for the preparation of the carbinols **4a–f***

To a cooled (0 °C) solution of biphenyl methanone (5 mmol) in anhydrous 1,4-dioxan (15 mL) was added sodium borohydride (10 mmol) and then the mixture was allowed to stir at room temperature under nitrogen for 2–6 h. The solvent was concentrated under reduced pressure and aqueous hydrochloric acid (1.5 N, 10 mL) was added to the residue. The oil formed was extracted with diethyl ether (2 × 50 mL) and washed with water (2 × 25 mL), the organic layers were combined and dried over the anhydrous Na_2SO_4 and the solvent concentrated under reduced pressure to obtain the title compounds **4a–f**.

*Biphenyl-4-yl-(5-phenyl-benzofuran-2-yl)methanol (**4a**)*

Pale yellow solid (90 %), m.p.: 148–153.5 °C. ^{1}H NMR (DMSO-d_6, δ ppm); 9.06 (s, 1H), 7.45–7.81 (m, 10H), 7.28 (d, $J = 7.1$ Hz, 4H), 7.24 (d, $J = 6.8$ Hz, 2H), 6.75 (s, 1H), 6.28 (d, $J = 5.2$ Hz, 1H), 5.84 (d, $J = 4.8$ Hz, 1H); Anal. calcd. for $C_{27}H_{20}O_2$ C, 86.06; H, 5.31; O, 8.50 %; found: C, 86.02; H, 5.27; O, 8.46 %. MW: 376.44; [*m*/*z*]+: 377.5.

*(4′-Ethyl-biphenyl-4-yl)-[5-(4-ethyl-phenyl)-benzofuran-2-yl]methanol (**4b**)*

White solid (88 %), m.p.: 131–135 °C. ^{1}H NMR (DMSO-d_6, δ ppm); 9.06 (s, 1H), 7.46–7.80 (m, 10H), 7.26 (d, $J = 6.8$ Hz, 4H), 6.75 (s, 1H), 6.28 (d, $J = 5.2$ Hz, 1H), 5.8 (d, $J = 4.8$ Hz, 1H), 2.61 (q, $J = 7.6$ Hz, 4H), 1.08 (t, $J = 7.2$ Hz, 6H); Anal. calcd. for $C_{31}H_{28}O_2$ C, 86.0; H, 6.47; O, 7.39 %; found: C, 85.97; H, 6.43; O, 7.35 %. MW: 432.5; [*m*/*z*]+: 433.4.

*(2′-Fluoro-biphenyl-4-yl)-[5-(2-fluoro-phenyl)-benzofuran-2-yl]methanol (**4c**)*

Pale yellow solid (92 %), m.p.: 102–106 °C. ^{1}H NMR (DMSO-d_6, δ ppm); 7.74 (s, 1H), 7.49–7.59 (m, 6H), 7.26–7.29 (m, 8H), 6.79 (s, 1H), 6.35 (d, $J = 4.8$ Hz, 1H), 5.91 (d, $J = 4.8$ Hz, 1H); Anal. calcd. for $C_{27}H_{18}F_2O_2$ C, 78.5; H, 4.36; O, 7.75 %; found: C, 78.1; H, 4.32; O, 7.72 %. MW: 412.42; [*m*/*z*]+: 413.4.

*(3′-Nitro-biphenyl-4-yl)-[5-(3-nitro-phenyl)-benzofuran-2-yl]methanol (**4d**)*

Pale yellow solid (86 %), m.p.: 115–119 °C. ^{1}H NMR (DMSO-d_6, δ ppm); 7.75 (s, 1H), 7.49–7.60 (m, 6H), 7.29–7.34 (m, 8H), 6.97 (s, 1H), 6.35 (d, $J = 4.7$ Hz, 1H), 5.97 (d, $J = 4.9$ Hz, 1H); Anal. calcd. for $C_{27}H_{18}N_2O_6$ C, 69.46; H, 3.85; N, 6.00; O, 20.58 %; found: C, 69.42; H, 3.82; N, 5.98; O, 20.54 %. MW: 466.44; [*m*/*z*]+: 467.3.

*(3′-Methanesulfonyl-biphenyl-4-yl)[5-(3-methanesulfonylphenyl)benzofuran-2-yl]methanol (**4e**)*

White solid (96 %), m.p.: 125–128 °C. ^{1}H NMR (DMSO-d_6, δ ppm); 7.7 (s, 1H), 7.45–7.55 (m, 6H), 7.24–7.32 (m, 8H), 6.98 (s, 1H), 6.30 (d, $J = 4.65$ Hz, 1H), 5.91 (d, $J = 4.75$ Hz, 1H); 3.04 (s, 6H); Anal. calcd. for $C_{29}H_{24}O_6S_2$ C, 65.33; H, 4.50; O, 18.02; S, 12.01 %; found: C, 65.30; H, 4.46; O, 18.00; S, 11.97 %. MW: 532.62; [*m*/*z*]+: 533.6.

*(2′-Ethoxy-biphenyl-4-yl)[5-(2-ethoxy-phenyl)benzofuran-2-yl]methanol (**4f**)*

Brown solid (82 %), m.p.: 152.5–157 °C. ^{1}H NMR (DMSO-d_6, δ ppm); 7.7 (s, 1H), 7.4–7.52 (m, 6H), 7.24–7.34 (m, 8H), 6.97 (s, 1H), 6.29 (d, $J = 4.6$ Hz, 1H), 5.94 (d, $J = 4.75$ Hz, 1H), 3.94 (q, $J = 6.66$ Hz, 4H), 1.24 (t, $J = 7.54$ Hz, 6H); Anal. calcd. for $C_{31}H_{28}O_4$ C, 80.07; H, 6.02; O, 13.77 %; found: C, 80.03; H, 6.00; O, 13.73 %. MW: 464.55; [*m*/*z*]+: 465.45.

Pharmacology

The newly synthesized compounds were screened for their antimicrobial and antioxidant properties to study the effect of functionalization at the carbonyl carbon and substitution at biphenyl ring on these activities.

Antimicrobial activity

The antimicrobial activities of the synthesized compounds against *E. coli*, *S. aureus*, *B. subtilis*,, and *C. albicans* were examined qualitatively and quantitatively by the presence or absence of inhibition zones and zone diameter. Each vial with one bead was inoculated into 10 mL Tryptone soya broth (TSB) in 50 mL conical flask, and were incubated at 37 °C for bacteria and 30 °C for fungi till they showed good growth. From the well grown flask 100 µL of the inoculum was spread uniformly on the pre-set media plates (Tryptone soya agar (TSA) and malt extract agar (MEA) respectively for bacteria and fungi). Sterile filter paper disks (5 mm diameter) were placed on the spread plates, from the stock solutions of the compounds 5 µL (250 µg) of the sample was loaded aseptically. Dimethyl sulfoxide (DMSO) was used as negative control and ampicillin (for bacteria) and nystatin (for fungi) as positive controls. TSA plates were incubated at 37 °C for 24 h and MEA plates were incubated at 30 °C for 3 days. The plates were checked for zone of inhibition, the compounds which showed good zone inhibition, were studied for minimum inhibitory concentration (MIC). MIC was performed at different concentrations 1, 10, 25, and 50 mg/mL. 100 µL of the inoculum was uniformly spread onto preset plates placed sterile filter paper disks (5 mm diameter) on the spread plates and 5 µL of the sample was loaded aseptically. TSA plates were incubated at 37 °C for 24 h and MEA plates were incubated at 37 °C for 3 days. The results given in Table 1 shows that compounds **1**, **2a**, **2f**, and **2g** exhibited antimicrobial activity with MIC ranging between 0.001 mg/mL to 0.500 mg/mL. Moreover compounds **2e**, **2h**, **4c**, and **4d** shows activity against *B. subtilis* and **4d** against *S. aureus* with MIC ranging between 0.050 mg/mL to 0.500 mg/mL.

Table 1 Zone of inhibition and MIC of 5-phenyl-1-benzofuran-2-yl derivatives

Zone of inhibition in mm (50 mg/mL concentration)					Minimum inhibitory concentration (MIC mg/mL)			
Compounds	*S. aureus*	*B. subtilis*	*E. coli*	*C. albicans*	*S. aureus*	*B. subtilis*	*E. coli*	*C. albicans*
1	23	24	17	15	0.050	0.050	0.050	0.050
2a	15	22	0	10	0.001	0.010	–	0.010
2e	0	7	0	0	–	0.050	–	–
2f	0	16	0	6	–	0.500	–	0.500
2g	10	16	0	6	0.250	0.050	–	0.500
2h	8	10	0	0	0.100	0.100	–	–
4c	0	6	0	0	–	0.050	–	–
4d	6	6	0	0	0.500	0.500	–	–
Ampicillin	16	15	20	0				
Nystatin	0	0	0	6				

Antioxidant studies

The target compounds were tested for 2,2-diphenyl-1-picryhydrazyl (DPPH) radical scavenging activity with butylated hydroxytoluene (BHT) as standard according to the previously reported procedure (Braca and co workers, 2001). This method is based on the reduction of free radical DPPH by free radical scavengers. The procedure involves the measurement of decrease in absorbance of DPPH at 517 nm, which is proportional to the activity of free radical scavenger added to DPPH reagent solution. A stock solution of test compounds (1 mg/mL) and DPPH (0.004 %) was prepared in 95:5 methanol:water. To 3 mL of freshly prepared DPPH solution in test tube, was added stock solution of test compound (100 µg) and reacted for 15 min and the absorbance was measured at 517 nm using UV–Visible spectrophotometer (Shimadzu UV-1800, Japan). BHT was used as a reference standard and dissolved in distilled water to make the stock solution with the same concentration (1 mg/mL). Ascorbic acid was used as control sample and 95 % methanol served as blank. % scavenging of the DPPH free radical was measured by using the following equation:

$$\begin{aligned} &\% \text{ Scavenging activity} \\ &= (\text{absorbance of the control} \\ &\quad - \text{absorbance of the test sample})/ \\ &\quad \text{absorbance of the control} \times 100. \end{aligned}$$

The results are tabulated in Table 2, compounds **3a**, **3g**, **3h**, **4a**, and **4b** show comparable activity with the standard.

In silico molecular docking studies

The ligands were drawn in ChemDraw Ultra 6.0 (Chem Office package) assigned with proper 2D orientation and the structure of each compound was analyzed for connection error in bond order. OSIRIS, an ADMET based Java library layer that provides reusable cheminformatics functionality which is an entirely in-house developed drug discovery informatics system was used to predict the total drug score via in silico (Thomas and co workers, 2009). Energy of the molecules was minimized using Dundee PRODRG2 server (Alexander *et al.*, 2004). The energy minimized compounds were then read as input for AutoDock 4.2, in order to carry out the docking simulation (Morris and co workers, 1998). All the heteroatoms were removed from the2VF5.pdb, to make complex receptor free of any ligand before docking. The Graphical User Interface program "AutoDock Tools" was used to prepare, run, and analyze the docking simulations. Kollman united atom charges, solvation parameters and polar hydrogen's were added to the receptor for the preparation of protein in docking simulation. Since ligands are not peptides,

Table 2 DPPH assay in % of 5-phenyl-1-benzofuran-2-yl derivatives

Compounds	DPPH assay in %	Compounds	DPPH assay in %
1	11.7	**3f**	24.2
2a	7.3	**3g**	55.2
2b	17.3	**3h**	60.3
2c	16.1	**3i**	11.4
2d	18.7	**3j**	21.2
2e	19.5	**3k**	5.5
2f	12.3	**3l**	16.4
2g	33.7	**4a**	79.5
2h	19.0	**4b**	55.7
2i	15.8	**4c**	21.3
3a	52.3	**4d**	19.9
3b	18.8	**4e**	39.8
3c	12.9	**4f**	19.3
3d	30.5	BHT	90.42
3e	34.7	–	–

Gasteiger charge was assigned and then non-polar hydrogens were merged. AutoDock requires pre-calculated grid maps, one for each atom type; present in the ligand being docked and it stores the potential energy arising from the interaction with macromolecule. This grid must surround the region of interest (active site) in the macromolecule. In the present study, the binding site was selected based on the amino acid residues, which are involved in binding with glucosamine-6-phosphate (D-fructose-6-P phosphate) of GlcN-6-P synthases obtained from PDB with ID 2VF5 which would be considered as the best accurate active region as it is solved by experimental crystallographic data (Wallace and co workers, 1995). The region of D-fructose-6-P phosphate bound within GlcN-6-P synthases was considered to be active site as the enzyme exhibits absolute specificity for L-glutamine as an amino donor and for D-fructose-6-P phosphate as an acceptor substrate. GlcN-6-P synthase catalyses a practically irreversible reaction, catalyzing the first committed step in an important branch of the glycolytic pathway, this amidotransferase is an obvious point of metabolic control and hence the target (Chmara *et al*., 1986; Badet *et al*., 1988). Therefore, the grid was centered at the region including all the 12 amino acid residues (Ala602, Val399, Ala400, Gly301, Thr302, Ser303, Cys300, Gln348, Ser349, Thr352, Ser347, and Lys603) that surround active site. The grid box size was set at 70, 64, and 56 Å for *x*, *y*, and *z*, respectively, and the grid center was set to 30.59, 15.822, and −3.497 for *x*, *y*, and *z* respectively, which covered all the 12 amino acid residues in the considered active pocket. Docking software AutoDock 4.2 Program supplied with AutoGrid 4.0 and AutoDock 4.0 was used to produce grid maps. The spacing between grid points was 0.375 angstroms. The Lamarckian Genetic Algorithm (LGA) was chosen to search for the best conformers. During the docking process, a maximum of 10 conformers was considered for each compound. All the AutoDock docking runs were performed in Intel Centrino Core2Duo CPU @ 2.20 GHz of IBM system origin, with 2 GB DDR2 RAM. AutoDock 4.0 was compiled and run under Windows XP operating system.

Results and discussion

The newly synthesized compounds were screened for their antimicrobial and antioxidant properties to study the effect of functionalization at the carbonyl carbon and substitution at biphenyl ring on these activities. The introduction of hydroxyl group at carbonyl carbon enhanced the antioxidant property (**3a**, **3g**, **3h**, **4a**, and **4b**), while antimicrobial activity decreased; biphenyl methanone **1**, **2a**, **2f,** and **2g** exhibited antimicrobial activity with minimal inhibitory concentration (MIC) ranging between 0.001 mg/mL to 0.500 mg/mL (Table 1), tertiary alcohols **3a**, **3g**, and **3h** and carbinols **4a** and **4b** exhibited the promising antioxidant property (Table 2). Biphenyl methanone **2a** when converted to corresponding carbinol (**4a**) and tertiary alcohols (**3a–d**); **3a** and **4a** have not shown antimicrobial

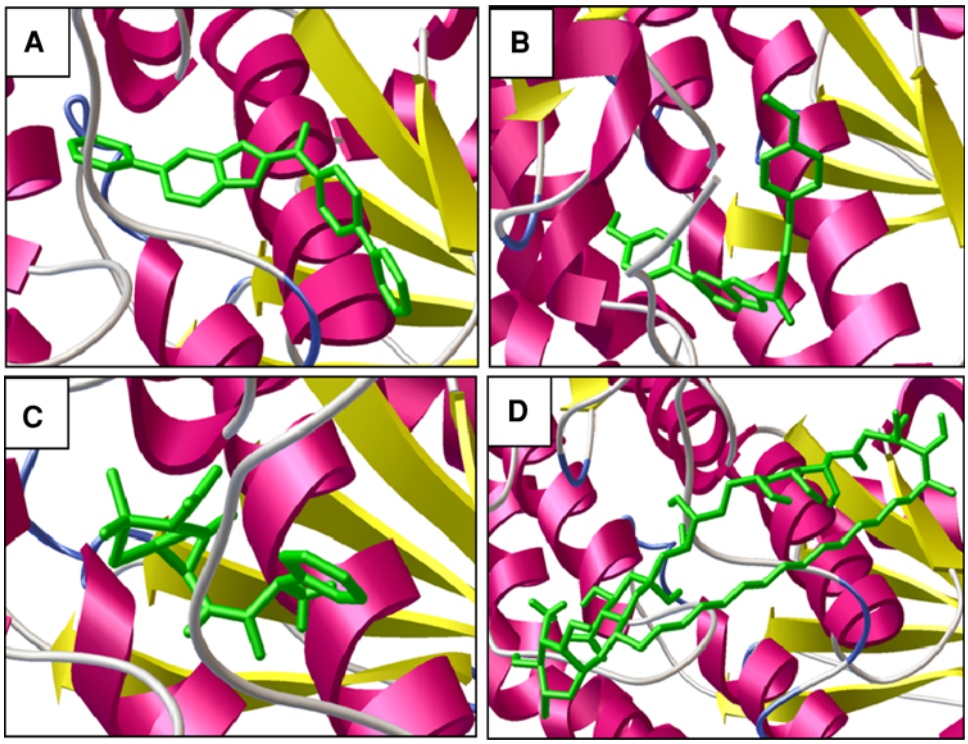


Fig. 1 Ligands **2a**, **2g**, ampicillin, and nystatin docked in best of its conformation in image **a**, **b**, **c**, and **d** respectively. (In all the images the ligands are represented in *green color* and the target protein GlcN-6-P in secondary structure and secondary colorization) (Color figure online)

activity, but antioxidant property correspondingly increased. The carbinol **4b** of 4-ehtyl biphenyl methanone (**2b**) and its tertiary alcohols **3e–h** have not shown antimicrobial activity, but antioxidant property correspondingly increased. 2-ethoxy-biphenyl derivatives (**2c**, **3i–l** and **4f**) were not active for these studies. The dibromo compound **1** with MIC of 0.05 mg/mL against antibacterial and antifungal strains (*S. aureus*, *B. subtilis*, *E. Coli*, and *C. albicans*, when bromo group was displaced with its bipheyl substituents, the derivatives (**2a–i**, **3a–l**, and **4a–f**) were inactive against *E.Coli*. The biphenyl compound **2a** (without substitution on biphenyl ring) and 4-vinyl (**2g**) were active against *S.aureus*, *B.subtilis*, and *C.albicans*; 3-methylsulphonyl (**2f**) derivative was active against *B.subtilis* and *C.albicans*; 2-acetyl derivative (**2h**) was active against *S.aureus* and *B.subtilis*; 3-nitro methanone derivative **2e** and its carbinol **4d** were active against *B.subtilis*, and *S.aureus* and *B.subtilis* respectively; 3-nitro methanone derivative **2e** and 2-fluoro carbinol **4c** were equally active against *B.subtilis*. Other methanone derivatives, 2-ethoxy (**2c**), 2-flouro (**2d**) and their carbinols (**4f** and **4c** respectively) and 2-chloro-5-cyano methanone derivative (**2i**) have not shown activity on any of the strains tested. Biphenyl methanones (**2a–i**) have displayed poor antioxidant activity but carbinol of **2a** and **2b** (**4a** and **4b**, respectively) and tertiary alcohols (**3a**, **3g** and **3h**) good activity against the standard used. The antimicrobial activity of biphenyl methanone (**2a–i**) shows that the activity has bettered with decreasing order of electron withdrawing nature ($NO2 > CN > CH_3CO$; **2e**, **2f**, and **2h**, respectively) or electron donating nature (vinyl > phenyl; **2g** and **2a**, respectively), but have not shown promising antioxidant activity. The functionalization (decrease in the electron withdrawing effect) at carbonyl carbon of biphenyl methanone reduced antimicrobial activity, but the antioxidant activity has bettered; the carbinols **4c** and **4d** have shown antimicrobial activity and tertiary alcohols (**3a–i**) have not shown antimicrobial activity, and carbinols

Table 3 Binding energy (kJ mol^{-1}), inhibition constant, and total internal energy (kJ mol^{-1})

Compound	Binding energy (kJ mol^{-1})	Inhibition constant (μM)
1	−6.58	15.02
2a	−10.16	08.09
2e	−7.37	03.96
2f	−6.14	03.55
2g	−8.22	07.10
2h	−7.32	01.31
4c	−7.47	03.36
4d	−7.56	02.28
Ampicillin	−7.66	05.44
Nystatin	−2.72	03.14

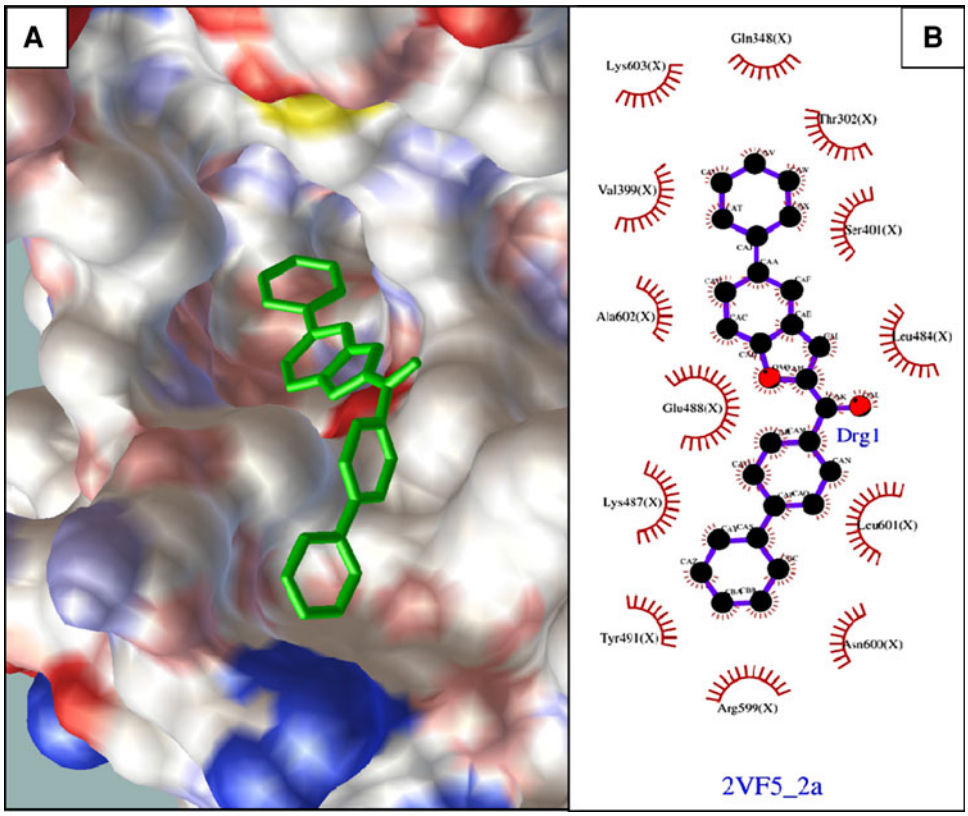


Fig. 2 The crevice of the portion of the target protein GlcN-6-P and ligand **2a** docked in best of its conformation. **a** Ligand molecule being shown in *ball* and *stick* in *green color* and the target protein molecule in molecular surface view colored by residue. **b** 2D LIGPLOT view of ligand molecule being shown in *ball* and *stick* and the surrounded amino acid residues of the active pocket crevice after docking (Color figure online)

(**3a**, **3g**, and **3h**) and tertiary alcohols (**4a** and **4b**) have exhibited antioxidant activity. The effect of increase in antioxidant activity of carbinols and tertiary alcohols could be due the introduction of hydroxyl group at carbonyl compound.

Considering GlcN-6-P synthase as the target receptor, comparative and automated docking studies with newly synthesized candidate lead compounds were performed to determine the best in silico conformation (Arulmoli and co workers, 2011). The Lamarckian genetic algorithm, inculcated in the docking program AutoDock 4.2, was employed to satisfy the purpose. The docking of receptor GlcN-6-P with newly synthesized candidate ligands exhibited well established bonds with one or more amino acids in the receptor active pocket. The active pocket consisted of 12 amino acid residues as Ala602, Val399, Ala400, Gly301, Thr302, Ser303, Cys300, Gln348, Ser349, Thr352, Ser347, and Lys603 using LIGPLOT. The synthesized ligand molecules having 2D structure were converted to energy minimized 3D structures and were further used for in silico protein–ligand docking. The ligands **1**, **2a**, **2e**, **2f**, **2g**, **2h**, **4c**, and **4d** and ampicillin and nystatin were considered for this study. The molecules **2a** (binding energy of -10.16 kJ mol^{-1}) and **2g** (binding energy of -8.22 kJ mol^{-1}) have showed considerably good binding energy, Fig. 1 shows the docked images. Table 3 shows the binding energy and inhibition constant of the compounds and the standards tested. Figure 2 shows the critical image view using LIGPLOT of molecule **2a** which promises to be the best among all the synthesized series.

Conclusion

In conclusion, the synthesized compounds **1**, **2a**, **2f**, and **2g** showed antimicrobial activity and **3a**, **3g**, **3h**, **4a** exhibited promising antioxidant activity. The most active compound **2a** possessed MIC of 0.001 mg/mL against *S.aureus* and 0.01 mg/mL against *B.subtilis* and *C.albicans* and compound **1** with MIC of 0.05 mg/mL against each of *S.aureus*, *B.subtilis*, *E.Coli*, and *C.albicans* and **4a** showed promising antioxidant activity by DPPH method.

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