Microwave-assisted Synthesis of Hybrid Heterocyclics as Biological Potent Molecules

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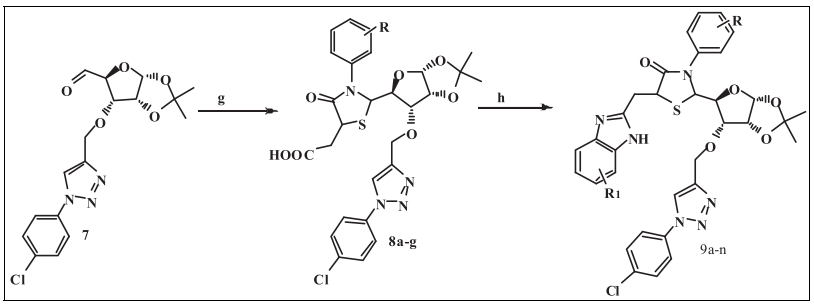

A series of novel 5-((1*H*-benzo[*d*]imidazol-2-yl)methyl)-2-((3a*R*,5*S*,6*S*,6a*R*)-2,2-dimethyl-6-((1-phenyl-1*H*-1,2,3-triazol-4-yl)methoxy)tetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)-3-phenylthiazolidin-4-ones **9a–n** has been synthesized from triazole-linked thiazolidinone derivatives **8a–g** with *o*-phenylenediamine and characterized by IR, NMR, MS, and elemental analyses. Further, these compounds were screened for their antibacterial activity against Gram-positive bacteria, namely, *Bacillus subtilis* (ATCC 6633), *Staphylococcus aureus* (ATCC 6538p), and *Micrococcus luteus* (IFC 12708), and Gram-negative bacteria, namely, *Proteus vulgaris* (ATCC 3851), *Salmonella typhimurium* (ATCC 14028), and *Escherichia coli* (ATCC 25922). Among the screened compounds, compounds **9b**, **9d**, **9h**, and **9i** are highly active against almost all selected bacterial strains; the remaining compounds showed moderate to good activity and emerged as potential molecules for further development.

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INTRODUCTION

1,2,3-Triazoles are one of the most important classes of heterocyclic organic compounds, which are reported to be present in a plethora of biological activities for diverse therapeutic areas [1]. The 1,2,3-triazole motif is associated with diverse pharmacological activities such as antibacterial, antifungal, hypoglycemic, antihypertensive, and analgesic properties. Polysubstituted five-membered aza-heterocyclics rank the most potent glycosidase inhibitors [2]. Further, this nucleus in combination with or in linking with various other classes of compounds such as amino acids, steroids, aromatic compounds, carbohydrates, and so forth became prominent in having various pharmacological properties [3]. 1,2,3-Triazole-modified carbohydrates have became easily available after the discovery of the Cu(I) catalyzed azide-alkynes 1,3-dipolar cycloaddition reaction [4] and quickly became a prominent class of non-natural sugars. The chemistry and biology of triazole-modified sugars are dominated by triazole glycosides [5]. Therefore, the synthesis and investigation of biological activity of 1,2,3-triazole glycosides is an important objective, which also received considerable attention from medicinal chemists.

Thiazoles are familiar group of heterocyclic compounds possessing a wide variety of biological activities, and their utility as medicine is very much established [6]. Thiazole nucleus is also an integral part of all the available penicillins, which have revolutionized the therapy of bacterial diseases [7]. Further, the chemistry of thiazolidinone ring system is one considerable interest as its core structure in various synthetic pharmaceuticals displaying a broad spectrum of biological activities [8]. The thiazolidinone nucleus also appears frequently in the structure of various natural products notably thiamine, compounds possessing cardiac and glycemic benefits such as troglitazone [9], and many metabolic products of fungi and primitive marine animals, including 2-(aminoalyl)-thiazole-4-carboxylic acids [10]. Numerous thiazolidinone derivatives have shown significant bioactivities such as antidiarrheal [11], anticonvulsant [12], antimicrobial [13], antidiabetic [14], antihistaminic [15], anticancer [16], anti-human immunodeficiency virus [17], Ca^{+2} channel blocker [18], platelet-activating factor antagonist [19], cardioprotective [20], antiischemic [21], COX inhibitory [22], antiplatelet-activating factor [23], non-peptide thrombin receptor antagonist [24], tumor necrosis factor-α antagonist [25], and nematicidal

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activities. Natural biological substances such as purine bases and vitamin B_{12} include benzimidazole moiety in their structure. Several benzimidazole derivatives are reported to exhibit antimicrobial [26–28], anticancer [29,30], antifungal [31,32], antiparasitic [33], antiviral [34], anti-inflammatory [35], and antihistaminic [36] activities.

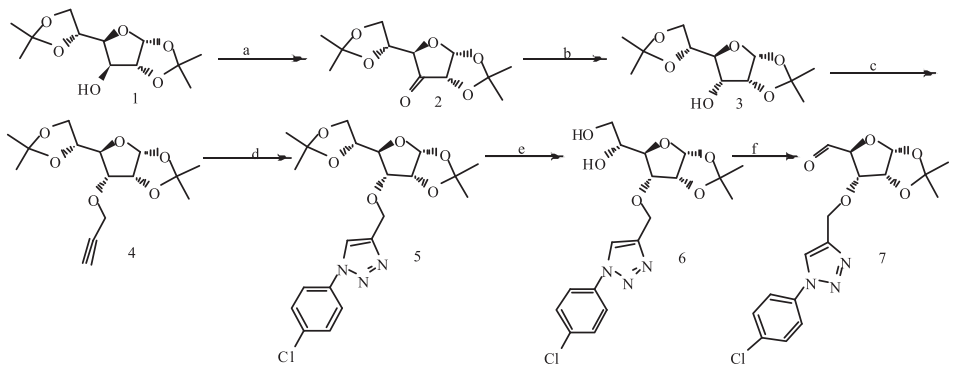
Microwave irradiation is an alternative heating technique based on the transformation of electromagnetic energy into heat. Often this method increases the rate of chemical reactions [37] and results in higher yields. Microwave energy couples directly with polar molecules or ions and leads to a rapid rise in the temperature of reaction medium [38,39]. Reactions that require hours or even days using conventional heating can usually be completed in minutes or seconds using microwaves. Several reactions have been performed under microwave-assisted conditions with significant rate enhancements, improved yield, and selectivity [39].

Following the successful introduction of antimicrobial agent microwave-assisted synthesis, inspired by the biological profile of triazoles, thiazolidinones, and benzimidazoles, and in the continuation of our work on biological active molecules [40–46], we have developed a series of novel hybrid heterocyclics and investigated the application of microwave irradiation for the synthesis of our hybrid molecules and evaluated their antimicrobial activity.

RESULTS AND DISCUSSION

The key intermediate **8** required for the synthesis of title compound was prepared according to the procedure outlined in the Scheme 1. Diacetone D-glucose (**1**) prepared from D(+)-glucose by treating with acetone in the presence of catalytic amount of sulfuric acid according to the literature procedure [47], reduction of **2** prepared by Swern oxidation of **1**, with $NaBH_4$ in aq ethanol at 0°C for 1 h gave **3** (77%), which on subsequent propargylation in dimethylformamide (DMF) in the presence of NaH for 1 h afforded propargyl ether **4** (80%). Now, the propargyl ether converted into triazole **5** (82%) by using 1,3-dipolar cycloaddition with *p*-chlorophenyl azide was carried out at ambient temperature in the presence of $CuSO_4$ and sodium ascorbate in a mixture of 1:1 *t*-BuOH–H_2O as reported by Sharpless. Acid hydrolysis of 5,6-acetonide **5** in 60% AcOH furnished the diol **6** (85%), which on oxidative cleavage with $NaIO_4$ gave the aldehyde **7**. Subsequently, one-pot synthesis of triazole-linked thiazolidinone glycosides was carried out by the condensation reaction between **7**, primary aromatic amine, and a thiomalic acid in the presence of $ZnCl_2$ under microwave irradiation/conventional heating (Scheme 2). Compound **8** on further condensation with *o*-phenelene diamine in presence of acid yielded compound **9**. In classical method, the reactions were performed in dry toluene and DMF at reflux for a long

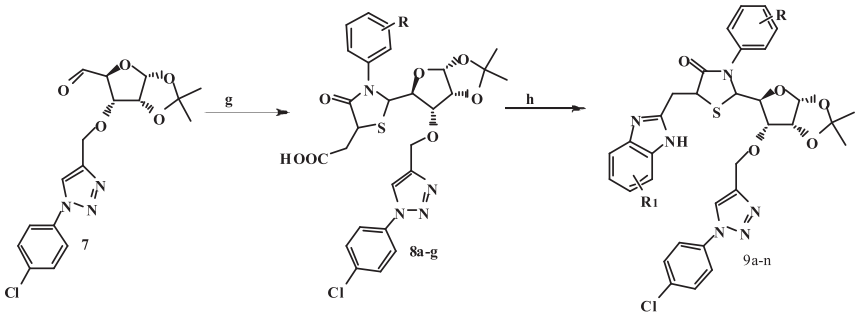
Scheme 1. Synthesis of compound **7**.



R = a) C_6H_5 b) 4 – Cl- C_6H_5; c) 4-NO_2- C_6H_5 d) 2-Me – C_6H_5 e) 4-Me - C_6H_5 f) 3-OH- C_6H_5 g) 4-OH- C_6H_5. h)R_1 = H,Cl

Reagents and conditions ; a) $COCl_2$, CH_2Cl_2, Et_3N, - 78 °C-rt, 1.5h, 83% ; b) $NaBH_4$, EtOH, H_2O, (19:1), 0 °C -rt , 78%; c) Propargyl bromide, NaH, DMF, 0 °C –rt; d) P-Chloro phenyl azide, Sodium ascorbate, $CuSO_4.5H_2O$, t -BuOH/H_2O, 0 °C -rt , 75% ; e) 60%, AcOH, rt , 69% ; f) $NaIO_4$, CH_2Cl_2 , 0 °C –rt, 75% ; g) Ar-NH_2 ,$SH(CHCOOH)_2$, $ZnCl_2$, Toluene , 80 °C , 75% ; MWI,90% h) 4-F- C_6H_4-CHO, AcOH /NaOAc, reflux, 82-88%; i) R'- OPD.HCl, reflux, 78- 84%.MWI 92%.

Scheme 2. Synthesis of compound **9a-n**.



R = a) C_6H_5 b) 4 – Cl- C_6H_5; c) 4-NO_2- C_6H_5 d) 2-Me – C_6H_5 e) 4-Me - C_6H_5 f) 3-OH- C_6H_5 g) 4-OH- C_6H_5. h)R_1 = H,Cl

Reagents and conditions ; a) $COCl_2$, CH_2Cl_2, Et_3N, - 78 °C-rt, 1.5h, 83% ; b) $NaBH_4$, EtOH, H_2O, (19:1), 0 °C -rt , 78%; c) Propargyl bromide, NaH, DMF, 0 °C –rt; d) P-Chloro phenyl azide, Sodium ascorbate, $CuSO_4.5H_2O$, t -BuOH/H_2O, 0 °C -rt , 75% ; e) 60%, AcOH, rt , 69% ; f) $NaIO_4$, CH_2Cl_2 , 0 °C –rt, 75% ; g) Ar-NH_2 ,$SH(CHCOOH)_2$, $ZnCl_2$, Toluene , 80 °C , 75% ; MWI,90% h) 4-F- C_6H_4-CHO, AcOH /NaOAc, reflux, 82-88%; i) R'- OPD.HCl, reflux, 78- 84%.MWI 92%.

time (2–4 h), often leading to degradation processes and consequent low yields of isolated products, whereas in the application of microwave-assisted technology, the reaction is completed in only 5–10 min, and the compounds, isolated by conventional workup, are obtained in satisfactory yields, often higher than those achieved by traditional methods. The structures of synthesized compounds were confirmed by IR, NMR, MS, and elemental analysis. In the IR spectrum of compound **9a**, disappearance of carboxylic acid carbonyl (C═O) absorption band at about 1710 cm^{-1}, which was present in compound **8a**, confirmed the cyclization of involvement of carboxylic acid system. In addition, the absorption bands corresponding to –N–H of the benzimidazole moiety and –N═N– of the triazole were observed at 3414 and 1610 cm^{-1}. In ^{1}H-NMR spectrum, the –NH proton of benzimidazole ring appeared at 9.32 ppm as a singlet, and four aromatic hydrogens of benzimidazole appeared as doublets at 7.44 and 7.21. These signals demonstrate that the cyclization step has occurred. In ^{13}C-NMR spectra, the prominent signals corresponding to the carbons of benzimidazole in compound **9a** observed at 151.4, 138.9, and 33.2 ppm are proof of their structure. Further, the compounds were subject to antibacterial testing.

Antibacterial activity. All the compounds **9a–n** were assayed for their antibacterial activity against Gram-positive bacteria, namely, *Bacillus subtilis* (ATCC 6633), *Staphylococcus aureus* (ATCC 6538p), and *Micrococcus luteus* (IFC 12708), and Gram-negative bacteria, namely, *Proteus vulgaris* (ATCC 3851), *Salmonella typhimurium* (ATCC 14028), and *Escherichia coli* (ATCC 25922) by the broth dilution method, recommended by the National Committee for Clinical Laboratory Standards [48]. The bacteria were grown overnight in Luria–Bertani broth at 37°C, harvested by centrifugation, and then washed twice with sterile distilled water. Stock solutions of the series of compounds were prepared in DMSO. Each stock solution was diluted with standard method broth (Difco) to prepare serial twofold dilutions in the range of 50 to 0.8 μg/mL. Ten microliters of the broth containing about 10^5 cfu/mL of test bacteria was added to each well of 96-well microtiter plate. Culture plates were incubated for 24 h at 37°C, and the growth was monitored visually and spectrophotometrically. The lowest concentration required to arrest the growth of bacteria was regarded as minimum inhibitory concentration (μg/mL), was determined for all the compounds, and was compared with the control. Amphicillin was also screened under identical conditions for comparison. Data of the compounds **9a–n** are presented in Table 1 as the minimum inhibitory concentration. Among the screened compounds **9a**–**n**, the imidazole moiety-bearing electron-withdrawing group on the fourth position of phenyl, namely, 4-chlorophenyl **9b**, is highly active against all the microorganisms employed (at 1.56 μg/mL) (except *E. coli*); it is almost equal to the standard. Compound **9d**, bearing electron-withdrawing group on the fourth position of phenyl, namely, 4-chlorophenyl, is also highly active but only against

Table 1

Antimicrobial activity of the synthesized compounds.

Compound	*Bacillus subtilis*	*Escherichia coli*	MIC (μg/mL)			
			Staphylococcus aureus	*Micrococcus luteus*	*Proteus vulgaris*	*Salmonella typhimurium*
9a	12.5	25.0	12.5	25.0	12.5	25.0
9b	6.25	12.5	12.5	12.5	6.25	12.5
9c	1.56	6.25	1.56	1.56	1.56	1.56
9d	6.25	6.25	6.25	6.25	12.5	25.0
9e	3.12	1.56	12.5	1.56	1.56	3.12
9f	12.5	12.5	6.5	3.12	12.5	6.25
9g	6.25	25.0	25.0	25.0	6.25	50.0
9h	12.5	25.0	12.5	1.56	1.56	12.5
9i	6.25	12.5	1.25	11.5	1.25	10.5
9k	15.7	19.6	17.0	0	17.9	18.5
9l	25.0	20.0	22.8	19.2	19.6	25.0
9m	20.7	18.5	20.4	15.7	22.8	21.5
9n	24.5	22.0	23.6	24.7	25.0	22.0
Ampicillin	1.56	12.5	1.56	1.56	3.12	3.12

MIC, minimum inhibitory concentration.

M. luteus and *P. vulgaris* at the same concentration as **9h**. Compound **9i**, bearing electron-withdrawing group on the fourth position of phenyl, namely, 4-chlorophenyl, also showed good antibacterial activity against *B. subtilis*, *S. aureus*, *M. luteus*, and *S. typhimurium*. The remaining compounds showed moderate to good activity.

EXPERIMENTAL

Commercial grade reagents were used as supplied. Solvents except analytical reagent grade were dried and purified according to literature when necessary. Reaction progress and purity of the compounds were checked by thin-layer chromatography (TLC) on precoated silica gel F254 plates from Merck (Merck, Bangalore, India), and compounds were visualized either by exposing to UV light or by dipping in 1% aq potassium permanganate solution. Silica gel chromatographic columns (60–120 mesh) were used for separations. Optical rotations were measured on a PerkinElmer 141 polarimeter (Perkin Elmer, Waltham, MA) by using a 2-mL cell with a path length of 1 dm with $CHCl_3$ or $CDCl_3$ as solvent. Microwave reactions are carried out in minilab microwave catalytic reactor (ZZKD, WBFY-201), and reaction mixture temperatures were measured through an immersed fiber optic sensor. All melting points are uncorrected and measured using Fisher–Johns apparatus. IR spectra were recorded as KBr disks on a PerkinElmer FT IR spectrometer. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian Gemini spectrometer (300 MHz for ^{1}H and 75 MHz for ^{13}C). Chemical shifts are reported as δ ppm against tetramethylsilane as internal reference, and coupling constants (*J*) are reported in Hertz units. Mass spectra were recorded on a VG micro mass 7070H spectrometer. Elemental analyses (C, H, and N) determined by a PerkinElmer 240 CHN elemental analyzer were within ±0.4% of theoretical.

(3aR,5R,6aS)-5-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyldihydrofuro[3,2-d][1,3]dioxol-6-(3aH)-one (2). Oxolylchlorode of 8.5 mL was dissolved in 20 mL of dry CH_2Cl_2 and cooled to −78°C, and 14 mL of DMSO was added to a solution of 5 g of alcohol **1** in 30 mL of CH_2Cl_2. The reaction mixture was stirred for 45 min, quenched with 40 mL Et_3N, and warmed to 25°C. The reaction mixture was extracted with CH_2Cl_2, and organic layer separated was washed with water (50 mL) and brine (50 mL), dried (Na_2SO_4), and evaporated. Residue obtained was purified by column chromatography (60–120 mesh silica gel, 10% ethyl acetate in petroleum ether) to afford **2** as quantitative yield (4.5 g, 87%) as a yellow syrup, which was used as such for the next reaction.

(3aR,5S,6R,6aR)-5-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[3,2-d][1,3]dioxol-6-ol (3). To a stirred solution of **2** (4.5 g, 19 mmol) in aq ethanol (EtOH : H_2O19: 1; 100 mL), $NaBH_4$ (0.37 g, 9.7 mmol) was added at 0°C, and then reaction mixture was stirred for1 h. Solvent was evaporated in vacuum, residue treated with saturated NH_4Cl solution (10 mL), and stirred at room temperature for an additional 10 min. The reaction mixture was extracted with EtOAc (2 × 50 mL), and organic layer separated was washed with water (50 mL) and brine (50 mL), dried (Na_2SO_4), and evaporated. Residue obtained was purified by column chromatography (60–120 mesh silica gel, 60% ethyl acetate in petroleum ether) to afford **3** (3.8 g, 80%) as a white solid; mp 82°C; $[\alpha]_D^{20}$ + 82.49 (*c* 1.62, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$, 298 K): δ 5.75 (d, 1H, *J* = 3.7 Hz, C_1H), 4.56 (d, 1H, *J* = 4.2 Hz, C_2H), 4.23

(m, 1H, C_5H), 4.07–3.91 (m, 3H, C_4H, 2 × C_6H), 3.74 (dd, 1H, J = 8.0, 4.3 Hz, C_3H), 2.44 (d, 1H, J = 8.4 Hz, OH), 1.56 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.36 (s, 6H, 2 × CH_3); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 112.8, 109.8, 103.9, 79.7, 79.0, 75.5, 72.5, 65.8, 26.6, 26.5, 26.3, 25.3; MS: m/z (M^+ + Na) 283.

(3aR,5R,6R,6aR)-5-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyl-6-(prop-2-ynyloxy)tetrahydrofuro[3,2-d][1,3] dioxole (4). Sodium hydride (60% in mineral oil, 0.64 g) was added to a stirred solution of **3** (3.6 g, 13.84 mmol) in DMF (80 mL) at 0°C and stirred for 30 min. This yellow mixture was cooled to 0°C and treated with propargyl bromide (4.2 g) in DMF (20 mL). The dark brown reaction mixture was stirred for an hour at room temperature and quenched (at 5–10°C) with saturated aq ammonium chloride (20 mL). The crude product was extracted with methylene chloride (3 × 30 mL), dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on silica gel (5% ethyl acetate : hexane) to afford **4** (3.1 g, 75%). Viscous oil $[\alpha]_D$ − 6.3 (c 1.7, $CHCl_3$). ^{1}HNMR (300 MHz, $CDCl_3$): δ 5.62 (d, J = 3.7 Hz, 1H, C_1H), 4.69 (t, J = 3.9 Hz, 1H, C_2H), 4.36 (dt, J = 3.1, 7.3 Hz, 1H, C_5H), 4.21 (s, 2H, CH_2), 4.09–3.96 (m, 3H, C_4H, 2X C_6H), 3.68 (dd, J = 8.9, 4.1 Hz, 1H, C_3H), 3.19 (s, 1H, CH), 1.56 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.36 (s, 6H, 2 × CH_3); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 112.7, 109.5, 103.8, 80.2, 77.6, 77.2, 74.6, 66.2, 57.2, 26.6, 26.2. MS: m/z (M^+ + Na) 321.

1-(4-Chlorophenyl)-4-(((3aR,5R,6R,6aR)-5-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[3,2-d][1,3]dioxol-6-yloxy)methyl)-1H-1,2,3-triazole (5). To a solution containing (3 g, 10.06 mmol) the alkyne **4** *p*-chlorophenyl azide (1.8 g, 11.76 mmol) in dichloromethane (30 mL) and water (30 mL) were added $CuSO_4{\cdot}5H_2O$ (1.8 g, 8.15 mmol) and sodium ascorbate (1.2 g). The resulting suspension was stirred at room temperature for 4–6 h. After this time, the mixture was diluted with 20 mL dichloromethane and 20 mL water. The organic phase was separated, dried with sodium sulfate, and concentrated at reduced pressure, and the crude residue was purified by column chromatography silica gel (60–120 mesh, 35% EtOAc in hexane) to afford **5** (3.2 g, 75%) as a white powder mp 159–161°C. $[\alpha]_D$ − 91.3 (c 1.7, $CHCl_3$). ^{1}HNMR (300 MHz, $CDCl_3$): δ 8.05 (s, 1H, Ar–H), 7.56 (d, J = 9.2 Hz, 2H, Ar–H), 7.45 (d, J = 8.9 Hz, 2H, Ar–H), 5.59 (d, J = 3.7 Hz, 1H, C_1H), 4.65 (t, J = 3.9 Hz, 1H, C_2H), 4.59 (s, 2H, CH_2), 4.39 (dt, J = 3.1, 7.3 Hz, 1H, C_5H), 4.09–3.96 (m, 3H, C_4H, 2 × C_6H), 3.71 (dd, J = 8.9, 4.1 Hz, 1H, C_3H), 1.54 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.34 (s, 6H, 2 × CH_3); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 144.1, 134.5, 122.4, 119.5, 112.5, 109.6, 103.6, 80.0, 77.4, 74.2, 67.5, 66.2, 26.6, 26.2, 24.9. MS: m/z (M^+ + H) 452. *Anal.* Calcd for $C_{21}H_{26}ClN_3O_6$: C, 55.81; H, 5.80; N, 9.30. Found: C, 55.75; H, 5.75; N, 9.21.

(R)-1-((3aR,5R,6R,6aR)-6-((1-(4-Chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-2,2-dimethyltetrahydrofuro[3,2-d][1,3] dioxol-5-yl)ethane-1,2-diol (6). A mixture of **5** (3 g, 6.65 mmol) in 60% aq AcOH (25 mL) was stirred at room temperature for 12 h. Reaction mixture was neutralized with anhyd $NaHCO_3$ (15 g) and extracted with EtOAc (3 × 40 mL). The combined organic layers were dried (Na_2SO_4), evaporated, and residue purified by column chromatography (60–120 mesh silica gel, 41% ethyl acetate in petroleum ether) to afford **6** (2.6 g, 82%) as a pale yellow solid; mp 168–171°C. ^{1}HNMR (300 MHz, $CDCl_3$): δ 8.03 (s, 1H, Ar–H), 7.54 (d, J = 9.2 Hz, 2H, Ar–H), 7.43 (d, J = 8.9 Hz, 2H, Ar–H), 5.51 (d, J = 3.7 Hz, 1H, C_1H), 4.56 (t, J = 3.9 Hz, 1H, C_2H), 4.59 (s, 2H, OCH_2), 3.98–3.93 (m, 2H, C_4H, C_5H), 4.01–3.92 (m, 3H, C_3H, 2 × C_6H), 2.44 (bs, 1H, OH), 1.54 (s, 3H, CH_3), 1.50 (bs, 1H, OH), 1.34 (s, 3H, CH_3); ^{13}C-NMR (75 MHz, $CDCl_3$): δ144.2, 134.2, 122.1, 119.2, 112.2, 109.2, 103.1, 79.8, 77.1, 74.1, 67.2, 66.2, 64.2, 70.6, 26.6, 26.2, 24.9. MS: m/z (M^+ + H) 412. *Anal.* Calcd for $C_{18}H_{22}ClN_3O_6$: C, 52.49; H, 5.38; N, 10.21. Found: C, 52.35; H, 5.25; N, 10.11.

2-((3aR,5S,6S,6aR)-6-((1-(4-Chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-3-phenylthiazolidin-4-one (8a–g). To a solution of diol **6** (0.200 g, 0.48 mmol) in CH_2Cl_2 (5 mL), $NaIO_4$ (0.130 g, 0.61 mmol) was added at 0°C and stirred at room temperature for 6 h. The reaction mixture was filtered and washed with CH_2Cl_2 (2 × 10mL). It was dried (Na_2SO_4) and evaporated to give aldehyde **7** (150 g) in quantitative yield as a yellow liquid, which was used as such for the next reaction. To a stirred mixture of **7** (0.150 g, 0.395 mmol), aromatic amine (0.395 mmol) and thiomalic acid (0.125 g, 0.86 mmol) in dry toluene (5 mL), anhyd $ZnCl_2$ (0.100 g, 0.751 mmol) was added after 2 min and irradiated in microwave bath reactor at 280 W for 4–7 min at 110°C. After cooling, the filtrate was concentrated to dryness under reduced pressure, and the residue was taken up in ethyl acetate. The ethyl acetate layer was washed with 5% sodium bicarbonate solution and finally with brine. The organic layer was dried over Na_2SO_4 and evaporated to dryness at reduced pressure. The crude product thus obtained was purified by column chromatography on silica gel (60–120 mesh) with hexane–ethyl acetate as eluent. Under conventional method, the reaction mixture in toluene (10 mL) was refluxed at 110°C for the appropriate time (Table 2).

2-(2-((3aR,5S,6S,6aR)-6-((1-(4-Chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3] dioxol-5-yl)-4-oxo-3-phenylthiazolidin-5-yl)acetic acid (8a). mp 211–214°C. ^{1}HNMR (300 MHz, $CDCl_3$): δ 11.44 (s,

Table 2

Synthesis of compounds **8a–g** and **9a–n**.

Compound	R	R^1	Molecular formula	Reaction time		Yield	
				A (h)	B (min)	A	B
8a	C_6H_5	—	$C_{27}H_{27}ClN_4O_7S$	3.5	5	63	79
8b	4-Cl–C_6H_4	—	$C_{27}H_{26}Cl_2N_4O_7S$	2.5	6	65	82
8c	4-NO_2–C_6H_4	—	$C_{27}H_{26}Cl_2N_5O_9S$	3.0	7	61	79
8d	2-CH_3−C_6H_4	—	$C_{28}H_{29}ClN_4O_7S$	2.5	5	70	81
8e	4-CH_3–C_6H_4	—	$C_{28}H_{29}ClN_4O_7S$	2.0	5	67	82
8f	3-OH–C_6H_4	—	$C_{27}H_{27}ClN_4O_8S$	3.0	5	77	87
8g	4-OH–C_6H_4	—	$C_{27}H_{27}ClN_4O_8S$	2.5	4	79	90
9a	C_6H_5	H	$C_{33}H_{31}ClN_6O_5S$	4.5	8	65	85
9b	C_6H_5	Cl	$C_{30}H_{30}Cl_2N_6O_5S$	3.0	4	63	76
9c	4-Cl–C_6H_4	H	$C_{33}H_{30}Cl_2N_6O_5S$	4.0	2	70	88
9d	4-Cl–C_6H_4	Cl	$C_{33}H_{29}Cl_3N_6O_5S$	4.5	2	68	81
9e	4-NO_2–C_6H_4	H	$C_{33}H_{30}ClN_7O_7S$	4.2	4	68	85
9f	4-NO_2–C_6H_4	Cl	$C_{33}H_{29}Cl_2N_7O_7S$	4.0	3	72	90
9g	2-CH_3−C_6H_4	H	$C_{34}H_{33}ClN_6O_5S$	5.0	25	69	87
9h	2-CH_3−C_6H_4	Cl	$C_{34}H_{32}Cl_2N_6O_5S$	4.5	10	70	85
9i	4-CH_3–C_6H_4	H	$C_{34}H_{33}ClN_6O_5S$	4.1	9	65	91
9j	4-CH_3–C_6H_4	Cl	$C_{34}H_{32}Cl_2N_6O_5S$	3.6	5	75	92
9k	3-OH	H	$C_{33}H_{31}ClN_6O_6S$	4.1	8	69	88
9l	3-OH	Cl	$C_{33}H_{30}Cl_2N_6O_6S$	3.9	6	65	89
9m	4-OH	H	$C_{33}H_{31}ClN_6O_6S$	3.9	9	71	85
9n	4-OH	Cl	$C_{33}H_{30}Cl_2N_6O_6S$	3.7	8	68	88

A, conventional heating; B, microwave irradiation.

1H, CO_2H), 8.09 (s, 1H, Ar–H), 7.55 (d, J = 9.2 Hz, 2H, Ar–H), 7.48 (d, J = 8.9 Hz, 2H, Ar–H), 6.73–7.35 (m, 5H, Ar–H), 6.15 (s, 1H, CHS), 5.73 (d, J = 4.2 Hz, 1H, C_1H), 4.69 (t, J = 3.9 Hz, 1H, C_2H), 4.65 (t, 1H, CH), 4.52 (s, 2H, OCH_2), 3.92–3.89 (m, 1H, C_4H), 3.31 (dd, J = 9.1, 4.2 Hz, 1H, C_3H), 2.38 (d, 2H, CH_2), 1.53 (s, 3H, CH_3), 1.30 (m, 3H, CH_3); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 170.9, 143.8, 141.2, 134.2, 128.2, 126.8, 122.1, 118.8, 104.2, 80.4, 77.9, 73.8, 66.1, 52.0, 37.2, 33.9, 25.9; MS: m/z (M^+ + H) 545. *Anal.* Calcd for $C_{27}H_{27}ClN_4O_7S$: C, 55.24; H, 4.64; N, 9.54. Found: C, 55.12; H, 4.59; N, 9.39.

2-(3-(4-Chlorophenyl)-2-((3a*R*,5*S*,6*S*,6a*R*)-6-((1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-4-oxothiazolidin-5-yl)acetic acid (8b). mp 259–261°C. ^{1}HNMR (300 MHz, $CDCl_3$): δ 11.44 (s, 1H, CO_2H), 7.98 (s, 1H, Ar–H), 7.45 (d, J = 9.2 Hz, 4H, Ar–H), 7.39 (d, J = 8.9 Hz, 4H, Ar–H), 6.14 (s, 1H, CHS), 5.73 (d, J = 4.2 Hz, 1H, C_1H), 4.69 (t, J = 3.9 Hz, 1H, C_2H), 4.65 (t, 1H, CH), 4.52 (s, 2H, OCH_2), 3.92–3.89 (m, 1H, C_4H), 3.20 (dd, J = 9.1, 4.2 Hz, 1H, C_3H), 2.34 (d, 2H, CH_2), 1.53 (s, 3H, CH_3), 1.30 (m, 3H, CH_3); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 170.6, 143.2, 141.6, 134.6, 128.8, 126.9, 122.2, 118.4, 104.5, 80.6, 77.6, 73.2, 66.4, 52.3, 36.9, 33.2, 25.6; MS: m/z (M^+ + H) 621. *Anal.* Calcd for $C_{27}H_{26}Cl_2N_4O_7S$: C, 52.18; H, 4.22; N, 9.01. Found: C, 52.02; H, 4.09; N, 8.95.

2-(2-((3a*R*,5*S*,6*S*,6a*R*)-6-((1-(4-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-3-(4-nitrophenyl)-4-oxothiazolidin-5-yl)acetic acid (8c). mp 256–258°C. ^{1}HNMR (300 MHz, $CDCl_3$): δ 11.45 (s, 1H, CO_2H), 8.21 (d, J = 8.4 Hz, 2H), 8.01 (s, 1H, Ar–H), 7.49 (d, J = 9.1 Hz, 2H, Ar–H), 7.41 (d, J = 8.5 Hz, 2H, Ar–H), 6.79 (d, J = 9.6 Hz, 2H, Ar–H), 6.14 (s, 1H, CHS), 5.69 (d, J = 4.2 Hz, 1H, C_1H), 4.65 (t, 1H, CH), 4.53 (t, J = 3.9 Hz, 1H, C_2H), 4.52 (s, 2H, OCH_2), 3.90–3.86 (m, 1H, C_4H), 3.19 (dd, J = 9.1, 4.2 Hz, 1H, C_3H), 2.30 (d, 2H, CH_2), 1.49 (s, 3H, CH_3), 1.25 (m, 3H, CH_3); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 190.2, 173.2, 143.6, 141.9, 134.5, 128.2, 126.5, 122.2, 118.2, 104.3, 80.4, 77.2, 73.1, 66.2, 52.1, 36.4, 33.1, 25.4; MS: m/z (M^+ + H) 632. *Anal.* Calcd for $C_{27}H_{26}Cl_2N_5O_9S$: C, 51.31; H, 4.15; N, 11.08. Found: C, 51.19; H, 4.09; N, 10.95.

2-(2-((3a*R*,5*S*,6*S*,6a*R*)-6-((1-(4-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-4-oxo-3-o-tolylthiazolidin-5-yl)acetic acid (8d). mp 247–249°C. ^{1}HNMR (300 MHz, $CDCl_3$): δ 11.45 (s, 1H, CO_2H), 8.22 (d, J = 8.4 Hz, 2H, Ar–H), 8.06 (s, 1H, Ar–H), 7.50 (d, J = 9.1 Hz, 2H, Ar–H), 7.42–6.85 (m, 4H, Ar–H), 6.14 (s, 1H, CHS), 5.65 (d, J = 4.2 Hz, 1H, C_1H), 4.60 (t, 1H, CH), 4.53 (t, J = 3.9 Hz, 1H, C_2H), 4.54 (s, 2H, OCH_2), 3.92–3.86 (m, 1H, C_4H), 3.22 (dd, J = 9.1, 4.2 Hz, 1H, C_3H), 2.34 (d, 2H, CH_2), 2.21 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 1.29 (m, 3H, CH_3); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 191.4, 173.4, 144.6, 142.9, 133.9, 125.4, 122.2, 119.2, 105.6, 80.6, 77.4, 73.4, 66.5, 53.1, 36.3, 33.2, 25.2, 16.2; MS: m/z (M^+ + H) 600. *Anal.* Calcd for

$C_{28}H_{29}ClN_4O_7S$: C, 55.95; H, 4.86; N, 9.32. Found: C, 54.19; H, 4.62; N, 9.15.

2-(2-((3aR,5S,6S,6aR)-6-((1-(4-Chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-4-oxo-3-p-tolylthiazolidin-5-yl)acetic acid (8e). mp 197–199°C. ^{1}HNMR (300 MHz, $CDCl_3$): δ 11.45 (s, 1H, CO_2H), 8.20 (d, J = 8.4 Hz, 2H, Ar–H), 8.04 (s, 1H, Ar–H), 7.54 (d, J = 9.1 Hz, 2H, Ar–H), 7.36 (d, J = 8.33 Hz, 2H, Ar–H), 7.12 (d, J = 8.3 Hz, 2H, Ar–H), 6.14 (s, 1H, CHS), 5.65 (d, J = 4.2 Hz, 1H, C_1H), 4.60 (t, 1H, CH), 4.53 (t, J = 3.9 Hz, 1H, C_2H), 4.54 (s, 2H, OCH_2), 3.92–3.86 (m, 1H, C_4H), 3.22 (dd, J = 9.1, 4.2 Hz, 1H, C_3H), 2.34 (d, 2H, CH_2), 2.21 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 1.29 (m, 3H, CH_3); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 191.4, 173.4, 144.6, 142.9, 133.9, 125.4, 122.2, 119.2, 105.6, 80.6, 77.4, 73.4, 66.5, 53.1, 36.3, 33.2, 25.2, 16.2; MS: m/z (M^+ + H) 600. *Anal.* Calcd for $C_{28}H_{29}ClN_4O_7S$: C, 55.95; H, 4.86; N, 9.32. Found: C, 54.19; H, 4.62; N, 9.15.

2-(2-((3aR,5S,6S,6aR)-6-((1-(4-Chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-3-(3-hydroxyphenyl)-4-oxothiazolidin-5-yl)acetic acid (8f). mp 227–229°C. ^{1}HNMR (300 MHz, $CDCl_3$): δ 11.42 (s, 1H, CO_2H), 8.24 (d, J = 8.7 Hz, 2H, Ar–H), 8.03 (s, 1H, Ar–H), 7.56 (d, J = 9.2 Hz, 2H, Ar–H), 7.14–6.70 (m, 4H, Ar–H), 6.14 (s, 1H, CHS), 5.76 (d, J = 3.6 Hz, 1H, C_1H), 5.42 (s, 1H, OH), 4.96 (d, J = 5.2 Hz, 1H, CH), 4.51 (t, J = 3.9 Hz, 1H, C_2H), 4.54 (s, 2H, OCH_2), 3.93–3.96 (m, 1H, C_4H), 3.26 (dd, J = 9.1, 4.2 Hz, 1H, C_3H), 2.34 (d, 2H, CH_2), 1.53 (s, 3H, CH_3), 1.38 (m, 3H, CH_3); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 175.6, 171.6, 158.3, 144.2, 143.2, 134.6, 134.4, 130.6, 128.6, 122.2, 120.1, 119.4, 114.6, 111.8, 107.6, 106.8, 81.8, 78.6, 74.8, 64.9, 54.9, 41.1, 38.9, 35.3; MS: m/z (M^+ + H) 545. *Anal.* Calcd for $C_{27}H_{27}ClN_4O_8S$: C, 53.78; H, 4.52; N, 9.29. Found: C, 53.52; H, 4.35; N, 8.99.

2-(2-((3aR,5S,6S,6aR)-6-((1-(4-Chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-3-(4-hydroxyphenyl)-4-oxothiazolidin-5-yl)acetic acid (8g). mp 256–258°C. ^{1}HNMR (300 MHz, $CDCl_3$): δ 11.39 (s, 1H, CO_2H), 8.22 (d, J = 8.7 Hz, 2H, Ar–H), 8.06 (s, 1H, Ar–H), 7.52 (d, J = 9.2 Hz, 2H, Ar–H), 7.14–6.87 (m, 4H, Ar–H), 6.14 (s, 1H, CHS), 5.76 (d, J = 3.6 Hz, 1H, C_1H), 5.42 (s, 1H, OH), 4.96 (d, J = 5.2 Hz, 1H, CH), 4.51 (t, J = 3.9 Hz, 1H, C_2H), 4.54 (s, 2H, OCH_2), 3.93–3.96 (m, 1H, C_4H), 3.26 (dd, J = 9.1, 4.2 Hz, 1H, C_3H), 2.34 (d, 2H, CH_2), 1.53 (s, 3H, CH_3), 1.38 (m, 3H, CH_3); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 173.6, 171.6, 154.1, 143.2, 142.1, 133.6, 131.4, 129.6, 128.1, 122.6, 120.5, 115.4, 112.6, 111.8, 107.6, 106.8, 81.8, 78.6, 76.8, 65.9, 56.9, 42.1, 36.9, 34.3; MS: m/z (M^+ + H) 545. *Anal.* Calcd for $C_{27}H_{27}ClN_4O_8S$: C, 53.78; H, 4.52; N, 9.29. Found: C, 53.42; H, 4.25; N, 9.19.

5-((1H-Benzo[d]imidazol-2-yl)methyl)-2-((3aR,5S,6S,6aR)-2,2-dimethyl-6-((1-phenyl-1H-1,2,3-triazol-4-yl)methoxy)tetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-3-phenylthiazolidin-4-one (9a–n). A mixture of **7** (0.01 mol) and substituted *o*-phenylenediamine (2 mmol) catalytic amount of HCl was grounded thoroughly and transferred to a 50-mL flask. After adding a few drops of DMF, the mixture was irradiated in a microwave oven at 180 W for 4–7 min at 110°C. The progress of reaction was monitored by TLC, with a mixture of ethanol and water (9:1) as the eluent. On completion, the reaction mixture was cooled, ice-cold distilled water was added, and stirred for a while wherein a precipitate was observed. The precipitate was collected by filtration, washed with water, dried, and recrystallized from ethanol water. In classical method, reaction mixtures were grounded thoroughly and transferred to a 50-mL flask. The mixture was refluxed in DMF (20 mL) over a hot plate stirrer. The progress of reaction was monitored by TLC. After completion of the reaction, the product was purified by column chromatography on silica gel (60–120 mesh) with hexane–ethyl acetate as eluent.

5-((1H-Benzo[d]imidazol-2-yl)methyl)-2-((3aR,5S,6S,6aR)-6-((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-3-phenylthiazolidin-4-one (9a). mp 221–223°C. ^{1}HNMR (500 MHz, DMSO): δ 9.32 (s, 1H, –NH), 8.06 (s, 1H, Ar–H), 7.52 (d, J = 9.2 Hz, 4H, Ar–H), 7.44 (d, J = 8.9 Hz, 2H, Ar–H), 7.21 (d, J = 8.4 Hz, 2H, Ar–H), 6.73–7.35 (m, 5H, Ar–H), 6.15 (s, 1H, CHS), 5.73 (d, J = 4.2 Hz, 1H, C_1H), 4.69 (t, J = 3.9 Hz, 1H, C_2H), 4.65 (t, 1H, CH), 4.52 (s, 2H, OCH_2), 3.92–3.89 (m, 1H, C_4H), 3.31 (dd, J = 9.1, 4.2 Hz, 1H, C_3H), 2.38 (d, 2H, CH_2), 1.53 (s, 3H, CH_3), 1.30 (m, 3H, CH_3); ^{13}C-NMR (75 MHz, DMSO): δ 151.4, 143.8, 141.2, 134.2, 128.2, 126.8, 122.1, 118.8, 104.2, 80.4, 77.9, 73.8, 66.1, 53.0, 37.2, 33.9, 25.9; MS: m/z (M^+ + H) 545. *Anal.* Calcd for $C_{33}H_{31}ClN_6O_5S$: C, 60.13; H, 4.74; N, 12.75. Found: C, 60.01; H, 4.54; N, 12.55.

5-((5-Chloro-1H-benzo[d]imidazol-2-yl)methyl)-2-((3aR,5S,6S,6aR)-6-((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-3-phenylthiazolidin-4-one (9b). mp 227–229°C. ^{1}HNMR (500 MHz, DMSO): δ 9.27 (s, 1H, –NH), 8.20 (s, 1H, Ar–H), 8.04 (s, 1H, Ar–H), 7.51 (d, J = 9.2 Hz, 2H, Ar–H), 7.44 (d, J = 8.9 Hz, 2H, Ar–H), 7.21 (d, 2H, Ar–H), 6.73–7.35 (m, 5H, Ar–H), 6.15 (s, 1H, CHS), 5.73 (d, J = 4.2 Hz, 1H, C_1H), 4.69 (t, J = 3.9 Hz, 1H, C_2H), 4.65 (t, 1H, CH), 4.52 (s, 2H, OCH_2), 3.92–3.89 (m, 1H, C_4H), 3.31 (dd, J = 9.1, 4.2 Hz, 1H, C_3H), 2.38 (d, 2H, CH_2), 1.53 (s, 3H, CH_3), 1.30 (m, 3H, CH_3); ^{13}C-NMR (75 MHz, DMSO): δ 151.4, 143.8, 141.2, 134.2, 128.2, 126.8, 122.1, 118.8, 104.2, 80.4, 77.9, 73.8, 66.1, 53.0, 37.2, 33.9, 25.9; MS: m/z (M^+ + H) 694. *Anal.* Calcd for $C_{30}H_{30}Cl_2N_6O_5S$: C, 57.14; H, 4.36; N, 12.12. Found: C, 56.98; H, 4.14; N, 12.01.

5-((1H-Benzo[d]imidazol-2-yl)methyl)-3-(4-chlorophenyl)-2-((3aR,5S,6S,6aR)-6-((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)

methoxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl) thiazolidin-4-one (9c). mp 248–250°C. ^{1}HNMR (500 MHz, DMSO): δ 9.17 (s, 1H, –NH), 8.05 (s, 1H, Ar–H), 7.50 (d, *J* = 9.2 Hz, 4H, Ar–H), 7.42 (d, *J* = 8.9 Hz, 2H, Ar–H), 7.20 (d, 2H, Ar–H), 7.10–6.95 (m, 4H, Ar–H), 6.13 (s, 1H, CHS), 5.71 (d, *J* = 4.2 Hz, 1H, C_1H), 4.66 (t, *J* = 3.9 Hz, 1H, C_2H), 4.60 (t, 1H, CH), 4.50 (s, 2H, OCH_2), 3.92–3.89 (m, 1H, C_4H), 3.31 (dd, *J* = 9.1, 4.2 Hz, 1H, C_3H), 2.38 (d, 2H, CH_2), 1.53 (s, 3H, CH_3), 1.30 (m, 3H, CH_3); ^{13}C-NMR (75 MHz, DMSO): δ 151.1, 143.8, 141.2, 138.9, 134.2, 128.2, 126.8, 122.1, 118.8, 104.2, 80.4, 77.9, 73.8, 66.1, 53.0, 37.2, 33.9, 25.9; MS: *m*/*z* (M^+ + H) 693. *Anal.* Calcd for $C_{33}H_{30}Cl_2N_6O_5S$: C, 57.13; H, 4.36; N, 12.12. Found: C, 56.81; H, 4.14; N, 12.01.

5-((5-Chloro-1H-benzo[d]imidazol-2-yl)methyl)-3-(4-chlorophenyl)-2-((3aR,5S,6S,6aR)-6-((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)thiazolidin-4-one (9d). mp 232–234°C. ^{1}HNMR (500 MHz, DMSO): δ 9.27 (s, 1H, –NH), 8.26 (s, 1H, Ar–H), 8.04 (s, 1H, Ar–H), 7.51 (d, *J* = 9.2 Hz, 4H, Ar–H), 7.44 (d, *J* = 8.9 Hz, 4H, Ar–H), 7.21 (d, 1H, Ar–H), 7.11 (d, 1H, Ar–H), 6.15 (s, 1H, CHS), 5.73 (d, *J* = 4.2 Hz, 1H, C_1H), 4.69 (t, *J* = 3.9 Hz, 1H, C_2H), 4.65 (t, 1H, CH), 4.52 (s, 2H, OCH_2), 3.92–3.89 (m, 1H, C_4H), 3.31 (dd, *J* = 9.1, 4.2 Hz, 1H, C_3H), 2.38 (d, 2H, CH_2), 1.53 (s, 3H, CH_3), 1.30 (m, 3H, CH_3); ^{13}C-NMR (75 MHz, DMSO): δ 151.1, 143.5, 141.0, 134.1, 128.4, 126.2, 122.0, 116.8, 102.2, 80.1, 77.6, 73.2, 66.0, 53.0, 37.6, 33.1; MS: *m*/*z* (M^+ + Na) 749. *Anal.* Calcd for $C_{33}H_{29}Cl_3N_6O_5S$: C, 54.14; H, 4.01; N, 11.54. Found: C, 53.98; H, 3.94; N, 11.31.

5-((1H-Benzo[d]imidazol-2-yl)methyl)-2-((3aR,5S,6S,6aR)-6-((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-3-(4-nitrophenyl)thiazolidin-4-one (9e). mp 256–258°C. ^{1}HNMR (500 MHz, DMSO): δ 9.17 (s, 1H, –NH), 8.21 (d, *J* = 8.4 Hz, 2H), 8.01 (s, 1H, Ar–H), 7.49 (d, *J* = 9.1 Hz, 2H, Ar–H), 7.41 (d, *J* = 8.5 Hz, 2H, Ar–H), 7.30–7.34 (m, 4H, Ar–H), 6.79 (d, *J* = 9.6 Hz, 2H, Ar–H), 6.14 (s, 1H, CHS), 5.69 (d, *J* = 4.2 Hz, 1H, C_1H), 4.65 (t, 1H, CH), 4.53 (t, *J* = 3.9 Hz, 1H, C_2H), 4.52 (s, 2H, OCH_2), 3.90–3.86 (m, 1H, C_4H), 3.19 (dd, *J* = 9.1, 4.2 Hz, 1H, C_3H), 2.30 (d, 2H, CH_2), 1.49 (s, 3H, CH_3), 1.25 (m, 3H, CH_3); ^{13}C-NMR (75 MHz, DMSO): δ 190.2, 173.2, 143.6, 141.9, 134.5, 128.2, 126.5, 122.2, 118.2, 104.3, 80.4, 77.2, 73.1, 66.2, 52.1, 36.4, 33.1, 25.4; MS: *m*/*z* (M^+ + H) 704. *Anal.* Calcd for $C_{33}H_{30}ClN_7O_7S$: C, 56.70; H, 4.29; N, 13.92. Found: C, 56.49; H, 4.09; N, 13.75.

5-((5-Chloro-1H-benzo[d]imidazol-2-yl)methyl)-2-((3aR,5S,6S,6aR)-6-((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-3-(4-nitrophenyl)thiazolidin-4-one (9f). mp 247–248°C. ^{1}HNMR (500 MHz, DMSO): δ 9.14 (s, 1H, –NH), 8.36 (s, 1H, Ar–H), 8.19 (d, *J* = 8.4 Hz, 2H), 8.01 (s, 1H, Ar–H), 7.49 (d, *J* = 9.1 Hz, 2H, Ar–H), 7.41 (d, *J* = 8.5 Hz, 2H, Ar–H), 7.34 (d, *J* = 9.3 Hz, 2H, Ar–H), 6.79 (d, *J* = 9.6 Hz, 2H, Ar–H), 6.14 (s, 1H, CHS), 5.69 (d, *J* = 4.2 Hz, 1H, C_1H), 4.65 (t, 1H, CH), 4.53 (t, *J* = 3.9 Hz, 1H, C_2H), 4.52 (s, 2H, OCH_2), 3.90–3.86 (m, 1H, C_4H), 3.19 (dd, *J* = 9.1, 4.2 Hz, 1H, C_3H), 2.30 (d, 2H, CH_2), 1.49 (s, 3H, CH_3), 1.25 (m, 3H, CH_3); ^{13}C-NMR (75 MHz, DMSO): δ 190.2, 173.2, 143.6, 141.9, 134.5, 128.2, 126.5, 122.2, 118.2, 104.3, 80.4, 77.2, 73.1, 66.2, 52.1, 36.4, 33.1; MS: *m*/*z* (M^+ + H) 739. *Anal.* Calcd for $C_{33}H_{29}Cl_2N_7O_7S$: C, 53.60; H, 3.96; N, 13.27. Found: C, 53.49; H, 3.79; N, 12.95.

5-((1H-Benzo[d]imidazol-2-yl)methyl)-2-((3aR,5S,6S,6aR)-6-((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-3-o-tolylthiazolidin-4-one (9g). mp 247–249°C. ^{1}HNMR (300 MHz, DMSO): δ 9.19 (s, 1H, –NH), 8.06 (s, 1H, Ar–H), 7.50 (d, *J* = 9.1 Hz, 2H, Ar–H), 7.42 (d, 2H, Ar–H), 7.38 (d, *J* = 8.5 Hz, 2H, Ar–H), 7.34 (d, 2H, Ar–H), 7.29–7.32 (m, 4H, Ar–H), 6.14 (s, 1H, CHS), 5.65 (d, *J* = 4.2 Hz, 1H, C_1H), 4.60 (t, 1H, CH), 4.53 (t, *J* = 3.9 Hz, 1H, C_2H), 4.54 (s, 2H, OCH_2), 3.92–3.86 (m, 1H, C_4H), 3.22 (dd, *J* = 9.1, 4.2 Hz, 1H, C_3H), 2.34 (d, 2H, CH_2), 2.21 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 1.29 (m, 3H, CH_3); ^{13}C-NMR (75 MHz, DMSO): δ 191.4, 173.4, 144.6, 142.9, 133.9, 125.4, 122.2, 119.2, 105.6, 80.6, 77.4, 73.4, 66.5, 53.1, 36.3, 33.2; MS: *m*/*z* (M^+ + H) 674. *Anal.* Calcd for $C_{34}H_{33}ClN_6O_5S$: C, 60.66; H, 4.94; N, 12.48. Found: C, 60.26.; H, 4.62; N, 12.15.

5-((5-Chloro-1H-benzo[d]imidazol-2-yl)methyl)-2-((3aR,5S,6S,6aR)-6-((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-3-o-tolylthiazolidin-4-one (9h). mp 257–248°C. ^{1}HNMR (500 MHz, DMSO): δ 9.17 (s, 1H, –NH), 8.29 (s, 1H, Ar–H), 8.06 (s, 1H, Ar–H), 7.50 (d, *J* = 9.1 Hz, 2H, Ar–H), 7.42 (d, *J* = 8.1 Hz, 2H, Ar–H), 7.38 (d, *J* = 8.5 Hz, 2H, Ar–H), 7.34 (d, 2H, Ar–H), 7.29 (d, *J* = 9.2 Hz, 1H, Ar–H), 7.14 (d, *J* = 8.6 Hz, 1H, Ar–H), 6.14 (s, 1H, CHS), 5.65 (d, *J* = 4.2 Hz, 1H, C_1H), 4.60 (t, 1H, CH), 4.53 (t, *J* = 3.9 Hz, 1H, C_2H), 4.54 (s, 2H, OCH_2), 3.92–3.86 (m, 1H, C_4H), 3.22 (dd, *J* = 9.1, 4.2 Hz, 1H, C_3H), 2.34 (d, 2H, CH_2), 2.21 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 1.29 (m, 3H, CH_3); ^{13}C-NMR (75 MHz, DMSO): δ 191.4, 173.4, 144.6, 142.9, 133.9, 125.4, 122.2, 119.2, 105.6, 80.6, 77.4, 73.4, 66.5, 53.1, 36.3, 33.2; MS: *m*/*z* (M^+ + H) 708. *Anal.* Calcd for $C_{34}H_{32}Cl_2N_6O_5S$: C, 57.71; H, 4.56; N, 11.88. Found: C, 57.26.; H, 4.22; N, 11.45.

5-((1H-Benzo[d]imidazole-2-yl)methyl)-2-((3aR,5S,6S,6aR)-6-((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxolol-5-yl)-3-p-tolylthiazolidine-4-one (9i). mp 207–209°C. ^{1}HNMR (300 MHz, DMSO): δ 9.12 (s, 1H, –NH), 8.20 (d, *J* = 8.4 Hz, 2H, Ar–H), 8.04 (s, 1H, Ar–H), 7.59 (d, *J* = 9.4 Hz, 2H, Ar–H), 7.44 (d, *J* = 9.1 Hz, 2H, Ar–H),

7.32 (d, *J* = 8.9 Hz, 2H, Ar–H), 7.21 (d, *J* = 8.3 Hz, 2H, Ar–H), 7.12 (d, *J* = 8.3 Hz, 2H, Ar–H), 6.14 (s, 1H, CHS), 5.65 (d, *J* = 4.2 Hz, 1H, C_1H), 4.60 (t, 1H, CH), 4.53 (t, *J* = 3.9 Hz, 1H, C_2H), 4.54 (s, 2H, OCH_2), 3.92–3.86 (m, 1H, C_4H), 3.22 (dd, *J* = 9.1, 4.2 Hz, 1H, C_3H), 2.34 (d, 2H, CH_2), 2.21 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 1.29 (m, 3H, CH_3); ^{13}C-NMR (75 MHz, DMSO): δ 192.4, 175.4, 142.6, 139.9, 136.7, 132.9, 124.4, 121.2, 117.2, 104.6, 82.6, 78.4, 73.1, 64.5, 52.1, 35.3, 31.2, 25.2, 21.4, 16.2; MS: *m*/*z* (M^+ + H) 673. *Anal.* Calcd for $C_{34}H_{33}ClN_6O_5S$: C, 60.66; H, 4.94; N, 5.27. Found: C, 60.49; H, 4.62; N, 5.15.

5-((6-Chloro-1*H*-benzo[*d*]imidazol-2-yl)methyl)-2-((3a*R*,5*S*,6*S*,6a*R*)-6-((1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)-3-*p*-tolylthiazolidin-4-one (9j). mp 217–219°C. ^{1}HNMR (300 MHz, DMSO): δ 9.12 (s, 1H, –NH), 8.22 (d, *J* = 8.4 Hz, 2H, Ar–H), 8.02 (s, 1H, Ar–H), 7.56 (d, *J* = 9.4 Hz, 2H, Ar–H), 7.42 (d, *J* = 9.1 Hz, 2H, Ar–H), 7.31 (d, *J* = 8.9 Hz, 2H, Ar–H), 7.20 (d, *J* = 8.3 Hz, 1H, Ar–H), 7.12 (d, *J* = 8.3 Hz, 2H, Ar–H), 6.15 (s, 1H, CHS), 5.63 (d, *J* = 4.2 Hz, 1H, C_1H), 4.61 (t, 1H, CH), 4.53 (t, *J* = 3.9 Hz, 1H, C_2H), 4.51 (s, 2H, OCH_2), 3.92–3.89 (m, 1H, C_4H), 3.23 (dd, *J* = 9.1, 4.2 Hz, 1H, C_3H), 2.35 (d, 2H, CH_2), 2.20 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 1.25 (m, 3H, CH_3); ^{13}C-NMR (75 MHz, DMSO): δ 192.4, 171.4, 142.6, 140.9, 131.9, 125.4, 123.8, 121.2, 118.2, 102.6, 81.6, 76.4, 72.4, 61.5, 52.1, 33.3, 25.2, 23.2, 16.2; MS: *m*/*z* (M^+ + H) 707. *Anal.* Calcd for $C_{34}H_{32}Cl_2N_6O_5S$: C, 57.71; H, 4.56; N, 4.88. Found: C, 57.59; H, 4.42; N, 4.75.

5-((1*H*-Benzo[*d*]imidazol-2-yl)methyl)-2-((3a*R*,5*S*,6*S*,6a*R*)-6-((1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)-3-(3-hydroxyphenyl)thiazolidin-4-one (9k). mp 237–239°C. ^{1}HNMR (300 MHz, DMSO): δ 9.09 (s, 1H, NH), 8.21 (d, *J* = 8.7 Hz, 2H, Ar–H), 8.03 (s, 1H, Ar–H), 7.52 (d, *J* = 9.2 Hz, 2H, Ar–H), 7.14–7.10 (m, 4H, Ar–H), 6.12 (s, 1H, CHS), 5.74 (d, *J* = 3.6 Hz, 1H, C_1H), 5.40 (s, 1H, OH), 4.96 (d, *J* = 5.2 Hz, 1H, CH), 4.49 (t, *J* = 3.9 Hz, 1H, C_2H), 4.50 (s, 2H, OCH_2), 3.93–3.90 (m, 1H, C_4H), 3.21 (dd, *J* = 9.1, 4.2 Hz, 1H, C_3H), 2.31 (d, 2H, CH_2), 1.51 (s, 3H, CH_3), 1.35 (m, 3H, CH_3); ^{13}C-NMR (75 MHz, DMSO): δ 173.6, 158.1, 142.2, 140.2, 133.6, 131.4, 130.1, 125.6, 121.2, 120.1, 116.4, 114.1, 111.8, 105.6, 106.2, 80.8, 76.6, 73.8, 63.9, 52.9, 40.1, 36.9, 32.3, 28.1; MS: *m*/*z* (M^+ + H) 675. *Anal.* Calcd for $C_{33}H_{31}ClN_6O_6S$: C, 58.71; H, 4.63; N, 5.25. Found: C, 58.62; H, 4.55; N, 5.19.

5-((5-Chloro-1*H*-benzo[*d*]imidazol-2-yl)methyl)-2-((3a*R*,5*S*,6*S*,6a*R*)-6-((1-(4-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)-3-(3-hydroxyphenyl)thiazolidin-4-one (9l). mp 247–249°C. ^{1}HNMR (300 MHz, DMSO): δ 9.09 (s, 1H, NH), 8.21 (d, *J* = 8.7 Hz, 2H, Ar–H), 8.03 (s, 1H, Ar–H), 7.52 (d, *J* = 8.2 Hz, 1H, Ar–H), 7.14–7.10 (m, 4H, Ar–H), 6.12 (s, 1H, CHS), 5.74 (d, *J* = 3.6 Hz, 1H, C_1H), 5.40 (s, 1H, OH), 4.96 (d, *J* = 5.2 Hz, 1H, CH), 4.49 (t, *J* = 3.9 Hz, 1H, C_2H), 4.50 (s, 2H, OCH_2), 3.93–3.90 (m, 1H, C_4H), 3.21 (dd, *J* = 9.1, 4.2 Hz, 1H, C_3H), 2.31 (d, 2H, CH_2), 1.51 (s, 3H, CH_3), 1.35 (m, 3H, CH_3); ^{13}C-NMR (75 MHz, DMSO): δ 172.6, 156.1, 141.2, 140.2, 131.6, 130.4, 129.1, 124.6, 123.2, 121.1, 115.4, 113.1, 112.8, 104.6, 103.2, 82.8, 75.6, 72.8, 62.9, 53.9, 41.1, 37.9, 33.3, 26.1; MS: *m*/*z* (M^+ + Na) 729. *Anal.* Calcd for $C_{33}H_{30}Cl_2N_6O_6S$: C, 55.86; H, 4.26; N, 5.25. Found: C, 55.62; H, 4.15; N, 5.09.

5-((1*H*-Benzo[*d*]imidazol-2-yl)methyl)-2-((3a*R*,5*S*,6*S*,6a*R*)-6-((1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)-3-(4-hydroxyphenyl)thiazolidin-4-one (9m). mp 266–268°C. ^{1}HNMR (300 MHz, DMSO): δ 8.20 (d, *J* = 8.7 Hz, 2H, Ar–H), 8.02 (s, 1H, Ar–H), 7.49 (d, *J* = 9.2 Hz, 2H, Ar–H), 7.14–7.09 (m, 4H, Ar–H), 6.16 (s, 1H, CHS), 5.73 (d, *J* = 3.6 Hz, 1H, C_1H), 5.41 (s, 1H, OH), 4.94 (d, *J* = 5.2 Hz, 1H, CH), 4.51 (t, *J* = 3.9 Hz, 1H, C_2H), 4.54 (s, 2H, OCH_2), 3.96–3.92 (m, 1H, C_4H), 3.24 (dd, *J* = 9.1, 4.2 Hz, 1H, C_3H), 2.33 (d, 2H, CH_2), 1.53 (s, 3H, CH_3), 1.38 (m, 3H, CH_3); ^{13}C-NMR (75 MHz, DMSO): δ 171.2, 153.1, 142.2, 141.1, 136.6, 134.4, 129.6, 128.4, 122.2, 120.1, 114.4, 112.2, 111.3, 105.6, 103.8, 80.8, 76.6, 74.8, 65.3, 57.0, 42.5, 36.4, 34.1; MS: *m*/*z* (M^+ + H) 675. *Anal.* Calcd for $C_{33}H_{31}ClN_6O_6S$: C, 58.72; H, 4.62; N, 5.28. Found: C, 58.52; H, 4.39; N, 5.19.

5-((5-Chloro-1*H*-benzo[*d*]imidazol-2-yl)methyl)-2-((3a*R*,5*S*,6*S*,6a*R*)-6-((1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)-3-(4-hydroxyphenyl)thiazolidin-4-one (9n). mp 246–248°C. ^{1}HNMR (300 MHz, DMSO): δ 8.19 (d, *J* = 8.3 Hz, 2H, Ar–H), 8.02 (s, 1H, Ar–H), 7.38 (d, *J* = 9.2 Hz, 1H, Ar–H), 7.11–7.09 (m, 4H, Ar–H), 6.12 (s, 1H, CHS), 5.70 (d, *J* = 3.4 Hz, 1H, C_1H), 5.40 (s, 1H, OH), 4.83 (d, *J* = 5.1 Hz, 1H, CH), 4.50 (t, *J* = 3.5 Hz, 1H, C_2H), 4.52 (s, 2H, OCH_2), 3.94–3.92 (m, 1H, C_4H), 3.22 (dd, *J* = 9.1, 4.2 Hz, 1H, C_3H), 2.30 (d, 2H, CH_2), 1.51 (s, 3H, CH_3), 1.34 (m, 3H, CH_3); ^{13}C-NMR (75 MHz, DMSO): δ 154.1, 141.2, 140.1, 134.6, 132.4, 128.6, 126.4, 121.2, 120.8, 113.4, 112.6, 110.3, 105.2, 103.2, 80.2, 76.2, 74.2, 65.1, 57.0, 42.1, 36.2, 34.1; MS: *m*/*z* (M^+ + H) 709. *Anal.* Calcd for $C_{33}H_{30}Cl_2N_6O_6S$: C, 55.85; H, 4.24; N, 9.88. Found: C, 55.72; H, 4.19; N, 9.69.

CONCLUSION

In conclusion, a series of a new class of hybrid heterocyclics **9a–n** have been synthesized and evaluated for their antibacterial activity; most of the compounds showed appreciable antibacterial activity.

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