Synthesis and Biological Evaluation of Novel Pyrane Glycosides

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Abstract

A series of novel (5R)-5-((2S,3S)-3-((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-3,6-dihydro-2H-pyran-2-yl)-3-(4-fluorophenyl)-2,6-diphenyl-3,3a,5,6-tetrahydro-2H-pyrazolo[3,4-d]thiazoles 11a–g and (5R)-5-((2S,3S)-3-((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-3,6-dihydro-2H-pyran-2-yl)-3-(4-fluorophenyl)-6-phenyl-3,3a,5,6-tetrahydroisoxazolo[3,4-d]thiazoles 12a–g were synthesized by the reaction of chalcone derivatives of (R,Z)-2-((2S,3S)-3-((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-3,6-dihydro-2H-pyran-2-yl)-5-(4-fluorobenzylidene)-3-phenylthiazolidin-4-ones 10a–g with phenylhydrazine and hydroxylamine hydrochloride. The chemical structures of newly synthesized compounds were elucidated by IR, NMR, MS and elemental analysis. The compounds 11a–g and 12a–g were evaluated for their antibacterial activity and antifungal activity.

Keywords: Glycosides; click reaction; cyclisation; thiazolopyrazoles; thiazoloisoxazoles; antimicrobial activity

1. Introduction

Carbohydrates, are the most ample class of biomolecules, a vital source of energy and structural components having an important role in biological processes. Carbohydrates, besides being the most abundant class of bio-molecules, a vital source of energy and structural components, have an important role in biological processes, organic synthesis and chemical industries.1 They have been mostly used in chemical industries and their large scale applications include their use as feedstocks in different chemical industries, like pharmaceutical, food, cosmetic and detergent industries.2 In the formation of glyconjugates (glycolipids, glycoproteins and polysaccharides) and in many biological processes they play decisive role in cell physiology such as intercellular recognition, bacterial and viral infection, cancer metastasis, apoptosis and neuronal proliferation, etc.3

Their fascinating properties, such as hydrophilicity, lowered toxicity and emphasized bioactivities, in addition of carbohydrate affiliation to many systems make them often very effective.4 Organic chemists have linked carbohydrates to various biologically potent compounds to enhance their biological applications, such as steroids, aminoacids and other therapeutic agents.5 One of the chemical reactions which is involved in making such links is carbohydrate affiliation with a potential compound through a triazole ring.6 To obtain cyclised products with biological potential a process according to an efficient method is used, being an alkyne-azide cyclization reaction and the introduction of a triazole ring.7 The strategy of linking a carbohydrate moiety with another species via a triazole ring is gaining importance in organic synthesis, natural products chemistry and biochemistry.8 The combination of biocompatibility and presence of stereogenic centres stemming from the carbohydrate, together with the polar nature and possible hydrogen bonding ability of a triazole ring, makes gluco-based triazoles very fascinating for organic synthetic chemists.

The derivatives of thiazolidinone are known to possess significant pharmacological9 and biological activities,10 like sedative,11 anti inflammatory,12 anti tubercular,13 anticancer,14 anti tumor,15 anti-HIV,16 anti bacterial,17 anti fungal,18 analgesic, hypotermic,19 anesthetic,20 nematicidal,21 and CNS stimulant.22 Furthermore, thiazolidinones have been used for the treatment of cardiac diseases,23 diabetic complications, like contract nephropathy, neuropathy,24 and as a selective anti platelet activating fac-
Moreover, isoxazole derivatives are an important class of bioactive molecules, which exhibit significant activities, such as anti fungal. The cardinal derivatives include such having antidepressant activity, hampering protein kinases, possessing antiviral, anti-inflammatory, anticonvulsant, insecticidal, antitubercular, immunomodulatory, and hypolipemic activities. Additionally, derivatives of pyrazole are considered as feasible antimicrobial agents.

We have developed a series of novel triazole-linked pyrene glycosides; additionally we screened them for their antimicrobial activity, connected with the affluent introduction of pyrazoles, thiazolidinones, and triazoles as shown by parts of our previous work on biologically active heterocycles. We have also developed a series of novel triazole-linked pyrene glycosides and evaluated their antimicrobial activity.

2. Results and Discussion

For the synthesis, the title compound was prepared according to the procedure outlined in the Scheme 1, where the key intermediate 8 is required. From 3,4,6-tri-O-acetyl-D-glucal (1) by treating with triethylsilane and boron trifluoride diethyl etherate, diacetyl-D-glucal (2) was prepared, giving with NaOMe in methanol at 0 °C after 1 h compound 3 (77%), which has on subsequent treatment with TBDMSCl in dichloromethane in the presence of NEt₃ after 12 h afforded TBS ether 4 (80%), which on treatment with propargyl bromide in toluene in the presence of tetrabutylammonium hydrogensulphate produced diether 5. After deprotection of TBS ether 5, the propargyl ether 6 was converted into triazole 7 (82%) by using 1,3-di-polar cycloaddition with para-chlorophenyl azide carried out at ambient temperature in the presence of CuSO₄ and sodium ascorbate in a mixture of 1:1 CH₂Cl₂–H₂O. The synthesis of triazole-linked thiazolidinone glycosides was carried out by the condensation reaction of 8, obtained by the oxidation of 7 with IBX in acetonitrile. Compound 8 was in the next step reacted with R-substituted primary aromatic amine and thioglycolic acid in the presence of ZnCl₂ under microwave irradiation (Scheme 1) furnishing set of compound 9a–g. These compounds were isolated by conventional work-up, when the reaction was completed in only 5–10 minutes, the 9a–g were obtained in satisfactory yields. Then the compounds 9a–g were reacted with para-fluorobenzaldehyde in the presence of anhydrous NaOAc in glacial AcOH at reflux temperature giving chalcone derivatives of triazole-linked thiazolidinone glycosides 10a–g. Further, these compounds upon cyclocondensation with arylhydrazines in the presence of anhydrous NaOAc in glacial AcOH at reflux temperature gave 11a–g in good yields. Compound 10a–g on cyclocondensation with hydroxylamine hydrochloride in the presence of anhydrous NaOAc in glacial AcOH at reflux temperature gave compounds 12a–g. By IR, NMR, and MS the structures of the synthesized compounds were confirmed and then evaluated for their antimicrobial activity.

3. Antimicrobial Activity

By the filter paper disc method, the antimicrobial activity of the synthesized compounds 11a–g and 12a–g has been evaluated against Staphylococcus aureus ATCC6538P, Bacillus subtilis ATCC6633, Pseudomonas aeruginosa ATCC9027, and Echerichia coli ATCC8739. Antifun-

| Compounds | Gram positive | Gram Negative | Fungi |
|-----------|---------------|---------------|------|
|           | Staphylococcus | Pseudomonas   | Candida |
|           | aureus subtilis| aeruginosa    | albicans |
|           | Echerichia    | coliflor     | Candida |
|           | coliflor albicans | albicans | albicans | Albicans | albicans |
| 11a       | 17             | 18            | 20    | 15   | 13   |
| 11b       | 24             | 20            | 19    | 14   | 12   |
| 11c       | 15             | 15            | 14    | 15   | 14   |
| 11d       | 20             | 10            | 7     | 14   | 15   |
| 11e       | 15             | 11            | 9     | 21   | 15   |
| 11f       | 16             | 19            | 17    | 9    | 7    |
| 11g       | 22             | 15            | 14    | 22   | 16   |
| 12a       | 16             | 19            | 18    | 17   | 14   |
| 12b       | 20             | 19            | 18    | 15   | 13   |
| 12c       | 10             | 15            | 16    | 14   | 13   |
| 12d       | 20             | 6             | 10    | 14   | 12   |
| 12e       | 16             | 12            | 10    | 20   | 17   |
| 12f       | 17             | 19            | 18    | 7    | 8    |
| 12g       | 20             | 16            | 15    | 21   | 16   |
| Ampicillin | 22             | 20            | 19    | _    | _    |
| Micostatin | _              | _             | _     | 22   | 16   |
gal activity of the synthesized compounds has been tested against *Candida albicans* ATCC2091, and *Aspergillus niger*, at a concentration of 500 μg/mL in DMF.

To culture the bacteria and fungi, nutrient agar and potato dextrose agars were used, respectively. The plates were cultured by the bacteria or fungi and incubated for 24 h at 37 °C for bacteria and for 72 h at 27 °C for fungi and then the inhibition zones of microbial growth surrounding the filter paper disc (5 mm) were measured in millimeters. Ampicillin and mycostatin, at a concentration 500 μg/mL, were used as standard against bacteria and fungi, respectively. All test results are shown in Table 1. From the data it is clear that compounds 11b, 12b, 11d, 12d, 11g, and 12g possess high activity, while compounds 11a, 12a, 11c, 11e, 12e, 11f, and 12f possess moderate activity against Gram positive bacteria. The compounds 11a, 12a, 11b, 12b, 11f, and 12f showed high activity as Gram negative microorganisms are concerned, while compounds 11c, 12c, 11g and 12g display moderate activity. Compounds 11e, 12e, 11g, and 12g also exerted high activity, while compounds 11a, 12a, 11c, 12c, 11d, 12d, 11b, and 12b have moderate activity against fungi.

4. Experimental

All the used reagents were supplied as commercially available. According to the literature, when necessary, the solvents used (except analytical reagent and grade) were dried and purified. By thin-layer chromatography (TLC)

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**Reagents and conditions:**

- (a) BF$_3$, Et$_2$O, Et$_3$SiH, CH$_2$Cl$_2$;
- (b) MeOH, NaOMe;
- (c) TBDMSCl, Et$_3$N, CH$_2$Cl$_2$;
- (d) propargyl bromide, NaH, n-Bu$_4$N-HSO$_4$, 35% NaOH, toluene;
- (e) TBAF, THF;
- (f) 4-Cl-C$_6$H$_4$-N$_3$, CuSO$_4$, sodium ascorbate, CH$_2$Cl$_2$, H$_2$O (1:1);
- (g) IBX, CH$_3$CN;
- (h) R-C$_6$H$_4$-NH$_2$, AcOH, SHCH$_2$COOH, ZnCl$_2$, C$_6$H$_6$;
- (i) 4-F-C$_6$H$_4$-CHO, NaOAc, AcOH;
- (j) PhNH$_2$NH$_2$, NaOAc, AcOH;
- (k) NH$_2$OH, NaOAc, AcOH.
on pre-coated silica gel F254 plates from Merck the reaction progress and purity of the compounds was checked. They were is visualized either by exposure to UV light or dipping in 1% aqueous potassium permanganate solution. Silica gel chromatographic columns (60–120 mesh) were used for separations. Optical rotations were measured on an Perkin–Elmer FT IR spectrometer. By using Fisher–Johns apparatus all the melting points were measured and are corrected. IR spectra were recorded as KBr disks on a Perkin–Elmer FT IR spectrometer. Microwave reactions were carried out in mini lab microwave catalytic reactor (ZKKD, WBF-201). On Varian Gemini spectrometer (300 MHz for 1H and 75 MHz for 13C) the 1H NMR and 13C NMR spectra were recorded; chemical shifts are reported as δ in ppm against TMS as the internal reference, coupling constants (J) are reported in Hz units. On a VG micro mass spectrometer mass spectra were recorded. Elemental analysis (C, H, N) were determined by a Perkin–Elmer 240 CHN elemental analyzer and were within ± 0.4% of theoretical values.

((2R,3S)-3-Acetoxy-3,6-dihydro-2H-pyran-2-yl)methyl Acetate (2)

Tri-O-acetyl-D-glucal (1) (6.0 g, 22.04 mmol) was dissolved in anhydrous dichloromethane (10 mL). The solution was cooled to about 0 °C, and triethylsilane (3.06 g, 26.44 mmol) was added and the mixture was stirred for five minutes. Then boron trifluoride diethyl etherate (690 μL of a 40 w% solution in diethyl ether, 11.02 mmol) was added drop wise and the reaction mixture was stirred for 90 min. The mixture was poured into a saturated solution of NaHCO3. Then the organic layer was washed with water and dried over Na2SO4 and concentrated under reduced pressure.

Column chromatography on silica gel (PE/EtOAc, 3:1) yielded the title compound 2 (4.48 g, 20.84 mmol, 95%) as a colorless syrup. [α]D20 = +115.5 (c = 1.00, CHCl3).

1H NMR (300 MHz, CDCl3) δ 5.87–5.84 (m, 2H, =CH), 4.95 (t, 1H, OCH), 4.03–3.99 (m, 1H, CH), 4.15–4.09 (m, 4H, OCH2), 2.20 (s, 6H, CO CH3); 13C NMR (75 MHz, CDCl3) δ 100.2, 127.2, 125.8, 78.3, 76.2, 74.2, 64.0, 62.5, 21.1; MS m/z (M++H) 215. Anal. calcd. for C10H14O5: C, 56.07; H, 6.35; Found: C, 56.42; H, 6.35.

((2R,3S)-3-(Prop-2-ynoxyloxy)-3,6-dihydro-2H-pyran-2-yl)methoxy)silane (5)

To a solution of alcohol 4 (3.50 g, 13.10 mmol) in toluene (3.2 mL) was added 35% aqueous solution of NaOH (6.4 ml), propargyl bromide (80% solution in toluene, 363 μL, 2.4 mmol, 1.5 equiv), and n-Bu4NHSO4 (360 mg, 1.6 mmol, 1 equiv). After 6 h of vigorous stirring at rt, Et2NH (6.4 mL) was added. The reaction mixture was stirred for 1 h, poured into ice water, cautiously neutralized by addition of a 3M solution of hydrochloric acid, and extracted with EtOAc. The combined organic extracts were washed with brine, dried over MgSO4, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (hexane/EtOAc 85:15) to afford propargyl ether 5 as a colorless oil (3.1 g, 83%). 1H NMR (300 MHz, CDCl3) δ 6.03–5.80 (m, 2H, =CH), 4.69 (t, J = 3.9 Hz, 1H, CH), 3.68 (dd, J = 8.9 Hz, 4.1 Hz, 1H, OCH), 3.99–3.89 (m, 6H, CH2), 3.20 (s, 1H, CH), 0.96 (s, 9H, t-Bu), 0.23 (s, 6H, CH3); 13C NMR (75 MHz, CDCl3) δ 127.2, 124.9, 78.0, 76.2, 74.2, 64.2, 63.2, 58.5, 25.3, 18.5; MS m/z (M++H) 283. Anal. calcd. for C15H24O3Si: C, 63.78; H, 9.28. Found: C, 63.62; H, 8.95.

((2R,3S)-3-(Prop-2-ynoxyloxy)-3,6-dihydro-2H-pyran-2-yl)methanol (6)

To a stirred solution of 5 (3 g, 10.600 mmol) in tetrahydrofuran, catalytic amount of TBAF was added and stirred the reaction mixture at room temperature for 15 min, extracted the product with ethyl acetate (50 mL). The combined organic extracts were washed with brine, dried over MgSO4, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (60–120 mesh, hexane/EtOAc 70:30) to afford alcohol 6 as a yellow oil (1.5 g, 83%). 1H NMR (300 MHz, CDCl3) δ 5.95–5.75 (m, 2H, =CH), 4.65 (dd, J = 3.9 Hz, 1H, CH), 4.52 (brs, 1H, OH), 4.09–4.11 (m, 4H, OCH2), 3.64 (dd, J = 4.1 Hz, 8.9 Hz, 1H, OCH), 3.76 (dd, J = 6.8 Hz, 2H, OCH2), 3.28 (s, 1H, CH); 13C NMR (75 MHz, CDCl3) δ 127.2, 125.6, 78.3, 76.1, 74.1, 64.2, 61.4, 58.0; MS m/z (M++H) 169. Anal. calcd. for C3H12O2: C, 64.27; H, 7.10. Found: C, 64.02; H, 6.95.
(2R,3S)-3-((4-Chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-3,6-dihydro-2H-pyran-2-yl)methanol (7)

The a solution containing alkyne 6 (1.4 g, 8.28 mmol), para-chlorophenylazide (1.25 g, 8.11 mmol) in dichloromethane (10 mL) and water (10 mL) were added CuSO₄ · 5H₂O (0.110 g) and sodium ascorbate (0.114 g). The resulting suspension was stirred at room temperature for 6 h. Then, the mixture was diluted with 5 mL dichloromethane and 5 mL water. The organic phase was separated, dried with sodium sulfate and concentrated under reduced pressure. The crude product was purified by using column chromatography on silica gel (60–120 mesh, hexane/EtOAc 65:35) to afford 7 (2 g, 75%) as a white powder. M.p. 149–151.0°C. 1H NMR (300 MHz, CDCl₃) δ 8.05 (s, 1H, Ar-H), 7.51 (d, 2H, Ar-H), 7.40 (d, 2H, Ar-H), 7.36–7.32 (m, 2H, Ar-H), 7.25 (d, 2H, Ar-H), 7.10–6.20 (m, 5H, Ar-H), 6.84 (d, 2H, CH-S), 4.55 (s, 2H, OCH₂), 3.80 (t, 2H, OCH₂), 3.72 (s, 2H, CH₂); 13C NMR (75 MHz, CDCl₃) δ 170.5, 144.2, 139.2, 134.2, 129.2, 125.5, 122.0, 119.5, 85.4, 72.4, 65.8, 64.2, 62.4; MS m/z 144.1, 141.8, 125.6, 124.4, 119.4, 116.5, 85.4, 72.6, 65.8, 63.6, 51.5, 34.6; MS m/z (M++Na) 252. Anal. calcd. for C₁₂H₁₀ClN₃O₃S: C, 55.70; H, 5.01; N, 13.06. Found: C, 55.65; H, 4.95; N, 13.16. 13C NMR (75 MHz, CDCl₃) δ 170.4, 144.1, 139.2, 134.2, 129.2, 125.5, 122.0, 119.5, 85.4, 72.4, 65.8, 63.6, 51.5, 34.6; MS m/z (M++Na) 252. Anal. calcd. for C₁₂H₁₀ClN₃O₃S: C, 55.70; H, 5.01; N, 13.06. Found: C, 55.65; H, 4.95; N, 13.16.

(R)-2-((2S,3S)-3-((1-(4-Chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-3,6-dihydro-2H-pyran-2-yl)-3-phenylthiazolidin-4-ones 9a–g

At room temperature for about 30 min, to the solution of alcohol 7 (1.9 g, 5.90 mmol) in CH₂Cl₂ (10 mL), a catalytic amount of IBX was added at 0 °C and stirred. The reaction mixture was filtered and washed with CH₂Cl₂ (2 × 10 mL). The resulting suspension was stirred at room temperature for 6 h. Then, the mixture was diluted with 5 mL dichloromethane and 5 mL water. The organic phase was separated, dried with sodium sulfate and concentrated under reduced pressure. The crude product was purified by using column chromatography on silica gel (60–120 mesh, hexane/EtOAc 65:35) to afford 7 (2 g, 75%) as a white powder. M.p. 149–151.0°C. 1H NMR (300 MHz, CDCl₃) δ 8.05 (s, 1H, Ar-H), 7.51 (d, 2H, Ar-H), 7.40 (d, 2H, Ar-H), 7.36–7.32 (m, 2H, Ar-H), 7.25 (d, 2H, Ar-H), 7.10–6.20 (m, 5H, Ar-H), 5.80–5.71 (m, 2H, =CH), 4.90 (d, J = 5.2 Hz, 1H, CH-S), 4.55 (s, 2H, OCH₂), 4.09–3.94 (m, 2 × CH₂), 3.79 (d, J = 6.6 Hz, 2H, OCH₂), 3.72 (s, 2H, CH₂); 13C NMR (75 MHz, CDCl₃) δ 170.4, 144.1, 141.8, 134.1, 128.2, 125.6, 122.4, 119.4, 85.6, 72.6, 66.4, 64.0, 51.4, 33.9; MS m/z (M++H) 469. Anal. calcd. for C₂₃H₂₁ClN₅O₅S: C, 55.65; H, 4.95; N, 11.66.
(R,Z)-2-((2S,3S)-3-((1-(4-Chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-3,6-dihydro-2H-pyran-2-yl)-3-(4-fluorobenzylidene)thiazolidin-4-one (10a). M.p. 235–237 °C. Yield 82% (0.224 g). 1H NMR (300 MHz, CDCl3) δ 8.07 (s, 1H, Ar-H), 7.80 (s, 1H, CH=C), 7.72 (d, J = 9.6 Hz, 2H, Ar-H), 7.40 (d, J = 9.2 Hz, 2H, Ar-H), 7.45 (d, J = 8.9 Hz, 2H, Ar-H), 7.19 (d, J = 8.2 Hz, 2H, Ar-H), 7.02–6.80 (m, 5H, Ar-H), 5.80–5.74 (m, 2H, =CH), 4.90 (d, J = 5.2 Hz, 1H, CH-S), 4.52 (s, 2H, OCH2), 4.09–3.94 (m, 2H, 2 × CH), 3.79 (d, J = 6.6 Hz, 2H, OCH2). 13C NMR (75 MHz, CDCl3) δ 170.4, 162.1, 144.2, 139.2, 134.2, 130.4, 129.2, 125.5, 124.1, 122.2, 119.4, 85.4, 72.8, 65.4, 51.2; MS m/z (M++Na) 632. Anal. calcd. for C30H23ClFN4O3S: C, 59.12; H, 3.80; N, 9.19. Found: C, 59.01; H, 3.45; N, 8.96.

(R,Z)-2-((2S,3S)-3-((1-(4-Chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-3,6-dihydro-2H-pyran-2-yl)-5-(4-fluorobenzylidene)thiazolidin-4-one (10c). M.p. 221–223 °C. Yield 75% (0.216 g). 1H NMR (300 MHz, CDCl3) δ 8.29 (d, J = 8.7 Hz, 2H, Ar-H), 8.09 (s, 1H, Ar-H), 7.69 (d, J = 9.1 Hz, 2H, Ar-H), 7.65 (s, 1H, CH=C), 7.61 (d, J = 9.4 Hz, 2H, Ar-H), 7.46 (d, J = 8.5 Hz, 2H, Ar-H), 7.18 (s, J = 8.3 Hz, 2H, Ar-H), 6.84 (d, J = 9.8 Hz, Ar-H), 5.86–5.79 (m, 2H, =CH), 4.96 (d, J = 5.2 Hz, CH-S), 4.55 (s, 2H, OCH2), 4.05–3.95 (m, 2H, 2 × CH), 3.85 (d, J = 6.9 Hz, 2H, OCH2). 13C NMR (75 MHz, CDCl3) δ 171.5, 162.1, 144.0, 141.8, 134.2, 130.4, 128.5, 127.2, 125.6, 123.2, 119.4, 116.4, 85.4, 72.6, 66.5, 64.0, 51.6, 34.5; MS m/z (M++H) 620. Anal. calcd. for C30H23ClFN4O3S: C, 58.11; H, 3.74; N, 11.29. Found: C, 57.98; H, 3.55; N, 11.09.

(R,Z)-2-((2S,3S)-3-((1-(4-Chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-3,6-dihydro-2H-pyran-2-yl)-5-(4-fluorobenzylidene)-3-0-tolythiazolidin-4-one (10d). M.p. 201–203 °C. Yield 85% (0.217 g). 1H NMR (300 MHz, CDCl3) δ 8.08 (s, 1H, Ar-H), 7.69 (d, J = 8.5 Hz, 2H, Ar-H), 7.62 (s, 1H, CH=C), 7.56 (d, J = 9.2 Hz, 2H, Ar-H), 7.49 (d, J = 8.7 Hz, 2H, Ar-H), 7.45–7.39 (m, 4H, Ar-H), 7.10 (d, J = 9.1 Hz, 2H, Ar-H), 5.76 (m, 2H, =CH), 4.93 (d, J = 5.2 Hz, 1H, CHS), 4.60 (s, 2H, OCH2), 4.05–3.96 (m, 2H, CH2), 3.90 (t, 2H, OCH2), 2.1 (s, 3H, CH3). 13C NMR (75 MHz, CDCl3) δ 170.8, 162.9, 144.6, 137.2, 133.2, 130.6, 130.4, 128.2, 125.9, 122.7, 119.2, 116.2, 115.4, 84.4, 72.1, 65.3, 63.1, 52.5, 32.0, 17.5; MS m/z (M++H) 589. Anal. calcd. for C31H26ClFN4O3S: C, 63.21; H, 4.45; N, 9.51. Found: C, 62.75; H, 4.25; N, 9.29.

Similarly all the compounds (10b–e) prepared according to above procedure.

General Procedure for the Synthesis of 10a–g

In anhydrous glacial acetic acid (20 mL), a mixture of compound 9a (0.235 g, 0.501 mmol), para-fluorobenzaldehyde (0.065 g, 0.524 mmol) and sodium acetate (0.01 mol) was refluxed for about 3 h. The reaction mixture was concentrated and then poured into ice cold water; the solid thus separated, then it was filtered, and washed with water and crystallized from glacial acetic acid, to afford pure 10a as a yellow solid.
M.p. 205–215 °C. Yield 66% (0.209 g). ¹H NMR (300 MHz, CDCl₃) δ 8.02 (s, 1H, Ar-H), 7.69 (s, 1H, CH =C), 7.65 (d, J = 9.1 Hz, 2H, Ar-H), 7.54 (d, J = 9.2 Hz, 2H, Ar-H), 7.42 (d, J = 8.7 Hz, 2H, Ar-H), 7.35 (d, J = 8.2 Hz, 2H, Ar-H), 7.18 (d, J = 8.8 Hz, 2H, Ar-H), 6.80 (d, J = 9.4 Hz, 2H, Ar-H), 5.70–5.69 (m, 2H, =CH), 4.94 (s, 1H, CHS), 4.55 (s, 2H, OCH₂), 4.04–3.98 (m, 2H, CH); ¹³C NMR (75 MHz, CDCl₃) 139.8, 134.9, 134.8, 130.4, 128.8, 127.2, 125.6, 123.2, 119.4, 115.3, 85.1, 72.6, 66.1, 63.2, 51.2, 21.6; MS m/z (M⁺+H) 589. Anal. calcld. for C₃₆H₃₀ClFN₆O₂S: C, 63.21; H, 4.45; N, 9.51. Found: C, 62.98, H, 4.25; N, 9.33.

(R,Z)-2-((2S,3S)-3-(((1-(4-Chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-3,6-dihydro-2H-pyran-2-yl)-5-(4-fluorobenzylidene)-3-(3-hydroxyphenyl)thiazolidin-4-one (10g). M.p. 218–219 °C. Yield 82% (0.219 g). ¹H NMR (300 MHz, CDCl₃) δ 9.42 (brs, 1H, PhOH), 8.08 (s, 1H, Ar-H), 7.71 (d, J = 9.7 Hz, 2H, Ar-H), 7.65 (s, 1H, CH=C), 7.59 (d, J = 9.3 Hz, 2H, Ar-H), 7.44 (d, J = 8.6 Hz, 2H, Ar-H), 7.15 (d, J = 8.4Hz, 2H, Ar-H), 6.80–6.78 (m, 4H, Ar-H), 5.70–5.68 (m, 2H, =CH), 4.92 (d, J = 5.2 Hz, 1H, CHS), 4.64 (s, 2H, OCH₂), 4.10 (t, 2H, OCH₂), 4.01–3.98 (m, 2H, 2 × CH), 3.85 (d, J = 6.9 Hz, 2H, OCH₂); ¹³C NMR (75 MHz, CDCl₃) 170.9, 162.1, 158.2, 143.8, 139.8, 134.5, 130.8, 128.6, 125.6, 124.1, 122.4, 119.5, 115.7, 114.8, 106.5, 85.4, 72.5, 66.4, 63.4, 51.5; MS m/z (M⁺+H) 591. Anal. calcld. for C₃₆H₃₀ClFN₆O₂S: C, 60.96; H, 4.09; N, 9.48. Found: C, 60.58; H, 3.85; N, 9.13.

(R,Z)-2-((2S,3S)-3-(((1-(4-Chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-3,6-dihydro-2H-pyran-2-yl)-5-(4-fluorobenzylidene)-3-(3-hydroxyphenyl)thiazolidin-4-one (10f). M.p. 283–285 °C. Yield 62% (0.203 g). ¹H NMR (300 MHz, CDCl₃) δ 9.42 (brs, 1H, PhOH), 8.05 (s, 1H, Ar-H), 7.85 (d, J = 9.3 Hz, 2H, Ar-H), 7.65 (s, 1H, CH=C), 7.56 (d, J = 9.2 Hz, 2H, Ar-H), 7.46 (d, J = 8.4 Hz, 2H, Ar-H), 7.32 (d, J = 8.6 Hz, 2H, Ar-H), 7.19 (d, J = 8.3 Hz, 2H, Ar-H), 7.02 (d, J = 8.8 Hz, 2H, Ar-H), 5.89–5.80 (m, 2H, =CH), 4.96 (d, J = 5.4 Hz, 1H, CHS), 4.66 (s, 2H, OCH₂), 4.09 (d, J = 2H, OCH₂), 4.04–3.98 (m, 2H, CH); ¹³C NMR (75 MHz, CDCl₃) d 170.5, 162.1, 158.2, 143.8, 139.8, 134.5, 130.8, 128.6, 125.6, 124.1, 122.4, 119.5, 115.7, 114.8, 106.5, 85.4, 72.5, 66.4, 63.4, 51.5; MS m/z (M⁺+H) 591. Anal. calcld. for C₃₆H₃₀ClFN₆O₂S: C, 60.96; H, 4.09; N, 9.48. Found: C, 60.58; H, 3.85; N, 9.23.

General Procedure for the Synthesis of 11a–g

To the anhydrous sodium acetate (0.191 mmol) a mixture of compound 10a (0.191 mmol), phenyl hydrazine (0.191 mmol), in glacial acetic acid (10 mL), was refluxed for about 7 h. Then the reaction mixture was concentrated and cooled at room temperature, the solid was separated and filtered, then it was washed thoroughly with water, the crude product was obtained and it was purified by column chromatography on silica gel with hexane–ethyl acetate as the eluent to afford pure compounds 11.
(5R)-5-((2S,3S)-3-((1-(4-Chlorophenyl)-1H-1,2,3-triazol-4-yl) methoxy)-3,6-dihydro-2H-pyran-2-yl)-3-(4-fluorophenyl)-2-phenyl-6-o-tolyl-3,3a,5,6-tetrahydro-2H-pyrazolo[3,4-d][thiazole](11d). M.p. 205–215 °C. Yield 67% (0.078 g). IR (KBr) ν 3099, 3018, 2875, 1635, 1576, 1460, 1374, 1370, 1132, 1332, 1306, 1340, 1282, 1259, 1227, 119.2, 116.2, 115.4, 84.2, 76.1, 65.3, 63.1, 52.5, 32.0, 17.5; MS m/z (M’+Na) 701. Anal. calcd. for C30H25ClFN5O3S: C, 65.43; H, 4.75; N, 12.37. Found: C, 65.15; H, 4.45; N, 12.09.

(5R)-5-((2S,3S)-3-((1-(4-Chlorophenyl)-1H-1,2,3-triazol-4-yl) methoxy)-3,6-dihydro-2H-pyran-2-yl)-3-(4-fluorophenyl)-2-phenyl-6-o-tolyl-3,3a,5,6-tetrahydro-2H-pyrazolo[3,4-d][thiazole](11e). M.p. 218–219 °C. Yield 89% (0.105 g). IR (KBr) ν 3084, 3013, 2928, 1621, 1576, 1460, 1374, 1370, 1132, 1332, 1306, 1340, 1282, 1259, 1227, 119.2, 116.2, 115.4, 84.2, 76.1, 65.3, 63.1, 52.5, 32.0, 17.5; MS m/z (M’+H) 681. Anal. calcd. for C36H30ClFN6O3S: C, 63.48; H, 4.44; N, 12.34. Found: C, 63.18; H, 4.15; N, 12.13.

4-((5R)-5-((2S,3S)-3-((1-(4-Chlorophenyl)-1H-1,2,3-triazol-4-yl) methoxy)-3,6-dihydro-2H-pyran-2-yl)-3-(4-fluorophenyl)-2-phenyl-3,3a-dihydro-2H-pyrazolo[3,4-d][thiazol-6(5H)-yl]phenol (11f).

M.p. 283–285 °C. Yield 65% (0.074 g). IR (KBr) ν 3369, 3092, 1635, 1602, 1492, 1372, 1274, 1120, 723 cm–1; 1H NMR (300 MHz, CDCl3) δ 9.40 (brs, 1H, Ph-OH), 8.08 (s, 1H, Ar-H), 7.85 (d, J = 9.3 Hz, 2H, Ar-H), 7.52 (d, J = 9.2 Hz, 2H, Ar-H), 7.48 (d, J = 8.4 Hz, 2H, Ar-H), 7.32 (d, J = 8.6 Hz, 2H, Ar-H), 7.19 (d, J = 8.3 Hz, 2H, Ar-H), 7.02 (d, J = 8.8 Hz, 2H, Ar-H), 6.85–6.80 (m, 5H, Ar-H), 5.89–5.85 (m, 2H, =CH), 4.86 (d, J = 5.4 Hz, 1H, CHS), 4.56 (s, 2H, OCH2), 4.08 (d, J = 2H, OCH2), 4.05–3.99 (m, 2H, CH); 13C NMR (75 MHz, CDCl3) δ 170.5, 162.3, 154.1, 144.4, 143.8, 134.9, 134.8, 130.4, 128.8, 127.2, 125.6, 123.2, 120.8, 119.4, 116.4, 115.9, 85.4, 72.6, 66.5, 64.0, 51.6; MS m/z (M’+H) 681. Anal. calcd. for C36H36ClFN6O3S: C, 63.18; H, 4.15; N, 12.03.

General Procedure for Synthesis of Compounds 1a–g

In anhydrous glacial acetic acid (10 mL), a mixture of compound 10a (0.191 mol), hydroxylamine hydrochloride (0.4 mol) and sodium acetate (0.191 mol) was refluxed according to the above procedure. Similarly all the compounds 1a–g prepared according to the above procedure.

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(5R)-6-(4-Chlorophenyl)-5-((2S,3S)-3-((1-(4-chlorophenyl)-1H-1,1,2,3-triazol-4-yl)ethoxy)-3,6-dihydro-2H-pyran-2-yl)-3-(4-fluorophenyl)-3,3a,5,6-tetrahydrothiazolo[4,5-c]isoxazoles (12b). M.p. 242–244 °C. Yield 85% (0.100 g). IR (KBr) v 3076, 3019, 1620, 1563, 1424, 1312, 1220, 1215, 1151, 764 cm⁻¹; 1H NMR (300 MHz, CDCl₃) δ 8.03 (s, 1H, Ar-H), 7.67 (d, J = 8.3 Hz, 2H, Ar-H), 7.50 (d, J = 8.4 Hz, 4H, Ar-H), 7.44 (s, 1H, CH-N), 7.40 (d, J = 6.8 Hz, 4H, Ar-H), 7.29 (d, J = 8.1 Hz, 2H, Ar-H), 5.82–5.78 (m, 2H, =CH), 5.70 (d, J = 2.2 Hz, 1H, CH-O), 4.69 (d, J = 2.2 Hz, 1H, CHS), 4.50 (s, 2H, OCH₂); 13C NMR (75 MHz, CDCl₃) δ 164.5, 162.1, 144.4, 136.2, 129.6, 127.2, 126.0, 124.7, 122.0, 119.1, 117.5, 115.7, 85.4, 73.1, 66.0, 63.8, 61.0, 40.2; MS m/z (M⁺H) 624. Anal. calcld. for C₃₀H₂₄ClFN₆O₅S: C, 61.63; H, 4.50; N, 11.59. Found: C, 57.51; H, 3.49; N, 11.46.

(5R)-5-((2S,3S)-3-((1-(4-Chlorophenyl)-1H-1,1,2,3-triazol-4-yl)ethoxy)-3,6-dihydro-2H-pyran-2-yl)-3-(4-fluorophenyl)-6-(2-tolyl)-3,3a,5,6-tetrahydrothiazolo[4,5-c]isoxazoles (12c). M.p. 251–254 °C. Yield 75% (0.095 g). IR (KBr) v 3089, 3010, 1619, 1608, 1537, 1442, 1349, 1336, 1221, 1131, 754 cm⁻¹; 1H NMR (300 MHz, CDCl₃) δ 8.23 (d, J = 8.3 Hz, 2H, Ar-H), 8.06 (s, 1H, Ar-H), 7.55 (d, J = 9.1 Hz, 2H, Ar-H), 7.44 (s, 1H, CH-N), 7.40 (d, J = 9.4 Hz, 2H, Ar-H), 7.36 (d, J = 8.5 Hz, 2H, Ar-H), 7.15 (d, J = 8.3 Hz, 2H, Ar-H), 6.86 (d, J = 9.8 Hz, 2H, Ar-H), 5.84–5.80 (m, 2H, =CH), 5.72 (d, J = 2.2 Hz, 1H, CH-O), 4.70 (d, J = 2.2 Hz, 1H, CHS), 4.53 (s, 2H, OCH₂), 4.07–3.98 (m, 2H, 2x CH), 3.83 (d, J = 6.9 Hz, 2H, OCH₂); 13C NMR (75 MHz, CDCl₃) δ 164.0, 161.8, 150.5, 144.4, 133.9, 128.5, 127.3, 126.9, 124.7, 122.0, 119.5, 115.4, 84.4, 73.4, 65.9, 63.6, 61.0, 40.5; MS m/z (M⁺Na) 657. Anal. calcld. for C₃₁H₂₇ClFN₅O₃S: C, 66.3, 63.9, 61.2, 40.1, 21.3; MS m/z (M⁺H) 604. Anal. calcld. for C₂₉H₂₂ClFN₄O₃S: C, 61.63; H, 4.50; N, 11.59. Found: C, 61.48; H, 4.35; N, 11.43.
5. Conclusions

A series of novel pyranose glycosides 11a–g and 12a–g was prepared and evaluated for their antimicrobial activity; we found out that compounds 11b, 12b, 11d, 12d, 11g, and 12g possess high activity, while compounds 11a, 12a, 11c, 11e, 12e, 11f, and 12f possess moderate activity against Gram positive strains. As far as Gram negative microorganisms are concerned, compounds 11a, 12a, 11f, 12f, 11b, and 12b showed high activity while compounds 11c, 12c, 11g, and 12g display moderate activity. Compounds 11e, 12e, 11g, and 12g also exerted high activity while compounds 11a, 12a, 11c, 12c, 11d, 12d, 11b, and 12b have moderate activity against fungi.

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**Povzetek**

Z reakcijo med halkonskimi derivati \((R,Z)-2-((2S,3S)-3-((1-(4-klorofenil)-1H-1,2,3-triazol-4-il)metoksi)-3,6-dihidro-2H-piran-2-il)-5-(4-fluorobenziliden)-3-feniltiazolidin-4-onov 10a–g fenilhidrazinom ali hidroksilamin hidrokloridom smo pripravili serijo novih \((5R)-5-((2S,3S)-3-((1-(4-klorofenil)-1H-1,2,3-triazol-4-il)metoksi)-3,6-dihidro-2H-piran-2-il)-3-(4-fluorofenil)-2,6-difenil-3,3a,5,6-tetrahidro-2H-pirazolo[3,4-d]tiazolov 11a–g in \((5R)-5-((2S,3S)-3-((1-(4-klorofenil)-1H-1,2,3-triazol-4-il)metoksi)-3,6-dihidro-2H-piran-2-il)-3-(4-fluorofenil)-5-fenil-3,3a,5,6-tetrahidroizoksazolo[3,4-d]tiazolov 12a–g*. Kemijske strukture novih pripravljenih spojij smo določili z IR, NMR, MS in elementno analizo. Za spojine 11a–g in 12a–g smo določili tudi učinkovitost delovanja proti bakterijam in glivam.