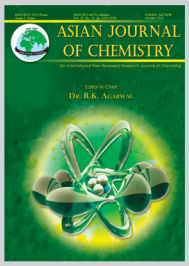
Asian Journal of Chemistry; Vol. 24, No. 6 (2012), 2651-2656

ASIAN JOURNAL OF CHEMISTRY

www.asianjournalofchemistry.co.in



Synthesis of Substituted Thiazolidinone Derivatives and Study on their Activity

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(*Received*: 14 June 2011; *Accepted*: 17 January 2012) AJC-10965

A series of S-glycosidic linkage bearing thiazolidinones have been prepared. The synthesized derivatives characterized by elemental and spectral analysis (IR, ^{1}H NMR and mass). Furthermore, compounds also evaluated to check their antimicrobial potency against selected panels of microbes. The most potent derivative also screened for its lethal dose.

Key Words: S-Glycosides, Triazoles, Thiazolidinones, Antibacterial, Antifungal, Lethal dose.

INTRODUCTION

The treatment of infectious diseases still remains an important and challenging problem because of a combination of factors including emerging infectious diseases and the increasing number of multi-drug resistant microbial pathogens with particular relevance for gram positive bacteria[1-5]. Substituted thiazolidinone derivatives have occupied a unique position in heterocyclic chemistry due to their biological activities. 4-Thiazolidinone ring system which is a core structure in various synthetic pharmaceuticals display a broad spectrum of biological activity, including antibacterial and antifungal properties[6-11]. On the other hand, a recent survey of novel small-molecule therapeutics revealed that the majority of them result from an analogue-based approach and that their market value represents two-thirds of all drug sales[12]. Several reports are available to clarify the biological utility[13-19] of 1,2,4 triazoles. Glycosides are well famed for their extensive existence in the animals as well as in plants and taken on an important biological function[20]. Many active ingredients in natural drugs belong to the class of glycosides. Since last decades, the glycosides attracted researchers for their significant antibacterial and anticancer activities to attempt to improve the biological activity of these compounds by the glycosylation in order to increase their solubility in water and guidance quality[21,22]. During past decades, a great deal of modified N-glycosides[23,24], C-glycosides[25,26] and S-glycosides have been emphasized[27] but only a few S-glycosides bearing 1,2,4-triazole have been reported. In view of this, we focused our attention to the synthesis of novel thiazolidinone possessing 1,2,4-triazoles, tetra-O-acetyl-α-D-glucopyanosyl bromide and S-glycosides to investigate their antibacterial and antifungal activities.

EXPERIMENTAL

All the chemicals used for the preparation of desired derivatives, were obtained from Sisco Research Laboratories (SRL), Mumbai, India, Qualigen Fine Chemicals, Mumbai, India; E. Merck Ltd., New Delhi, India. The melting point of the compounds was determined in open glass capillaries with the help of thermonic melting points apparatus (Campbell Electronics, Mumbai, India) and are uncorrected. The homogeneity of all the newly synthesized compounds were routinely checked by TLC on silica gel G plates and spots were located by using iodine chamber. Elemental analysis was performed in Heraeus CHN rapid analyzer. The results were found within the ± 0.4 % of theoretical values. Infrared spectra were recorded on KBr pellets on a Perkin Elmer system 2000 FTIR spectrometer and ^{1}H NMR spectra on Bruker DPX 200 using TMS as internal standard. Compound **1(a-g)** were prepared by reported methods in literature.

General method of synthesis of 3-Aryl-4-amino-5-mercapto triazoles 1(a-h): The starting triazoles were prepared according to the reported method[28-31].

General method of synthesis of 5-Aryl-4-{(1-phenylethylidene)amino}-3-thio-4*H*-1,2,4-triazole 2(a-h): Methanolic solution of 3-aryl-4-amino-5-mercapto triazoles (0.01 mol) and acetophenone (0.01 mol) was refluxed for 3-4 h. Excess of methanol was distilled off to get oily viscous

residue which was triturated with petroleum ether (40-60 ºC) to afford crude **2(a-h)**. Crude products was recrystallized with appropriate solvents.

2a: Yield 68 % (methanol), m.p. 188 ºC. IR (KBr, ν_{max}, cm^{-1}): 1620 (C…C of aromatic ring), 1602(SH), 1556 (C=N), 1520 (N-N), 1304 (C-N). ^1H NMR ($CDCl_3$, δ ppm): 12.70 (s, 1H, HS-), 6.70-7.89 (m, 10H, ArH), 1.60 (s, 3H, $-CH_3$). MS: $[M]^+$ 294.37 at m/z. Anal. calcd. (%) for $C_{16}H_{14}N_4S$: C, 65.28; H, 4.79; N, 19.03; found (%): C, 65.18; H, 4.75; N, 19.05.

2b: Yield 61 % (AcOH-water), m.p. 160 ºC. IR (KBr, ν_{max}, cm^{-1}): 1624 (C…C of aromatic ring), 1605 (SH), 1549 (C=N), 1525 (N-N), 1302 (C-N). ^1H NMR ($CDCl_3$, δ ppm): 12.78 (s, 1H, HS-), 10.40 (s, 1H, HO-), 6.56-7.70 (m, 9H, ArH), 1.56 (s, 3H, $-CH_3$). MS: $[M]^+$ 310.37 at m/z. Anal. calcd. (%) for $C_{16}H_{14}N_4OS$: C, 61.92; H, 4.55; N, 18.05; found (%): C, 61.98; H, 4.65; N, 18.00.

2c: Yield 66 % (AcOH-water), m.p. 210 ºC. IR (KBr, ν_{max}, cm^{-1}): 1620 (C…C of aromatic ring), 1600(SH), 1550 (C=N), 1520 (N-N), 1304 (C-N). ^1H NMR ($CDCl_3$, ν ppm): 12.70 (s, 1H, HS-), 10.36 (s, 1H, HO-), 6.61-7.78 (m, 9H, ArH), 1.48 (s, 3H,$-CH_3$). MS: $[M]^+$ 310.37 at m/z. Anal. calcd. (%) for $C_{16}H_{14}N_4OS$: C, 61.92; H, 4.55; N, 18.05; found (%): C, 62.00; H, 4.54; N, 18.04.

2d: Yield 60 % (AcOH-water), m.p. 133 ºC. IR (KBr, ν_{max}, cm^{-1}): 1620 (C…C of aromatic ring), 1601(SH), 1548 (C=N), 1522 (N-N), 1304 (C-N). ^1H NMR ($CDCl_3$, δ ppm): 12.73 (s, 1H, HS-), 10.45 (s, 1H, HO-), 6.55-7.83 (m, 9H, ArH), 1.52 (s, 3H, $-CH_3$). MS: $[M]^+$ 310.37 at m/z. Anal. calcd. (%) for $C_{16}H_{14}N_4OS$: C, 61.92; H, 4.55; N, 18.05; found (%): C, 61.90; H, 4.57; N, 18.08.

2e: Yield 59 % (ethanol), m.p. 186 ºC. IR (KBr, ν_{max}, cm^{-1}): 1620 (C…C of aromatic ring), 1604 (SH), 1550 (C=N), 1520 (N-N), 1302 (C-N), 1170 (C-O-C). ^1H NMR ($CDCl_3$, δ ppm): 12.70 (s, 1H, HS-), 6.70-7.89 (m, 9H, ArH), 4.10 (q, 2H, $-CH_2-$ CH_3), 2.02 (t, 3H, CH_2-CH_3), 1.60 (s, 3H, $-CH_3$). MS: $[M]^+$ 338.43 at m/z. Anal. calcd. (%) for $C_{18}H_{18}N_4OS$: C, 63.88; H, 5.36; N, 16.56; found (%): C, 63.90; H, 5.47; N, 16.58.

2f: Yield 64 % (ethanol), m.p. 192 ºC. IR (KBr, ν_{max}, cm^{-1}): 1620 (C…C of aromatic ring), 1599 (SH), 1555 (C=N), 1523 (N-N), 1304 (C-N), 1174 (C-O-C). ^1H NMR ($CDCl_3$, δ ppm): 12.74 (s, 1H, HS-), 6.56-7.70 (m, 9H, ArH), 4.15 (q, 2H, $-CH_2-CH_3$), 2.07 (t, 3H, CH_2-CH_3), 1.63 (s, 3H,$-CH_3$). MS: $[M]^+$ 338.43 at m/z. Anal. calcd. (%) for $C_{18}H_{18}N_4OS$: C, 63.88; H, 5.36; N, 16.56; found (%): C, 63.90; H, 5.47; N, 16.58.

2g: Yield 60 % (ethanol), m.p. 162 ºC. IR (KBr, ν_{max}, cm^{-1}): 1624 (C…C of aromatic ring), 1610 (SH), 1552 (C=N), 1525 (N-N), 1306 (C-N), 675 (C-Cl). ^1H NMR ($CDCl_3$, δ ppm): 12.79 (s, 1H, HS-), 7.89-6.60 (m, 9H, ArH), 1.62 (s, 3H, $-CH_3$). MS: $[M]^+$ 328.82 at m/z. Anal. calcd. (%) for $C_{16}H_{13}N_4SCl$: C, 58.44; H, 3.98; N, 17.04; found (%): C, 58.40; H, 3.97; N, 17.08.

2h: Yield 67 % (ethanol), m.p. 162 ºC. IR (KBr, ν_{max}, cm^{-1}): 1620 (C…C of aromatic ring), 1604 (SH), 1550 (C=N), 1522 (N-N), 1304 (C-N), 672 (C-Cl). ^1H NMR ($CDCl_3$, δ ppm): 12.68 (s, 1H, HS-), 7.84-6.62 (m, 9H, ArH), 1.56 (s, 3H, $-CH_3$). MS: $[M]^+$ 328.82 at m/z. Anal. calcd. (%) for $C_{16}H_{13}N_4SCl$: C, 58.44; H, 3.98; N, 17.04; found (%): C, 58.42; H, 3.95; N, 17.10.

General method of synthesis of 4-(4-acetoxymethyl-4-phenylethylidenyl)amino-5-aryl-3-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosylthio)-1,2,4-triazole 3(a-h): Compounds **2(a-h)** (0.01 mol) was dissolved in the solution of KOH (0.01 mol) in ethanol. The mixture was stirred at room temperature for 0.5 h. Compound of tetra-O-acetyl-α-D-glucopyanosyl bromide (1 mol) was then filtered and washed with water. The crude product was purified by column chromatography on silica gel with hexane and ethyl acetate as eluent to afford compounds **3(a-h)**.

3a: Yield 70 % (methanol), m.p. 199 ºC. IR (KBr, ν_{max}, cm^{-1}): 1624 (C…C of aromatic ring), 1560 (C=N), 1525 (N-N), 1307 (C-N). ^1H NMR ($CDCl_3$, δ ppm): 7.70-6.50 (m, 10H, ArH), 4.95-3.85 (m, 7H, 7 × H, glycosidic ring), 2.15-1.96 (s, 12H, 4 × 3H, $CH_3C=O$), 1.67 (d, 2H, CH_2-$OCOCH_3$), 1.45 (s, 3H, $-CH_3$). MS: $[M]^+$ 622.69 at m/z. Anal. calcd. (%) for $C_{31}H_{34}N_4O_8S$: C, 59.79; H, 5.50; N, 9.00; found (%): C, 59.88; H, 5.55; N, 9.15.

3b: Yield 61 % (methanol), m.p. 159 ºC. IR (KBr, ν_{max}, cm^{-1}): 1620 (C…C of aromatic ring), 1553 (C=N), 1522 (N-N), 1304 (C-N). ^1H NMR ($CDCl_3$, δ ppm): 10.50(s, 1H, HO-), 7.75-6.57 (m, 9H, ArH), 5.00-4.05 (m, 7H, 7 × H, glycosidic ring), 2.18-1.91 (s, 12H, 4 × 3H, $CH_3C=O$), 1.62 (d, 2H, CH_2-$OCOCH_3$), 1.42 (s, 3H, $-CH_3$). MS: $[M]^+$ 638.69 at m/z. Anal. calcd. (%) for $C_{31}H_{34}N_4O_9S$: C, 58.30; H, 5.37; N, 8.77; found (%): C, 58.40; H, 5.50; N, 8.74.

3c: Yield 68 % (methanol), m.p. 145 ºC. IR (KBr, ν_{max}, cm^{-1}): 1620 (C…C of aromatic ring), 1556 (C=N), 1526 (N-N), 1305 (C-N). ^1H NMR ($CDCl_3$, δ ppm): 10.54(s, 1H, HO-), 7.79-6.58 (m, 9H, ArH), 5.00-4.12 (m, 7H, 7 × H, glycosidic ring), 2.10-1.89 (s, 12H, 4 × 3H, $CH_3C=O$), 1.60 (d, 2H, CH_2-$OCOCH_3$), 1.39 (s, 3H, $-CH_3$). MS: $[M]^+$ 638.69 at m/z. Anal. calcd. (%) for $C_{31}H_{34}N_4O_9S$: C, 58.30; H, 5.37; N, 8.77; found (%): C, 58.35; H, 5.39; N, 8.71.

3d: Yield 64 % (methanol), m.p. 139 ºC. IR (KBr, ν_{max}, cm^{-1}): 1620 (C…C of aromatic ring), 1549 (C=N), 1524 (N-N), 1309 (C-N). ^1H NMR ($CDCl_3$, δ ppm): 10.50(s, 1H, HO-), 7.80-6.60 (m, 9H, ArH), 5.05-4.10 (m, 7H, 7 × H, glycosidic ring), 2.08-1.90 (s, 12H, 4 × 3H, $CH_3C=O$), 1.68 (d, 2H, CH_2-$OCOCH_3$), 1.34 (s, 3H, $-CH_3$). MS: $[M]^+$ 638.69 at m/z. Anal. calcd. (%) for $C_{31}H_{34}N_4O_9S$: C, 58.30; H, 5.37; N, 8.77; found (%): C, 58.44; H, 5.40; N, 8.79.

3e: Yield 59 % (methanol), m.p. 162 ºC. IR (KBr, ν_{max}, cm^{-1}): 1620 (C…C of aromatic ring), 1548 (C=N), 1525 (N-N), 1306 (C-N), 1173 (C-O-C). ^1H NMR ($CDCl_3$, δ ppm): 7.80-6.59 (m, 9H, ArH), 4.98-4.02 (m, 7H, 7 × H, glycosidic ring), 3.86 (q, 2H, $-CH_2-CH_3$), 2.72 (t, 3H, CH_2-CH_3), 2.20-1.92 (s, 12H, 4 × 3H, $CH_3C=O$), 1.66 (d, 2H, CH_2-$OCOCH_3$), 1.30 (s, 3H, $-CH_3$). MS: $[M]^+$ 666.74 at m/z. Anal. calcd. (%) for $C_{33}H_{38}N_4O_9S$: C, 59.45; H, 5.74; N, 8.40; found (%): C, 59.50; H, 5.77; N, 8.51.

3f: Yield 56 % (methanol), m.p. 190 ºC. IR (KBr, ν_{max}, cm^{-1}): 1620 (C…C of aromatic ring), 1550 (C=N), 1520 (N-N), 1304 (C-N). ^1H NMR ($CDCl_3$, δ ppm): 7.73-6.52 (m, 9H, ArH), 4.93-4.00 (m, 7H, 7 × H, glycosidic ring), 3.80 (q, 2H,$-CH_2-CH_3$), 2.68 (t, 3H, CH_2-CH_3), 2.18-1.86 (s, 12H, 4 × 3H, $CH_3C=O$), 1.60 (d, 2H, CH_2-$OCOCH_3$), 1.27 (s, 3H, $-CH_3$). MS: $[M]^+$ 666.74 at m/z. Anal. calcd. (%) for $C_{33}H_{38}N_4O_9S$: C, 59.45; H, 5.74; N, 8.40; found (%): C, 59.44; H, 5.71; N, 8.43.

3g: Yield 51 % (methanol), m.p. 158 ºC. IR (KBr, ν_{max}, cm^{-1}): 1624 (C…C of aromatic ring), 1553 (C=N), 1522 (N-N), 1306 (C-N), 670 (C-Cl). ^1H NMR ($CDCl_3$, δ ppm): 7.86-6.66 (m, 9H, ArH), 5.00-4.10 (m, 7H, 7 × H, glycosidic ring), 3.72 (q, 2H, $-CH_2-CH_3$), 2.73 (t, 3H, CH_2-CH_3), 2.20-1.81 (s, 12H, 4 × 3H, $C_H3C=O$), 1.52 (d, 2H, $CH_2-OCOCH_3$), 1.29 (s, 3H, $-CH_3$). MS: $[M]^+$ 657.13 at m/z. Anal. calcd. (%) for $C_{31}H_{33}N_4O_8SCl$: C, 56.66; H, 5.06; N, 8.53; found (%): C, 56.62; H, 5.07; N, 8.58.

3h: Yield 54 % (methanol), m.p. 181 ºC. IR (KBr, ν_{max}, cm^{-1}): 1621 (C…C of aromatic ring), 1550 (C=N), 1519 (N-N), 1301 (C-N), 673(C-Cl). ^1H NMR ($CDCl_3$, δ ppm): 7.92-6.74 (m, 9H, ArH), 4.93-4.00 (m, 7H, 7 × H, glycosidic ring), 2.18-1.80 (s, 12H, 4 × 3H, $CH_3C=O$), 1.55 (d, 2H, $CH_2-OCOCH_3$), 1.23 (s, 3H, $-CH_3$). MS: $[M]^+$ 657.13 at m/z. Anal. calcd. (%) for $C_{31}H_{33}N_4O_8SCl$: C, 56.66; H, 5.06; N, 8.53; found (%): C, 56.63; H, 5.06; N, 8.51.

General procedure for preparation of [{5-Aryl-3-(2, 3, 4, 6-tetra-O-acetyl-β-D-gluco- pyranosylthio)-1,2,4-triazolo}-3-(2-methyl-2-phenyl)]thiazolidin-4-one 4(a-h): A solution of compound **3(a-h)** (0.01 mol) and anhydrous $ZnCl_2$ in dry benzene (50 mL), thioglycolic acid (0.02 mol) was added dropwise with stirring at ambient temperature and the reaction mixture was refluxed for 6-10 h. The reaction mixture was cooled and poured on crushed ice. The crude product was purified by column chromatography on silica gel with hexane and ethyl acetate as eluent to afford compounds **4(a-h)**.

4a: Yield 55 % (methanol), m.p. 123 ºC. IR (KBr, ν_{max}, cm^{-1}): 1625 (C…C of aromatic ring), 1551 (C=N), 1522 (N-N), 1302 (C-N), 715 (C-S-C). ^1H NMR ($CDCl_3$, δ ppm): 7.78-6.56 (m, 10H, ArH), 4.99-3.95 (m, 7H, 7 × H, glycosidic ring), 3.50 (d, 2H, $NH-CH_2$), 2.25-1.99 (s, 12H, 4 × 3H, $CH_3C=O$), 1.62 (d, 2H, $CH_2-OCOCH_3$), 1.45 (s, 3H, $-CH_3$). MS: $[M]^+$ 698.76 at m/z. Anal. calcd. (%) for $C_{32}H_{34}N_4O_{10}S_2$: C, 55.00; H, 4.90; N, 8.02; found (%): C, 55.14; H, 4.93; N, 8.00.

4b: Yield 54 % (DMF-water), m.p. 146 ºC. IR (KBr, ν_{max}, cm^{-1}): 1621 (C…C of aromatic ring), 1554 (C=N), 1520 (N-N), 1304 (C-N), 718 (C-S-C). ^1H NMR ($CDCl_3$, δ ppm): 10.45 (s, 1H, HO-), 7.80-6.70 (m, 9H, ArH), 4.90-4.02 (m, 7H, 7 × H, glycosidic ring), 3.45 (d, 2H, $N-CH_2$), 2.15-1.93 (s, 12H, 4 × 3H, $CH_3C=O$), 1.60(d, 2H, $CH_2-OCOCH_3$), 1.36 (s, 3H,$-CH_3$). MS: $[M]^+$ 714.76 at m/z. Anal. calcd. (%) for $C_{32}H_{34}N_4O_{11}S_2$: C, 53.77; H, 4.79; N, 7.84; found (%): C, 53.54; H, 4.73; N, 8.00.

4c: Yield 52 % (DMF-water), m.p. 134 ºC. IR (KBr, ν_{max}, cm^{-1}): 1624 (C…C of aromatic ring), 1553 (C=N), 1522 (N-N), 1304 (C-N). ^1H NMR ($CDCl_3$, δ ppm): 10.50(s, 1H, HO-), 7.75-6.57 (m, 9H, ArH), 5.00-4.05 (m, 7H, 7 × H, glycosidic ring), 2.18-1.91 (s, 12H, 4 × 3H, $CH_3C=O$), 1.62 (d, 2H, $CH_2-OCOCH_3$), 1.42 (s, 3H, $-CH_3$). MS: $[M]^+$ 714.76 at m/z. Anal. calcd. (%) for $C_{33}H_{34}N_4O_{11}S_2$: C, 53.77; H, 4.79; N, 7.84; found (%): C, 53.70; H, 4.70; N, 7.80.

4d: Yield 50 % (DMF-water), m.p. 165 ºC. IR (KBr, ν_{max}, cm^{-1}): 1620 (C…C of aromatic ring), 1549 (C=N), 1524 (N-N), 1309 (C-N). ^1H NMR ($CDCl_3$, δ ppm): 10.50(s, 1H, HO-), 7.80-6.60 (m, 9H, ArH), 5.05-4.10 (m, 7H, 7 × H, glycosidic ring), 2.08-1.90 (s, 12H, 4 × 3H, $CH_3C=O$), 1.68 (d, 2H, $CH_2-OCOCH_3$), 1.34 (s, 3H, $-CH_3$). MS: $[M]^+$ 714.76 at m/z. Anal. calcd. (%) for $C_{33}H_{34}N_4O_{11}S_2$: C, 53.77; H, 4.79; N, 7.84; found (%): C, 53.75; H, 4.74; N, 7.83.

4e: Yield 58 % (ethanol), m.p. 194 ºC. IR (KBr, ν_{max}, cm^{-1}): 1625 (C…C of aromatic ring), 1548 (C=N), 1525 (N-N), 1306 (C-N), 1173 (C-O-C). ^1H NMR ($CDCl_3$, δ ppm): 7.80-6.59 (m, 9H, ArH), 4.98-4.02 (m, 7H, 7 × H, glycosidic ring), 3.86 (q, 2H, $-CH_2-CH_3$), 2.72 (t, 3H, CH_2-CH_3), 2.20-1.92 (s, 12H, 4 × 3H, $CH_3C=O$), 1.66 (d, 2H, $CH_2-OCOCH_3$), 1.30 (s, 3H, $-CH_3$). MS: $[M]^+$ 742.82 at m/z. Anal. calcd. (%) for $C_{34}H_{38}N_4O_{11}S_2$: C, 54.98; H, 5.16; N, 7.54; found (%): C, 54.95; H, 5.23; N, 7.51.

4f: Yield 57 % (ethanol), m.p. 212 ºC. IR (KBr, ν_{max}, cm^{-1}): 1619 (C…C of aromatic ring), 1550 (C=N), 1520 (N-N), 1304 (C-N). ^1H NMR ($CDCl_3$, δ ppm): 7.72-6.50 (m, 9H, ArH), 4.93-4.00 (m, 7H, 7 × H, glycosidic ring), 3.83(q, 2H, $-CH_2-CH_3$), 2.72 (t, 3H, CH_2-CH_3), 2.18-1.86 (s, 12H, 4 × 3H, $CH_3C=O$), 1.60 (d, 2H, $CH_2-OCOCH_3$), 1.27 (s, 3H, $-CH_3$). MS: $[M]^+$ 740.84 at m/z. Anal. calcd. (%) for $C_{34}H_{38}N_4O_{11}S_2$: C, 54.98; H, 5.16; N, 7.54; found (%): C, 54.90; H, 5.20; N, 7.55.

4g: Yield 53 %; (AcOH-water), m.p. 205 ºC. IR (KBr, ν_{max}, cm^{-1}): 1624 (C…C of aromatic ring), 1553 (C=N), 1522 (N-N), 1306 (C-N), 670(C-Cl). ^1H NMR ($CDCl_3$, δ ppm): 7.77-6.54 (m, 9H, ArH), 4.98-4.02 (m, 7H, 7 × H, glycosidic ring), 2.24-1.92 (s, 12H, 4 × 3H, $CH_3C=O$), 1.61 (d, 2H, $CH_2-OCOCH_3$), 1.24 (s, 3H, $-CH_3$). MS: $[M]^+$ 733.21 at m/z. Anal. calcd. (%) for $C_{32}H_{33}N_4O_{10}S_2Cl$: C, 52.42; H, 4.54; N, 7.64; found (%): C, 54.39; H, 4.55; N, 7.59.

4h: Yield 50 % (AcOH-water),mp 175 0C. IR (KBr, ν_{max}, cm^{-1}): 1621 (C…C of aromatic ring), 1550 (C=N), 1519 (N-N), 1301 (C-N), 673(C-Cl). ^1H NMR ($CDCl_3$, δ ppm): 7.86-6.66 (m, 9H, ArH), 5.00-4.10 (m, 7H, 7 × H, glycosidic ring), 2.20-1.81 (s, 12H, 4 × 3H, $CH_3C=O$), 1.52(d, 2H, $CH_2-OCOCH_3$), 1.29 (s, 3H, $-CH_3$). MS: $[M]^+$ 731.24 at m/z. Anal. calcd. (%) for $C_{32}H_{33}N_4O_{10}S_2Cl$: C, 52.42; H, 4.54; N, 7.64; found (%): C, 54.40; H, 4.59; N, 7.60.

General procedure for preparation of [{5-Aryl-3-(β-D-glucopyranosylthio)-1,2,4-triazolo}-3-(2-methyl-2-phenyl)]thiazolidin-4-one 5(a-h): Compounds **4(a-h)** (0.2 mmol) was added to NaOMe (5.0 mol) in methanol and stirred at room temperature for 1-3 h. The solution was concentrated and the crude product was purified by recrystallization with appropriate solvents.

5a: Yield 50 % (ethanol), m.p. 206 ºC. IR (KBr, ν_{max}, cm^{-1}): 1625 (C…C of aromatic ring), 1556 (C=N), 1527 (N-N), 1308 (C-N), 713 (C-S-C). ^1H NMR ($CDCl_3$, δ ppm): 7.84-6.60 (m, 10H, ArH), 4.90-4.02 (m, 7H, 7×H, glycosidic ring), 3.65-3.45 (s, 4H, 4X H, OH), 2.40 (s, 2H, $S-CH_2$), 1.42 (s, 3H, $-CH_3$). MS: $[M]^+$ at m/z. Anal. calcd. (%) for $C_{24}H_{26}N_4O_6S_2$: calcd. (%) C: 54.32; H: 4.94; N: 10.56; found (%) C: 54.30; H: 4.95; N: 10.59. MS: $[M]^+$ at m/z 530.62.

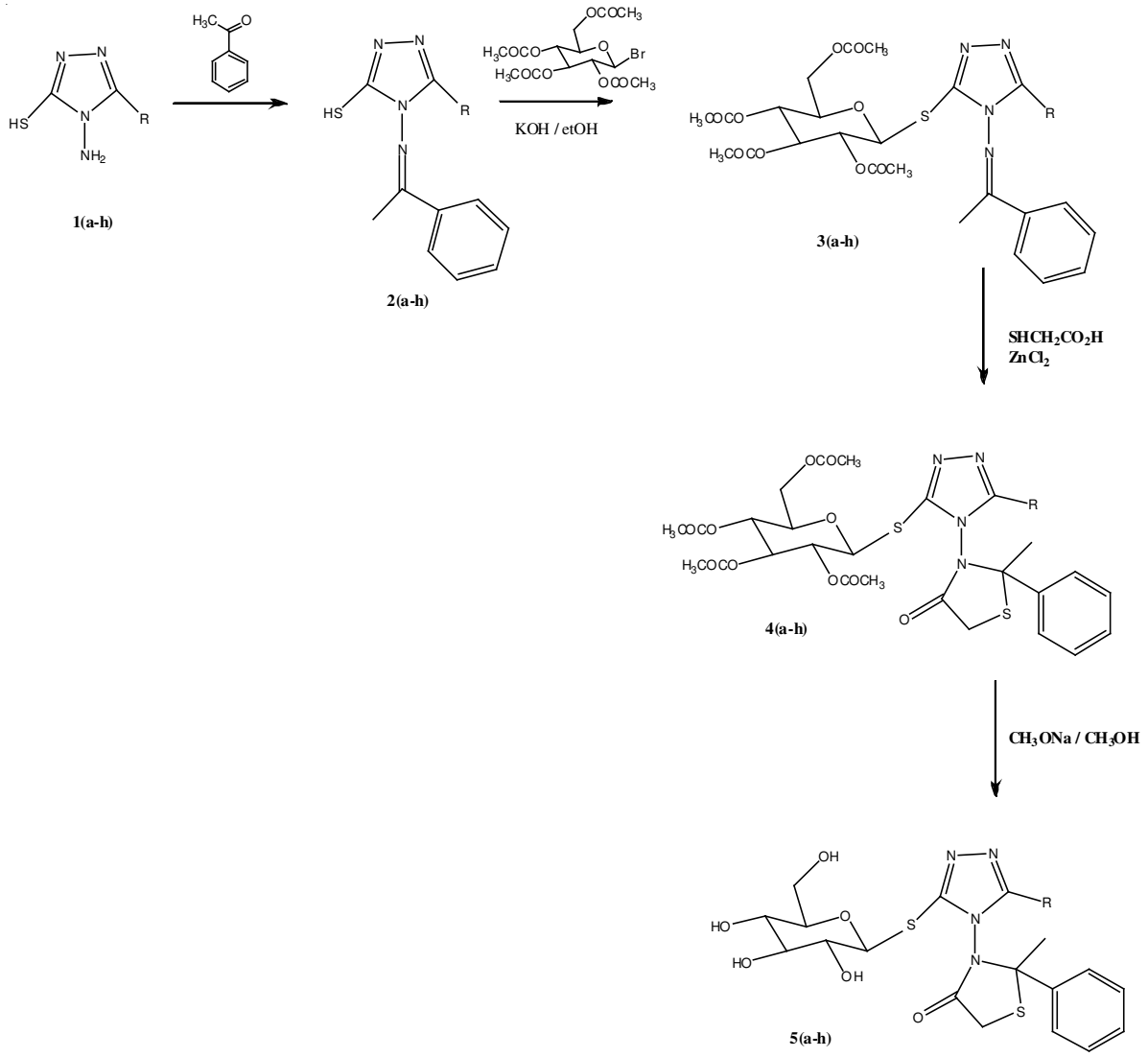
5b: Yield 48 % (DMF-water), m.p. 146 ºC. IR (KBr, ν_{max}, cm^{-1}): 1621 (C…C of aromatic ring), 1554 (C=N), 1520 (N-N), 1304 (C-N), 718 (C-S-C). ^1H NMR ($CDCl_3$, δ ppm): 10.45 (s, 1H, HO-), 7.80-6.70 (m, 9H, ArH), 4.90-4.02 (m, 7H, 7 × H, glycosidic ring), 3.65-3.45 (s, 4H, 4X H, OH), 2.42 (s, 2H, $S-CH_2$), 1.36 (s, 3H, $-CH_3$). MS: $[M]^+$ 546.62 at m/z. Anal. calcd. (%) for $C_{24}H_{26}N_4O_7S_2$: C, 52.73; H, 4.79; N, 10.25; found (%): C: 52.70; H: 4.80; N: 10.29.

5c: Yield 45 % (DMF-H_2O), m.p. 176 ºC. IR (KBr, ν_{max}, cm^{-1}): 1621 (C…C of aromatic ring), 1554 (C=N), 1520 (N-N), 1304 (C-N), 718 (C-S-C). ^1H NMR ($CDCl_3$, δ ppm): 10.50 (s, 1H, HO-),7.85-6.73 (m, 9H, ArH), 4.87-4.00 (m, 7H, 7 × H, glycosidic ring), 3.65-3.45 (s, 4H, 4X H, OH), 2.48 (s, 2H, S-CH_2), 1.30 (s, 3H, -CH_3). MS: $[M]^+$ 546.62 at m/z. Anal. calcd. (%) for $C_{24}H_{26}N_4O_7S_2$: C, 52.73; H, 4.79; N, 10.25; found (%): C: 52.70; H: 4.80; N: 10.29.

5d: Yield 41 % (DMF-H_2O), m.p. 145 ºC. IR (KBr, ν_{max}, cm^{-1}): 1623 (C…C of aromatic ring), 1552 (C=N), 1521 (N-N), 1303 (C-N), 716 (C-S-C). 1H NMR ($CDCl_3$, δ ppm): 10.54 (s, 1H, HO-),7.82-6.71 (m, 9H, ArH), 4.86-4.04 (m, 7H, 7 × H, glycosidic ring), 3.61-3.42 (s, 4H, 4X H, OH), 2.48 (s, 2H, S-CH_2), 1.36 (s, 3H, -CH_3). MS: $[M]^+$ 546.62 at m/z. Anal. calcd. (%) for $C_{24}H_{26}N_4O_7S_2$: C, 52.73; H, 4.79; N, 10.25; found (%): C: 52.70; H: 4.79; N: 10.25.

5e: Yield 49 % (ethanol), m.p. 196 ºC. IR (KBr, ν_{max}, cm^{-1}): 1625 (C…C of aromatic ring), 1548 (C=N), 1525 (N-N), 1306 (C-N), 1175 (C-O-C), 676 (C-S-C). ^1H NMR ($CDCl_3$, δ ppm): 7.80-6.59 (m, 9H, ArH), 4.98-4.05 (m, 7H, 7 × H, glycosidic ring), 3.86 (q, 2H, -CH_2-CH_3), 3.60-3.40 (s, 4H, 4X H, OH), 2.70 (t, 3H, CH_2-CH_3), 2.50 (s, 2H, S-CH_2), 1.30 (s, 3H, -CH_3). MS: $[M]^+$ 574.67 at m/z. Anal. calcd. (%) for $C_{26}H_{30}N_4O_7S_2$: C, 54.34; H, 5.26; N, 9.75; found (%): C, 54.40; H, 5.22; N, 9.73.

5f: Yield 44 % (ethanol), m.p. 184 ºC. IR (KBr, ν_{max}, cm^{-1}): 1622 (C…C of aromatic ring), 1544 (C=N), 1524 (N-N), 1304 (C-N), 1173 (C-O-C), 676(C-S-C). ^1H NMR ($CDCl_3$, δ ppm): 7.85-6.63 (m, 9H, ArH), 5.00-4.10 (m, 7H, 7 × H, glycosidic ring), 3.89 (q, 2H, -CH_2-CH_3), 3.58-3.30 (s, 4H, 4X H, OH), 2.75(t, 3H, CH_2-CH_3), 2.41 (s, 2H, S-CH_2), 1.35 (s, 3H, -CH_3). MS: $[M]^+$ 574.67 at m/z. Anal. calcd. (%) for $C_{26}H_{30}N_4O_7S_2$:



Ar = C_6H_5, 2-OH.C_6H_4, 3-OH.C_6H_4, 4-O H.C_6H_4, 4-C_2H_5O.C_6H_4, 2-C_2H_5O.C_6H_4, 2-Cl.C_6H_4, 4-Cl.C_6H_4

Scheme-I

TABLE-1
ANTIBACTERIAL AND ANTIFUNGAL DATA FOR THE SYNTHESIZED COMPOUNDS

	Antibacterial activity data (mm)				Antifungal activity data (mm)			
Compound No.	*S. aureus*	*E.coli*	*K. pneumoniae*	*P. vulgaris*	*A. fumigatus*	*C. glabrata*	*C. albacans*	*C. krusei*
4a	4	4	–	–	–	5	6	5
4b	8	8	6	–	–	–	7	7
4c	4	–	–	–	–	–	–	5
4d	6	8	8	6	–	–	6	–
4e	8	–	–	–	–	8	–	–
4f	–	8	8	–	10	5	6	–
4g	–	12	6	8	8	8	8	8
4h	8	10	–	6	8	6	6	–
5a	6	6	–	–	–	6	–	–
5b	8	6	8	–	–	8	8	8
5c	10	8	10	8	10	11	6	8
5d	12	14	18	16	16	10	12	–
5e	12	10	14	10	14	12	15	6
5f	14	10	14	16	12	10	8	8
5g	18	22	24	26	18	16	12	16
5h	16	20	22	18	14	12	10	12
Ampicillin trihydrate	16	20	20	20	–	–	–	–
Fluconazole (std.)	–	–	–	–	20	15	16	15
DMF (control)	–	–	–	–	–	–	–	–

–: Means no activity.

C, 54.34; H, 5.26; N, 9.75; found (%): C, 54.45; H, 5.23; N, 9.71.

5g: Yield 40 %; (AcOH-water), m.p. 175 ºC. IR (KBr, ν_{max}, cm^{-1}): 1624 (C…C of aromatic ring), 1553 (C=N), 1522 (N-N), 1306 (C-N), 670(C-Cl). 1H NMR ($CDCl_3$, δ ppm): 7.77-6.54 (m, 9H, ArH), 4.98-4.02 (m, 7H, 7×H, glycosidic ring), 3.56-3.31 (s, 4H, 4X H, OH), 2.40 (s, 2H, S-CH_2), 1.32 (s, 3H, -CH_3). MS: $[M]^+$ 565.06 at m/z. Anal. calcd. (%) for $C_{24}H_{25}ClN_4S_2O_6$: C, 51.01; H, 4.46; N, 9.92; found (%): C, 51.09; H, 4.50; N, 9.99.

5h: Yield 43 %; (AcOH-water), m.p. 163 ºC. IR (KBr, ν_{max}, cm^{-1}): 1625 (C…C of aromatic ring), 1554 (C=N), 1524 (N-N), 1304 (C-N), 672 (C-Cl). ^{1}H NMR ($CDCl_3$, δ ppm): 7.80-6.60 (m, 9H, ArH), 4.97-4.00 (m, 7H, 7 × H, glycosidic ring), 3.62-3.19 (s, 4H, 4X H, OH), 2.35 (s, 2H, S-CH_2), 1.38 (s, 3H, -CH_3). MS: $[M]^+$ 565.06 at m/z. Anal. calcd. (%) for $C_{24}H_{25}ClN_4S_2O_6$: C, 51.01; H, 4.46; N, 9.92; found (%): C, 51.02; H, 4.45; N, 9.92.

RESULTS AND DISCUSSION

The synthetic route for the synthesis is outlined in **Scheme-I**. Reaction of 3-aryl-4-amino-5-mercapto triazoles **1(a-h)** with acetophenone afforded 5-aryl-4-{(1-phenylethylidene)amino}-3-thio-4*H*-1,2,4-triazole **2(a-h)** which undergo glycosylation in ethanolic-KOH yielded 4-(4-acetoxymethyl-4-phenylethylidenyl)amino-5-aryl-3-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl-thio)-1,2,4-triazole **3(a-h)**. Reaction of thioglycolic acid with compounds **3(a-h)** in presence of anhydrous zinc chloride resulted into thiazolidinone derivatives *i.e.*, [{5-aryl-3-(2, 3, 4, 6-tetra-O-acetyl-β-D-glucopyranosylthio)-1,2,4-triazolo}-3-(2-methyl-2-phenyl)]-thiazolidin-4-one **4(a-h)**. Deprotection of hydroxyl gp. of **4(a-h)**, carried out by means of sodium methoxide, yielded [{5-aryl-3-(β-D-glucopyranosylthio)-1,2,4-triazolo}-3-(2-methyl-2-phenyl)]thiazolidin-4-one **5(a-h)**.

Antimicrobial tests: Preliminary antimicrobial susceptibility test for the newly synthesized compounds were screened for their antibacterial and antifungal activity. Disk diffusion method[32,33] was used for determination of the preliminary antibacterial activity. Ampicillin trihydrate and fluconazole were used as standard drugs. On the other hand, the newly prepared compounds were screened for their *in vitro* antifungal activity by the serial plate dilution method[34,35]. The inhibitory values of the tested compounds against the tested bacterial and fungal strains were recorded in mm (Table-1).

Acute toxicity: Lethal doses (LD_{50}) of compounds were determined in albino mice. After 24 h of drug administration, mortality in each group was observed and from the data obtained LD_{50} was calculated by the method of Carrol[32]. Data revealed that compound **5g** does not show any toxicity up to dose of 9.25 mg/kg body weight in mice.

Conclusion

Hence, it is cleared from the study of biological activity data that the incorporation of thiazolidinone ring enhance antifungal and antibacterial activities. Presence of chloro group as substituent brought remarkable increase in biological activities. Compound **5g** was the most potent compound with lesser amount of toxicity.

ACKNOWLEDGEMENTS

The authors are thankful for SAIF, Punjab University, India for spectral, elemental analysis and L.L.R.M. Medical College, India for biological activities.

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