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Microwave Assisted Synthesis of S-Glycosides Containing 1,5 – Benzodiazepines

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Abstract: *2-(4'-mercapto-3'-nitrophenyl)-4-(aryl/hetero aryl)-1H-1,5-benzodiazepines 2a-j were synthesized by condensation of O-Phenylenediamine with substituted propane1,3-diones using silica as solid support under microwave irradiation. A number of their S-glycosides derivatives 3-4 a-j were synthesized with different α-acetobromo sugars in presence of K_2CO_3 and acetone under microwave condition. On further deacetylation of peracetate glycosides produce glucosyl-, and galactosyl-, containing 1,5 benzodiazepine derivatives 5-6 a-j. these compounds were evaluated for biological activity.*

Keywords: *β-diketones; 1, 5-benzodiazepine; Solid support, Microwave, Thio-Glycosides.*

1. INTRODUCTION

Carbohydrate containing compounds have gained much attention in the last years because of the saccaride parts of glucolipids, glycoprotein and other glycoconjugates as they are responsible for their function in various biological processes i.e. cell growth regulation, cell differentiation, immunological response, metastasis inflation and bacterial infection [1-6].

Thio- sugars has been investigated as new therapeutics for biological interest because of their ability to act as enzyme inhibitors [7].Thus, thio sugar based drug designing prompt the synthetic and medicinal chemists to develop the new bioactive molecule for carbohydrate drug design [8 , 9] . In recent reports revealed that the thio glycoside shows active therapeutics against infectious disease and cancers [10] . The therapeutic nature of Thio sugar has been investigated as antagonist activity [11, 12] and inhibitors of protein glycosylation [13]

Benzodiazepines are an important class of biologically active molecule [14,15] attract attention of medicinal chemists due to widely used as anticonvulsant [16] antipsychotic [17], and anti-inflammatory agent [18,19] have been reported.

Microwave irradiation of organic reactions has rapidly gained in popularity as it accelerates a variety of synthetic transformations. The microwave-enhanced procedures with or without the use of catalyst are particularly eco-friendly and the protocol has the advantages of short reaction time and high yield. [20-25]

While the diverse chemical space accessible by O-glycosides contributes to a remarkably vast array of biological functions and in continuation of our laboratory's previous work [26,27] aimed at introduction of carbohydrate moieties into biologically versatile rings to improve their pharmacological activity. We report here the synthesis of a new series of S-glycosides based 1,5-benzodiazepines in which is glycosidic used as a carrier for the benzodiazepine ring moiety under microwave irradiation.

2. METHODS

2.1. Silica Supported Microwave Assisted Synthesis of 1, 5- Benzodiazepine

3 mmol of a substituted β- diketone and 3.2 mmol of *O*-phenylenediamine were mixed along with few drops of ethanol to form a homogenous paste. Approx 1g of finely powdered SiO_2, and a drop of

glacial acetic acid was added to the above paste and mixed thoroughly to homogenize. The reaction mixture was placed in a closed pyrax vessel and excess of ethanol (if any) was allowed to evaporate and closed it. The reaction mixture was then irradiated in microwave to obtain the product in high yield. Progress of the reaction was monitored by using TLC strips.

The microwave assisted synthesis reduces the timing of the reaction and gives the high quality of yield comparable to the conventional method. (**Table 2**)

2.2. Synthesis of Thio-(Tetra-O-Acetyl Gluco/Galacto Pyranosyl) Containing 1,5-Benzodiaze-Pine

2-(4'- Mercapto 3'-nitro phenyl)-4-(phenyl) 1H- 1, 5-benzodiazepine **2a** (1mol) and potassium carbonate (0.5mol) α-acetobromo sugars(gluco/galacto) (0.55mol) in dry acetone (5 ml) in a closed pyrax vessel was irradiated by MW for 2.5 to 4 min. The reaction mixture was cooled and then it was filtered off and washed the reaction mixture with dry acetone , collected the filtrate was concentrate under reduced pressure The resulting brown syrup was dissolved in methanol: chloroform (5:15) and chromatographed on 60-120 mesh silica gel eluting with 10% methanol in chloroform to obtained title compound. A brown syrupy 2-[3'-Nitro 4'-thio-(tetra –*O*- acetyl- β-D- glucopyranosyl) phenyl]-4 – phenyl-1H – 1,5 benzodiazepines was obtained 2.5 g 80% . The compound was optically active and specific rotation $[\alpha]^{30}_{D}$ methanol was found to be -5.66. Comparable study of the conventional and MW-assisted synthesis of Thio-(tetra-*O*-acetyl glucopyranosyl) containing benzodiazepine are given in **Table 3.**

2.3. Synthesis of Thiosugar Containing 1,5- Benzodiazepine

2-[3'-Nitro 4'-thio-(*β*-D- gluco pyranosyl) phenyl)-4 - phenyl 1*H* - 1,5 benzodiazepines. Deacetylation of 2-[3'-Nitro 4'-thio-(2",3",4",6"- tetra-O- acetyl-*β*-D- gluco/ galacto pyranosyl) phenyl] -4 - (phenyl) 1*H* – 1,5 benzodiazepines (0.109 mmols)have been achieved through, by taking acetylated compound in absolute methanol(4mL) and anhydrous zinc acetate (0.126 mmols)was refluxed for 7 hr. The reaction mixture was cooled down to room temperature and filtered through cation exchange resin; the solvent was removed under vaccum. The residue was purified by silica gel chromatography (CH_2Cl_2 :MeOH 10:2 v/v) to get the brown coloured semisolid. The spectral data of various compounds are given below. The reaction mixture was neutralized with ion -exchange resin (Amberlite IR-120, SD Fine H^+ form) filtered and concentrated in vaccu to afford viscous 2-[3'-Nitro 4'-S-(β-D- glucopyranosyl) thio phenyl)-4 – phenyl- 1*H* – 1,5 benzodiazepine as solid yield . The compound was found to be optically active and its specific rotation in methanol was given with analysis data .

2.4. Pharmacology: Antimicrobial Activity

Microbial strains used were *Staphyloccocus aureus* (ATCC 25923), *Bacillus subtilis* (ATCC 6633), *Escherechia coli* (ATCC 25922), *Pseudonomas aeruginosa* (ATCC 27853) standard drug used in study, Gentamycin, and Fluconazole (Matrix, Sinnar), were used after proper authentication.

2.4.1. In-Vitro Antibacterial Activity

Synthesized compounds were screened for their *in-vitro* antimicrobial activity against the standard strains (mentioned above). The cultures were obtained in *Mueller–Hinton Broth* (Difco) for all the bacteria after 18–24 h of incubation at 37± 1°C. Testing was carried out in *Mueller–Hinton Broth* at pH 7.4 and two fold dilution technique was applied. A set of tubes containing only inoculated broth was kept as negative controls. Gentamycin was used as positive control. In order to evaluate antibacterial activity compounds, minimum inhibitory concentrations (MICs) were determined. After incubation for 18–24 h at 37±1 °C, the last tube with no growth of microorganism was considered to represent MIC expressed in μg/mL. After incubation for 18–24 h at 37±1 °C, the last tube with no growth of microorganism was considered to represent MIC expressed in μg/mL.

2.4.2. In-Vitro Anti-Fungal Assay

The yeasts were maintained in *Sabouraud Dextrose Broth* after incubation for 48 h at 25 ±1 °C. Testing was performed in *Sabouraud Dextrose Broth* at pH 7.4 and the two fold dilution technique was applied. A set of tubes containing only inoculated broth was kept as controls. After incubation for 48 h at 25 ±1 °C, the last tube with no growth of yeast was recorded to represent MIC expressed in μg/mL. Fluconazole was used as standard antifungal drug.

The antibacterial and antifungal activity data are given in **Table 1.**

3. RESULT AND DISCUSSION

3.1. Physical Measurements

All the starting compounds (Alfa-Asser Comp.) were used in synthetic process. Melting points were determined through open capillary tube were uncorrected. FT-IR spectra were recorded on Perkin-Elmer spectrum Rx-I spectrophotometer. Bruker II-400 NMR spectrophotometer (^{1}H-400MHz,and ^{13}C 100MHz) were used for ^{1}H and ^{13}C NMR spectra in which TMS has been used as internal standard in DMSO and $CDCl_3$ .The chemical shift (δ) were measured in ppm. Mass spectra were determined by using Hitachi Perkin –Elmer RMU 6D mass spectrometer. Elemental analyses were carried out by using Perkin-Elmer 2400CHN analyzer. We have used laboratory Microwave Organic Reactor model CEM- 908010 Max Power Level 300 watts for our synthesis purpose.

3.1.1. Microwave Assisted Synthesis of 1, 5- Benzodiazepine

2-(4'-Mercapto-3'-Nitro Phenyl)-4-(Phenyl)-1*H*-1, 5-Benzodiazepine (2a): mp128^{0}C IR(KBr): 3408 cm^{-1} (-NH),1610 cm^{-1} (C=N), 1525 and 1350 cm^{-1} (-NO_2), 2630 cm^{-1} (-SH); ^{1}H NMR (DMSO-d_6) : δ_H 4.78 (s, 1H, -C=CH-) 3.71 (s, 1H, NH), 3.25 (s, 1H, SH), 8.29-7.24 (m, 12H, Ar-H), MS (EI) : m/z (%) 374 (24.49, M+1), Anal. Calcd. For $C_{21}H_{15}N_3O_2S$ (373.43): C, 67.54; H, 4.05; N, 11.25; Found: C, 66.95; H, 4.16; N, 11.43.

2-(4'-Mercapto-3'-Nitro Phenyl)-4-(2"-Chlorophenyl)-1*H*-1,5-Benzodiazepine(2b): mp 123^{0}C. IR (KBr) : 3410 cm^{-1} (NH), 1605 cm^{-1} (C=N), 1525 and 1347 cm^{-1} (NO_2), 2625 cm^{-1} (SH); ^{1}H NMR (DMSO-d_6): δ_H 4.70 (s, 1H,-C=CH-), 3.65 (s, 1H, NH), 3.20 (s, 1H, SH), 8.35-7.12 (m, 11H, Ar-H),; MS (EI): m/z(%) 409 (38.29, M+2), Anal. Calcd. For $C_{21}H_{14}N_3O_2SCl$ (407.87): C, 61.84 ; H, 3.46; N, 10.30; Found: C, 60.83; H, 3.06; N, 9.79.

2-(4'-Mercapto-3'-Nitrophenyl)-4-(4"-Fluorophenyl)-1*H*-1,5-Benzodiazepine(2c): mp 112^{0}C; IR (KBr): 3405 cm^{-1} (NH), 1612 cm^{-1} (C=N), 1532 and 1347 cm^{-1} (NO_2), 2623 cm^{-1} (SH); ^{1}H NMR (DMSO-d_6) : δ_H 4.72 (s, 1H, -C=CH-), 3.71 (s, 1H NH), 3.25(s, 1H, SH) 8.15-7.2 (m, 7H, Ar-H); MS (EI): m/z (%) 392 (21.65, M+1), Anal. Calcd. For $C_{21}H_{14}N_3O_2SF$ (391.48): C, 64.44; H, 3.61; N, 10.74; Found: C, 63.86; H, 3.45; N, 10.33.

2-(4'-Mercapto-3'-Nitrophenyl)-4-(3"-Methoxyphenyl)-1*H*-1,5-Benzodiazepine (2d): mp 118 ^{0}C IR (KBr): 3415 cm^{-1} (NH), 1615 cm^{-1} (C=N), 1530 and 1343 cm^{-1} (NO_2), 2624 cm^{-1} (SH); ^{1}H NMR (DMSO-d_6): δ_H 4.65 (s, 1H, -C=CH-), 3.72 (s, 1H, NH), 3.25 (s, 1H, SH), 8.30-7.15 (m, 11H, Ar-H); 3.80 (s, 3H, -CH_3); MS (EI) : m/z (%) 404 (25.3, M+1), Anal. Calcd. for $C_{22}H_{17}N_3O_3S$ (403.45): C, 65.49; H, 4.25; N, 10.42; Found: C, 64.88; H, 4.39; N, 10.12;.

2-(4'-Mercapto-3'-Nitro Phenyl)-4-(2"-Pyridinyl)-1*H*-1,5-Benzodiazepine (2e): mp 115 ^{0}C IR (KBr**)**: 3414 cm^{-1} (NH), 1616 cm^{-1}(C=N), 1535 and 1348 cm^{-1}(NO_2), 2618 cm^{-1} (SH) ; ^{1}H NMR (DMSO-d_6) : δ_H 4.65 (s, 1H, -C=CH-), 3.58 (s, 1H, NH), 3.26(s, 1H, SH), 8.6-7.15 (m, 11H, Ar-H); MS (EI): m/z (%) 375 (24.49, M+1), Anal. Calcd. for $C_{20}H_{14}N_4O_2S$ (374.42): C, 64.16; H, 3.77; N, 14.96; Found: C, 64.45; H, 3. 9; N, 14.99.

2-(4'-Mercapto-3'-Nitrophenyl)-4-(Thiophen-2"-Yl)-1*H*-1,5-Benzodiazepine (2f): mp 115 ^{0}C IR (KBr**)**: 3414 cm^{-1} (NH), 1616 cm^{-1}(C=N), 1535 and 1348 cm^{-1}(NO_2), 2618 cm^{-1} (SH) ; ^{1}H NMR (DMSO-d_6) : δ_H 4.82 (s, 1H, -C=CH-), 3.68 (s, 1H, NH), 3.25(s, 1H, SH), 7.1-6.80 (m, 10H, Ar-H); MS (EI): m/z (%) 380(24.49, M+1), Anal. Calcd. For $C_{19}H_{13}N_3O_2S_2$ (379.46) C, 60.14; H, 3.45; N, 11.07; Found: C, 60.45; H, 3.69; N, 11.29.

3.1.2. Synthesis of Thio-(tetra-O-acetyl gluco pyranosyl) Containing1,5- benzodiazepine

2-[3'-Nitro-4'-Thio-(Tetra-*O*-Acetylglucopyranosyl)Phenyl]-4-(Phenyl)-1*H*-1,5-Benzodiazepine (**3a**): $[\alpha]^D_{30}$= -5.66

IR (KBr) : 1753 cm^{-1} (C=O ester), 3414 cm^{-1} (NH), 1616 cm^{-1} (C=N), 1535 and 1348 cm^{-1}(NO2), ^{1}H NMR (DMSO-d_6): δ_H 4.75(s, 1H, -C=CH-), 3.60 (s, 1H, NH), 8.29-7.54 (m, 12H, Ar-H); 5.82 (d, 1H, βH-1' $J_{1',2'}$ = 9.2 Hz), 5.08 (t, 1H, H-2', $J_{2',3'}$ = 9.2 Hz), 5.36 (t, 1H, H-3', $J_{3',4'}$= 10.3 Hz), 5.12 (t, 1H, H-4', $J_{4',5'}$ = 9.1Hz), 3.95 (m, 1H, H-5'), 4.23 (dd, 1H, H-6' $J_{6',6''}$ = 12.6Hz, $J_{6',5'}$ = 2.6Hz), 4.13 (dd, 1H, H-6" $J_{6'',5'}$ = 2.5Hz), 2.09, 2.05, 2.01, 1.98 (each s, each 3H ,4Ac); MS (EI) : m/z (%) 704 (35.4, M+1), 374 (67, B+1), 331(39.75, sugar moiety), 169 (100, $C_8H_9O_4^+$), 229 (3.1), 187 (4.2)

Anal. Calcd. for $C_{35}H_{33}N_3O_{11}S$ (703.72) : C, 59.74; H, 4.73; N, 5.97; Found : C, 59.89; H, 4.67; N, 5.67.

2-[3'-Nitro-4'-Thio-(Tetra-*O*-Acetylglucopyranosyl)Phenyl]-4-(2"-Chlorophenyl)-1*H*-1,5-Benzodiaze -Pine (3b): $[A]^{D}_{30}$ = -4.24

IR (KBr) : 1746 cm^{-1} (C=O ester), 3403 cm^{-1} (NH), 1610 cm^{-1} (C=N), 1525 and 1350 cm^{-1} (NO_2); ^1H NMR (DMSO-d_6): δ_H 4.75 (s, 1H, -C=CH-), 3.61 (s, 1H, NH), 8.35-7.15 (m, 11H, Ar-H); 5.80 (d, 1H, β H-1' $J_{1'2'}$ = 9.0 Hz), 5.05 (t, 1H, H-2', $J_{2'3'}$ = 9.4 Hz), 5.35 (t, 1H, H-3', $J_{3'4'}$ = 10.3 Hz), 5.12 (t, 1H, H-4', $J_{4'5'}$ = 9.1 Hz), 3.93 (m, 1H, H-5'), 4.23 (dd, 1H, H-6' $J_{6'6"}$ = 12.6 Hz , $J_{6'5'}$ = 2.6 Hz), 4.13 (dd, 1H, H-6" $J_{6"5'}$ = 2.5 Hz), 2.05, 2.03, 1.98, 1.94 (each s, each 3H , 4Ac); MS (EI) : m/z (%) 739 (32.5, M+2), 331 (41.6, sugar moiety), 169 (100, $C_8H_9O_4^+$), 271 (5.4) , 211 (3.7).

Anal. Calcd. For $C_{35}H_{32}ClN_3O_{11}S$ (738.16) : C, 56.95; H, 4.37; N, 5.69; Found: C, 56.89; H, 4.13; N, 5.67.

2-[3'-Nitro-4'-Thio-(Tetra-*O*-Acetylglucopyranosyl)Phenyl]-4-(4"-Fluorophenyl)-1*H*-1,5-Benzodiaze -Pine (3c) : $[A]^{D}_{30}$ = -9.12

IR (KBr) : 1749 cm^{-1} (C=Oester), 3414 cm^{-1} (NH), 1618 cm^{-1} (C=N), 1528 and 1345 cm^{-1} (NO_2), ^1H NMR (DMSO-d_6) : δ_H 4.78 (s, 1H, -C=CH-), 3.62 (s, 1H, NH), 8.15-7.4 (m, 11H, Ar-H); 5.82 (d, 1H, β H-1' $J_{1'2'}$ = 9.3 Hz), 5.08 (t, 1H, H-2, $J_{2'3'}$ = 9.5 Hz), 5.35 (t, 1H, H-3, $J_{3'4'}$ = 10.5 Hz), 5.13 (t, 1H, H-4', $J_{4'5'}$ = 9.1 Hz), 3.94 (m, 1H, H-5'), 4.21 (dd, 1H, H-6', $J_{6'6"}$ = 12.6 Hz, $J_{6'5'}$ = 4.5 Hz), 4.12 (dd, 1H, H-6", $J_{6"5'}$ = 2.5 Hz), 2.05, 2.02, 1.98, 1.96 (each s, each 3H, 4Ac); MS (EI) : m/z (%) 722 (31.8, M+1), 392 (63, B+1), 331 (41.2, sugar moiety), 169 (100, $C_8H_9O_4^+$),271 (4.5), 229(3.4), 211 (2.6).

Anal. Calcd. For $C_{35}H_{32}FN_3O_{11}S$ (721.71) : C, 58.25; H, 4.47; N, 5.82; Found: C, 57.89; H, 4.25; N, 5.43.

2-[3'-Nitro-4'-Thio-(Tetra-*O*-Acetylglucopyranosyl) Phenyl]-4-(3"-Methoxyphenyl)-1*H*-1,5-Benzodi Azepine (3d) : $[A]^{D}_{30}$ = -5.34

IR (KBr) : 1752 cm^{-1} (C=O ester), 3409 cm^{-1} (NH), 1610 cm^{-1} (C=N), 1538 and 1352 cm^{-1} (NO_2), ^1H NMR (DMSO-d_6) : δ_H 4.70 (s, 1H, -C=CH-), 3.62 (s, 1H, NH), 8.30-7.25 (m, 11H, Ar-H) 3.63 (s, 3H, $-CH_3$); 5.81 (d, 1H, β H-1' $J_{1'2'}$ = 9.1 Hz), 5.06 (t, 1H, H-2', $J_{2'3'}$ = 9.5 Hz), 5.35 (t, 1 H, H-3', $J_{3'4'}$ = 10.4 Hz), 5.12 (t, 1H, H-4', $J_{4'5'}$ = 9.2 Hz), 3.95 (m, 1H, H-5'), 4.25 (dd, 1H, H-6' $J_{6'6"}$ = 12.7 Hz, $J_{6'5'}$ = 2.6 Hz), 4.13 (dd, 1H, H-6" $J_{6"5'}$ = 2.5 Hz), 2.09, 2.06, 2.01, 1.98 (each s, each 3H, 4Ac); MS (EI) : m/z (%) 734 (33.6, M+1), 404 (64, B+1), 331 (35.75, sugar moiety), 169 (100, $C_8H_9O_4^+$), 271 (5.3), 211(4.2).

Anal. Calcd. For $C_{36}H_{35}N_3O_{12}S$ (733.74) : C, 58.93; H, 4.81; N, 5.73; Found: C, 58.34; H, 4.34; N, 5.23.

2-[3'-Nitro-4'-Thio-(Tetra-*O*-Acetylglucopyranosyl) Phenyl] -4- (2"-Pyridinyl)-1*H*-1,5-Benzodiaze- Pine (3e) : $[A]^{D}_{30}$ = -3.98

IR (KBr) :1746 cm^{-1} (C=Oester) , 3412 cm^{-1} (NH), 1615 cm^{-1} (C=N), 1545 and 1352 cm^{-1} (NO_2), ^1H NMR (DMSO-d_6) : δ_H 4.74 (s, 1H, -C=CH-), 3.61 (s, 1H, NH), 8.64-7.15 (m, 11H, Ar-H); 5.81 (d, 1H, β H-1' $J_{1'2'}$ = 9.2 Hz), 5.06 (t, 1H, H-2', $J_{2'3'}$ = 9.3 Hz), 5.34 (t, 1H, H-3', $J_{3'4'}$ = 10.3 Hz), 5.11 (t, 1H, H-4', $J_{4'5'}$ = 9.0 Hz), 3.92 (m, 1H, H-5'), 4.25 (dd, 1H, H-6', $J_{6'6"}$ = 12.5 Hz, $J_{6'5'}$ = 2.9 Hz), 4.15 (dd, 1H, H-6", $J_{6"5'}$ = 2.6 Hz), 2.07, 2.05, 2.01, 1.99 (each s, each 3H , 4Ac) MS (EI) : m/z (%) 705 (33, M+1), 331 (43.6, sugar moiety), 169 (100, $C_8H_9O_4^+$), 271(5.7), 211 (4.1), 109(45.7).

Anal. Calcd. For $C_{34}H_{32}N_4O_{11}S$ (704.7) : C, 57.95; H, 4.58; N, 7.95; Found : C, 57.56; H, 4.35; N, 6.99.

2-[3'-Nitro-4'-Thio-(Tetra-*O*-Acetylglucopyranosyl)Phenyl]-4-(Thiophen-2"-Yl)-1*H*-1,5-Benzo Diazepine (2f) : $[A]^{D}_{30}$ = -3.98

IR (KBr) :1746 cm^{-1} (C=Oester) , 3412 cm^{-1} (NH), 1615 cm^{-1} (C=N), 1545 and 1352 cm^{-1} (NO_2), ^1H NMR (DMSO-d_6) : δ_H 4.74 (s, 1H, -C=CH-), 3.61 (s, 1H, NH), 7.2-6.80 (m, 10H, Ar-H); 5.84 (d, 1H, β H-1' $J_{1'2'}$ = 9.2 Hz), 5.07 (t, 1H, H-2', $J_{2'3'}$ = 9.4 Hz), 5.33 (t, 1H, H-3', $J_{3'4'}$ = 10.1 Hz), 5.13 (t ,1H, H-4', $J_{4'5'}$ = 9.0), 3.91 (m, 1H, H-5'), 4.25 (dd, 1H, H-6' $J_{6'6"}$ = 12.5 Hz, $J_{6'5'}$ = 3.1 Hz), 4.14 (dd, 1H, H-6" $J_{6"5'}$=2.5 Hz), 2.07, 2.04, 2.01, 1.97 (each s, each 3H ,4Ac); MS (EI) : m/z (%) 710 (33.8, M+1), 331(35.6, sugar moiety), 169 (100,$C_8H_9O_4^+$), 271(6.4), 211(3.89).

Anal. Calcd. For $C_{33}H_{31}N_3O_{11}S_2$ (709.74) : C, 55.84; H, 4.40; N, 5.92; Found : C, 55.06; H, 4.15; N, 5.59.

3.1.3. Synthesis of Thio-(Tetra-O-Acetylgalactopyranosyl) Containing 1,5-Benzodiazepine.

2-[3'-Nitro-4'-Thio-(Tetra-*O*-Acetylgalactopyranosyl)Phenyl]-4-(Phenyl)-1*H*-1,5-Benzodi Azepine (**4a**): $[A]^D_{30}$= -5.46

^{1}H NMR (DMSO-d_6) : δ_H 4.88 (s, 1H, -C=CH-) 3.71 (s, 1H, NH), , 8.19-7.10 (m, 12H, Ar-H),5.86 (d, 1H, βH-1' $J_{1'2'}$ = 10.2 Hz), 5.28 (t, 1H, H-2', $J_{2'3'}$ = 10.2 Hz), 5.36 (t, 1H, H-3', $J_{3'4'}$= 3.6 Hz), 5.12 (t, 1H, H-4', $J_{4'5'}$ = `3.4Hz), 4.19-4.06(3H, H-5', H-6', H-6") , 2.09, 2.05, 2.01, 1.98 (each s, each 3H ,4Ac); MS (EI) : m/z (%) 704 (35.4, M+1), 331(39.75, sugar moiety), 169 (100, $C_8H_9O_4^+$)

Anal. Calcd. For $C_{35}H_{33}N_3O_{11}S$ (703.72) : C, 59.74; H, 4.73; N, 5.97; Found : C, 59.89; H, 4.67; N, 6.07.

2-[3'-Nitro-4'-Thio-(Tetra-*O*-Acetylgalactopyranosyl)Phenyl]-4-(2"-Chlorophenyl)-1*H*-1,5-Benzodiazepine (4b): $[A]^D_{30}$ = -4.44

^{1}H NMR (DMSO-d_6): δ_H 4.70 (s, 1H,-C=CH-), 3.65 (s, 1H, NH), 8.30-7.15 (m, 11H, Ar-H),; 5.82 (d, 1H, β H-1' $J_{1'2'}$ = 10.1 Hz), 5.08 (t, 1H, H-2, $J_{2'3'}$ = 10.0 Hz), 5.35 (t, 1H, H-3, $J_{3'4'}$ = 3.5 Hz), 5.13 (t, 1H, H-4', $J_{4'5'}$ = 3.2 Hz), 4.19-4.06(3H, H-5', H-6', H-6") 2.05, 2.02, 1.98, 1.96 (each s, each 3H, 4Ac) MS (EI) : m/z (%) 739 (32.5, M+2), 409 (62, B+2), 331 (41.6, sugar moiety), 169 (100, $C_8H_9O_4^+$)

Anal. Calcd. For $C_{35}H_{32}ClN_3O_{11}S$ (738.16) : C, 56.95; H, 4.37; N, 5.69; Found: C, 56.89; H, 4.2; N, 5.77.

2-[3'-Nitro-4'-Thio-(Tetra-*O*-Acetylgalactopyranosyl)Phenyl]-4-(4"-Fluorophenyl)-1*H*-1,5-Benzodiazepine (4c) : $[A]^D_{30}$ = -9.56

^{1}H NMR (DMSO-d_6) : δ_H 4.72 (s, 1H, -C=CH-), 3.71 (s, 1H NH), 3.25(s, 1H, SH) 8.15-7.1 (m, 11H, Ar-H); 5.80 (d, 1H, β H-1' $J_{1'2'}$ = 10.2 Hz), 5.05 (t, 1H, H-2', $J_{2'3'}$ = 9.9 Hz), 5.35 (t, 1H, H-3', $J_{3'4'}$ = 3.6 Hz), 5.12 (t, 1H, H-4', $J_{4'5'}$ = 3.8 Hz), 4.19-4.06 (3H, H-5', H-6', H-6") , 2.05, 2.03, 1.98, 1.94 (each s, each 3H , 4Ac) MS (EI) : m/z (%) 722 (31.8, M+1), 392 (45.5, B+1), 331 (41.2, sugar moiety), 169 (100, $C_8H_9O_4^+$)

Anal. Calcd. For $C_{35}H_{32}FN_3O_{11}S$ (721.71) : C, 58.25; H, 4.47; N, 5.82; Found: C, 57.89; H, 4.65; N, 5.73.

2-[3'-Nitro-4'-Thio-(Tetra-*O*-Acetylgalactopyranosyl)Phenyl]-4-(3"-Methoxyphenyl)-1*H*-1,5-Benzodiazepine (**4d**) : $[A]^D_{30}$ = -5.54

^{1}H NMR (DMSO-d_6) δ_H 4.55 (s, 1H, -C=CH-), 3.72 (s, 1H, NH), 8.40-7.15 (m, 11H, Ar-H); 3.85 (s, 3H, -CH_3); 5.81 (d, 1H, β H-1' $J_{1'2'}$ = 10.0 Hz), 5.06 (t, 1H, H-2', $J_{2'3'}$ = 10.2 Hz), 5.35 (t, 1 H, H-3', $J_{3'4'}$ = 3.4 Hz), 5.12 (t, 1H, H-4', $J_{4'5'}$ = 3.2 Hz), 4.19-4.06(3H, H-5', H-6', H-6") , 2.09, 2.06, 2.01, 1.98 (each s, each 3H, 4Ac) ; MS (EI) : m/z (%) 734 (33.6, M+1),404 (54, B+1), 331 (35.75, sugar moiety), 169 (100, $C_8H_9O_4^+$)

Anal. Calcd. For $C_{36}H_{35}N_3O_{12}S$ (733.74) : C, 58.93; H, 4.81; N, 5.73; Found: C, 58.64; H, 4.84; N, 5.83.

2-[3'-Nitro-4'-Thio-(Tetra-*O*-Acetylgalactopyranosyl)Phenyl]-4- (2"- Pyridinyl) -1*H*-1,5-Benzodiazepine(**4e**) : $[A]^D_{30}$ = -6.35

^{1}H NMR (DMSO-d_6) : δ_H 4.65 (s, 1H, -C=CH-), 3.58 (s, 1H, NH), 3.26(s, 1H, SH), 8.3-7.10 (m, 11H, Ar-H); 5.82 (d, 1H, β H-1', $J_{1'2'}$ = 10.1 Hz), 5.08 (t, 1H, H-2', $J_{2'3'}$ = 10.1 Hz), 5.33 (t, 1H, H-3', $J_{3'4'}$ = 3.8 Hz), 5.13 (t, 1H, H-4', $J_{4'5'}$ = 4.0 Hz), 5.19-4.26(3H, H-5', H-6', H-6") , 2.04, 2.06, 2.04, 2.01 (each s, each 3H ,4Ac); MS (EI) : m/z (%) 705 (30.4, M+1), 375(52.2,B+1), 331 (39.75, sugar moiety), 169 (100, $C_8H_9O_4^+$),

Anal. Calcd. For $C_{34}H_{32}N_4O_{11}S$ (704.7) : C, 57.95; H, 4.58; N, 7.95; Found : C, 57.76; H, 4.35; N, 8.09.

2-[3'-Nitro-4'-Thio-(Tetra-*O*-Acetylgalactopyranosyl) Phenyl]-4-(3"-Thiophenyl)-1*H*-1,5-Benzodiazepine(**4f**) : $[A]^D_{30}$ = -4.96

^{1}H NMR (DMSO-d_6) : δ_H 4.62 (s, 1H, -C=CH-), 3.58 (s, 1H, NH), 7.1-6.7 (m, 10H, Ar-H) ; 5.65 (d, 1H, β H-1', $J_{1'2'}$ = 10.3 Hz), 5.08 (t, 1H, H-2', $J_{2'3'}$ = 10.1 Hz), 5.33 (t, 1H, H-3', $J_{3'4'}$ = 3.7 Hz), 5.13 (t, 1H, H-4', $J_{4'5'}$ = 3.9 Hz), 5.46-4.38 (3H, H-5', H-6', H-6") , 2.09, 2.06, 2.04, 2.01 (each s, each 3H ,4Ac); MS (EI) : m/z (%) 710 (35.4, M+1), 380(50.4, B+1), 331 (39.75, sugar moiety), 169 (100, $C_8H_9O_4^+$)

Anal. Calcd. For $C_{33}H_{31}N_3O_{11}S_2$ (709.74) : C, 55.84; H, 4.40; N, 5.92; Found : C, 55.96; H, 4.55; N, 6.10.

3.1.4. Synthesis of S- Glucosyl Containing Benzodiazepine

2-[3'-Nitro-4'-Thio-(B-D-*O*-Gluco Pyranosyl) Phenyl]-4-(Phenyl)-1*H*-1,5-Benzodiazepine (**5a**) : $[A]^D_{30}$ = -6.95

IR (KBr) : 3449 cm^{-1} (υ_{-OH}),1610 cm^{-1} ($\upsilon_{C=N}$), 1548 and 1355 cm^{-1} (υ_{NO2}); ^{1}H NMR (DMSO-d_6) : δ_H 3.75 (s, 1H, NH dis appeared with D_2O), 4.71 (s, 1H, -C=CH-), 8.61-7.34 (m, 12H, H ar) ; 5.41 (d, 1H, β H-1', $J_{1'2'}$ = 10.1 Hz), 3.26-4.43 (m, 6H, H-2', H-3', H-4', H-5', H-6', H-6"), 4.59 (brs, 1H, D_2OExch., -OH), 4.85-5.60 (m, 3H, D_2O Exch., -OH); ^{13}C NMR (DMSO-d_6) : δ 149.7 (C-2), 81 (C-3), 164.4 (C-4), 141 (C-5a), 122.9 (C-6), 120.1 (C-7), 127.9 (C-8), 117.6 (C-9), 138.3 (C-9a), 132.1 (C'-1), 121.8 (C'-2), 149.0 (C'-3), 126.8 (C'-4), 130.4 (C'-5), 132.8 (C'-6), 133.2 (C"-1), 129.5 (C"-2), 128.4 (C"-3), 131.5 (C"-4), 128.7 (C"-5), 129.6 (C"-6), 84.5 (β C-1'), 74.3 (C-2'), 78.4 (C-3'), 72.6 (C-4'), 79.3 (C-5'), 62.9 (C-6') ; MS (EI) : m/z 557 (M+ Na), 536 (M+1)$^+$, 163 (sugar moiety);

2-[3'-Nitro-4'-Thio-(B-D-*O*-Glucopyranosyl)Phenyl]-4-(2"-Chlorophenyl)-1*H*-1,5-Benzodi Azepine (**5b**) : $[A]^D_{30}$ = -7.62

IR (KBr) : 3452 cm^{-1} (υ_{-OH}), 1612 cm^{-1} ($\upsilon_{C=N}$), 1545 and 1348 cm^{-1} (υ_{NO2}); ^{1}H NMR (DMSO-d_6) : δ_H 3.73 (s, 1H, NH disappeared with D_2O), 4.68 (s, 1H, -C=CH-), 7.76-7.41 (m, 11H, Har); 5.43 (d, 1H, β H-1', $J_{1'2'}$ = 9.1 Hz), 3.24-4.45 (m, 6H, H-2', H-3', H-4', H-5', H-6', H-6"), 4.61 (brs, 1H, D_2O Exch., -OH), 4.83-5.61 (m, 3H, D_2OExch., -OH); ^{13}C NMR (DMSO-d_6) δ_C 149.4 (C-2), 82 (C-3), 164.3 (C-4), 41.5 (C-5a), 122.8 (C-6), 120.0 (C-7), 128.2 (C-8), 117.5 (C-9), 138.1 (C-9a), 132.0 (C'-1), 121.6 (C'-2), 148.9 (C'-3), 126.8 (C'-4), 130.3 (C'-5), 132.7 (C'-6), 128.5 (C"-1), 134.7 (C"-2), 128.8 (C"-3), 129.6 (C"-4), 130.5 (C"-5), 128.7 (C"-6), 84.6 (β C-1'), 72.1 (C-2'), 73.9 (C-3'), 70.4 (C-4'), 74.4 (C-5'), 64.8 (C-6'),MS (EI) : m/z 591(M+ Na), 570 (M+1)$^+$, 163(sugar moiety)

2-[3'-Nitro-4'-Thio-(B-D-*O*-Glucopyranosyl) Phenyl] – 4 - (4"-Fluoropheny)-1*H*-1,5-Benzodi Azepine (**5c**) : $[A]^D_{30}$ = -11.1

IR (KBr) : 3451 cm^{-1} (υ_{-OH}), 1618 cm^{-1} ($\upsilon_{C=N}$), 1542 and 1352 cm^{-1} (υ_{NO2}); ^{1}H NMR (DMSO-d_6) : δ_H 3.74 (s, 1H, NH disappeared with D_2O), 4.70 (s, 1H, -C=CH-), 7.64- 7.40 (m, 11H, Har),7; 5.44 (d, 1H, β H-1', $J_{1'2'}$ = 9.1 Hz), 3.27-4.45 (m, 6H, H-2', H-3', H-4', H-5', H-6', H-6"), 4.57 (brs, 1H, D_2O Exch., -OH), 4.88-5.63 (m, 3H, D_2OExch., -OH); ^{13}C NMR (DMSO-d_6) δ_C 149.8 (C-2), 83 (C-3), 164.6 (C-4), 141 (C-5a), 123.1 (C-6), 120.1 (C-7), 128.1 (C-8), 117.6 (C-9), 138.2 (C-9a), 131.9 (C'-1), 121.7 (C'-2), 149.2 (C'-3), 126.7 (C'-4), 130.5 (C'-5), 132.6 (C'-6), 125.1 (C"-1), 129.4 (C"-2), 114.3 (C"-3), 163.4 (C"-4), 129.5 (C"-5), 114.6 (C"-6), 84.5 (β C-1'), 72.6 (C-2'), 73.8 (C-3') , 70.7 (C-4'), 74.6 (C-5'), 64.8 (C-6'); MS (EI) : m/z 575 (M + Na), 554 (M+1)$^+$, 163 (sugar moiety)

2-[3'-Nitro-4'-Thio-(B-D-*O*-Glucopyranosyl) Phenyl]-4-(3"-Methoxyphenyl)-1*H*-1,5- Benzodi Azepine (**5d**) : $[A]^D_{30}$ = -7.14

IR (KBr**)** : 3444 cm^{-1} (υ_{-OH}), 1616 cm^{-1} ($\upsilon_{C=N}$), 1552 and 1348 cm^{-1} (υ_{NO2}); ^{1}H NMR (DMSO-d_6) : δ_H 3.71 (s, 1H, NH disappeared with D_2O), 4.69 (s, 1H, -C=CH-), 7.90-6.87 (m, 11H, Har), , 3.84 (s, 3H, -CH_3); 5.45 (d, 1H, β H-1', $J_{1'2'}$ = 9.1 Hz), 3.25-4.44 (m, 6H, H-2', H-3', H-4', H-5', H-6', H-6"), 4.57 (brs, 1H, D_2OExch., -OH), 4.84-5.63 (m, 3H, D_2O Exch., -OH); ^{13}C NMR (DMSO-d_6) δ_C 149.7 (C-2), 82 (C-3), 164.5 (C-4), 142 (C-5a), 123.3 (C-6), 120.2 (C-7), 128.3 (C-8), 117.8 (C-9), 138.4 (C-9a), 132.1 (C'-1), 121.9 (C'-2), 149.2 (C'-3), 126.9 (C'-4), 130.6 (C'-5), 132.7 (C'-6), 127.5 (C"-1), 114.4 (C"-2), 159.7 (C"-3), 114.3 (C"-4), 127.4 (C"-5), 120.9 (C"-6), 31.3 (C-methoxy), 84.5 (β C-1'), 72.5 (C-2'), 73.8 (C-3'), 70.6 (C-4'), 74.4 (C-5'), 64.7 (C-6') ; MS (EI): m/z 587 (M + Na), 566 (M+1)$^+$, 163 (sugar moiety)

2-[3'-Nitro-4'-Thio-(B-D-O-Gluco Pyranosyl) Phenyl]-4-(2"- Pyridinyl)-1*H*-1,5-Benzodiazepine (**5e**) : $[A]^{D}_{30}$ = -9.67

IR (KBr) : 3448 cm^{-1} (υ_{-OH}), 1608 cm^{-1} ($\upsilon_{C=N}$), 1540 and 1352 cm^{-1} (υ_{NO2}); ^{1}H NMR (DMSO-d_6) : δ_H 3.75 (s, 1H, NH, NH disappeared with D_2O), 4.70 (s, 1H, -C=CH-),8.52-7.40 (m, 11H , Har); 5.45 (d, 1H, β, H-1', $J_{1'2'}$ = 9.1 Hz), 3.26-4.45 (m, 6H, H-2', H-3', H-4', H-5', H-6', H-6"), 4.60 (brs, 1H, D_2O Exch., -OH), 4.87-5.62 (m, 3H, D_2OExch., -OH); ^{13}C NMR (DMSO-d_6) δ_C : 149.5 (C-2), 83 (C-3), 164.4 (C-4), 141 (C-5a), 123.1 (C-6), 120.1 (C-7), 128.1 (C-8), 117.6 (C-9), 138.2 (C-9a), 132.2 (C'-1), 121.8 (C'-2), 149.0 (C'-3), 126.8 (C'-4), 130.4 (C'-5), 132.8 (C'-6), 145.4 (C"-2 pyridine), 125.7 (C"-3 pyridine), 134.8 (C"-4 pyridine), 126.7 (C"-5 pyridine), 145.5 (C"-6 pyridine), 84.3 (β, C-1'), 72.4 (C-2'), 73.8 (C-3'), 70.6 (C-4'), 74.7 (C-5'), 64.9 (C-6'); MS (EI) : m/z 558 (M + Na), 537 (M+1)$^+$, 163 (sugar moiety)

2-[3'-Nitro-4'-Thio-(B-D-*O*-Glucopyranosyl) Phenyl]-4-(3"-Thiophenyl)-1*H*-1,5-Benzodiaze Pine (**5f**) : $[A]^{D}_{30}$ = -5.32

IR (KBr) : 3447 cm^{-1} (υ_{-OH}), 1609 cm^{-1} ($\upsilon_{C=N}$), 1546 and 1351 cm^{-1} (υ_{NO2}); ^{1}H NMR (DMSO-d_6) : δ_H 3.71 (s, 1H, NH disappeared with D_2O), 4.73 (s, 1H, -C=CH-), 7.92-7.66 (m, 9H, Har), 6.79 (m , 2H, Har); 5.45 (d, 1H, β H-1', $J_{1'2'}$ = 9.1 Hz), 3.24-4.45 (m, 6H, H-2', H-3', H-4', H-5', H-6', H-6"), 4.57 (brs, 1H, D_2OExch., -OH), 4.83-5.64 (m, 3H, D_2OExch., -OH); ^{13}C NMR (DMSO-d_6) δ 149.5 (C-2), 83.1 (C-3), 163.8 (C-4), 142.2 (C-5a), 122.7 (C-6), 121.2 (C-7),128.3(C-8), 115.8 (C-9), 137.4 (C-9a), 131.1 (C'-1), 122.8 (C'-2), 148.2 (C'-3), 125.9 (C'-4), 131.6 (C'-5), 132.9 (C'-6), 125.2 (C"-2), 127.5 (C"-3), 127.5 (C"-4), 125.6 (C"-5), 84.1 (β C-1'), 71.5 (C-2'), 73.5 (C-3'), 70.4 (C-4'), 74.6 (C-5'), 64.3 (C-6'); MS (EI) : m/z 563 (M + Na), 542 (M+1)$^+$, 163 (sugar moiety)

3.1.5. Synthesis f S- Galactosyl Containing 1,5-Benzodiazepine

2-[3'-Nitro-4'-Thio-(B-D-*O*-Galactopyranosyl) Phenyl]-4-(Phenyl)-1*H*-1,5-Benzodiazepine (**6a**) : $[A]^{D}_{30}$ = -5.85

^{1}H NMR (DMSO-d_6) : δ_H 8.1- 7.4 (m, 12H, Har) , 3.75 (s, 1H, NH disappeared with D_2O), 4.71 (s, 1H, -C=CH-),; 5.44 (d, 1H, β H-1', $J_{1'2'}$ = 9.9 Hz), 3.10-4.25 (m, 6H, H-2', H-3', H-4', H-5', H-6', H-6"), 4.40 (brs, 1H, D_2OExch., -OH), 4.55-5.40 (m, 3H, D_2O Exch., -OH); ^{13}C NMR (DMSO-d_6) : δ 149.2 (C-2), 83.1 (C-3), 163.9 (C-4), 142 (C-5a), 122.7 (C-6), 120.3 (C-7), 127.8 (C-8), 117.4 (C-9), 138.2 (C-9a), 132.0 (C'-1), 121.9 (C'-2), 149.1 (C'-3), 126.7 (C'-4), 130.3 (C'-5), 132.6 (C'-6), 133.1 (C"-1), 129.3 (C"-2), 128.5 (C"-3), 131.6 (C"-4), 128.8 (C"-5), 129.5 (C"-6), 84.5 (β C-1'), 74.3 (C-2'), 78.4 (C-3'), 72.6 (C-4'), 79.3 (C-5'), 62.9 (C-6') ; MS (EI) : m/z 557 (M + Na), 536 (M+1)$^+$, 163 (sugar moiety)

2-[3'-Nitro-4'-Thio-(B-D-*O*-Galactopyranosyl) Phenyl]-4-(2"-Chlorophenyl)-1*H*-1,5-Benzodiaze Pine (**6b**) : $[A]^{D}_{30}$ = -6.42

^{1}H NMR (DMSO-d_6) : δ_H 7.96-7.40(m , 11H, Har) 3.70 (s, 1H, NH disappeared with D_2O), 4.62 (s, 1H, -C=CH-), 5.43 (d, 1H, β H-1', $J_{1'2'}$ = 9.8 Hz), 3.20-4.50 (m, 6H, H-2', H-3', H-4', H-5', H-6', H-6"), 4.61 (brs, 1H, D_2O Exch., -OH), 4.83-5.61 (m, 3H, D_2OExch., -OH); ^{13}C NMR (DMSO-d_6) δ_C 148.8 (C-2), 82.3 (C-3), 163.9 (C-4), 41.8 (C-5a), 123.1 (C-6), 120.1 (C-7), 127.9 (C-8), 117.4 (C-9), 137.9 (C-9a), 131.8 (C'-1), 121.4 (C'-2), 148.8(C'-3), 127.1 (C'-4), 130.1 (C'-5), 132.5 (C'-6), 129.1 (C"-1), 134.5 (C"-2), 128.6 (C"-3), 128.9 (C"-4), 130.4 (C"-5), 128.6 (C"-6), 84.4 (β C-1'), 72.1 (C-2'), 73.9 (C-3'), 70.4 (C-4'), 74.4 (C-5'), 64.8 (C-6'), MS (EI) : m/z 591 (M + Na), 570 (M+1)$^+$, 163(sugar moiety)

2-[3'-Nitro-4'-Thio-(B-D-*O*-Galactopyranosyl) Phenyl]-4-(4"-Fluoropheny)-1*H*-1,5-Benzodiaze Pine (**6c**) : $[A]^{D}_{30}$ = -10.5

^{1}H NMR (DMSO-d_6) : δ_H 7.8- 7.4 (m, 11H, Har) 3.76 (s, 1H, NH disappeared with D_2O), 4.77 (s, 1H, -C=CH-), 5.44 (d, 1H, β H-1', $J_{1'2'}$ = 9.8 Hz), 3.15-4.45 (m, 6H, H-2', H-3', H-4', H-5', H-6', H-6"), 4.57 (brs, 1H, D_2O Exch., -OH), 4.88-5.63 (m, 3H, D_2OExch., -OH); ^{13}C NMR (DMSO-d_6) δ_C 149.7 (C-2), 82.9 (C-3), 164.6 (C-4), 140.9 (C-5a), 122.8 (C-6), 120.3 (C-7), 128.2 (C-8), 117.4 (C-9), 137.9(C-9a), 132.0 (C'-1), 121.9 (C'-2), 149.1 (C'-3), 126.6 (C'-4), 130.3 (C'-5), 132.2 (C'-6), 125.3 (C"-1), 129.2 (C"-2), 113.9 (C"-3), 163.3 (C"-4), 129.4 (C"-5), 114.3 (C"-6), 84.5 (β C-1'), 72.6 (C-2'), 73.8 (C-3') , 70.7 (C-4'), 74.6 (C-5'), 64.8 (C-6'); MS (EI) : m/z 575 (M + Na), 554 (M+1)$^+$, 163 (sugar moiety)

2-[3'-Nitro-4'-Thio-(B-D-*O*-Galactopyranosyl) Phenyl]-4-(3"-Methoxyphenyl)-1*H*-1,5-Benzodi Azepine (**6d**) : $[A]^{D}_{30}$ = -7.14

^{1}H NMR (DMSO-d_6) : δ_H 7.8-6.6 (m, 11H, Har) 3.71 (s, 1H, NH disappeared with D_2O), 4.69 (s, 1H, -C=CH-), 3.84 (s, 3H, $-CH_3$); 5.40 (d, 1H, β H-1', $J_{1'2'}$ = 9.7 Hz), 3.21-4.42 (m, 6H, H-2', H-3', H-4', H-5', H-6', H-6"), 4.57 (brs, 1H, D_2OExch., -OH), 4.84-5.63 (m, 3H, D_2O Exch., -OH); ^{13}C NMR (DMSO-d_6) δ_C 148.7 (C-2), 82.3 (C-3), 164.3 (C-4), 142.2 (C-5a), 123.1 (C-6), 119.9 (C-7), 128.1 (C-8), 117.7 (C-9), 137.9 (C-9a), 132.4 (C'-1), 121.7 (C'-2), 148.9 (C'-3), 126.8 (C'-4), 130.4 (C'-5), 132.9 (C'-6), 128.1 (C"-1), 114.3 (C"-2), 159.8 (C"-3), 114.5 (C"-4), 127.7 (C"-5), 121.0 (C"-6), 31.5 (C-methoxy), 84.6 (β C-1'), 72.5 (C-2'), 73.8 (C-3'), 70.6 (C-4'), 74.4 (C-5'), 64.7 (C-6') ; MS (EI): m/z 587 (M + Na), 566 ($M+1)^+$, 163 (sugar moiety)

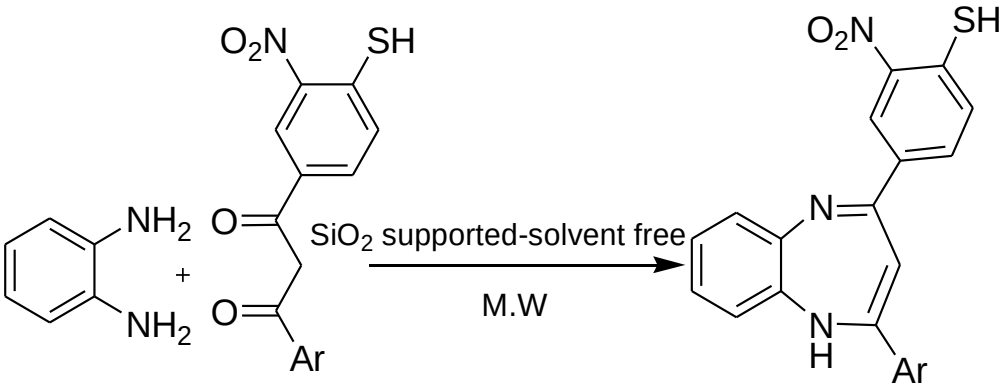
2-[3'-Nitro-4'-Thio-(B-D-*O*-Galacto Pyranosyl) Phenyl]-4-(2'-Pydinyl)-1*H*-1,5- Benzodiazepine (**6e**) : $[A]^{D}_{30}$ = -12.6

^{1}H NMR (DMSO-d_6) : δ_H 8.70-8.55 (m, 7H, Har) , 4.75 (s,1H, -C=CH-), 3.74 (s, 1H, NH disappeared with D_2O), , 8.27 (m, 2H, Pyridine), 7.60 (m, 2H, Pyridine), 5.42 (d, 1H, β H-1', $J_{1'2'}$ = 9.9 Hz), 3.27-4.44 (m, 6H, H-2', H-3', H-4', H-5', H-6', H-6"), 4.55 (brs, 1H, D_2O Exch., -OH), 4.84-5.25 (m, 3H, D_2O Exch., -OH); ^{13}C NMR (DMSO-d_6 δ_C : 148.9 (C-2), 83.2 (C-3), 164.4 (C-4), 141.3 (C-5a), 123.2 (C-6), 121.2 (C-7), 128.2 (C-8), 117.3 (C-9), 138.1 (C-9a), 132.0 (C'-1), 121.9 (C'-2), 148.9 (C'-3), 126.7 (C'-4), 130.5(C'-5), 132.8 (C'-6), 149.4 (C"-2 pyridine) , 121.5 (C"-3 pyridine) , 129.5 (C"-4 pyridine), 120.6 (C"-5 pyridine) , 148.7 (C"-6 pyridine) , 84.6 (β C-1'), 72.4 (C-2'), 73.6 (C-3'), 70.7 (C-4'), 74.4 (C-5'), 64.9 (C-6'); MS (EI) : m/z 558 (M + Na), 537 $(M+1)^+$, 163 (sugar moiety)

2-[3'-Nitro-4'-Thio-(B-D-*O*-Galactopyranosyl) Phenyl]-4-(3"-Thiophenyl)-1*H*-1,5-Benzodiazepine (**6f**) : $[A]^{D}_{30}$ = -3.45

^{1}H NMR (DMSO-d_6) : δ_H 7.96-6.7 (m, 10H Har), 4.70 (s, 1H, -C=CH-), 3.72 (s, 1H, NH disappeared with D_2O), 5.43 (d, 1H, β H-1', $J_{1'2'}$ = 9.9 Hz), 3.27-4.45 (m, 6H, H-2', H-3', H-4', H-5', H-6', H-6"), 4.59 (brs, 1H, D_2OExch., -OH), 4.83-5.62 (m, 3H, D_2OExch., -OH); ^{13}C NMR (DMSO-d_6 δc 149.5 (C-2), 82.1 (C-3), 164.4 (C-4), 142.2 (C-5a), 123.2 (C-6), 120.3 (C-7), 128.5 (C-8), 117.5 (C-9), 138.4 (C-9a), 132.6 (C'-1), 121.8 (C'-2), 149.3 (C'-3), 126.6 (C'-4), 130.5 (C'-5), 132.7 (C'-6), 122.5 (C"-2), 129.7 (C"-3), 129.5 (C"-4), 122.6 (C"-5), 84.4 (β C-1'), 72.7 (C-2'), 73.9 (C-3'), 70.4 (C-4'), 74.3 (C-5'), 64.8 (C-6'), MS (EI) : m/z 563 (M + Na), 542($M+1)^+$, 163 (sugar moiety)

2-(4'-mercapto-3'-nitrophenyl)-4-(aryl/hetero aryl)-1*H*-1,5-benzodiazepineswere synthesized by condensation of *O*-Phenylenediamine with 1-(4'-mercapto-3'-nitrophenyl)-3-(aryl/hetero aryl)-propane1,3-diones in ethanolic solution with trace of glacial acetic acid in presence of nitrogen atmosphere. The same reaction when carried out using silica as solid support under microwave irradiation resulted in high yield of the product in a short period of time (**Scheme 1) (1a-f).** Proposed mechanism for the synthesis of benzodiazepine is given in Fig 1.



Scheme1. *Synthesis of 1,5-Benzodiazepine*

Ar = a. Phenyl b. o- Chloro phenyl c. p- Fluorophenyl d. m- Methoxyphenyl

e. 2-Pyridyl f. 2- Thiophenyl

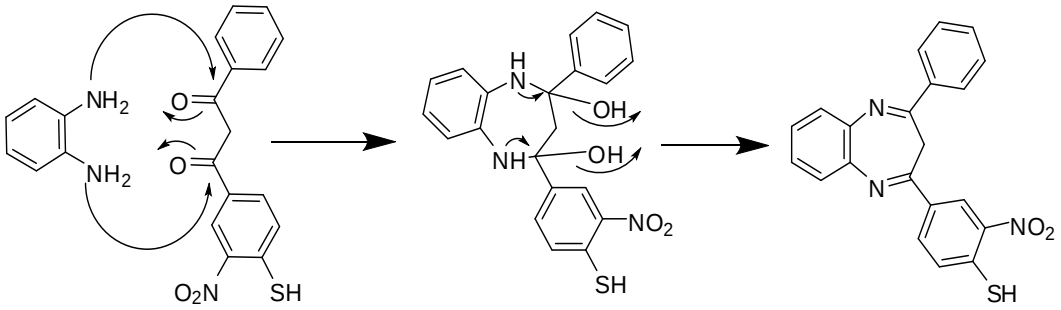


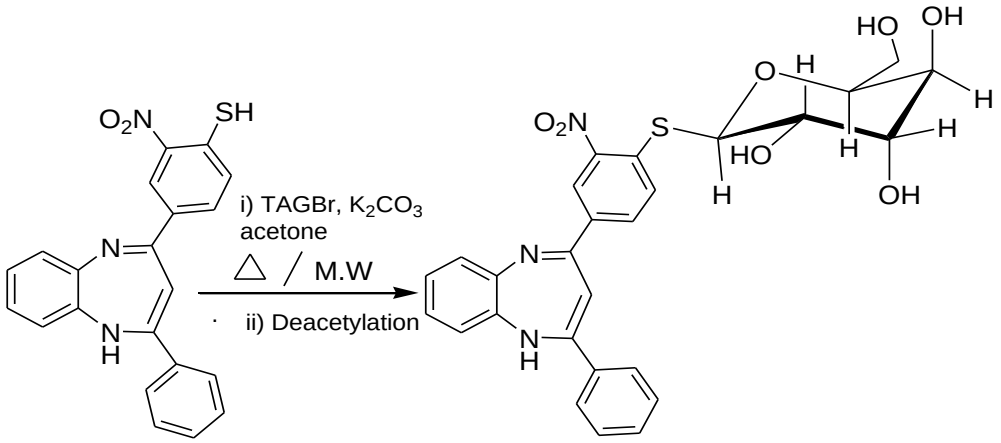
Fig1. *Mechanism of 1,5-Benzodiazepine*

It is proposed and seems to be feasible that the carbonyl bond being highly polar is attacked by the lone pair electron from nitrogen of amine. A simultaneous attack by both the amines of o-phenylenediamine leads to the formation of a –NH-C bond with simultaneous removal of a hydroxyl anion which ultimately takes up a proton resulting in a condensation product.

Synthesis of benzodiazepine using this solvent free approach was found to be efficient and economical. No solvent was required except the minor quantity used in preparing paste of the two reactants to homogenize. The progress of the reaction was monitored by TLC on regular interval.

Glycosides reported in the present work were synthesized without using any heavy metal salts such as Ag_2CO_3, HgO, $HgBr_2$, $Hg(CN)_2$, AgOTf and $HgCl_2$ because it requires laborious chromatographic purifications The glucosylation was carried out by using Modified Koenigs-Knorr method[28]·The glucosylation of aglycone moiety was synthesized with the help of per-acetate sugar bromide as glucosyl donor. Aglycone was added to the solution of α-per-acetate bromo sugar in dry acetone in presence of K_2CO_3 for microwave irradiation. The resulting mixture contain 2-[3'nitro-4'- thio(tetra-*O*-acetylglycopyranosyl)phenyl]-4-(aryl/heteroaryl)-1H-1,5-benzodiazepines **2.** Experiments with other alkali metal carbonates as possible substitutes for K_2CO_3 proved less successful (results not shown in the table). Thus, the Na_2CO_3-assisted reactions were shown to be considerably slower as a result of which the desired S- glycoside was obtained in poor yield (only 20%) with the hydrolytic product reponderating (>70%). Use of Cs_2CO_3 on the other hand, led to the formation of partially deacetylated products, thus giving the desired product S-glycosides in only low yields. Further, no reaction was observed in attempts with $BaCO_3$, and hence the unchanged starting material was recovered.

These benzodiazepine derivatives on glucosylation with tetra-O-acetyl glucopyranosyl bromide and tetra-O-acetyl galactopyranosyl bromide yielded corresponding 2-[3'nitro-4'-thio(tetra-*O*-acetyl glucopyranosyl) phenyl]-4-(aryl/heteroaryl)-1*H*-1,5-benzodiazepines and 2-[3'nitro-4'-thio(tetra-*O*-acetylgalactopyranosyl) phenyl]-4-(aryl/heteroaryl)-1*H*-1,5-benzodiazepines respectively. Deacetylation of above *S*-glycosylated moiety with anhydrous zinc acetate in methanol afforded2-[3'-nitro-4'-thio(glucopyranosyl) phenyl]-4-(aryl/heteroaryl)-1*H*-1,5-benzodiazepines **(Scheme 2).**

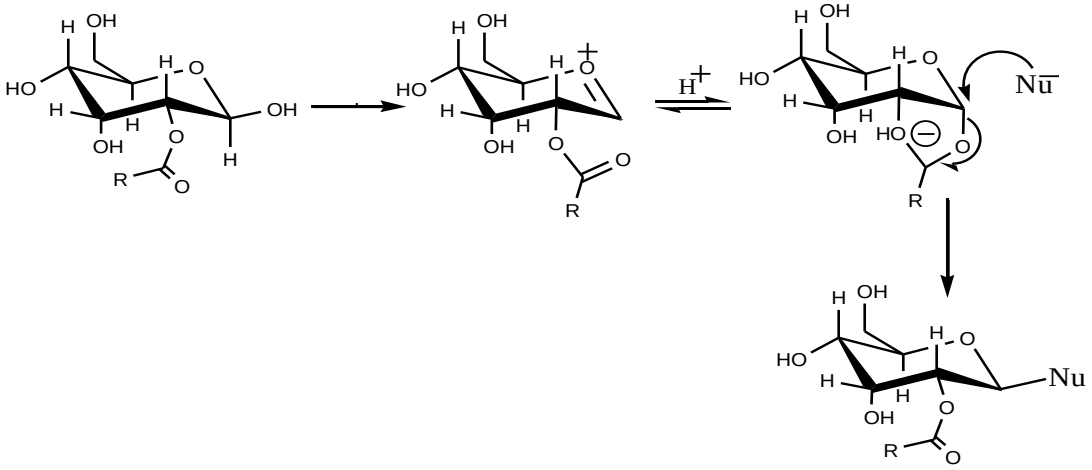


Scheme2. *Synthesis of Glucose containing 1, 5-benzodiazepine.*

Different instrumental techniques were used to elucidate the structure of the above aglycon moiety. The IR spectra generally indicate the presence of ν_{NH} 3408 cm^{-1} and $\nu_{C=N}$ 1620 cm^{-1} show the

characteristic frequencies of newly formed functional groups. NMR spectral data of the newly synthesized compound confirmed by the δ value. More spectra data were given in the experimental portion.

A strong absorption peak at 1760cm^{-1} was assigned to C=O stretch of O-acetyl groups of glucose moiety. A sharp peak at 2854cm^{-1} was assigned to glucosidic –CH stretch. The main advantage of this reaction was that the distereoselectivity was high in favour of β-anomer, improves the overall yield and regioselectivity. The one mechanism suggested is mainly focused in **scheme 3.**



Scheme3. *Neighbouring group participation*

Spectral data were used to elucidate the configuration of the *β*-anomer. When the six- membered ring of a sugar moity is in a chair conformation , the germinal coupling contants are 12.0 Hz., Axial-axial vicinal protons generally have coupling constants of 8.0-12.0 Hz, While axial-equatorial vicinal protons and equatorial-equatorial vicinal protons have J values of 0- 5.0 Hz [29]. Therefore, the large coupling constants (10- 10.3 Hz) of the anomeric protons are typical for *β*-configurated glucopyranose. The chemical shift and coupling constant of the anomeric proton was in accordance with the reported value for the *β*-glucosides [30] Large coupling constants of the anomeric proton in *S*- glucosides derivatives corresponds to the diaxial orientation of the H-1' and H-2' protons, indicating the *β*-configuration of the anomer.

The EI-MS mass spectra of **2a** showed the characteristic dissociation of poly-*O*-acetylated *S*-glucosides glycosidic bond fragments with m/z 331 (aglycon moiety) and the 163(the carbohydrate moiety).

Various *β*-diketones have been prepared by using conventional methods described in literature [31,32].

2-[3'nitro-4'-thio (glucopyranosyl) phenyl] -4-(aryl/heteroaryl)-1*H*-1,5-benzodiazepines **3**.were prepared by deacetylation of acetylated β-glucosides **2** with anhydrous zinc acetate in absolute methanol.

The IR spectrum of deacetylated product **3a** are characterized by the absence of $\upsilon_{c=o}$ ester stretching vibration at 1750-1744cm^{-1} region and the presence of strong bond at 3450-3435cm^{-1} showed the presence of characteristic absorption peak(br, -OH peak of carbohydrate residue), 2855 cm^{-1}(glucosidic –CH) ,indicating the formation of glucosides. The ^{1}H NMR and ^{13}C NMR data show the presence of carbohydrate moiety. The chemical shift of the anomeric proton shows β-linkage at δ 5.82(-CH) indicating the linkage of carbohydrate unit. Signals due to hydroxyl protons of the carbohydrate were not observed because of the fast exchange of all non-hydrogen bonded OH groups and the acidic phenolic functions. The mass spectral (EI-MS) studies shows that molecular ion peak at m/z 536(M+1)$^{+}$, was dominated by m/z 373(100%) with the loss of 163 amu corresponding to the intact anhydro-sugar moiety. The molecular ion peak at m/z 373.confirmed the molecular formula of the glucosides.

The analytical and spectral data (IR,^{1}H NMR, ^{13}CNMR and mass spectra) were consistent with the assigned structure. The analytical data of 3a was compatible with the molecular formula. The mass spectrum of **3a** was compatible with the molecular formula.

The microwave assisted synthesis reduces the timing of the reaction and gives the high quality of yield comparable to the conventional method. Comparison of Microwave assisted synthesis and conventional synthesis.

Table1. *Comparison of the conventional and MW-assisted silica supported synthesis of 1,5-benzodiazepine.*

Compd	conventional method		microwave	
	Time (h)	Yield (%)	Time (s), Power (W)	Yield (%)
1a	12	65	160, 60	88
1b	12	62	160, 60	86
1c	12	58	180, 60	86
1d	12	62	160, 60	82
1e	12	51	160, 60	90
1f	12	65	140, 60	89

Table2. *Comparison of the conventional and MW-assisted synthesis of Thio-(tetra-O-acetyl glucopyranosyl) containing benzodiazepine.*

Compd	conventional method		Microwave	
	Time (h)	Yield (%)	Time (s), Power (W)	Yield (%)
3a	18	81	150,120	80
3b	18	85	160, 120	90
3c	18	92	150, 120	85
3d	18	83	175,120	75
3e	18	88	170,120	90
3f	18	78	160,120	85

4. PHAMACOLOGICAL ACTIVITY

The antimicrobial activity screening shows that, synthesized scaffold exhibited antibacterial activity with MIC in the range 0.5-28.250 µg/mL and antifungal activity with MIC in the range 4.50-18.125 µg/mL. Compound 5d was found to potent of all tested compounds with MIC in the range 0.5-2.250 against bacterial mentioned strains. Compound 5d exhibited MIC of 0.5 against B. *substilis* and *S.Faecalis*. Antibacterial evaluation reveals that compounds 2-(4'-Mercapto-3'-nitrophenyl)-4-(4"-substitutedphenyl)-1*H*-1,5-benzodiazepines 2(a-i) exhibited antibacterial activity MIC in the range 2.00- 28.250 g/mL. in the series compound 2d exhibited potent activity with MIC of 2-3.5 against bacterial strains indicating importance of electron releasing methoxy group on para position of phenyl ring, for their antibacterial activity. Where as 3, 4-dimethoxy substitueted compound (2g) results in very weak activity. Galactosyl derivatives of series 2(a-f) i.e compounds 6(a-f) generates compounds with no further increase in potency. Antibacterial screening reveals that glucopyranosyl derivatives that is compounds 6(a-f) generates potent antimicrobial agents as compared to parent compounds 2(a-f). compound 5d was found to be potent in the series with MIC in the range of 0.5 – 2.250. glucosydation of compound 2d that is 5d generates potent compound in the series, indicating further importance of methoxy group at para position of phenyl ring of glucosyl derivatives and importance of glycosidation may be by increased oral bioavailability.

Table3. *The zone of inhibition and minimum inhibitory concentrations (MICs) were determined in comparison with the standard drug fluconazole*

Compd. / Micro Organisms	Minimum Inhibitory Concentration (µg/mL)						
	Bacteria					Fungi	
	B. substilis	S. aureus	S. faecalis	E. Coli	P. aeruginosa	C. albicans	A. niger
Gentamycin	0.4	0.6	0.7	0.4	0.6	NT	NT
Fluconazole	NT	NT	NT	NT	NT	2.0	2.0
DMSO	Nil	Nil	Nil	Nil	Nil	Nil	Nil
2a	12.250	17.50	13.250	8.125	23.125	07.250	08.125
5a	8.125	11. 50	7.50	5.750	15.50	05.125	06.125
6a	8.250	11.125	7.750	5.125	15.00	05.750	06.50
2b	04.50	4.125	4.50	12.50	28.250	05.125	08.50
5b	03.125	2.750	3.125	8.750	20.50	04.250	06.250
6b	03.750	2.50	3.50	8.50	19.750	04.50	06.50
2c	03.125	05.50	3.125	12.250	14.250	14.250	11.125
5c	02.125	04.750	3.0	9.50	10.50	10.125	8.750
6c	02.50	04.250	3.125	9.25	9.750	10.50	8.50

2d	2.125	2.50	2.00	3.5	2.00	8.250	10.50
5d	2.0	2.250	1.5	2.75	1.75	6.5	7.750
6d	2.25	2.2	1.5	2.75	1.6	6.75	7.50
2e	04.50	4.725	4.50	11.50	23.250	06.125	09.50
5e	03.225	3.750	3.125	7.750	14.50	04.25	06.25
6e	03.350	3.50	3.25	7.50	14.750	04.35	06.75
2f	12.50	13.50	11.125	14.50	10.25	8.50	9.125
5f	9.75	11.5	9.75	10.750	8.50	6.75	8.75
6f	9.5	11.125	9.6	10.50	8.75	6. 5	8.60

5. CONCLUSION

Use of solid support over the solvent medium has shown a significant increase in yield of a biologically important heterocyclic moiety i.e. the benzodiazepine. This method of using a trace quantity of glacial acetic acid along with a neutral silica powder proved economical as compared to the earlier reported method which used some expensive metal catalysts. The microwave assisted synthesis reduces the timing of the reaction and gives the high quality of yield comparable to the conventional method.(Table1&2). The glucose containing molecules are more effective than galactosyl containing molecules.(Table3)

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