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SYNTHESIS AND BIOLOGICAL ACTIVITIES OF GLYCOCONJUGATED SPIRO TRIONES

V. N. Ingle[1]*, P. K.Gaidhane[2], K. M. Hatzade[1], V. D. Umare[1] , V. S. Taile[1]

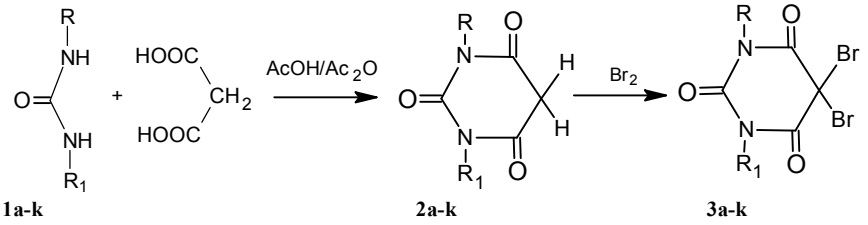
[1]Department of Chemistry, University campus, Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur, India.

[2]Department of Chemistry, Govindrao Wanjari College of Engineering and Technology, Nagpur, India.

Tel: +91 9822026274 , E-mail: Pravin.kg@rediffmail.com

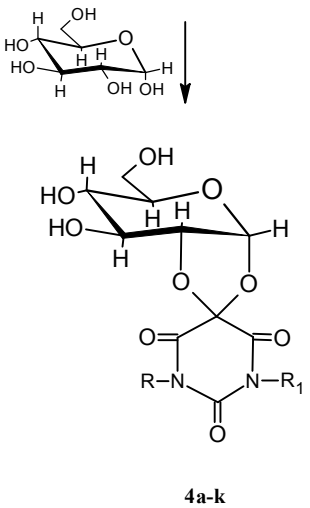
Abstract : Malonic acid undergoes condensation readily with ureas to yield barbituric acids **2** which on bromination give 5,5-dibromobarbituric acids **3**. Reaction of α-D-glucose with these 5,5-dibromo barbituric acids afforded 2,3-α-D-glucopyrano-1,4-dioxo-7,9-diaza-spiro[4,5]deca-6,8,10-triones **4**. The structures of the products have been assigned on the basis of ^{1}H NMR, ^{13}C NMR, ES-MS, optical activity and elemental analysis. The compounds are found to have antibacterial and antifungal activities.

Key words: Barbituric acid, 5, 5-dibromo barbituric acid, α-D-glucose, dioxolane, triones.



1a-k **2a-k** **3a-k**

	R	R_1
a)	H	H
b)	Phenyl	H
c)	Phenyl	Phenyl
d)	*o*-tolyl	H
e)	*o*-tolyl	*o*-tolyl
f)	*p*-tolyl	H
g)	*p*-tolyl	*p*-tolyl
h)	*o*-anisyl	H
i)	*o*-anisyl	*o*-anisyl
j)	*p*-anisyl	H
k)	*p*-anisyl	*p*-anisyl



4a-k

Scheme 1

1. Introduction

DRUGS modified with carbohydrates have been the subjects of considerable interest in carbohydrate chemistry because many carbohydrate derivatives exhibit variety of biological and therapeutic properties. Certain glycoconjugates are more readily excretable and resistant to significant metabolic transformation.[1-6] Thus, a modification of carbohydrates via carbon-oxygen bond formation receives increasing attention among synthetic organic chemists and also provides valuable synthons suitable for the synthesis of complex molecules since carbohydrate derivatives contain a large number of chiral centers and functional groups. Spirocarbocyclic systems enhance the biological potency of compounds.[7] Many spiro compounds possess antiparasitic and analgesic activities.[8] Spiroheterocycles are also used as intermediates for aldose reductase inhibitors, and some new spiroheterocycles are also found to have activity as herbicides and pesticides.[9]

It has been found that incorporation of various heterocycles in pyrimidine (triones) nucleus enhances biological activities. Barbituric acids have been reported to possess a wide spectrum of biological activities as sedatives and hypnotics, antitumor, antiviral, anti-inflammatory, antisclerotics, and bacteriostatics.[10-12] 1,3-Dioxolanes are found to be associated with a number of biological activities like antispasmodics,[13] sedatives, analgesic, tranquilizer and anesthesia.[14]

In continuation of our work on the synthesis of galactopyranosyl-derived spiro barbiturates[15] and synthetic utility of spiro compounds, herein we report the synthesis and screening results of 2,3-α-D-glucopyrano-1,4-dioxo-7,9-diaza-spiro[4,5]deca-6,8,10-triones **4** in antibacterial and antifungal assays.

2. Results and discussion

Substituted ureas **1** were prepared as described in the literature.[16] The barbituric acids **2** were prepared by the Biltz and Wittek method[15,17] in which ureas **1** are condensed with malonic acid in acetic acid-acetic anhydride. 5,5-Dibromo barbituric acids **3** were prepared by adding bromine to barbituric acids in suitable solvents.[15,18,19] Glacial acetic acid was found to be the most convenient solvent for bromition of N-substituted barbituric acids.

These acids gave a positive test for bromine. The rate of dioxolane formation-etherification-depends on the presence of substituents attached to nitrogen atoms in barbituric acids. It is fast in the case of 1-aryl and 1,3-diaryl barbituric acids. The replacement of N-hydrogen by aryl groups increases the solubility of barbituric acids in organic solvents. In the ^{1}H NMR spectrum, **3a** exhibited a singlet for NH at δ 11.68 ppm, while the ^{13}C NMR spectrum showed peaks at 165 (C-6, C-4,), 149 (C-2), and 45 ppm (C-5, C-Br). The IR spectrum showed absorption bands at 3203 (NH), 1714 (C=O), 1183 (C-N-C) and 587 cm^{-1} (C-Br). The reaction of 5,5-dibromo barbituric acid **3a** with α-D-glucopyranose afforded **4a**. The negative test for bromine, the absence of C-Br absorption band in the spectrum and the presence of strong band at 1263 cm^{-1} for C-O-C is fully consistent with structure of 2,3-α-D-glucopyrano-1,4-dioxo-7,9-diaza-spiro[4,5]deca-6,8,10-triones **4a**. The IR spectrum showed characteristic bands at 3131 (OH), 3061 (NH), 2856 (glucosidic CH), 1707 (C=O), 1263 and 1152 cm^{-1} (C-N-C) groups. The ^{1}H NMR spectrum of **4a** showed signals at δ 10 (s, 1H, N-H), 3.79, (H, CH_2) and 3.76-3.40 ppm (H, glucosidic CH). In the proton-decoupled ^{13}C NMR, the anomeric carbon C-1' and C-2' resonated at 103 and 84 ppm respectively. The ES-MS spectrum showed a molecular ion peak at 304 (M^+) and was dominated by m/z 126 ($C_4O_3N_2H_2$) with the loss of 178 amu corresponding to the loss of an intact sugar moiety, $C_6H_{10}O_6$. Also the molecular ion peak at 304 (M^+) confirms the molecular formula $C_{10}O_9N_2H_{12}$. All the compounds gave satisfactory C, H, and N elemental analysis.

2.1. Microbial activity

2.1.1. Antimicrobial activity

The synthesized compounds were screened for their antibacterial activities by the using the cup-plate method against B. *subtilis* (gram-positive) and E. *coli* (gram-negative) at concentrations of 100 µg/mL in DMF. Pure Norfloxacine was taken as standard antibiotic for the comparison of the results. The sterilized nutrient agar media (30 mL) was inoculated with the test organism and poured optically in to the Petridishes. Then four holes of 6 mm diameter were punched carefully by the using sterile cork-border and these were completely filled with different test solution. The plates were then incubated for 24 h at 37^{0}C and zones of inhibitions were measured. Similar procedure was adopted for pure Ciprofloxacin and the corresponding zone diameters were compared. The screening results indicate that compounds **4a-k** showed moderate to excellent bactericidal activities against both organisms (Table **2**).

2.1.2. Antifungal activity

The antifungal activity of synthesized compounds was evaluated by the using above same method (cup-plate technique) against A. *niger* and C. *albicans* at concentration 100 µg/mL in DMF. The plates were incubated for 8 days at 37^{0}C. The zones of inhibitions were measured. Similarly a commercial fungicide Gentamycine was also tested under similar condition with a view of comparing the results. The compounds showed significant fungitoxicity against both the test fungi (Table **2**).

3. Conclusion

In present communication, a new class of spiro barbiturates with 1, 3-dioxolane moiety was prepared through the spiro system by exploiting the reactivity of gem-dibromo functionality in 5, 5-dibromo barbituric acid with α-D-glucopyranose. They show moderate to excellent antimicrobial activity.

4. Experimental

4.1. General methods

Melting points were determined in open glass capillaries and are uncorrected. Optical rotations were measured at

29^0C. Elemental analysis ware determined using the Perkin Elmer 2400 CHN analyzer. FT-IR spectra were recorded using (KBr) disc on Perkin-Elmer spectrum Rx-I spectrometer. ^{1}H NMR and ^{13}C NMR on Brucker AC-300 F (300 MHz) NMR spectrometer by using DMSO and $CDCl_3$ as solvent and tetramethylsilane as an internal standard. Mass spectra were recorded on 70-S Mass spectrometer using *m*-nitro benzyl alcohol (NBA) matrix.

*Barbituric acid **2a***

Urea **1a** (0.9 g, 0.015 mol) and malonic acid (2.08 g, 0.02 mol) are dissolved in 5 mL of glacial acetic acid in a flask fitted with dropping funnel, reflux condenser and stirrer. The mixture was heated to 65^0C and 4 mL of acetic anhydride was added during 30 min. The reaction mixture was heated with stirring at 90^0C for 3 h. The solvent was removed by distillation under vacuum at 60^0C and the residue was treated with 0.2 N NaOH. The clear solution was acidified with 0.2 N HCl to obtained barbituric acid **2a**. mp 255^0C (water) (Yield 50 %).

Similarly, 1-aryl-and 1,3-diaryl barbituric acids **(2b-k)** were prepared by the reaction of substituted ureas **(1b-k)** with malonic acid. Compounds gave satisfactory C, H and N analysis (Table **1**).

*5,5-Dibromobarbituric acid **3a***

This was prepared by adding molecular bromine (2.55 g, 0.016 mol) to barbituric acids **2a** (1.28 g, 0.01mol) in H_2O (60 mL) at 50^0C with vigorous shaking. The compound was cooled, and filtered.

The compound **3a** was crystallized from aq methanol, mp 235^0C (Yield 70 %); (Found: C, 16.93; H, 1.03; N, 9.97 %. $C_4H_2O_3N_2Br_2$ requires C, 16.78; H, 0.69; N, 9.79%) *vmax* (KBr)/cm^{-1} 3202 (-NH), 1714 (C=O), 1183 (C-N-C), 587 (C-Br). *λmax*/nm($\xi/M^{-1}cm^{-1}$) (300 MHz, $CDCl_3$+DMSO-d_6). δ_H 11.68 (s, N-H). δ_C 165 (s, C-4, C-6), (s, C=O), 149 (s, C-2) (s, C=O), 45 (C-5) (C-Br).

Similarly, 5,5-dibromo-1-aryl-and 1,3-diaryl barbituric acids **(3b-k)** were prepared by adding bromine to 1-aryl-and 1,3-diaryl barbituric acids **(2b-k)** in suitable solvents.

*5,5-Dibromo-1-phenyl barbituric acid **3b***

The compound **3a** was crystallized from glacial acetic acid, mp 184^0C (Yield 68 %), (Found: C, 33.54; H, 1.89; N, 7.93 %. $C_{10}H_6O_3N_2Br_2$ requres C, 33.14; H, 1.65; N, 7.73%). *vmax* (KBr)/cm^{-1} 3181 (-NH), 3056 (Ar-CH), 1731 (C=O), 1179 (C-N-C), 710 (Ar-H), 574 (C-Br). *max*/nm(ξ/M^{-1} cm^{-1}) (300 MHz, $CDCl_3$+DMSO-d_6). δ_H 11.53 (s, 1H, N-H), 6.5-9.1 (m, 5H, Ar-H). δ_c 161 (C-4) (s, C=O), 158 (C-6) (s, C=O), 150 (C-2) (s, C=O), 47 (C-5) (C-Br);

*5,5-Dibromo-1,3-diphenyl barbituric acid **3c***

The compound **3c** was crystallized from benzene, mp 152^0C (Yield 71 %). (Found: C, 43.97; H, 2.59; N, 6.74 %. $C_{16}H_{10}O_3N_2Br_2$ requires C, 43.83; H, 2.28; N, 6.39 %) *vmax* (KBr)/cm^{-1} 3071 (Ar-CH), 1720 (C=O), 1181 (C-N-C), 714 (Ar-H), 579 (C-Br). *λmax*/nm (ξ/M^{-1} cm^{-1}). δ_H 6.5-9.1 (m, 5H, Ar-H). δ_C159 (C-4) (s, C=O), 157 (C-6) (s, C=O), 151 (C-2) (s, C=O), 46 (C-5) (C-Br).

*5,5-Dibromo-1-o-tolyl barbituric acid **3d***

The compound **3d** was crystallized from glacial acetic acid, mp 174^0C (Yield 69 %). (Found: C, 23.89; H, 1.79; N, 5.39 %. $C_{11}H_8O_3N_2Br_2$ requires C, 23.78; H, 1.44; N, 5.04) *vmax* (KBr)/cm^{-1} 3184 (-NH), 3049 (Ar-CH), 1733 (C=O), 1178 (C-N-C), 710 (Ar-H), 576 (C-Br). *λmax*/nm ($\xi/M^{-1}cm^{-1}$) (300 MHz, $CDCl_3$+DMSO-d_6) δ_H 11.23 (s, 1H, N-H), 6.5-9.1 (m, 5H, Ar-H), 2.32 (s, 3H, CH_3). δ_c 163 (C-4) (s, C=O), 156 (C-6) (s, C=O), 149 (C-2) (s, C=O), 49 (C-5) (C-Br), 21 (Ar-CH_3).

*5,5-Dibromo-1,3-di-o-tolyl barbituric acid **3e***

The compound **3e** was crystallized from methanol, mp 190^0C (Yield 71 %). (Found: C, 32.82; H, 2.41; N, 4.67 %. $C_{18}H_{14}O_3N_2Br_2$ requires C, 32.54; H, 2.17; N, 4.34 %). *vmax* (KBr)/cm^{-1}3023 (Ar-CH), 1730 (C=O), 1175 (C-N-C), 715 (Ar-H), 580 (C-Br). *λmax*/nm ($\xi/M^{-1}cm^{-1}$) (300 MHz, $CDCl_3$+DMSO-d_6). δ_H 6.5-9.0 (m, 10H, Ar-H), 2.29 (s, 6H, CH_3); δ_C 160 (C-4) (s, C=O), 159 (C-6) (s, C=O), 154 (C-2) (s, C=O), 46 (C-5) (C-Br), 19 (Ar-CH_3).

*5,5-Dibromo-1-o-tolyl barbituric acid **3f***

The compound **3f** was crystallized from glacial acetic acid, mp 105^0C (Yield 69 %); (Found: C, 23.87; H, 1.81; N, 5.42 %. $C_{11}H_8O_3N_2Br_2$ requires C, 23.78; H, 1.44; N, 5.04%). *vmax* (KBr)/cm^{-1} 3184 (-NH), 3049 (Ar-CH), 1733 (C=O), 1178 (C-N-C), 710 (Ar-H), 576 (C-Br). *λmax*/nm ($\xi/M^{-1}cm^{-1}$) (300 MHz, $CDCl_3$+DMSO-d_6) δ_H 11.23 (s, 1H, N-H), 6.5-9.1 (m, 5H, Ar-H), 2.32 (s, 3H, CH_3). δ_C 163 (C-4) (s, C=O), 156 (C-6) (s, C=O), 149 (C-2) (s, C=O), 49 (C-5) (C-Br), 21 (Ar-CH_3).

*5,5-Dibromo-1,3-di-o-tolyl barbituric acid **3g***

The compound **3g** was crystallized from glacial acetic acid, mp 265^0C (Yield 75 %). (Found: C, 32.83; H, 2.43; N, 4.66 %. $C_{18}H_{14}O_3N_2Br_2$ requires C, 32.54; H, 2.17; N, 4.34 %). *vmax* (KBr)/cm^{-1}3023 (Ar-CH), 1730 (C=O), 1175 (C-N-C), 715 (Ar-H), 580 (C-Br). *λmax*/nm ($\xi/M^{-1}cm^{-1}$) (300 MHz, $CDCl_3$+DMSO-d_6) δ_H 6.5-9.0 (m, 10H, Ar-H), 2.29 (s, 6H, CH_3). δ_C 160 (C-4) (s, C=O), 159 (C-6) (s, C=O), 154 (C-2) (s, C=O), 46 (C-5) (C-Br), 19 (Ar-CH_3).

*5,5-Dibromo-1-o-anisyl barbituric acid **3h***

The compound **3h** was crystallized from benzene mp 181^0C (Yield 74 %). (Found: C, 23.37; H, 1.73; N, 4.98 %. $C_{11}H_8O_4N_2Br_2$ requires C, 23.11; H, 1.40; N, 4.90 %). *vmax* (KBr)/cm^{-1} 3186 (-NH), 3059 (Ar-CH), 1747 (C=O), 1175 (C-N-C), 710 (Ar-H), 575 (C-Br). *λmax*/nm (ξ/M^{-1} cm^{-1}) (300 MHz, $CDCl_3$+DMSO-d_6) δ_H 11.33 (s, 1H, N-H), 6.5-9.0 (m, 5H, Ar-H), 3.79 (s, 3H, OCH_3). δ_c 164 (C-4) (s, C=O), 157 (C-6) (s, C=O), 152 (C-2) (s, C=O), 59 (Ar-OCH_3), 48 (C-5) (C-Br).

*5,5-Dibromo-1,3-di-o-anisyl barbituric acid **3i***

The compound **3i** was crystallized from glacial acetic acid, mp 164^0C (Yield 72 %) (Found: C, 31.99; H, 2.37; N, 4.34 %. $C_{18}H_{14}O_4N_2Br_2$ requires C, 31.95; H, 2.07; N, 4.14 %). *vmax* (KBr)/cm^{-1} 3063 (Ar-CH), 1734 (C=O), 1175 (C-N-C), 715 (Ar-H), 571 (C-Br).

λmax/nm (ξ/$M^{-1}cm^{-1}$) (300 MHz, $CDCl_3$+DMSO-d_6) δ_H 6.5-9.0 (m, 10H, Ar-H), 3.82 (s, 6H, OCH_3). δ_c 162 (C-4) (s, C=O), 154 (C-6) (s, C=O), 150 (C-2) (s, C=O), 57 (Ar-OCH_3), 49 (C-5) (C-Br).

*5,5-Dibromo-1-o-anisyl barbituric acid **3j***

The compound **3j** was crystallized from glacial acetic acid, mp 166^{0}C (AcOH) (Yield 76 %). (Found: C, 23.39; H, 2.79; N, 4.97 %. $C_{11}H_8O_4N_2Br_2$ requires C, 23.11; H, 1.40; N, 4.90 %). *vmax* (KBr)/cm^{-1} 3186 (-NH), 3059 (Ar-CH), 1747 (C=O), 1175 (C-N-C), 710 (Ar-H), 575 (C-Br). *λmax*/nm (ξ/M^{-1} cm^{-1}) (300 MHz, $CDCl_3$+DMSO-d_6) δ_H 11.33 (s, 1H, N-H), 6.5-9.0 (m, 5H, Ar-H), 3.79 (s, 3H, OCH_3). δ_c 164 (C-4) (s, C=O), 157 (C-6) (s, C=O), 152 (C-2) (s, C=O), 59 (Ar-OCH_3), 48 (C-5) (C-Br).

*5,5-Dibromo-1,3-di-o-anisyl barbituric acid **3k***

The compound **3k** was crystallized from glacial acetic acid, mp 270^{0}C (Yield 69 %). (Found: C, 31.98; H, 2.93; N, 4.37 %. $C_{18}H_{14}O_4N_2Br_2$ requires C, 31.95; H, 2.07; N, 4.14 %). *vmax* (KBr)/cm^{-1} 3063 (Ar-CH), 1734 (C=O), 1175 (C-N-C), 715 (Ar-H), 571 (C-Br). *λmax*/nm (ξ/M^{-1} cm^{-1}) (300 MHz, $CDCl_3$+DMSO-d_6) δ_H 6.5-9.0 (m, 10H, Ar-H), 3.82 (s, 6H, OCH_3). δ_C162 (C-4) (s, C=O), 154 (C-6) (s, C=O), 150 (C-2) (s, C=O), 57 (Ar-OCH_3), 49 (C-5) (C-Br).

*2,3-α-D-Glucopyrano-1,4-dioxo-7,9-diaza-spiro[4,5]deca-6,8,10-triones **4a***

A mixture of 5,5-dibromo barbituric acid **3a** (2.85 g, 0.01mol), α-D-glucose(1.80 g, 0.01mol), pyridine (0.79 g, 0.01 mol) and alcohol (25 mL) was refluxed for 3 h. The excess of solvent was distilled off and the syrup poured on to crushed ice to obtain **4a**. The compound was filtered, washed with alcohol and dried.

The compound **4a** was crystallized from glacial acetic acid, mp >285 ^{0}C (Yield 80 %); [α] $^{29}_D$ 51.72 (Found: C, 39.71; H, 3.81; N, 7.34 %. $C_{10}O_9N_2H_{12}$ requires C, 39.47; H, 3.94; N, 7.36%). *vmax* (KBr)/cm^{-1} 3131 (-OH), 3061 (-NH), 2956 (glucosidic-CH), 1708 (C=O), 1263 (C-O-C), 1176 (C-N-C), 1152 (C-O). *λmax*/nm (ξ/M^{-1} cm^{-1}) (300 MHz, $CDCl_3$+DMSO-d_6) δ_H 11.72 (s, 1H, N-H); 9.79 (s, 1H, O-H), 5.5-5.3 (m, 2H, 3'and 4'-H); 5.05-5.12 (m,1H, 2'-H, anomeric proton), 4.68 (d, 1H, 1'-H, anomeric proton), 4.11 (dd, 2H, 6'-H_2), 3.77-3.82 (m, 1H, 5'-H). δ_C 165 (C-6) (s, C=O), 163 (C-4) (s, C=O), 148 (C-2) (s, C=O), 119 (C-5, spiro C-atom), 102 (C-1', anomeric C-atom), 82 (C-2', anomeric C-atom), 78 (C-5'), 75 (C-3'), 62 (C-4'), 55 (C-6'); EI-MS: m/z 304 (M^+, $C_{10}O_9N_2H_{12}$), 126 ($C_4O_3N_2H_2$).

When the reaction of α-D-glucopyranose was extended with several other 5,5-dibromo-1-aryl-and 1,3-diaryl barbituric acids **(3b-k),** then corresponding 2,3-α-D-glucopyrano-1,4-dioxo-7-aryl-7,9-diaza-and 7,9-diaryl-7,9-diaza-spiro[4,5]deca-6,8,10-triones **(4b-k)** have been synthesized.

*2,3-α-D-glucopyrano-7-phenyl-1,4-dioxo-7,9-diaza-spiro[4,5]deca-6,8,10-triones **4b***

The compound **4b** was crystallized from glacial acetic acid, mp 164^{0}C (Yield 82 %) [α] $^{29}_D$ 58.71 (c0.1 .in methanol). (Found: C, 50.92; H, 4.56; N, 7.47 %. $C_{16}O_9N_2H_{16}$ requires C, 50.52; H, 4.21; N, 7.36 %) *vmax* (KBr)/cm^{-1} 3178 (-NH), 3201 (-OH), 3052 (Ar-CH), 2861 (glucosidic-CH), 1728 (C=O), 1268 (C-O-C), 1172 (C-N-C), 1158 (C-O), 710 (Ar-H). *λmax*/nm (ξ/M^{-1} cm^{-1}) (300 MHz, $CDCl_3$+DMSO-d_6) δ_H 11.31 (s, N-H), 9.81 (s, O-H), 6.5-8.5 (m, 5H, Ar-H), 5.5-5.2 (m, 2H, 3'and 4'-H), 5.03-5.11 (m,1H, 2'-H, anomeric proton), 4.62 (d,1H,1'-H, anomeric proton), 4.09 (dd, 2H, 6'-H_2), 3.76-3.84 (m, 1H, 5'-H). δ_C 162 (C-4) (s, C=O), 160 (C-6) (s, C=O), 154 (C-2) (s, C=O), 120-160 (aromatic C-atom), 118 (C-5, spiro C-atom), 103 (C-1', anomeric C-atom), 85 (C-2', anomeric C-atom), 77 (C-5'), 75 (C-3'), 64 (C-4'), 57 (C-6'). FAB-MS: m/z 380 (M^+, $C_{16}O_9N_2H_{16}$), 202 ($C_{10}O_3N_2H_6$), 125 ($C_4O_3N_2H$).

*2,3-α-D-Glucopyrano-7,9-diphenyl-1,4-dioxo-7,9-diaza-spiro[4,5]deca-6,8,10-triones **4c***

The compound **4c** was crystallized from glacial acetic acid, mp 198^{0}C (Yield 79 %) [α] $^{29}_D$ 66.72 (c 0.1 in methanol). (Found: C, 57.92; H, 4.59; N, 6.37 %. $C_{22}O_9N_2H_{20}$ requires C, 57.89; H, 4.38; N, 6.14 %) *vmax* (KBr)/cm^{-1}3244 (-OH), 3048 (Ar-CH), 2912 (glucosidic-CH), 1730 (C=O), 1270 (C-O-C), 1169 (C-N-C), 1151 (C-O), 719 (Ar-H). *λmax*/nm (ξ/$M^{-1}cm^{-1}$) (300 MHz, $CDCl_3$+DMSO-d_6) δ_H 9.66 (s, 1H, O-H), 6.5-8.5 (m, 5H, Ar-H), 5.5-5.3 (m, 2H, 3'and 4'-H); 5.02-5.09 (m,1H, 2'-H, anomeric proton), 4.66 (d,1H,1'-H, anomeric proton), 4.10 (dd, 2H, 6'-H_2), 3.79-3.84 (m, 1H, 5'-H). δ_C 164 (C-4) (s, C=O) 162 (C-6) (s, C=O), 149 (C-2) (s, C=O), 120-160 (aromatic C-atom), 118 (C-5, spiro C-atom), 103 (C-1', anomeric C-atom), 83 (C-2', anomeric C-atom), 76 (C-5'), 74 (C-3'), 62 (C-4'), 54 (C-6'). EI-MS: m/z 456 (M^+, $C_{22}O_9N_2H_{20}$), 278 ($C_{16}O_3N_2H_{10}$), 201 ($C_{11}O_3N_2H_5$), 124 ($C_2O_3N_2$).

*2,3-α-D-Glucopyrano-7-o-tolyl-1,4-dioxo-7,9-diaza-spiro[4,5]deca-6,8,10-triones **4d***

The compound **4d** was crystallized from glacial acetic acid, mp 228^{0}C (Yield 82 %) [α] $^{29}_D$ 102.67 (c 0.1 .in methanol). (Found: C, 51.95; H, 4.66; N, 7.12 %. $C_{17}O_9N_2H_{18}$ requires C, 51.64; H, 4.56; N, 7.08 %). *vmax* (KBr)/cm^{-1} 3211 (-OH), 3180 (-NH), 3052 (Ar-CH), 2864 (glucosidic-CH), 1731 (C=O), 1265 (C-O-C), 1175 (C-N-C), 1159 (C-O), 710 (Ar-H). *λmax*/nm (ξ/$M^{-1}cm^{-1}$) (300 MHz, $CDCl_3$+DMSO-d_6) δ_H 11.27 (s, N-H), 9.79 (s, O-H), 6.5-8.5 (m, 4H, Ar-H), 5.6-5.2 (m, 2H, 3'and 4'-H), 5.03-5.13 (m,1H, 2'-H, anomeric proton), 4.62 (d, 1H, 1'-H, anomeric proton), 4.09 (dd, 2H, 6'-H_2), 3.75-3.80 (m, 1H, 5'-H), 2.23 (s, 3H, CH_3). δ_C 162 (C-4) (s, C=O), 160 (C-6) (s, C=O), 154 (C-2) (s, C=O), 120-160 (aromatic C-atom), 119 (C-5, spiro C-atom), 103 (C-1', anomeric C-atom), 87 (C-2', anomeric C-atom), 79 (C-5'), 72 (C-3'), 65 C-4'), 58 (C-6'), 20 (Ar-CH_3). EI-MS: m/z 394 (M^+, $C_{17}O_9N_2H_{18}$), 216 ($C_{11}O_3N_2H_8$), 201 ($C_{10}O_3N_2H_5$), 125 ($C_4O_3N_2H$).

*2,3-α-D-Glucopyrano-7,9-di-o-tolyl-1,4-dioxo-7,9-diaza-spiro[4,5]deca-6,8,10-triones **4e***

The compound **4e** was crystallized from glacial acetic acid, mp 252^{0}C (Yield 78 %) $[\alpha]^{29}_D$ 121.38 (c 0.1 .in methanol). (Found: C, 59.21; H, 4.78; N, 5.98 %. $C_{24}O_9N_2H_{24}$ requires C, 59.50; H, 4.95; N, 5.78 %). *vmax*(KBr)/cm^{-1} 3214 (-OH), 3061 (Ar-CH), 2890 (glucosidic-CH), 1729 (C=O), 1269 (C-O-C), 1173 (C-N-C), 1148 (C-O), 710 (Ar-H). *λmax*/nm (ξ/M^{-1}cm^{-1}) (300 MHz, $CDCl_3$+DMSO-d_6) δ_H 11.23 (s, N-H), 9.79 (s, O-H), 6.5-8.5 (m, 8H, Ar-H), 5.5-5.1 (m, 2H, 3'and 4'-H); 5.03-5.11 (m,1H, 2'-H, anomeric proton), 4.69 (d,1H,1'-H, anomeric proton), 4.11 (dd, 2H, 6'-H_2), 3.73-3.79 (m, 1H, 5'-H), 2.30 (s, 6H, CH_3). δ_C 164 (C-4) (s, C=O), 161 (C-6) (s, C=O), 157 (C-2) (s, C=O), 120-160 (aromatic C-atom), 119 (C-5, spiro C-atom), 103 (C-1', anomeric C-atom), 89 (C-2', anomeric C-atom), 78 (C-5'), 73 (C-3'), 64 (C-4'), 55 (C-6'), 20 (Ar-CH_3); EI-MS: m/z 484 (M^+, $C_{24}O_9N_2H_{24}$), 306 ($C_{18}O_3N_2H_{14}$), 291 ($C_{17}O_3N_2H_{11}$), 215($C_{11}O_3N_2H_7$), 200 ($C_{10}O_3N_2H_4$), 124 ($C_4O_3N_2$).

2,3-α-D-Glucopyrano-7-o-tolyl-1,4-dioxo-7,9-diaza-spiro[4,5]deca-6,8,10-triones ***4f***

The compound **4f** was crystallized from glacial acetic acid, mp 105^{0}C (Yield 81 %) $[\alpha]^{29}_D$ -97.72 (c 0.1 .in methanol). (Found: C, 51.95; H, 4.66; N, 7.12 %. $C_{17}O_9N_2H_{18}$ requires C, 51.64; H, 4.56; N, 7.08 %). *vmax* (KBr)/cm^{-1} 3211 (-OH), 3180 (-NH), 3052 (Ar-CH), 2864 (glucosidic-CH), 1731 (C=O), 1265 (C-O-C), 1175 (C-N-C), 1159 (C-O), 710 (Ar-H). *λmax*/nm (ξ/M^{-1}cm^{-1}) (300 MHz, $CDCl_3$+DMSO-d_6) δ_H 11.27 (s, N-H), 9.79 (s, O-H), 6.5-8.5 (m, 4H, Ar-H), 5.6-5.2 (m, 2H, 3'and 4'-H), 5.03-5.13 (m,1H, 2'-H, anomeric proton), 4.62 (d, 1H, 1'-H, anomeric proton), 4.09 (dd, 2H, 6'-H_2), 3.75-3.80 (m, 1H, 5'-H), 2.23 (s, 3H, CH_3). δ_C 162 (C-4) (s, C=O), 160 (C-6) (s, C=O), 154 (C-2) (s, C=O), 120-160 (aromatic C-atom), 119 (C-5, spiro C-atom), 103 (C-1', anomeric C-atom), 87 (C-2', anomeric C-atom), 79 (C-5'), 72 (C-3'), 65 (C-4'), 58 (C-6'), 20 Ar-CH_3); EI-MS: m/z 394 (M^+, $C_{17}O_9N_2H_{18}$), 216 ($C_{11}O_3N_2H_8$), 201 ($C_{10}O_3N_2H_5$), 125 ($C_4O_3N_2H$).

2,3-α-D-Glucopyrano-7,9-di-o-tolyl-1,4-dioxo-7,9-diaza-spiro[4,5]deca-6,8,10-triones ***4g***

The compound **4g** was crystallized from glacial acetic acid, mp 265^{0}C (Yield 79 %) $[\alpha]^{29}_D$ 80.87 (c 0.1 .in methanol). (Found: C, 59.21; H, 4.78; N, 5.98 %. $C_{24}O_9N_2H_{24}$ requires C, 59.50; H, 4.95; N, 5.78 %). *vmax*(KBr)/cm^{-1} 3214 (-OH), 3061 (Ar-CH), 2890 (glucosidic-CH), 1729 (C=O), 1269 (C-O-C), 1173 (C-N-C), 1148 (C-O), 710 (Ar-H). *λmax*/nm (ξ/M^{-1}cm^{-1}) (300 MHz, $CDCl_3$+DMSO-d_6) δ_H 11.23 (s, N-H), 9.79 (s, O-H), 6.5-8.5 (m, 8H, Ar-H), 5.5-5.1 (m, 2H, 3'and 4'-H); 5.03-5.11 (m,1H, 2'-H, anomeric proton), 4.69 (d,1H,1'-H, anomeric proton), 4.11 (dd, 2H, 6'-H_2), 3.73-3.79 (m, 1H, 5'-H), 2.30 (s, 6H, CH_3). δ_C 164 (C-4) (s, C=O), 161 (C-6) (s, C=O), 157 (C-2) (s, C=O), 120-160 (aromatic C-atom), 119 (C-5, spiro C-atom), 103 (C-1', anomeric C-atom), 89 (C-2', anomeric C-atom), 78 (C-5'), 73 (C-3'), 64 (C-4'), 55 (C-6'), 20 (Ar-CH_3); EI-MS: m/z 484 (M^+, $C_{24}O_9N_2H_{24}$), 306 ($C_{18}O_3N_2H_{14}$), 291 ($C_{17}O_3N_2H_{11}$), 215($C_{11}O_3N_2H_7$), 200 ($C_{10}O_3N_2H_4$), 124 ($C_4O_3N_2$).

2,3-α-D-Glucopyrano-7-o-anisyl-1,4-dioxo-7,9-diaza-spiro[4,5]deca-6,8,10-triones ***4h***

The compound **4h** was crystallized from glacial acetic acid, mp 137^{0}C (Yield 80 %) $[\alpha]^{29}_D$ 66.29 (c 0.1 in methanol). (Found: C, 49.54; H, 4.36; N, 6.92 %. $C_{17}O_{10}N_2H_{18}$ requires C, 49.75; H, 4.14; N, 6.82 %). *vmax*(KBr)/cm^{-1} 3219 (-OH), 3184 (-NH), 3054 (Ar-CH), 2871 (glucosidic-CH), 1744 (C=O), 1269 (C-O-C), 1174 (C-N-C), 1146 (C-O), 710 (Ar-H). *λmax*/nm (ξ/M^{-1}cm^{-1}) (300 MHz, $CDCl_3$+DMSO-d_6) δ_H 11.31 (s, N-H), 9.81 (s, O-H), 6.5-8.5 (m, 5H, Ar-H), 5.6-5.2 (m, 2H, 3'and 4'-H), 5.03-5.16 (m,1H, 2'-H, anomeric proton), 4.67 (d,1H,1'-H, anomeric proton), 4.12 (dd, 2H, 6'-H_2), 3.78-3.83 (m, 1H, 5'-H), 3.92 (s, 3H, OCH_3). δ_C 166 (C-4) (s, C=O), 163 (C-6) (s, C=O), 158 (C-2) (s, C=O), 120-160 (aromatic C-atom), 119 (C-5, spiro C-atom), 102 (C-1', anomeric C atom), 87 (C-2', anomeric C-atom), 78 (C-5'), 73 (C-3'), 66 (C-4'), 59 (C-6'), 57 (CH_3, Ar-OCH_3). EI-MS: m/z 410 (M^+, $C_{17}O_{10}N_2H_{18}$), 232 ($C_{11}O_4N_2H_8$), 201 ($C_{10}O_3N_2H_5$), 125 ($C_4O_3N_2H$).

3-α-D-Galactopyrano-7,9-di-o-anisyl-1,4-dioxo-7,9-diaza-spiro[4,5]deca-6,8,10-triones ***4i***

The compound **4i** was crystallized from glacial acetic acid, mp 118^{0}C (Yield 81 %) $[\alpha]^{29}_D$ 35.85 (c 0.1 .in methanol). (Found: C, 55.61; H, 4.94; N, 5.72 %. $C_{24}O_{11}N_2H_{24}$ requires C, 55.81; H, 4.65; N, 5.42 %). *vmax* (KBr)/cm^{-1} 3212 (-OH), 3059 (Ar-CH), 2868 (glucosidic-CH), 1737 (C=O), 1271 (C-O-C), 1172 (C-N-C), 1153 (C-O), 710 (Ar-H). *λmax*/nm (ξ/M^{-1}cm^{-1}) (300 MHz, $CDCl_3$+DMSO-d_6) δ_H 11.39 (s, N-H), 9.87 (s, O-H), 6.5-8.5 (m, 8H, Ar-H), 5.6-5.2 (m, 2H, 3'and 4'-H), 5.03-5.13 (m,1H, 2'-H, anomeric proton), 4.65 (d, 1H, 1'-H, anomeric proton), 4.12 (dd, 2H, 6'-H_2), 4.03 (s, 6H, OCH_3), 3.78 (m, 1H, 5'-H). δ_C 166 (C-4) (s, C=O), 163 (C-6) (s, C=O), 158 (C-2) (s, C=O), 120-160 (aromatic C-atom), 119 (C-5, spiro C-atom), 102 (C-1', anomeric C-atom), 87 (C-2', anomeric C-atom), 78 (C-5'), 73 (C-3'), 66 (C-4'), 59 (C-6'), 56 (CH_3, Ar-OCH_3). EI-MS: m/z 516 (M^+, $C_{24}O_{11}N_2H_{24}$), 338 ($C_{18}O_5N_2H_{14}$), 307 ($C_{17}O_4N_2H_{11}$), 231 ($C_{11}O_4N_2H_7$), 200 ($C_{10}O_3N_2H_4$), 124 ($C_4O_3N_2$).

2,3-α-D-Glucopyrano-7-o-anisyl-1,4-dioxo-7,9-diaza-spiro[4,5]deca-6,8,10-triones ***4j***

The compound **4j** was crystallized from glacial acetic acid, mp 166^{0}C (Yield 76 %)$[\alpha]^{29}_D$ 129.68 (c 0.1 in methanol). (Found: C, 49.54; H, 4.36; N, 6.92 %. $C_{17}O_{10}N_2H_{18}$ requires C, 49.75; H, 4.14; N, 6.82 %). *vmax* (KBr)/cm^{-1} 3219 (-OH), 3184 (-NH), 3054 (Ar-CH), 2871 (glucosidic-CH), 1744 (C=O), 1269 (C-O-C), 1174 (C-N-C), 1146 (C-O), 710 (Ar-H). *λmax*/nm (ξ/M^{-1}cm^{-1}) (300 MHz, $CDCl_3$+DMSO-d_6) δ_H 11.31 (s, N-H), 9.81 (s, O-H), 6.5-8.5 (m, 5H, Ar-H), 5.6-5.2 (m, 2H, 3'and 4'-H), 5.03-5.16 (m,1H, 2'-H, anomeric proton), 4.67 (d,1H,1'-H, anomeric proton), 4.12 (dd, 2H, 6'-H_2), 3.78-3.83 (m, 1H, 5'-H), 3.92 (s, 3H, OCH_3). δ_C 166 (C-4) (s, C=O), 163 (C-6) (s, C=O), 158 (C-2) (s, C=O), 120-160 (aromatic C-atom), 119 (C-5, spiro C-atom), 102

(C-1', anomeric C atom), 87 (C-2', anomeric C-atom), 78 (C-5'), 73 (C-3'), 66 (C-4'), 59 (C-6'), 57 (CH_3, Ar-OCH_3); EI-MS: m/z 410 (M^+, $C_{17}O_{10}N_2H_{18}$), 232 ($C_{11}O_4N_2H_8$), 201 ($C_{10}O_3N_2H_5$), 125 ($C_4O_3N_2H$).

3-α-D-Glucopyrano-7,9-di-o-anisyl-1,4-dioxo-7,9-diaza-spiro[4,5]deca-6,8,10-triones ***4k***

The compound **4k** was crystallized from glacial acetic acid, mp 270^{0}C (Yield 82 %) [α] $^{29}_D$ 58.34 (c 0.1 .in methanol). (Found: C, 55.61; H, 4.94; N, 5.72 %. $C_{24}O_{11}N_2H_{24}$ requires C, 55.81; H, 4.65; N, 5.42 %). *vmax* (KBr)/cm^{-1}3212 (-OH), 3059 (Ar-CH), 2868 (glucosidic-CH), 1737 (C=O), 1271 (C-O-C), 1172 (C-N-C), 1153 (C-O), 710 (Ar-H). *λmax*/nm (ξ/M^{-1}cm^{-1}) (300 MHz, $CDCl_3$+DMSO-d_6) δ_H 11.39 (s, N-H), 9.87 (s, O-H), 6.5-8.5 (m, 8H, Ar-H), 5.6-5.2 (m, 2H, 3'and 4'-H), 5.03-5.13 (m,1H, 2'-H, anomeric proton), 4.65 (d, 1H, 1'-H, anomeric proton), 4.12 (dd, 2H, 6'-H_2), 4.03 (s, 6H, OCH_3), 3.78 (m, 1H, 5'-H). δ_C 166 (C-4) (s, C=O), 163 (C-6) (s, C=O), 158 (C-2) (s, C=O), 120-160 (aromatic C-atom), 119 (C-5, spiro C-atom), 102 (C-1', anomeric C-atom), 87 (C-2', anomeric C-atom), 78 (C-5'), 73 (C-3'), 66 (C-4'), 59 (C-6'), 56 (CH_3, Ar-OCH_3). EI-MS: m/z 516 (M^+, $C_{24}O_{11}N_2H_{24}$), 338 ($C_{18}O_5N_2H_{14}$), 307 ($C_{17}O_4N_2H_{11}$), 231 ($C_{11}O_4N_2H_7$), 200 ($C_{10}O_3N_2H_4$), 124 ($C_4O_3N_2$).

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Table 1. Characterization data of compound 2a-k

Product	R	R_1	Mol. Formula	mp (^{0}C)	Yield (%)	% found(Calcd) C	H	N
2a	H	H	$C_4H_4O_3N_2$	255	50	37.82 (37.50)	3.83 (3.12)	21.98 (21.87)
2b	C_6H_5	H	$C_{10}H_8O_3N_2$	262	48	59.69 (59.40)	3.98 (3.96)	13.93 (13.86)
2c	C_6H_5	C_6H_5	$C_{16}H_{12}O_3N_2$	238	52	69.23 (69.06)	4.54 (4.31)	10.37 (10.07)
2d	*O*-CH_3-C_6H_4	H	$C_{11}H_{10}O_3N_2$	181	44	33.69 (33.41)	2.84 (2.53)	7.39 (7.08)
2e	*O*-CH_3-C_6H_4	*O*-CH_3-C_6H_4	$C_{18}H_{16}O_3N_2$	210	47	44.91 (44.62)	3.72 (3.30)	5.86 (5.78)
2f	*p*-CH_3-C_6H_4	H	$C_{11}H_{10}O_3N_2$	243	44	33.57 (33.41)	2.91 (2.53)	7.33 (7.08)
2g	*p*-CH_3-C_6H_4	*p*-CH_3-C_6H_4	$C_{18}H_{16}O_3N_2$	233	49	44.93 (44.62)	3.77 (3.30)	5.85 (5.78)
2h	*O*-OCH_3-C_6H_4	H	$C_{11}H_{10}O_4N_2$	253	41	32.42 (32.11)	2.76 (2.43)	6.97 (6.81)
2i	*O*-OCH_3-C_6H_4	*O*-OCH_3-C_6H_4	$C_{18}H_{16}O_5N_2$	186	43	41.96 (41.86)	3.42 (3.10)	5.84 (5.42)
2j	*P*-OCH_3-C_6H_4	H	$C_{11}H_{10}O_4N_2$	190	49	32.47 (32.11)	2.81 (2.43)	6.96 (6.81)
2k	*P*-OCH_3-C_6H_4	*P*-OCH_3-C_6H_4	$C_{18}H_{16}O_5N_2$	220	48	41.93 (41.86)	2.81 (3.10)	5.79 (5.42)

Table 2. Data for in vitro antibacterial and antifungal activities of compounds 4a-k

	Diameter of inhibition zone (in mm) against			
	Bacterial Strains		Fungal Strains	
products	*E.coli*	*B.subtilis*	*A. niger*	*C. albicans*
4a	25	17	21	19
4b	23	25	23	20
4c	21	15	23	16
4d	28	15	23	20
4e	21	21	22	20
4f	18	13	17	- -
4g	24	16	22	18
4h	11	14	16	16
4i	15	18	24	21
4j	13	11	- -	17
4k	14	--	21	21

- - = no inhibition of growth.

Diameter of zone of inhibition from 22-28 (in mm) shows excellent activity, that of 16-21 (in mm) exhibits moderate activity and that of 11-15 (in mm) shows poor activity for bacterial strains.

Diameter of zone of inhibition from 20-24 (in mm) shows excellent activity, that of 15-19 (in mm) exhibits moderate activity and that of 11-14 (in mm) shows poor activity for Fungal Strains.

Ciprofloxacine 100 µg/mL used as standard against E. *coli*, and *B. subtilis*, diameter of zone of inhibition is 35 and 29 respectively.

Gentamycine100 µg/mL used as standard against A. *niger* and *C. albicans,* diameter of zone of inhibition is 25 and 21 respectivrly.

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