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Synthesis of Some Biologically Active Pyrazolylphthalazine Derivatives and Acyclo-*C*-nucleosides of 6-(2,4,6-trimethylphenyl)-1,2,4-triazolo[3,4-a]phthalazine

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1-Chloro-4-(2,4,6-trimethylphenyl)phthalazine (**2**) was used as a precursor for preparation of some novel pyrazolylphthalazine derivatives **6-13** and **15-19**. Moreover, the acyclonucleosides **20-23 a-e** were prepared by the reaction of hydrazinophthalazine derivative **3** with different aldoses. All new phthalazine derivatives were characterized using ^{1}H NMR, ^{13}C NMR, FTIR, mass spectrum and elemental analysis. The newly synthesized compounds showed highly activity against different species of bacteria and fungi, in addition to an excellent antiinflammatory property.

Keywords: C-nucleosides, Phthalazine derivatives, Biological activity.

INTRODUCTION

The synthesis of new series of heterocyclic molecules and the evaluation of their biological and antiinflammatory activities is the major objective of this research work. Heterocyclic molecules that contain nitrogen have received great attention as described by several published articles on their applications in diverse areas, particularly as drugs[1,2]. Phthalazines are examples of heterocycles, that are containing nitrogen, have a great biological interest[3-5]. They form the structural outline for numerous biologically active compounds. Therefore, they are considered a significant key elements in organic synthesis. Numerous reports in the literature have focused on the pharmacology of phthalazine derivatives. These reports have ensued in a great number of contributions in different areas of interest[6-11]. Phthalazine derivatives were described to possess anticonvulsant[12], cardiotonic[13], antimicrobial[14], antitumor[15-18], antihypertensive[19,20], antithrombotic[21], antidiabetic[22,23], antitrypanosomal[24], antiinflammatory[25-31] and vasorelaxant activities[20,32]. Moreover, phthalazines have recently been described to inhibit serotonin reuptake and are considered as antidepression agents[33]. Thus, a number of methods have been described for the synthesis of phthalazine derivatives[12,34-40]. However, the development of new synthetic methods for heterocycles molecules containing phthalazine ring is still considered as a scientific challenge. On the other hand, C-nucleosides were revealed to exhibit noticeable and versatile biological activities[41,42] and many of their derivatives have been synthesized recently as potential antimicrobial[43] and antiviral agents[44]. Thus, many reports[45-50] have recently performed in dealing with this class of nucleosides. In view of the aforementioned facts, we aim to incorporate a phthalazine moiety with other heterocyclic ring system to attain new functions in challenge to improve the antimicrobial activity of compounds containing the phthalazine ring system.

EXPERIMENTAL

Melting points were determined on a MEL-TEMP II melting point apparatus in open glass capillaries and are uncorrected. The infrared spectra were recorded for potassium bromide discs on a Pye-Unicam SP1025 spectrophotometer. NMR spectra were carried out at ambient temperature (-25 °C) with a Brucker AC-250 spectrometer or with a Varian Gemini 200 spectrometer at 250 MHz using tetramethylsilane (TMS) as an internal standard. Mass spectra (MS) were performed on a Hewlett-Packard 5995 gas chromatography-mass spectrometer system or on a Shimadzu GCMS-QP 1000 EX mass spectrometer. Homogeneity of the products and follow up of the reactions

were checked by ascending thin-layer chromatography TLC on plates pre-coated with silica gel G (E. Merck; layer thickness 0.25 mm), used without pretreatment.

General procedure for synthesis of compounds (4-6): As described from previous work[63] with some modifications; briefly: active methylene compounds (*viz* malononitrile, ethyl cyanoacetate, ethyl acetoacetate and acetylacetone, 0.01 mol) were added to an ethanolic sodium ethoxide solution (0.56 g of sodium in 50 mL ethanol) and left for stirring for 2 h. Compound **2** (0.01 mmol) was also added to an ethanolic sodium ethoxide solution (0.56 g of sodium in 50 mL ethanol) and stirred for 2 h. The reaction mixture was heated under reflux for 5 h. The ethanol was removed under reduced pressure and the residue was poured into cold water (100 mL) and extracted with ether. The extracted solvent was dried over anhydrous sodium sulphate and removed under reduced pressure to give the compounds **4-6**, respectively.

2-[4-(2,4,6-Trimethylphenyl)-phthalazin-1-yl]-malononitrile (4): Yield: 71 %; m.p. 173-174 °C; ^{1}H NMR (DMSO-d_6) δ: 2.37 (s, 3H, CH_3), 2.48 (s, 6H, $2CH_3$), 4.57 (s, 1H, CH), 7.08-8.02 (m, 6H, Ar-H); ^{13}C NMR (DMSO-d_6) δ: 20.2, 22.5, 27.1, 119.1, 123.4, 126.1, 127.1, 127.8, 129, 129.7, 133.1, 133.9, 138.2, 140.1, 152.2, 154.1; IR (KBr, ν_{max}, cm^{-1}): 2223 (2 CN); MS (70 eV) *m/z* (%): 312 (M^+, 10). Anal. calcd. for $C_{20}H_{16}N_4$: C, 76.90; H, 5.16; N, 17.94; found C, 76.94; H, 5.10; N, 17.90.

Ethyl 2-cyano-2-[4-(2,4,6-trimethylphenyl)phthalazin-1-yl]acetate (5a): Yield: 62 %; m.p. 215-216 °C; ^{1}H NMR (DMSO-d_6) δ: 1.35 (t, *J* = 10 Hz, 3H, CH_3), 2.32 (s, 3H, CH_3), 2.50 (s, 6H, 2 CH_3), 4.31 (q, *J* = 10 Hz, 2H, CH_2), 5.03 (s, 1H, CH), 7.02-8 (m, 6H, Ar-H); ^{13}C NMR (DMSO-d_6) δ: 15.2, 20.3, 22.8, 37.2, 66.1,117.3, 123.8, 125.1, 127.3, 127.9, 129.5, 130.7, 132.1, 133.4, 138.2, 140.6, 155.2, 157.1, 169.0; IR (KBr, ν_{max}, cm^{-1}): 2231 (CN), 1735 (CO); MS (70 eV) *m/z* (%): 359 (M^+, 20). Anal. calcd. for $C_{22}H_{21}N_3O_2$: C, 73.52; H, 5.89; N, 11.69; found C, 73.50; H, 5.91; N, 11.66.

Ethyl 2-[4-(2,4,6-trimethylphenyl)phthalazin-1-yl]-3-oxobutanoate (5b): Yield: 65 %; m.p. 188-189 °C; ^{1}H NMR (DMSO-d_6) δ: 1.24 (t, *J* = 10 Hz, 3H, CH_3), 2.35 (s, 3H, CH_3), 2.50 (s, 6H, 2 CH_3), 2.61 (s, 3H, $COCH_3$), 4.44 (q, *J* = 10 Hz, 2H, CH_2), 5.11 (s, 1H, CH), 7.04-7.98 (m, 6H, Ar-H); ^{13}C NMR (DMSO-d_6) δ: 15.6, 20.1, 22, 29.2, 63.0, 65.6, 123, 125.2, 126.8, 127.7, 129, 130.1, 132.7, 133, 137.2, 140, 155.9, 158.1, 167.0, 188.1; IR (KBr, ν_{max}, cm^{-1}): 1710, 1735 (2 CO); MS (70 eV) *m/z* (%): 376 (M^+, 9). Anal. calcd. for $C_{23}H_{24}N_2O_3$: C, 73.38; H, 6.43; N, 7.44; found C, 73.30; H, 6.47; N, 7.45.

3-[4-(2,4,6-Trimethylphenyl)phthalazin-1-yl]pentane-2,4-dione (6): Yield: 64 %; m.p. 163-164 °C; ^{1}H NMR (DMSO-d_6) δ: 2.31 (s, 3H, CH_3), 2.47 (s, 6H, 2 CH_3), 2.70 (s, 6H, $2COCH_3$), 5.01 (s, 1H, CH), 7.01-7.99 (m, 6H, Ar-H); ^{13}C NMR (DMSO-d_6) δ: 20.5, 22.4, 30.1, 77.9, 123.3, 125.4, 126.9, 128.5, 129.1, 130.4, 132.7, 133.5, 136.5, 140.1, 155, 158, 190; IR (KBr, ν_{max}, cm^{-1}): 1717 (2 CO); MS (70 eV) *m/z* (%): 346 (M^+, 18). Anal. calcd. for $C_{22}H_{22}N_2O_2$: C, 76.28; H, 6.40; N, 8.09; found C, 76.29; H, 6.46; N, 8.

General procedure for the synthesis of pyrazolylphthalazines 7-9: A mixture of **4**, **5a**, **5b**, **6** (0.005 mol) and hydrazine hydrate (0.005 mol) in absolute ethanol (20 mL) was heated under reflux for 6 h and then allowed to cool. The solid product was collected and recrystallized from the proper solvent to give the compounds **7-9**, respectively.

4-[4-(2,4,6-Trimethylphenyl)phthalazin-1-yl]-4*H*-pyrazole-3,5-diamine (7): Yield: 62 %; m.p. 209-210 °C; ^{1}H NMR (DMSO-d_6) δ: 2.38 (s, 3H, CH_3), 2.51 (s, 6H, 2 CH_3), 4.11 (s, 1H, CH), 5.10-5.40 (br s, 4H, $2NH_2$), 7.04-8.01 (m, 6H, Ar-H); ^{13}C NMR (DMSO-d_6) δ: 20.8, 22.7, 48.1, 124, 125.1, 126, 128.6, 129, 131, 132.4, 133.6, 136.5, 140.3, 154.5, 158.1, 170.2; IR (KBr, ν_{max}, cm^{-1}): 3467-3296 (NH_2); MS (70 eV) *m/z* (%): 344 (M^+, 10). Anal. calcd. for $C_{20}H_{20}N_6$: C, 69.75; H, 5.85; N, 24.40; found C, 69.71; H, 5.87; N, 24.44.

3-Amino-4-[4-(2,4,6-trimethylphenyl)phthalazin-1-yl]-1*H*-pyrazol-5(4*H*)-one (8a): Yield: 59 %; m.p. 239-240 °C; ^{1}H NMR (DMSO-d_6) δ: 2.36 (s, 3H, CH_3), 2.50 (s, 6H, $2CH_3$), 4.22 (s, 1H, CH), 4.40 (br s, 2H, NH_2), 6.92-8 (m, 7H, Ar-H + NH of pyrazole); ^{13}C NMR (DMSO-d_6) δ: 21, 22.6, 55.2, 122.6, 125, 126.3, 128.9, 129.7, 130.8, 132.8, 133, 136.6, 141, 155.4, 156.8, 159.1, 178.1; IR (KBr, ν_{max}, cm^{-1}): 3425-3211 (multiple bands, NH_2, NH), 1678 (CO), 1612 (C=N); MS (70 eV) *m/z* (%): 345 (M^+, 8). Anal. calcd. for $C_{20}H_{19}N_5O$: C, 69.55; H, 5.54; N, 20.28; found C, 69.50; H, 5.51; N, 20.30.

4-[4-(2,4,6-Trimethylphenyl)phthalazin-1-yl]-3-methyl-1*H*-pyrazol-5(4*H*)-one (8b): Yield: 61 %; m.p. 250-251 °C; ^{1}H NMR (DMSO-d_6) δ: 2.12 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 2.52 (s, 6H, $2CH_3$), 4.10 (s, 1H, CH), 6.96-8.09 (m, 7H, Ar-H + NH of pyrazole); ^{13}C NMR (DMSO-d_6) δ: 20.4, 21.8, 22.5, 52.2, 123, 125, 127.4, 128, 129.5, 131.2, 132.4, 133.8, 136.8, 140.4, 152.1, 154.8, 158.1, 176.9; IR (KBr, ν_{max}, cm^{-1}): 3224 (NH), 1679 (CO), 1611 (C=N); MS (70 eV) *m/z* (%): 344 (M^+, 15). Anal. calcd. for $C_{21}H_{20}N_4O$: C, 73.23; H, 5.85; N, 16.27; found C, 73.20; H, 5.87; N, 16.20.

1-(3,5-Dimethyl-1*H*-pyrazol-4-yl)-4-(2,4,6-trimethylphenyl)phthalazine (9): Yield: 60 %; m.p. 200-201 °C; ^{1}H NMR (DMSO-d_6) δ: 2.34 (s, 3H, CH_3), 2.49 (s, 6H, $2CH_3$), 2.55, 2.65 (2s, 6H, $2CH_3$ of pyrazole), 7.00-8.13 (m, 7H, Ar-H + NH of pyrazole); ^{13}C NMR (DMSO-d_6) δ: 16.1, 21, 22.3, 120, 123.3, 125.3, 126.9, 128.8, 129, 131.5, 132.3, 133.7, 136.6, 140.4, 144, 144.6, 154.2, 157.2; IR (KBr, ν_{max}, cm^{-1}): 3211 (NH), 1609 (C=N); MS (70 eV) *m/z* (%): 342 (M^+, 11). Anal. calcd. for $C_{22}H_{22}N_4$: C, 77.16; H, 6.48; N, 16.36; found C, 77.19; H, 6.40; N, 16.37.

General procedure for the synthesis of pyrazolylphthalazine derivatives 10-13: A solution of **3** (0.01 mol) and active methylene compounds, namely ethyl acetoacetate, ethyl cyanoacetate, diethylmalonate, acetylacetone (0.012 mol), in ethanol (25 mL) containing catalytic amount of piperidine (1 mL) was refluxed for 4 h. The solid compound obtained after cooling was crystallized from a suitable solvent to give the compounds **10-13**.

1-[4-(2,4,6-Trimethylphenyl)phthalazin-1-yl]-3-methyl-1*H*-pyrazol-5(4*H*)-one (10): Yield: 71 %; m.p. 270-271 °C; ^{1}H NMR (DMSO-d_6) δ: 2.30 (s, 3H, CH_3), 2.47 (s, 6H, $2CH_3$), 2.61 (s, 3H, CH_3), 3.83 (s, 2H, CH_2), 7.01-8.03 (m, 6H, Ar-H); ^{13}C NMR (DMSO-d_6) δ: 18.2, 21.8, 23, 45.5, 117.1, 121.3, 126, 128.3, 130.2, 130.9, 132, 133.4, 136.2, 139.3, 147, 153.5, 161.3, 175.1; IR (KBr, ν_{max}, cm^{-1}): 3246 (NH), 1709 (CO), 1615 (C=N); MS (70 eV) *m/z* (%): 344 (M^+, 19). Anal. calcd. for $C_{21}H_{20}N_4O$: C, 73.23; H, 5.85; N, 16.27; found C, 73.20; H, 5.83; N, 16.29.

3-Amino-1-[4-(2,4,6-trimethylphenyl)phthalazin-1-yl]-1*H*-pyrazol-5(4*H*)-one (11): Yield: 68 %; m.p. 223-224 °C; ^{1}H NMR (DMSO-d_6) δ: 2.33 (s, 3H, CH_3), 2.49 (s, 6H, $2CH_3$), 3.42 (s, 2H, CH_2), 4.47 (br s, 2H, NH_2), 7.04-8.04 (m, 6H, Ar-H); ^{13}C NMR (DMSO-d_6) δ: 21.3, 22.9, 75.2, 116.6, 121, 126.4, 129.3, 130.5, 130.9, 132.2, 133.5, 136.1, 139.53, 147.1, 154.5, 167.1, 175.9; IR (KBr, ν_{max}, cm^{-1}): 3379 (NH_2), 1712 (CO), 1612 (C=N); MS (70 eV) *m/z* (%): 345 (M^+, 14). Anal. calcd. for $C_{20}H_{19}N_5O$: C, 69.55; H, 5.54; N, 20.28; found C, 69.50; H, 5.58; N, 20.30.

1-[4-(2,4,6-Trimethylphenyl)phthalazin-1-yl]pyrazolidine-3,5-dione (12): Yield: 71 %; m.p. 236-237 °C; ^{1}H NMR (DMSO-d_6) δ: 2.33 (s, 3H, CH_3), 2.49 (s, 6H, $2CH_3$), 3.79 (s, 2H, CH_2), 7.04-8.04 (m, 6H, Ar-H), 9.88 (s, 1H, NH, exchangeable); ^{13}C NMR (DMSO-d_6) δ: 20.8, 23.1, 50.1, 116.7, 121, 126, 129.1, 130.4, 130.9, 132.1, 133.5, 137.1, 139.2, 147.1, 153.0, 166.1, 173.0; IR (KBr, ν_{max}, cm^{-1}): 3224 (NH), 1707-1666 (2CO), 1618 (C=N); MS (70 eV) *m/z* (%): 346 (M^+, 7). Anal. calcd. for $C_{20}H_{18}N_4O_2$: C, 69.35; H, 5.24; N, 16.17; found C, 69.36; H, 5.29; N, 16.10.

1-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-4-(2,4,6-trimethylphenyl)phthalazine (13): Yield: 70 %; m.p. 170-171 °C; ^{1}H NMR (DMSO-d_6) δ: 1.82 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 2.49 (s, 6H, $2CH_3$), 2.62 (s, 3H, CH_3), 6.13 (s, 1H, CH of pyrazole), 7.01-8.08 (m, 6H, Ar-H); ^{13}C NMR (DMSO-d_6) δ: 11.1, 15.3, 21.9, 23.2, 107.2, 118.1, 121.8, 126, 128.1, 130, 130.6, 131.1, 133.2, 136, 139, 142.2, 147.1, 152, 153.2; IR (KBr, ν_{max}, cm^{-1}): 1610 (C=N); MS (70 eV) *m/z* (%): 342 (M^+, 17). Anal. calcd. for $C_{22}H_{22}N_4$: C, 77.16; H, 6.48; N, 16.36; found C, 77.10; H, 6.50; N, 16.32.

3-[2-(4-(2,4,6-Trimethylphenyl)phthalazin-1-yl]hydrazinyl)propanenitrile (14): A solution of **3** (0.01 mol) and acrylonitrile (0.01mol) was refluxed in pyridine (25 mL) for 4 h. After cooling, the reaction mixture was poured onto ice and HCl and the solid formed was crystallized from benzene to give **14**. Yield: 66 %; m.p. 280-281 °C; ^{1}H NMR (DMSO-d_6) δ: 2.10 (s, 1H, $NHCH_2$, exchangeable with D_2O), 2.36 (s, 3H, CH_3), 2.48 (s, 6H, $2CH_3$), 3.12 (s, 2H, CH_2), 3.45 (s, 2H, CH_2), 7.02-8.02 (m, 6H, Ar-H) 8.11 (s, 1H, NH, exchangeable with D_2O); ^{13}C NMR (DMSO-d_6) δ: 17.1, 21.3, 23.2, 48.5, 117.2, 120.1, 121.0, 127.1, 129.4, 130.7, 131.5, 132, 133.5, 136.2, 139.9, 148, 157.1; IR (KBr, ν_{max}, cm^{-1}): 3290-3210 (NH), 2221 (CN), 1616 (C=N); MS (70 eV) *m/z* (%): 331 (M^+, 6). Anal. calcd. for $C_{20}H_{21}N_5$: C, 72.48; H, 6.39; N, 21.13; found C, 72.42; H, 6.34; N, 21.17.

2-[4-(2,4,6-Trimethylphenyl)phthalazin-1-yl]-2,5-dihydro-1*H*-pyrazol-3-amine (15): A solution of **14** (0.01 mol) in ethanol (25 mL) and sodium hydroxide (15 mL, 20 %) was refluxed for 8 h. The reaction mixture was cooled to room temperature and acidified with hydrochloric acid to give a solid product which was crystallized to give **15**. Yield: 51 %; m.p. 208-209 °C; ^{1}H NMR (DMSO-d_6) δ: 2.10 (s, 1H, $NHCH_2$, exchangeable with D_2O), 2.33 (s, 3H, CH_3), 2.49 (s, 6H, $2CH_3$), 4.10 (t, J = 7.1 Hz, 2H, CH_2 of pyrazol moiety), 4.55 (d, J = 7.1 Hz, 1H, methine proton of pyrazole), 6.23 (br s, 2H, NH_2), 7.01-8 (m, 6H, Ar-H) 9.91 (s, 1H, NH, exchangeable with D_2O); ^{13}C NMR (DMSO-d_6) δ: 21.5, 23.4, 48.7, 80.8, 117.4, 121.0, 126.1, 128.3, 130.3, 130.8, 131.4, 133.5, 136.2, 139.5, 146, 153.6, 159; IR (KBr, ν_{max}, cm^{-1}): 3380-3150 (NH and NH_2), 1615 (C=N); MS (70 eV) *m/z* (%): 331 (M^+, 19). Anal. calcd. for $C_{20}H_{21}N_5$: C, 72.48; H, 6.39; N, 21.13; found C, 72.48; H, 6.41; N, 21.15.

General procedure for the synthesis of pyrazolylphthalazine derivatives 16-19: To a solution of hydrazinophthalazine **3** (0.01 mol) in (30 mL) anhydrous ethanol, ethoxymethylenemalononitrile, tetracyanoethylene, ethyl (ethoxymethylene)cyanoacetate, or methyl *bis*(methylthio)-ethoxymethylene cyanoacetate (0.01mol) was added and the reaction mixtures were refluxed for 3-5 h, respectively. The products, which separated on cooling, were collected by filtration and recrystallized from a suitable solvent to give compounds **16-19**.

5-Amino-1-[4-(2,4,6-trimethylphenyl)phthalazin-1-yl]-1*H*-pyrazole-4-carbonitrile (16): Yield: 88 %; m.p. 261-262 °C; ^{1}H NMR (DMSO-d_6) δ: 2.36 (s, 3H, CH_3), 2.50 (s, 6H, $2CH_3$), 6.88 (br s, 2H, NH_2 exchangeable with D_2O), 7.05-8.03 (m, 6H, Ar-H), 8.21 (s, 1H, CH of pyrazole); ^{13}C NMR (DMSO-d_6) δ: 21.4, 23.1, 72, 116.1, 122, 125.3, 125.9, 126.3, 128, 129.1, 134.1, 134.9, 137.2, 139, 145.8, 152, 155.4, 165.3; IR (KBr, ν_{max}, cm^{-1}): 3407, 3204 (NH_2), 2212 (CN), 1605 (C=N); MS (70 eV) *m/z* (%): 354 (M^+, 10). Anal. calcd. for $C_{21}H_{18}N_6$: C, 71.17; H, 5.12; N, 23.71; found C, 71.10; H, 5.17; N, 23.75.

5-Amino-1-[4-(2,4,6-trimethylphenyl)phthalazin-1-yl]-1*H*-pyrazole-3,4-dicarbonitrile (17): Yield: 65 %; m.p. 216-217 °C; ^{1}H NMR (DMSO-d_6) δ: 2.32 (s, 3H, CH_3), 2.47 (s, 6H, $2CH_3$), 6.92 (br s, 2H, NH_2 exchangeable with D_2O), 7.05-8.04 (m, 6H, Ar-H); ^{13}C NMR (DMSO-d_6) δ: 21.1, 23, 89.1, 114.1, 116.7, 120.1, 122.1, 125.4, 126, 126.8, 127.3, 129.3, 134.5, 134.9, 137.5, 140, 152.1, 155.5, 162.2; IR (KBr, ν_{max}, cm^{-1}): 3411, 3202 (NH_2), 2224 (CN), 1610 (C=N); MS (70 eV) *m/z* (%): 379 (M^+, 8). Anal. calcd. for $C_{22}H_{17}N_7$: C, 69.64; H, 4.52; N, 25.84; found C, 69.64; H, 4.52; N, 25.84.

Ethyl 5-amino-1-[4-(2,4,6-trimethylphenyl)phthalazin-1-yl]-1*H*-pyrazole-4-carboxylate (18): Yield: 85 %; m.p. 200-201 °C; ^{1}H NMR (DMSO-d_6) δ: 1.35 (t, J = 6.9 Hz, 3H, CH_3), 2.34 (s, 3H, CH_3), 2.47 (s, 6H, $2CH_3$), 4.22 (q, J = 6.9 Hz, 2H, CH_2), 6.94 (br s, 2H, NH_2 exchangeable with D_2O), 7.02-8.16 (m, 7H, Ar-H + CH of pyrazole); ^{13}C NMR (DMSO-d_6) δ: 15.3, 21.4, 23.1, 55.3, 109.1, 121.6, 125.1, 126, 126.7, 127.3, 128.3, 133.1, 134.2, 134.9, 137, 139, 152, 155.1, 160.1, 167.8; IR (KBr, ν_{max}, cm^{-1}): 3464, 3354 (NH_2), 1729 (CO), 1605 (C=N); MS (70 eV) *m/z* (%): 401 (M^+, 14). Anal. calcd. for $C_{23}H_{23}N_5O_2$: C, 68.81; H, 5.77; N, 17.44; found C, 68.79; H, 5.770; N, 17.47.

Methyl 5-amino-1-[4-(2,4,6-trimethylphenyl)phthalazin-1-yl]-3-(methylthio)-1*H*-pyrazole-4-carboxylate (19): Yield: 87 %; m.p. 221-222 °C; ^{1}H NMR (DMSO-d_6) δ: 2.37 (s, 3H, CH_3), 2.50 (s, 6H, $2CH_3$), 3.81 (s, 3H, SCH_3), 4.01 (s, 3H, $COOCH_3$), 6.90 (br s, 2H, NH_2 exchangeable with D_2O), 7.01-8 (m, 6H, Ar-H); ^{13}C NMR (DMSO-d_6) δ: 14.5, 21.0, 22.3, 55.1, 99, 122, 125.3, 126.1, 126.9, 127, 129, 134.6, 134.9, 137.1, 140.1, 143.1, 152.3, 155.9, 159.4, 169.1; IR (KBr, ν_{max}, cm^{-1}): 3410, 3233 (NH_2), 1731 (CO), 1611 (C=N); MS (70 eV) *m/z* (%): 447 (M^+, 5). Anal. calcd. for $C_{24}H_{25}N_5O_2S$: C, 64.41; H, 5.63; N, 15.65; S, 7.16; found C, 64.40; H, 5.68; N, 15.66; S, 7.10.

General procedure for the synthesis of sugar hydrazone derivatives 20 a-e: To a solution of hydrazinophthalazine **3** (0.1 mol) in ethanol (50 mL) was added the respective sugar (0.1 mol) and catalytic amount of glacial acetic acid (0.1 mL). The mixture was heated under reflux on a water bath for 5 h. After cooling the separated solid was collected by filtration, dried and crystallized from the appropriate solvent to give **20 a-e**.

D-Glucose [4-(2,4,6-trimethylphenyl)phthalazine-1-yl]-hydrazone (20a): Yield: 60 %; m.p. 200-201 °C; ^{1}H NMR (DMSO-d_6) δ: 2.35 (s, 3H, CH_3), 2.51 (s, 6H, $2CH_3$), 3.21-3.60 (protons of the alditol congregated with the solvent absorption), 3.72-3.85 (m, 2H, CH_2OH), 4.42-5.12 (m, 5H, 5OH, D_2O exchangeable), 6.77 (d, 1H, N=CH), 7.01-8.11 (m, 7H, Ar-H and NH); ^{13}C NMR (DMSO-d_6) δ: 21.1, 22.9, 65.5, 66.3, 71.2, 73.0, 73.8, 117, 118.3, 127.1, 127.5, 129, 129.8, 132.1, 133.2, 137.1, 139.1, 144.1, 154.1, 165.7; IR (KBr, ν_{max}, cm^{-1}): 3418-3211 (OH, NH), 1618 (C=N); MS (70 eV) *m/z* (%): 440 (M^+, 6). Anal. calcd. for $C_{23}H_{28}N_4O_5$: C, 62.71; H, 6.41; N, 12.72; found C, 62.70; H, 6.45; N, 12.70.

D-Galactose [4-(2,4,6-trimethylphenyl)phthalazine-1-yl]-hydrazone (20b): Yield: 91 %; m.p. 181-182 °C; ^{1}H NMR (DMSO-d_6) δ: 2.33 (s, 3H, CH_3), 2.51 (s, 6H, $2CH_3$), 3.20-3.66 (protons of the alditol congregated with the solvent absorption), 3.70-3.81 (m, 2H, CH_2OH), 4.41-5.17 (m, 5H, 5OH, D_2O exchangeable), 6.70 (d, 1H, N=CH), 7.04-8.09 (m, 7H, Ar-H and NH); ^{13}C NMR (DMSO-d_6) δ: 21, 22.8, 65.1, 67.1, 72, 73.5, 73.9, 118, 118.9, 127.5, 127.9, 129, 129.7, 132.1, 133, 137, 139.6, 144, 153.1, 165; IR (KBr, ν_{max}, cm^{-1}): 3433-3234 (OH, NH), 1621 (C=N). Anal. calcd. for $C_{23}H_{28}N_4O_5$: C, 62.71; H, 6.41; N, 12.72; found C, 62.75; H, 6.40; N, 12.75.

D-Mannose [4-(2,4,6-trimethylphenyl)phthalazine-1-yl]-hydrazone (20c): Yield: 78 %; m.p. 213-214 °C; ^{1}H NMR (DMSO-d_6) δ: 2.30 (s, 3H, CH_3), 2.46 (s, 6H, $2CH_3$), 3.28-3.67 (protons of the alditol congregated with the solvent absorption), 3.75-3.81 (m, 2H, CH_2OH), 4.38-5.07 (m, 5H, 5OH, D_2O exchangeable), 6.75 (d, 1H, N=CH), 7.05-8.04 (m, 7H, Ar-H and NH); ^{13}C NMR (DMSO-d_6) δ: 20.2, 22.6, 65.2, 66.5, 71.2, 73.5, 73.9, 117.4, 118.8, 127.1, 128.5, 129, 130.8, 132.1, 134.2, 137.1, 140.1, 144.2, 154.6, 166.7; IR (KBr, ν_{max}, cm^{-1}): 3409-3210 (OH, NH), 1617 (C=N). Anal. calcd. for $C_{23}H_{28}N_4O_5$: C, 62.71; H, 6.41; N, 12.72; found C, 62.70; H, 6.48; N, 12.72.

D-Xylose [4-(2,4,6-trimethylphenyl)phthalazine-1-yl]-hydrazone (20d): Yield: 59 %; m.p. 207-208 °C; ^{1}H NMR (DMSO-d_6) δ: 2.30 (s, 3H, CH_3), 2.46 (s, 6H, $2CH_3$), 3.34-3.51 (protons of the alditol congregated with the solvent absorption), 3.61-3.73 (m, 2H, CH_2OH), 4.20-5.91 (m, 4H, 4OH, D_2O exchangeable), 6.69 (d, 1H, N=CH), 7-8.07 (m, 7H, Ar-H and NH); ^{13}C NMR (DMSO-d_6) δ: 20.8, 22.9, 65.1, 66.9, 73.2, 75.6, 116.1, 118, 126.2, 128, 129.2, 130.9, 131.1, 133.1, 136.1, 141.1, 144.1, 156.6, 168.3; IR (KBr, ν_{max}, cm^{-1}): 3438-3222 (OH, NH), 1617 (C=N). Anal. calcd. for $C_{22}H_{26}N_4O_4$: C, 64.37; H, 6.38; N, 13.65; found C, 64.30; H, 6.40; N, 13.60.

D-Arabinose [4-(2,4,6-trimethylphenyl)phthalazine-1-yl]-hydrazone (20e): Yield: 62 %; m.p. 179-180 °C; ^{1}H NMR (DMSO-d_6) δ: 2.32 (s, 3H, CH_3), 2.49 (s, 6H, $2CH_3$), 3.32-3.48 (protons of the alditol congregated with the solvent absorption), 3.60-3.71 (m, 2H, CH_2OH), 4.21-5.94 (m, 4H, 4OH, D_2O exchangeable), 6.66 (d, 1H, N=CH),7.02-8.10 (m, 7H, Ar-H and NH); ^{13}C NMR (DMSO-d_6) δ: 20.4, 23.2, 65.4, 66.7, 74.2, 75.3, 117.1, 118, 126.5, 128.4, 129.4, 131.2, 131.8, 133, 137.1, 140.1, 144.1, 156, 167.5; IR (KBr, ν_{max}, cm^{-1}): 3430-3205 (OH, NH), 1617 (C=N); MS (70 eV) *m/z* (%): 410 (M^+, 6). Anal. calcd. for $C_{22}H_{26}N_4O_4$: C, 64.37; H, 6.38; N, 13.65; found C, 64.32; H, 6.44; N, 13.61.

General procedure for synthesis of per-*O*-acetyl-sugar hydrazone derivatives (21 a-e): A cold solution of **20 a-e** (0.02 mol) in pyridine (50 mL) was treated with acetic anhydride (60 mL). The mixture was kept overnight at room temperature with occasional shaking. The mixture was poured onto ice-H_2O and the product was collected by filtration, washed repeatedly with water, dried and recrystallized from ethanol to give compounds **21 a-e**.

2,3,4,5,6-Penta-*O*-acetyl-D-glucose[1-acetyl-1-{4-(2,4,6-trimethylphenyl)phthalazine-1-yl}-hydrazone] (21a): Yield: 58 %; m.p. 60-61 °C; ^{1}H NMR (DMSO-d_6) δ: 2.02, 2.04, 2.10 (3s, 15 H, 5O Ac), 2.35 (s, 3H, CH_3), 2.46 (s, 6H, $2CH_3$), 2.53 (s, 3H, NAc), 4.15 (dd, 1H, H-6'), 4.26 (dd, 1H, H-6), 5.02-5.10 (m, 1H, H-5), 5.44-5.55 (m, 2H, H-4, H-3), 5.62 (dd, 1H, H-2), 6.74 (d, 1H, N=CH), 7.08-8.11 (m, 6H, Ar-H); ^{13}C NMR (DMSO-d_6) δ: 20, 20.8, 21.3, 22.1, 22.9, 62.2, 66.9, 68.6, 70.9, 72, 118, 118.5, 126.1, 127.2, 128.1, 129.3, 132, 133.1, 137.1, 139, 143.1, 154.1, 165.1, 174.2, 177.0; IR (KBr, ν_{max}, cm^{-1}): 1719 (OAc), 1674 (NAc), 1608 (C=N). Anal. calcd. for $C_{25}H_{30}N_4O_6$: C, 62.23; H, 6.27; N, 11.61; found C, 62.29; H, 6.25; N, 11.60.

2,3,4,5,6-Penta-*O*-acetyl-D-galactose[1-acetyl-1-{4-(2,4,6-trimethylphenyl)phthalazine-1-yl}-hydrazone] (21b): Yield: 80 %; m.p. 161-162 °C; ^{1}H NMR (DMSO-d_6) δ: 1.96, 1.99, 2.03, 2.08, 2.09 (5s, 15H, 5O Ac), 2.30 (s, 3H, CH_3), 2.48 (s, 6H, 2CH3), 2.55(s, 3H, NAc), 3.88(dd, 1H, H-6'), 4.28 (dd, 1H, H-6), 5.38-5.88 (m, 4H, H-5, H-4, H-3, H-2), 6.55 (d, 1H, N=CH), 7.03-8.10 (m, 6H, Ar-H); ^{13}C NMR (DMSO-d_6) δ: 19.6, 20.6, 21.4, 22.3, 22.8, 62, 66.5, 68.6, 70.7, 72.0, 118.1, 118.9, 126, 127.1, 128.1, 128.9, 132, 133.2, 137.1, 139.4, 144.6, 154.2, 165.8, 172.9, 176.8; IR (KBr, ν_{max}, cm^{-1}): 1723 (OAc), 1677 (NAc), 1611 (C=N); MS (70 eV) *m/z* (%): 482 (M^+, 8). Anal. calcd for $C_{25}H_{30}N_4O_6$: C, 62.23; H, 6.27; N, 11.61; found C, 62.30; H, 6.20; N, 11.64.

2,3,4,5,6-Penta-*O*-acetyl-D-mannose[1-acetyl-1-{4-(2,4,6-trimethylphenyl)phthalazine-1-yl}-hydrazone] (21c): Yield: 63 %; m.p. 58-60 °C; ^{1}H NMR (DMSO-*d*6) δ: 2.03, 2.06, 2.11 (3s, 15H, 5 OAc), 2.36 (s, 3H, CH_3), 2.49 (s, 6H, $2CH_3$), 2.55 (s, 3H, NAc), 4.14 (dd, 1H, H-6'), 4.28 (dd, 1H, H-6), 5.22-5.40 (m, 1H, H-5), 5.42 (m, 2H, H-4), 5.54 (dd, 1H, H-3), 5.66 (dd, 1H, H-2), 6.68 (d, 1H, N=CH), 7.04-8.08 (m, 6H, Ar-H); ^{13}C NMR (DMSO-d_6) δ: 20.4, 20.9, 21.8, 22.3, 23.9, 62.1, 66.2, 68.3, 70.5, 72.6, 118.2, 118.7, 126.1, 127.2, 128.6, 130.3, 132.1, 133.4, 137.3, 139.2, 143.9, 154.2, 166.3, 173.3, 176.4; IR (KBr, ν_{max}, cm^{-1}): 1713 (OAc), 1682 (NAc), 1615 (C=N). Anal. calcd. for $C_{25}H_{30}N_4O_6$: C, 62.23; H, 6.27; N, 11.61; found C, 62.25; H, 6.24; N, 11.66.

2,3,4,5,6-Penta-*O*-acetyl-D-xylose[1-acetyl-1-{4-(2,4,6-trimethylphenyl)phthalazine-1-yl}-hydrazone] (21d): Yield: 53 %; m.p. 97-98 °C; ^{1}H NMR (DMSO-d_6) δ: 1.91, 1.94, 2, 2.19 (4s, 12H, 4OAc), 2.35 (s, 3H, CH_3), 2.47 (s, 6H, $2CH_3$), 2.51 (s, 3H, NAc), 4.22 (dd, 1H, H-5'), 4.38 (dd, 1H, H-5), 5.38-5.40 (m, 1H, H-4), 5.78 (m, 2H, H-3), 6.01 (dd, 1H, H-2), 6.58 (d, 1H, N=CH), 7-8.04 (m, 6H, Ar-H); ^{13}C NMR

(DMSO-d_6) δ: 20.1, 20.9, 21.7, 22.4, 23.5, 62.4, 66.4, 68.9, 70, 116.2, 118.6, 126, 127.1, 128.4, 130, 132.1, 133.8, 138.3, 140.2, 143.7, 154, 166.8, 171.3, 175.4; IR (KBr, ν_{max}, cm^{-1}): 1726 (OAc), 1685 (NAc), 1610 (C=N). Anal. calcd. for $C_{24}H_{28}N_4O_5$: C, 63.70; H, 6.24; N, 12.38; found C, 63.65; H, 6.29; N, 12.34.

2,3,4,5,6-Penta-*O*-acetyl-D-arabinose[1-acetyl-1-{4-(2,4,6-trimethylphenyl)phthalazine-1-yl}hydrazone] (21e): Yield: 67 %; m.p. 110-111 °C; ^{1}H NMR (DMSO-d_6) δ: 1.90, 1.93, 2.01, 2.19 (4s, 12H, 4OAc), 2.37 (s, 3H, CH_3), 2.50 (s, 6H, $2CH_3$), 2.54 (s, 3H, NAc), 4.27 (dd, 1H, H-5'), 4.39 (dd, 1H, H-5), 5.39-5.45 (m, 1H, H-4), 5.79 (m, 2H, H-3), 6.11 (dd, 1H, H-2), 6.60 (d, 1H, N=CH), 7.01-8.09 (m, 6H, Ar-H); ^{13}C NMR (DMSO-d_6) δ: 20, 20.8, 21.9, 22.4, 23.7, 62.7, 66, 68.1, 70.8, 116.2, 117.6, 126, 127, 128.4, 130.5, 131.8, 133.4, 138.3, 140.1, 144.7, 154.2, 166, 171.4, 176.4; IR (KBr, ν_{max}, cm^{-1}): 1714 (OAc), 1680 (NAc), 1611 (C=N); MS (70 eV) *m/z* (%): 452 (M^+, 7). Anal. calcd for $C_{24}H_{28}N_4O_5$: C, 63.70; H, 6.24; N, 12.38; found C, 63.68; H, 6.28; N, 12.37.

General procedure for the synthesis of 1-(alditol-1-yl)-1,2,4-triazolo[4,3-a]phthalazines (22 a-e): A 2M solution of iron (III) chloride in absolute ethanol (2 mL) was added dropwise to a boiling solution of **20a-e** (0.01 mol) in ethanol (50 mL). Heating was continued for 20 min and the mixture was then kept overnight at room temperature. The product was filtered, washed repeatedly with water, dried and recrystallized from ethanol to give compounds **22a-e**.

4-(2,4,6-Trimethylphenyl)-1-(D-gluco-pentitol-1-yl)-1,2,4-triazolo[4,3-a]phthalazine (22a): Yield: 89 %; m.p. 86-87 °C; ^{1}H NMR (DMSO-d_6) δ: 2.34 (s, 3H, CH_3), 2.50 (s, 6H, $2CH_3$), 3.33-3.62 (protons of the alditol congregated with the solvent absorption), 3.73-3.90 (m, 2H, CH_2OH), 4.31-5.22 (m, 5H, 5OH, D_2O exchangeable), 7.09-8.09 (m, 6H, Ar-H); ^{13}C NMR (DMSO-d_6) δ: 20.5, 22.1, 63.4, 66.3, 70, 71.8, 73.5, 122.2, 126.7, 126.9, 127.7, 129, 130.8, 131.5, 132, 137.3, 138, 149.7, 154, 160.1; IR (KBr, ν_{max}, cm^{-1}): 3454-3219 (OH), 1605 (C=N); MS (70 eV) *m/z* (%): 438 (M^+, 9). Anal. calcd for $C_{23}H_{26}N_4O_5$: C, 63; H, 5.98; N, 12.78; found.C, 63.05; H, 5.96; N, 12.80.

4-(2,4,6-Trimethylphenyl)-1-(D-galacto-pentitol-1-yl)-1,2,4-triazolo[4,3-a]phthalazine (22b): Yield: 85 %; m.p. 81-82 °C; ^{1}H NMR (DMSO-d_6) δ: 2.31 (s, 3H, CH_3), 2.51 (s, 6H, $2CH_3$), 3.30-3.61 (protons of the alditol congregated with the solvent absorption), 3.74-3.92 (m, 2H, CH_2OH), 4.31-5.32 (m, 5H, 5OH, D_2O exchangeable), 7.01-8.10 (m, 6H, Ar-H); ^{13}C NMR (DMSO-d_6) δ: 20.6, 22.1, 63.8, 65.2, 70.1, 70.8, 72.2, 122.5, 126, 126.9, 128.9, 129.7, 130.8, 131.7, 132.2, 136.4, 138.1, 148.4, 154.2, 160.6; IR (KBr, ν_{max}, cm^{-1}): 3459-3279 (OH), 1606 (C=N). Anal. calcd. for $C_{23}H_{26}N_4O_5$: C, 63; H, 5.98; N, 12.78; found C, 63.03; H, 5.99; N, 12.82.

4-(2,4,6-Trimethylphenyl)-1-(D-manno-pentitol-1-yl)-1,2,4-triazolo[4,3-a]phthalazine (22c): Yield: 73 %; m.p. 106-107 °C; ^{1}H NMR (DMSO-d_6) δ: 2.39 (s, 3H, CH_3), 2.50 (s, 6H, $2CH_3$), 3.22-3.60 (protons of the alditol congregated with the solvent absorption), 3.70-3.86 (m, 2H, CH_2OH), 4.30-5.36 (m, 5H, 5OH, D_2O exchangeable), 7.02-8.13 (m, 6H, Ar-H); ^{13}C NMR (DMSO-d_6) δ: 20.1, 23.2, 63.0, 66.7, 70.3, 71.8, 72.5, 123.5, 126.1, 126.8, 128.0, 129.3, 130.4, 131.7, 132.5, 137.4, 138, 146.4, 154, 161.3; IR (KBr, ν_{max}, cm^{-1}): 3478-3210 (OH), 1602 (C=N); MS (70 eV) *m/z* (%): 438 (M^+, 6). Anal. calcd. for $C_{23}H_{26}N_4O_5$: C, 63; H, 5.98; N, 12.78; found C, 63.09; H, 5.90; N, 12.70.

4-(2,4,6-Trimethylphenyl)-1-(D-xylo-pentitol-1-yl)-1,2,4-triazolo[4,3-a]phthalazine (22d): Yield: 60 %; m.p. 125-126 °C; ^{1}H NMR (DMSO-d_6) δ: 2.30 (s, 3H, CH_3), 2.48 (s, 6H, $2CH_3$), 3.20-3.60 (the protons of the alditol congregated with the solvent absorption), 3.65-3.77 (m, 2H, CH_2OH), 3.91-5.14 (m, 4H, 4OH, D_2O exchangeable), 7-8.03 (m, 6H, Ar-H); ^{13}C NMR (DMSO-d_6) δ: 20.2, 22.8, 63.0, 66.1, 73.8, 74.5, 124, 126.3, 127.1, 128.5, 129.6, 130.8, 131.4, 132.3, 136.6, 138.1, 147.2, 154.0, 160.1; IR (KBr, ν_{max}, cm^{-1}): 3455-3266 (OH), 1607 (C=N). Anal. calcd. for $C_{22}H_{24}N_4O_4$: C, 64.69; H, 5.92; N, 13.72; found C, C, 64.67; H, 5.90; N, 13.76.

4-(2,4,6-Trimethylphenyl)-1-(D-arabino-pentitol-1-yl)-1,2,4-triazolo[4,3-a]phthalazine (22e): Yield: 63 %; m.p. 92-93 °C; ^{1}H NMR (DMSO-d_6) δ: 2.33 (s, 3H, CH_3), 2.49 (s, 6H, $2CH_3$), 3.16-3.54 (the protons of the alditol congregated with the solvent absorption), 3.60-3.79 (m, 2H, CH_2OH), 3.90-5.24 (m, 4H, 4OH, D_2O exchangeable), 7.11-8 (m, 6H, Ar-H); ^{13}C NMR (DMSO-d_6) δ: 21, 23.5, 64.3, 66.7, 72.9, 74.4, 124.1, 127.3, 127.6, 128.5, 129.5, 130.4, 131.7, 132, 137.6, 139.2, 147, 154.2, 161.2; IR (KBr, ν_{max}, cm^{-1}): 3472-3196 (OH), 1604 (C=N); MS (70 eV) *m/z* (%): 408 (M^+, 11). Anal. calcd. for $C_{22}H_{24}N_4O_4$: C, 64.69; H, 5.92; N, 13.72; found C, C, 64.60; H, 5.91; N, 13.70.

General procedure for the synthesis of (penta-*O*-acetyl-sugar-1-yl)-1,2,4-triazolo[4,3-a]phthalazines (23 a-e): A cold solution of **22 a-e** (0.01 mol) in dry pyridine (10 mL) was treated with acetic anhydride (10 mL) and the mixture was kept overnight at room temperature with occasional shaking. The mixture was poured onto crushed ice and the product was collected by filtration, washed repeatedly with water, dried and recrystallized from ethanol to give compounds **23 a-e**.

4-(2,4,6-Trimethylphenyl)-1-(1,2,3,4,5-penta-*O*-acetyl-D-gluco-pentitol-1-yl)-1,2,4-triazolo[4,3-a]phthalazine (23a): Yield: 75 %; m.p. 70-71 °C; ^{1}H NMR (DMSO-d_6) δ: 1.99, 2.01, 2.03 (3s, 15H, 5OAc), 2.39 (s, 3H, CH_3), 2.50 (s, 6H, $2CH_3$), 3.98-4.01 (m, 2H, CH_2OAc), 4.23-5.59 (m, 4H, 4CHOAc), 7.03-8.10 (m, 6H, Ar-H); ^{13}C NMR (DMSO-d_6) δ: 19, 19.8, 21.5, 22.6, 62.1, 67.1, 69.2, 70.6, 77.4, 125.0, 127.3, 128, 128.5, 129.8, 130.8, 131.9, 133, 137.6, 140.2, 148, 154.2, 160.2, 174.2; IR (KBr, ν_{max}, cm^{-1}): 1724 (OAc), 1601 (C=N). Anal. calcd. for $C_{33}H_{36}N_4O_{10}$: C, 61.10; H, 5.59; N, 8.64; found C, 61.11; H, 5.58; N, 8.60.

4-(2,4,6-Trimethylphenyl)-1-(1,2,3,4,5-penta-*O*-acetyl-D-galacto-pentitol-1-yl)-1,2,4-triazolo[4,3-a]phthalazine (23b). Yield: 80 %; m.p. 63-64 °C; ^{1}H NMR (DMSO-d_6) δ: 1.98-2.25 (m, 15H, 5O Ac), 2.38 (s, 3H, CH_3), 2.51 (s, 6H, $2CH_3$), 3.94-4.03 (m, 2H, CH_2OAc), 4.21-5.55 (m, 4H, 4CHOAc), 7-8.11 (m, 6H, Ar-H); ^{13}C NMR (DMSO-d_6) δ: 19.03, 20, 21.56, 23, 62.2, 68.1, 69.1, 70.6, 76. 5, 123, 1276.3, 128, 128.6, 129.8, 130.2, 132.3, 133.1, 137.1, 141.2, 147, 154.2, 160, 174.5; IR (KBr, ν_{max}, cm^{-1}): 1730 (OAc), 1606 (C=N); MS (70 eV) *m/z* (%): 648 (M^+, 6). Anal. calcd. for $C_{33}H_{36}N_4O_{10}$: C, 61.10; H, 5.59; N, 8.64; found.C, 61.17; H, 5.55; N, 8.64.

4-(2,4,6-Trimethylphenyl)-1-(1,2,3,4,5-penta-*O*-acetyl-D-manno-pentitol-1-yl)-1,2,4-triazolo[4,3-a]phthalazine

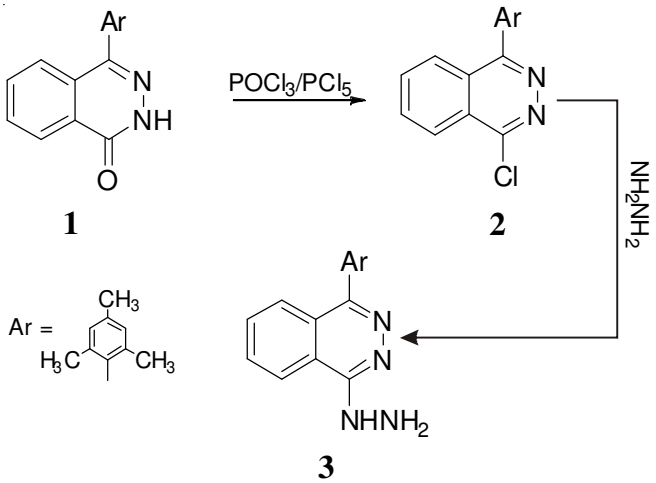
(23c). Yield: 60 %; m.p. 71-72 °C; ^{1}H NMR (DMSO-d_6) δ: 1.96-2.28 (m, 15H, 5OAc), 2.33 (s, 3H, CH_3), 2.48 (s, 6H, $2CH_3$), 3.90-4 (m, 2H, CH_2OAc), 4.20-5.57 (m, 4H, 4CHOAc), 7.01-8.13(m, 6H, Ar-H); ^{13}C NMR (DMSO-d_6) δ: 18.9, 19.7, 21.2, 22.9, 63, 67.2, 69.2, 70.6, 77.7, 126, 127.1, 128.2, 128.7, 129.6, 130.8, 131.8, 133, 137, 141.2, 147.6, 153.1, 159.2, 173.8; IR (KBr, ν_{max}, cm^{-1}): 1735 (OAc), 1601 (C=N). Anal. calcd. for $C_{33}H_{36}N_4O_{10}$: C, 61.10; H, 5.59; N, 8.64; found.C, 61.14; H, 5.50; N, 8.60.

4-(2,4,6-Trimethylphenyl)-1-(1,2,3,4,5-penta-*O*-acetyl-D-xylo-pentitol-1-yl)-1,2,4-triazolo[4,3-a]phthalazine (23d). Yield: 55 %; m.p. 68-69 °C; ^{1}H NMR (DMSO-d_6) δ: 1.86-2.17 (m, 12H, 4OAc), 2.36 (s, 3H, CH_3), 2.49 (s, 6H, $2CH_3$), 3.94-4 (m, 2H, CH_2OAc), 4.23-5.22 (m, 3H, 3CHOAc), 7.11-8.14 (m, 6H, Ar-H); ^{13}C NMR (DMSO-d_6) δ: 19.1, 20, 21.4, 23.8, 63.2, 68.1, 69.4, 75.8, 125.6, 127.2, 127.9, 128.7, 129.1, 130, 131.3, 132.9, 137.3, 141.4, 148.6, 152.2, 157.7, 172.9; IR (KBr, ν_{max}, cm^{-1}): 1721 (OAc), 1607 (C=N); MS (70 eV) *m/z* (%): 576 (M^+, 9). Anal. calcd. for $C_{30}H_{32}N_4O_8$: C, 62.49; H, 5.59; N, 9.72; found.C, 62.40; H, 5.62; N, 9.70.

4-(2,4,6-Trimethylphenyl)-1-(1,2,3,4,5-penta-*O*-acetyl-D-arabino-pentitol-1-yl)-1,2,4-triazolo[4,3-a]phthalazine (23e). Yield: 65 %; m.p. 93-94 °C; ^{1}H NMR (DMSO-d_6) δ: 1.89-2.14 (m, 12H, 4OAc), 2.31 (s, 3H, CH_3), 2.47 (s, 6H, $2CH_3$), 3.90-3.99 (m, 2H, CH_2OAc), 4.21-5.20 (m, 3H, 3CHOAc), 7.10-8.10 (m, 6H, Ar-H); ^{13}C NMR (DMSO-d_6) δ: 19.2, 20.01, 21, 22.8, 64.1, 68, 69, 74.1, 125.7, 127, 127.9, 128.7, 129, 130.3, 131.6, 132.5, 138.3, 141, 148.1, 152, 157, 175.2; IR (KBr, ν_{max}, cm^{-1}): 1733 (OAc), 1604 (C=N). Anal. calcd. for $C_{30}H_{32}N_4O_8$: C, 62.49; H, 5.59; N, 9.72; found C, 62.44; H, 5.60; N, 9.71.

RESULTS AND DISCUSSION

The key precursor 1-chloro-4-(2,4,6-trimethylphenyl) phthalazine **2** was prepared in moderate yield upon refluxing of phthalazinone derivative **1** and a mixture of phosphorous oxychloride/phosphorous pentachloride on a water bath, which upon subsequent reaction with hydrazine hydrate in refluxing ethanol afforded the target compound, hydrazinophthalazine derivative **3** (**Scheme-I**)[51].



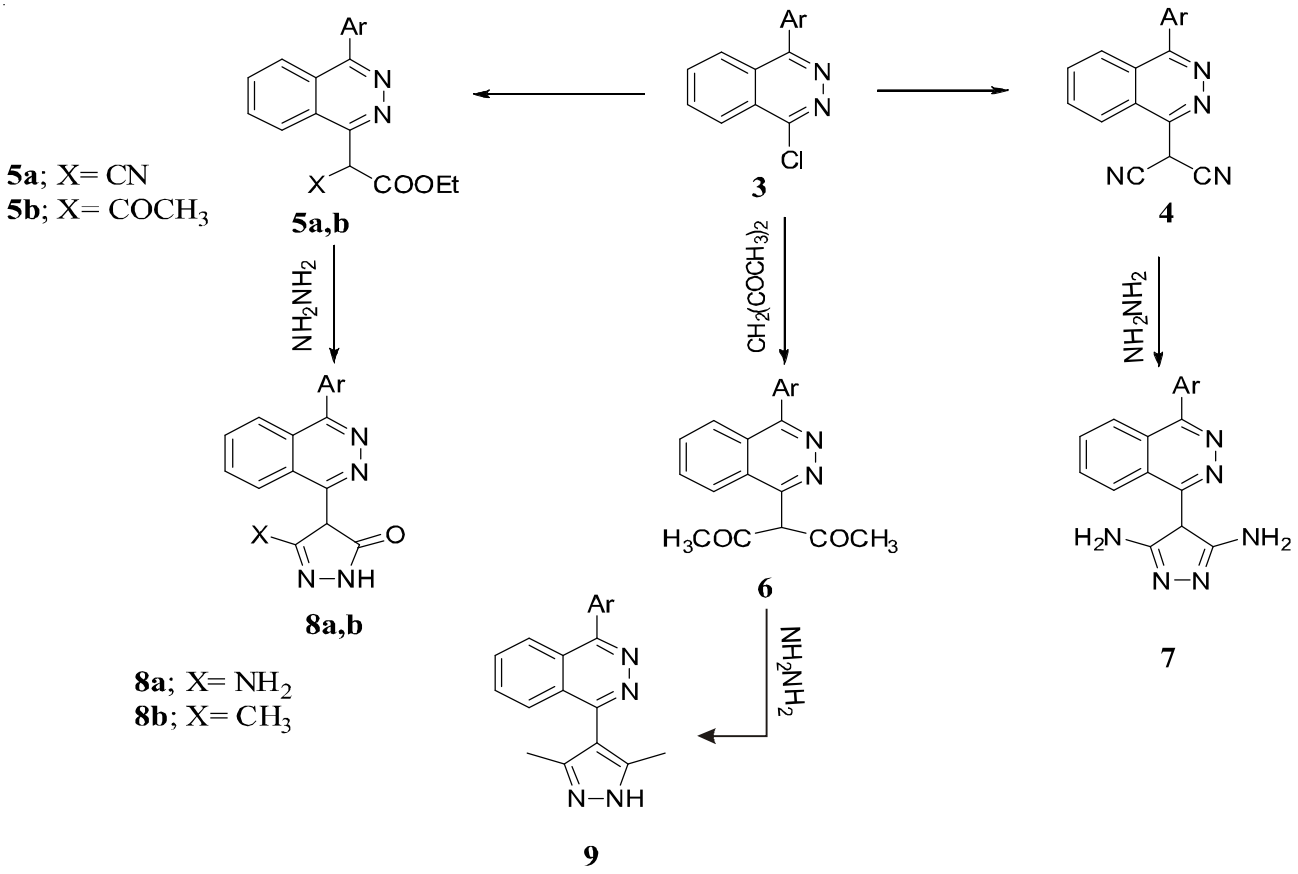
Scheme-I: Synthesis of hydrazinophthalazine derivative **3**

The chemical behavior of chlorophthalazine derivative **2** towards active methylene compounds was studied with respect to the synthesis of highly substituted pyrazoles[52,53]. Thus, the treatment of compound **2** with different active methylene compounds namely,malononitrile, ethyl cyanoacetate, ethyl acetoacetate and acetylacetone afforded the corresponding phthalazine derivatives **4-6**, respectively. The IR spectrum of compound **4** and **5a** revealed the presence of a CN group at 2223 and 2231 cm^{-1}, respectively. The ^{1}H NMR spectrum of compounds **4-6** displayed a CH proton as a singlet signalat δ 4.57-5.11 ppm. The ^{13}C NMR spectrum of compound **6** gave characteristic signals in accordance with the assigned structure. Cyclocondensation of compounds **4-6** with hydrazine hydrate in refluxing absolute ethanol yielded the pyrazolylphthalazine derivatives **7-9**, respectively. The infrared spectrum of compound **7** showed the absence of nitrile functional group and the presence of only NH_2 groups (**Scheme-II**).

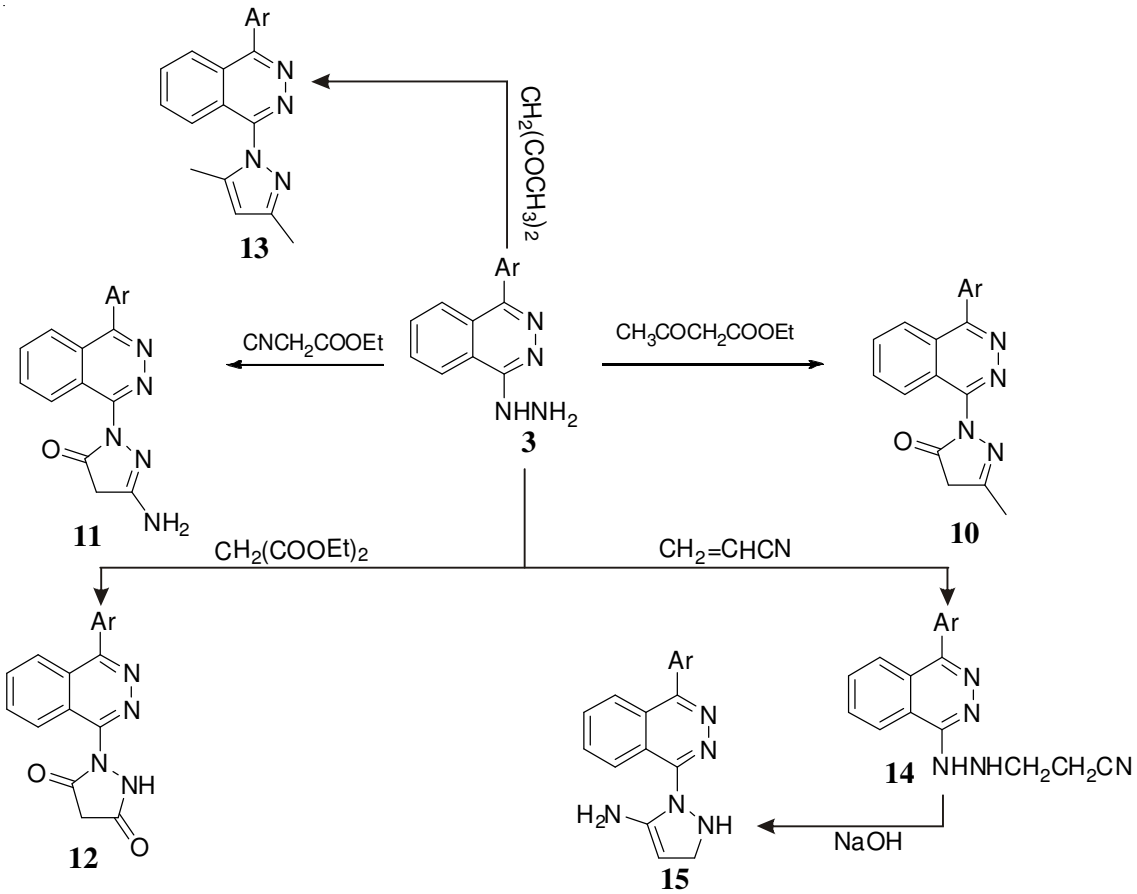
In this study, our attention was also directed towards the synthesis of pyrazolylphthalazine derivatives in order to attain possible potential antihypertensive agents[54]. Thus, hydrazinophthalazine derivative **3** was subjected to react with different active methylene compounds namely, ethyl acetoacetate, ethyl cyanoacetate, diethyl malonate and acetylacetone to afford the corresponding pyrazolylphthalazine derivatives[10-13], respectively. The IR spectra of compounds[10-12] revealed the presence of a CO group 1707-1666 cm^{-1} region. The ^{1}H NMR spectrum of **11** showed a signal at 4.47 for assigned NH_2 (exchangeable with D_2O). The mass spectrum of **13** showed a peak corresponding to its molecular ion at *m/z* 342. Moreover, treatment of **3** with acrylonitrile in refluxing pyridine afforded the corresponding propionitrile derivative **14**, which underwent acid hydrolysis to give pyrazolylphthalazine derivative **15** (**Scheme-III**). The IR spectrum of compound **14** showed the presence of an absorption band for CN group at 2221 cm^{-1}. The mass spectrum of **15** showed a peak corresponding to its molecular ion at *m/z* 331.

Similarly, the hydrazinophthalazine derivative **3** has been reacted with ethoxymethylenemalononitrile, tetracyanoethylene, *bis*(methylthio)-methylenemalononitrile, or ethyl(ethoxymethylene)-cyanoacetate in refluxing ethanol to produce the corresponding pyrazole derivatives **16-19**, respectively. The structures of the latter compounds were confirmed on the basis of their elemental analysis and spectral data. The IR spectrum of compounds **16** and **17** showed absorption bands characteristic for NH_2 and C≡N groups, while those of compounds **18** and **19** revealed absorption bands characteristic for NH_2 and C=O. Moreover, the ^{1}H NMR spectrum of compounds **16-19** showed signals at δ = 6.88, 6.92, 6.94 and 6.90 ppm for assigned NH_2 (exchangeable with D_2O), respectively. The mass spectrum of compounds **16-19** gave the molecular ion peaks at *m/z* = 354, 379, 401 and 447, respectively (**Scheme-IV**).

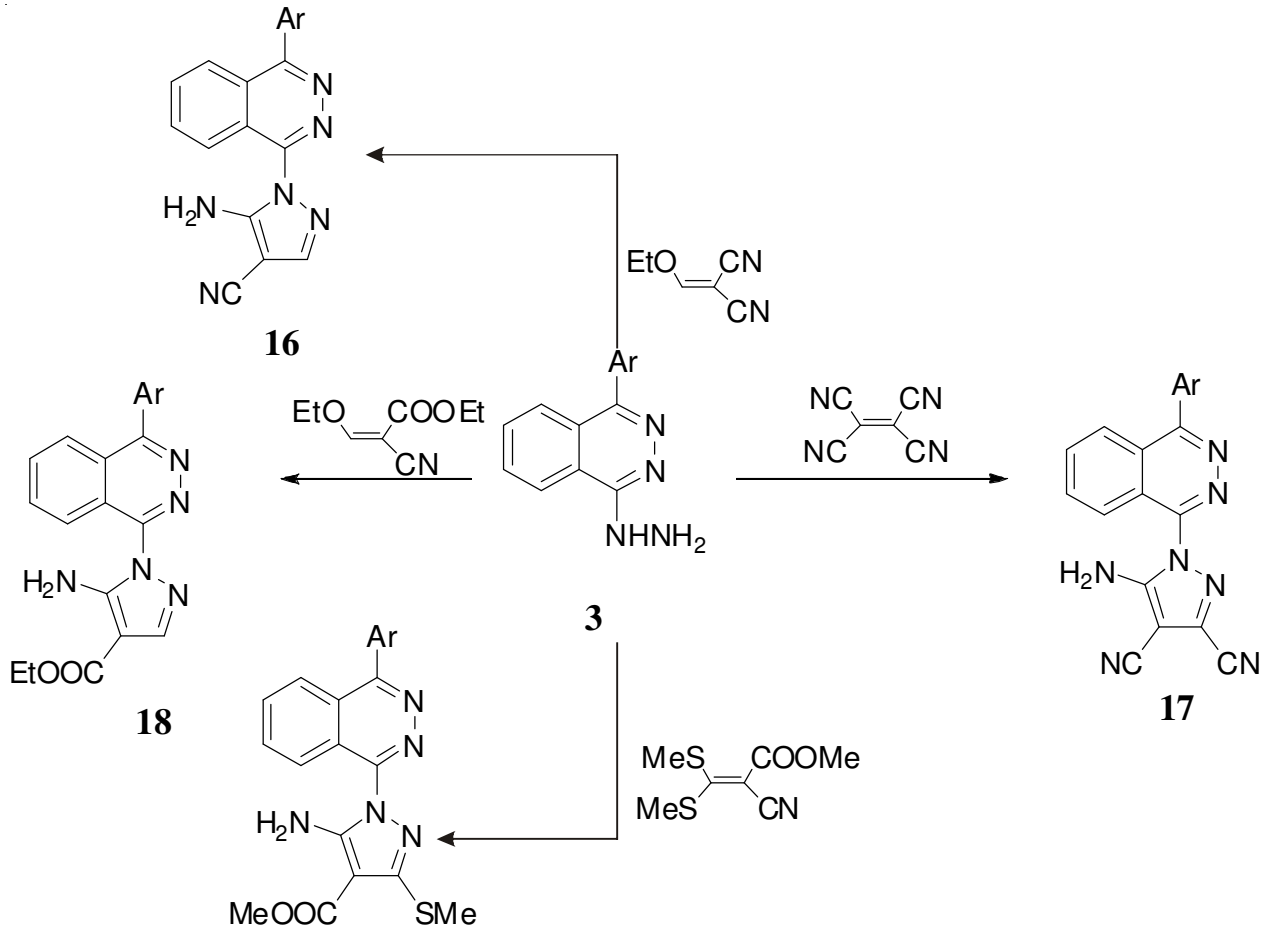
The scope of this examination was further prolonged towards the synthesis of acyclo-*C*-nucleoside derivatives. Thus, condensation of hydrazinophthalazine derivative **3** with equimolar amount of different aldohexose and aldopentose namely, D-glucose, D-galactose, D-mannose, D-xylose and D-arabinose, respectively in refluxing ethanol in presence of catalytic amount of acetic acid gave the corresponding sugar



Scheme-II: Synthesis of pyrazolylphthalazine derivatives **4-9**



Scheme-III: Synthesis of pyrazolylphthalazine derivatives **10-13** and **15**

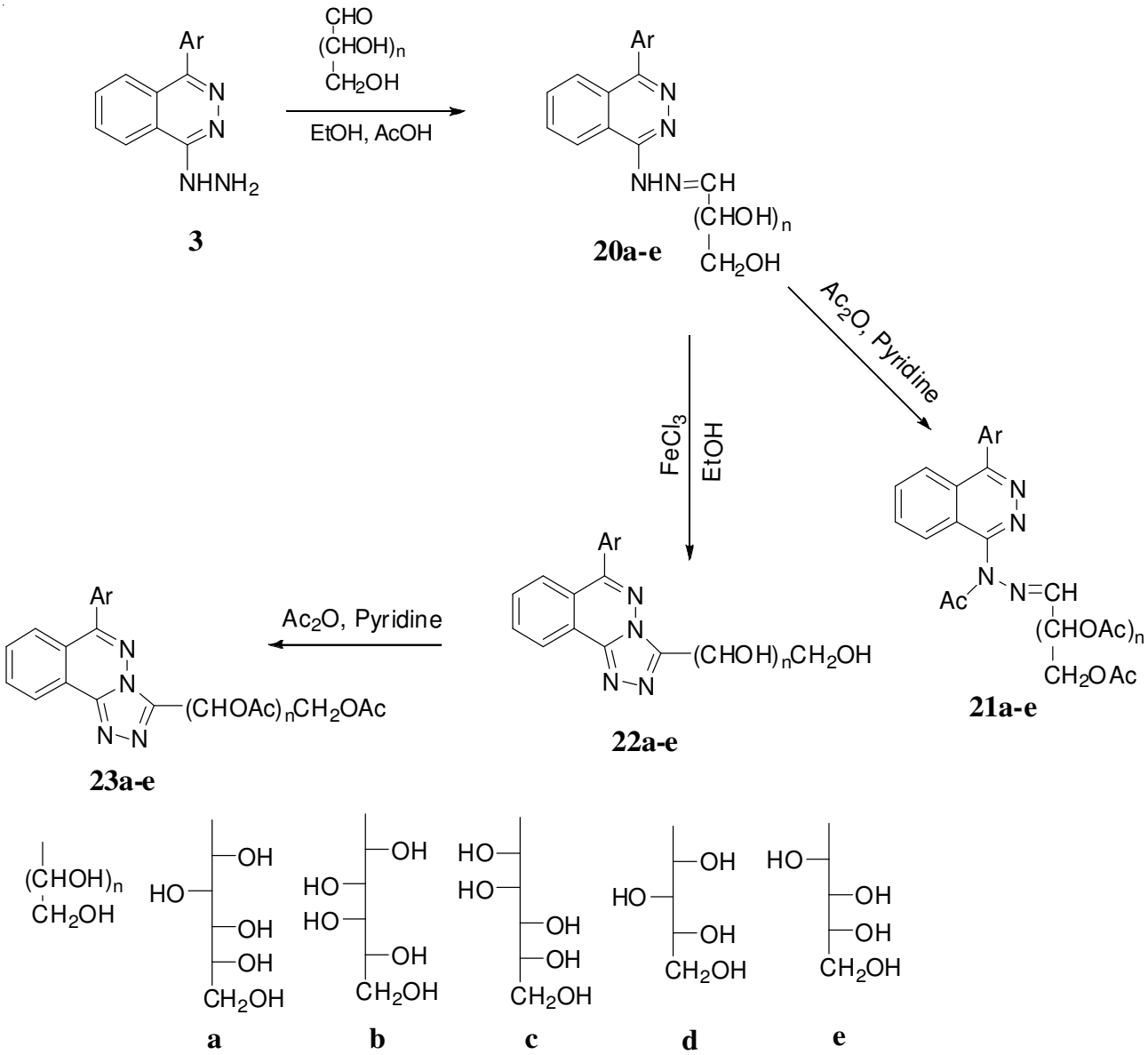


Scheme-IV: Synthesis of pyrazolylphthalazine derivatives **17-19**

hydrazones **20a-e**. The IR spectrum of compounds **20a-e** showed characteristic absorption bands 3438-3205 cm^{-1} region corresponding to the OH and NH groups. Acetylation of the sugar hydrazones **20a-e** with acetic anhydride in dry pyridine at room temperature afforded the corresponding per-acetyl derivatives **21a-e**, whose IR spectra showed the disappearance of the OH groups and appearance of absorption bands in the carbonyl frequency region at 1726-1713 and 1685-1674 cm^{-1} due to (OAc) and (NAc) groups, respectively. Their ^{1}H NMR spectra showed signals corresponding to *O*-acetyl groups in addition to NAc groups; whereas no signals could be found for NH groups confirming that per-*O*- and *N*-acetylation had taken place. The spectra also showed the presence of the CH=N proton as doublet at low field at δ 6.55-6.74 ppmin addition to the rest of the alditol-1-yl side chain. The sugar hydrazone **20a-e** on oxidative cyclization with iron(III) chloride in ethanolic solution afforded the corresponding triazolo[4,3-a]phthalazine derivatives **22a-e**. This oxidation may take place by the electrophilic attack of the hard acid site of iron(III) chloride[55] on the hardest basic site of the sugar hydrazone **20a-e**, followed by the elimination of hydrogen chloride and formation of possibly a nitrilimine that undergoes 1,5-electrocyclization to give **22a-e**. Their IR spectra showed characteristic absorption bands at 3478-3196 cm^{-1} corresponding to the OH groups. The mass spectrum of **22a** showed a peak corresponding to its molecular ion at *m/z* 438, in addition to ion peak at *m/z* 287 presumably attributed to the triazolophthalazine ring. The ^{1}H NMR spectrum of compound **22b** showed a doublet at low field at δ 3.90 ppm which was assigned to H-1, followed by the rest of the aldito-1-yl side chain at higher field. The spectra of **22c-e** showed a similar pattern. Acetylation of **22a-e** with acetic anhydride in pyridine afforded the polyacetoxyalkyl derivatives **23a-e** (**Scheme-V**), whose IR spectra showed the presence of only one absorption band in the carbonyl frequency region (OAc) and devoid any band for OH. The ^{1}H NMR spectra confirmed the presence of the OAc groups. The mass spectrum of **23b** and **23d** showed a peak corresponding to its molecular ion at *m/z* 648 and 576, which when combined with the elemental analysis led to the assignment of the molecular formula $C_{33}H_{36}N_4O_{10}$ and $C_{30}H_{32}N_4O_8$, respectively.

Biological activities

Antibacterial: Antimicrobial activity of the newly synthesized compounds **7-13**, **15-19**, **22a-e** and **23a-e** were assessed against *Escherichia coli*, *Staphylococcus aureus*, *Bacillus subtilis*, *Salmonella typhi* bacterial strains, *Aspergillumsniger* and *Candida albicans* fungal strains in term of disk diffusion method[62]. As described by El-Hashash *et al.*[62], amoxicillin and ketoconazole were used as a standard drugs for the bacteria and fungi, respectively. Preliminary screening of phthalazine-derivatives



Scheme-V: Synthesis of acyclo-*C*-nucleosides of 6-(2,4,6-trimethylphenyl)-1,2,4-triazolo[3,4-a]phthalazine **22** and **23a-e**

and standard drugs were accomplished at fixed concentrations (500 µg/mL). The antimicrobial activity was noted after 24 h, by calculating the inhibition zone diameter for bacteria and after 72 h in case of fungi. Each test was repeated twice. Based on the results of inhibition zone, the minimum inhibitory concentration (MIC) of compounds **7-13**, **15-19**, **22a-e** and **23a-e** against all strains; bacterial and fungal was determined by liquid dilution method[62]. As described by El-Hashash *et al.*[62] stock solutions of the tested compounds with 500, 250, 200, 100, 62.5, 50, 25 and 12.5 µg mL^{-1} concentrations were dilutedusing DMSO as solvent. The same concentrations of standard drugs *e.g.*, amoxicillin and ketoconazole, were also prepared. Inoculums of both bacterial and fungal culture were also prepared. To a series of test tubes containing 1 mL each of phthalazine compound solution with different concentrations and 0.2 mL of the inoculums was added. Further 3.8 mL of sterile water was added to each of the test tubes. These tubes were incubated for 24 h at 37 °C and the turbidity for all tubes was observed. This method was repeated by changing phthalazine compounds with standard drugs *e.g.*, amoxicillin and ketoconazole for comparison. The minimum inhibitory concentration at which no growth was detected (Table-1). The comparison of the MICs (in µg/mL) of potent compounds and standard drugs against tested strains are presented in the Table-1.

Antiinflammatory activity: A series of phthalazin-4-yl acetic acid derivatives[56] was prepared and showed antiinflammatory activity in the carrageenin and edema test. Recently, several groups have studied the structure-activity relationship of novel series of 4-arylsubstituted phthalazinones[28,57] and showed that the presence of 4-aryl substituted on the phthalazinone nucleus contributes to a good antiinflammatory and nociceptive activities. It is also well known that some heteroaryl acetic acids possess antiinflammatory activities[58,59]. Substitution of the acetamide side chain on the lactam nitrogen in the phthalazinone derivatives[25] resulted in compounds having considerably high antinociceptive and antiinflammatory activities without gastric lesion and bleeding at the given dose. It was of interest to prepare a number of 4-aryl-oxophthalazine-

TABLE-1
ANTIMICROBIAL ACTIVITY OF
COMPOUNDS **7-13, 15-19, 22a-e** AND **23a-e**

Compounds	Minimum inhibitory concentration (MIC) in µg/mL					
	Bacterial strains			Fungal strains		
	S. aureus	*B. subtilis*	*S. typhi*	*E. coli*	*A. niger*	*C. albican*
7	50	25	25	50	125	125
8a	50	50	25	25	250	125
8b	50	100	200	200	250	-
9	500	250	-	500	500	-
10	250	500	200	200	-	500
11	50	25	25	50	62.5	125
12	100	100	250	100	500	125
13	500	200	250	-	250	250
15	25	25	25	50	62.5	125
16	50	50	25	25	62.5	250
17	25	50	50	50	125	62.5
18	25	25	50	50	62.5	62.5
19	50	25	25	25	125	125
22a	25	25	25	25	62.5	62.5
22b	25	25	50	25	62.5	62.5
22c	25	50	25	25	62.5	62.5
22d	50	25	25	50	100	62.5
22e	25	25	50	50	62.5	125
23a	100	50	25	25	100	100
23b	25	25	25	100	62.5	62.5
23c	25	100	250	25	125	62.5
23d	50	25	50	25	250	250
23e	25	100	25	50	62.5	125
Amoxicillin	62.5	6.25	6.25	6.25	-	-
Ketaconazole	-	-	-	-	31.25	31.25

2-yl acetic acid derivatives for pharmacological screening. Various pyrazole derivatives including the drugs butazolidin, celebrex were reported as effective antiinflammatory agents[60,61]. Consequently, it was worthwhile to incorporate pyrazole moieties in the 2 position of phthalazinone nucleus in a hope to yield safe and potent antiinflammatory compounds. Compounds **7-13**, **17-19**, **22b,d** and **23a,d** were screened for their antiinflammatory activity.

The screening was conducted in acute inflammatory model. As described by Ramtohul *et al.*[36] Carrageenan induced rat paw oedema method was used as follow: Carrageenan (an irritant) at a concentration of 1 mg mL^{-1} was injected subcutaneously into the hind paw of the rat to produce oedema. Different groups of animals were administered with standard drug indomethacin, the test samples and the vehicle used for the preparation of samples. The increase in the paw volume was measured before and after 3 h of administration and the results were compared. Ninety healthy albino rats of body weight 170-250 g were selected and made into nine groups of six animals each. All the animals were kept on fasting for 18 h. One group of animals was kept as control, which received 2 % w/v acacia mucilage, which was used to suspend the sample. Another group received the standard drug Indomethacin 1.5 mg kg^{-1} body weight intraperitonially. Remaining seven groups of animals received seven different test compounds (1.5 mg kg^{-1} body weight) intraperitonially. After 0.5 h, 0.1 mL of w/v carrageenan was injected subcutaneously into the right hind paw of the rats. A mark was made at the right hind paw, which was dipped in the plethismograph up to the mark and the volume was measured immediately and after 3 h. The change in paw volume was compared with that in the vehicle treated control animals. The percentage inhibition of oedema was calculated using the formula:

$$\% \text{ Oedema inhibition} = 100 - (V_{test}/V_{control}) \times 100$$

The percentage of inhibition was compared with that of the standard drug indomethacin. Interestingly five compounds exhibited good antiinflammatory activity against indomethacin (Table-2).

TABLE-2
ANTI-INFLAMMATORY ACTIVITY OF
COMPOUNDS **7-13, 17-19, 22b,d** AND **23a,d**

Compounds	Paw oedema Volume Mean + S.E mL	Percentage inhibition of Paw oedema	Dose (mg kg^{-1} p.o)
2 (%) Gumacacia (control)	0.62 ± 0.029		10 mL kg^{-1}
Indomethacine	0.25 ± 0.012	59.67	1.5
7	0.56 ± 0.018	30.64	50
8a	0.55 ± 0.013	11.29	50
9	0.56 ± 0.020	9.67	50
10	0.52 ± 1.78	9.67	50
11	0.55 ± 0.015	16.12	50
12	0.56 ± 0.020	9.67	50
13	0.55 ± 0.015	16.12	50
17	0.56 ± 0.018	30.64	50
18	0.56 ± 0.018	30.64	50
19	0.46 ± 0.18	25.8	50
22b	0.56 ± 0.018	30.64	50
22d	0.46 ± 0.19	25.8	50
23a	0.56 ± 0.018	30.64	50
23d	0.56 ± 0.019	30.64	50

Conclusion

We reported here the successful synthesis of some novel pyrazolylphthalazine derivatives and acyclo-C-nucleosidesof 6-(2,4,6-trimethylphenyl)-1,2,4-triazolo[3,4-a]phthalazine. Most of the newly synthesized compounds were tested for their antimicrobial and antiinflammatory activity. The antimicrobial activity study showed that all the compounds tested displayed moderate to good antibacterial and antifungal activities against pathogenic strains. In case of antiinflammatory activity, compounds exhibited good activity among the tested compounds.

ACKNOWLEDGEMENTS

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