Synthesis of some new N-glycosyl and 4-aryl-2-((1-(piperidin-1-ylmethyl)-1H-benzo[d] imidazol-2-yl)methyl)phthalazin-1(2H)-one

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Abstract: A series of 2-((1H-benzo[d]imidazol-2-yl)methyl)-4-arylphthalazin-1(2H)-one(3) and 2-((1-substituted-1H-benzo[d]imidazol-2-yl)methyl)-4-arylphthalazin-1(2H)-one(4) were synthesized starting from 4-arylphthalazin-1(2H)-one(1). Moreover, the N-glycosyl of 2-((1H-benzo[d]imidazol-2-yl)methyl)-4-arylphthalazin-1(2H)-one(5a,b) were synthesized by interaction of phthalazinone derivative(3) with acetobromo-α-D-glucose. Deacetylation of acetylated N-nucleosides 5a,b using ammonia solution in methanol afforded the corresponding deacetylated N-glycosyl 6a,b respectively. The structures of the synthesized compounds were confirmed by 1HNMR, 13CNMR, MS, IR spectroscopy and by elemental analysis.

Keywords: N-glycosyl; phthalalazine; antimicrobial activity, Benzimidazole.

1. Introduction
Phthalazines are classes of nitrogen heterocycles that are of considerable interest because of their widespread pharmacological and therapeutic properties. [1-3]. Phthalazines have been reported to possess antimicrobial, [6] antitumor, [7-10] antihypertensive, [11,12] antithrombotic, [13] antidiabetic, [14,15] Anti-T. cruzi, [16] anti-inflammatory,[17-23] and vasorelaxant activities. [12,24]. On the other hand, benzimidazole ring displays an important heterocyclic pharmacophore and privileged scaffold in drug discovery[25]. This compound carrying different substituents encompassing a diversified range of biological activities[26,25] include anticancer, antiviral, antibacterial, antifungal, anti-inflammatory, antihistaminic, antihypertensive. The diverse biological activities of phthalazinenucleus, and benzimidazolepharmacophores envisaged us to plan a new lead compounds that may exhibit wide pharmacological activities. By combining these pharmacophore components in a molecule to give a compact system, we designed and synthesized a series of phthalazin-1(2H)-one derivatives containing benzimidazole moieties.

2. Experimental
Melting points were determined on the Electrothermal 9100 melting point apparatus (Electrothermal, UK) and are uncorrected. The IR spectra (KBr) were recorded on an FT-IR NEXCES spectrophotometer (Shimadzu, Japan). The 1H-NMR spectra were measured with a Jeol ECA 500 MHz (Japan) in DMSO-d6 and chemical shifts were recorded in δ ppm relative to TMS. Mass spectra (EI) were run at 70 eV with a Finnigan SSQ 7000 spectrometer. The purity of the compounds was checked on Aluminium plates coated with silica gel (Merck). The elemental analysis for C, H, N and S was performed by a Costech model 4010 and the percentage values agreed with the proposed structures within ± 0.4% of the theoretical values.

General procedure for preparation of [4-aryl-1(2H)-oxo-phthalazin-2-yl]acetic acid ethyl ester (2a-d)
A mixture of phthalazinone(1) (0.01 mol), 5 g ethyl bromoacetate (0.03 mol) and 4.1 g potassium carbonate (0.03 mol) in 30 mL dry acetone was heated under reflux for 30 h, cooled at room temperature and poured into water. The obtained solid was filtered off and crystallized from petroleum ether 40–60 °C to give 2.
[4-(2,4,6-Trimethylphenyl)-1(2H)-oxo-phthalazin-2-yl]acetic acid ethyl ester (2a). [27] M.p. 124-125°C; yield 80%; 1H NMR (DMSO-d6) δ: 1.48 (t, J = 10 Hz, 3H, CH3CH2), 2.39 (s, 3H, CH2CO), 2.51 (s, 6H, 2CH3), 4.18 (q, J = 10 Hz, 2H, CH2CH3), 4.79 (s, 2H, CH2CO), 7.10-8.0 (m, 6H, Ar–H); IR (KBr) ν: 1731 and 1659 cm⁻¹; MS (70 eV) m/z (%): 356 (M+, 11).

[4-(3-Chloro-4-methylphenyl)-1(2H)-oxo-phthalazin-2-yl]acetic acid ethyl ester (2b)

M.p. 145-146°C; yield 78%; 1H NMR (DMSO-d6) δ: 1.53(t, J = 7.6 Hz, 3H, CH3CH2), 4.32 (q, J = 7.6 Hz, 2H, CH2CO), 7.08–8.04 (m, 7H, 7H, Ar–H); IR (KBr) ν: 1742, 1681 cm⁻¹; MS (70 eV) m/z (%): 350 (M+, 10). Anal. calcd. for C25H22N4O: C, 75.02; H, 5.20; N, 7.32.

[4-(3-Chloro-4-methylphenyl)-1(2H)-oxo-phthalazin-2-yl]acetic acid ethyl ester (2c)

M.p. 199-200°C; yield 66%; 1H NMR (DMSO-d6) δ: 2.40 (s, 3H, CH3), 4.15 (s, 1H, NH exchangeable with D2O), 4.66 (s, 2H, CH2CO), 7.01–8.10 (m, 11H, Ar–H); IR (KBr) ν: 3236 (NH), 1682 (CO) cm⁻¹; MS (70 eV) m/z (%): 491 (M+, 10). Anal. calcd. for C25H22N4O: C, 75.78; H, 6.72; N, 14.20.

General procedure for preparation of 2-((1H-benzo[d]imidazol-2-yl)methyl)-4-aryl phthalazin-1(2H)-one (3a-d).

A mixture of ester 2 (0.01 mol) and o-phenylenediamine (0.01 mol) was heated in hydrochloric acid at 100°C for 4hrs, cooled and poured into ice cold 10% aqueous sodium carbonate. The solid product, which separated out, was collected and washed with water and recrystallized from the proper solvent to give 3.

2-((1H-Benz[d]imidazol-2-yl)methyl)-4-(4,2,4,6-trimethylphenyl)phthalazin-1(2H)-one (3a).

M.p. 230-231°C; yield 70%; 1H NMR (DMSO-d6) δ: 2.34 (s, 3H, CH3), 2.50 (s, 6H, 2CH3), 4.11 (s, 1H, NH exchangeable with D2O), 4.75 (s, 2H, CH2CO), 7.05–8.12 (m, 10H, Ar–H); IR (KBr) ν: 3310 (NH), 1660 (CO) cm⁻¹; MS (70 eV) m/z (%): 394 (M+, 33). Anal. calcd. for C25H22N4O: C, 76.12; H, 5.62; N, 14.20; found C, 76.18; H, 5.60; N, 14.23.

2-((1H-Benz[d]imidazol-2-yl)methyl)-4-(3,4-dichlorophenyl)phthalazin-1(2H)-one (3b).

M.p. 214-215°C; yield 68%; 1H NMR (DMSO-d6) δ: 4.22 (s, 1H, NH exchangeable with D2O), 4.83 (s, 2H, CH2CO), 7.02–8.15 (m, 11H, Ar–H); IR (KBr) ν: 3322 (NH), 1675 (CO) cm⁻¹. Anal. calcd. for C22H14Cl2N4O: C, 72.62; H, 3.35; Cl, 16.78; N, 13.30; found C, 72.68; H, 3.30; Cl, 16.85; N, 13.28.

2-((1H-Benz[d]imidazol-2-yl)methyl)-4-(3-chloro-4-methylphenyl)phthalazin-1(2H)-one (3c).

M.p. 230-231°C; yield 81%; 1H NMR (DMSO-d6) δ: 7.65 (s, 1H, CH3), 4.15 (s, 1H, NH exchangeable with D2O), 4.77 (s, 2H, CH2CO), 7.02–8.11 (m, 10H, Ar–H); IR (KBr) ν: 3236 (NH), 1682 (CO) cm⁻¹; MS (70 eV) m/z (%): 400 (M+, 19). Anal. calcd. for C22H14Cl2N4O: C, 76.18; H, 5.60; N, 13.30.

2-((1H-Benz[d]imidazol-2-yl)methyl)-4-((biphenyl-4-yl)-phthalazin-1(2H)-one (3d).

M.p. 256-257°C; yield 70%; 1H NMR (DMSO-d6) δ: 4.05 (s, 1H, NH exchangeable with D2O), 4.70 (s, 2H, CH2CO), 7.03–8.15 (m, 17H, Ar–H); IR (KBr) ν: 3236 (NH), 1678 (CO) cm⁻¹. Anal. calcd. for C28H20N4O: C, 78.49; H, 4.70; N, 13.08; found C, 78.55; H, 4.73; N, 13.05.

General procedure for preparation of 4-aryl-2-((1-(piperidin-1-ylmethyl)-1H-benzo[d]imidazol-2-yl)methyl)phthalazin-1(2H)-one (4a-d).

The compound 3 (0.02 mol) was suspended in minimum quantity of dimethylformamide. To that solution slightly more than 0.02 mole formaldehyde and 0.025 mole piperidine was added with vigorous stirring. The reaction mixture was heated on water bath for one hour and kept overnight at room temperature. The solid thus separated was filtered and recrystallized from the proper solvent to give 4.

4-(2,4,6-Trimethylphenyl)-2-((1-piperidin-1-ylmethyl)-1H-benzo[d]imidazol-2-yl)methyl)phthalazin-1(2H)-one (4a).

M.p. 140-141°C; yield 60%; 1H NMR (DMSO-d6) δ: 1.60-2.08 (m, 6H, -CH2-CH2-CH2-), 2.33 (s, 3H, CH3), 2.36 (t, 4H, 2CH2), 2.51 (s, 6H, 2CH3), 4.77 (s, 2H, CH2CO), 7.02–8.11 (m, 10H, Ar–H); IR (KBr) ν: 1662 (CO) cm⁻¹; MS (70 eV) m/z (%):491 (M+, 10). Anal. calcd. for C31H33N5O: C, 75.73; H, 6.77; N, 14.25; found C, 75.78; H, 6.72; N, 14.20.

4-(3,4-Dichlorophenyl)-2-((1-piperidin-1-ylmethyl)-1H-benzo[d]imidazol-2-yl)methyl)phthalazin-1(2H)-one (4b).

M.p. 133-134°C; yield 60%; 1H NMR (DMSO-d6) δ: 1.62-2.11 (m, 6H, -CH2-CH2-CH2-), 2.39 (t, 4H, 2CH2), 4.79 (s, 2H, CH2CO), 7.02–8.15 (m, 11H, Ar–H); IR (KBr) ν: 1677 (CO) cm⁻¹; MS (70 eV) m/z (%): 466 (M+, 130).
4-(3-Chloro-4-methylphenyl)-2-((1-(piperidin-1-ylmethyl)-1H-benzo[d]imidazo-2-yl)methyl)phthalazin-1(2H)-one (4c)

M.p. 159-160°C; yield 66%; 1H NMR (DMSO-d6) δ: 1.64-2.09 (m, 6H, -CH2-CH2-CH2-), 2.30 (s, 3H, CH3), 2.37 (t, 4H, 2CH2), 4.70 (s, 2H, CH2CO), 7.00-8.13 (m, 11H, Ar–H); IR (KBr) v: 1674 (CO) cm⁻¹. Anal. calcd. for C25H22ClN2O: C, 69.94; H, 5.67; Cl, 7.12; N, 14.06; found C, 69.90; H, 5.68; Cl, 7.18; N, 14.02.

General procedure for preparation of N-nucleoside[28] 5a,b.

A mixture of 3a or 3b (0.01 mol) and (0.01 mol) potassium carbonate was stirred in dry acetone/DMF (20 mL) for 2 h, then acetonbromo-α-D-glucose (0.011 mol) was added. The reaction mixture was stirred at 25°C overnight then refluxed for 5 h, filtered off and the solvent was then evaporated under reduced pressure. The product was dried and crystallized from the proper solvent or chromatographed on silica gel column to give 5a and 5b respectively.

4-(2,4,6-Trimethylphenyl)-2-((1-(1H-imidazol-2-yl)methyl)phthalazin-1(2H)-one (6a)

M.p. 180-181°C; yield 62%; 1H NMR (DMSO-d6) δ: 1.60-2.08 (m, 6H, -CH2-CH2-CH2-), 2.38 (t, 4H, 2CH2), 4.70 (s, 2H, CH2CO), 7.01-8.13 (m, 17H, Ar–H); IR (KBr) v: 1660 (CO) cm⁻¹; MS (70 eV) m/z (%): 525 (M⁺, 21). Anal. calcd. for C31H29N3O: C, 77.69; H, 5.94; N, 13.32; found C, 77.77; H, 5.90; N, 13.34.

General procedure for preparation of N-glycosyl 6a,b.

Triethylamine (1 mL) was added to a solution of N-nucleoside 5a,b (0.01 mol) in MeOH (30 mL) and 4 drops of water. The mixture was stirred overnight at 25°C, evaporated under reduced pressure and the residue was co-evaporated with MeOH until the triethylamine was removed. The residue was crystallized from proper solvent.

4-(2,4,6-Trimethylphenyl)-2-((1-β-D-galactopyranosyl)-1H-benzo[d]imidazo-2-yl)methyl)phthalazin-1(2H)-one (6a)

M.p. 237-238°C; yield 74%; 1H NMR (DMSO-d6) δ: 2.37 (s, 3H, CH3), 2.50 (s, 6H, 2CH3), 3.19 (m, 6H, H-6″), 3.52 (m, 1H, H-5″); yield 74%; 1H NMR (DMSO-d6) δ: 1.77, 1.90, 1.93, 2.04 (4s, 12H, 4CH3CO), 2.32 (s, 3H, CH3), 2.51 (s, 6H, 2CH3), 4.01(m, 1H, H-5″), 4.22 (dd, 1H, J5″,6″ = 1.64, J6″,6‴ = 12.71 Hz, H-6‴), 4.44 (dd, 1H, J5″,6″ = 5.36, J6″,6‴ = 12.71 Hz, H-6‴), 4.70 (s, 2H, CH2CO), 5.201 (t, 1H, J3″,4″ = 9.63, J4″,5″ = 9.94 Hz, H-4″), 5.32 (t, 1H, J2″,3″ = 9.38 Hz, H-2″), 5.49 (t, 1H, J3″,4″ = 9.58 Hz, H-3″), 6.28 (d, 1H, J5″,6″ = 1.64, J6″,6‴ = 12.70 Hz, H-6‴), 4.48 (dd, 1H, J5″,6″ = 5.36, J6″,6‴ = 12.70 Hz, H-6‴), 4.79 (s, 2H, CH2CO), 5.22 (t, 1H, J3″,4″ = 9.60, J4″,5″ = 9.92 Hz, H-4″), 5.39 (t, J1″,2″ = 9.30 Hz, H-2″), 5.50(t, 1H, J3″,4″ = 9.52 Hz, H-3″), 6.41 (d, 1H, J1″,2″ = 9.81 Hz, H-1″), 7.01-8.16 (m, 11H, Ar–H); IR (KBr) v: 1744, 1677, cm⁻¹. Anal. calcd. for C31H29N3O12: C, 57.53; H, 4.29; Cl, 9.43; N, 7.45; found C, 57.56; H, 4.33; Cl, 9.40; N, 7.41.

3. Results and Discussion

3.1. Synthesis

Treatment of phthalazin-1(2H)-one derivatives 1a-e with ethyl bromoacetate in boiling acetone in presence of K2CO3 gave the corresponding phthalazine acetic acid ethyl esters 2a-d. The
The structure of compound 2a-d was confirmed on the basis of their elemental analysis and spectral data. The IR spectrum showed a characteristic absorption band at $\nu = 1731$-$1742$ cm$^{-1}$ corresponding to CO of ester, CO of cyclic amide at $\nu = 1659$-$1681$ cm$^{-1}$ and devoid any band for NH. The 1H NMR spectrum of compound 2a-d showed a triplet signal at $\delta = 1.48$-$1.53$ assigned for CH$_3$CH$_2$, a quartet signal at $\delta = 4.18$-$4.32$ assigned for CH$_2$CH$_3$, a singlet at $\delta = 4.79$-$4.51$ assigned for CH$_2$CO. Cyclocondensation of acetic acid ethyl esters 2a-d with o-phenylenediamine in HCl gave 2-((1H-benzo[d]imidazol-2-yl)methyl)-4-arylphthalazin-1(2H)-one (3a-d). The $^1$H-NMR spectrum of compounds 3a-d showed NH at $\delta = 4.05$-$4.22$. Compounds 3a-d were allowed to undergo the Mannichaminoalkylation with pipridine and paraformaldehyde in absolute ethanol to give Mannich bases 4a-d respectively. Compound 4a displayed characteristic $>$N-CH$_2$N$<$ signal at $\delta = 4.77$ ppm. Glycosylation of 2-((1H-benzo[d]imidazol-2-yl)methyl)-4-arylphthalazin-1(2H)-one (3a,b) with one equivalent of acetobromo-$\alpha$-D-glucose in dry acetone in presence of K$_2$CO$_3$ afforded N-nucleoside (5a,b). The structure of compounds 5a and 5b were based on the spectroscopic data. Thus, the $\beta$-configuration of compounds 5a and 5b were supported by their $^1$H-NMR spectra, which revealed the anomeric proton as doublet at $\delta = 6.28$ and 6.41 ppm with coupling constant $J = 9.90$ and 9.81 Hz, respectively. Deacetylation of compounds 5a and 5b in the presence of methanol/Et$_3$N and few drops of water, led to the formation of the free glycosides 6a and 6b. The $^1$H-NMR spectra of these latter compounds showed the absence of the CH$_3$CO and the appearance of the D$_2$O exchangeable OH protons at $\delta = 3.52$-$5.58$ ppm. Their IR spectra indicated the presence of broad band at 3447, 3423 cm$^{-1}$ for OH groups.

4. Conclusions

We reported here the successful synthesis of a series of some new A series of 2-((1H-benzo[d]imidazol-2-yl)methyl)-4-arylphthalazin-1(2H)-one (3) and 4-aryl-2-((1-(piperidin-1-ylmethyl)-1H-benzo[d]imidazol-2-yl)methyl)phthalazin-1(2H)-one(4) were synthesized starting from 4-arylphthalazin-1(2H)-one (1).

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