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

Ibrahim E. El-Shamy[1(*)], Hadeer M. Bakeer[1], Khalid M. Al-Shamrani [2], A. M. Abdel-Mohsen [3, 4(*)], and Mohammed M. Al-Shehri[2]

[1] Chemistry Department, Faculty of Science, Fayoum University, Fayoum, Egypt.
[2] Research Institute of petrochemical, king Abdulaziz City for Science and Technology, Riyadh, 11442, Kingdom of Saudi Arabia.
[3]Central European Institute of Technology (CEITEC), Brno University of Technology, Brno 66100, Czech, Republic.
[4]Textile Research Division, National Research Center, Dokki, Giza, P.O. 12622, Giza 12522, Egypt.
iei00@fayoum.edu, egabdel-mohsen@ceitec.vutbr.cz, abdo_mohsennrc@yahoo.com

Abstract: A series of 2-((1*H*-benzo[d]imidazol-2-yl)methyl)-4-arylphthalazin-1(2*H*)-one **(3)** and 2-((1-substituted-1H-benzo[*d*]imidazol-2-yl)methyl)-4-arylphthalazin-1(2*H*)-one **(4)** were synthesized starting from 4-arylphthalazin-1(2H)-one **(1)**. Moreover, the *N*-glycosyl of 2-((1*H*-benzo[d]imidazol-2-yl)methyl)-4-arylphthalazin-1(2*H*)-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.
[Ibrahim E. El-Shamy, Hadeer M. Bakeer, A. M. Abdel-Mohsen, Mohammed M. Al-Shehri and Khalid M. Al-Shamran. **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.** *Life Sci J* 2014;11(4):94-99]. (ISSN:1097-8135). http://www.lifesciencesite.com. 11

Keywords: N-glycosyl; phthalazinone; antimicrobial activity, Benzamidazole.

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 phthalazinenucluse, 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(2*H*)-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(2*H*)-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 ^{o}C to give **2**.

[4-(2,4,6-Trimethylphenyl)-1(2*H*)-oxo-phthalazin-2-yl]acetic acid ethyl ester (2a).[27] M.p.124–125 ^{o}C; ; yield 80%; 1H NMR (DMSO-d6) δ: 1.48(t, J =10 Hz, 3H,CH3CH2), 2.39 (s, 3H, CH3), 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) v: 1731 and 1659 cm-1; MS (70 eV) m/z (%): 350(M+, 15), 305 (100). Anal. calcd. for C21H22N2O3: C 71.98, H 6.33, N 7.99; found C 71.93, H 6.31, N 8.03.

[4-(3,4-Dichlorophenyl)-1(2*H*)-oxo-phthalazin-2-yl]acetic acid ethyl ester (2b)

M.p. 145-146^{o}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,CH2CH3), 4.68 (s, 2H, CH2CO), 7.08–8.04 (m, 7H, Ar–H); IR (KBr) v: 1742, 1681 cm^{-1}. Anal. calcd. for C18H14Cl2N2O3: C, 57.31; H, 3.74; Cl, 18.80; N, 7.43; found C, 57.28; H, 3.70; Cl, 18.78; N, 7.48.

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

M.p. oC; yield 81%; 1H NMR (DMSO-d6) δ: 1.48(t, J =8.9 Hz, 3H,CH3CH2), 2.39 (s, 3H, CH3), 4.17 (q, J =8.9 Hz, 2H,CH2CH3), 4.44 (s, 2H, CH2CO), 7.00–8.01 (m, 7H, Ar–H); IR (KBr) v: 1740, 1668 cm-1; MS (70 eV) m/z (%):356 (M+, 11). Anal. calcd. for C19H17ClN2O3: C, 63.96; H, 4.80; Cl, 9.94; N, 7.85;found C, 63.99; H, 4.76; Cl, 9.98; N, 7.80.

[4-(Biphenyl-4-yl)-1(2*H*)-oxo-phthalazin-2-yl]acetic acid ethyl ester (2d)

M.p. oC; yield 76%; 1H NMR (DMSO-d6) δ: 1.42(t, J =8.0 Hz, 3H,CH3CH2), 4.19 (q, J = 8.0 Hz, 2H,CH2CH3), 4.51 (s, 2H, CH2CO), 7.03–8.12 (m, 13H, Ar–H); IR (KBr) v: 1739, 1672 cm-1. Anal. calcd. for C24H20N2O3: C, 74.98; H, 5.24; N, 7.29; found C, 75.02; H, 5.20; N, 7.32.

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^{o}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 with methanol to give **3**.

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

M.p. 230-231oC; 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) v: 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-((1*H*-Benzo[d]imidazol-2-yl)methyl)-4-(3,4-dichlorophenyl)-phthalazin-1(2*H*)-one (3b).

M.p. 214-215^{o}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) v: 3322 (NH), 1675(CO) cm-1. Anal. calcd. for C22H14Cl2N4O: C, 62.72; H, 3.35; Cl, 16.83; N, 13.30; found C, 62.78; H, 3.30; Cl, 16.85; N, 13.28.

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

M.p. 199-200^{o}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) v: 3236 (NH), 1670(CO) cm-1; MS (70 eV) m/z (%):400 (M+, 19). Anal. calcd. for C23H17ClN4O: C, 68.91; H, 4.27; Cl, 8.84; N, 13.98; found C, 68.95; H, 4.26; Cl, 8.80; N, 14.00.

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

M.p. 256-257^{o}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) v: 3255 (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 pipredine 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)-1*H*-benzo[*d*] imidazol-2-yl)methyl) phthalazin-1(2*H*)-one (4a).

M.p. 140-141^{o}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) v: 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^{o}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) v: 1677 (CO) cm-1; MS (70

eV) m/z (%):518 (M+, 15). Anal. calcd. for $C_{28}H_{25}Cl_2N_5O$: C, 64.87; H, 4.86; Cl, 13.68; N, 13.51; found C, 64.89; H, 4.82; Cl, 13.63; N, 13.54.

4-(3-Chloro-4-methylphenyl)-2-((1-(piperidin-1-ylmethyl)-1H-benzo[d] imidazol-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 $C_{29}H_{28}ClN_5O$: 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.

4-(Biphenyl-4-yl)-2-((1-(piperidin-1-ylmethyl)-1H-benzo[d]imidazol-2-yl)methyl) phthalazin-1(2H)-one (4d)

M.p. 180-181oC; 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 $C_{34}H_{31}N_5O$: 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*-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 acetobromo-α-D-glucose (0.011 mol) was added. The reaction mixturewas 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-(2',3',4',6'-tetra-*O*-acetyl-*β*-D-galactopyranosyl)-1*H*-benzo [*d*]imidazol-2-yl)methyl)phthalazin-1(2*H*)-one (5a).

M.p. 88-89°C; yield 68%; 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), 5.20 (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, J1',2' = 9.90 Hz, H-1'), 7.00–8.12 (m, 10H, Ar–H); IR (KBr) v: 1741, 1672, cm^{-1}. Anal. calcd. for $C_{39}H_{40}N_4O_{10}$: C, 64.63; H, 5.56; N, 7.73; found C, 64.68; H, 5.52; N, 7.70.

4-(3,4-Dichlorophenyl)-2-((1-(2',3',4',6'-tetra-*O*-acetyl-*β*-D-galactopyranosyl)-1*H*-benzo[d] imidazol-2-yl)methyl)phthalazin-1(2*H*)-one (5b)

M.p. 110-111°C; yield 63%; 1H NMR (DMSO-d6) δ: 1.75, 1.92, 1.95, 2.07 (4s, 12H, 4CH3CO), 4.04(m, 1H, H-5'), 4.24 (dd, 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, 1H, J2',3' = 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 $C_{36}H_{32}Cl_2N_4O_{10}$: 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.

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*]imidazol-2-yl)methyl) phthalazin-1(2H)-one (6a).

M.p. 237-238oC; yield 74%; 1H NMR (DMSO-d6) δ: 2.37 (s, 3H, CH3), 2.50 (s, 6H, 2CH3), 3.19 (m, 6H, H-6' , H-6'', H-5' , H-4', H-3' and H-2'), 3.52 (t, 1H, J = 3.60 Hz, OH-6', exchangeable with D2O), 4.40 (d, 1H, J = 4.24 Hz, OH-4', exchangeable with D2O), 4.75 (s, 2H, CH2CO), 5.21 (d,1H, J = 4.44 Hz, OH-3', D2O exchangeable), 5.53 (d, 1H, J = 4.92 Hz, OH-2', exchangeable with D2O), 6.04 (d, 1H, J1',2' = 8.44 Hz, H-1'), 7.05–8.12 (m, 10H, Ar–H); IR (KBr) v: 3446, 1660 cm^{-1}; Anal. calcd. for $C_{31}H_{32}N_4O_6$: C, 66.89; H, 5.79; N, 10.07; found C, 66.92; H, 5.75; N, 10.05.

4-(3,4-Dichlorophenyl)-2-((1-(*β*-D-galactopyranosyl)-1*H*-benzo[d]imidazol-2-yl)methyl) phthalazin-1(2*H*)-one (6b)

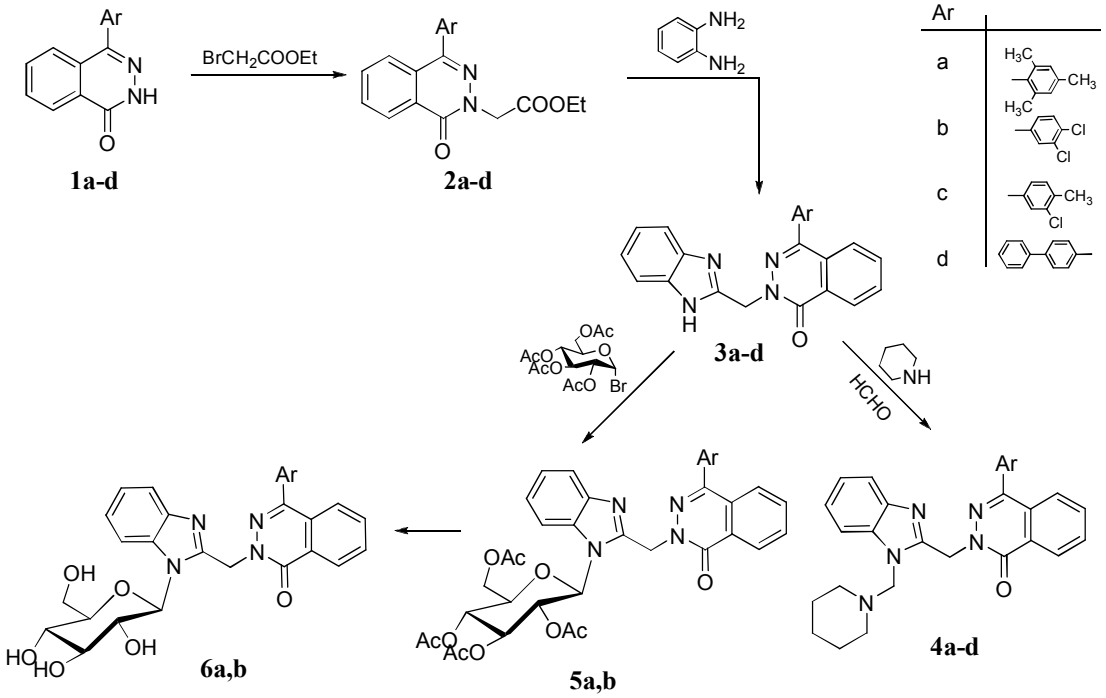
M.p. 268-269°C; yield 74%; 1H NMR (DMSO-d6) δ: 3.20 (m, 6H, H-6' , H-6'', H-5' , H-4', H-3' and H-2'), 3.53 (t, 1H, J = 3.60 Hz, OH-6', exchangeable with D2O), 4.45 (d, 1H, J = 4.24 Hz, OH-4', exchangeable with D2O), 4.81 (s, 2H, CH2CO), 5.23 (d,1H, J = 4.44 Hz, OH-3', D2O exchangeable), 5.58 (d, 1H, J = 4.92 Hz, OH-2', exchangeable with D2O), 6.07 (d, 1H, J1',2' = 8.44 Hz, H-1'), 7.01–8.10 (m, 11H, Ar–H); IR (KBr) v: 3423, 1678 cm-1; MS (70 eV) m/z (%):582 (M+, 8). Anal. calcd. for $C_{28}H_{24}Cl_2N_4O_6$: C, 57.64; H, 4.15; Cl, 12.15; N, 9.60; found C, 57.69; H, 4.10; Cl, 12.11; N, 9.62.

3. Results and Discussion

3.1. Synthesis

Treatment of phthalazin-1(2*H*)-one derivatives **1a-e** with ethyl bromoacetate in boiling acetone in presence of K_2CO_3 gave the corresponding phthalazine acetic acid ethyl esters **2a-d**. 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 ν = 1731-1742 cm-1 corresponding to CO of ester, CO of cyclic amide at ν = 1659-1681 cm^{-1} and devoid any band for NH. The 1H NMR spectrum of compound **2a-d** showed a triplet signal at δ 1.48-1.53 assigned for CH_3CH_2, a quartet signal at δ 4.18-4.32 assigned for CH_2CH_3, a singlet at δ 4.79-4.51 assigned for CH_2CO. Cyclocondensation of acetic acid ethyl estes**2a-d** with *o*-phenylenediamine in HCl gave 2-((1H-benzo[*d*]imidazol-2-yl)methyl)-4-arylphthalazin-1(2*H*)-one **(3a-d)**. The ^{1}H-NMR spectrum of compounds **3a-d** showed NH at δ 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 δ 4.77 ppm. Glycosylation of 2-((1*H*-benzo[*d*]imidazol-2-yl)methyl)-4-arylphthalazin-1(2H)-one **(3a,b)** with one equivalent of acetobromo-α-D-glucose in dry acetone in presence of K_2CO_3 afforded N-nucleoside **(5a,b)**. The structure of compounds **5a** and **5b** were based on the spectroscopic data. Thus, the β-configuration of compounds **5a** and **5b** were supported by their ^{1}H-NMR spectra, which revealed the anomeric proton as doublet at δ 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_3N 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_3CO and the appearance of the D_2O exchangeable OH protons at δ 3.52-5.58 ppm. Their IR spectra indicated the presence of broad band at 3447, 3423 cm^{-1} for OH groups.



Scheme 1.Phthalazin-1(2H)-one derivative

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(2*H*)-one **(3)** and 4-aryl-2-((1-(piperidin-1-ylmethyl)-1H-benzo[*d*] imidazol-2-yl)methyl)phthalazin-1(2*H*)-one**(4)** were synthesized starting from 4-arylphthalazin-1(2*H*)-one **(1)** .

Acknowledgements

This work was financially supported by the project "CEITEC– Central European Institute of Technology – excellent teams (CZ.1.07/2.3.00/30.0005)" financed from European Social Fund.

Corresponding Authors:

1. Dr. Abdel-Mohsen M. Abdel-Mohsen
Central European Institute of Technology (CEITEC), Brno University of Technology, Czech Republic, andTextile Research Division, National Research Center, Dokki, Giza, P.O. 12622, Giza 12522, Egypt.
E-mail: abdo_mohsennrc@yahoo.com, abdel-mohsen@ceitec.vutbr.cz
2. Dr. Ibrahim E. El-Shamy
Chemistry Department, Faculty of Science, Fayoum University, Fayoum, Egypt
E-mail: iei00@fayoum.edu.eg

References

1. M. Napoletano, G. Norcini, F. Pellacini, F. Marchini, G. Morazzoni, P. Ferlenga and L. Pradella,The synthesis and biological evaluation of a novel series of phthalazine PDE4 inhibitors I.,Bioorg. Med. Chem. Lett., **2000**, 10, 2235.
2. M. Agrawal, P. Kharkar, S. Moghe, T. Mahajan, V. Deka, C. Thakkar, A. Nair, C. Mehta, J. Bose, A. Kulkarni-Almeida, D. Bhedi, R. A. Vishwakarma., Discovery of thiazolyl-phthalazinoneacetamides as potent glucose uptake activators via high-throughput screening., Bioorg. Med. Chem. Lett., **2013**, 23, 5740.
3. M. R.Ciria, A. M. Sanz, M. J. R. Yunta, F. G.Contreras, P. Navarro, I. Fernandez, M. Pardo, C. Cano, C., Synthesis and cytotoxic activity of N,N-bis-{3-[N-(4-chlorobenzo[g]-phthalazin-1-yl)]aminopropyl}-N-methylamine: a new potential DNA bisintercalator., Bioorg. Med. Chem., **2003**, 11, 2143.
4. Soliman R, Gabr M, Abouzeit-har MS and Sharabi FM. Formation of thiazoles, thiazines, and thiadiazines from 1-phthalazine thiosemicarbazides as potential anticonvulsants., J.Pharma. Sci., 1981, 70, 94.
5. Nomoto, Y.; Obase, H.; Takai, H.; Teranishi, M.; Nakamura, J.; Kubo, K., Studies on cardiotonic agents. II.: Synthesis of novel phthalazine and 1, 2, 3-benzotriazine derivatives Chem. Pharm. Bull. **1990**, 38, 2179-2183.
6. A. H. Abd El-Wahab, H. M. Mohamed, A. M. El-Agrody, M. A. El-Nassag, A. H. Bedair. Synthesis, reactions and biological evaluation of benzyltriazolophthalazine derivatives, Eur. J. Chem., **2013**, 4, 10.
7. Juan Li, Yan-Fang Zhao, Xiao-Ye Yuan, Jing-XiongXu and Ping Gong, Synthesis and anticancer activities of novel 1,4-disubstituted phthalazines , Molecules, **2006**, 11, 574.
8. V. M. Loh Jr., X-l. Cockcroft, K. J. Dillon, L. Dixon, J. Drzewiecki, P. J. Eversley, S. Gomez, J. Hoare, F. Kerrigan, I. T.W. Matthews, K. A. Menear, N. M.B. Martin, R. F. Newton, J. Paul, G. C. Smith, J. Vile, A. J. Whittle, Phthalazinones. Part 1: The design and synthesis of a novel series of potent inhibitors of poly(ADP-ribose)polymerase, Bioorg. Med. Chem. Lett. **2005**, 15, 2235-2239.
9. S. L. Zhang, Y. J. Liu, Y. F. Zhao, Q. T. Guo, P. Gong, Synthesis and antitumor activities of novel 1,4-substituted phthalazine derivatives , Chin. Chem. Lett., **2010**, 21, 1071.
10. S. Zhang, Y. Zhao, Y. Liu, D. Chen, W. Lan, Q. Zhao, C. Dong, L. Xia, P. Gong, S. Zhang, Synthesis and antitumor activities of novel 1,4-disubstituted phthalazine derivatives, Eur. J. Med. Chem., **2010**, 45, 3504.
11. A. Akashi, T. Chiba, A. Kasahara, Antihypertensive activity of 1-[2-(1,3-dimethyl-2-butenylidene)-hydrazino]-phthalazine (DJ-1461), a new phthalazine derivative, Eur. J. Pharm., **1974**, 29, 161.
12. E. del Olmo, B. Barboza, M. Ybarra, Jose'LuisLo'pez-Pe'rez, R. Carro'n, M A. Sevilla, C. Boselli, A. S. Feliciano. Vasorelaxant activity of phthalazinones and related compounds, Bio. Med. Chem. Lett., **2006**, 16, 2786.
13. Johnsen, M.; Rehse, K.; Petz, H.; Stasch, J.; Bischoff, E. Arch. Pharmacol. **2003**, 336, 591-597.
14. Madhavan, G. R.; Chakrabarti, R.; Kumar, S. K.; Misra, P.; Mamidi, R. N.; Balraju, V.; Ksiram, K.; Babu, R. K.; Suresh, J.; Lohray, B. B.; Lohray, V. B.; Iqbal, J.; Rajagopalan, Novel phthalazinone and benzoxazinone containing thiazolidinediones as antidiabetic and hypolipidemic agents R. Eur. J. Med. Chem. **2001**, 36, 627-637.
15. Lenz, E. M.; Wilson, I. D.; Wright, B.; Partidge, E. A.; Roddgers, C. T.; Haycock, P. R.; Lindon, J. C.; Nicholson, J. K. J. Pharm. Biomed. Anal. **2002**, 28, 31-43.
16. M. Sánchez-Moreno, F. Gómez-Contreras, P. Navarro, C. Marín, F. Olmo, M. J. R. Yunta, A. M. Sanz, M. J. Rosales, C. Cano, L. Campayo. Phthalazine Derivatives containing imidazole rings behave as Fe-SOD inhibitors and show remarkable Anti-T. cruziactivity in immunodeficient-mouse mode of infection , J. Med. Chem., **2012**, 55, 9900.
17. X-Y. Sun, C. Hu, X-Q. Deng, C-X. Wei, Z-G. Sun, Z-S. Quan. Synthesis and anti-inflammatory activity evaluation of some novel 6-alkoxy (phenoxy)-[1,2,4]triazolo[3,4-a]phthalazine-3-amine derivatives, Eur. J. Med. Chem., **2010**, 45, 4807.

18. Mosaad S.M. Abdalla, Mohamed I. Hegab, Nageh A. Abo Taleb, Sherifa M. Hasabelnaby, A. Goudah. Synthesis and anti-inflammatory evaluation of some condensed [4-(3,4-dimethylphenyl)-1(2H)-oxo-phthalazin-2-yl]acetic acid hydrazide, Eur. J. Med. Chem., **2010**, 45, 1267.
19. N. Kaila, A. Huang, A. Moretto, B. Follows, K. Janz, M. Lowe, J. Thomason, T. S. Mansour, C. Hubeau, K. Page, P. Morgan, S.Fish, X. Xu, C. Williams, E. Saiah. Diazineindole acetic acids as potent, slective, and orally bioavailable antagonists of Chemoattractant Receptor homologous molecule expressed on Th2 Cells (CRTH2) for the treatment of allergic inflammatory diseases, J. Med. Chem., **2012**, 55, 5088.
20. Van der Mey, M.; Hatzelmann, A.; Van Klink, G. P.; Van der Lann, I. J.; Sterk, G. J.; Thibaut, U.; Timmerman, H., Novel Selective PDE4 Inhibitors. 1. Synthesis, structure–activity relationships, and molecular modeling of 4-(3,4-dimethoxyphenyl)-2H-phthalazin-1-ones and analogues, J. Med. Chem. **2001**, 44, 2511.
21. L. H. Pettus, S. Xu, G-Q. Cao, P. P. Chakrabarti, R. M. Rzasa, K. Sham, R. P. Wurz, D. Zhang, S. Middleton, B. Henkle, M. H. Plant, C. J. M. Saris, L. Sherman, L. Wong, D. A. Powers, Y. Tudor, V. Yu, M. R. Lee, R. Syed, F. Hsieh, A. S. Tasker, 3-Amino-7-phthalazinylbenzoisoxazoles as a novel class of potent, selective, and orally available inhibitors of p38α Mitogen-Activated protein kinase, J. Med. Chem., **2008**, 51, 6280.
22. Nargues S. Habib, Ahmed M. Farghaly, Fawzia A. Ashour, Adnan A. Bekhit, Heba A. Abd El Razik, TarekAbd El Azeim, Synthesis of some triazolophthalazinederivatives for their anti-Inflammatory and antimicrobial Activities, Archiv der Pharmazie, **2011**, 344, 530.
23. Brad, H.; Guo-Qiang, C.; Partha, P. C.; James, R. F.; Liping, P.; Robert, M. R.; Anthony, B. R.; Andreas, R.; Kelvin, S.; Maya, T.; Ryan, P. W.; Shimin, X.; Dawei, Z.; Faye, H.; Matthew, R. L.; Rashed, S.; Vivian, L.; Daved, G.; Matthew, H. P.; Bradley, H.; Lisa, S.; Scot, M.; Lu, M.W.; Andrew, S. T. Discovery of Highly Selective and Potent p38 Inhibitors Based on a Phthalazine Scaffold, J. Med. Chem. **2008**, 51, 6271.
24. F. M. Awadallah, W. I. El-Eraky, D. O. Saleh, Synthesis, vasorelaxant activity, and molecular modeling study of some new phthalazine derivatives, Eur. J. Med. Chem., **2012**, 52, 14.
25. Sharma S, Gangal S, Rauf A. Convenient one-pot synthesis of novel 2-substituted benzimidazoles, tetrahydrobenzimidazoles and imidazoles and evaluation of their in vitro antibacterial and antifungal activities, Eur J Med Chem., **2009**, 44, 1751.
26. Bishop BC, Chelton ETJ, Jones AS. The antibacterial activity of some fluorine-containing benzimidazoles, Biochem Pharmacol, **1964**, 13,751.
27. M. A. El-Hashash, A. Y. El-Kady, M. A. Taha, and I. E. El-Shamy, Chin. J. Chem., **2012**, 30, 616.
28. H. A. El-Sayed, A. H. Moustafa, A. Z. Haikal, R. Abu-El-Halawa, S. H. El-Ashry, Synthesis, antitumor and antimicrobial activities of 4-(4-chlorophenyl)-3-cyano-2-(β-O-glycosyloxy)-6-(thien-2-yl)-nicotinonitrile,**2011**, 46, 2948.

2/19/2014