Synthesis and behavior of 4- arylphthalazin-1(2H)thione derivatives towards carbon and nitrogen electrophiles

M.A.El-Hashash; A.H-Moustafa ;R.S.Ali

Abstract– 4-methylphenylphthalazin -1(2H)- thione (4-a) has been reacted with alkylating agents namely propargl bromide, allyl bromide, epichlorohydrin- 2,3,4,6-tetracetyl-β -D-glucopyranosyl bromide, and peracetylated ribose and yielded the S-alkylatedproducts. Interaction of 4-(3,4-dimethylphenyl) phthalizin-(2H)-one with D-glucono-1,5 lactone and 2,3,4,6- tetracetoxy-α- D-glucopyranosyl bromide yielded the N-nucleosides 10 and 11 respectively.

Treatment of (3,4-dimethylphenyl) phthalizin-1- (2H)-thione(4b) with hydrazine hydrate afforded the hydrazine derivative 12. Hetero ring opening of D-glucono-1, 5 –lactone by the hydrazine derivative 12 gave the N-nucleoside derivative 17.

Furthermore, reaction of the hydrazine derivative with D-glucose gave the corresponding hydrazone 13. Treatment of hydrazone 13 with acetic anhydride followed by bromination gave acetylated cyclic C-nucleoside 15 which converted to free C-nucleoside via its reaction with ammonium hydroxide and methanol.

Index Terms— methylphthalazine – D-glucopyranosylbromide – peracetylatedribose - D-glucono-1,5 lactone -2,3,4,6- tetracetoxy-α- D-glucopyranosyl bromide - N-nucleoside- acetylated cyclic C-nucleoside.

1 INTRODUCTION

Nitrogen containing heterocyclic molecules constitutes the largest portion of chemical entities, which are part of many natural products, fine chemicals, and biologically active pharmaceuticals. Phthaiazin-1(2H)-ones are important building blocks in the construction of new molecular systems for biologically active molecules [1-3].

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The development of new and efficient methodologies for synthesis of potentially bioactive phthaiazin-1(2H)- one derivative is important**.**

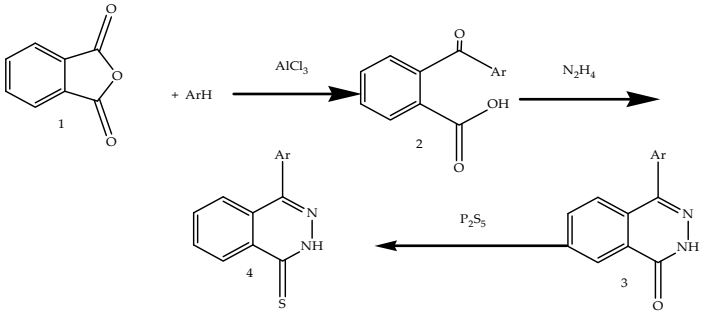
Phthaiazin-1(2H)- ones are of considerable interest due to their antidiabetic[4], antiallergic[5], vasrelaxant[6], PDE4 inhibitors[7], VEGF (vascular endothelial growth factor) receptor tyrosine kinesis for the treatment of cancer[8,9], antiasthmatic agents with dual activities of thromboxane A2 (TXA2) synthetase inhibition and bronchodialation[10], herbicidal[11], like activities. A number of established drug molecules like hydralazine[12,13], budralazine[14,15], azelastine[16,17], ponalrestat[18] and zopolrestat[19] are prepared from the corresponding phthalazinones.

Due to the nature of the phthalazine nucleus. Synthesis of new derivatives becomes an important issue. There has been little reported in the literature concerning phthaiazin-

1(2H)- thione. It was for that reason that we decide to synthesis new phthaiazin-1(2H)-thione derivatives.

Results and discussion

In this article we report the synthesis of new 4-arylphthaiazin-1(2H)-thione derivatives 4a and b according to (scheme 1). Compound 3 was obtained by cyclization of acylbenzoic acid 2 using hydrazine hydrate. The later was made through a friedel-crafts reaction between aromatic hydrocarbon and phthalic anhydride.

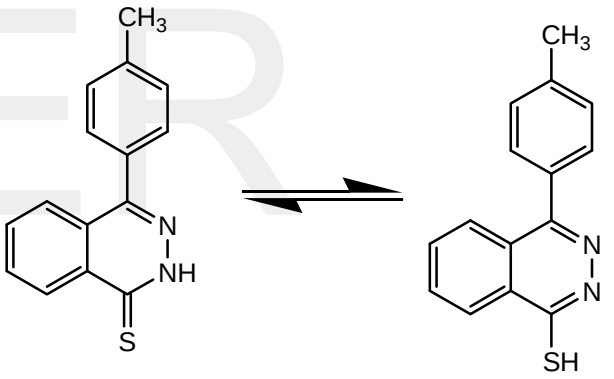


a- Ar= $C_6H_4.CH_3$(4)

b-Ar=$C_6H_3(CH_3)_2$(3,4)

Scheme (1)

Reation of compound 3 with phosphorus penta sulphide in boiling xylene afforded 4 arylphthaiazin-1(2H)-thione (4a) and (4b).IR spectrum displayed absorption bands in the region 3450-3460 and 1240-1255 Cm^{-1} NH and C=S groups. ^{1}HNMR showed a signal at δ 12.72ppm for NH or SH group in tautomer form^{13}CNMR spectrum showed a signal at δ179.5 ppm characteristic for C= S group. Alkylation of compound 4a with alkylhalides namely, propargyl, allyl bromide and epichlorohydrin in presence of K_2CO_3 anhydrous and dry acetone yielded the S-alkylphthalazine derivatives 5a-c scheme 2. Assignment of structures 5a-c are based on correct elemental analysis. The IR spectra are consistent with the proposed structure and revealed the absence of NH and C=S groups.^{1} HNMR spectra of compound 5a showed triplet signal at δ3.21 PPm with coupling constant (J=1.5 HZ,longe range coupling) characteristic for the acetylinic proton (≡C-H),in addition to doublet signal at δ4.32 ppm assigned for the presence of SCH_2 group. Its ^{13}CNMR showed the absence of signal at 179.5 PPm indicate the formation of S-alkyl not N-alkyl compound, in addition two signals at δ21.4 for SCH_2, and at 74.0,80.5 PPm characteristic for C ≡C carbon. ^{1}HNMR spectrum and elemental analysis for compound 5b are agreement with the proposed structure (cf. experimental section). ^{1}HNMR srectrum of compound 5c are showed two doublet of doublet at 4.33 and 4.51 PPm characterized for the diasterorotopic proton of CH_2Oof oxirane ring, and two doublet of doublet at 3.95 and 4.15 PPm for the diasterotopic proton of SCH_2 in addition to multiplet signal at 6.22 for sterogenic proton of oxirane ring. The alkylation of compound 4a proceeds according to the expected mechanism. The reaction take place via SN^2 mechanism in which the lone pair of sulphur attacks the alkyl halide moiety, and the function of K_2 CO_3 is pulling of the bromide ion and abstract hydronium H^+ from SH group.Here the authors offer a speculation to explain the activities of the thioamide and iminothiol equilibrium based on their thermodynamic and kinetic control under the experimental conditions



Firstly, in the presence of K_2 CO_3 anhydrous and acetone the conjugate base of the iminothiol tautomer is more thermodynamically stable than the conjugate base derived from thioamide tautomervia the back donation involving the vacant d-orbital of the sulpher atom. Therefore, the iminothiol tautomer is more predominate under such conditions.

Secondly, sulphur anion is strong nucleophile than nitrogen anion (nucleophilicity is kinetic control). Thus, the iminothiol tautomer is more thermodynamically ana kinetically favored than the thio amide tautomer, which practically spells out the reactivity of the iminothiol tautomer.

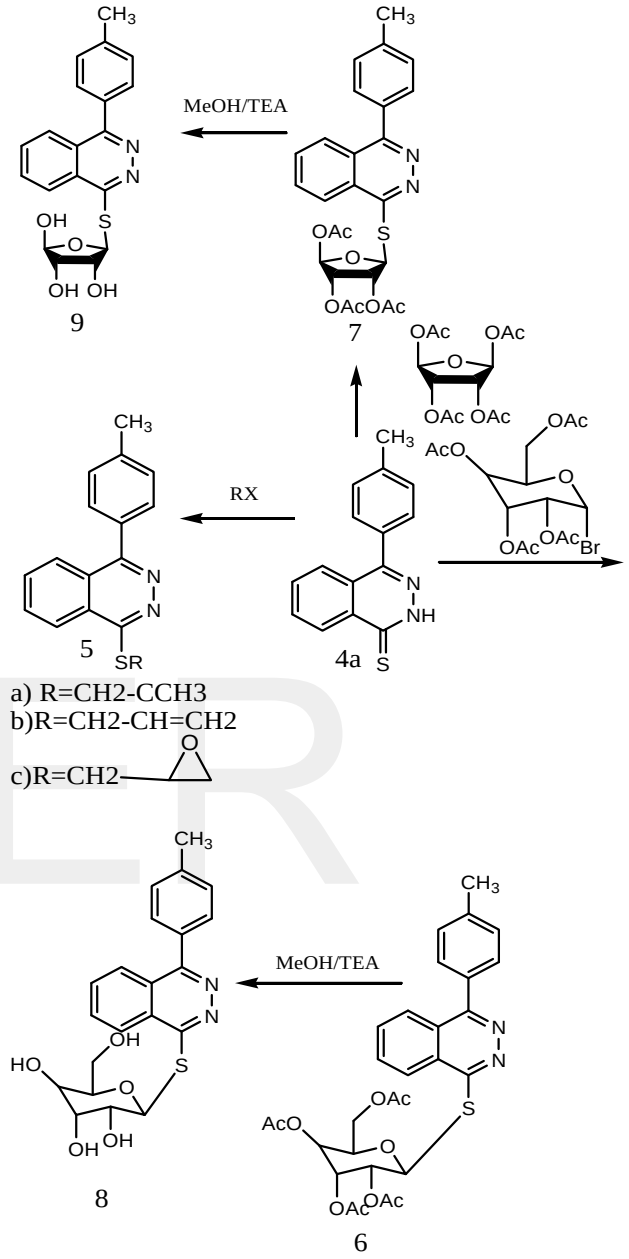
Compound 4a undergoes alkylation with 2,3,4,6-tetra acetoxy-β -D- glucopyranosyl bromide and peracetylated ribose in presence of anhydrous K_2 CO_3 and dry acetone to give 4-(4-methylphenyl)-1-(2,3,4,6-tetra acetoxy) -β -D-

glucopyranosyl) thiophthalazine (6) and 4-(4-methyl-phenyl)-1-(2,3,5triacetoxy)βDribofuranosyl)thiophthalazine (7) with very low yield Ca 10% riboside 7 was obtained by MW irradiation of 4a with peracetylated ribose for 5 min.

The IR spectra for S-nucleosides 6 and 7 showed absorption bands at 1737 and 1739 Cm^{-1} for acetoxy groups. ^{1}HNMR spectrum of glycoside 6 showed signals at δ81.81 , 1.93 , 1.95 and 2.02 for 4-acetoxy groups and at δ6.35 PPm as doublet signal characteristic for anomeric proton with coupling constat (j=9.6HZ) indicate the formation of B-configuration. While ^{1}HNMR spectrum of ribose 7 showed signals at δ 2,03 and 2.07 and 2.09 characteristic for 3-acetoxy groups and doublet signal at 6.44 PPm characteristic for anomeric proton. The elemental analysis data assigned structure of S-nucleosides 6 and 7.(cf.experemental part.

The deprotection of S-nucleosides 6 and 7 in presence of MeOH/TEA and few drops of water afforded the free nucleosides 8 and 9 respectively in 85% yields.

The IR spectra are in agreement with the structureand revealed the absence of V of acetoxy groups and presence of bands at 3595 and 3415 cm^{-1} for free VOH groups of free nucleosides.^{1}HNMR spectra of nucleosides 8 and 9 showed the absence of the methyl protons for the acetoxy groups and presence of signals for the OH groups which exchandeable whith D_2O, in addition to signals at δ 5.72 and 6.25 PPm with coupling constant (j=6.6,3.8 HZ) characteristic for the anomeric protons.



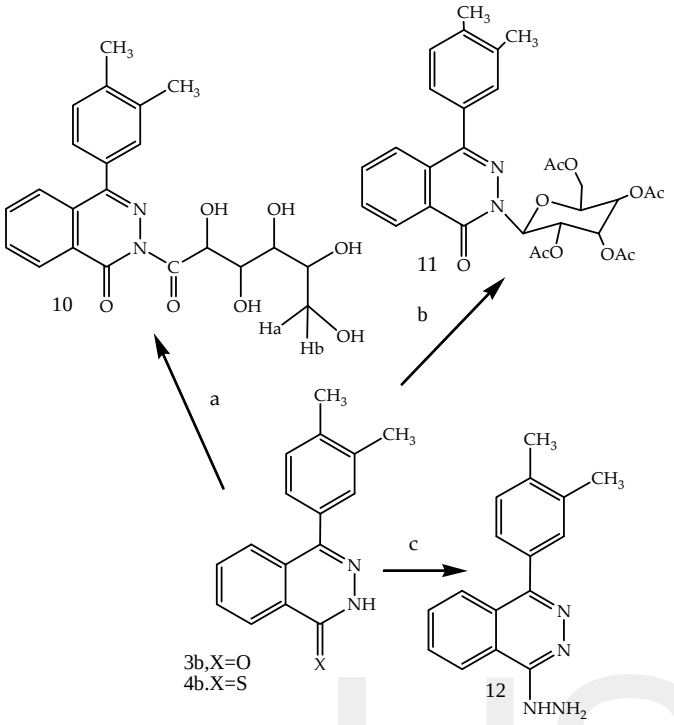
Scheme(2):Alkylation with functionalized alkyl halides

In this investigation the outher sought to investigate heteroting opening of D-glucono-1,5-lactone with phthalazinone derivative 3b with the aim of obtaining N-nucleoside incorporated with phthalazinone moiety.

Actually, some N-ucleoside was shown to exhibit prominent and versatile biologically activity[20,21] .

Indeed, the phthalazinone 3b was allowed to react with with D-glucono-1,5- lactone in pyridine afforded N-nucleoside derivative, 2-g;uconyl-4(3,4-dimethylphenyl)-2H- phtha;azin-1-one (10). Additionally, when

phthalazinone 3b was glycosidated by coupling with



Scheme(3)

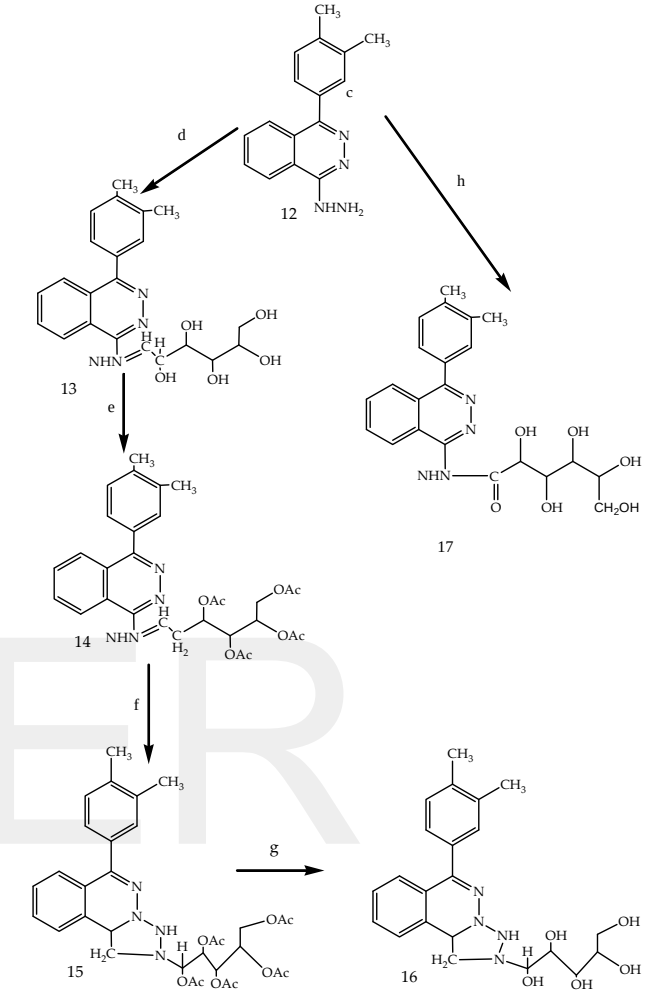
a)D-glucono-1,5-lactone/pyridine
b)2,3,4,6-tetraacetoxy-α-D-glucopyraosylbromide(α-ABG),Na2CO3/DMF c) N2H4/ethanol

2,3,4,6-tetr acetoxy-α D-glucopyranosylbomide (α-ABG) in the presence of sodium carbonate solution in N,N-dimethyl formamide, it gave 2-(2,3,4,6-tetra acetoxy)-β- D-glucopyranosyl) -4-(3,4) dimethyl-phenyl)-2H-phthalaz-ine-1-one(11)

[1]HNMRof nucleoside 11 reveald signals at 1.89, 2.03, 2.05 and 2.11(4S, 12H, 4H3CCO) attributable to glycosadated moiety ,and at 6.1 ppm as doublet characteristic for anomeric proton with coupling constant (J=8.2 HZ). The

Elemental analysis data assigned structures of N-nucleosides 10 and 11 cf .experimental part.

The hydrazinophthalazine 12 was obtained from the interaction of the thione 4b with hydrazine hydrate in boiling ethanol. Interaction of the hydrazinephthalazine 12 with –D-glucose in the presence of catalytic amount of glacial acetic acid yielded the hydrazon 13. Here the authors sought to convert the hydrazon 13 to the corresponding C-nucleosides via acetylation of the hydrazon derivative at room temperature and gave O-acetylated derivative 14. Oxidative cyclization of compound 14 by using bromine acetic acid afforded the O-acylated cyclic C-nucleoside15.



Scheme(4):Synthesis of N-nucleoside and C-nucleoside analogues

d) D-glucose/AcOH e) Ac2O/pyridine f) Br2/AcOH

g) NH4OH/MeOH f) D-glucono-1,5-lactone/pyridine

Deprotenation of 15 using ammonium hydroxide solution in methanol gave the target free cyclic C-nucleosides 16. This reaction was suggested to proceed via dimroth type rearrangement where the triazolo [1, 5-a]phthalazine was converted to triazolo[3,4-a]phthalazine.[1] HNMR spectrum of compound 16 revealed signals of the D2O exchangeable OH protons at δ3.10-3.50 and 3.7 (m, 2H, proton of triazole moiety) and the absence of the acetyl protons. The IR data of compound 16 showed also the absence of the acetyl function and the appearance of the characteristic OH's band at3370cm. Finally, the hydrazinophthalazine 12react

with D-glucono-1,5-lacton in pyridine and gave the heteroring opening adduct 17(scheme 3)

EXPERMENTAL

Melting points are uncorrected. IR spectra (KBr disc)were recorded on FTIR-400,(Perkin- Elmer) spectrophotometer

.^{1}H,^{13}CNMR spectra were recorded on a Varian 200,500 MHZ and 300MHZ all chemical shifts were reported as δ ppm scale using TMS as the standard and coupling constant values are given in HZ. The elemental analysis was determined at Microanalysis center, Cairo University.

General procedure for synthesis of (4-arylphthalazin-1(2H)-thion(4a and b).

The phthalazines (3a and b) (0.01 mol) in dry xylene (30mL) was treated with phosphorus penta sulphide (0.01 mol) and then the reaction mixture was stirred under reflux for 1 hour. Filtered off and concentrate the solvent and the solid obtained was crystallized from

4-(4-Methylphenyl)phthalazin-1-(2H)-thione(4a):

Yield 96% mp 230-231˚C IR (KBr) 3450 (ν NH), 1243 (ν C=S).HNMR(DMSO-d6)δ2.39(s,3H,CH_3), 7.31(d,2H,J=8.00 HZ , ArH),7.43(d,2H,J=7.80HZ,ArH),7.65-8.32(m,4H,ArH)12,72(s,1H,NH).^{13}CNMRδ21.40(CH_3),123.6,124.2,125.3,127.1,129.6,130.2,133.3,133.5,134.1,139.3,1.0and 179.5 (Ar-C, C=N and C=S). Anal. Calculated for $C_{15}H_{12}N_2S$ (252.33): C, 71.41, H, 4.79, N, 11.10 Found: C, 71.48; H, 4.75; N, 11.13.

4-(3,4- Dimethylphenyl)phthalazine-1(2H)thionee(4b):

Yield 87%mp187-188 ˚C IR (KBr) 3460(ν NH), 1255(ν C=S).^{1}HNMR (DMSO-d_6) δ 2.23 (s,3H,4-Ar-CH_3) 2.41(s,3H,3-Ar-CH_3),7.28(s,1H,ArH),7.45(d,2H,J=7.82HZ,ArH),7.66-8.31(m,4H,ArH),12.51(s,1H,SH) Anal. Calculated for $C_{16}H_{14}N_2S$ (266.36): C, 72.15; H, 5.30; N, 10.52 Found C, 72.35; H, 5.15; N, 10 .90.

General procedure for synthesis of compounds [5a-c]

A mixture of the appropriate alkyl halide namely propargyl bromide, allyl bromide and epichlorohydrin (0.02 mol), thione 4a (0.01 mol) and anhydrous potassium carbonate (0.04 mol) in dry acetone (50 mol) was heated under reflux for 15 hrs. The excess solvent was removed by evaporation, then the reaction mixture was diluted with water, the solid that obtained was filtered off and crystallized from ethanol.

1-(prop-2-ynylthio)-4-(4-Methylphenyl)phthalazine(5a):

Yield 65%; mp 133-134 ˚C.^{1}HNMR (DMSO-d_6) 82.43 (s,3H, ArCH), 3.21 (t,1H,J=1.5 HZ,acetylenic proton),4.32 (d,2H,J=2.4 HZ,SCH), 7.39 (d,2H,j=7.6 HZ, ArH), 7.58 (d,2H,J=7.90 HZ,ArH),8.00-8.32 (m,4H,ArH). ^{13}CNMR : 8 19.50 and 21.40 (SCH and CH), 74 and 80.50 (C C), 123.6, 124.6, 125.2, 127.1, 129.6, 130.2, 133.2, 134.0, 139.3, 157.0 and 157.7(ArC and 2 C=N). Anal. Calculated for $C_{18}H_{14}N_2S$ (290.38):C,74,75,H,4.86;N,9.65Found : C,74.52;H,4.88;N,9.98.

1-[allylthio]-4-(4-Methylphenyl)phthalazine (5b):

Yield 70%; mp 144-146 ˚C. ^{1}HNMR (DMSO-d_6) δ 82.34 (s,3H,ArCH),4.12 (m,2H,SCH), 5.50-5.18 (m,2H,terminal olefinic proton), 6.00 (m,1H,olefinic proton), 7.28 (d,2H,J=7.8 HZ,ArH), 7.49 (d,2H,J=7.70HZ,ArH),7.99-8.28 (m,4H,ArH). Anal. Calculated for $C_{18}H_{16}N_2S$ (292.40):C,73.94,H,5.52;N,9.58Found : C,73.90;H,5.56;N,9.49.

1-(oxiran-2-ylmethylthio)-4-[4-Methylphenyl)phthalazine (5c):

Yield 65% mp˚ 118-120 ˚C. ^{1}HNMR (DMSO-d_6) δ2.34 (s 3H,ArCH_3),2.62,3.95 (DD,2H,J=9.10,1.80HZ,CH_3S)4.23,4.51(DD,2H,J=7.10,5.3 HZ,diasterotopic protonsofoxiranering),6.22(m,1H,sterogenc protons of oxiran ring),7.35 (d,2H,J=706HZ,ArH),7.46(d,2H,J=7.90 HZ,ArH),7.57-8.32(m,4H,ArH).^{13}CNMR: δ21.4(CH_3),32.8(SCH_2),53.3 and 55.3 and 55.80 (CH_2O and CHO of oxiran ring) 127.1,127.6 ,128.6 , 129.5 , 129.8, 132.2, 132.4,134.1, 139.2 , 146.7 , 157.5 and 158.2 (Ar-C and 2 C=N) . Anal. Calculated for $C_{18}H_{16}N_2OS$ (308.40): C, 70.10 , H, 5.23; N, 9.08 Found: c, 70.12; H, 5.20; N, 9.09.

4-(4-Methylphenyl)-1-(2,3,4,6-tetraacetoxy-β-D-glucopyranosylthio)phthalazine(6):

A Solution of 2,3,4,6,-tetraacetoxy-B-D-glucopyranosyl bromide (0.015 mol),anhydrous potassium carbonate (0.02 mol)and compound 4a (0.01 mol) in dry acetone (50 mL) was heated under reflux for 24 hrs. The excess solvent was removed by distillation, then the reaction was dilute with water, the solid that obtaind was filtered off and crystallized from ethanol. Yield 25% , mp 95-97˚C . IR (KBr)1737(νC=Oacetoxysugar).1HNMR(DMSO-d6)δ 1.81,m1.93,1.95and2.02(4s,12H,4-CH3CO),2.49(s.3H, ArCH_3),4.01(m,2H,H5andH-6),4.36(m,2H,CH_2OCOCH_3),

5(t,1H,J=9.8HZ,H-4),5.63(t,1H,J=9.8HZ,H-2)5.76(t,1H,J= 8.65HZ,H-3),6.35(d,1H,J=9.6HZ,H-1),7.378.94(m,8H,ArH) .Anal.CalculatedforC29H36N2O9S(582.17):C,59.78; H,5.19;N,4.81 Found; C,59.79;H,5.18;N,4.80.

4-(4-Methylphenyl-1-(2,3,5-triacetoxy-β-D-ribofuraosyl-thio) phthalazine(7);

Method A

A mixture of thione 4a (0.01mol),anhydrous potassium carbonate(0.02mol), peracetaylated ribose (0.015mol) in dry acetone 50 mL) was heated under reflux for 24 hrs.the excess solvent was removed by distillation, then the reaction mixture was diluted with water, the solid that separated was crystallized from ethanol to give riboside 7(yield Ca 10%).

Method B:

A mixture of thione 4a (0.01mol), and peracetaylated ribose (o.o15mol),was dissolved in methylene chloride, then 1 gm silica gel (200-400mesh)was added, the solvent was removed by evaporation and dried residue was irradiated for 5 minute in a domestic microwave oven. The product was extracted with methylene chloride evaporated to dryness and purified by recrystalization from ethanol.

Yield 20% mp 92-94 ˚C. IR(KBr) 1739($\nu_{c=o}$ acetoxy group).^{1}HNMR(DMSO-d_6) δ2.03,2.07 and 2.09 (3s,9H,3-CH_3CO),2.49(s,3H,CH_3),4.05(dd,1H,J 5.5=11.2 HZ,H-5),4.1(dd,1H,J 4,5=4.6,J 5.5=11.2HZ,H-5)4.32(m,1H,H-4), 5.38(t,1H,J2.3=3HZ,H-2),6.44(d,1H,J1.2=2.4HZ,H-1), 7.37 (d,2H,J=7.8 HZ\,ArH),7.50(d,2H,J=7.8 HZ ,ArH), 7.78-8.08(m,4H,ArH).Anal.Culculated for $C_{25}H_{24}N_2O_7S$ (496.53) ;C,60.47;H,4.87;N,5.64 Found: C,60.19;H.4.12;N,5.48.

4-(4-Methylphenyl)-1-(B-D-gluconopyranosylthio) phthalazine(8);

A mixture of compound 6 (0.01mol)in methanol (20mL),triethylamine(1mL) and few drops of water was stirred over night at room temperature and then the solvent was evaporated under reduced pressure. The residue was crystallized from ethanol. Yield 85%: mp 140-142˚C.IR (KBr) 3395(ν_{OH}).HNMR (DMSO-d6/D2O) 2.38(3s,3H,Ar-H), 3.04(m,1H,H-3),3.22(m,1H,H-2),3.38(m,2H,H-6,H-6), 3.63(m,1H,H-5),4(m,1H,H-4),5.72(d,1H,J1.2=6.60HZ, H-1), 7.358.92(m, 8H, ArH).Anal.CulculateforC21H22O5S (414.47):C,60.58;H,5.35;N,6.76 Found: C,60.59;H,5.38;N,6.80.

4-(4-METHYLPHENYL)-1-(B-D-ribofuranosylthio) phthalazine(9):

A mixture of compound 7 (0.01mol) in methanol (20 mL), triethylamine(1mL) and few drops of water was stirred over night at room temperature and then the solvent was evaporated under reduced pressure. The residue was crystallized from ethanol. Yield 85%mp 137-139˚C.^{1}HNMR(DMSO-d_6/D_2O)2.39(s,3H,CH_3),3.5-3.6(m,2H,H-5,H-5), 3.98 (m,1H,H-4), 4.13 (dd,1H, J3,4=4.8 HZ,J2,3=5.4HZ,H-3),4.259dd,1H,J=5HZ,H2) ,6.25 (d,1H,J 1,2=3.8HZ,H-1),7.37(d,2H,J=7.8HZ,ArH) ,7.50 (d,2H, J=7.8HZ,ArH),7.78-8.81(m,4H,ArH).Anal. Culculated for $C_{19}H_{18}N_2O_4S$(370.42):C,61.61;H,4.90;N,7.56Found: C,61.50; H,5.10;N,7.28.

4-(3,4-Dmethylphenyl)2-gluconyl-(2H)phthalazine-1-one(10):

A mixture of compound 3a (0.01mol), D-glucono-1,5-lactone (0.015)in pyridine(30mL)was heated under refluxe for 2 hours. The reaction mixture after cooling was poured on to ice/hydrochloric acid. The solid that obtaind was filtered off and crystallized from ethanol.yield 72%; mp 288˚C.IR(KBr) 1665,1675($\nu_{C=O}$),3390(ν_{OH}). ^{1}HNMR(DMSO-d_6)δ2.20,2.38(s,2Ar-CH_3),3.559(m,3H,4-H,5-H,5-H)3.64(M,3H,1-H,2-H,3-H),3.84(m,4H,2-OH,3-OH,4-OH,5-OH),4.81(s,1H,1-OH),7,37-8.22(m,7H,ArH).Anal. Culculeted for $C_{22}H_{24}N_2O_7$(428): C,61.68;H,5.60;N,6.54 Found C,61.62; H, 5.60;N,6.56.

2-(2,3,4,6-Tetraacetoxy-B-D-glucopyranosyl)-4-(3,4-dimethylphenyl)-2H-phthalazine-1-one(11):

A mixture of compound 3a (0.01 mol),2.3.4.6-Tetraacetoxy--D-glucopyranosyl bromide (0.015mol),Na2CO3(0.02mol) in DMF(40mL) was heated under reflux for 6 hours. The reaction mixture was diluted with water and thesolid that obtaind was filtered off and crystallized from ethylacetat/hexane. Yield 45%; mp180˚C.IR (KBr) 1665, 1745, 3370 of ν_{max} carbonyl groups and ν_{OH}. ^{1}HNMR(DMSO-d_6/D_2O)δ2.22,2.40(2s,6H,Ar-CH_3), 4.1.1,4.26(2dd,2H,GERMINAL PROTONS OF 6-Ha and with coupling constant at 3.05,5.35 and12.25HZ

corresponding to j5,6b,j6b,6a respectively),5.12-5.61(m,3H,2-H,3-H,4-H),6.11(d,J=5.35HZ,1-H),7.37-8.22(m,7H,ArH_.Anal.Culculatedfor $C_{30}H_{32}N_2O_{10}$ (580) C,62.06;H,5.51;N,4.82 Found : C,62.08; H,5.54; N,4.81.

1-(3,4-dimethylphenyl)-2H-phthalazine-1-one(12):

A mixture of thione 4b (0.01mol),hydrazine hydrate "(0.03mol?) in ethanol (50mL) was heated under reflux for 5 hours. The reaction mixture was allowed to cool and separaterd solid that obtaind was filtered off and crystallized from dioxin. Yield 70%; mp 268-270°C .IR(KBr) 3389,3450 (ν_{NH}). EIMS m/s (264). Anal. Calculated for $C_{16}H_{16}N_4$(264):C,72.72;H,6.06;N,21.20Found: C,72.69;H,6.05;N,21.25.

6-{[4-(3,4-Dimethylphenyl)-phthalazine-1-yl]-hydrazono}-hexane-1,2,3,4,5-pentaol(13)

A mixture of hydrazine 12 (0.01mol) and α-D-glucose(0.01)in ethanol (50mL) was refluxed for 8 hours. The reaction mixture was allwed to co ol and separated sold was filtered off and crystallized from ethanol. Yield 70% mp235-237°C.IR(KBr)1629(ν_{CN}),3148(ν_{NH}),3432(ν_{OH}). Anal. Culculated for $C_{22}H_{26}N_4O_5$(426): C,61.97;H,6.10;N,13.14 Found: C,61.92;H,6.15;N,13.13. :C,60.56;H,5.36;N,8.83 Found: C,60.46;H,5.37;N,8.85.

Aceticacid2,3,4,5-Tetraacetoxy-1-{[4-(3,4-Dimethylphenyl)-phthalazine-1-yl]-hydrazonomethyl}pentylester(14).

A solution of compound 14 (0.01mol) in a mixture of acetic anhydride (10 mL) was stirred at room temperature 24 hours. The reaction mixture was poured into ice-water with stirring and the solid that separated was collected by filtration and crystallized from ethanol. . Yield 65% mp 166-167°C.IR (KBr)1248(ν_{O-C}),1605($\nu_{C=N}$),1720($\nu_{C=O}$) and 3100 (ν_{NH}) Anal.Calculated for $C_{30}H_{34}N_4O_{10}$(578.61) : C,62.27; H,.5.92;N,9.68 Found: C,60.31;H,5.64;N,8.83.

(1S)-Per-O-acetyl-1-C-[4-(3,4-Dimethylphenyl)-1,2,4-triazolo[3,4-a]phthalazine-2-yl]-D-arabinitol(15).

To a solution of compound 14 (0.01mol) in glacial acetic acid (20mL),bromine (0.01mol),in glacial acetic acid(5mL),was added drop with at room temperature. The reaction mixture was heated under reflux for 1 hour, cooled, poured into water with stirring. The solid that separated was crystallized from ethanol. Yield 55%; mp 210-212°C.IR(KBr) 1640(νC=N) ,1735($\nu_{C=O}$) .^{1}HNMR(DMSO-d_6) δ 1.9-2.2(m,15H,5OCOCH$_3$),2.28 and 2.46(2s,6H,Ar-CH$_3$),4.05(m,2H,methyl-eneprotons),4.2-5.5(m,4H, 4CHOAC)7.1-8.2(m.7H,ArH). Anal.Calculated for $C_{32}H_{38}N_4O_{10}$:C,60,18;H,6.00;N,8.77Found: C,60.46;H,5.37;N,8.85.

(1S)-C-[4-(3,4-Dimethylphenyl)-1,2,4-triazolo[3,4-a]phthalazine-2-yl]-D-arabinitol(16).

To asoluion of compound 15 (0.01mol) in anhydrous methanol (30mL), ammonium hydroxide solution (5ml,35%) was added,then the reaction mixture was stirred at room temperature for 3 hours. The reactionmixture was evaporated under reduced pressure and the residue was purified on silica gel column using chloroform methanol (4:1) as eluentto give 16. Yield 55%; mp above 300° C. IR(KBr) 1644($\nu_{C=N}$) ,3341(ν_{OH}) .Anal. Culculated for $C_{22}H_{28}N_4O_5$ (428): C,61.67;H,6.59;N,13.08 Found: C,62.28;H,5.64;N,13.14.

2,3,4,5,6-Pentahydroxyhexanoicacid-N-{4-(3,4-dimethylphenyl)phthalazine-1- yl]hydrazid (17).

A mixture of compound 12 (0.01mol) and D-glucono-1,5-lactone (0.01mol) in pyridine (20mL) was refluxed for 2 hours. The reaction mixture was allowed to cool then poured into ice/HCl. The solid that separated, filtered off and crystallized from ethanol. Yield 85%; mp above 300°C . IR(KBr) 1675($\nu_{C=O}$) ,3300(ν_{OH}) . Anal. Culculated for $C_{22}H_{26}N_4O_6$ (442): C,59.72;H,5.88;N,12.66 Found: C,59.72;H,5.80;N,12.61.

REFERANCES:

[1]B.AbEL-Fattah,M.I.Al-Ashmawi,S.El-Feky,E.Roder, Egypt.J.Pharm.Sci.29(1988)259-268.

[2]B.E.Bayoumy,S.A.El-Feky,M.El-Mobayed,Egypt. J.Chem.33(1991)267-275.

[3]M.A.Khalil,S.M.El-Khawss,M.G.Kassem, Sci. Pharma 48 (1980)334-349.

[4]O.M.Boland,C.C.Blackwell,B.F.Clarke,D.J.Ewing,Diabetes42(1993)231-340.

[5]Y.Hamamoto,K.Nagi,M.Muto,C.Asgami,Exp.Depart-ment.2(1993)231-235.

[6]E.DelOlmo,Barboza,M.I.Ybarra,J.L.LopezPerez,R.Carron, M.A.Sevilla,C.Boselli,A.San Feliciano,Bioorg.MED.chem . Lett.16(2006)2786-2790.

[7]M.Napoletano.G.Norcini,F.Marcini,G.Morazzoni,P.Ferlenga,L.Pradella,Bioorg.Med.Chem.Lett.10(2000)2235-2238.

[8]G.Bold,K.H.Altmann,J.Frei,M.Lang,P.W.Manley,P. Traxler,B.Wietfeld,J.Brueggen,E.Bunchdunger,R.Cozens,S.Ferrari,P.Furet,F.Hofmann,G.Martiny-Baron,J.Mestan,J.Roesel,M.Sills,D.Stover,F.Acemoglu, E.Boss,R.Emmenegger,L.Laesser,E.Masso,R.Roth, C.Schlachter,W.Vetterli,D.Wyss,J.M.Wood,J.Med.Chem.43 (2000)2310-2323.

[9]J.M.Atif,M.Kunhi,A.A.Bekhit,M.P.Subramanian, K.Al-Hussein,H.Y.Aboul-Enein,F.M.Al-Khodairy,Asian Pac.J.CancerPrev.7(2006)249-252.

[10]M.Yamaguchi,K.Kamei,T.Koga,M.Akima,A.Maruyama, T.Kuroki,N.Ohi,J.Chem.36(1993)4052-4060.

[11]Y.X.Li.Y.P.Lue,Z.Xi.C.W.Niu,Y.Z.He,G.F.Yang,J.Agric. FoodChem.54(2006)9135-9139.

[12]F.H.H.Leenen,D.L.Smith,R.M.Faraks,R.A.Reeves, A.Marquez-Julin,Am.J.Med.82(1987)969-978.

[13]J.M.Leiro,E.Alvarez,J.A.Arranz,E.Cano,F.O.rallo,Int. Immunopharmacol 4(2004)263-177.

[14]S.Tanaka,M.Tanaka,A.Akashi,Stroke 20(1989)1724-1729.

[15]R.Moroi,K.Ono,T.Saito,T.Akimoro,M.Sano,Chem. Pharm.Bull.25(1977)830-835.

[16]J.P.Kemp,E.O.Meltzer,H.A.Orgel,M.J.Welch,G.A.Buchol tz,E.Middleton,S.L.Spector,J.J.Newton,J.L.Perhach JR.,Allergy.Clin.Immunol79(1987)893-899.

[17]G.Scheffler,J.Engel,B.Kutscher,W.S.Sheldrick,P.Bell.Archiv.der.pharmazie.321?(1988)205-208.

[18]P.F.Kador,J.H.Kinoshita,N.E.Sharpless,J.Med.Chem.28 (1985)841-849.

[19]B.L.Mylair,E.R.Larson,T.A.Beyer,W.J.Zembrowski,C.E. Aldinger,M.F.Deem,T.W.Siegel,D.H.Singleton,J.Med.Chem. 34(1991)108-122.

[20]H.Hall,D.W.Covington,J.R.Wheaton,R.A.Lzydor, X.Zhou.Pharmazie,56,168(2001).