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Facile Synthesis and Structural Characterization of Some Phthalazin-1(2H)-one Derivatives as Antimicrobial Nucleosides and Reactive Dye

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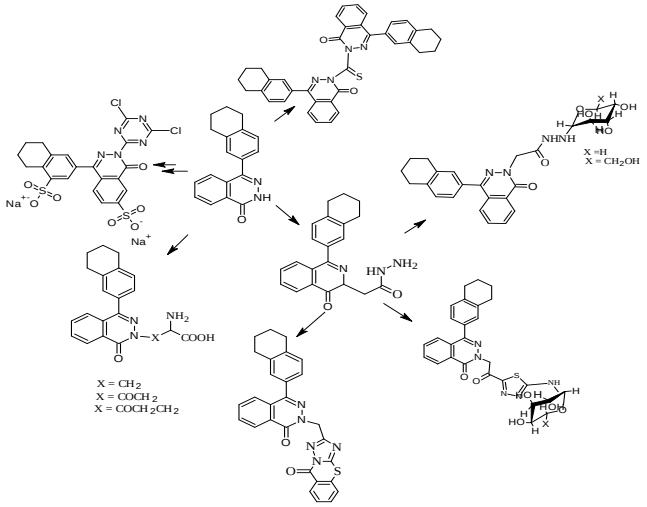
Abstract: ***A new series of 2, 4-disubstituted phthalazin-1(2H)-one derivatives was synthesized via nucleophilic attach of N-2 of phthalazin-1(2H)-one derivatives on different monosuccharides. Synthesis of phthalazinone nucleosides were very effective as antimicrobial. . Also the phthalazinonemoiety can be used in synthesis of reactive nucleosides and dyes that was chemically bonded with proteins and fibers respectively as afforded highly stability of dyestuff wool and cotton textiles. The structure of the prepared compounds were elucidated by physical and spectral data like FT-IR ,[1]H-NMR and [13]C-NMR***



Keywords: phthalazin-1(2H) one, allyl-, propargyl-phthalazinone, nucleosides, reactive dye

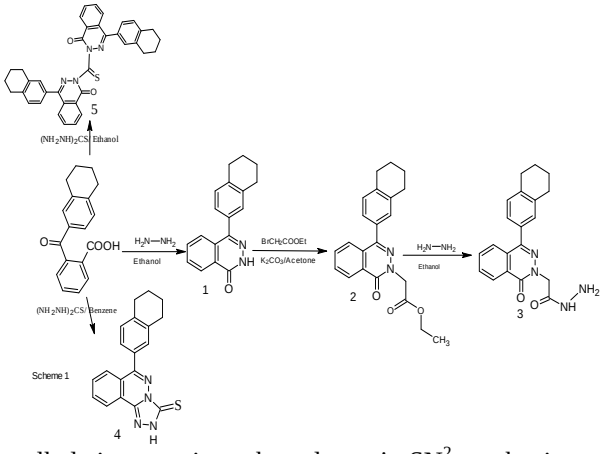
1. Introduction

Phthalazines as N-heterocycles have received considerable attention in the literature as a consequence of their exciting biological properties and their role as pharmacophore[1]. Some of phthalazinones were screened in vitro for their antimicrobial activity and The energy gap between HOMO and LUMO has been calculated to reflect the chemical reactivity and kinetic stability of compounds [2].A Novel series of N-substituted-4-phenylphthalazin-1-ones bearing different anilines at the N-2 of phthalazin-1-one scaffold *via* acetyl-flexible linker as anticancer agents with the compounds were synthesized by insertion of methylene (CH_2) bridge at C4-position of phthalazinone moiety to provide a flexibility that increase their anti-proliferative activity against three human tumor cell[3]. Similarly, heterocycles containing the phthalazine moiety are of interest because they show some pharmacological and biological activities [4-6]. Phthalazine derivatives were reported to possessanticonvulsant [7], antitumor, **5**[8], antihypertensive [9], antithrombotic [10], antidiabetic[11], antitrypanosomal,**5**[12], anti-inflammatory **3** and **4**[13], cardiotonic[14] and vasorelaxant activities[15]. Therefore, a number of methods have been reported for the synthesis of phthalazinederivatives [16-22]. Despite the available methods, the development of new synthetic methods for the efficient preparation of phthalazinone derivative is therefore an interesting challenge. In addition phthalazinone and its derivatives were bis-phenol–like monomers which can be polymerized with the activated aryl dihalidemonomers to give amorphous polymers **1[**23] with high glass transition temperature and excellent thermo-stability, which are soluble in common organic solvents [23,24]. Recently [25-27] a series of poly (phthalazinone ether sulfoneketone (PPESK)) copolymers used as potential polymer in proton exchange membrane fuel cells [PEMFCs].Corrosion of metals is a major industrial problem that has attracted many investigation and researchers [28, 29]. The use of inhibitors is one of the most practical methods to protect metal against corrosion [30]. The adsorption on the metal surface depends mainly on the physicochemical properties of the inhibitor group, such as the functional group, molecular electronic structure and the molecular size [31-33]. A number of heterocyclic compounds containing nitrogen, oxygen and sulphur either in the aromatic or long chain carbon system have been reported to be effective inhibitors [34, 35]. The planarity and the lone pair of electron in the hetero atoms are important features that determine the adsorption of molecules on the metallic surface [36]. The inhibition efficiency has been closely related to the inhibitor adsorption

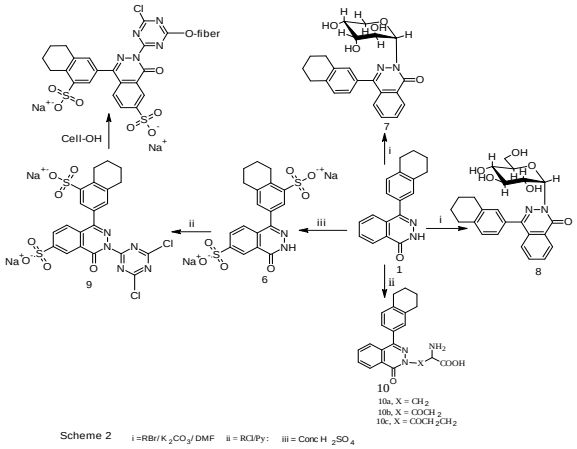
abilities and the molecular properties for different kinds of organic compounds [37, 38]. The adsorption process depends on the electronic characteristic of the of organic molecules (adsorbate), and nature of themetal surface [39]. It may take place in the presence lone pair electrons of heteroatom (P, Se, S, N, O) and/or aromatic rings in the adsorbed molecules [40].

2. Results and Discussion

In this articles the authors could be reported [41] the synthesis of 4-(1,2,3,4-Tetrahydronaphthalyl)-1-(2H)-phthalazinones**1**was obtained from ring closure of 2-tetrahydronaphthalenoyl benzoic acidusing hydrazine hydrate(Scheme 1).Assignment of structures **1** could be based on correct IR, ^{1}H-NMR and ^{13}C-NMR spectroscopes and was listed in the experimental. The ester of phthalazin-1(2H)-one derivative**2** was obtained by treatment of **1** with ethylbromoacetate in the presence of anhydrous K_2CO_3 and dry acetone.



The alkylation reaction takes place *via* SN^2 mechanism and the role of anhydrous K_2CO_3 in pull of bromide ion as KBr and abstract of hydronium ion (H^+) and converted to $KHCO_3$. IR spectra of **2** showed bands in the region 1649 cm^{-1} attributable to *v*co of cyclic amide group in addition to 1750cm^{-1} attributable to *v*co of ester group, this indicate that the reaction takes place *via* N-alkylation and not O-alkylation of the phthalazinone derivatives. In this investigation, the authors can be used to the hydrazide**3** a useful intermediate for construction of different heterocyclic compounds containing mixed and non-mixed systems. In this regard, the (2H) phthalazin-1-one ring has attracted our attention in regard to synthesis of hydrazide derivatives. Thus, when the phthalazin-1(2H)-one ester**2** was allowed to react with hydrazine hydrate in the presence of boiling ethanol yielded the corresponding the hydrazide**3**(Scheme 1). Structure of hydrazide**3** was established on the basis of IR, ^{1}H-NMR and elemental analysis data. IR spectra exhibit two carbonyl groups for amide groups, which agreed well with the proposed structure. Synthesis of phthalazinone carrying electrophilic and nucleophilic sites were very effective to decrease the basicity of the hydrazide **3** to encourge in the stability of structure, for example in industrial binder of pigments i.e. pH doesn't change(the phthalazinone moiety is considered as chromophore) and as pro-drug to increase their biological activities. Also, the authors can be reported the ring closure of 2-tetrahydronaphthalenoyl benzoic acid using thiocarbonicdihydrazide. When 2-aroylbenzoic acid 1 was allowed to react with thiocarbonicdihydrazide under different solvent condition, afforded the new synthesized compounds **4**, and **5**(Scheme 1).The reactions tookplace in a normal route to yielded the corresponding 2-phthalazinonyl thiohydrazide intermediate. The course of the reaction intermediate was depended upon solvent of the reaction. In polar aprotic solvent e.g. dioxane, the reaction course tookplace intramolecular cyclization to yielded the corrosponded triazolethione derivative **4**. But, in polar protic solvent condition e.g. ethanol, the reaction course tookplace intermolecular ring closure of the intermediate with another aroylbenzoic molecule, means 2 mole of 2-aroylbenzoic acid can be reacted with 1 mole of thiocarbonic dihydrazide, afforded the diphthalazinonyl thione **5**.the phthalazinone moiety considered as chromophore and play an important role in the field of the dying. It was characterized as synthesis of the reactive dye (Scheme 2), when it allowed to sulphonate with concentrated sulfuric acid, it was affording **6** to enhance the chromophoric moiety. Also, Glycosylheterocycles and their nucleoside analogueshave multiple potential applications. Significant progress with such analogues has let to advances in cancer chemotherapy and anti HBV and HIV applications. The lack of an effective therapy to treat hepatitis B virus and HIV infections , particularly in chronic cases has focused considerable effort into the synthesis of nucleoside analogues possessing antiviral activity[22-24]. Some analogues having either modified bases and/or glycosyl residues have shown promise in antiparasite chemotherapy[25,26] for cytokinin activities[42,43] as antihypertensive agent[44], as biochemical tools[45,46] and as inhibitors of cellular enzymes[47,48]. An area of intensive research is in the design of nucleoside analogues where in theglycone moieties are altered while biological activity is retained. This type of novel design of nucleoside analogue pertains to modified nucleo-bases which are of neither the purine nor pyrimidine types. We have reported the synthesis and biological activity of nucleoside analogues incorporating modified nucleobases [49, 50]. In this regard, the (2H) phthalazin-1-one ring has attracted our attention in synthesis of cyclo-nucleoside derivatives. Thus, when the phthalazin-1(2H)-one derivatives **1** was allowed to react with α-D-arabino- and/or gluco-pyranosyl bomide in the presence K_2CO_3/ dry DMFyielded the corresponding N-cyclonucleosides 2-(α-D-arabino- and/or gluco-pyranosyl)-4-phenyl phthalazin-one(**7** and **8**) respectively(Scheme 2). Structure of **7**and**8** were established on the basis of IR, ^{1}H-NMR and elemental analysis data. IR spectra exhibit carbonyl group for cyclic amide, which agreed well with the proposed structure.

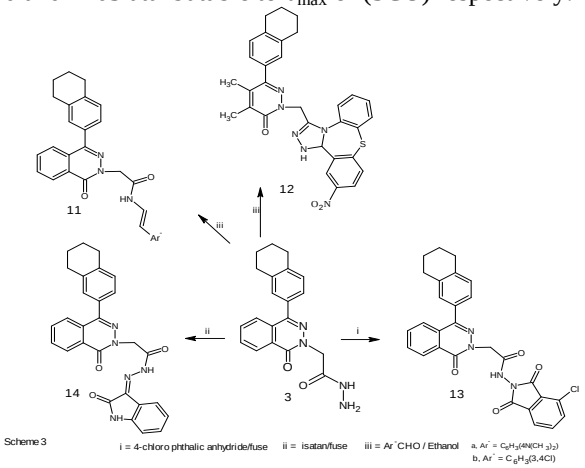


Scheme 2 i =RBr/ K_2CO_3/ DMF ii = RCl/Py: iii = Conc H $_2SO_4$

Moreover, Creation of the builder **9**, when the sulphonatedphthalazinone**6** was allowed to react with 2,4,6-trichloro-1.3.5-triazine(TCT) in the presence of pyridine, it was afforded **9** that be ready reacted with the fibers. The phthalazinonemoiety can be used in synthesis of reactive dyes that was chemically bonded with fibers as afforded highly stability of dying wool and cotton textiles. Assignments of structure**9**can be based on correct elemental analyses, IR, and ^{1}H- NMR spectral data.

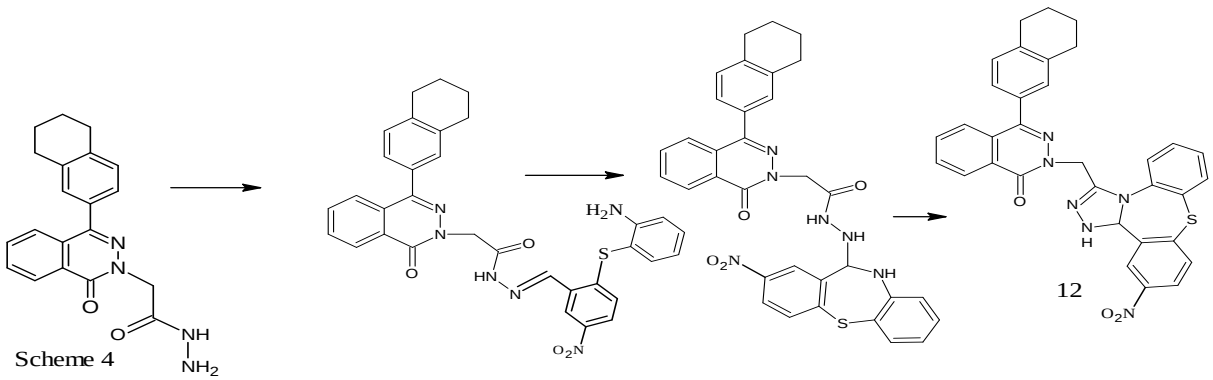
Reactions of the phthalazinone**1**within preferred alkyl halide to yielded α-amino acids carrying phthalazinone bases **10**(Scheme 2). It's important to improve the amino acid in which as carrying a pro-drug precursor. A novel synthesized bases for protein that can be used for enzymatic reaction and drug delivery. When the phthalazinone**1** was allowed to react with alkyl halide of α-amino acids e.g. β-chloroalanine, Aspartic and/or Glutamic acidmonochloride, to yield the target compounds **10**. Assignments of structures **10** are based on correct elemental analyses, IR and ^{1}H- NMR spectral data, the IR spectrum exhibits strong absorption bands at 1661-1665, 1684 and 1686 attributable to υ_{CO}, the ^{1}HNMR of compound **10** showed signals at 2.2 (dt, 1H, CH(NH_2)COOH) and 6.4 and 8.2(s, 3H, NH_2 and COOH, D_2O exchangeable). The biological activities of the compounds **10** could be became more effective than the phthalazinone itself, and the reverse result occurred within the compounds **6** and **7** that can't be expected. It's well-known that N-nucleosides could be preferred as a bioactive molecule, but a negative result occurred. Table 1 outlined the results of biological activity of the compounds **1**, **6**,**7**, **10a**, **10b**, and **10c**.Otherwise, the importance of presence the acetyl group in the derivatives **10b** and **10c**, the felexibility of the target for matching with piptide structures that can be used to destruct the tumer cell formed.

On the other hand, refluxing of [1(2H)-oxo-4-(1,2,3,4-teterahydronaphthalen-1-yl)phthalazin-2-yl]acetic acid hydrazide**(3)** with aromatic aldehydes e.g. 4-N,N-dimethyl aminobenzaldehyde and/or *p*-chlorobenzaldehyde in boiling ethanol afforded N-arylidine derivatives **11** in good yields**,** the ^{1}H-NMR spectrum of **11a** should exhibit at δ 8.75 assigned for the methylidene proton, the mass spectrum of compound **11b** should the ion peak at m/z 570(48.46%) corresponding to $M^{\cdot+}$. Repeating of the above reaction of hydrazide with 4-nitro-2-(2-aminothio phenyl)benzaldehyde, affording unexpected product of 1, 3-thiazepino-1, 2, 4-triazole **12**(Scheme 3). Moreover, when the hydrazide**3** was submitted to react with phthalaic anhydride and/or is a tin in an oil bath at 150^{0}C, it yielded [4-(3-methyl-4-bromo)phenyl-1(2H)-oxo-phthalazin-2-yl]-N-phthalimidoacetamide**13** and/or indol-2-on-3-yl-acetyl hydrazone**14**respectively. IR spectra of compounds **13**and**14** revealed strong absorption bands at the regions 1655,1690, 1735 and 1790 cm^{-1}attributable to υ_{max} of (4CO), and 1660, 1670 and 1705 attributable to υ_{max} of (3CO) respectively.



Scheme 3 i = 4-chloro phthalic anhydride/fuse ii = isatan/fuse iii = Ar$^-$CHO / Ethanol a, Ar$^-$ = C_6H_3(4N(CH $_3$)$_2$) b, Ar$^-$ = C_6H_3(3,4Cl)

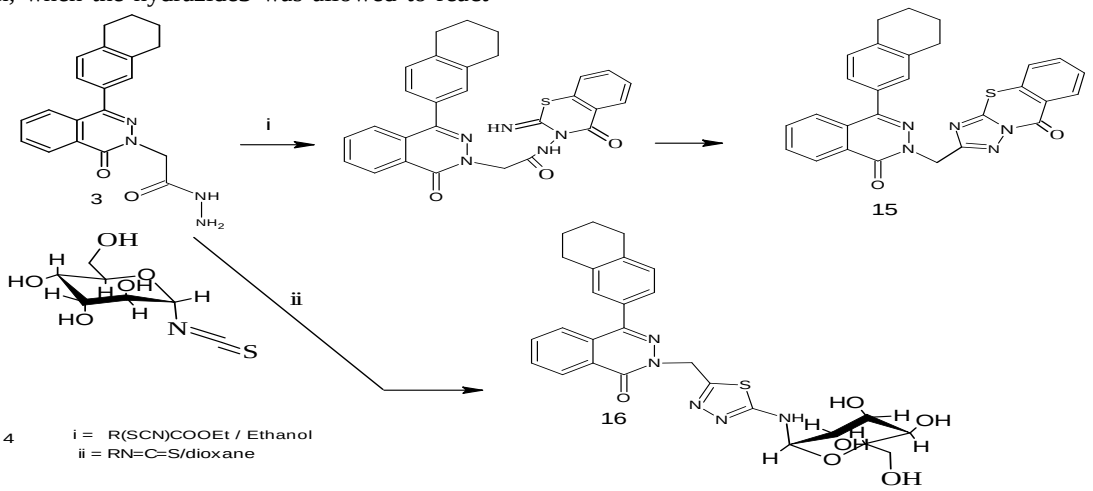
The authors can be explained formation of dibenzothiazepinotriazole, when the hydrazide**3** was allowed to react with new carbon electrophile e.g. ethyl-2-thiocyanatobenzoate in boiling ethanol affording an important species of 4-oxo-benzothiazino-1,2,4-triazole derivatives **15**.The reaction possibly proceeds according to the following mechanism (Scheme 4).



Scheme 4

The ^{1}H-NMR of compound The authors can be reported synthesis and characterization, when the hydrazide**3** was

allowed to react with new carbon electrophile e.g. ethyl-2-thiocyanatobenzoate in boiling ethanol affording an important species of 4-oxo-benzothiazino-1,2,4-triazole derivatives **15** (Scheme 4). **15** should signals at δ 4.75 for CH_2 of inserted between the two heterocyclic moieties.The mass spectrum of compound **15** should the prominent ion peak at m/z 491(2.25%) and 493(2.48%) attributable to $M^{\cdot+}$ and $M^{\cdot+}$+2 respectively. To continue and enhancement the chromophoric moiety, when the phthalazinonehydrazide derivative **3** was allowed to react with alkyl- and/or aryl-isothiocyanate namely methyl, ethyl, cyclohexyl, and phenylisothiocyanate afforded thiocarbamate[51, 52]**.**But in one pot reaction, when the hydrazide**3** was allowed to react with 1-glucosyl bromide and ammonium isothiocyanate afforded the novel N-nucleoside **16**. The reaction could be formed glucosylisothiocyanate intermediate *via* mixed the glycosyl bromide with ammonium isothiocyanate that can be scavenged by the hydrazide derivative **3** to afford the target compounds **16** that its structure was verified by spectral tools.(Scheme4). The ^{1}H-NMR of compound **16** exhibits signal at δ 5.7 and 9.90 assigned for 5H of OH and NHthat both are D_2O exchangeable. The phthalazinone moiety that incorporated with triazole and/or thiadiazole moieties **15** and **16** can be also flexible and used in synthesis of anticancer agents.



Scheme 4 i = R(SCN)COOEt / Ethanol
ii = RN=C=S/dioxane

3. Antimicrobial Evaluation

Compounds 1, 2, 3, 4, 5, 6, 7, 8, and 10were tested for antimicrobial activity against *Escherichiacoli* (Gram negative bacterium), *Staphylococcusaureus* (Grampositivebacterium), *Aspergillusflavus* and *Candida albicans* (fungi) using the disc diffusion method. The antimicrobiale valuation was done in the Micro analytical Center at Cairo University.

3.1Generaldisc Diffusion (agar-based) Method

Standard discs of tetracycline(antibacterial agent) and amphotericin B(antifungal agent) served as positive controls and references for antimicrobial activities respectively, but filter discs impregnated with10µL of solvent (chloroform, ethanol, DMF) were used as a negative control. The agar used is Mueller-Hintonagar that is rigorously tested for composition and pH. The depth of the agar in the plateisa factor to be considered in this method. Blank paper discs (Schleicher and Schuell,Spain) with a diameter of 8.0mm were impregnated with 10 µL of the tested concentration of the stock solutions. When a filter paper disc impregnated with a tested.

Chemical is placed on agar, the chemical will diffuse from the disc into the agar. This diffusion will place the chemical in the agaronly around the disc. The solubility of the chemical and its molecular size will determine the size of the area of chemical in filtration around the disc. If an organism is placed on the agar it will not grow in the area susceptible to the chemical around the disc. This area of no growth around the disc is the"zone of inhibition "or" clear zone". For disc diffusion, the zone diameters were measured with slipping calipers of the National Committee for Clinical Laboratory Standards (NCCLS)[20].Agar-based method is a good alternative method being simpler and faster than broth–based methods [21,22].

3.2 Antibacterial Activity

Concentration of 1mg/mL of test compounds was prepared by dissolving the compounds in its proper solvent. For each concentration, 0.2 mL of synthesized compounds (1mg/mL) was added to each hole. The plates were allowed to stand at room temperature for two hours and then incubated. The organisms were grown in nutrient agar at 37oCfor 24 hours. After incubation period, the growth inhibition zones diameters were carefully measured in mm. The clear zone around the wells was measured as inhibition zones. The absence of a clear zone around the well was taken as in activity. Result so fanti bacterial activity ested against *E.coli* (G^-) and *S.Aureus* (G^+) showed that all of the selected compounds were anti bacterially active and comparatively efficient

3.3 Antifungal Activity

The samples were dissolved, each in its proper solvent, then 0.5 mL sample of each compound (1 mg/mL) plus 0.1 mL of the tested fungal suspension were mixed thoroughly with 20 mL of agar medium, which was maintained at 45oC. The inoculated medium was poured into sterile Petri-dishes, allowed to solidify, and incubated at 25oC for seven days. Results of antifungal activity tested showed that compounds 2, 3, 6, 10a and 10b were active against both fungi, none was active with A. flavus, 4, 5, 8 and 10cwere active only with C. albicans, whereas the rest of compounds were totally inactive.

All the results for the antimicrobial evaluation are given in (Table 1) showing the inhibition zone diameter in mm/mg sample. Both compounds 3 and 6 showed the highest inhibition with *S. aureus* whereas compounds 3, 6 and 10showed the highest inhibition towards *C.albicans*. In conclusion all the products 1, 2, 3, 4, 5,6, 7, 8, 10a, 10b, and 10c were antibacterially active and comparatively efficient. In addition, compounds 2, 3, 6, 10a and 10b were active against both fungi, 4, 5, and10cwereactiveonlywith*C. albicans*, and the rest were inactive. The antimicrobial activity of the products compared to those of tetracycline (TC) and amphotericin B (ATB) are given in Fig 1.

4. Conclusion

The aim of this work is synthesis of some important phthalazinone derivatives to study influence of the molecular structure on the inhibiting efficiencies of organic compounds in *E. coli, S. Aureus, P. Flavus, and C. Albicans*. Nitrogen based compounds are effective antibacterial(*Staph.aureus and Escherichia coli),* and antifungal activities(*Pseud. flavusand Candida albicans).*It's found the presence of lone pair of electrons on the nitrogen atom of the additional atom delocalized and thus produces a delocalization energy that stabilized the phthalazinone compounds. The investigated phthalazine derivatives have been shown inhibiting properties for antimicrobial reagents. The structure and composition of most of synthesized phthalazine derivatives can be influence their inhibiting efficiency for microbes.

Table 1: *In vivo* antimicrobial activity by agar diffusion method of tested compounds

	Inhibition zone diameter (mm / mg sample)				
Compound	*E.coli*	*S.aureus*	*A.flavus*	*C.albicans*	Controlsolvent
Tetracycline TC	33	31	00	00	----
AmphotericinB	00	00	17	21	----
1	10	10	00	00	Chloroform
2	09	10	09	10	DMF
3	16	16	12	15	Ethanol
4	14	16	00	12	Ethanol
5	14	15	00	12	Ethanol
6	18	18	17	16	Ethanol
7	08	08	00	00	Chloroform
8	12	12	00	12	Ethanol
10a	08	21	08	18	Ethanol

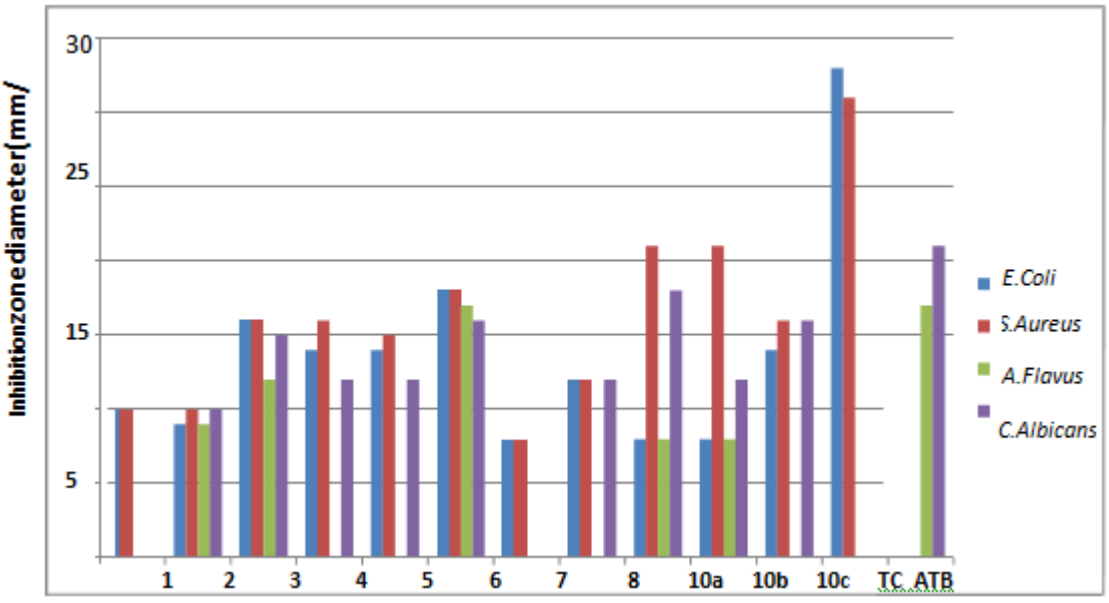


Figure 1: Graphical representation for the antimicrobial activity of the tested compounds

5. Experimental

Melting points are corrected. IR spectra (KBr disc) were recorded on infrared spectrometer FT-IR 400D (Perkin-Elmer) spectrophotometer. ^{1}H-NMR ,^{13}C-NMR spectra are recorded on a varian 200 & 500MHz and avarian 300 MHz. All chemical shifts were reported as (δ) ppm scale using TMS as internal standard and coupling constant values are given in Hz. Elemental analyses were carried out at the Microanalytical Center,National Research Center, Cairo University, Giza, Egypt

4-(5,6,7,8-tetrahydronaphthalen-2-yl)phthalazin-1(2*H*)-one(1)

Hydrazine hydrate (0.015 mol) was added to a solution of 2-(B-tetroyl) benzoic acid (0.01 mol) in absolute ethanol and the reaction mixture was heated under refluxed for 3h. The solid that separated after cooling was filtered off and recrystallized from ethanol to give the phthalazinon**2** , 80% yield as colorless crystals, m.p. 225-226℃; The ^{1}H-NMR spectrum showed signal at 1.8 (m ,4H, β -methylene group) , 2.87 (m , 4H, α – methylene group of tetryl moiety) 7.3 – 7.7 (m , 7H , ArH) , 10.5 (s , 1H , NH , exchangeable with D_2O) . IR (KBr) *v*: 3296 (NH), 1665 (C=O) , 1605 (C=N) cm^{-1}. EIMS (70 eV) *m/z* (%) : 276 (M $^+$, 100) , 248 (43) , 220 (15) , 131 (25) , 105 (15) .Anal calcd for $C_{18}H_{16}N_2O$: C , 78.23 ; H , 5.84 ; N 10.14 ; found C , 78.4 ; H 5.7 ; N 10.2 .

Ethyl2-(1-oxo-4-(5,6,7,8-tetrahydronaphthalen-2-yl)phthalazine-2(1*H*)-yl)acetate (2) .

A mixture of compound **1d** (0.01 mol), 5mL ethylbromoacetate , and 4.1g anhydrous K_2CO_3 (0.03 mol) in dry acetone (30 mL) was heated under reflux for 24 h .The solvent was evaporated and the residue was diluted with water , the solid obtained was filtered off, dried and crystallized from pet.ether(80-100^{0}C). Yield 84% as white crystals. m.p. 110-112 ℃. ^{1}HNMR (DMSO-d_6, 300 MHz) δ: 1.27 (t, J= 7.2 H_Z, 3H, $CH_2\underline{CH_3}$), 1.8 (m , 4H, tetralin), 2.8 (m, 4H, tetralin), 4.2 (q, J= 7.5 H_Z, 2H , $O\underline{CH_2}CH_3$) ,5.0 (s, 2H,CH_2), 7.3-7.7 (m , 8H , Ar-H). IR (KBr) *v*:1750, 1649 (C=O), 1584 (C=N) cm^{-1} . EIMS (70 eV) *m/z* (%):362 (M $^+$, 78), 290 (100), 134 (22), 77 (39). Anal calcd for $C_{22}H_{22}N_2O_3$: C,72.92;H , 6.07; N , 7.73; found C , 73.2 ; H, 5.95; N , 8.10

2-(1-oxo-4-(5,6,7,8-tetrahydronaphthalen-2-yl)phthalazine-2(1*H*)-acetohydrazide (3)

A mixture of **2** (4.01g) and hydrazine hydrate (2 mL) in boiling ethanol (50mL) was refluxed 1h and cooled at room temperature. The solid that formed was filtered off , dried and crystallized from ethanol. Yield 78%. Off white crystal. m.p. 232-234^{0}C. IR (KBr) ν (cm^{-1}) 1658(CO), 3324, 3417($NHNH_2$). ^{1}HNMR (DMSO-*d6)*: 1.8 (m, 4H, β -methylene group), 2.87 (m, 4H, α –methylene group of tetrylmoiety), 4.26(s, 2H, NH_2 exchangeable protons with D_2O), 4.76 (s, 2H, CH_2CO), 7.53-8.64 (m, 7H, Ar-H), 9.28(s, 1H, NH exchangeable with D_2O). ^{13}C-NMR δ 54.3, 64.5, 69.9, 126.8, 127.0, 128.0, 129.0, 129.5, 129.9, 132.2, 133.8, 135.5, 146.1, 158.9, 163.2 168.2 and 172.9. Anal. Calc. for $C_{17}H_{15}N_4O_2Br$(M.wt.379) C, 52.73; H, 3.90; N 14.47; found C, 52.75; H ,3.92; N ,14.44.

6-(5,6,7,8-tetrahydronaphthalen-2-yl)–[1,2,4]triazolo[3,4-a] phthalazine -3(2*H*)thio(4)

Thiocarbonicdihydrazide(0.015 mol) was added to a solution of phthalazinone**1** (0.01 mol) in benzene (30mL) and the reaction mixture was heated under refluxed for 3h. The solid that separated after cooling was filtered off and recrystallized from benzene to give**4** , 80% yield as colorless crystals, m.p. 184-186℃; The ^{1}H-NMR spectrum showed signal at 1.8 (m , 4H, β -methylene group), 2.87 (m , 4H, α – methylene group of tetryl moiety), 7.3 – 7.7 (m, 7H, ArH) , 11.2 (s, 1H, NH , exchangeable with D_2O) . IR (KBr) *v* : 3296 (NH) , 1605 (C=N),1115 (C=S) cm^{-1}. EIMS (70 eV) *m/z* (%) : 332 (M $^+$, 100) , 248 (43) , 220 (15) , 131 (25) , 105(15) .Anal calcd for $C_{19}H_{16}N_4S$: C, 68.65 ; H, 4.85 ; N, 16.85 ; S, 9.65 ; found C, 67.59 ; H, 4.83 ; N, 16.70 ; S, 9.57 .

2,2$^-$thiocarbonylbis(4-(5,6,7,8-tetrahydronaphthalen-2-yl)phthalazin-1(2*H*)-one (5)

Thiocarbonicdihydrazide (0.015 mol) was added to a solution of phthalazinone**1** (0.01 mol) in absolute ethanol (30mL) and the reaction mixture was heated under refluxed for 3h. The solid that separated after cooling was filtered off and recrystallized from ethanol to afford**5** , 80% yield as colorless crystals, m.p. 198-200℃; The ^{1}H-NMR spectrum showed signal at 1.8-1.9 (m ,8H, β -methylene group) , 2.87 (m , 8H, α –methylene group of tetryl moiety) 7.1 – 7.9 (m , 14H , ArH). IR (KBr) *v* : 3296 (NH) , 1665 (C=O) , 1605 (C=N) cm^{-1}. EIMS (70 eV) *m/z* (%) : 594.72 (M $^+$, 100) , 248 (43) , 220 (15) , 131 (25) , 105 (15).Anal calcd for $C_{37}H_{30}N_4O_2S$: C , 74.72 ; H, 5.08 ; N, 9.42 ; S,5.39; found C, 74.4 ; H 4.7 ; N, 9.2; S, 5.02.

Sodium-4-oxo-1-(4-sulfonato-5,6,7,8-tetrahydronaphthalen-2-yl)-3,4-dihydrophthalazine-6-sulfonate (6)

Sulphonation of phthalazinone**1**(2.2g; 0.01 mol) with concentrated H_2SO_4(0.02 mol) was heated under reflux 30 min., and then pour prohibition and slowly the reaction mixture upon solution of concentrated Na_2CO_3. Yield 80%. m.p. 202-204^{0}C. IR(KBr) 1650(amide)(CO),1592-1519(SO_2).^{1}HNMR (DMSO-*d6)*: δ 1.8 (m , 4H, β -methylene group), 2.87 (m , 4H, α – methylene group of tetryl moiety), 7.67-8.28(m, 6H, Ar-H), 9.23 (bs, 2H, H of sulphonic groups that replaced Na). Anal. Calc. for $C_{18}H_{14}Na_2S_2O_7$: C ,45.00; H ,2.94 ; N, 5.83; S, 13.35; found: C, 44.54; H, 2.87, N, 5.77; S, 13.08.

2-(α-D-Arabinopyranosyl)-4-phenylphthalazinone(7) and 2-(α-D-gluco-pyranosyl)-4-phenyl phtha- lazinone(8)

A mixture of 1 (2.2g; 0.01 mol), 1-bromo-α-D-arabinopyranoand/or1-bromo-α-D-glucopyranose (0.01 mol) and anhydrous K2CO3(3g; 0.02 mol) in dry DMF (30 mL) was stirring at room temperature 24h. The excess solvent was evaporated under reduced pressure, and the reaction mixture was diluted with water. The solid that obtained was crystallized from dioxane

(4-(5,6,7,8-tetrahydronaphthalen-2-yl)-2-((2S,3R,4R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl) tetrahydro-2H-pyran2-yl)phthalazin-1(2H)-one(7)

Yield 90%. m.p. 124-126^{0}C. IR(KBr) 1652 (amide) (CO). ^{1}HNMR (DMSO-*d6)*: δ 1.8 (m, 4H, β -methylene group), 2.22-2.39(m, 5H, H of arabinose moiety), 2.87 (m, 4H, α – methylene groupof tetrylmoiety), 4.36-4.51(m, 3H, OH), 7.46-8.23 (m, 7H, Ar-H).Anal. Calc. for $C_{24}H_{23}N_2O_6$: C, 68.57; H, 5.71; N, 6.66; found: C, 68.49, H, 5.65; N, 6.61.

(4-(5,6,7,8-tetrahydronaphthalen-2-yl)-2-((2S,3R,4R,5S,6R)-2,3,4,6-tetrahydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran2-yl)phthalazin-1(2*H*)-one(8)

Yield 90%.m.p. 132-134^{0}C. IR(KBr) 1652 (amide) (CO). ^{1}HNMR (DMSO-*d6)*: δ 1.8 (m, 4H, β -methylene group), 2.12-2.62(m, 7H, H of glucose moiety), 2.87 (m, 4H, α – methylene group of tetryl moiety), 4.36-4.51(m, 4H, OH),

7.46-8.23 (m, 7H, Ar-H).Anal. Calc. for $C_{25}H_{26}N_2O_6$: C, 66.66; H, 6.00; N, 6.22; found: C, 66.53, H, 6.02; N ,6.25.

Sodium-3-(4,6-dichloro-1,3,5-triazin-2-yl)-4-oxo-1-(4-sulfonato-5,6,6,8-tetrahydronaphthalen -2-yl)- 3,4-dihydrophthalazine-6-sulfonate (9)

A mixture of phthalazinonedisulphonated (0.01 mol) and 2,4,6-trichlorotriazine(0.01 mol) in pyridine and refluxing for 2h. Pour the reaction mixture after cooling on petroleum ether. Teatment the aqueous layer with conc. HCl. Filter the solid product **9** in the acid form**.** Yield80%.m.p.256-258^{0}C.IR(KBr) 1650(amide)(CO), 1592-1519(SO_2). ^{1}HNMR (DMSO-*d6)*: δ 1.8 (m, 4H, β -methylene group), 2.87 (m, 4H, α –methylene group of tetryl moiety), 7.67-8.28(m, 7H, Ar-H), 9.23 (bs, 2H, H of sulphonic groups that replaced Na). Anal. Calc. for $C_{21}H_{13}Cl_2N_5Na_2S_2O_7$: C ,40.14; H, 2.09; Cl,11.28; N 11.15; Na, 7.32;O,17.82 ; S,10.21 found: C ,40.05; H ,2.02 ; Cl,11.15 ;N, 11.9; Na,7.28 ; O,17.76 ; S,10.17

Synthesis of phthalazinone amino acids 10

A mixture of compound**1** (0.01 mol), chloride of α-amino acids namely; β-chloroalanine, 2-amino-4-chloro-4-oxobutanoic acid (chloride of aspartic), and 2-amino-5-chloro-5-oxobutanoic acid (chloride of glutamic) in pyridine (30 mL) and few drops of water was heated under reflux for 4 h. The solvent was evaporated and the residue was diluted with water, the solid obtained was filtered off, dried and crystallized from pet.ether(80-100^{0}C).

2-amino-3-(1-oxo-4-(5,6,7,8-tetrahydronaphthalen-2-yl)phthalazin-2(1*H*)-yl) propanoic acid (10a)

Yield 84% as white crystals. m.p. 210-212 ^{0}C. IR(KBr) ν(cm^{-1}) 1751, 1658(CO). ^{1}HNMR spectrum (DMSO-d6) : δ 1.8 (m , 4H, β -methylene group), 2.87 (m , 4H, α –methylene group of tetryl moiety), 4.14-4.19(2dd, 2H, CH_2N),4.56(dd, 1H, CH), 5.6(bs, 2H, NH_2), 7.33–8.28 (m, 7H, Ar-H), 8.3(s, 1H, COOH). ^{13}C-NMR δ 33.6, 53.8 (N-CH_2), 75.5, 78.8, 125.8, 127.0, 127.8,128.9, 129.1, 129.7, 129.9, 132.7, 134.3, 134.9, 137.3, 147.2 and 157.9 (Ar-C), 163.5(C=N),190.3(C=O). (M.wt. 363.41) % Anal. Calc for $C_{21}H_{21}N_3O_3$: C,69.41;H,5.82 ; N,11.56 ; found C,69.37, H,5.77; N,11.50.

2-amino-4-oxo-4-(1-oxo-4-(5,6,7,8-tetrahydronaphthalen-2-yl)phthalazin-2(1*H*)-yl)butanoic acid 10b

Yield 84% as white crystals. m.p. 232-234 ^{0}C. IR(KBr) ν(cm^{-1}) 1751, 1658(CO). ^{1}HNMR spectrum (DMSO-d6) : δ 1.8 (m , 4H, β -methylene group), 2.87 (m , 4H, α –methylene group of tetryl moiety), 3.46-3.49(2dd, 2H, CH_2CO),4.67(dd, 1H, CH), 5.6(bs, 2H, NH_2), 7.33–8.28 (m, 7H, Ar-H), 8.3(s, 1H, COOH). ^{13}C-NMR δ 33.6, 53.8 (N-CH_2), 75.5, 78.8, 125.8, 127.0, 127.8,128.9, 129.1, 129.7, 129.9, 132.7, 134.3, 134.9, 137.3, 147.2 and 157.9 (Ar-C), 163.5(C=N),190.3(C=O). Anal. (M.wt. 391.42) % Anal. Calc for $C_{22}H_{21}N_3O_4$: C ,67.51;H ,5.41 ; N, 10.74 ; found C ,67.44, H, 5.39; N, 10.67.

2-amino-5-oxo-5-(1-oxo-4-(5,6,7,8-tetrahydronaphthalen-2-yl)phthalazin-2(1*H*)-yl)pentanoic acid 10c

Yield 84% as white crystals. m.p. 226-228 ^{0}C. IR(KBr) ν(cm^{-1}) 1751, 1658(CO). ^{1}HNMR spectrum (DMSO-d6) : δ 1.8 (m , 4H, β -methylene group), 2.1(m, 2H, CH_2), 2.87 (m , 4H, α –methylene group of tetryl moiety), 2.94(t, 2H, CH_2CO), 4.62(s, 1H, CH), 5.6(bs, 2H, NH_2), 7.33–8.28 (m, 7H, Ar-H), 8.3(s, 1H, COOH). ^{13}C-NMR δ 33.6, 53.8 (N-CH_2), 75.5, 78.8, 125.8, 127.0, 127.8,128.9, 129.1, 129.7, 129.9, 132.7, 134.3, 134.9, 137.3, 147.2 and 157.9 (Ar-C), 163.5(C=N),190.3(C=O). (M.wt. 405.45) % Anal. Calc for $C_{23}H_{23}N_3O_4$: C ,68.13;H ,5.72 ; N, 10.36 ; found C ,68.10, H, 5.65; N, 10.30.

Synthesis of Arylidine derivatives 11

A mixture of hydrazide**3**(3.87g, 0.01mol), appropriate aromatic aldehyde (0.01 mol) namely 3,4-dichlorobenzaldehydand4-dimethylaminobenzaldehyde was refluxed in absolute ethanol(30mL) and few drops acetic acid for 9h. After cooling, the separated solid was collected by filtration, dried and crystallized from proper solvent

(Z)-N$^-$-(dimethylamino)benzylidene)-2-(4-(5,6,7,8-tetrahydronaphthalen-2-yl)phthalazine-2(1*H*)-acetohydrazide(11a)

Yield 96%, white crystals crystallized from benzene. m.p. 184-186^{0}C. IR(KBr) ν(cm^{-1}) 1620(C=N), 1673(CO) and 3170(NH). ^{1}HNMR (DMSO-*d6)*: δ 1.8 (m, 4H, β -methylene group), 2.87 (m, 4H, α – methylene group of tetryl moiety), 4.01(s, 2H, methylene proton of gly. precusor), 6.7(s, 1H, CH=), 7.11-8.21 (m, 11H, Ar-H), 12.04(s, 1H, NH exchangeable with D_2O). ^{13}C-NMR δ 35.9(methyl of Ar), 64.2 (methylene N-CH_2), 122.4, 126.9, 127.2, 127.7, 128.4, 128.7, 129.0, 129.5, 130.1, 130.6, 131.2, 132.5, 133.9, 134.5, 138.2, 143.5, 160.6, 165.4, 166.5, 167.2, 168.2, 169.0 (C=N, C=O). MS: m/z = 472, 470. Anal. Calc. for $C_{29}H_{31}N_5O$ (M.wt.465.59): % C ,74.81; H, 6.71; N ,10.03 ; O, 3.44; found: C ,74.78; H, 6.67;N,10.01;O,3.40

(Z)-N$^-$-(dichlorobenzylidene)-2-(4-(5,6,7,8-tetrahydronaphthalen-2-yl)phthalazine-2(1*H*)-acetohydrazide (11b)

Yield 98%, orange crystals crystallized from benzene. m.p. 224-226^{0}C. IR(KBr) ν(cm^{-1}) 1604(C=N), 1666(CO) and 3170(NH). ^{1}HNMR (DMSO-*d6)*: δ 1.8 (m , 4H, β -methylene group), 2.87 (m , 4H, α –methylene group of tetryl moiety), 2.7(s, 6H, N(CH_3)$_2$), 4.51(s, 2H, methylene proton of gly. precusor), 6.7(s, 1H, CH=), 7.11-8.21 (m, 10H, Ar-H), 12.04(s, 1H, NH exchangeable with D_2O). ^{13}C-NMR δ 35.9(methyl of Ar), 55.4, 56.2(2methyl of N(CH_3)$_2$), 62.2 (methylene N-CH_2), 122.4, 126.9, 127.2, 127.7, 128.4, 128.7, 129.0, 129.5, 130.1, 130.6, 131.2, 132.5, 133.9, 134.5, 138.2, 143.5, 160.6, 165.4, 166.5, 167.2, 168.2, 169.0 (C=N, C=O). MS:m/z=472, 470. Anal. Calc.for $C_{26}H_{24}N_4OCl_2$(M.wt.491.41): %C, 65.99; H, 4.92;Cl,14.43; N ,11.40; O, 3.26.; found: C, 65.96; H, 4.88;Cl,14.39; N ,11.35; O, 3.21 .

(E)-N-(2-(2-aminophenylthio)-5-nitrobenzylidene)-2-(4-(5,6,7,8-tetrahydronaphthalen-2-yl)phthalazin-2(1*H*)-yl)acetohydrazide (12)

A mixture of hydrazide**3**(3.87g, 0.01mol), 4-nitro-2-(2-aminothiophenyl)benzaldehyde was refluxed in absolute ethanol(30mL) and few drops acetic acid for 9 h. After cooling, the separated solid was washed with light petrol(b.p 40-60^{0}C), collected by filtration, dried and crystallized from benzene.Yield 90%, green crystals. m.p. 240-242^{0}C. IR(KBr) ν(cm^{-1}) 1658 (CO) and 3090-3100(NH), 3345-3420(NH_2).

^{1}HNMR (DMSO-*d6)*: δ 1.8 (m , 4H, β -methylene group), 2.87 (m , 4H, α – methylene group of tetryl moiety), 4.21(s, 2H, methylene proton),6.98-8.20 (m, 14H, Ar-H), 10.04(s, 1H, NH exchangeable with D_2O). ^{13}C-NMR δ 35.9(methyl of Ar), 64.2 (methylene N-CH_2), 85.7(S-CH), 122.4, 126.9, 127.2, 127.7, 128.0, 128.4, 128.7, 129.0, 129.5, 130.1, 130.6, 131.2, 131.8, 132.3, 132.5, 133.9, 134.5, 138.2, 139.2, 140.2, 143.5, 160.6, 165.4, 166.5, 167.2, 167.8, 168.5(C=N, C=O). (M.wt.590.69): % Anal. Calc. for $C_{33}H_{30}N_6O_3S$: C, 67.10; H, 5.12; N ,14.23; S, 5.43; found: C, 67.7; H, 5.9; N, 14.18; S, 5.37.

N-(4-chloro-1,3-dioxoisoindolin-2-yl)-2-(1-oxo-4-(5,6,7,8-tetrahydronaphthalen-2-yl) phthalazin-2(1H)-yl)acetamide (13)

A mixture of hydrazide**3**(3.87g, 0.01mol),4-chlorophthalic anhydride(1.4g, 0.01mol) was heated in an oil bath at 180^{0}C for 1 h. The fused mixture was then treated with ethanol and filtered. The crude product was crystallized from dioxane. Yield 92%, white crystals. m.p. 262-263^{0}C. IR(KBr) ν(cm^{-1}) 1650, 1690, 1735, 1790(4CO). ^{1}HNMR (DMSO-*d6)*: δ 1.8 (m , 4H, β -methylene group), 2.87 (m , 4H, α – methylene group of tetryl moiety), 4.20(s, 2H, methylene proton of gly. precusor), 7.26-8.11Anal.Calc.$C_{28}H_{21}ClN_4O_4$for (M.wt.512): %C 65.56; H,4.13; N,10.92;Cl,6.91;O,12.48; found: C,65.51, H,4.9, N,10.86;Cl,6.84;O,12.4365.56, H 4.13, N 10.92, Cl6.91;O,12.48; 58.04, H 3.31, N 10.83, Br 15.45; found: C 58.01, H 3.33, N 10.85, Br 15.46. (m, 11H, Ar-H), 9.11(s, 1H, NH exchangeable with D_2O). ^{13}C-NMR δ 38.3-47.8(methylene groups), 49.7 (methylene N-CH_2), 126.9, 127.7, 128.7, 129.1, 129.5, 129.8, 130.1, 130.6, 131.2, 131.7, 132.5, 133.9, 134.2, 134.5, 138.2, 139.4, 143.5, 145.6, 158.7, 160.6, 165.4, 168.2, 169.0 (C=N, 3C=O). MS: m/z = 518, 516, Anal. Calc. for $C_{25}H_{17}N_4O_4Br$ (M.wt.517): %C 58.04, H, 3.31; N, 10.83; Br, 15.45; found: C, 58.01; H, 3.33; N, 10.85; Br, 15.46.

(Z)-N-(2-oxoindolin-3-ylidene)-2-(4-(5,6,7,8-tetrahydronaphthalen-2-yl)phthalazin-2 (1*H*)-yl)acetohydrazide (14)

Amixture of hydrazide**3**(3.87g, 0.01mol), isatin(1.4g, 0.01mol) and few drops of acetic acid in ethanol (20mL) was refluxed 10 h. After cooling, the obtained solid was collected and filtered. The crude product was crystallized from ethanol. Yield 96%, white crystals. m.p. 218-220^{0}C. IR(KBr) ν(cm^{-1}) 1660, 1670, 1705(3CO). ^{1}HNMR (DMSO-*d6)*: δ 1.8 (m , 4H, β -methylene group), 2.87 (m , 4H, α – methylene group of tetryl moiety), 4.06(s, 2H, methylene proton of gly. precusor), 7.19-8.25 (m, 11H, Ar-H), 9.8 and 11.7(s, 2H, 2NH exchangeable with D_2O). ^{13}C-NMR δ 41.1-47.4(methylene groups), 55.7 (methylene N-CH_2), 126.9, 127.7, 128.7, 129.1, 129.5, 129.8, 130.1, 130.6, 131.2, 131.7, 132.5, 133.9, 134.2, 134.5, 138.2, 139.4, 140.3, 143.5, 145.6, 158.7, 162.1, 165.7, 168.4(C=N, 2C=O). MS: m/z = 517, 515. (M.wt.516) Anal. Calc. for $C_{28}H_{25}N_5O_2$: C, 72.55; H ,5.44; N, 15.11; O, 6.90; found: C ,72.48; H 5.38; N, 15.9; O, 6.87.

2-((1-oxo-4-(5,6,7,8-tetrahydronaphthalen-2-yl)phthalazin-2(1*H*)-yl)methyl)-9H-benzo[e][1,2,4]triazolo[5,1-b][1,3]thiazin-9-one (15)

A mixture of hydrazide**3**(3.87g, 0.01mol), ethyl-2-thiocyanatobenzoate(0.01 mole) was refluxed in absolute ethanol(30mL) for 9 h. After cooling, the separated solid was collected by filtration, dried and crystallized from ethanol. Yield 96%, white crystals. m.p. 184-186^{0}C. IR(KBr) ν(cm^{-1}) 1620(C=N), 1673 (CO) and 3170(NH). ^{1}HNMR (DMSO-*d6)*: δ 1.8 (m , 4H, β -methylene group), 2.87 (m , 4H, α – methylene group of tetryl moiety), 4.01(s, 2H, methylene proton of gly. precusor), 6.7(s, 1H, CH=), 7.11-8.21 (m, 11H, Ar-H). ^{13}C-NMR δ 35.9(methyl of Ar), 64.2 (methylene N-CH_2), 122.4, 126.9, 127.2, 127.7, 128.4, 128.7, 129.0, 129.5, 130.1, 130.6, 131.2, 132.5, 133.9, 134.5, 138.2, 143.5, 160.6, 165.4, 166.5, 167.2, 168.2, 169.0 (C=N, C=O). MS: m/z = 472, 470. (M.wt.491.56)Anal. Calc. for $C_{28}H_{21}N_5O_2S$: C, 68.41; H,4.31; N,14.25; S,6.52; found: C, 68.38; H,4.27; N,14.20; S,6.48.

4-(5,6,7,8-tetrahydronaphthalen-2-yl)-2-((2S,3R,4R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-ylamino)-1,3,4thiadiazol-2-yl)methyl)phthalazin1(2*H*)-one(16)

In one pot reaction of a mixture of hydrazide (0.774g, 0.002mol), D (+)glucosyl bromide (0.34g;0.002mol), ammonium isocyanate (0.03 mol) in pyridine(20mL) was refluxed for 6h. After cooling, the reaction mixture poured onto ice/H_2O. The solid that formed was filtered off, dried and crystallized from ethanol. Yield 86%, colourless crystals. m.p. 290-292^{0}C. IR(KBr) ν(cm^{-1}) 1650(CO), 3233(NH), 3440(OH). ^{1}HNMR (DMSO-*d6)*: δ 1.8 (m , 4H, β -methylene group), 2.12-2.62(m, 7H, H of glucose moiety), 2.87 (m , 4H, α – methylene group of tetryl moiety), 4.20(s, 2H, methylene protons),4.60(bs, 4H, OHglu), 6.9-7.8 (m, 7H, Ar-H), 9.80(s, 1H, NH exchangeable with D_2O). ^{13}C-NMR δ 39.45- 46.5(methylene groups of Ar), 52.8(methylene), 122.3, 125.7, 126.9, 127.7, 128.7, 129.1, 130.2, 131.7, 132.5, 133.9, 134.2, 134.5, 136.5, 138.2, 139.4, 140.2, 143.5, 145.6,158.7, 160.6, 165.4, 168.2 (3C=N, C=O). Anal. Calc. for $C_{27}H_{29}N_5O_6S$ (M.wt.551.61): % C ,58.79; H, 5.30; N, 12.70; found % C , 58.74; H, 5.32; N, 12.67.

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