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

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A NEW series of 2,4-disubstituted phthalazin-1(2H)-one derivatives were 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 phthalazinone moiety can be used in synthesis of reactive nucleosides and dyes that were chemically bonded with proteins and fibers respectively as afforded highly stability of dyestuff wool and cotton textiles. The structure of the prepared compounds was elucidated by physical and spectral data like FT-IR, ^{1}H- and ^{13}C-NMR.

Keywords: Phthalazin-1 (2*H*) one, Allyl-, Propargyl - Phthalazinone, Epchlorohydrin, Nucleosides, Reactive dye

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. 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 possess anticonvulsant [7], antitumor [8], antihypertensive [9], antithrombotic [10], antidiabetic [11], antitrypanosomal [12], anti-inflammatory [13], cardiotonic [14] and vasorelaxant activities [15]. Therefore, number of methods have been reported for the synthesis of phthalazine derivatives [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 dihalide monomers to give amorphous polymers [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 sulfone ketone(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 investgation 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]. Number of heterocyclic compounds containing nitrogen, oxygen and sulfur 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 the metal 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].

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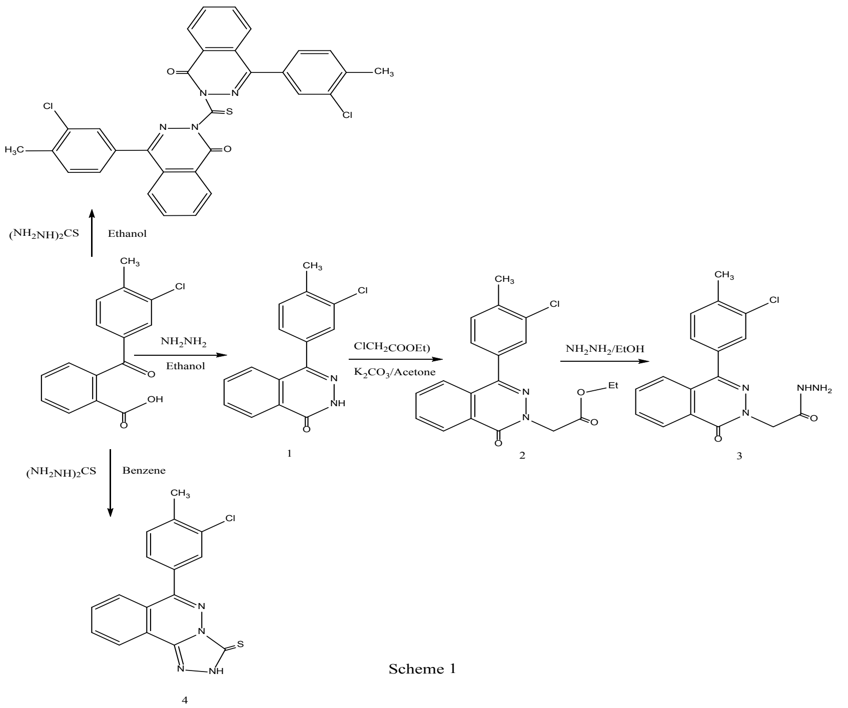
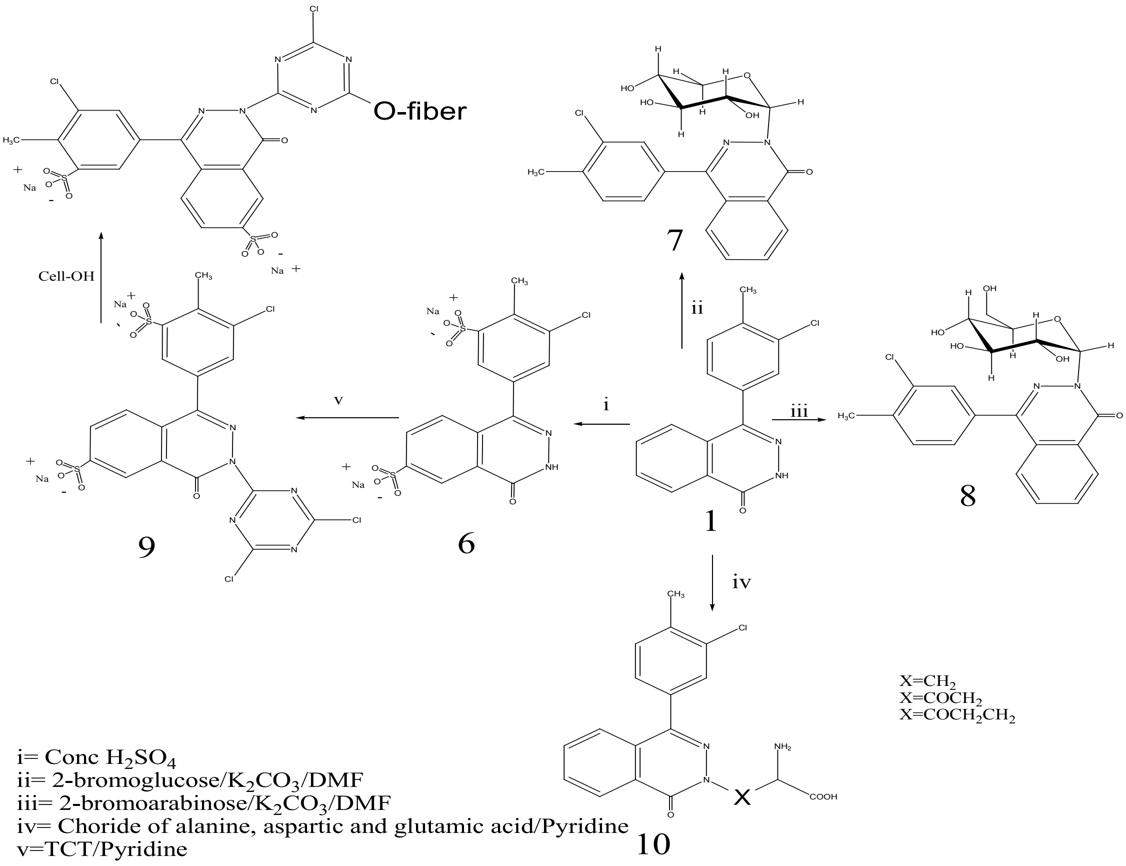
Results and Discussion

In this article the authors could be reported [41] the synthesis of 4-(3-chloro-4-methylphenyl)-1-(2*H*)-phthalazinones 1 was obtained from ring closure of 3-chloro-4-methylphenyl benzoic acid using hydrazine hydrate (Scheme 1). Assignment of structures 1 could be based on correct IR, ^{1}H-NMR and ^{13}C-NMR spectroscopes and were listed in the experimental. The ester of phthalazin-1(2*H*)-one derivatives 2 was obtained by treatment of 1 with ethyl chloroacetate 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 chloride ion as KCl and abstract of hydronium ion (H^+) and converted to $KHCO_3$. IR spectrum of 2 showed bands in the region 1649 cm^{-1} attributable to *v* CO of cyclic amide group in addition to 1750 cm^{-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 (2*H*) phthalazin-1-one ring has attracted our attention in regard to synthesis of a hydrazide derivatives. Thus, when the phthalazin-1(2*H*)-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 spectrum 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 3-chloro-4-methylphenyl benzoic acid using thiocarbonic dihydrazide. When 2-aroylbenzoic acid 1 was allowed to react with thiocarbonic dihydrazide 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.* benzene, 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, Glycosyl heterocycles and their nucleoside analogues have 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 the a glycone 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 (2*H*) phthalazin-1-one ring has attracted our attention in synthesis of a cyclo-nucleoside derivatives. Thus, when the phthalazin-1(2*H*)-one derivatives 1 was allowed to react with α-D-arabino- and/or gluco-pyranosyl bomide in the presence K_2CO_3/ dry DMF yield 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 spectrum exhibit carbonyl group for cyclic amide, which agreed well with the proposed structure. Moreover, Creation of the builder 9, when the sulphonated phthalazinone 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. So, the phthalazinone moiety 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 halide of amino acid to yield α-amino acids carrying phthalazinone bases 10



Scheme 1



i= Conc H_2SO_4
ii= 2-bromoglucose/K_2CO_3/DMF
iii= 2-bromoarabinose/K_2CO_3/DMF
iv= Choride of alanine, aspartic and glutamic acid/Pyridine
v=TCT/Pyridine

Scheme2

Reactions of the phthalazinone 1 within preferred halide of amino acid to yield 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 halide of α-amino acids e.g. β-chloroalanine, Aspartic and/or Glutamic acid monochloride, 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 *v* CO , the ^{1}HNMR of compound 10 showed signals at 2.2 (dt, 1H, $\underline{CH}(NH_2)$ 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 7 and 8 that can't be expected.

On the other hand, refluxing of [1(2*H*)-oxo-4-(3-chloro-4-methylphenyl)phthalazin-2-yl] acetic acid hydrazide (3) with aromatic aldehydes e.g. 4-N,N-dimethyl aminobenzaldehyde and/or 4-chlorobenzaldehyde in boiling ethanol afforded N-arylidine derivatives 11 in good yields, the ^{1}H-NMR spectrum of 11a exhibited at δ 8.75 assigned for the methylidene proton, the mass spectrum of compound 11b showed the ion peak at m/z 570(48.46%) corresponding to $M^{.+}$. 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 isatin in an oil bath at 150^{0}C, it yielded [4-(3-chloro 4-methyl-)phenyl-1(2*H*)-oxo-phthalazin-2-yl]-N-phthalimido-acetamide 13 and/or indol-2-on-3-yl-acetyl hydrazone 14 respectively. IR spectrum of compounds 13 and 14 revealed strong absorption bands at the regions 1655,1690, 1735 and 1790 cm^{-1} attributable to υ (4CO), and 1660, 1670 and 1705 attributable to υ of (3CO) respectively.

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).

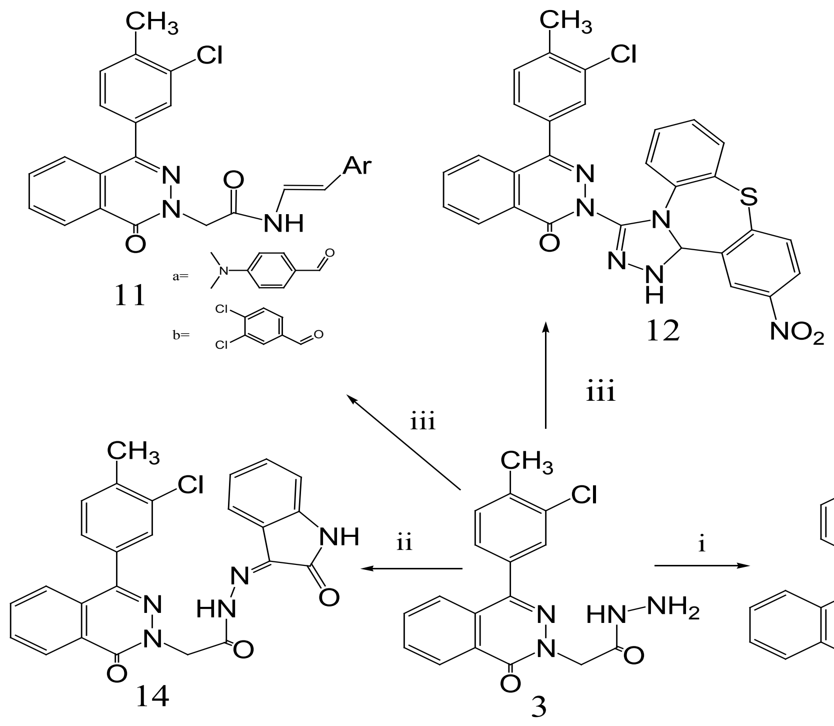
The ^{1}H-NMR of compound. The authors can be reported synthesis and characterization, when the hydrazide 3 was allowed to react with new carbon electrophile e.g ethyl-2-thiocyanatobenzoate in boiling ethanol affording an important species of 4-oxo-benzothiazino-1,2,4-triazole derivatives 15 (Scheme 4). 15 showed signals at δ 4.75 for CH_2 of inserted between the two heterocyclic moieties. The mass spectrum of compound 15 showed the prominent ion peak at m/z 491(2.25%) and 493(2.48%) attributable to $M^{.+}$ and $M^{.+}$+2 respectively. To continue and enhancement the chromophoric moiety, when the phthalazinone hydrazide derivative 3 was allowed to react with alkyl- and/or aryl-isothiocyanate namely methyl, ethyl, cyclohexyl, and phenyl isothiocyanate afforded thiocarbamate [51, 52]. But in one pot reaction, when the hydrazide 3 was allowed to react with 2-glucosyl bromide and ammonium isothiocyanate afforded the novel N-nucleoside 16. The reaction could be formed glucosyl isothiocyanate 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. (Scheme 4). The ^{1}H-NMR of compound 16 exhibited signal at δ 5.7 and 9.90 assigned for 5H of OH and NH that 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.

Antimicrobial evaluation

Compounds 1, 2, 3, 4, 5, 6, 7, 8, and 10 were tested for antimicrobial activity against *Escherichia coli* (Gram negative bacterium), *Staphylococcu*s *aureus* (Gram positive bacterium), *Aspergillus flavus* and *Candida albicans* (fungi) using the disc diffusion method. The antimicrobial evaluation was done in the Microanalytical Center at Cairo University

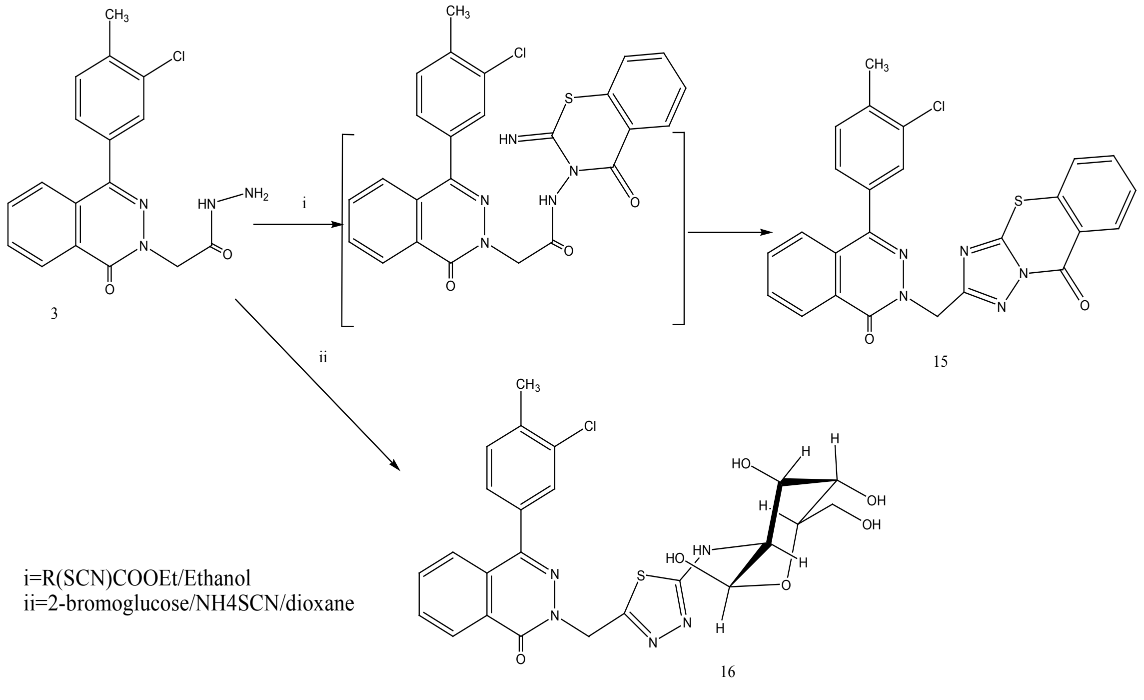
Generaldiscdiffusion(agarbased)method

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 with 10µL of solvent (chloroform, ethanol, DMF) were used as a negative control. The agar used is Mueller - Hinton agar that



i=Phthalic anhyride/fuse
ii=Isatan/fuse
iii=Ar⁻CHO/Ethanol

Scheme3



i=R(SCN)COOEt/Ethanol
ii=2-bromoglucose/NH4SCN/dioxane

Scheme 4

is rigorously tested for composition and pH. The depth of the agar in the plate is a factor to be considered in this method. Blank paper discs (Schleicher and Schuell, Spain) with a diameter of 8.0 mm 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 agar only around the disc. The solubility of the chemical and its molecular size will determine the size of the area of chemical infiltration 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]. 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.

Antibacterial Activity

Concentration of 1 mg/mL of test compounds were prepared by dissolving the compounds in its proper solvent. For each concentration, 0.2 mL of synthesized compounds (1 mg/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 37^{O}C for 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 inactivity.

Results of antibacterial activity tested against *E. Coli* (G$^-$) and *S. Aureus* (G$^+$) showed that all of the selected compounds were antibacterially active and comparatively efficient.

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 45^{O}C. The inoculated medium was poured into sterile Petri-dishes, allowed to solidify, and incubated at 25^{O}C 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 10c were 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 10 showed 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, and 10c were active only with *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..

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. flavus and Candida albicans)*. It's found the presence of lone pair of electrons on the nitrogen atom of the additional atom delocalized and thus produce 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.

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

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*	Control solvent
Tetracycline TC	32	35	00	00	----
Amphotericin B	00	00	18	20	----
1	11	10	00	00	Chloroform
2	07	12	07	12	DMF
3	16	16	12	15	Ethanol
4	14	17	00	14	Ethanol
5	15	16	00	14	Ethanol
6	16	17	16	15	Ethanol
7	09	09	00	00	Chloroform
8	13	13	00	11	Ethanol
10a	08	21	09	17	Ethanol
10b	08	21	09	17	Ethanol
10c	13	17	00	17	Ethanol

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-(3-Chloro-4-methylphenyl)phthalazin-1(2H)-one (1)

Hydrazine hydrate (0.015 mol) was added to a solution of 3-chloro-4-methylphenyl 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. 220-222℃; The ^{1}H-NMR spectrum showed signal at 2.35 (methyl group), 7.3 – 7.7 (m, 7H, ArH) , 10.5 (s , 1H , NH , exchangeable with D_2O) . IR (KBr) ν cm^{-1}: 3296 (NH), 1665 (C=O), 1605 (C=N) . Ms: *m/z* : 276 (M^+, 100), 248 (43), 220 (15), 131 (25), 105 (15). Anal calcd for $C_{15}H_{11}N_2$ O Cl(270)(%): C, 66.66; H, 4.07; N 10.37; found C, 66.45; H 4.02; N 10.12

Ethyl2-(1-oxo-4-(3-chloro-4-methylphenyl)phthalazine-2(1H)-yl)acetate (2)

A mixture of compound 1 (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℃. IR (KBr) ν cm^{-1}: 1750, 1649 (C=O), 1584 (C=N) ; ^{1}H-NMR (DMSO-d_6) δ ppm: 1.27 (t, J= 7.2 H_Z, 3H, $CH_2\underline{CH_3}$), 2.14 (s, 3H, CH_3), 4.12 (q, J= 7.5 H_Z, 2H, $O\underline{CH_2}CH_3$) ,5.3 (s, 2H, CH_2), 7.3-7.7 (m, 7H, Ar-H). Ms : m/z 362 (M^+, 78%), 290 (100%), 134 (22%), 77 (39%). Anal calcd for $C_{19}H_{17}N_2O_3$ Cl(356)(%): C, 64.04; H, 5.05; N, 7.86; found C, 64.01; H, 5.01; N, 7.66.

2-(1-Oxo-4-(3-chloro-4-methylphenyl) phthalazine-2(1H)-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. Mp 160-162^{0}C. IR(KBr) ν cm^{-1} : 1658(C=O), 3324,3417($NHNH_2$). ^{1}H-NMR (DMSO-d6) δ ppm: 1.8 (m, 3H, CH_3), 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), 8.4(s, 1H, NH exchangeable with D_2O). 13C NMR ($CDCl_3$) δ ppm: 171.5, 159.7, 139.6,.139.5, 135.9, 135.7,133.5,132.5,132.5,2.4,130.5,129.3,129.3 ,127.6,127.6,127.2,55.6,and15.2 (CS) Anal. Calc. for $C_{17}H_{15}N_4O_2Cl$(343) (%) C 59.47, H 4.66, N 16.32; found C 59.23, H 4.23, N 16.26.

(3-Chloro-4-methylphenyl)–[1,2,4]triazolo[3,4-a] phthalazine-3(2H)thione (4)

Thiocarbonic dihydrazide (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 3hr. The solid that separated after cooling was filtered off and recrystallized from benzene to give 4, 80% yield as colorless crystals, m.p. 164-166 ℃; IR (KBr) *ν cm*$^{-1}$: 3296 (NH), 1605 (C=N), 1115 (C=S) ^{1}H-NMR (DMSO-d6) δ ppm 2.35 (m , 3H, CH_3), 7.3 – 7.7 (m, 7H, ArH) , 11.2 (s, 1H, NH , exchangeable with D_2O) . Ms : m/z 332 (M$^+$, 100%) , 248 (43%) , 220 (15%) , 131 (25%) , 105(15%) . Anal calcd for $C_{16}H_{11}N_4S\,Cl$ (326)(%) : C, 58.89; H, 3.37; N, 17.17 ; S, 9.81 ; found C, 57.57 ; H, 3.52 ; N, 17.70 ; S, 9.67 .

Thiocarbonylbis(4-(3-chloro-4-methylphenyl) phthalazin) -1 (2H)-one (5)

Thiocarbonic dihydrazide (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. 210-212 ℃; The IR (KBr) *ν* cm^{-1}: 3296 (NH), 1665 (C=O), 1605 (C=N). ^{1}H-NMR (DMSO-d6) δ ppm at 2.2 (m ,6H, 2CH_3), 7.1 – 7.9 (m , 14H , ArH), 9.5(bs, 1H, NH). Ms : m/z 594.72 (M $^+$, 100%), 248 (43%), 220 (15%), 131 (25%), 105 (15%). Anal calcd for $C_{31}H_{20}N_4\,O_2S\,Cl_2$(550)(%): C, 63.91; H, 3.43; N, 9.62; S, 5.49; found C, 63.6; H 3.23; N, 9.1; S, 5.52.

Sodium-4-oxo-1-(5-sulfonato-3-chloro-4-methylphenyl)-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%. Mp = 184-186 ^{0}C. IR (KBr) *ν* cm^{-1} 1650(amide) (CO), 1592-1519 (SO_3). ^{1}H-NMR (DMSO-*d6)* δ ppm at 2.28 (m , 6H, 2CH_3), 7.67-8.28(m, 6H, Ar-H), . Anal. Calc. for $C_{15}H\ _9N_2Na_2S_2O_7Cl_2$ (421) (%): C ,40.00; H ,2.0; N, 6.22; S, 14.22; found: C, 39.89; H, 2.12, N, 6.08; S, 14.09.

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-arabinopyranose and/or 1-bromo-α-D-glucopyranose (0.01 mol) and anhydrous K_2CO_3(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-(3-Chloro-4-methylphenyl)-2-((2S,3R,4R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran2-yl)phthalazin-1(2 H)-one(7)

Yield 90%. Mp 150-152^{0}C.IR (KBr) *ν* cm^{-1} 1652 (amide) (CO). ^{1}H-NMR (DMSO-*d6)* δ ppm at 2.39 (m, 3H, CH_3), 2.22-2.39(m, 6H, H of arabinose moiety), 4.36-4.51(m, 3H, OH), 7.46-8.23 (m, 7H, Ar-H). Anal. Calc. for $C_{20}H_{19}N_2O_6Cl$(354): C, 57.69; H, 4.08; N, 6.73; found: C, 57.21, H, 4.32; N ,6.51.

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

Yield 90%. Mp 170-172^{0}C IR (KBr) *ν* cm^{-1} : 1652 (amide) (CO). ^{1}H-NMR (DMSO-d6) δ ppm at: 2.33 (m, 3H, CH_3), 2.12-2.62(m, 7H, H of glucose moiety), 4.36-4.51(m, 4H, OH), 7.46-8.23 (m, 7H, Ar-H). Anal. Calc. for $C_{21}H_{21}N_2O_6Cl$(464) : C, 58.74; H, 4.89; N, 6.52; found: C, 58.33, H, 4.46; N ,6.24

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

A mixture of phthalazinone disulphonated (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**.** Yield 80%. Mp = 234-236 ^{0}C. IR (KBr) *ν* cm^{-1} : 1650(amide) (CO), 1592-1519(SO_2). ^{1}H-NMR (DMSO-d6) δ ppm at: 2.4 (m, 3H, CH_3), 7.67-8.28(m, 7H, Ar-H). Anal. Calc. for $C_{18}H_8Cl_3N_5Na_2S_2O_7$(597) : C ,36.18; H, 1.34; N 11.72; S,10.72 found: C ,36.06; H ,1.2 ; ;N, 11.8; S,10.37

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-(3-chloro-4-methylphenyl) phthalazin-2(1H)-yl) propanoic acid (10a)

Yield 84% as white crystals. Mp 210-212 ^{0}C. IR (KBr) *ν* cm^{-1} : 1751, 1658(CO). ^{1}H-NMR (DMSO-d6) δ ppm at: 2.35 (m, 3H, CH_3), 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 ($CDCl_3$) δ ppm: 33.6(CH2), 53.8 (N-CH2), 20.6,53.3, 127.2, 127.5, 127.6, 129.2, 129.3, 130.5, 130.9, 132.2, 132. 3.133.3.134.7.134.5,138.3,158.0(C=N), and 172.8 (C=O) Anal. Calc for $C_{18}H_{16}N_3O_3Cl$ (357) : C ,60.50;H ,4.48 ; N, 11.76 ; found C ,60.16, H, 4.26; N, 11.11.

2-Amino-4-oxo-4-(1-oxo-4-(3-chloro-4-methylphenyl)phthalazin-2(1H)-yl)butanoic acid (10b)

Yield 84% as white crystals. Mp 232-234 ^{0}C. IR (KBr) υ cm^{-1}: 1751, 1658(CO). ^{1}H-NMR (DMSO-*d6)* δ ppm at: δ 2.33 (m, 3H, CH_3), 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 ($CDCl_3$) δ ppm: 33.6, 53.8 (N-CH2), 20.6,53.3, 127.2, 127.5, 127.6, 129.2, 129.3, 130.5, 130.9, 132.2, 132.3.1 33.3.134.7.134.5,138.3,158.0(C=N), 174.9(C=O) and 1752 (C=O) Anal. (M.wt. 385) % Anal. Calc for $C_{19}H_{16}N_3O_4Cl$(385) : C ,59.22;H ,4.51 ; N, 10.52 ; found C ,58.63, H, 4.27; N, 10.09.

2-Amino-5-oxo-5-(1-oxo-4-(3-chloro-4-methylphenyl) phthalazin-2(1H)-yl)pentanoic acid (10c)

Yield 84% as white crystals. Mp 226-228 ^{0}C. IR (KBr) υ cm^{-1}: 1751, 1658(CO). ^{1}H-NMR (DMSO-d6) δ ppm at: δ 2.35 (m, 3H, CH_3), 2.1(m, 2H, CH_2), 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 ($CDCl_3$) δ ppm: 20.5, 36.4, 127.2, 127.2, 127.6, 129.2, 129.3, 130.5, 131.2, 131.3, 130.6, 132.3, 134.7, 134.5, 138.3, 158.0 (C=N),,174.5(C=O) and 175.2 (C=O). Anal. Calc for $C_{20}H_{18}N_3O_4Cl$(405.45) % : C ,60.15;H ,4.51 ; N, 10.52 ; found C ,59.86, H, 4.25; N, 10.9.

Synthesis of Arylidine derivatives 11

A mixture of hydrazide **3**(3.87g, 0.01mol), appropriate aromatic aldehyde(0.01 mol) namely 3,4-dichlorobenzaldehyde and 4-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.

N^{-}-(4-Dimethylamino)benzylidene)-2-(3-chloro-4-methylphenyl)phthalazine-2(1H)-acetohydrazide(11a

Yield 96%, white crystals crystallized from benzene. Mp 184-186^{0}C. IR (KBr) υ cm^{-1}: 1620(C=N), 1673(CO) and 3170(NH). ^{1}H-NMR (DMSO-d6) δ ppm at: δ 2.29 (m, 3H, CH_3), 2.7(s, 6H, $N(CH_3)_2$), 4.01(s, 2H, methylene proton), 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 ($CDCl_3$) δ ppm: 35.9 (methyl of Ar), 56.2(2methyl of $N(CH_3)_2$), 64.2 (methylene N-CH_2), 122.4, 126.9, 127.2, 127.7, 128.4, 128.7, 129.7, 129.9, 130.6, 130.6, 131.5, 132.8, 133.9, 134.8, 136.2, 160.6, 168.4, 166.5, 167.2, 168.2, 169.0 (C=N, C=O). MS: m/z = 472, 470. Anal. Calc. for $C_{27}H_{23}N_7O_2Cl$ (512) % C ,63.28; H, 4.49; N ,19.14; found: C ,62.88; H, 4.29; N ,19.05

N^{-}-(4-Chlorobenzylidene)-2-(4-(3-chloro-4-methylphenyl)phthalazine-2(1H)-acetohydrazide (11b)

Yield 98%, orange crystals crystallized from benzene. Mp 224-226^{0}C. IR(KBr) ν(cm^{-1}) 1604(C=N), 1666(CO) and 3170(NH). ^{1}H-NMR (DMSO-*d6)* δ ppm at: 1.8 (m , 3H, CH_3), 4.51(s, 2H, methylene proton), 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 ($CDCl_3$) δ ppm: 35.9(methyl of Ar), 55.4, 62.2 (methylene N-CH_2), 122.2, 122.8, 124.2, 124.7, 126.4, 126.5, 127.0, 127.5, 129.1, 129.2, 129.6, 132.6, 134.7, 134.9, 136.2, 143.2, 148.6, 155.4, 156.5, 167.9, 174.2, 174.0 (C=N, C=O). MS: m/z = 472, 470. Anal. Calc. for $C_{26}H_{17}N_4OCl_3$(496): C, 60.48; H, 3.42 N ,8.46 found: C, 60.21; H, 3.36; N ,8.39.

(E)-N-(2-(2-Aminophenylthio)-5-nitrobenzylidene)-2-(4-(3-chloro-4-methylphenyl) phthalazin-2 (1H)-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. Mp 240 (NH2)3420,(3345-3100), 1658 (CO) and 3090-3100(NH), 3345-3420(NH_2). ^{1}H-NMR (DMSO-d6) δ ppm at: 1.8 (m , 3H, CH_3), 4.21(s, 1H, CH), 6.98-8.20 (m, 14H, Ar-H), 10.04(s, 1H, NH exchangeable with D_2O). ^{13}C NMR ($CDCl_3$) δ ppm: 35.9(methyl of Ar), 64.2 (methylene N-CH_2), 85.7(S-CH), 122.3, 126.4, 127.5, 127.9, 128.0, 128.1, 128.6, 129.0, 129.4, 129.5, 129.6, 130.2, 130.8, 131.3, 131.5, 132.7, 134.3, 138.1, 139.4, 140.3, 143.6, 160.7, 165.4, 165.6, 166.3, 167.9, 168.7(C=N, C=O). Anal. Calc. for $C_{30}H_{19}N_6O_3SCl$(590.69): C, 62.60; H, 3.82; N ,14.60; S, 5.56; found: C, 61.96; H, 5.38; N, 14.17; S, 5.37.

2-[4-(3-Chloro-4-methylphenyl)-1-oxo-2H-phthalzin-2-yl]-N-(1,3-dioxo-1,3-dihydro-isoindol-2-yl) acetamide (13)

A mixture of hydrazide 3(3.87g, 0.01mol), phthalic 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. Mp 268-270^{0}C. IR(KBr) ν(cm^{-1}) 1650, 1690, 1735, 1790(4CO). ^{1}H-NMR (DMSO-*d6)* δ ppm at: 2.32 (m , 3H, CH_3), 4.20(s, 1H, CH of gly. precusor), 7.26-8.11 (m, 11H, Ar-H), 9.11(s, 1H, NH exchangeable with D_2O). ^{13}C NMR ($CDCl_3$) δ ppm: 38.3-47.8 (methylene groups), 47.6 (methylene N-CH_2), 124.5, 126.3, 127.5, 128.3, 128.8, 128.9, 130.2, 130.3, 131.6, 131.9, 132.8, 132.9, 133.8, 133.9, 138.5, 139.3, 143.4, 145.7, 158.7, 160.2, 164.3, 168.5, 170.3 (C=N, 3C=O). Ms: *m/z* 472, 470, Anal. Calc. for $C_{25}H_{17}N_4O_4Cl_1$ (435) C 68.96, H 3.21, N 12.87, found: C 69.07, H 2.94, N 12.65.

N-(2-Oxoindolin-3-ylidene)-2-(4-(3-chloro-4-methylphenyl)phthalazin-2(1H)-yl) acetohydrazide (14)

A mixture 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. Mp 218-220^{0}C. IR(KBr) ν(cm^{-1})1660, 1670, 1705(3CO). ^{1}H-NMR (DMSO-d6) δ ppm at: 1.8 (m , 4H, β -methylene group), 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 ($CDCl_3$) δ ppm: 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* 473, 471. Anal. Calc. for $C_{25}H_{18}N_5O_3Cl$(471) : C, 63.69; H ,3.82; N, 14.86; found: C ,63.18; H 3.31; N, 14.02.

2-((1-Oxo-4-(3-chloro-4-methylphenyl) phthalazin-2(1H)-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. Mp 184-186^{0}C. IR (KBr) ν cm^{-1} 1620(C=N), 1673 (CO) and 3170(NH). ^{1}H-NMR (DMSO-*d6)* δ ppm at: 1.8 (m, 3H, CH_3), 4.01(s, 2H, methylene proton of gly. precusor), 7.11-8.21 (m, 11H, Ar-H). ^{13}C NMR ($CDCl_3$) δ ppm: 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* 487.5, 485.5. Anal. Calc. for $C_{25}H_{16}N_5O_2SCl$ (475): C, 61.85; H,3.29; N,14.43; S,6.59; found: C, 61.32; H,3.01; N,14.130; S,6.48.

4-(3-Chloro-4-methylphenyl)-2-((2S,3R,4R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-ylamino)-1,3,4thiadiazol-2-yl)methyl)phthalazin1(2H)-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. Mp 290-292^{0}C. IR(KBr) ν cm^{-1} 1650(CO), 3233(NH), 3440(OH). ^{1}H-NMR (DMSO-*d6)* δ ppm at: δ 1.8 (m , 3H, CH_3), 2.12-2.62(m, 7H, H of glucose 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 ($CDCl_3$) δ ppm: 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 $C_{24}H_{24}N_5O_6S$ Cl (530) % C , 54.33; H, 4.71; N, 13.20; S; 6.03 found % C , 53.95; H, 4.12; N, 13.08 ;S, 5,89

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التركيب التجميعي والخصائص الهيكلية لبعض المشتقات الفثالازينية المضادة للميكروباتو الصبغ التفاعلية

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تم توليف سلسلة جديدة من المشتقات من فثالازين1- (2H)عن طريق عن طريق الاضافة النيوكلوفيلية بذرة النيتروجين فى المشتقات فثالازين 1- (2H) على مختلف السكريات الأحادية. كان توليف نوكلوسيدس فثالازينون فعالة جدا كمضادات للميكروبات. كما يمكن استخدام مشتقات الفثالازينون في تركيب النيوكليوسيدات التفاعلية والأصباغ التي هى مرتبطة كيميائيا مع البروتينات والألياف على التوالي لكى يعطى الاستقرار على الاصواف المصبوغة والمنسوجات القطنية. تم توضيح هيكل المركبات المعدة بواسطة البيانات الفيزيائية والطيفية مثل الرنين المغناطيسي النووي للهيدروجين و الرنين المغناطيسي النووي لذرة الكربون.