Regular Article

Facile Synthesis, Characterization, and Antimicrobial Evaluation of Novel Heterocycles, Schiff Bases, and *N*-Nucleosides Bearing Phthalazine Moiety

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The present work describes convenient synthesis of the novel Schiff bases **5a** and **b** by reacting phthalazinones **4a** and **b** with 4-methoxybenzaldehyde. Reaction of the Schiff bases with phenylisothiocyanate afforded diazetidine derivatives **7a** and **b**. Also, compounds **4a** and **b** reacted with 2-bromoglucoside tetraacetate giving peracetylated *N*-glycosides **6a** and **b**, which were deacetylated to afford *N*-glycosylated phthalazinones **8a** and **b**. On the other hand, when compound **3** was treated with POCl₃/PCl₅ and/or ethyl chloroacetate, chlorophthalazine and ethyl acetate derivatives **9** and **10** were obtained, respectively. Hydrazinolysis of compounds **9** and **10** produced the hydrazino and hydrazide derivatives **11** and **12**, respectively. When compound **11** reacted with 2-furaldehyde, acetic anhydride, and/or carbon disulphide, it gave compounds **13–15**, respectively. Treatment of the hydrazide **12** with aromatic aldehydes, acetic anhydride, ethyl acetoacetate, acetyl acetone, ammonium thiocyanate, and/or phthalic anhydride furnished compounds **17–21**. Meanwhile, reacting Schiff base **22** with the chlorophthalazine derivative **9** produced compound **23**, which on treatment with furoyl chloride produced compound **24**. The structures of the novel compounds were confirmed by IR, ¹H-NMR, ¹³C-NMR, MS, and elemental analysis. The newly synthesized compounds were tested against *Bacillus subtilis* and *Staphylococcus aureus* as Gram-positive bacteria, *Escherichia coli* and *Pseudomonas aeruginosa* as Gram-negative bacteria, and *Candida albicans* and *Aspergillus niger* as fungi strains. Compounds **5a** and **b**, **23**, and **24** showed greater antimicrobial activity than the stranded compounds, suggesting that they could be considered as promising antimicrobial agents.

Key words phthalazin-1-one; *N*-glycosylated phthalazinone; Schiff base; diazetidine; antimicrobial activity

Phthalazines as *N*-heterocycles have received considerable attention in the literature as a consequence of their role as pharmacophore.^{1,2)} Recently, they are derived from a wide range of biologically active natural products, troponoid family.³⁾ A novel series of *N*-substituted-4-phenyl/benzyl-phthalazin-1-ones, phthalazine-1,4-dione showed antitumor activity.^{4–7)} It is well known that phthalazinone derivatives like other members of isomeric diazine series have considerable biological and pharmaceutical activities. Indeed, several phthalazinone derivatives have been reported to possess anti-rheumatic,⁸⁾ antihyperglycemic,⁹⁾ anticonvulsant,¹⁰⁾ antihypertensive,¹¹⁾ antithrombotic,¹²⁾ antitrypanosoma,¹³⁾ antioxidant,¹⁴⁾ anti-inflammatory¹⁵⁾ and β -adrenergic blocking activities.¹⁶⁾ Besides, they can be used as Potent Vasodilators,¹⁷⁾ and α 1-adrenoceptor antagonists.¹⁸⁾ A number of established drug molecules like Hydralazine,¹⁹⁾ Azelastine,²⁰⁾ Ponalrestat²¹⁾ and Zopolrestat²²⁾ were prepared from the corresponding phthalazinones. Moreover, many substituted and fused phthalazine and phthalazinone derivatives exhibited antimicrobial activity.^{23–26)}

On the basis of the above findings and in continuation of our research interest in the synthesis of novel biologically active heterocycles,^{27–31)} and with the aim of preparing new derivatives of phthalazine with potential pharmacological activity, we report here the synthesis of novel Schiff bases containing phthalazine moiety, phthalazinone and fused phthalazine derivatives, followed by evaluation of their antimicrobial activity against different strains of bacteria and fungi, where most of synthesized compounds exhibited a moderate to a strong antimicrobial activities. Some of the tested compounds

showed antimicrobial activity higher than the reference compounds.

Results and Discussion

Chemistry The reaction of commercially available 2-(4-methoxyphenyl)acetyl)benzoic acid (**1**) with hydroxyl amine and/or hydrazine hydrate, afforded 4-(4-methoxybenzyl)-1*H*-benzo[*d*][1,2]oxazin-1-one (**2**)³²⁾ and phthalazinone derivative **3**,^{33,34)} respectively. Treatment of **2** with binucleophiles e.g., 1,4-phenylenediamine and 4,4'-diaminobiphenyl afforded the *N*-substituted phthalazinone derivatives **4a** and **b**, respectively (Chart 1).

Compounds **4a** and **b** may be formed through the nucleophilic attack of the amino group (of the diamine) on the carbonyl group of benzoxazine causing ring opening followed by elimination of water molecule and ring closure. The structure of these compounds were elucidated depending on their IR spectra which displayed peaks in the region 3348–3283 attributable to NH₂ groups, and ¹H-NMR which showed signals at δ 6.39 (s, 2H, NH₂, D₂O exchangeable) for **4a** and 6.23 (s, 2H, NH₂, D₂O exchangeable) for **4b**, respectively.

When compounds **4a** and **b** were refluxed with 4-methoxybenzaldehyde in absolute ethanol and/or 2-bromo-2-deoxy-1,3,4,6-tetra-*O*-acetyl- α -D-glucopyranose in dioxane,³⁵⁾ the Schiff bases **5a** and **b** and the *N*- α -D-glucosetetraacetate phthalazinone derivatives **6a** and **b** were obtained, respectively, in a good yield (Chart 2).

Formation of the Schiff bases **5a** and **b** occurs through the nucleophilic attack of the amino on the carbonyl group of the aldehyde followed by elimination of water molecule. The IR

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spectra of **5a** and **b** devoid any bands for the NH_2 group and the mass spectra showed molecular ion peaks at m/z 475 and 551, respectively.

The structure of compounds **6a** and **b** was confirmed from the IR spectra which showed three peaks in the region 1660–1685 attributable to three $\text{C}=\text{O}$ groups of phthalazinone and peracetyl moieties, respectively. Also, their $^1\text{H-NMR}$ spectra displayed signals at δ 2.08–2.29 (s, 12H, 4COCH_3), and 2.05–2.24 (s, 12H, 4COCH_3), respectively.

When the Schiff bases **5a** and **b** were allowed to react with phenylisothiocyanate, diazetidine derivatives **7a** and **b** were obtained. The proposed structure **7a** and **b** were elucidated from the IR spectra which displayed peaks in the region 1319–1322 attributable to $\text{C}=\text{S}$ group, $^1\text{H-NMR}$ spectra which showed peaks at δ 6.56–6.61 corresponding to the

benzylic protons of the diazetidine ring. Also by the mass spectra which showed molecular ion peaks at m/z 610 and 686, respectively.

Moreover, the hydrolysis of **6a** and **b**, using sodium carbonate, afforded the deacetylated glucose phthalazinone derivatives **8a** and **b**³⁵⁾ (Chart 2). The structures of **8a** and **b** were assigned by their IR spectra which displayed peaks at ν (cm^{-1}) 3384–3261 (OH bonded and non-bonded) and mass spectra that showed a molecular ion peaks at m/z 519 and 595, respectively.

On the other hand, the phthalazinone derivative **3** was subjected to react with a mixture of $\text{POCl}_3/\text{PCl}_5$ ³⁶⁾ and/or ethyl chloroacetate, in presences of potassium carbonate,³⁴⁾ producing 1-chlorophthalazine and phthalazinone ethyl acetate derivatives **9** and **10**, respectively.

The formation of **9** takes place *via* the reaction of $\text{POCl}_3/\text{PCl}_5$ with the hydroxyl group of the enol form of compound **3**. The structure of **9** was indicated from its IR spectrum which devoid any bands for the $\text{C}=\text{O}$ and NH groups. While the formation of product **10** is believed to proceed *via* $\text{S}_{\text{N}}2$ mechanism through nucleophilic attack of the lone pair of nitrogen atom on the electronically deficient carbon attached to chlorine atom followed by elimination of HCl molecule. The structure of **10** was confirmed as a result of the presence of two absorption bands at 1745, 1684 (in the IR spectra) attributable to two $\text{C}=\text{O}$ groups of the ethyl ester and phthalazinone moieties. Also, the $^1\text{H-NMR}$ showed δ 1.34 (t, 3H, CH_3 , $J=6.1$ Hz) and 4.39 (q, 2H, CH_2 , $J=8.2$ Hz), indicating the presence of ethyl ester group.

When both compounds **9** and **10** were further reacted with hydrazine hydrate in boiling ethanol, the hydrazino phthalazine³⁷⁾ and phthalazinone acetohydrazide³⁴⁾ derivatives **11** and **12** were produced, respectively (Chart 3).

Formation of compound **11** takes place through nucleophilic attack of hydrazine molecule on the carbon atom (attached to the chlorine atom) followed by elimination of HCl molecule. The IR spectrum of **11** showed peaks at 3379, 3285, 3147 (NH_2 , NH).

On the other hand, the hydrazide **12** is formed *via* tetrahe-

Chart 1

Reagents and conditions: (i) 4-Methoxybenzaldehyde/EtOH/reflux 3 h (74–80%), (ii) 2-bromo-2-deoxy-1,3,4,6-tetra-*O*-acetyl- α -D-glucopyranose/dioxane/reflux 4 h (56–58%), (iii) PhNCS /toluene/reflux/6 h (68–72%), (iv) Na_2CO_3 solution/MeOH (43–48%).

Chart 2

Reagents and conditions: (i) POCl₃/PCl₅/reflux 4 h (84%), (ii) ClCH₂CO₂C₂H₅/K₂CO₃/dry acetone/reflux 24 h (80%), (iii) N₂H₄·H₂O/EtOH/reflux 3 h (85, 90%).

Chart 3

dral mechanism through the attacking of nucleophilic hydrazine molecule on the *sp*² carbon of the carbonyl functionality of the ester group in compound **10** with the elimination of an ethanol molecule. The structure of hydrazide **12** was supported by its spectroscopic data, where the IR spectrum displayed peaks at 3350, 3211, 3130 (NH₂, NH) and the ¹H-NMR indicated the absence of any peaks for the ethyl group.

The 1-hydrazinophthalazine derivative **11** was used as a key starting material to synthesize different interesting phthalazine and fused phthalazine derivatives. Thus, condensation of **11** with 2-furaldehyde in boiling ethanol, produced the hydrazone derivative **13**.³⁸⁾ While, 1,2,4-triazolo[3,4-*a*]-phthalazines **14**, and **15** have been prepared upon the reaction of **11** with carbon electrophiles namely, acetic anhydride and carbon disulphide, respectively.

Compound **13** is formed through condensation reaction between the carbonyl group of the aldehyde and the amino group of the hydrazino-derivative. The IR spectrum of **13** devoid any peaks for the NH₂ group, and the ¹H-NMR showed a peak at δ 6.39 for the methine proton (–N=CH–).

A plausible explanation for the formation of product **14** consists in acetylation of the hydrazino group followed by 1,3-proton shift, attacking of lone pair of N-1 on the acetyl carbonyl group and finally elimination of a water molecule. The structure was elucidated by the spectroscopic data, where the IR showed the absence of any absorption bands for NH or NH₂, and the ¹H-NMR showed a peak at δ 2.44 (s, 3H), corresponding to the methyl group.

Compound **15** is possibly formed through the attacking of the nucleophilic amino group on the electronically deficient carbon of carbon disulfide, 1,3-proton shift then attacking of N-1 on C=S functionality with the elimination of H₂S molecule. The IR spectrum of **15** showed a peak at 1271 (C=S) and devoid any bands for NH and NH₂ groups. Also the ¹H-NMR displayed a peak at δ 11.96 (s, 1H, D₂O exchangeable) attributable to the SH group.

Compound **15** was confirmed chemically *via* its reaction with hydrazine hydrate to furnish the corresponding hydrazine derivative **16** (Chart 4).

Compound **16** may take place by the nucleophilic attack of the hydrazine molecule on the carbon atom (bearing the SH group), followed by elimination of H₂S molecule. The

structure of **16** gets support from its spectroscopic data which showed absorption bands (ν cm^{–1}) at 3364, 3260, 3174 attributable to both NH and NH₂ and δ values (ppm) at 5.65 (s, 2H, NH₂, D₂O exchangeable) and 11.11 (s, 1H, NH, D₂O exchangeable).

Meanwhile, the hydrazide **12** could be used as versatile synthon for preparing different hydrazones and building up many ring systems by reacting the hydrazide group with different reagents. Thus, reaction of **12** with different aldehydes such as furan-2-carboxaldehyde, piperonal and 2-methoxybenzaldehyde, in boiling ethanol, gave the hydrazones **17a–c**,³⁹⁾ respectively. This reaction takes place through a condensation reaction between the NH₂ group of hydrazide **12** and the carbonyl group of the aldehyde. The structures of hydrazones **17a–c** were supported by their IR spectra which devoid any peaks for the NH₂ group, and the ¹H-NMR spectra which displayed peaks at δ 6.16–6.31 (s, 1H) for the methine proton N=CH–.

Reaction of **12** with acetic anhydride and/or ethyl acetoacetate afforded the 1,3,4-oxadiazole derivatives **18a** and **b**, respectively.

According to our speculation, product **18a** is formed through acylation of the hydrazine group of compound **12**, 1,3-proton shift followed by cyclization with the elimination of a water molecule. The IR spectrum of this compound devoid any peaks for NH and NH₂ groups and its ¹H-NMR spectrum showed a peak at δ 2.55 (s, 3H) attributable to the methyl group. While compound **18b** is believed to be formed through nucleophilic attack of the amino group on the electronically deficient carbonyl carbon of the ester group with elimination of EtOH molecule, 1,3-proton shift and finally cyclization with elimination of water molecule. The structure of **18b** was elucidated from its IR spectrum which displayed absorption bands at 1672, 1660 for two C=O groups, and the ¹H-NMR spectrum which showed peaks at δ 2.01 (s, 3H), for –COCH₃ and 3.92 (s, 2H) for –CH₂–CO– of the acetonyl group.

On the other hand, treatment of **12** with acetyl acetone and/or ammonium thiocyanate in ethanol, produced pyrazole and 1,3,4-triazole derivatives **19** and **20**, respectively. The 1,3-dioxoisindoline derivative **21** was obtained upon fusion of the hydrazide **12** with phthalic anhydride in an oil bath at 170°C (Chart 5).

Reagents and conditions: (i) 2-Furaldehyde/EtOH/reflux 3 h (76%), (ii) Ac₂O/heat 1 h (62%), (iii) CS₂/KOH/abs. EtOH/reflux 6 h (60%), (iv) N₂H₄·H₂O/EtOH/reflux 3 h (54%).

Chart 4

Product **19** may be formed as a result of a condensation process between the hydrazide moiety of compound **12** and a molecule of acetyl acetone followed by cyclization of the lactim form (of the condensation product) with elimination of water molecule. The presence of two bands for two C=O groups in the IR spectrum of compound **19** supported its proposed structure. Also, its ¹H-NMR displayed peaks at δ 2.12 (s, 3H) for the COCH₃ group, 2.79 (s, 3H) for the methyl group attached to the pyrazole ring and 3.89 (s, 1H, pyrazole).

It is well known that ammonium thiocyanate isomerizes to thiourea under the effect of heat.⁴⁰⁾ So, the mercaptotriazole **20** could be obtained from the attacking of thiourea on the carbonyl of the hydrazide moiety followed by cyclization as a result of elimination of ammonia molecule. The structure of compound **20** was confirmed by the IR spectrum which showed a band at 1265 (C=S) and the ¹H-NMR spectrum which displayed two peaks at 10.76, 12.22, (2s, 2H, D₂O exchangeable) corresponding to NH and SH, respectively.

On the other hand, compound **21** is formed as a result of nucleophilic attack of the amino group on one of the carbonyl functionalities of phthalic anhydride accompanied by the cleavage of the five membered ring then cyclization with the elimination of water molecule to form the 1,3-dioxoisindoline ring. The structure of **21** was elucidated depending the IR spectrum which indicated the presence of four absorption bands at 1770, 1742, 1680, 1660 (CO). Also, the mass spectrum showed a molecular ion peak at m/z 468 (14.2%).

When Dapson (4,4'-sulfonyldianiline) was reacted with 4-methoxyacetophenone in equimolar amount, the mono imino-compound **22** was obtained in fair yield. It should

be noted that there is a possibility for the formation of di-iminated compound, but we isolated only the mono-derivative, where the IR of the product showed bands at 3430 and 3321 (NH₂). This may be attributed to the use of only one mole of 4-methoxyacetophenone.

Compound **22** was allowed to react with 1-chlorophthalazine derivative **9** in the presence of pyridine, producing the phthalazine derivative **23** through the nucleophilic attack of the amino group on the carbon atom (bearing chlorine atom) followed by elimination of HCl molecule. The IR of **23** showed only one absorption band at 3230 attributable to the NH group.

Reaction of **23** with 2-furoyl chloride, in dry pyridine, afforded the phthalazine derivative **24** (Chart 6), whose structure was inferred by the IR spectrum which exhibited a strong peak at 1674 attributable to the C=O group attached to the furoyl moiety and the mass spectrum which showed a molecular ion peak at m/z 722 (25.7%).

Compound **24** was formed *via* tetrahedral mechanism through the attacking of the lone pair of the NH group of **23** on the *sp*² carbon of the carbonyl functionality of furoyl chloride, followed by elimination of HCl molecule.

Antimicrobial Activity The antimicrobial screening of the synthesized compounds has been evaluated by using agar diffusion method according to Cheesbrough.⁴¹⁾ The synthesized compounds have been tested for their antibacterial activity against *Bacillus subtilis* (ATCC-6633), *Staphylococcus aureus* (ATCC-25923), *Escherichia coli* (ATCC-25922) and *Pseudomonas aeruginosa* (ATCC-9027), and antifungal activity against *Candida albicans* (ATCC-24433), *Aspergillus niger*

Reagents and conditions: (i) Ar'CHO/EtOH/reflux 3 h (74–85%), (ii) Ac₂O and/or CH₃COCH₂CO₂Et/EtOH/reflux 4 h (69–77%), (iii) CH₃COCH₂COCH₃/EtOH/reflux 3 h (71%), (iv) NH₄SCN/EtOH/reflux 3 h (61%), (v) phthalic anhydride/fusion at 170°C/for 1 h (58%).

Chart 5

Reagents and conditions: (i) 4-methoxyacetophenone/EtOH/reflux 4 h (63%), (ii) compound **9**/ethanol/drops of pyridine/reflux 6 h (58%), (iii) 2-furoyl chloride/dry pyridine/reflux 3 h (78%).

Chart 6

(ATCC-16404), at a concentration of 100 µg/mL in dimethyl sulfoxide (DMSO). Nutrient agar and potato dextrose agars were used to culture the bacteria and fungi, respectively. The plates were inoculated by the bacteria or fungi and incubated for 24 h at 37°C for bacteria and for 72 h at 28°C for fungi and then the inhibition zones of microbial growth surrounding the filter paper disc (5 mm) were measured in millimeters. Ampicillin and Nystatin, at a concentration 100 µg/mL, were used as standard against bacteria and fungi, respectively. The

obtained results are compiled in Table 1.

From the above table, it is clear that most of the compounds have moderate to strong antimicrobial activity. Compounds **5a**, **b**, **23** and **24** showed antimicrobial activity higher than the standard compounds, which means that they could be considered as promising antimicrobial agents.

The minimum inhibition concentration for the most potent compounds are recorded in Table 2 using the two fold dilution method.

Table 1. Antimicrobial Screening Results of the Tested Compounds (Inhibition Zones)

Cmpd No.	Antibacterial activity (mm)				Antifungal activity (mm)	
	Gram-positive bacteria		Gram-negative bacteria		<i>Candida albicans</i>	<i>Aspergillus niger</i>
	<i>Bacillus subtilis</i>	<i>Staphylococcus aureus</i>	<i>Escherichia coli</i>	<i>Pseudomonas aeruginosa</i>		
3	17	14	13	14	16	13
4a	14	13	11	10	12	10
4b	13	10	12	12	14	11
5a	27	26	22	22	24	20
5b	28	26	21	20	23	18
6a	20	17	14	15	17	13
6b	17	16	13	14	14	11
7a	16	18	17	17	14	12
7b	18	17	16	18	19	15
8a	22	19	18	16	16	11
8b	19	18	15	13	14	12
9	14	12	10	10	15	13
10	17	15	12	11	15	10
11	11	14	10	12	11	12
12	23	21	18	18	20	17
13	19	16	16	13	18	15
14	15	14	12	12	10	11
15	19	17	14	15	11	11
16	16	18	17	19	15	14
17a	23	20	18	15	17	13
17b	22	20	19	18	18	15
17c	18	19	16	13	10	11
18a	17	18	18	15	16	14
18b	18	16	14	17	15	11
19	21	18	15	14	12	16
20	22	20	17	18	19	15
21	16	19	17	17	15	12
23	28	25	22	21	23	21
24	26	24	22	20	24	19
Ampicillin	25	22	20	19	—	—
Nystatin	—	—	—	—	22	18

Cmpd No: compound number; mm: millimeter.

Table 2. MICs for the Most Potent Compounds ($\mu\text{g/mL}$)

Cmpd No.	Gram-positive bacteria		Gram-negative bacteria		Fungi	
	<i>Bacillus subtilis</i>	<i>Staphylococcus aureus</i>	<i>Escherichia coli</i>	<i>Pseudomonas aeruginosa</i>	<i>Candida albicans</i>	<i>Aspergillus niger</i>
5a	12.5	12.5	50	50	25	50
5b	12.5	12.5	50	50	25	50
23	12.5	25	50	50	25	50
24	12.5	25	50	50	25	50

The inhibitory capability of the most active compounds (**5a**, **b**, **23** and **24**) was demonstrated in Figs. 1A and B. These potent compounds showed higher activity against Gram-positive bacteria (*Bacillus subtilis* and *Staphylococcus aureus*) compared with Gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*). On the other hand less activity was showed against both fungal strains *Candida albicans* and *Aspergillus niger*.

Experimental

All melting points are uncorrected and were determined on a Gallen Kamp electric melting point apparatus. The microanalyses were within $\pm 0.4\%$ of theoretical values and were

carried out at the Microanalytical Centre, National Research Centre, Cairo, Egypt. IR spectra (in KBr) were recorded on Shimadzu FT-IR 8101 PC using the OMNIC program and are reported as frequency of absorption in cm^{-1} . ^1H -NMR spectra were recorded on a Bruker spectrophotometer at 400 MHz using tetramethylsilane (TMS) as internal standard. ^{13}C -NMR spectra were recorded on the same spectrometer at 100 MHz. Electron Ionization (EI)-MS were measured on a Shimadzu-GC-MS-QP-1000 EX mass spectrometer instrument operating at 70 eV. The purity of the new synthesized compounds was checked by 0.2 mm layer thickness Fluka aluminum-backed TLC plates with detection by UV quenching at 254 nm. Biological evaluation was carried out at Microbiology Depart-

Fig. 1. Antimicrobial Activity of the Most Potent Compounds against Different Bacterial (A) and Fungal (B) Strains

B. s.: *Bacillus subtilis*; *S. a.*: *Staphylococcus aureus*; *E. c.*: *Escherichia coli*; *P. a.*: *Pseudomonas aeruginosa*; *C. a.*: *Candida albicans* and *A. n.*: *Aspergillus niger*. Nys: nystatin; Amp: ampicillin.

ment, Ain Shams University, Faculty of Science, Ain Shams University, Cairo, Egypt. Reagents and solvents were used as obtained from the supplier without further purification.

4-(4-Methoxybenzyl)phthalazin-1(2H)-one (3) This compound was previously prepared by Olmo *et al.*,³³ but no spectroscopic data or chemical analysis was recorded in their paper for this compound. Herein, this compound was prepared according to different previously reported methodology.³⁴

Yield 93%. mp 254–256°C. IR (KBr), ν cm^{-1} : 3199 (NH), 1661(CO), 1610 (C=N). $^1\text{H-NMR}$ (400MHz, DMSO- d_6) δ : 3.69 (s, 3H, OCH₃), 4.22 (s, 2H, CH₂Ar), 7.33–8.34 (m, 4H, ArH), 12.74 (s, 1H, NH, D₂O exchangeable). $^{13}\text{C-NMR}$ (100MHz, DMSO- d_6) δ ppm: 35.13, 55.79, 113.39, 122.51, 126.15, 127.36, 128.56, 130.23, 132.19, 133.62, 153.44, 154.33, 156.09, 163.14. MS: m/z 266 [M^+] (100%). Anal. Calcd for C₁₆H₁₄N₂O₂ (266): C, 72.18; H, 5.26; N, 10.52. Found: C, 72.49; H, 5.09; N, 10.90.

General Procedure for the Synthesis of the Phthalazinones 4a and b A mixture of 4-(4-methoxybenzyl)-1H-benzo[d][1,2]oxazin-1-one (**2**) (2.67 g, 0.01 mol) and 1,4-phenylene diamine, and/or 4,4'-benzidine (0.01 mol) was heated under reflux in absolute ethanol (20 mL) for 6 h. The resulting mixture was cooled and then poured onto an ice/water mixture. The separated solid was filtered, washed with water, air-dried and crystallized from ethanol.

2-(4-Aminophenyl)-4-(4-methoxybenzyl)phthalazin-1(2H)-one (4a)

Yield 76%. mp 168–170°C. IR (KBr), ν (cm^{-1}): 3348, 3287 (NH₂), 1665 (C=O), 1619 (C=N). $^1\text{H-NMR}$ (400MHz, DMSO- d_6) δ : 3.70 (s, 3H, OCH₃), 4.23 (s, 2H, CH₂Bz), 6.39 (s, 2H, NH₂, D₂O exchangeable), 7.18–8.26 (m, 12 H, ArH). $^{13}\text{C-NMR}$ (100MHz, DMSO- d_6) δ ppm: 35.01, 56.22, 114.51, 120.81,

122.51, 126.68, 127.31, 128.72, 129.62, 130.18, 131.18, 133.41, 146.92, 147.58, 154.01, 156.02, 158.12, 162.90. MS: m/z 357 [M^+] (27.9). Anal. Calcd for C₂₂H₁₉N₃O₂ (357): C, 73.95; H, 5.32; N, 11.76. Found: C, 74.31; H, 5.54; N, 12.05.

2-(4'-Amino-[1,1'-biphenyl]-4-yl)-4-(4-methoxybenzyl)-phthalazin-1(2H)-one (4b)

Yield 68%. mp 182–184°C. IR (KBr), ν (cm^{-1}): 3339, 3283 (NH₂), 1669 (C=O), 1622 (C=N). $^1\text{H-NMR}$ (400MHz, DMSO- d_6) δ : 3.74 (s, 3H, OCH₃), 4.25 (s, 2H, CH₂Bz), 6.23 (s, 2H, NH₂), 7.08–8.19 (m, 16H, ArH). $^{13}\text{C-NMR}$ (100MHz, DMSO- d_6) δ ppm: 35.42, 54.91, 114.41, 120.82, 122.01, 122.99, 125.11, 126.72, 127.32, 128.69, 130.21, 131.01, 132.12, 133.39, 134.78, 137.21, 140.11, 146.89, 150.01, 154.09, 156.58, 162.81. MS: m/z 433 [M^+] (35.7). Anal. Calcd for C₂₈H₂₃N₃O₂ (433): C, 77.60; H, 5.31; N, 9.70. Found: C, 77.44; H, 5.04; N, 10.02.

General Procedure for the Synthesis of the Schiff Bases 5a and b A mixture of compounds **4a** and **b** (0.01 mol) and 4-methoxybenzaldehyde (1.36 g, 0.01 mol) was heated under reflux in absolute ethanol (20 mL) for 3 h. The resulting mixture was cooled and then poured onto an ice/water mixture. The separated solid was filtered, washed with water, dried and then crystallized from ethanol.

4-(4-Methoxybenzyl)-2-(4-((4-methoxybenzylidene)amino)-phenyl)phthalazin-1(2H)-one (5a)

Yield 80%. mp 200–202°C. IR (KBr), ν (cm^{-1}): 1668 (C=O), 1615 (C=N). $^1\text{H-NMR}$ (400MHz, DMSO- d_6) δ : 3.65, 3.78 (2s, 6H, 2OCH₃), 4.22 (s, 2 H, CH₂Bz), 6.68 (s, 1H, =CH–), 7.18–8.19 (m, 16 H, ArH). $^{13}\text{C-NMR}$ (100MHz, DMSO- d_6) δ ppm: 35.23, 54.89, 55.12, 116.49, 120.81, 122.51, 126.59, 127.31, 129.22, 130.44, 132.04, 133.19, 134.39, 136.55, 140.81, 142.51, 146.59, 148.68, 149.31, 151.72, 153.59, 155.62,

158.18, 164.92. MS: m/z 475 [M^+] (40%). *Anal.* Calcd for $C_{30}H_{25}N_3O_3$ (475): C, 75.79; H, 5.26; N, 8.84. Found: C, 76.16; H, 5.00; N, 8.55.

4-(4-Methoxybenzyl)-2-(4'-((3-methoxybenzylidene)amino)-[1,1'-biphenyl]-4-yl)phthalazin-1(2H)-one (**5b**)

Yield 74%. mp 212–214°C. IR (KBr), ν (cm^{-1}): 1667 (C=O), 1617 (C=N). 1H -NMR (400 MHz, DMSO- d_6) δ : 3.62, 3.79 (2s, 6H, 2OCH₃), 4.19 (s, 2H, CH₂Bz), 6.75 (s, 1H, =CH–); 7.24–8.22 (m, 20H, ArH). ^{13}C -NMR (100 MHz, DMSO- d_6) δ ppm: 35.77, 54.96, 55.80, 116.41, 119.19, 120.62, 122.69, 123.87, 125.11, 126.19, 126.72, 127.32, 128.69, 130.21, 131.01, 132.12, 133.39, 134.42, 135.78, 136.44, 137.21, 138.88, 140.11, 146.89, 150.01, 154.00, 158.54, 165.58. MS: m/z 551 [M^+] (35.7%). *Anal.* Calcd for $C_{36}H_{29}N_3O_3$ (551): C, 78.40; H, 5.26; N, 7.62. Found: C, 78.07; H, 5.00; N, 7.29.

Synthesis of 1,3-Diazetidine Derivatives 7a and b Equimolar amounts of **5a** and **b** (0.01 mol) and phenyl isothiocyanate (1.35 g, 0.01 mol) in 25 mL toluene was refluxed for 6 h. The solvent was distilled off and the residue was washed with ethanol followed by water, and the product was crystallized from ethanol.

4-(4-Methoxybenzyl)-2-(4-(2-(4-methoxyphenyl)-3-phenyl-4-thioxo-1,3-diazetidin-1-yl)phenyl)-phthalazin-1(2H)-one (**7a**)

Yield 68%. mp 278–280°C. IR (KBr), ν (cm^{-1}): 1664 (C=O), 1614 (C=N), 1319 (C=S). 1H -NMR (400 MHz, DMSO- d_6) δ : 3.61, 3.76 (2s, 6H, 2 OCH₃), 4.21 (s, 2H; CH₂Bz), 6.56 (s, 1H, benzylic H), 7.15–8.20 (m, 21H, ArH). ^{13}C -NMR (100 MHz, DMSO- d_6) δ ppm: 35.33, 55.44, 56.05, 95.46, 115.91, 116.19, 120.62, 122.69, 126.67, 128.23, 128.89, 129.73, 130.32, 130.91, 131.91, 132.21, 133.66, 134.40, 135.66, 136.41, 137.03, 137.79, 141.14, 144.87, 153.23, 154.55, 158.89, 166.67, 174.21. MS: m/z 610 [M^+] (59.1%). *Anal.* Calcd for $C_{37}H_{30}N_4O_3S$ (610): C, 72.79; H, 4.92; N, 9.18; S, 5.25. Found: C, 73.15; H, 5.21; N, 9.55; S, 5.63.

4-(4-Methoxybenzyl)-2-(4'-(2-(4-methoxyphenyl)-3-phenyl-4-thioxo-1,3-diazetidin-1-yl)-[1,1'-biphenyl]-4-yl)-phthalazin-1(2H)-one (**7b**)

Yield 72%. mp 284–286°C. IR (KBr), ν (cm^{-1}): 1671 (C=O), 1522 (C=N), 1322 (C=S). 1H -NMR (400 MHz, DMSO- d_6) δ : 3.64, 3.73 (2s, 6H, 2 OCH₃), 4.24 (s, 2H; CH₂Bz), 6.61 (s, 1H, benzylic H), 7.13–8.25 (m, 25H, ArH). ^{13}C -NMR (100 MHz, DMSO- d_6) δ ppm: 35.45, 55.23, 55.89, 96.12, 115.78, 117.02, 121.82, 122.56, 126.88, 127.49, 128.12, 128.78, 129.33, 129.81, 130.24, 130.98, 131.66, 132.29, 133.69, 134.51, 135.72, 136.32, 137.22, 138.12, 138.82, 139.39, 140.51, 141.32, 142.67, 152.88, 154.34, 159.61, 165.58, 174.99. MS: m/z 686 [M^+] (66.3%). *Anal.* Calcd for $C_{43}H_{34}N_4O_3S$ (686): C, 75.22; H, 4.96; N, 8.16; S, 4.67. Found: C, 74.90; H, 5.23; N, 7.88; S, 5.00.

Synthesis of Acetylated Derivatives 6a and b and Deacetylated Derivatives 8a and b A mixture of phthalazinones **2a** and **b** (0.01 mol) and 2-bromo-2-deoxy-1,3,4,6-tetra-*O*-acetyl- α -D-glucopyranose (4.1 g, 0.01 mol) in 100 mL 1,4-dioxane was heated with frequent stirring under reflux for 4 h. The mixture was cooled to room temperature and the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate, washed sequentially with saturated NaHCO₃ (3×20 mL), then with water and dried over MgSO₄. The purification and separation was achieved by column chromatography (EtOAc–hexane, 3:1) giving the acetylated products **6a** and **b** as a white solid which was later on recrystallized using diethyl ether–hexane as a solvent.

A solution of **6a** and **b** in MeOH (50 mL) was treated with sodium carbonate solution (2.12 g, 0.05 mol in 20 mL water). After stirring for 30 min, a white solid syrupy began to settle. The residue was then purified by column chromatography (EtOAc–hexane, 3:1) giving the deacetylated derivatives each as a white solid, which was crystallized by dichloromethane–diethyl ether as a solvent, affording **8a** and **b**, respectively.

6-(Acetoxymethyl)-3-((4-(4-(4-methoxybenzyl)-1-oxophthalazin-2(1H)-yl)phenyl)amino)-tetrahydro-2H-pyran-2,4,5-triyl Triacetate (**6a**)

Yield 58%. mp 124–126°C. IR (KBr), ν (cm^{-1}): 3334 (NH); 1685, 1671, 1660 (C=O), 1H -NMR (400 MHz, DMSO- d_6) δ : 2.08–2.29 (s, 12H, 4 COCH₃), 3.65 (s, 3H, OCH₃), 4.18 (s, 2H, CH₂Bz), 4.32–5.87 (m, 7H, CH₂OAc and pyran-H), 7.18–8.28 (m, 12H, ArH), 11.03 (s, 1H, NH, D₂O exchangeable). ^{13}C -NMR (100 MHz, DMSO- d_6) δ ppm: 22.02, 22.81, 36.11, 55.37, 61.39, 70.89, 71.91, 72.38, 73.10, 92.89, 115.44, 118.89, 121.11, 122.42, 126.59, 127.32, 128.42, 130.38, 131.11, 132.42, 136.59, 136.71, 143.19, 146.90, 154.01, 160.58, 171.20, 174.21. MS: m/z [687 (1.4%)]. *Anal.* Calcd for $C_{36}H_{37}N_3O_{11}$ (687): C, 62.88; H, 5.39; N, 6.11. Found: C, 63.24; H, 5.08; N, 5.78.

6-(Acetoxymethyl)-3-((4'-(4-(4-methoxybenzyl)-1-oxophthalazin-2(1H)-yl)-[1,1'-biphenyl]-4-yl)amino)-tetrahydro-2H-pyran-2,4,5-triyl Triacetate (**6b**)

Yield 56%. mp 164–166°C. IR (KBr), ν (cm^{-1}): 3311 (NH); 1683, 1673, 1662 (C=O), 1H -NMR (400 MHz, DMSO- d_6) δ : 2.05–2.24 (s, 12H, 4 COCH₃), 3.68 (s, 3H, OCH₃), 4.24 (s, 2H, CH₂Bz), 4.34–5.84 (m, 7H, CH₂OAc and pyran-H), 7.22–8.24 (m, 16H, ArH), 10.89 (s, 1H, NH, D₂O exchangeable). ^{13}C -NMR (100 MHz, DMSO- d_6) δ ppm: 21.82, 23.01, 35.89, 55.90, 61.01, 70.22, 71.39, 72.54, 74.45, 88.21, 114.89, 115.55, 120.78, 122.01, 125.11, 126.59, 127.72, 128.29, 130.22, 131.43, 132.62, 133.41, 134.38, 137.20, 140.78, 142.01, 145.11, 146.72, 154.00, 160.59, 172.20, 173.92. MS: m/z 763 [M^+] (10.9%). *Anal.* Calcd for $C_{42}H_{41}N_3O_{11}$ (763): C, 66.06; H, 5.37; N, 5.50. Found: C, 66.43; H, 5.70; N, 5.16.

4-(4-Methoxybenzyl)-2-(4-((2,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-3-yl)amino)-phenyl)-phthalazin-1(2H)-one (**8a**)

Yield 48%. mp 158–160°C. IR (KBr), ν (cm^{-1}): 3384, 3278 (OH bonded and non-bonded), 3185 (NH), 1664 (C=O). 1H -NMR (400 MHz, DMSO- d_6) δ : 3.20–3.61 (m, 6H, glucose-H), 3.78 (s, 3H, OCH₃), 4.15 (s, 2H, CH₂Bz), 4.28, 4.44, 4.59, 4.74 (s, 4H, 4OH of glucose, D₂O exchangeable), 5.21 (d, 1H, H_{anom} , $J=7.9$ Hz), 7.13–8.31 (m, 12H, Ar-H), 9.37 (s, 1H, NH, D₂O exchangeable). ^{13}C -NMR (100 MHz, DMSO- d_6) δ ppm: 35.01, 55.99, 61.87, 63.89, 70.21, 73.38, 74.11, 94.62, 115.34, 116.88, 121.11, 124.44, 128.61, 129.70, 130.89, 131.52, 131.78, 132.05, 132.57, 135.39, 144.18, 153.90, 156.03, 160.59. MS: m/z 519 [M^+] (25.2%). *Anal.* Calcd for $C_{28}H_{29}N_3O_7$ (519): C, 64.74; H, 5.59; N, 8.09. Found: C, 65.09; H, 5.81; N, 8.43.

4-(4-Methoxybenzyl)-2-(4'-(2,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-3-yl)amino)-[1,1'-biphenyl]-4-yl)phthalazin-1(2H)-one (**8b**)

Yield 43%. mp 188–190°C. IR (KBr), ν (cm^{-1}): 3379, 3261 (OH bonded and non-bonded), 3191 (NH), 1669 (C=O). 1H -NMR (400 MHz, DMSO- d_6) δ : 3.23–3.66 (m, 6H, glucose-H), 3.82 (s, 3H, OCH₃), 4.10 (s, 2H, CH₂Bz), 4.33, 4.51, 4.66, 4.79 (s, 4H, 4OH of glucose, D₂O exchangeable), 5.32 (d, 1H, H_{anom} , $J=8.3$ Hz), 7.09–8.41 (m, 16H, Ar-H), 9.88 (s, 1H, NH,

D₂O exchangeable). ¹³C-NMR (100 MHz, DMSO-*d*₆) δ ppm: 35.47, 56.23, 60.99, 64.12, 71.87, 74.81, 75.43, 95.59, 114.91, 116.64, 121.52, 122.79, 124.78, 126.23, 127.83, 128.57, 129.54, 130.58, 131.33, 131.97, 132.21, 132.88, 134.41, 137.39, 138.68, 154.48, 156.87, 161.24. MS: *m/z* 595 [*M*⁺] (34.2%). *Anal.* Calcd for C₃₄H₃₃N₃O₇ (595): C, 68.57; H, 5.55; N, 7.06. Found: C, 68.89; H, 5.84; N, 6.73.

Synthesis of 1-Chloro-4-(4-methoxybenzyl)phthalazine (9) Compound **3** (2.66 g, 0.01 mol) was added to a mixture of 5 mL POCl₃ and 2 g PCl₅. The reaction mixture was refluxed for 4 h, then poured drop wise of ice/water mixture with vigorous stirring. The precipitate so formed was filtered off, washed with water several times, dried then recrystallized from ethanol.

Yield 84%. mp 155–157°C. IR (KBr), ν (cm⁻¹): 3059–2993 (CH), 1610 (C=N). ¹H-NMR (400 MHz, DMSO-*d*₆) δ : 3.66 (s, 3H, OCH₃), 4.27 (s, 2H, CH₂Bz), 7.12–8.09 (m, 8H, ArH). ¹³C-NMR (100 MHz, DMSO-*d*₆) δ ppm: 35.59, 56.33, 115.53, 124.19, 125.34, 126.86, 127.76, 128.89, 130.11, 132.34, 133.73, 154.32, 156.31, 159.03. MS: *m/z* 284 [*M*⁺] (28.9%), 286 [*M*+2] (10.1%). *Anal.* Calcd for C₁₆H₁₃N₂OCl (284): C, 67.61; H, 4.58; N, 9.86; Cl, 12.50. Found: C, 67.93; H, 4.31; N, 10.23, Cl, 12.12.

Synthesis of Ethyl-2-(4-(4-methoxybenzyl)-1-oxo-phthalazin-2-yl)acetate (10) A mixture of phthalazinone derivative **3** (2.66 g, 0.01 mol), ethylchloroacetate (2.44 g, 0.02 mol) and anhydrous potassium carbonate (5.52 g, 0.04 mol) in dry acetone (50 mL) was refluxed for 24 h. The excess solvent was then removed by distillation and the residue was diluted with water. The obtained solid was filtered off and crystallized from benzene.

Yield 80%. mp 102–104°C. IR (KBr), ν (cm⁻¹): 3042–2885 (CH), 1745, 1684 (CO), 1614 (C=N). ¹H-NMR (400 MHz, DMSO-*d*₆) δ : 1.34 (t, 3H, CH₃, *J*=6.1 Hz), 3.71 (s, 3H, OCH₃), 4.21 (s, 2H, CH₂Ar), 4.39 (q, 2H, CH₂, *J*=8.2 Hz), 5.1 (s, 2H, NCH₂CO), 7.17–7.99 (m, 8H, ArH). ¹³C-NMR (100 MHz, DMSO-*d*₆) δ ppm: 15.19, 36.11, 51.21, 56.09, 63.22, 115.67, 123.89, 125.56, 126.77, 127.59, 129.09, 130.32, 131.92, 133.45, 153.99, 156.82, 159.79, 171.01. MS: *m/z* 352 [*M*⁺] (100%). *Anal.* Calcd for C₂₀H₂₀N₂O₄ (352): C 68.18, H 5.68, N 7.95. Found: C 67.85, H 5.40, N 8.32.

Synthesis of 1-Hydrazinyl-4-(4-methoxybenzyl)phthalazine (11) A solution of **9** (2.84 g, 0.01 mol) and hydrazine hydrate (0.5 mL, 0.01 mol) in ethanol (30 mL) was heated under reflux for 3 h. The solid that separated after cooling was filtered off and recrystallized from ethanol.

Yield 90%. mp 194–196°C. IR (KBr) ν (cm⁻¹): 3379, 3285, 3147 (NH₂, NH), 3048–2864 (CH), 1618 (C=N). ¹H-NMR (400 MHz, DMSO-*d*₆) δ : 3.73 (s, 3H, OCH₃), 4.28 (s, 2H, CH₂Ar), 6.34 (s, 2H, NH₂, D₂O exchangeable), 7.16–7.91 (m, 8H, ArH), 9.19 (s, 1H, NH, D₂O exchangeable). ¹³C-NMR (100 MHz, DMSO-*d*₆) δ ppm: 36.96, 54.55, 115.97, 118.34, 121.12, 124.41, 127.44, 129.66, 130.54, 131.71, 133.11, 150.03, 156.82, 160.56. MS: *m/z* 280 [*M*⁺] (43.6%). *Anal.* Calcd for C₁₆H₁₆N₄O (280): C, 68.57; H, 5.71; N 20.00. Found, C, 68.94; H, 6.05; N, 19.68.

Synthesis of 2-(4-(4-Methoxybenzyl)-1-oxophthalazin-2-yl)acetohydrazide (12) A solution of ester **10** (3.52 g, 0.01 mol) and hydrazine hydrate (1.0 mL, 0.02 mol) in ethanol (30 mL) was refluxed for 3 h. The reaction mixture was concentrated and the obtained solid was filtered off and recrystal-

lized from ethanol.

Yield 85%. mp 252–254°C. IR (KBr) ν (cm⁻¹): 3350, 3211, 3130 (NH₂, NH), 3050–2879 (CH), 1666, 1651 (CO), 1614 (C=N). ¹H-NMR (400 MHz, DMSO-*d*₆) δ : 3.63 (s, 3H, OCH₃), 4.14 (s, 2H, CH₂Ar), 4.68 (s, 2H, CH₂CO), 5.55 (brs, 2H, NH₂, D₂O exchangeable), 7.21–7.98 (m, 8H, ArH), 10.13 (1H, NH, D₂O exchangeable). ¹³C-NMR (100 MHz, DMSO-*d*₆) δ ppm: 36.43, 56.33, 58.61, 116.27, 124.02, 125.88, 127.12, 128.34, 129.45, 130.72, 131.77, 133.32, 134.21, 152.87, 155.15, 159.02, 172.25. MS: *m/z* 338 [*M*⁺] (29.6%). *Anal.* Calcd for C₁₈H₁₈N₄O₃ (338): C, 63.91; H 5.32; N, 16.57. Found: C, 64.22; H, 5.03; N, 16.20.

Synthesis of 1-(2-(Furan-2-ylmethylene)hydrazinyl)-4-(4-methoxybenzyl)phthalazine (13) A solution of **11** (2.8 g, 0.01 mol) and furfural (0.96 g, 0.01 mol) in ethanol (20 mL) was heated under reflux for 3 h. The solid that separated after cooling was filtered off and recrystallized from ethanol. Yield 76%. mp 140–142°C. IR (KBr) ν (cm⁻¹): 3190 (NH), 3055–2878 (CH), 1614 (C=N). ¹H-NMR (400 MHz, DMSO-*d*₆) δ : 3.63 (s, 3H, OCH₃), 4.18 (s, 2H, CH₂Ar), 6.39 (s, 1H, –N=CH–), 6.51 (m, 2H, H3, H4-furan) 7.13–8.10 (m, 9H, H5-fur + ArH), 10.77 (s, 1H, NH, D₂O exchangeable). ¹³C-NMR (100 MHz, DMSO-*d*₆) δ ppm: 37.05, 54.09, 111.71, 113.21, 115.22, 117.39, 121.89, 123.79, 128.11, 129.41, 130.30, 131.96, 133.11, 134.67, 142.55, 150.03, 151.62, 156.21, 162.99. MS: *m/z* 358 [*M*⁺] (22.8%). *Anal.* Calcd for C₂₁H₁₈N₄O₂ (358): C, 70.39; H, 5.03; N, 15.64. Found: C, 70.69; H, 5.28; N, 13.00.

Synthesis of 6-(4-Methoxybenzyl)-3-methyl-[1,2,4]-triazolo[3,4-*a*]phthalazine (14) A mixture of **11** (2.8 g, 0.01 mol) and acetic anhydride (10 mL) was heated for one hour on a water bath. Excess acetic anhydride was distilled off and solid was washed with water several times, then recrystallized from ethanol.

Yield 62%. mp 162–164°C. IR (KBr) ν (cm⁻¹): 3052–2891 (CH), 1614 (C=N). ¹H-NMR (400 MHz, DMSO-*d*₆) δ : 2.44 (s, 3H, CH₃), 3.65 (s, 3H, OCH₃), 4.23 (s, 2H, CH₂Ar), 7.12–8.18 (m, 8H, ArH). ¹³C-NMR (100 MHz, DMSO-*d*₆) δ ppm: 14.44, 36.18, 55.01, 113.21, 123.43, 124.93, 127.34, 128.89, 129.76, 130.44, 131.71, 133.53, 134.67, 148.21, 156.21, 158.86. MS: *m/z* 304 [*M*⁺] (19.9%). *Anal.* Calcd for C₁₈H₁₆N₄O (304): C, 71.05; H, 5.26; N, 18.42. Found: C, 70.76; H, 5.02; N, 18.70.

Synthesis of 6-(4-Methoxybenzyl)-[1,2,4]triazolo[3,4-*a*]phthalazine-3-thiol (15) A mixture of **11** (2.8 g, 0.01 mol), carbon disulfide (3.8 g, 0.05 mol) and anhydrous potassium hydroxide (0.5 g) in absolute ethanol (20 mL) was refluxed on a water bath for 6 h. The reaction mixture after cooling and concentration was poured into crushed ice. The solid that separated out was filtered off and recrystallized from dioxane.

Yield 60%. mp 144–146°C. IR (KBr) ν (cm⁻¹): 3039–2874 (CH), 1614 (C=N), 1271 (C=S). ¹H-NMR (400 MHz, DMSO-*d*₆) δ : 3.62 (s, 3H, OCH₃), 4.26 (s, 2H, CH₂Ar), 7.13–8.09 (m, 8H, ArH), 11.96 (s, 1H, SH, D₂O exchangeable). ¹³C-NMR (100 MHz, DMSO-*d*₆) δ ppm: 35.98, 54.89, 115.00, 123.73, 124.69, 127.03, 128.71, 129.18, 130.19, 132.09, 133.48, 149.31, 155.89, 158.18, 160.86. MS: *m/z* 322 [*M*⁺] (19.9%). *Anal.* Calcd for C₁₇H₁₄N₄OS (322): C, 63.35; H, 4.35; N, 17.39; S, 9.94. Found: C, 63.70; H, 4.08; N, 17.75; S, 10.30.

Synthesis of 3-Hydrazinyl-6-(4-methoxybenzyl)-[1,2,4]-triazolo[3,4-*a*]phthalazine (16) Hydrazine hydrate (1 mL, 0.02 mol) was added to a solution of **15** (3.22 g, 0.01 mol) in 25 mL ethanol. The reaction mixture was heated under reflux

for 3 h. The solid that separated after cooling and concentration was filtered off and recrystallized from ethanol.

Yield 54%. mp 168–170°C. IR (KBr) ν (cm⁻¹): 3364, 3260, 3174 (NH₂, NH), 3057–2891 (CH), 1614 (C=N). ¹H-NMR (400 MHz, DMSO-*d*₆) δ : 3.66 (s, 3H, OCH₃), 4.24 (s, 2H, CH₂Ar), 5.65 (s, 2H, NH₂, D₂O exchangeable), 7.05–8.06 (m, 8H, ArH), 11.11 (s, 1H, NH, D₂O exchangeable). ¹³C-NMR (100 MHz, DMSO-*d*₆) δ ppm: 35.21, 55.44, 115.55, 123.61, 124.18, 127.44, 128.65, 129.39, 130.21, 132.00, 133.66, 148.21, 156.56, 158.45, 159.98. MS: *m/z* 320 [M⁺] (30.2%). *Anal.* Calcd for C₁₇H₁₆N₆O (320): C, 63.75; H, 5.00; N, 26.25. Found: C, 64.02; H, 5.29; N, 25.90.

Synthesis of the Hydrazones 17a–c A solution of acetohydrazide **12** (3.38 g, 0.01 mol) and aromatic aldehydes namely, furan-2-carboxaldehyde, piperonal and 2-methoxybenzaldehyde (0.01 mol) in ethanol (30 mL) was refluxed for 3 h. The reaction mixture allowed to cool and the obtained solid was filtered off and recrystallized from suitable solvent.

N'-(Furan-2-ylmethylene)-2-(4-(4-methoxybenzyl)-1-oxophthalazin-2(1*H*)-yl)acetohydrazide (**17a**)

Yield 74%. mp 180–182°C. Solvent (benzene). IR (KBr) ν (cm⁻¹): 3170 (NH), 3041–2896 (CH), 1680, 1662 (CO), 1614 (C=N). ¹H-NMR (400 MHz, DMSO-*d*₆) δ : 3.72 (s, 3H, OCH₃), 4.27 (s, 2H, CH₂Ar), 5.02 (s, 2H, CH₂C=O), 6.16 (s, 1H, N=CH), 6.48–6.77 (m, 2H, furH), 7.07–8.13 (m, 9H, ArH and C5-furan-H), 9.99 (s, 1H, NH, D₂O exchangeable). ¹³C-NMR (100 MHz, DMSO-*d*₆) δ ppm: 35.66, 54.44, 58.89, 109.25, 113.33, 117.28, 122.84, 127.09, 128.11, 129.66, 130.57, 131.98, 133.23, 134.71, 138.43, 146.09, 148.23, 152.56, 156.21, 159.88, 168.99. MS: *m/z* 416 [M⁺] (13.5%). *Anal.* Calcd for C₂₃H₂₀N₄O₄ (416): C, 66.35; H, 4.81; N, 13.46. Found: C, 66.01; H, 5.06; N, 13.74.

N'-(Benzo[d]1,3-dioxo-5-ylmethylene)-2-(4-(4-methoxybenzyl)-1-oxophthalazin-2(1*H*)-yl)acetohydrazide (**17b**)

Yield 85%. mp 186–188°C. Solvent (ethanol). IR (KBr) ν (cm⁻¹): 3186 (NH), 3052–2890 (CH), 1676, 1665 (CO), 1611 (C=N). ¹H-NMR (400 MHz, DMSO-*d*₆) δ : 3.79 (s, 3H, OCH₃), 4.22 (s, 2H, CH₂Ar), 5.11 (s, 2H, CH₂C=O), 5.63 (s, 2H, O-CH₂-O), 6.25 (s, 1H, N=CH), 7.14–8.18 (m, 11H, ArH), 10.11 (s, 1H, NH, D₂O exchangeable). MS: *m/z* 470 [M⁺] (41.6%). *Anal.* Calcd for C₂₆H₂₂N₄O₅ (470): C, 66.38; H, 4.68; N, 11.91. Found: C, 66.07; H, 4.97; N, 12.25.

2-(4-(4-Methoxybenzyl)-1-oxophthalazin-2(1*H*)-yl)-*N'*-(2-methoxybenzylidene)acetohydrazide (**17c**)

Yield 82%. mp 192–194°C. Solvent (toluene). IR (KBr) ν (cm⁻¹): 3191 (NH), 3058–2895 (CH), 1679, 1660 (CO), 1618 (C=N). ¹H-NMR (400 MHz, DMSO-*d*₆) δ : 3.62, 3.79 (s, 6H, 2OCH₃), 4.14 (s, 2H, CH₂Ar), 5.06 (s, 2H, CH₂C=O), 6.31 (s, 1H, N=CH), 7.10–8.08 (m, 12H, ArH), 10.32 (s, 1H, NH, D₂O exchangeable). ¹³C-NMR (100 MHz, DMSO-*d*₆) δ ppm: 35.66, 54.44, 56.36, 59.04, 113.45, 115.22, 117.39, 122.76, 124.52, 127.23, 128.65, 129.81, 130.42, 131.78, 132.56, 133.19, 133.89, 134.37, 147.27, 153.42, 154.56, 156.18, 159.23, 169.58. MS: *m/z* 456 [M⁺] (32.8%). *Anal.* Calcd for C₂₆H₂₄N₄O₄ (456): C, 68.42; H, 5.26; N, 12.28. Found: C, 68.09; H, 5.00; N, 12.60.

Synthesis of Compounds 18a and b A solution of **12** (3.38 g, 0.01 mol) and acetic anhydride or ethyl acetoacetate (0.01 mol) in ethanol (30 mL) was refluxed for 4 h. The reaction mixture allowed to cool and the obtained solid was filtered off and crystallized from suitable solvent.

4-(4-Methoxybenzyl)-2-((5-methoxy-1,3,5-oxadiazol-2-yl)-methyl)phthalazin-1(2*H*)-one (**18a**)

Yield 77%. mp 172–174°C. Solvent (benzene). IR (KBr) ν (cm⁻¹): 3044–2876 (CH), 1672 (CO), 1619 (C=N). ¹H-NMR spectrum (400 MHz, DMSO-*d*₆) δ : 2.55 (s, 3H, CH₃), 3.73 (s, 3H, OCH₃), 4.14 (s, 2H, CH₂Ar), 4.64 (s, 2H, CH₂), 7.07–8.23 (m, 8H, ArH). ¹³C-NMR (100 MHz, DMSO-*d*₆) δ ppm: 22.06, 35.32, 50.44, 56.11, 113.31, 122.22, 125.66, 128.32, 129.14, 130.59, 131.85, 132.77, 134.37, 154.39, 156.55, 159.23, 161.19, 165.87. MS: *m/z* 362 [M⁺] (29.9%). *Anal.* Calcd for C₂₀H₁₈N₄O₃ (362): C, 66.30; H, 4.97; N, 15.47. Found: C, 66.00; H, 5.21; N, 15.16.

Synthesis of 4-(4-Methoxybenzyl)-2-((5-(2-oxopropyl)-1,3,5-oxadiazol-2-yl)methyl)phthalazin-1(2*H*)-one (**18b**)

Yield 69%. mp 188–190°C. Solvent (dioxane). IR (KBr) ν (cm⁻¹): 3050–2885 (CH), 1672, 1660 (CO), 1614 (C=N). ¹H-NMR (400 MHz, DMSO-*d*₆) δ : 2.01 (s, 3H, COCH₃), 3.74 (s, 3H, OCH₃), 3.92 (s, 2H, CH₂C=O), 4.11 (s, 2H, CH₂Ar), 4.69 (s, 2H, CH₂), 7.07–8.23 (m, 8H, ArH). MS: *m/z* 404 [M⁺] (18.7%). *Anal.* Calcd for C₂₂H₂₀N₄O₄ (404): C, 65.35; H, 4.95; N, 13.86. Found: C, 65.71; H, 5.17; N, 14.14.

Synthesis of 2-((4-Acetyl-5-methyl-4*H*-pyrazol-3-yl)-methyl)-4-(4-methoxybenzyl)-phthalazin-1(2*H*)-one (19**)**

A solution of **12** (3.38 g, 0.01 mol) and acetyl acetone (1.5 g, 0.015 mol) in ethanol (30 mL) was heated under reflux for 3 h. The reaction mixture allowed to cool and the obtained solid was filtered off and crystallized from ethanol.

Yield 71%. mp 178–180°C. IR (KBr) ν (cm⁻¹): 3051–2893 (CH), 1675, 1663 (CO), 1620 (C=N). ¹H-NMR (400 MHz, DMSO-*d*₆) δ : 2.12 (s, 3H, COCH₃), 2.79 (s, 3H, CH₃), 3.66 (s, 3H, OCH₃), 3.89 (s, 1H, pyrazole), 4.17 (s, 2H, CH₂Ar), 4.71 (s, 2H, CH₂), 7.10–8.26 (m, 8H, ArH). ¹³C-NMR (100 MHz, DMSO-*d*₆) δ ppm: 15.06, 27.32, 35.86, 50.21, 53.34, 56.76, 115.01, 122.88, 125.76, 128.44, 129.21, 130.34, 131.96, 132.89, 134.76, 144.99, 154.23, 156.12, 159.14, 161.19, 198.01. MS: *m/z* 402 [M⁺] (16.9%). *Anal.* Calcd for C₂₃H₂₂N₄O₃ (402): C, 68.66; H, 5.47; N, 13.93. Found: C, 68.93; H, 5.70; N 14.29.

Synthesis of 2-((5-Mercapto-4*H*-1,2,4-triazol-3-yl)-methyl)-4-(4-methoxybenzyl)phthalazin-1(2*H*)-one (20**)** A solution of **12** (3.38 g, 0.01 mol) and ammonium thiocyanate (2.28 g, 0.03 mol) in ethanol (30 mL) was heated under reflux for 3 h. The solid that separated out after cooling was filtered off and crystallized from benzene.

Yield 61%. mp 218–220°C. IR (KBr) ν (cm⁻¹): 3179 (NH), 3061–2892 (CH), 1678 (CO), 1614 (C=N), 1265 (C=S). ¹H-NMR (400 MHz, DMSO-*d*₆) δ : 3.75 (s, 3H, OCH₃), 4.14 (s, 2H, CH₂Ar), 4.57 (s, 2H, CH₂), 7.04–8.22 (m, 8H, ArH), 10.76, 12.22, (2s, 2H, NH and, SH D₂O exchangeable). ¹³C-NMR (100 MHz, DMSO-*d*₆) δ ppm: 36.21, 50.29, 56.76, 115.76, 122.69, 125.91, 128.66, 129.01, 130.43, 131.78, 132.89, 134.59, 153.55, 154.45, 156.66, 158.34, 159.14. MS: *m/z* 379 [M⁺] (10.4%). *Anal.* Calcd for C₁₉H₁₇N₅O₂S (379): C, 60.16; H, 4.49; N, 18.47; S, 8.44. Found: C, 60.50; H, 4.21; N, 18.09; S, 8.10.

Synthesis of *N*-(1,3-Dioxoisindolin-2-yl)-2-(4-(4-methoxybenzyl)-1-oxophthalazin-2(1*H*)-yl)-acetamide (21**)**

A mixture of hydrazide **12** (3.38 g, 0.01 mol) and phthalic anhydride (1.5 g, 0.01 mol) was heated in an oil bath at 170°C for 1 h. The reaction mixture was allowed to cool and the solid obtained was crystallized from ethanol.

Yield 58%. mp 262–264°C. IR (KBr) ν (cm⁻¹): 3182 (NH), 3051–2880 (CH), 1770, 1742, 1680, 1660 (CO), 1614 (C=N).

¹H-NMR (400MHz, DMSO-*d*₆) δ : 3.62 (s, 3H, OCH₃), 4.11 (s, 2H, CH₂Ar), 4.59 (s, 2H, CH₂), 7.07–8.27 (m, 12H, ArH), 12.23 (s, 1H, NH, D₂O exchangeable). ¹³C-NMR (100MHz, DMSO-*d*₆) δ ppm: 35.74, 54.34, 58.71, 115.54, 122.99, 124.02, 125.69, 127.11, 128.71, 129.12, 130.66, 131.65, 132.77, 133.44, 134.34, 152.79, 154.32, 156.43, 158.88, 168.11. MS: *m/z* 468 [M⁺] (14.2%). *Anal.* Calcd for C₂₆H₂₀N₄O₅ (468): C, 66.67; H, 4.27; N, 11.97. Found: C, 66.34; H, 4.02; N, 12.31.

Synthesis of 4-((4-((1-(4-Methoxyphenyl)ethylidene)-amino)phenyl)sulfonyl)aniline) (22) A mixture of dapsone (4,4'-sulfonyldianiline) (2.48 g, 0.01 mol) and 4-methoxyacetophenone (1.50 g, 0.01 mol) in 25 mL absolute ethanol was heated under reflux for 4 h. The solid that separated out on cooling was filtered and crystallized from ethanol.

Yield 63%. mp 176–178°C: IR (KBr) ν (cm⁻¹): 3430, 3321 (NH₂), 1610 (C=N), 1160 (S=O). ¹H-NMR (400MHz, DMSO-*d*₆) δ : 2.11 (s, 3H, CH₃), 3.74 (s, 3H, OCH₃), 6.45 (s, 2H, NH₂, D₂O exchangeable), 7.10–8.11 (m, 12H, 3 ArH). MS: *m/z* 380 [M⁺] (33.3%). *Anal.* Calcd for C₂₁H₂₀N₂O₃S (380): C, 66.32; H, 5.26; N, 7.37; S, 8.42. Found: C, 66.66; H, 5.55; N, 7.06; S, 8.07.

Synthesis of 4-(4-Methoxybenzyl)-N-(4-((4-((1-(4-methoxyphenyl)ethylidene)amino)phenyl)-sulfonyl)phenyl)-phthalazin-1-amine (23) Chlorophthalazine derivative **9** (2.84 g, 0.01 mol) and the Schiff base **22** (3.80 g, 0.01 mol) were dissolved in 30 mL absolute ethanol and 0.5 mL pyridine was added. The reaction mixture was heated under reflux for 6 h. The resulting mixture was cooled and poured onto ice/water. The solid that separated out was filtered, washed with water, air-dried and crystallized from ethanol.

Yield 58%. mp 270–272°C: IR (KBr) ν (cm⁻¹): 3230 (NH), 1619 (C=N), 1155 (S=O). ¹H-NMR (400MHz, DMSO-*d*₆) δ : 2.17 (s, 3H, CH₃), 3.67, 3.84 (2s, 6H, 2OCH₃), 4.21 (s, 2H, CH₂Ar), 7.09–8.08 (m, 20H, Ar-H), 9.94 (s, 1H, NH, D₂O exchangeable). ¹³C-NMR (100MHz, DMSO-*d*₆) δ ppm: 22.79, 36.46, 55.11, 57.52, 113.89, 114.12, 115.33, 117.52, 120.87, 123.31, 124.19, 127.49, 128.99, 129.62, 130.51, 131.68, 132.23, 132.75, 133.43, 135.32, 136.32, 138.7, 144.83, 147.64, 153.91, 155.29, 163.88, 165.22, 167.31. MS: *m/z* 628 [M⁺] (13.2%). *Anal.* Calcd for C₃₇H₃₂N₄O₄S (628): C, 70.70; H, 5.10; N, 8.91; S, 5.10. Found: C, 71.01; H, 5.37; N, 9.32; S, 5.43.

Synthesis of N-(4-(4-Methoxybenzyl)phthalazin-1-yl)-N-(4-((4-((1-(4-methoxyphenyl)-ethylidene)amino)phenyl)-sulfonyl)phenyl)furan-2-carboxamide (24) A mixture of compound **23** (3.14 g, 0.005 mol) and 2-furoyl chloride (0.65 g, 0.005 mol) was refluxed in 30 mL of dry pyridine for 3 h. The excess solvent was distilled off and the reaction solution was cooled, then poured into crushed ice with frequent stirring leaving a crude product which was filtered off, washed with water, dried and crystallized from ethanol.

Yield 78%. mp 284–286°C: IR (KBr) ν (cm⁻¹): 1674 (C=O), 1602 (C=N), 1157 (S=O). ¹H-NMR (400MHz, DMSO-*d*₆) δ : 2.14 (s, 3H, CH₃), 3.70, 3.85 (2s, 6H, 2OCH₃), 4.16 (s, 2H, CH₂Ar), 6.82–8.23 (m, 23H, ArH and furan-H). ¹³C-NMR (100MHz, DMSO-*d*₆) δ ppm: 22.48, 36.05, 55.82, 58.49, 112.62, 113.45, 114.78, 116.56, 117.72, 120.61, 122.24, 123.60, 124.29, 125.91, 127.48, 128.58, 129.87, 130.25, 131.54, 132.33, 132.89, 134.67, 136.34, 140.78, 142.78, 146.31, 147.42, 149.24, 153.89, 156.32, 158.68, 161.78, 163.31, 166.39. MS: *m/z* 722 [M⁺] (25.7%). *Anal.* Calcd for C₄₂H₃₄N₄O₆S (722): C, 69.81; H, 4.71; N, 7.76; S 4.43. Found: C, 70.14; H, 5.00; N, 8.08; S, 4.09.

Conclusion

In this paper, several new heterocyclic compounds that contain a phthalazine and phthalazinone moieties were synthesized using simple methods. The structures of the newly synthesized compounds were elucidated by different spectral methods and they were tested for their antimicrobial activities. Most of these compounds showed promising activities against different bacteria and fungi strains.

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