Reaction of Phthalaldehydic Acid with Different Substituted Aniline as well as Hydrazine Derivatives

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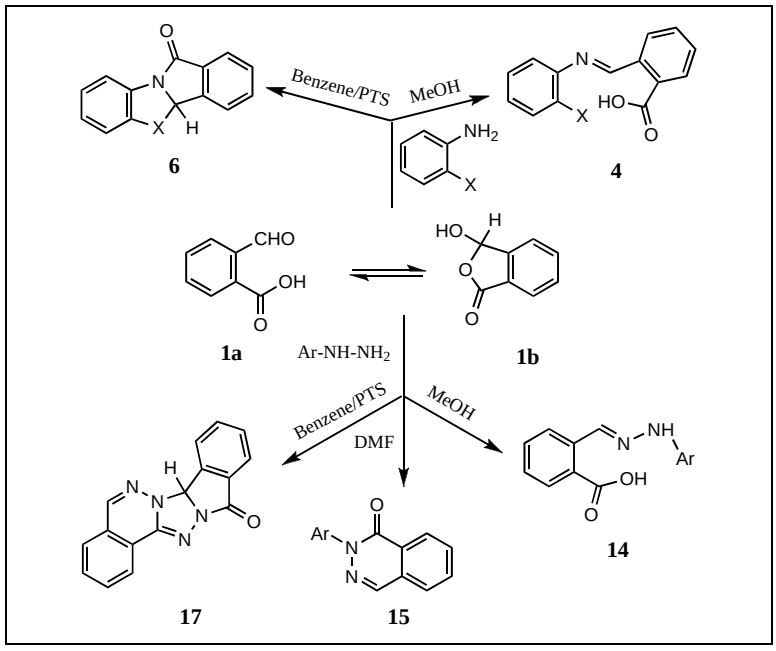

Phthalaldehydic acid **1** is often represented as having two tautomeric forms **1a** and **1b**. The reaction of phthalaldehydic acid with different aryl amine and heterocyclic aryl hydrazine derivatives afforded different products depending on the reaction conditions such as solvent and temperature.

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INTRODUCTION

Phthalaldehydic acid **1** (namely, 2-formyl benzoic acid) and its derivatives represent an important member in aromatic hydrocarbon, chemistry for their wide usages in the preparation of 3-substituted phthalides [1-4], heterobicyclic, tricyclic and tetracyclic systems [5-7], in addition to their broad spectrum of biological activities [8,9]. Reported among these activities, were anorexic, anti HIV, anti-inflammatory, analgesic or anti-allergic effects [8, 10-12]. Some have been used in therapy, in particular as nootropic agents [13]. Derivatives of phthalaldehydic acid **1** also show activities as hypnotics, sedatives, muscle relaxants [14], and the non-nucleosidic HIV-reverse transcriptase inhibitors [8,15]. Also related compounds are important herbicides for bud growth inhibition [16,17] and plant regulation [18].

The bi-functionality at ortho-position of this molecule gives it the ability for introducing heterocycle moieties. Several procedures have been applied in that aspect [5-7, 19a].

Our interest was focused on studying the reaction of phthalaldehydic acid with different aryl amine and heterocyclic aryl hydrazine derivatives in various solvents. The change of solvent had a great effect on the type of products obtained. The microbiological activity of the obtained compounds was also evaluated.

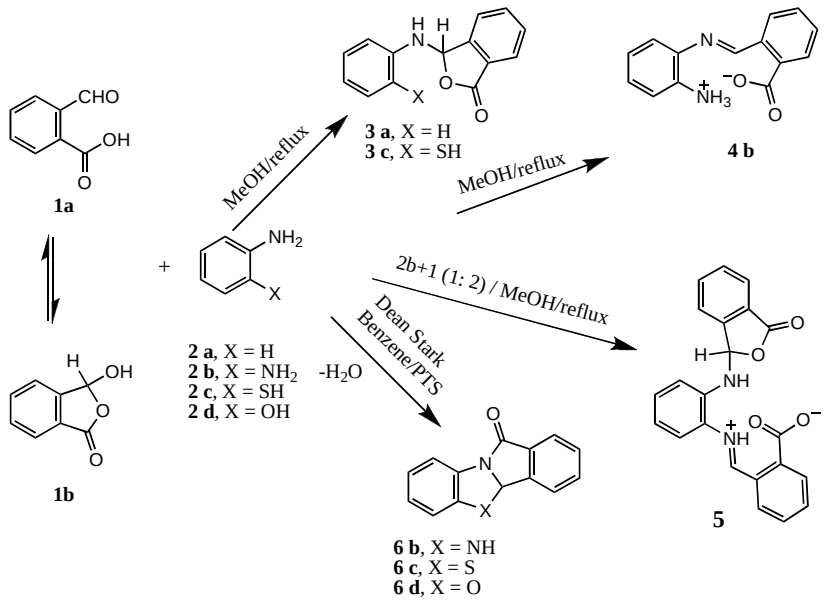
RESULTS AND DISCUSSION

Chemistry. Phthalaldehydic acid **1** is often represented as having an aldehyde and an acid group **1a**. However, the tautomeric structure 3-hydroxy phthalide form **1b** was suggested by Racine in 1886 [20]. On the basis of spectroscopic evidence, **1** exists in both the open **1a** and ring form **1b** depending upon the solvent and temperature [19]. At 500 MHz **1** is shown to exist in the two tautomeric forms **1a** and **1b** in $CDCl_3$ by exhibiting both the CH hydrogen at δ 6.65 ppm and CHO hydrogen at δ 10.58 ppm. Examination of the influence of acid such as *p*-toluenesulfonic acid on this equilibrium revealed a complete shift to the cyclic form **1b** by displaying the CH at δ 6.01 ppm and no aldehydic hydrogen was detected.

The reaction of phthalaldehydic acid **1** with aniline **2a** was described previously [1-4]. The 3-anilino phthalide **3a** was the only product obtained when methanol was used as solvent, by allowing the reaction mixture to undergo reflux for 3 hours. The ir, melting point and elemental analysis were in accordance with the reported data [1-4].

The same reaction was performed using *o*-substituted aniline **2b-d** under the same conditions. Reactive equimolar amount of *o*-phenylene diamine **2b** with **1** in methanol as a solvent, led to formation of the Schiff's base **4b**. The zwitter ion form of **4b** (Scheme 1) was observed in solid and in solution states. The ir spectrum of **4b** in KBr showed one broad absorption peak at 3066-2600 cm^{-1} due to the ammonium (NH_3^+) group, and one absorption peaks at 1638 cm^{-1} due to the carbonyl (COO^-) group of the carboxylate. The ^1H nmr spectrum of **4b** in dimethyl sulfoxide-d_6 showed a broad peak at δ 3.58 corresponding to NH_3^+ group which is D_2O exchangeable. The ^{13}C nmr spectrum of **4b** showed eleven resolved carbon signals. No signals in the sp^3-carbon region were observed; the carbon signal of the imino group (CH=N) and the carbonyl (C=O) were observed at δ 151.77 and 169.99, respectively, which rules out the existence of any ring tautomer. The rest of the carbon signals correspond to the remaining carbon atoms.

Scheme 1



When two equivalents of **2b** are allowed to react with phthalaldehydic acid **1** under the same conditions mentioned above, only one product was obtained. Its structure was assigned as 2-[(*E*)-({2-[(3-Oxo-1,3-dihydro-2-benzofuran-1-yl)amino]phenyl}imino)methyl] benzoic acid **5** on the basis of its spectroscopic data (Scheme 1). The formed product **5** contains the two tautomeric forms (**1a** and **1b**) as observed from its spectral data. Thus, the ir spectrum of **5** showed an absorption peak at 3072 cm^{-1} due to the NH group and a broad absorption peak at 2921-2630 cm^{-1} due to the NH^+ group, and two absorption peaks at 1776, 1708 cm^{-1} due to the (C=O) group of the ring form, and the (C=O) group corresponding to the (COO^-) group respectively. The ^1H nmr spectrum of **5** showed two broad peaks at δ 4.36 and 6.08 corresponding to the NH and NH^+ group which are D_2O exchangeable, and a singlet corresponding to the –CH group of the ring form at δ 7.36. The ^{13}C nmr spectrum of **5** showed twenty two resolved carbon signals. The carbon signal of the -CH group of the ring part of **5** was observed at δ 84.32, the carbon signal of the imino group (CH=N) was observed at δ 154.67. The carbon signals of the two carbonyl groups were observed at δ 167.52 and 168.24. The rest of the resolved signals were corresponding to the rest of the carbon atoms. The HMQC confirmed that the carbon signal at δ 84.32 is correlated to the singlet CH signal at δ 7.36, which confirmed the proposed structure.

The reaction of *o*-amino thiophenol **2c** with phthalaldehydic acid **1** using methanol as solvent gave the corresponding cyclized product **3c** (Scheme 1) as observed from its spectral data. The ir spectrum of **3c** showed absorption peak at 3409 cm^{-1} due to the NH group, and an absorption peak at 1717 cm^{-1} due to the carbonyl group of the ring form. The ^1H nmr spectrum of **3c** showed a singlet at δ 1.60 and 7.25 corresponding to SH and NH groups which are D_2O exchangeable, a singlet at δ 6.99 corresponding to the CH group of the ring form. The ^{13}C nmr spectrum of **3c** showed fourteen resolved carbon signals. The carbon signal of the CH group of the ring form was resolved at δ 64.54 and

the carbon signal of the carbonyl group was observed at δ 163.86. The remaining signals were in accordance with the remaining carbon atoms.

On the other hand, the reaction of *o*-amino phenol **2d** with phthalaldehydic acid **1** using methanol as solvent gave more than one product on TLC which couldn't be isolated as a pure product.

We extended our work to use different solvent system such as dry benzene in presence of *p*-toluenesulfonic acid (PTS) using Dean Stark trap [6]. The reaction of o-substituted anilines **2b-2d** with phthalaldehydic acid **1** in dry benzene in presence of *p*-toluenesulfonic acid using Dean Stark trap afforded a tetracyclic product **6** (Scheme 1) as a single product in nearly all cases as observed from spectral analysis. The only exception is in the case of *o*-aminophenol **2d**, where the product **6d** was isolated as an isomeric mixture in a ratio 2:3 (Scheme 1) as evident from its spectral data. On the other hand the reaction of *o*-phenylene diamine **2b** and *o*-amino thiophenol **2c** gave in excellent yield with high stereoselectivity only one product **6b** and **6c** respectively. The ir spectrum of compound **6d** showed absorption peak at 1780 cm^{-1} due to the carbonyl group. Its ^{1}H nmr spectrum showed two singlet peaks at δ 6.57 and δ 6.90 in ratio 2:3 corresponding to the CH groups of the two isomeric products of **6d**. Its ^{13}C nmr spectrum showed eleven resolved carbon signals. The carbon signals of the CH groups were observed at δ 98.30 and 99.11 and the carbonyl carbon signals were observed at δ 167.95 and 168.26. The rest of the resolved carbon signals are corresponding to the aromatic carbon atoms of the two isomeric mixtures. The two isomers of compound **6d** were separated by a mass selective detector (GC/MS) using an HP-5MS column. 1 micrometer split less injection at inlet temperature 250°C and detector temperature 280°C. They showed 2 peaks at retention time (t_R) 5.97 and 6.50 min, and in ratio 47.999 % and 52.001 % respectively. The two isomers showed the same molecular ion peak at m/z 223. The ir spectrum of **6c** showed one absorption peak at 1719 cm^{-1} due to the carbonyl group. The ^{1}H nmr spectrum of **6c** showed only one singlet at δ 7.29 corresponding to the CH group. The ^{13}C nmr spectrum of **6c** showed two resolved carbon signals corresponding to the CH and C=O groups at δ 69.26 and 168.63 respectively. The rest of the resolved carbon signals were consistent with the expected product. The ir and nmr spectra of compound **6b** were in agreement with the proposed structure **6b**.

The energy minimization of the tetracyclic products **6, 9** and **17** were processed utilizing PM3/MOPAC [21] and the observed structure for **6b** is represented as a prototype (Figure 1).

The bi-functional system 4-amino-5-(3-chlorophenyl)-2,4-dihydro-[1,2,4]triazole-3-thione **7** reacted with phthalaldehydic acid **1** using methanol as solvent under the same conditions used for the aniline derivatives to afford the corresponding Schiff's base **8** (Scheme 2) as observed

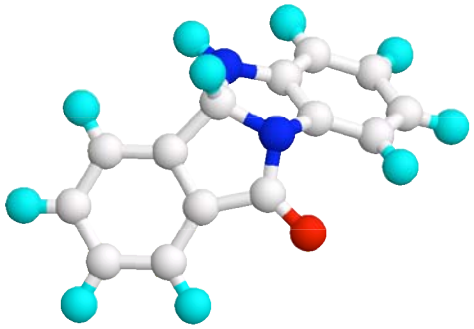
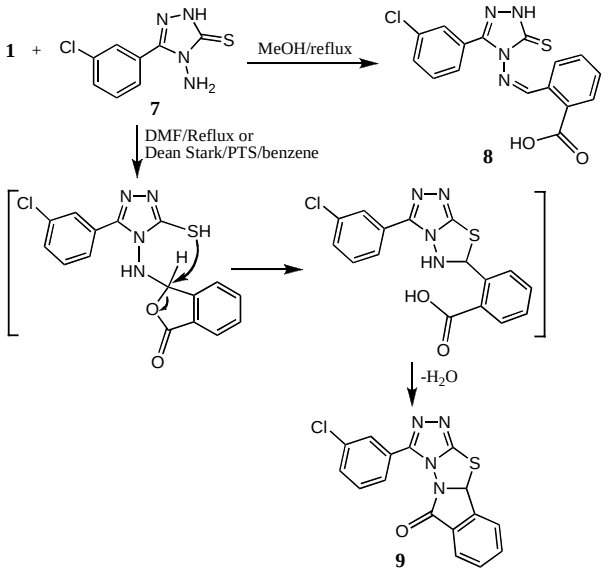


Figure 1

from its spectral data. While using dimethyl formamide (DMF) as solvent gave a tetracyclic product **9** in yield 82 % with high stereoselectivity, only one product was obtained as observed from its spectral data. The ir spectrum of **9** showed one absorption peak at 1784 cm^{-1} corresponding to the carbonyl group. The ^{1}H nmr spectrum of **9** showed a singlet at δ 7.61 corresponding to one proton for the CH group. As expected from the proposed structure **9** the ^{13}C nmr spectrum showed sixteen resolved carbon signals with the CH of the ring form resolved at δ 84.51. The reaction of **7** and phthalaldehydic acid **1** in dry benzene in presence of *p*-toluenesulfonic acid using Dean Stark trap gave also the same tetracyclic product **9** as in case of using DMF as a solvent but in much better yield (94 %) (Scheme 2). The formation of **9** could be explained due to the attacking of the amino group in **7** at the tautomeric carbon atom to generate the transient intermediate, in which the sulphur atom attacks the tautomeric carbon followed by elimination of one equivalent of water to form the product **9** (Scheme 2).

Scheme 2



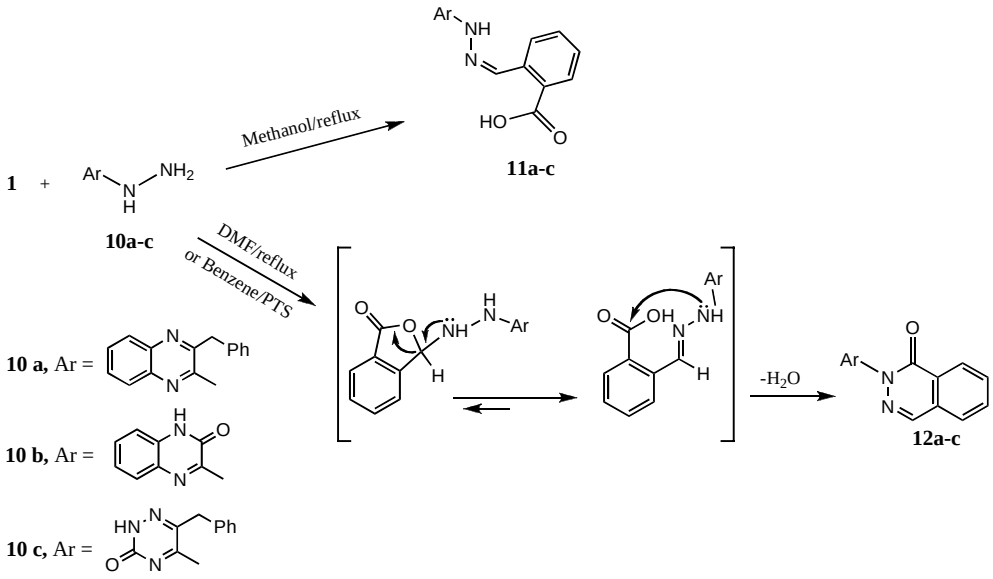
This mechanism is the same predicted for the formation of the previously prepared compound **6**.

As extension to our work the reaction of phthalaldehydic acid **1** with hetero aryl hydrazine derivatives was studied. The reaction of phthalaldehydic acid **1** with (3-benzyl-quinoxalin-2-yl)-hydrazine **10a**, 3-hydrazino-1*H*-quinoxalin-2-one **10b** or 6-benzyl-5-hydrazino-2*H*-[1,2,4]-triazin-3-one **10c** gave two different products (Scheme 3) depending on the reaction conditions used. The Schiff's base **11** was obtained when using methanol as solvent, where the cyclized product **12** was isolated when dimethyl formamide (DMF) was used as solvent (Scheme 3). The structures of **11a-c** and **12a-c** were established by ir, ^{1}H nmr, ^{13}C nmr and elemental analyses.

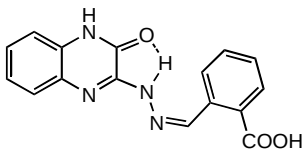
The probable reaction mechanism for the formation of compound **12** is through attack of the NH_2 group in **10** at the tautomeric carbon atom to generate the transient intermediate, which rearranges to afford the trans-imine intermediate, followed by elimination of one equivalent of water to form the product **12** [7a].

The reaction of phthalaldehydic acid **1** with 1-hydrazinophthalazine **13** using methanol as solvent gave the Schiff's base **14** in good yield and the spectral data were identical to that reported in the literature [22]. On the other hand, when the reaction was performed using DMF as solvent the cyclized product **15** was obtained in good yield and the spectral data were identical to the reported data by R. N. Castle and *et al.* [23] (Scheme 4).

Scheme 3



The reaction of the hydrazines **10a** and **10c** with phthalaldehydic acid **1** in dry benzene in presence of *p*-toluenesulfonic acid using Dean Stark trap afforded the cyclized products **12a** and **12c** respectively. While the hydrazine **10b** when reacting with phthalaldehydic acid **1** under the same previously mentioned conditions gave only the Schiff's base **11b**. The Schiff's base obtained is highly insoluble and contains hydrogen bonding (Figure 2). This probably prevents further ring closure.



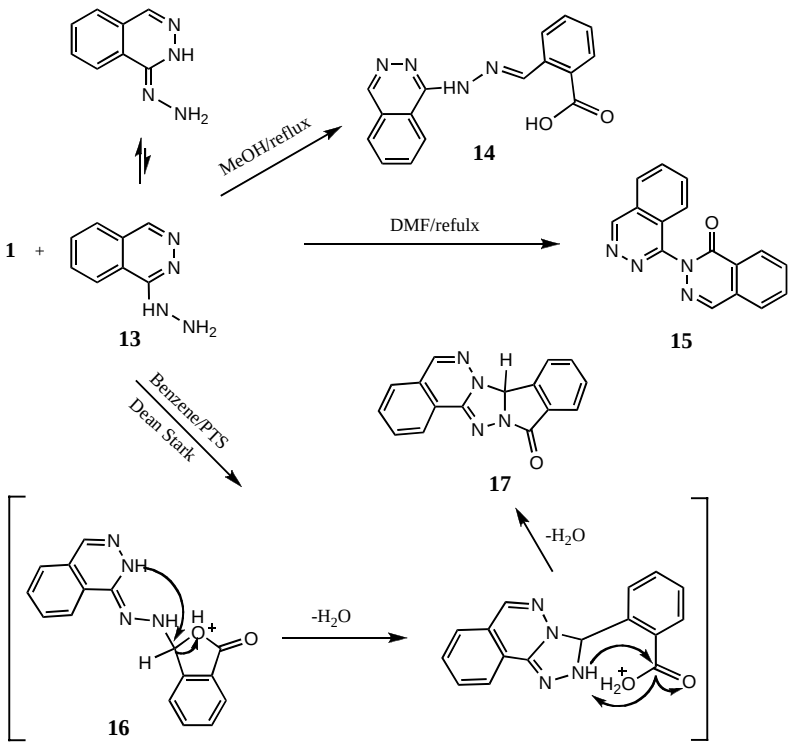
11b

Figure 2

The reaction of 1-hydrazinophthalazine **13** with phthalaldehydic acid **1** in dry benzene in presence of *p*-toluenesulfonic acid using Dean Stark trap gave the corresponding pentacyclic product **17** as an isomeric mixture in ratio 1:2 (Scheme 4) as observed from its spectral data. A possible explanation for the formation of **17** was based on the unique reactivity of compound **13** having the N-2 nitrogen atom [19a,24-28]. Hydralazine is known to adopt the tautomeric form where the nitogen ring is in the second nucleophilic reactivity. Using hydralazine-HCl with phthaladehydic acid in aqueous medium was reported to undergo the formation of the intermediate **16** under such acidic condition [19a].

A plausible explanation for the formation of compound **17** could be through the dehydration of the intermediate **16** under acidic condition as shown in Scheme 4. The ir spectrum of compound **17** showed absorption peak at 1778 cm^{-1} due to the carbonyl group. The ^{1}H nmr spectrum of **17** showed two singlet peaks at δ 7.04 and δ 7.12 in ratio 1:2

Scheme 4



corresponding to the CH group of the two isomeric products of **17**. The ^{13}C nmr spectrum of **17** showed two resolved carbon signals corresponding to the CH group at δ 99.89 and 102.18 and also the two carbonyl carbon signals were observed at δ 168.30 and 168.46. The two isomers of compound **17** were separated by a mass selective detector (GC/MS) using an HP-5MS column. 1 micrometer split less injection at inlet temperature 250 ℃ and detector temperature 280 ℃. They showed 2 peaks at retention time (t_R) 5.99 and 6.52 min, and in ratio 56.6 % and 43.4 % respectively. The two isomers showed the same molecular ion peak at m/z 274.

Biology. Four test organisms representing different groups of microorganisms were used to evaluate the bioactivity of the designed products. The utilized test organisms were: *Escherichia coli (E. coli)* ATCC 25922 and *Pseudomonas aeruginosa (P. aeruginosa)* as Gram-negative bacteria, *Staphylococcus aureus* (*S. aureus*) ATCC 19433 as an example of Gram-positive bacteria, and *Candida albicans* (*C. albicans*) as yeast-like fungi. The inhibition zone results are given in Table 1. It is apparent from the data listed in Table 1 that some of the synthesized compounds showed antibacterial activity comparable to that of ampicillin, ciprofloxacin and clotrimazole. However, concerning the activity against gram-positive bacteria, compounds **3a, 6d, 11c, 12c** and **17** showed excellent activity higher and comparable to that of both ampicillin and ciprofloxacin, where compounds **6c, 8, 9, 11a, 11b and 14,** exhibit good activity which is higher and comparable to that of ampicillin. On the other hand, the activity against the gram-negative bacteria (*Escherichia coli*) of a number of the designed compounds **3a, 5, 6b, 6d, 8, 11a, 11c, 12a, 12b, 15**, showed higher and comparable activity to that of ampicillin. Concerning the data of antifungal activity, the synthesized compounds showed moderate activity against *Candida albicans*, comparable to that of clotrimazole. The microdilution susceptibility test in Müller-Hinton Broth (Oxoid) and Sabouraud Liquid Medium (Oxoid) were also used for the determination of antibacterial and antifungal activity [31,32]. The minimal inhibitory concentration (MIC) listed in (Table 1) showed that the test compounds **4b** and **12a** have antifungal activity about 25% of that of Clotrimazole (Canesten®, Bayer). The test Compound **11a** has antimicrobial activity against *S.aureus* 25% of that of ampicillin, while its activity is about 50% of that of ciprofloxacin. Compounds **3a**, **8**, **11b** and **12a** have antimicrobial activity against *E. coli* 50% to that of ampicillin, while the activity of these compounds is about 25% of that of ciprofloxacin. From the data given in Table 1 we also notice that compounds **3a, 4b, 6b, 8**, **12a** and **12c** have antibacterial activity against *P. aeruginosa* about 50% of that of ciprofloxacin.

EXPERIMENTAL

Chemistry. Melting points were determined with a Mel-Temp apparatus and are uncorrected. Magnetic resonance

spectra (^{1}H nmr and ^{13}C nmr spectra) were recorded on a JEOL 500 MHz spectrometer with chemical shift values reported in δ units (part per million) relative to an internal standard. Infrared (ir) data were obtained on a Perkin-Elmer 1600 series Fourier transform instrument as KBr pellets. Elemental analyses were performed on Perkin-Elmer 2400 elemental analyzer, and the found values were within ±0.3% of the theoretical values. Agilet mass selective detector using a HP-5MS column was used for separation of some compounds. Reaction progress and product purity was ascertained by TLC on silica gel-protected aluminium sheets (Type 60 GF254, Merck) and the spots were detected by exposure to UV-lamp at λ 254 nm for few seconds. The compounds were named using Chem. Draw Ultra version 9.0, Cambridge soft Corporation.

Table 1

In Vitro antimicrobial activity of the test compounds, and evaluation of the antimicrobial activity of the test compounds, and determination of the IZ (inhibition zone) and the MIC (minimal inhibitory concentration).

Test compound	*Escherichia coli*		*Staphylococcus aureus*		*Candida albicans*		*Pseudomanas aerogenisa*	
	IZ	MIC	IZ	MIC	IZ	MIC	IZ	MIC
Ampicillin	18	25	22	12.5	-----	------	-----	-----
Clotrimazole	----	-----	-----	------	29	12.5	-----	------
Ciprofloxacin	28	12.5	30	25	-----	------	38	25
3a	19	50	36	100	18	100	20	50
3c	17	100	-----	------	17	100	18	>200
4b	17	100	-----	------	17	50	23	50
5	19	100	16	100	16	>200	20	100
6b	19	100	20	100	22	100	20	50
6c	17	100	27	100	18	200	18	>200
6d	20	200	30	100	18	200	17	>200
8	18	50	26	100	16	>200	22	50
9	17	100	29	100	17	100	21	100
11a	18	100	27	50	16	>200	17	>200
11b	16	50	28	100	17	>200	22	100
11c	18	100	33	100	18	100	18	>200
12a	18	50	------	------	18	50	20	50
12b	18	>200	------	------	16	>200	20	>200
12c	16	>200	36	100	16	>200	20	50
14	16	>200	26	100	15	>200	18	>200
15	19	100	------	------	17	>200	20	100
17	17	>200	36	>200	17	>200	18	>200

General procedure for the reaction of aniline and aniline derivatives with phthalaldehydic acid 1 in methanol. A Solution of (10 mmol) of the aniline or aniline derivatives in 20 mL methanol was refluxed with (1.50 g, 10 mmol) phthalaldehydic acid for 3 hours in presence of 2 drops of acetic acid. The product which separated out on concentration was collected by filtration, dried and recrystallized from ethanol..

3-Anilino-2-benzofuran-1(3*H*)-one (3a). Compound **3a** was obtained as colorless needles, 2.05 g (91 %) yield, mp 179-180°C (Lit 179-180°C) [1-4], ir (KBr): 3332 (NH), 1740 (C=O) cm^{-1}; ^{1}H nmr (DMSO-d$_6$): δ 6.54 (d, 1H, C*H*, *J* = 9.9 Hz), 6.79 (m, 1H, Ar*H*), 6.84 (d, 1H, Ar*H*, *J* = 8.4 Hz), 6.94 (t, 1H, Ar*H*, *J* = 7.7 Hz), 7.13 (d, 1H, N*H*, D$_2$O exchangeable), 7.20 (t, 1H, Ar*H*, *J* = 7.7 Hz), 7.27 (m, 1H, Ar*H*), 7.69 (m, 2H, Ar*H*), 7.83 (m, 2H, Ar*H*). ^{13}C nmr (DMSO-d$_6$): δ 88.53, 114.39, 114.84, 119.84, 124.62, 125.43, 129.64, 131.04, 134.91, 145.67, 146.38, 169.70. *Ana*l. Calcd for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.78; H, 5.06; N, 6.03.

2-{(*E*)-[(2-Aminophenyl)imino]methyl}benzoic acid (4b). Compound **4b** was obtained as white crystal, 2.14 g (89 %) yield, mp 264-265°C. ir (KBr): 3066-2600 (NH_3^+), 1638 (COO^-) cm^{-1}. ^{1}H nmr (DMSO-d$_6$): δ. 3.58 (br.s, 3H, N*H*$_3^+$, D$_2$O exchangeable), 7.19 (m, 2H, Ar*H*), 7.54-7.59 (m, 4H, Ar*H* + C*H*), 7.65 (t, 1H, Ar*H, J* = 6.9 Hz), 7.76, 7.81 (2d, 2H, Ar*H, J* = 7.7 Hz). ^{13}C nmr (DMSO-d$_6$): δ 115.62, 122.55, 130.08, 130.17, 130.57, 130.66, 131.46, 133.73, 139.41, 151.77, 169.29. *Anal.* Calcd for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 70.23; H, 5.24; N, 11.43.

3-[(2-Mercaptophenyl)amino]-2-benzofuran-1(3*H*)-one (3c). Compound **3c** was obtained as colorless needles, 2.41 g (94 %) yield, mp 164-165°C. ir (KBr): 3409 (NH), 1717 (C=O) cm^{-1}, ^{1}H nmr (CDCl$_3$): δ 1.60 (s, 1H, S*H*, D$_2$O exchangeable), 6.99 (s, 1H, C*H*), 7.09 (t, 1H, Ar*H, J* = 7.7 Hz), 7.18-7.22 (m, 2H, Ar*H*), 7.25 (s, 1H, N*H*, D$_2$O exchangeable), 7.54-7.60 (m, 2H, Ar*H*), 7.64-7.68 (m, 2H, Ar*H*), 7.94 (d, 1H, Ar*H, J* = 7.6 Hz). ^{13}C nmr (CDCl$_3$): δ 64.54, 113.83, 118.40, 118.91, 120.49, 121.17, 121.27, 125.25, 127.99, 128.52, 131.15, 131.81, 138.39, 163.86. *Anal.* Calcd for $C_{14}H_{11}NO_2S$: C, 65.35; H, 4.31; N, 5.44. Found: C, 65.52; H, 4.13; N, 5.61.

2-[(*E*)-({2-[(3-Oxo-1,3-dihydro-2-benzofuran-1-yl)-amino]phenyl}imino)methyl]benzoic acid (5). A Solution of (1.08 g, 10 mmol) of the *o*-phenylenediamine in 20 mL methanol was refluxed with (3.0 g, 20 mmol) phthalaldehydic

acid **1** for 3 hours in presence of 2 drops of acetic acid. The product which separated out on concentration was collected by filtration, dried and recrystallized from ethanol. Compound **5** was obtained as white powder, 3.45 g (93 %) yield, mp 183-184°C. ir (KBr): 3072 (NH), 2921-2630 (NH^+), 1776 (C=O cyclic), 1708 (C=O carboxylate) cm^{-1}, ^1H nmr (DMSO-d_6): δ 4.36, 6.08 (2 br.s, 2H, N*H* + N*H*$^+$, D_2O exchangeable), 7.00 (t, 1H, C*H, J* = 7.7 Hz), 7.19 (t, 1H, Ar*H, J* = 7.7 Hz), 7.36 (s, 1H, C*H*), 7.59 (d, 1H, Ar*H, J* = 6.9 Hz), 7.63-7.67 (m, 3H, Ar*H*), 7.69-7.80 (m, 5H, Ar*H*), 7.99 (d, 1H, Ar*H, J* = 6.9 Hz), 8.05 (d, 1H, Ar*H, J* = 7.7 Hz). ^{13}C nmr (DMSO-d_6) (HMQC, HMBC): δ 84.32, 111.05, 120.42, 120.46, 123.23, 123.31, 123.78, 124.61, 125.94, 126.98, 130.67, 130.96, 131.21, 131.93, 132.38, 132.75, 135.71, 143.68, 144.49, 154.67, 167.52, 168.24. *Anal*. Calcd for $C_{22}H_{16}N_2O_4$: C, 70.96; H, 4.33; N, 7.52. Found: C, 71.17; H, 4.61; N, 7.26.

General procedure for the reaction of aniline derivatives with phthalaldehydic acid 1 for the preparation of 6. The aniline derivatives (10 mmol), phthalaldehydic acid **1** (1.50 g, 10 mmol) and *p*-toluene sulfonic acid (1.90 g, 10 mmol) were dissolved in benzene (40 ml). The mixture was heated at reflux under Dean-stark conditions for 12 hours. The resultant solution was allowed to cool, and the product which separated out on concentration was collected by filtration, dried and recrystallized from ethanol.

4*b*,5-Dihydro-isoindolo[2,1-*a*]benzimidazole-11(11*H*)-one (6). Compound **6b** was obtained as colorless crystals, 2.05 g (92 %) yield, mp 230-231°C. ir (KBr): 3435 (NH), 1765 (C=O) cm^{-1}. ^1H nmr (DMSO): δ. 5.55 (s, 1H, C*H*), 7.55-7.59 (m, 2H, Ar*H* + N*H*, D_2O exchangeable), 7.71, 7,78 (2t, 2H, Ar*H, J* = 7.7 Hz), 7.90-7.96 (m, 4H, Ar*H*), 8.11 (d, 1H, Ar*H, J* = 7.7 Hz). ^{13}C nmr (DMSO): δ 51.11, 113.50, 116.20, 123.56, 125.55, 126.20, 129.78, 130.33, 133.20, 136.33, 138.36, 145.93, 146.42, 154.71. *Anal*. Calcd for $C_{14}H_{10}N_2O$: C, 75.66; H, 4.54; N, 12.60. Found: C, 75.43; H, 4.33; N, 12.82.

Isoindolo[1,2-*b*]benzothiazol-11(4*bH*)-one (6c) [33]. Compound **6c** was obtained as colorless needles, 2.18 g (91 %) yield, mp 160-161°C. ir (KBr): 1719 (C=O) cm^{-1}. ^1H nmr (DMSO-d_6): δ. 7.12, 7.19 (2t, 2H, Ar*H, J* = 7.7 Hz), 7.29 (s, 1H, C*H*), 7.36 (d, 1H, Ar*H, J* = 7.7 Hz), 7.51 (d, 1H, Ar*H, J* = 8.5 Hz), 7.64, 7.74 (2t, 2H, Ar*H, J* = 7.7 Hz), 7.78, 7.85 (2d, 2H, Ar*H, J* = 7.7 Hz). ^{13}C nmr (DMSO-d_6): δ 69.26, 118.66, 123.88, 124.99, 125.05, 126.24, 126.54, 130.70, 131.89, 134.28, 136.31, 136.56, 143.97, 168.63. *Anal*. Calcd for $C_{14}H_9NOS$: C, 70.27; H, 3.79; N, 5.85. Found: C, 70.43; H, 3.94; N, 5.61.

Isoindolo[1,2-*b*]benzoxazole-11(4*bH*)-one (6d). Compound **6d** was obtained as colorless needles, 1.99 g (89 %) yield, mp 204-205°C. ir (KBr): 1780 (C=O) cm^{-1}. **6d^1 (isomer 1, 40%):** ^1H nmr ($CDCl_3$): δ 6.57 (s, 1H, C*H*), 7.61 (t, 2H, Ar*H, J* = 7.7 Hz), 7.65 (m, 1H, Ar*H*), 7.70-7.76 (m, 2H, Ar*H*), 7.79 (t, 1H, Ar*H, J* = 7.7 Hz), 7.92 (dd, 2H, Ar*H, J* = 7.7, 11.0 Hz). ^{13}C nmr ($CDCl_3$): δ 98.30, 124.01, 124.52, 125.70, 125.83, 126.61, 126.87, 131.56, 135.07, 144.14, 167.95. **6d^2 (isomer 2, 60%)**: ^1H nmr ($CDCl_3$): δ 6.90 (s, 1H, C*H*), 7.61 (t, 2H, Ar*H, J* = 7.7 Hz), 7.65 (m, 1H, Ar*H*), 7.70-7.76 (m, 2H, Ar*H*), 7.79 (t, 1H, Ar*H, J* = 7.7 Hz), 7.92 (dd, 2H, Ar*H, J* = 7.7, 11.0 Hz). ^{13}C nmr ($CDCl_3$): δ 99.11, 124.01, 124.52, 125.70, 125.83, 126.61, 126.87, 131.50, 135.01, 144.14, 168.26. *Anal*. Calcd for $C_{14}H_9NO_2$: C, 75.33; H, 4.06; N, 6.27. Found: C, 75.43; H, 4.24; N, 6.03. The two isomers **6d^1** and **6d^2**.were separated using GC/MS: isomer **6d^1,** t_R 5.97 min (47.999 %), m/e 223 (M^+, 7 %); isomer **6d^2,** t_R.6.50 min (52.001 %), m/e 223 (M^+, 9 %).

2-((*Z*)-{[3-(3-Chlorophenyl)-5-thioxo-1,5-dihydro-4*H*-1,2,4-triazol-4-yl]imino})benzoic acid (8). A Solution of (2.27 g, 10 mmol) of 4-amino-5-(3-chlorophenyl)-2,4-dihydro[1,2,4]-triazole-3-thione **7** in 20 mL methanol was refluxed with (1.50 g, 10 mmol) phthalaldehydic acid **1** for 3 hours in presence of 2 drops of acetic acid. The product which separated out on concentration, collected by filtration, dried and recrystallized from ethanol. Compound **8** was obtained as yellow powder, 2.22 g (62 %) yield, mp 186-187°C. ir (KBr): 3300-2596 (OH), 3111 (NH), 1705 (C=O) cm^{-1}. ^1H nmr (DMSO-d_6): δ 7.52, 7.58 (2 m, 2H, Ar*H*), 7.70 (m, 3H, Ar*H*), 7.81 (d, 1H, Ar*H*, *J* = 7.6 Hz), 7.88 (s, 1H, C*H*), 7.98 (d, 1H, Ar*H, J* = 5.4 Hz), 8.03 (d, 1H, Ar*H, J* = 6.1 Hz), 10.53 (s, 1H, O*H*, D_2O exchangeable), 14.31 (br.s, 1H, N*H*, D_2O exchangeable). *Anal*. Calcd for $C_{16}H_{11}ClN_4O_2S$: C, 53.56; H, 3.09; N, 15.61. Found: C, 53.33; H, 3.24; N, 15.43.

3-(3-Chlorophenyl)[1,2,4]triazolo[4',3':4,5][1,3,4]thiadiazolo-[2,3-*a*]isoindol-6(10*bH*)-one (9).

***Method A*:** A Solution of (2.27 g, 10 mmol) of **7** in 10 mL DMF was refluxed with (1.50 g, 10 mmol) phthalaldehydic acid **1** for 3 hours in presence of 2 drops of acetic acid. The product which separated out on concentration, collected by filtration, dried and recrystallized from ethanol. The product was poured into water, collected by filtration, dried and recrystallized from ethanol. Compound **9** was obtained as colorless crystals, 2.77 g (82 %) yield, mp 220-221°C. ir (KBr): 1784 (C=O) cm^{-1}. ^1H nmr: δ 7.61 (s, 1H, C*H*), 7.68 (t, 1H, Ar*H, J* = 6.9 Hz), 7.78 (m, 1H, Ar*H*), 7.92 (m, 2H, Ar*H*), 7.98 (m, 1H, Ar*H*), 8.12 (s, 1H, Ar*H*), 8.33 (d, 2H, Ar*H, J* = 6.1 Hz). ^{13}C nmr: δ 84.51, 124.29, 125.43, 126.91, 127.17, 127.24, 127.99, 129.64, 131.01, 133.40, 135.24, 135.43, 140.53, 146.12, 159.80, 169.29. *Anal*. Calcd for $C_{16}H_9ClN_4OS$: C, 56.39; H, 2.66; N, 16.44. Found: C, 56.43; H, 2.89; N, 16.32.

***Method B*:** Compound **7** (10 mmol), phthalaldehydic acid **1** (1.50 g, 10 mmol) and *p*-toluene sulfonic acid (1.90 g, 10 mmol) were dissolved in benzene (40 ml). The mixture was heated at reflux under Dean-stark conditions for 12 hours. The resultant solution was allowed to cool, the product that separated out on concentration was collected by filtration, dried and recrystallized from ethanol. Compound **9** was obtained as colorless crystals, 3.19 g (94 %) yield, 220-221°C. The spectral data are identical to the one given above.

General procedure for the reaction of hydrazine derivatives with phthalaldehydic acid 1 for the preparation of Schiff's base 11.

Method A: A Solution of (10 mmol) of the hydrazine derivatives in 20 mL methanol was refluxed with (1.50 g, 10 mmol) phthalaldehydic acid **1** for 3 hours in presence of 2 drops of acetic acid. The product that separated out on concentration was collected by filtration, dried and recrystallized from ethanol.

Method B: The hydrazine derivative **10** (10 mmol) when allowed to react with (1.50 g, 10 mmol) phthalaldehydic acid **1** in presence of p-toluene sulfonic acid (1.90 g, 10 mmol) in benzene (40 ml), and the mixture was heated at reflux under Dean-stark conditions for 12 hours. The resultant solution was allowed to cool, and the product that separated out on concentration was collected by filtration, dried and recrystallized from ethanol.

2-{(*E*)-[(3-Benzylquinoxalin-2-yl)hydrazono]methyl}benzoic acid (11a). Using Method A, compound **11a** was obtained as yellow powder, 3.74 g (98 %) yield, mp 195-196°C. ir (KBr): 3138-2816 (OH), 3217 (NH), 1709 (C=O) cm^{-1}. ^1H nmr (DMSO-d_6): δ 4.17 (s, 2H, CH_2), 7.17 (t, 2H, Ar*H, J* = 6.9 Hz), 7.26 (t, 3H, Ar*H, J* = 7.7 Hz), 7.35 (m, 3H, Ar*H*), 7.49-7.61 (m, 4H, Ar*H*), 7.85 (d, 1H, Ar*H, J* = 6.9 Hz), 8.47 (br.s, 1H, N*H*, D_2O exchangeable), 9.15 (s, 1H, C*H*), 11.40 (br.s, 1H, O*H*, D_2O exchangeable). ^{13}C nmr (DMSO-d_6) (DEPT, HMQC): δ 39.50 (CH_2), 115.61 (CH), 122.78 (CH), 126.82 (CH), 128.57 (CH), 128.80 (CH), 129.52 (CH), 129.75 (C, quart.), 129.96, 130.73, 132.14 (C, quart.), 135.50 (C, quart.), 138.39 (C, quart.), 146.58 (C quart.), 155.44 (CH), 159.55 (C=N), 168.84 (C=O). *Anal.* Calcd for $C_{23}H_{18}N_4O_2$: C, 72.24; H, 4.74; N, 14.65. Found: C, 72.43; H, 4.84; N, 14.43.

2-{(*E*)-[(3-Oxo-3,4-dihydroquinoxalin-2-yl)hydrazono]-methyl}benzoic acid (11b). By Method A compound **11b** was obtained as yellow powder, yield 2.75 g (89 %), mp 273-274°C. ir (KBr): 3300-2827 (OH), overimposed 3217 and 3094 (2NH), 1726 (C=O carboxyle), 1688 (C=O amide) cm^{-1}. ^1H nmr (DMSO-d_6): δ 7.16 (m, 4H, Ar*H*), 7.49 (m, 2H, Ar*H*), 7.61 (t, 1H, Ar*H, J* = 7.7 Hz), 7.85 (d, 1H, Ar*H, J* = 7.7 Hz), 8.07 (br.s, 1H, N*H*, D_2O exchangeable), 9.21 (s, 1H, C*H*), 11.40 (br.s, 1H, O*H*, D_2O exchangeable), 12.36 (br.s, 1H, N*H*, D_2O exchangeable). ^{13}C nmr (DMSO-d_6): δ 115.56, 124.00, 125.30, 126.14, 127.41, 129.30, 129.75, 130.75, 131.08, 132.39, 133.33, 135.55, 146.55, 146.83, 151.37, 168.69. *Anal.* Calcd for $C_{16}H_{12}N_4O_3$: C, 62.33; H, 3.92; N, 18.17. Found: C, 62.47; H, 4.09; N, 17.96.

Using Method B, the same product was obtained in 2.87 g (93.1%) yield.

2-{(*E*)-[(6-Benzyl-3-oxo-2,3-dihydro-[1,2,4]triazin-5-yl)-hydrazono]methyl}benzoic acid (11c). Using Method A compound **11c** was obtained as yellow powder, 2.97 g (85 %) yield, mp 219-220°C. ir (KBr): 3380 (NH), 3340-2800 (OH) and overimposed 3216 (NH), 1708 (C=O carboxyl), 1698 (C=O amide) cm^{-1}. ^1H nmr (DMSO-d_6): δ 3.86 (s, 2H, CH_2), 7.16-7.29 (m, 6H, Ar*H*), 7.51, 7.56 (2t, 2H, Ar*H, J* = 7.7 Hz), 7.83 (d, 1H, Ar*H, J* = 7.7 Hz), 8.63 (br.s, 1H, N*H*, D_2O exchangeable), 9.10 (s, 1H, C*H*), 11.02 (br.s, 1H, O*H*, D_2O exchangeable), 11.58 (s, 1H, N*H*, D_2O exchangeable). *Anal.* Calcd for $C_{18}H_{15}N_5O_3$: C, 61.89; H, 4.33; N, 20.05. Found: C, 62.11; H, 4.54; N, 19.88.

General procedure for the preparation of compound 12.

Method A: A Solution of the hydrazines derivatives **10** (10 mmol) in 10 mL dimethylformamide was refluxed with (1.50 g, 10 mmol) phthalaldehydic acid **1** for 3 hours in presence of 2 drops of acetic acid. The product was poured into water, collected by filtration, dried and recrystallized from ethanol.

Method B: The hydrazine derivative **10** (10 mmol) was also allowed to react with (1.50 g, 10 mmol) phthalaldehydic acid **1** in presence of *p*-toluene sulfonic acid (1.90 g, 10 mmol) in benzene (40 ml). The mixture was heated at reflux under Dean-stark conditions for 12 hours. The resultant solution was allowed to cool, and the product that separated out on concentration was collected by filtration, dried and recrystallized from ethanol.

2-(3-Benzylquinoxalin-2-yl)phthalazin-1(2*H*)-one (12a). Using Method A, compound **12a** was obtained as pale brown crystals, 2.84 g (78 %) yield, mp 145-146°C. ir (KBr): 1672 (C=O) cm^{-1}. ^1H nmr (DMSO-d_6): δ 4.26 (s, 2H, CH_2), 6.86 (d, 2H, Ar*H, J* = 6.9 Hz), 6.99 (m, 3H, Ar*H*), 7.90 (m, 2H, Ar*H*), 8.00 (m, 2H, Ar*H*), 8.07 (d, 1H, Ar*H, J* = 8.0 Hz), 8.16 (d, 1H, Ar*H, J* = 8.0 Hz), 8.26 (d, 2H, Ar*H, J* = 7.4 Hz), 8.47 (s, 1H, Ar*H*). ^{13}C nmr (DMSO-d_6): δ 40.81, 126.52, 127.00, 127.65, 128.02, 128.75, 129.05, 129.21, 130.08, 131.27, 132.08, 133.35, 135.13, 137.39, 140.13, 140.40, 142.06, 148.61, 154.32, 159.4. *Anal.* Calcd for $C_{23}H_{16}N_4O$: C, 75.81; H, 4.43; N, 15.38. Found: C, 76.04; H, 4.64; N, 15.12.

Using Method B the same product was obtained in yield 3.36 g (92.2 %).

3-(1-Oxophthalazin-2(1*H*)-yl)quinoxalin-2(1*H*)-one (12b). Using Method A, compound **12b** was obtained as pale buff powder, 2.15 g (74 %) yield, mp 200-201°C. ir (KBr): 3437 (NH), 1690 (C=O, NH-CO), 1674 (C=O, N-CO) cm^{-1}. ^1H nmr (DMSO-d_6): δ 7.40 (m, 2H, Ar*H*), 7.65 (br. s, 1H, Ar*H*), 7.83 (m, 1H, Ar*H*), 7.93 (m, 1H, Ar*H*), 8.03 (m, 2H, Ar*H*), 8.27 (m, 1H, Ar*H*), 8.60 (m, 1H, Ar*H*), 12.78 (br.s, 1H, N*H*, D_2O exchangeable). ^{13}C nmr (DMSO-d_6): δ 116.35, 124.58, 126.39, 127.59, 128.07, 129.48, 130.14, 130.86, 132.47, 133.35, 133.68, 135.15, 140.19, 151.08, 152.02, 159.18. *Anal.* Calcd for $C_{16}H_{10}N_4O_2$: C, 66.20; H, 3.47; N, 19.30. Found: C, 65.94; H, 3.24; N, 19.43.

2-(6-Benzyl-3-oxo-2,3-dihydro-1,2,4-triazin-5-yl)phthalazin-1(2*H*)-one (12c). Using Method A, compound **12c** was obtained as pale yellow crystals, 2.68 g (81 %) yield, 204-205°C. ir (KBr): 3230 (NH), 1701 (C=O, NH-CO), 1645 (C=O, N-CO) cm^{-1}. ^1H nmr (DMSO-d_6): δ 4.21 (s, 2H, CH_2), 7.26-7.27 (m, 5H, Ar*H*), 7.43 (m, 2H, Ar*H*), 7.52 (m, 2H, Ar*H*), 7.71 (m, 1H, Ar*H*), 11.35 (s, 1H, N*H*, D_2O exchangeable). *Anal.* Calcd for $C_{18}H_{13}N_5O_2$: C, 65.25; H, 3.95; N, 21.14. Found: C, 65.44; H, 3.84; N, 21.25.

Using Method B the same product was obtained in yield 2.32 g (70.1%).

2-[(*E*)-(Phthalazin-1-ylhydrazono)methyl] benzoic acid (14). A Solution of (1.60 g, 10 mmol) of the hydralazine **13** in 20 mL methanol was refluxed with (1.50 g, 10 mmol) phthal-aldehydic acid **1** for 3 hours in presence of 2 drops of acetic acid. The product which separated out on concentration was collected by filtration, dried and recrystallized from ethanol. Compound **14** was obtained as yellow powder, 2.48 g (85 %) yield, mp 199-200°C (Lit 198°C)[23b, 34]. ir (KBr): 3494-3266 (OH), 3051 (NH), 1692 (C=O) cm^{-1}. ^1H nmr (DMSO-d_6): δ 7.46 (t, 1H, Ar*H, J* = 7.7 Hz), 7.57 (t, 1H, Ar*H, J* = 7.7 Hz), 7.69-7.78 (m, 4H, Ar*H* + N*H*), 7.83 (d, 1H, Ar*H, J* = 7.7 Hz), 8.12 (s, 1H, Ar*H*), 8.31 (d, 1H, Ar*H, J* = 7.7 Hz), 8.65 (d, 1H, Ar*H, J* = 8.4 Hz), 9.10 (s, 1H, C*H*), 12.18 (br.s, 1H, N*H*, D_2O exchangeable). ^{13}C nmr (DMSO-d_6) (HMQC, HMBC): δ 124.44, 126.43, 127.05, 127.62, 128.58, 129.75, 130.52, 131.32, 132.00, 132.41, 133.04, 135.76, 138.55, 149.38, 152.35, 169.08. *Anal.* Calcd for $C_{16}H_{12}N_4O_2$: C, 65.75; H, 4.14; N, 19.17. Found: C, 65.54; H, 4.36; N, 19.02.

1'*H*-1,2'-Biphthalazinyl-1'-one (15). A Solution of the hydralazine **13** (1.60 g, 10 mmol) in 10 mL dimethylformamide was refluxed with (1.50 g, 10 mmol) phthalaldehydic acid **1** for 3 hours in presence of 2 drops of acetic acid. The product was poured into water and the solid collected by filtration, dried and recrystallized from ethanol. Compound **15** was obtained as white crystals, 2.30 g (84 %) yield, mp 279-280°C (Lit 279-281°C) [19,23]. ir (KBr): 1661 (C=O) cm^{-1}. ^1H nmr (DMSO-d_6): δ 7.87 (d, 1H, Ar*H, J* = 8.4 Hz), 7.95-8.02 (m, 2H, Ar*H*), 8.05-8.10 (m, 3H, Ar*H*), 8.34 (t, 2H, Ar*H, J* = 7.7 Hz), 8.69 (s, 1H, Ar*H*), 9.87 (s, 1H, Ar*H*). ^{13}C nmr: δ 124.07, 126.61, 127.69, 127.88, 128.18, 128.77, 130.35, 133.43, 134.33, 134.74, 135.16, 140.36, 153.49, 155.77, 159.77. *Anal.* Calcd for $C_{16}H_{10}N_4O$: C, 70.06; H, 3.67; N, 20.43. Found: C, 69.93; H, 3.44; N, 20.67.

Isoindolo[2',1':1,5][1,2,4]triazolo[3,4-*a*]phthalazin-7(11*bH*)-one (17). The hydralazine **13** (10 mmol), phthalaldehydic acid **1** (1.50 g, 10 mmol) and *p*-toluene sulfonic acid (1.90 g, 10 mmol) were dissolved in benzene (40 ml). The mixture was heated at reflux under Dean-stark conditions for 12 hours. The resultant solution was allowed to cool and the product that separated out on concentration was collected by filtration, dried and recrystallized from ethanol. Compound **17** was obtained as colorless needles, 2.52 g (92 %) yield, mp 198-199°C. ir (KBr): 1778 (C=O) cm^{-1}. **17^1 (isomer 1, 67%)**: ^{1}H nmr: δ 7.04 (s, 1H, C*H*), 7.69-7.32 (m, 4H, Ar*H*), 7.81-7.84 (m, 1H, Ar*H*), 7.86-7.91 (m, 4H, Ar*H*). ^{13}C nmr: δ 99.89, 124.69, 125.08, 125.45, 125.72, 126.44, 132.10, 135.81, 144.80, 168.30. **17^2 (isomer 2, 33%)**: ^{1}H nmr: δ 7.12 (s, 1H, C*H*), 7.69-7.32 (m, 4H, Ar*H*), 7.81-7.84 (m, 1H, Ar*H*), 7.86-7.91 (m, 4H, Ar*H*). ^{13}C nmr: δ 102.18, 124.69, 125.08, 125.45, 125.72, 126.40, 132.02, 135.63, 145.19, 168.46. *Anal*. Calcd for $C_{16}H_{10}N_4O$: C, 70.06; H, 3.67; N, 20.43. Found: C, 69.83; H, 3.59; N, 20.62. The two isomers **17^1** and **17^2**.were separated using GC/MS: isomer **17^1,** t_R.5.99 min (56.554) %, m/e 274 (M^+, 11 %); isomer **17^2,** t_R.6.52 min (43.446 %), m/e 274 (M^+, 8 %).

Biology. Inhibition Zone Measurement (IZ): Compounds **3a, 3c, 4b, 5, 6b-d, 8, 9, 11a-c, 12a-c, 14, 15** and **17** were *in vitro* evaluated for antimicrobial activity against the following four test organisms: *Escherichia coli (E. coli)* ATCC 25922 and *Pseudomonas aeruginosa (P. aeruginosa)* as Gram-negative bacteria, *Staphylococcus aureus* (*S. aureus*) ATCC 19433 as Gram-positive bacteria, and *Candida albicans* (*C. albicans*) as yeast-like fungi. Agar-diffusion method was used for the determination of antibacterial and antifungal activity [30]. Standard sterilized filter paper discs (5 mm diameter) impregnated with a solution of test compound in DMF (1mg/mL) was placed on an agar plate seeded with the appropriate test organisms in triplicate. The test organisms Ampicillin trihydrate, ciprofloxacin and clotrimazole were used as standard antibacterial and antifungal agents, respectively. Dimethylformamide (DMF) alone showed no inhibition zone. The plates were incubated at 37°C for 24 h. The results were recorded for each tested compound as the average diameter of inhibition zone of bacterial growth around the discs in mm (Table 1).

Minimal Inhibitory Concentration (MIC) measurements: The MIC measurement was carried out for compounds that showed significant growth inhibition zones using the twofold serial dilution technique. The compounds were prepared in concentration range (400, 200, 100, .12.5 μg/ml). The micro-dilution susceptibility test in Müller-Hinton Broth (Oxoid) and Sabouraud Liquid Medium (Oxoid) were used for the determination of antibacterial and antifungal activity [31,32]. The same test organisms were utilized. Ampicillin, ciprofloxacin and clotrimazole were used as standard antibacterial and antifungal agents, respectively. Solutions of the test compounds, ampicillin trihydrate and clotrimazole were prepared in DMSO at concentration of 1600 μg/ml. The microorganism suspensions at 10^6 CFU/ml (Colony Forming Unit/ml) concentrations were inoculated to the corresponding wells. Plates were incubated at 37°C for 24 h to 48 h. The incubation chamber was kept sufficiently humid. At the end of the incubation period, the minimal inhibitory concentrations (MIC) were determined (Table 1).

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