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Synthesis and Antimicrobial Activity of some Novel Isoindoline-1,3-Dione Derivatives

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ABSTRACT

New phthalimido derivatives incorporated with chalcone, pyrazole, pyrazoline, and pyrimidine moieties were synthesized and evaluated for their antimicrobial activities against bacterial and fungal strains. 2-{4-[1-Acetyl-5-(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazol-3-yl]phenyl} isoindoline-1,3-dione (**7**) showed broad spectrum antibacterial activity against both G+ and G- bacteria. While, (E)-2-{4-[3-(4-chlorophenyl)acryloyl]phenyl}isoindoline-1,3-dione (**4b**) showed promising antifungal activity.

Keywords

Phthalimide; Chalcones; Pyrazole; Pyrazoline; Antimicrobial agents

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INTRODUCTION

Despite of increasing synthesis of antimicrobial agents, a big problem is still present. Resistance to antimicrobial agents is considered as the real challenge in the course of treatment of infectious diseases. Structural modification of already known antimicrobial drugs by introducing different nuclei and moieties results in a strategy for the development of novel drugs.

Phthalimides are bicyclic non-aromatic nitrogen heterocycles. They are considered as starting materials and intermediates for the synthesis of different alkaloids [1] .Phthalimides have been received a great deal of attention due to their biological activities such as antibacterial [2-4] **1**, antifungal [3], anti-inflammatory [5-7], antitumor [8-11], anti HIV-1 [12,13] and anxiolytic activities [14], **Figure 1**.

Moreover, chalcones are also known to have a diverse array of biological activities among with antiallergic [15], anti-inflammatory [16,17], anticancer [18], antimalarial[19] and antimicrobial activities [20,21].

Also, chalcones are considered as useful synthons in the synthesis of many bioactive molecules such as: pyrazolines and pyrimidines.

Both pyrazolines [2] **1**, pyrazoles [22] **2** and pyrimidines [2] **1** have been proved to posses antibacterial [22,23] , antifungal [22,23] and antimicrobial [24, 25] activities, **Figure 1**.

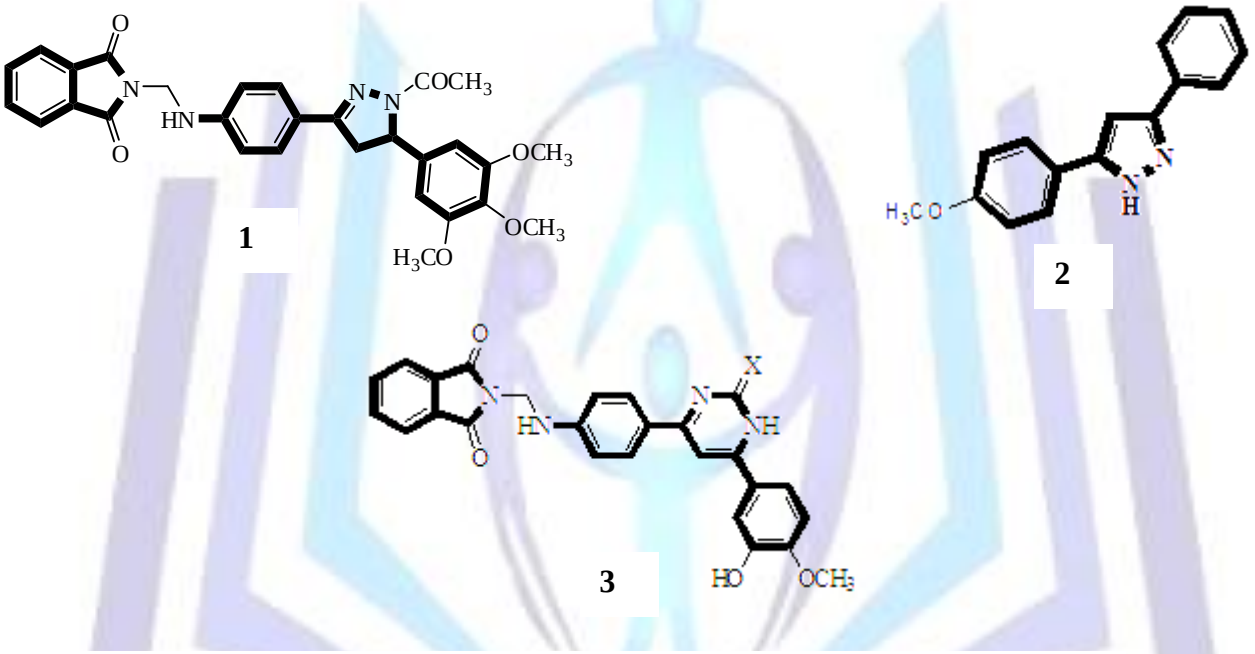

Fig.1: Previously synthesized antimicrobial agents with the required pharmacophores.

Prompted by all the above facts, we thought it is worthwhile to synthesize new compounds containing phthalimide scaffold attached to chalcone function as well as different heterocyclic rings like pyrazole, pyrazoline and pyrimidine which have been found to have an interesting profile of antimicrobial activity. The design of the new compounds is illustrated in **Figure 2**.

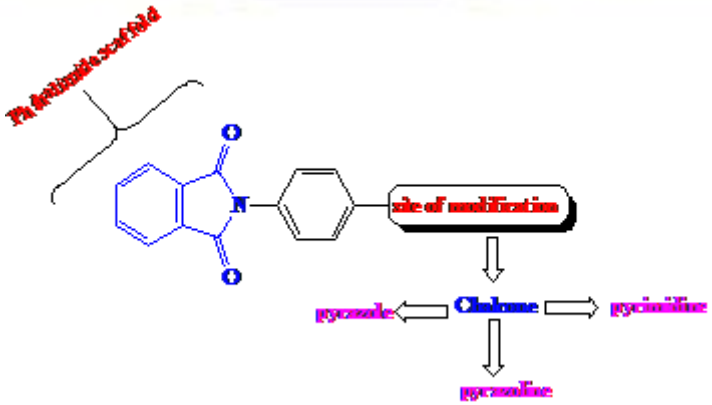

Fig. 2: General design for the newly synthesized compounds 3-8a&b.

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MATERIALS AND METHODS

Chemistry

Melting points were determined using a Griffin apparatus and were uncorrected. IR spectra were recorded on Shimadzu IR 435 spectrophotometer and values were represented in cm^{-1}, Cairo University, Cairo, Egypt, ^{1}H NMR and ^{13}C NMR were carried out on Bruker 400 MHz spectrophotometer, Beni Suef University, Beni Suef, Egypt, using TMS as an internal standard and chemical shifts were recorded in ppm on

δ scale. The electron impact (EI) mass spectra were recorded on Hewlett Packard 5988 spectrometer, Microanalytical center, Cairo University, Cairo, Egypt. Thin-layer chromatography (TLC) was performed on Merk TLC aluminium sheets silica gel 60 F254 with detection by UV quenching at 254nm to follow the course of reactions and to check the purity of products. All reagents and solvents were purified and dried by standard techniques.

General procedure for preparation of 2-(4-acetylphenyl)isoindoline-1,3-dione (3)

A mixture of phthalic anhydride **(1)** (1.48g, 0.01mol) and *p*-aminoacetophenone **(2)** (1.35g, 0.01mol) in glacial acetic acid (30 mL) was heated under reflux for 10hrs. The solid separated on hot was filtered, dried and crystallized from propanol as colorless crystals, m.p. 244-246 ^{o}C, yield 70%. Analysis: for $C_{16}H_{11}NO_3$, M.Wt. 265.26, calculated: C, 72.45; H, 4.18; N, 5.28. Found: C, 72.31; H, 4.10; N, 5.26. IR (KBr, cm^{-1}): 1782, 1714, 1677 (3C=O). ^{1}H NMR (DMSO-d_6, *δ ppm*): 2.63 (s, 3H, CH_3), 7.64 (d, 2H, *J*= 8.4 Hz, $H_{aromatic}$), 7.93 (m, 2H, $H_{aromaic}$), 8.00 (m, 2H, $H_{aromatic}$), 8.12 (d, 2H, *J*= 8.4 Hz, $H_{aromatic}$). MS: (*m/z*) 266 [$(M+1)^{+\cdot}$, 5.87%], 265 [$(M)^{+\cdot}$, 26.65%], 76 [$(C_6H_4)^{+\cdot}$, 100%].

***General procedure for preparation of* compounds 4a-d**

A mixture of compound **3** (2.65g, 0.01 mol) and the appropriate aldehyde (0.01 mol) in 5% ethanolic potassium hydroxide (30 mL) was stirred at room temperature for 24hrs. The reaction mixture was poured onto ice cold water and neutralized with dilute hydrochloric acid. The separated solid was filtered off, dried and crystallized from acetone to give compounds **4a-d**.

(E)-2-{4-[3-(4-Hydroxyphenyl)acryloyl]phenyl}isoindoline-1,3-dione (4a)

As brown crystals, m.p. 214-216^{o}C, yield 59%. Analysis: for $C_{23}H_{15}NO_4$, M.Wt. 369.37, calculated: C, 74.79; H, 4.09; N, 3.79. Found: C, 74.66; H, 3.95; N, 3.51. IR (KBr, cm^{-1}): 3247 (OH), 1713, 1670, 1652 (3C=O). ^{1}H NMR (DMSO-d_6, *δ ppm*): 7.53 (d, 2H, *J*= 6 Hz, $H_{aromatic}$), 7.57 (m, 4H, $H_{aromatic}$), 7.61 (m, 4H, $H_{aromatic}$), 7.67 (d, 1H, *J*= 14 Hz, =CH), 7.89 (d, 1H, *J*= 10.4 Hz, =CH), 7.93 (d, 2H, *J*= 7.6 Hz, $H_{aromatic}$), 10.71 (s, 1H, OH, exchangeable with D_2O). MS: (*m/z*) 370 [$(M+1)^{+\cdot}$, 48.97%], 369 [$(M)^{+\cdot}$, 41.38%], 119 [$(C_7H_5NO)^{+\cdot}$, 100%].

(E)-2-{4-[3-(4-Chlorophenyl)acryloyl]phenyl}isoindoline-1,3-dione (4b)

As yellow crystals, m.p. 220-222 ^{o}C, yield 65%. Analysis: for $C_{23}H_{14}ClNO_3$, M.Wt. 387.82, calculated: C, 71.23; H, 3.64; N, 3.61. Found: C, 71.52; H, 3.34; N, 3.59. IR (KBr, cm^{-1}): 1779, 1713, 1655 (3C=O). ^{1}H NMR (DMSO-d_6, *δ ppm*): 7.26 (m, 4H, $H_{aromatic}$), 7.46 (d, 2H, *J*= 7.64 Hz, $H_{aromatic}$), 7.63 (d, 1H, *J*= 14.8 Hz, =CH), 7.84 (d, 1H, *J*= 15.2 Hz, =CH), 7.91 (m, 4H, $H_{aromatic}$), 7.97 (m, 2H, $H_{aromatic}$). MS: (*m/z*) 389 [$(M+1)^{+\cdot}$, 7.42%], 388 [$(M)^{+\cdot}$, 5.79%], 80 [$(C_4O_2)^{+\cdot}$, 100%].

(E)-2-{4-[3-(4-(Dimethylamino)phenyl)acryloyl]phenyl}isoindoline-1,3-dione (4c)

As dark brown crystals, m.p. 153-155 ^{o}C, yield 49 %. Analysis: for $C_{25}H_{20}N_2O_3$, M.Wt. 396.15, calculated: C, 75.74; H, 5.08; N, 7.07. Found: C, 75.63; H, 4.97; N, 6.87. IR (KBr, cm^{-1}): 1714, 1670, 1652 (3C=O). ^{1}H NMR (DMSO-d_6, *δ ppm*): 3.01 (s, 6H, 2CH3), 7.56 (m, 4H, , $H_{aromatic}$), 7.67 (d, 1H, *J*= 14.8 Hz, =CH), 7.83 (d, 1H, *J*= 14 Hz, =CH), 8.12 (m, 8H, $H_{aromatic}$). MS: (*m/z*) 397 [$(M+1)^{+\cdot}$, 55.56%], 396 [$(M)^{+\cdot}$, 73.74%], 82 [$(C_4H_2O_2)^{+\cdot}$, 100%].

(E)-2-{4-[3-(4-Nitrophenyl)acryloyl]phenyl}isoindoline-1,3-dione (4d)

As dark yelow crystals, m.p. 195-197 ^{o}C, yield 62 %. Analysis: for $C_{23}H_{14}N_2O_5$, M.Wt. 398.37, calculated: C, 69.34; H, 3.54; N, 7.03. Found: C, 69.61; H, 3.33; N, 6.95. IR (KBr, cm^{-1}): 1713, 1669, 1653 (3C=O). ^{1}H NMR (DMSO-d_6, *δ ppm*): 7.39 (d, 2H, *J*= 6 Hz, $H_{aromatic}$), 7.73 (d, 1H, *J*= 14.8 Hz, =CH), 7.88 (d, 1H, *J*= 15.6 Hz, =CH), 7.92 (m, 5H, $H_{aromatic}$), 8.20 (m, 5H, $H_{aromatic}$). MS: (*m/z*) 399 [$(M+1)^{+\cdot}$, 0.86%], 398 [$(M)^{+\cdot}$, 56.03%], 80 [$(C_4O_2)^{+\cdot}$, 100%].

General procedure for preparation of 2-{4-[3-(4-chlorophenyl)-1H-pyrazol-5-yl]phenyl}isoindoline-1,3-dione (5)

A mixture of the chalcone derivative **4b** (3.87g, 0.01 mol) and hydrazine hydrate 99% (2.5g, 0.05 mol) in absolute ethanol (30 mL) was heated under reflux for 8hrs. The reaction mixture was poured onto ice cold water. The formed solid was filtered off, dried and crystallized from ethanol to give compound **5**. As white crystals, m.p. 239-241 ^{o}C, yield 45 %. Analysis: for $C_{23}H_{14}ClN_3O_2$, M.Wt. 399.83, calculated: C, 69.09; H, 3.53; N, 10.51. Found: C, 69.22; H, 3.75; N, 10.55. IR (KBr, cm^{-1}): 2334 (NH), 1713, 1655 (2C=O). ^{1}H NMR (DMSO-d_6, *δ ppm*): 7.51 (d, 2H, *J*= 8 Hz, $H_{aromatic}$), 7.59 (m, 4H, $H_{aromatic}$), 7.67 (m, 4H, $H_{aromatic}$), 7.78 (s, 1H, $H_{pyrazole}$), 7.87 (d, 2H, *J*= 8.4 Hz, $H_{aromatic}$), 10.51 (s, 1H, NH, exchangeable with D_2O). ^{13}C NMR (DMSO-d_6, *δ ppm*): 100.79, 123.20, 126.25, 127.33, 129.39, 129.78, 130.41, 132.69, 132.70, 133.22, 134.34, 138.99, 147.72, 149.45, 168.38. MS: (*m/z*) 401 [$(M+1)^{+\cdot}$, 22.39%], 104 [$(C_7H_6N)^{+}$, 100%].

General procedure for preparation of 5-(4-chlorophenyl)-3-[4-(1,3-dioxoisoindolin-2-yl)phenyl]-1H-pyrazole-1-carbaldehyde (6)

A mixture of the chalcone derivative **4b** (3.87g, 0.01 mol) and hydrazine hydrate 99% (2.5g, 0.05 mol) in formic acid (30 mL) was heated under reflux for 10hrs. The reaction mixture was poured onto ice cold water. The formed solid was filtered off, dried and crystallized from ethanol to give compound **6**. As yellow crystals, m.p. 237-239^{o}C, yield 49 %. Analysis: for $C_{24}H_{14}ClN_3O_3$, M.Wt. 427.84, calculated: C, 67.38; H, 3.30; N, 9.82. Found: C, 67.52; H, 3.71; N, 9.73. IR (KBr, *cm*$^{-1}$): 1726, 1712, 1654 (3C=O). ^{1}H NMR (DMSO-d_6, *δ ppm*): 7.38 (d, 2H, *J*= 8.4 Hz, $H_{aromatic}$), 7.76 (m, 2H, $H_{aromatic}$), 7.94 (m, 7H, $H_{aromatic}$), 8.16 (m, 2H, $H_{aromatic}$), 8.87 (s, 1H, CHO). ^{13}C NMR (DMSO-d_6, *δ ppm*): 103.21, 124.38, 126.66, 127.86, 129.94, 130.25, 130.49, 130.63, 130.75, 132.03, 140.83, 145.50, 148.44, 167.31, 187.77. MS: (*m/z*) 427 [$(M)^{+\cdot}$, 23.85%], 69 [$(C_2HN_2O)^{+}$, 100%].

General procedure for preparation of 2-{4-[1-acetyl-5-(4-chlorophenyl)-4,5-dihydro-1H-pyrazol-3-yl]phenyl}isoindoline-1,3-dione (7)

A mixture of the chalcone derivative **4b** (3.87g, 0.01 mol) and hydrazine hydrate 99% (2.5g, 0.05 mol) in glacial acetic acid (30 mL) was heated under reflux for 10hrs. The reaction mixture was poured onto ice cold water. The formed solid was filtered off, dried and crystallized from ethanol to give compound **7**. As brown crystals, m.p. 278-280 ^{o}C, yield 52 %. Analysis: for $C_{25}H_{18}ClN_3O_3$, M.Wt. 443.88, calculated: C, 67.65; H, 4.09; N, 9.47. Found: C, 67.42; H, 3.81; N, 9.33. IR (KBr, *cm*$^{-1}$): 1727, 1690, 1658 (3C=O). ^{1}H NMR (DMSO-d_6, *δ ppm*): 2.28 (2, 3H, CH_3), 3.11 (dd, 1H, $H^4_{pyrazoline}$, *J*= 18.4, 4 Hz), 3.81 (dd, 1H, $H^4_{pyrazoline}$, *J*= 11.6, 6 Hz), 5.51 (dd, 1H, $H^5_{pyrazoline}$, *J*= 10.8, 7.6 Hz), 7.19 (d, 2H, *J*= 8 Hz, $H_{aromatic}$), 7.36 (d, 2H, *J*= 8 Hz, $H_{aromatic}$), 7.66 (m, 4H, $H_{aromatic}$), 7.71 (d, 2H, *J*= 8.8 Hz, $H_{aromatic}$), 7.88 (d, 2H, *J*= 8 Hz, $H_{aromatic}$). MS: (*m/z*) 444 [$(M)^{+\cdot}$, 11.42%], 313 [$(C_{19}H_{11}N_3O_2)^{+\cdot}$, 100%].

General procedure for preparation of compounds 8a&b

A mixture of the chalcone derivative **4b** (3.87g, 0.01 mol) and urea or thiourea (0.01 mol) in absolute ethanol (30 mL) containing sodium hydroxide (1g) was heated under reflux for 10hrs. The reaction mixture was poured onto ice cold water, neutralized with dilute hydrochloric acid. The formed solid was filtered off, dried and crystallized from ethanol to give compounds **8a&b**.

2-{4-[6-(4-chlorophenyl)-2-oxo-1,2-dihydropyrimidin-4-yl]phenyl}- isoindoline-1,3-dione (8a)

As brown crystals, m.p. 258-260 ^{o}C, yield 45 %. Analysis: for $C_{24}H_{14}ClN_3O_3$, M.Wt. 427.07, calculated: C, 67.38; H, 3.30; N, 9.82. Found: C, 67.12; H, 3.52; N, 9.76. IR (KBr, *cm*$^{-1}$): 3347 (NH), 1730, 1686 (2C=O). ^{1}H NMR (DMSO-d_6, *δ ppm*): 7.58 (m, 4H, $H_{aromatic}$), 7.67 (m, 4H, $H_{aromatic}$), 7.89 (m, 4H, $H_{aromatic}$), 8.21 (s, 1H, $H_{pyrimidine}$), 10.75 (s, 1H, NH, exchangeable with D_2O). MS: (*m/z*) 427 [$(M)^{+\cdot}$, 10.27%], 77 [$(C_6H_5)^{+\cdot}$, 100%].

2-{4-[6-(4-chlorophenyl)-2-thioxo-1,2-dihydropyrimidin-4-yl]phenyl}- isoindoline-1,3-dione (8b)

As brown crystals, m.p. 232-234 ^{o}C, yield 49 %. Analysis: for $C_{24}H_{14}ClN_3O_2S$, M.Wt. 443.90, calculated: C, 64.94; H, 3.18; N, 9.47. Found: C, 65.10; H, 3.35; N, 9.52. IR (KBr, *cm*$^{-1}$): 3348 (NH), 1731, 1685 (2C=O), 1229 (C=S). ^{1}H NMR (DMSO-d_6, *δ ppm*): 7.62 (m, 4H, $H_{aromatic}$), 7.82 (m, 4H, $H_{aromatic}$), 7.92 (m, 4H, $H_{aromatic}$), 8.00 (s, 1H, $H_{pyrimidine}$), 10.69 (s, 1H, NH, exchangeable with D_2O). MS: (*m/z*) 444 [$(M)^{+\cdot}$, 15.16%], 77 [$(C_6H_5)^{+\cdot}$, 100%].

Antimicrobial evaluation

A. Determination of antimicrobial activities:

The MIC and MBCs of test compounds were determined against four reference bacterial strains: two gram positive bacteria, *Staphylococcus aureus* (ATCC 6538) and *Bacillus subtilis* (ATCC 6633), and two gram negative bacteria, *Escherichia coli* (ATCC 5087) and *Pseudomonas aeruginosa* (ATCC 9027). *Candida albicans* (ATCC 60193) and *Aspergillus niger* (ATCC 171809) were choose as standard strains of fungi. All assays were conducted in triplicates under strict aseptic conditions.

B. Determination of the Minimum Inhibitory Concentrations (MICs):

The preliminary MICs were firstly determined by the microbroth dilution method as per Clinical Laboratory Standard Institute guidelines (CLSI, 2009) [26]. Briefly, 100 µL of double strength DMSO (Sigma-Aldrich, Germany) were placed in each well of 96-well microtiter plate. Aliquot of 100 µL of the solution to be tested were added to the first column. Then 2-fold dilutions were carried out from one well to the next up to final well in each row for each tested compound. MICs were then determined using agar disc diffusion technique according to Kirby Bauer disc diffusion method with some modifications according to (CLSI 2009) [26]. A total of 15 mL of molten (45^{o}C) Nutrient agar (sigma-Aldrich, Germany) were added into sterilized petri-dishes, allowed to solidify then 33.3µL of each bacteria and fungi suspension (10^5 CFU mL^{-1}) were surface inoculated. Finally, discs were wet with 10µL of each dilution of the tested solution then placed into each plate and were allowed to stand for 10 min and then all plates were transferred and incubated at 37^{o}C for 24h for bacterial strains and 30^{o}C for 48h fungal strains under aerobic conditions. The zones of inhibitions were then measured in mm.

The results are summarized in **Table 1.** The zones of inhibition for most active compounds are represented in **Figure 3.**

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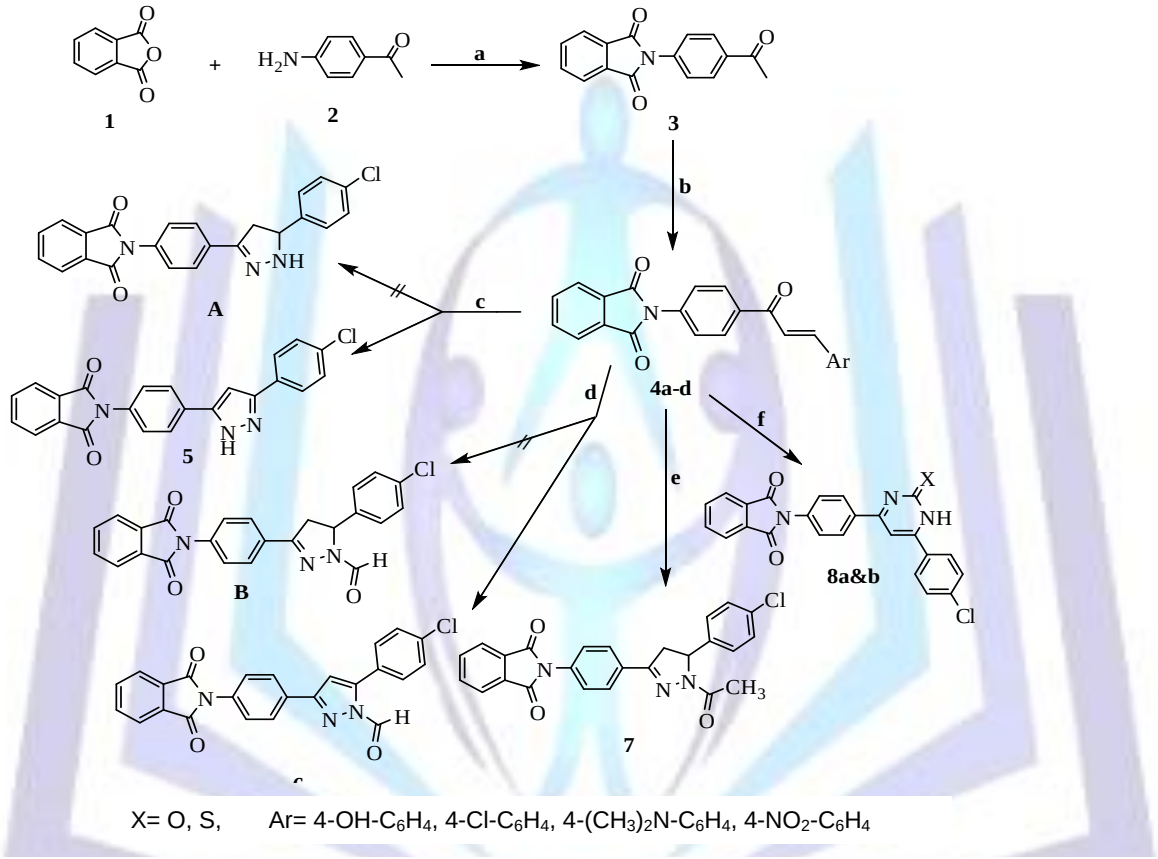
RESULTS AND DISCUSSION

Chemistry:

In the present work, starting from 2-(4-acetylphenyl)isoindoline-1,3-dione **(3)**, different compounds of phthalimide derivatives were prepared.

Thus, the reaction of **3** with different aromatic aldehydes, namely: 4-hydroxy, 4-chloro, 4-*N*,*N*-dimethylamino and 4-nitrobenzaldehyde resulted in the formation of chalcone derivatives **4a-d**. Merging pyrazole moiety with phthalimide core in **5** and **6** was obtained from the reaction of compound **4b** with hydrazine hydrate 99% in either absolute ethanol or

formic acid, respectively rather than pyrazoline derivatives **A** and **B**, sequentially (confirmed by IR, ^{1}H NMR, ^{13}C NMR and Mass spectroscopy). On the other hand, compound **7** was yielded from **4b** and hydrazine hydrate 99% in glacial acetic acid. Finally, compound **4b** reacted with both urea and thiourea to give 2-thio(oxo)- 1,2-dihydropyrimidine derivatives **8a&b**, respectively. (**Scheme 1**)



Scheme 1: *Reagents and Conditions:* **a,** gl. acetic acid, reflux 10hrs; **b,** ArCHO, KOH, absolute ethanol, stirring 24hr; **c,** NH_2NH_2, absolute ethanol, reflux 8hrs; **d,** NH_2NH_2, formic acid, reflux 10hrs; **e,** NH_2NH_2, gl. acetic acid, reflux 10hrs; **f,** urea or thiourea, NaOH, absolute ethanol, reflux 10hrs.

Biological activity

Antimicrobial activity

All of the newly synthesized compounds were evaluated for their *in vitro* antibacterial activity against two gram positive bacterial strains (*S. aureus* and *B. subtlis*), and two strains of gram negative bacteria (*E. coli* and *P. aeruginosa*). They were also tested for their in vitro antifungal activity against two mycotic strains namely, *C. albicans* and *A. niger*. Determination of the preliminary antibacterial and antifungal activity were investigated using agar-diffusion method. The results were recorded for each tested compound as the average diameter of inhibition zones (IZ) of bacterial or fungal growth around the discs in mm, **Table 1**.

Based on the data obtained from **Table 1**, Pyrazoline derivative **7** was the most active among test compounds as antibacterial agent showing broad spectrum antibacterial activities against (G+) and (G–) strains.

While, the tested compounds (**4a**, **4b**, **4d** and **8a**) showed narrow spectrum (G+) antibacterial activities for (*S. aureus* and *B. subtils*).

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One of the tested compounds **4b** exhibited antifungal activities against *C. albicans* and *A. niger* (IZ = 20, 12mm, respectively).

The chalcone derivative **4b**, pyrazoline containing compound **7** and pyrimidinone derivative **8a** possessed activity against spore forming organisms (*A. niger* and/or *B. subtilis*).

No antimicrobial activities were detected in the tested compounds { (4-*N*,*N*-dimethylamino chalcone derivative) **4c**, (Pyrazole analogue) **5**, (*N*-formyl pyrazole derivative) **6** and (thioxopyrimidinone analogue) **8b**} for *S. aureus*, *B. subtilis, E. coli*, *P. aeruginosa*, *C. albicans* and *A. niger* during whole concentrations.

Table 1: Antimicrobial activity of the newly synthesized compounds against G+, G- and fungal strains expressed as IZ (mm).

Compd. no.	Gram +ve		Gram -ve		Fungi	
	S. aureus	***B. subtilis***	***P.aeruginosa***	***E. coli***	***C. albicans***	***A. niger***
4a	11	0	0	0	0	0
4b	12	0	0	0	20	12
4c	0	0	0	0	0	0
4d	11	0	0	0	0	0
5	0	0	0	0	0	0
6	0	0	0	0	0	0
7	10	11	10	15	0	0
8a	12	13	0	0	0	0
8b	0	0	0	0	0	0

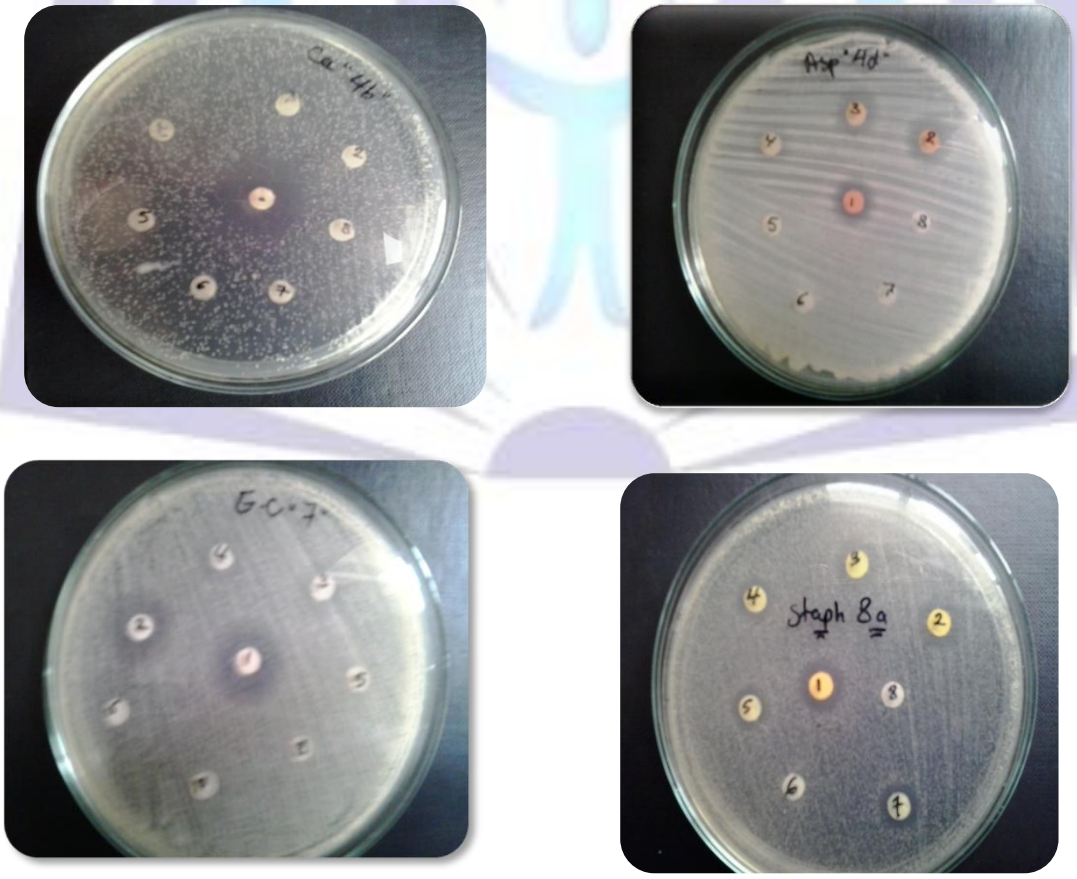

Figure 3: Zone of inhibition at different concentrations (mm) by paper disc diffusion.

CONCLUSION

Antibacterial and antifungal activities for all the newly synthesized phthalimido derivatives were *in vitro* evaluated. The most active compound as antibacterial agent against both G+ and G- strains was **7**. Chalcone derivative **4b** possessed potent antimicrobial activity against fungi and G+ organisms. Moreover, the two other chalcone derivatives **4a** and **4d** shared their activities with **8a** against G+ bacteria.Whereas, no antimicrobial activities were observed in compounds **4c**, **5**, **6** and **8b**.

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