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Der Pharma Chemica, 2013, 5(5):97-108
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

Synthesis, characterization and antimicrobial activity of some novel isoindole-1,3-dione derivatives

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ABSTRACT

The present investigation, represents the synthesis of new derivativescontaining2-((4-acetyl phenyl amino)methyl)isoindoline-1,3-dione moiety incorporated with different heterocycles such as pyrazoline, isoxazoline, pyrimidine, pyridones and iminopyridine. Spectral techniques of IR, ^{1}H NMR, Mass spectroscopy and elemental analyses were used to characterize the synthesized compounds.Most of the synthesized compounds were tested for their antimicrobial activity against a variety of gram positive and gram negative bacteria as well as fungal isolates using Ciprofloxacin and Ketoconazole as reference drugs. Some of the tested compounds showed potent activity and could be considered as promising antibacterial and antifungal agents.

Keywords: Phthalimide, Heterocyclic derivatives, Antibacterial agents, Antifungal agents

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INTRODUCTION

Infectious and parasitic diseases are responsible for 23% of percentage of worldwide deaths and the second ranking cause of death according to the World Health Organization. The other issue related to infectious diseases are their emerging resistance to the used antimicrobial agents [1]. Therefore, the need to the discovery of new antimicrobial agents is a necessity. Phthalimides are a class of compounds well known for a long time and they have attracted the scientists' attention in the past decades, mainly due to their variety of applications in different fields particularly as organic synthesis [2-5] and pharmaceuticals [6-37]. Manyreports showed that compounds containing phthalimide subunit **1** (scheme 1) have been described as a scaffold to design new prototypes of drug-candidates with different biological activities and are used in different diseases as infectious diseases [6-10], tuberculosis [11,12], AIDS [13-15], tumors [16-19], multiple myeloma [21-23], inflammatory diseases [24-26], asthma [27], hyperlipidemia [28-30], diabetes [31], convulsion [32,33], depression [34] and anxiety [35]. Also some phthalimide derivatives have inhibitory activity against Rho kinase [36] and acetyl cholinesterase [37]. Based on the previous outcomes, we synthesized a series of phthalimide derivatives attached to various heterocyclic rings that have been proved to possess antibacterial and antifungal activity such as pyrazoline [38], oxazoline [39], pyrimidine [40], morpholine [41], piperazine [42], pyridine [43,44] and pyrane [45] as well as chalcones [46] and carboximde [47] functionalities aiming to synergize the antimicrobial activity,. The newly synthesized derivatives were then evaluated for their antimicrobial activity against different gram negative, gram positive bacteria, yeasts and fungi.

MATERIALS AND METHODS

Chemistry

Melting points were determined using an electro-thermal capillary melting point apparatus and remained uncorrected. Microanalyses were carried out at the Micro Analytical Center, Cairo University. Infrared spectra were acquired with a Jasco FT/IR-6100 using KBr discs.^{1}H NMR spectra were acquired with Jeol EX 500 MHz spectrometers, using TMS as internal standard. Mass spectra were acquired with a Jeol JMS-AX 500. All reactions were followed and checked by TLC (aluminium-backed sheets, Merck plates) with chloroform-methanol 9:1 (v/v) as a mobile phase, the spots were detected by exposure to UV analysis lamp λ 254/366 nm for few seconds. Iodine vapour was used for detection the plates.

2-{[(4-acetylphenyl)amino]methyl}-1H-isoindole-1,3(2H)-dione (***2***)
This compound was prepared according to the reported method [48]

General procedure for preparation of compounds $\mathbf{3_{a-e}}$
A mixture of compound **2**(1g, 3.4mmol) and the appropriate aldehydes, namely:vanillinaldehyde, veratraldehyde, 3,4,5-trimethoxybenzaldehyde, N,N-dimethylaminobenzaldehyde and 4-chlorobenzaldehyde (3.4mmol) in 5% ethanolic sodium hydroxide (15 mL) was heated under reflux and stirring for 10h. The reaction mixture was poured onto ice/water and neutralized with diluted hydrochloric acid. The formed solid was filtered off,washed with water, air dried and recrystallized from the proper solvent to give the title compounds $\mathbf{3_{a-e}}$.

2-[({4-[3-(4-hydroxy-3-methoxyphenyl)prop-2-enoyl]phenyl}amino)methyl]-1H-isoindole-1,3(2H)-dione($\mathbf{3_a}$)
Crystallized from methanol, red crystals, m.p.134°C, yield 70%. Analysis: for $C_{25}H_{20}N_2O_5$, M.Wt.428.14, calculated: C, 70.08; H, 4.71; N, 6.54. Found: C, 70.12; H, 4.59; N, 6.50. IR (KBr, cm^{-1}): 3474 (OH), 3343 (NH), 3061 (CH aromatic), 2954 (CH aliphatic), 1774, 1712, 1660 (3C=O). ^{1}H NMR (DMSO-d_6, δ *ppm*): 3.91 (3H, s, OCH_3), 5.10 (2H, s, CH_2), 6.52-6.60 (2H, dd, HC=CH), 7.15-7.92 (11H, m, $H_{aromatic}$), 8.65 (1H, s, NH exchangeable with D_2O), 9.96 (1H, s, OH exchangeable with D_2O). MS: (*m/z*) ~ $[M+1]^+$429 (37.5%).

2-[({4-[3-(3,4-dimethoxyphenyl)prop-2-enoyl]phenyl}amino)methyl]-1H-isoindole-1,3(2H)- dione ($\mathbf{3_b}$*)*
Crystallized from methanol, dark yellow crystals, m.p. 95°C, yield 60%. Analysis: for $C_{26}H_{22}N_2O_5$, M.Wt.442.15, calculated: C, 70.58; H, 5.01; N, 6.33. Found: C, 70.72; H, 5.20; N, 6.15. IR (KBr, cm^{-1}): 3357 (NH), 3059 (CH aromatic), 2939 (CH aliphatic), 1770, 1711, 1660 (3C=O). ^{1}H NMR (DMSO-d_6, δ *ppm*): 3.95 (3H, s, OCH_3), 3.97 (3H, s, OCH_3), 5.28 (2H, s, CH_2), 6.89-7.00 (2H, dd, HC=CH), 7.16-8.18 (11H, m, $H_{aromatic}$), 9.86 (1H, s, NH exchangeable with D_2O). MS: (*m/z*) ~$[M-CH_3]^+$ 427 (10.5%).

2-[({4-[3-(3,4,5-trimethoxyphenyl)prop-2-enoyl]phenyl}amino)methyl]-1H-isoindole-1,3(2H)-dione($\mathbf{3_c}$*)*
Crystallized from methanol, dark red crystals, m.p. 157°C, yield 63%. Analysis: for $C_{27}H_{24}N_2O_6$, M.Wt.472.16, calculated: C, 68.63; H, 5.12; N, 5.93. Found: C, 68.78; H, 5.03; N, 6.11. IR (KBr, cm^{-1}): 3362 (NH), 3058 (CH aromatic), 2945 (CH aliphatic), 1771, 1713, 1656 (3C=O).^{1}H NMR (DMSO-d_6, δ *ppm*): 3.87 (3H, s, OCH_3), 3.94 (6H, s, $2OCH_3$), 5.21 (2H, s, CH_2), 6.51-6.62 (2H, dd, HC=CH), 6.82-7.96 (10H, m, $H_{aromatic}$), 9.65 (1H, s, NH exchangeable with D_2O). MS: (*m/z*) ~$[M+3]^+$ 475 (4.8%),.

2-[({4-[3-(4-{dimethylamino}phenyl)prop-2-enoyl]phenyl}amino)methyl]-1H-isoindole-1,3(2H)-dione ($\mathbf{3_d}$*)*
Crystallized from isopropanol, brick red crystals, m.p. 112°C, yield 75%. Analysis: for $C_{26}H_{23}N_3O_3$, M.Wt.425.17, calculated: C, 73.39; H, 5.45; N, 9.88. Found: C, 73.52; H, 5.29; N, 9.65. IR (KBr,cm^{-1}): 3352 (NH), 3065 (CH aromatic), 2952 (CH aliphatic), 1770, 1709, 1658 (3C=O). ^{1}H NMR (DMSO-d_6, δ *ppm*): 3.08 (6H, s, $2CH_3$), 5.10 (2H, s, CH_2), 6.50-6.61 (2H, dd, HC=CH), 6.67-7.86 (12H, m, $H_{aromatic}$), 9.74 (1H, s, NH exchangeable with D_2O). MS: (*m/z*) ~$[M]^+$ 425 (5.1%).

2-[({4-[3-(4-chlorophenyl)prop-2-enoyl]phenyl}amino)methyl]-1H-isoindole-1,3(2H)-dione ($\mathbf{3_e}$*)*
Crystallized from methanol, yellow crystals, m.p. 96°C, yield 65%. Analysis: for $C_{24}H_{17}ClN_2O_3$, M.Wt.416.09, calculated: C, 69.15; H, 4.11; N, 6.72. Found: C, 68.96; H, 4.23; N, 6.84. IR (KBr, cm^{-1}): 3367 (NH), 3060 (CH aromatic), 2934 (CH aliphatic), 1772, 1711, 1653 (3C=O). ^{1}H NMR (DMSO-d_6, δ *ppm*): 5.02 (2H, s, CH_2), 6.49-6.60 (2H, dd, HC=CH), 7.16-7.91 (12H, m, $H_{aromatic}$), 9.73 (1H, s, NH exchangeable with D_2O). MS: (*m/z*) ~$[M]^+$ 416 (5%), 418 (1.5%).

General procedure for preparation of compounds $\mathbf{4}_{a-d}$

A mixture of the chalcone derivatives $\mathbf{3}_{c,e}$(1mmol) and hydrazine hydrate 99% (0.25 mL, 5mmol)in glacial acetic acid (15 mL) was refluxed for 4 h. Upon reaction completion, the reaction mixture waspoured onto ice/water and the formed precipitate was filtered off and recrystallized from the proper solvents to obtain the desired derivatives $\mathbf{4}_{a,b}$, respectively.The derivative $\mathbf{3}_{d}$was treated with hydrazine hydrate inabsolute ethanol (10 mL) and heated under reflux for 8h. Then the reaction mixture was cooled andconcentrated, the formed precipitate was filtered off, dried and crystallized from isopropanol to give compound $\mathbf{4}_{d}$.

2-[({4-[5-(3,4,5-trimethoxyphenyl)-1-acetyl-4,5-dihydro-1H-pyrazol-3-yl] phenyl}amino)methyl]-1H-isoindole-1,3(2H)-dione (***4****a*)

Crystallized from methanol, buff crystals, m.p. 118°C, yield 70%. Analysis: for $C_{29}H_{28}N_4O_6$, M.Wt. 528.20, calculated: C, 65.90; H, 5.34; N, 10.60. Found: C, 66.21; H, 5.25; N, 10.92. IR (KBr, *cm*$^{-1}$): 3339 (NH), 3039 (CH aromatic), 2934 (CH aliphatic), 1772, 1714, 1658 (3C=O), 1593 (C=N). ^{1}H NMR (DMSO-d_6, *δ ppm*): 2.05-2.08, 2.16-2.21 (2H, dd, dd, C_4-H_2 of pyrazoline), 2.32 (3H, s, CH_3), 3.76 (3H, s, OCH_3), 3.84 (6H, s, $2OCH_3$), 3.92 (1H, t, C_5-H of pyrazoline), 5.43 (2H, s, CH_2), 6.45 (1H, s, NH exchangeable with D_2O), 6.97-8.16 (10H, m, $H_{aromatic}$).

2-[({4-[5-(4-chlorophenyl)-1-acetyl-4,5-dihydro-1H-pyrazol-3-yl]phenyl} amino)methyl]-1H-isoindole-1,3(2H)-dione (***4****b*)

Crystallized from methanol, buff crystals, m.p. 223°C, yield 60%. Analysis: for $C_{26}H_{21}ClN_4O_3$, M.Wt.472.13, calculated: C, 66.03; H, 4.48; N, 11.85. Found: C, 65.86; H, 4.75; N, 11.98.IR (KBr, *cm*$^{-1}$): 3255 (NH), 3097 (CH aromatic), 2924 (CH aliphatic), 1771, 1713, 1691 (3C=O), 1593 (C=N). ^{1}H NMR (DMSO-d_6, *δ ppm*): 1.80 (3H, s, CH_3), 1.94-2.03, 2.17-2.25 (2H, dd,dd,C_4-$H_2$of pyrazoline), 3.84 (1H, t, C_5-Hof pyrazoline), 5.47 (2H, s, CH_2), 7.17-8.14 (12H, m, $H_{aromatic}$), 9.65 (1H, s, NH exchangeable with D_2O). MS: (*m/z*) ~[M-CH_3]$^+$ 457 (9.8%), 459 (3.3%).

2-{[(4-{5-[4-(dimethylamino)phenyl]-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl}phenyl)amino]methyl}-1H-isoindole-1,3(2H)-dione (***4****c*)

Crystallized frommethanol, buff crystals, m.p.117°C, yield 88%. Analysis: for $C_{32}H_{29}N_5O_2$, M.Wt.515.23, calculated: C, 74.54; H, 5.67; N, 13.58. Found: C, 74.73; H, 5.95; N, 13.40. IR (KBr, *cm*$^{-1}$): 3286 (NH), 3091, 3029 (CH aromatic), 2937 (CH aliphatic), 1787, 1712 (2C=O), 1597 (C=N).^{1}H NMR (DMSO-d_6, *δ ppm*): 1.85-1.89, 2.24-2.28 (2H, dd, dd, C_4-$H_2$of pyrazoline), 3.13 (6H, s, $2CH_3$), 3.66 (1H, t, C_5-Hof pyrazoline), 5.06 (2H, s, CH_2), 6.66-7.93 (17H, m, $H_{aromatic}$), 9.56 (1H, s, NH exchangeable with D_2O). MS: (*m/z*) ~[M-2]$^+$ 513 (50%).

2-{[(4-{5-[4-(dimethylamino)phenyl]-4,5-dihydro-1H-pyrazol-3-yl}phenyl) amino]methyl}-1H-isoindole-1,3(2H)-dione (***4****d*)

Crystallized from isopropanol, light brown crystals, m.p.222°C, yield 65%. Analysis: for $C_{26}H_{25}N_5O_2$, M.Wt.439.20, calculated: C, 71.05; H, 5.73; N, 15.93. Found: C, 70.83; H, 5.49; N, 16.26. IR (KBr, *cm*$^{-1}$): 3359 (NH), 3092 (CH aromatic), 2936 (CH aliphatic), 1770, 1712 (2C=O), 1596 (C=N). ^{1}H NMR (DMSO-d_6, *δ ppm*): 2.72-2.79, 2.83-2.90 (2H, dd, dd, C_4-$H_2$of pyrazoline), 2.99 (6H, s, $2CH_3$), 3.46 (1H, t, C_5-Hof pyrazoline), 5.23 (2H, s, CH_2), 6.76-8.12 (12H, m, $H_{aromatic}$), 7.39, 8.53 (2H, 2s, 2NH exchangeable with D_2O).

General procedure for preparation of compounds $\mathbf{5}_{a,b}$

A mixture of compounds $\mathbf{3}_{a,e}$ (1mmol) and hydroxylamine hydrochloride (0.07g, 1mmol) in ethanol (15mL) containing sodium hydroxide (0.1g) was heated under reflux for 8h. The reaction mixture was then cooled, poured onto ice water, filtered off and dried under vacuum at room temperature to give compounds $\mathbf{5}_{a,b}$, respectively.

2-[({4-[5-(4-hydroxy-3-methoxyphenyl)-4,5-dihydro-1,2-oxazol-3-yl]phenyl} amino)methyl]-1H-isoindole-1,3(2H)-dione (***5****a*)

Crystallized frommethanol, light brown crystals, m.p. 221°C, yield 65%. Analysis: for $C_{25}H_{21}N_3O_5$, M.Wt.443.15, calculated: C, 67.71; H, 4.77; N, 9.48. Found: C, 67.48; H, 4.91; N, 9.74. IR (KBr, *cm*$^{-1}$):3441 (OH), 3380 (NH), 3059 (CH aromatic), 2928 (CH alphatic),1779, 1711 (2C=O), 1595 (C=N). ^{1}H NMR (DMSO- d_6, *δ ppm*): 3.65-3.82 (2H, dd, dd, C_4-$H_2$of isoxazoline), 3.85 (3H, s, OCH_3), 4.25 (1H, t, C_5-Hof isoxazoline), 5.20 (2H, s, CH_2), 6.07 (1H, s, NH exchangeable with D_2O), 6.55-7.92 (11H, m, $H_{aromatic}$), 9.85 (1H, s, OH exchangeable with D_2O). MS: (*m/z*)~[M-1]$^+$ 442 (7.8).

2-[({4-[5-(4-chlorophenyl)-4,5-dihydro-1,2-oxazol-3-yl]phenyl}amino) methyl]-1H-isoindole-1,3(2H)-dione (***5$_b$***)
Crystallized frommethanol, orange brown crystals, m.p. 165°C, yield 60%. Analysis: for $C_{24}H_{18}ClN_3O_3$, M.Wt.431.10, calculated: C, 66.75; H, 4.20; N, 9.73. Found: C, 66.85; H, 4.42; N, 9.51. IR (KBr, *cm*$^{-1}$):3362 (NH), 3061 (CH aromatic), 2924 (CH alphatic), 1771, 1708 (2C=O), 1593 (C=N).^{1}H NMR (DMSO-d$_6$, *δ ppm*): 2.34-2.59 (2H, dd, dd, C_4-$H_2$of isoxazoline), 3.82 (1H, t, C_5-Hof isoxazoline), 5.18 (2H, s, CH_2), 6.04 (1H, s, NH exchangeable with D_2O), 6.51-8.12 (12H, m, $H_{aromatic}$). MS: (*m/z*) ~[M]$^+$ 431 (24.1%), 433 (7.3%).

General procedure for preparation of compounds ***6$_{a-d}$***
A mixture of the chalcone derivatives **3$_{a,b}$** (1mmol) and urea or thiourea (1mmol) in ethanol (20mL) containing sodium hydroxide (0.1g) was refluxed for 10h. The reaction mixture was concentrated under vacuum, cooled and neutralized with dilute HCl. The formed product was filtered off and washed with water to affordcompounds**6$_{a-d}$**, respectively.

2-((4-(6-(4-hydroxy-3-methoxyphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl) phenylamino)methyl)isoindoline-1,3-dione (***6$_a$***)
Crystallized frommethanol, brown crystals, m.p. 200°C, yield 60%. Analysis: for $C_{26}H_{20}N_4O_5$, M.Wt. 468.14, calculated: C, 66.66; H, 4.30; N, 11.96. Found: C, 66.52; H, 4.65; N, 11.63. IR (KBr, *cm*$^{-1}$):3449 (OH), 3382, 3220 (2NH), 3068 (CH aromatic), 2928 (CH aliphatic), 1771, 1712, 1659 (3C=O), 1595 (C=N).^{1}H NMR (DMSO-d$_6$, *δ ppm*): 3.86 (3H, s, CH_3), 5.43 (2H, s, CH_2), 6.57-7.88 (12H, m, $H_{aromatic}$), 6.27, 8.56 (2H, 2s, 2NH exchangeable with D_2O), 9.63 (1H, s, OH exchangeable with D_2O).

2-((4-(6-(4-hydroxy-3-methoxyphenyl)-2-thio-1,2-dihydropyrimidin-4-yl) phenylamino)methyl)isoindoline-1,3-dione (***6$_b$***)
Crystallized fromethanol, brown crystals, m.p. 208°C, yield 58%. Analysis: for $C_{26}H_{20}N_4O_4S$, M.Wt. 484.12, calculated: C, 64.45; H, 4.16; N, 11.56; S, 6.62. Found: C, 64.09; H, 4.59; N, 11.67; S, 6.81. IR (KBr, *cm*$^{-1}$):3336 (OH), 3421, 3365 (2NH), 3065 (CH aromatic), 2924 (CH aliphatic), 1773, 1715 (2C=O), 1596 (C=N), 1225 (C=S).^{1}H NMR (DMSO-d$_6$, *δ ppm*): 3.84 (3H, s, OCH_3), 5.41 (2H, s, CH_2), 2.07, 6.09 (2H, 2s, 2NH exchangeable with D_2O), 6.65-8.31 (12H, m, $H_{aromatic}$), 9.65 (1H, s, OH exchangeable with D_2O). MS: (*m/z*) ~ [M+1]$^+$ 485 (23.8%).

2-((4-(6-(3,4-dimethoxyphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)phenyl amino)methyl)isoindoline-1,3-dione (***6$_c$***)
Crystallized from ethanol, brown crystals, m.p. 123°C, yield 65%. Analysis: for $C_{27}H_{22}N_4O_5$, M.Wt. 482.16, calculated: C, 67.21; H, 4.60; N, 11.61. Found: C, 67.53; H, 5.03; N, 11.38. IR (KBr, *cm*$^{-1}$): 3420, 3358 (2NH), 3059 (CH aromatic), 2948 (CH aliphatic), 1771, 1714, 1660 (3C=O), 1596 (C=N).^{1}H NMR (DMSO-d$_6$, *δ ppm*): 3.86 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 5.41 (2H, s, CH_2), 6.55-8.12 (12H, m, $H_{aromatic}$), 6.09, 7.78 (2H, 2s, 2NH exchangeable with D_2O).

2-((4-(6-(3,4-dimethoxyphenyl)-2-thio-1,2-dihydropyrimidin-4-yl)phenyl amino)methyl)isoindoline-1,3-dione(***6$_d$***)
Crystallized fromethanol, red crystals, m.p. 157°C, yield 65%. Analysis: for $C_{27}H_{22}N_4O_4S$, M.Wt.498.14, calculated: C, 65.05; H, 4.45; N, 11.24; S, 6.43. Found: C, 65.01; H, 4.75; N, 11.02; S, 6.57. IR (KBr, *cm*$^{-1}$):3443, 3323 (2NH), 3013 (CH aromatic), 2914 (CH aliphatic), 1712, 1658 (2C=O), 1606 (C=N), 1221 (C=S).^{1}H NMR (DMSO-d$_6$, *δ ppm*): 3.82 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 5.28 (2H, s, CH_2), 6.72-8.05 (12H, m, $H_{aromatic}$), 6.20, 9.63 (2H, 2s, 2NH exchangeable with D_2O).MS: (m/z) ~ [M+1]$^+$ 498 (16.7%).

General procedure for preparation of compounds ***7$_{a,b}$***
A mixture of the acetyl compound **2** (1g, 3.4mmol) and semicarbazide HCl and/or thiosemicarbazide (3.4mmol) in absolute ethanol (15 mL) was heated under reflux for 8h. The formed compoundswere filtered off, washed several times with water and dried. Crystallization was performed from the appropriate solvents to give derivatives **7$_{a,b}$**.

*2-[1-(4-{[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]amino}phenyl) ethylidene]hydrazinecarboxamide (****7$_a$****)*
Crystallized from glacial acetic acid, orange crystals, m.p. 187°C, yield 70%. Analysis: for $C_{18}H_{17}N_5O_3$, M.Wt.351.13, calculated: C,61.53; H, 4.88; N, 19.93. Found: C, 61.58; H, 4.65; N, 20.21. IR (KBr, *cm*$^{-1}$):3384, 3317, 3210 (NH_2, 2NH), 3037 (CH aromatic), 2942 (CH aliphatic), 1751, 1721, 1671 (3C=O), 1595 (C=N).^{1}H NMR (DMSO-d$_6$, *δ ppm*): 2.14 (3H, s, CH_3), 5.06 (2H, s, CH_2), 6.57-7.96 (8H, m, $H_{aromatic}$), 8.78, 9.56 (2H, 2s, 2NH exchangeable with D_2O), 9.36 (2H, s, NH_2 exchangeable with D_2O).

*2-[1-(4-{[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]amino}phenyl) ethylidene]hydrazinecarbothioamide (**7_b**)*
Crystallized from glacial acetic acid, yellow crystals, m.p. 205°C, yield 70%. Analysis: for $C_{18}H_{17}N_5O_2S$, M.Wt.367.11, calculated: C, 58.84; H, 4.66; N, 19.06; S, 8.73. Found: C, 59.17; H, 4.85; N, 19.32; S, 8.56. IR (KBr, *cm*$^{-1}$):3474, 3355, 3318 (NH_2, 2NH), 3062 (CH aromatic), 2934 (CH aliphatic), 1772, 1716 (2C=O), 1267(C=S).^{1}H NMR (DMSO-d_6, *δ ppm*): 1.28 (3H, s, CH_3), 5.39 (2H, s, CH_2), 7.28-8.06 (8H, m, $H_{aromatic}$), 8.82, 9.98 (2H, 2s, 2NH exchangeable with D_2O), 9.65 (2H, s, NH_2 exchangeable with D_2O). MS: (*m/z*) ~ $[M+3]^+$ 370 (11.8%).

*General procedure for preparation of compounds**$8_{a,b}$***
A mixture ofthe acetyl compound**2** (1g, 3.4mmol), sulphur (0.11g, 3.4mmol) and the appropriate secondary amine, namely morpholine or N-methylpiprazine (3.4mmol) in dioxane (10 mL)was refluxed gently till the evolution of H_2S subsided and then refluxed vigorously for 12h. The reaction mixture was filtered off, poured onto warm ethanol (10mL). Then theformed solid product was filtered off and air dried to give the title compounds **$8_{a,b}$**.

*2-((4-(2-morpholino-2-thioxoethyl)phenylamino)methyl)isoindoline-1,3-dione(**8_a**)*
Crystallized frombenzene/petroleum ether(1:1), pale brown crystals, m.p. 276°C, yield 65%. Analysis: for $C_{21}H_{21}N_3O_3S$, M.Wt.395.13, calculated: C, 63.78; H, 5.35; N, 10.63; S, 8.11. Found: C, 63.85; H, 5.41; N, 10.84; S, 8.35. IR (KBr, *cm*$^{-1}$):3348 (NH), 3063 (CH aromatic), 2937 (CH aliphatic), 1711, 1665 (2C=O), 1220 (C=S).^{1}HNMR(DMSO-d_6, *δ ppm*): 3.01 (2H, s, CH_2), 3.66 (4H, t, N-$(CH_2)_2$of morpholine), 3.82 (4H, t, O-$(CH_2)_2$of morpholine), 5.12 (2H, s, CH_2), 6.72-8.31 (8H, m, $H_{aromatic}$), 7.67 (1H, s, NH exchangeable with D_2O). MS: (*m/z*) ~ $[M]^+$ 395 (19.4%).

*2-((4-(2-(4-methylpiperazin-1-yl)-2-thioxoethyl)phenylamino)methyl)isoindoline-1,3-dione(**8_b**)*
Crystallized frombenzene/petroleum ether (1:1), pale brown crystals, m.p. 188°C, yield 70%. Analysis: for $C_{22}H_{24}N_4O_2S$, M.Wt.408.16, calculated: C, 64.68; H, 5.92; N, 13.71; S, 7.85. Found: C, 64.55; H, 5.78; N, 13.63; S, 7.91. IR (KBr, *cm*$^{-1}$): 3366 (NH), 3059 (CH aromatic), 2923 (CH aliphatic), 1769, 1713 (2C=O), 1220 (C=S).^{1}H NMR (DMSO- d_6, *δ ppm*): 1.91 (3H, s, CH_3), 2.22 (4H, t, N-$(CH_2)_2$of piperazine), 2.93 (2H, s, CH_2), 3.08 (4H, t, N-$(CH_2)_2$of piperazine), 5.17 (2H, s, CH_2), 7.36-8.01 (8H, m, $H_{aromatic}$), 8.63 (1H, s, NH exchangeable with D_2O).

*General procedure for preparation of compounds**$9_{a,b}$***
A mixture of compound **2** (1gm, 3.4mmol), malononitrile (0.23g, 3.4mmol) and the appropriate aldehydes, namely: 4-dimethylaminobenzaldehyde or 3,4-dimethoxybenzaldeyde (3.4mmol) in n-butanol (15 mL) containing few drops of piperidine was heated under reflux for 5h. The separated solid was filtered off, washed with cold water then with cold ethanol and air dried to give compounds **$9_{a,b}$**, respectively.

*2-amino-6-(4-{[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]amino} phenyl)-4-[4-(dimethylamino)phenyl]-4H-pyran-3-carbonitrile (**9_a**)*
Crystallized fromacetic acid, dark orange crystals, m.p. 175°C, yield 60%. Analysis: for $C_{29}H_{25}N_5O_3$, M.Wt. 491.20, calculated: C, 70.86; H, 5.13; N, 14.25. Found: C, 70.65; H, 5.47; N, 14.39. IR (KBr, *cm*$^{-1}$):3364, 3201 (NH_2, NH), 3058 (CH aromatic), 2921 (CH aliphatic), 2207 (C≡N), 1771, 1716 (2C=O).^{1}H NMR (DMSO- d_6, *δ ppm*): 3.11 (6H, s, $2CH_3$), 4.35 (1H, d, CHof pyrane), 5.27 (2H, s, CH_2), 6.85-8.05 (13H, m, $H_{aromatic}$ and CH of pyrane), 6.1 (2H, s, NH_2 exchangeable with D_2O), 11.3 (1H, s, NH exchangeable with D_2O).

*2-amino-6-(4-{[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]amino} phenyl)-4-(3,4-dimethoxyphenyl)-4H-pyran-3-carbonitrile (**9_b**)*
Crystallized fromethanol, brown crystals, m.p. 200°C, yield 60%. Analysis: for $C_{29}H_{24}N_4O_5$, M.Wt. 508.17, calculated: C, 68.49; H, 4.76; N, 11.02. Found: C, 68.72; H, 5.00; N, 11.24. IR (KBr, *cm*$^{-1}$):3455, 3365 (NH_2, NH), 3062 (CH aromatic), 2935 (CH aliphatic), 2191 (C≡N), 1773, 1725 (2C=O).^{1}H NMR (DMSO- d_6, *δ ppm*): 3.79 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 4.10 (1H, d, CHof pyrane), 5.00 (2H, s, CH_2), 6.52-7.88 (11H, m, $H_{aromatic}$), 9.80 (1H, s, NH exchangeable with D_2O), 11.3 (2H, s, NH_2 exchangeable with D_2O).

*General procedure for preparation of compounds**$10_{a,b}$***
A mixture of compound **2** (1g, 3.4mmol), malononitrile (0.23g, 3.4mmol), anhydrous ammonium acetate (1.5g, 20mmol) and the appropriate aldehydes, namely: 4-dimethylaminobenzaldehyde or 3,4-dimethoxybenzaldeyde (3.4mmol) in n-butanol (15 mL) was heated under reflux for 6h. The separated solid was filtered off, washed with cold water then with cold ethanol, dried to give the corresponding compounds ***$10_{a,b}$***.

6-(4-{[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]amino}phenyl)-4-[4-(dimethylamino)phenyl]-2-imino-1,2-dihydropyridine-3-carbonitrile (***10$_a$***)
Crystallized fromacetic acid, brown crystals, m.p. 215°C, yield 60%. Analysis: for $C_{29}H_{24}N_6O_2$, M.Wt. 488.20, calculated: C, 71.30; H, 4.95; N, 17.20. Found: C, 71.51; H, 5.20; N, 17.47. IR (KBr, cm^{-1}):3438, 3354, 3203 (3NH), 3060 (CH aromatic), 2926 (CH aliphatic), 2191 (C≡N), 1773, 1720 (2C=O), 1601 (C=N).^{1}H NMR (DMSO- d_6, *δ ppm*): 3.01 (6H, s, $2CH_3$), 5.17 (2H, s, CH_2), 6.82-8.05 (13H, m, $H_{aromatic}$ and CH of pyridine), 4.52, 6.00, 9.89 (3H, 3s, 3NH exchangeable with D_2O). MS: (*m/z*) ~ $[M]^+$ 488 (11.5%).

6-(4-{[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]amino}phenyl)-4-(3,4-dimethoxyphenyl)-2-imino-1,2-dihydropyridine-3-carbonitrile (***10$_b$***)
Crystallized frommethanol, orange crystals, m.p. 179°C, yield 65%. Analysis: for $C_{29}H_{23}N_5O_4$, M.Wt. 505.18, calculated: C, 68.90; H, 4.59; N, 13.85. Found: C, 69.23; H, 4.50; N, 14.16. IR (KBr, cm^{-1}):3453, 3358, 3212 (3NH), 3062 (CH aromatic), 2957 (CH aliphatic), 1772, 1723 (2C=O), 2204 (C≡N), 1598 (C=N).^{1}H NMR (DMSO- d_6, *δ ppm*): 3.81 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 5.40 (2H, s, CH_2), 6.54-7.91 (12H, m, $H_{aromatic}$ and CH of pyridine), 2.37, 7.23, 11.34 (3H, 3s, 3NH exchangeable with D_2O). MS: (*m/z*) ~$[M+3]^+$ 508 (28%).

General procedure for preparation of compounds ***11$_{a-c}$***
A mixture of compound **2** (0.59g, 2mmol), ethyl cyanoacetate (0.23 mL, 2mmol), anhydrous ammonium acetate (1.24g, 16mmol) and appropriate aldehydes namely: 4-chlorobenzaldeyde, vanillinaldehyde or 3,4-dimethoxy benzaldeyde (2 mmol) in n-butanol (10 mL) was heated under reflux for 7h. The reaction mixture was concentrated to half its volume. After cooling the separated crystalline solid was isolated by filtration and recrystallized to give compounds **11$_{a-c}$**.

4-(4-chlorophenyl)-6-(4-{[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]amino}phenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (***11$_a$***)
Crystallized fromethanol, orange crystals, m.p. 217°C, yield 55%. Analysis: for $C_{27}H_{17}ClN_4O_3$, M.Wt. 480.10, calculated: C, 67.43; H, 3.56; N, 11.65. Found: C, 67.56; H, 3.76; N, 11.74. IR (KBr, cm^{-1}):3368, 3349 (2NH), 3065 (CH aromatic), 2925 (CH aliphatic), 2215 (C≡N), 1771, 1728, 1660 (3C=O).^{1}H NMR (DMSO- d_6, *δ ppm*): 5.10 (2H, s, CH_2), 6.87-8.14 (13H, m, $H_{aromatic}$ and CH of pyridine), 7.25, 9.65 (2H, 2s, 2NH exchangeable with D_2O). MS: (*m/z*) ~$[M+1]^+$481 (14.6%), 483(5.2%).

4-(4-hydroxy-3-methoxyphenyl)-6-(4-{[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]amino}phenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (***11$_b$***)
Crystallized fromacetic acid, light brown crystals, m.p.>300°C, yield 65%. Analysis: for $C_{28}H_{20}N_4O_5$, M.Wt. 492.14, calculated: C, 68.29; H, 4.09; N, 11.38. Found: C, 68.50; H, 4.35; N, 11.22. IR (KBr, cm^{-1}):3384 (OH), 3367, 3205 (2NH), 3061 (CH aromatic), 2932 (CH aliphatic), 2211 (C≡N), 1773 1728, 1664 (3C=O).^{1}H NMR (DMSO- d_6, *δ ppm*): 3.83 (3H, s, OCH_3), 5.26 (2H, s, CH_2), 6.53-8.20 (12H, m, $H_{aromatic}$ and CH of pyridine), 7.25, 9.65 (2H, 2s, 2NH exchangeable with D_2O), 11.32 (1H, s, OH exchangeable with D_2O). MS: (*m/z*) ~$[M-2]^+$ 490 (4.1%).

4-(3,4-dimethoxyphenyl)-6-(4-{[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]amino}phenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (***11$_c$***)
Crystallized fromethanol, yellow crystals, m.p. 186°C, yield 60%. Analysis: for $C_{29}H_{22}N_4O_5$, M.Wt. 506.16, calculated: C, 68.77; H, 4.38; N, 11.06. Found: C, 68.64; H, 4.54; N, 11.43. IR (KBr, cm^{-1}):3373, 3204 (2NH), 2219 (C≡N), 3061 (CH aromatic), 2936 (CH aliphatic), 1774, 1729, 1660 (3C=O).^{1}H NMR (DMSO- d_6, *δ ppm*): 3.75 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 5.19 (2H, s, CH_2), 7.14-8.27 (12H, m, $H_{aromatic}$ and CH of pyridine), 8.66, 11.31 (2H, 2s, 2NH exchangeable with D_2O).

Antimicrobial evaluation
The newly synthesized chemical compounds were individually tested against highly pathogenic strains of gram positive (*Staphylococcus aureus* (ATCC 9213), *Bacillus subtilis* (ATCC 6633), *Bacillus megaterium* (ATCC 9885)) and gram negative (*Klebsiella pneumonia* (ATCC 13883), *Pseudomonas aeruginosa* (ATCC 27953), *Escherichia coli* (ATCC 25922)) bacterial pathogens, two yeasts (*Saccharomyces cerevisiae*, *Candida albicans* (NRRLY-477) and fungus (*Aspergillus niger* (local isolate)). The using 100 µL of suspension containing 1x108 colony-forming unit/mL (CFU/mL) of pathological tested bacteria, 1 x106 CFU/mL of yeast and 1 x106 CFU/mL of fungi spread on nutrient agar (NA), Sabourand dextrose agar (SDA) and Potato dextrose agar medium (PDA) respectively .

Determination of antimicrobial activity by Agar-diffusion method

Antimicrobial tests were carried out by the agar well diffusion method of *Perez et al*. [49]. After the preparation of agar media, they were left to cool and solidify; wells (10 mm in diameter) were made in the solidified agar and loaded with 100 µL of the tested compound solution prepared by dissolving 100 mg of the chemical compound in 1mL of dimethyl sulfoxide (DMSO). The inculcated plates were then incubated for 24 h at 37°C for bacteria and 48h at 28°C for fungi. Negative controls were prepared using DMSO employed for dissolving the tested compounds. Ciprofloxacin (50mg/mL) and Ketoconazole (50mg/mL) were used as standard drugs for antibacterial and antifungal activity, respectively. After incubation time, antimicrobial activity was evaluated by measuring the zone of inhibition (IZ) against the test organisms and compared with that of the standard. Antimicrobial activities were expressed as inhibition diameter zones in millimeters (mm). The experiment was carried out in triplicate and the average zone of inhibition was calculated.

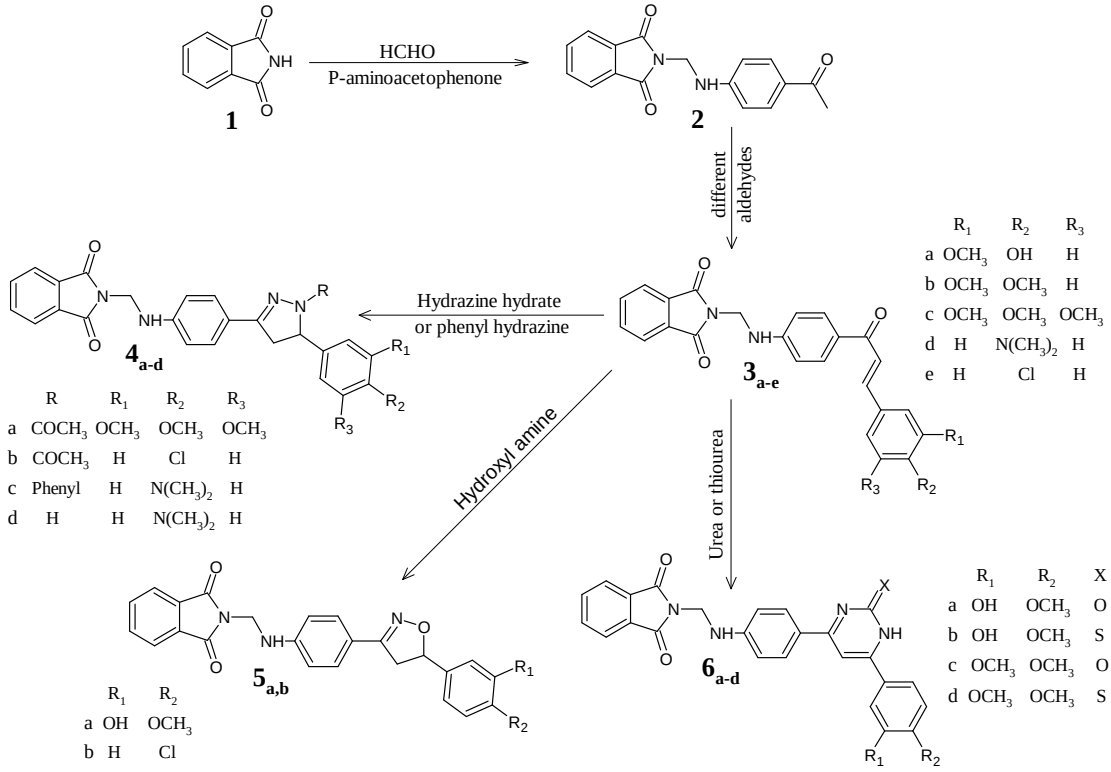
Minimal inhibitory concentration (MIC) measurement

The bacteriostatic activity of the active compounds (having inhibition zones (IZ) ≥ 16 mm) was then evaluated using the two fold serial dilution technique of *Scott et al*. [50]. Two fold serial dilutions of the tested compounds solutions were prepared using the proper nutrient broth. The final concentrations of the solutions were 200, 100, 50 mg/mL. Each 5 mL received 0.1 mL of the appropriate inoculum and incubated at 37°C for 24h. The lowest concentration showing no growth was taken as the minimum inhibitory concentration (MIC).

RESULTS AND DISCUSSION

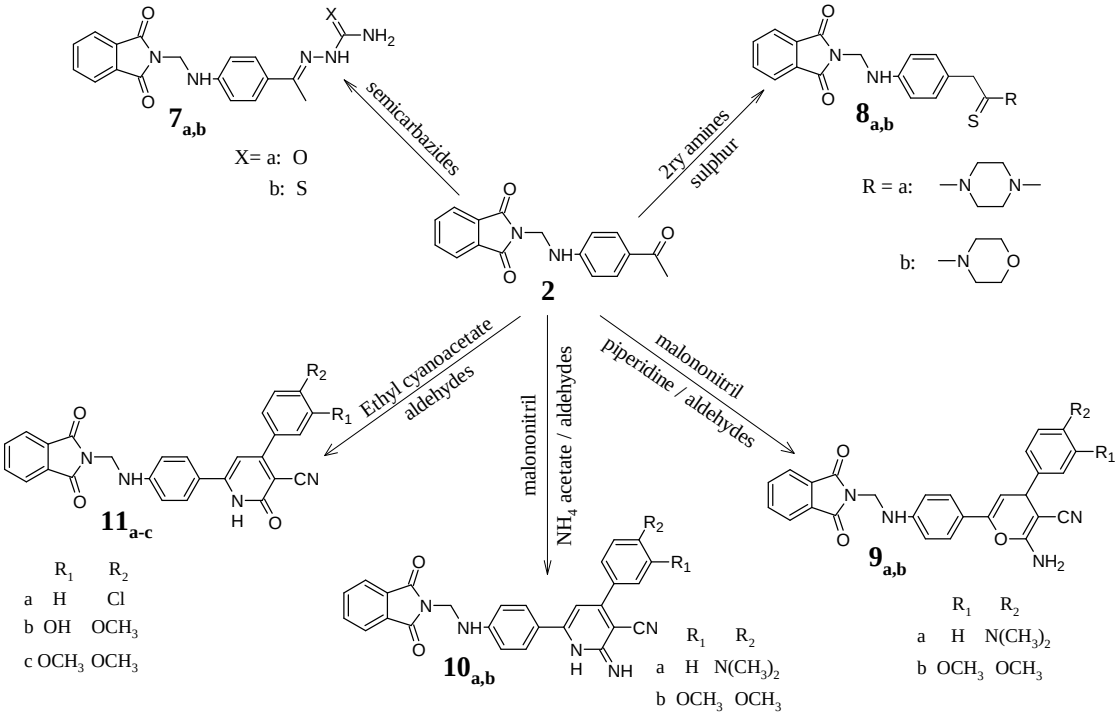
Chemistry

In this study, we synthesized a series of phthalimide derivatives attached to different five and six membered heterocyclic compounds based on 2-{[(4-acetylphenyl)amino]methyl}-1*H*-isoindole-1,3(2*H*)-dione **2**, that was used as a key starting material. The reaction of **2** with different aromatic aldehydes resulted in the formation of a variety of chalcones $\mathbf{3}_{\mathbf{a-e}}$, which were then cyclized into 4,5-dihydro-pyrazole derivatives$\mathbf{4}_{\mathbf{a-d}}$, through their reaction with hydrazine hydrate or phenyl hydrazine in either glacial acetic acid or absolute ethanol, respectively. When the derivatives $\mathbf{3}_{\mathbf{a-c}}$were treated with hydroxylamine they yielded isoxazoline derivatives $\mathbf{5}_{\mathbf{a,b}}$. Compounds $\mathbf{3}_{\mathbf{a,b}}$also reacted with both urea and thiourea to give 2-thio(oxo)-1,2-dihydropyrimidine derivatives$\mathbf{6}_{\mathbf{a-d}}$.



Scheme 1

Upon the treatment of the acetyl compound **2** with semicarbazide HCl or thiosemicarbazide, hydrazinecarbox(thio)amide derivatives**7$_{a,b}$**were obtained. Derivatives **8$_{a,b}$**were also obtained as a product of the reaction of compound **2** with cyclic secondary amines, morpholine or 4-methyl piperazine, in the presence of sulphur. Depending on the reaction conditions, the acetyl compound **2** reacted withdifferent aromatic aldehydes and malononitrile in the presence of piperidine to give the pyrane derivatives **9$_{a,b}$**. While in the presence of anhydrous ammonium acetate, 2-imino-1,2-dihydropyridine-3-carbonitrile derivatives **10$_{a,b}$** were obtained. Finally, the reaction of compound **2** with different aldehydes and ethyl cyanoacetate gave the pyridone derivatives **11$_{a-c}$**.



Scheme 2

Biological activity

Antimicrobial activity

Most of the newly synthesized compounds were evaluated for their *in vitro*antibacterial activity against three strains of gram positive bacteria (*S. aureus*, *B. subtilis*, *B. megaterium*), and three strains of gram negative bacteria (*K. pneumonia*, *P. aeruginosa*, *E. coli*) using ciprofloxacin as a standard drug (50 µg/mL). They were also evaluated for their *in vitro* antifungal activity against three mycotic strains (*S. cerevisiae*, *C. albicans*, *A. niger*) using fluconazole as a standard antifungal drug (50 µg/mL). Agar-diffusion method [49] was used in this investigation for determination of the preliminary antibacterial and antifungal activity. 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. The minimum inhibitory concentration (MIC) measurement was determined for the compounds that showed significant growth inhibition zones (≥ 16 mm) using the two-fold serial dilution method [50]and 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**.

Table 1: Antimicrobial activity against the pathological strains expressed as IZ (mm) based on well diffusion assay of chemical compounds

M.O.* / Compd.**	*Gram positive bacteria*			*Gram negative bacteria*			*Yeast*		*Fungi*
	S. aureus	*B. subtilis*	*B. megaterium*	*K. pneumoniae*	*P. aeruginosa*	*E. coli*	*S. cerevisiae*	*C. albicans*	*A. niger*
3a	18	15	18	24	28	21	22	24	-ve
3d	17	-ve	-ve	24	26	17	17	14	-ve
3e	15	15	13	24	23	16	23	26	-ve
4a	-ve	18	13	26	18	18	22	24	14
4b	-ve	-ve	15	22	18	20	30	18	-ve
4c	-ve	-ve	12	28	14	20	26	24	-ve
4d	19	22	20	29	30	31	20	21	-ve
5a	-ve	-ve	17	20	19	18	18	16	-ve
6a	36	34	37	37	38	38	35	33	27
6c	18	N.A.	15	21	17	18	24	15	-ve
6d	37	37	35	39	38	39	30	32	25
7b	15	16	14	26	28	16	22	20	-ve
8b	-ve	19	16	25	18	16	28	28	15
9a	-ve	18	12	24	16	16	30	24	-ve
9b	-ve	N.A.	-ve	28	15	19	18	16	-ve
10a	-ve	16	-ve	-ve	19	13	18	18	-ve
10b	15	17	16	16	19	-ve	15	24	-ve
11a	15	15	15	24	22	22	19	30	-ve
11b	-ve	27	-ve	22	21	-ve	14	13	-ve
Ciprofloxacin	20	22	24	25	24	23	-	-	-
Ketoconazole	-	-	-	-	-	-	23	22	24

** M.O.: microorganism* *** Compd: compound* *N.A.: no activity*

The minimum inhibitory concentrations (MIC) were recorded for compounds that showed promising growth inhibition using the two-fold serial dilution method. The MIC (µg/mL) values against the tested bacterial and fungal isolates were recorded in **Table 2**.

Table 2: Antimicrobial activity against the pathological strains expressed as MIC (µg/mL) based on two fold serial dilution technique of chemical compounds

M.O.* / Compd.**	*Gram positive bacteria*			*Gram negative bacteria*			*Yeast*		*Fungi*
	S. aureus	*B. subtilis*	*B. megaterium*	*K. pneumoniae*	*P. aeruginosa*	*E. coli*	*S. cerevisiae*	*C. albicans*	*A. niger*
3a	200	-	200	50	50	200	100	50	-
3d	200	-	-	100	50	200	200	-	-
3e	-	-	-	50	100	200	100	50	-
4a	-	-	-	50	-	200	100	100	-
4b	200	100	200	50	50	25	200	100	-
4c	-	200	-	50	200	200	100	100	-
4d	-	-	-	22	200	200	50	200	-
5a	-	-	200	200	200	200	200	200	-
6a	25	25	25	25	25	25	25	25	25
6c	200	-	-	21	200	200	100	-	-
6d	25	25	25	25	25	25	25	25	50
7b	-	200	-	50	50	200	100	200	-
8b	-	200	-	50	200	200	50	50	-
9a	-	200	-	50	200	200	50	100	-
9b	-	-	-	50	-	200	200	200	-
10a	-	200	-	-	200	-	200	200	-
10b	-	200	200	200	200	-	-	50	-
11a	-	-	-	50	100	200	200	50	-
11b	-	50	-	100	200	-	-	-	-
Ciprofloxacin	25	25	25	25	25	25	-	-	-
Ketoconazole	-	-	-	-	-	-	25	25	25

** M.O.: microorganism* *** Compd: compound*

Based on the data obtained from Table **1** and Table **2**, it is obvious that most of the tested compounds were highly active against gram negative bacteria (*K. pneumonia*, *P. aeruginosa*, *E. coli*) and yeasts (*S. cerevisiae*, *C. albicans*) while having moderate or low activity against gram positive bacteria (*S.aureus,B.subtilis*, *B. megaterium*). All the tested compounds exhibited no activity against the tested fungus (*A. niger*) except the derivatives $\mathbf{6_a}$, $\mathbf{6_d}$ which

showed potent antifungal activity (IZ = 27, 25mm, respectively) and the derivatives **4_c**, **8_b**which were weakly active (IZ = 14, 15mm, respectively).The chalcone derivatives **3_a**, **3_d**, **3_e** possessed moderate to good activity against the tested gram negative bacteria *K. pneumoniae*, *P. aeruginosa*, *E. coli*, and yeasts *S. cerevisiae*, *C. albicans*with MIC ranging from 50-200µg/mL, while *S. aureus*, *B. subtilis*, *B. megaterium* were less susceptible to these compounds especially derivative **3_e**which showed a very weak antibacterial activity against the gram positive bacteria.The pyrazoline derivative**4_a** possessed moderate antibacterial and antifungal activity. Unlike its parent compound, derivative **4_d** was highly active against most of the tested microorganisms(IZ = 22-31 mm) and was inactive against A. *niger*, whilst the other dihydropyrazole derivatives **$4_{b,c}$**were inactive against gram positive bacteria, but exerted moderate to good activity against gram negative bacteria (IZ = 14-28 mm) and potent antifungal activity towards the tested yeasts (IZ = 18-30 mm) in comparison to the standard drugs.The isoxazoline derivative **5_a** showed weak to moderate antimicrobial activity. In contrast to the five membered derivatives of chalcones, the six membered dihydropyrimidone derivatives **6_a**, **6_d**, with the exception of **6_c**, they exerted a significant increase in the antibacterial and antifungal activity towards all the tested microorganisms even the resistant *A. niger*,and they were more potent than the standards (Ciprofloxacin, Ketoconazole)thus they can be considered as promising antimicrobial agents. As for the compound **7_b**, it was highly active against two gram negative bacteria *K. pneumoniae*, *P. aeruginosa*(IZ = 26, 28 mm) but less active on *E. coli* and *S. cerevisiae*, *C. albicans*. In contrast with the previous derivative, compound **8_b** was more potant as antifungal agent against *S. cerevisiae*, *C. albicans*, and also towards *K. pneumoniae*(IZ = 28, 25 mm) while *P. aeruginosa* and *E. coli* were less susceptible to its action. The pyrane derivatives **9_a** possessed high antimicrobial activity on *K. pneumoniae*, *S. cerevisiae* and *C. albicans*, but moderate activity against *B. subtilisP. aeruginosa* and *E. coli*, while the dimethoxy derivative **9_b** showed high activity towards *K. pneumoniae* but lesser activity against *E. coli* and the yeasts. The imino dihydropyridine derivativesdid not have any significant activity, except for compound **10_b** which was highly active against *C. albicans*(IZ = 24 mm). While the dihydropyridone derivative **11_a**no or moderate antimicrobial activity. However thechloro-analogue**11_b** showed significant activity against *B. subtilis*, a gram positive bacterium, and moderate activity aganist *K. pneumoniae* and *P. aeruginosa*, gram negative bacteria.

CONCLUSION

In the summary,we synthesized 26 novel phthalimide compounds and tested their antimicrobial activity against a variety of gram positive and gram negative bacteria as well as fungal isolates using Ciprofloxacin and Ketoconazole as reference drugs. Only compounds **6_a**, **6_d** were active against all of the tested microorganisms and showed potent antibacterial and antifungal activity (MIC = 25 µg/mL), even more potent than the used standards. While compound **4_b** possessed moderate to potent antimicrobial activity towards all microorganism (MIC = 25-200 µg/mL) except *A. niger*. Most of the tested derivatives (at least 16 of the tested derivatives) were active against *K. pneumonia, P. aeruginosa*, *E. coli, S. Cerevisiae* and *C. albicans*.While *B. subtilis* was the most susceptible gram positive bacterium (10 compounds showed antibacterial activity against it), whereas *K. pneumonia* was the most sensitive microorganism (10 derivatives exerted MIC of 50µg/mL and 2 derivatives possessed MIC of 25µg/mL).

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