Synthesis, Characterization and Antimicrobial Evaluation of Newly Synthesized Compounds With Phthalimide Skeleton

Kamelia Amin¹, Afaf El-Masry², Neama Mohamed³, Ghada Awad³ and Basma Habib³,*

¹Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Cairo University, ²Department of Therapeutical Chemistry and ³Department of Natural and Microbial Products, National Research Centre, Cairo, Egypt.

Introduction

Phthalimide containing compounds have attracted the interest of scientists since the thalidomide incidence in the middle of the last century [1]. Furthermore, many literatures have investigated the phthalimide derivatives due to their diverse range of biological activities such as antimicrobial [2-5], antiviral [6,7], anticancer [8,9], anti-inflammatory [10,11], antiepileptic [12,13], antihyperlipidimic [14,15], antihyperglycemic [16], anxiolytic [17], etc.

Microbial infectious diseases are one of the most serious global problems and represent major socio-economic challenge facing humanity. One of its complications is the development of antimicrobial resistance (AMR) as a consequence of misuse of the antimicrobial medicines or when a microorganism mutates or acquires a resistance gene. A World Health Organization report in 2014 stated that we are already facing this major threat in every region of the world. Thus, the discovery of new antimicrobial agents is an urgent need to overcome the threat of the resistant microbes.

In the view of these observation, it was of interest to synthesize several 2-[(4-(substituted phenyl)amino)methyl]-1H-isooindole-1,3(2H)-dione derivatives and screen them for their antimicrobial activities.

Results and Discussion

Chemistry

In this study, we synthesized a series of phthalimide derivatives based on 2-[(4-(bromoacetyl)phenyl)amino)methyl]-1H-isooindole-1,3(2H)-dione (1) as a key starting material. Compound 1 was synthesized by treatment of the compound A namely 2-[(4-Acetylphenyl)amino)methyl]-1H-isooindole-1,3(2H)-dione with bromine water in the presence of glacial acetic acid as a reacting medium at room temperature.

The treatment of α-bromoketone (1) with thiourea in absolute ethanol via Hantzsch thiazole synthesis yielded 1,3-thiazole derivative (2). Condensation of compound 2 with different aldehydes, aromatic aldehydes or monosaccharide, in ethanol with the presence of basic catalyst gave Schiff bases 3 (4a,b). The cyclization of Schiff bases (4a,b) with thioglycolic acid in dioxane at room temperature afforded the thiazolidin-4-one derivatives.
(5a,b). Furthermore, condensation of the amino derivative (2) with several anhydrides, namely, succinic, maleic and phthalic anhydride in glacial acetic acid under reflux yielded the pyrrole derivatives (6a-c), respectively. (Scheme 1)

Similar to the synthesis of derivative (2), the hydrazino-thiazole derivative (7) was synthesized via condensation of key substance (1) with thiosemicarbazide.

The condensation of compound 7 with different aromatic aldehydes gave Schiff’s bases (8a-d). Staudinger synthesis was used for the preparation of the azetidin-2-ones (9a,b) and their 3-chloro derivatives (10a,b) by reacting compounds 8a,c with acetyl chloride and chloroacetyl chloride, respectively. While the formation of thiazolidinone derivatives (11a,b, 12a,b) was achieved via reaction of the imine derivatives (8b,d) with thioglycolic acid and/or thiolactic acid, respectively (Scheme 2).

On the other hand, compound 1 was refluxed with selenium dioxide in absolute ethanol to afford ethyl 2-oxoacetate derivative (13) after the removal of the selenium metal, which on reacting with o-phenylenediamine gave the phthalimido quinoxaline derivative (14).

Treatment of bromoacetyl compound 1 with malononitrile in ethanolic solution containing sodium hydroxide afforded the new isoindolyl dinitrile derivative (15). Compound 15 was then cyclized using acetic acid and concentrated hydrochloric acid gave 2-amino furan-3-carbonitrile derivative (16). While on reacting compound 15 with hydrazine hydrate or phenyl hydrazine in ethanolic solution furnished the diaminopyrazole derivatives (17a,b) (Scheme 3).

Antimicrobial results

In this work, 22 newly synthesized compounds (1, 2, 3, 4b, 5a,b, 6b,c, 7, 8a,b,d, 9a,b, 10a,b, 11a, 12a, 14, 15, 16 and 17a) were screened for their in vitro antibacterial and antifungal activities by using the agar well diffusion and broth dilution methods against a panel of Gram positive bacteria [Staphylococcus aureus ATCC9213, Bacillus subtilis ATCC6633, Bacillus megaterium ATCC9885], Gram negative bacteria [Klebsiella pneumoniae ATCC13883, Pseudomonas aeruginosa ATCC27953, Escherichia coli ATCC25922], Fungi [Saccharomyces cerevisiae, Candida albicans NRRLY-477, Aspergillus niger Local isolate]. Ciprofloxacin and Ketoconazole were the reference drugs used in the evaluation of the antibacterial and antifungal activity of the tested compounds, respectively.

Based on the results recorded in Tables 1 & 2 and expressed in terms of IZ and MIC, the antibacterial and antifungal activities of the newly synthesized compounds in comparison to the used standard drugs, Ciprofloxacin and Ketoconazole, respectively, clarified that most of the compound tested showed IZ and MIC ranging from 39 to 12 mm and from 25 to 200 μg/ml, respectively. Substantially, most of the tested compounds showed remarkable activity against the Gram negative bacteria and were active against the fungi. The bacteria were less susceptible to their antibacterial effect, while the A. niger was the most resistible microorganism. While, K. pneumonia and S. cerevisiae were the most sensitive bacterium and fungus, respectively.

The key intermediate, bromo-acetyl (compound 1) was moderately active against bacteria and yeast but no activity against S. aureus and A. niger. In contrast, its amino thiazole derivative (2) showed good antifungal activity especially against A. niger but lower antibacterial activity. The other tested phthalimide-thiazole derivatives exerted diversity in their activity, Schiff’s base.

Scheme 3
<table>
<thead>
<tr>
<th>Tested compounds</th>
<th>Gram positive bacteria</th>
<th>Gram negative bacteria</th>
<th>Fungi</th>
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<tbody>
<tr>
<td></td>
<td>S. aureus</td>
<td>B. subtilis</td>
<td>B. megaterium</td>
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<tr>
<td>1</td>
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<td>2</td>
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<td>Ketoconazole</td>
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*The experiment was carried out in triplicate and the average zone of inhibition was calculated; N.A. (no activity).
TABLE 2. Minimum inhibitory concentration (μg/ml) of compounds 1 – 17a against the pathological strains based on two fold serial dilution technique.

<table>
<thead>
<tr>
<th>Tested compounds</th>
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<th>Fungi</th>
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<td>Ciprofloxacin</td>
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<tr>
<td>Ketoconazole</td>
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</table>
(3) showed insignificant antimicrobial activity. The thiazole Schiff’s base (4b), containing sugar moiety, possessed remarkable antimicrobial activity (MIC = 25-200 μg/ml) which was higher than the parent amino thiazole derivative (2), while its corresponding thiazolidinone derivative (5b) showed moderate activity. However the thiazole azetidine (10b) and thiazolidinone (12a) were also active against the tested pathogens, but they only showed weak to moderate activity (MIC = 100-200 μg/ml). While, the thiazolidinone derivative (12a) had no antifungal activity.

Unpredictably, the quinoxaline derivative (14) exhibited good antifungal activity particularly against A. niger (MIC = 50 μg/ml). In addition, the dinitrile compound 15 showed prominent antimicrobial activity (MIC = 25 μg/ml) against all the test pathogens. The cyanofuran derivative 16 exhibited poor activity (MIC = 200 μg/ml) against the used Gram negative bacteria, while diaminopyrazole derivative 17a exhibited good antifungal activity (MIC = 50 μg/ml) against S. cervesia and C. albicans and weak antibacterial effects (MIC = 200 μg/ml).

In conclusion, a total of 22 novel phthalimide compounds were subjected to antimicrobial screening. From the tested phthalimide derivatives, the dinitrile derivative (15), showed promising antimicrobial activity (MIC = 25 μg/ml) against all tested microorganisms and can be regarded as promising lead structures for development of enhanced antimicrobial candidates. Two other derivatives, thiazole derivative 4b and azetidinone derivative (10c), were moderately active as antimicrobial agents (MIC = 50-200 μg/ml).

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 Jasco FT/IR-6100 using KBr discs. 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 vapor was used for the detection of the plates.

2-{{[4-Acetylphenyl]amino}methyl}-1H-isoindole-1,3(2H)-dione (A)

This compound was prepared according to the reported method [18].

Preparation of 2-{{[4-(Bromoacetyl)phenyl]amino}methyl}-1H-isoindole-1,3(2H)-dione (1)

To a solution of compound A (0.74 g, 2.5 mmol) in glacial acetic acid (10 ml), bromine water (1 ml) was added dropwise with vigorous stirring during ½ hr. The reaction mixture was kept overnight and then poured on crushed ice. The separated product was filtered off, washed several times with water, vacuum dried and crystallized from isopropanol, light yellow crystals (Scheme 1), mp 109-111 °C, yield 72%, Analysis for C_{14}H_{12}BrN_{2}O_{3}, M.Wt. 350.08, calculated: C: 43.10 H: 3.04 N: 7.72 Br: 31.84, found: C: 43.50 H: 3.29 N: 7.51 Br: 31.51. IR (KBr; cm^{-1}): 3445, 3373 (NH), 3025 (CH aromatic), 2925 (CH aliphatic), 1770, 1712 (2C=O), 1619, 1518, 1411 (C=N). 1H NMR (DMSO, δ ppm): 9.17 (3H, 2s, NH 2, NH exchangeable with D 2O). MS: (m/z) ~ [M+1]+ 373 (18%), 375 (19%).

Preparation of 2-{{[4-(2-Amino-1,3-thiazol-4-yl)phenyl]amino}methyl}-1H-isoindole-1,3(2H)-dione (2)

A mixture of compound 1 (0.75 g, 2 mmol) and thiourea (0.15 g, 2 mmol) in absolute ethanol (15 ml) was heated under reflux for 3 hr. The reaction mixture was cooled, poured onto ice water and the formed precipitate was filtered off, washed several times with water and vacuum dried, the formed powder was then crystallized from benzene/ethanol (10 ml / 0.5 ml), dark yellow crystals (Scheme 1), mp 167-9 °C, yield 84%, Analysis for C_{18}H_{14}N_{4}O_{2}S, M.Wt. 350.08, calculated: C: 61.70 H: 4.03 N: 15.99 S: 8.38, found: C: 61.85 H: 4.29 N: 16.20 S: 8.78. IR (KBr; cm^{-1}): 3445, 3346 (NH), 3025 (CH aromatic), 2925 (CH aliphatic), 1770, 1712 (2C=O), 1611 (C=N). 1H NMR (DMSO, δ ppm): 9.17 (3H, 2s, NH 2, NH exchangeable with D 2O). MS: (m/z) ~ [M+1]+ 373 (18%), 375 (19%).

Preparation of 2-{{[4-(2-Amino-1,3-thiazol-4-yl)phenyl]amino}methyl}-1H-isoindole-1,3(2H)-dione (3)

A mixture of equimolecular amounts of compound 2 (0.35 g, 1 mmol) and 4-dimethylamino-benzaldehyde (0.15 g, 1 mmol) in absolute ethanol (15 ml) was heated under reflux for 18 hr. The formed solid was filtered off, air dried and crystallized from acetone, greenish...
brown crystals (Scheme 1), mp 102-4 °C, yield 67%. Analysis: for C\textsubscript{23}H\textsubscript{22}N\textsubscript{4}O\textsubscript{6}S, M.Wt. 482.13, calculated: C: 56.24 H: 4.72 N: 11.08 S: 6.52 found: C: 56.72 H: 4.95 N: 14.33 S: 6.91. IR (KBr; cm\textsuperscript{-1}): 3538 (NH), 3045 (CH aromatic), 2915 (CH\textsubscript{aliphatic}), 1769, 1716 (2C=O), 1594 (C=N). 1\textsuperscript{H} NMR (DMSO, \(\delta\) ppm): 3.00 (6H, s, 2CH\textsubscript{2}), 5.21 (2H, s, CH\textsubscript{2}), 6.74-7.95 (14H, m, Haromatic, Hthiazole), 9.62 (1H, s, NH exchangeable with D\textsubscript{2}O). MS: (m/z) ~ [M+1]+ 482 (2%).

General procedure for preparation of compounds (4a, b)

A mixture of compound 2 (0.35 g, 1 mmol) dissolved in absolute ethanol (5 ml) and dimethylformamide (0.5 ml) and the respective monosaccharide, namely, D-arabinose or D-mannose (1 mmol) dissolved in absolute ethanol (5 ml) and anhydride, maleic anhydride and/or phthalic anhydride (1 mmol) in glacial acetic acid was heated under reflux for 8 hr. The reaction mixture was then cooled, poured on ice water, washed with sodium carbonate solution (4 N) then with water. The separated solid was filtered off, washed with water till carbonate-free then cold ethanol then ether and dried under vacuum at room temperature to give the corresponding compounds 4a, b, respectively (Scheme 1).

2-\{[4-(2-[2,3,4,5-Tetrahydroxypropylidene]amino)-1,3-thiazol-4-yl]phenyl]amino\} methyl-1H-isooindole-1,3(2H)-dione (5a)

Crystallized from acetic acid, dark yellow crystals, mp 173-5 °C, yield 65%. Analysis: for C\textsubscript{24}H\textsubscript{24}N\textsubscript{4}O\textsubscript{7}S, M.Wt. 481.14, calculated: C: 56.65 H: 4.79 N: 11.83 S: 6.65 found: C: 57.43 H: 4.47 N: 9.55 S: 11.23. IR (KBr; cm\textsuperscript{-1}): 3675-3209 (4OH), 3365 (NH), 3095 (CH aromatic), 2927 (CH\textsubscript{aliphatic}), 1769, 1716, 1656 (3C=O), 1610 (C=N). 1\textsuperscript{H} NMR (DMSO, \(\delta\) ppm): 2.52-2.89 (4H, m, 4OH), 3.38-4.38 (7H, m, 3CH, 2CH\textsubscript{2}), 5.14 (2H, s, CH\textsubscript{2}), 6.15 (1H, s, CH of thiazolidinone), 6.92-8.20 (9H, m, H\textsubscript{aromatic}, H\textsubscript{thiazole}). 8.95 (1H, s, NH exchangeable with D\textsubscript{2}O).

General procedure for preparation of compounds (5a, b)

A solution of compounds 4a, b (4 mmol) and thioglycolic acid (0.6 ml, 8 mmol) in dioxane (10 ml) was stirred at room temperature for 10-12 hr. The solvent was evaporated and the residue was washed with sodium carbonate solution (4 N) then with water. The separated solid was filtered off, washed with water till carbonate-free then cold ethanol then ether and dried under vacuum at room temperature to give the corresponding compounds 5a, b, respectively (Scheme 1).

2-\{[4-\{2-\{4-Oxo-2-(1,2,3,4-tetrahydroxybutyl)-1,3-thiazolidin-3-yl\}-1,3-thiazol-4-yl\}phenyl]amino\} methyl-1H-isooindole-1,3(2H)-dione (5b)

Crystallized from acetic acid, dark yellow crystals, mp 175-8 °C, yield 60%. Analysis: for C\textsubscript{25}H\textsubscript{26}N\textsubscript{4}O\textsubscript{8}S\textsubscript{2}, M.Wt. 586.12, calculated: C: 53.23 H: 4.47 N: 9.55 S: 10.96 found: C: 53.16 H: 4.78 N: 9.58 S: 11.23. IR (KBr; cm\textsuperscript{-1}): 3658-3216 (5OH), 3446 (NH), 3095 (CH\textsubscript{aromatic}), 2924 (CH\textsubscript{aliphatic}), 1770, 1717, 1656 (3C=O), 1610 (C=N). 1\textsuperscript{H} NMR (DMSO, \(\delta\) ppm): 2.49-2.68 (5H, m, 5OH), 3.43-4.38 (8H, m, 4CH, 2CH\textsubscript{2}), 5.14 (2H, s, CH\textsubscript{2}), 6.14 (1H, s, CH of thiazolidinone), 6.89-8.16 (9H, m, H\textsubscript{aromatic}, H\textsubscript{thiazole}). 8.67 (1H, s, NH exchangeable with D\textsubscript{2}O).
2-[[4-{2-(2,5-Dioxopyrrolidin-1-yl)-1,3-thiazol-4-yl}phenyl]amino]methyl]-1H-isindole-1,3(2H)-dione (6a)

Crystallized from ethanol, dark green crystals, mp 124-5 °C, yield 55%. Analysis: for C_{22}H_{16}N_{4}O_{4}S, M.Wt. 432.09, calculated: C: 61.10 H: 3.63 N: 11.39 S: 6.89. IR (KBr; cm^{-1}): 3350, 3226 (NH 2, 2NH), 3059 (CH aromatic), 2926 (CH aliphatic), 1774, 1719 (4C=O), 1593 (C=N). 1H NMR (DMSO, δ ppm): 0.86 (3H, s, NH exchangeable with D 2O), 5.10 (2H, s, CH 2), 6.74-7.93 (9H, m, H aromatic, Hthiazole), 9.14 (1H, s, NH exchangeable with D2O).

2-[[4-{2-(2,5-Dioxo-2,5-dihydro-1H-pyrrole-1-yl)-1,3-thiazol-4-yl}phenyl]amino]methyl]-1H-isindole-1,3(2H)-dione (6b)

Crystallized from methanol, dark green crystals, mp 132-4 °C, yield 65%. Analysis: for C_{22}H_{16}N_{4}O_{4}S, M.Wt. 430.07, calculated: C: 61.39 H: 4.33 N: 11.66 S: 7.45. IR (KBr; cm^{-1}): 3358, 3036 (NH), 3039 (CH aromatic), 2925 (CH aliphatic), 1770, 1714 (2C=O), 1611 (C=N). 1H NMR (DMSO, δ ppm): 1.12 (3H, s, CH 3, OCH 3), 3.83 (3H, s, OCH 3), 3.87 (3H, s, OCH 3), 5.00 (2H, s, CH 2), 6.93-7.95 (9H, m, H aromatic, Hthiazole), 9.85 (1H, s, NH exchangeable with D 2O). MS: (m/z) ~ [M]+ 430 (28.6%).

2-[[4-{2-(2,5-Dioxo-2,5-dihydro-1H-pyrrole-1-yl)-1,3-thiazol-4-yl}phenyl]amino]methyl]-1H-isindole-1,3(2H)-dione (6c)

Crystallized from methanol, brownish green crystals, mp 187-9 °C, yield 55%. Analysis: for C_{23}H_{18}N_{5}O_{2}S, M.Wt. 499.13, calculated: C: 62.77 H: 4.37 N: 13.78 S: 6.56. IR (KBr; cm^{-1}): 3562-3324 (OH, 2NH), 3358 (NH), 3039 (CH aromatic), 2925 (CH aliphatic), 1770, 1714 (2C=O), 1610 (C=N). 1H NMR (DMSO, δ ppm): 3.84 (3H, s, OCH 3), 5.17 (2H, s, CH 2), 6.95-7.88 (13H, m, H aromatic, Hthiazole), 9.63, 9.77 (2H, 2s, NH exchangeable with D 2O), 10.27 (1H, s, OH exchangeable with D 2O). MS: (m/z) ~ [M]+ 499 (2.6%).

2-[[4-{2-(4-{2-[(4,3-Dimethoxybenzylidene)hydrazinyl]-1,3-thiazol-4-yl}phenyl]amino]methyl]-1H-isindole-1,3(2H)-dione (6b)

Crystallized from acetic acid, brown crystals, mp 187-9 °C, yield 55%. Analysis: for C_{23}H_{18}N_{5}O_{2}S, M.Wt. 513.10, calculated: C: 63.14 H: 4.51 N: 13.64 S: 6.24. IR (KBr; cm^{-1}): 3456, 3366 (2NH), 3065 (CH aromatic), 2925 (CH aliphatic), 1770, 1711 (2C=O), 1608 (C=N). 1H NMR (DMSO, δ ppm): 3.83 (3H, s, OCH 3), 3.87 (3H, s, OCH 3), 5.14 (2H, s, CH 2), 7.08-8.12 (13H, m, H aromatic, Hthiazole), 9.63, 9.84 (2H, 2s, NH exchangeable with D 2O). MS: (m/z) ~ [M]+ 513 (2.3%).
SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL EVALUATION OF NEWLY ... 683

178-9 °C, yield 70%. Analysis: for C_{27}H_{24}N_{6}O_{2}S, M.Wt. 496.17, calculated: C: 65.30 H: 4.87 N: 16.92 S: 6.46 found: C: 65.04 H: 4.98 N: 17.08 S: 6.38. IR (KBr; cm^{-1}): 3434, 3372 (2NH), 3065 (CH aromatic), 2923 (CH aliphatic), 1771, 1713 (2C=O), 1596 (C=N). ¹H NMR (DMSO, δ ppm): 3.01 (6H, s, 2CH₃), 5.18 (2H, s, CH₂), 6.73-8.05 (14H, m, H aromatic, H thiazole), 5.66, 9.67 (2H, 2s, 2NH exchangeable with D₂O). MS: (m/z) ~ [M+] 496 (11.1%).

2-[[4-[[2-[[4-Chlorobenzylidene] hydrazinyl]-1,3-thiazol-4-yl]phenyl]amino] methyl]-1H-isoindole-1,3(2H)-dione (8d)
Crystallized from dioxane, brown crystals, mp 237-9 °C, yield 60%. Analysis: for C_{25}H_{18}ClN_{5}O_{2}S, M.Wt. 487.09, calculated: C: 61.54 H: 3.72 N: 7.27 S: 6.56 found: C: 61.70 H: 3.58 N: 7.13 S: 6.82. IR (KBr; cm^{-1}): 3456, 3368 (2NH), 3034 (CH aromatic), 2917 (CH aliphatic), 1769, 1708 (2C=O), 1608 (C=N). ¹H NMR (DMSO, δ ppm): 5.09 (2H, s, CH₂), 7.23-8.21 (14H, m, H aromatic, H thiazole), 5.66, 9.96 (2H, 2s, 2NH exchangeable with D₂O). MS: (m/z) ~ [M] + 487 (1.9%), 489 (0.6%).

General procedure for preparation of compounds (9a,b)
A mixture of compounds 8a,c (1 mmol) and triethylamine (0.2 g, 2 mmol) was dissolved in dioxane (0.5 ml) and cooled. To this cooled solution, acetyl chloride (0.07 ml, 1 mmol) was added slowly at 0 °C. The mixture was stirred for 24 hr and set aside for 48 hr at room temperature. The formed solution was concentrated then the obtained product was poured on ice water. The separated solid was filtered off, washed with water and vacuum dried to give compounds 9a,b, respectively (Scheme 2).

2-[[4-[[2-[[4-(4-Dimethylaminophenyl)-2-oxoazetidin-1-yl]amino]-1,3-thiazol-4-yl]phenyl]amino] methyl]-1H-isoindole-1,3(2H)-dione (9b)
Crystallized from acetone, dark brown crystals, mp 162-4 °C, yield 42%. Analysis: for C_{29}H_{26}N_{6}O_{3}S, M.Wt. 538.18, calculated: C: 64.67 H: 4.87 N: 15.60 S: 5.95 found: C: 64.61 H: 5.04 N: 15.83 S: 6.08. IR (KBr; cm^{-1}): 3445, 3365 (2NH), 3093 (CH aromatic), 2920 (CH aliphatic), 1770, 1712, 1654 (3C=O), 1599 (C=N). ¹H NMR (DMSO, δ ppm): 2.35-3.12 (2H, dd, CH₂-C=O), 3.01 (6H, s, 2CH₃), 4.22 (1H, t, CH-N), 5.23 (2H, s, CH₂), 6.95-7.96 (13H, m, H aromatic, H thiazole), 5.73, 9.74 (2H, 2s, 2NH exchangeable with D₂O). MS: (m/z) ~ [M]+ 538 (61.1%).

General procedure for preparation of compounds (10a,b)
A solution of chloroacetyl chloride (0.13 g, 12 mmol) in dry dioxane was added dropwise below 10 °C to a well stirred solution of compounds 8a,c (1 mmol) and triethylamine (0.3 g, 3 mmol). The reaction mixture was stirred for 6-7 hr, then the excess dioxane is removed and the residue was poured onto ice water, the resulting solid was filtered off, washed and vacuum dried to give compounds 10a,b (Scheme 2).

2-[[4-[[2-[[3-Chloro-4-[4-(dimethylamino)phenyl]-2-oxoazetidin-1-yl]amino]-1,3-thiazol-4-yl]phenyl]amino] methyl]-1H-isoindole-1,3(2H)-dione (10b)
Crystallized from acetone, dark brown crystals, mp 176-7 °C, yield 55%. Analysis: for C_{29}H_{25}ClN_{6}O_{3}S, M.Wt. 572.14, calculated: C: 64.61 H: 5.04 N: 15.83 S: 6.08. IR (KBr; cm^{-1}): 3445, 3365 (2NH), 3093 (CH aromatic), 2920 (CH aliphatic), 1771, 1714, 1668 (3C=O), 1609 (C=N). ¹H NMR (DMSO, δ ppm): 2.23-3.12 (2H, dd, CH₂-C=O), 3.01 (6H, s, 2CH₃), 4.22 (1H, t, CH-N), 5.23 (2H, s, CH₂), 6.95-7.96 (13H, m, H aromatic, H thiazole), 5.73, 9.74 (2H, 2s, 2NH exchangeable with D₂O). MS: (m/z) ~ [M]+ 572 (31.3%).

2-[[4-[[2-[[3-Chloro-4-[4-(dimethylamino)phenyl]2-oxoazetidin-1-yl]amino]-1,3-thiazol-4-yl]phenyl]amino]methyl]-1H-isoindole-1,3(2H)-dione (10b)
Crystallized from acetone, dark brown crystals, mp 176-7 °C, yield 55%. Analysis: for C_{29}H_{25}ClN_{6}O_{3}S, M.Wt. 572.14, calculated: C:
60.78 H: 4.40 N: 14.67 S: 5.60 found: C: 60.96 H: 4.29 N: 14.69 S: 5.38. IR (KBr; cm\(^{-1}\)): 3456, 3366 (2NH), 3092 (CH aromatic), 2919 (CH aliphatic), 1773, 1711, 1673 (3C=O), 1606 (C=N). \(^1\)H NMR (DMSO, \(\delta \) ppm): 2.51(1H, d, CH-N), 3.01 (6H, s, 2CH\(_3\)), 3.10 (1H, d, HC-Cl), 6.97-7.91 (13H, m, H aromatic, Hthiazole), 5.64, 9.63 (2H, 2s, 2NH exchangeable with D\(_2\)O). MS: (m/z) \~ [M]+ 572 (8.1%).

General procedure for preparation of compounds (11a,b)

A mixture of compounds 8b,d (1 mmol) and thioglycolic acid (0.2 ml, 2 mmol) in benzene (10 ml) was heated under reflux for 8-10 hr. The formed solid was filtered off and air dried to give compounds 11a,b, respectively (Scheme 2).

2-({[4-(2-{[2-(3,4-Dimethoxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]amino}-1,3-thiazol-4-yl) phenyl] amino} methyl)-1H-isoindole-1,3(2H)-dione (11a)

Crystallized from dioxane, brown crystals, mp 109-11°C, yield 70%. Analysis: for C\(_{29}\)H\(_{25}\)N\(_5\)O\(_5\)S\(_2\), M.Wt. 587.13, calculated: C: 59.27 H: 4.29 N: 11.92 S: 10.91 found: C: 59.54 H: 4.45 N: 12.31 S: 10.78. IR (KBr; cm\(^{-1}\)): 3447, 3369 (2NH), 3075 (CH aromatic), 2927 (CH aliphatic), 1772, 1711, 1660 (3C=O), 1612 (C=N). \(^1\)H NMR (DMSO, \(\delta \) ppm): 3.15-3.29 (2H, dd, CH\(_2\)thiazolidinone), 3.85 (3H, s, OCH\(_3\)), 3.89 (3H, s, OCH\(_3\)), 4.97 (1H, s, CH thiazolidinone), 5.18 (2H, s, CH\(_2\)), 6.80-8.03 (12H, m, Haromatic, Hthiazole), 5.66, 9.80 (2H, 2s, 2NH exchangeable with D\(_2\)O). MS: (m/z) \~ [M]+ 589 (11.1%).

2-({[4-(2-{[5-Methyl-2-(3,4-dimethoxy-phenyl)-4-oxo-1,3-thiazolidin-3-yl]amino}-1,3-thiazol-4-yl) phenyl] amino} methyl)-1H-isoindole-1,3(2H)-dione (11b)

Crystallized from acetic acid, dark brown crystals, mp 138-40°C, yield 65%. Analysis: for C\(_{30}\)H\(_{27}\)N\(_5\)O\(_5\)S\(_2\), M.Wt. 601.15, calculated: C: 59.63 H: 4.45 N: 12.31 S: 10.78 found: C: 59.54 H: 4.45 N: 12.31 S: 10.78. IR (KBr; cm\(^{-1}\)): 3459, 3365 (2NH), 2930 (CH aliphatic), 2972 (CH\(_2\)), 1789, 1715, 1660 (3C=O), 1612 (C=N). \(^1\)H NMR (DMSO, \(\delta \) ppm): 1.41 (3H, d, CH\(_3\) thiazolidinone), 3.62 (1H, q, CH thiazolidinone), 3.83 (3H, s, OCH\(_3\)), 5.14 (2H, s, CH\(_2\)), 6.80-8.03 (12H, m, Haromatic, Hthiazole), 5.66, 9.65 (2H, 2s, 2NH exchangeable with D\(_2\)O). MS: (m/z) \~ [M]+ 602 (64.5%).

General procedure for preparation of compounds (12a,b)

A mixture of compounds 8b,d (1 mol) and thiolactic acid (0.2 ml, 2 mmol) was fused at 140°C on sand bath for 6-8 hr. The solid mass was crystallized from the proper solvent to give the corresponding compounds 12a,b, respectively (Scheme 2).

2-({[4-(2-{[5-Methyl-2-(3,4-dimethoxy-phenyl)-4-oxo-1,3-thiazolidin-3-yl]amino}-1,3-thiazol-4-yl) phenyl] amino} methyl)-1H-isoindole-1,3(2H)-dione (12a)

Crystallized from acetic acid, dark brown crystals, mp 138-40°C, yield 65%. Analysis: for C\(_{28}\)H\(_{21}\)N\(_5\)O\(_5\)S\(_2\), M.Wt. 575.09, calculated: C: 58.38 H: 3.85 N: 12.13 found: C: 58.50 H: 3.99 N: 11.83. IR (KBr; cm\(^{-1}\)): 3436, 3347 (2NH), 2927 (CH\(_2\)), 1789, 1715, 1660 (3C=O), 1612 (C=N). \(^1\)H NMR (DMSO, \(\delta \) ppm): 1.40 (3H, d, CH\(_3\) thiazolidinone), 3.60 (1H, q, CH thiazolidinone), 4.40 (1H, s, CH thiazolidinone), 5.19 (2H, s, CH\(_2\)), 7.00-7.97 (13H, m, Haromatic, Hthiazole), 7.83, 10.0 (2H, 2s, 2NH exchangeable with D\(_2\)O). MS: (m/z) \~ [M]+ 575 (8.1%), 577 (2.6%).

Preparation of Ethyl (4-{{[1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl]methyl}amino} phenyl) (oxo)acetate (13)

To a solution of selenium dioxide (0.34 g, 3 mmol) in absolute ethanol (10 ml), compound I (0.75 g, 2 mmol) was added. The mixture was heated under reflux for 15 hr. The precipitated selenium metal was removed by filtration and the filtrate was evaporated and the residue was crystallized from ethanol, yellow crystals (Scheme 3), mp 134-6 °C, yield 71%. Analysis: for C\(_{29}\)H\(_{17}\)Cl\(_2\)N\(_2\)O\(_4\), M.Wt. 532.11, calculated: C: 64.77 H: 4.58 N: 7.95, found: C: 64.89 H: 4.50 N: 8.11. IR (KBr; cm\(^{-1}\)): 3371 (NH), 3074 (CH\(_\text{aromatic}\)).
SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL EVALUATION OF NEWLY ...

2921 (CH$_{aliphatic}$), 1772, 1716, 1670 (4C=O). 1H NMR (DMSO, δ ppm): 1.41 (3H, t, CH$_3$), 3.95 (2H, q, OCH$_2$), 5.24 (2H, s, CH$_2$), 7.73-8.31 (8H, m, H$_{aromatic}$), 9.47 (1H, s, NH exchangeable with D$_2$O).

Preparation of 2-((4-(3-Oxo-3,4-dihydro-quinoxalin-2-yl)phenyl) amino) methyl)-1H-isoindole-1,3 (2H)-dione (14)

A solution of benzene-1,2-diamine (0.15 g, 1.4 mmol) in ethanol (5 ml) was added to the solution of compound 13 (0.35 g, 1 mmol) in ethanol (10 ml) and the mixture was heated on steam bath for 8 hr. The solution was diluted with water and the formed precipitate was filtered off, washed with cold alcohol, crystallized from ethanol, light yellow crystals (Scheme 3), mp 215-6 °C, yield 68%. Analysis: for C$_{23}$H$_{16}$N$_4$O$_3$, M.Wt. 396.14, calculated: C: 69.69 H: 4.07 N: 14.13, found: C: 69.21 H: 4.31 N: 14.33. IR (KBr; cm$^{-1}$): 3426, 3323 (2NH), 3091 (CH aromatic), 2926 (CH aliphatic), 1769, 1715, 1656 (3C=O), 1610 (C=N). 1H NMR (DMSO, δ ppm): 5.49 (2H, s, CH$_2$), 7.31-8.20 (12H, m, H aromatic), 8.45, 9.67 (2H, 2s, 2NH exchangeable with D$_2$O). MS: (m/z) ~ [M-1]$^+$ 395 (79.3%).

Preparation of 2-[(4-[(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl] amino) phenyl]-2-oxoethyl propanedinitrile (15)

A mixture of compound 1 (0.75 g, 2 mmol) and malononitrile (0.13 g, 2 mmol) in absolute ethanol (10 ml) was treated with sodium hydroxide solution (2 ml, 40%) dropwise with stirring for about 10 min. After complete addition, the reaction mixture was diluted with water (5 ml). The formed precipitate was filtered off, washed several times with water and air dried to give compound 15, buff crystals (Scheme 3), mp 135-7 °C, yield 65%. Analysis: for C$_{20}$H$_{14}$N$_4$O$_3$, M.Wt. 358.11, calculated: C: 64.03 H: 3.94 N: 15.63, found: C: 64.35 H: 4.11 N: 15.84. IR (KBr; cm$^{-1}$): 3448 (NH), 3032 (CH aromatic), 2925 (CH aliphatic), 2199 (2C≡N), 1774, 1716, 1667 (3C=O). 1H NMR (DMSO, δ ppm): 2.96 (2H, d, CH$_2$), 4.03 (1H, t, CH), 5.12 (2H, s, CH$_2$), 7.33-8.30 (8H, m, H$_{aromatic}$), 9.58 (1H, s, NH exchangeable with D$_2$O). MS: (m/z) ~ [M+$^+$]$^+$ 398 (79.3%).

Preparation of 2-Amino-5-(4-[(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl) methyl]amino) phenyl)furan-3-carbonitrile (16)

A solution of compound 15 (0.36 g, 1 mol) in acetic acid (5 ml) was heated under reflux with 0.5 ml concentrated hydrochloric acid for 10 h. The reaction mixture was cooled and diluted with water, and then the formed solid was filtered off, dried under vacuum and then crystallized from ethanol, light brown crystals (Scheme 3), mp 102-3 °C, yield 75%. Analysis: for C$_{20}$H$_{14}$N$_4$O$_3$, M.Wt. 358.11, calculated: C: 66.94 H: 4.75 N: 18.02, found: C: 66.58 H: 4.96 N: 18.29. IR (KBr; cm$^{-1}$): 3467, 3363, 3220 (NH, 2NH), 3069 (CH$_{aromatic}$), 2922 (CH$_{aliphatic}$), 1773, 1716, 1660 (3C=O), 1603 (C=N). 1H NMR (DMSO, δ ppm): 3.02 (2H, s, COCH$_2$), 5.27 (2H, s, CH$_2$), 7.03-7.89 (8H, m, H$_{aromatic}$), 5.69, 8.75, 9.63, 10.74 (6H, 4s, 2NH, 2NH$_2$ exchangeable with D$_2$O). MS: (m/z) ~ [M+$^+$]$^+$ 395 (79.3%).

General procedure for preparation of compounds (17a,b)

To a solution of compound 15 (0.36 g, 1 mmol) in ethanol (8 ml), hydrazine hydrate or phenyl hydrazine (1.5 mmol) was added. The reaction mixture was refluxed for 13-15 hr. The formed precipitate was then filtered off and air dried to give compounds 17a,b (Scheme 3).

2-[(4-{(3,5-Diamino-1H-pyrazol-4-yl)acetyl} phenyl)amino)methyl]-1H-isoindole-1,3(2H)-dione (17a)

Crystallized from methanol, light brown crystals, mp 212-4 °C, yield 55%. Analysis: for C$_{20}$H$_{18}$N$_6$O$_3$, M.Wt. 390.13, calculated: C: 61.53 H: 4.65 N: 15.63, found: C: 61.20 H: 4.67 N: 15.84. IR (KBr; cm$^{-1}$): 3448 (NH, NH$_2$), 3168 (2NH, 2NH$_2$), 3019 (CH aromatic), 2898 (CH$_{aliphatic}$), 1774, 1720, 1658 (3C=O), 1610 (C=N). 1H NMR (DMSO, δ ppm): 5.06 (2H, s, CH$_2$), 4.80 (2H, s, NH$_2$ exchangeable with D$_2$O), 8.77 (1H, s, NH exchangeable with D$_2$O), 6.57-8.19 (m, 9H, H$_{aromatic}$, H$_{furan}$).

Preparation of 2-Amino-5-(4-[(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl] amino) phenyl)furan-3-carbonitrile (16)

A solution of compound 15 (0.36 g, 1 mol) in acetic acid (5 ml) was heated under reflux with 0.5 ml concentrated hydrochloric acid for 10 h. The reaction mixture was cooled and diluted with water, and then the formed solid was filtered off, dried under vacuum and then crystallized from ethanol, light brown crystals (Scheme 3), mp 102-3 °C, yield 75%. Analysis: for C$_{20}$H$_{18}$N$_6$O$_3$, M.Wt. 390.13, calculated: C: 61.53 H: 4.65 N: 15.63, found: C: 61.20 H: 4.67 N: 15.84. IR (KBr; cm$^{-1}$): 3438, 3383, 3220 (NH, 2NH$_2$), 3069 (CH$_{aromatic}$), 2922 (CH$_{aliphatic}$), 1773, 1716, 1660 (3C=O), 1603 (C=N). 1H NMR (DMSO, δ ppm): 5.69, 8.75, 9.63, 10.74 (6H, 4s, 2NH, 2NH$_2$ exchangeable with D$_2$O). MS: (m/z) ~ [M+$^+$]$^+$ 393 (19.4%).

Antimicrobial evaluation

Most of the newly synthesized compounds diluted with water, and then the formed solid was filtered off, dried under vacuum and then crystallized from ethanol, light brown crystals (Scheme 3), mp 102-3 °C, yield 75%. Analysis: for C$_{20}$H$_{18}$N$_6$O$_3$, M.Wt. 390.13, calculated: C: 61.53 H: 4.65 N: 15.63, found: C: 61.20 H: 4.67 N: 15.84. IR (KBr; cm$^{-1}$): 3448 (NH, NH$_2$), 3168 (2NH, 2NH$_2$), 3019 (CH$_{aromatic}$), 2898 (CH$_{aliphatic}$), 1774, 1720, 1658 (3C=O), 1610 (C=N). 1H NMR (DMSO, δ ppm): 5.06 (2H, s, CH$_2$), 4.80 (2H, s, NH$_2$ exchangeable with D$_2$O), 8.77 (1H, s, NH exchangeable with D$_2$O), 6.57-8.19 (m, 9H, H$_{aromatic}$, H$_{furan}$).

 Egyptians J. Chem. 60, No.4 (2017)
were individually tested against highly pathogenic strains of gram positive (Staphylococcus aureus (ATCC 29213), 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, yeasts (Saccharomyces cerevisiae, Candida albicans (NRRLY-477)) and fungus (Aspergillus niger (local isolate)) using 100 μl of suspension containing 1x10⁸ colony-forming unit/mL (CFU/ml) of pathological tested bacteria, 1 x 10⁶ CFU/ml of yeast and 1 x 10⁶ CFU/ml of fungi spread on nutrient agar (NA), Sabourand dextrose agar medium (SDA) and Potato dextrose agar medium (PDA), respectively.

**Agar well diffusion assay**

Antimicrobial screening was carried out by the agar well diffusion method of Perez et al.[19]. After the preparation of nutrient agar media (sabourand dextrose agar (SDA) and potato dextrose agar medium (PDA) for bacteria and fungi, respectively), they were left to cool and solidify; 100 μL of suspension containing 1 x 10⁸ CFU/ml of pathological tested bacteria, 1 x 10⁶ CFU/ml of fungi were spread on nutrient agar. Then, wells (10 mm in diameter) were made in the solidified agar and loaded with 100 μl of tested compound solutions [prepared by dissolving 100 mg of the chemical compound in 1 ml of dimethyl sulfoxide (DMSO)]. The inculcated plates were then incubated for 24 hr at 37°C for bacteria and 48 hr at 28 °C for fungi. Negative controls were prepared using the solvent employed for dissolving the tested compound (DMSO). Ciprofloxacin (50 mg/ml) and Ketoconazole (50 mg/ml) were used as standard for antibacterial and antifungal activities, respectively. After the incubation time, the antimicrobial activity was evaluated by measuring the diameter (mm) of the inhibition zone (IZ) of the selected compounds against the test organisms. The experiments were carried out in triplicate and the average inhibition zone was calculated (Table 1).

**Broth dilution method**

The bacteriostatic activity of the active compounds (IZ ≥ 16 mm) was then evaluated using the two-fold serial dilution technique.[20] 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, 25 mg/ml. Each 5 ml received 0.1 ml of the appropriate inoculum and incubated at 37°C for 24 hr. The lowest concentration showing no growth was taken as MIC (Table 2).

**References**

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In an attempt to prepare new antibacterial agents, a series of new derivatizations of the thiazolidin-2-one and thiazole rings have been prepared. The structures of these compounds have been confirmed by infrared, nuclear magnetic resonance, and mass spectra. Most of the compounds were screened for their antibacterial activity by the agar well diffusion assay and the broth dilution method. The results show that the most active compound is the derivative 2-(3,4-dihydrobenzo[1,2]thiazole-1-carboxylic acid).