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Synthesis of some novel azaheterocycles utilizing 3-(4-nitrobenzylidene)-5-phenylfuran-2(3*H*)-one with expected antimicrobial activity

Mohamed. F. El-Shehry,[1*] Khadiga. M. Abu-Zied,[2] Ewies. F. Ewies,[3] Samir.M.Awad,[4] Maysa. E. Mohram[5]

[1]*Pesticide Chemistry Department, National Research Centre, Dokki, Egypt*
[2]*Photochemistry Department, National Research Centre, Dokki, Egypt*
[3]*Organomettalic and Organometalloid Chemistry Department, National Research Centre, Dokki, Egypt*
[4] *Pharmaceutical Organic Chemistry Departement, Helwan University, Egypt*
[5] *Microbial Chemistry Department, National Research Centre, Dokki, Egypt*

ABSTRACT

3-(4-Nitrobenzylidene)-5-phenylfuran-2(3H)-one ***2*** *was prepared and converted into a variety of heterocyclic systems of synthetic and biological importance via reaction with nitrogen nucleophiles. Benzylamine reacted with the furanone* ***2****; the product was found to depend on the reaction conditions. Thus, at room temperature the open-chain N-benzylamide* ***3*** *was obtained, whereas under refluxing conditions the 3-(4-Nitrobenzylidene)-5-phenyl-1-benzyl-2(3H)-pyrrolone* ***4*** *was obtained. Hydrazine hydrate affected ring opening of the furanone to give the corresponding acid hydrazide* ***5****. The latter was used as key starting materials for the synthesis of aminotriazole* ***17*** *and 1,3,4-oxadiazole derivatives* ***15a-c****. The structural elucidation of products is reported and also some of the products were screened for their antimicrobial activity.*

Keywords: 2(3*H*)-Furanones, 2(3*H*)-pyrrolones, acid hydrazide, pyridazin-3(4*H*)-one, pyrrolo [2,3-*c*] pyrazole, 5-thioxo-1*H*-1,2,4-triazol-3-yl, 1,3,4-oxadiazoles derivatives.

INTRODUCTION

The furanone ring system, also known as butyrolactone or butenolide, is a widely recognized component of natural products exhibiting a wide range of interesting biological activities. Different classes of synthetic furanones and pyrrolones possess an extensive spectrum of pharmacological activities.[1,2] In particular, compounds bearing 2(3*H*)-furanone and 2(3*H*)-pyrrolone rings are known to exhibit important activities such as anti-inflammatory, analgesic, cardiotonic, anticonvulsant and COX-2 inhibition activities in addition to antioxidant, cytotoxic, antifungal, antibacterial and antiviral activities.[3-13] In continuation to our interest in the chemistry of 2(3*H*)-furanone and 2(3*H*)-pyrrolone rings we report here the results of our work aimed at exploring the potential utility of 2(3*H*)-furanone in the heterocyclic synthesis. Conversion of **2** into the corresponding pyridazones, oxadiazoles and some novel azaheterocyclec derivatives with anticipating potential biological interest.[14-17]

MATERIALS AND METHODS

All melting points were determined on a Gallenkamp melting point apparatus. The IR spectra were recorded on a Perkin Elmer 317 Grating IR spectrophotometer, using KBr pellets. The ^{1}H and ^{13}C NMR spectra were measured on a Joel E.C.A-500 MHz instrument in DMSO-d_6 as solvents and using TMS as internal standard. The mass spectra were performed on a Joel JMS-A X 500 spectrometer. Elemental analyses were carried out at the Microanalysis Laboratory, Cairo University, Cairo, Egypt. Giza, Egypt. TLC: Merck 0.2 mm silica gel 60 F154 anal aluminium plates. Compound **1**, was prepared according to the reported method.[18]

3-(4-Nitrobenzylidene)-5-phenylfuran-2(3*H*)-one (2)
A solution of 3-benzoylpropionic acid **1** (0.53g, 3 mmol) and 4-nitrobenzaldehyde (0.45g, 3 mmol) in acetic anhydride (15 mL) with triethylamine (3 drops) was refluxed for 4 h under anhydrous conditions. After completion of reaction, the contents were poured into crushed ice in small portions while stirring. A colored solid mass separated out, which was filtered, washed with water and crystallized from a mixture of methanol to give **2**.

Yield 72%; mp: 135-137 °C. IR (KBr): ν 1770 (lactone CO) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 6.59 (s, 1H, furanone H-4), 7.19-8.21 (m, 10H, ArH and olefinic H). ^{13}C NMR (DMSO-d_6): δ 107.6, 116.4, 123.7, 126.4, 127.5, 129.8, 130.3, 135.2, 141.2, 145.6, 148.2, 155.1, 177.5. MS m/z (%): 293 [M^+]. Analysis for $C_{17}H_{11}NO_4$ (293.27) Calcd: C, 69.62; H, 3.78; N, 4.78. Found: C, 69.70; H, 3.72; N, 4.73

2-(4-Nitrobenzylidene)-*N*-benzyl-4-oxo-4-phenylbutanamide (3)
Furanone **2** (0.88g, 3 mmol) and benzylamine (0.43g, 4 mmol) were stirred in dry benzene for 3 h. On completion of reaction, excess benzene was distilled off and a solid mass so obtained was washed with petroleum ether and dried. The compound obtained was used without crystallization to give **3**.

Yield 68 %; mp: 185-186 °C. IR (KBr): ν 3350 (NH), 1715, 1665 (2CO) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 3.94 (s, 2H, CH_2CO), 4.15 (s, 2H, $PhCH_2$), 7.17-8.20 (m, 15H, ArH and olefinic H), 9.57 (s, 1H, NH, D_2O-exchangeable). ^{13}C NMR (DMSO-d_6): δ 40.6, 43.3, 124.8, 127.3, 128.5, 129.1, 129.9, 130.5, 137.2, 138.3, 140.2, 143.6, 147.8, 168.7, 170.7. MS m/z (%): 400 [M^+]. Analysis for $C_{24}H_{20}N_2O_4$ (400.43) Calcd: C, 71.99; H, 5.03; N, 7.00. Found: C, 71.94; H, 5.10; N, 7.09

3-(4-Nitrobenzylidene)-5-phenyl-1-benzyl-2(3*H*)-pyrrolone (4)
(**Method A**): Compound **3** (1.2g, 3 mmol) was refluxed in 6 N hydrochloric acid (20 mL) for 2 h. The contents were then cooled and a solid mass so obtained was collected, washed with water and crystallized from methanol to give **4**.
(**Method B**): Furanone **2** (0.88g, 3 mmol) and benzylamine (0.43g, 4 mmol) were refluxed in ethanol (15 mL) for 3 h. The reaction mixture concentrated to half its volume and the solid product was filtered off, washed with petroleum ether and dried to give **4**.

Yield 70 %; mp: 148-150 °C. IR (KBr): ν 1656 (CO) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 4.84 (s, 2H, benzyl CH_2), 6.59 (s, 1H, pyrrolone H-4), 7.10-8.12 (m, 15H, ArH and olefinic H). ^{13}C NMR (DMSO-d_6): δ 50.6, 105.4, 124.1, 124.5, 124.8, 125.3, 127.2, 127.5, 128.6, 130.2, 133.7, 136.2, 145.1, 146.5, 148.9, 179.7. MS m/z (%): 382 [M^+]. Analysis for $C_{24}H_{18}N_2O_3$ (382.41) Calcd: C, 75.38; H, 4.74; N, 7.33. Found: C, 75.44; H, 4.79; N, 7.27

2-(4-Nitrobenzylidene)-4-oxo-4-phenylbutanehydrazide (5)
Furanone **2** (1.47g, 5 mmol) and hydrazine hydrate (2 mL) in ethanol (10 mL) were stirred at 25°C for 3h. After The reaction mixture was poured onto crushed ice, a precipitate was obtained, which was filtered, dried and recrystallized from methanol to give **5**.

Yield 77 %; mp: 168-170 °C. IR (KBr): ν 3380, 3310 (NH_2, NH), 1710, 1660 (2 CO) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 3.96 (s, 2H, CH_2CO), 6.87 (br s, 2H, NH_2, D_2O-exchangeable), 7.10-8.09 (m, 10H, ArH and olefinic H), 9.70 (s, 1H, NHCO, D_2O-exchangeable). ^{13}C NMR (DMSO-d_6): δ 33.6, 124.7, 127.4, 129.1, 129.9, 130.5, 131.9, 137.5, 139.3, 143.2, 147.3, 167.7, 171.9. MS m/z (%): 325 [M^+]. Analysis for $C_{17}H_{15}N_3O_4$ (325.32) Calcd: C, 62.76; H, 4.65; N, 12.92. Found: C, 62.70; H, 4.59; N, 12.98

General procedure for the synthesis of (6) and (7)
Furanone **2** (1.47g, 5 mmol) and hydrazine hydrate (2 mL) or phenylhydrazine (0.5 mL) in ethanol (15 mL) were refluxed for 2h. After cooling the reaction mixture was poured onto crushed ice, a precipitate was obtained, which was filtered, dried and recrystallized from methanol to give the corresponding pyridazinone derivatives **6** and **7**, respectively.

4-(4-Nitrobenzyl)-6-phenylpyridazin-3(2*H*)-one (6)
Yield 78 %; mp: 194-196 °C. IR (KBr): ν 3262 (NH), 1655 (CO) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 4.10 (s, 2H, CH_2), 6.74 (s, 1H, pyridazinone H-5), 7.13-8.04 (m, 9H, ArH), 10.14 (br s, 1H, NH, D_2O-exchangeable). ^{13}C NMR (DMSO-d_6): δ 42.7, 124.2, 124.8, 125.1, 128.4, 129.1, 132.6, 141.6, 143.5, 145.8, 147.3, 169.8. MS m/z (%): 307 [M^+]. Analysis for $C_{17}H_{13}N_3O_3$ (307.30) Calcd: C, 66.44; H, 4.26; N, 13.67. Found: C, 66.49; H, 4.20; N, 13.70

4-(4-Nitrobenzylidene)-1,2-dihydro-1,6-diphenylpyridazin-3(4*H*)-one (7)
Yield 57 %; mp: 120-122 °C. IR (KBr): ν 3230 (NH), 1680 (CO) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 6.82 (s, 1H, pyridazinone H-5), 7.02-8.31 (m, 15H, ArH and olefinic H), 9.12 (br s, 1H, NHCO, D_2O-exchangeable). ^{13}C NMR (DMSO-d_6): δ 103.6, 122.3, 124.1, 124.8, 125.7, 126.3, 127.6, 129.2, 129.7, 131.4, 134.6, 135.2 138.8, 145.1, 147.8, 171.7. MS m/z (%): 383 [M^+]. Analysis for $C_{23}H_{17}N_3O_3$ (383.40) Calcd: C, 72.05; H, 4.47; N, 10.96. Found: C, 72.11; H, 4.40; N, 10.91

General procedure for the synthesis of (8) and (9)
A mixture of furanone **2** (1.47g, 5 mmol), and thiosemicarbazide or thiourea (0.009 mmol) were refluxed at 80 ºC in sodium ethoxide (Na 0.5 g, 20 mmol in 30 mL dry ethanol) for 12 h. After cooling, the reaction mixture was poured into acidic ice water and neutralized with HCl (pH ~ 7). The solid was filtered off, washed with water, dried and crystallized from DMF to give **8** or **9**, respectively.

3-(4,5-Dihydro-5-thioxo-1*H*-1,2,4-triazol-3-yl)-4-(4-nitrophenyl)-1-phenylbut-3-en-1-one (8)
Yield 65 %; mp: 248-250 °C. IR (KBr): ν 3365, 3230 (2NH), 1680 (CO) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 4.18 (s, 2H, -$COCH_2$), 7.08-8.15 (m, 10H, ArH and olefinic H), 8.50, 10.63 (2br s, 2H, 2NH`s, D_2O-exchangeable). ^{13}C NMR (DMSO-d_6): δ 33.6, 124.4, 128.3, 128.7, 129.8, 130.1, 131.5, 135.6, 136.7, 144.2, 148.9, 149.3, 160.7, 180.7. MS m/z (%): 366 [M^+]. Analysis for $C_{18}H_{14}N_4O_3S$ (366.39) Calcd: C, 59.01; H, 3.85; N, 15.29. Found: C, 59.08; H, 3.90; N, 15.23

6-(4-Nitrophenyl)-5-(2-oxo-2-phenylethyl)-2-thioxotetrahydro-pyrimidin-4(1*H*)-one (9)
Yield 70 %; mp: > 300 °C. IR (KBr): ν 3403, 3290 (2NH), 1682 (CO), 1255 (C=S) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 3.44 (m, 1H, pyrimidinone H-5), 4.17 (d, 1H, pyrimidinone H-6), 4.88 (m, 2H, -$COCH_2$), 7.18-8.27 (m, 9H, ArH), 9.52, 11.15 (br s, 2H, 2NH`s, D_2O-exchangeable). ^{13}C NMR (DMSO-d_6): δ 37.5, 43.4, 66.9, 115.3, 126.9, 127.4, 128.3, 128.6, 129.6, 135.1, 138.7, 142.7, 146.4, 148.3, 169.4, 175.8, 182.3. MS m/z (%): 369 [M^+]. Analysis for $C_{18}H_{15}N_3O_4S$ (369.39) Calcd: C, 58.53; H, 4.09; N, 11.38. Found: C, 58.59; H, 4.13; N, 11.33

Synthesis of (10a) and (11a)
A mixture of pyrrolone **4** (0.38g, 1 mmol), and hydrazine hydrate (3 mmol) was refluxed in ethanol for 2 h. The solid precipitated formed after concentrated of the reaction mixture was cooled, filtered off and recrystallized from ethanol to give **10a**. The solid product was refluxed at 80 ºC in sodium ethoxide (Na 0.5 g, 20 mmol in 30 mL dry ethanol) for 2 h. The reaction mixture was poured onto ice and acidified with 2 M HCl. The formed solid product was collected by filtration, washed with water, dried and finally recrystallized from the appropriate solvent, to afford pyrrolo[2,3-*c*]pyrazole **11a**.

1-Benzyl-3-(1-(4-nitrophenyl)-1-hydrazinomethyl)-5-phenyl-1*H*-pyrrol-2(3*H*)-one (10a)
Yield 65 %; mp: 181-183 °C. IR (KBr): ν 3369, 3261 (NH, NH_2), 1654 (CO) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 3.33-3.39 (m, 3H, $NHNH_2$), 4.22 (dd, *J* = 5.35 Hz, 1H, pyrrole H-3), 4.29 (d, *J* = 6.10 Hz, 1H, -CHNH), 4.81 (s, 2H, CH_2), 7.22-8.07 (m, 15H, ArH and pyrrole H-4). ^{13}C NMR (DMSO-d_6): δ 40.2, 40.3, 72.9, 123.4, 125.9, 127.3, 127.9, 128.6, 128.9, 131.7, 132.9, 139.6, 145.2, 146.8, 149.1, 173.4. MS m/z (%): 414 [M^+]. Analysis for $C_{24}H_{22}N_4O_3$ (414.46) Calcd: C, 69.55; H, 5.35; N, 13.52. Found: C, 69.49; H, 5.40; N, 13.58

6-Benzyl-2,3,3*a*,6-tetrahydro-3-(4-nitrophenyl)-5-phenylpyrrolo[2,3-*c*]pyrazole (11a)
Yield 70 %; mp: 166-168 °C. ^{1}H NMR (DMSO-d_6): δ 3.65 (dd, *J* = 5.8 Hz, 1H, pyrazole H-4), 4.24 (d, *J* = 6.3 Hz, 1H, pyrazole H-3), 4.85 (s, 2H, CH_2), 7.22-8.07 (m, 15H, ArH and pyrrole H-4), 10.20 (br s, 1H, NH, D_2O-exchangeable). ^{13}C NMR (DMSO-d_6): δ 72.9, 98.4, 109.2, 122.8, 124.5, 124.7, 125.7, 127.8, 128.8, 129.0, 129.5, 131.4, 133.6, 140.0, 145.1, 146.6, 154.3. MS m/z (%): 396 [M^+]. Analysis for $C_{24}H_{20}N_4O_2$ (396.44) Calcd: C, 72.71; H, 5.08; N, 14.13. Found: C, 72.68; H, 5.13; N, 14.18

General procedure for the synthesis of (11a), (11b), (12) and (13)
The procedure described above for synthesis of **11a** was followed except for use of (hydrazine hydrate, phenylhydrazine, thiosemicarbazide or thiourea) (3 mmol) with pyrrolone **4** (0.38g, 1 mmol) in one-step sequence to afford the corresponding pyrrolo[2,3-*c*]pyrazole **11a**, **11b**, pyrrolo[2,3-*c*]pyrazole **12** and pyrrolo[2,3-*d*]pyrimidine **13** derivatives**,** respectively.

6-Benzyl-2,3,3*a*,6-tetrahydro-3-(4-nitrophenyl)-2,5-diphenylpyrrolo[2,3-*c*]pyrazole (11b)
Yield 53 %; mp: 154-156 °C. ^{1}H NMR (DMSO-d_6): δ 3.73 (dd, *J* = 5.3 Hz, 1H, pyrazole H-4), 4.30 (d, *J* = 5.9 Hz, 1H, pyrazole H-3), 4.86 (s, 2H, CH_2), 7.12-8.14 (m, 20H, ArH and pyrrole H-4). ^{13}C NMR (DMSO-d_6): δ 70.5, 99.2, 112.3, 121.7, 123.5, 124.3, 124.4, 125.6, 127.7, 127.5, 128.7, 128.2, 132.3, 132.8, 140.3, 143.6, 145.2, 146.1, 154.4. MS m/z (%): 472 [M^+]. Analysis for $C_{30}H_{24}N_4O_2$ (472.54) Calcd: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.30; H, 5.09; N, 11.90

6-Benzyl-3,3a-dihydro-3-(4-nitrophenyl)-5-phenylpyrrolo[2,3-*c*]pyrazole-2(6*H*)-carbothioamide (12)
Yield 60 %; mp: 158-160 °C. IR (KBr): ν 3336 (NH_2), 1599 (C=N), 1254 (C=S) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 3.22 (dd, *J* = 5.7 Hz, 1H, pyrrole H-3), 4.29 (d, *J* = 6.1 Hz, 1H, pyrazole H-3), 4.83 (s, 2H, CH_2), 7.10-8.13 (m, 15H, ArH and pyrrole H-4), 8.15 (br s, 2H, NH_2, D_2O-exchangeable). ^{13}C NMR (DMSO-d_6): δ 47.2, 70.2, 94.6, 119.4, 123.7, 125.7, 126.4, 127.3, 128.1, 128.4, 128.6, 128.9, 135.3, 138.1, 140.4, 146.7, 146.9, 147.4, 148.5, 158.3, 178.4. MS m/z (%): 455 [M^+]. Analysis for $C_{25}H_{21}N_5O_2S$ (455.53) Calcd: C, 65.92; H, 4.65; N, 15.37. Found: C, 65.97; H, 4.59; N, 15.41

7-Benzyl-3,4-dihydro-4-(4-nitrophenyl)-6-phenyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2(7*H*)-thione (13)
Yield 70 %; mp: 170-172 °C. IR (KBr): ν 3346, 3240 (2NH), 1255 (C=S) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 4.45 (s, 2H, CH_2), 4.82 (s, 1H, pyrimidine H-4), 6.58 (s, 1H, pyrrole H-4), 7.11-8.11 (m, 14H, ArH), 9.03, 10.20 (br s, 2H, 2NH, D_2O-exchangeable). ^{13}C NMR (DMSO-d_6): δ 51.7, 70.4, 91.7, 115.4, 126.1, 126.4, 126.7, 127.4, 128.3, 128.8, 128.9, 129.4, 135.3, 136.1, 138.6, 143.2, 147.2, 148.4, 154.13, 174.3. MS m/z (%): 440 [M^+]. Analysis for $C_{25}H_{20}N_4O_2S$ (440.52) Calcd: C, 68.16; H, 4.58; N, 12.72. Found: C, 68.11; H, 4.78; N, 12.74

General procedure for the synthesis of (14a) and (15a-c)
(**Method A**): A mixture of an equimolar quantity of aromatic acids (benzoic, 4-chlorobenzoic or 2,4-dichlorophenoxy acetic) acid (2 mmol) and acid hydrazide **5** (2 mmol) in 15 mL of $POCl_3$ was refluxed for 3-6 h. The progress of the reaction was monitored by TLC using ethyl acetate: acetone (9:1) as eluent. The reaction mixture was cooled and poured carefully on to crushed ice (200g) with constant stirring and neutralized with sodium bicarbonate solution (10%, w/v). The resulting solid thus obtained was collected by filtration, washed well with cold water, dried and recrystallized from methanol to give **15a-c**.
(**Method B**): To a solution of the acid hydrazide **5** (2 mmol) in benzene (30 mL) was added to benzoyl chloride (2 mmol) and the mixture stirred at 25°C for 5 h. The solid separated out was collected and recrystallized from ethanol to yield **14a**. Compound **14a** (1 mmol) in $POCl_3$ (10 mL) were individually refluxed for 1-3 h., then allowed to cool, poured onto crushed ice and washed with aqueous (1.0 N) $NaHCO_3$. The solid precipitate was filtered off, washed with water and recrystallized from ethanol to produce compounds **15a**.

***N*^{1}-[*α*-Aracyl-*β*-(phenyl)acroyl-*N*^{2}-[benzoyl]hydrazine (14a)**
Yield 70 %; mp: 266-268 °C. IR (KBr): ν 3435, 3215 (2NH), 1729, 1668, 1654 (3CO) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 4.14 (s, 2H, CH_2), 7.12-8.12 (m, 15H, ArH and olefinic H), 8.33, 9.20 (2br s, 2H, 2NH`s, D_2O-exchangeable). ^{13}C NMR (DMSO-d_6): δ 33.7, 124.1, 127.7, 127.9, 128.2, 128.6, 129.5, 130.0, 132.2, 134.7, 135.1, 138.6, 142.8, 147.3, 163.9, 168.7, 178.7. MS m/z (%): 429 [M^+]. Analysis for $C_{24}H_{19}N_3O_5$ (429.42) Calcd: C, 67.13; H, 4.46; N, 9.79. Found: C, 67.09; H, 4.41; N, 9.75

4-(4-Nitrophenyl)-1-phenyl-3-(5-phenyl-1,3,4-oxadiazol-2-yl)but-3-en-1-one (15a)
Yield 80 %; mp: 222-224 °C. IR (KBr): ν 1729 (CO) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 4.86 (s, 2H, CH_2), 7.03-8.16 (m, 15H, ArH and olefinic H). ^{13}C NMR (DMSO-d_6): δ 37.6, 125.8, 128.3, 129.2, 129.7, 130.4, 132.5, 133.2, 137.9, 139.6, 144.2, 148.5, 153.8, 156.4, 170.4. MS m/z (%): 411 [M^+]. Analysis for $C_{24}H_{17}N_3O_4$ (411.41) Calcd: C, 70.07; H, 4.16; N, 10.21. Found: C, 70.12; H, 4.13; N, 10.27

3-(5-(4-Chlorophenyl)-1,3,4-oxadiazol-2-yl)-4-(4-nitrophenyl)-1-phenylbut-3-en-1-one (15b)
Yield 75 %; mp: 265-267 °C. IR (KBr): ν 1725 (CO) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 4.83 (s, 2H, CH_2), 7.08-8.20 (m, 14H, ArH and olefinic H). ^{13}C NMR (DMSO-d_6): δ 40.1, 67.1, 115.2, 122.9, 127.3, 128.3, 128.7, 129.7, 133.9, 134.5, 135.8, 139.5, 142.8, 147.3, 155.7, 158.1, 177.9. MS m/z (%): 445 [M^+]. Analysis for $C_{24}H_{16}ClN_3O_4$ (445.85) Calcd: C, 64.65; H, 3.62; N, 9.42. Found: C, 64.60; H, 3.67; N, 9.47

3-(5-((2,4-Dichlorophenoxy)methyl)-1,3,4-oxadiazol-2-yl)-4-(4-nitrophenyl)-1-phenylbut-3-en-1-one (15c)
Yield 70 %; mp: 293-295 °C. IR (KBr): ν 1727 (CO) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 4.12 (s, 2H, CH_2), 5.41 (s, 2H, phenoxy CH_2), 7.00-8.02 (m, 13H, ArH and olefinic H). ^{13}C NMR (DMSO-d_6): δ 35.3, 65.7, 117.5, 122.0, 125.3, 127.4, 128.7, 129.1, 129.6, 130.7, 131.8, 137.2, 139.5, 140.8, 144.6, 152.5, 154.3, 160.2, 176.5. MS m/z (%): 510 [M^+]. Analysis for $C_{25}H_{17}Cl_2N_3O_5$ (510.33) Calcd: C, 58.84; H, 3.36; N, 8.23. Found: C, 58.89; H, 3.32; N, 8.27

3-(4,5-Dihydro-5-thioxo-1,3,4-oxadiazol-2-yl)-4-(4-nitrophenyl)-1-phenylbut-3-en-1-one (16)
A mixture of **5** (0.9 g, 3 mmol), carbon disulfide (0.5 mL, 6 mmol) and KOH (30%, 15 mL) in 50 mL ethanol was refluxed on water bath for 4 hr. The mixture was cooled and poured into crushed ice and made acidic by HCl. The resulting solid was, filtered, and the separated product was purified by recrystallization from acetic acid to give **16**.

Yield 55 %; mp: 197-199 °C. IR (KBr): ν 3231 (NH), 1726 (CO) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 4.82 (s, 2H, CH_2), 7.13-8.11 (m, 10H, ArH and olefinic H), 11.32 (br s, 1H, NH, D_2O-exchangeable). ^{13}C NMR (DMSO-d_6): δ 35.2, 125.7, 128.4, 129.3, 129.7, 130.1, 135.6, 137.0, 139.2, 144.5, 148.5, 156.8, 177.4, 180.7. MS m/z (%): 367 [M^+]. Analysis for $C_{18}H_{13}N_3O_4S$ (367.38) Calcd: C, 58.85; H, 3.57; N, 11.44. Found: C, 58.89; H, 3.53; N, 11.47

3-(4,5-Dihydro-5-thioxo-1*H*-1,2,4-triazol-3-yl)-4-(4-nitrophenyl)-1-phenylbut-3-en-1-one (17).
A mixture of **16** (0.4 g, 1 mmol) and 80% hydrazine hydrate (0.6 mL, 20 mmol) in absolute ethanol (25 mL) were refluxed for 3h. After the completion of the reaction the solvent and excess of hydrazine hydrate were removed under reduced pressure using rotary evaporator. The residue was washed with diethyl ether and recrystallized from ethanol to give **17**.

Yield 60 %; mp: 185-187 °C. IR (KBr): ν 3340, 3228 (NH_2, NH), 1665 (CO) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 4.23 (s, 2H, CH_2), 6.45 (br s, 2H, NH_2 exchangeable), 7.02-8.13 (m, 10H, ArH and olefinic H), 10.43 (br s, 1H, NH exchangeable). ^{13}C

NMR (DMSO-d_6): δ 33.8, 124.6, 128.2, 128.6, 129.3, 130.5, 134.1, 136.7, 144.2, 144.9, 148.5, 163.3, 175.6. MS m/z (%): 381 [M^+]. Analysis for $C_{18}H_{15}N_5O_3S$ (381.41) Calcd: C, 56.68; H, 3.96; N, 18.36. Found: C, 56.63; H, 3.92; N, 18.41

Antimicrobial activity

The antibacterial and antifungal activities[19-22] were carried out in the Microbial Chemistry Department, National Research Centre, using the diffusion plate method. A filter paper sterilized disc saturated with the measured quantity (25 µL) of the sample (1 mg/mL) is placed on a plate (9 cm diameter) containing a solid bacterial medium (nutrient agar) or a fungal medium (potato dextrose agar) which has been seeded with the spore suspension of the test organism. After incubation at 37°C for 24 h for bacteria (in case of fungi, at 25°C for 72 h), the diameter of the clear zone of inhibition surrounding the sample is taken as a measure of the inhibitory power of the sample against the particular test organism (% inhibition = sample inhibition zone (cm) / plate diameter x 100). All measurements were done in methanol as a solvent which has zero inhibition activity. The antimicrobial activity of the tested compounds were examined with Gram positive bacteria *Bacillus subtilis*, *Bacillus cereus*, and *Staphylococcus aureus*, and Gram negative bacteria *Escherichia coli*, *Pseudomonas aeruginose* and fungus *Candida albicans*. The obtained results are compared with the reference antibiotics that were purchased from Egyptian markets.[19-22]

Table 1. The anti bacterial and antifungal activities of the tested compounds

Compd. No.	Inhibition zone diameter mm/mg sample					
	Microorganism					
	Gram positive bacteria			Gram negative bacteria		Fungi
	B. cereus	*S. aureus*	*S. typhimurium*	*P. aeruginosa*	*E. coli*	*C. albicans*
2	-	-	-	-	-	23
3	-	5	-	-	4	-
5	-	7	-	-	-	-
6	-	6	-	-	-	-
7	-	4	-	-	-	-
8	-	12	-	-	-	-
9	-	17	-	-	-	-
10a	-	5	-	-	7	-
11b	-	8	-	-	8	10
12	-	9	-	-	6	-
13	-	7	-	-	-	8
15a	-	8	-	-	11	-
15b	-	21	-	-	8	-
15c	-	11	-	-	10	-
16	-	14	-	-	-	-
Reference Antibiotic*	25	32	40	45	15	35

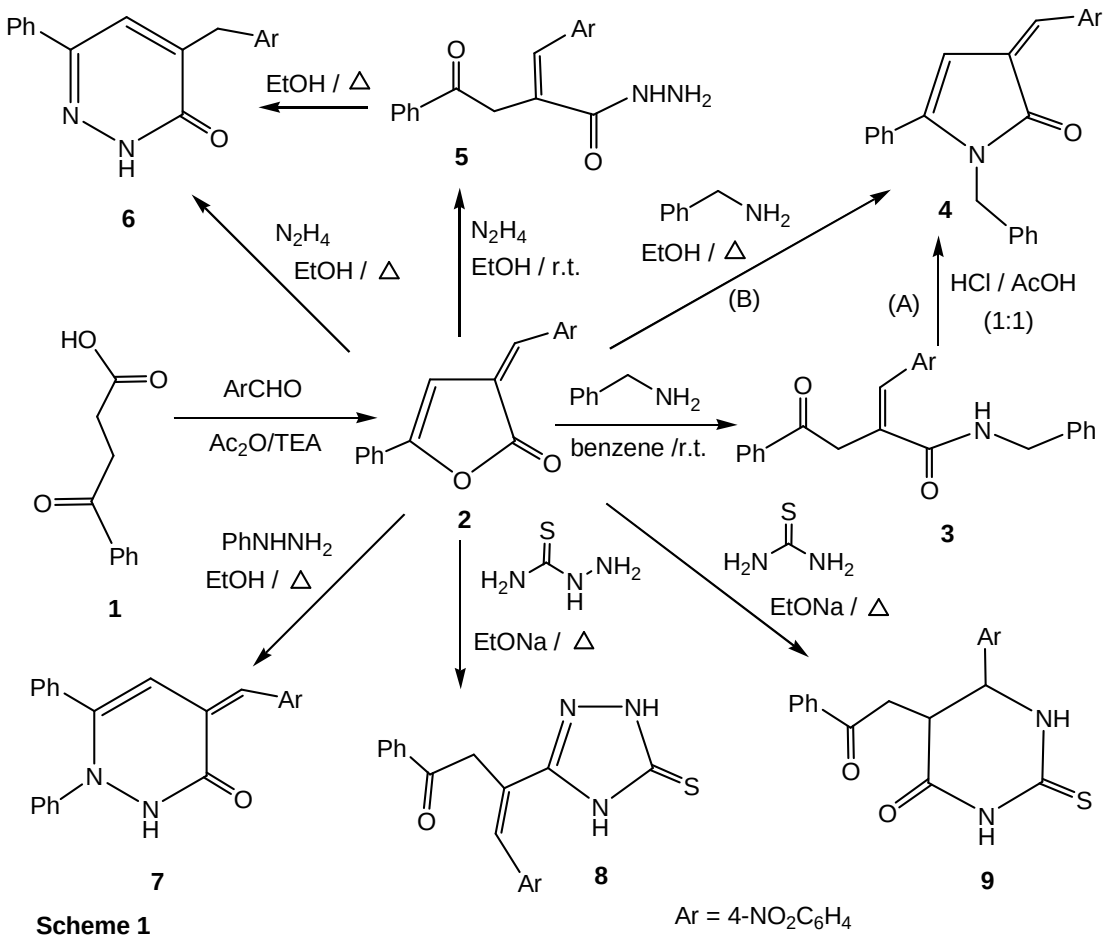
** Reference antibiotics are Nizo-arm (antifungal) and Penicillin (antimicrobial)*

From table 1 some of the tested compounds showed different antimicrobial activities. It is worth nothing that all the screened materials have no antimicrobial activity against *Bacillus cereus*, *Salmonella typhimurium* and *Pseudomonas aeroginosa*. The clear inhibition zone reached 47 and 73% in case of compounds **10a** and **15a** against *Escherichia coli* (Gram negative) respectively. Also, it reached 37, 53 and 65% in compounds **8**, **9** and **15b** respectively against *Staphylococcus aureus* (Gram positive). Compound **2** exhibits antifungal activity against *Candida albicans*; its clear inhibition zone reached 66%. On the other hand, the other tested compounds have no or low antibacterial or antifungal activities**.**

RESULTS AND DISCUSSION

3-(4-Nitrobenzylidene)-5-phenylfuran-2(3*H*)-one **2** was isolated in almost quantitative yield upon condensation reaction of 4-nitrobenzaldehyde with 3-benzoylpropionic acid **1** under perkin reaction conditions.[4,23] The 3-(4-nitrobenzylidene)-5-phenyl-1-benzyl-2(3*H*)-pyrrolone **4** was synthesized either by treatment of **2** with benzylamine in benzene at room temperature to give N-benzyl-γ-ketoamide **3**, which was then cyclized in 6 M HCl (method A) or by heating benzylamine with **2** in ethanol (method B) to give the corresponding benzylpyrrolone **4**.

Treating the furanone **2** with hydrazine hydrate in ethanol at room temperature, led to the formation of acid hydrazide **5**. Also, compound **6** was prepared by refluxing compound **2** with hydrazine hydrate in absolute ethanol.

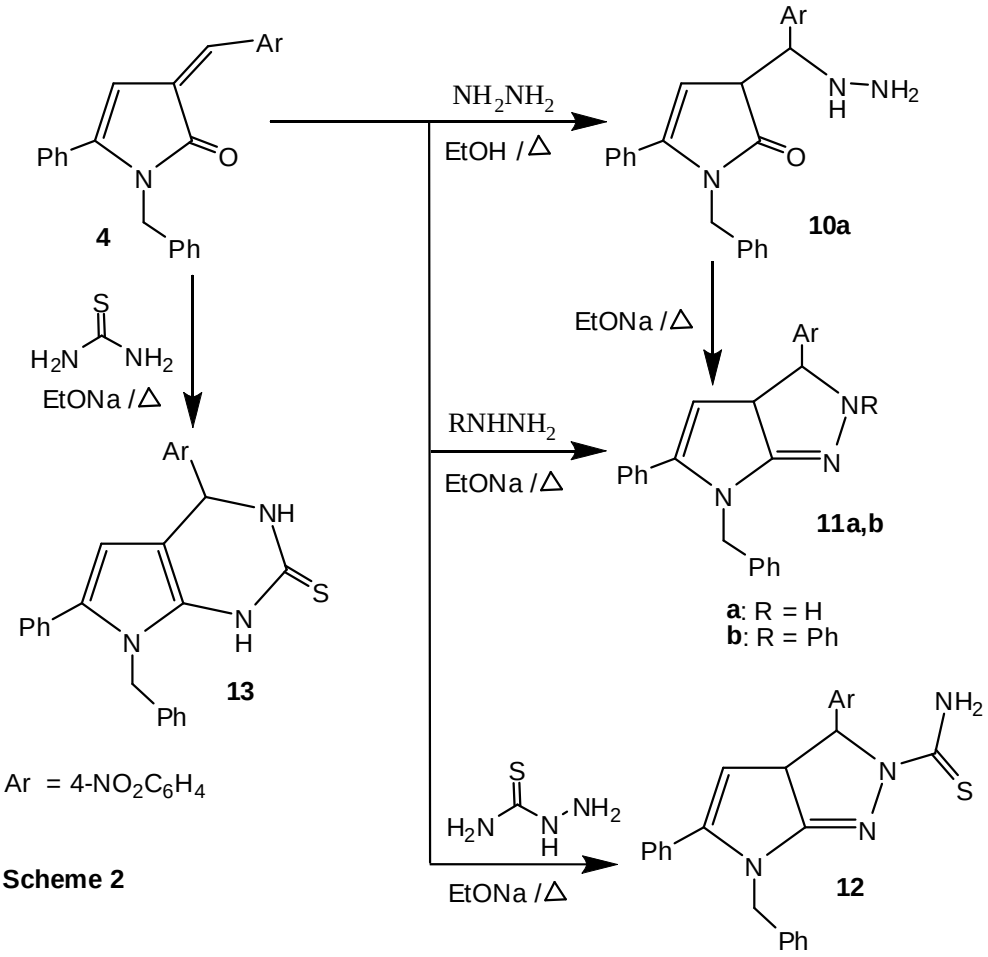


Scheme 1

However, refluxing of **2** with (hydrazine hydrate or phenyl hydrazine) in ethanol gave pyridazinone derivatives **6** and **7**, respectively. On the other hand, when **2** was condensed with thiosemicarbazide or thiourea in boiling sodium ethoxide yielded 4,5-dihydro-5-thioxo-1*H*-1,2,4-triazole **8** and pyrimidinethione **9** derivatives, respectively. (Scheme 1)

Moreover, when hydrazine hydrate was subjected to reaction with **4** in refluxing ethanol under an inert atmosphere, **10a** was obtained via Michael addition, which undergo intramolecular cyclization under refluxing in sodium ethoxide, workup of the reaction mixture furnished pyrrolo[2,3-*c*]pyrazole derivative **11a**.

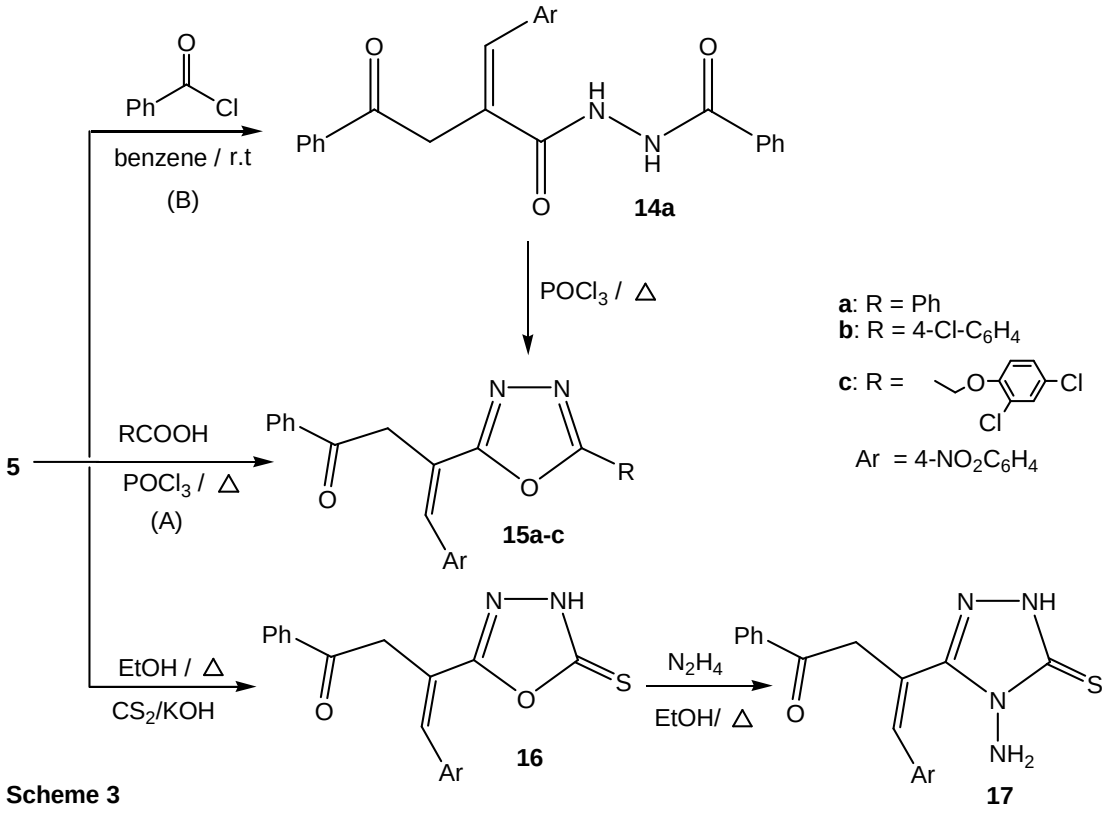
On the other hand, pyrrolo[2,3-*c*]pyrazole **11a**, **11b**, pyrrolo[2,3-*c*]pyrazole-2(6*H*)-carbothioamide **12** and pyrrolo[2,3-*d*]pyrimidine-2(7*H*)-thione **13** derivatives were obtained, respectively in one-step sequence by heating **4** with hydrazine hydrate, phenylhydrazine, thiosemicarbazide or thiourea using sodium ethoxide.[23-26] (Scheme 2)



Scheme 2

The 1,3,4-oxadiazole derivatives **15a-c** were prepared by the reaction of aromatic acids (benzoic, 4-chlorobenzoic or 2,4-dichlorophenoxy acetic acid) with hydrazide **5** in the presence of $POCl_3$ (method A).[27] The interaction of **5** with benzoyl chloride in dry benzene did not afford the expected 5-phenyl [1,3,4]oxadiazole derivative **15a**, however the *N*-benzyl carboxylic acid hydrazide **14a** derivative was shown to be the reaction product. When, compounds **14a** was subjected to cyclodehydration in boiling phosphorus oxychloride, the corresponding oxadiazoles **15a** obtained by (method B) was identical in all respects (m.p., mixed m.p. and TLC) with that obtained from (method A).

Moreover, The hydrazide **5** was utilized as the key starting material for the synthesis of the amino-1,2,4-triazole and 1,3,4-oxadiazole derivatives, it was converted into the corresponding 1,3,4-oxadiazole derivative **16** by treatment with carbon disulphide in aqueous potassium hydroxide. Aminotriazole derivative **17** was obtained in one-pot reaction by heating equimolar quantities of oxadiazole **16** with hydrazine hydrate, according to Reid and Heindel procedure with slight modification.[28] (Scheme 3). All the synthesized compounds were characterized by spectroscopic data, i.e., IR, ^{1}H-NMR, ^{13}C-NMR, mass and elemental analysis. The results are given in the supplementary material to this paper.



Scheme 3

CONCLUSION

In summary, we have reported an effective and simple reaction for the synthesis of novel nitrogenated heterocyclic compounds such as pyrrolone, pyridazinone, triazole, pyrimidine and oxadiazole derivatives utilizing furanone ring. It is proved, that most of the synthesized compounds exhibited moderate activity against bacteria, no activity against *Bacillus cereus*, *Salmonella typhimurium* and *Pseudomonas aeroginosa* and less activity on fungi.

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