SYNTHESIS OF NOVEL ANTIBACTERIAL AND ANTIFUNGAL \(\alpha\)-AMINO ACIDS AND HETEROCYCLIC COMPOUNDS

Maher A. El-Hashash[a], Sameh A. Rizk[a]*

Keywords: (E)-4-aryl-4-oxo-2-butenoic acid, furanones, thiadiazoles, pyridazinones, imidazolo[2,3-b]1,3,4-thiadiazoles, thiadiazolopyrimidines, bezoxazinones, fused quinoxalinylquinazolinones

Utility of (E)-4-(acetylamino)phenyl-4-oxo-2-butenoic acid with new sulfur reagents e.g. 2-amino-5-aryl-thiadiazoles to afford the corresponding adducts (3, 4, 5, 6). Reaction of the latter compounds with different electrophilic and nucleophilic reagents affords some important heterocycle such as various furanones, thiadiazoles, pyridazinones, imidazolo[2,3-b]1,3,4-thiadiazoles, thiadiazolopyrimidines, bezoxazinones, fused quinoxalinylquinazolinones

*Corresponding Authors
*E-mail: Samehrizk2006@gmail.com
[a] Chemistry department, Science Faculty, Ain-Shams University

INTRODUCTION

Amino acids are the smallest units of proteins and are useful components in a variety of metabolic activities. There are numerous advantages of taking amino acids as dietary supplements, also provide many useful biological activities In vitro data [1] about amino acids include muscle protein maintenance, potentiation of immune function, affecting neuronal activities in the brain, tissue repair acceleration, protecting liver from toxic agents, pain relief effect, lowering blood pressure, modulating cholesterol metabolism, stimulating insulin of growth hormone secretion and so on. It is important to be note that they are part of complex pathway and biological systems. Amino acids have proven to play a significant role in the synthesis of novel drug candidate with the use of non-proteinogenic and unnatural amino acids [2-7]. Over the last decade the synthesis of non-proteinogenic unnatural amino acids has received significant attention of organic chemists, who have tried to find out cost effective and less time consuming synthetic pathways. From this point of view the authors have made an attempt to investigate the reaction of 4-aryl-4oxo-but-2-enoic acids with 2-amino-1,3,4-thiadiazole under aza-michael reaction conditions which produced adducts 3-6 as \(\alpha\)-amino acid types with acetic anhydride at different condition and \(\text{N}_2\text{H}_4\) to give the corresponding furanone, imidazolo[2,3-b]1,3,4-thiadiazole, 1,3,4-thiadiazolopyrimidine and pyridazinone derivatives, respectively with an aim to obtain some interesting heterocyclic compounds with non-mixing and mixing system. Hence, keeping these reports in view and continuation of our earlier search work [13] for aza-Michael adducts.

EXPERIMENTS

All melting points are uncorrected. Elemental analyses were carried out in the Microanalytical Center, the center for research, Cairo, Egypt. By Elementar Viro El Microanalysis IR spectra (KBr) were recorded on IR spectrometer ST-IR DOMEM Hartman Braun, Model: MBB 157, Canada and \(^1\)H-NMR spectra recorded on a varian 300 MHz (Germany 1999) using TMS as internal standard. The mass spectra were recorded on Shimadzu GCMS-QP-1000 EX mass spectrometer at 70e.v. homogeneity of all compounds synthesized was checked by TLC.

Compounds 3-6

A solution of 4-(4-Acetaminophenyl)-4-oxo-2-butenoic acid (0.01 mol) and 5-aryl-2-amino-1,3,4-thiadiazole (0.016 mol) in 30 ml ethanol was refluxed for 3 h. The crude product was washed by petroleum ether (b.p 40–60°C), and then crystallized from ethanol to give the following compounds.

4-(4-Acetaminophenyl)-4-oxo-2-(5-phenyl-2-thiadiazolylamino)butanoic acid (3)

Yield 80%, Mp 160-162 °C, IR for CO for acid and ketone groups (1695 – 1665) cm\(^{-1}\), \(^1\)H NMR (DMSO-d\(_6\)) 2.5 (s,3H,CH\(_3\)CO), 3.4 (2 dd, CH\(_2\)-C=O J=15.2, J=7.7) (diastereotopic protons), 4.2 (dd,CH-COOH,methine proton), 6.7 (s, NH), 7.6-8.1 (m, 9H, ArH), 8.2 (s, 1H, COOH), 8.6 (s, 1H, C=O-NH). EIMS m/z 410 (M\(^+\)). Anal.Calc. for (C\(_{20}\)H\(_{18}\)N\(_4\)O\(_4\)S\(_2\)): C 58.53, H 4.39; Found: C 58.50, H 4.40.

4-(4-Acetaminophenyl)-4-oxo-2-(5-(4-chlorophenyl)-2-thiadiazolyl) butanoic acid (4)

Yield 75%, Mp. 174-174 °C, IR for CO for acid and ketone groups (1695–1665 cm\(^{-1}\), \(^1\)H NMR (DMSO-d\(_6\)) exhibits signals at 2.5(s, 3H, CH\(_3\)CO), 3.4 (2 dd, CH\(_2\)=C=O, J=15.2, J=7.7) (diastereotopic protons), 4.2 (dd,CH-COOH,methine proton), 6.7 (s, NH), 7.6-8.1 (m, 8H, ArH), 8.2 (s, 1H, COOH), 8.6 (s, 1H, C=O-NH). EIMS m/z 358 (M\(^+\)-CO\(_2\) + CH\(_2\)=CO). Anal.Calc. for (C\(_{20}\)H\(_{16}\)N\(_4\)O\(_4\)Cl): C 52.53, H 4.39; Found: C 52.50, H 4.40.
Yield 70%. M.p. 180-182 °C. IR: CO for acid and ketone groups are at 1694-1660 cm⁻¹. ¹H-NMR spectrum in DMSO-d₆ exhibits signals at 2.5 (s, 3H, CH₃CO), 3.4 (2 dd, CH₂-C=O, J=7.7), 4.2 (dd, CH-COOH, methine proton), 6.7 (s, NH), 7.6-8.1 (m, 11H, ArH and olefinic protons), 9.5 (s, 1H, COOH), 10.2 (s, 1H, C=O-NH). m/z: 392 (M⁻CO₂). Anal. Calc. for (C₂₂H₂₀N₄SO₄): C 60.55, H 4.58; Found: C 60.50, H 4.60.

Yield 35%. M.p. 150-152 °C. IR: CO for imide, acid and ketone groups at are at 1770, 1690 and 1660 cm⁻¹. ¹H-NMR spectrum (DMSO-d₆) exhibits signals at 2.5 (s, 3H, CH₃CO), 3.4 (2 dd, CH₂-C=O, J=15.2, J=7.7) (diastereotopic protons), 4.2 (dd, CH-COOH, methine proton), 6.7 (s, NH), 7.6-8.1 (m, 8H, ArH), singlet at 10.2 was assigned for the two acidic protons of acetamido and pyridazinone moieties. EIMS: m/z: 406 (M⁺). Anal. Calc. C₂₀H₁₇N₄O₃S: C 54.59, H 4.43; Found: C 54.50, H 4.43.

Yield 70-75 %. IR(KBr) 1674, 1708 (CO), 3177 (NH). ¹H NMR (DMSO-d₆): δ 2.2 (s, 3H, CH₃), 3.7 (2dd, 2H, CH₂-C=NC=N), 4.2 (2dd, CH, methine proton) 6.7 (s, NH, NH of thiadiazole moiety), 7.43-7.81 (m, 9H, ArH, ArH), singlet at 10.2 was assigned for the two acidic protons of acetamido and pyridazinone moieties. EIMS: m/z: 405 (M⁻Cl). Anal. Calc. C₂₀H₁₇N₄O₂Cl: C 54.54, H 3.86; Found: C 54.50, H 3.86.

Yield 70-75 %, IR(KBr) 1674, 1708 (CO), 3177 (NH). ¹H NMR (DMSO-d₆): δ 2.2 (s, 3H, CH₃), 3.7(2dd, 2H, CH₂-C=NC=N), 4.2 (2dd, CH, methine proton) 6.7 (s, NH, NH of thiadiazole moiety), 7.43-7.81 (m, 9H, ArH, ArH), singlet at 10.2 was assigned for the two acidic protons of acetamido and pyridazinone moieties. EIMS: m/z: 405 (M⁻Cl). Anal. Calc. C₂₀H₁₇N₄O₂Cl: C 54.54, H 3.86; Found: C 54.50, H 3.86.

Yield 70-75 %. IR(KBr) 1674, 1708 (CO), 3177 (NH). ¹H NMR (DMSO-d₆): δ 2.2 (s, 3H, CH₃), 3.7 (2dd, 2H, CH₂-C=NC=N), 4.2 (2dd, CH, methine proton) 6.7 (s, NH, NH of thiadiazole moiety), 7.43-7.81 (m, 9H, ArH, ArH), singlet at 10.2 was assigned for the two acidic protons of acetamido and pyridazinone moieties. EIMS: m/z: 405 (M⁻Cl). Anal. Calc. C₂₀H₁₇N₄O₂Cl: C 54.54, H 3.86; Found: C 54.50, H 3.86.

Ethyl N-[6-(4-acetaminophenyl)-3-oxo-4-thiadiazolyl-2-yl]glycinate (13)

Boiling of 3 (g; 0.005 mol) with acetic anhydride (9.4 mL ) on a hot plate was heated under reflux for 4 h. The reaction mixture was poured on to H₂O and the solid compound was separated and crystallized form ethanol. M.wt=453 (C₂₀H₁₃N₄O₃SBr), M. 230 °C, yield 65%, calcd/Found: C 52.98/52.80, H 3.81/3.79, Br 17.66/17.45, S 7.06/6.88. IR: v<sub>CO</sub> are at 1772 ,1668 cm⁻¹. ¹H-NMR (DMSO-d₆) exhibits signals at 5.2 (s, 2H, CH₂-N), 6.7 (s, 1H, bridgeCH, 1,3-double bond shift), 7.2-7.7 (m, 10H, ArH).

Pyridazinones 10-12

An equimolar mixture of compound 7 (2.75 g;5mmol) and hydrazine hydrate (1.7mL,0.015 mol) was refluxed in boiling ethanol for 3 h and the solid that separated out was filtered off, dried and then crystallized from ethanol .

6-(Acetaminophenyl)-4-(5-phenyl-2-amino-1,3,4-thiadiazole)-2,3,4,5-tetrahydro-3(2H)-pyridazinones (10)

Yield 70-75 %. IR(KBr) 1674, 1708 (CO), 3177 (NH). ¹H NMR (DMSO-d₆): δ 2.2 (s, 3H, CH₃), 3.7 (2dd, 2H, CH₂-C=NC=N), 4.2 (2dd, CH, methine proton) 6.7 (s, NH, NH of thiadiazole moiety), 7.43-7.81 (m, 9H, ArH, ArH), singlet at 10.2 was assigned for the two acidic protons of acetamido and pyridazinone moieties. EIMS: m/z: 405 (M⁻Cl). Anal. Calc. C₂₀H₁₇N₄O₂Cl: C 54.54, H 3.86; Found: C 54.50, H 3.86.

6-(Acetaminophenyl)-4-(5-(4-chlorophenyl)-2-amino-1,3,4-thiadiazole)-2,3,4,5-tetrahydro-3(2H)-pyridazinones (11)

Yield 70-75 %. IR(KBr) 1674, 1708 (CO), 3177 (NH). ¹H NMR (DMSO-d₆): δ 2.2 (s, 3H, CH₃), 3.7 (2dd, 2H, CH₂-C=NC=N), 4.2 (2dd, CH, methine proton) 6.7 (s, NH, NH of thiadiazole moiety), 7.43-7.81 (m, 9H, ArH, ArH), singlet at 10.2 was assigned for the two acidic protons of acetamido and pyridazinone moieties. EIMS: m/z: 405 (M⁻Cl). Anal. Calc. C₂₀H₁₇N₄O₂Cl: C 54.54, H 3.86; Found: C 54.50, H 3.86.

6-(Acetaminophenyl)-4-(5-(3-styryl-2-amino-1,3,4-thiadiazole)-2,3,4,5-tetrahydro-3(2H)-pyridazinones (12)

Yield 70-75%. IR(KBr) 1674, 1708 (CO), 3177 (NH). ¹H NMR (DMSO-d₆): δ 2.2 (s, 3H, CH₃), 3.7 (2dd, 2H, CH₂-C=NC=N), 4.2 (2dd, CH, methine proton) 6.7 (s, NH, NH of thiadiazole moiety), 7.43-7.81 (m, 9H, ArH, ArH), singlet at 10.2 was assigned for the two acidic protons of acetamido and pyridazinone moieties. EIMS: m/z: 405 (M⁻Cl). Anal. Calc. C₂₀H₁₇N₄O₂Cl: C 54.54, H 3.86; Found: C 54.50, H 3.86.

Ethyl N-[6-(4-acetaminophenyl)-3-oxo-pyridazin-4-yl]-N-[5-(5-phenyl-1,3,4-thiadiazol-2-yl)] glycinate (13)

An equimolar mixture of compound 10 (2.0 g; 5 mmol) and ethylchloroacetate (1.4 mL, 0.015 mol) in 50 mL dry pyridine was refluxed for 3 h. The reaction mixture was poured on to ice/HCl and the solid that separated out was filtered off, dried and then crystallized from ethanol .

11.36 (brs, 2H, NH of acetamido and pyridazinone moieties). Anal.: Calcd. for C_{24}H_{24}N_{6}SO_{4}: C 58.53, H 4.87, N 17.07; Found: C 52.40, H 4.76, N 17.00.

3-Oxo-4-(5-phenyl-1,3,4-thiadiazol-2-yl)-6-(4-acetyl-aminophenyl)-1,2,3,4-tetrahydro-1,4-oxazino[2,3-c]pyridazine (14)

An equimolar mixture of compound 10 (2.0 g; 5 mmol), ethylchloroacetate (1.4 mL, 0.015 mol) and anhydrous K_{2}CO_{3} (4 g) in 50 mL dry acetone was refluxed for 24 h. The reaction mixture was then poured on to H_{2}O/ice. The solid that separated out was filtered off, dried and then, crystallized from benzene. Yield 65 %. Mp. 162-164 °C. IR (KBr) 1630 (C=N), 1650, 1685 (CO), 3320, 3188 (NH). 1H NMR (DMSO-d_{6}): δ 2.08(s, 3H, CH_{3}), 3.72-3.76(m, 3H, CH_{2}CH), 5.933 (s, 2H, OCH_{2}CO), 7.46-7.92 (m, 9H, Ar-H), 11.36 (brs, 1H, NH of acetamido moiety). Anal.: Calcd. for C_{22}H_{18}N_{6}SO_{3}: C 59.19, H 4.03, N 18.83; Found: C 59.30, H 4.00, N 18.70.

1-((2-(4-Acetylaminophenyl))-2-oxo)ethyl-7-oxo-quinoxalino-[1,2-b]-quinazoline (16)

A mixture of benzoxazinone 15 (0.01 mol) and o-phenylene diamine (0.01mol) in ethanol (50 mL) was heated and refluxed for 5h. The reaction mixture was allowed to cool and the product was filtered, dried and recrystallized from ethanol. Yield 70 %. Mp. 126-128 °C. IR (KBr) 1709, 1735 (CO), 3423 (NH). 1H-NMR (DMSO-d_{6}): δ 2.5 (s, 3H, CH_{3}), 3.4 (m, 3H, CH_{2}-CH), 6.2 (s, 1H, pyrazine moiety), 7.46-8.11 (m, 12H, Ar-H), 12.40 (brs, 1H, NH of acetamido moiety). Anal.: Calcd. for C_{25}H_{20}N_{4}O_{3}: C 70.75, H 4.71, N 13.20; Found: C 70.70, H 4.64, N 13.15.

RESULTS AND DISCUSSION

When 4-(4-acetylaminophenyl)-4-oxo-but-2-enoic acid (1) was allowed to react with 2-amino 5-aryl thiadiazole derivatives (2), it produced 3-(4-acetamidobenzoyl)-2-(5-aryl 2-thiadiazolylamino)propanoic acids (3-6) as α-amino acid types that differ in biological activity by differing the aryl groups. Outline in Table 1 the presence of halogen atom enhances the antibacterial activity rather than chromophore moiety -CH=CH- (Scheme 1).

![Scheme 1](image1)

The recent efforts made for the development of new ascorbic acid analogues in obtaining anti-oxidant agents resulted in the synthesis of lactone derivatives related to ascorbic acid, the NH group in the position 3 is acting as OH group in ascorbic acid, we also have found out that some 3,5-diaryl-2(3H) furanone possess significant anti-inflammatory and anti-oxidant activities.

![Scheme 2](image2)

Ar = C_{6}H_{4}(4-NHOCH_{3})

![Scheme 3](image3)

Ar = Ph, C_{6}H_{4}(4-Cl), PhCH=CH-
These results prompted us that lactones can be obtained by the lactonization of hydroxyl acids. Thus, the adduct 3 (new α-amino acid) with design and synthesize new furanones. The synthesis of freshly distilled acetic anhydride afforded 2-(5-acetaminophenyl)-2-oxo-furan-3-ylaminio-5-phenyl 1,3,4-thiadiazole (7) and 2-phenyl-4-oxo-5-(4-acetylamino benzoylmethyl)imidazo[2,1-b]1,3,4-thiadiazole derivatives (8). The $^1$H-NMR spectrum of compounds 8 and 9 showed singlet peak at 6.7 corresponding to bridged CH,1,3-double bond shift that explained the proton spend apart of life time as methine proton. Fused thiadiazolo pyrimidine 9 can be synthesized by the treatment of aza-adducts 3 with boiling acetic anhydride, through decarboxylation followed by ring closure (Scheme 2).

It was reported$^{16}$ that the pyridazineone substituted 1,3,4-thiadiazolene were fungicidally active and their activity was influenced by the nature of the substituents. Thus, when the above reaction of pyridazinone 10 with ethylchloroacetate is carried out in the presence of acidic hydrante and dry acetone$^{89}$ it produced 1,4 oxazino[2,3-c]pyridazine derivatives 14 (Scheme 3).

In one pot reaction, 4-(4-acetaminophenyl)-4-oxo-but-2-enoic acid (1) was allowed to react with phosphorous pentachloride and then refluxed with anthranilic in the presence of acetic anhydride produced benzoazinone 15$^{90}$. The preparation of quinoxaline and its derivatives plays an important role in organic synthesis$^{17}$, displaying a broad spectrum of biological activities$^{18}$, as a building blocks in the synthesis of organic semiconductors$^{19}$, rigid subunits in macro cyclic receptors or molecular recognition$^{20}$ and chemically controlled switches$^{21}$.

Treatment of the benzoazinone 15 with o-phenylene diamine in boiling ethanol can be produced with new derivative of quinoxaline 16 (Scheme 4).

### Table 1. Antibacterial and Antifungal activities for some important synthesize compounds

<table>
<thead>
<tr>
<th>Compound / Ar</th>
<th>Escherichia coli G</th>
<th>Staphylococcus aureus G</th>
<th>Aspergillus flavus (Fungus)</th>
<th>Candida albicans (Fungus)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3/C$_6$H$_5$</td>
<td>14</td>
<td>14</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>4/C$_6$C$_6$H$_4$</td>
<td>16</td>
<td>16</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>5/Phtalimidomethyl</td>
<td>14</td>
<td>14</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>6/β-styryl</td>
<td>14</td>
<td>13</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>16</td>
<td>16</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>11</td>
<td>18</td>
<td>16</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>13</td>
<td>12</td>
<td>14</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>14</td>
<td>14</td>
<td>13</td>
<td>12</td>
<td>13</td>
</tr>
</tbody>
</table>

The antimicrobial screening of all the synthesized compounds can be done using the agar diffusion assay. Tetracycline (Antibacterial agent): 32-30, Amphotericin (Antifungal agent): 18-16.

### REFERENCES


![Scheme 4.](image)


Received: 11.03.2013.

Accepted: 20.04.2013.