SYNTHESIS OF NOVEL ANTIBACTERIAL AND ANTFUNGAL
α-AMINO ACIDS AND HETEROCYCLIC COMPOUNDS

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Keywords: (E)-4-aryl-4-oxo-2-butenolic acid , furanones, thiadiazoles, pyridazinones, imidazolo[2,3-b]1,3,4-thiadiazoles, thiadiazolopyrimidines, benzoxazinones, fused quinoxalinylquinazolines

Utility of (E)-4-(acetylamino)phenyl-4-oxo-2-butenolic acid with new sulfur reagents e.g. 2-amino-5-aryl-thiadiazole 2 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, benzoxazinones, fused quinoxalinylquinazolines

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 horm

Compounds 3-6

A solution of 4-(4-Acetaminophenyl)-4-oxo-2-butenolic 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-phenoxy-2-thiadiazolyl)butanoic acid (3)

Yield 80% , Mp 160-162 °C ,IR for CO for acid and ketone groups (1695 – 1665 ) cm⁻¹, ¹H NMR (DMSO-d₆) 2.5 (s,3H,CH₃CO),3.4 (2 dd , CH₂=C=O J=15.2, J=7.7) (diastereotopic protons) , 4.2(dd,CH-CH₂O-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 (C₂₀H₁₄N₂S₄O₄): C 58.53, H 4.39; Found: C 58.50, H 4.40.

4-(4-Acetaminophenyl)-4-oxo-2-(5-(4-chlorophenyl)-2-thiadiazole-azo)butanoic acid(4)

Yield 75%. Mp. 174-174 °C . IR for CO for acid and ketone groups are at 1695–1630 cm⁻¹. ¹H NMR (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-CH₂O-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). m/z 358 (M⁺-CO₂ +CH₂=CO). Anal.Calc. for (C₂₀H₁₄N₂S₄O₄Cl): C 54.05, H 3.83; Found: C 54.00, H 3.80.

4-(4-Acetaminophenyl)-4-oxo-2-(5-styryl-2-thiadiazolyl amino)butanoic acid (5)

Yield 70%. Mp. 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, CH₂C=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, 11H, ArH and olefinic protons), 9.5 (s, 1H, COOH), 10.2 (s, 1H, C=O-NH). m/z: 392 (M⁻CH₃CO). Anal. Calc. for (C₂₂H₂₀N₄S₄O₇): C 50.39, H 2.24, N 11.62.

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 (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=O), 4.2 (2 dd, CH, methine proton) 6.7 (s, NH, NH of thiadiazole moiety), 7.43-7.81 (m, 9H, Ar-H), 11.59 (brs, 2H, NH of acetamido and pyridazinone moieties). EIMS: m/z: 406 (M⁺); Anal.: Calc. C₂₁H₁₇N₆O₅S: C 59.11, H 4.43; Found: C 59.20, H 4.43.

6-(Acetaminophenyl)-4-(5-(4-chlorophenyl)-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=N), 4.2 (2 dd, CH, methine proton) at 6.5 ppm assigned for NH of thiadiazole moiety.) 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: 405 (M⁻Cl). Anal.: Calc. for 11 C₂₀H₁₅N₆O₅S: C 54.54, H 3.86; Found: C 54.50, H 3.86.

6-(Acetaminophenyl)-4-(5-(styryl-2-amino-1,3,4-thiadiazole)-2,3,4,5-tetrahydro-3(2H)-pyridazinones (13)

Yield 70-75%. IR(KBr) 1674, 1708 (CO), 3177 (NH). ¹H NMR (DMSO-d₆): δ 2.2 (s, 3H, CH₃), 3.7 (2 dd, 2H, CH₂-C=N), 4.2 (2 dd, CH, methine proton), singlet broad band at 6.5 ppm assigned for NH of thiadiazole moiety.) 7.6-8.1(m, 11H, ArH and olefinic protons), singlet at 10.2 assigned for two acidic protons of acetamido and pyridazinone moieties. EIMS m/z: 432 (M⁺). Anal. Calc. for 11 C₂₁H₁₆N₆O₅S: C 61.11, H 4.62; Found: C 61.18, H 4.60.

Ethyl N-[6-(4-acetaminophenyl)-3-oxo-pyridazin-4-yl]-N-[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.

Yield 35 %. Mp. 190-192. IR(KBr) 1630 (C=N), 1650, 1743 (CO), 3320, 3188 (NH). ¹H NMR (DMSO-d₆): δ 1.12 (t, 3H, CH₃), 2.08 (s, 3H, CH₃), 3.72-3.86 (m, 3H, CH₂CH₃), 4.13 (s, 2H, CH₂-N), 4.80 (q, 2H, CH₂-O), 7.46-7.92 (m, 9H, Ar-H), 7.6-8.1 (m, 11H, Ar-H).
Synthesis and antimicrobial activities of novel α-amino acids and heterocycles

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RESULTS AND DISCUSSION

When 4-(4-acetamidophenyl)-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).

 nutshell, the recent efforts made for the development of new ascorbic acid analogues in obtaining antioxidant and anti-inflammatory agents. 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 antioxidant activities.

Scheme 1.

The recent efforts made for the development of new ascorbic acid analogues in obtaining antioxidant and anti-inflammatory agents have resulted 2(3H)-furanones as a new antioxidant and anti-inflammatory agents. 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 antioxidant activities.

Scheme 2.

Scheme 3.
These results prompted us that lactones can be obtained by the lactonization of hydroxyl acids. Thus, the adduct 3 (new \(\alpha\)-amino acid) with design and synthesize new furanones. The synthesis of freshly distilled acetic anhydride afforded 2-(5-acetaminophenyl-2-oxo-furan-3-yl)amino-5-phenyl 1,3,4-thiadiazole (7) and 2-phenyl-4-oxo-5-(4-acetylaminobenzoylmethyl)imidazo-[2,1-b]-1,3,4-thiadiazole derivatives (8). The 1H-NMR spectrum of compounds 8 and 9 showed singlet peak at 6.7 corresponding to bridged CH1,3-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 pyridazinone substituted 1,3,4-thiadiazolene were fungicidally active and their activity was influenced by the nature of the substituents. Thus, when the acid 1a was allowed to react with hydrazine hydrate in boiling ethanol, 13. Reaction of the pyridazinone derivative 13 with ethylchloroacetate in boiling pyridine produced glycinate ester derivative 14. But, when the above reaction of pyridazinone 10 with ethylchloroacetate is carried out in the presence of anhydrous carboxylic and dry acetonitriene it produced 1,4 oxazino[2,3-c]pyridazine derivatives 14 (Scheme 3).

In one pot reaction, 4-(4-acetaminophenyl)-4-oxo-but-2-enolic acid (1) was allowed to react with phosphoryl pentachloride and then refluxed with anthranilic acid in the presence of acetic anhydride produced benzoazinone 15.\(^{16}\) 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 synthesized compounds

<table>
<thead>
<tr>
<th>Compound / Ar</th>
<th>Escherichia coli G</th>
<th>Staphylococcus aureus G(^a)</th>
<th>Aspergillus flavus (Fungus)</th>
<th>Candida albicans (Fungus)</th>
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<tr>
<td>3/C(\text{H}_2\text{O})</td>
<td>14</td>
<td>14</td>
<td>12</td>
<td>10</td>
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<tr>
<td>4/-C(\text{Cl}\text{H}_2\text{O})</td>
<td>16</td>
<td>16</td>
<td>13</td>
<td>12</td>
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<tr>
<td>5/Phthalimidoethyl</td>
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<td>14</td>
<td>12</td>
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<td>6/(\beta)-styril</td>
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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-url)
Synthesis and antimicrobial activities of novel \( \alpha \)-amino acids and heterocycles

Section A - Research Paper


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