Synthesis, characterization and evaluation of antibacterial activity of some new derivatives of Veronal

Ahmed W. Radh

Department of Chemistry, College of Pharmacy, Kufa University, Najf-Iraq

ABSTRACT

Reaction of veronal with acetic anhydride gave N,N-1,3-diacetyl veronal (As) which was reacted with some aromatic aldehydes to give chalcones (ch1-ch7). Sulphadiazine converted to diazonium salt will be reacted with sodium azide and sodium acetate to form 4-azido-N-(pyrimidin-2-yl)phenylsulfonamid (Az). 1,2,3-triazole derivatives (T1-T7) were prepared by cycloaddition reactions between compound (Az) with chalcones. All compounds were characterized by C.H.N.S. analyses, F.T.I.R spectra and $^1$H-NMR spectrum. Some of the prepared compounds were screened for antibacterial activity.

Keywords: veronal, 1,2,3-triazoline, azide, chalcone and antibacterial activity.

INTRODUCTION

Barbiturates are drugs that act as central nervous system depressants, while barbituric acid itself does not have any effect on the central nervous system.[1] The derivatives of barbituric acid have diverse applications such as sedatives, hypnotics and anticonvulsants under a variety conditions and are also employed for anesthesia.[2] Recently, new biomedical applications have been developed for cancer and AIDS therapy.[3] Five member nitrogenheterocycles play an important role in biological activity particularly[4], the 1,2,3- triazoles. The use of triazoles shows great importance with applications in the field of pharmaceutical, medicinal chemistry and agrochemicals.[5]

1,2,3- Triazole present in many heterocyclic compounds is exhibiting different biological activity such as antibacterial[6], activity against gram positive and negative bacteria[7], herbicidal[8], anti-allergic[9], anti-HIV[10], anti-fungal[11], anti-viralactivity against many viruses[12]. Triazoles of small molecular weights are drug available so far for treating anti inflammatory [13], and anti convulsant[14] effects.

MATERIALS AND METHODS

Melting points were determined by using Electro thermal melting point apparatus. I.R spectra were recorded by using Shimadzu FT.1R-8400S infrared spectrophotometer by KBr disc, Kufa University. $^1$H-NMR were determined on Bruker spectrometer, at (400MHZ) with DMSO-\textit{d6} as solvent, Iran, Kashan university.
Synthesis of N,N-1,3-diacetyl-Veronal (As)

A mixture of veronal (0.001 mol) and acetic anhydride (10 mL) with few drops of concentrated sulfuric acid was refluxed for 2 hours at (60-70°C). The initial content of the reaction is a suspension, then it was clear solution after the temperature reached above (60°C). Then, the reaction was completed depended on TLC by using (benzene: ethanol, 4:1). After the reaction has been completed the reaction mixture was added in to crushed ice water with stirring. The formed solid product was separated by filtration, and recrystallized from ethanol. Yield 79% , (m.p.163-165)

TLC ( Benzene :Ethanol ) ( 4:1 ) ( Rf, 0.7 ); Anal. Calc. for C₁₂H₁₆N₂O₃ C% (53.73); H % (6.01); N% (10.44) Found C% (53.23); H % (6.008); N% (10.367); I.R spectra: (C-Harm) (3095) cm⁻¹ , (C-Halp) asy (2954) cm⁻¹, (C-Halp) sy (2870) cm⁻¹. \( ^1H \)-NMR spectrum, (δ ppm), (DMSO-d₆) ((6H) (-CH₃) 0.73), ((4H), (-CH₂-) 2.34), ((3H) (-CO-CH₃) 2.55).

General procedure for synthesis chalcones (ch1- ch7)

To a stirred mixture of ( 0.01 mol) of (As) and (0.02 mol) of aromatic aldehydes in (25 mL) ethanol at room temperature, 20% NaOH aqueous solution was added portion-wise in ice bath after which stirring was continued for further (2-3) hr. Then, the reaction was completed depended on TLC by using (benzene: ethanol, 4:1). The color precipitate formed was filtered and washed with 3% aqueous HCl, then with distilled water and re-crystallized from ethanol.

The following compounds were synthesized:

1,3-Bis-(4-dimethylamino)phenyl)acryloyl)Veronal (ch1)

T.L.C. ( B:E) ( 4:1 ) ( Rf, 0.66 ) , (m.p. 63-65, Rf 0.75, yield 82%); Anal. Calc. for C₂₀H₂₄N₂O₃ C% 67.91; H % 6.46; N% 5.46; Found C% 67.61; H % 6.41; N% 5.31. I.R spectra: 3051(C-Harm), 2966(C-Hal) 1660(C=Oamid), 1600(C=C), 1058(C-N); \( ^1H \)-NMR spectrum, (δ ppm), (DMSO-d₆) ((6H) (-CH₃) 0.73), ((4H), (-CH₂-) 2.336), ((6H) (N-(CH₃)₂) 3.107), ((2H) (CO-CH=CH) 6.729), ((2H) (CO-CH=CH) 7.360), ((Ar-H) ) 6.543-7.682);

1,3-Bis-(4-bromophenyl)acryloyl)Veronal (ch2)

TLC ( Benzene : Ethanol ) ( 4:1 ) ( Rf, 0.71 ), (m.p. 73-75, yield=80%); Anal. Calc. for C₂₁H₂₁Br₂N C% 51.58; H % 3.68; N%4.56; Found C% 51.44; H % 3.551; N%4.56. I.R spectra 3050(C-Har),2967(C-Hal) 1665(C=Oamid), 1600(C=C), 638(C-Br); \( ^1H \)-NMR spectrum, (δ ppm), (DMSO-d₆) ((6H) (-CH₃) 0.701), ((4H), (-CH₂-) 2.334), ((2H) (CO-CH=CH) 6.769), ((2H) (CO-CH=CH) 7.370), ((Ar-H ) 6.555-7.881).

1,3-Bis-(3-hydroxyphenyl)acryloyl ) Veronal (ch3)

TLC ( Benzene : Ethanol ) ( 4:1 ) ( Rf, 0.62 ), (m.p. 82-8482-84, yield 85%); Anal. Calc. for C₂₀H₂₂N₂O₃ C% 65.54, N%5.88, H% 5.08%; Found C% 65.33, N%5.82, H% 5.003; I.R spectra: 3412(O-H), 3057(C-Har),2972(C-Hal),1691(C=O) ,1566(C=C) ; \( ^1H \)-NMR spectrum, (δ ppm), (DMSO-d₆) ((6H) (-CH₃) 0.701), ((4H), (-CH₂-) 2.201), ((2H) (CO-CH=CH) 6.898), ((2H) (CO-CH=CH) 7.342), ((Ar-H ) 6.876-7.872), ((1H) (OH)8.831)

1,3-Bis-(4-nitrophenyl)acryloyl Veronal (ch4)

TLC ( Benzene : Ethanol ) ( 4:1 ) ( Rf, 0.72 ), (m.p. 82-84, yield 87% ) Anal. Calc. for C₂₀H₂₂N₂O₅ C% 58.43, N%5.10, H% 4.15); Found C% 58.32, H % 4.12 ; I.R spectra: 3060(C-Har),2972(C-Hal) 1698(C=Oamid) 1584(C=C), 1349(NO₂); \( ^1H \)-NMR spectrum, (δ ppm), (DMSO-d₆) ((6H) (-CH₃) 0.701), ((4H), (-CH₂-) 2.203), ((2H) (CO-CH=CH) 6.888), ((2H) (CO-CH=CH) 7.351), ((Ar-H ) ) 6.823-8.272).

1,3-Bis-(4-hydroxy-3-methoxyphenyl)acryloyl)Veronale (ch5)

T.L.C. ( B:E ) ( 4:1 ) ( Rf, 0.55 ), (m.p. 96-98, yield 83% ) Anal. Calc. for C₂₆H₂₃Cl₂N C% 60.83; H % 4.32; N%5.46; Found C% 60.53, N % 5.31, H% 4.215; I.R spectra: 3055(C-Har),2977(C-Hal) 1675(C=Oamid)}
1600(C=O), 680(C-Cl); $^1$H-NMR spectrum, (δ ppm), (DMSO-$d_6$) ((6H) (-CH$_3$) 0.701), ((4H), (-CH$_2$) 2.332), ((2H) (CO-CH=CH) 6.733), ((2H) (CO-CH=CH) 7.343), ((Ar-H) ) 6.663-7.882).

- 1,3-Bis-(4-hydroxyphenyl)acryloyl ) Veronal. (ch7)

TLC ( Benzene : Ethanol ) ( 4:1 ) ( Rf, 0.57 ) , (m.p.102-104, yield 74%); Anal. Calc. for C$_{26}$H$_{24}$N$_2$O$_7$: C% 65.54, N%5.88, H%5.08; Found  C% 65.42, N%5.86, H% 5.01). **IR spectra**: 3425(O-H), 3065(C-Har) 2980(C-Hal),1680 (C=O) ,1570 (C=C) ; $^1$H-NMR spectrum, (δ ppm), (DMSO-$d_6$) ((6H) (-CH$_3$) 0.701), ((4H), (-CH$_2$) 2.204), ((2H) (CO-CH=CH) 6.889), ((2H) (CO-CH=CH) 7.35), ((Ar-H) ) 6.872-7.882), ((1H) (OH)8.84)

![Scheme 1](image)

**Synthesis 4-azido-N-(pyrimidin-2-yl)phenylsulfonamid(Az)**

Sulphadiazine (0.01mole) was dissolved in (1.7ml) of concentrated hydrochloric acid and (10 ml) of distilled water. The mixture was cooled at (0-5 °C) in ice-water bath. Then a solution of sodium nitrite (0.01mol) was dissolved in (5 ml) of distilled water then it will be cooled at (0-5 °C). This solution was added a drop wise to the mixture with stirring. The diazonum salt solution was added portion wise to solution of (0.01mol) of sodium azide and (0.01mol) of sodium acetate and controlled temperature at (0-5°C).The mixture was stirred for 30 mint. The mixture was left over night. (Az) compound was precipitated and filtered, washed well with distilled water and re-crystallized from ethanol.

(m.p. 223-225, yield 90% ); Anal. Calc. for C$_{10}$H$_{8}$N$_6$O$_2$S C% 43.47; H% 2.92; S%30.42; S% 11.61 Found  C% 43.32, N% 30.25, H% 2.88 S% 11.31) **IR spectra**: Aromatic (1424-1615)cm$^{-1}$ (N-H) str. Amide ((3420)cm$^{-1}$ (N$_3$) str. ((2113)cm$^{-1}$ (C=O) str. Pyrimidine(1540) cm$^{-1}$; $^1$H-NMR spectrum, (δ ppm), (DMSO-$d_6$) (Ar-H) (6.96-7.68), (HC=O) pyrimidine (8.87), (N-H) Sulfone ( 11.32)
Scholar Research Library

Synthesis of 1,2,3-triazoline derivatives (T1-T7)

4-azido-N-(pyrimidin-2-yl) phenylsulfonamid(Az) (0.02mol) was dissolved in DMF as solvent (50ml). The chalcons compounds (0.01 mol) was added to the solution. The mixture was heated at 110 °C for 24 hrs. Then removing the solvent, the residue was washed with diethyl ether and recrystallized from ethanol., the reaction was completed depended on TLC by using (benzene: methanol, 4:1).

1,3-bis(oxomethylene)bis(5-(4-(dimethylamino)phenyl)-4,5-dihydro-1,2,3-triazoline-4,1(diyl))bis(N-(pyrimidin-2-yl)benzenesulfonamide)Veronal

TLC ( Benzene : Methanol ) ( 4:1 ) ( Rf, 0.46 ) , (m.p. 265-267, yield 75% ); Chemical Formula: C_{54}H_{50}N_{16}O_{11}S_{2} Anal. Calc.C%, 55.44; H%, 4.65; N%, 20.26, S%, 5.11; Found.C% 54.81; H % 4.41; N%19.116; S% 5.116; I.R spectra : 1. Inter: C-Har.,3051) cm\(^{-1}\), (C-Hal. 2960 cm\(^{-1}\), (C=O amid 1670) cm\(^{-1}\), (C=N) Pyrimidine(1545) cm\(^{-1}\), (Aromatic) (1424-1615)cm\(^{-1}\) (N-H) Amide (3420)cm\(^{-1}\).; \(\delta\) ppm, (DMSO-d6) ((6H) (-CH\(_3\)) 0.703), ((4H), (-CH\(_2\)-) 2.343), ((6H) (N-(CH\(_3\)) 3.121), ((Ar-H) ) 6.543-7.882 ), (HC=N) pyrimidine (8.84), (N-H) Sulfone ( 11.22 )

1,3-bis(oxomethylene)bis(5-(4-bromophenyl)-4,5-dihydro-1,2,3-triazoline-4,1(diyl))bis(N-(pyrimidin-2-yl)benzenesulfonamide)Veronal

TLC (benzene: methanol 4:1)( Rf, 0.39 ), (m.p. 231-233, yield 80% ) Chemical Formula: C_{50}H_{38}Br_{2}N_{14}O_{11}S_{2} Anal. Calc.C%, 47.84; H%, 3.32; N%, 16.98; S%, 5.55 Found C% 47.14; H % 3.111; N%16.56, S%, 5.05 I.R spectra: 1. Inter: (N-H) Amide ((3430)cm\(^{-1}\), (C-Har., 3060) cm\(^{-1}\), (C-Hal., 2965 cm\(^{-1}\), (C=O amid 1666) cm\(^{-1}\),(C=N) Pyrimidine(1545) cm\(^{-1}\) (Aromatic) (1420-1610)cm\(^{-1}\) , (C-Br ,710) cm\(^{-1}\) **H-NMR spectrum.** \(\delta\) ppm, (DMSO-d6) ((6H) (-CH\(_3\)) 0.702), ((4H), (-CH\(_2\)-) 2.34), ((Ar-H) ) 6.559-7.899), (HC=N) pyrimidine (8.86), (N-H) Sulfone ( 11.31 ).

1,3-bis(oxomethylene)bis(5-(3-hydroxyphenyl)-4,5-dihydro-1,2,3-triazoline-4,1(diyl))bis(N-(pyrimidin-2-yl)benzenesulfonamide)Veronal

TLC (benzene: methanol 4:1) ( Rf, 0.45 ) , (m.p. 288-290, yield 81% ) Chemical Formula: C_{50}H_{46}Br_{2}N_{16}O_{9}S_{2} Anal. Calc.C%, 53.69; H%, 3.92; N%, 19.06, S%, 6.23 Found C% 52.73, H% 3.103); S%, 5.43 **I.R spectrum.** (O-H .3380) cm\(^{-1}\), (C-Har., 3077) cm\(^{-1}\), (C-Hal., 2975 )cm\(^{-1}\), (C=O amid 1665) cm\(^{-1}\),(C=N) Pyrimidine (1530) cm-1 , (Aromatic) (1424-1595)cm\(^{-1}\) (N-H) Amide (3380)cm\(^{-1}\) **H-NMR spectrum.** \(\delta\) ppm, (DMSO-d6) ((6H) (-CH\(_3\)) 0.701), ((4H), (-CH\(_2\)-) 2.207), ((Ar-H) ) 7.116-7.92),((HC=N) pyrimidine (8.84), ((1H) (OH) 8.81 )

**Scholar Research Library**
1,3-bis(oxomethylene)bis(5-(4-nitrophenyl)-4,5-dihydro-1,2,3-triazoline-4,1(diyl))bis(N-(pyrimidin-2-yl)benzenesulfonamide)Veronal

TLC (benzene: methanol 4:1) (Rf, 0.46) , (m.p. 211-213, yield 78%) Chemical Formula: C₅₀H₅₇O₁₅S₄ Anal. Calc.C%, 50.83; H%, 3.52; N%, 20.62, S%, 5.90 Found C% 50.32, N% 20.24, H%3.12 ; S%, 5.43. I.R spectra: (N-H) Amide ((3350)cm⁻¹ , (C-Har., 3050) cm⁻¹ , (C-Hal., 2970 )cm⁻¹ , (C=O amid 1688) cm⁻¹ , (Aromatic) (1420-1600)cm⁻¹(C=N) Pyrimidine (1533) cm-1, (NO₂,1350) cm⁻¹. ¹H-NMR spectrum, (δ ppm), (DMSO-d₆) ((6H) (-CH₃) 0.704), ((4H), (-CH₂-) 2.201), ((Ar-H) ) 7.123-8.21), (HC=N)pyrimidine (8.88) (N-H) Sulfone ( 11.30)

1,3-bis(oxomethylene)bis(5-(4-hydroxy-3-methoxyphenyl)-4,5-dihydro-1,2,3-triazoline-4,1(diyl))bis(N-(pyrimidin-2-yl)benzenesulfonamide)Veronal

TLC (benzene: methanol 4:1) (Rf, 0.41) , (m.p. 312-314 yield 77%) Chemical Formula: C₅₂H₄₅O₁₅S₄ Anal. Calc.C%, 52.94; H%, 4.07; N%, 18.01, S%, 5.89 Found C% 52.53, N% 17.31, H% 3.81; S%, 5.29. I.R spectra: (O-H ,3400) cm⁻¹ , (C-Har., 3060) cm⁻¹ , (C-Hal., 2970 )cm⁻¹ , (C=O amid 1690) cm⁻¹, (C=N) Pyrimidine (1540) cm⁻¹ , (Aromatic) (1415-1600)cm⁻¹ (N-H) Amide ((3400)cm⁻¹, ¹H-NMR spectrum, (δ ppm), (DMSO-d₆) ((6H) (-CH₃) 0.702), ((4H), (-CH₂-) 2.21), ((3H) (O-CH₃) 3.334), ((Ar-H) ) 6.961-8.171), ((IH) (OH)8.593) , (HC=N)pyrimidine (8.85), (N-H) Sulfone ( 11.31)

Where G₁

-4-N,N-dimethyl
-4-bromo
-3-hydroxy
-4-nitro
-4-hydroxy-3-methoxy
-4-chloro
-4-hydroxy

Scheme(3)
1,3-bis(oxomethylene)bis(5-(4-hydroxyphenyl)-4,5-dihydro-1,2,3-triazoline-4,1(diyl))bis(N-(pyrimidin-2-yl)benzenesulfonamide)

**Veronal**

TLC (benzene: methanol 4:1) (Rf, 0.51) , (m.p. 198-200, yield 83%)  Chemical Formula: C₅₀H₄₆N₁₆O₉S₂  Anal. Calc. C%, 53.69; H%, 3.92; N%, 19.06, S%, 5.66  I.R spectra: (O-H, 3380) cm⁻¹, (N-H) Amide ((3380) cm⁻¹, (C-Har., 3050) cm⁻¹, (C-Hal., 2980) cm⁻¹, (C=O amid 1670) cm⁻¹, (C=N) Pyrimidine (1535) cm⁻¹, (Aromatic) (1410-1600)cm⁻¹ 1H-NMR spectrum, (δ ppm), (DMSO-d₆)  (6H) (-CH₃) 0.701, (4H), (-CH₂-) 2.204, ((Ar-H) ) 7.188-7.892, ((1H) (OH) 8.81)  (HC=N) pyrimidine (8.85), (N-H) Sulfone (11.31)

**Veronal**

TLC (benzene: methanol 4:1) (Rf, 0.44) , (m.p. 177-179, yield 85%)  Chemical Formula: C₄₆H₃₈Cl₂N₁₄O₉S₂  Anal. Calc. C%, 51.83; H%, 3.59; N%, 18.40, S%, 5.25  I.R spectra: (C-Har., 3050) cm⁻¹, (C-Hal., 2970) cm⁻¹, (C=O amid 1660) cm⁻¹, (Aromatic) (1430-1600)cm⁻¹ 1H-NMR spectrum, (δ ppm), (DMSO-d₆)  (6H) (-CH₂-) 0.701, (4H), (-CH₂-) 2.33, ((Ar-H) 6.963-7.882), ((HC=N) pyrimidine (8.87), (N-H) Sulfone (11.32)

**RESULTS AND DISCUSSION**

In this research the synthesis of some new 1,2,3-triazoline derivatives were achieved from veronal. The first compound (As) prepared by reaction veronal and acetic anhydride with a few drops of concentrated sulfuric acid (scheme 1). The synthesized compound (As) was analyzed and characterized by using (C.H.N.S) analysis, and the result of experimental percentages of elements was a good agreement with the calculated percentages. This is good evidence for formatted compound. The F.T.I.R spectra of this compound showed disappearance of absorption band at (3375) cm⁻¹ of the symmetric stretching vibration of (-NH-) group. The absorption band at 1690 cm⁻¹ was due to stretching vibration of carbonyl groups. All of these absorption bands are another good evidence to formation (As).

**Chalcones compounds**

Chalcones are synthesized by Claisen-Schmidt condensation of 1,3-diacetyl veronal and aromatic aldehyde by base catalyzed followed by dehydration to yield chalcones.

The chalcone compounds were characterized by bayer test (KMnO₄ test) and the result was positive, that is good evidence for formatted chalcon compounds (ch1-ch7) The (C.H.N.S) analysis of these compounds accepted agreement with the calculated percentage of elements, F.T.I.R spectra and the ¹H-NMR spectrum good evidence to formation compounds (ch1-ch7) (scheme 1).

Sulphadiazine was converted to diazonium salt by reaction with concentrated hydrochloric acid and sodium nitrite. Diazonium salt was directly introduced azide compound by reaction with sodium azid and sodium acetate. The (C.H.N.S) analysis of synthesized compound (Az) was accepted agreement with the calculated percentage of elements. The F.T.I.R spectra of this compound and ¹H-NMR spectrum good evidence for formatted compound (scheme 2).

Chalcones compounds (ch1-ch7) condense with azide compound (Az) to give 1,2,3-triazoline derivatives (T1-T7). The (C.H.N.S) analysis of synthesized compounds [were accepted agreement with the calculated percentage of elements. The F.T.I.R spectra of these compounds and ¹H-NMR spectrum considered good evidence for formatted our compounds (scheme 3).

**Antibacterial activity test**

Triazoline derivatives (T1-T7) were screened for antifungal activity against Escherichia coli, Pseudomonas aeruginosa, and Staphylococcus aureus in Muller Hinton agar. (15,16) by measuring the inhibition zone in (mm).

Azithromycin (250 µg/ µL) that used as a standard drug. Each bacteria isolate was inoculated on to the Muller-Hinton Agar [sterilize in autoclave] by dipping a cotton swab in to the suspension and streaking over the surface of the agar plates. Then, in the solidified medium, four holes were made (6 mm). These holes were filled with (0.5
ml) of the prepared compounds ((250 µg/ µL) of the compound dissolved in 1ml of DMSO solvent). These plates were incubated at 37 °C and measured of zone inhibition after 48 hours. The results are presented in Table 2.

Table 1 Antibacterial activities of compounds T1-T7.

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>Escherichia coli</th>
<th>Staphylococcus aureus</th>
<th>Pseudomonas aeruginosa</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Zone of inhibition (mm)</td>
<td>% Inhibition</td>
<td>Zone of inhibition (mm)</td>
</tr>
<tr>
<td>T1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>T2</td>
<td>35</td>
<td>175</td>
<td>35</td>
</tr>
<tr>
<td>T3</td>
<td>50</td>
<td>250</td>
<td>25</td>
</tr>
<tr>
<td>T4</td>
<td>0</td>
<td>0</td>
<td>30</td>
</tr>
<tr>
<td>T5</td>
<td>30</td>
<td>150</td>
<td>0</td>
</tr>
<tr>
<td>T6</td>
<td>0</td>
<td>0</td>
<td>30</td>
</tr>
<tr>
<td>T7</td>
<td>45</td>
<td>225</td>
<td>25</td>
</tr>
<tr>
<td>S.T.</td>
<td>20</td>
<td>100</td>
<td>28</td>
</tr>
</tbody>
</table>

S.T., standard (Azithromycin)

Results data of (inhibition zone %) of compounds in Table 2 we observe important results: The first that the compounds (T3) and (T7) gave good activity against Escherichia coli, Pseudomonas aeruginosa, and Staphylococcus aureus while compound (T1) gave good activity against Staphylococcus aureus. But (T4) and (T6) gave good activity against Staphylococcus aureus. Also we showed compound (T2) has good activity against Escherichia coli, and Staphylococcus aureus. (T5) compound gave good activity against Escherichia coli and Pseudomonas aeruginosa.

REFERENCES