Synthesis, Characterization and Antibacterial Activity of Some Novel 1,2,3-Triazole-Chalcone Derivatives from N-Acetyl-5H-Dibenzo [b,f] Azepine-5-Carboxamide

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Abstract

This work involves preparation of a series of 1,2,3-triazole derivatives. In the first step, the reaction of N-acetyl-5H-dibenzo [b,f] carboxamide with different benzaldehyde derivatives to yield chalcone compounds A-D was carried out. In the second step, compounds A-D reacted with 4,4’-sulfonylbis(azidobenzene) (G) to produce 1,2,3-triazole derivatives A₁-D₁. All the prepared compounds were characterized by Fourier-transform infrared spectroscopy (FTIR) and melting point, some of them were characterized by proton nuclear magnetic resonance (¹H-NMR) spectroscopy analysis. Biological activity test was done to evaluate the antibacterial activity of eight synthesized derivative compounds against two multi-drug resistant pathogenic bacteria isolated from patients infected with burn infection; Staphylococcus aureus and Pseudomonas aeruginosa. Three concentrations were selected 50, 100 and 150 mg/mL from each of the synthesized derivative compounds. The derivative compound D₁ with the concentrations of 100 and 150 mg/mL exhibited excellent effect against P. aeruginosa with inhibition zone diameters of 28.10 ± 0.5 and 28 ± 0.05 mm, respectively.

Keywords: Chalcone; Azide; 1,2,3-Triazole; Biological activity; Anti-inflammatory

Introduction

Triazole is one of the most important heterocyclic compounds due to its wide range of pharmaceutical applications and synthetic media [1]. Wolff and coworkers discovered that 1,2,3-tetrazolium could be prepared by a 1,3-dipole addition reaction, where the reactivity of alkenes in this type of cycloaddition was significantly influenced by the electronic properties of the double bond, and the reaction with electron deficient alkenes required long reaction time of weeks or even months [2]. Chalcone derivatives containing α,β-unsaturated carbonyl have a wide range of biological activities in medical and pharmaceutical...
drugs such as oxidation resistors, anti-inflammatory, antimicrobial, anti-tubercular and anticancer [3-7]. Synthesis and biological evaluation of 1,2,3-triazole tethered pyrazoline and chalcone derivatives were reported by Hussaini et al. It was indicated that some of the prepared compounds had significant activities against the prostate cancer cell line DU145 and caused accumulation of cells in G2/M phase and inhibited tubulin polymerization. Furthermore, these compounds reduced the mitochondrial membrane potential, and thereby indicating their ability to trigger apoptosis [8]. In the present study, novel 1,2,3-triazol-chalcone derivatives from N-acetyl-5H-dibenzo azepine-5-carboxamide were synthesized and characterized. Biological screening of the prepared compounds were also investigated.

Table 1 Physical properties of A–D compounds

| Compound | Structural formula | Molecular formula | M.P. (°C) | Yield (%) | Rf  |
|----------|--------------------|-------------------|-----------|-----------|-----|
| A        | ![Structural formula A] | C_{27}H_{20}N_{2}O_{2} | 238 - 240 | 90        | 0.82|
| B        | ![Structural formula B] | C_{24}H_{20}N_{2}O_{3} | 240 - 246 | 78        | 0.75|
| C        | ![Structural formula C] | C_{24}H_{20}N_{2}O_{2} | 245 - 250 | 75        | 0.63|
| D        | ![Structural formula D] | C_{23}H_{18}N_{2}O_{2} | 239 - 244 | 86        | 0.80|

Experimental

General synthesis procedure for chalcone derivatives (A)-(D) [9]

A solution of N-acetyl-5H-dibenzo [b,f] azepine-5-carboxamide (0.01 mol) in absolute ethanol (50 mL) was refluxed with various aromatic aldehydes in the presence of 10% NaOH (5 ML) for 3 h; the concentration was cooled and poured onto ice. The solids thus obtained recrystallization ethanol solvent. The reaction showed by thin layer chromatography (TLC) that was completed by using benzene : methanol = 4 : 1 as a solvent. 1-(E)-N-(2(2-hydroxynaphthalen-1-yl)vinyl)-5H-dibenzo [b,f] azepine-5-carboxamide (A). 2-(E)-N-(4-hydroxy-3-methoxystyryl)5H-dibenzo [b,f] azepine-5-carboxamide (B). 3-(E)-
N-(4-methoxystyryl)-5H-dibenzo[bf]azepine-5-carboxamide (C). 4-(E)-N-(4-hydroxystyryl)-5H-dibenzo[bf]azepine-5-carboxamide (D).

**General synthesis procedure of 4, 4’sulfonylbis azidobenzene (G)** [10]

Dapsone (0.001 mol) was dissolved in 10 mL of dilute HCl in a round bottomed flask. Reaction was cooled to 0-5 °C. Sodium nitrite (0.002 mol) was added in small portion (4 portions) to the reaction mass by maintaining the temperature at 0-5 °C, and the reaction was maintained for 15 min. A solution of sodium azide (0.002 mol) was added in a dropwise manner to the reaction mixture at 0 °C. The reaction mixture was stirred for 20 min at 0 °C. The product was extracted by using chloroform followed by washing with water up to neutral pH. Organic layer was dried with anhydrous sodium sulfate and then the solvent was removed to yield aryl azide derivatives with melting point (m.p.) = 188-190 °C.

**General synthesis procedure of 1, 2, 3-triazole derivatives (A1)-(D1)** [10]

A solution of unsaturated compounds (2 eq) dimethyl sulfoxide DMSO (5 mL) was added to the suspension of sodium ascorbate (1.2 eq) and CuSO4·5H2O (1.2 eq) in DMSO (4 mL). The mixture was stirred for 10 min and the aryl azide was added to the mixture derivatives (2.2 eq). The mixture was heated to 50 °C with 28-h stirring. The reaction mixture was diluted with distilled water (30 mL), extracted with EtOAc (3×30 mL), dried over Na2SO4, and evaporated. Ethanol solvent was used in recrystallization, and TLC was used to prove that the reaction was completed by using benzene : methanol = 4 : 1 as a solvent. 1-N,N’-(1,1’-(sulfonylbis(4,1-phenylene))bis(4-(2-hydroxynaphthalen-1-yl)-4,5-

| Compound | Structural formula | Molecular formula | M.P. (°C) | Yield (%) | Rf |
|----------|--------------------|-------------------|----------|-----------|----|
| A1       | ![Structural formula](image) | C66H48N10O6S2 | 238-240  | 85        | 0.71 |
| B1       | ![Structural formula](image) | C60H48N10O8S2 | 210-216  | 80        | 0.67 |
| C1       | ![Structural formula](image) | C60H48N10O6S2 | Decomposition above 170-174 | 77 | 0.81 |
| D1       | ![Structural formula](image) | C58H44N10O6S2 | Decomposition above 165-167 | 86 | 0.73 |
dihydro-1H-1,2,3-triazole-5,1-diyl)bis(5H-dibenzo [b,f] azepine-5-carboxamide) (A<sub>1</sub>). 2-N,N'-((1,1'-(sulfonylbis(4,1-phenylene))bis(4-(4-hydroxy-3-methoxy phenyl)-4,5-dihydro-1H-1,2,3-triazole-5,1-diyl))bis(5H-dibenzo [b,f] azepine-5-carboxamide) (B<sub>1</sub>). 3-N,N'-(1,1'-(sulfonylbis(4,1-phenylene))bis(4-(4-methoxyphenyl)-4,5 dihydro-1H-1,2,3-triazole-5,1-diyl))bis(5H-dibenzo [b,f] azepine-5-carboxamide) (C<sub>1</sub>). 4-N,N'-(1,1'-(sulfonylbis(4,1-phenylene))bis(4-(4-hydroxyphenyl)-4,5-dihydro-1H-1,2,3-triazole-5,1-diyl))bis(5H-dibenzo [b,f] azepine-5-carboxamide) (D<sub>1</sub>).

**Biological activity test**

Biological activity testing was done to evaluate the antibacterial activity of eight synthesized derivative compounds against two multi-drug resistant pathogenic bacteria isolated from patients infected with burn infection: *Staphylococcus aureus* (*S. aureus*) as gram-positive bacterium and *Pseudomonas aeruginosa* (*P. aeruginosa*) as gram-negative bacterium. These pathogenic bacteria were provided from medical laboratory of Faculty of Science, University of Kufa, Iraq. Antibacterial activity test was performed by using

![Scheme 1 Equation of synthesis of chalcone derivatives (A)-(D).](http://www.nanobe.org)
agar well diffusion method [12, 14]. Briefly, three concentrations were selected (50, 100 and 150 mg/mL) from each crud synthesized derivative compound. By crock-poorer (Oxoid, UK), four wells were made in Muller-Hinton agar surface (Oxoid, UK) swabbed with two pathogenic bacteria according to 0.5 McFarland turbidity. Forty µL of each dilution was transferred to each well and left at 20 °C for 2 h and incubated at 37 °C overnight. Triplicates were done for each test. The inhibition zone around each well was measured in millimeters.

**Statistical analysis**

SPSS V.8 windows software was used in statistical analysis to make comparisons between diameters of inhibition zones (mm) according to T-test. P-value < 0.05 was considered indicative of statistical significance [12].

**Results and Discussion**

**Synthesis of chalcone derivatives (A)-(D)**

The compounds (A)-(D) were synthesized by treatment of N-acetyl-5H-dibenzo[b,f] azepine-5-carboxamide with different benzaldehyde derivatives in the presence of ethanol and 10% NaOH.

The prepared compounds (A)-(D) were characterized by Fourier-transform infrared spectroscopy (FTIR), and the band located at 1602-1683 cm$^{-1}$ was due to the stretching vibration (C=C) of vinyl group of all compounds [15-17]. Other information of functional groups is shown in Table 3.

**Synthesis of 4, 4'-sulfonylbis (azidobenzene) (G)**

The compound (G) was synthesized by treatment of a Dapsone with HCl and NaNO$_2$ to form diazonium salts at 0-5 °C, followed by reaction of diazonium salts with NaN$_3$ at the same temperature. The FTIR spectra showed the typical azide (N3) group absorption at 2105 cm$^{-1}$, and disappearance bands at 3328 and 3449 cm$^{-1}$ due to amine group [18, 19].

**Synthesis of 1,2,3-triazoline derivatives (A$_1$)-(D$_1$)**

The compounds (A$_1$)-(D$_1$) were synthesized by 1,3-dipole cycloaddition reaction catalyzed with CuSO$_4$·5H$_2$O of unsaturated compounds.

The prepared compounds (A$_1$)-(D$_1$) were characterized by FTIR, which showed the disappearance of azide and two asymmetric absorption bands located at 1315-1334 cm$^{-1}$ ascribing to the (SO$_2$) [20-22] in azide. Other information of functional groups is listed as follows:

Proton nuclear magnetic resonance ($^1$H-NMR) spectrum (300 MHz, DMSO-d$_6$ of compound (A) showed the following characteristic chemical shifts, 8.04-7.20 (m, 8H, Ar-H) (Fig. 5). $^1$H-NMR (301 MHz, DMSO-d$_6$) of compound (D) showed δ 9.36 (s, 1H, NH-amide), 8.64 (s, $^1$H, CH=CH), 8.10-7.31 (m, 16H, Ar-H), 7.28 (d, 1H, OH), 6.62 (d, 1H, NH) (Fig. 6). $^1$H-NMR (301 MHz, DMSO-d$_6$) of compound (B$_1$)

![Scheme 2](image-url)  
**Scheme 2** Equation of synthesis of 4, 4'-sulfonylbis (azidobenzene).

| Comp. | Ar             | $\nu$ (C=C) alkenes (cm$^{-1}$) | $\nu$ (C-H)St. Aromatic Aliphatic (cm$^{-1}$) | $\delta$(C-H) bending: (817) (cm$^{-1}$) | Other (cm$^{-1}$) |
|-------|----------------|---------------------------------|-----------------------------------------------|-------------------------------------------|------------------|
| A     | HO             | 1602.85                         | 2926.01                                       | 889.18                                    | $\nu$(O-H): -3415.93 |
| B     | OCH$_3$        | 1666.85                         | 2983.88                                       | 866.04                                    | $\nu$(O-H): -3385.07 $\nu$(O-CH$_3$): -2848.51 |
| C     | OCH$_3$        | 1654.92                         | 2833.43                                       | 864.11                                    | $\nu$(O-CH$_3$): -2850.32 |
| D     | OH             | 1683.86                         | 2983.88                                       | 866.04                                    | $\nu$(O-H): -3431.36 |

http://www.nanobe.org
showed 7.86 - 7.02 (m, 34H, Ar-H), δ 9.34 (s, 2H, NH-amide), 8.53 (s, 2H, CH=N in triazole ring), 6.62 (d, 2H, OH), 5.59 (d, 2H, NH-ring), 3.70 (s, 6H, O-CH₃) (Fig. 7). \(^1\)H-NMR (301 MHz, DMSO-\(d_6\)) of compound (D₁) showed δ 8.53 (s, 2H, NH-amide), 7.99- 7.32 (m, 34H, Ar-H), 7.04 (d, 2H, OH), 5.40 (d, 2H, NH-ring) (Fig. 8).

Antibacterial activity test of derivative compounds (50 mg/mL) against \(S\). \(aureus\) onto Muller-Hinton agar surface was conducted (Fig 9). Antibacterial activity test of derivative compounds (150 mg/mL) against \(P\). \(aeruginosa\) onto Muller-Hinton agar surface was conducted (Fig. 10).

**Biological activity**

According to inhibition zones’ diameters, derivative compounds (C₁), (D) and (D₁) had good antibacterial activity against pathogenic bacteria with high inhibition zones in all concentrations (50, 100 and 150 mg/mL) (Fig. 1 and 2). The derivative compound (D₁) with concentrations of 100 and 150 mg/mL had excellent effect against \(P\). \(aeruginosa\) with inhibition zone diameters of 28.10 ± 0.5 and 28 ± 0.05 mm, respectively. All inhibition zones diameters in mm against two pathogenic bacteria are shown in Table 4.
Fig. 1 FTIR spectrum of amide compound.

Fig. 2 FTIR spectrum of compound (A).

Fig. 3 FTIR spectrum of compound (B₁).
Fig. 4 FTIR spectrum of compound (D₁).

Fig. 5 $^1$H-NMR spectrum (300 MHz, DMSO-$d_6$) of compound (A).
Fig. 6 $^1$H-NMR (301 MHz, DMSO-$d_6$) of compound (D).

Fig. 7 $^1$H-NMR (301 MHz, DMSO-$d_6$) of compound (B$_1$).
Conclusions

In this study, 1,2,3-triazole derivatives prepared were stable by resonance with high melting points relatively. And there were good antibacterial activities against *Pseudomonas aeruginosa* and *Staphylococcus aureus*.
Conflict of Interests

The authors declare that no competing interest exists.

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