Synthesis, Identification and Studying Biological Activity of Some Heterocyclic Derivatives from 3, 5-Dinitrosalicylic Acid

R Kais¹ and S Adnan²

¹Department of Chemistry, College of Education, University of Al-Qadisiyah, Iraq. E-mail: rafid.kais@qu.edu.iq

²Department of Chemistry, College of Education, University of Al-Qadisiyah, Iraq

Abstract

The study deals with synthesizing new thiadiazole compound (2-(5-amino-1,3,4-thiadiazol-2-yl)-4,6-dinitrophenol)(1) by reaction of 3,5-dinitrosalicylic acid with thiosemicarbazide in Phosphoric chloride, then it is (1) reacted with 2-Bromobenzaldehydeto getting Schiff base (2-(5-((2-bromobenzylidene)amino)-1,3,4-thiadiazol-2-yl)-4,6-dinitrophenol)(2). The compound (2) will reacted with (chloroacetylchloride, thioglycolic acid, glycine, sodium azide, phthalic anhydride) to give ( -lactam, thiazolidine, imidazolidine, tetrazole, oxazepine) derivatives respectively. The new synthesized compounds have been identified by their melting points, ¹H-NMR, ¹³C-NMR and FT-IR spectra. Then the biological activity studied for all the synthesized derivatives toward two type of bacteria.

Keywords: thiadiazole, Schiff bases, -lactam, thiazolidine, imidazolidine, tetrazole, oxazepine.

1. Introduction

Thiadiazole is a heterocyclic compound formed from both nitrogen atoms and one sulfur atom as part of the aromatic five membered rings [1]. The sulfur atom of the thiadiazole very imparts it used as anti-parasitic, anti-convulsan, anti-coagulant, anti-cancer, and anti-tubercular [2].
imine group (–RC=NR–) in Schiff bases are prepared by the condensation between the amine (R–NH₂) and carbonyl (RCOR) compounds[3]. Schiff bases have been displayed to exhibit a wide range of biological activities. These biological activities include antifungal, antibacterial, antimalarial, anti-proliferative, anti-inflammatory, antiviral, and antipyretic properties [4].

Imidazolidines are compounds of highly conserved five-member ring which formed of nitrogen-containing pharmacophores[5]. Imidazolidines are very important structure blocks in biologically active compounds because it carriers of pharmacologically active carbonyl compounds [6].

Thiazolidines are five member rings with a thin group and amine group. The group is always at the first place and amine group at third place [7]. Thiazolidinones are very important group of heterocyclic compounds that having various biological uses as: antibacterial anticonvulsant, anti-inflammatory, FSH receptor agonist, anticancer, antiviral, antifungal and antihistaminic activities [8].

Azetidinones are carbonyl derivative of azetidine which contain the carbonyl group at position 2, also called 2-azetidinone or -lactam[9]. Its most important class of antibiotics in human medicine and share [9].

Tetrazoles are artificial, five-membered heterocycles consisting of four nitrogen atoms and one carbon atom with different substitutions[10]. Tetrazole derivatives applications as antihypertensive, antialergic and antibiotic [11].

Oxazepine is seven membered heterocycle have oxygen and nitrogen in addition to the five carbon atoms[12]. These compounds have been synthesized by condensation of Schiff bases and anhydrides[13]. Oxazepine derivatives have biological activities such as antibacterial, hypnotic muscle relaxant, inflammatory and antiepileptic[14].

2. Experimental

2.1 Materials and methods

FTIR Spectra was done in the range of (4000-400 cm⁻¹) by using KBr disk which were recorded on a SHIMADZU FTIR-8400S fourier transform proton nuclear magnetic resonance were recorded on fourier transformation bruker spectrometer, operating at (400 MHz) with
(DMSO-d$_6$) measurements were made at Department of chemistry, university of Tehran in Iran. Elemental analysis measured on EAS superuser elemental analyser system GmbH, access: VarioELsuperuser.

2.2 Procedure

2.2.1 synthesis of 2- (5-amino-1,3,4-thiadiazol-2-yl)-4,6-dinitrophenol (1)

A mixture of the corresponding 3,5-dinitrosalicylic acid (0.0043 mol), thiosemicarbazide (0.39 g, 0.0043 mol) and phosphorous oxychloride (8 ml) was gently refluxed for 3 h. After cooling, water (40 ml) was added slowly then the reaction mixture was refluxed for 4 h and filtered. The solution was neutralized with concentrated potassium hydroxide solution and the precipitate was filtered and recrystallized from ethanol [15].

2.2.2 synthesis of 2-(5-((2-bromobenzylidene) amino)-1,3,4-thiadiazol-2-yl)-4,6 dinitrophenol (2)

A mixture of equimolar quantities (0.0035 mol) of compound (1) and (0.0035 mol) of 2-bromobenzaldehyde and (3 drops) of glacial acetic acid was refluxed for (6) h in 30 ml of ethanol. The reaction mixture was cooled and kept for (24 hs). The precipitate was filtered and recrystallized from ethanol [16].

2.2.3 synthesis of 2-(2-bromophenyl)-3-(5-(2-hydroxy-3,5-dinitrophenyl)-1,3,4-thiadiazol-2-yl)imidazolidin-4-one (3)

A mixture of Schiff bases (2) (0.0011 mol) and glycine (0.0011 mol) was dissolved in THF (15 mL) and refluxed for 48 hs. The reaction was cooled and recrystallized from absolute ethanol [17].

2.2.4 synthesis of 2-(2-bromophenyl)-3-(5-(2-hydroxy-3,5-dinitrophenyl)-1,3,4-thiadiazol-2-yl)thiazolidin-4-one (4)

Mercapto acetic acid (0.0011 mol) in 1,4-dioxane (20 ml) was added to (0.0011 mol) of Schiff bases (2). Then added to mixture (0.5 gm) anhydrous zinc chloride with stirring then the mixture was refluxed for 16 hours. The reaction mixture was cooled and kept for (24 hs). The crystals found was filtered, dried and recrystallized from ethanol [18].

2.2.5 synthesis of 4-(2-bromophenyl)-3-chloro-1-(5-(2-hydroxy-3,5-dinitrophenyl)-1,3,4 thiadiazol-2-yl)azetidin-2-one (5)

To Triethylamine (0.0003 mol) in 1,4-dioxane, chloroacetyl chloride (0.00012 mol) was added drop wise to a solution of the compounds (2) (0.0011 mol) and at 10 °C temperature.
The reaction mixture was stirred for 12 h. The solid obtained was recrystallized from ethanol[20].

2.2.6 synthesis of 2-(5-(5-(2-bromophenyl)-2,5-dihydro-1H-tetrazol-1-yl)-1,3,4-thiadiazol-2-yl)-4,6-dinitrophenol(6) Compounds of (2) (0.0011mole) was dissolved in (20mL) dioxane and mixed with(0.0011mole) sodium azide. These mixtures were refluxed for(48)h at T=55 °C . The crystals found was filtered, dried and recrystallized from ethanol[21].

2.2.7 synthesis of 3-(2-bromophenyl)-4-(5-(2-hydroxy-3,5-dinitrophenyl)-1,3,4-thiadiazol-2-yl)-3,4-dihydrobenzo[e][1,3]oxazepine-1,5-dione (7)

A mixture of Schiff base (2) (0.0011mole) and phthalicanhydride (0.0011mole) was dissolved in (20mL) 1,4-dioxane. The mixture was refluxed for 28hrs in water bath at (70 °C), the precepitate was filtered and recyrstallized from ethanol[22].
3. Results and Discussion

3.1 The compound (1) (1-(4-((5-methyl-4-nitro-1H-imidazol-2-yl)diazenyl)phenyl)ethan-1-one) is brown solid yield 85%, m.p. 258°C.

The infrared spectrum of compound 1 (figure 1) showed band at (3571.92) cm⁻¹ for (OH), (3093.61) cm⁻¹ for (NH), (3001.31) cm⁻¹ for (C-H) aromatic, (2885.31, 2962.46) cm⁻¹ for (C-H) aliphatic, (1674.10) cm⁻¹ for (C=N), (1612.38) cm⁻¹ for (C=C), (640.32) cm⁻¹ for (C-S).
The $^1$H-NMR (DMSO-$d_6$) spectrum data ‘figure 2’ of compound (1) show: 4.7 ( $\text{S, 2H, NH}_2$), 5.4 ( $\text{S, 1H, OH}$), 7 – 7.4 ( $\text{m, 2H, Ar-H}$), 2.48-2.5 ( DMSO ).

The $^{13}$C-NMR (DMSO-$d_6$) spectrum data ‘figure 3’ of compound (1) show: 134 ( C$_1$ ), 130 ( C$_2$ ), 129 ( C$_8$ ), ( 124 – 126 ) C$_\text{arom}$, 38.9-40.04 ( DMSO ).
3.2 The compound (2) 2-(5-((2-bromobenzylidene)amino)-1,3,4-thiadiazol-2-yl)-4,6-dinitrophenol was obtained as yellow solid yield 79%, m.p (230°C).

The infrared spectrum of 'figure 4' compound (2) showed band at, (1581.52, 1380) cm\(^{-1}\) for (NO\(_2\)), (1627.81) cm\(^{-1}\) for (C=C), (1674.10) cm\(^{-1}\) for (CH=N), (3371.34) cm\(^{-1}\) for (OH).

The \(^1\)H-NMR (DMSO-d\(_6\)) spectrum 'figure 5' data of compound (2) show: 9.7 (S, 1H, OH), 8.8 (S, 1H, CH), 6.9 – 8 (m, 6H, Ar-H), 2.4 (DMSO).

The \(^{13}\)C-NMR (DMSO-d\(_6\)) spectrum data ‘figure 6’ of compound (2) show: 131 (C\(_9\)), 147.12 (C\(_5, C_7\)), 158.56 (C\(_8\)), 173.23 (C\(_1\)), (126.59 – 128) C\(_{arom.}\), 38.8-40.9 (DMSO).
3.3 The compound (3) 2-(2-bromophenyl)-3-(5-(2-hydroxy-3,5-dinitrophenyl)-1,3,4-thiadiazol-2 yl)imidazolidin-4-onewas obtained as yellow solid yield 78% , m.p(204) °C.

The infrared spectrum data of ‘figure 7’ compound (3) showed band at, (2864.45, 2968.45) cm⁻¹ for (C-H aliphatic), (3163.04) cm⁻¹ for (NH), (1664.73) cm⁻¹ for (C=O), (1596.95) cm⁻¹ for (C=N), (1527.52) cm⁻¹ for (C=C)aromatic.
The $^1$H-NMR (DMSO-d$_6$) spectrum data ‘figure 8’ of compound (3) show: 3.5 (S, 2H, CH$_2$), 9.7 (S, 1H, OH), 3.8 (S, 1H, CH), 4.6 (S, 1H, NH), 6.9 – 8.8 (m, 7H, Ar-H), 2.49 (DMSO).

The $^{13}$C-NMR (DMSO-d$_6$) spectrum data ‘figure 9’ of compound (3) show: 41 (C$_4$), 62 (C$_5$), 171 (C$_3$), 167 (C$_2$), 160 (C$_{13}$), (125 – 132) C$_{arom}$, 38.8-40.07 (DMSO).

Figure 7. FT-IR for Compound (3)
3.4 The compound (4) 2-(2-bromophenyl)-3-(5-(2-hydroxy-3,5-dinitrophenyl)-1,3,4-thiadiazol-2-yl)thiazolidin-4-one was obtained as red solid yield 75%, m.p (101)°C.

The infrared spectrum data ‘figure 10’ of compound (4) showed two band at, (2862.17, 2923.88) cm⁻¹ for (C-H aliphatic), (3047.32) cm⁻¹ for (C-H) aromatic, (1720.39) cm⁻¹ for (C=O), (1550.66) cm⁻¹ for (C=C) aromatic, (1581.52) cm⁻¹ for (C=N), (3402.20) cm⁻¹ for (OH), (3220.21) cm⁻¹ for (NH).

The ¹H-NMR (DMSO-d₆) spectrum data ‘figure 11’ of compound (4) show: 2.4 (S, 2H, CH₂), 9.6 (S, 1H, OH), 3.1 (S, 1H, CH), 6.6 – 7.6 (m, 7H, Ar-H), 2.81-2.87 (DMSO). The ¹³C-NMR (DMSO-d₆) spectrum data ‘figure 12’ of compound (4) show: 40.5 (C₄), 52 (C₅), 189 (C₇), 171 (C₂), 170 (C₁), 150 (C₁₃), (111 – 131) C arom, 38.8-40 (DMSO).
3.5 The compound (5) 4-(2-bromophenyl)-3-chloro-1-(5-(2-hydroxy-3,5-dinitrophenyl)-1,3,4 thiadiazol-2-yl)azetidin-2-one was obtained as brown solid yield 88% , m.p( 117) °C.

The infrared spectrum data ‘figure 13’ of compound (5) showed two bands at, (2885.31, 2939.31) cm⁻¹ for (C-H aliphatic), (3080) cm⁻¹ for (C-H) aromatic , (1720.39) cm⁻¹ for (C=O), (1596.95) cm⁻¹ for (C=N), (848.62) cm⁻¹ for (C-Cl), (3363.62) cm⁻¹ for (OH).

The ¹H-NMR (DMSO-d₆) spectrum data ‘figure 14’ of compound (5) showed : 1.2 (d, 2H, CH-N), 10.8 (S, 1H, OH), 3 (d, 1H, CH-Cl), 6.5 – 7.6 (m, 7H, Ar-H), 2.48-2.5 (DMSO)
The $^{13}$C-NMR (DMSO-d$_6$) spectrum data ‘figure 15’ of compound (5) show: 59 (C$_4$), 45 (C$_5$), 174 (C$_3$), 169 (C$_2$), 168 (C$_1$), (125 – 133) C$_{arom}$, 38.8-40.07 (DMSO).
3.6 The compound (6) 2-(5-(5-(2-bromophenyl)-2,5-dihydro-1H-tetrazol-1-yl)-1,3,4-thiadiazol-2-yl)-4,6-dinitrophenol was obtained as brown solid yield 78%, m.p (141) °C.

The infrared spectrum data ‘figure 16’ of compound (6) showed band at, (3240.19) cm⁻¹ for (NH), (3371.34) cm⁻¹ for (OH), (1627.81) cm⁻¹ for (C=N), (1604.66) cm⁻¹ for (C=C).

The ¹H-NMR (DMSO-d₆) spectrum data ‘figure 17’ of compound (6) show: 9.7 (S, 1H, OH), 3 (S, 1H, CH), 4.1 (S, 1H, NH), 7 – 8.8 (m, 6H, Ar-H), 2.48-2.49 (DMSO).

The ¹³C-NMR (DMSO-d₆) spectrum data ‘figure 18’ of compound (6) show: 62.7 (C₃), 160 (C₂), 152 (C₁₁), 145 (C₁₂, C₁₄), (109 – 131) C arom., 38.79-40.04 (DMSO).
3.7 The compound (7) 3-(2-bromophenyl)-4-(5-(2-hydroxy-3,5-dinitrophenyl)-1,3,4-thiadiazol-2-yl)-3,4-dihydrobenzo[e][1,3]oxazepine-1,5-dione was obtained as yellow solid yield 90%, m.p (238) °C.

The infrared spectrum data ‘figure 19’ of compound (7) showed tow band at, (2893.02, 2970.17) cm\(^{-1}\) for (C-H aliphatic), (3078.18) cm\(^{-1}\) for (C-H aromatic), (1689.53) cm\(^{-1}\) for (C=O oxa.), (1558.94) cm\(^{-1}\) for (C=C aromatic), (1589.23) cm\(^{-1}\) for (C=N), (3433.06) cm\(^{-1}\) for (OH).
The $^1$H-NMR (DMSO-d$_6$) spectrum data ‘figure 20’ of compound (7) show : 4.4 ( S, 1H , CH), 9.7 ( S, 1H , OH), 7.1 – 8.6 ( m , 10H , Ar-H ), 2.49 ( DMSO). The $^{13}$C-NMR (DMSO-d$_6$) spectrum data ‘figure 21’ of compound (7) show : 64.32 ( C$_5$ ), 165.12, 168.35 ( C$_3$, C$_4$ ), 155.51 ( C$_{13}$ ), 138.43, 146.22 ( C$_{14}$, C$_{16}$ ), ( 127.68 – 133.71 ) C$_{arom}$, 38.81-40.06 ( DMSO).
Figure 20. $^1$H-NMR of Compound (7)

Figure 21. $^{13}$C-NMR of Compound (7)
Table 1. Analytical and physical data of compounds

| NO. | molecular formula | Color  | M.P °C | RF | yield % | C% | H% | N% |
|-----|-------------------|--------|--------|----|---------|----|----|----|
| 1   | C₈H₅N₅O₅S      | Brown  | 258    | 0.3| 85      | 33.93| 33.71| 1.79| 1.68| 24.73| 24.59|
| 2   | C₁₅H₈BrN₅O₅S   | Yellow | 230    | 0.5| 79      | 40.02| 39.89| 1.79| 1.75| 17.75| 17.67|
| 3   | C₁₇H₁₁BrN₆O₆S  | Yellow | 204    | 0.6| 78      | 40.25| 40.16| 2.19| 2.16| 16.57| 16.46|
| 4   | C₁₇H₁₀BrN₅O₆S₂ | Red    | 101    | 0.3| 75      | 38.94| 38.88| 1.92| 1.78| 13.36| 13.19|
| 5   | C₁₇H₉BrClN₅O₆S | Brown  | 117    | 0.3| 88      | 38.77| 38.65| 1.76| 1.58| 13.30| 13.55|
| 6   | C₁₅H₉BrN₈O₆S   | Brown  | 141    | 0.5| 78      | 36.53| 36.48| 1.48| 1.39| 22.72| 22.67|
| 7   | C₂₃H₁₂BrN₅O₆S  | Yellow | 238    | 0.5| 90      | 46.17| 46.06| 2.02| 2.01| 11.70| 11.65|

4. Antimicrobial activity

In this study we investigated antimicrobial activity of compounds(1-7) which were screened for antibacterial activity against microorganisms representing Gram-positive bacteria [Staphylococcus aureus] and Gram-negative bacteria [Escherichia coli] by agar diffusion method. DMSO is used as solvent. All the compounds were inoculated using a loop onto plates containing Nutrient Agar (NA) media and incubated at 37°C for 24 hours. To carry out...
agar diffusion assay the bacterial suspensions were prepared in sterile distilled water. The results of the antimicrobial activity of the compounds(1-7) against all tested bacterial are shown in figure22 and Table 2.

**Table2. Antibacterial activity of synthesized compounds (1-7)**

| Compounds | Activity index | Zone Of Inhibition (mm) |
|-----------|----------------|-------------------------|
|           |                | Eschericha coli         |
|           |                | Gram(-)                 |
|           |                | Staphylococcus aureus   |
|           |                | Gram(+)                 |
| 1         | 18             | 18                      |
| 2         | 16             | 15                      |
| 3         | 17             | 15                      |
| 4         | 15             | 14                      |
| 5         | 23             | 14                      |
| Standard  |                |                         |
| Amoxycilline | 17          | 17                      |
| Celecoxib   | 15           | 15                      |
| Ciprofloxacin | 30           | 30                      |
Figure 22. effect of compounds (1-7) on growing bacteria (Escherichia coli (A), Staphylococcus aureus (B))
A= Amoxycillin, B= Celecoxib, C= Ciprofloxacin, D= DMSO

5. Conclusions
We can prepare heterocyclic derivatives from 3,5-dinitrosalicylic acid such as thiadiazole, -lactam, thiazolidine, imidazolidine, tetrazole, oxazepine, then studying the biological activity for them, shown compound (7) has more biological activity.

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