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Synthesis, Characterization, and Evaluation of the Antibacterial Activity of Novel 5-aryl-2-amino 1,3,4 Thiadiazole Derivatives

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Abstract

The antibiotic resistant crisis is a worldwide phenomenon that threatens the global health. The misuse and overuse of antibiotics as well as the inadequate development of new antibacterial drugs have all drove the evolution of resistance. Thus, the development and discovery of novel antibacterial agents is a critical field within medicinal chemistry. In this study, a series of novel 1,3,4 thiadiazole derivatives containing imine group was synthesized. The chemical structures had been identified by ^{1}H-NMR, FT-IR, Elemental Analysis (CHNS), and some physicochemical properties. The antibacterial activity of the synthesized compounds was evaluated against two gram-positive (*Staphylococcus aureus, Enterococcus faecalis*), and two gram negative (*Escherichia coli, Klebsiella pneumonia*) bacteria. Among the synthesized compounds, compounds **e4**, **e5**, and **e6** were found to exhibit good antibacterial activity against the tested bacterial strains.

Keywords: Antibacterial, 1,3,4thiadiazole, Imine, *Escherichia coli.*

1. Introduction

Antibacterial drugs are crucial tools in decreasing morbidity and mortality associated with life-threatening infections [1]. However, a global issue has took a place as a result of misuse and overuse of these agents [2]. The multidrug-resistant bacterial strain has been developed along with the decline in the discovery of new antibacterial drugs [3]. The mechanism of bacterial resistance was found to be related to the chemical structure of the antibacterial drugs and the pathway through which they exhibit their activity [4]. Thus, there is an urgent need to overcome this global crisis. The development and discovery of novel antibacterial agents is a critical field within medicinal chemistry. With this in mind, it is commendable to examine new agents with new chemical structures for their antibacterial activity compared to known old agents.

1, 3, 4-thiadiazole rings are an important functional group in medicinal chemistry. They are five-membered aromatic heterocyclic compounds with one sulfur and two nitrogen atoms [5]. Many studies have seen that molecules with thiadiazole moiety in their structures exert many pharmacological activities. For example, anti-inflammatory[6], anticancer[7,8], anticonvulsant [9], antituberculosis[10], and antidiabetic[11, 12]. Furthermore, many pieces of researches supported that this group exhibits promising activity against a wide range of bacterial strains [13, 14].

On the other hand, Schiff bases are promising groups in pharmaceutical chemistry. They contain azomethine group (-HC=N-)[15]. They have been shown to be an attractive moiety for many researchers because of their wide range of biological activity. For example, compounds containing Schiff base might act as anticancer[16], antitoxins[17, 18], analgesic, anti-inflammatory[19], and anti-tuberculosis [20]. In addition to that, in the field of antibacterial discovery, Schiff bases play an important role. It has been found that their derivatives exhibit good antibacterial activity compared to reference antibiotics [21].

Interestingly, agents that combine those two pharmacologically active moieties have shown good antibacterial activities compared to standard antibiotics [22, 23]. This might be due to the multiple mechanisms of action associated with their structures. Therefore, the aim of this study is to synthesize novel products with both 1, 3, 4-thiadiazole, and Schiff base in their structure and evaluate their antibacterial activities. **Figure 1** showed the proposed chemical structure of the synthesized compounds.

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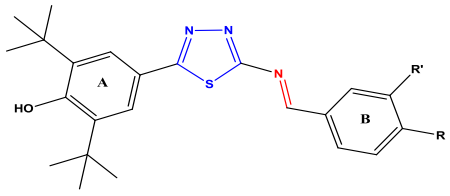


Figure 1: The proposed chemical structure of the synthesized compounds.

2. Experiments

2.1. Chemicals and instruments

All reagents and anhydrous solvents were used as received from the commercial suppliers, (Sigma-Aldrich, Munich, Germany, BDH, Pool Dorset, England, and Fluka, Newport News, USA). Melting points were determined by the capillary method using Electrothermal IA9000, Essex, UK and they are uncorrected. Thin-layer chromatography (TLC) was run on silica gel (60) F254 Merck (Germany), exposed to UV254 nm light, and the eluent used is n-hexane: ethyl acetate (1:1) for compounds (c), ethyl acetate: toluene: ammonia for compounds (e1-6), to check the purity of the compounds, as well as, monitoring the progress of reactions. FT-IR spectra were recorded by using a Shimadzu model (Kyoto, Japan) spectrophotometer on a KBr disk, (v = cm-1). CHNS microanalysis was done by using a Euro EA3000 elemental analyzer (Carlo Erba, Milan, Italy). 1HNMR spectra were recorded on Inova model Ultra shield 500MHz, at (Tehran University, Iran), using tetramethylsilane (TMS) as an internal standard. The chemical shift was expressed as (δ= ppm), DMSO-d6 was used as a solvent.

2.2. Chemical synthesis

Chemical synthesis of all new thiadiazole derivatives is depicted in **Scheme 1**

2.2.1: synthesis of 4-(5-amino-1,3,4-thiadiazol-2-yl)-2,6-di-tert-butylphenol (Compound c)

Drops of conc H_2SO_4 were added to a mixture of 10mmole of (3,5-di-tert-butyl-4-hydroxybenzoic acid) (compound a) and 10mmole of thiosemicarbazide (b) in 10ml of methanol. The solution was reflex for 4h. The product was neutralized with sod. bicarbonate and the precipitate were washed several times with ethyl acetate and recrystallized from methanol [24].

Yellow crystal, yield 74 %, m.p. 220 ^{o} C, R_f =0.34 using n-hexane: ethyl acetate (1:1), Molecular Formula: $C_{16}H_{23}N_3OS$, Molecular Weight: 305.44. IR (KBr disc, v =cm-1): 3336.85 and 3200 (N-H) str. of 1° amine; 3101.54 br (O-H) of phenol; 2954.95, 2908.65, and 2870.08 (C-H) str. of CH_3.

2.2.2: Synthesis of 1,3,4-thiadiazol-2- imine derivatives (Compounds e1-6)

5mmole of different types of aromatic aldehydes solution containing drops of acid was added to the solution of compound c (5mmole) in 10ml methanol. The mixture was reflex for 10h. The formed precipitate was filtered and recrystallized from methanol[25].

(E)-4-(5-(benzylideneamino)-1,3,4-thiadiazol-2-yl)-2,6-di-tert-butylphenol (Compound e1): Orange powder, m.p.230-231, 65 yield%, R_f =0.5. IR (KBr disc, v =cm-1). Elemental analysis: Cal. For ($C_{23}H_{27}N_3OS$), molecular weight: 393.55, C: 70.20; H: 6.92; N: 10.68; S: 8.15; Obs. C: 70.4; H: 6.82; N: 10.60; S: 8.0. ^{1} HNMR (500MHz, DMSO-d6, δ=ppm); 0.98 (18H, s, aliph C**H**$_3$); 4.97 (1H, s, phenolic-O**H**); 7.11(2H, s, Aromatic –**H**, ring A); 7.26 (1H, t, Aromatic-**H**, Ring B, *J*=6Hz); 7.33 (2H, dd, Aromatic -**H**, Ring B, *J*=6, and 7 Hz); 7.52 (2H, d, Aromatic-**H**, Ring B, *J*=7Hz); 9.3 (1H, s, C**H**=N).

(E)-2,6-di-tert-butyl-4-(5-(3-methoxybenzylideneamino)-1,3,4-thiadiazol-2-yl)phenol (Compound e2)*:* yellow powder, m.p. 256-259, 88 yield%, R_f =0.77. IR (KBr disc, v =cm-1): 3143.97 br. phenol (O-H) str.; 2991.59, and 2964.59 (C-H) str. of CH_3; 1579.7 (C=N) str.; 1523.76, 1516.05, and 1452.4 Ar. (C=C) str.; 1288.45 asym (C-O); 1097.5 sym (C-O). Elemental analysis: Cal. For ($C_{24}H_{29}N_3O_2S$) molecular weight: 423.58, C: 68.06; H: 6.90; N: 9.92; S: 7.57; Obs. C:67.01; H: 6.81; N:9.89; S:7.6. ^{1} HNMR (500MHz, DMSO-d6, δ=ppm: 1.11 (18H, s, aliph C**H**$_3$); 3.7 (3H, s, OC**H**$_3$); 5.22 (1H, s, phenolic-O**H**); 7 (1H, d, Aromatic –**H** (CH□C**H**□C-OCH$_3$), ring B, *J*=6.1 Hz); 7.21 (1H, dd, Aromatic –**H** (CH□C**H**□CH), ring B, *J*=6.1, and 8.5 Hz); 7.4 (1H, d, Aromatic –**H** (N=CHC□C**H**□CH), ring B, *J*=8.5Hz); 7.5(1H, s, Aromatic –**H**, (N=CHC□C**H**□C-OCH$_3$), ring B); 7.68 (2H, s, Aromatic –**H**, ring A); 9.25 (1H, s, C**H**=N).

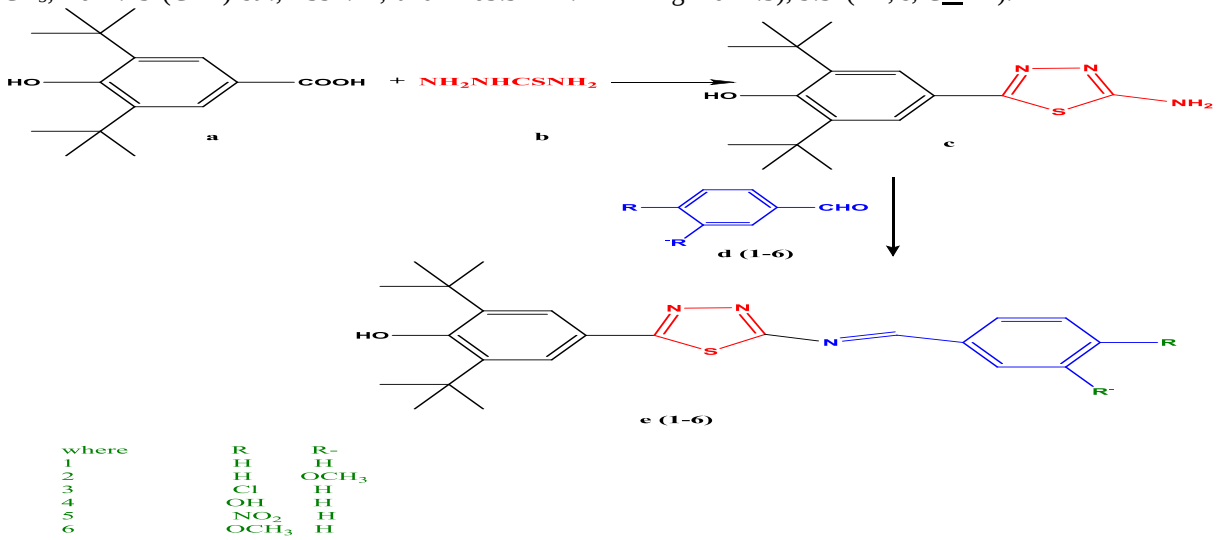
(E)-2,6-di-tert-butyl-4-(5-(4-chlorobenzylideneamino)-1,3,4-thiadiazol-2-yl)phenol (Compound e3)*:* yellow powder, m.p. 268-269, 80 yield%, R_f =0.76. IR (KBr disc, v =cm-1): 3100 phenol (OH) str.; 2997.38, 2960.73, and 2910.58 (C-H) str. of CH_3; 1622.13 (C=N) str.; 1591.27, and 1458.18 Ar. (C=C) str. Elemental analysis: Cal. For ($C_{23}H_{26}ClN_3OS$) molecular weight: 427.99, C: 64.55; H: 6.12; Cl: 8.28; N: 9.82; S: 7.49; Obs. C: 64.58; H: 6.11; CI: 8.2; N: 9.84; S: 7.5.^{1} HNMR (500MHz, DMSO-d6, δ=ppm: 1.29 (18H, s, aliph C**H**$_3$); 4.96 (1H, s, phenolic-O**H**); 7.2(2H, s, Aromatic –**H**, ring A); 7.78 (2H, d, Aromatic –**H** (C**H**□C-CI), ring B, *J*=6.5Hz); 8.11 (2H, d, Aromatic

–**H** (N=CHC□C**H)**, ring B, *J*=6.5Hz) ; 9.54 (1H, s, C**H**=N).

(E)-2,6-di-tert-butyl-4-(5-(4-hydroxybenzylideneamino)-1,3,4-thiadiazol-2-yl)phenol (Compound e4)*:* yellow powder, m.p. 244-246, 75yield%, R_f =0.88. IR (KBr disc, v =cm-1): 3159.4 br. phenol (OH) str.; 2958.8, 2908.65, and 2872.01 (C-H) str. of CH_3; 1602.85 (C=N) str.; 1535.34, 1510.26, and 1462.04 Ar. (C=C) str. Elemental analysis: Cal. For ($C_{23}H_{27}N_3O_2S$) molecular weight: 409.55, C: 67.45; H, 6.65; N: 10.26; S: 7.83; Obs. C 67.22; H: 6.66; N: 10.21; S: 7.81. [1] HNMR (500MHz, DMSO-d6, δ=ppm: 0.94 (18H, s, aliph C**H**$_3$); 5.28 (H, s, phenolic-O**H,** ring A); 6.21 (1H, s, phenolic –O**H**, ring B); 7.34 (2H, d, Aromatic –**H**, (C**H**□C-OH), ring B, *J*=7.3 Hz); 7.52 (2H, s, Aromatic –**H**, ring A); 7.82 (2H, d, Aromatic –**H** (N=CHC□C**H)**, ring B, *J*=7.3 Hz); 9.1 (1H, s, C**H**=N).

(E)-2,6-di-tert-butyl-4-(5-(4-nitrobenzylideneamino)-1,3,4-thiadiazol-2-yl)phenol (Compound e5)*:* Orange powder, m.p. 260-261, 89yield%, R_f =0.85. IR (KBr disc, v =cm-1): 3101.2 phenol (OH) str.; 2960.73, and 2910.58 (C-H) str. of CH_3; 1622.13 (C=N) str.; 1591.27, and 1463.97 Ar. (C=C) str. Elemental analysis: Cal. For ($C_{23}H_{26}N_4O_3S$), molecular weight: 438.55, C: 62.99; H: 5.98; N: 12.78; S: 7.31; Obs. C: 62.97; H: 5.96. N: 12.79; S: 7.28. [1] HNMR (500MHz, DMSO-d6, δ=ppm: 1.29 (18H, s, aliph C**H**$_3$); 5.26 (2H, s, phenolic-O**H**); 7.65 (2H, s, Aromatic –**H**, ring A), 7.93 (2H, d, Aromatic –**H** (N=CHC□C**H)**, ring B, *J*= 6.2 Hz); 8.62 (2H, d, Aromatic –**H** (C**H**□C-NO_2), ring B, *J*= 6.2 Hz) ; 9.55(1H, s, C**H**=N).

(E)-2,6-di-tert-butyl-4-(5-(4-methoxybenzylideneamino)-1,3,4-thiadiazol-2-yl)phenol (Compound e6)*:* Orange powder, m.p. 250-252, 71yield%, R_f =0.75. IR (KBr disc, v =cm-1): 3161.33 phenol (OH) str.; 2960.73, 2908.65, and 2872.01 (C-H) str. of CH_3; 1602.85 (C=N) str.; 1533.41, 1489.05, and 1467.83 Ar. (C=C) str; 1288.45 asym (C-O) str; 1093.64 sym (C-O) str. Elemental analysis: Cal. For ($C_{24}H_{29}N_3O_2S$) molecular weight: 423.58 C: 68.06; H: 6.90; N: 9.92; S: 7.57; Obs. C:68.07; H: 6.93; N: 9.94; S: 7.56. [1]HNMR (500MHz, DMSO-d6, δ=ppm: 1.3(18H, s, aliph C**H**$_3$); 3.82 (3H, s, OC**H**$_3$); 5.11 (1H, s, phenolic-O**H**); 7.01 (2H, d, Aromatic –**H** (C**H**□C-OCH_3), ring B, *J*=7.3Hz); 7.58 (2H, s, Aromatic –**H**, ring A); 8.22 (2H, d, Aromatic-**H** (N=CHC□C**H)**, ring B *J*=7.3); 9.51(1H, s, C**H**=N).



Scheme 1: Chemical synthesis of thiadiazole –imine derivatives (compounds e1-6)

2.2. Antibacterial Activity

Antibacterial activities of the newly synthesized compounds (c and e1-6) in two different concentrations (0.250 and 0.125 mg/ml) were assessed using the disk diffusion method. Their activities were evaluated against Gram-positive bacteria (*Staphylococcus aureus* and *Enterococcus faecalis*); and Gram-negative bacteria (*Escherichia coli* and *Klebsiella pneumonia*). Those organisms were grown on Mueller-Hinton agar. Filter paper disks impregnated with a known concentration of the synthesized compounds were placed on these agars. Then, the petri dishes were incubated at 37 °C for 24 hours. Amoxicillin and Meropenem were used as standards. The zone of inhibition was measured and the results have been summarized in **Table1**.

3. Results and discussion

3.1. Chemistry

4-(5-amino-1,3,4-thiadiazol-2-yl)-2,6-di-tert-butylphenol (compound c) was synthesized by reacting equal mmole of 3,5-di-tert-butyl-4-hydroxybenzoic acid and thiosemicarbazide in methanol under reflux, drops of conc. H_2SO_4 was added to catalyze the cyclization. Compound c characterized by FT-IR spectroscopy due to absent C=O of compound a carboxylic acid, and appearance of two bands of 1^oNH_2 at 3336.85 and 3200.

1,3,4-thiadiazol-2- imine derivatives (compounds e1-6) were synthesized by reacting compound c which was prepared in the first step with different types of aromatic aldehydes. The reaction is accomplished under reflex.
FT-IR spectra of compounds (e1-6) displayed a distinct band at 1579.7, 1622.13, 1602.85, 1622.13, and 1602.85 respectively related to the formed C=N group.

^{1}HNMR spectroscopy displayed characterized signals for synthesized compounds.
Compounds (e1-6) showed a distinct singlet peak at δ= 9.3, 9.25, 9.54, 9.1, 9.55, and 9.51 respectively. This indicates the imine group (H-C=N) formation.

3.2. Biological activity

Novel thiadiazole derivatives (**e1-6**) were tested for their antibacterial activity against gram-positive bacterial strains: *Staphylococcus aureus, Enterococcus faecalis and* gram negative bacterial strains: *Escherichia coli*, and *Klebsiella pneumonia*. Amoxicillin and Meropenem were used as standards. The inhibition zone values were reported in **Table 1**.

According to the results of this study, all thiadiazole derivatives have antibacterial activity against most tested bacterial types. Compound **C** showed weak antibacterial activity against *Enterococcus faecalis* and *E. coli*; however, no activity against *Staphylococcus aureus* and *Klebsiella pneumonia* was seen. Similar activity was found by compound **e1 (**with no substituted at ring B) against all the bacterial species. Compound **e2** (with methoxy group at *m* position of ring B) showed good activity against both *Staphylococcus aureus* and *Escherichia coli* .Despite that, weak activity against *Klebsiella pneumonia* and no activity against *Enterococcus faecalis* were observed.

Both compounds **e4** and **e6** (with hydroxyl and methoxy groups at *p* position of ring B respectively) appear to exhibit good activity against *Staphylococcus aureus* and weak activity against *Enterococcus faecalis.* However, they showed distinguished activity against *Escherichia coli* as compared with standard Meropenem. At the same time, the activity against *Klebsiella pneumonia* by **e4** was distinguished, while weak activity was seen by **e6**.

These results referred to the importance of electron-donating group at para position in improving the antibacterial activity than at meta position. In addition, the resonance stability provided by the hydroxide group seems to play an important role in the antibacterial activity.

On the other hand compound **e3** (with *p*-Cl at ring B) showed no antibacterial activity against *Staphylococcus aureus*, weak activity against both *Enterococcus faecalis* and *Escherichia coli*, and good activity against *Klebsiella pneumonia*. However, compound **e5** (with *p*-NO_2 at ring B) shows weak activity toward both *Staphylococcus aureus*, and *Enterococcus faecalis.* Despite that, distinguished activity toward both *Escherichia coli* and *Klebsiella pneumonia* has been observed.

The mesoionic properties of the five-member ring thiadiazole that involve delocalization of positive and negative charge, and the presence of sulfur atom with high effect on lipophilicity and subsequently pharmacokinetic properties have played an important role in enhancing bacterial cell membrane penetration by the synthesized compounds and then interaction with different biological targets [26]. Furthermore, it seems that the ability of electron-donating groups to form H-bond with target protein in a better manner than electron-withdrawing groups. This could play an important role in increasing the antibacterial activity of the newly synthesized derivatives. In addition, as thiadiazole ring is rich with heteroatoms, this might provide numerous points through which it can interact potentially with the biological targets.

Table1: Antibacterial activity of synthesized compounds.

Compound	R	R-	Conc.	*Staphyloco*	*Enterococc*	*E. coli*	*Klebsiella*

			mg/ml	*ccus aureus*	*us faecalis*		*pneumonia e*
c	-	-	0.250	0 mm	7 mm	6 mm	0 mm
	-	-	0.125	0 mm	7 mm	6 mm	0 mm
e1	H	H	0.250	0 mm	7 mm	6 mm	0 mm
			0.125	0 mm	7 mm	6 mm	0 mm
e2	H	OMe	0.250	14 mm	0 mm	17 mm	6 mm
			0.125	9 mm	0 mm	17 mm	0 mm
e3	Cl	H	0.250	0 mm	9 mm	7 mm	17 mm
			0.125	0 mm	8 mm	7 mm	17 mm
e4	OH	H	0.250	20 mm	9 mm	24 mm	25 mm
			0.125	17 mm	0 mm	20 mm	23 mm
e5	NO2	H	0.250	7 mm	10 mm	20 mm	20 mm
			0.125	0 mm	9 mm	20 mm	9 mm
e6	OMe	H	0.250	15 mm	9 mm	23 mm	8 mm
			0.125	8 mm	0 mm	18 mm	6.5 mm
Meropenem	-	-	0.250	13 mm	19 mm	30 mm	22 mm
			0.125	11 mm	15 mm	27 mm	18 mm
Amoxicillin	-	-	0.250	0 mm	0 mm	0 mm	9 mm
			0.125	0 mm	0mm	0mm	0mm

4. Conclusion

New series of novel compounds that combine both thiadiazole and schiff bases in their structures were synthesized. Those agents were analyzed through FT-IR, ^{1}H-NMR, and elemental analysis CHNS. The compounds with electron donating groups at para position seemed to exhibit higher antibacterial activity.

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