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Research Article

A simple and efficient route for the synthesis of 3-amino aryl -5-aryl -1,2,4-triazoles and investigation of the antibacterial activity

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ABSTRACT

Heterocycles containing nitrogen element have many medicinal properties. Among them, triazoles show significant anticancer and antifungal properties. Because of the beneficial properties of these compounds, chemists have always sought an easier and more effective way to synthesize these compounds. In this study, ten new 3-aminoaryl-5-aryl-1,2,4-triazole derivatives were prepared through the reaction of N-acyl-N'-aryl thioures and hydrazine hydrate under reflux conditions. The progress of the reaction was observed by thin layer chromatography ($CHCl_3$-EtOH 10:1 (v:v)) on 60 HF_{254} silica gel plates, which were examined under UV 254 and 365 nm light. In most of the articles reported on the synthesis of triazole derivatives, the final and pure product is obtained by chromatography on 10*10 cm RP $18F_{254S}$ plates. In this research, triazole derivatives prepared by recrystallization from ethanol three times, high purity products were obtained. The structures of the synthesized compounds were confirmed by analyzes Ft-IR, ^{1}HNMR and ^{13}CNMR. The antibacterial properties of the synthesized compounds were investigated by the well diffusion method. All compounds showed good antibacterial properties against *Staphylococcus aureus* and *Escherichia coli* bacteria. Compounds 3g and 3f showed the highest resistances against bacteria *S. aureus*, and compounds 3g and 3e showed the highest resistance against bacteria *E. coli*.

1. Introduction

Heterocyclic compounds, both natural and synthetic, show interesting biological activities and are often key components in various biological processes. Heterocyclic compounds containing nitrogen atom have attracted considerable attention due to their wide range of medicinal activities. For example, a number of 1,2,4-triazole derivatives are known as antibacterial, antifungal (Lipshutz, 1986), antituberculosis (Prasanna et al., 2013), anticancer (Uzgoren-Baran et al., 2012), antiproliferative (2012). Potts, 1961) anticonvulsant (Li et al., 2013), anti-inflammatory (Patel et al., 2014), analgesic (Rehman et al., 2014; Muniyappan et al., 2020; Bozorov et al. al., 2020; Bozorov et al., 2014; Lakkola et al., 2019; Zhang et al., 2014). For example, fluconazole is used as an antimicrobial drug, while verozol, letrozole, and anastrozole are nonsteroidal drugs used to treat cancer, and lorcolezole is used as an anticonvulsant (Sambasiva et al., 2014; Peterson et al., 2010;

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Oza et al., 2010). The synthesis of triazole derivatives has attracted much attention from researchers due to their various applications. triazole rings (Malah et al., 2020), in a wide range of drugs due to their antiviral activity and other activities, including histamine H1/H2 receptor blockers, cholinesterase active agents, CNS stimulants, anxiety Ants and sedatives (Matin et al., 2022) are included. The electrophilic and nucleophilic centers in N-acyl-N'-aryl thioureas make them useful synthons for the synthesis of various heterocycles.

In recent decades, the literature has been enriched with progressive findings about the synthesis and pharmacological activities of 3,5-disubstitutal – 1,2,4-triazoles ring which is a core structure in various synthetic pharmaceuticals displaying a wide variety of biological activities.

The use of amidines and amidates (Ueda et al., 2009; Castanedo et al., 2011; Xu et al., 2010), oxamides (Batchelor et al., 2008), *S*-methylilisothioureas (Yin et al., 2009) isocyanides (Sarnpitak et al., 2013), *N*-cyanobenimidate (Lee et al., 2012) benzamides derivaties (Sudheendran et al., 2014) and Suzuki_Miyaura reaction (Katkevica et al., 2013) in reasonable yieldes has been repoted.

Due to rapid genetic changes, microorganisms develop resistance to many antibiotics and therapeutic agents (Palma et al., 2020; Duval et al., 2019; Holmes et al., 2016; Donadu et al., 2020). In the last few decades, benzotriazole and its derivatives are of great importance in medicinal chemistry.

The effectiveness of triazole derivatives as drug precursors has attracted the attention of all researchers for a long time. Benzotriazole derivatives act as agonists for many biologically active proteins (Sahu et al., 2013).

Different derivatives synthesized by different researchers showed antimicrobial activity such as antibacterial, antifungal, antiviral, antihelminthic, antiprotozoal and antimicrobial (Karaca Gençer et al., 2017).

The antimicrobial activity of triazole derivatives has been widely investigated since the late 1980s, and together with all azole rings, it has become one of the most prominent research activities in recent years. In the early 20th century, the discovery and development of antibacterial drugs was one of the most important scientific achievements (Appna et al., 2019). Despite investment in antimicrobial drug discovery, no new drug classes have been discovered in the past 20 years.

In addition, the problem of treating infections due to increasing resistance to antibiotics highlighted the necessity of creating new drugs. For decades, scientists have studied various nitrogen rings and determined that when triazoles are part of larger heterocyclic systems, they exhibit biological activity, particularly antibacterial activity.

Escherichia coli is a Gram-negative, facultatively anaerobic, rod-shaped bacterium commonly found in the lower intestine of warm-blooded organisms (Tenaillon et al., 2010; Wells., 2000). Staphylococcus aureus is a gram-positive spherically shaped bacterium that causes a wide range of clinical diseases (Masalha et al., 2001). Infections caused by this pathogen are common in both community-acquired and hospital-acquired environments.

Staphylococcus aureus and Escherichia coli are the most important causes of food-related diseases in the world (Vogt et al., 2005). It has been reported that this bacterium can be found in foods such as milk, other dairy products, vegetables and fermented and raw meats. The enterotoxin of Staphylococcus aureus is resistant to heat and if it is present in food, it is not destroyed by heat.

In this research, we will introduce a simple and effective method for the synthesis of triazole derivatives with high efficiency.

2. Materials and Methods

Compounds were obtained from Merck and used without further purification. The melting points were taken on an Electerothermal-9100 capillary melting point apparatus and are uncorrected. TLC was performed using Silica gel 60 HF_{254} fluorescent plates (Merck), which were examined under UV 254 and 365 nm light. Infrared spectra (ν/cm^{-1}) were recorded on Shimadzu IR-470, using KBr disks. ^{1}H and ^{13}C-NMR spectra were recorded on DRX-400 MHz NMR Spectrometer at 293 K in DMSO-d_6. Spectra were internally referenced to TMS. Peaks are reported in ppm up field of TMS. Elemental analyses (C, H, N) were performed with a Heraeus CHN-O-Rapid analyzer.

3.1. General procedure for the preparation 3-amino aryl -5-aryl-1,2,4-triazole derivatives

To a stirred solution of thiourea (1mmol) in 15 ml of CH_2Cl_2 was added dropwise a mixture of hydrazine hydrate (1.5 mmol) in 5 ml CH_2Cl_2 under reflux condition for 12h. The progress of reaction was monitored by TLC ($CHCl_3$:EtOH 10 : 1). After completion of reaction, the mixture was cooled and the solvent was removed under reduced pressure, and the residue was recrystallized from EtOH.

3.2. Spectral data of synthesized 3-amino aryl -5-aryl-1,2,4-triazole derivatives

3-(4-Ethyl phenyl) amino-5-(4-methyl phenyl)-4H-1,2,4-triazole(3a)

White crystals; yield: 0.26 g (92%); mp 246-248ºC. IR (KBr): 3325, 3275 (NH); 2915 (CH aliph); 1610 (C=N); 1560 (C=C). ^{1}H-NMR (DMSO-d_6): 1.15 (3H, t, $^3J_{HH}$=7.6, CH_3); 2.35 (3H, s, CH_3); 2.52 (2H, q, $^3J_{HH}$=7.6, CH_2); 3.42 (H, brs, NH); 7.08 (2H, d, $^3J_{HH}$=8.4, 2CH); 7.31 (2H, d, $^3J_{HH}$=8.0, 2CH); 7.50 (2H, d, $^3J_{HH}$=8.4, 2CH); 7.89 (2H, d, $^3J_{HH}$=8.0, 2CH); 9.17 (H, s, NH arom). ^{13}C-NMR (DMSO-d_6): 16.4 (CH_3); 21.4 (CH_3); 27.9 (CH_2); 116.4 (C); 126.2 (2CH); 128.4 (2CH); 129.9 (2C); 134.9 (C); 139.5 (C=N); 140.1 (C=N). Anal. Calcd. for $C_{17}H_{18}N_4$ (278): C, 73.38; H, 6.48; N, 20.14. Found: C, 73.41; H, 6.39; N, 20.20.

3-(2-Methyl phenyl) amino-5-(4-methyl phenyl)-4H-1,2,4-triazole(3b)

White crystals; yield: 0.23 g (87%); mp 238-240ºC. IR (KBr): 3325, 3275 (NH); 2915 (CH aliph); 1600 (C=N); 1560 (C=C). ^{1}H-NMR (DMSO-d_6): 2.29 (3H, s, CH_3); 2.36 (3H, s, CH_3); 6.86 (H, brs, CH); 7.16 (2H, brs, 2CH); 7.30 (2H, brs, 2CH); 7.87 (2H, d, $^3J_{HH}$=8.0, 2CH); 7.92 (H, brs, CH); 12.32 (H, brs, NH); 13.64 (H, brs, NH arom).Anal. Calcd for $C_{16}H_{16}N_4$ (264): C, 72.73; H, 6.06; N, 21.25. Found: C, 72.71; H, 6.09; N, 21.29.

3-(4-Methyl phenyl) amino-5-(4-Chloro phenyl)-4H-1,2,4-triazole(3c)

White crystals; yield:0.27 g (90%); mp 262-264ºC. IR (KBr): 3400, 3280 (NH); 2940 (CH aliph); 1610 (C=N); 1560 (C=C). ^{1}H-NMR (DMSO-d_6): 2.24 (3H, s, CH_3); 7.08 (2H, d, $^3J_{HH}$=7.2, 2CH); 7.49 (2H, d, $^3J_{HH}$=7.6 Hz, 2CH); 7.58 (2H, d, $^3J_{HH}$=5.6, 2CH); 8.99 (2H, d, $^3J_{HH}$=8.0, 2CH); 9.22 (H, s, NH); 12.71 (H, s, NH arom). Anal. Calcd for $C_{15}H_{13}ClN_4$ (284.5): C, 63.27; H, 4.57; N, 19.68; Cl, 12.49. Fond: C, 63.30; H, 4.59; N, 19.60; Cl, 12.52.Cl,

3-(4-Ethyl phenyl) amino-5-(4-Chloro phenyl)-4H-1,2,4-triazole(3d)

White crystals; yield: 0.28 g (93%); mp 270-271ºC. IR (KBr): 3453 (NH); 2964 (CH aliph); 1620 (C=N). ^{1}H-NMR (DMSO-d_6): 1.16 (3H, t, $^3J_{HH}$=7.6, CH_3); 2.53 (2H, q, $^3J_{HH}$=7.6, CH_2); 7.10 (2H, d, $^3J_{HH}$=8.4, 2CH); 7.50 (2H, d, $^3J_{HH}$=8.8, 2CH); 7.58 (2H, d, $^3J_{HH}$=8.4 Hz, 2CH); 8.00 (2H, d, $^3J_{HH}$=8.8, 2CH); 9.25 (H, s, NH); 13.16 (H, brs, NH arom). ^{13}C-NMR (DMSO-d_6): 16.4 (CH_3); 27.9 (CH_2); 116.4 (C); 126.2 (2CH); 128.4 (2CH); 129.9 (2C); 134.9 (C); 139.5 (C); 140.1 (C).

Anal. Calcd for $C_{16}H_{15}ClN_4$ (298.5): C, 64.32; H, 5.03; N, 18.79; Cl, 11.89. Found: C, 64.36; H, 5.10; N, 18.75; Cl, 11.93.

3-(2-Methyl phenyl) amino-5-(4-Chloro phenyl)-4H-1,2,4-triazole(3e)

White crystals; yield: 0.26 g (91%); mp 208-209ºC. IR (KBr): 3449 (NH); 2925 (CH aliph); 1607 (C=N); 1543 (C=C). ^{1}H-NMR (DMSO-d_6): 2.32 (3H, s, CH_3); 6.98 (H, brs, NH); 7.05 (H, t, $^3J_{HH}$=6.8, CH); 7.20 (H, d, $^3J_{HH}$=6.4, CH); 7.24 (H, t, $^3J_{HH}$=6.4, CH); 7.41 (2H, d, $^3J_{HH}$=8.0 Hz, 2CH); 7.68 (H, d, $^3J_{HH}$=7.2, CH); 7.88 (2H, d, $^3J_{HH}$=8.0, 2CH); 8.20 (H, brs, NH arom). Anal. Calcd for $C_{15}H_{13}ClN_4$ (284.5): C, 63.27; H, 4.57; N, 19.68; Cl, 12.49; Fond: C, 63.30; H, 4.59; N, 19.60; Cl, 12.52.

3-(4-Ethyl phenyl) amino-5-(4-Fluoro phenyl)-4H-1,2,4-triazole(3f)

White crystals; yield: 0.27 g (96%0); mp 258-260ºC. IR (KBr): 3449 (NH); 2926 (CH aliph); 1614 (C=N); 1556 (C=C). ^{1}H-NMR (DMSO-d_6): 1.18 (3H, t, $^3J_{HH}$=7.6, CH_3); 2.54 (2H, q, $^3J_{HH}$=7.6, CH_2); 7.11 (2H, d, $^3J_{HH}$=7.2, 2CH); 7.36 (2H, t, $^3J_{HH}$=8.8, 2CH); 7.51 (2H, d, $^3J_{HH}$=8.4, 2CH); 8.01 (2H, m, 2CH); 9.21 (H, s, NH); 12.36 (H, brs, NH arom). ^{13}C-NMR (DMSO-d_6): 16.2 (CH_3); 28.0 (CH_2); 114.9

(CH); 115.1 (CH); 116.2 (CH); 116.4 (CH); 116.6 (C); 126.3 (2CH); 128.3 (2CH); 128.4 (2CH); 130.0 (C); 130.1 (C); 135.3 (C=N); 139.8 (C=N); 161.9 (C-F); 164.4 (C-F). Anal. Calcd for $C_{16}H_{15}FN_4$ (282): C, 68.09; H, 5.32; N, 19.86; F, 6.74. Found: C, 69.02; H, 5.36; N, 19.91; F, 6.67.

3-(Phenyl) amino-5-(4-Ethyl phenyl)-4H-1,2,4-triazole(3g)

White crystals; yield: 0.25 g (93%); mp 222-224ºC. IR (KBr): 3431, 3246 (NH); 3040(CH arom); 1616 (C=N); 1492 (C=C). ^{1}H-NMR (DMSO-d_6): 1.16 (3H, t, $^3J_{HH}$=7.6, CH_3); 2.53 (2H, q, $^3J_{HH}$=7.6, CH_2); 7.10 (2H, d, $^3J_{HH}$=8.0, 2CH); 7.50 (5H, m, 5CH); 7.99 (2H, d, $^3J_{HH}$=8.4, 2CH); 9.18 (H, brs, NH); 13.68 (H, brs, NH arom). Anal. Calcd for $C_{16}H_{16}N_4$ (264): C, 72.73; H, 6.06; N, 21.25. Found: C, 72.80; H, 6.12; N, 21.19.

3-(2-Methyl phenyl) amino-5-(phenyl)-4H-1,2,4-triazole(3h)

White crystals; yield: 0.22 g (88%); mp 217-218ºC. IR (KBr): 3453, 3163 (NH); 3032(CH arom); 1684 (C=N); 1537 (C=C). ^{1}H-NMR (DMSO-d_6): 2.51 (3H, s, CH_3); 7.38 (9H, m, 9CH arom); 10.19 (H, brs, NH); 11.16 (H, s, NH arom). ^{13}C-NMR (DMSO-d_6): 19.9 (CH_3); 125.9 (CH); 127.8 (CH); 128.2 (2CH); 128.4 (2CH); 129.0 (C); 131.0 (C); 131.2 (CH); 134.6 (CH); 136.3 (CH); 137.8 (C); 170.8 (C=N); 180.9 (C=N). Anal. Calcd for $C_{15}H_{14}N_4$ (250): C, 72.00; H, 5.60; N, 22.40. Found: C, 72. 07; H, 5.57; N, 22.37.

3-(2-Methyl phenyl) amino-5-(4-Ethyl phenyl)-4H-1,2,4-triazole(3i)

White crystals; yield: 0.24 g (86%); mp 252-254ºC. IR (KBr): 3447 3302 (NH); 2923 (CH aliph); 1611 (C=N); 1545 (C=C). ^{1}H-NMR (DMSO-d_6): 1.16 (3H, t, $^3J_{HH}$=7.6, CH_3); 2.51 (3H, s, CH_3); 2.57 (2H, q, $^3J_{HH}$=7.6, CH_2); 7.10 (2H, d, $^3J_{HH}$=8.0 Hz, 2CH); 7.34 (3H, brs, 3CH); 7.52 (2H, d, $^3J_{HH}$=8.4 Hz, 2CH); 7.67 (H, brs, CH); 9.08 (H, brs, NH); 13.36 (H, brs, NH arom). Anal. Calcd for $C_{17}H_{18}N_4$ (278): C, 73.38; H, 6.48; N, 20.14. Found: C, 73.41; H, 6.39; N, 20.17

3-(4-Methyl phenyl) amino-5-(4-ethyl phenyl)-4H-1,2,4-triazole(3j)

White crystals; yield: 0.24 g (85%); mp 255-256ºC. IR (KBr): 3439 (NH); 2964 (CH aliph); 1628 (C=N); 1430 (C=C). ^{1}H-NMR (DMSO-d_6): 1.16 (3H, t, $^3J_{HH}$=7.6, CH_3); 2.37 (3H, s, CH_3); 2.52 (2H, q, $^3J_{HH}$=10.4, CH_2); 7.10 (2H, d, $^3J_{HH}$=8.0, 2CH); 7.33 (2H, d, $^3J_{HH}$=7.6, 2CH); 7.51 (2H, d, $^3J_{HH}$=8.4, 2CH); 7.88 (2H, d, $^3J_{HH}$=8.0, 2CH); 9.13 (H, s, NH); 13.62 (H, brs, NH arom). Anal. Calcd for $C_{17}H_{18}N_4$ (278): C, 73.38; H, 6.48; N, 20.14. Found: C, 73.41; H, 6.39; N, 20.20.

3.3. Biology

3.3.1. Agar well diffusion assay testing

Preparation of McFarland half standard solution

At first, in order to determine the concentration of inoculum for bacterial culture on the plate, barium sulfate standard turbidity equivalent to McFarland's half standard was used. To prepare the standard half McFarland solution, 0.5 cc of 0.048 M barium chloride solution ($BaCl_2.2H_2O$) was added to 99.5 cc of 0.36 N sulfuric acid solutions with a high speed stirrer. Standard absorbance of McFarland half solution at 625 nm should be between 0.8-0.13.

4 cc of the prepared suspension was poured into screw-capped tubes (the same size as the tubes used to prepare the bacterial solution ready for inoculation). Before using this solution every time, it should be stirred well and vigorously with a vortex. If suspended particles of barium are seen, another new solution should be made.

Cultivation of standard concentration of desired bacteria

Using Inoculating Loops, a small amount of the desired bacteria that was already grown in solid culture medium was removed and poured into a test tube containing 4 cc of liquid culture medium. Then it was incubated for 24 hours at 37 ˚C. During this time, bacteria have grown strongly and the turbidity of the solution has increased. We take some of the solution (about 1 cc) with a sampler and pour it into another test tube containing 4 cc of liquid culture medium. The obtained turbidity should exactly match the turbidity of the 0.5 McFarland solutions. Then the loop was inserted into the test tube to be

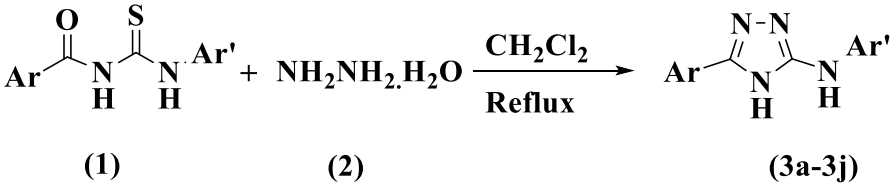
coated with bacteria and the bacteria were cultivated linearly on the solid culture medium. In the next step, wells with a diameter of 2 mm were created using a Pasteur tube.

3.3.2. Sample preparation and antibacterial test by well method

0.002 g of each sample was poured into the microtube. Then 1 cc of Solvent X was added to it and mixed well by vortex. In each of the created wells, the concentration prepared from each sample is poured so that the well is completely filled. Then the prepared plates were incubated for 24 hours at 37 ˚C. After this time, the halo formed around the well was measured with a ruler and reported.

3. Results and Discussion

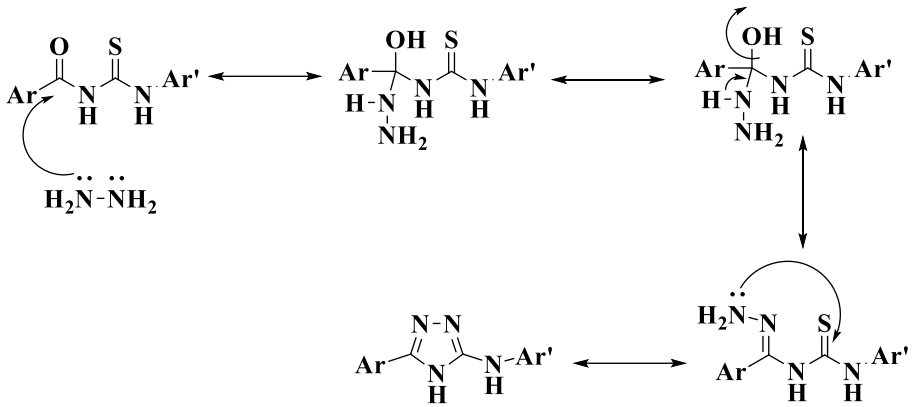
Due to the diverse biological activity of 1,2,4-triazoles and our continuing interest in the development of new strategies toward the synthesis of heterocyclic compounds (Yavari et al., 2007; Pourshamsian et al., 2010; Montazeri et al., 2011; Montazeri et al., 2012; Pourshamsian et al., 2012a; 2013b; 2014c) we report a simple and efficient reaction, between *N*-acyl-*N*- aryl thioureas **1** and hydrazine hydrate (2), which leads to 3-aminosubstituted 5 aryl-1,2,4-triazoles (3a-3j) in good yields (Scheme 1). The progress of reaction was monitored by TLC ($CHCl_3$:EtOH 10:1). The selection of suitable and reactive raw materials in the positions desired by the chemist will lead to the synthesis of compounds with the least by-products and will result in an easier work-up. The electrophilic and nucleophilic centers in N-acyl-N'-aryl thioureas make them useful compounds for the synthesis of various heterocycles. The advantage of this method was that all the products were recrystallized three times from ethanol and reached a high purity of the desired product, and there was no need to purify the product using a chromatography column.



	Ar	Ar′	Yield (%)
3a	4-Et-C6H5	4-Me-C6H5	92
3b	4-Me-C6H5	2-Me-C6H5	87
3c	4-Cl-C6H5	4-Me-C6H5	90
3d	4-Cl-C6H5	4-Et-C6H5	93
3e	4-Cl-C6H5	2-Me-C6H5	91
3f	4-F-C6H5	4-Et-C6H5	96
3g	4-Et-C6H5	Ph	93
3h	Ph	2-Me-C6H5	88
3i	4-Et-C6H5	2-Me-C6H5	86
3j	4-Me-C6H5	4-Et-C6H5	85

Scheme 1. The reaction has been carried out and the yield percentage of the synthesized products

The structures of compounds 3a-3j were deduced from their elemental analyses and their IR, ^{1}H- and ^{13}C-NMR spectra. The structure of product **3a** was supported by NMR spectroscopy. The ^{1}H-NMR spectrum of compound **3a** gave a triplet due to three protons of the CH_3 group (δ = 1.15), singlet due to three protons of the CH_3 (δ = 2.35), quarted due to two protons of the CH_2 group (δ = 2.52). Four doublet at (δ = 7.08, 7.31, 7.50, and 7.89) are to aromatic protons. A singlet at (δ = 7.30) is due to NH proton and another singlet at (δ = 9.17) is due to NH aromatic proton. Elemental analysis also gave satisfactory results for all the compounds. Spectral data of other compounds are given in section 4. The ^{13}C-NMR spectrum of compound 1a showed 13 signals which confirmed with structures. The proposed mechanism is showed in Scheme 2.



Scheme 2: Proposed mechanism for the synthesis of 3-aminosubstituted 5 aryl-1,2,4-triazoles

Antibacterial activities of 3-amino aryl -5-aryl -1,2,4-triazoles

The antibacterial properties of all the synthesized compounds were investigated at a concentration of 2000 µg/ml. The antibacterial activity of the compounds was performed using the agar well diffusion method against E. coli and S. aurous bacteria. The results are reported in Table 1 and Figure 1. As can be deduced from Table 1, compounds 3g and 3f showed the highest resistances against bacteria *S. aureus*, and compounds 3g and 3e showed the highest resistance against bacteria *E. coli*.

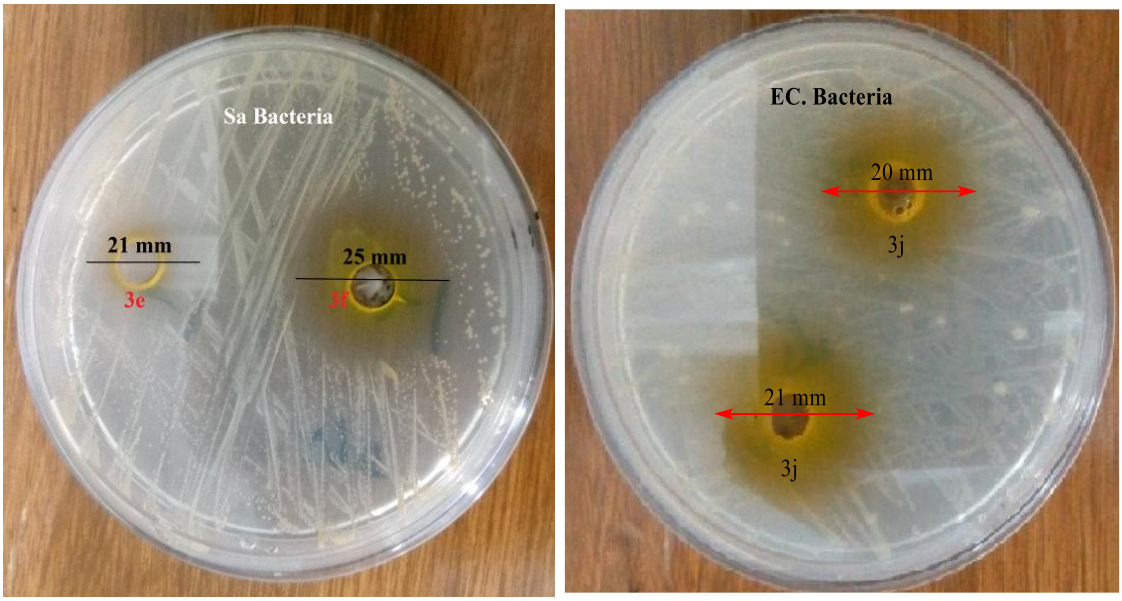


Figure 1. Perform antibacterial test by agar well diffusion method

Table 1. Inhibition zones (mm) of synthesized 3-amino aryl -5-aryl -1,2,4-triazoles against bacteria by agar well diffusion method

Entry	Product	Against *S. aureus* bacteria	Against *E. coli* bacteria	Sample concentration µg/ml
1	3a	11	9.5	2000
2	3b	14	11	2000
3	3c	17	10	2000
4	3d	21	11	2000
5	3e	21	22	2000
6	3f	25	20	2000
7	3g	26	22	2000
8	3h	15	14	2000
9	3i	17	15	2000
10	3j	24	20.5	2000

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Refereces

Appna N.R., Nagiri R.K., Korupolu R.B., Kanugala S., Chityal G.K., Thipparapu G., Banda N. (2019) Design and Synthesis of Novel 4-Hydrazone Functionalized/1,2,4-Triazole Fused Pyrido[2,3-d]Pyrimidine Derivatives, Their Evaluation for Antifungal Activity and Docking Studies. Med. Chem. Res. 28;1509–1528.

Batchelor, D.V., Beal, D.M., Brown, T.B., Ellis, D., Gordon, D.W., Johnson, P.S., Mason, H.J., Ralph, M.J., Underwood, T.J., Wheeler, S. (2008) Acid-Mediated Synthesis of 3-N,N-Dialkyl-amino-1,2,4-Triazoles. Synfacts, 2421-2424.

Bozorov, K., Zhao, J., Aisa, H.A. (2019) 1,2,3-Triazole-containing hybrids as leads in medicinal chemistry: A recent overview. Bioorg. Med. Chem. 27; 3511-3531.

Castanedo, G.M., Seng, P.S., Blaquiere, N., Trapp, S., Staben, S.T. (2011) Rapid synthesis of 1, 3, 5-substituted 1, 2, 4-triazoles from carboxylic acids, amidines, and hydrazines. J. Org. Chem. 76; 1177-1179.

Donadu M.G., Le N.T., Ho D.V., Doan T.Q., Le A.T., Raal A., Usai M., Marchetti M., Sanna G., Madeddu S. (2020) Phytochemical Compositions and Biological Activities of Essential Oils from the Leaves, Rhizomes and Whole Plant of Hornstedtia Bella Škorničk. Antibiotics. 9;334.

Duval R.E., Grare M., Demoré B. (2019) Fight against Antimicrobial Resistance: We Always Need New Antibacterials but for Right Bacteria. Molecules. 24:3152.

Holmes A.H., Moore L.S.P., Sundsfjord A., Steinbakk M., Regmi S., Karkey A., Guerin P.J., Piddock L.J.V. (2016) Understanding the Mechanisms and Drivers of Antimicrobial Resistance. Lancet. 357;176–187.

Katkevica, S., Salum, P., Jirgensons, A. (2013) Synthesis of 5-substituted 3-mercapto-1,2,4-triazoles via Suzuki–Miyaura reaction. Tetrahedron let. 54; 4524-4525.

Lakkkula, R., Roy, A., Mukkanti, K., Sridhar, G. (2019) Synthesis and anticancer activity of 1,2,3-triazole fused N-arylpyrazole derivatives. Russ. J. Gen. Chem. 89; 831-835.

Lee, J., Hong, M., Jung, Y., Cho, E.J., Rhee, H. (2012) Synthesis of 1, 3, 5-trisubstituted-1, 2, 4-triazoles by microwave-assisted N-acylation of amide derivatives and the consecutive

reaction with hydrazine hydrochlorides. Tetrahedron. 65; 2045-2051.

Lipshutz, B.H. (1986) Five-membered heteroaromatic rings as intermediates in organic synthesis. Chem. Rev. 86; 795-819.

Li, Y.D., Mao, W.T., Fan, Z.J., et al. (2013) Synthesis and biological evaluation of novel 1,2,4-triazole containing 1,2,3-thiadiazole derivatives. Chinese Chem. Lett. 24; 1134-1136.

Malah, T.E., Nour, F.F., Satti, A.A.E., Hemdan, B.A., El-Sayed, W.A. (2020) Design, synthesis, and antimicrobial activities of 1,2,3-triazole glycoside clickamers. Molecules, 25; 790

Masalha M., Borovok I., Schreiber R., Aharonowitz Y., Cohen G. (2001) Analysis of transcription of the Staphylococcus aureus aerobic class Ib and anaerobic class III ribonucleotide reductase genes in response to oxygen. J. Bacteriol. 183;7260–7272.

Matin, M.M., Matin, Priyanka., Rahman, R., Hadda, T.B., et al. (2022) Triazoles and Their Derivatives: Chemistry, Synthesis, and Therapeutic Applications. Front Mol Biosci. 9; 864286.

Montazeri, A., Montazeri, N., Pourshamsian, Kh., Tcharkhtchi, A. (2011) The effect of sonication time and dispersing medium on the mechanical properties of multiwalled carbon nanotube (MWCNT)/epoxy composite. Int. J. Polymer Anal. Charact. 16; 465-476.

Montazeri, N., Pourshamsian, Kh., Yosefiyan, S., Momeni, S. (2012) Pentafluorophenylammonium triflate-CuCl2: A mild, efficient and reusable heterogeneous catalyst system for facile synthesis of 4(3H)-quinazolinones under solvent-free conditions. J. Chem. Sci. 124; 883–887.

Muniyappan., G. Kathavarayan, S., Balachandran, C., et al. (2020) Synthesis, anticancer and molecular docking studies of new class of benzoisoxazolyl-piperidinyl-1, 2, 3-triazoles. J. King Saud Univ. Sci. 32; 3286-3292.

Oza, V., Ashwell, S., Brassil, P., Breed, J., Deng, C., Ezhuthachan, J., Haye, H., Horn, C., Janetka, J., Lyne, P., Newcombe, N., Otterbien, L., Pass, M., Read, J., Roswell, S., et al., (2010) Discovery of a novel class of triazolones as checkpoint kinase inhibitors-hit to lead exploration. Bioorg. Med. Chem. Lett. 20; 5133-5138.

Karaca Gençer H., Acar Çevik U., Levent S., Sağlık B.N., Korkut B., Özkay Y., Ilgın S., Öztürk Y. (2017) New Benzimidazole-1,2,4-Triazole Hybrid Compounds: Synthesis, Anticandidal Activity and Cytotoxicity Evaluation. Molecules. 2017;22:507.

Patel, R.V., Park, S.W. (2014) Access to a new class of biologically active quinoline based 1,2,4-triazoles. European J. Med. Chem. 71; 24-30.

Palma E., Tilocca B., Roncada P. (2020) Antimicrobial Resistance in Veterinary Medicine: An Overview. Int. J. Mol. Sci. 21;1914.

Peterson, L.B., Blagg, B.S. (2010) Click chemistry to probe Hsp90: Synthesis and evaluation of a series of triazole-containing novobiocin analogues. Bioorg. Med. Chem. Lett. 20; 3957-3960.

Prasanna, B.N., Mohana, K.N., Mallesha, L. (2013) Synthesis and antiproliferative activity of some new fluorinated Schiff bases derived from 1,2,4-triazoles. J. Fluorine Chem. 156; 15-20.

Potts, K.T. (1961) The Chemistry of 1, 2, 4-Triazoles. Chem. rev. 61; 87.

Pourshamsian, Kh., Montazeri, N., Rad-Moghadam, K., Ali-Asgari, S. (2010) A simple and efficient synthesis of some novel thiazolidine one derivatives. J. Heterocyclic. Chem. 47; 1439-1442.

Pourshamsian, Kh., Montazeri, N., Mohamadi_Zeydi, M., Fotokkiani, F. (2012) An Efficient Synthetic Route for Synthesis of Thiazolidine-4-ones Derivatives. Asian J. Chem. 24; 5242_5244.

Pourshamsian, Kh., Montazeri, N., Ahmadi, S., Noghani, T. (2013) Microwave Assisted, One Pot Synthesis of Alkyl-3-amino-2-arylimino-1, 3-thiazolan-4-ones-5-ylidene Acetate. Asian J. Chem. 25; 306-308.

Pourshamsian, Kh. (2014) ZnO-NPs as an efficient reusable heterogeneous catalyst

for synthesis of 1,4-Dihydropyrimidine derivatives in solvent-free conditions. Int. J. Nano Dimens. 6; 99-104.

Rehman, S., Rahman, M. Tripathi, V.K., Singh, J., Ara, T. et al. (2014) Synthesis and biological evaluation of novel isoxazoles and triazoles linked 6-hydroxycoumarin as potent cytotoxic agents. Bioorg. Med. Chem. Lett. 24; 4243-4246.

Sambasiva,P. Kurumurthy, C., Veeraswamy, B., Santhosh,G., Poornachandra, Y., Ganes h,C., Vasamsetti, S.B., Kotamraju, S., N arsaiah, B. (2014) Synthesis of novel 1,2,3-triazole substituted-N-alkyl/aryl nitrone derivatives, their anti-inflammatory and anticancer activity. Eur. J. Med. Chem. 80; 184-191.

Sahu N., Sahu J.K., Kaushik A. (2013) A Review on "Triazoles": Their Chemistry and Pharmacological Potentials. Curr. Res. Pharm. Sci. 3;108–113.

Sarnpitak, P., Krasavin, M. (2013) Synthesis of 1,2,4-triazoles employing isocyanides. Tetrahedron. 69; 2289-2295.

Sudheendran, K., Schmidt, D., Frey, W., Conrad, J., Beifuss, U. (2014) Facile synthesis of 3,5-diaryl-1,2,4-triazoles via copper-catalyzed domino nucleophilic substitution/oxidative cyclization using amidines or imidates as substrates. Tetrahedron, 70; 1635-1645.

Tenaillon O., Skurnik D., Picard B., Denamur E. (2010) The population genetics of commensal Escherichia coli. Nat. Rev. Microbiol. 8; 207-217.

Ueda, S., Nagasawa, H. (2009) Facile synthesis of 1,2,4-triazoles via a copper-catalyzed tandem addition-oxidative cyclization. J. Am. Chem. Soc. 113;15080-15081.

Uzgoren_Baran, A., Tel, B.C., Sarigol, D. (2012) Thiazolo[3,2-b]-1,2,4-triazole-5(6H)-one substituted with ibuprofen: Novel non-steroidal anti-inflammatory agents with favorable gastrointestinal tolerance. European J. Med. Chem. 57; 398-406.

Vogt R., Dippold L. (2005). Escherichia coli O157:H7 outbreak associated with consumption of ground beef (2002) Public Health Rep. 120;174–178.

Wells, J.C. (2000) Longman Pronunciation Dictionary. Harlow [England], Pearson Education Ltd.

Xu, Y., Mclaughlin, M., Bolton, E.N., Reamer, R.A. (2010) Practical synthesis of functionalized 1, 5-disubstituted 1, 2, 4-triazole derivatives. J. Org. Chem. 75; 8666-8669.

Yavari, I., Ali-Asgari, S., Pourshamsian, Kh., Bagheri., M. (2007) Efficient synthesis of functionalized bis-(4-oxo-1, 3-thiazolan-5-ylidene) acetates. J. Sulfur Chem. 28; 477-482.

Yin, P., Ma, W.B., Chen, Y., Huang, W.C., Deng, Y., He, L. (2009) Highly efficient cyanoimidation of aldehydes. Org. Lett. 11; 5482-5485.

Zhang, W., Li, Z., Zhou, M., Wu, F., Hou, X., Luo, H., Liu, H., Han, X., Yan, G., Ding, Z., Li, R. (2014) Synthesis and biological evaluation of 4-(1,2,3-triazol-1-yl)coumarin derivatives as potential antitumor agents. Bioorg. Med. Chem. Lett. 24; 799-807.