International Journal of Science and Research (IJSR)
ISSN (Online): 2319-7064
Index Copernicus Value (2015): 78.96 | Impact Factor (2015): 6.391

Synthesis of Bis-Heterocyclic Compounds and Study their Antimicrobial Activity

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Abstract: ***According to our recent previous published work, new series of triazole based Schiff's bases (6a-j) have been synthesized from the reaction of benzaldehyde derivatives. Characterization of the synthesized bis-heterocyclic compounds was achieved by ^{1}H NMR, ^{13}C NMR, and FT-IR spectroscopic methods. The antimicrobial activity of compounds 5, and 6a-j were studied against a gram negative bacteria (Escherichia Coli)and a gram positive bacteria (Staphylococcus Aureus).As expected, results revealed that most of studied compounds display high antibacterial activity against both kinds of bacteria, especially against Escherichia Coli. Generally, the antibacterial activity increased with increasing compound concentration and most synthesized compounds can be considered as antibacterial agents even better than the reference in the case of Escherichia Coli. Particularly, synthesized Compounds 5, 6f, and 6jhave been indicated as the most effective candidates against Staphylococcus Aureus, while the highest antibacterial activity against Escherichia Coli have been revealed by compounds 6e, 6f, and 6j.In this study it was found that antibacterial activity of synthesized compounds is proven firstly by the bis-heterocyclic character and secondly by variation of benzene ring substitution.***

Keywords: Triazole, Antibacterial activity, Schiff`s bases, Bis-heterocyclic compounds

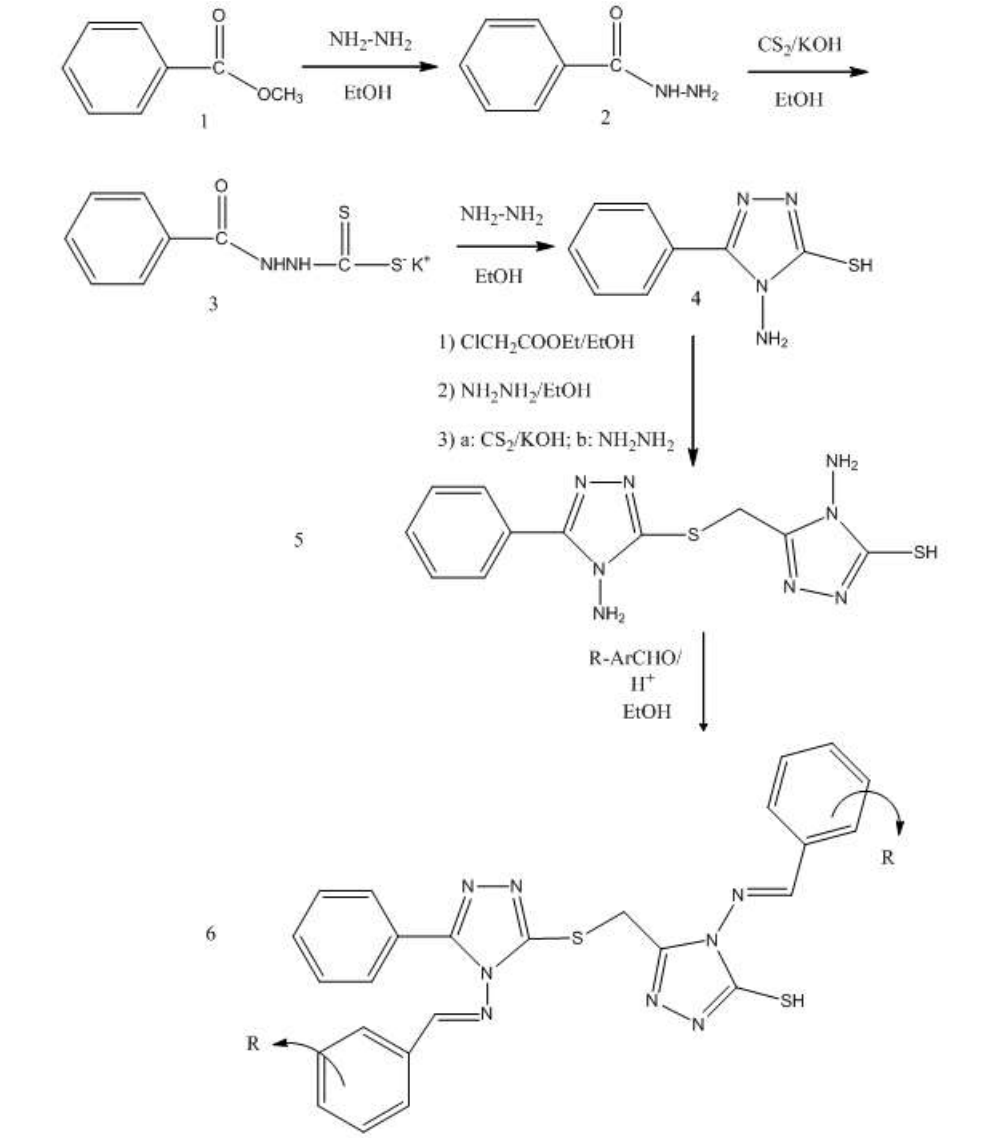
1. Introduction

Nowadays, among other disciplines synthetic heterocyclic chemistry can be considered as an important element to provide antibiotics to the market [1]. Heterocyclic compounds comprised in their structure triazole ring have been essential structural fragments due to their broad spectrum anti-microbial activity [2, 3], anti-pesticidal activity [4], corrosion inhibition [5, 6], and other industrial applications [7, 8].

During the development of a variety of antibiotics, confrontations have appeared against microbial diseases. As bacteria have turning out to be more resistant towards antibiotic, antibiotics overuse and mistreatment have resulted leading to a markedly universal health failure. Broad spectrum potency is reasonably preferred for newly found antibacterial agents [9]. Hence, recent efforts have been presented toward investigating more potential antibacterial agents.Thus, bis-heterocyclic compounds have being shown as highly active compounds to eliminate above mentioned restrictions and confront difficulties [10, 11, 12].

Schiff's bases are also considered as one of the most applied, commonly benefited for industrial uses, and exhibit a wide range of biological activities [13, 14].These remarkable observations and promised preliminary results from our previous published work are motives to synthesize bis-heterocyclic compounds comprising Schiff bases together with 1, 2, 4-triazole ring which predictable to be high potentially anti-microbialactive compounds [15].Scheme 1 shows the synthetic route applied in this work.

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No.	6a	6b	6c	6d	6e	6f	6g	6h	6i	6j
R	H	p-Br	m-Br	p-Cl	p-NO_2	p-OH	p-OCH_3	p-CH_3	p-NH_2	p-N $(CH_3)_2$

Scheme 1: Synthetic route to compounds 6a-j [18]

2. Materials and Methods

Aimed compounds were synthesized according to our published work [15, 16]. FT-IR spectra were done on Shimadzu model FT-IR-8400S.Spectrometer 400 MHz, Avance III 400, Bruker was used to create ^{1}H NMR and ^{13}C NMR spectra. All Compounds were characterized by FT-IR, and (^{1}H NMR, ^{13}C NMR) for compounds **5, 6b, 6c, 6d, and 6f**.On the other hand, the biological activities for compounds **5, and 6 (a-j)** were determined according to well diffusion method [17].

3. Results and Discussion

Chemistry

The products **5 and 6 (a-j)** have been characterized as follows:

4-amino-5-{[(4-amino-5-phenyl-*4H*-1, 2, 4-triazol-3-yl)sulfanyl]methyl}-*4H*-1, 2, 4-triazole-3-thiol (5) [15]

FT-IR (cm^{-1}): (3452, 3417, 3398, and 3278) due to symmetrical and asymmetrical stretching bands which confirm the existence of two NH_2 groups, 3155 cm^{-1} represents (N-H) bond, 3068, 1612, and 601attributed to CH-arom., C=N, and C-S bond, respectively.

^{1}H NMR (δ/ppm): 3.66 (4H, *s*, NH_2), 4.69 (1H, *s*, NH), 5.54 (2H, *s*, CH_2), 7.66-8.04 (5H, *m*, CH aromatic ring), and 13.89 (1H, *s*, SH).

^{13}C NMR (δ/ppm) shows signals at: 32.48 (1C, CH_2), 128.01-132.25 (6C, aromatic ring), 149.41 (1C, ph-C=N), 160.42 (1C,

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H_2C-C=N), 169.94 (1C, C=S), 179.12 (1C, N=C-S), and 180.09 (1C, N=C-SH).

4- [(E)-benzylideneamino]-5-{[(4-((E)-benzylideneamino)-5-phenyl-*4H*-1, 2, 4-triazol-3-yl)sulfanyl]methyl}-*4H*-1, 2, 4-triazole-3-thiol (6a) [15]

FT-IR (cm^{-1}): 3059, 1612, (1500, 1446), 686 attributed to CH arom., C=N group, C=C, and C-S bond, respectively;

4- [(E)-(4-bromobenzylidene)amino]-5-({[4-((E)-(4-bromobenzylidene)amino)-5-phenyl-*4H*-1, 2, 4-triazol-3-yl]sulfanyl}methyl)-*4H*-1, 2, 4-triazole-3-thiol (6b) [15]

FT-IR (cm^{-1}): 3043, 1624, (1566, 1500), (779, 945), 682, and 544 due to CH-arom., C=N, C=C, 1, 3-disubstituted benzene ring, C-S, and C-Br, respectively.

^{1}H NMR (δ/ppm): 4.80 (2H, *s*, CH_2), 7.00-8.24 (13H, *m*, CH of e aromatic rings), (9.85, and10.01) forboth (1H, *s*, N=CH), and 13.91 (1H, *s*, SH).

^{13}C NMR (δ/ppm): 32.88 (1C, CH_2), 122.17- 135.98 (18C, 3 aromatic rings), 149.84 and 151.93 (2C, CH=N), 155.04 (1C, ph-C=N), 156.54 (1C, H_2C-C=N), 160.53 (1C, N=C-S), and 182.25 (1C, N=C-SH).

4- [(E)-(3-bromobenzylidene)amino]-5-{[(4-((E)-(3-bromobenzylidene)amino)-5-phenyl-*4H*-1, 2, 4-triazol-3-yl)sulfanyl]methyl}-*4H*-1, 2, 4-triazole-3-thiol (6c)

FT-IR (cm^{-1}): 3097, 1608, (1500, 1446), 686, 767, and 545 attributed to CH-arom., C=N, C=C, C-S, 1, 4-disubstituted benzene ring, and C-Br, respectively.

^{1}H NMR (/ppm): 4.97 (2H, *s*, CH_2), 7.37-8.70 (13H, *m*, CH of three aromatic rings), (9.75, and10.03) for both (1H, *s*, N=CH), and 13.87 (1H, *s*, SH).

^{13}C NMR (/ppm): 30.05 (1C, CH_2), 122.42-132.88 (18C, 3 aromatic rings), 149.55 and 151.58 (2C, HC=N), 160.46 (1C, ph-C=N), 160.70 (1C, H_2C-C=N), 174.20 (1C, N=C-S), and 183.02 (1C, N=C-SH).

4- [(E)-(4-chlorobenzylidene)amino]-5-{[(4-((E)-(4-chlorobenzylidene)amino)-5-phenyl-*4H*-1, 2, 4-triazol-3-yl)sulfanyl]methyl}-*4H*-1, 2, 4-triazole-3-thiol (6d)

FT-IR (cm^{-1}): 3047, 1624, 2560, 821, and 497 attributed toCH-arom., C=N group, S-H, 1, 4-disubstituted benzene ring, C-Cl, respectively.

^{1}H NMR (/ppm): 4.67 (2H, *s*, CH_2), 7.16-7.91 (13H, *m*, CH of three aromatic rings), (8.09 and9.95) for both (1H, *s*, N=CH), and 13.85 (1H, *s*, SH).

^{13}C NMR (δ/ppm): 33.06 (1C, CH_2), 126.60-144.36 (18C, 3 aromatic rings), 144.94 and 155.61 (2C, HC=N), 156.39 (1C, ph-C=N), 160.54 (1C, H_2C-C=N), 168.55 (1C, N=C-S), and 179.14 (1C, N=C-SH).

4- [(E)-(4-nitrobenzylidene)amino]-5-{[(4-((E)-(4-nitrobenzylidene)amino)-5-phenyl-*4H*-1, 2, 4-triazol-3-yl)sulfanyl]methyl}-*4H*-1, 2, 4-triazole-3-thiol (6e)

FT-IR (cm^{-1}): 2999, 1608, 2762, (1500, 1485), 848, and (1346, 1439) attributed to CH-arom., C=N, CH-aliph., C=C, 1, 4-disubstituted benzene ring, NO_2, respectively

4- [(E)-{ (3-{[(4-((E)-(4-hydroxybenzylidene)amino]-5-mercapto-*4H*-1, 2, 4-triazol-3-yl)methyl]sulfanyl}-5-phenyl-*4H*-1, 2, 4-triazol-4-yl)imino]methyl}phenol (6f)

FT-IR (cm^{-1}): 3450, 3062, 1624, and 833 attributed to O-H bond, C=N, CH-arom., and 1, 4-disubstituted benzene ring, respectively.

^{1}H NMR (δ/ppm): 4.98 (2H, *s*, CH_2), 7.11-8.03 (13H, *m*, CH of three aromatic rings), (9.53 and9.60) for both (1H, *s*, OH), (9.89, 9.98) for both (1H, *s*, CH=N), and 13.97 (1H, *s*, SH).

^{13}C NMR (δ/ppm): 34.05 (1C, CH_2), 112.08-144.79 (18C, 3 aromatic rings), 153.57 and 154.05 (2C, HC=N), 164.74 (1C, ph-C=N), 167.16 (1C, H_2C-C=N), 169.65 (1C, N=C-S), and 180.05 (1C, N=C-SH).

4- [(E)-(4-methoxybenzylidene)amino]-5-{[(4-((E)-(4-methoxybenzylidene)amino)-5-phenyl-*4H*-1, 2, 4-triazol-3-yl)sulfanyl]methyl}-*4H*-1, 2, 4-triazole-3-thiol (6g)

FT-IR (cm^{-1}): 3053, 2628, 1600, (1504, 1485), 833, and 547, attributed to CH-arom., S-H, C=N, C=C, 1, 4-disubstituted benzene ring, and C-S, respectively; 1350, 1161 for $CH_{3bend.}$, and C-O, respectively.

4- [(E)-(4-methylbenzylidene)amino]-5-{[(4-((E)-(4-methylbenzylidene)amino)-5-phenyl-*4H*-1, 2, 4-triazol-3-yl)sulfanyl]methyl}-*4H*-1, 2, 4-triazole-3-thiol (6h)

FT-IR (cm^{-1}): 3072, 1604, (1500, 1485), 1354, and 810 attributed to CH-arom., C=N, C=C arom., $CH_{3bend.}$, and 1, 4-disubstituted benzene ring, respectively.

4- [(E)-(4-(dimethylamino)benzylidene)amino]-5-{[(4-((E)-(4-(dimethylamino)benzylidene)amino)-5-phenyl-*4H*-1, 2, 4-triazol-3-yl)sulfanyl]methyl}-*4H*-1, 2, 4-triazole-3-thiol (6i)

FT-IR (cm^{-1}): 3078, 1597, (1500, 1485), 1350, 1165, and 813 attributed to CH-arom., C=N, C=C, $CH_{3bend.}$, C-N, and 1, 4-disubstituted benzene ring respectively.

4- [(E)-(2-aminobenzylidene)amino]-5-{[(4-((E)-(2-aminobenzylidene)amino)-5-phenyl-*4H*-1, 2, 4-triazol-3-yl)sulfanyl]methyl}-*4H*-1, 2, 4-triazole-3-thiol (6j)

FT-IR (cm^{-1}): (3244, 3394), 3035, 2560, and 1604 attributed to NH_2, CH-arom., S-H, and C=N, respectively.

Biological Activity

The antibacterial effect of synthesized compounds was examined on the two types of bacteria using the concentrations (5, 10, 25, 50) µg/mL. Results are visualized in figures 1 and 2. All compounds including Amoxicillin as a reference have MIC of (5 µg/mL) towards (gram *-ve* bacteria, *E. coli*) and (gram *+ve* bacteria, *S. aureus*). As expected, results revealed that most of studied compounds display high antibacterial activity against both kinds of bacteria, especially against *E.Coli*. Generally, the antibacterial activity increased with increasing compound concentration. Particularly, Compounds 5, 6f, and 6j have been indicated as the most effective candidates against *S.Aureus*, while the highest antibacterial activity against *E. Coli* have been revealed by compounds 6d, 6f, and 6j. In this study, benzene ring substitution has been proved as the most crucial factor to determine the antibacterial activity.

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There is a relationship between the antibacterial ability of triazoleas antibiotic and the formation of a stable complex between cleaved DNA and topoisomerase. This effect has a considerable harmful consequence for the cell ability to handle with DNA damage by drug [18]. The most effective factors in the DNA damage might be the geometrical structures of compounds and the substituent's on the compounds [19].

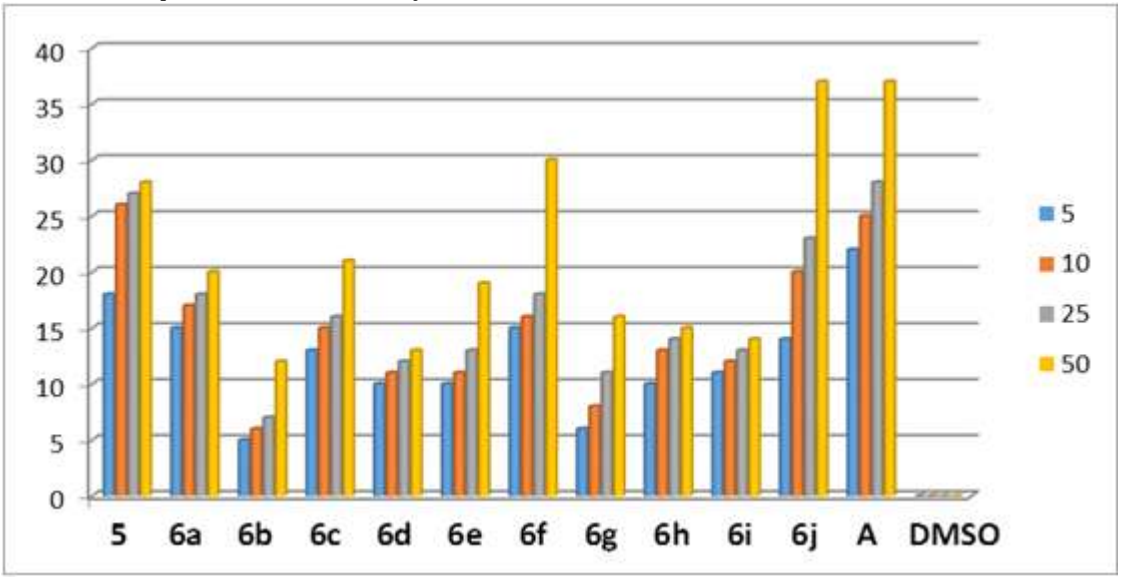


Figure 1: Inhibition zones in (mm) for compounds 5, 6 (a-j) against *S. aureus*, amoxicillin as reference; concentrations = 5, 10, 25, 50 (µg/mL), DMSO is the solvent

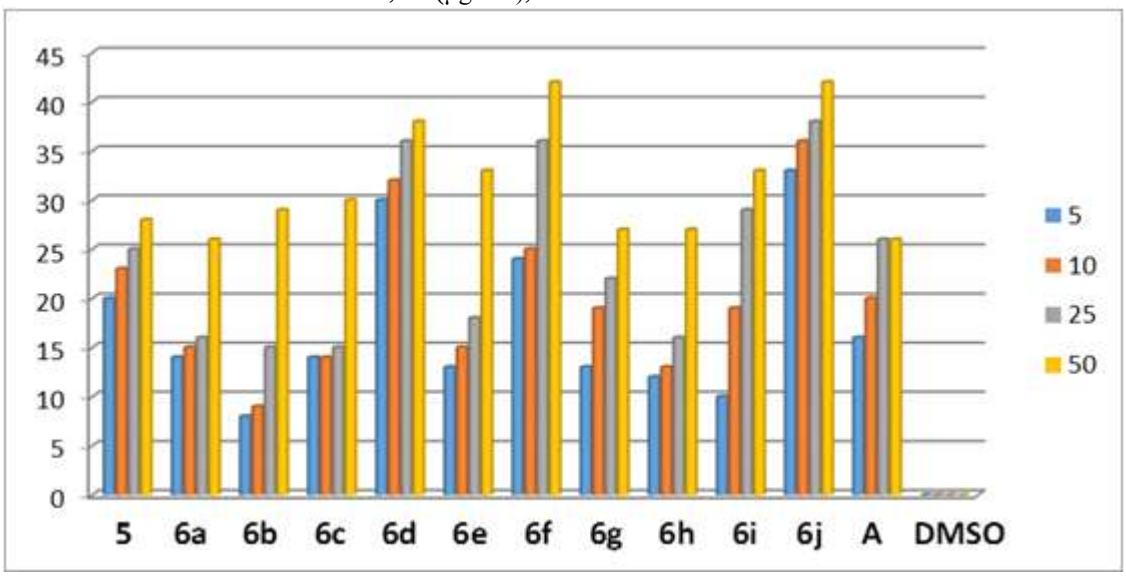


Figure 2: Inhibition zones in (mm) for compounds 5, 6 (a-j) against *E. coli*, amoxicillin as reference; concentrations = 5, 10, 25, 50 (µg/mL), DMSO is the solvent

4. Conclusions

Generally, most of synthesized compounds showed excellent antimicrobial activity towards both bacteria: (gram *-ve*, *E. coli*) and (gram *+ve*, *S. aureus*) that might be due to their bis-functional character.Thereupon, compounds**6f**with *p*-hydroxy and **6j**with *p*-dimethylamino substituent's were the most active against both bacteria and compound**6d**with*o*-chlorosubstituentagainst*E. coli*. As expected, it is indicated that ring substitution was the most significant effect on the antibacterial potentiality of the designed bis-heterocyclic compounds.

5. Acknowledgment

The Authors thank the department of biotechnology of the College of Science Baghdad University and the department of

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chemistry of the College of Science Al-Nahrain University for support and providing all required accomplishing this work.

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