EGYPTIAN ACADEMIC JOURNAL OF
BIOLOGICAL SCIENCES
PHYSIOLOGY & MOLECULARBIOLOGY

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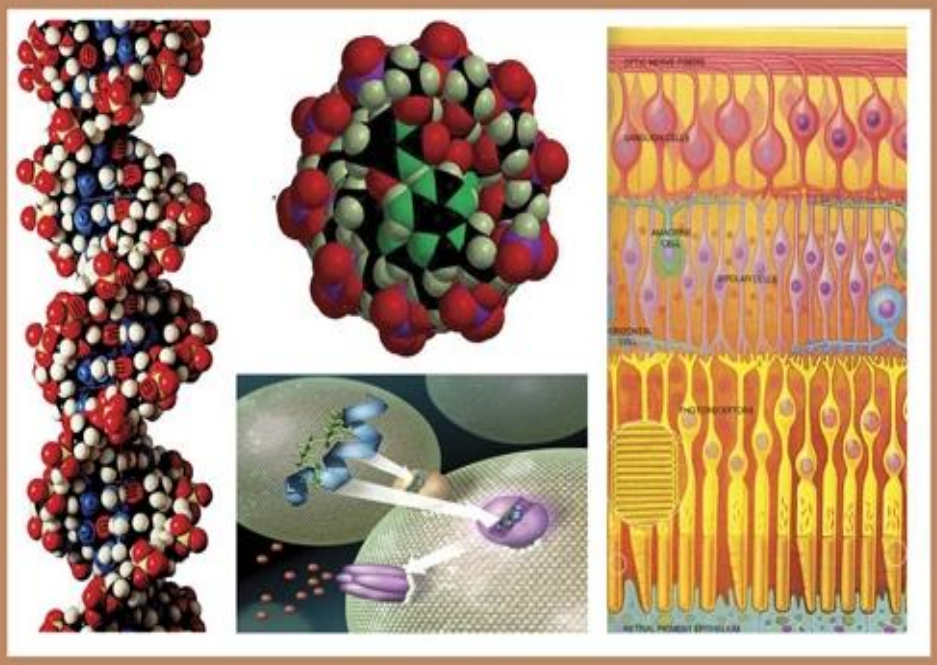

ISSN
2090-0767

WWW.EAJBS.EG.NET

Vol. 15 No. 1 (2023)

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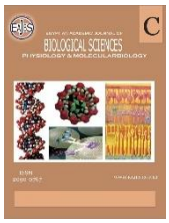
Citation: *Egypt.Acad.J.Biolog.Sci. (C.Physiology and Molecular biology) Vol. 15(1) pp67-77 (2023)*
DOI: 10.21608/EAJBSC.2023.309591

Egypt. Acad. J. Biolog. Sci., 15(1):67-77 (2023)

Egyptian Academic Journal of Biological Sciences
C. Physiology & Molecular Biology
ISSN 2090-0767
www.eajbsc.journals.ekb.eg



Synthesis, Characterization and Study of Anti-Bacterial Activity of Some New Bis-Heterocyclic Derivatives

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ARTICLE INFO
Article History
Received:12/6/2022
Accepted:25/7/2023
Available:1/8/2023

Keywords:
1,2,3-triazole, dapsone, Anti-bacterial activity, Click chemistry.

ABSTRACT

In this research, some new 1,2,3-triazole derivatives of dapsone, have been prepared. The first step includes the preparation of Azo derivative by reaction of dapsone with the 4-Aminoacetophenone to produce azo compounds (**A**), then, the amino group of dapsone is converted to a diazonium salt and reacted with sodium azide to obtain the compound (**B**) Then, Chalcones (**D1-D3**); has been prepared through the reaction of an aromatic ketone with different aldehydes. The second step involves the reaction of chalcones derivatives (**D1-D3**) with compound **(B)** in the presence of copper (I) to obtain a 1,2,3-triazoline compound (**H5** – **H7**). Different spectroscopy methods, such as FT-IR, ^{1}H-NMR, and ^{13}C-NMR, were used to identify synthesized compounds.

The potential antibacterial activity of the synthesized heterocyclic derivatives has been finally tested as a third stage, using two types of bacteria (*Staphylococcus aureus* and *Escherichia coli*).

INTRODUCTION

Sulpha medicines, commonly referred to as sulphonamides, are chemical substances with a sulphonamide moiety (-SO_2NH-)(Qadir *et al*., 2015) in their structure. Sulpha medications were designed to be used as antimicrobial agents in the past (García Ruano *et al*., 2008), and they remain commonly employed today as preventive and restorative mixtures as a function against various bacterial contaminations in different application areas like eye diseases, flu, meningitis, actinomyces contaminations, and urinary lot infections(Ebrahimi *et al*., 2013). The sulphonamide is also functioning as an anti-microbial to treat incurable diseases, such as a specialist inhibitor against cancer cells(Owa & Nagasu, 2000), antagonist against thyroid(Zafar *et al*., 2021), antagonist against hypoglycemia, antagonist against inflammation(Supuran *et al*., 2003), and several other uses in various sectors(Ibrahim *et al*., 2014). Sulphonamide compounds are designed similarly to para-amino benzoic corrosives, which call for the conjunction of folate in bacterial cells. Para benzoic acid is shielded from exposure by sulphonamides(Sahoo & Kumar, 2016). The Chemistry of Heterocycles describes the 1,2,3-triazole as an unsaturated, aromatic, five-membered, excessive nitrogen heterocycle with a six-electron ring structure made up of two double-bonded carbon atoms and three regular nitrogen atoms. Three categories are used to categorize them: monocyclic 1,2,3-triazoles, benzotriazoles, and 1,2,3-triazolium salts[9]. Monocyclic 1,2,3-triazoles are further split into three subclasses based on the location of the NH proton. While the nonaromatic 4H-1,2,3-triazole is not in equilibrium, the aromatic 1H- and 2H-1,2,3-triazoles are, both in the gas phase and solution. Additionally, in this research, some new 1,2,3-triazole derivatives of dapsone, have been prepared (Owa & Nagasu, 2000).

MATERIALS AND METHODS

Experimental General Considerations:

All solvents and chemicals were of the highest analytical grade and used as supplied from commercial sources. The infrared spectra were characterized with FT-IR spectrophotometer (FTIR-8400s, Shimadzu). Nuclear magnetic resonance (NMR) spectra were characterized using Bruker 400 MHz spectrometers at ambient temperature.

Preparation of Azo Compounds (A) (Khalil A *et al*., 2019):

Take (0.02mol,2.72g) from the aromatic amine compounds (*p*-amino acetophenone) and dissolved in the beaker containing 4 mL of concentrated HCl and 10 mL of distilled H_2O and then the solution was cooled in an ice water bath. The $NaNO_2$ solution was prepared in another beaker by dissolving (0.02 mol., 1.38 g) in 5ml of distilled H_2O and also cooled at (0^0c) and then added slowly to solution one at the same temperature with constant stirring by the magnetic stirrer. The formed Diazonium salt solution was maintained at ($0\ ^0$c) and added drop-wise to (0.02mol., 5 g) Dapsone solution prepared in 10% sodium hydroxide solution. The pH was kept between (8-9) at temperature (0^0c) and then the mixture was stirred for 30 min. The final product was precipitated, filtered out and washed with distilled water several times and then recrystallized with ethanol**.**

A: Chemical Formula: $C_{28}H_{24}N_6O_4S$, M.Wt: 540, Yield 80%, m.p. 136-138 C, Colour: Brawn, R*f* = 0.7 (Toluene: ethanol, 2:1). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.34 (d, *J* = 1.9 Hz, 1H), 8.00 – 7.98 (m, 2H), 7.84 – 7.78 (m, 3H), 7.03 (d, *J* = 8.4 Hz, 1H), 5.21 (d, *J* = 7.1 Hz, 1H), 5.13 (d, *J* = 7.1 Hz, 1H), 2.54 (s, 2H).**^{13}C NMR** (100 MHz, DMSO-*d6*) δ 196.78, 155.88, 151.21, 137.26, 131.64, 129.31, 128.80, 128.43, 122.74, 121.82, 116.05,26.35,40.76,40.58,40.10,39.98,39.88,39.76.

Preparation of Azide Compound (B) (Huisgen *et al* ,1956):

Take (0.011mol,6.5g) from Azo compounds and dissolved them in the beaker containing 10 mL of ethanol and then the solution was cooled at 0-5C in an iced water bath and added to the solution 5ml from concentrated hydrochloric acid. The sodium nitrite solution was prepared in another beaker by dissolving (0.011 mol., 1.52 g) in 5ml of distilled water and also cooled at (00C) and then added slowly to solution one at the same temperature with containing stirring by the magnetic stirrer. The formed diazonium salt solution was kept at ($0\ ^0$c) and added to the solution slowly another solution was prepared from (0.011mol,1.44g) Sodium azide in distilled water and then the mixture was stirred for 20 min. The final product was precipitated, filtered out and washed with distilled water several times and then recrystallized with ethanol**.**

B: Chemical Formula: $C_{28}H_{20}N_{10}O_4S$ M.Wt: 592.59, Yield 80%, M.p. 114-116 C, Color: Yellow, R*f* = 0.7 (Toluene: ethanol, 2:1). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.54 (d, *J* = 1.9 Hz, 1H), 8.10 (dd, *J* = 8.4, 1.8 Hz, 1H), 8.08 – 7.95 (m, 2H), 7.95 – 7.93 (m, 2H), 7.63 (d, *J* = 8.4 Hz, 1H), 2.53 (s, 2H). **^{13}C NMR** (100 MHz, DMSO-*d*6) δ 196.78, 157.53, 138.46, 138.38, 137.92, 137.30, 129.20, 127.82, 123.71, 121.86, 120.16, 40.78, 40.56, 40.32, 40.01, 39.98, 39.87, 26.37.

General Synthesis of Chalcone Derivatives (Gaonkar *et al*. ,2008, Ngo *et al*., 2014):

To a stirred mixture of (0.01 mole,1.16 ml) of acetophenone or (0.01 mole,1.35g) of 4-aminoacetophnone and (0.01 mol) of different aromatic benzaldehydes (4-Choro benzaldehyde 1.40g), 4-(N, N-dimethyl amino)benzaldehyde 1.49g), (4- hydroxyl benzaldehyde 1.22g) in (25 mL) ethanol in ice water path, 30% NaOH aqueous solution was added portion-wise after which stirring was continued for further (12) h. TLC showed that the reaction was completed by using (Toluene: ethanol) (Toluene4:1). The coloured precipitate synthesised was filtered and washed with 3% aqueous HCl, then the

compound was washed with distilled water and recrystallized from ethanol.

D1: Chemical formula: **$C_{15}H_{11}ClO$**, M.wt 242.70 g/mol. (yield 85%), melting point: 80-82 ^oC, (R_f: 0.63), Color: Pale-yellow. **FT.IR data (cm^{-1}):** 3053 (C-H aromatic), 1485 (C=C aromatic), 1589 (C=C aliphatic), 1655 (C=O).). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.95 – 7.90 (m, 1H), 7.75 – 7.71 (m, 1H), 7.55 – 7.50 (m, 1H), 7.46 – 7.35 (m, 1H) 6.75 – 6.67 (m, 3H). **^{13}C NMR** (100 MHz, DMSO-*d*6) δ 190.02, 144.84, 138.30, 136.84, 134.78, 129.87, 129.65, 129.16, 128.98, 128.66, 121.55, 40.88, 40.65, 40.58, 40.20, 39.90, 39.87.

D2: Chemical formula: **$C_{17}H_{17}NO$**, M.wt 251.33 g/mol. (yield 86%), melting point: 84-86 ^oC, (R_f: 0.66), Colour: Yellow.

FT.IR data (cm^{-1}): 3052 (C-H aromatic), 2900(C-H aliphatic), 1650(C=O), 1564 (C=C aromatic),1487(C=C aliphatic), 1323(3^o amine), 981(C-N). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.91 – 7.86 (m, 4H), 7.75 – 7.72 (m, 3H), 7.56 (d, *J* = 15.6 Hz, 1H), 7.52 – 7.36 (m, 4H), 6.70 – 6.67 (m, 3H), 3.02 (s, 6H).**^{13}C NMR** (100 MHz, DMSO-*d*6) δ 189.68, 152.32, 144.84, 134.82, 130.74, 130.13, 129.68, 129.05, 128.66, 121.21,111.18,40.23,40.15,40.01,39.95,39. 87,39.70.

D3: Chemical formula: **$C_{15}H_{12}O_2$**, M.wt 224.26 g/mol. (yield 88%), melting point: 76-78 ^oC, (R_f: 0.69), Colour: Yellow.

FT.IR data (cm^{-1}): 3352 (-OH group), 3055 (C-H aromatic), 2926 (C-H aliphatic), 1653(C=O), 1579 - 1488 (C=C aromatic, aliphatic).**^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.58 (s, 1H), 7.98 – 7.90 (m, 2H), 7.86 (d, *J* = 15.6 Hz, 1H), 7.75 – 7.71 (m, 2H), 7.57 (d, *J* = 15.5 Hz, 1H), 7.53 (ddt, *J* = 7.1, 6.4, 0.8 Hz, 2H), 7.46 – 7.35 (m, 1H), 6.91 – 6.88 (m, 2H). **^{13}C NMR** (100 MHz, DMSO-*d*6) δ 189.80, 161.14, 144.80, 134.77, 131.55, 130.51, 129.68, 128.96, 128.66, 121.52, 118.44, 40.73, 40.67, 40.59, 40.53, 39.97, 39.83.

Synthesis of 1,2,3-Triazoline Compounds (H5-H7):

In 15 mL of DMSO containing (1.68 mmol, 0.5g) from compound **B** (1.2equiv) of the prepared chalcones (**D_1**, **D_2** and **D_3**) are added after several minutes, the catalyst is added (monovalent copper and sodium ascorbate in a ratio of 5%mol and 10%mol respectively). Then the temperature is raised to 50 ^oC and the reaction is left to when finished (as indicated by TLC, (Toluene: ethanol) (4:1) The product is then rinsed with distilled water after the solvent is evaporated using a rotary evaporator. Utilizing a glacial acetic acid and acetone (2:3) combination, the products were recrystallized.

H5: Chemical formula: **$C_{15}H_{12}O_2$**, M.wt 224.26 g/mol. (yield 78%), melting point: 63-65 oC, (Rf: 0.54), Colour yellow: **FT.IR data (cm^{-1}):** 3055(C-H aromatic),1665(C=O ketone),1586 (C=C aromatic), 1486 (N=N azo), 1407 (asy S=O), 1211(N-N group), 1153(sy SO2), 1000(S-N), 823(C-Cl). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.31 (d, *J* = 1.8 Hz, 1H), 8.07 – 8.01 (m, 2H), 7.95 – 7.85 (m, 3H), 7.82 – 7.75 (m, 3H), 7.54 – 7.47 (m, 4H), 7.37 – 7.29 (m, 2H), 7.28 (ddt, *J* = 8.7, 6.2, 2.2 Hz, 1H), 5.66 (dt, *J* = 7.9, 0.9 Hz, 1H), 4.18 (d, *J* = 7.9 Hz, 1H), 2.55 (s, 2H).**^{13}C NMR** (100 MHz, DMSO-*d*6) δ 196.85, 190.49, 156.12, 139.60, 138.87, 137.28, 135.22, 134.85, 133.76, 133.65, 130.20, 129.68, 129.43, 129.24, 128.46, 127.83, 127.01, 124.98, 121.82, 118.56, 72.36, 69.27, 26.38, 40.91, 40.77, 40.34, 39.97, 39.79, 39.57.

H6: Chemical formula: **$C_{15}H_{12}O_2$**, M.wt 224.26 g/mol. (yield 77%), melting point: 66-68 oC, (Rf: 0.52), Colour: yellow. **FT.IR data (cm^{-1}):** 3059 (C-H aromatic), 1668 (C=O ketone), 1578 (C=C aromatic), 1515 (N=N azo),(1438 asy SO2),1269(N-N group), 1152(sy SO2), 817(C-S).**^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.35 (d, *J* = 1.9 Hz, 1H), 8.04 – 7.97 (m, 2H), 7.93 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.85 – 7.76 (m, 5H), 7.45 (ddt, *J* = 8.2, 2.6, 1.3 Hz, 2H), 7.37 – 7.30 (m, 2H), 7.33 – 7.24 (m, 1H), 6.88 – 6.81 (m, 2H), 5.66 (dt, *J* = 7.9, 0.9 Hz, 1H), 4.22 (d, *J* = 7.9 Hz, 1H), 3.01 (s, 4H), 2.55 (s, 2H).

^{13}C NMR (100 MHz, DMSO-*d*6) δ 196.79, 190.83, 156.12, 153.05, 144.88, 138.92, 137.27, 134.85, 133.80, 130.85, 129.75,

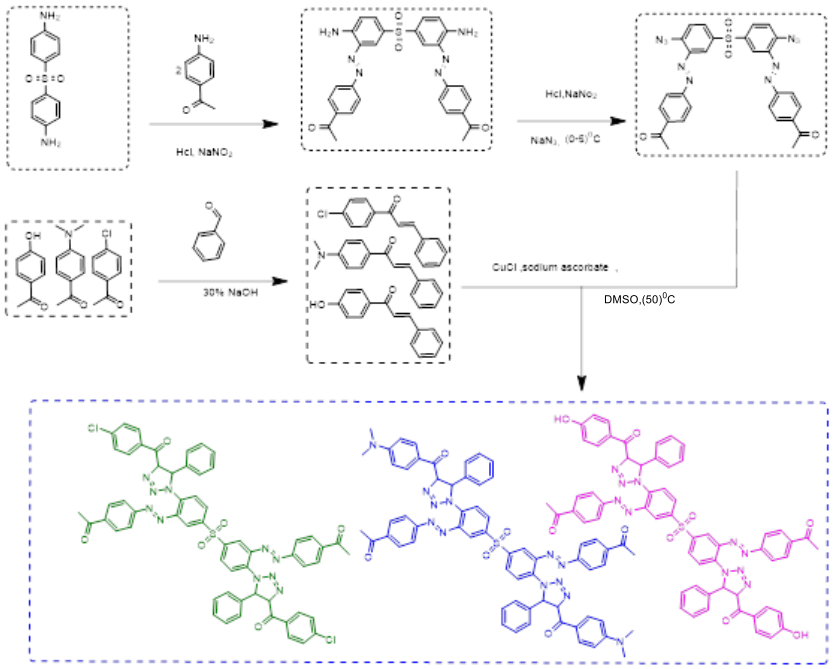
129.45, 128.38, 128.05, 127.75, 126.98, 124.99, 121.84, 118.66, 110.77, 72.36, 69.26, 40.23, 26.39, 40.78, 40.56, 40.31, 39.90,39.76,39.48.

H7: Chemical formula: **$C_{15}H_{12}O_2$**, M.wt 224.26 g/mol. (yield 76%), melting point: 60-62 ^oC, (R_f: 0.57), Colour: yellow.

FT.IR data (cm^{-1}): 3353 (O-H aromatic), 3067 (C-H aromatic), 1668 (C=O ketone), 1580 (C=C aromatic), 1506 (N=N azo), (1438 asy SO2),1265(N-N group), 1147(sy SO2). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.38 (s, 1H), 8.33 (d, J = 1.8 Hz, 1H), 8.00 – 7.89 (m, 3H), 7.91 – 7.84 (m, 2H), 7.79 (d, J = 8.4 Hz, 1H), 7.74 – 7.68 (m, 2H), 7.46 (ddt, J = 8.1, 2.6, 1.2 Hz, 2H), 7.37 – 7.30 (m, 2H), 7.28 (ddt, J = 8.6, 4.2, 2.2 Hz, 1H), 6.96 – 6.89 (m, 2H), 5.66 (dt, J = 7.9, 1.0 Hz, 1H), 5.45 (d, J = 7.9 Hz, 1H), 2.55 (s, 2H).**^{13}C NMR** (100 MHz, DMSO-d6) δ 196. 86, 190.86, 162.18, 156.12, 138.87, 137.28, 135.22, 134.85, 133.76, 131.06, 129.65, 129.41, 129.01, 128.46, 127.83, 127.01, 124.98, 121.82, 118.56, 115.83, 72.36, 69.27, 27.77, 40.94,40.73,40.37,39.97,39.71,39.32.

RESULTS AND DISCUSSION

The first prepared azo compound **(A)** by reaction Aromatic amine 4-amino acetophenone was converted to diazonium chlorides with concentrated hydrochloric acid and sodium nitrite got in a solid state in good yield, The azide derivative of the azo dye **(B)** is formed by first forming the azo dapson diazonium ion, then proceeding with the reaction via an azide attack on the diazonium ion, as suggested by Huisgen and Ugi(Huisgen & Ugi, 1956). the amine group (-NH_2) of the dapson is linked to the benzene ring, this provides a strong driving force for the reaction to occur with high yield. The chalcones derivatives (**D_1**, **D_2** and **D_3**) have been synthesized by the Claisen–Schmidt condensation strategy which is the most popular one, with simplicity and higher yields as compared to other traditional methods. It is done between a ketone containing alpha-hydrogen (aceto-phenone) and aromatic aldehyde**.** Later by adopting 1,3-Dipolar cycloadditions reaction of the azide derivative with the prepared chalcones (**D_1**, **D_2** and **D_3**), using the copper chloride (CuCl) as a catalyst, we prepared a kind of heterocyclic compounds (**H_5**, **H_6** and **H_7**) linking two important classes in medicinal chemistry. These reactions have simple conditions and straightforward work-up steps.



Scheme 1: Step of synthesis of 1,2,3-Triazoline compounds.

All prepared compounds were characterized by ^{1}H NMR and ^{13}C NMR spectroscopy. The ^{1}H NMR spectrum of D1 in DMSO-d_6 (Fig. 1) shows the multiple signals in the range of 7.95 – 7.35 ppm for CH in the benzene ring. The spectrum also shows a doublet at (6.75-6.67) for CH=CH. For Compound D_2, the ^{1}H NMR spectrum in DMSO-d_6 (Fig. 2) shows multiple signals in the range of 7.91 – 7.36 ppm for CH in the benzene ring. The spectrum also shows a doublet at (6.70-6.67) ppm for CH=CH group. The single signal at 3.02 ppm for CH_3 group. The ^{1}H NMR spectrum of D_3 in DMSO-d_6 (Fig. 3) shows multiple signals in the range of 7.98 – 7.35 ppm for CH in the benzene ring. The spectrum also shows a doublet at (6.91-6.88) ppm for CH=CH group. The single signal at 9.58 ppm for OH group.

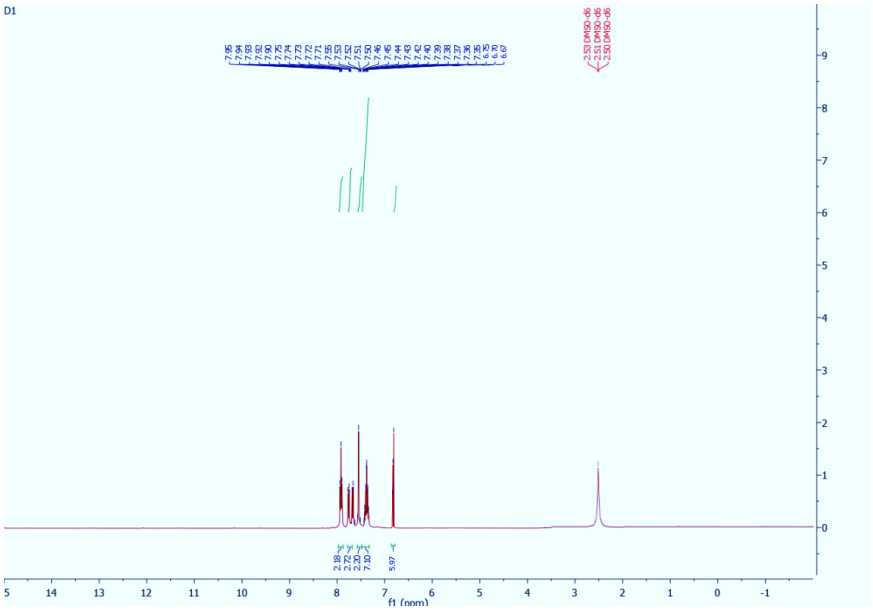


Fig. 1: ^{1}HNMR spectrum of compound D_1

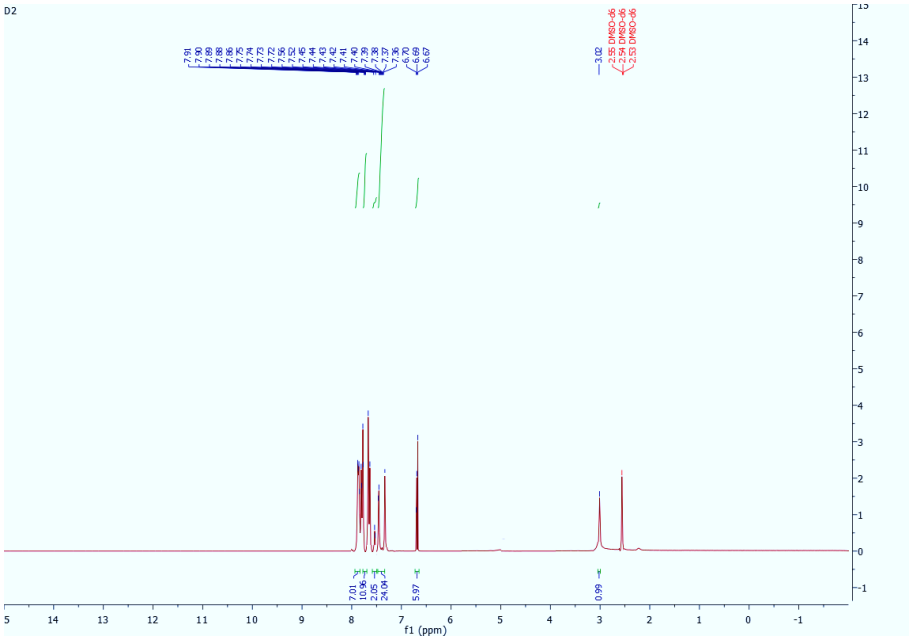


Fig. 2: ^{1}HNMR spectrum of compound D_2.

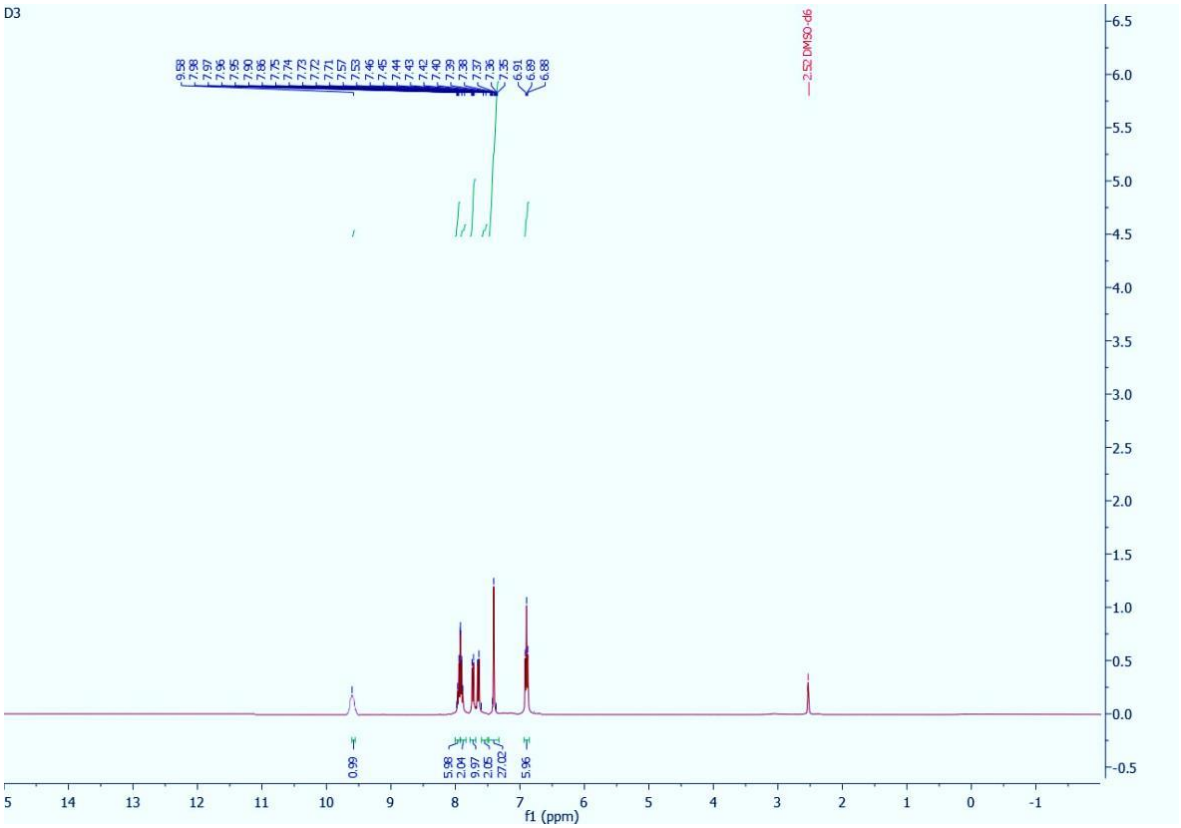


Fig. 3:[1]HNMR spectrum of compound D_3.

The ^{1}H NMR spectrum of H_5 in DMSO-d_6 (Fig. 4) shows multiple signals in the range of 8.28 – 7.28 ppm for CH in the benzene ring. The spectrum also shows doublet at (5.66 and 4.31 ppm) for CH in the triazoline ring. The methyl group appeared at 2.57 ppm. For Compound H_6, the ^{1}H NMR spectrum in DMSO-d_6 (Fig. 5) shows the multiple signals in the range 8.35 – 7.25 ppm for CH in benzene ring. The ^{1}H NMR spectrum of H_7 in DMSO-d_6 (Fig. 6) shows the multiple signals in the range 8.33 – 7.28 ppm for CH in benzene ring. The spectrum also shows doublet at (6.86 and 4.36 ppm) for CH in triazoline ring. The acetyl group appeared at 2.57 ppm. The single signal at 8.35 ppm for OH group.

The mass spectrum of [$C_{85}H_{42}C_2N_{10}O_6$] shows a molecular ion peak [M+] at m/z 1078.00 which is in accordance with the proposed formula of the compound (H_5) (Fig.7).

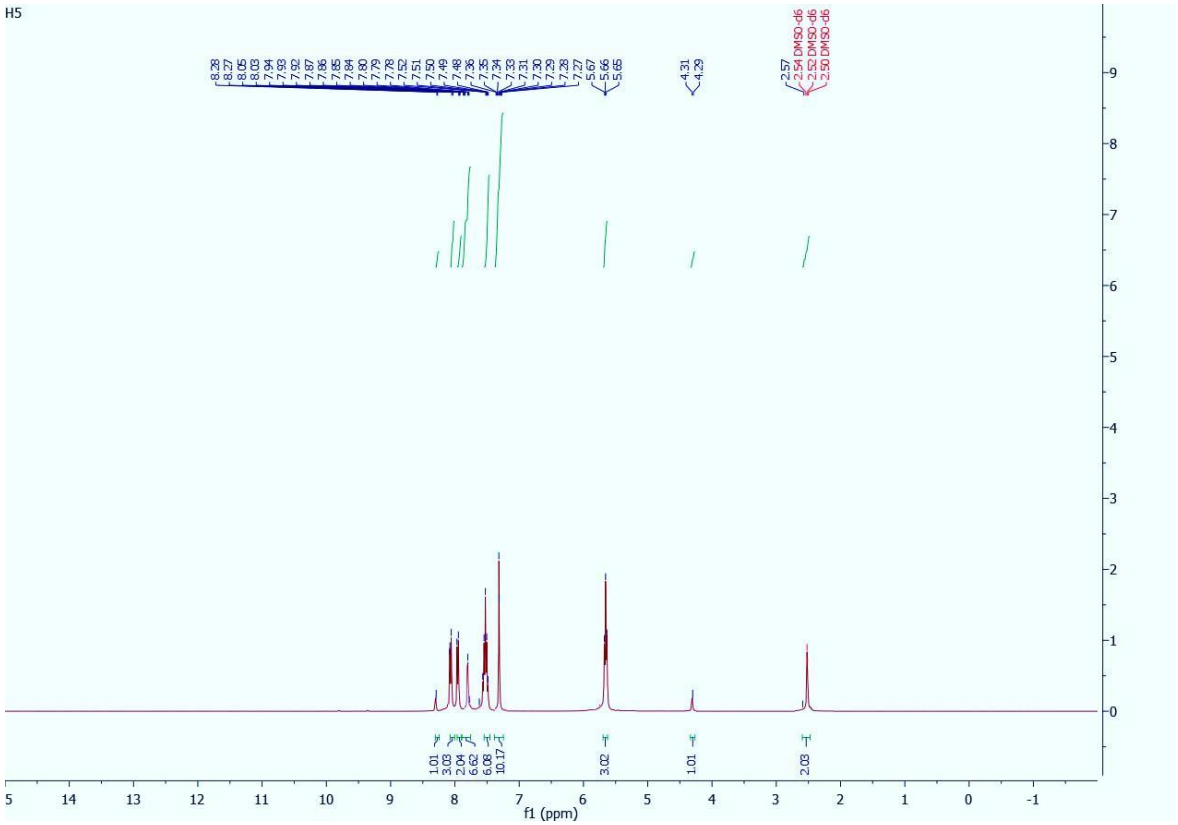


Fig. 4: ^{1}HNMR spectrum of compound H_5

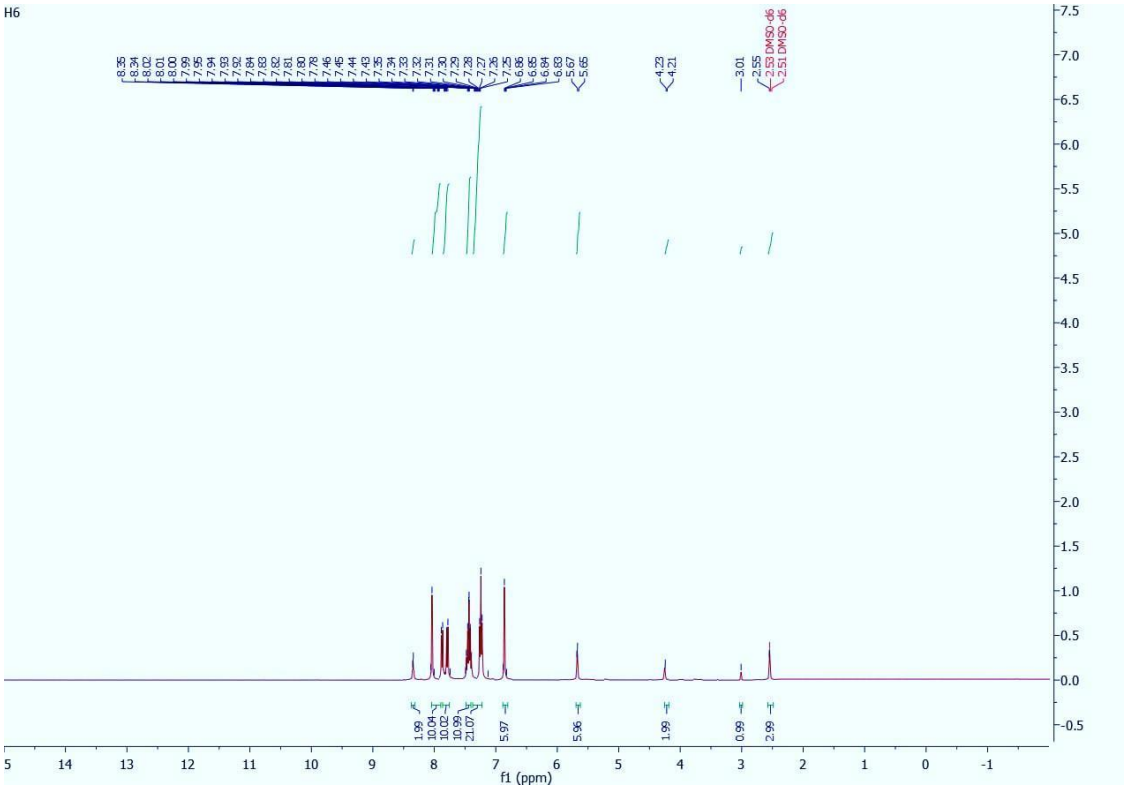


Fig. 5: ^{1}HNMR spectrum of compound H_6.

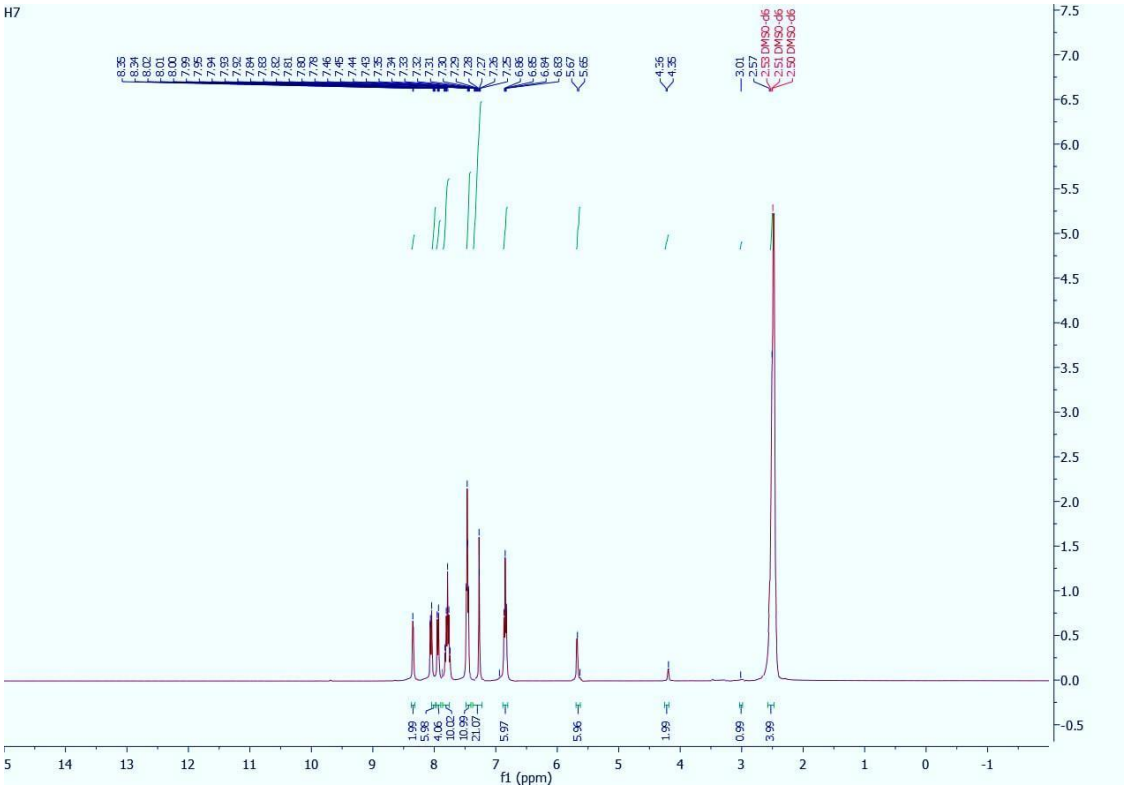


Fig. 6: ^{1}HNMR spectrum of compound H_7.

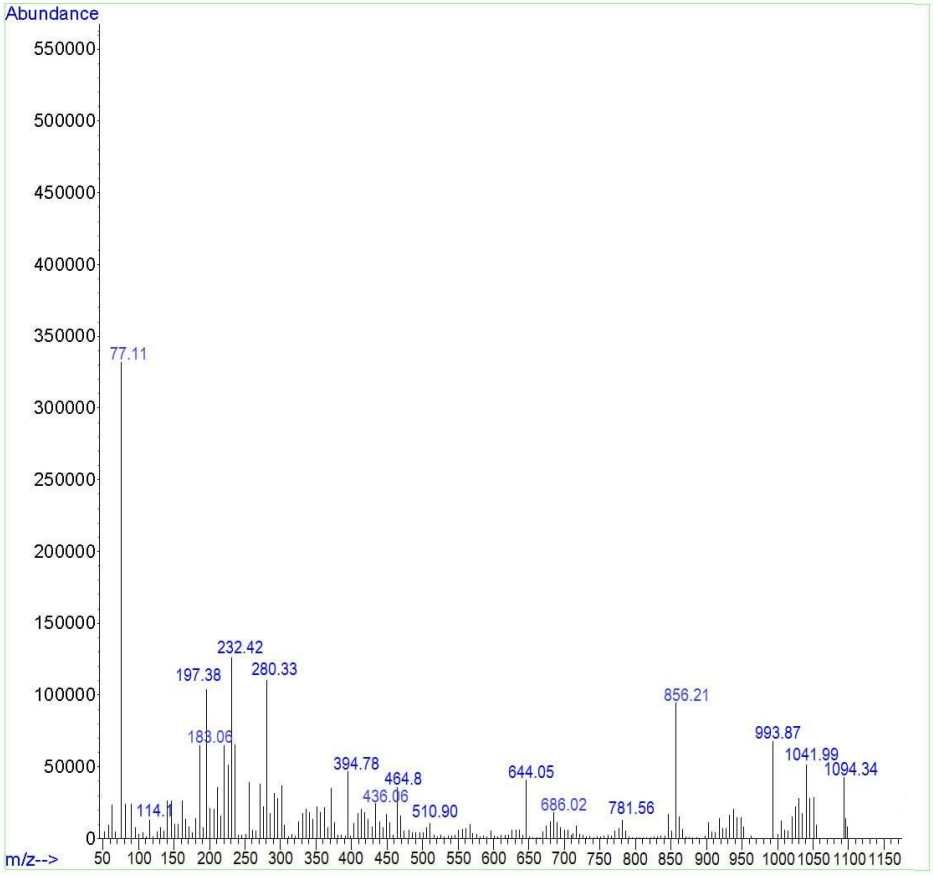


Fig. 7: MASS spectrum of compound H_7.

Antibacterial Study of The Prepared Heterocyclic:

The synthesized heterocyclic compounds were tested using *Escherichia coli* as Gram-negative and *Staphylococcus aureus* as Gram-positive bacteria for their anti-bacterial efficacy by a diffusion method in a Mueller-Hinton agar medium. After 24hrs of incubation, the inhibition zones were measured. The anti-bacterial activity of the synthesized compounds (**H_5**, **H_6** and **H_7**) was studied as a function against one gram-positive bacteria *Staphylococcus aureus* and one gram-negative bacteria *Escherichia coli*. The anti-bacterial activity has been initially checked as the recognized growth inhibition zones by disk-diffusion approach employing Mueller Hinton Broth (MBH) environment. Then, Minimum inhibitory concentrations (MIC) were recognized for the produced compounds. DMSO was employed as a negative control for anti-bacterial activity. The observed minimum inhibitory concentration (MIC) anti-bacterial data of the synthesized compounds (**H_5**, **H_6** and **H_7**). The anti-bacterial activity findings showed that the tested compounds exhibited various degrees of inhibition against Gram-positive and Gram-negative bacteria both tested microorganisms were found to be the sensitive bacteria. All prepared compounds increase their effectiveness with increasing concentration. Compounds (**H_5**, **H_6** and **H_7**) and the dapsone-1,2,3-triazoles skeleton observed the best anti-bacterial activity against *Staphylococcus aureus* with MIC values Beside this, compounds **(H_6 and H_7)** showed the most anti-bacterial activity against *Staphylococcus aureus* with MIC value 32 µg/mL. in Figure 9. On the other hand, also, compounds (**H_5**, **H_6** and **H_7**) give moderate activity against the selected bacteria *Escherichia coli.* are given in Figure 8.

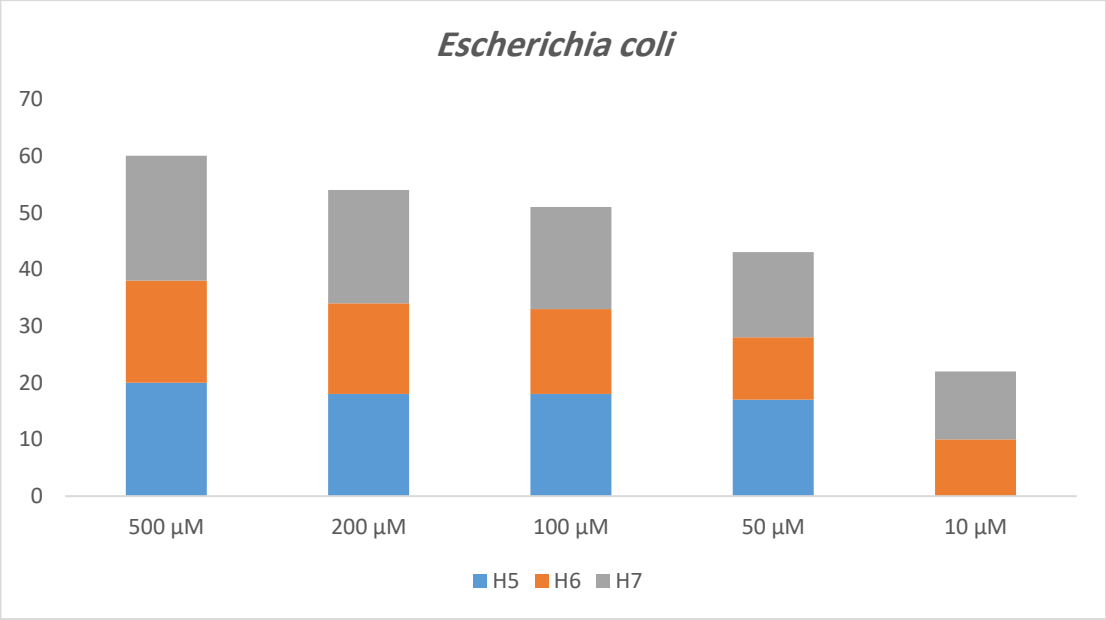


Fig. 8: Biological activity of the synthesized heterocyclic in this study**.**

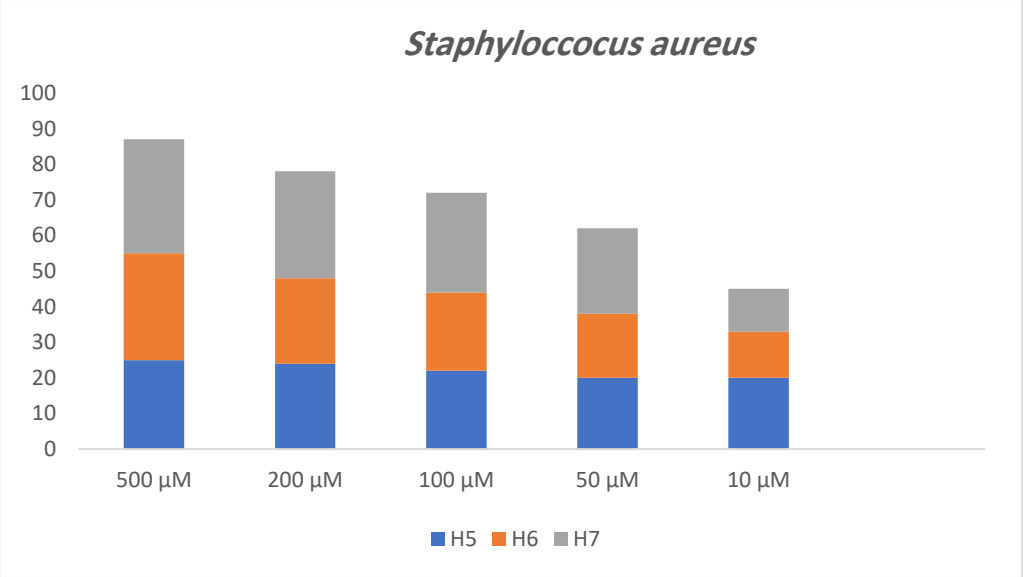


Fig. 9: Biological activity of the synthesized heterocyclic in this study.

Conclusions

In conclusion, Successful synthesis of new heterocyclic compounds attached-dapsone it can be concluded that:

1. Different building blocks were prepared as raw materials for cycloaddition reactions using simple strategies and readily available materials.
2. 1,3-Dipolar cycloaddition reactions pose a flexible and efficient method for the synthesis of a wide range of heterocyclic compounds.
3. The use of copper sulphate pentahydrate is far superior to CuCl because it is much easier to get rid of and produces better results.
4. Some of the dapsone-based heterocyclic compounds synthesized have demonstrated good biological activity against Gram-negative and Gram-positive bacteria.

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