Synthesis and antibacterial screening of some new 1'2'3 -triazole derivatives from dapsone

[1]Hasan Mohammed Marhoon., [2]Ezzat Hussein Zimam

University of Kufa, Faculty of Science, Department of Chemistry., Iraq

E-mail: h.alarbawee@gamil.com[1]

E-mail: ezat_ahlam@yahoo.com [2]

Abstract

In our relentless pursuit of developing innovative antibacterial derivatives, we have successfully generated and evaluated a novel series of 1,2,3-triazole derivatives derived from azo dapsone. The synthesis process commenced with the fusion of the dapsone core with the triazole framework, establishing a solid foundation for our synthetic endeavors. Subsequently, the azo dapsone nucleus underwent functionalization using sodium azide, resulting in the creation of an azide derivative (B).

To synthesize the desired end 1,2,3-triazoles, a click reaction was employed, combining the azide compound with triple bond derivatives. The structures of all the synthesized compounds were meticulously characterized through the utilization of advanced techniques such as Nuclear Magnetic Resonance (NMR) and Infrared (IR) spectroscopy.

Following the successful synthesis and characterization, our focus shifted to evaluating the in vitro antibacterial activity of these compounds against two significant bacterial strains: the gram-positive bacterium Staphylococcus aureus and the gram-negative bacterium Escherichia coli. Among the compounds synthesized, one compound in particular, designated as (H_2), exhibited exceptional potency against Staphylococcus aureus with a minimal inhibitory concentration (MIC) of 25 µg/mL, surpassing the activity of all other prepared compounds. Similarly, compound (H_1)

displayed remarkable efficacy against Escherichia coli with an MIC of 22 µg/mL, outperforming the other end compounds.

These findings demonstrate the tremendous potential of our synthetic approach in generating dapsone derivatives with enhanced antibacterial activity. Our research represents a significant step forward in the development of novel and potent antibacterial agents.

Keywords: 1,2,3-triazole synthesis, dapsone, Antibacterial derivatives, Click chemistry.

Introduction

The realm of five-membered heterocyclic compounds, including thiazides, thiadiazols, triazoles, 1,3,4-oxadiazoles, and benzimidazole rings, has captured significant attention owing to their remarkable biological activity[1]. Particularly intriguing is their potential as antiviral agents, exhibiting promising effectiveness against a wide spectrum of viruses[2]. As researchers delve into the therapeutic applications of these compounds, triazole-based derivatives have emerged as a captivating area of exploration, with the potential to serve as antibacterial, antiviral, antifungal, anticancer, and antihypertensive medications.

Of particular interest is the 1,2,3-triazole ring, which acts as a versatile linker, elevating the biological activity by facilitating the creation of hybrid molecules[3]. In the field of medicinal chemistry, 1,2,3-triazole derivatives have gained prominence due to their advantageous pharmacological properties. They have served as foundations for the development of diverse compounds with noteworthy antibacterial[4–7] . antitumoral[8,9] . anticancer[10–12] ,antityrosinase[13], and anti-inflammatory [14] activities. Notable drugs based on the 1,2,3-triazole scaffold include Rufinamide, an anticonvulsant, Cefatrizine, an antibiotic, and Tazobactam, an antifungal agent.

The global prevalence of microbial infections, coupled with the escalating challenges posed by bacterial resistance to existing antibacterial agents, necessitates the urgent development of novel and effective antimicrobial medications[15,16] .In line with our ongoing research on the creation of innovative antibacterial compounds [17,18] .we have embarked on a new investigation involving the synthesis of novel 1,2,3-triazole compounds derived from sulfamethoxazole. These compounds have undergone rigorous testing against two highly virulent bacterial strains. Our endeavor not only aims to contribute to the growing body of knowledge surrounding the diverse biological activities exhibited by the 1,2,3-triazole system, but also seeks to address the pressing need for potent antibacterial agents.

Materials and Methods

To facilitate our experimental procedures, a range of reagents, solvents, and starting materials were sourced from reputable chemical suppliers such as Sigma Aldrich Chemicals, Thomas Baker, Merck, Fluke, and industrial suppliers. In order to monitor the progress of the reactions, thin-layer chromatography (TLC) plates coated with silica gel SG-40 from Merck Company were employed, offering a visual representation of the reaction outcomes.

To analyze the chemical structures and confirm the formation of desired compounds, Fourier transformation infrared (FTIR) spectra were recorded using Bruker ALPHA at the University of Kufa, Faculty of Science. Additionally, 1H nuclear magnetic resonance (NMR) spectra were acquired on a Bruker apparatus, operating at a frequency of 400 MHz for 1H NMR and 100 MHz for 13C NMR. These analytical techniques provided valuable insights into the molecular composition and structural characteristics of the synthesized compounds, enhancing the precision and reliability of our research.

Synthesis of Azo compounds (A)[19]

In a precise and controlled manner, we began by taking 0.02 mol (2.72 g) of the aromatic amine compound, specifically p-aminoacetophenone, and dissolved it in a beaker containing 4 mL of concentrated HCl and 10 mL of distilled water. To maintain optimal conditions, the solution was cooled in an iced water bath, ensuring a stable temperature.

In a separate beaker, we prepared a sodium nitrite solution by dissolving 0.02 mol (1.38 g) of sodium nitrite in 5 mL of distilled water. Similar to the previous step, this solution was also cooled to a temperature range of 0-5 ℃. The sodium nitrite solution was then gently added to the aromatic amine solution while maintaining the same temperature, with continuous stirring using a magnetic stirrer. This process resulted in the formation of a diazonium salt solution, which was carefully kept at a temperature range of 0-5.℃

Next, the diazonium salt solution was slowly added drop-wise to a solution of 0.02 mol (5 g) of Dapsone prepared in a 10% sodium hydroxide solution. It was crucial to maintain a pH level between 8 and 9 throughout this step, while also ensuring the temperature remained within the range of 0-5 ℃. The mixture was stirred for a duration of 30 minutes, allowing for the desired reactions to take place . The final product was precipitated, filtered out and washed with distilled water several times and then recrystallized with ethanol.

To obtain the final product, the resulting mixture was subjected to precipitation. This precipitate was subsequently filtered and thoroughly washed using distilled water multiple times, ensuring the removal of any impurities. Finally, the product underwent recrystallization by employing ethanol, further purifying and refining its composition.

By adhering to these meticulous steps, we were able to successfully synthesize the desired product, achieving our intended chemical transformation.

1,1'-(((1E,1'E)-(sulfonylbis (6-amino-3,1-phenylene)) bis(diazene-2,1-diyl))bis(4,1-phenyl-ene)) bis (ethan-1-one) (A):

Chemical Formula:$C_{28}H_{24}N_6O_4S$, M.Wt: 540, Yield 80%, M.p. 136-138 C, Color :Brawn, Rf = 0.7 (Toluene: ethanol, 2:1). **FT.IR data (cm^{-1}):** 3333-3352 (N-H_2), 1667 (C=O ketone), 1585 (C=C aromatic), 1493 (N=N azo), 1431(-SO_2),1098 (C-O aliphatic). **^{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-*d*6) 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.

Synthesis azide compound (B)[20]

In a carefully prepared mixture of distilled water and hydrolic acid, in a 1:3 ml ratio, we dissolved 15 mmol of 4-aminoacetophenone, creating an interesting solution. To maintain optimal conditions, the mixture was cooled using an ice-salt bath, reducing the temperature to an ice-cold 0 °C. At the same time, an aqueous solution of $NaNO_2$, which also consisted of 15 mmol, was prepared and cooled to the same temperature range.

The real magic began as we cautiously added the $NaNO_2$ solution drop by drop to the azo dapsone solution. With each addition, a fascinating transformation took place, turning the solution into a captivating shade of slightly-yellow. This step was performed meticulously until the desired reaction was achieved. To further advance our experimentation, the solution was left to stir for a duration of 45 minutes, allowing for important chemical interactions to occur.

Meanwhile, we diligently prepared an aqueous solution of NaN3, with a quantity equivalent to 2 times the previously used reagents. The NaN_3 solution was added in batches, unveiling an intriguing display of bubbles during each addition. This captivating phenomenon added an element of excitement to our scientific endeavor.

Following the completion of the solution's addition, the mixture was left to stir for an extended period of 2 hours, ensuring that all components were thoroughly integrated.

To unveil the final outcome, the resulting sediment was meticulously filtered and subjected to multiple washes using distilled water. This careful purification process helped to eliminate any impurities, leaving us with a product of great interest and potential.

Through these meticulous steps, we embarked on a captivating scientific journey, exploring the transformative power of carefully prepared mixtures and reactions. The discoveries made in this endeavor contribute to the broader landscape of scientific understanding.

1,1'-(((1E,1'E)-(sulfonyl bis (6-azido-3,1-phenylene))bis(diazene-2,1-diyl))bis (4,1-pheny-lene))bis(ethan-1-one) (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). **FT.IR data (cm^{-1}):** 3052(C-H aromatic), 2097 (N_3), 1680 (C=O ketone), 1581 (N=N azo), 1408(-SO_2) ,1095 (C-O aliphatic). **^{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.

Synthesis of (prop-2-yn-1-yloxy) derivatives (C1-C3)[21,22]

In our quest for chemical exploration, we embarked on a fascinating journey involving phenol derivatives, namely 4-hydroxy-3-methoxy benzyldehyde, 4-nitrophenol, and 3-hydroxyquinolone. To initiate the transformative process, we dissolved 15 mmol of these compounds in acetone. Intriguingly, we introduced 2equivalents of anhydrous potassium carbonate (K_2CO_3) into the mixture, setting the stage for an exciting reaction.

To maintain control and precision, we carefully cooled the reaction below 15°C, creating an environment conducive to our desired chemical transformations. In a calculated manner, we added 2.7 equivalents of a 3-bromo-1-propyne solution in small, measured increments, allowing the reaction to progress in distinct stages. The resulting mixture was then subjected to reflux, where the combination was heated to optimize reaction conditions. Monitoring the reaction's progress became a crucial step, with TLC serving as our faithful companion in ensuring completeness.

As the journey unfolded, we bid farewell to the solvent by subjecting it to reduced pressure, resulting in a residue. This residue was dissolved in distilled water, initiating the process of extraction. We skillfully employed ethyl acetate, adding it twice to accomplish efficient extraction. To ensure the purity of our desired product, we relied on anhydrous magnesium sulfate to effectively dry the organic layer, removing any lingering traces of moisture.

The pursuit of our desired product persisted as we directed our attention to elution. By skillfully employing reduced pressure, we gradually removed the solvent, allowing the desired product to manifest. To further refine its composition, we turned to the trustworthy technique of column chromatography. Employing a carefully balanced mixture of hexane and ethyl acetate as the eluent, we navigated the chromatographic journey, separating and purifying our product with precision.

In this captivating endeavor, we witnessed the fascinating transformation of phenol derivatives, employing meticulous techniques and strategic manipulations to extract and purify our desired product. The discoveries made along this path deepen our understanding of the intricate world of chemical reactions and bring us closer to unlocking new possibilities in the realm of science.

3-(prop-2-yn-1-yloxy) quinoline (1w): Product **C_1** was obtained as a brawn crystal, (yield 86%), melting point: 127-129 ^{o}C, (R_f: 0.76), **FTIR data** (cm^{-1}): 3277(≡C-H), 3104(C-H aromatic), 2923(C-H aliphatic), 2121 (C≡C group), 1587(C=C aromatic), 1266(C-O aromatic), 1011(C-O aliphatic),**^{1}H-NMR** (400 MHz, DMSO-d_6) δ 8.24 (d, 2H, Ar-), 7.20 (d, 2H, Ar-), 4.99 (d, 2H, O-CH_2-C≡C), 3.70 (s, 1H, -C≡C-H).

1-nitro-4-(prop-2-yn-1-yloxy) benzene (C_2): Product C_2 was obtained as a yellow crystal. (yield 88%), melting point: 108-110 oC, (Rf : 0.80), Chemical Formula: $C_9H_7NO_3$ Molecular Weight: 177.16**, FTIR data (cm^{-1}):** 3240(≡C-H), 3104(C-H aromatic), 2923(C-H aliphatic), 2117(C≡C group), 1580(C=C aromatic), 1490(asy NO_2), 1382(sy NO_2), 1239(C-O aromatic), 1012(C-O aliphatic). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.18 – 8.11 (m, 1H), 7.18 – 7.12 (m, 1H), 4.80 (d, *J* = 2.9 Hz, 1H), 3.57 (t, *J* = 2.9 Hz, 0H).

3-methoxy-4-(prop-2-yn-1-yloxy) benzaldehyde (C_3): Product **C_3** was obtained as a yellow solid. (yield84%), melting point: 68-70 ^{o}C, (R_f: 0.74), Chemical Formula: C11H10O3 Molecular Weight: 190.20, **FTIR data (cm^{-1}):** 3245(≡C-H), 3078(C-H aromatic), 2982, 2927(C-H aliphatic), 2829, 2731(C-H aldehyde "FERMI doublet"), 2113(C≡C group), 1686(C=O aldehyde), 1587,1509(C=C aromatic), 1259(C-O aromatic), 1037(C-O aliphatic). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.86 (t, *J* = 1.0 Hz, 1H), 7.45 (ddd, *J* = 8.4, 1.9, 1.0 Hz, 1H), 7.39 (dd, *J* = 2.0, 1.0 Hz, 1H), 7.11 (d, *J* = 8.4 Hz, 1H), 4.82 (d, *J* = 2.9 Hz, 2H), 3.89 (s, 3H), 3.57 (t, *J* = 3.0 Hz, 1H).

Synthesis of 1,2,3-triazoles derivatives (H1-H3)[23]

In a thrilling chemical transformation, we embarked on a journey involving compounds C1-C3, as well as compound B. To initiate this captivating process, we dissolved 0.55 mmol of compound B in 20 mL of DMSO, creating a solution brimming with potential. As we delved deeper into our experiment, we introduced 1.2

equivalents of compounds C1-C3 into the mixture, setting the stage for an extraordinary reaction.

With precision and finesse, we allowed the mixture to stir for a brief but pivotal 10 minutes. At this critical juncture, we added 5 mol% of CuCl(1) and 10 mol% of sodium ascorbate, unleashing their catalytic prowess upon our concoction. This transformative combination brought about a symphony of chemical reactions, setting the stage for a captivating display of molecular rearrangements.

With anticipation in the air, we patiently left the reaction to stir at ambient laboratory temperature, allowing time for the magic to unfold. Monitoring the reaction's progress was of utmost importance, and we relied on the trusty technique of thin-layer chromatography (TLC) to guide us. It was through this visual aid that we ascertained the completion of the reaction, signaled by the desired product's appearance. The solvent, a witness to the chemical ballet, was subsequently removed using a rotary evaporator, leaving behind a tantalizing sediment.

To further refine our creation, we embarked on a process of washing and recrystallization. Guided by our expertise, we washed the sediment and embarked on a captivating recrystallization process. The chosen solvents, glacial acetic acid and ethanol in a 1:3 ratio, played their part in bringing ourcompound into a wonderful crystalline form.

The discoveries made in this pursuit expand our understanding of the intricacies of chemical reactions and pave the way for future advancements in the realm of science.

1,1'-(((1E,1'E)-(sulfonylbis(6-(4-((quinolin-8-yloxy)methyl)-1H-1,2,3-triazol-1-yl)-3,1-phenylene))bis(diazene-2,1-diyl))bis(4,1-phenylene))bis (ethan-1-one)(H_1).

(yield 88%), melting point: 100-102 ^{o}C, (R_f : 0.61), FT.IR data (cm^{-1}): 3067 (C-H aromatic), 1668 (C=O ketone), 1587 (C=C aromatic), 1512 (N=N azo),1436 (S=O), 1012 (C-O aliphatic).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.51 (d, *J* = 1.9 Hz, 1H), 8.33 – 8.20 (m, 2H), 8.10 (dd, *J* = 8.4, 1.8 Hz, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 7.97 – 7.91 (m, 4H), 7.53 – 7.45 (m, 2H), 7.43 – 7.16 (m, 1H), 7.15 (dd, *J* = 7.8, 0.8 Hz, 1H), 5.41 (s, 1H), 2.55 (s, 2H).**^{13}C NMR** (100 MHz DMSO-*d6*) δ 196.80, 155.54, 152.98, 147.97, 147.74, 140.64, 137.44, 137.30, 137.26, 136.73, 129.98, 129.41, 129.09, 127.06, 126.85, 126.73,125.60, 121.81, 121.74, 118.83, 117.56, 111.43, 59.96,40.87,40.55,40.39,39.85,39.70,39,25,26.35,25.00.

1,1'-(((1E,1'E)-(sulfonylbis(6-(4-((4-nitrophenoxy)methyl)-1H-1,2,3-triazol-1-yl)-3,1-phenylene))bis(diazene-2,1-diyl))bis(4,1-phenylene))bis(ethan-1-one)(H_2):

(yield 88%), melting point: 84-86 oC, (*Rf* : 0.63), **FT.IR data (cm^{-1}):** 3145(C-H triazole),3098 (C-H aromatic), 1684 (C=O ketone), 1588 (C=C aromatic),), 1503 (N=N azo), 1436 (S=O), 1011 (C-O aliphatic, 949(S-N).**^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.53 (d, *J* = 1.8 Hz, 1H), 8.23 – 8.17 (m, 2H), 8.15 – 8.08 (m, 2H), 8.09 – 8.05 (m, 3H), 7.96 – 7.93 (m, 2H), 7.20 – 7.17 (m, 2H), 5.26 (s, 1H), 2.56 (s, 2H).**^{13}C NMR** (100 MHz, DMSO-*d6*) δ 196.83, 163.73, 155.54, 148.34, 141.50, 137.67, 137.28, 137.26, 136.73, 129.94, 129.40, 126.85, 125.90, 121.81, 118.83, 117.56, 115.15, 58.49, 40.81, 40.50, 40.23, 39.90, 39.77, 39.44, 26.37.

4,4'-((((sulfonylbis(2-((E)-(4-acetylphenyl)diazenyl)-4,1-phenylene))bis(1H-1,2,3-triazole-1,4-diyl))bis(methylene))bis(oxy))bis(3-methoxybenzaldehyde). (H_3):

(yield 87%), melting point: 79-81 °C, (R_f : 0.60), FTIR: FT.IR data (cm^{-1}): 3144 (C-H triazole), 3084 (C-H aromatic), 1666 (C=O ketone), 1581 (C=C aromatic), 1511 (N=N azo), 1410 (S=O), 1258 (C-O aromatic),1087(C-O aliphatic), 952(S-N), 883(C-S)**^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.91 (t, *J* = 1.0 Hz, 1H), 8.63 (d, *J* = 1.9 Hz, 1H), 8.26 (s, 1H), 8.22 (dd, *J* = 8.5, 2.0 Hz, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 8.06 – 7.99 (m, 4H), 7.86 (ddd, *J* = 8.4, 2.0, 1.0 Hz, 1H), 7.21 (dd, *J* = 2.0, 1.0 Hz, 1H), 7.10 (d, *J* = 8.4 Hz, 1H), 5.26 (s, 1H), 3.12 (s, 2H), 2.58 (s, 2H).**^{13}C NMR** (100 MHz, DMSO-d_6) δ 196.78, 192.30, 155.54, 151.27, 149.77, 147.97, 137.44, 137.28, 137.26, 136.73, 132.71, 129.98, 129.40, 126.85, 126.20, 121.81, 118.83, 117.56, 115.21, 111.84, 59.73, 56.24, 40.90, 40.72, 40.33, 39.89, 39.56, 39.33, 26.34.

Antibacterial Study

Two strains of *Staph aureus and E. coli* have been chosen. Bacterium is used for all experiments, and grown in Muller Hinton agar. All types of bacteria have been grown at 36 h and have been incubated at 37 °C. After serial optimization to reach $1.5x10^{-8}$ bacteria per ml, it is used spectrophotometry experiment to compare the OD_{600} with viable count (CFU). It is around OD_{600} 0.4 equal $1x10^8$.Different concentrations have been prepared as following (10,50,100,200 & 500) µM in (DMSO) of all prepared heterocyclic in our study, added separately to the wells on the pits that already have bacterial growth. The plates were incubated for 24 h to test the anti-bacterial effects; a ruler is used to measure the inhibition zone to the nearest millimeter (mm).

Results and Discussion Chemistry.

Illuminating the Synthetic Path: Pioneering 1,2,3-Triazole Derivatives from Sulfamethoxazole. Through a well-crafted strategy, vividly illustrated in Scheme 1, we have triumphed in synthesizing an exquisite array of 1,2,3-triazole derivatives

from sulfamethoxazole. This remarkable achievement was realized through a captivating cycloaddition reaction between 4-azido-N-(5-methylisoxazol-3-yl) benzene sulfonamide and O-propargyl derivatives adorned with alkyl chains.Our journey commenced with the creation of the azide derivative of sulfamethoxazole (1). The orchestration of this intricate transformation involved the initial formation of the sulfamethoxazole diazonium ion, followed by an exhilarating azide attack on this ion. Inspired by the pioneering insights of Huisgen and Ugi [24], we harnessed the inherent stability of nitrogen and the electron-withdrawing prowess of the (-SO_2-) group nestled within the benzene ring. This synergistic combination served as a compelling driving force, culminating in remarkable yields.Because nitrogen is very stable and is lost as a gas, and the amine group (-NH2) of the sulfadiazine is linked to the benzene ring, which contains the electronwithdrawing group (-SO_2-), this provides a strong driving force for the reaction to occur with high yield. The propargyl derivative is prepared through the Williamson reaction, in which anhydrous potassium bicarbonate (K_2CO_3) is used as catalyst, which has a sufficient base to extract the proton of the hydroxyl group [25], as it provides a good nucleophilic (phenoxied ion) to attack the carbon atom associated with the halogen present in propagel bromide where the mechanism of this reaction is classified as SN_2 reaction, as a result, acetone one of the best solvents for this type of reactions. This harmonious dance of molecules and bonds unveiled the captivating compounds we sought.As our journey reached its pinnacle, the grand finale awaited—a spellbinding 1,3-dipolar cycloaddition reaction. In this moment of alchemical brilliance, the enigmatic 4-azido-N-(5-methylisoxazol-3-yl) benzene sulfonamide joined forces with the alluring O-propargyl derivatives (C_1-C_3). Guided by the ethereal presence of copper monochloride and sodium ascorbate, harmoniously within the realm of DMSO, the mesmerizing transformation

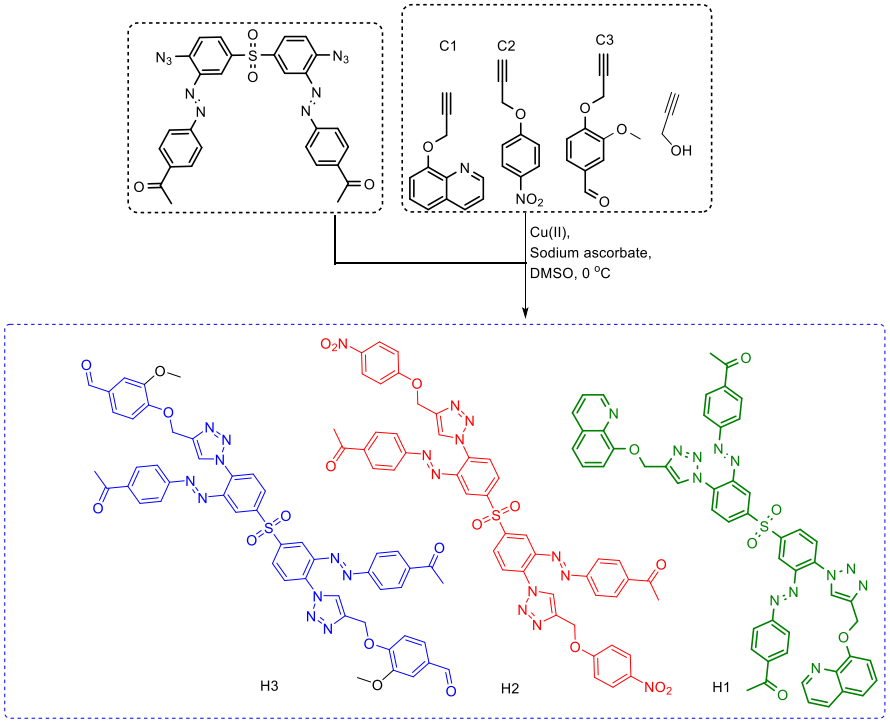
yielded the coveted 1,2,3-triazole compounds (H_1-H_3), emerging with impressive yields, like stars illuminating the night sky.

To bestow validity upon our creations, we turned to the art of characterization. Armed with the indispensable tools of infrared, ^{1}HNMR and ^{13}C NMR, and mass analysis, we ventured into the intricate landscapes of structural analysis. Within the reverberating spectra of compounds (H_1-H_3), we marveled at the distinctive signatures of the 1,2,3-triazole nucleus. The FTIR spectra unveiled characteristic bands within the range of 1500–1300 cm−1, speaking eloquently of the resolute C=C and N=N bonds. The unmistakable resonance of the (NH) group of sulfonamide echoed within the range of 3300–3350 cm−1, while the vibrant presence of the alkyl chains radiated with intensity in the range of 2800-2900 cm−1.

Delving deeper into the wondrous realm of NMR, we discovered a symphony of signals within the 1HNMR spectra of compounds (H_1-H_3). Protons resonating within the 1,2,3-triazole nucleus gracefully danced between 8.35 ppm and 8.41 ppm, while aromatic protons found their melodic expression in the realm of 7.83–7.20 ppm. A mesmerizing signal at 6.16 ppm bore witness to the ethereal presence of methylene groups attached to the oxazole ring, while a resolute single signal at 8.47 ppm spoke of the enchanting world of imine protonation. Meanwhile, a singular singlet signal emerged, resonating within the range of 11.41-11.46 ppm, serenading us with the soulful tones of the sulfonamide proton.

In the ethereal realm of ^{13}C NMR spectra, a resplendent tapestry unfolded. As expected, all the anticipated carbon signals corresponding to sulfamethoxazole-1,2,3-triazole derivatives emerged with distinction. The signals of methyl carbons adorned the landscape between 12 ppm and 15 ppm, while the sonorous tones of aromatic carbons resonated at 125 ppm and 143 ppm, elegantly corresponding to the 1,2,3-triazole nucleus.

With these analytical revelations, our journey of synthesis and discovery concluded, leaving behind a trail of meticulously characterized and truly captivating compounds, bearing the hallmarks of our relentless pursuit of scientific excellence.



Scheme 1. Synthetic Route of heterocyclic compound

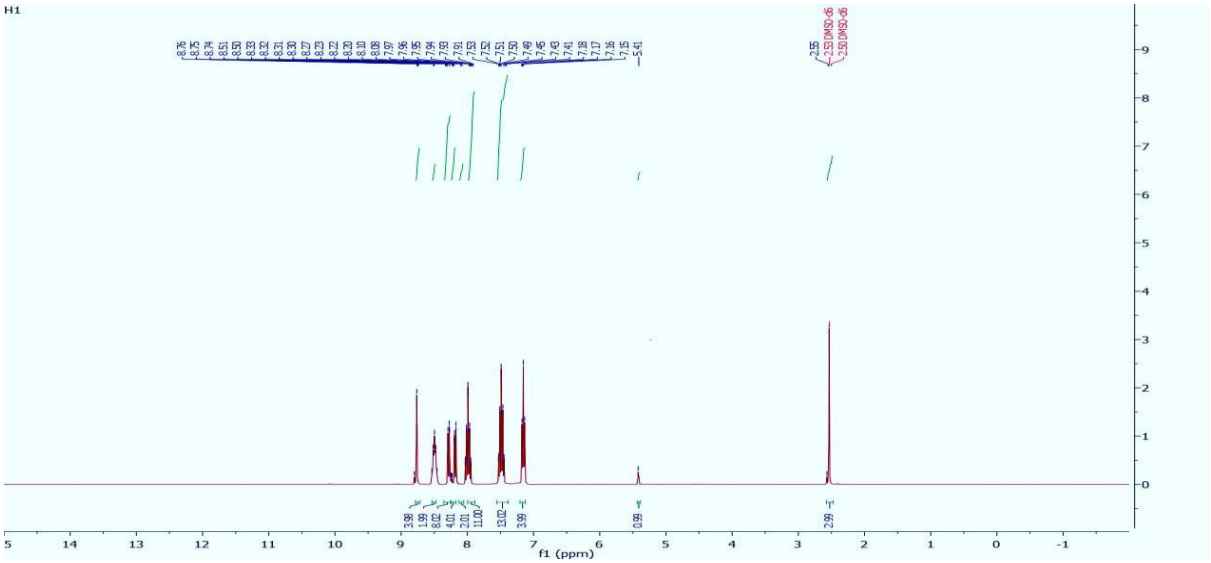


Figure 1 ^{1}HNMR spectrum of compound C_1

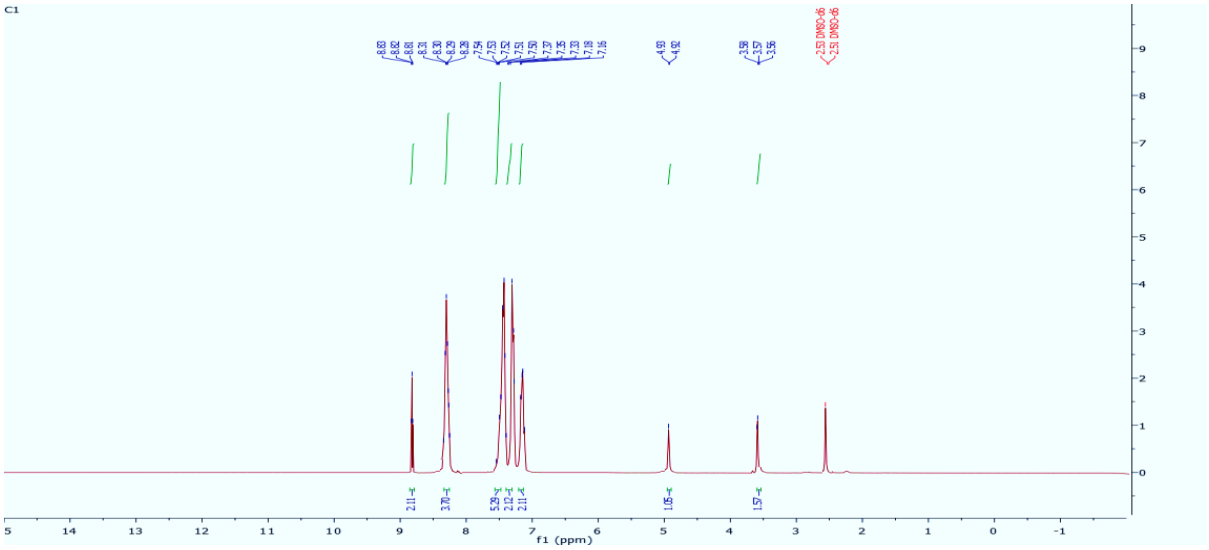


Figure 1 ^{1}HNMR spectrum of compound H_1

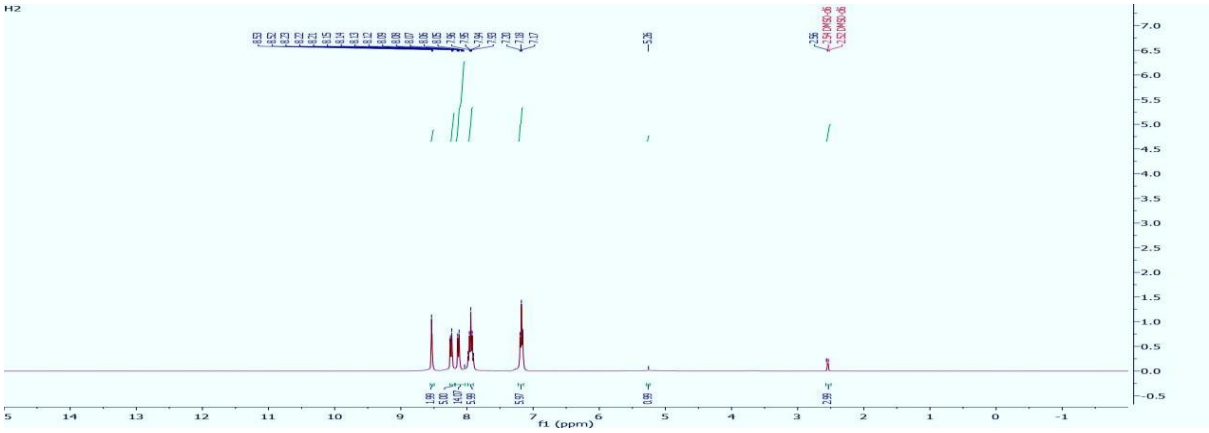
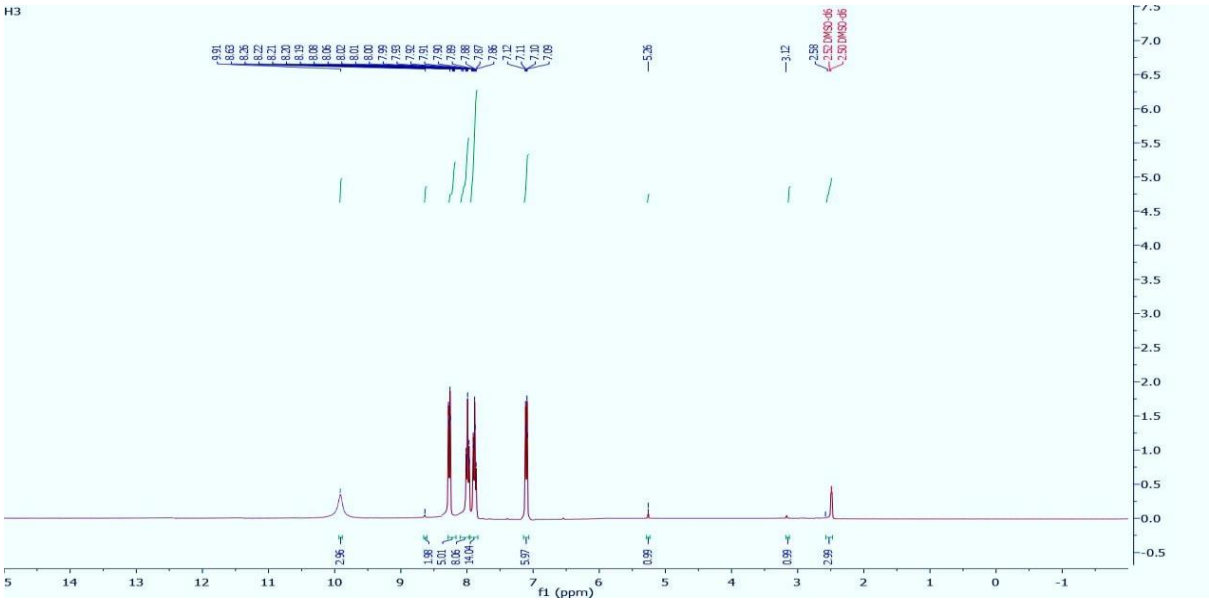


Figure 5 ^{1}HNMR spectrum of compound H_2



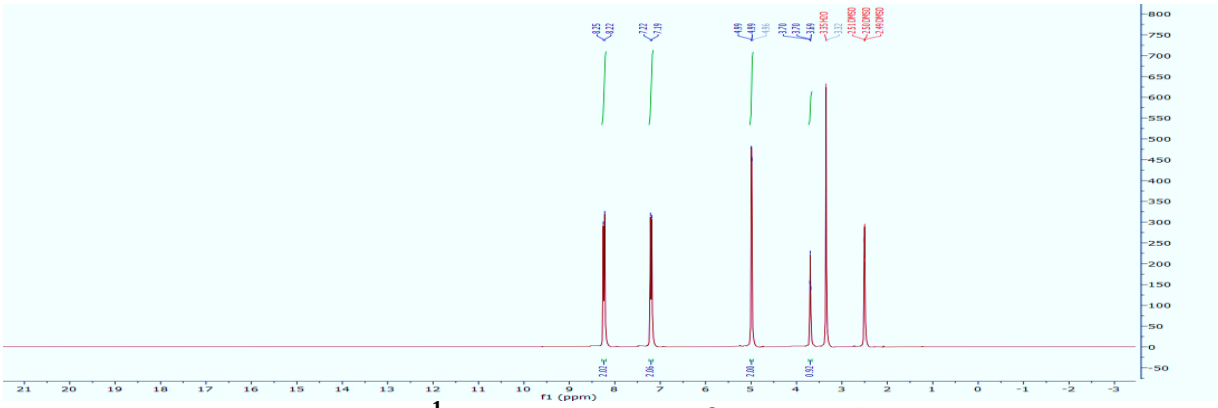
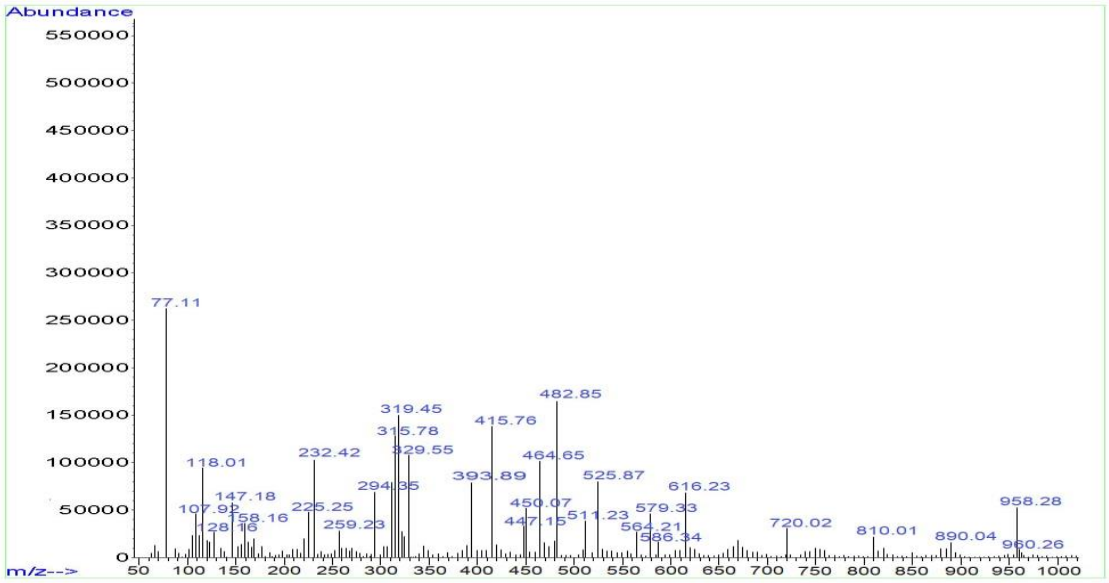


Figure 6 ^{1}HNMR spectrum of compound H_3

The mass spectrum of [$C_{52}H_{38}N_{12}O_6S$] shows a molecular ion peak [M+] at m/z 995.01 which is in accordance with the proposed formula of the compound (H_1)



Exploration of antibacterial efficacy

Unleashing the Antibacterial Potential: Evaluation of Compounds (H1-H3) against Staphylococcus aureus and Escherichia coli.

In our quest to combat bacterial infections, we embarked on a comprehensive study to assess the antibacterial activity of the synthesized compounds (H_1-H_3) against two common strains, Staphylococcus aureus (Gram-positive) and Escherichia coli (Gram-negative). The growth inhibition zones were meticulously examined using the disc

diffusion method with Mueller Hinton Broth (MBH) medium, serving as our litmus test.

To determine the minimum inhibitory concentrations (MIC), the compounds were put through rigorous evaluation. As a negative control, we employed DMSO to benchmark the antibacterial activity. The fascinating findings regarding the MIC antibacterial values for the synthesized compounds (H_1-H_3) are visually presented in Fig. 1 and Fig. 2.

Our findings revealed intriguing degrees of inhibition against both Gram-positive and Gram-negative bacteria. Notably, all the prepared compounds exhibited enhanced effectiveness with increasing concentration. Compounds (H_1-H_3), adorned with alkyl or phenyl groups on the dapson-1,2,3-triazole scaffold, showcased the most promising antibacterial activity against Staphylococcus aureus, as illustrated in Fig. 1. In particular, compound (H_2) emerged as a standout performer, demonstrating remarkable activity against Staphylococcus aureus, with an MIC value of 25 µg/mL.

On the other hand, compound (H_1) demonstrated exceptional efficacy against the selected bacteria Escherichia coli, with an MIC value of 22 µg/mL. These findings open new avenues for further exploration and development of compounds with potent antibacterial properties, potentially paving the way for novel therapeutic interventions in the fight against infectious diseases.

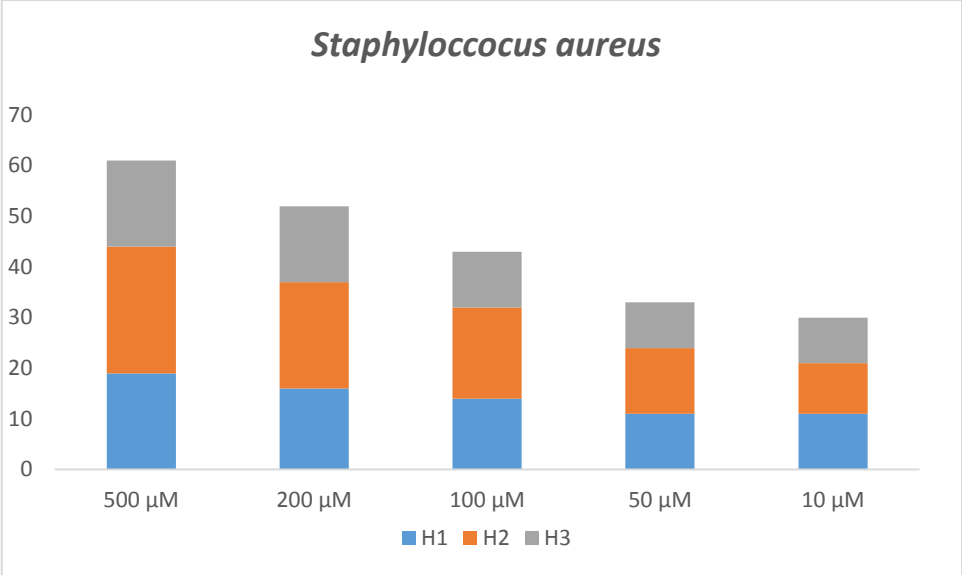


Fig. 7: The biological activity of end products (H_1-H_3) against staphylococcus aureusa

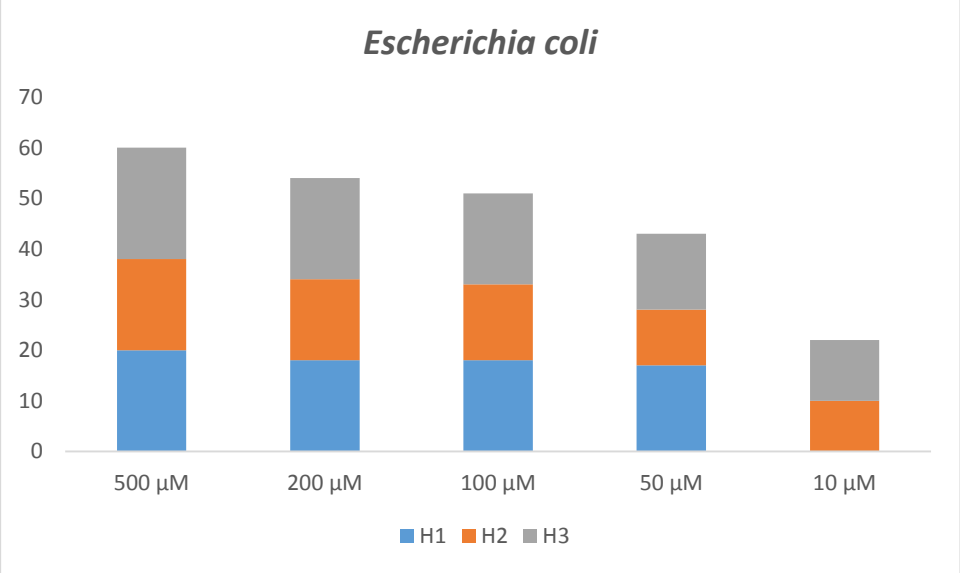


Fig.8: The biological activity of end products (H_1-H_5) against Escherichia coli

Conclusion

Unveiling the Potential: Novel 1,2,3-Triazole Derivatives from Azo Dapsone.

In this captivating scientific endeavor, we set out to unlock the hidden potential of 1,2,3-triazole derivatives derived from azo dapsone. Through meticulous preparation,

comprehensive characterization, and rigorous biological evaluation, we embarked on a journey that promises to shape the future of antibacterial research.

The synthesized compounds (H_1-H_3) underwent meticulous screening to unravel their in vitro antibacterial activity against two notorious pathogenic strains. Our findings were nothing short of remarkable.

Compound (H_2) stood out as the beacon of hope in our battle against Staphylococcus aureus. Its potency surpassed that of the other prepared compounds, offering a glimmer of promise in combating this formidable pathogen. With each breakthrough, we edged closer to a potential solution.

Meanwhile, the spotlight also shone brightly on compound (H_1), showcasing its exceptional efficacy against Escherichia coli. This compound emerged as a formidable contender, outshining the other compounds in its ability to combat this relentless bacterial strain.

In conclusion, our endeavors in synthesizing, characterizing, and biologically evaluating these 1,2,3-triazole derivatives have unraveled a world of possibilities. The discovery of compound (H_2)'s potency against Staphylococcus aureus and compound (H_1)'s effectiveness against Escherichia coli ignites a renewed sense of hope in the fight against pathogenic bacteria.

As we draw the curtains on this our research, we eagerly anticipate further exploration and refinement of these compounds, paving the way for innovative antibacterial interventions that may shape the future of healthcare. The journey has just begun, and with each step, we move closer to conquering the challenges posed by infectious diseases.

References

[1] A.S. Saghyan, H.M. Simonyan, S.G. Petrosyan, A.V. Geolchanyan, G.N. Roviello, D. Musumeci, V. Roviello, Thiophenyl-substituted triazolyl-thione L-

alanine: asymmetric synthesis, aggregation and biological properties, Amino Acids 46 (10) (2014) 2325–2332.

[2] S.S. Tawfik, M. Liu, A.A. Farahat, Antiviral activity of thiadiazoles, oxadiazoles, triazoles and thiazoles, Organic Chemistry. (2020) 180–218.

[3] C. H Zhou, Y. Wang, Recent researches in triazole compounds as medicinal drugs, Curr. Med. Chem. 19 (2) (2012) 239–280.

[4] N. Boechat, M. de L.G. Ferreira, L.C.S. Pinheiro, A.M.L. Jesus, M.M.M. Leite, C.C.S. Júnior, A.C.C. Aguiar, I.M. Andrade, A.U. Krettli, New Compounds Hybrids 1 H -1,2,3-Triazole-Quinoline Against Plasmodium falciparum, Chem. Biol. Drug Des. 84 (2014) 325–332, doi:10.1111/cbdd.12321.

[5] M. Aarjane, S. Slassi, B. Tazi, M. Maouloua, A. Amine, Novel series of acridone-1,2,3-triazole derivatives: microwave-assisted synthesis, DFT study and antibacterial activities, J. Chem. Sci. 131 (2019) 1–11, doi:10.1007/ s12039-019-1653-2.

[6] K. Sri, S. Praveena, N. Yadagiri, S. Murthy, S. Pal, Syntheses and biological activities of 1,4-disubstituted-1,2,3-triazoles, Available Online Www.jocpr.com, Jornal of. Chemistry. Pharm. Res. 7 (2015) 506–522 www.jocpr.com. (accessed February 1, 2021).

[7] N. Kuntala, J.R. Telu, V. Banothu, S.B. Nallapati, J.S. Anireddy, S. Pal, Novel benzoxepine-1,2,3-triazole hybrids: synthesis and pharmacological evaluation as potential antibacterial and anticancer agents, Medchemcomm 6 (2015) 1612–1619, doi:10.1039/c5md00224a.

[8] O. Grytsai, O. Valiashko, M. Penco-Campillo, M. Dufies, A. Hagege, S. Martial, G. Pagès, C. Ronco, R. Benhida, Synthesis and biological evaluation of 3-amino1,2,4-triazole derivatives as potential anticancer compounds, Bioorg. Chem. 104 (2020) 104271, doi:10.1016/j.bioorg.2020.104271.

[9] M.A. Almehmadi, A. Aljuhani, S.Y. Alraqa, I. Ali, N. Rezki, M.R. Aouad, M. Hagar, Design, synthesis, DNA binding, modeling, anticancer studies and DFT calculations of Schiff bases tethering benzothiazole-1,2,3-triazole conjugates, *Journal of Molecular Structure*. 1225 (2021) 129148, doi:10.1016/j.molstruc.2020.129148.

[10] C.P. Kaushik, J. Sangwan, R. Luxmi, D. Kumar, D. Kumar, A. Das, A. Kumar, D. Singh, Design, synthesis, anticancer and antioxidant activities of amide linked 1,4-disubstituted 1,2,3-triazoles, *Journal of Molecular Structure*. (2020) 129255, doi:10. 1016/j.molstruc.2020.129255.

[11] K.S.S. Praveena, E.V.V. Shivaji Ramarao, N.Y.S. Murthy, S. Akkenapally, C. Ganesh Kumar, R. Kapavarapu, S. Pal, Design of new hybrid template by linking quinoline, triazole and dihydroquinoline pharmacophoric groups: a greener approach to novel polyazaheterocycles as cytotoxic agents, Bioorganic Med. Chem. Lett. 25 (2015) 1057–1063, doi:10.1016/j.bmcl.2015.01.012.

[12] J. Mareddy, S.B. Nallapati, J. Anireddy, Y.P. Devi, L.N. Mangamoori, R. Kapavarapu, S. Pal, Synthesis and biological evaluation of nimesulide based new class of triazole derivatives as potential PDE4B inhibitors against cancer cells, Bioorganic Med. Chem. Lett. 23 (2013) 6721–6727, doi:10.1016/j.bmcl.2013.10. 035.

[13] Z. Peng, G. Wang, Q.-.H. Zeng, Y. Li, Y. Wu, H. Liu, J. Jing Wang, Y. Zhao, Synthesis, antioxidant and anti-tyrosinase activity of 1,2,4-triazole hydrazones as antibrowning agents, Food Chem (2020) 128265, doi:10.1016/j.foodchem.2020. 128265.

[14] M.J. Assarzadeh, A. Almasirad, A. Shafiee, M.N. Koopaei, M. Abdollahi, Synthesis of new thiazolo[3,2-b][1,2,4]triazole-6(5H)-one derivatives as potent analgesic and anti-inflammatory agents, Med. Chem. Res. 23 (2014) 948–957, doi:10.1007/s00044-013-0697-y.

[15] E.A. Scott, E. Bruning, R.W. Nims, J.R. Rubino, M.K. Ijaz, A 21st century view of infection control in everyday settings: moving from the Germ Theory of Disease to the Microbial Theory of Health, Am. J. Infect. Control. (2020), doi:10. 1016/j.ajic.2020.05.012.

[16] S.E. Walsh, J.Y. Maillard, A.D. Russell, C.E. Catrenich, D.L. Charbonneau, R.G. Bartolo, Development of bacterial resistance to several biocides and effects on antibiotic susceptibility, J. Hosp. Infect. 55 (2003) 98–107, doi:10.1016/ S0195-6701(03)00240-8.

[17] M. Aarjane, S. Slassi, A. Ghaleb, B. Tazi, A. Amine, Synthesis, biological evaluation, molecular docking and in silico ADMET screening studies of novel isoxazoline derivatives from acridone, Arab. J. Chem. (2021) 103057, doi:10.1016/j. arabjc.2021.103057.

[18] M. Aarjane, S. Slassi, B. Tazi, M. Maouloua, A. Amine, Synthesis, antibacterial evaluation and molecular docking studies of novel series of acridone1,2,3-triazole derivatives, Struct. Chem. 31 (2020) 1523–1531, doi:10.1007/ s11224-020-01512-0.

[19] Khalil A. , Hafiza A. N., Sajidah P. , Habib-ur-Rehman S., Syed S. A. ., Salma S., Areeba A., Javaria J., M. M. Ahmad and Muhammad A., Journal of Molecular Structure, (2019) , 1198 , 126885.

[20] Ehab K. Obaid, Rahmah H. Abdullah, Hussein Abdulkadim Hasan, Najlaa N. Hussein, Maha A. Khalaf, and Ali Jabbar Radhi, Synthesis and study biological activity of new heterocyclic compounds based on sugar, AIP Conf. Proc., 2290, 030028-1–030028-7, (2020).

[21] Batool, T. *et al.* A convenient method for the synthesis of (Prop-2-Ynyloxy) benzene derivatives via reaction with propargyl bromide, their optimization, scope and biological evaluation. *PLoS One* **9**, e115457 (2014).

[22] Diamanti, A. *et al.* Mechanism, kinetics and selectivity of a Williamson ether synthesis: elucidation under different reaction conditions. *React. Chem. Eng.* (2021).

[23] Yuqin Jiang, Duanyang Kong, Jinglin Zhao, Weiwei Zhang, Wenjing Xu, References Wei Li, Guiqing Xu. A simple, efficient thermally promoted protocol for Huisgen-click reaction catalyzed by CuSO4· 5H2O in water. Tetrahedron Lett. 55, 2410–2414 (2014).

[24] Huisgen, R. & Ugi, I. Zur Lösung eines klassischen Problems der organischen Stickstoff- Chemie. Angew. Chemie 68, 705–706 (1956).

[25] [Yina Pájaro, Ángel Sathicq, Esneyder Puello-Polo, Astrid Pérez, Gustavo Romanelli, , Jorge Trilleras. An Efficient K2CO3-Promoted Synthesis of 1- Bromo-2-aryloxyethane Derivatives and Evaluation of Larval Mortality against Aedes aegypti. J. Chem. 2017, (2017).