The International Science of Health Journal
Vol.2, No. 3 September 2024
e-ISSN: 2986-6820; p-ISSN: 2986-6855, Pages 01-10
DOI: https://doi.org/10.59680/ishel.v2i2.1259
Available online at: https://jurnal.stikeskesdam4dip.ac.id/index.php/ishel

Modification of Sulfadiazine Antibacterial to Promising Anticancer Schiff Base Derivatives: Synthesis and *in Vitro* Studies

Tasnim Tariq Mohammed[1] , Aula Hassoon Obaid[2] , Ghasaq Farouq Hammeed[3] , Abbas K. Abbas[4],
[1]College of Medicine, Fallujah University, Al-Anbar, Iraq
[2]College of Medicine, Fallujah University, Al-Anbar, Iraq
[3]Department of Optics, College of Health & Medical Technology, Sawa University, Al-Muthana. Iraq
[4]Muthana Agriculture Directorate, Ministry of Agriculture, Al-Muthanna, Iraq
tasnim.tariq@uofallujah.edu.iq , ulaa.hassoun@uofallujah.edu.iq , ghasaq@sawauniversity.edu.iq , Abbaschemist1991@gmail.com

Abstract: *The study displays a novel approach for synthesizing imine-sulfadiazine compounds (A and B) by reacting Sulfadiazine with various aldehydes, including 2-chlorobenzaldehyde and 4-pentoxybenzaldehyde. The derivatives (A and B) were characterized using spectroscopic techniques, specifically FT-IR spectroscopy. The synthesized compounds were assessed in vitro against various bacteria, including Streptococcus pneumoniae and E. coli, using the zone inhibition method. The results indicated that specific derivatives possess enhanced antibacterial characteristics compared to the effectiveness of the regular medications. The derivative A was assessed for its anticancer activity against breast cancer MCF-7 cells using the MTT assay, which yielded a favorable outcome within 24 hours.*

Keywords: *Antibiotic; Sulfadiazine; Drugs; Bacteria; Cancer*

1. INTRODUCTION

Bacterial infections remain a large and dealing with risk to public health, resulting in significant illness and death on a global scale for many millennia [1]. Despite persistent endeavors to develop and present novel antibacterial medications, the rate and dissemination of bacterial diseases have never ceased [2]. The main barrier to achieving comprehensive control over bacterial infections is creating bacterial strains resistant to many drugs. Hence, it is crucial to prioritize identifying innovative antibacterial compounds that possess distinct structures or functions through novel mechanisms [3].

Sulfonamide is a frequently used functional group in medicinal chemistry [4], including in the structures of medically important compounds. Besides being the initial synthetic antibacterial drug, sulfonamides also possess a diverse range of biological actions, including inhibition of carbonic anhydrase, activation of insulin release, and anti-inflammatory effects [5-7].

Antibacterial sulfonamides, such as sulfathiazole, sulfadiazine, and sulfisoxazole (Fig. 1), disrupt the bacterial folate pathway to exert their mechanism of action [8].

Received May 22, 2024; Revised June 26, 2024; Accepted July 20, 2024; Online Available:July 23, 2024
** Tasnim Tariq Mohammed , tasnim.tariq@uofallujah.edu.iq*

Figure 1. Structures of antibacterial sulfa drugs [9].

While sulfonamides were initially the first category of chemicals to exhibit selective action against bacteria, their clinical application is currently quite restricted. There are several significant reasons for this restriction. One reason is that numerous additional and more potent antibacterial agents were found subsequent to their approval in the 1930s. The second, and arguably the most crucial, factor is the swift development of medication resistance against sulfonamides [10].

Another factor that limits the use of sulfonamides is their significant toxicity and the frequent occurrence of allergic adverse effects in patients. Sulfathiazole is a sulfa medication with antibacterial properties that acts quickly [11]. Despite being supplanted by less harmful alternatives, it is still found in commercial goods alongside other antibacterial substances, particularly for the management of vaginal infections [12].

Molecular modification is a commonly used approach in drug design involving chemical changes to a lead product [13]. This strategy focuses on enhancing a substance's pharmacological and pharmacokinetic characteristics, including increasing its potency, reducing its toxicity, and improving its chemical qualities. Fourteen Modifying the molecular structure of current chemical frameworks is a possible approach to address drug resistance in antibacterial, antitubercular, and anticancer treatments. Given the global rise in antibiotic resistance, it may be worthwhile to reevaluate the use of affordable sulfonamides in treating infectious diseases by making necessary changes to their structure [14].

Schiff bases are formed through the condensation reaction between primary (aromatic) amines and aldehydes or ketones, resulting in the formation of the azomethine (imino) group (-CR=N-). Azomethine groups are essential for the bioactivity of flexible pharmacophores used in many pharmacological activities. For instance, naturally occurring and artificially synthesized Schiff bases have demonstrated significant potential as antibacterial and antitubercular agents [15].

In this study, we modification of pure sulfadiazine drug to produce imine derivatives (A and B), characterization of these derivatives by FTIR spectroscopy. Evolution the biological activity and anticancer MCF-7cell line by used MTT assay.

2. METHODS

Synthesis of imine- sulfadiazine derivatives (A and B)

Dissolve (0. 441 g, 0.1 mmol) of sulfadiazine in 15 ml of ethanol. 0.1 moles of corresponding aldehydes, such as 2-chlorobenzaldehyde and 4-pentoxybenzaldehyde were added to this solution. The resulting mixture was refluxed for 3 h. The precipitates were collected, washed several times with absolute ethanol, dried under vacuum, and kept [16].

Investigation of the antimicrobial activity of Imine- sulfadiazine derivatives (A and B).

Several bacterial strains, including *Streptococcus pneumonia,* and *E. coli*, were cultivated on Muller-Hinton agar plates using sterile loop and streaking techniques, beginning with the broth culture. Subsequently, a distinct well was generated within the agar medium. A volume of 100 µl of the suitable dilution of imine-sulfadiazine compounds (A and B) was supplied to each well, resulting in efficient absorption. The container was sealed tightly and placed in an incubator set at 37 ºC for the 24 h to evaluation the following day [16]. The microbial suspensions were uniformly spread across the surface of the media using a sterilized triangular loop. A sterilized stainless-steel cylinder with a diameter of 12 mm was used to produce cavities. The different synthetic chemicals were successively introduced into the cavities using a micropipette at different concentrations (0.1, 0.001, and 0.00001 M). Subsequently, they were granted permission to disperse for a duration of sixty minutes. DMSO functioned as the solvent for all compounds, while sterile distilled water functioned as the solvent exclusively for pure amoxicillin. The plates were incubated at a temperature of 37 degrees Celsius for a duration of 48 hours. The diameter of the zone of inhibition surrounding the cups was measured in ml following incubation [17].

Assessment of the detrimental effects of the inhibitor using the MTT Assay on the MCF-7 Cell Line

The cytotoxicity of derivative (A) was assessed using the MTT assay. Pre-assembled kit (Intron Biotech) contents of Kit A:

MTT solution refers to a solution that contains MTT, a compound commonly used in biological assays. 3-(4,5-dimethylthiazol-2yl) 2,5-diphenyl tetrazolium bromide, with a molecular weight of 414. 10 mL in total, divided into 10 vials.

There are two bottles, each containing 50 mL of solubilization solution.

Procedure:

The process was executed in accordance with the instructions provided by the manufacturer.

1- The cells, with a density of 4.5 x 105, were cultivated on 96-well plates with a final volume of 200 µL of complete culture media per well. The plates were coated with a sterile parafilm, gently mixed, and placed in an incubator at a temperature of 37 °C and a carbon dioxide concentration of 5% for a duration of 24 hours [18].

2-After the incubation period, the liquid in the container was taken out, and 200 µl of a diluted form of derivative (A) at concentrations of 25, 50, 100, 200, and 400 µg/mL was introduced into the small compartments. Each concentration and control was subjected to triplicate analysis. The plates were cultured for 48 hours at a temperature of 37°C and in an atmosphere containing 5% carbon dioxide [19].

Following exposure to the derivative (A), a volume of 10 µL of MTT solution was applied to each well. The plates were incubated for an additional 4 hours at a temperature of 37°C and a carbon dioxide concentration of 5%.

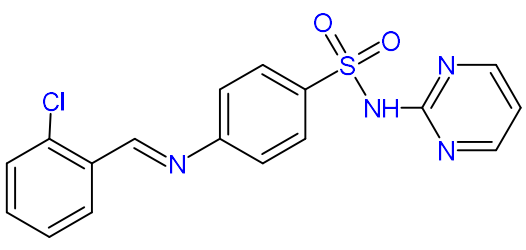
4- The medium was thereafter extracted, and 100 µL of DMSO solubilization solution was introduced into each well and allowed to incubate for 5 minutes.

The absorbance was quantified using an ELISA reader (Bio-rad, Germany) at a wavelength of 575 nm.

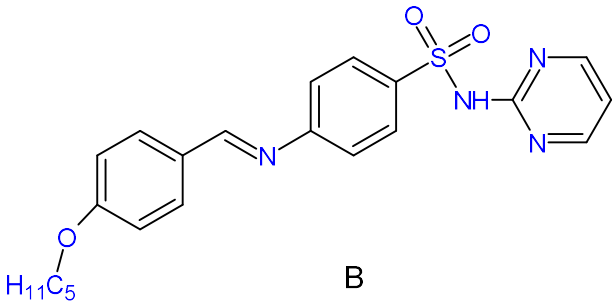
The optical density values were subjected to statistical analysis in order to determine the IC50 value.

3. RESULTS AND DISCUSSION

According to scheme 1, the titled products (A and B) were prepared through a one-pot synthesis between sulfadiazine, and different substituted benzaldehyde. Acetic acid has been utilized as a catalyst.



A



B

Figure 1. Chemical structures of synthesized derivatives (A and B).

Imine derivative (A): Molecular Formula: $C_{17}H_{13}ClN_4O_2S$, Color: Light yellow powder, M.p.: 155-158 °C, Yield: 77 %. FTIR (cm^{-1}): 3043 (C-H aromatic), 1649 (C=N) [20], 1591 (C=C aromatic), 3391 (N-H) [17].

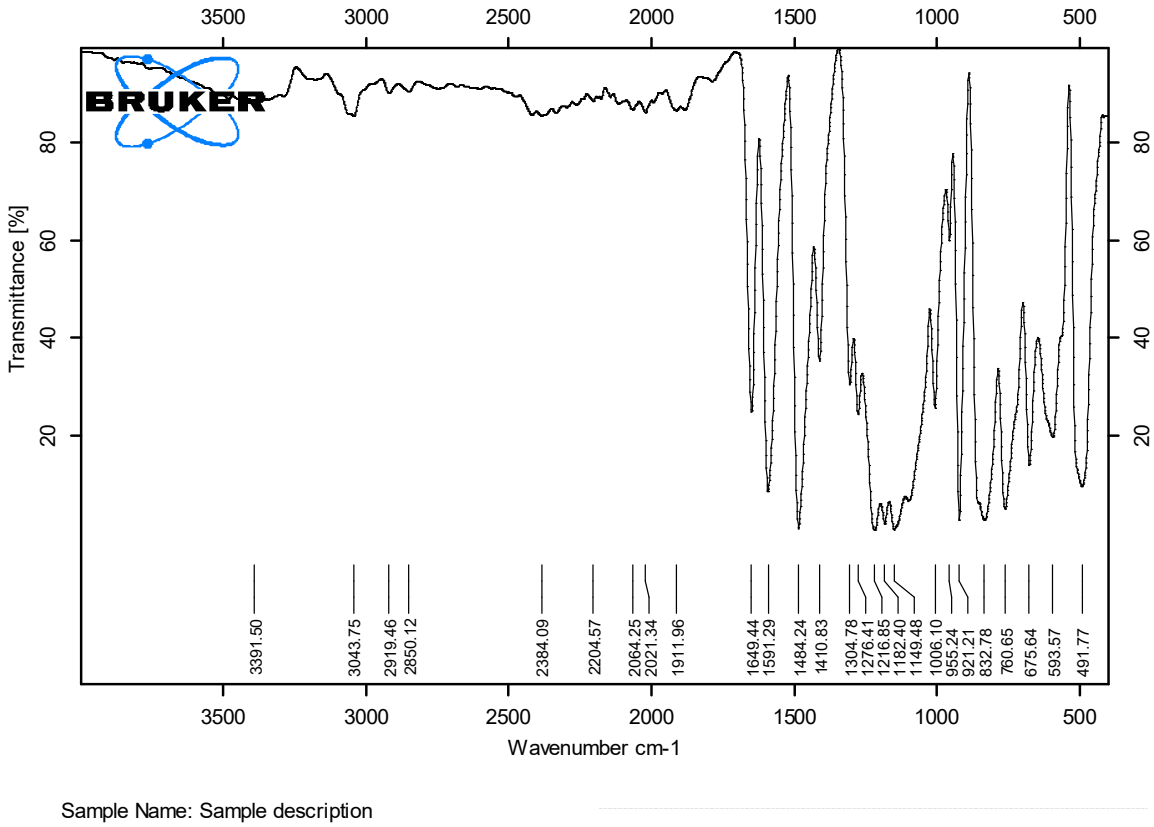


Figure 1. FTIR of derivative A.

Imine derivative (B): Molecular Formula: $C_{22}H_{24}N_4O_3S$, Color: yellow powder, M.p.: 173-16 °C, Yield: 74 %. FTIR (cm^{-1}): 3044 (C-H aromatic), 1649 (C=N) [21], 1589 (C=C aromatic), 3377 (N-H).

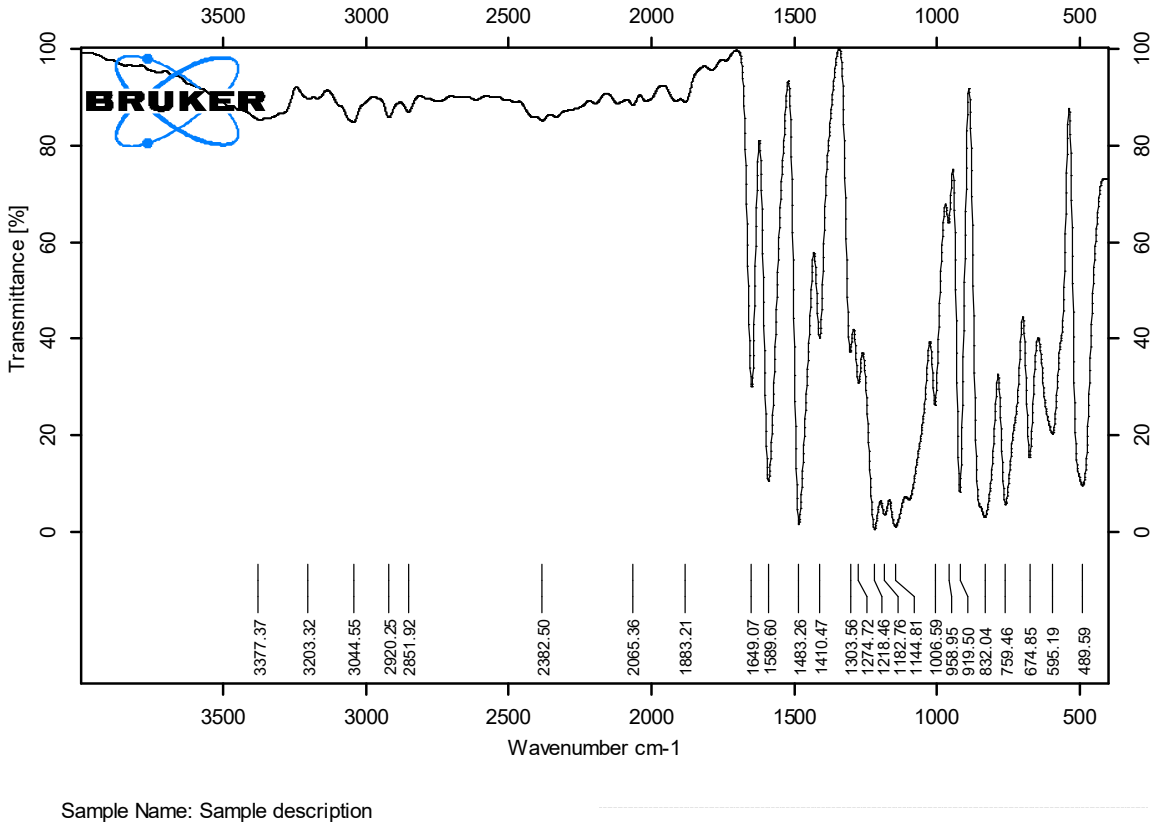


Figure 2. FTIR of derivative B.

Biological activity: Sulfadiazine functions as an inhibitor of competition of the bacterial enzyme dihydropteroate synthase [22]. This type of enzyme is required for the accurate processing of para-aminobenzoic acid (PABA), which is crucial for the synthesis of folic acid. The restrained response is essential in these organisms for the production of folic acid [23].

The penicillin G have been highest biological activity against *S. aureus* by zone inhibition 33 mm at 0.1 M. while derivative A more than derivative B because have chlorine atom in his structure. The less effect on zone inhibition was derivative B at 0.00001 M by 10 mm.

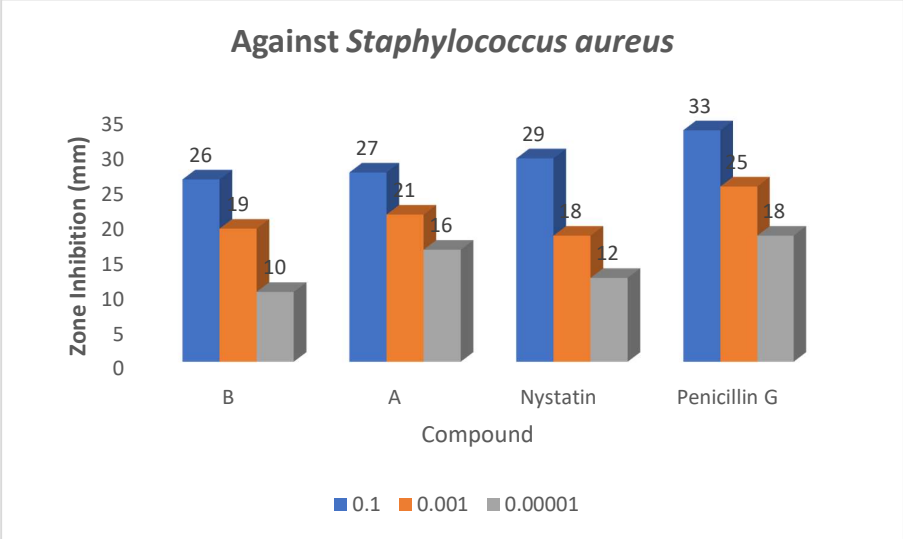


Figure 3. Biological activity of nystatin, penicillin G, derivatives A and B *against S. aureus*.

The derivative A have been highest biological activity against *E. Coli* by zone inhibition 31 mm at 0.1 M. while penicillin G more than nystatin and derivative B because have more active groups in his structure. The less effect on zone inhibition was nystatin at 0.00001 M by 11 mm.

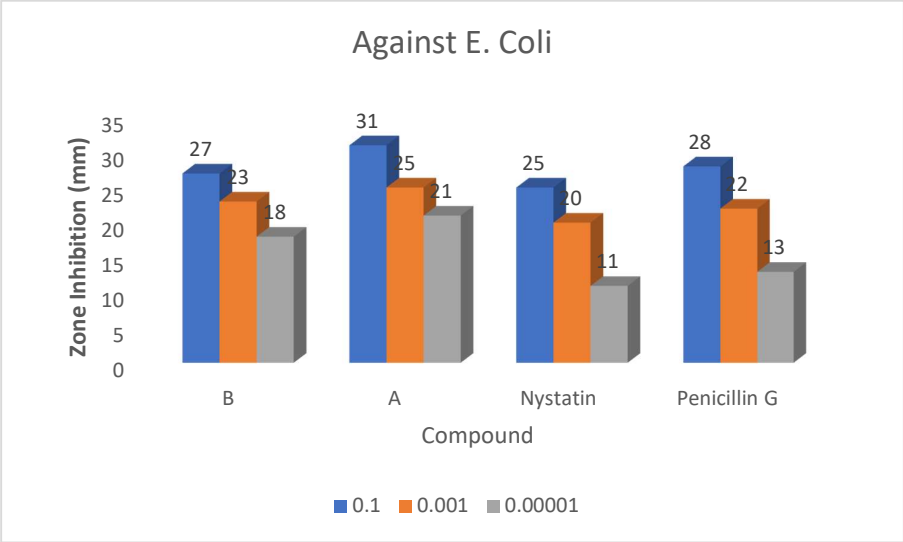


Figure 4. Biological activity of nystatin, penicillin G, derivatives A and B *against E. Coli*.

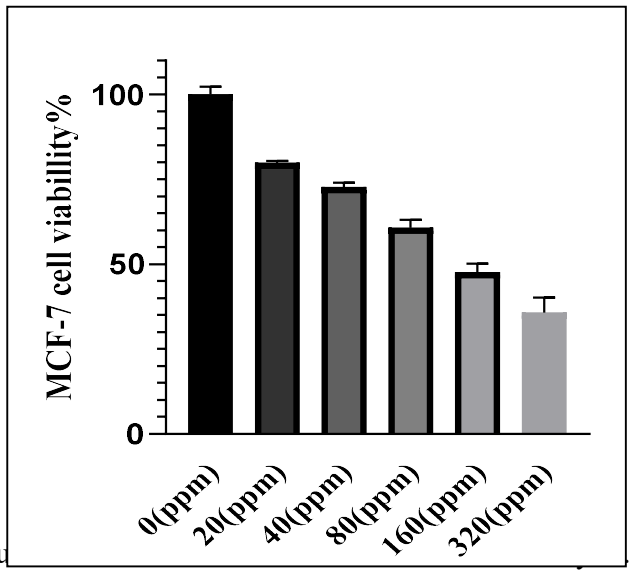
The cytotoxicity of the synthesized derivative A was evaluated as an anticancer agent using the viability assessment method MTT.

The MTT test was used to evaluate the cytotoxicity of derivative A towards the MCF-7 cell line. The vitality of the cells was evaluated 24 hours after treatment with various doses of each derivative, ranging from 0 to 320 g/ml. Figure 5 illustrates the outcomes of derivative A, which

has a value of 33.24 at 24 hours. These values were measured on a scale ranging from 0 to 100. The findings exhibited a correlation between the dosage and the impact on the MCF-7 cell line.

Table 1: Cell viability rates of derivative (A) induced MCF-7 cell.

Concentration (PPM)	After 24 h	
	Mean	SD
0	100	2.364490
20	77.78457	1.4857221
40	71.23910	1.9758853
80	63.38814	2.230095
160	48.63535	2.771974
320	33.24087	3.197403



Figu

4. CONCLUSION

The derivatives synthesized have biological activity as antibacterial and anticancer, these derivatives characterize by FTIR spectroscopy. The results showed the derivative A have bigger biological activity by used inhibition zone, and tested by MTT technique as anti-MCF-7 cancer cell. In future, we will synthesize new derivatives of different drugs.

REFERENCES

Boulechfar, C., et al. (2023). Schiff bases and their metal complexes: A review on the history, synthesis, and applications. Inorganic Chemistry Communications, 150, 110451. https://doi.org/10.1016/j.inoche.2022.110451

Çakmak, R., Başaran, E., & Şentürk, M. (2022). Synthesis, characterization, and biological evaluation of some novel Schiff bases as potential metabolic enzyme inhibitors. Archiv der Pharmazie, 355(4), 2100430. https://doi.org/10.1002/ardp.202100430

Cheong, M. S., et al. (2020). Influence of sulfonamide contamination derived from veterinary antibiotics on plant growth and development. Antibiotics, 9(8), 456. https://doi.org/10.3390/antibiotics9080456

Deusenbery, C., Wang, Y., & Shukla, A. (2021). Recent innovations in bacterial infection detection and treatment. ACS Infectious Diseases, 7(4), 695-720. https://doi.org/10.1021/acsinfecdis.0c00639

Egbujor, M. C., Garrido, J., Borges, F., & Saso, L. (2023). Sulfonamide a valid scaffold for antioxidant drug development. Mini-Reviews in Organic Chemistry, 20(2), 190-209. https://doi.org/10.2174/1570193X19666210817123236

El-Gaby, M., et al. (2020). Sulfonamides: Synthesis and the recent applications in Medicinal Chemistry. Egyptian Journal of Chemistry, 63(12), 5289-5327. https://doi.org/10.21608/ejchem.2020.23710.2401

Han, Y., et al. (2021). Sulfonamide derivatives as potential anti-cancer agents and their SARs elucidation. European Journal of Medicinal Chemistry, 226, 113837. https://doi.org/10.1016/j.ejmech.2021.113837

Kalelkar, P. P., Riddick, M., & García, A. J. (2022). Biomaterial-based antimicrobial therapies for the treatment of bacterial infections. Nature Reviews Materials, 7(1), 39-54. https://doi.org/10.1038/s41578-021-00361-6

Manohar, P., Loh, B., Nachimuthu, R., Hua, X., Welburn, S. C., & Leptihn, S. (2020). Secondary bacterial infections in patients with viral pneumonia. Frontiers in Medicine, 7, 420. https://doi.org/10.3389/fmed.2020.00420

Matela, G. (2020). Schiff bases and complexes: A review on anti-cancer activity. Anti-Cancer Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Cancer Agents), 20(16), 1908-1917. https://doi.org/10.2174/1871520620666200518150854

Mondal, S., & Malakar, S. (2020). Synthesis of sulfonamide and their synthetic and therapeutic applications: Recent advances. Tetrahedron, 76(48), 131662. https://doi.org/10.1016/j.tet.2020.131662

Raju, S. K., et al. (2022). Biological applications of Schiff bases: An overview. GSC Biological and Pharmaceutical Sciences, 21(3), 203-215. https://doi.org/10.30574/gscbps.2022.21.3.0058

Schneider, P., et al. (2020). Rethinking drug design in the artificial intelligence era. Nature Reviews Drug Discovery, 19(5), 353-364. https://doi.org/10.1038/s41573-019-0050-4

Subbaiah, M. A., & Meanwell, N. A. (2021). Bioisosteres of the phenyl ring: Recent strategic applications in lead optimization and drug design. Journal of Medicinal Chemistry, 64(19), 14046-14128. https://doi.org/10.1021/acs.jmedchem.1c00605

Uddin, N., et al. (2020). Synthesis, characterization, and anticancer activity of Schiff bases. Journal of Biomolecular Structure and Dynamics, 38(11), 3246-3259. https://doi.org/10.1080/07391102.2019.1685411

Wan, Y., Fang, G., Chen, H., Deng, X., & Tang, Z. (2021). Sulfonamide derivatives as potential anti-cancer agents and their SARs elucidation. European Journal of Medicinal Chemistry, 226, 113837. https://doi.org/10.1016/j.ejmech.2021.113837

Yousif, M. N., et al. (2022). Recent advances in the chemistry and biological activity of sulfonamide derivatives. Mini-Reviews in Organic Chemistry, 19(6), 695-707. https://doi.org/10.2174/1570193X19666220311113425

Zhang, Z.-X., & Willis, M. C. (2022). Sulfondiimidamides as new functional groups for synthetic and medicinal chemistry. Chem, 8(4), 1137-1146. https://doi.org/10.1016/j.chempr.2022.01.015