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Molecular Docking, Synthesis and Antibacterial activity of sulphdiazine drug modification and studying their PC3 by MTT

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Abstract: In this study, we report a novel imine-amoxicillin synthesis (A1-A3) by reacts Sulfadiazine with different aldehydes such as 2-bromobenzaldehyde, 4-propoxybenzaldehyde, and 4-butoxybenzaldehyde. The derivatives (A1-A3) were characterized by spectroscopic technique, such as FT-IR and ^{1}H-NMR spectroscopy. All the synthesized derivatives were evaluated *in vitro* against different microorganisms such as *Bacillus subtilis, Streptococcus pneumonia, E. coli*, and *Bacillus subtilis* by zone inhibition method. The findings demonstrated that certain derivatives exhibit superior antibacterial properties in comparison to the efficacy of the original drug. The evaluation of derivative 1 as anticancer (breast cancer) by MTT assay and give a positive result after 24 h more than 48 h.

Keywords: Imine, Sulfadiazine, Schiff base, Drug.

Introduction

Over the past few decades, there has been an increase of drug-resistant human pathogenic microorganisms [1]. This can be attributed to the overuse and broad use of antimicrobial medicines, as well as erroneous diagnosis. Some of the drug-resistant microorganisms include methicillin-resistant Staphylococcus aureus, vancomycin-resistant Enterococci, and azole-resistant Candida species [2]. The management of these infections is a significant obstacle, particularly in patients with weakened immune systems. To address this issue, it is imperative to explore novel and potent antimicrobial medicines. There are two basic techniques to achieve this: discovering an entirely novel antimicrobial pharmacophore and altering the structure of a well-known antimicrobial drug [3].

Drugs that include sulphur are often displayed. Sulfur-containing scaffolds are present in a wide variety of natural products and medicines [4], playing important functions and exhibiting various biological effects [5, 6]. For many years, sulphur has maintained its status as a small, ring-shaped atom that has been able to surpass 362 FDA-approved medications that contain sulphur, oxygen, or nitrogen [7]. This is achieved through the use of sulfonamide, sulfones, and compounds that have C-S bonds. The discussion will present recent advancements. Sulfonamides, also known as sulfanilamide's, are a significant group of manufactured antimicrobial medications that are widely used in pharmacology to treat a wide range of bacterial illnesses in both humans and animals [8].

Sulfadiazine, a sulfonamide medication, eradicates germs responsible for infections, particularly those affecting the urinary system. Antibiotics are ineffective against colds, flu, and other viral infections [9].

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Sulfadiazine is a type of antibiotic known as a sulfonamide. Sulfonamides are artificial bacteriostatic antibiotics that have a broad range of effectiveness against most gram-positive and many gram-negative microorganisms. Nevertheless, numerous variations of a particular species can exhibit resistance [10-12]. Sulfonamides hinder bacterial reproduction by functioning as competitive inhibitors of p-aminobenzoic acid in the folic acid metabolic pathway. The bacterial susceptibility is uniform across different sulfonamides, and resistance to one sulfonamide implies resistance to all. Oral absorption of most sulfonamides is efficient [13]. Parenteral delivery is challenging due to the high alkalinity and tissue irritation caused by soluble sulfonamide salts. Sulfonamides exhibit extensive distribution in all tissues [14]. Elevated concentrations are attained in pleural, peritoneal, synovial, and ocular fluids. While these medications are no longer employed for the treatment of meningitis, cerebrospinal fluid (CSF) levels are elevated in cases of meningeal infections. Pus hinders the antimicrobial activity [15].

In this study, we synthesis a new imine derivative via reaction sulfonamides with different aldehydes and characterize by FTIR and 1H-NMR. Finally, tested the biological activity of these derivatives and evaluation the anticancer activity by MTT assay.

Materials and Methods

Materials: All chemicals that used in this study from sigma Aldrich company for chemical materials.

Methods

Synthesis of imine- sulphdiazine derivatives (A1-A3)

Dissolve (0. 441 g, 1.0 mmol) of sulphdiazine in 20 ml of ethanol. Added 1.0 mole of corresponding aldehydes, such as 2-bromobenzaldehyde, 4-propoxybenzaldehyde, and 4-butoxybenzaldehyde to this solution. The resulting mixture was reflux for 4 h. The precipitates collected, and washed several times with absolute ethanol, dried under vacuum and kept [16, 17].

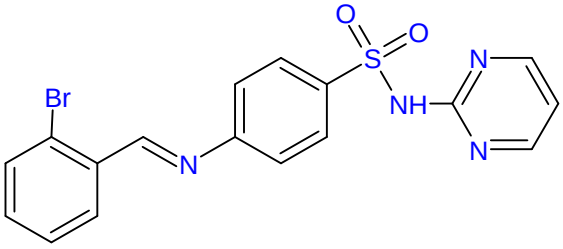
Investigation of the antimicrobial activity of Imine- sulphdiazine derivatives (A1-A3).

The several bacterial strains, including *Bacillus subtilis, Streptococcus pneumonia, E. coli,* and *Bacillus subtilis,* 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- sulphdiazine compounds (A1 – A3) was supplied to each well, resulting in efficient absorption. The container was sealed tightly and placed in an incubator set at a temperature of 37 ºC for the duration of the night, with the intention of examining it the following day [18].

Results and Discussion

The spectroscopic result, the appeared azomethine group in FTIR and disappeared amine group of amoxicillin drug and appeared proton of azomethine group of imine- sulphdiazine at 1HNMR.

Imine derivative (A1): Molecular Formula: $C_{21}H_{22}N_4O_3S$, Color: Dark yellow powder, M.p.: 188-190 °C, Yield: 79%. FTIR (cm^{-1}): 3042 (C-H aromatic), 1651 (C=N), 1590 (C=C aromatic), 3339 (N-H). 1H-NMR (ppm): 8.73 (s, 1H, N=CH), 7.17-8.57 (m, 8H, Ar) [19] [20].



Imine derivative (A2): Molecular Formula: $C_{17}H_{13}BrN_4O_2S$, Color: yellow powder, M.p.: 162-165 °C, Yield: 71%. FTIR (cm^{-1}): 3086 (C-H aromatic), 1652 (C=N), 1593 (C=C aromatic), 3340 (N-H).

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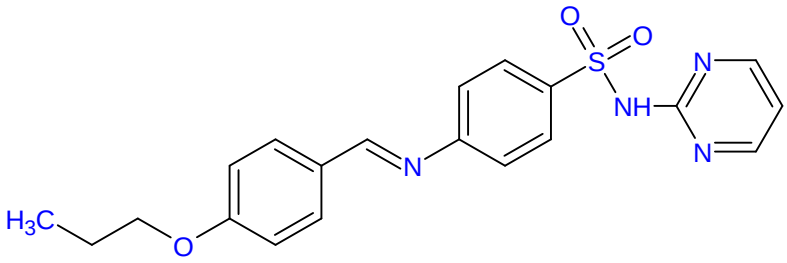
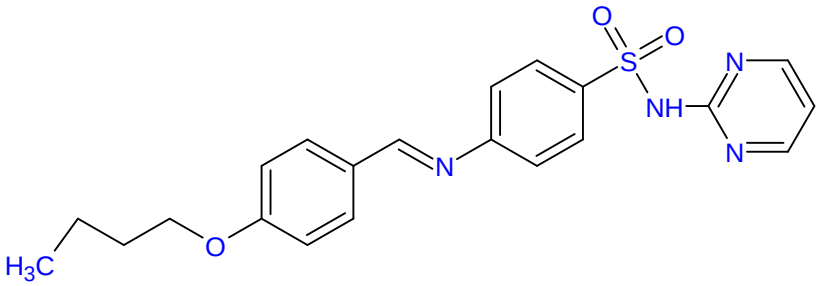
1H-NMR (ppm): 8.81 (s, 1H, N=CH), 6.97-8.07 (m, 11H, Ar), 3.66 (t, 2H, OCH_2), 1.31-1.72 (m, 5H, CH_2 and CH_3) [19, 21].



Imine derivative (A3): Molecular Formula: $C_{21}H_{22}N_4O_3S$, Color: yellow powder, M.p.: 173-175 °C, Yield: 76%. FTIR (cm^{-1}): 3071 (C-H aromatic), 1633 (C=N), 1590 (C=C aromatic). 1H-NMR (ppm): 8.81 (s, 1H, N=CH), 7.17-8.04 (m, 11H, Ar), 3.99 (t, 2H, OCH_2), 0.96-1.77 (m, 7H, CH_2 and CH_3) [22].



Bioactivity: Table 1 shows the results of a screening process conducted on a new set of imine-amoxicillin compounds (A1-A3) to determine their antimicrobial or antibacterial capabilities in a laboratory setting. After examining the inhibitory zone data for *Bacillus subtilis, Streptococcus pneumoniae*, *E. coli*, and *Bacillus subtilis*, it is clear that most of the new Imine-amoxicillin combination showed better antibacterial effectiveness than the original amoxicillin molecule. There is a direct relationship between the concentration and the level of bioactivity. Derivative A1 had the most significant impact on *Streptococcus pneumonia* bacteria [23]. Derivative A2 had the least impact on *E. coli* bacteria, as indicated in table 1.

Table 1: This study investigates the antibacterial properties of imine - sulphdiazine derivatives (A1-A3).

Derivative	Zone inhibition (mm)			
	E. coli	*Bacillus subtilis*	*Bacillus subtilis*	*Streptococcus pneumonia*
A1	13	15	11	17
A2	9	12	15	16
A3	16	13	13	12

The biggest effect on Fungal was on *Aspergillus nigaer* by derivative A. The derivative A more biological activity from amoxicillin drug which that more activity from derivative C, as shown in table 2.

Table 2: The present study investigates the antifungal properties of imine-sulphdiazine derivative (A1-A3).

Derivative	Zone inhibition (mm)

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	Candida	*Aspergillus nigaer*
A1	19	24
A3	15	18

Sulfadiazine functions as a competitive inhibitor of the bacterial enzyme dihydropteroate synthase. This enzyme is necessary for the accurate processing of para-aminobenzoic acid (PABA), which is vital for the synthesis of folic acid. The restrained response is essential in these organisms for the production of folic acid [24].

The effect of derivative (A1) analyzed as shown in figure 7, after 48 h, increase concentration (PPM), decrease breast cancer viability % more than 24 h. All result that obtained shown in table 3. However, it is important to acknowledge that the impacts of sulfadiazine can vary depending on the individual cellular types involved. In cancer cells, sulfadiazine has been observed to cause oxidative stress, as evidenced by the rise in MDA levels [25]. This may potentially trigger the onset of apoptosis in cancer cells. On the other hand, in regular cells (THLE2), sulfadiazine seems to decrease MDA levels while enhancing the function of antioxidant enzymes, suggesting that it can effectively remove harmful free radicals in these cells [26].

Table 3: The IC50 rates of derivative (A1) induced breast cancer cell.

Concentration (PPM)	After 24 h		After 48 h	
	Mean	SD	Mean	SD
0	100	2.322349	100	3.932492
20	78.7895	2.241244	41.9806	3.089231
40	56.7513	3.986991	25.0377	2.342935
80	36.8906	3.170353	12.1439	1.029182
160	16.5532	2.963243	8.9348	1.868221
320	6.8795	2.656903	2.2401	0.338213

S (Kcal/mol)	**RMSD (Å)**
-5.6656	**1.3911**

Ligand Interactions Report

Fri Apr 12 21:41:08 2024 (MOE 2015.10)

5NQI: RNA / 5NQI

Ligand	Receptor			Interaction	Distance	E (kcal/mol)
N 24	N3	A	2670 (A)	H-donor	3.13	-3.2
6-ring	C1'	C	2649 (A)	pi-H	4.49	-0.6
6-ring	O2'	5HM	2651 (A)	pi-H	3.42	-2.1

Interactions

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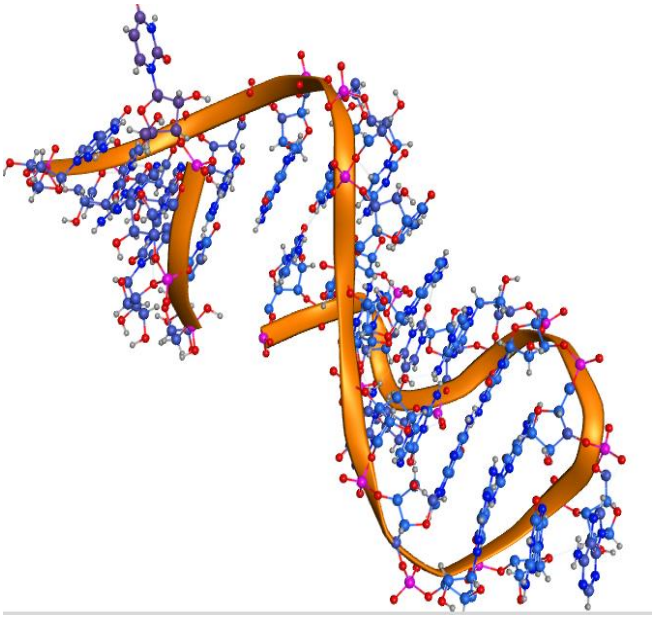
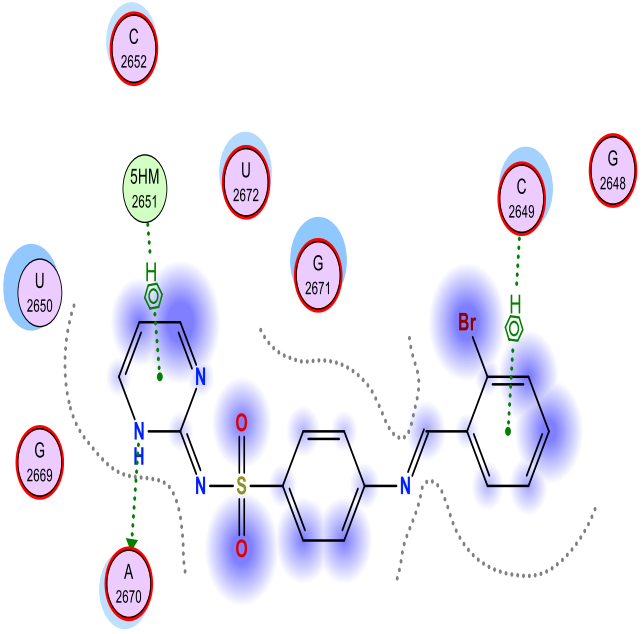
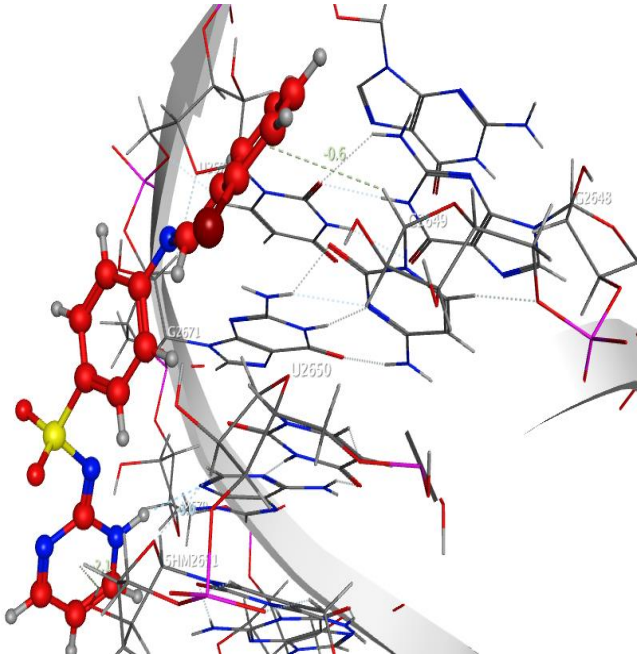


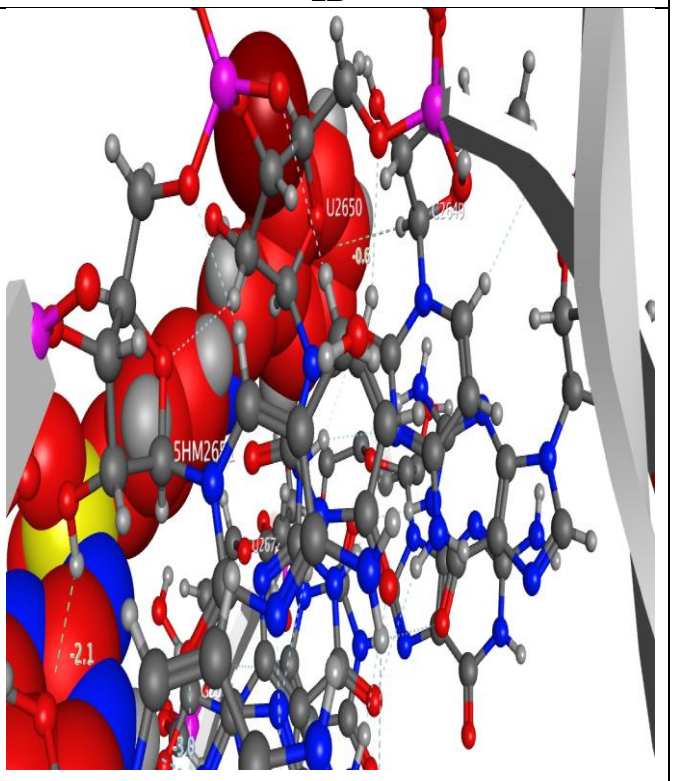
Protein ID (5NQI)



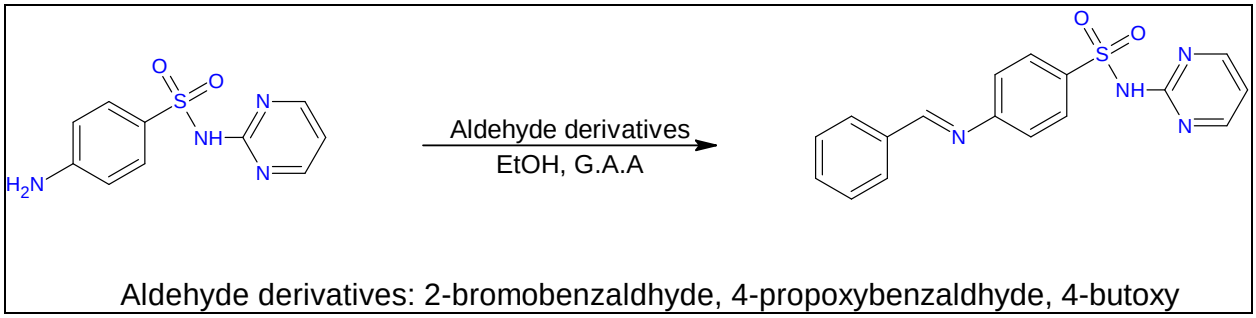
2D



3D



Map



Aldehyde derivatives: 2-bromobenzaldhyde, 4-propoxybenzaldhyde, 4-butoxy

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Scheme 1: Routs of imine- sulphdiazine derivatives (A1-A3).

Conclusion

Imine derivative derivatives (A1-A3) were synthesized and characterized by FTIR and 1H-NMR. Chemical reactions between sulphdiazine drug and aldehyde derivatives began the synthesis. The antimicrobial activity of imine derivatives, against *Staphylococcus epidermidis*, *Pseudomonas aeruginosa*, and *Escherichia coli* were tested *in vitro*. The findings demonstrated that certain derivatives exhibit superior antibacterial properties in comparison to the efficacy of the original drug. In future, we will synthesize a new derivative and tested *in vitro*. The evaluation of derivative 1 as anticancer (breast cancer) by MTT assay and give a positive result.

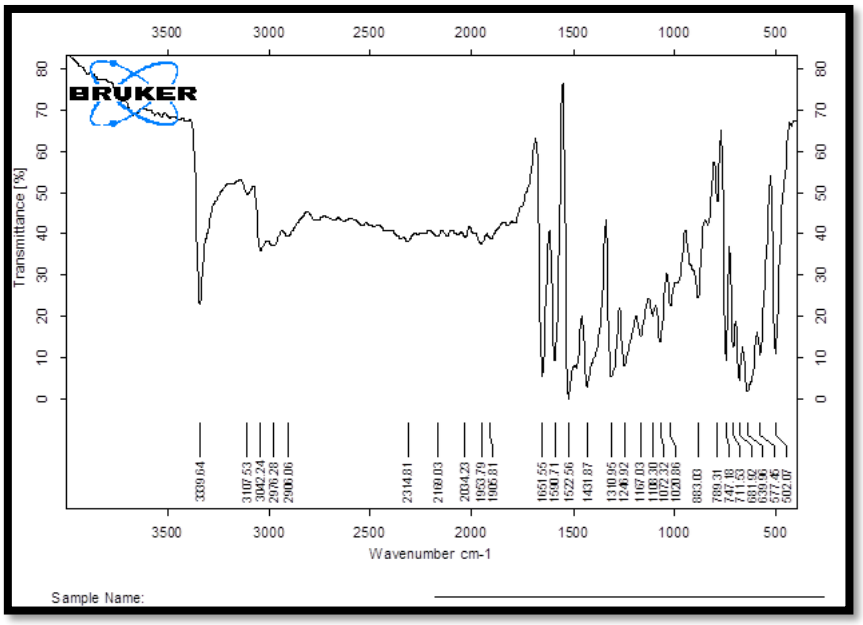

Figure 1: FTIR of derivative A1.

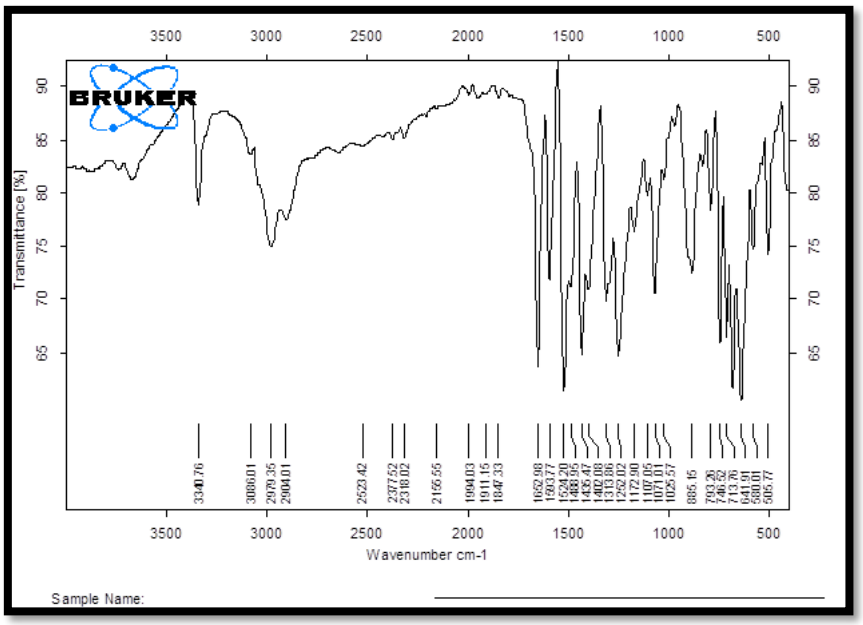

Figure 2: FTIR of derivative A2.

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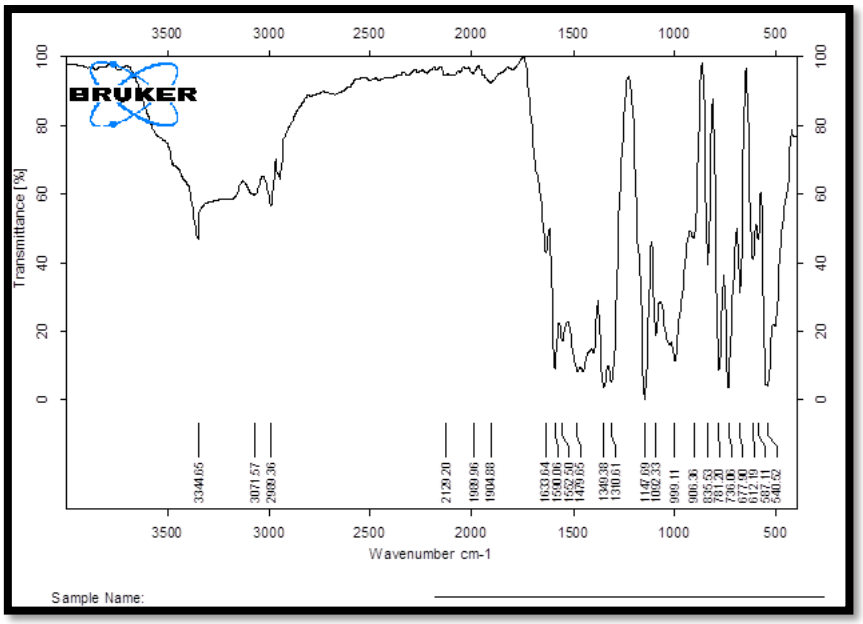

Figure 3: FTIR of derivative A3.

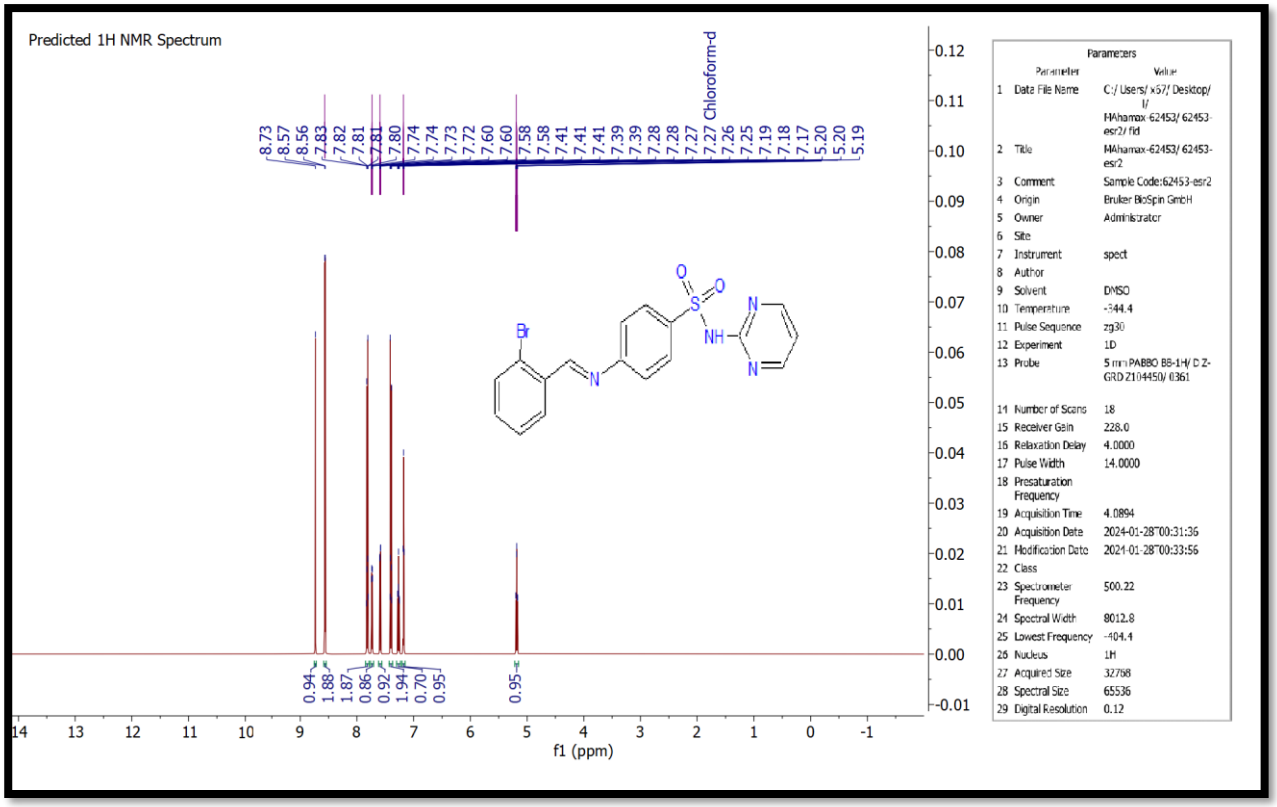

Figure 4: 1HNMR of derivative A1.

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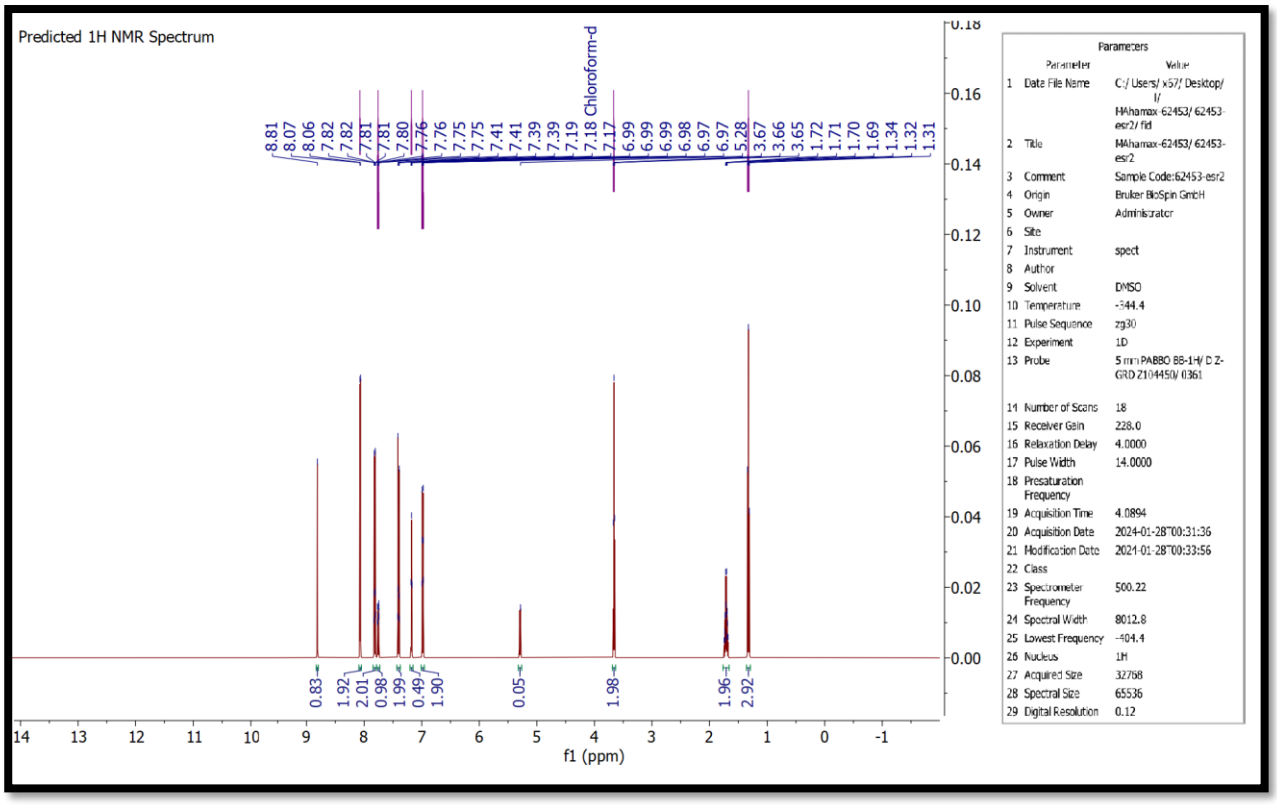

Figure 5: 1HNMR of derivative A2.

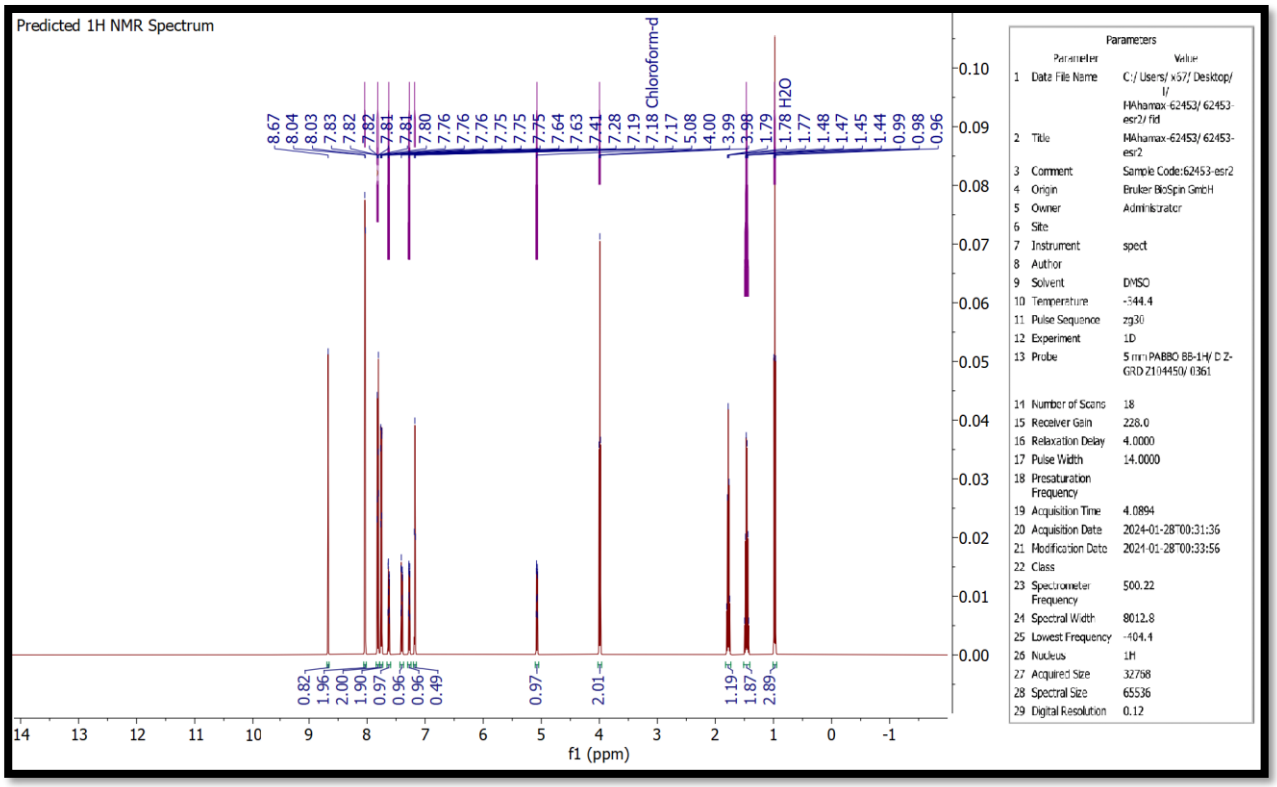

Figure 6: 1HNMR of derivative A3.

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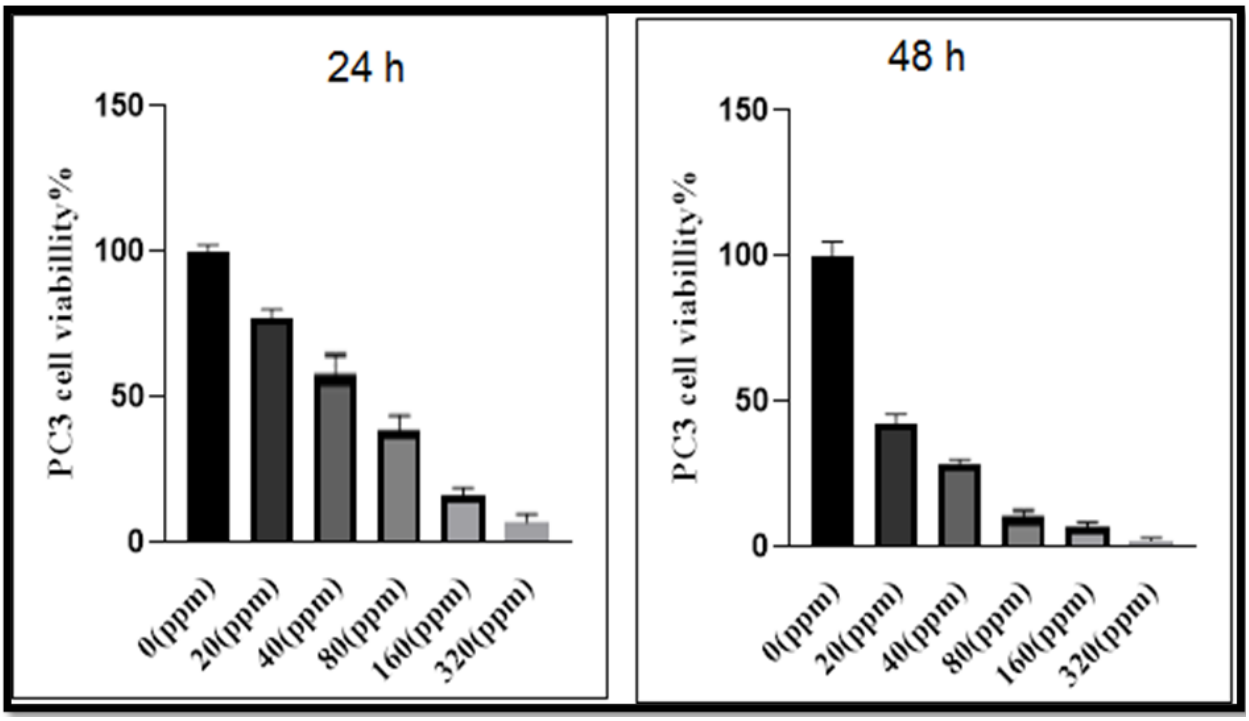

Figure 7: Effect of derivative (A) on breast cancer cell viability.

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