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FULL PAPER

Synthesis and characterization of some new heterocyclic compounds (hydroqinazoline and thiazinone) prepared from Schiff bases derived from flucytosine drug and study of biological activity

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A series of some new heterocyclic six–membered compounds has been synthesized from Flucytosine drug, containing a terminal primary amine group, and was used to prepare a number of new Schiff base compounds bearing the numbers (A1-A4) through interaction with different aldehydes and ketones and using ethanol absolute as a solvent. After that, it was possible to prepare several organic compounds using Schiff bases (A1-A4) prepared in the first step, which contain azomethine group react with (2-aminobenzoic acid and 2-mercaptobenzoic acid) to prepare hydroqinazoline (A5-A8) and thiazinone derivatives (A9-A12). These reactions are followed by TLC and the measurement of melting points for the derivatives. These compounds were determined by FT-IR and by ^{1}H-NMR and ^{13}C-NMR spectra, along with studying the biological activity of the prepared derivatives.

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KEYWORDS

Flucytosine; Schiff bases; hydroqinazoline; thiazinone; biological activity.

Introduction

The current crop of antifungal medications is highly diverse concerning their spectrums of action, potencies, therapeutic indices, rates of resistance evolution, and recommended administration routes [1]. For its use in chemotherapy against cancer, the fluorinated pyrimidine flucytosine (Figure 1) was initially created as an antimetabolic drug and the drug's antimicrobial effects are broad-ranging [2].

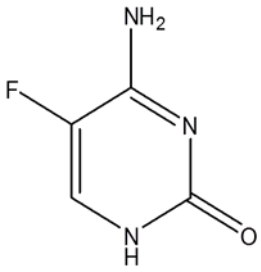


FIGURE 1 Synthetic formula of Flucytosine

It has been shown that the presence of the azomethine molecule is essential for bioactivity. Examples include the potential antibacterial, anti-tubercular, antifungal, anti-parasitic, antiviral, antioxidant, and anticancer effects of Schiff bases of both natural and synthetic origins [3,4].

Several variations of this medication have been developed because of its usefulness:

The typical formula for imines in Schiff compounds [5] is (R1R2C=NR3), where R1, R2, and R3 can be any of the following: alkyl, aryl, cyclo alkyl, or heterocyclic groups (referenced as "R1," "R2," and "R3" in the subsequent text) [6]. Hugo Schiff, a German scientist, created the first Schiff bases [7], in 1864, by condensing the amino group of primary amines and amino acids with the carbonyl group of aldehydes or ketones. This process resulted in the formation of the Schiff bases. These compounds, called heterocyclic compounds, each contain one nitrogen atom, one sulphur atom, and four carbon atoms in different locations along a six-member ring [8-10]. However, (N-C-S)-linked derivatives of these compounds have been used in pharmaceutical chemistry and medicine, and it has been shown that these derivatives display a wide range of biological activities, including antitubercular [11], antimicrobial [12], fungicidal [13], and anti-inflammatory effects. These derivatives have been shown to display these biological activities [14].

In addition, anti-inflammatory [15], antibiotic, antipyretic, anti-hypertonic, and diuretic activities are some pharmacological and medical effects displayed by the quinazoline derivatives that make up a significant family of fused heterocycles. These derivatives of quinazoline are also known as quinazolinones [16].

These unique chemicals were produced by reacting Schiff base derivatives with anhydride, 2-mercapto benzoic acid, and 2-amino benzoic acid. Ultimately, this process resulted in the production of all of these chemicals.

Experimental

After they have been obtained from commercial providers, reagents and reactants do not require any additional purification steps before being used. The cleaning of the solvents took place in preparation. To analyze the reaction route and ensure that the derivatives are pure, thin-layer chromatography was performed on silica gel-G (Merck grade) using a mixture of ethanol and benzene as the mobile phase. All of the melting points have been provided in degrees Celsius, and no adjustments have been made to them. The melting points were recorded in open capillaries using a melting point apparatus manufactured by Stuart (SMP30, England).

The derivatives' infrared (I.R.) spectra were obtained using a Shimadzu Prestige-21 Spectrophotometer with potassium bromide (KBr) pellets, and the values were represented in cm^{-1}. The ^{1}H-NMR and ^{13}C-NMR spectra were obtained using a Bruker spectrometer (Avance III, Bruker 300MHz NMR spectrophotometers with TMS as an internal standard, with values expressed in ppm).

The general method for preparing Schiff base compounds (A1-A4) [14]

Flusytosine as well as several heterocyclic aromatic aldehydes and ketones were grounded together in a mortar and pestle at 1:1. These compounds included N, N-dimethyl benzaldehyde, p-hydroxy benzaldehyde, 4-bromo benzaldehyde, p-nitro acetophenone, p-chloro acetophenone, and p-hydroxy acetophenone. Next, ethanol was added to the reaction combination, and then microwaved. Higher yields were achieved in a shorter time (12-20 min). Thin-layer chromatography was utilized to examine the reaction route and ensure the purity of the derivatives, as displayed in Scheme 1.

Preparations of hydroquinazoline derivatives (A5-A8) [15]

The Schiff bases (A1-A4) (0.01 mol) were reacted with 3 ccs of dimethylformamide (DMF) and a solution of 2-amino benzoic acid (0.01 mol) in dioxane. For 30-37 hours, this mixture was cooked in a water bath at a slow and steady boil. Thin-layer chromatography was used to check the purity of the compounds and trace the reaction's course, as depicted in Scheme 2.

Preparations of thiazinone derivatives (A9-A12) [16]

A combination of 20 mL of dry benzene and 3 mL of DMF was used to dissolve 0.01 mol of Schiff base (A1-A4) and 0.01 mol of 2-mercapto benzoic acid. Thin layer chromatography was used to check on the reaction's purity and track its progress after (a few droplets) of triethyl amine were added, and the mixture was refluxed for 30-35 hours, as demonstrated in Scheme 3.

After undergoing TLC (ethanol: benzene) (2:3), filtering, extracting, drying, and recrystallizing with pure ethanol, the desired compound was obtained.

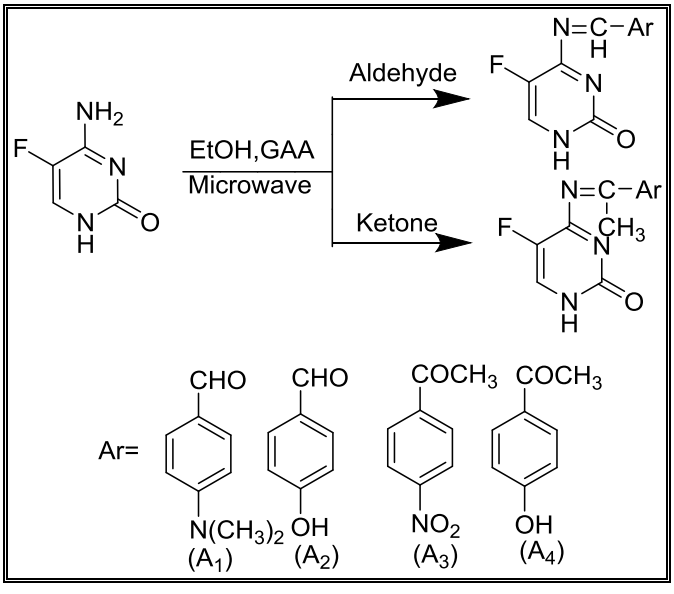
Table 1 provides the physicochemical information for the synthesized substances.

Biological activity assay [17]

The antibacterial activity of the synthesized compounds (A1-A12) has been tested using the good diffusion method on nutrient agar medium against four different types of bacteria, including gram-positive (*Staphylococcus aureus* and *Enterococcus faecalis*) and gram-negative (*E. coli* and *Klebsiella pneumonia*). All derivatives were dissolved in water at concentrations of 0.001 g to 0.01 g per 10 ml of DMSO. The findings were expressed as the minimal inhibitory concentration (MIC), demonstrating the compounds' potency against the target microorganisms (Flucytosine drug). Data from the biochemical study are presented in Table 2.

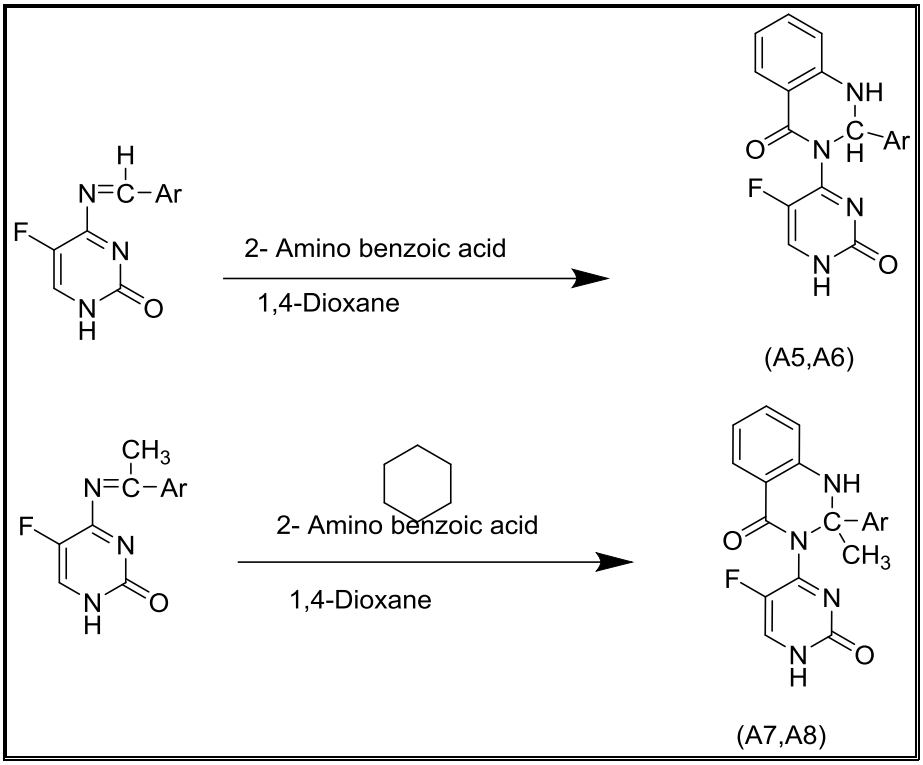
Results and discussion

Flusytosine was used to synthesize Schiff bases (A1-A4) by reacting with a wide range of substituted aromatic aldehydes and ketones in an acidic medium (glacial acetic acid) and pure ethanol (Scheme 1).



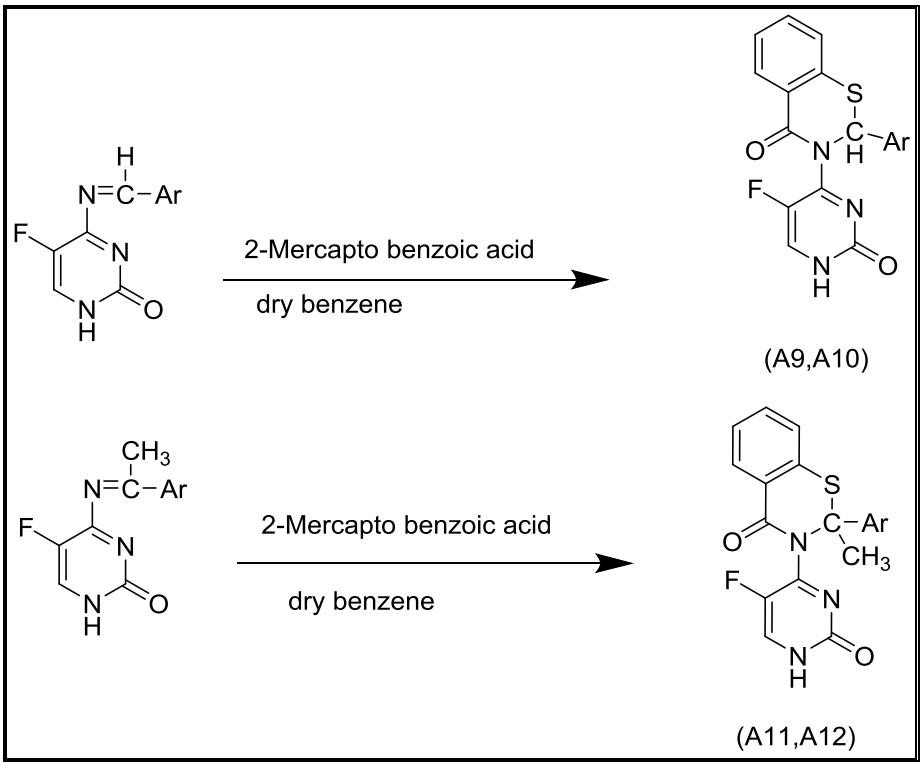
SCHEMEE 1 Preparation of new derivatives of Schiff bases from flucytosine

The second stage is to make various heterogeneous organic compounds by reacting Schiff's base compounds with 2-amino benzoic acid, as depicted in Scheme 2.



SCHEME 2 Preparation of new derivatives of hydro quinazoline from Schiff bases

Third, using Schiff's base compounds as starting materials, several heterogeneous organic compounds were made by reacting 2-mercapto benzoic acid with thiazinone(A9) through thiazinone(A12) according to Scheme 3.



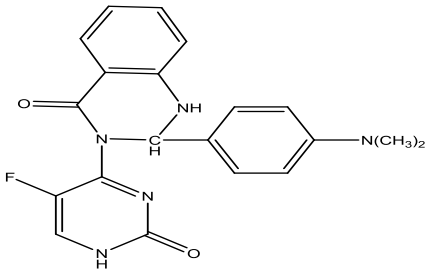
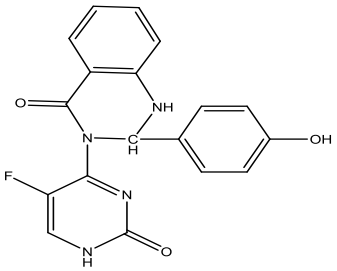
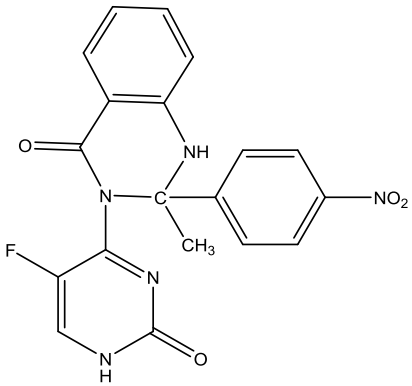
SCHEME 3 Preparation of new derivatives of thiazinone from Schiff bases

The v (NH2) group absorption band at (3400) cm^{-1} disappeared in the FTIR spectra of compounds (A1-A4) as the value of the substituted groups changed, and the (-C=N) absorption band appeared in the region (1672-1685) cm^{-1}. The remaining FTIR spectral readings (A1–A4) were done for the compounds (1-4) as in Figures 1-4.

Using FTIR spectral data, we can see that the (C=N) band disappears and the (C=O) band appears between 1658 and 1683 cm^{-1} and the (-N.H.) absorption band occurs between 3107 and 3348 cm^{-1} for molecules A5 through A8. To see the remaining FTIR spectral data for substances (A5-A8), (Figures 5, 7, 9, and 11).

For compounds (A9) through (A12), the (C=N) band disappeared, and the (C=O) amide bands at (1585–1606) cm^{-1} and the (C-S) band at (657–675) cm^{-1} emerged in the FTIR spectra. Different FTIR spectral measurements for the compounds are displayed in Figures12, 13, 15, 17, 19 and 20. Details of compounds is depicted in Table 3. The results are agreed with [18-20].

TABLE 1 Compound structures and ^{1}H-NMR Spectral data ($^{\delta}$ppm) for compounds

Compound No.	Compound Structures	^{1}H-NMR Spectral data ($^{\delta}$ppm)
A5		1.68 (S,6H,2CH_3) 7.68-7.96 (m,4H,Ar-H) 9.68 (S,C-H aldehyde) 10.52 (S,1H,NH-C-H) 10.81 (S,1H,NH C=O)
A6		7.59-7.74 (m,4H,Ar-H) 9.41 (S,C-H aldehyde) 10.08 (S,1H,NH-C-H) 10.62 (S,1H,NH C=O) 11.11 (S,1H,OH)
A7		1.96 (S,3H, CH_3) 7.18-7.26 (m,4H,Ar-H) 10.69 (S,1H,NH-C-H) 10.99 (S,1H,NH C=O)

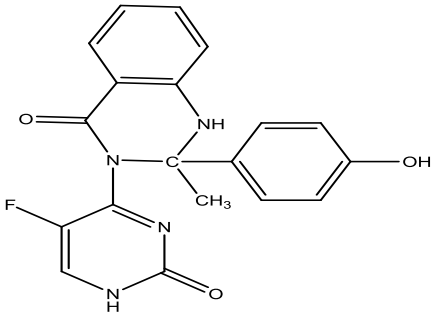
A8		1.89 (S,3H, CH_3) 7.12-7.13 (m,4H,Ar-H) 10.51 (S,1H,NH-C-H) 10.83 (S,1H,NH C=O) 11.58 (S,1H,OH)

TABLE 2 Details of compounds (A1-A12)

No.	M.F.	M.WT gm.\mol	M.P.	Rf	Color	%Yield
A1	$C_{13}H_{13}N_4OF$	260	75-77	0.50	Dark brown	79%
A2	$C_{11}H_8N_3O_2F$	233	120-122	0.52	Light brown	77%
A3	$C_{12}H_9N_4O_3F$	276	88-90	0.75	Orange	80%
A4	$C_{12}H_{10}N_3O_2F$	247	106-108	0.60	Yellow	86%
A5	$C_{20}H_{18}N_5O_4F$	379	lukewarm	0.64	Light red	72%
A6	$C_{18}H_{13}N_4O_3F$	352	lukewarm	0.67	Red	77%
A7	$C_{19}H_{14}N_5O_4F$	395	lukewarm	0.51	Dark red	80%
A8	$C_{19}H_{17}N_4O_2F$	366	lukewarm	0.48	Light red	69%
A9	$C_{20}H_{17}N_4O_2F\ S$	396	lukewarm	0.50	Dark red	61%
A10	$C_{18}H_{12}N_3O_3F\ S$	369	lukewarm	0.59	Dark red	71%
A11	$C_{19}H_{13}N_4O_4F\ S$	412	lukewarm	0.63	Red	75%
A12	$C_{19}H_{14}N_3O_3F\ S$	383	lukewarm	0.52	Dark red	64%

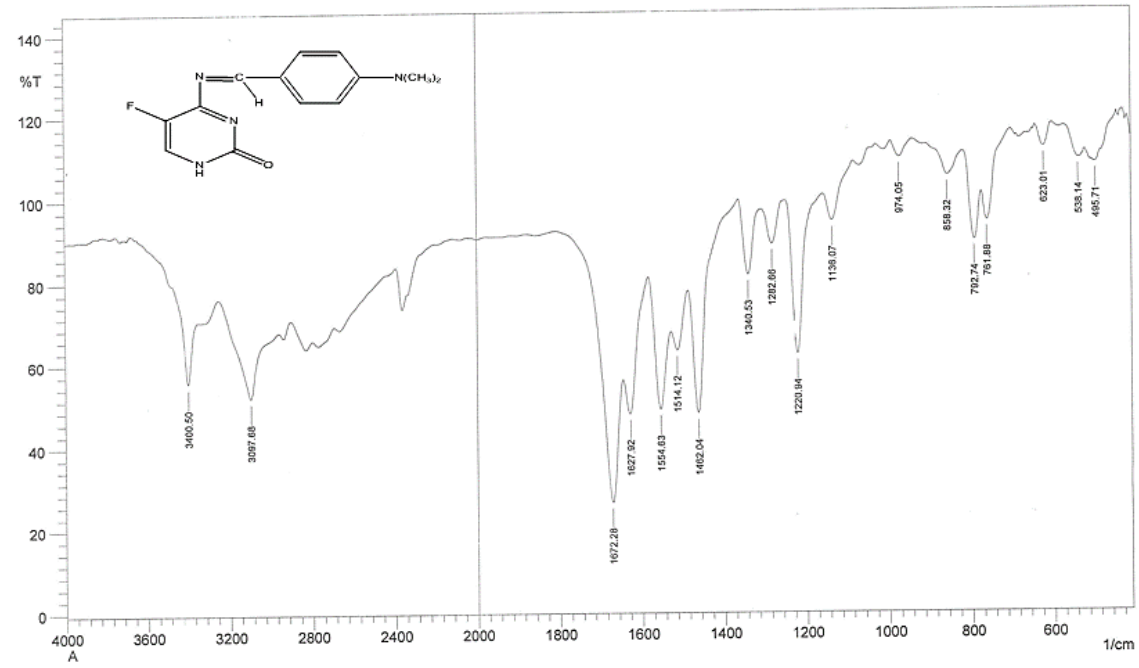


FIGURE 1 FT-IR Band of compound (1)

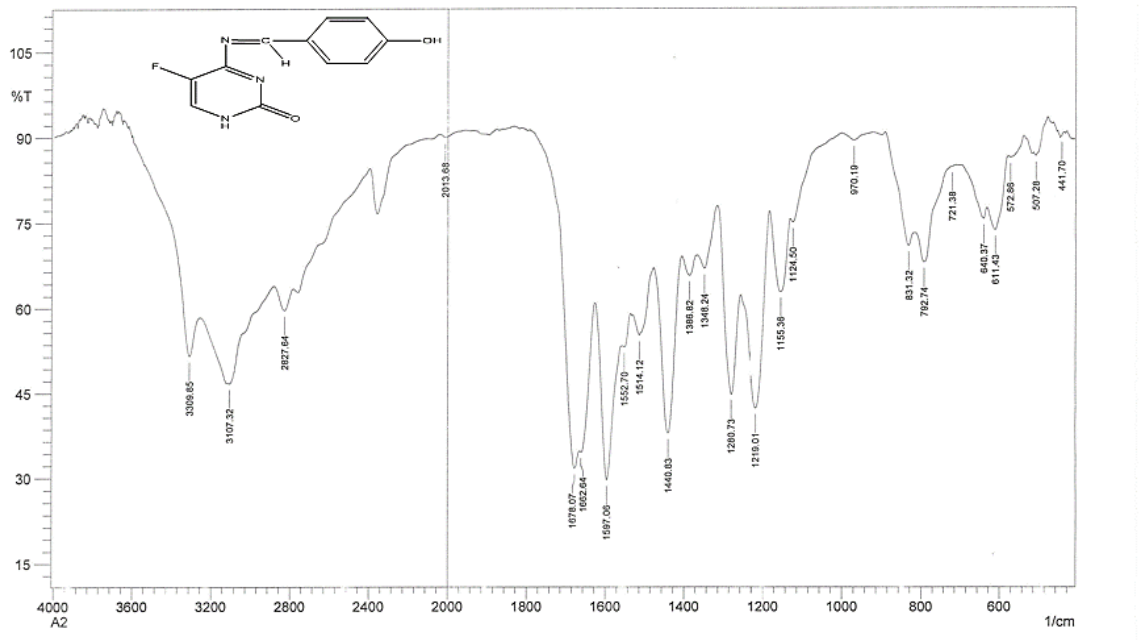


FIGURE 2 FT-IR Band of compound (2)

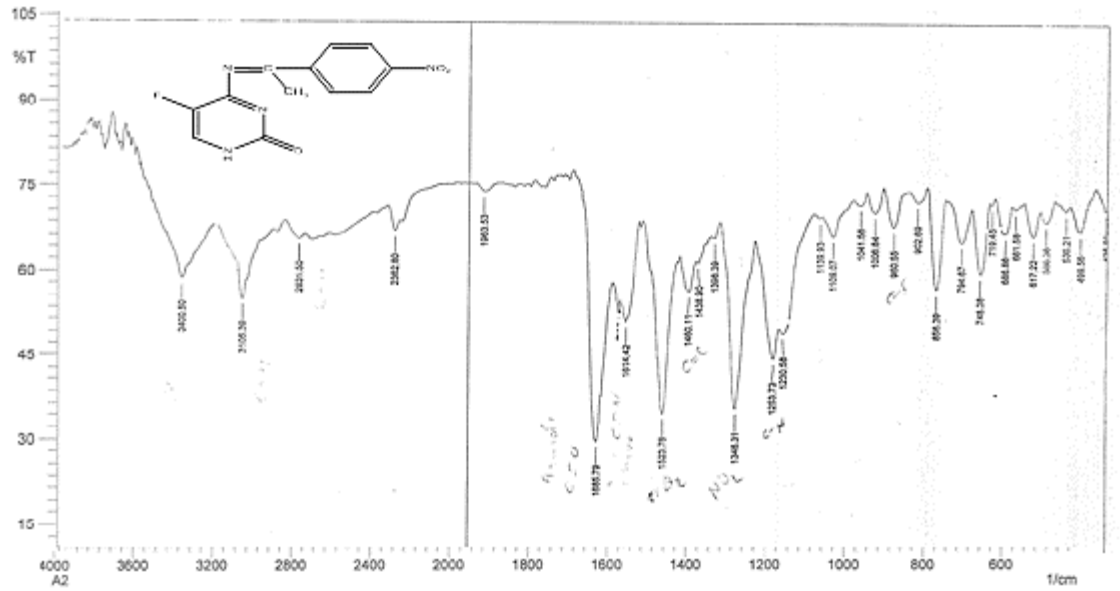


FIGURE 3 FT-IR Band of compound (3)

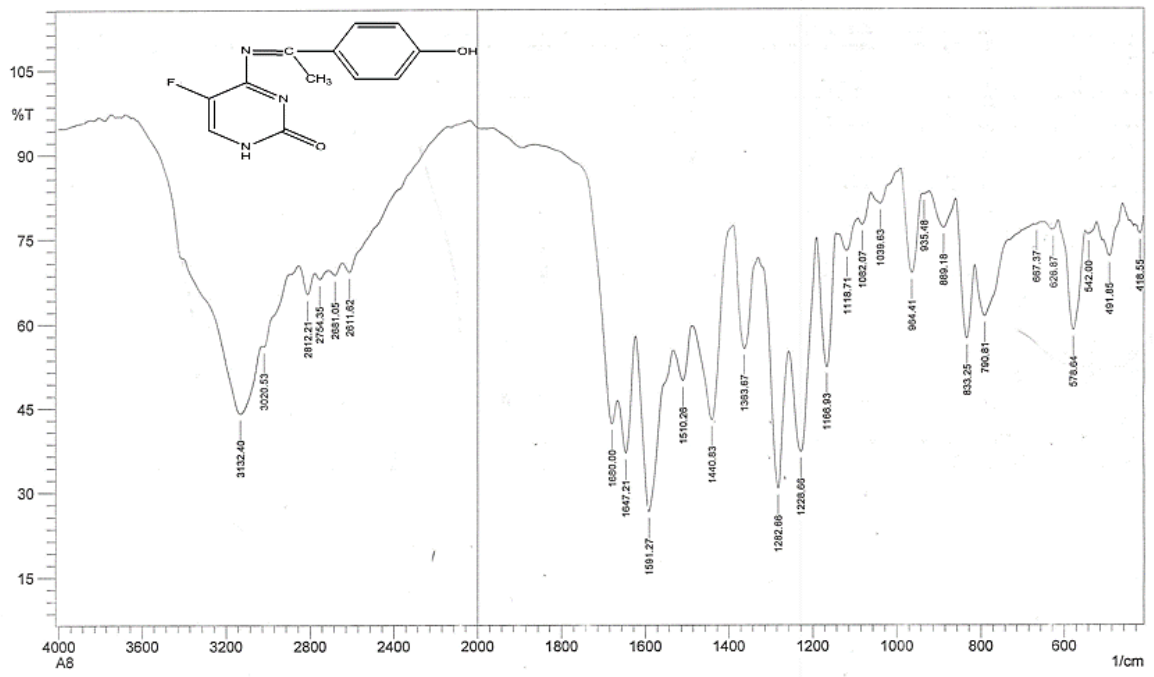


FIGURE 4 FT-IR Band of compound (4)

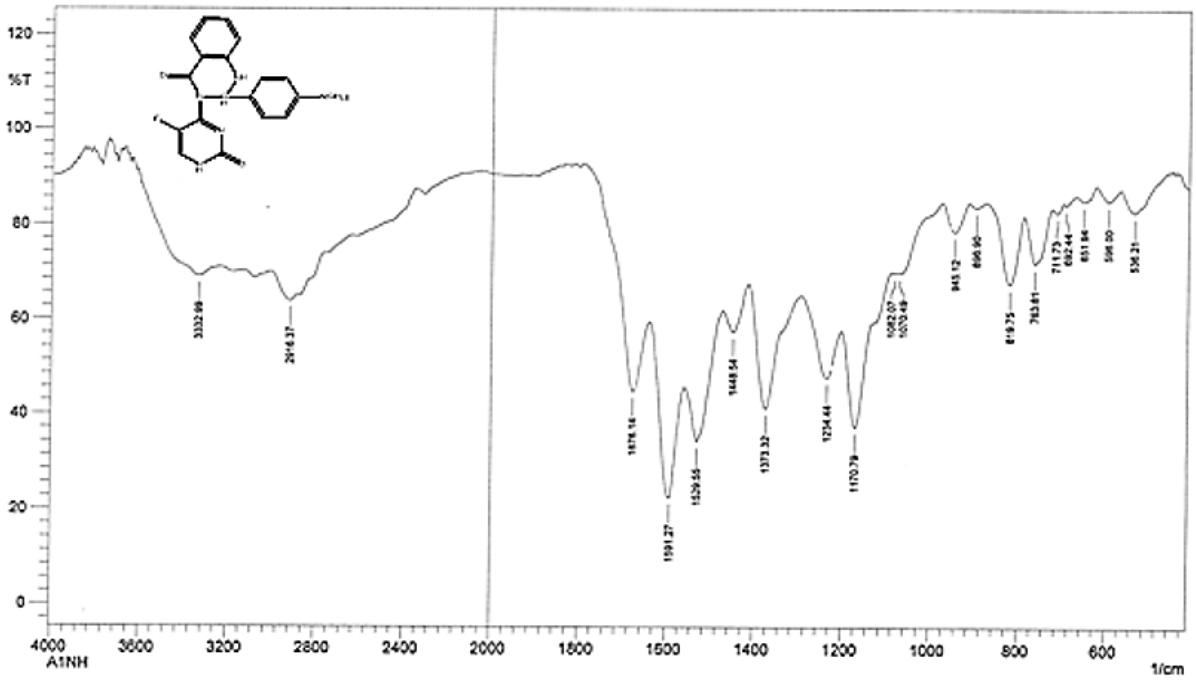


FIGURE 5 FT-IR Band of compound (5)

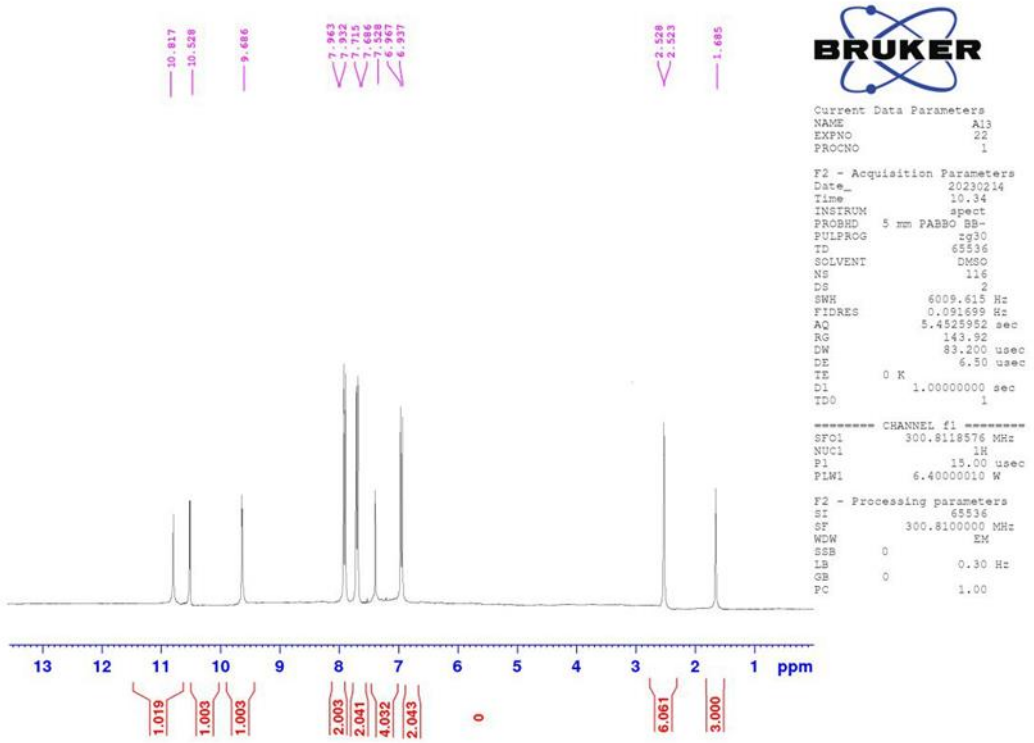


FIGURE 6 [1]HNMR band of compound (5)

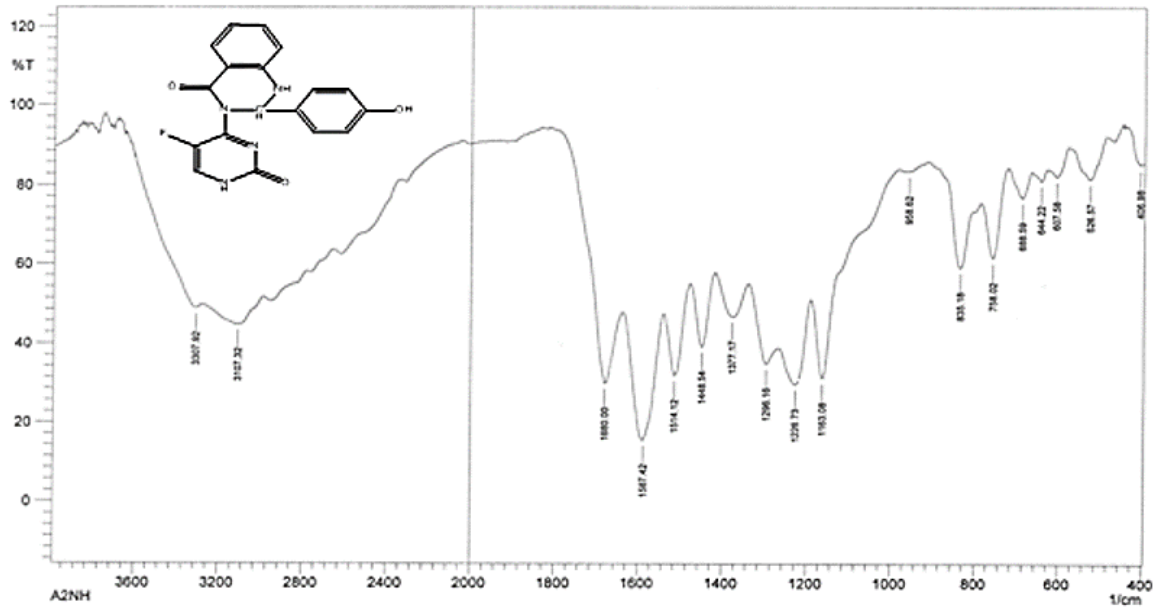


FIGURE 7 FT-IR Band of compound (6)

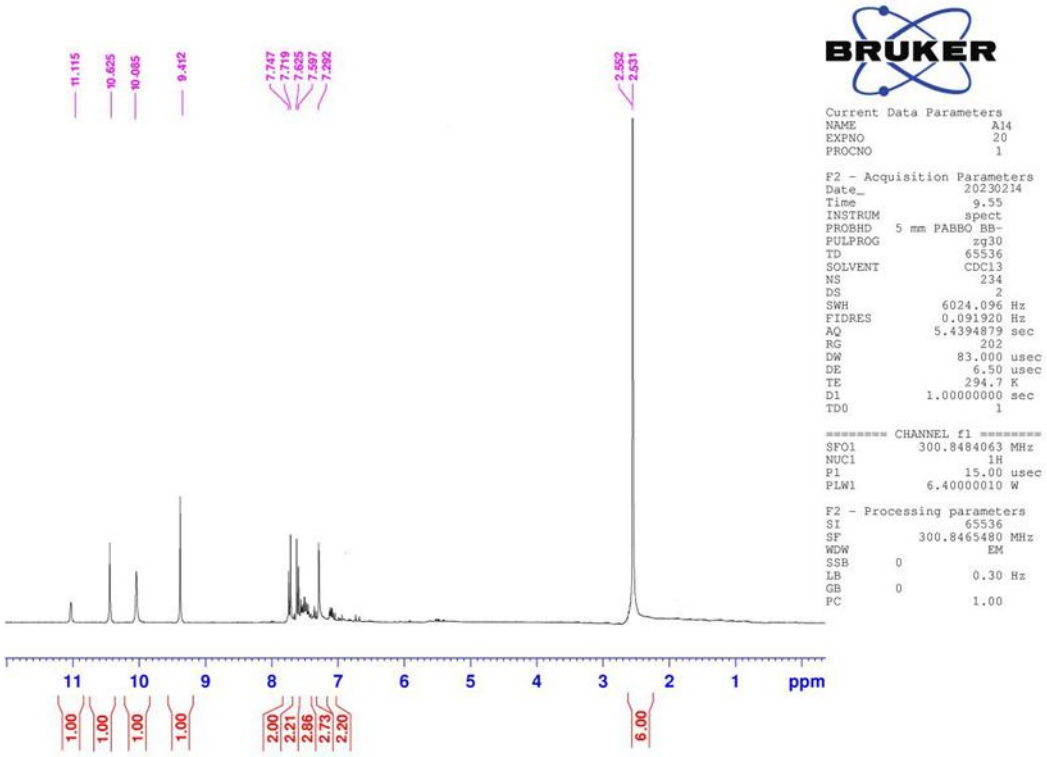


FIGURE 8 [1]HNMR band of compound (6)

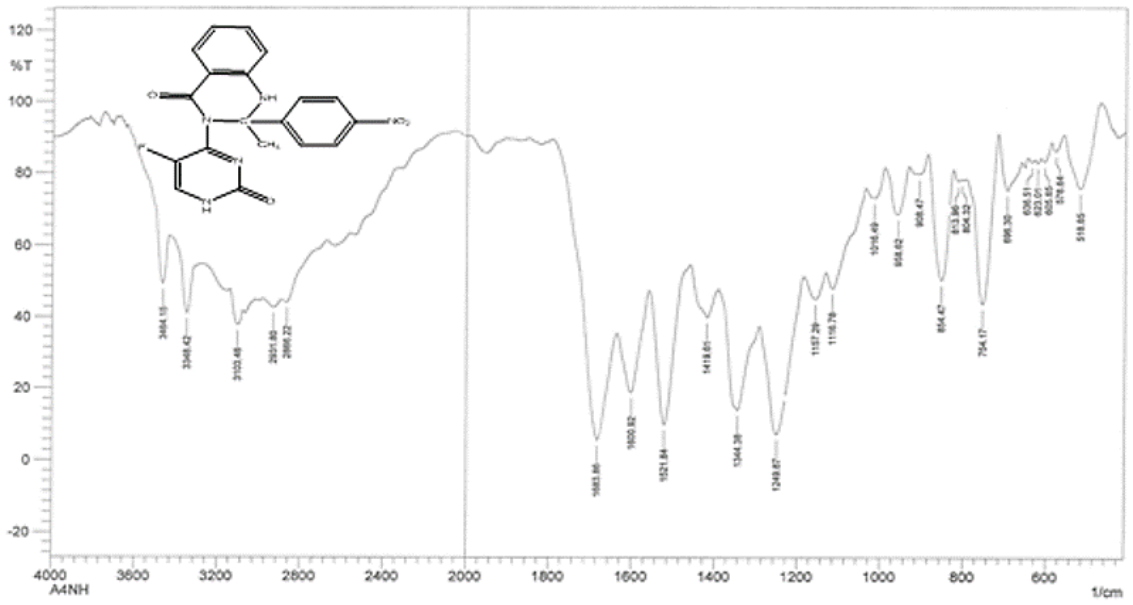


FIGURE 9 FT-IR Band of compound (7)

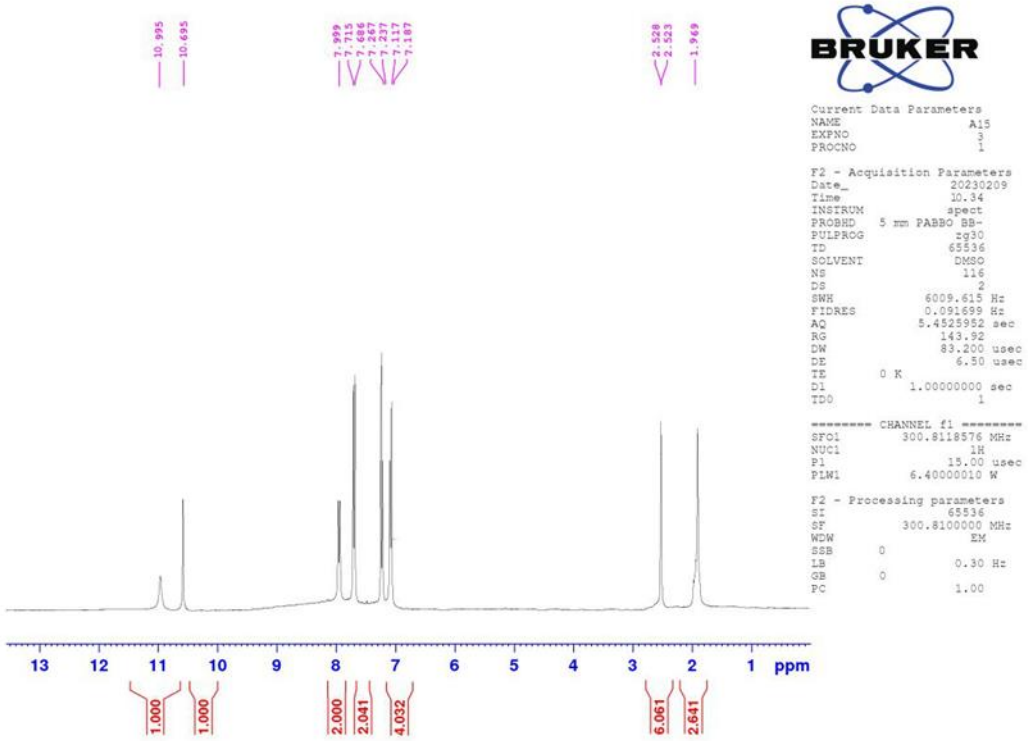


FIGURE 10 [1]HNMR band of compound (7)

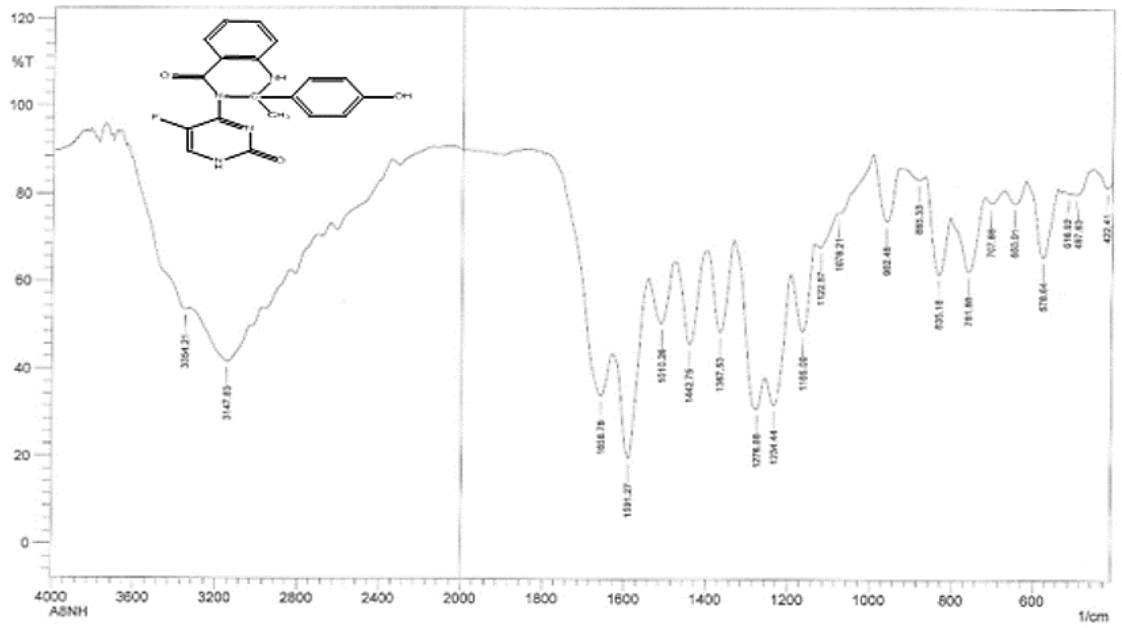


FIGURE 11 FT-IR Band of compound (8)

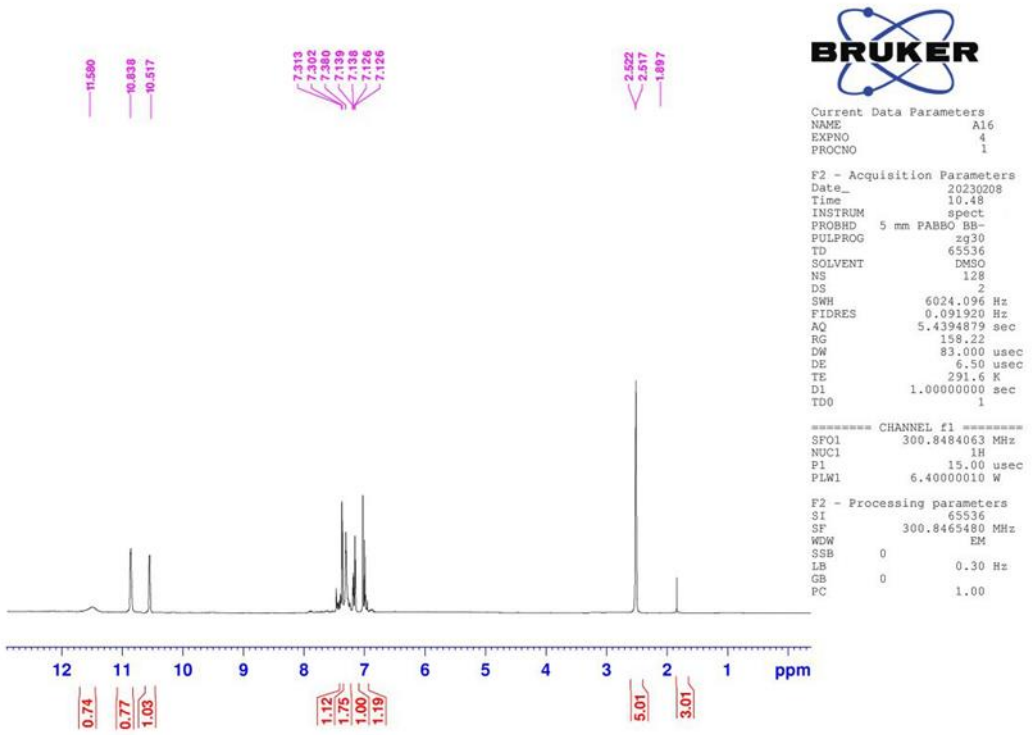


FIGURE 12 [1]HNMR band of compound (8)

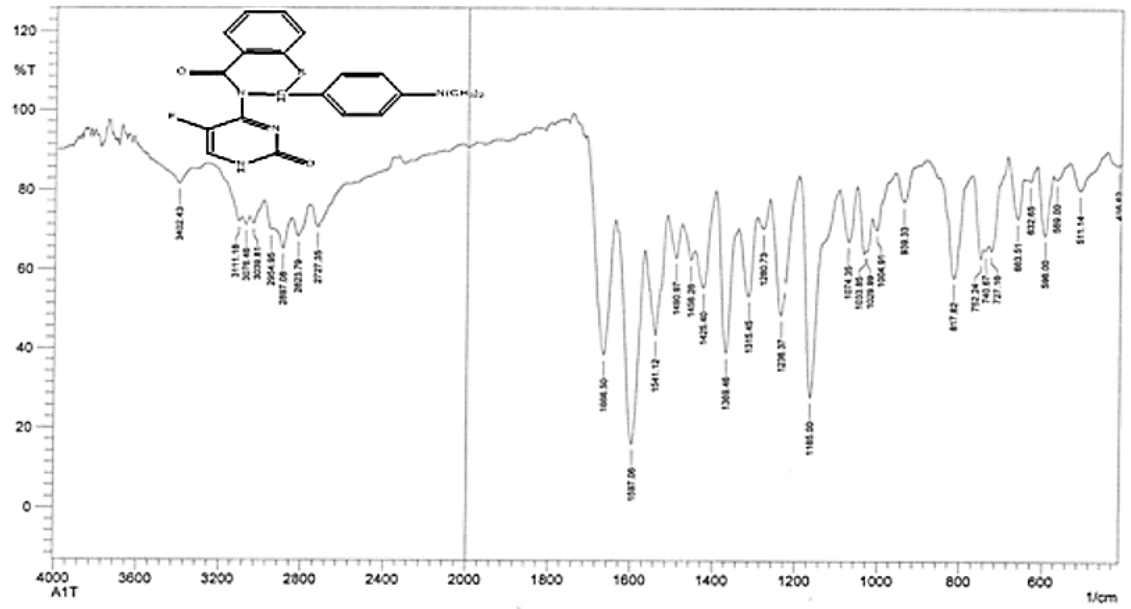


FIGURE 13 FT-IR Band of compound (9)

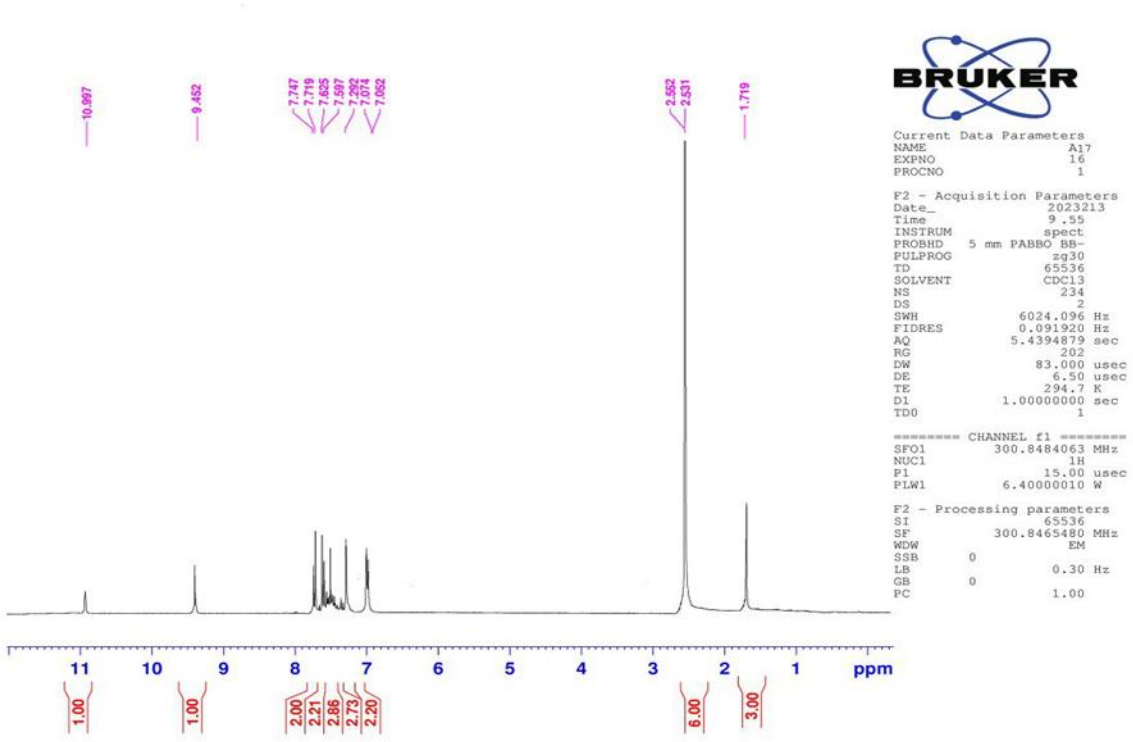


FIGURE 14 ^{1}HNMR band of compound (9)

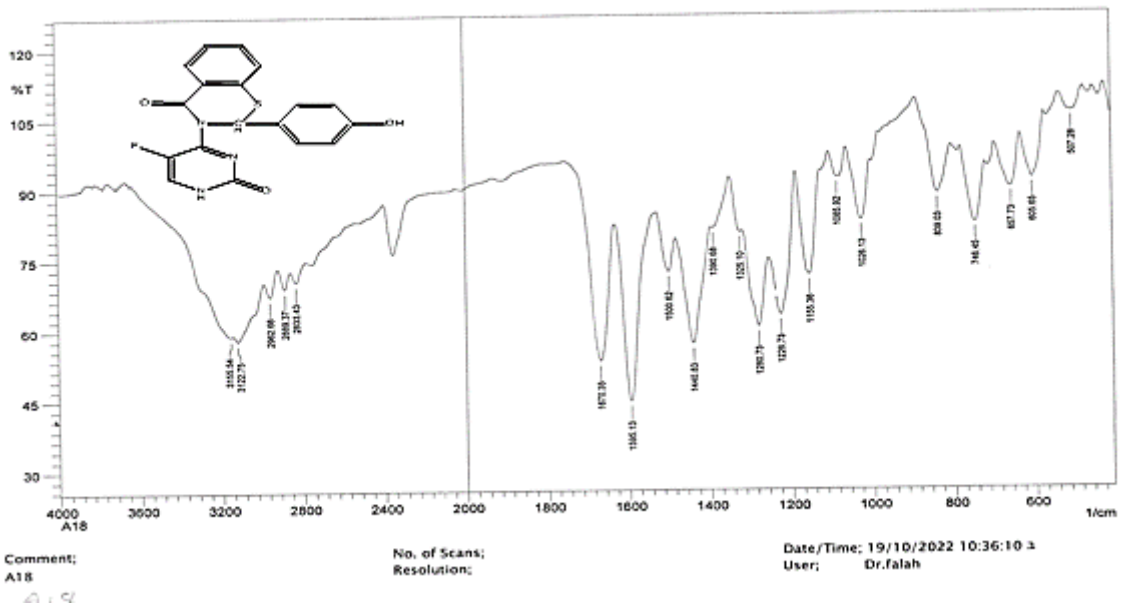


FIGURE 15 FT-IR Band of compound (10)

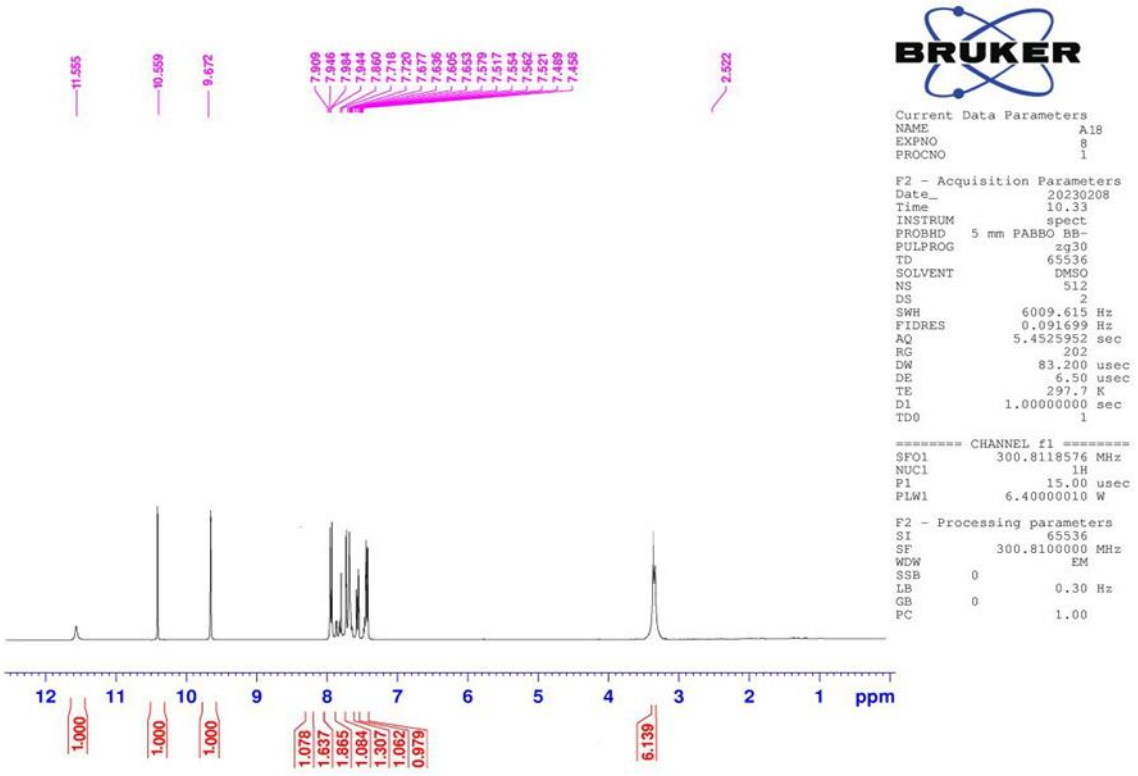


FIGURE 16 [1]HNMR band of compound (10)

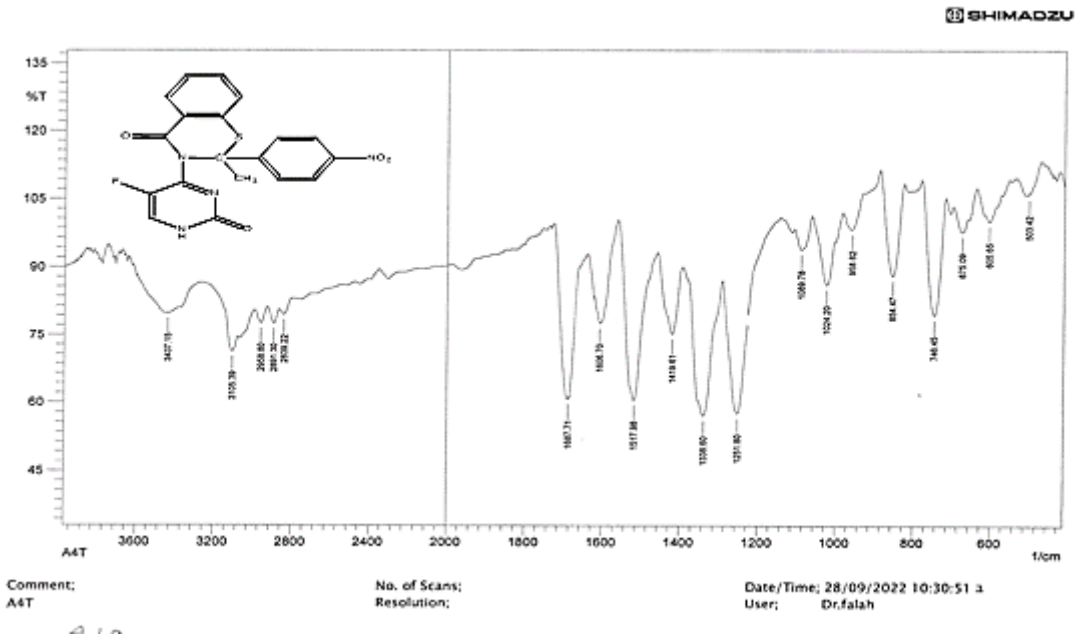


FIGURE 17 FT-IR Band of compound (11)

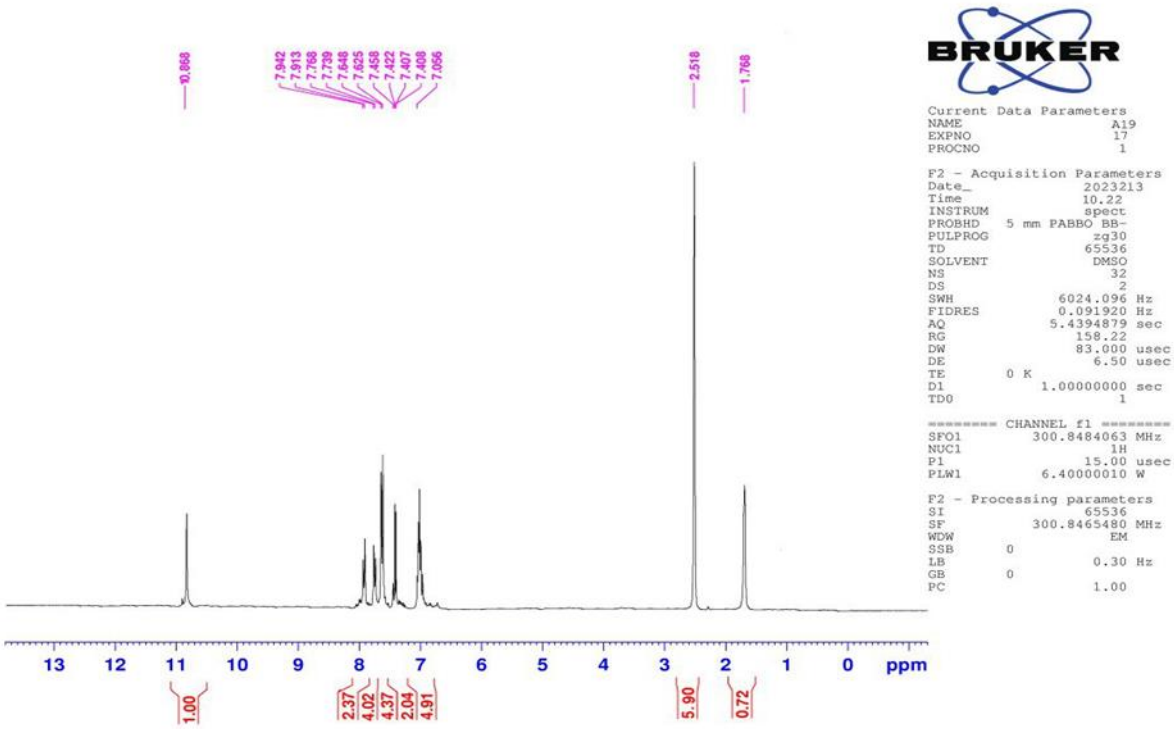


FIGURE 18 ^{1}HNMR band of compound (11)

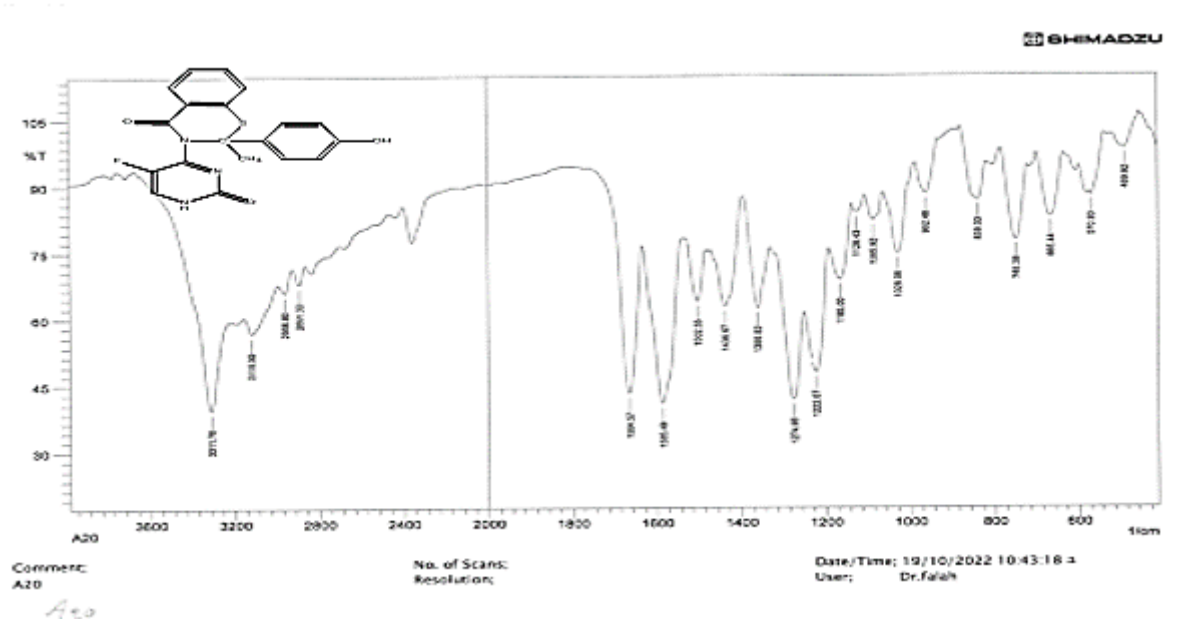


FIGURE 19 FT-IR Band of compound (12)

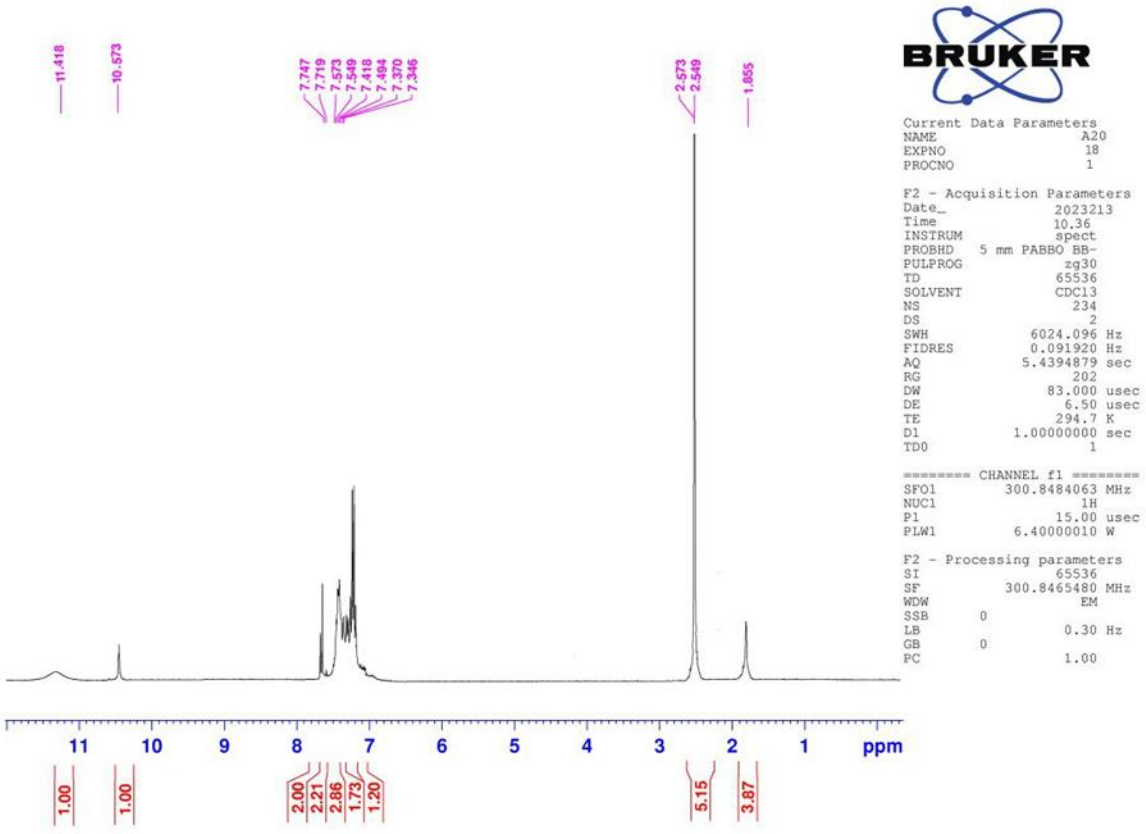
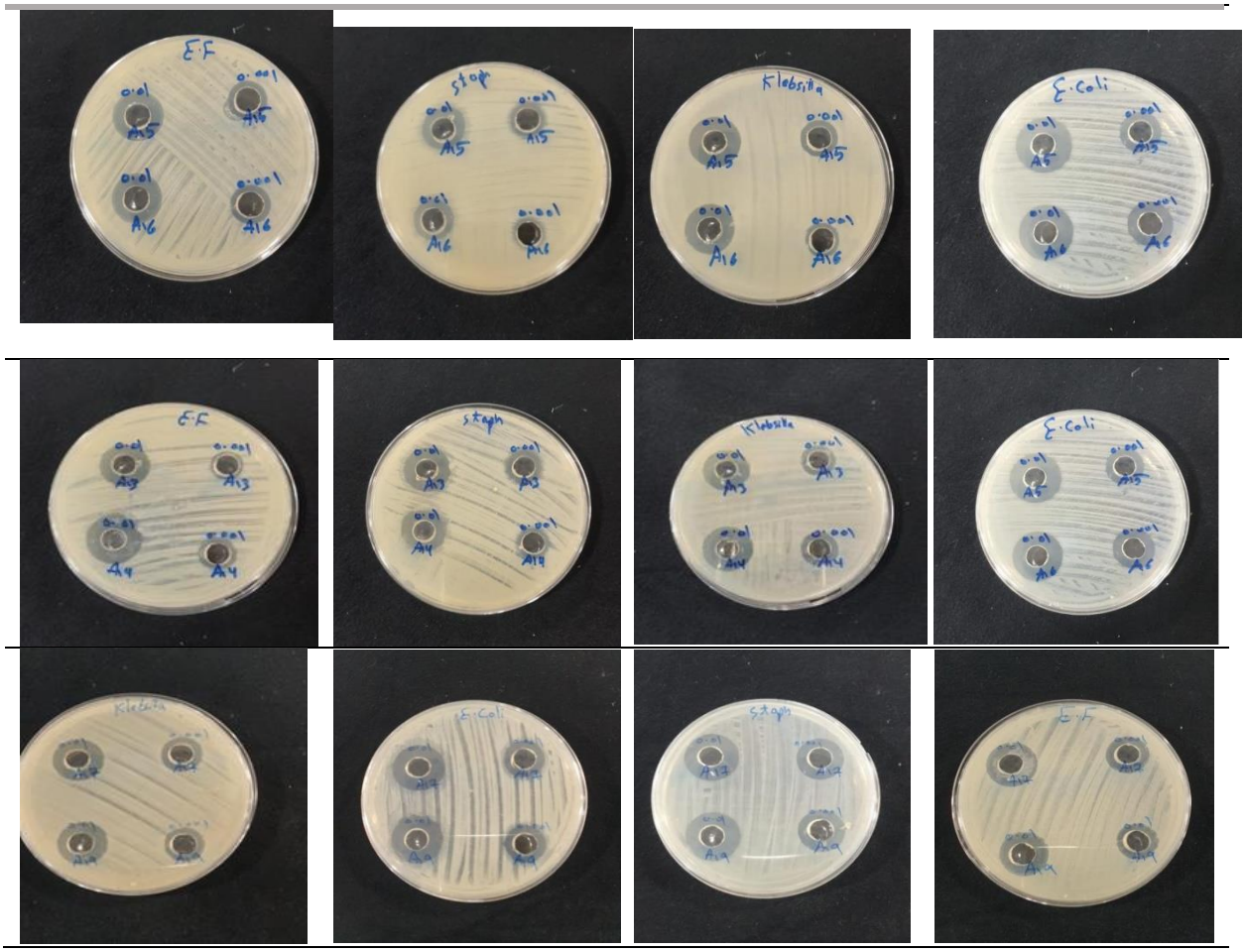


FIGURE 20 ^{1}HNMR band of compound (12)

TABLE 3 Details of compounds

No. of compound	*Staph*		E.F		*E.Coli*		*Klebsiella*	
	C1 10^{-2}mm	C2 10^{-3}mm	C1 10^{-2}mm	C2 10^{-3}mm	C1 10^{-2}mm	C2 10^{-3}mm	C1 10^{-2}mm	C2 10^{-3}mm
A1	19	0	20	0	19	0	19	0
A2	19	0	20	0	19	0	18	0
A3	20	0	18	0	20	0	19	0
A4	18	0	19	9	21	0	20	0
A5	19	14	18	11	21	14	19	15
A6	18	12	20	13	21	14	20	13
A7	17	13	18	14	20	16	19	11
A8	15	11	18	13	20	17	18	15
A9	21	18	19	16	20	16	18	16
A10	24	20	20	16	22	18	21	14
A11	20	17	18	15	19	15	17	18
A12	20	14	22	16	20	18	24	14



Conclusion

The target compounds have been successfully synthesized in this study. Characterization and identification of the compounds were checked using their physical characteristics, as well as their FT-IR spectra, ^{1}H-NMR spectra, and ^{13}C-NMR spectra. It was determined whether the synthesized

chemicals had an antibacterial effect on various gram-positive and gram-negative bacterial strains. Some synthesized compounds do not exhibit any activity against any bacteria, while others exhibit very good antibacterial activity against some bacteria.

Acknowledgements

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Conflict of Interest

There is no conflict of Interest.

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