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Docking, Ultrasonic Synthesis Of Some Heterocycle Compound Derived From N-Amino Phthalimide And Evaluation Of The Antibacterial Efficacy

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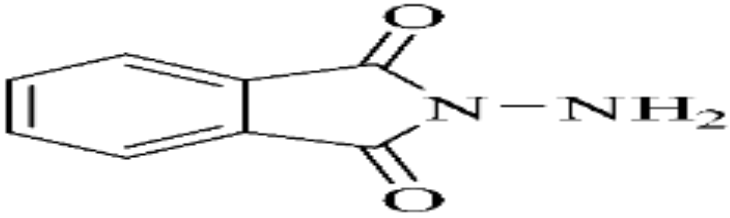
ABSTRACT
This research deals with the synthesis of some heterocyclic nitrogen compounds derived from N-amino phthalimide as a basic starting point using the ultrasound method which is considered a green chemistry method. Ultrasound synthesis technology was used to significantly accelerate the formation of these heterocyclic compounds compared with conventional methods. Meanwhile, docking simulations were conducted to evaluate their binding affinity to (coagulation factor X) using advanced computer programs. Their pharmacological potential was also evaluated using molecular docking studies. The results show that the prepared compounds have multiple promising pharmacological properties, making them strong candidates for drug development. The prepared compounds were characterized by various chemical and physical spectroscopic techniques, including FT-IR spectroscopy and nuclear magnetic resonance spectroscopy (^{1}H-NMR, ^{13}C-NMR). Finally, the antibacterial activity of the compounds was studied on four Gram-positive Staphylococcus aureus and bacillas and Gram-negative bacteria: E. coli and klebsiella in different concentration. Some compounds have shown activity against these bacteria.
Key word*: N-aminophthalimide ,Ultrasonic synthesis , Docking Studies Pipridine, Coagulation factor X*

INTRODUDTION

Heterocyclic nitrogen compounds represent an important class of organic molecules due to their wide These compounds are often (Aatif et al., 2022) .applications in medicinal chemistry and Pharmacology (Qadir .essential components of biologically active molecules, making them critical for drug Development These compounds are known for their ability to interact with biological receptors, enzymes, et al., 2022) proteins, giving them antibacterial, antifungal, and anticancer properties (Kumar et al., 2023). N— amino phthalimide It consists of a benzene ring and a heterocyclic ring fused together. The molecule is solid at room temperature, with a melting point of about 162°C (Homsi and Kasideh, 2015).



(Kushwaha .Its derivatives have shown potential in many chemical reactions and drug Design strategies The nitrogen atom in the heterocyclic ring of these compounds often plays an and Kaushik, 2016) allowing it to target specific proteins (Homsi and Kasideh, 2015) .important role in their Biological activity Molecular docking is a or enzymes associated with diseases such as cancer and inflammation computational technique used to predict how a small molecule (ligand) will bind to a receptor (protein, It allows researchers to enzyme) (Jakhar et al., 2020) It plays a pivotal and essential role in drug discover assess how well a candidate drug binds to its target receptor before exerimental testing(Yuriev and Ramsland, 2013) . Ultrasonic synthesis is a Technique that uses high-frequency sound waves(usually above 20 kHz) to accelerate chemical reactions(Yang et al., 2021). The use of ultrasonic energy in chemical reactions enhances the cavitation process resulting in the formation of bubbles that collapse generating high shear forces and high local temperature(Lal et al., 2023). This mechanical energy helps break bonds

which enhances the speed of chemical reactions and leads to better yields in shorter reaction times(Cai et al., 2021). This method has proven its efficiency in organic synthesis, especially in the synthesis of heterocyclic compounds offering many advantages compared to traditional methods (Askari et al., 2013). In this study, five N-amino phthalimide derivatives were prepared and tested in the laboratory against four types of bacteria, two Gram-negative and two Gram-positive.

MATERIALS AND METHODS

All the chemicals in the study are produced by Fluke and BDH, and some are locally produced and of high purity. The melting and decomposition points of the prepared compounds were measured in the Chemistry Department, College of Science, University of Mosul, using a Melting Point Apparatus, model (SMP30). The infrared spectra were measured by a Bruker FTIR device in the region between (4000-400 cm^{-1}). The measurement was carried out in the central laboratory of the College of Science, University of Mosul. The ^{1}H-NMR and ^{13}C-NMR were measured using a Bruker Ascend device (100 MHz for carbon) (400 MHz for proton). The measurement was carried out at the University of Basra, College of Education for Pure Sciences, Department of Chemistry, using DMSO solvent and using TMS as an internal reference. The antibacterial activity was carried out in a laboratory at the University of Mosul/ College of Science/ Life Sciences.

Preparation of compound (K_1, K_3, K_4)

These compounds (K_1, K_3, K_4) were prepared by reacting equal moles mixture of (N-aminophthalimide) (0.031 mmol, 0.05 g), Urea (0.031mmol, 0.02 g), and (0.25 ml) pipridine dissolved using ethanol solvent (10 mL). The reaction was heated for (1 hours) at a temperature of (72-75 °C) using ultrasonic technology with a small amount of (zirconyl chloride octahydrate $ZrOCl_2.8H_2O$) as a catalyst. Then the reaction was cooled to room temperature and the material was poured on ice to obtain a precipitate. Then the solution was filtered. Recrystallization with ethanol and dried at room temperature to give the desired compounds. Table 1 shows some of the physical properties of the prepared compounds.

Preparation of compound (K_2, K_5)

A mixture equimolar of N-aminophthalimide (0.31 mmole) and acetyl chloride (0. 31 mmole) and pipridin (0.5 ml) in ethanol (25 ml) The reaction mixture was heated for (30 mint) at (72 – 75 C°) in Ultrasonic technique. Then The reaction mixture was left for two hours at room temperature to allow a precipitate to form at the bottom of the flask. The precipitate was then separated from the filtrate by decantation. Table 1 shows some of the physical properties of the prepared compounds.

Table (1): physical properties of the prepared compounds (K_1, K_5).

.Comp .No	Molecular Formula	M.Wt	M.P °C	%Yield	Color
K	$C_9H_6N_4O_1$	186.14	260 - 262	80	white
K	$C_{10}H_6N_2O_2$	186.17	211 - 210	71	red
K	$C_9H_8N_4O_1S_1$	220.25	235 – 230	77	brown
K	$C_9H_8N_4O_1$	188.19	203 - 199	65	Yalow
K	$C_{10}H_7N_3O_1$	185.19	277 – 270	87	white

RESULT AND DISCUSSION:

In this research, we prepared the compounds (K_1, K_2, K_3, K_4, K_5) according to the method During the direct reaction of N-amino phthalimide with various ammonia derivatives (urea, thio urea, semecarbazol, acetonitrile) and a acetyl chloride In the presence of (zirconyl chloride octahydrate $ZrOCl_2.8H_2O$) as a catalyst as in scheme (1).

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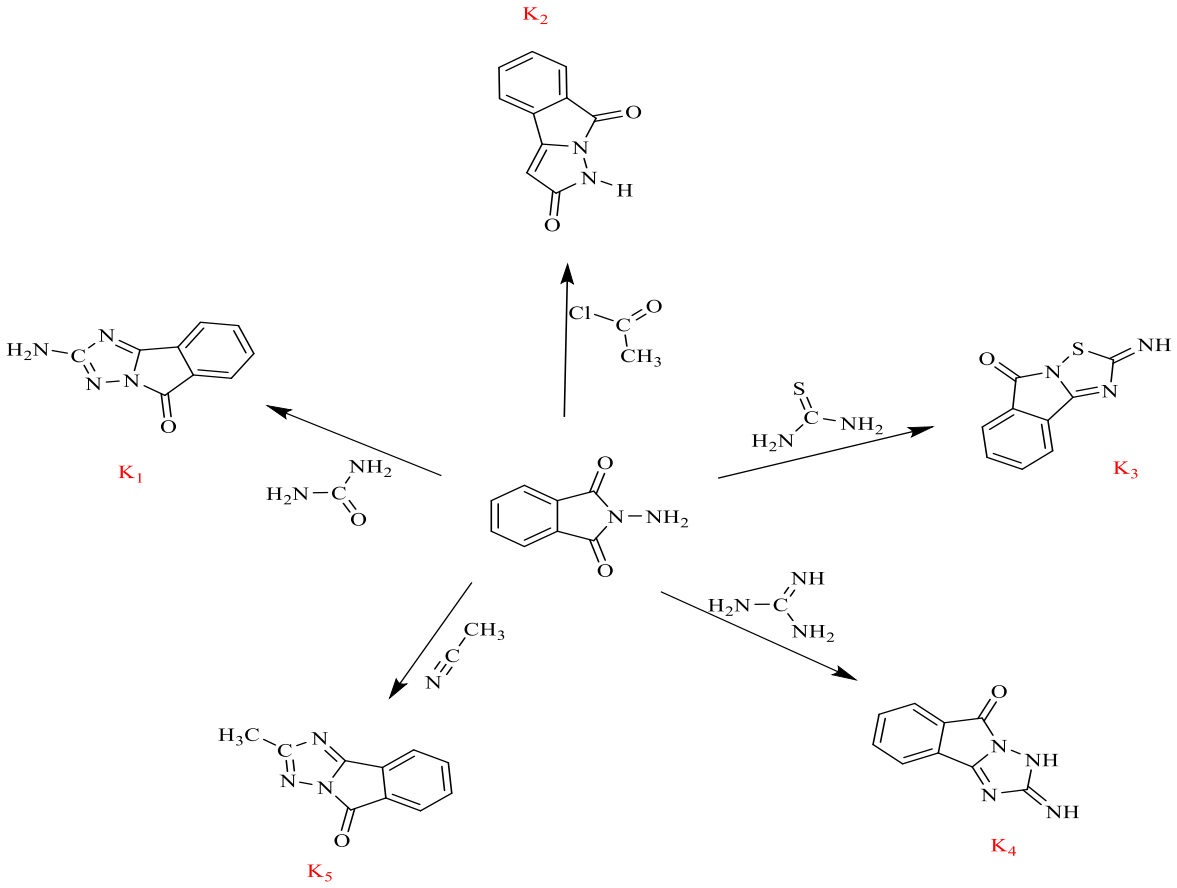
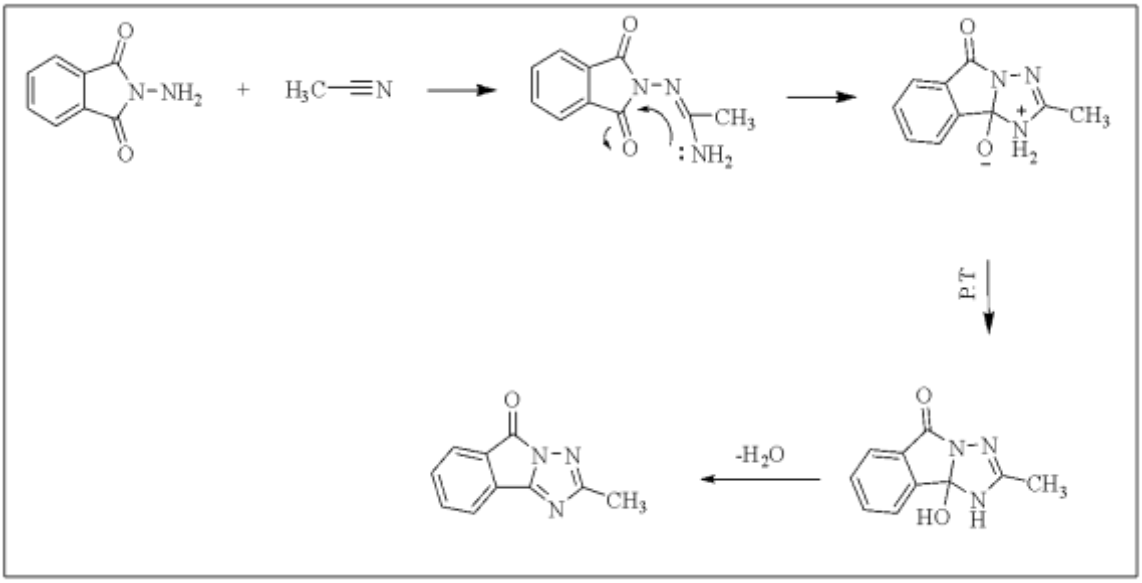


Scheme (1) The diagram shows all the reactions performed in the research.



The predicted nuclear substitution reaction mechanism for these reactions.

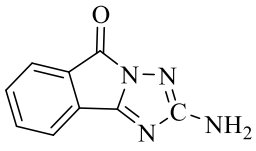
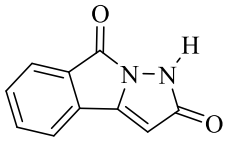
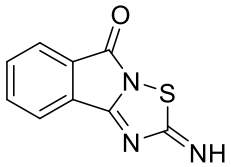
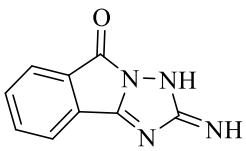
The prepared compounds (K_1 – K_5) yielded 65% - 87%, respectively, FT-IR spectroscopy was used to identify these compounds, and characteristic bands were observed at specific wavenumbers. These included bands at 1783 cm^{-1}- 1738 cm^{1} attributed to C=O stretching, bands at 1551 cm^{-1}-1662 cm^{-1}, attributed to C=N stretching as shown in (Table 2) and fig.(1, 5)

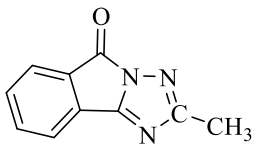
Table (2) FT-IR absorption spectra data (cm^{-1}) of the prepared compounds.

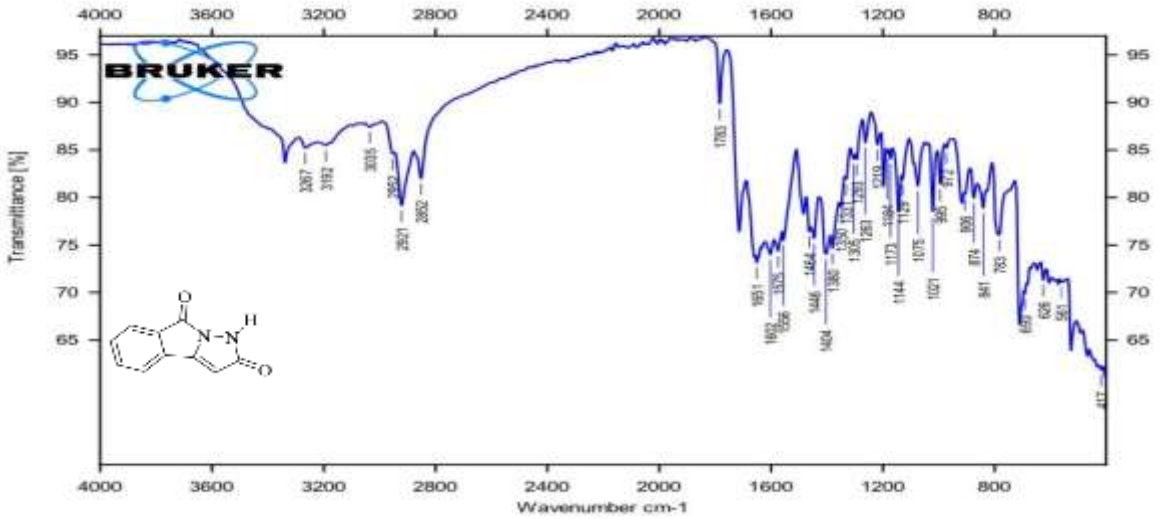
Comp. No.	vC=O	vC=N	vN-H
K1	1783	1662	3267
K2	1738	1653	3317
K3	1715	1661	3338
K4	1634	1653	3176
K5	1738	1651	3266

The ^{1}H-NMR spectra of the compounds (K_1, K_2, K_3, k_4, K_5) showed signals in the 3.41 and ppm (1H, S) attributed to the CH group, and multiple signals at 7.81-8.05 ppm corresponding to aromatic protons. Additionally, a signal was observed at 4.96 and 4.71 ppm (1H, S) representing the NH group. and 6.31 for NH_2 (as shown in Table 3) and fig. (6, 7) . The ^{13}C-NMR spectra of the compounds (K_1, K_2, K_3, k_4, K_5) exhibited signals at specific chemical shifts, including 158.24-167.37 ppm (C=O), 143.89-169.68 ppm (C=N), and 29.47 ppm (CH_3) (as shown in Table 3) and fig. (8, 9).

Tabel (3) ^{1}H-NMR and ^{13}C-NMR spectra of the compounds (K_1, K_2, K_3, k_4, K_5)

NO.	Structure	^{1}HNMR, DMSO-d6, δ (ppm)	^{13}C-NMR, DMSO-d6, δ (ppm)
K1		6.31 (1H, s, NH_2) 7.71-8.04 (4H, m, Aromatic protons)	128.34-129.18-130.61-135.02-135.81-137.74 (C- aromatic rings); 158.24-(C=O amide); 143.89-162.68-(C=N);
K2		5.95 (1H, s, CH) 11.4 (1H, s, NH) 7.39-7.62 (4H, m, Aromatic protons)	123.01-123.58-128.61-130.92-132.01-133.74 (C- aromatic rings); 161.35-165.91(C=O amide); 149.93-(C–N);
K3		4.71 (1H, s, CH) 7.87 (1H, s, NH) 7.81-7.55 (4H, m, Aromatic protons)	123.35-125.58-127.61-130.52-133.01-134.74 (C- aromatic rings); 167.35-(C=O amide); 155.10-169.68-(C=N);
K4		9.36 (1H, s , C=NH) 4.20 (1H, s, NH) 7.68-8.17 (4H, m, Aromatic protons)	116.32-123.74-128.44-130.23-130.67-132.74 (C- aromatic rings); 166.7-(C=O amide); 145.92-160.70-(C=N);

K5		1.19 (1H, s, CH_3) 3.41 (1H, s, CH) 4.96 (1H, s, NH) 7.86-8.05 (4H, m, Aromatic protons)	123.25-123.36-125.22-127.60-129.22-133.01 (C- aromatic rings); 167.37-(C=O amide); 29.47(CH_3); 155.08-(C=N);



FT-IR for prepared compound

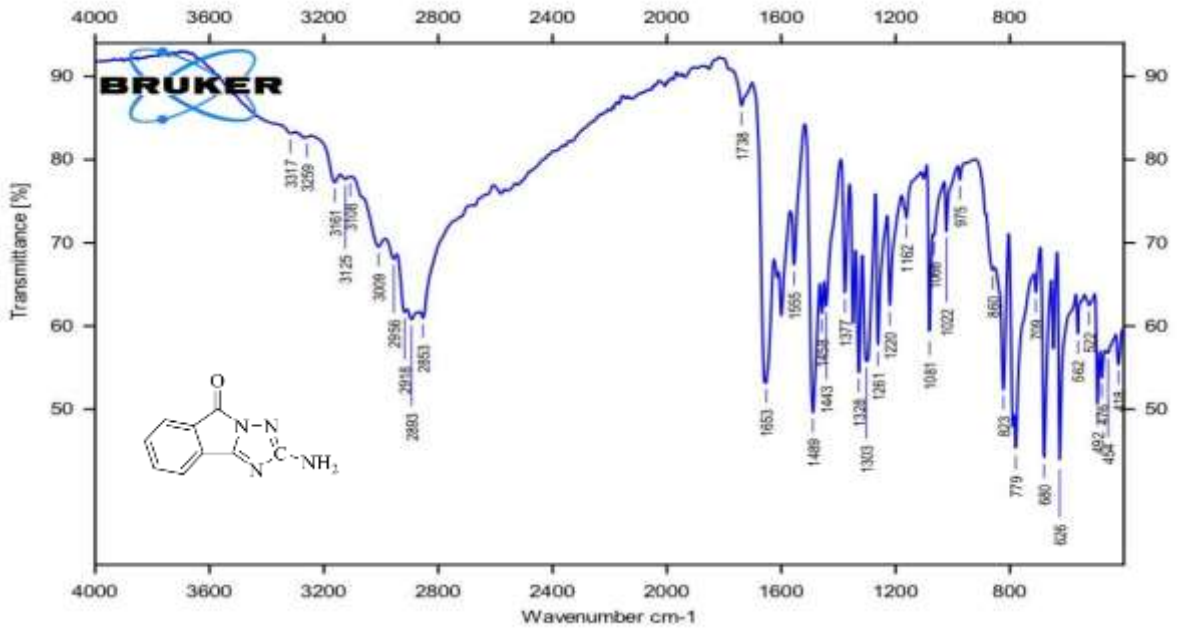


Fig. 2: FT-IR spectrum for K2

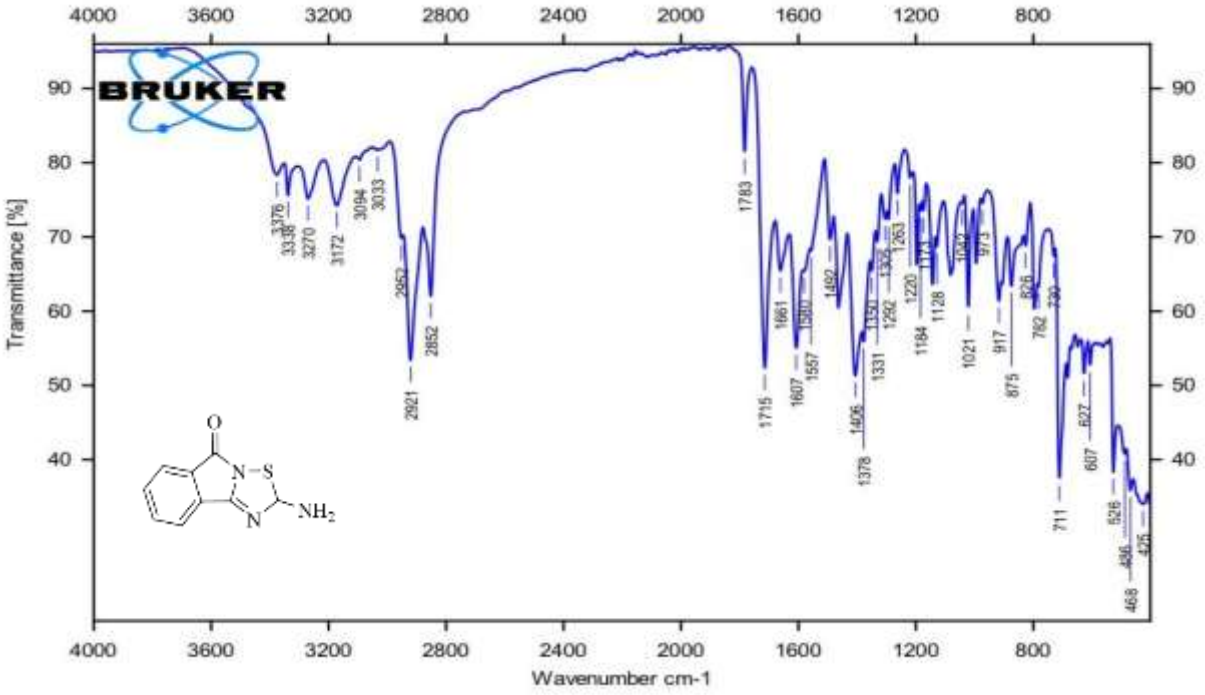
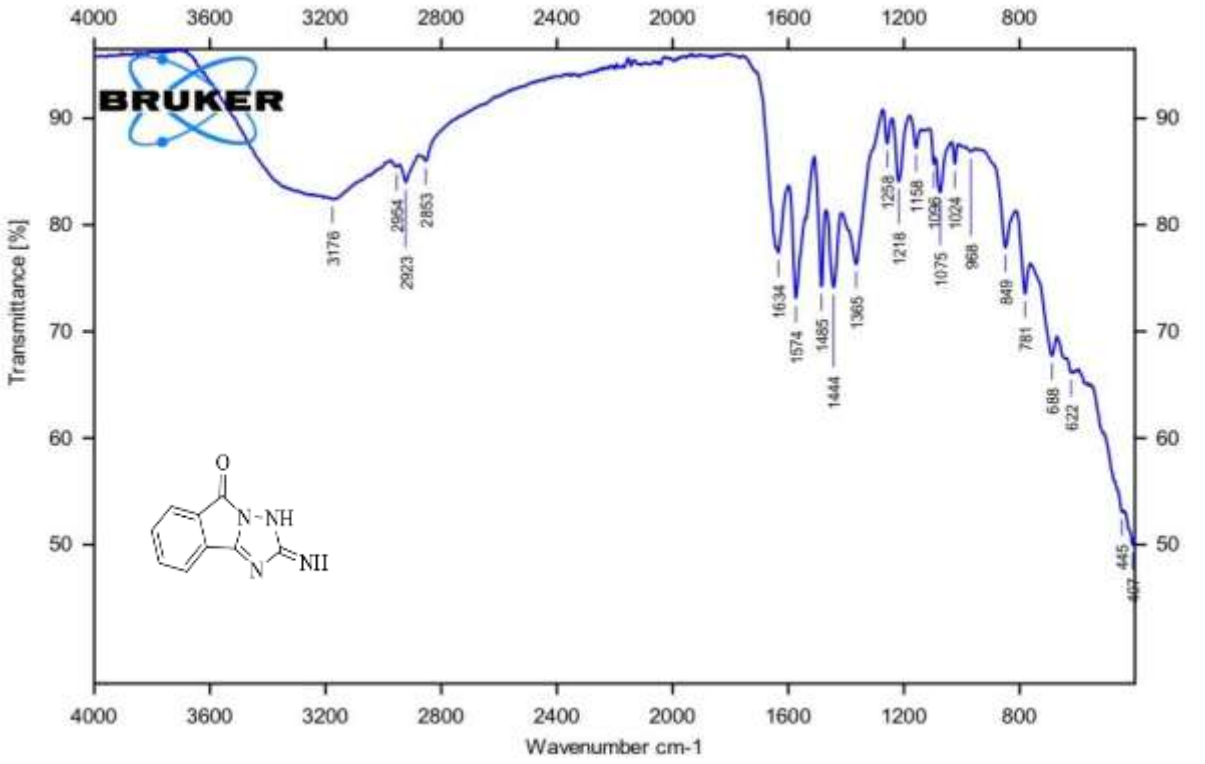


Fig. 3: FT-IR spectrum for K3



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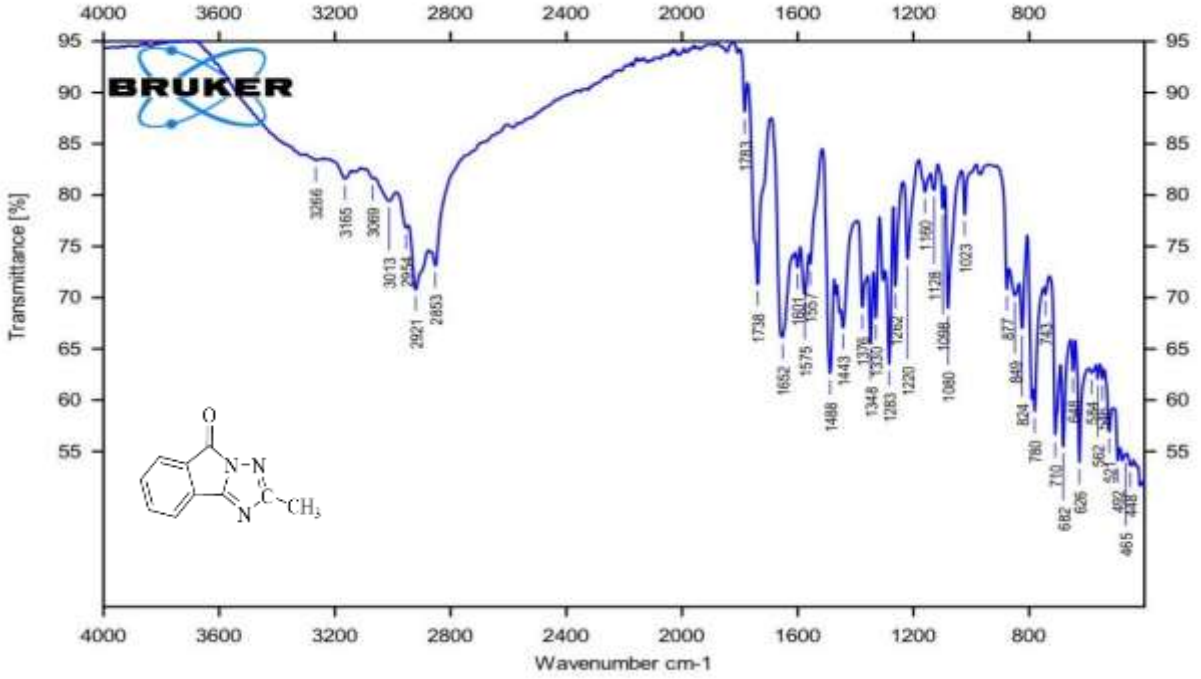
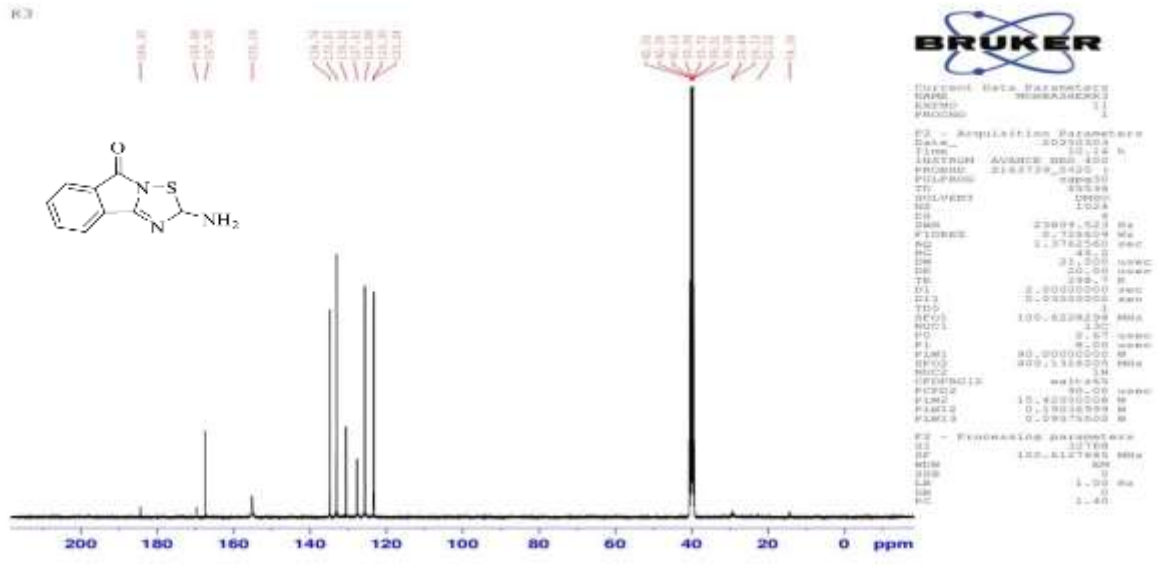


Fig. 5: FT-IR spectrum K5

The compounds wer [R as shown in the (Table



2- 3) and Fig. (1, 9).

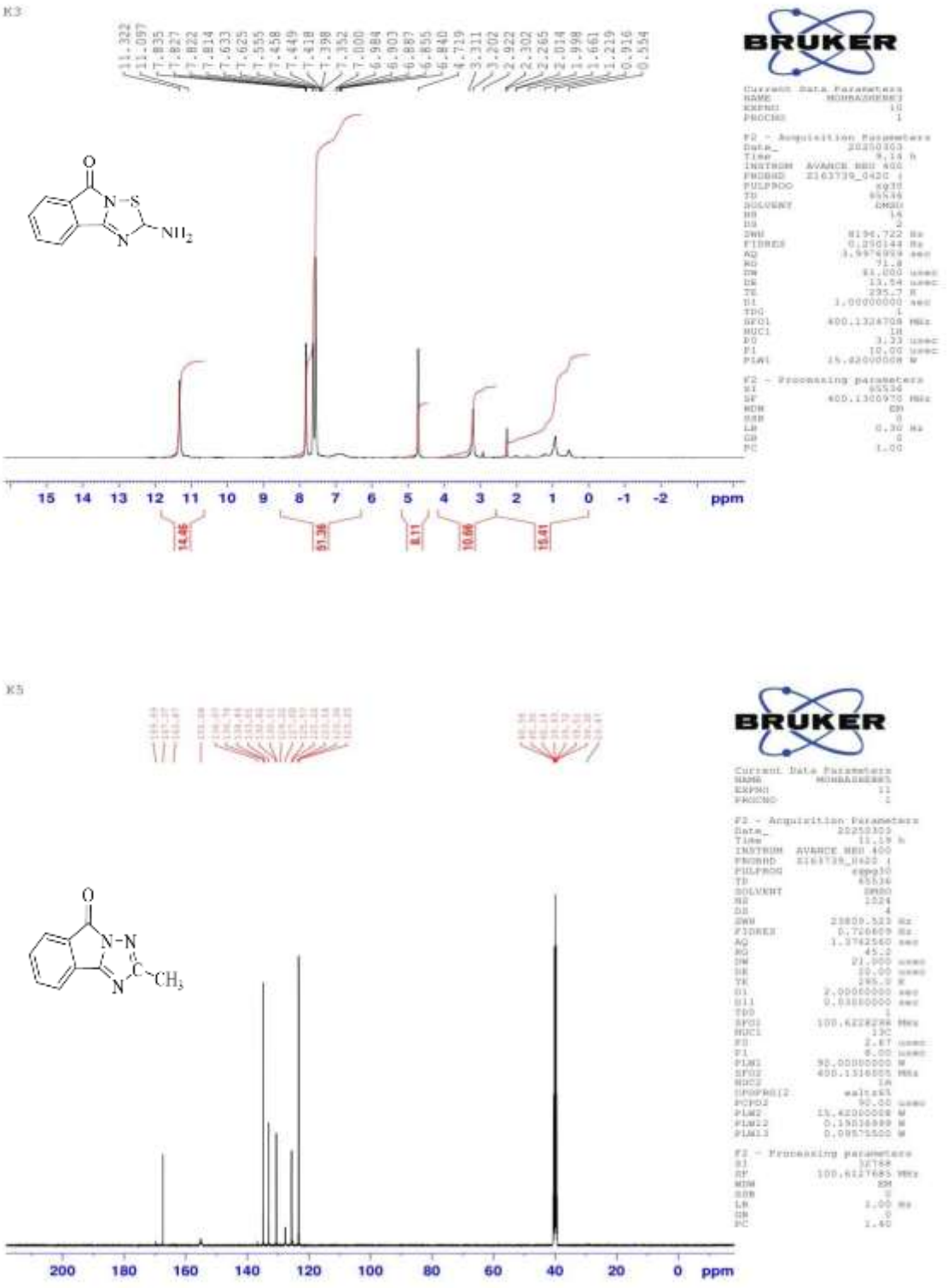


Fig. 8: ^{13}C-NMR spectrum for K5

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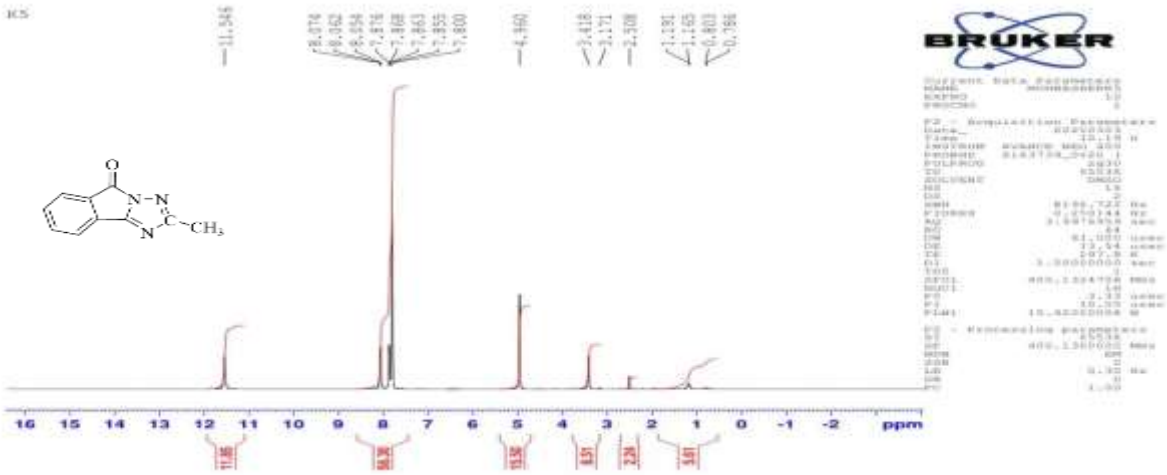

Molecular docking s

The molecular docking program data studio discovery was performed on all newly synthesized N-amino phthalimide derivatives, with the crystal structure of the enzyme (coagulation factor X) (PDB ID: 1FJS) as a target molecule. All compounds were found to interact with amino acids. The most effective compounds (k4) were found to be the most active. The table shows the docking scores of the studied compounds. The docking program reveals that all compounds bind to the active site of the amino acid of this protein via several types of bonds, including: van der Waals force, carbon-hydrogen bond, pi-sigma bond, pi-sulfur bond, and, most importantly, hydrogen bonding. Docking is commonly used to determine the best binding orientation for a molecule bound to a protein molecule to predict binding energy and biological activity based on ΔG [Kcal/mol], as shown in (Table 4) and fig. (10, 14).

Table (4). Data on molecular docking results of N-aminophalimide derivatives.

Compound No.	Molecular Formula	M.wt.	ΔG[Kcal/mol] 1FJS
K1	$C_9H_6N_4O_1$	186.14	-7.5
K2	$C_{10}H_6N_2O_2$	186.17	-7.9
K3	$C_9H_8N_4O_1S_1$	220.25	-6.8
K4	$C_9H_8N_4O_1$	188.19	-8.5
K5	$C_{10}H_7N_3O_1$	185.19	-7.4

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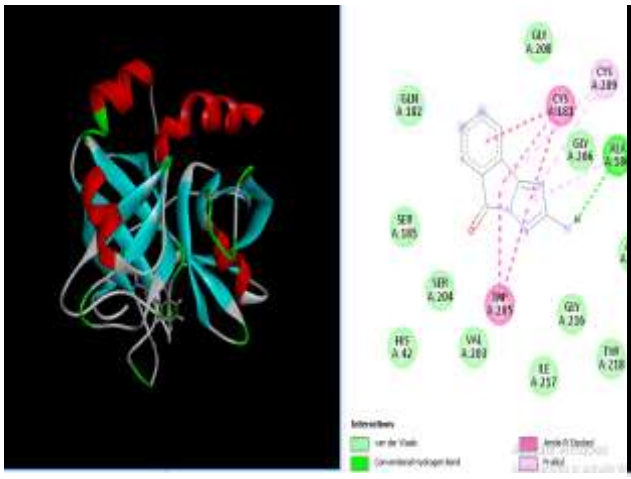

figure 10, -2D and 3D compound K1, with Amino acids of (1FJS)

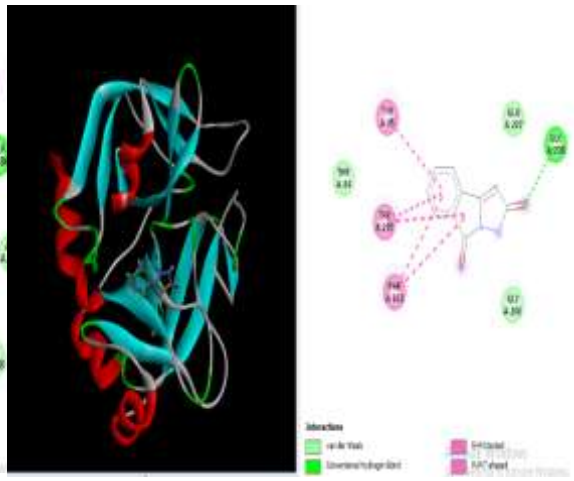

figure 11, -2D and 3D compound K2, with Amino acids of (1FJS)

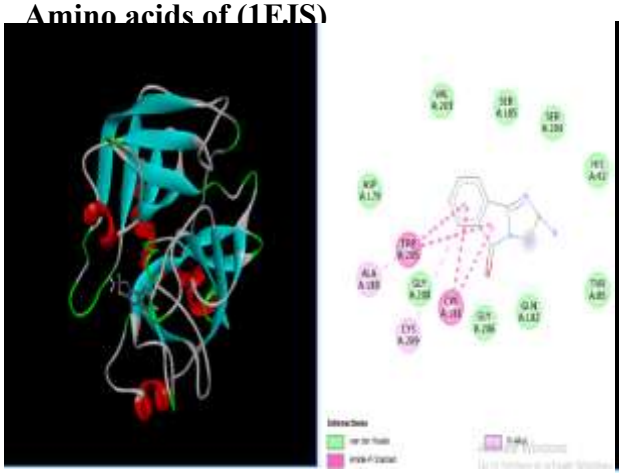

figure 12, -2D and 3D compound K3, with Amino acids of (1FJS)

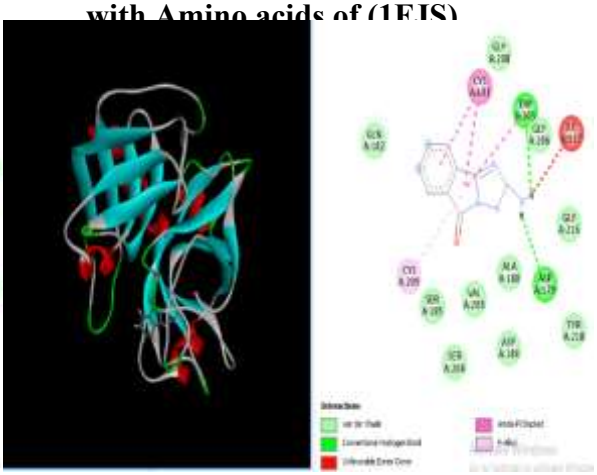

figure 13, -2D and 3D compound K4, with Amino acids of (1FJS)

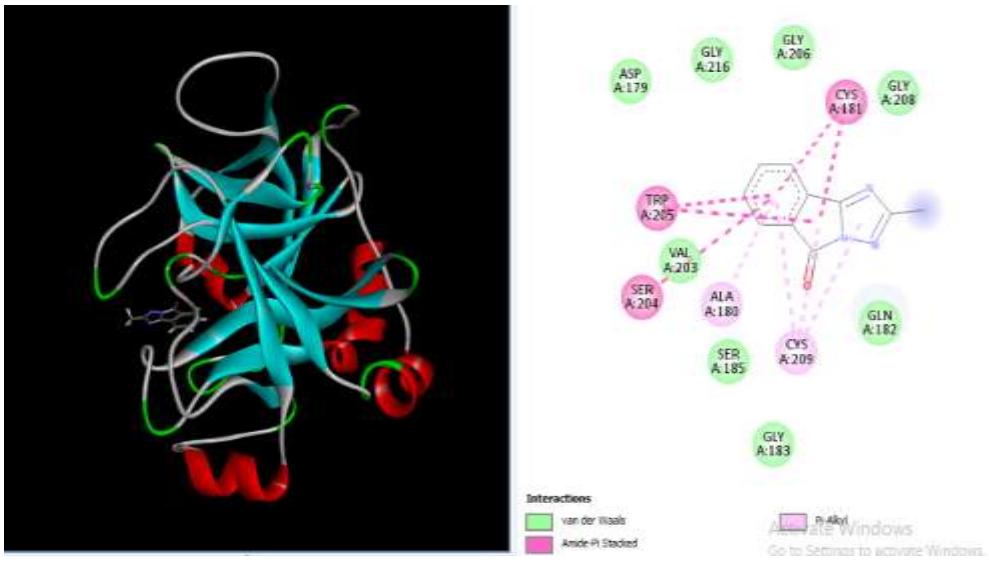

figure 14, -2D and 3D compound K5, with Amino acids of (1FJS)

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terial activity:

The bacterial activity of the prepared compounds was conducted, as this study included testing their effect on some types of identified bacteria. These isolated bacteria are considered the main causes of many diseases in humans. The study included four types of bacteria Gram-positive Staphylococcus aureus and bacillus and Gram-negative bacteria: E. coli and klebsiella in different concentration.The study method relied on making holes in the medium (Nutrient agar) using a cork piercer sterilized with absolute ethanol. Then, the bacteria were spread on the surface of the agar using a glass spreader to complete the bacterial culture and wipe the plate homogeneously to ensure the complete spread of bacteria on the culture medium. After that, the solutions (prepared compounds) were placed in an amount of mg/hole. DMF was added in a separate hole as a control sample. Then, the dishes were closed and placed in the incubator for a full day at a temperature of 37°C. After the specified period, the diameter of the inhibition zone was measured with a ruler. The compounds prepared in our
study showed good efficacy, while some compounds did not show efficacy.

Some pictures illustrating the bacterial activity process carried out with the help of the Department of Life Sciences at the University of Mosul.

Table (5) shows the results of the bacterial activity of the prepared compounds

Comp No	Concentration	E.clic	bacillus	staph	klebsiella
K	0.03	9	R	10	8
K	0.02	R	R	12	13
K	0.03	R	R	11	9
K	0.02	12	R	11	10
K_5	0.03	14	R	10	14

CONCLUSION

Spectral studies (IR), (13C-NMR) (1H-NMR) of each of the prepared compounds proved the correctness of the proposed structure for all the prepared compounds, and the bacterial activity was applied against four types of pathogenic bacteria. The results showed that compound K5 has a higher activity than the rest of the compounds. Some of them were also proven to be very effective against specific types of bacteria. In addition, the molecular binding study of these prepared compounds proved a high theoretical activity with the enzyme (coagulation factor X) PDB ID: 1FJS, which is considered an important coagulation factor in the human bode.

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