BioMed Visions Journal

Volume 1 | Issue 2 Article 5

June 2025

In Silico Screening for Computational Exploration of Interactions, Synthesis, and Comparative Evaluation of Novel Furan-2-Quinolone Derivatives as Potent Anticoagulants

Karm A. Khalaf
College of Pharmacy, Al - Noor University, 41000, Mosul, Iraq, karm.anez@alnoor.edu.iq

Noor A. Majeed
College of Technical College, Al - Noor University, Mosul, Iraq

Adnan O. Omar
Department of Chemistry, College of Science, University of Mosul, Mosul, Iraq

Recommended Citation

Khalaf, Karm A.; Majeed, Noor A.; and Omar, Adnan O. (2025) "In Silico Screening for Computational Exploration of Interactions, Synthesis, and Comparative Evaluation of Novel Furan-2-Quinolone Derivatives as Potent Anticoagulants," *BioMed Visions Journal*: Vol. 1: Iss. 2, Article 5.
DOI: https://doi.org/10.63100/3078-6738.1009

BIOMED VISIONS JOURNAL 2025;1:59–65

ORIGINAL STUDY

In Silico Screening for Computational Exploration of Interactions, Synthesis, and Comparative Evaluation of Novel Furan-2-Quinolone Derivatives as Potent Anticoagulants

Karm A. Khalaf [a,*], **Noor A. Majeed** [b], **Adnan O. Omar** [c]

[a] College of Pharmacy, Al - Noor University, 41000, Mosul, Iraq
[b] College of Technical College, Al - Noor University, Mosul, Iraq
[c] Department of Chemistry, College of Science, University of Mosul, Mosul, Iraq

ABSTRACT

There is an urgent need for the design and development of new and safer drugs for the treatment of (Blood coagulation). New derivatives of furan-2-qoinoline as anti-coagulation drug bearing furan, quinolone, were synthesized with the aim of developing new drug inhibitors (Factor Xa enzyme) respectively. In our study, synthesis of the new organic compounds derived from Furo-2-quinolone substituted by treated with ammonia derivatives like hydrazine, give K6, and (1-Amino-4,6-dimethyl furo[3,2-g] quinoline-2-one) K6 then react with Formaldehyde to form K6a. And evaluated their effects on coagulation in the docking (MCULE). then compared this compound, with the Rivaroxaban. compound give the result based on docking program analysis. And chose the novel compound that showed the highest negative AG value, indicating strong interaction and effective inhibition of (Factor Xa) enzymes. This enzyme plays a crucial role in the series of chemical reactions that lead to blood clotting. The results showed that the prepared organic compound exhibited strong binding and inhibition towards these enzymes. Therefore, this theoretical study, based on the docking MCULE program, indicates that the new organic compound K6a is a more potent anticoagulant than and Rivaroxaban. This is because this compound inhibits the activity of Factor Xa, preventing the formation of thrombin. Without thrombin, fibrin (the protein that forms the basis of a blood clot) cannot form. As a result, blood clot formation is reduced, helping to prevent clots in blood vessels.

Keywords: Anticoagulant, Factor Xa enzyme inhibition, Furo-2-quinolone derivatives, Docking analysis, Novel drug development

1. Introduction

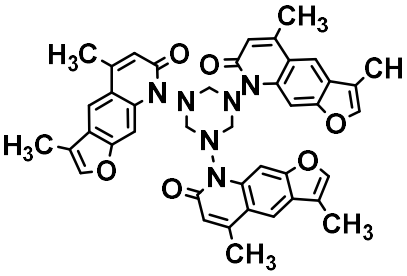
A chemical class with a quinolone nucleus presents characteristics of the Furo-2-quinolones (Kocsis, Domokos and Szabo, 2016). Such compounds are in a category of chemicals with the quinolone nucleus and find vast importance in scientific research because they are endowed with many types of biological activity and have possible pharmaceutical properties (Dube, Legoabe and Beteck, 2023). They are investigated for the action on different biological systems mainly and in relationship to its possible application within the field of pharmaceuticals (Saalim, Villegas-Moreno and Clark, 2020). The introduction of the quinoline ring and the furan ring into the field of medical science continues to be one of the front-line attractions for research (Basco et al., 1994). This chemical challenge will deal with the bridging of molecular structures of quinoline and furan to create a new compound with high pharmacological

Received 6 November 2024; revised 29 January 2025; accepted 5 February 2025.
Available online 16 June 2025

* Corresponding author.
E-mail address: karm.anez@alnoor.edu.iq (K. A. Khalaf).

https://doi.org/10.63100/3078-6738.1009

Table 1. Shows IR Spectrum & physical data of compounds.

No.	M.P	%	Color	IR(KBr) V cm^{-1} C=O	C=C	C-N-C	N-N
	230–233	70	Yellow	1706	1654 1633	1388 1348	1184

potentials (Senerovic et al., 2020). This association paves the way towards the exploration of new, potent treatment modalities because researchers want to explore more about the biological potentials correlated with these interlinked structures (Grygorenko et al., 2020). Advances in this field would further help new drug development to be carried out using methodologies in organic chemistry, thereby increasing the scope of medical treatment.

2. Materials and methods

This study aimed to develop new furan-2-quinoline derivatives as potential anticoagulants targeting the Factor Xa enzyme, essential for blood clotting. The compound K6 was synthesized by treating furo-2-quinolone with ammonia derivatives, such as hydrazine as shown in Scheme 1, and then reacting it with formaldehyde to produce K6a. The anticoagulant activity of K6a was evaluated using the MCULE docking program and compared with Rivaroxaban. The results showed that K6a had the highest negative AG value, indicating strong interaction and effective inhibition of Factor Xa. By inhibiting this enzyme, K6a as shown in Table 1 prevents thrombin formation, reducing fibrin production and minimizing blood clot formation. The findings suggest that K6a is more potent than Rivaroxaban, making it a promising candidate for further research.

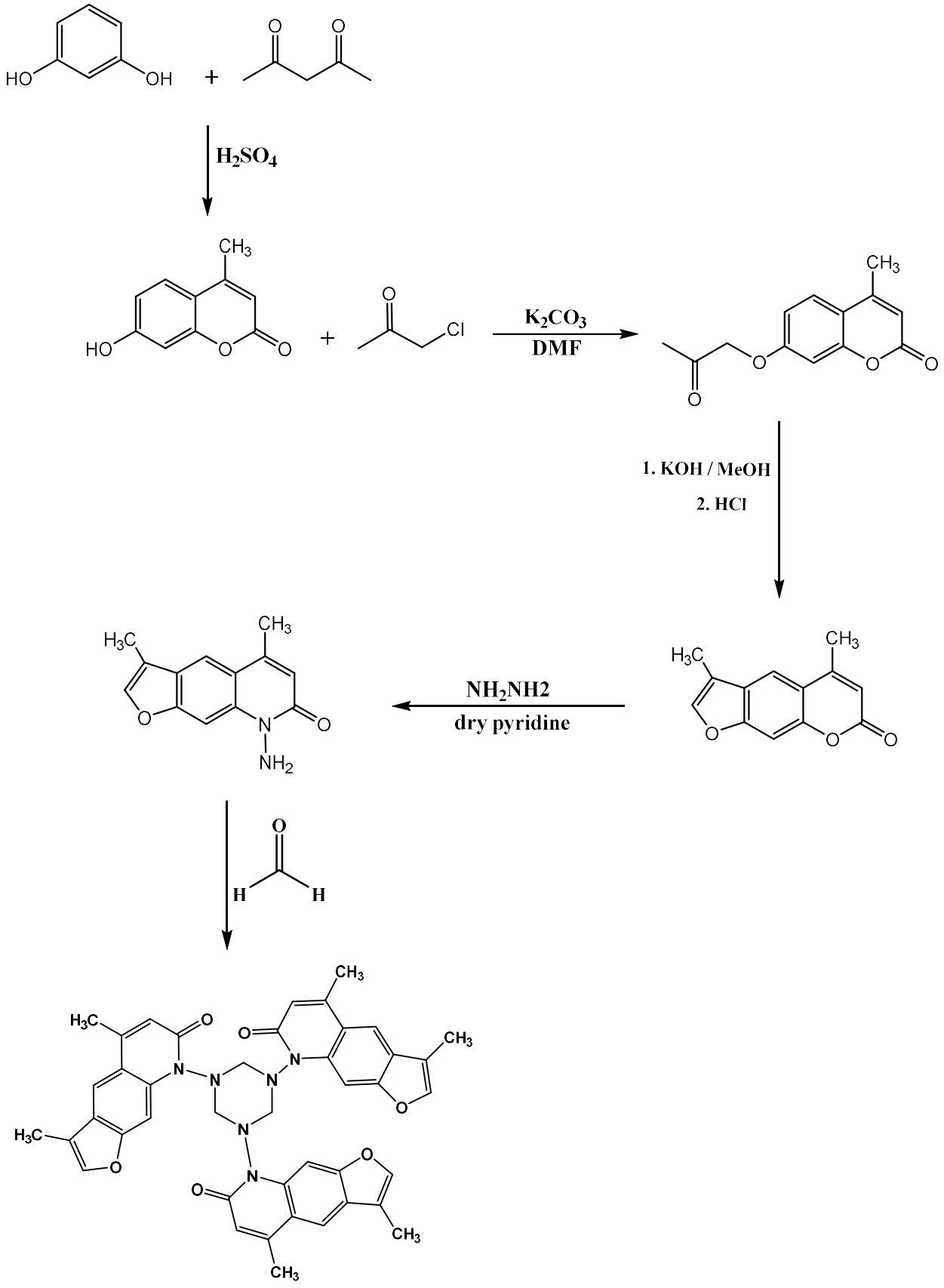
2.1. Experimental part

A mixture of resorcinol (0.01 mol, 1.1 g) and acetylacetone (0.01 mol, 1.3 mL) was added dropwise to 10 mL of concentrated sulfuric acid in an ice-cooled bath maintained at 0°C, ensuring that the temperature did not exceed 10°C. The reaction mixture was stirred continuously, forming a dense yellow-colored solution. After completion of the addition, stirring continued at room temperature for 24 hours. The reaction mixture was then poured onto a mixture of water and crushed ice with stirring, leading to the formation of a precipitate. The precipitate was collected by filtration, washed with water until neutral, dried, and recrystallized from ethanol or chloroform to obtain 7-hydroxy-4-methyl coumarin (K1) (Hussien et al., 2016).

Compound K1 (0.0156 mol, 3.0 g) was dissolved in a minimal amount of N,N-dimethylformamide (DMF), followed by the addition of chloroacetone (0.0156 mol, 2.5 mL) and dry potassium carbonate (5 g). The reaction mixture was stirred under dry conditions for 5 hours, forming a viscous solution. Water (250 mL) was then added, and stirring continued for 15 minutes until a precipitate was observed. The precipitate was collected by filtration, washed several times with water, dried, and recrystallized using ethanol to yield 7-acetonyloxy-4-methyl coumarin (K2) (Ibraheem, Al-Bayati and Hameed, 2016).

A solution of K2 (0.0065 mol, 2.0 g) in 75 mL of (1N) potassium hydroxide solution in methanol was stirred for 6 hours. The solution was then cooled to room temperature and acidified with (1N) hydrochloric acid until a precipitate formed. To ensure complete precipitation, the solution was further cooled in an ice bath for 1 hour. The resulting solid was filtered, washed several times with cold water until the wash water became neutral, dried, and recrystallized using ethanol, yielding 4,6-dimethyl furo[3,2-g] coumarin (K3) (Yin et al., 2022).

K3 (0.02 mol) was dissolved in 30 mL of dry pyridine under gentle stirring and heating. The solution was then cooled, and hydrazine hydrate (0.025 mol, 13 mL) was added dropwise. The reaction mixture was stirred and allowed to react for 6 hours. After cooling, the mixture was cautiously added to 100 mL of a (4 mol/L) hydrochloric acid solution, resulting in the formation of a precipitate. The solid product was filtered, washed with cold water until the wash water became neutral, dried, and recrystallized using ethanol to obtain 1-amino-4,6-dimethyl



Scheme 1. Showing a summary of the preparation of a new organic compound.

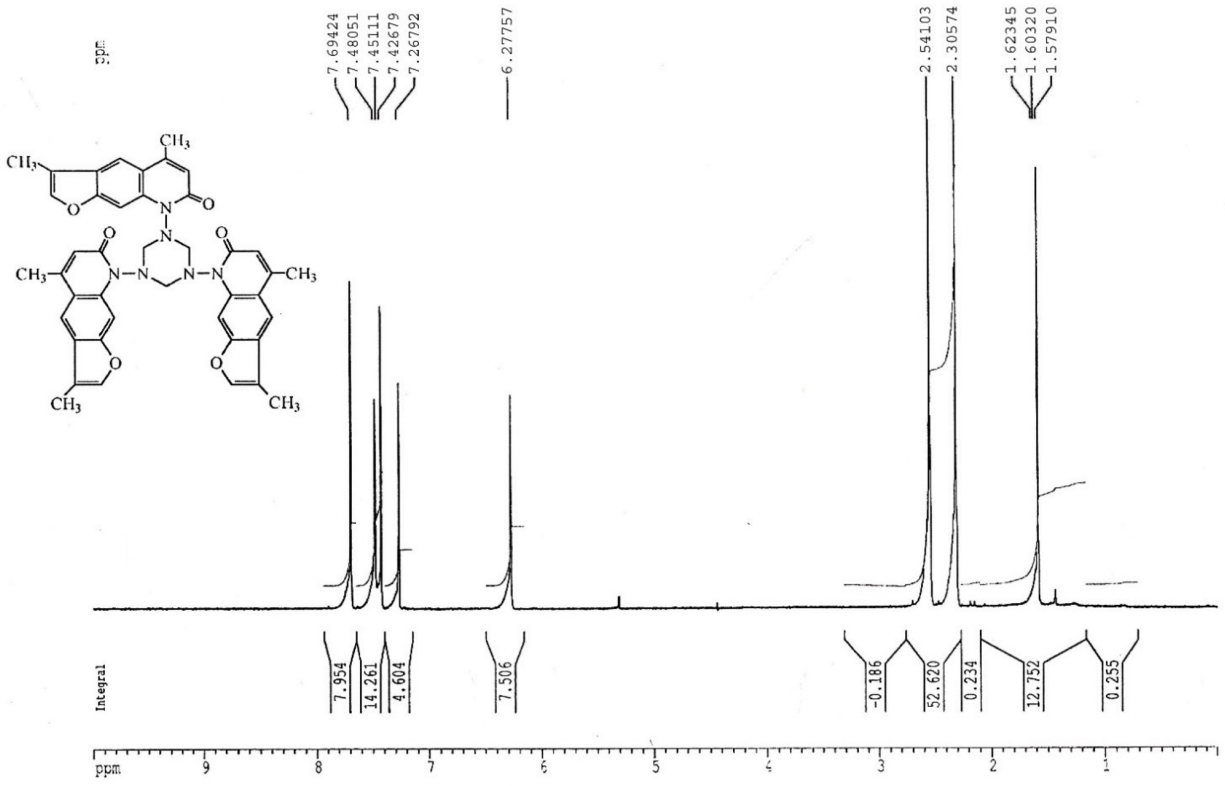


Fig. 1. Show the 1H-NMR of K6a.

furo[3,2-g] quinoline-2-one (K6) (Al-Bayati, Ahamad and Ahamed, 2015).

Finally, K6 (0.01 mol) was dissolved in 50 mL of ethanol under gentle heating. Formaldehyde (40%, 0.075 mol) was then added dropwise at room temperature with continuous stirring. The reaction mixture was stirred for 30 minutes at room temperature and then left undisturbed for another 30 minutes

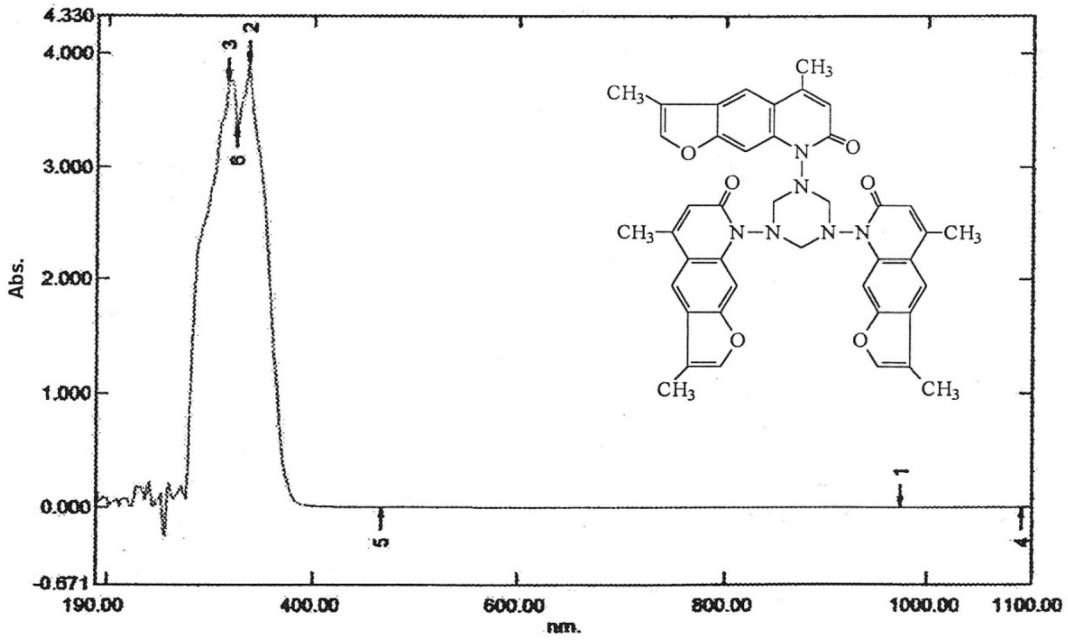
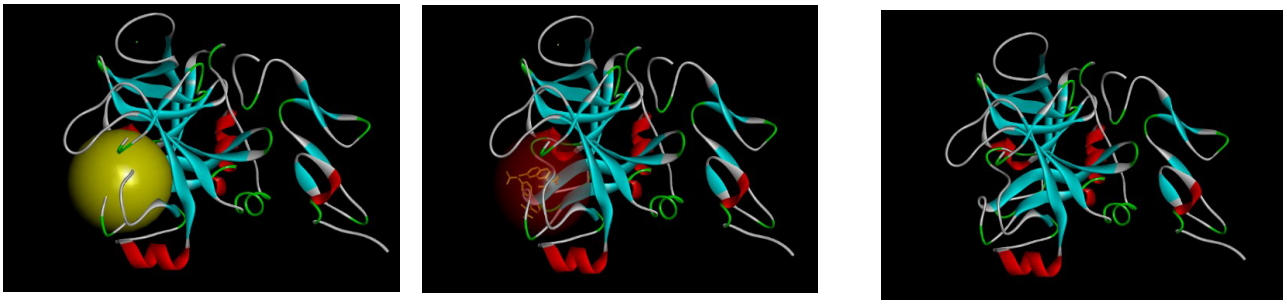


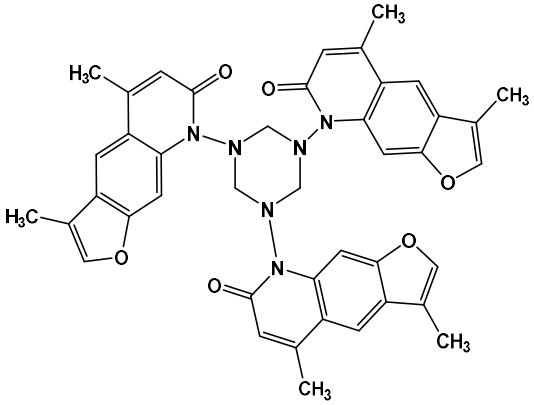
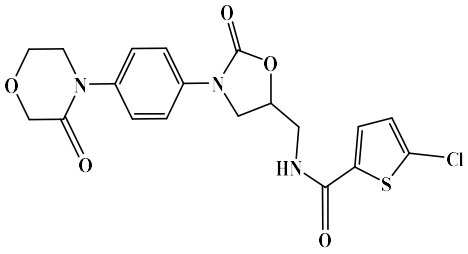
Fig. 2. Show the UV-spectrum of K6a.



(1) (2) (3)

Fig. 3. 1-Structure of Factor Xa Enzyme retrieved from PDB database, 2-preparation of enzyme in discovery studio visualizer: Solvent removal and active site identification, 3-Enzyme docking preparation: Removal of old ligand.

Table 2. The interaction of Factor Xa with new organic compound K6a and Rivaroxaban.

No.	Structure	Name	G[Kcal/mol] [1FAX]
1		Novel	–10.4
3		Rivaroxaban	–8.3

until crystal formation was observed. The resulting solid was filtered, washed with cold ethanol, dried, and recrystallized from petroleum ether to yield 1,3,5-tris-(4,6-dimethyl furo[3,2-g] quinolin-2-one-1-yl)-2,4,6-trihydro-1,3,5-triazine (K6a). The final compound was confirmed using proton-NMR and UV spectroscopy (Choodum and Nic Daeid, 2011).

2.2. Molecular docking study

A theoretical study to evaluate the drug potential of the new compound K6a as an inhibitor of the enzyme Factor Xa, comparing it theoretically with the drug Rivaroxaban, where Factor Xa is an enzyme that plays a crucial role in the series of chemical reactions leading to blood clotting (Remko, Remková and Broer, 2016). Rivaroxaban treatment inhibits the activity of Factor Xa, preventing the formation of thrombin. Without thrombin, fibrin (the protein essential for blood clot formation) cannot form (Samama, 2011). As a result, the formation of blood clots decreases, helping prevent clots in blood vessels (Esmon, 2013). Through the inhibition of Factor Xa.

2.3. Enzyme study

In a theoretical study of the enzyme, the structure of Factor Xa enzyme was downloaded from the PDB database (Sahu et al., 2022). Subsequently, the enzyme was imported into Discovery Studio Visualizer as illustrated in Fig. 1. Within this software, the enzyme was prepared by removing the solvent and

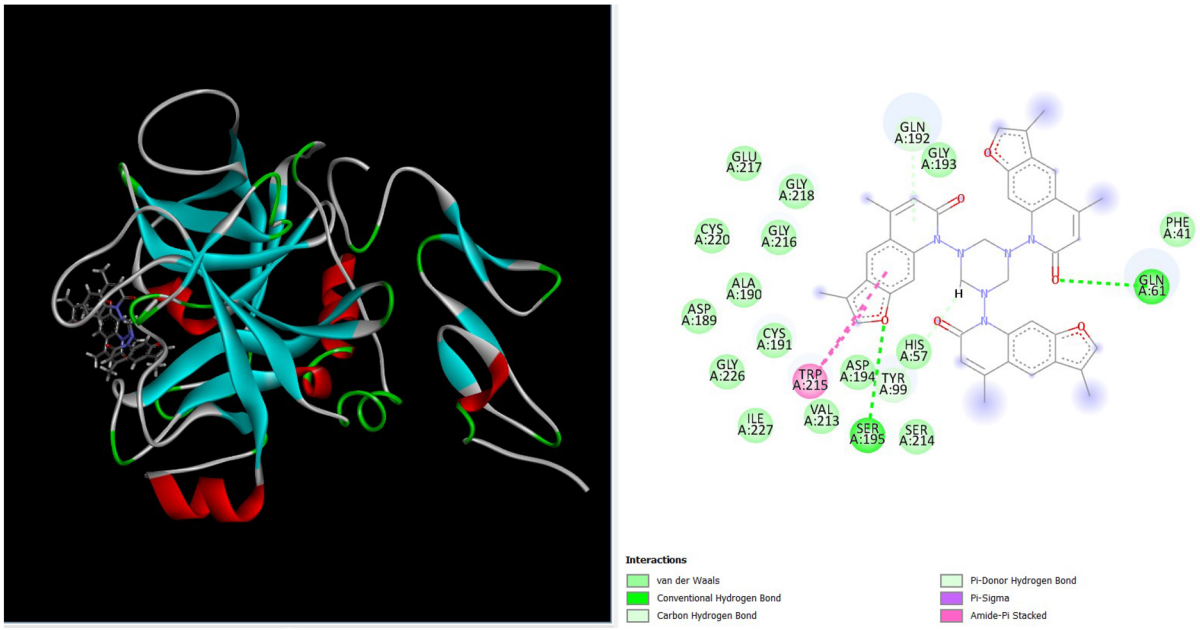


Fig. 4. 2D and 3D Molecular docking figure contacting compound K6a, with Amino acids of (Factor Xa).

identifying the active site coordinates **x**,9.76 **y**,6.71 **z**,24.87 as shown in Fig. 2. The old ligand was then removed from the enzyme and it was prepared for docking, as depicted in Fig. 3.

2.4. Factor Xa [1FAX]

Docking was performed using the MCULE program on the Factor Xa enzyme (1FAX) retrieved from the protein databank, with the new organic compound K6a and the drug Rivaroxaban (Sabbagh, AlBeik and Hadid, 2023). The theory suggests that the new organic compound K exhibits greater activity compared to Rivaroxaban, as indicated in Table 2. The interaction of active site of the receptor (Factor Xa) contains amino acid with new organic compound K6a and Rivaroxaban enzyme inhibition rates ΔG[Kcal/mol]. Two-dimensional and three-dimensional images illustrate the interaction of compound K6a with enzyme (Beno et al., 2015). as shown in Fig. 4, and similarly,

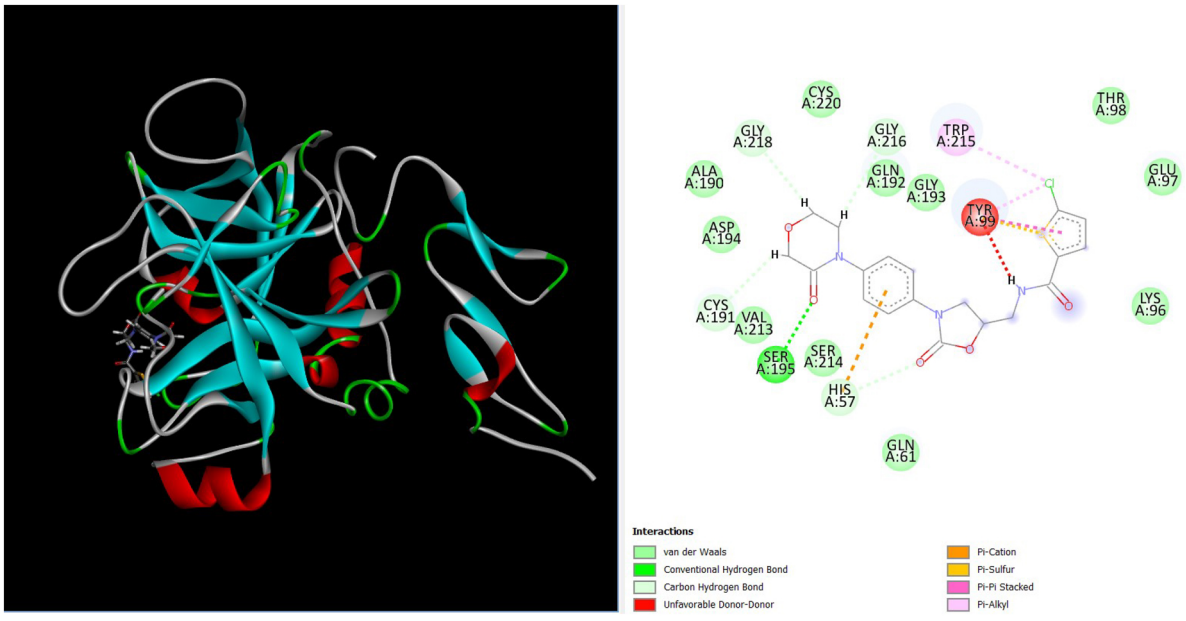


Fig. 5. 2D and 3D Molecular docking figure contacting compound Rivaroxaban, with Amino acids of (Factor Xa).

the interaction of Rivaroxaban with the enzyme, as depicted in Fig. 5.

3. Result and discussion

The study addresses the urgent need for safer anticoagulant drugs. New derivatives of furan-2-quinoline were synthesized to inhibit Factor Xa, a key enzyme in blood clotting. The compound K6a was developed by reacting furo-2-quinolone with ammonia derivatives like hydrazine Using the docking program MCULE, K6a was compared with the existing anticoagulant Rivaroxaban. The results showed that K6a had a higher negative AG value, indicating a stronger interaction and more effective inhibition of Factor Xa. This inhibition prevents thrombin formation, reducing blood clot formation. Thus, K6a is identified as a potentially more potent anticoagulant than Rivaroxaban.

Conflicts of interest

There are no Conflicts of Interest.

Funding statement

None.

Acknowledgment

I dedicate this research to all those who tirelessly strive to make new contributions in the fields of scientific research, especially in drug development and healthcare improvement. To my professors and colleagues at the College of Pharmacy and the College of Science, whose support and knowledge have inspired me. And to my family, who have been a constant source of strength and support throughout my academic journey.

References

Kocsis, B., Domokos, J. and Szabo, D. (2016) Chemical structure and pharmacokinetics of novel quinolone agents represented by avarofloxacin, delafloxacin, finafloxacin, zabofloxacin and nemonoxacin. *Ann Clin Microbiol Antimicrobials*, 15(1). https://doi.org/10.1186/s12941-016-0150-4.

Dube, P. S., Legoabe, L. J. and Beteck, R. M. (2023) Quinolone: A versatile therapeutic compound class. *Mol Divers*, 27(3), 1501–26. https://doi.org/10.1007/s11030-022-10581-8.

Saalim, M., Villegas-Moreno, J. and Clark, B. R. (2020) Bacterial alkyl-4-quinolones: Discovery, structural diversity and biological properties. *Molecules*, 25(23). https://doi.org/10.3390/molecules25235689.

Basco, L. K., Mitaku, S., Skaltsounis, A. L., Ravelomanantsoa, N., Tillequin, F., Koch, M., *et al.* (1994) Against *Plasmodium falciparum. Antimicrob Agents Chemother*, 38(5).

Senerovic, L., Opsenica, D., Moric, I., Aleksic, I., Spasić, M. and Vasiljevic, B. (2020) Quinolines and quinolones as antibacterial, antifungal, anti-virulence, antiviral and anti-parasitic agents. *Adv Exp Med Biol*, 1282, 37–69. https://doi.org/10.1007/5584_2019_428.

Grygorenko, O. O., Volochnyuk, D. M., Ryabukhin, S. V. and Judd, D. B.. (2020) The symbiotic relationship between drug discovery and organic chemistry. *Chem Eur J*, 26(6), 1196–1237. https://doi.org/10.1002/chem.201903232.

Hussien, F. A. H., Keshe, M., Alzobar, K., Merza, J. and Karam, A. (2016) Synthesis and nitration of 7-hydroxy-4-methyl coumarin via Pechmann condensation using eco-friendly media. *Int Lett Chem Phys Astron*, 69, 66–73. https://doi.org/10.56431/p-zj1ao8.

Ibraheem, H. H., Al-Bayati, R. I. and Hameed, S. M. (2016) Synthesis and characterization of new heterocyclic compounds derived from coumarin. *J Sci*, 27. www.mjs-mu.com.

Yin, H., Wu, Y., Gu, X., Feng, Z., Wang, M., Feng, D., *et al.* (2022) Synthesis of pyrano[3,2-c] quinolones and furo[3,2-c] quinolones via acid-catalyzed tandem reaction of 4-hydroxy-1-methylquinolin-2(1H)-one and propargylic alcohols. *RSC Adv*, 12(33), 21066–78. https://doi.org/10.1039/d2ra03416f.

Al-Bayati, R. I., Ahamad, M. R. and Ahamed, L. S. (2015) Synthesis and biological activity investigation of some quinoline-2-one derivatives. *Am J Org Chem*, 5(4), 125–35. https://doi.org/10.5923/j.ajoc.20150504.03.

Choodum, A. and Daeid, N. N. (2011) Rapid and semi-quantitative presumptive tests for opiate drugs. *Talanta*, 86(1), 284–92. https://doi.org/10.1016/j.talanta.2011.09.015.

Remko, M., Remková, A. and Broer, R. (2016) Theoretical study of molecular structure and physicochemical properties of novel factor Xa inhibitors and dual factor Xa and factor IIa inhibitors. *Molecules*, 21(2). https://doi.org/10.3390/molecules21020185.

Samama, M. M. (2011) The mechanism of action of rivaroxaban – An oral, direct factor Xa inhibitor – Compared with other anticoagulants. *Thromb Res*, 127(6), 497–504. https://doi.org/10.1016/j.thromres.2010.09.008.

Esmon, C. T. (2013) Targeting factor Xa and thrombin: Impact on coagulation and beyond. *Thromb Haemost*, 111(4), 625–33. https://doi.org/10.1160/TH13-09-0730.

Sahu, D., Bishwal, S. C., Malik, M. Z., Sahu, S., Kaushik, S. R., Sharma, S., *et al.* (2022) Troxerutin-mediated complement pathway inhibition is a disease-modifying treatment for inflammatory arthritis. *Front Cell Dev Biol*, 10. https://doi.org/10.3389/fcell.2022.845457.

Sabbagh, G., AlBeik, L. and Hadid, I. (2023) In silico and in vitro anticoagulant activity detection of quercetin, rutin, and troxerutin as new potential inhibitors of factor Xa. *Egypt J Chem*, 66(2), 151–66. https://doi.org/10.21608/ejchem.2022.140123.6144.

Beno, B. R., Yeung, K. S., Bartberger, M. D., Pennington, L. D. and Meanwell, N. A. (2015) A survey of the role of noncovalent sulfur interactions in drug design. *J Med Chem*, 58(11), 4383–438. https://doi.org/10.1021/jm501853m.