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Synthesis, Biological Activities and in Silico ADMET Study of Coumarin-3,4-Dihydropyrimidin-2(1*H*)-Ones

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Abstract: The synthesis of hybrid molecules represents a promising pathway for the development of new drugs. Dihydropyrimidinones (DHPMs) have demonstrated significant therapeutic and pharmacological properties, particularly as the foundational structure of several calcium channel blockers and antihypertensive agents. A wide range of biological effects, including antiviral, antitumor, antibacterial, and anti-inflammatory activities, have been described for these compounds. Functionalized DHPMs have shown significant activities against bacteria, viruses, and tumors. The synthesis of DHPMs has attracted considerable interest among organic and medicinal chemists. The most common method for synthesizing DHPMs and their corresponding dihydropyrimidinethiones (DHPMTs) involves the multicomponent Biginelli reaction. Several studies have been reported in the literature on the synthesis and biological evaluation of various pyrimido-fused heterocycles, such as pyrimido[4,5-d]pyridazin-8(7*H*)-ones, pyrano[2,3-d]pyrimidines, pyrido[2,3-d]pyrimidines, and 2,4-diaminopyrido[2,3-d]pyrimidines. As part of our interest in the synthesis of fused heterocycles, and given the importance of hybrid molecules and their synthesis which addresses several drawbacks, we describe in this work a simple strategy for the synthesis of a new series of coumarin-dihydropyrimidinone hybrid molecules. In silico toxicity predictions indicated that these compounds should have good oral bioavailability. The compounds were screened for their antimicrobial activity, and the results showed that compound 5b was the most active against the bacterium *Staphylococcus aureus*. Additionally, the compounds were docked with the FtsZ protein from *S. aureus.*

Keywords: Coumarin, Dihyropyrimididnone, Antibacterial activity, Molecular docking FtsZ protein

Introduction

Researchers in the medical, pharmaceutical, and chemical fields play a pivotal role in designing and preparing bioactive compounds to address various health issues such as cancer and bacterial infectious diseases. Consequently, there is a growing interest in the synthesis of pyrimidinone derivatives due to their promising biological applications as antimalarial, antibacterial, antifungal, anti-HIV, antiviral, anticancer, and anti-inflammatory agents(Santelli-Rouvier et al., 2004 ; Bhattacharjee et al., 2004). Correspondingly, the corresponding dihydropyrimidinones (DHPMs) have demonstrated significant therapeutic and pharmacological properties, serving as the integral backbone of several calcium channel blockers, antihypertensive agents, and α1a-antagonists. A broad spectrum of biological effects, including antiviral, antitumor, antibacterial, and anti-inflammatory activities, has been reported for these compounds (Ashok et al ., 2007). Furthermore, coumarin cores are recognized for their wide range of biological activities such as antibacterial, anticancer, anticoagulant, anti-inflammatory, and anti-HIV properties (Feng et al.,2020).

The most prevalent method for synthesizing DHPMs is through the multicomponent Biginelli reaction. This reaction involves heating a mixture of three components – a,β-ketoester, an aldehyde, and urea in ethanol with a catalytic amount of HCl. Multicomponent reactions (MCRs) are convergent processes where three or more starting materials react to yield a product (Biginelli et al., 1893). Given the biological significance of DHPMs and coumarins, and as part of our ongoing program for synthesizing bioactive compounds (Benazzouz et al., 2021 ; Halit et al., 2022), a new series of 4-aryl-6-methyl-5-(2-oxo-2*H*-chromene-3-carbonyl)-3,4-dihydropyrimidin-2(1*H*)-ones has been synthesized under mild conditions using 3-(acetoacetyl) coumarin derivatives 1a-c as key synthons, Selected compound were evaluated for their antibacterial activity. Molecular docking analysis was performed to better understand the enzyme binding mode making the design of better possible, and in silico properties prediction were studied.

Experimental

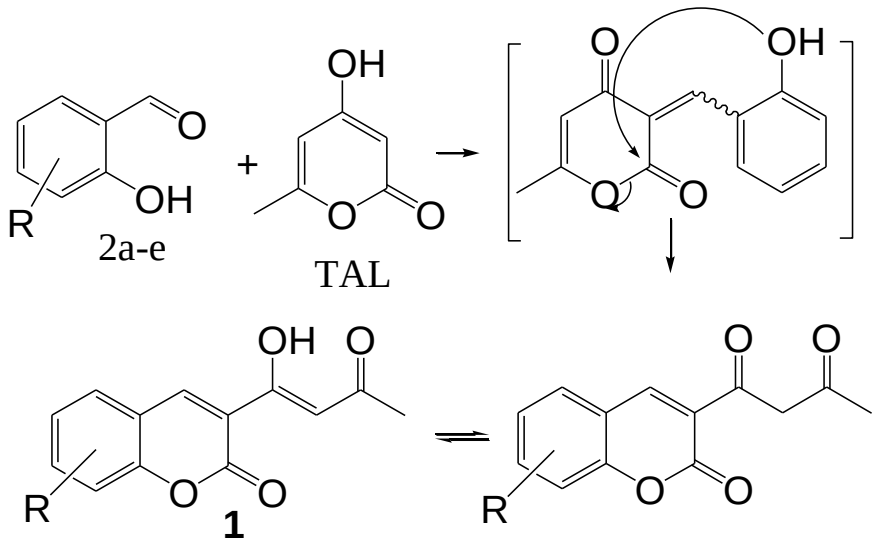
Materials

Melting points were determined on a Stuart scientific SPM3 apparatus fitted with a microscope and are uncorrected. 1H and 13C NMR spectra were recorded in DMSO-d6 solutions on Bruker Avance 300 (300.13 MHz for 1H and 75.47 MHz for 13C) spectrometer. Chemical shifts are reported in parts per million (d, ppm) using TMS as internal reference and coupling constants (J) are given in hertz (Hz). 13C assignments were made using NOESY, HSQC, and HMBC (delays for one bond and long-range JC/H couplings were optimized for 145 and 7 Hz, respectively) experiments. Mass spectra are obtained with ESIþ. Positive-ion ESI mass spectra were acquired using a Q-TOF 2 instrument [diluting 1 mL of the sample chloroform solution (w10^{-5} M) in 200 mL of 0.1% trifluoroacetic acid/methanol solution. Nitrogen was used as nebulizer gas and argon as collision gas. The needle voltage was set at 3000 V, with the ion source at 80 °C and desolvation temperature at 150 °C. Cone voltage was 35 V.

The antimicrobial activities against both Gram-positive bacteria, such as Staphylococcus aureus (ATCC 25923), and Gram-negative bacteria, including *Escherichia coli* (ATCC 25922) and *Pseudomonas aeruginosa* (ATCC 27853), were assessed in vitro.

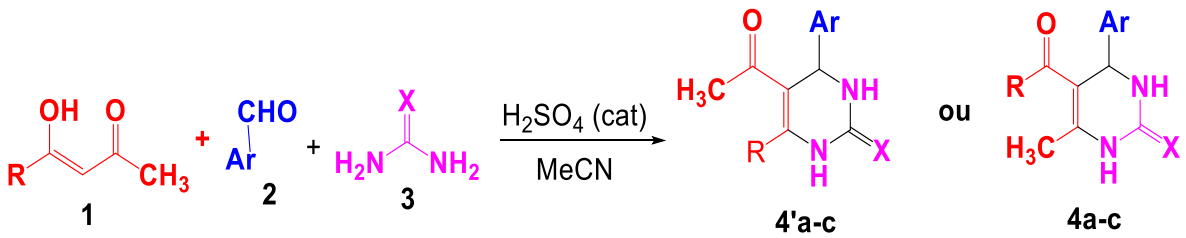
Chemistry

The starting materials 3-acetoacetylcoumarin derivatives were prepared according to the synthetic methods in Scheme 1 from substituted salicylaldehydes and 4-hydroxy-6-methyl-2*H*-pyran-2-one (triacetic acid lactone = TAL) through a tandem microwave-assisted Knoevenagel condensation and intramolecular translactonization process in an organobasic medium (Makhloufi-Chebli et al.,2008).



Scheme1. Synthesis of 3-acetoacetylcoumarin derivatives

A mixture of the appropriate 3-acetoacetylcoumarins 1 (1 mmol), benzaldehydes 2 (1 mmol), urea/thiourea 3 (1.5 mmol), and sulfuric acid (20 drops) in 10 mL of acetonitrile was stirred and refluxed for the appropriate amount of time (12-18 h). After completion of the reaction as indicated by thin layer chromatography (TLC), using a 1:4 mixture of $CHCl_3$/ methanol as eluant, the mixture was cooled to room temperature, then ice and water was added to afford the pure product. The solid was separated by filtration and washed with cold water, dried, washed with diethyl ether, and recrystallized from ethanol or ethyl acetate. (Scheme 2 and Table 1).



Scheme 2. Synthesis of 3-acetoacetylcoumarin derivatives

Screening for Antibacterial Activity

The activity of the synthesized compounds against the tested microorganisms was determined using the standardized disc agar diffusion method. The microorganisms utilized in the test included Gram-negative bacteria such as *Escherichia coli* (ATCC 25922) and *Pseudomonas aeruginosa* (ATCC 27853), as well as Gram-positive bacteria like *Staphylococcus aureus* (ATCC 25923). The tested compounds were dissolved in dimethyl sulfoxide (DMSO) with a concentration of 10^{-1} M. Subsequently, 25 µL of the tested sample was dispensed onto filter paper discs measuring 6 mm in diameter. These discs were gently placed on the surface of the agar plates and then incubated at 37°C for 24 hours. DMSO was utilized as the negative control. Following incubation, the diameters of the inhibition zones formed were measured in millimeters, and the mean values were recorded.

Computational Method

The FtsZ protein from S. aureus (FtsZ, PDB ID 4DXD) has been previously shown to be the target of antibacterial coumanins derivatives (Duggirala et al., 2014). Thus the synthesized compounds were docked with this bacterial protein to to explain their antibacterial activity. The protein *S. aureus* FtsZ (PDB ID 4DXD determined at 2.01 Å of resolution) was downloaded from the Protein Data Bank (Tan et al.,2012), corresponding to the protein S. aureus FtsZ complexed with inhibitor (PC190723). It is noteworthy that FtsZ protein is an important and vital cell division protein, which is found in S. aureus. However, we removed the bound ligand and crystallographic water molecules except those participating in the catalysis, and all missing hydrogens were added using AutoDockTools. The active site radius was taken to be 8 Å from the center of the co-crystallized ligand . Thus, the active site residues were found to be Gln192, Val207, Asn263, Val297, Leu200, Asn208, Leu209, Val203, Thr309 and Ile311. Then, the Gasteiger charges were assigned and nonpolar hydrogens were merged with their corresponding carbons (Terrachet et al., 2020; Benazzouz et al., 2021).

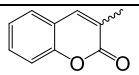
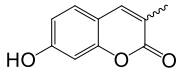
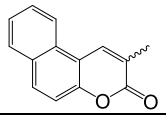
In silico predictive models are frequently applied to get an early estimation of the ADMET profile (Absorption, distribution, metabolism, excretion, and toxicity), this estimation has become a standard step nowadays in drug discovery. Thus, SwissADME server was used to predict the ADMET profile of the tested compounds.

Results and Discussion

Caracterization

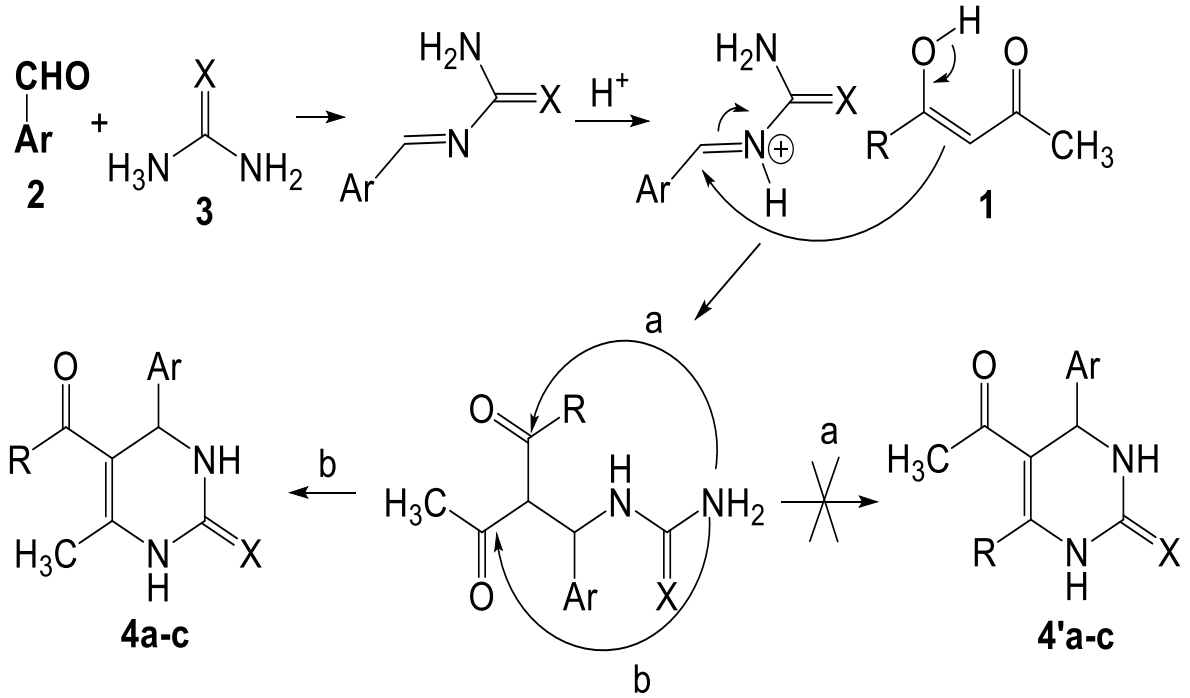
The coumarin-DHPMs derivatives **4a-c** were synthesized as outlined in Scheme 1 . The reaction of 3-acetoacetylcoumarine derivatives **1 ,** 4-nitrobenzaldehyde **2** and urea **3** gave the corresponding 4-aryl-6-methyl-5-(2-oxo-2H-chromene-3-carbonyl)-3,4-dihydropyrimidin-2(1*H*)-ones in good yields (42-70%) (Benazzouz et al., 2015). Structures of all prepared compounds were confirmed by IR, 1 H NMR and 13 C NMR analysis and their data are reported in Table 1.

Table 1. Synthesis of 4-aryl-6-methyl-5-(2-oxo-2*H*-chromene-3-carbonyl)-3,4-dihydropyrimidin-2(1*H*)-ones

Product	R	Ar	Yield (%)	Mp (°C)
4a		4-$NO_2C_6H_5$	**50**	**260**
4b		4-$NO_2C_6H_5$	**42**	**235**
4c		4-$NO_2C_6H_5$	**70**	**225**

The mechanism of the Biginelli reaction, along with the structure of the synthons used, suggests the formation of two possible dihydropyrimidinones/thiones (compounds of type 4a-c, or 4'a-c). This process initiates with the formation of an imine through the condensation of benzaldehyde with urea/thiourea, which then reacts with the 1,3-dicarbonyl compound after the nitrogen of the imine is protonated. In the final step of the mechanism, there are two possible cyclization sites, which, upon dehydration, can lead to the formation of DHPMs 4a-c (Scheme 3).

Scheme 3. Mechanism proposal for the formation of 4-aryl-6-methyl-5-(2-oxo-2*H*-chromene-



3-carbonyl)-3,4-dihydropyrimidin-2(1*H*)-ones.

The structures and purities of the obtained products were determined through elemental analysis, NMR (including extensive 2D NMR analyses, such as HSQC, HMBC, and NOESY), and mass spectrometry data. As an illustrative example, the 1H NMR spectrum of 4b displayed a singlet at δH 2.05 ppm and a doublet at δH 5.38 ppm, which were assigned to the proton resonances of the methyl group and H-6, respectively. Additionally, five other singlets were observed, attributed to H-4' (δH 8.01 ppm), H-8' (δH 6.75 ppm), NH (δH 8.11 and 9.58 ppm), and OH-7 (δH 10.92 ppm) protons. The remaining aromatic and benzopyranone protons appeared as doublets at δH 6.80, 7.52, 7.59, and 8.17 ppm.The HMBC connectivities of 4b were crucial in confirming the structure of the obtained isomer, particularly the correlation between H-40 and the ketone carbonyl carbon, which was also correlated with H-6 (Fig. 1). These correlations are consistent only with the structure 4b and not with 4'b. The HMBC connectivities of 4b facilitated the unequivocal assignment of all carbon resonances (Figure. 1).

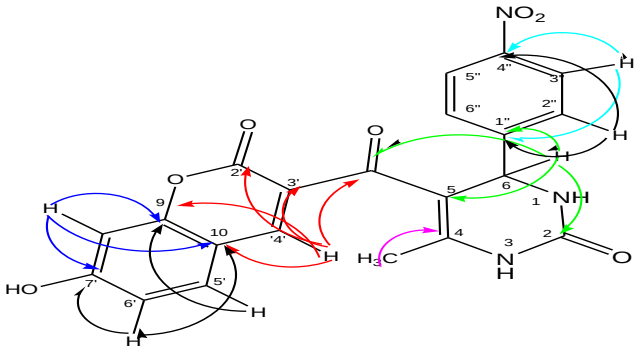


Figure 1. The HMBC connectivities of 4b

Table 2. 1H NMR data of DHPM-coumarins

Chemical shift δ (ppm)	**4a**	**4b**	**4c**
(d, CH_3 3H)	2.08	2.05	2.13
d, 1H, NH-1	8.10	8.11	9.32
(s, 1H, NH-3	9.69	9.58	9.71
d, 1H, H-5’	7.54	7.59	8.06
d, 1H, H-6	5.42	5.38	5.47
(s, OH)	/	10.92	/

Table 3. Elemental analysis and mass spectrometry data DHPM-coumarins

Compound	**m/z $(M+H)^+$**	**Anal calcd C% H% N%**	**Found C% H% N%**
4a	406	$C_{21}H_{15}N_3O_6$ 62.22, 3.73, 10.37	C 62.42, H 3.67, N 10.25.
4b	422	$C_{21}H_{15}N_3O_7$ C 59.86, H 3.59, N 9.97	C 59.68, H 3.70, N 9.75.
4c	456	$C_{25}H_{17}N_3O_6$ C 65.93, H 3.76, N 9.23	C 65.84, H 3.88, N 9.29.

B**iological Evaluation**

The results obtained indicate that the hybrid molecules 4a and 4b exhibit moderate inhibitory activity against all three tested strains. Compound 4c is inactive against all three tested strains. The activity of compound 4b is likely attributed to the presence of the hydroxyl (OH) group substituted on the benzene ring of the coumarin. This group can generate stable free radicals that participate in the redox cycle in the presence of oxygen from the air, potentially leading to lysosome destabilization and a decrease in mitochondrial membrane potential [30]

Table 4. Antimicrobil activity via disc diffusion method

Compounds	**Zone d’inhibition (mm)**		
	E.coli	*P. aeruginosa*	*S.aureus*
4b	9	8	11
4a	8	7	5
4c	7	5	8
DMSO	5	5	5

The Bioactivity Scores Prediction

The bioactivity scores of DHPMs-coumarins toward G protein-coupled receptor (GPCR) ligand, ion channel modulator, a kinase inhibitor, nuclear receptor ligand, protease inhibitors, and enzyme inhibitor were predicted by using the Molinspiration bioactivity score v2018.03 web (https:// www. molin spira tion. com/ cgi- bin/prope rties) (Ghannay et al.,2020).The predicted results are written in Table 5.

The rule for the bioactivity scores estimation is the following: when the bioactivity score was more than 0.00; the compound was considered active. While if the bioactivity score in the range between -0.50 and 0.00; the compound was moderately active. But if the bioactivity score was less than -0.50, the compound was inactive.

Table 5. The bioactivity scores prediction of the compounds 4a-c

The bioactivity score	**4a**	**4b**	**4c**
GPCR ligand	-0.68	-0.64	-0.59
Ion channel modulator	-0.63	-0.60	-0.59
Kinase inhibitor	-0.85	-0.79	-0.66
Nuclear receptor ligand	-0.48	-0.34	-0.35
Protease inhibitor	-0.74	-0.73	-0.71
Enzyme inhibitor	-0.51	-0.44	-0.42

The three DHPM-coumarin compounds showed inactivity against G protein-coupled receptor (GPCR) ligands, ion channel modulators, and kinase inhibitors, with bioactivity scores below -0.50. In terms of nuclear receptor inhibition, all compounds exhibited moderate activity, with bioactivity scores ranging from -0.35 to -0.48. Regarding enzyme inhibition, compounds 4b and 4c demonstrated moderate activity with bioactivity scores of -0.42 and -0.44, respectively, while the remaining compounds were found to be inactive.

In Silico Drug Likeness Analysis

To be considered as a drug with favorable pharmacokinetic properties, compounds must meet certain criteria outlined by Lipinski's rule. The drug likeness results of potential inhibitors, as determined using the SwissADME web server, are presented in Table 6

Table 6. Probabilities for Drug-Likeness properties of synthesized compounds,predicted by SwissADME web server

Property or rule	**4a**	**4b**	**4c**
MW (g/mol)	405.36	421.36	441.39
Solubility (Log S)	soluble	Soluble	Moderately Soluble
Log P	3.21	2.92	2.46
HBA	6	7	6
HBD	2	3	2
TPSA ($Å^2$)	134.23	154.46	134.23
Lipinski	Yes	Yes	Yes
Ghose	Yes	Yes	Yes
Veber	Yes	No	Yes
Egan	No	No	No
Muegge	Yes	No	Yes
Bioavailability Score	0,55	0.55	0,55

To adhere to Lipinski's rule, the number of hydrogen bond acceptors (HBA) should be less than or equal to 10, the n-octanol and water partition coefficient (LogP) should not exceed 5, the molecular weight (MW) should be less than or equal to 500 daltons, and the number of hydrogen bond donors (HBD) should be less than or equal to 5. The analysis of in silico results indicated that compounds 4a-c did not violate Lipinski's rule. The n-ON values range from 4 to 6, LogP values range from 2.46 to 3.91, and the number of hydrogen bond donors ranges from 0 to 1 for all synthesized compounds. It is predicted that all coumarin-DHPMs derivatives are soluble, and the total polar surface area (TPSA $\leq$ 160), which is a good indicator of drug bioavailability, falls within acceptable ranges for all compounds. (Benazzouz et al., 2021)

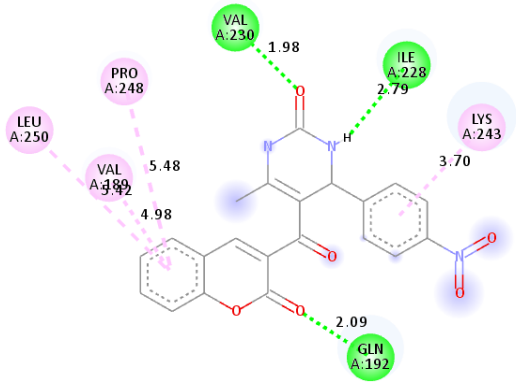
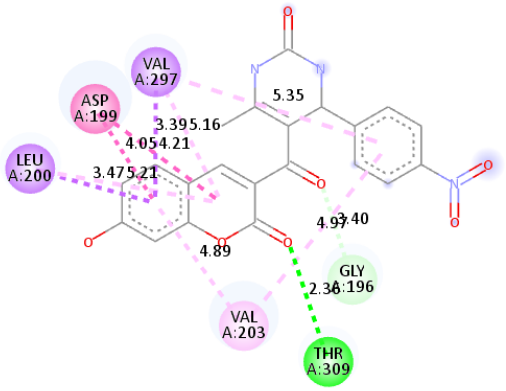
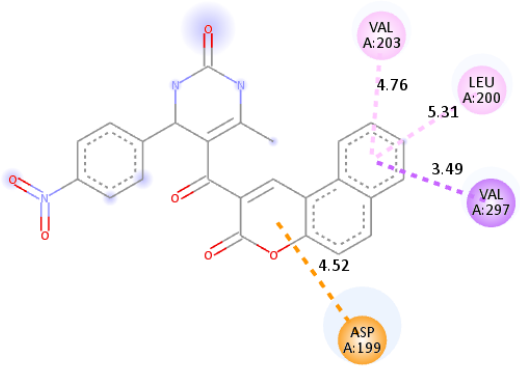
In Silico Prediction of ADMET Properties

In silico studies were conducted to evaluate the pharmacokinetic properties and safety potential of the synthesized coumarin-DHPMS derivatives. These derivatives demonstrated promising pharmacokinetic profiles in terms of human intestinal absorption (HIA), with the compounds showing high absorption values. The permeability through the colorectal carcinoma cell line (PCaCo-2) indicated favorable transport of drug metabolic compounds, falling within an acceptable range of 0 (poor absorption) to +1 (better absorption)(Seltur et al., 2017).

Table 7. ADMET properties of synthesized compounds, predicted by admetSAR and SwissADME web servers

Property	**3a**	**3b**	**3c**
PCaco-2	0.6470	0.8078	0.7648
HIA	+	+	+
PG Inhibitor	No	No	No
BBB	penetrate	No- penetrate	penetrate
CYP2C9 substrate	No	No	No
CYP2D6 Inhibitor	No	No	No
CYP3A4 Inhibitor	Yes	Yes	Yes
Carcinogenicity	No	No	No
hERG	Weak	Weak	Weak

Table 8. Docking energies, interactions observed in the docked conformations of synthesized compounds with The FtsZ protein from S. Aureus

Compounds	**Docking energy**	**2D diagram of ligand-protein Interactions**
4a	-7.6	
4b	-8.7	
4c	-9.1	

Furthermore, 4a and 4b were predicted to be non-inhibitors of important enzymes such as P-glycoprotein and cytochrome P450 isoforms 2D6, 2C19, and 3A4. This is significant as cytochrome P450 proteins play a crucial

role in drug metabolism, and inhibition of these isoforms could lead to potential drug interactions, accumulation, and toxicity.Moreover, the investigated compounds exhibited no evidence of carcinogenicity and displayed weak blocking activity against the Human Ether-a-go-go-Related Gene (hERG). It's noteworthy that the hERG gene encodes a potassium channel protein (Kv11.1) essential for cardiac action potential regulation. Inhibition of this gene could potentially lead to arrhythmic attacks or shocks. Therefore, the lack of significant inhibition against hERG suggests a favorable safety profile for the synthesized compounds.

Binding Mode of Studied Compounds

In this study, molecular docking study was performedin an effort to evaluate the binding interactions of the investigated with The FtsZ protein from *S. aureus*, and predict the best The FtsZ protein inhibitor among them. The molecules were docked in the active site of The FtsZ protein from *S. aureus* and the results are summarized in table 8. To investigate the potential mode of action and inhibition capacity of the synthesized compounds against various target macromolecules, molecular docking studies were conducted. The compounds were docked into the active site of S. aureus (PDB ID: 4DXD). The estimated binding energies and interacting residues, along with their respective denotations, are summarized in Table 8.The synthesized compounds were subjected to a molecular docking study for the analysis of their interactions with FtsZ protein from *S. aureus* PDB ID 4DXD. Binding energies varied between -9.1 kcal.mol^{-1} to -7.6 kcal.mol^{-1}.

In the active site of the receptor macromolecule 4DXD, the best binding conformations of compounds 4a-c were observed. Specifically, compound **4b** formed conventional hydrogen bonds with Thr309 (d= 2.36 Å). Furthermore, it engaged in significant interactions with essential active residues, including Gly192, Val297, Asp199, Leu200, and Val203 of the receptor macromolecule.

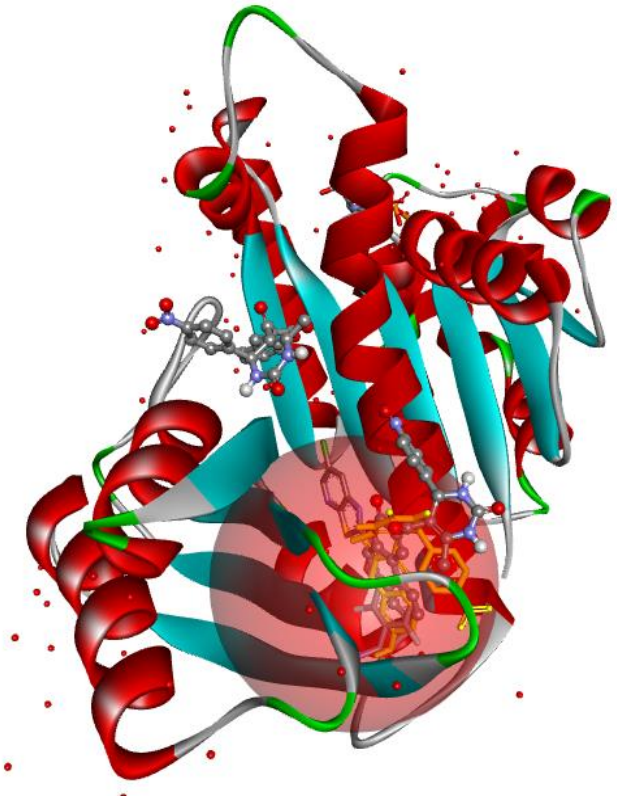


Figure 2. Superimposition of docked conformations of the compounds, **4a-c** on the crystal structure of ligand PC190723

The experimental results are in agreement with the docking predictions regarding the superposition of structures **4a-c** and the reference within the protein's active site. As shown in Figure 2, it is evident that compound **4a** is indeed bound to the molecule, but it is considerably distant from the active site. In contrast, compound **4b** is firmly anchored within the active site and binds perfectly to the key amino acids of the activity. However, molecule **4c** binds to some amino acids within the active site but extends beyond the boundaries of the key amino acids.

Conclusion

We have shown that the three-component reaction of 3-(acetoacetyl)coumarin derivatives, 4-nitro benzaldehydes, and urea, catalyzed by sulfuric acid provides a simple one-pot entry for the synthesis in very good yield of a series of new 4-aryl-6-methyl-5-(2-oxo-2*H*-chromene-3-carbonyl)-3,4-dihydropyrimidin-2(1*H*)-ones. The compounds were evaluated for antibacterial activity. The compounds with OH groups on the coumarin ring showed good activity.The results of the antibacterial activity show that only **4b** is active against bacteria *Staphylococcus aureus* compared to antibiotic used as reference. Indeed, **4b** showed good interactions with the active site amino acids of the FtsZ from *S. aureus* protein. In addition, all synthesized compounds have satisfactory calculated drug likeness parameters values, which make them promising candidates.

Scientific Ethics Declaration

The authors declare that the scientific ethical and legal responsibility of this article published in EPSTEM journal belongs to the authors.

Acknowledgements or Notes

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References

Ashok, M., Holla, B. S., & Kumari, N. S. (2007). Convenient one pot synthesis of some novel derivatives of thiazolo[2,3-b] dihydropyrimidinone possessing 4-methylthiophenyl moiety and evaluation of their antibacterial and antifungal activities.. *European Journal of Medicinal Chemistry, 42*(3), 380-385.

Benazzouz, A., Makhloufi-Chebli, M., Khatir-Hamdi, N., Boutemeur-Khedis, B., & Silva, A. M. S. (2015). A facile synthesis of new coumarin-3,4-dihydropyrimidin-2(1H)-ones/thiones dyads. *Tetrahedron*, 71, 3890-3894.

Benazzouz-Touami, A., Chouh, A., Halit, S., Terrachet-Bouaziz, S., & Makhloufi-Chebli, M. (2022). New coumarin-pyrazole hybrids: Synthesis, docking studies and biological evaluation as potential cholinesterase inhibitors. *Journal of Molecular Structures, 1249*, 1315.

Benazzouz-Touami, A., Hikem-Oukacha, D., Lamara, K. O., Halit, S., Terrachet-Bouaziz, S. (2021). Synthesis, biological activities and molecular docking study of 3-(3-oxobutanoyl)-2h-chromen-2-one derivatives. *Chemical Data Collections, 36*, 100792.

Bhattacharjee, A. K., Hartell, M. G., & Nichols, D. A. (2004). Structure-activity relationship study of antimalarial indolo [2,1-b] quinazoline-6,12-diones (tryptanthrins). Three dimensional pharmacophor modeling and identification of new antimalarial candidates *European Journal of Medicinal Chemistry, 39*(1), 59-67.

Biginelli, P. (1893). Aldehyde-urea derivatives of aceto- and oxaloacetic acids. *Gazzetta Chimica Italiana, 23*, 360-413.

Hammad S ., Bouaziz-Terrachet S., Meghnem, R., & .Meziane, D. (2020). Pharmacophore development, drug-likeness analysis, molecular docking, and molecular dynamics simulations for identification of new CK2 inhibitors. *J Mol Model, 26*(6) 160.

Duggirala, S., Nankar, R. P., Rajendran, S., & Doble, M. (2014). Phytochemicals as inhibitors of bacterial cell division protein FtsZ: Coumarins are promising candidates. *Applied Biochemistry Biotechnology, 174*(1), *283-296.*

Feng, D., Zhang, A., Yang, Y., & Yang, P. (2020) Coumarin-containing hybrids and their antibacterial activities. *Archiv der Pharmazie, 353*(6), 1-12.

Ghannay, S., Bakari, S., Msaddek, M., Vidal, S., & Kadri, A. (2020). Design, synthesis, molecular properties and *in vitro* antioxidant and antibacterial potential of novel enantiopure isoxazolidine derivatives. *Arabian Journal of Chemistry, 13*(1), 2121-2131.

Halit, S., Benazzouz-Touami, A., Makhloufi-Chebli, M., Terrachet, S., Ighilahriz, K., & Robert, A. M. S. (2022). Design, synthesis, biological evaluation of isonicotinoylpyrazolyl-coumarin derivatives and computational study. *Journal of Molecular Structure, 1265*,133487.

Makhloufi-Chebli, M., Hamdi, M., Silva, A. M. S., & Balegroune, F. (2008). Translactonisation intramoleculaire assistee par micro-ondes. Synthese des coumarines. *Journal of the Algerian Chemical Society*, *18*(1), 91-101.

Santelli-Rouvier, C., Pradines, B., & Berthelot, M. (2004). Arylsulfonyl acridinyl derivatives acting on Plasmodium falciparum. *European Journal of Medicinal Chemistry*, *39*(9), 735-744.

Setlur, A. S., Naik, S. Y., & Skariyachan, S. (2017). Herbal lead as ideal bioactive drug targets of Ebola virus in comparison with known chemical analogue: A computational drug discovery . *Interdiscipliner Sciences : Computational Life Sciences*, *9*(2), 254-277.

Tan, C. M., Therien, A. G., Lu, J., Lee, S. H., Caron, A., Gill, C. J., & Roemer, T. (2012). Restoring methicillin-resistant staphylococcus aureus susceptibility to β-Lactam Antibiotics. *Sci Transl Med*., 4(126).

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