



National Journal of Biological Sciences

Received: 24th July, 2025

Revised: 29th September, 2025

Accepted: 30th November, 2025

Published: 29th December, 2025

DOI: <https://doi.org/10.37605/v6i2/5>

RESEARCH PAPER

TITLE:

A COMPUTATIONAL STUDY ON CHEMICAL PROPERTIES OF COUMALIC ACID FOR ITS BIOLOGICAL USE AS ANTI-INFLUENZA DRUG

Authors: Muhammad Aziz¹, *Asim Nisar Sheikh², Kanwal Rasheed³

AFFILIATIONS

1. Institute of Biochemistry University of Balochistan, Quetta, Pakistan.
2. Pakistan Chemical Computational Society, Pakistan.
3. Department of Chemistry, COMSATS University Islamabad, Lahore Campus, Pakistan.

***Corresponding author:**

Email: asimnisarsheikh@yahoo.com

Tel: +923134381853.

A Computational Study on Chemical Properties of Coumalic Acid for its Biological Use as Anti-Influenza Drug

Muhammad Aziz¹, *A.N. Sheikh², Kanwal Rasheed³

Email: asimnisarsheikh@yahoo.com

ABSTRACT

Current study is designed to compute the molecular properties of Coumalic acid which highlights its role as an inhibitory neuraminidase, after attachment with Amino acid. This interrupts the life cycle of zoonotic orthomyxo-viruses which are considered as the main cause of influenza. Computational methodology is applied to investigate Coumalic acid neuraminidase's inhibitory activity. Molecular docking results reveal the concern molecule is a potential neuraminidase inhibitor that merges with the acid to active the site of neuraminidase. Pharmacodynamics tests like oral toxicity prediction reveal the compound belongs to class-III. Consulting with Globally Harmonized System, cytotoxicity, cardiac toxicity and the stress response become inactive as Coumalic acid enters in to blood brain barrier also suitable and plays a vital role as a cyclooxygenase-II inhibitor, which means Coumalic acid minimizes the effects of inflammation in humans. Computational quantum mechanical modeling is applied to calculate the molecular softness, molecular hardness, electrophilic index ionization energy, electronic properties, chemical potential, electronegativity and electron affinity which are tabulated.

Keywords: DFT, Virtual screening, drug, Flu viruses, 6-Oxopyran-3-carboxylic acid, Cell physiology,

1. INTRODUCTION

Influenza virus belongs to Negarnaviricota phylum (**Mehta and Spearman, 2024**). Influenza has an ability to spread quickly from person to person through air when someone infected with the flu coughs or sneezes. Seasonal influenza (**Zaraket et al., 2018**) is an infection caused by influenza viruses and people with cardiovascular diseases become their victim more easily (**Panhwar et al., 2019**). Many studies show that inflammatory response is also triggered by influenza virus (**Garcia et al., 2017**). So, select a drug which does not play a role in cardiac toxicity and suppresses the inflammatory effect too. Inflammation is characterized by redness, swelling, heat, and pain, and stop tissue working, which results in inflammatory cells begin in infected tissue (**Takeuchi & Akira, 2010**). Flu infection becomes severe illness if not treat, however it is not life threatening in healthy adults and synthetic drugs are used for the prevention of influenza (**Laborda, Wang, & Voglmeir, 2016**). Viruses have a capacity to create protections against past medication after modifies their target protein and the effectiveness becomes questionable and useless. Therefore, the discovery of high effective drugs is an imperative need (**Rao, Nyquist, & Stillwell, 2019**).

Surface bounded toadstool shape Glycoprotein neuraminidase plays a vital role

in the growth and life cycle of concern virus (Wang *et al.*, 2017). So, the drug which blocks the further development of influenza viruses and attach with neuraminidase also known sialidase inhibitor (Glanz, Myasoedova, Grechko, & Orekhov, 2019) can be considered as a suitable candidate against influenza virus. So, treatment of flu through drug is possible (Stiver *et al.*, 2003). Study molecular interaction provides the edge to examine the 3D virtual model confirmation. The field now a days as chemical computational prediction is a product of the digital age (Engkvist *et al.*, 2018). Through digital molecular study it is possible to see the actual issue in a comprehensible way beforehand (Daina, Blatte *et al.*, 2017). With the advancement in technology, the practice of chemicals on animals and harming the animal is no longer required (Doke & Dhawale, 2015) and the sale of products tested on animals is also banned in developing countries. There are many alternatives to animal testing methods for the evaluation of chemical toxicity. Computer-aided design can shorten the cycle of drug development (Lindert *et al.*, 2016), molecular docking technologies have been widely used for aforementioned purpose. In Silico drug-target interactions study become easy using computational docking mechanism. It makes the process easy to find multiples inhibitors (Ferrari, Wei, Costantino, & Shoichet, 2004).

Determination of chemical properties using DFT is essential to understand chemical and biological activities of the compounds against the biological target. It helps in characterizing the electrophilic or

nucleophilic nature, their ionization, potential and affinity towards the target protein.

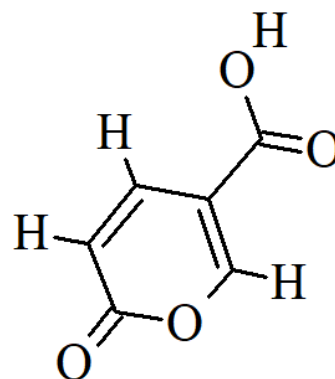


Fig S1. Molecular Structure of Coumalic Acid.

1.1. Ligand Chemistry

Generally, molecules comprising functional groups have certain properties that are similar to known drugs. Therefore, calculating the molecular property is significant parameters for oral drug, and it is shown to be an important feature in drug discovery and development. Coumalic acid contains total 14 atoms. There are 10 non-H bond(s), four multiple bonds, one rotatable bond, four double bonds, one aromatic ring, four hydrogen atoms, six carbon atoms and four oxygen atoms and at the tip there is a hydroxyl group (Fig 1.1). Molecular formula is $C_6H_4O_4$. The molecular weight is 140 g/mol, Smiles OC(=O)C1=COC(=O)C=C1, 2-oxo-2H-pyran-5-carboxylic acid is the scientific name.

2. COMPUTATIONAL METHODOLOGY

Structure of Coumalic acid is drawn through Avogadro 1.2 (Hanwell *et al.*, 2012). Different types of force fields are applied to

optimize geometry. For Oral toxicity, cytotoxicity and stress response calculation ProTox-II is used (**Banerjee, Eckert, Schrey & Preissner, 2018**). Web based application is used to predict lipophilicity (**Daina, Michielin, & Zoete, 2017**). Protein structures, i.e. neuraminidase and Cox-2, are obtained from the protein data bank online database system. Gamess is used for the calculation of physicochemical parameters

(**M.S.Gordon *et al.*, 2005**). Calculation is performed in the basic set B3LYP (Becke3-Lee-Yang-Parr) 6-31G*. Quantitative structure–activity relationship model was used to predict the potential hERG blockage (**Braga *et al.*, 2015**). For blood brain barrier online system is use (**Liu *et al.*, 2014**), Figure 2.1 draws with the help of Chimera 1.13.1(**Pettersen EF1 *et al.*, 2004**).

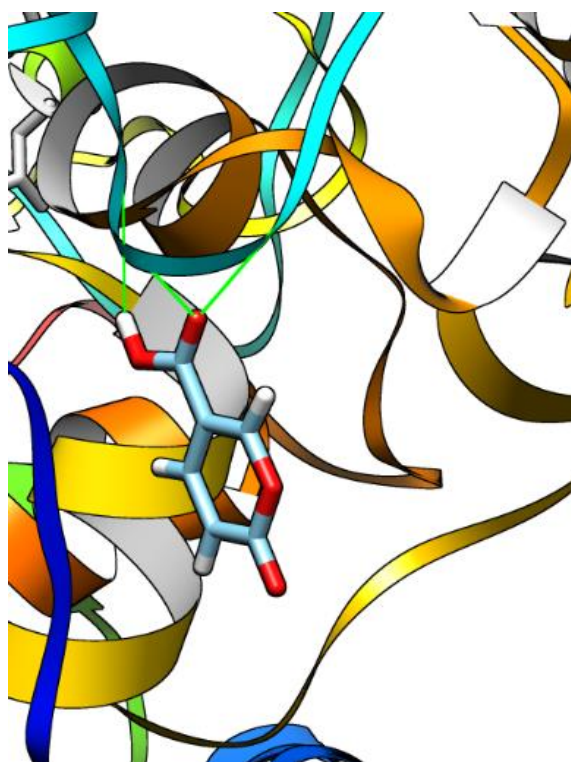


Fig S2. Interaction of Coumalic Acid with Targets.

3. RESULTS AND DISCUSSIONS

3.1 Molecular Docking

The virtual molecular docking of Coumalic acid with Neuraminidase (**UniProt *et al.*, 2008**) and the name of the organism is influenza B virus. The predicting results score, which is calculating from mcule

(**Kiss, Sandor, & Szalai, 2012**) shows that it's a good candidate for neuraminidases inhibitor.

After obtaining best score result, the above-mentioned ligand is studied with neuraminidase in Swiss docking online web system (**Grosdidier, Zoete, & Michielin,**

2011), which shows the Interrelating amino acids of neuraminidase given in table S1.

Table S1. Amino Acids⁺ Interacting Coumalic Acid Neuraminidase

Lys	Pro	Cyc	Gly	Hse	Phe	Glu	Hsd	Arg	Val	Asp	Leu
Position of Amino acid in Neuraminidase chain											
124	266	336	334	182	280	230	133	185	461	431	160
	82	317	330			413					
		121	411			125					
		230				78					
		126									
		278									

+ Where name of amino acid abbreviation.

Pilot study curbs Coumalic acid as a possible neuraminidase bound molecule; which stops further replication of flu virus, but the post-drug effect of title compound on human body is beyond the scope of this study. Computational studies carried out to show non-neglectable few parameters of pharmacodynamics.

3.2 Cyclooxygenase-2

Cox-2 or Cyclooxygenase-2 (1cx2, chain A obtain from Protein data bank) an enzyme that plays a key role in promoting inflammation. When cox-2 activity is blocked, direct inflammation is reduced. Cox-2 becomes active only at the site of inflammation i.e peripheral tissues. COX-2 inhibitor is a safe and promising therapeutic option not only for the treatment of inflammatory states but also for cancer (**J *et al.*, 2003**). Following Cox-2 amino acid Arg

44, Cys 47, Val 165, Lys 166, Gly 255 interact with Coumalic acid.

3.3 Cardiac Response

The hERG is a gene for potassium ion channels of cardiac myocytes. Any molecule that binds in the channel is known as hERG blockers (**Di & Kerns, 2016**) that can lead to cardiac arrhythmia (**Kerns & Di, 2008**). The drug which blocks off potassium channel is strongly associated with dysrhythmia conditions collectively known as drug-induced long-QT-syndrome (**Kudaibergenova, Perissinotti, & Noskov, 2018**). QSAR model reveals that it is a non-blocker. Binary prediction of non-blocker 60% and Multiclass Prediction is 80% non-blockers.

3.4 Oral Toxicity

According to LD₅₀:1120 mg/kg assessment, the concern molecule belongs to toxicity class-IV as defined by “The Globally

Harmonized System of Classification and Labelling of Chemicals” (GHS). The DL-AOT prediction and oral toxicity shows the same results (Madden *et al*, 2018).

3.5 Cytotoxicity

Inactive and Heat shock factor response also show inactive.

3.6 Lipophilicity

The ability to dissolve oil is known as Lipophilicity this property play a key role toward drug discovery (Arnott & Planey, 2012), Consensus Log Po/w 0.37.

3.7 Blood Brain Barrier

The prediction reveals the concern molecule is BBB+.

3.8 DFT Calculations

Table S2. DFT Based Physicochemical Results of Comalic Acid.

Parameter name	Symbolic Representation	Energy (eV)
Energy of HOMO	E_{HOMO}	-186.1
Energy of LUMO	E_{LUMO}	-53.8
First Energy Gap	$E_{\text{HOMO}} - E_{\text{LUMO}}$	-132.3
I (ionization energy)	$-E_{\text{HOMO}}$	186.1
E_a (electron affinity)	$-E_{\text{LUMO}}$	53
η hardness	$(I-A)/2$	66.1
μ (Chemical potential)	$-(I+A)/2$	-119.9
S (softness)	$1/\eta$	0.015
Ω (electrophilicity index)	$\mu^2/2\eta$	108.7
χ_m (Electronegativity)	$\frac{1}{2}(I+E_a)$ Kcal/mol	119.7

4. DISCUSSIONS

Identifying ligand binding on desired protein is an important step. Protein plays any

important role in replication of viruses. If the ligand binding ability is proved it means that the ligand is capable of cutting down the life

cycle of viruses. Through molecular docking application we are able to discover binding sites in protein (neuraminidase).

To know a molecules side effect during the early phase, reduce the risk of drug attrition due to cardio toxicity during pre-clinical stages.

Computer based models are used to predict the molecular side effects like oral toxicity, cytotoxicity, cardiac toxicity, lipophilicity, inflammation, and other miscellaneous effects play a vital role toward drug effeteness.

CONCLUSION

The results of current computer synthetic compound are useful to predict even complex amine precursors. These results show that drug will attach at the active site of glycoprotein of neuraminidase and stop the replication of virus. There is a need to test Neuraminidase inhibition/ Hemagglutination assay against the concern molecule, which does not play a role toward cardiac toxicity and is helpful in inflammation.

Conflicts of Interest The authors declare that there is no conflict of interest regarding the publication of this paper.

List of Abbreviation

QSAR= Quantitative structure activity relationship, hERG = Human Ether-a-go-go-related Gene, HOMO = Highest Occupied Molecular Orbital, LUMO = Lowest Unoccupied Molecular Orbital, DFT = Density functional theory.

REFERENCES

Arnott, J. A., & Planey, S. L. (2012). The influence of lipophilicity in drug discovery and design. *Expert*

Opinion on Drug Discovery, 7(10), 863-875. doi: 10.1517/17460441.2012.714363

Banerjee, P., Eckert, A. O., Schrey, A. K., & Preissner, R. (2018). ProTox-II: a webserver for the prediction of toxicity of chemicals. *Nucleic Acids Research*, 46, 257-263. doi: 10.1093/nar/gky318

Braga, R. C., Alves, V. M., Silva, M. F. B., Muratov, E., Fourches, D., Lião, L. M., . . . Andrade, C. H. (2015). Pred-hERG: A Novel web-Accessible Computational Tool for Predicting Cardiac Toxicity. *Molecular informatics*, 34(10), 698-701. doi: 10.1002/minf.201500040

Daina, A., Blatter, M.-C., Baillie Gerritsen, V., Palagi, P. M., Marek, D., Xenarios, I., . . . Zoete, V. (2017). Drug Design Workshop: A Web-Based Educational Tool To Introduce Computer-Aided Drug Design to the General Public. *Journal of Chemical Education*, 94(3), 335-344. doi: 10.1021/acs.jchemed.6b00596

Daina, A., Michielin, O., & Zoete, V. (2017). SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. *Scientific reports*, 7, 42717-42717. doi: 10.1038/srep42717

Di, L., & Kerns, E. H. (2016). Chapter 16 - hERG Blocking. In L. Di & E. H. Kerns (Eds.), *Drug-Like Properties (Second Edition)* (pp. 243-250). Boston: Academic Press.

- Doke, S. K., & Dhawale, S. C. (2015). Alternatives to animal testing: A review. *Saudi Pharmaceutical Journal*, 23(3), 223-229. doi: <https://doi.org/10.1016/j.jsps.2013.11.002>
- Engkvist, O., Norrby, P.-O., Selmi, N., Lam, Y.-h., Peng, Z., Sherer, E. C., . . . Smyth, L. A. (2018). Computational prediction of chemical reactions: current status and outlook. *Drug Discovery Today*, 23(6), 1203-1218. doi: <https://doi.org/10.1016/j.drudis.2018.02.014>
- Ferrari, A. M., Wei, B. Q., Costantino, L., & Shoichet, B. K. (2004). Soft Docking and Multiple Receptor Conformations in Virtual Screening. *Journal of medicinal chemistry*, 47(21), 5076-5084. doi: 10.1021/jm049756p
- Garcia, L. P. T. M. T. C. (2017). The inflammatory response triggered by Influenza virus: a two edged sword. *Inflammation Research*, 66(4), 288-302. doi: 10.1007/s00011-016-0996-0
- Glanz, V. Y., Myasoedova, V. A., Grechko, A. V., & Orekhov, A. N. (2019). Sialidase activity in human pathologies. *European Journal of Pharmacology*, 842, 345-350. doi: <https://doi.org/10.1016/j.ejphar.2018.11.014>
- Grosdidier, A., Zoete, V., & Michielin, O. (2011). SwissDock, a protein-small molecule docking web service based on EADock DSS. *Nucleic Acids Research*, 39(suppl_2), W270-W277. doi: 10.1093/nar/gkr366
- Hanwell, M. D., Curtis, D. E., Lonie, D. C., Vandermeersch, T., Zurek, E., & Hutchison, G. R. (2012). Avogadro: an advanced semantic chemical editor, visualization, and analysis platform. *Journal of Cheminformatics*, 4(1), 17. doi: 10.1186/1758-2946-4-17
- J, C. (2003). Cyclooxygenase-2 biology. *Curr Pharm Des.*, 9(27), 2177-2190.
- Kerns, E. H., & Di, L. (2008). Chapter 16 - hERG Blocking. In E. H. Kerns & L. Di (Eds.), *Drug-like Properties: Concepts, Structure Design and Methods* (pp. 209-214). San Diego: Academic Press.
- Kiss, R., Sandor, M., & Szalai, F. (2012). [Http://Mcule.com](http://Mcule.com): A public web service for drug discovery (Vol. 4).
- Kudaibergenova, M., Perissinotti, L. L., & Noskov, S. Y. (2018). Lipid roles in hERG function and interactions with drugs. *Neuroscience Letters*. doi: <https://doi.org/10.1016/j.neulet.2018.05.019>
- Laborda, P., Wang, S.-Y., & Voglmeir, J. (2016). Influenza Neuraminidase Inhibitors: Synthetic Approaches, Derivatives and Biological Activity. *Molecules (Basel, Switzerland)*, 21(11), 1513. doi: 10.3390/molecules21111513
- Lindert, S. P. L. a. S. (2016). Computational methods in drug discovery. *Beilstein J. Org. Chem.*, 12, 2694-2718. doi: 10.3762/bjoc.12.267
- Liu, H., Wang, L., Lv, M., Pei, R., Li, P., Pei, Z., . . . Xie, X.-Q. (2014). AlzPlatform: An Alzheimer's

- Disease Domain-Specific Chemogenomics Knowledgebase for Polypharmacology and Target Identification Research. *Journal of Chemical Information and Modeling*, 54(4), 1050-1060. doi: 10.1021/ci500004h
- MEHTA, D. & SPEARMAN, P. 2024. Chapter 116 - Influenza viruses. In: TANG, Y.-W., HINDIYEH, M. Y., LIU, D., SAILS, A., SPEARMAN, P. & ZHANG, J.-R. (eds.) *Molecular Medical Microbiology* (Third Edition). Academic Press.
- M.S.Gordon, M. W. S. e. b., C.E.Dykstra, G.Frenking, K.S.Kim, G.E.Scuseria (2005). Advances in electronic structure theory: GAMESS a decade later Theory and Applications of Computational Chemistry: the first forty years. *Elsevier, Amsterdam*, 1167-1189.
- Madden, J. C. (2018). Predictive Tools and Databases for Toxicokinetics. *Toxicology Letters*, 295, S7. doi: <https://doi.org/10.1016/j.toxlet.2018.06.027>
- Panhwar, M. S., Kalra, A., Gupta, T., Kolte, D., Khera, S., Bhatt, D. L., & Ginwalla, M. (2019). Effect of Influenza on Outcomes in Patients with Heart Failure. *JACC: Heart Failure*. doi: <https://doi.org/10.1016/j.jchf.2018.10.011>
- Pettersen EF1, G. T., Huang CC, Couch GS, Greenblatt DM, Meng EC, Ferrin TE. (2004). UCSF Chimera--a visualization system for exploratory research and analysis. *J Comput Chem.*, 25(13), 1605-1612. doi: 10.1002/jcc.20084
- Rao, S., Nyquist, A.-C., & Stillwell, P. C. (2019). 27 - Influenza. In R. W. Wilmott, R. Deterding, A. Li, F. Ratjen, P. Sly, H. J. Zar & A. Bush (Eds.), *Kendig's Disorders of the Respiratory Tract in Children (Ninth Edition)* (pp. 460-465.e462). Philadelphia: Content Repository Only!
- Stiver, G. (2003). The treatment of influenza with antiviral drugs. *Canadian Medical Association Journal*, 168(1), 49-57.
- Takeuchi, O., & Akira, S. (2010). Pattern Recognition Receptors and Inflammation. *Cell*, 140(6), 805-820. doi: <https://doi.org/10.1016/j.cell.2010.01.022>
- UniProt, C. (2008). The universal protein resource (UniProt). *Nucleic Acids Research*, 36(Database issue), D190-D195. doi: 10.1093/nar/gkm895
- Wang, Z., Cheng, L. P., Zhang, X. H., Pang, W., Li, L., & Zhao, J. L. (2017). Design, synthesis and biological evaluation of novel oseltamivir derivatives as potent neuraminidase inhibitors. *Bioorganic & Medicinal Chemistry Letters*, 27(24), 5429-5435. doi: <https://doi.org/10.1016/j.bmcl.2017.11.003>
- Zaraket, H., Melhem, N., Malik, M., Khan, W. M., Dbaiibo, G., & Abubakar, A. (2018). Review of seasonal influenza vaccination in the Eastern

Mediterranean Region: Policies, use
and barriers. *Journal of Infection and
Public Health*. doi:

<https://doi.org/10.1016/j.jiph.2018.10.009>