Ibn Al-Haitham Journal for Pure and Applied Sciences
Journal homepage: jih.uobaghdad.edu.iq
PISSN: 1609-4042, EISSN: 2521-3407
IHJPAS. 2024, 37(4)

DFT Calculation and Docking Affinity Evaluation of Novel Quinoline Derivatives as an Antibacterial Agent

Aya Ali Mohammed[1] and Ahlam Mohammed Farhan[2,*]
[1,2] Department of Chemistry, College of Science for Women, University of Baghdad, Baghdad, Iraq.
*Corresponding Author.

Received: 19 May 2023 Accepted: 25 June 2023 Published: 20 October 2024
doi.org/10.30526/37.4.3500

Abstract

The frightening growth of bacterial infections and their resistance to most first-line antibiotic drugs have made antibacterial therapy challenging. High accuracy, reduced time and effort, high cost, and a theoretical chemical study to find alternative treatments are preferable considerations. Chemical programs designed 150 fluoroquinolones in a theoretical study, and determined the top five based on their optimal binding affinity. The binding affinity (G) was calculated in Swiss Dock; a more negative G indicates a more suitable binding between the compound and the protein. This study selected the top five fluoroquinolones against each protein. The ΔG calculations indicate compound B has the highest inhibitory activity against *Staphylococcus aureus* (ΔG= -7.562 kcal/mol). Compound C has the strongest inhibitory activity against *E. coli* (ΔG= -8.562 kcal/mol) because it interacts with the Gyrase B protein. Compound A has the strongest inhibitory activity against *Streptococcus pyogenes* (ΔG= -6.762 kcal/mol) because it interacts with the cysteine protease Spe B. Compound D has the strongest inhibitory activity against *Klebsiella pneumoniae* (ΔG= -7.524 kcal/mol) because it interacts with the NDM-1 protein (ΔG= -6.999 kcal/mol) through their interaction with the azobenzene reductase protein. The HOMO-LUMO energy gaps of compounds (A-E) were theoretically estimated at B3LYP in conjunction with the base 6-311G (d, p) using DFT-based structural optimization. Compound E (ΔE Gap= 0.130 eV) is the one with the lowest energy gap. Compound C (ΔE Gap= 0.1609 eV) is the one that has the largest energy gap.

Keywords: Antibacterial, functional theory, HOMO-LUMO energy gaps, molecular docking, quinoline.

1. Introduction

Bacterial infections have a higher rate of morbidity and mortality, affecting millions of individuals as one of the most common causes of chronic diseases. Any bacterial infection appears to be a significant danger on a global scale [1]. Various bacterial strains have infected one-third of the world's population [2]. Even though it is the 21st century, a bacterium still poses a severe threat to human health, necessitating urgent research to develop chemicals with superior antibacterial properties and broad-spectrum activities. Therefore, it is crucial to develop new

pharmaceuticals that can treat diseases and inflammation while having reduced adverse effects on patients [3].

Recently, quinoline heterocyclic chemistry has gained attention in terms of biological and pharmacological effects. This system has proven to be an excellent scaffold for organic and pharmaceutical chemists. On the other hand, researchers have extensively explored quinoline derivatives as bioactive chemicals [4]. Quinoline and its derivatives have considerable applications in medicine and organic chemistry. These compounds are effective against malaria [5, 6], cancer [7, 8], bacteria [9, 10], fungi [11-13], viruses [14], inflammatory conditions [15], tumors [16], cancer cells [17], and tuberculosis [18].

Quinoline, also known as 1-aza-napthalene or benzo[b]pyridine, is a heterocyclic aromatic chemical that contains nitrogen. Its molecular weight is 129.16, and its chemical formula is C_9H_7N. The log P value is 2.04. The log P means The partition coefficient, also known as P, is defined as the ratio of solute concentrations between two solvents in a two-phase liquid phase. When one solvent is water and the other is a non-polar solvent, the log P value indicates whether the solvent is lipophilic or hydrophobic, with an acidic pKb of 4.85 and a basic pKa of 9.5. The quinoline serves as a weak tertiary base [19, 20]. **Figure 1** shows the quinoline structure.

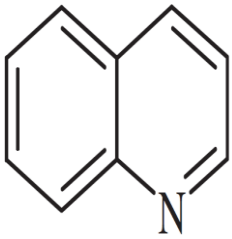


Figure 1. Quinoline structure [20].

A computational method plays a significant role in drug development by reducing the time and money needed in the drug design process. When designing novel drugs, using chemical and biological information ligands and/or targets to filter out molecules with undesirable qualities [21] is an effective filter-designing process. One of the most crucial issues in chemistry that has emerged recently is the understanding of chemical species reactivity. The development of theories that highlight the elements that influence reactivates is crucial for comprehending the reasons behind a reaction and its potential speed. Similarly, obtaining quantitative reactivity indexes is critical for rational design because they play an important role in calculating and forecasting reaction rates. To address these issues, chemists have made numerous attempts to develop quantitative reactivity signifiers. In chemistry, determining a molecule's reactivity (such as its nucleophilicities and electrophilicities) is crucial [22]. Several theories, such as Density Functional Theory (DFT), demonstrate that a molecule's nucleophilicity correlates with the energy of the highest occupied molecular orbital (HOMO) of the nucleophile, while its electrophilicity correlates with the energy of the lowest unoccupied molecular orbital (LUMO) of the electrophile [22]. Charge transfer within the molecule has occurred, as seen by the HOMO and LUMO energies [23]. The energy of HOMO (E-HOMO) primarily determines a molecule's ability to donate electrons. Adsorption and, hence, the increase in E-HOMO values may support adsorption and, consequently the ef. The molecule achieves this by directing its orbital electrons to an appropriate acceptor with an empty molecular orbital. On the other hand, the energy of LUMO (E-LUMO) describes a molecule's ability to accept electrons. d. Low E-LUMO values

indicate a higher likelihood of a molecule receiving electrons [24]. Molecular docking plays a significant role in understanding the binding interactions between a ligand and a protein receptor. This approach to drug design is very efficient in terms of the amount of time and money saved. Quinoline-containing compounds and these kinds of molecules are of crucial medical and pharmacological significance [25]. The DFT-optimized structures were used as an input for Swissdock. From the Protein Data Bank, crystal structures of receptor molecule 1NNI (Azobenzene Reductase from *Bacillus subtilis),* 2W9S (*Staphylococcus aureus* S1:DHFR in complex with trimethoprim), 3G7E (Crystal structure of *E. coli* Gyrase B co-complexed with prop-2-yn-1-yl {[5-(4-piperidin-1-yl-2-pyridin-3-yl-1,3-thiazol-5-yl)-1 hpyrazol-3-yl] methyl} carbamate inhibitor), and 4HL2 New Delhi Metallo-β-Lactamase-1 protein (NDM-1) of *Klebsiella pneumoniae,* 4RKX, and cysteine protease Spe B of *Streptococcus pyogenes* were obtained [26]. The study applies a theoretical approach to quinoline derivatives to predict and identify the most effective compounds. These compounds can be further evaluated experimentally for their anti-bacterial activity.

2. Materials and Methods

2.1 Computational Chemistry

Computational techniques are becoming more and more important and popular in drug development and discovery because they expedite researchers' time-consuming work and efforts. The docking procedure is one of these methods for predicting the ligand's conformation and orientation within the target's binding site. Accurate structural modeling and precise information about a compound's action are the primary objectives of docking investigations in general [27]. This procedure involves the use of three-dimensional conformations produced by the ChemDraw16.0 application included in the Chem Office software suite (Chem Office, 2016) [28].

3. Results and Discussion

3.1 The DFT studies

All synthetic molecules and natural compounds must have their electrical and structural properties optimized using the relatively quick and effective density functional theory. This study introduces density functional theory (DFT) and primarily explores the crucial elements associated with this topic. The DFT theory primarily presents and explores the key points in this study. The global reactivity parameters associated with each molecule have been calculated; in this case, E_{Homo} and E_{LUMO}, E gap (ΔE), the chemical potential (μ), the index of electrophilicity (ω), chemical hardness (η), softness (S), and electron affinity (EA). The equations below were used [29].

$$IP = -E_{HOMO} \quad (1)$$

$$EA = -E_{LUMO} \quad (2)$$

$$\mu = -\frac{1}{2}(E_{HOMO} + E_{LUMO}) \quad (3)$$

$$S = -\frac{2}{(E_{HOMO} - E_{LUMO})} \quad (4)$$

$$\eta = -\frac{1}{2}(E_{HOMO} - E_{LUMO}) \quad (5)$$

$$\omega = \frac{\mu 2}{2\eta} \quad (6)$$

The lowest unoccupied molecular orbital (LUMO) and the highest occupied molecular orbital (HOMO) are the boundary orbitals, and their characteristics are crucial for the chemical reactivity of any organic compound. The LUMO orbital often receives electrons, whereas the HOMO orbital typically loses them. Electrical activity correlates with the LUMO energy, whereas the ionization potential relates to the HOMO energy. This work examined the HOMO-LUMO distributions, their energies in eV units, and the corresponding quantum chemical descriptors of compounds (A, B, C, D, and E). The quantum chemical descriptors of these molecules were computed using the DFT/B3LYP approach and the basis set 6-311+G. Computational chemistry has predicted five active compounds, as shown in **Figure 2**. These compounds can be further evaluated experimentally for their antibacterial activity.

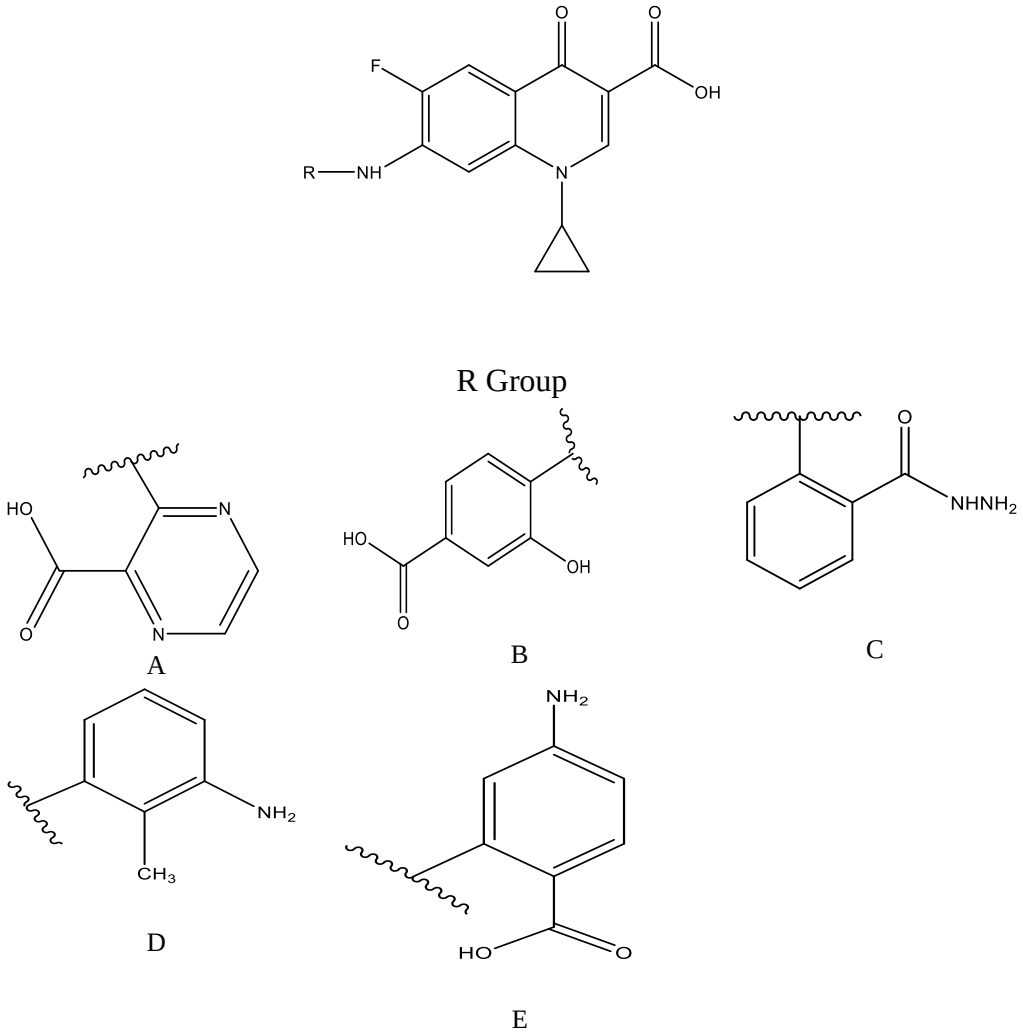


Figure 2. An overview of quinoline derivatives active.

The aim is to investigate the connection and correlation between the physicochemical and biological characteristics of synthesized molecules and their structural characteristics. We used Gaussian 09's implementation of the 6-311+G (d, p) basis set and the Gauss View 6.0 program suite to optimize the ground state molecular geometry of the (A, B, C, D, E) molecules [30]. Density functional theory, a method of optimization, yields the optimized structure, HOMO, and LOMO of compounds (A–E) as shown in **Figure 3**.

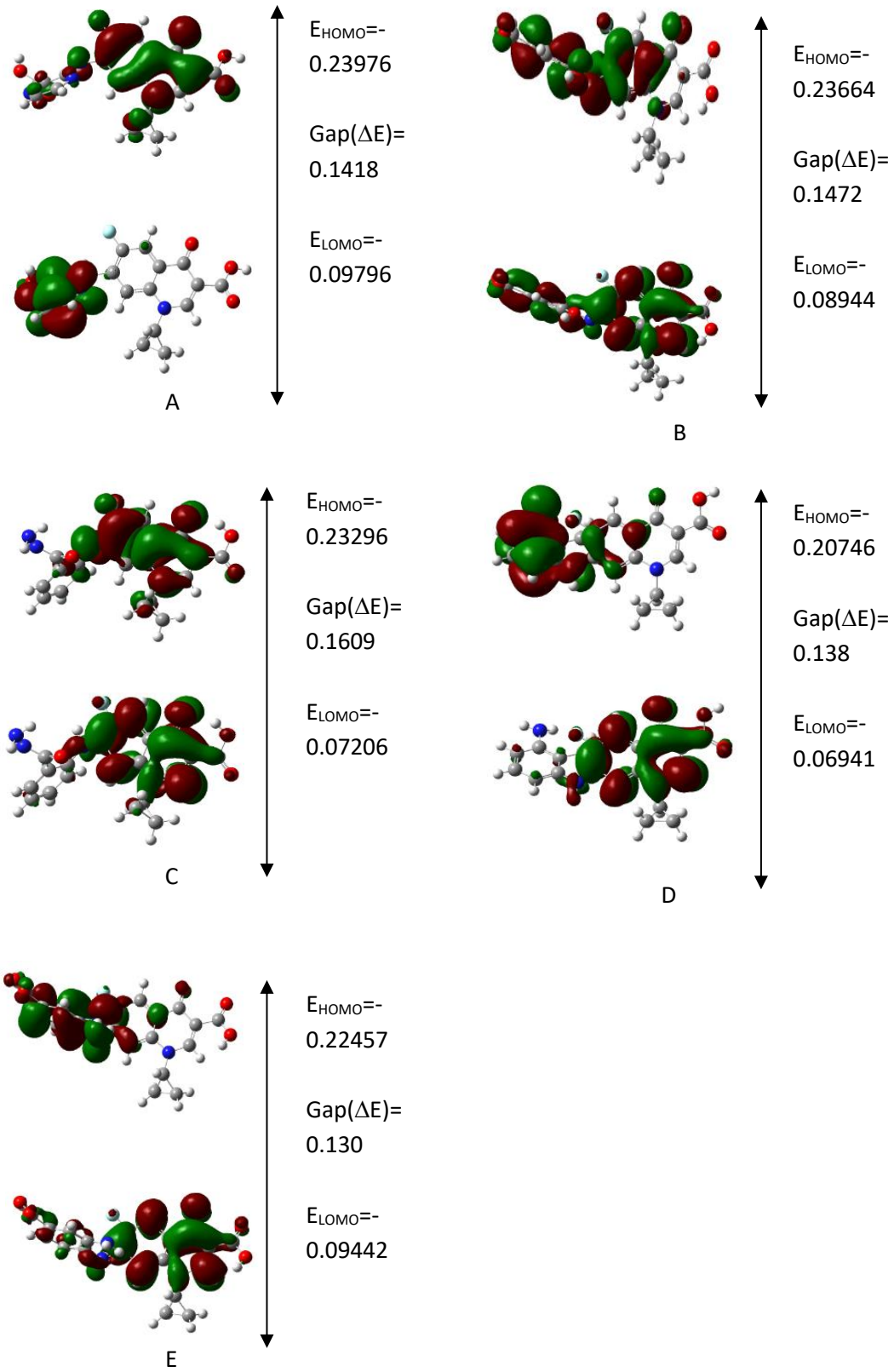


Figure 3. Optimized structure, HOMO, and LOMO of compounds (A-E) obtained from density functional theory.

HOMO (Highest Occupied Molecular Orbital) and LUMO (Lowest Unoccupied Molecular Orbital): For chemists and physicists, these electronic characteristics were crucial. The inner-maximum orbital, known as the LUMO, is described as an inner-maximum orbital where electrons can just be accepted [31].

HOMO stands for the ability to give an electron, while LUMO, an electron acceptor, stands for the ability to receive an electron. The energy gap between HOMO and LUMO governs the kinetic stability, chemical reactivity, and chemical hardness-softness of a molecule [32]. The HOMO-LUMO energy gap of Quinoline has been estimated to be at the DFT level. **Figure 3** shows the molecular orbitals and atomic orbital compositions.

Based on the results mentioned in **Table 1**, compound E (ΔE Gap= 0.130 eV) is the compound with the lowest energy gap. This allows the molecules with the shortest distance to be the softest. Compound C (ΔE Gap= 0.1609 eV) is the compound that has the largest energy gap. Compound D has the largest HOMO energy (EHOMO= -0.207 eV). Its higher energy allows it to be the strongest electron donor. Furthermore, compound A (ELUMO= 0.097 eV) has the lowest LUMO energy, indicating that it may be the strongest electron acceptor.

The HOMO and LUMO electron orbital energies relate to both IP (potential ionization) and EA (electron affinity), respectively. Compound D has the lowest potential ionization value (IP = 0.207 eV), rendering it the best electron donor. Compound A has the highest electron affinity value (EA= 0.09 eV), so it would be the best acceptor of electrons.

The chemical reactivity of a molecule varies depending on its chemical structure. Compound E has the lowest molecular hardness (softness) value among other molecules (η= 0.065 eV, S= 2.207 ev). The smallest orbital energy gap (ΔE= 0.130 eV) of E leads to the greatest chemical reactivity and the least kinetic stability as "the softest molecule.".

It has been compared orbital energies when considering a compound's chemical reactivity. The orbital HOMO has a higher energy and serves as an electron donor. The orbital LUMO acts as an acceptor for the less energetic electron. **Table 1** shows that the hardness value (a bigger difference between the HOMO and LUMO energies) of the final products makes them more stable, along with the intermediates.

Table1. Quantum chemical factors of compound.

Qualities	A	B	C	D	E
LUMO	-0.09796	-0.08944	-0.07206	-0.06941	-0.09442
HOMO	-0.23976	-0.23664	-0.23296	-0.20746	-0.22457
gap	0.1418	0.1472	0.1609	0.138	0.130
IP	0.23976	0.23664	0.23296	0.20746	0.22457
EA	0.09796	0.08944	0.07206	0.06941	0.09442
μ	0.1688	0.16304	0.1525	0.1384	0.1594
η	0.4515	0.455	0.464	2.150	0.453
S	2.214	2.197	2.155	2.150	2.207
Ω	0.332	0.325	0.309	0.306	0.314
χ	0.548	0.544	0.536	0.534	0.547

In *Escherichia coli*, compound C has the highest biological activity, with an energy gap value of 0.106 eV, while compound B in *Staphylococcus aureus* has the highest biological activity, with an energy gap value of 0.1472 eV. Compound A in *Streptococcus aureus* has the highest binding affinity, which means it has the highest biological activity with an energy difference of about ΔE = 0.1418 eV. Compound D had the highest biological activity in *Klebsiella pneumonia*, with an energy difference of ΔE = 0.138 eV. While compound E in *Bacillus subtilis* indicates the highest degree of docking to the highest biological activity, it has an energy gap value of about

$\Delta E = 0.130$ eV.

3.2 Molecular docking

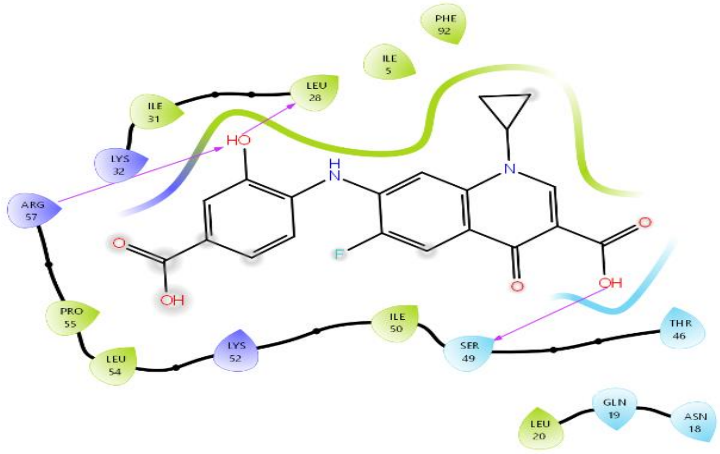
Drug molecules use molecular docking to demonstrate their binding activities to proteins [33]. Calculations using molecular docking, attempt to predict the most likely mode of interaction between a given protein and ligand [34]. Future *in vivo* and *in vitro* studies will limit the options for drugs to use, leading to this technique being considered highly helpful in the drug design field [35].

The docking investigation currently involves docking five chemicals with various types of proteins. The results in **Table 2** show that compound B had the best docking scores for *Staphylococcus aureus*. This demonstrated its strong binding affinity and accurate placement within the target protein's active site. This interacts with its necessary amino acids, indicating that these two molecules have significant levels of biological activity. **Figure 4** illustrates how the compounds with the highest scores on the list align their molecules with the essential amino acids in the active binding site protein.

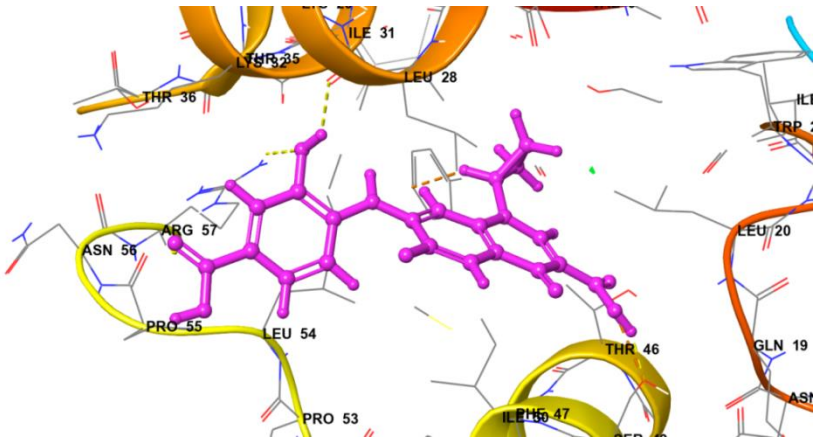
Table 2. Docking score of quinoline derivatives.

		A	B	C	D	E
Staphylococcus aureus	Docking Score (kcal/mol)	-6.987	-7.562	-6.758	-6.533	-6.687
	Binding Interaction	GLN19,LEU20, THR46,SER49, ILE50, LYS52, LEU54,PRO55, ARG57,LEU28, LYS29, ILE31, LYS32,PHE92	ILE5,LEU28,ILE31,LYS32, PHE92, ARG57,PRO55,LEU54,LYS52, ILE50, SER49, THR46, LEU20, GLN19, ASN18	ILE5,VAL6, ALA7,TYR98, PHE92,ASP27, LEU28,ILE31, LYS32, ARG57, LEU54,LYS5, ILE50,THR46, LEU20,TRP22	TYR98, PHE92, THR111,LEU, GLN19, LEU20,IE50, SER49, THR46, ILE5, VAL6, ALA7, ASP27, LEU28, ILE31	GLN19, LEU20, ILE5, PHE92, LEU28, ILE31, LYS32, ARG57, PRO55,LEU54, THR46, SER49, LYS52, ILE50
Streptococcus pyogenes	Docking Score (kcal/mol)	-6.762	-5.89	-5.852	-5.656	-5.74
	Binding Interaction	TRP389, ASP275, ALA283, H_20, SER282, GLY281, SER280,SER279, GLY339, HIE340, ALA341, CYS192, VAL193, GLN332, VAL334	CYS192,VAL19, H_2O,SER280, SER279, GLY281, SER282, ALA283, VAL334, GLN332, TYR389, ALA341, HIE340, GLY339, GLY338	ALA341, HIE340, GLY339, GLY284, VAL193, CYS192, ALA283, SER282, H_2O, SER280, GLY281, SER279, GLN332, GLY333, VAL334, GLN390, TYR389	GLY284, ALA283, SER282, GLY281, SER280, SER279, CYS192, VAL193, H_2O, TYR389, VAL334, GLY333, GLN332, ALA341, HIE340, GLY339, GLY338	ALA341, HIE340, GLY339, VAL193, CYS192, H_2O,GLY284, ALA283, SER282, GLY281, SER280, SER279, TYR389, GLN332, GLY333, VAL334
Escherichia coli	Docking Score	-6.77	-6.622	-8.562	-5.933	-8.295
	Binding Interaction	GLY102, LYS103,PHE10, GLU50,ASP49,ALA47, ASN46, HIS116, VAL43, THR165, H_2O	PRO79,ILE78, GLY77,ARG76, ASP73, VAL71, GLU50, ASP49, ALA47, ASN46, VAL43, THR165, VAL120,VAL167,	THR165,ASP73,ARG76, GLY77,ILE78, PRO79, ARG136, H_2O,VAL43, ASN46,	ARG136, PRO79,ILE78, GLY77,ARG7, H_2O,ASP73, VAL43, THR165, ASN46,	ASP73, H_2O, ARG76,GLY77, ILE78,PRO79, ARG136, TH165, VAL43,VAL12

			LEU132,LEU130, MET95, ILE54, ASP105, PHE104,LYS103, GLY102, GLY101	ALA47,ASP4, GLU50,ILE94,ALA53, GLY101, GLY102, LYS103, PHE104, ASP105, ASP106	ALA47, ASP49,ILE94, GLU50, GLY101, HIS116, GLY102, LYS103, PHE104, ASP105, ASP106, VAL111	0,ASN46, ALA47, HIS116, ILE94, ASP49, GLU50,GLY101,GLY102, LYS103, PHE104,ASP105, ASP106
Klebsiella Pneumoniae	Docking Score (kcal/mol)	-5.618	-7.437	-6.615	-7.524	-6.57
	Binding Interaction	LEU65, MET67, VAL73, ILE35, TRP93, MET154, GLU152,ASP124, GLN123,HIE122,ZN303, ZN302,LYS211, CYS208, HIS189, HIS250, ASN220, GLY219	ASN220, GLY219, LYS211, CYS208, HIS250, HIS189, Zn303, Zn302, MET154,GLY153, GLU152, LEU65, HIE122, GLN123, ASP124, TRP93	HIE122, GLN123, ASP124 TRP93, LEU65, MET67, VAL73,ILE35, GLY219, ASN220, CYS208, HIS250, HIS189, LYS211, Zn303,Zn302,GlU	MET67, LEU65, VAL73,ILE35, TRP93,GLY219, ASN220, CYS208, Zn303, Zn302, LYS211, ASP124, GLN123, HIE122, HIS189, HIS250	LEU65, MET67, VAL73, ILE35, LEU218, GLY219, ASN220, LYS211, HIS250, HIS189, CYS208, ZN303, ZN302,TRP93, ASP124,GLN12,HIE122,MET154, GLU152
Bacillus Subtilis	Docking Score (kcal/mol)	-6.155	-3.181	-4.594	-3.715	-6.999
	Binding Interaction	HIE75, TYR74, GLU73, PRO72, VAL104, ALA105, GLY106, THR9, ARG11, HIS13, GLY14, ARG15, THR16	SER76, HIE75, TYR74, GLU73, PRO72, THR9, ARG11, GLY14, ARG15, THR16, PRO138, VAL104, ALA105, GLY106, GLY107, GLY110, GLY111	THR9,ARG11,HIS13,GLY14, ARG15,THR16, VAL104, ALA105, GLY106, GLY110, GLY111, PRO72,GLU73, TYR74, HIE75	GLU73, TYR74,HIE75, SER76,ARG11 ARG15, GLU10, ALA105, GLY111, GLY110	THR9,ARG11, GLY14,ARG15,THR16,PRO72, GLU73,TYR74,HIE75,SER76, VAL104,ALA105,GLY106,GLY107,GLY110, GLY111



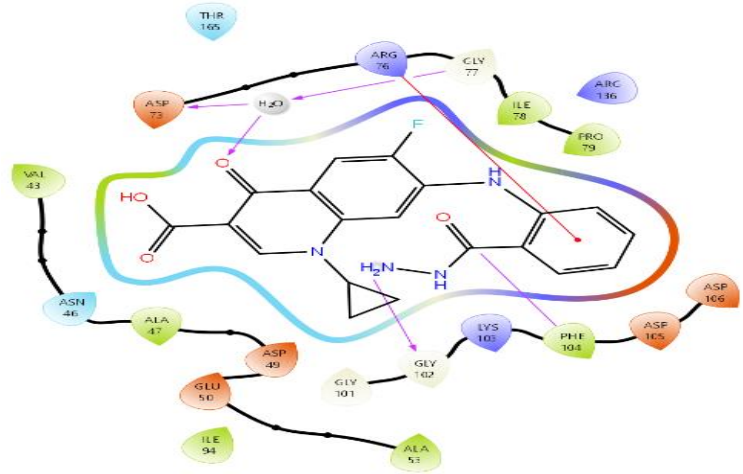
(a)



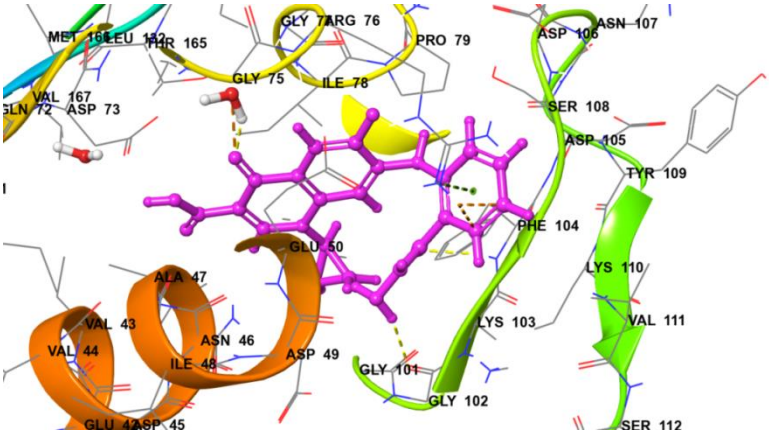
(b)

Figure 4. Compound B shows 2D (a) and 3D (b) structure of the highest scoring molecule.

It docks with ciprofloxacin with a score of -5.746 kcal/mol, while compound B has the highest score at -7.562 kcal/mol. It interacts with three H-bonds (SER49, LEU28, and ARG57) through a hydroxyl group. Also, there are hydrophobic interactions with the nearby amino acids (LEU28, ILE5, and PHE92). Compound C from *E. coli* has the best docking score (ΔG= -8.562 kcal/mol) compared to ciprofloxacin (ΔG= -7.022 kcal/mol). It interacts with five things: GLY77, H_2O, ASP73, GLY102, and PHE104; and it has a p-cation with ARG76, as shown in **Figure 5**.



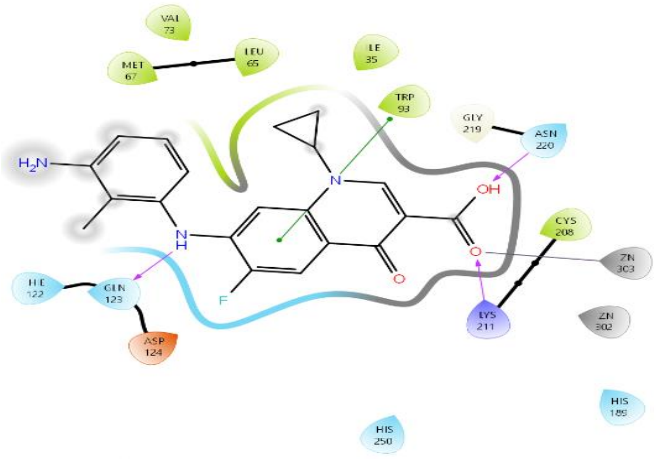
(a)



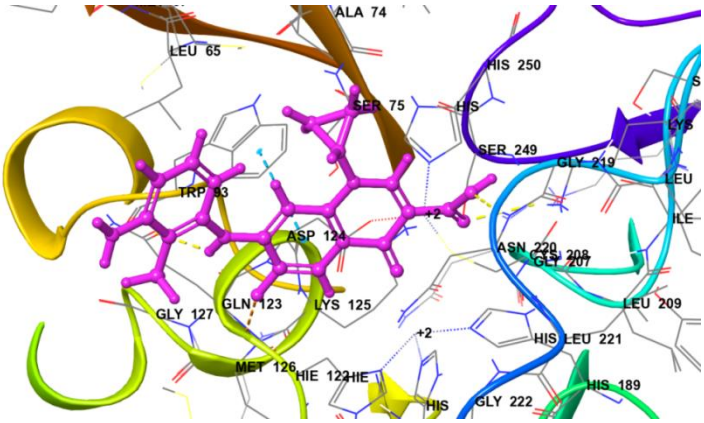
(b)

Figure 5. Compound C shows 2D (a) and 3D (b) structure of the highest scoring molecule.

Inside the active site of the target protein, compound D in *Klebsiella pneumonia*, which scores the highest docking result (ΔG= -7.524 kcal/mol) when compared with ciprofloxacin (ΔG= -6.762 kcal/mol), it interacts with and binds to different amino acids. These interactions are three H-bonds between (ASN220&GLN123&LYS211), ZN303&ZN302 (Chelation bond), and TRP93 (Pi-Pi stacking), as shown in **Figure 6**.



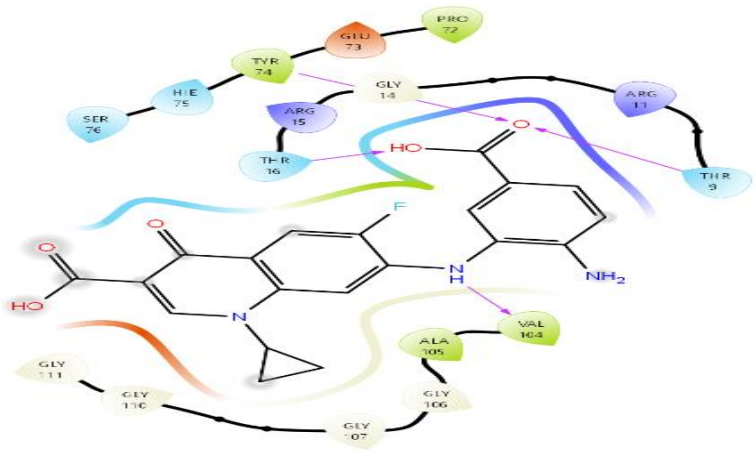
(a)



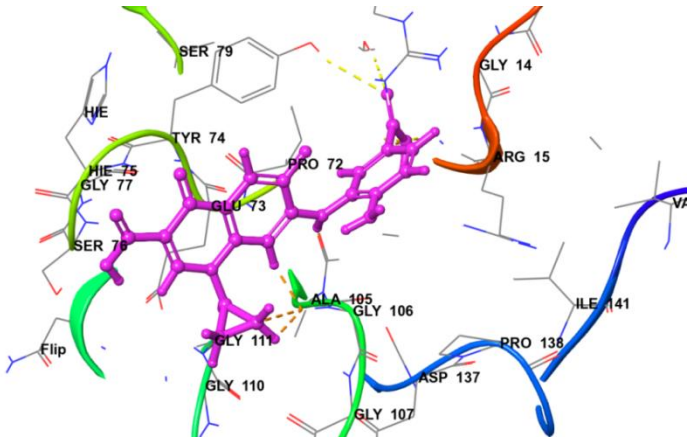
(b)

Figure 6. Compound D shows 2D (a) and 3D (b) structure of the highest scoring molecule.

Compound E in Bacillus subtilis has the highest docking score (ΔG= -6.99 kcal/mol) when compared with ciprofloxacin (ΔG= -2.874 kcal/mol), and it has interactions with four H-bonds with GLY14 and TYR74&THR9&VAL164, as shown in **Figure 7**.



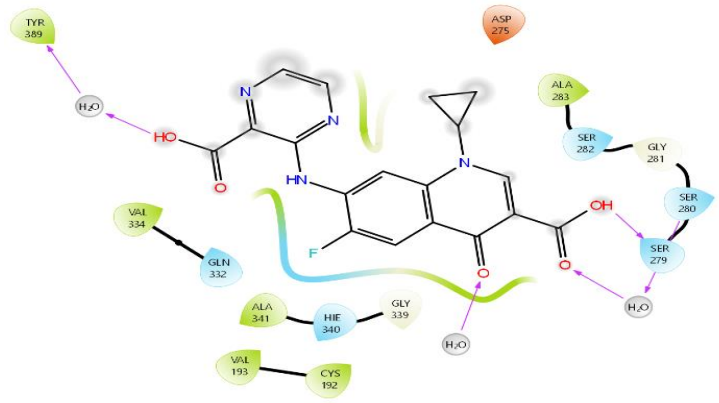
(a)



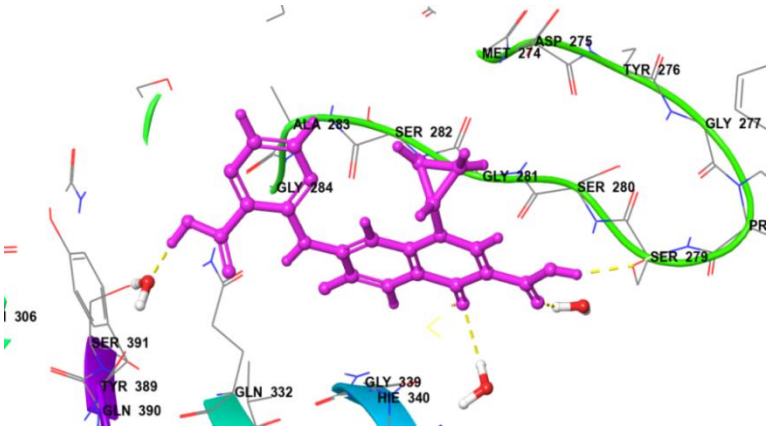
(b)

Figure 7. Compound E shows 2D (a) and 3D (b) structure of the highest scoring molecule.

Compound A in *streptococcus pyogenes* has the highest docking score (ΔG = -6.762 kcal/mol) when compared with ciprofloxacin (ΔG = -2.874 kcal/mol). **Figure 8** illustrates its interactions with five H-bonds, including TYR389, SER279, SER280, and H_2O with a hydroxyl group.



(a)



(b)

Figure 8. Compound A shows 2D (a) and 3D (b) structure of the highest scoring molecule.

4. Conclusion

Molecular Docking has been considered one of the most attractive approaches used in the drug design process. It enables researchers to virtually enhance binding affinity and develop more potent pharmacological agents before laboratory work. These chemicals have shown a strong affinity for binding. The active site was determined on the levitating ligand of the crystal

inside the protein active site, with varied chemical interactions in addition to higher docking scores for compounds A-E accordingly. The active site was determined by raising the ligand with the crystal. The prediction of the theoretical study for five compounds is Drug likeness compounds with anti-bacterial activity. Results show that compound C has the highest activity against *E. coli* through interaction with GyrB protein, compound B with *Staphylococcus aureus* through their interaction with S1: DHFR protein, and compound E against Bacillus subtilis through their interaction with Azobenzene Reductase protein. Moreover, compound D interacts with the NDM-1 protein to combat *Klebsiella pneumoniae,* while compound A interacts with the cysteine protease Spe B to combat *Streptococcus pyogenes*. Calculated chemical properties (such as ionization energy, electronic affinity, donating or accepting hydrogen bonds, etc.) indicate that these molecules have unique therapeutic properties that can be employed to overcome the problem of bacterial resistance. In the DFT, Compound E has the lowest energy gap, while Compound C has the largest energy gap.

Acknowledgment

The authors thank the staff of the laboratories of the College of Science for Women, University of Baghdad.

Conflict of Interest

There are no conflicts of interest.

Funding

None.

Ethical Clearance

This work has been approved by the Scientific Committee at the University of Baghdad/ College Science for Women.

References

1. Al Salman, J.; Al Dabal, L.; Bassetti, M.; Alfouzan, W.A.; Al Maslamani, M.; Alraddadi, B.; Elhoufi, A.; Enani, M.; Khamis, F.A.; Mokkadas, E.; Romany, I.; Somily, A.; Kanj, S. Management Of Infections Caused by WHO Critical Priority Gram-Negative Pathogens in Arab Countries of the Middle East: A Consensus Paper. *International Journal of Antimicrobial Agents* **2020**, *56(4)*, 106104. https://doi.org/10.1016/j.ijantimicag.2020.106104.
2. Jain, S.D.; Gupta, A. Chemistry of Fluoroquinones in the Management of Tuberculosis (TB): An Overview. *Asian Journal of Pharmaceutical Research* **2021**, *11(1)*, 55-59. http://dx.doi.org/10.5958/2231-5691.2021.00011.3.
3. Alabdali, A.Y.M.; Khalid, R.; Kzar, M.; Ezzat, M.O.; Huei, G.M.; Hsia, T.W.; Mogana, R.; Rahman, H.; Abd Razik, B.M.; Issac, P.K.; Chinnappan, S.; Khalivulla, S.I. Design, Synthesis, in Silico and Antibacterial Evaluation of Curcumin Derivatives Loaded Nanofiber as Potential Wound Healing Agents. *Journal of King Saud University-Science* **2022**, *34(7)*, 102205. https://doi.org/10.1016/j.jksus.2022.102205.
4. Dib, M.; Ouchetto, H.; Ouchetto, K.; Hafid, A.; Khouili, M. Recent Developments of Quinoline Derivatives and their Potential Biological Activities. *Current Organic Synthesis* **2021**, *18(3)*, 248-269. https://doi.org/10.2174/1570179417666201216162055.

5. Van de Walle, T.; Cools, L.; Mangelinckx, S.; D'hooghe, M. Recent Contributions of Quinolines to Antimalarial and Anticancer Drug Discovery Research. *European Journal of Medicinal Chemistry* **2021**, *226*, 113865. https://doi.org/10.1016/j.ejmech.2021.113865.
6. Uddin, A.; Chawla, M.; Irfan, I.; Mahajan, S.; Singh, S.; Abid, M. Medicinal Chemistry Updates on Quinoline-and Endoperoxide-Based Hybrids with Potent Antimalarial Activity. *RSC Medicinal Chemistry* **2021**, *12(1)*, 24-42. https://doi.org/10.1039/D0MD00244E.
7. Yadav, P.; Kumar, A.; Althagafi, I.; Nemaysh, V.; Rai, R.; Pratap, R. The Recent Development of Tetrahydro-Quinoline/Isoquinoline Based Compounds as Anticancer Agents. *Current Topics in Medicinal Chemistry* **2021**, *21(17)*, 1587-1622. https://doi.org/10.2174/1568026621666210526164208.
8. Jain, S.; Chandra, V.; Jain, P.K.; Pathak, K.; Pathak, D.; Vaidya, A. Comprehensive Review on Current Developments of Quinoline-Based Anticancer Agents. *Arabian Journal of Chemistry* **2019**, *12(8)*, 4920-4946. https://doi.org/10.1016/j.arabjc.2016.10.009
9. Bouzian, Younos, B.; Yusuf, S.; Karrouchi, K.; Luc V.M.; Karim, Ch.; Lhassane, M.; Hamou, A.N.; Ahmed, T.; El Mokhtar, E. Synthesis, Spectroscopic Characterization, DFT, Molecular Docking and in Vitro Antibacterial Potential of Novel Quinoline Derivatives. *Journal of Molecular Structure* **2021**, *1246*, 131217. https://doi.org/10.1016/j.molstruc.2021.131217.
10. El Shehry, M.F.; Ghorab, M.M.; Abbas, S.Y.; Fayed, E.A.; Shedid, S.A.; Ammar, Y.A. Quinoline Derivatives Bearing Pyrazole Moiety: Synthesis and Biological Evaluation as Possible Antibacterial and Antifungal Agents. *European Journal of Medicinal Chemistry* **2018**, *143*, 1463-1473. https://doi.org/10.1016/j.ejmech.2017.10.046.
11. Yaakov, B.D.; Shadkchan, Y.; Albert, N.; Kontoyiannis, D.P.; Osherov, N. The Quinoline Bromoquinol Exhibits Broad-Spectrum Antifungal Activity and Induces Oxidative Stress and Apoptosis in Aspergillus Fumigatus. *Journal of Antimicrobial Chemotherapy* **2017**, *72(8)*, 2263-2272. https://doi.org/10.1093/jac/dkx117.
12. Chen, Y.J.; Ma, K.Y.; Du, S.S.; Zhang, Z.J.; Wu, T.L.; Sun, Y.; Liu, Q-Y.; Yin , X-D.; Zhou, R.; Yan , Y-F.; Wang, R-X.; He, Y-H.; Chu, Q-R.; Tang, C. Antifungal Exploration of Quinoline Derivatives Against Phytopathogenic Fungi Inspired by Quinine Alkaloids. *Journal of Agricultural and Food Chemistry* **2021**, *69(41)*, 12156-12170. https://doi.org/10.1021/acs.jafc.1c05677.
13. Bhat, A.A.; Tandon, N.; Tandon, R. Pyrrolidine Derivatives as Antidiabetic Agents: Current Status and Future Prospects. *Chemistry Select* **2022**, *7(6)*, 202103757. https://doi.org/10.1002/slct.202103757.
14. Kaur, R.; Kumar, K. Synthetic and Medicinal Perspective of Quinolines as Antiviral Agents. *European Journal of Medicinal Chemistry* **2021**, *215*, 113220. https://doi.org/10.1016/j.ejmech.2021.113220.
15. Savegnago, L.; Vieira, A.I.; Seus, N.; Goldani, B.S.; Castro, M R.; Lenardão, E.J.; Alves, D. Synthesis and Antioxidant Properties of Novel Quinoline–Chalcogenium Compounds. *Tetrahedron Letters* **2013**, *54(1)*, 40-44. https://doi.org/10.1016/j.tetlet.2012.10.067.
16. Chen, Y.L.; Chen, I.L.; Lu, C.M.; Tzeng, C.C.; Tsao, L.T.; Wang, J.P. Synthesis and Anti-Inflammatory Evaluation of 4-Anilinofuro [2, 3-B] Quinoline and 4-Phenoxyfuro [2, 3-B] Quinoline Derivatives. *Part 3. Bioorganic and Medicinal Chemistry* **2004**, *12(2)*, 387-392. https://doi.org/10.1016/j.bmc.2003.10.051.
17. Joshi, P.V.; Sayed, A.A.; RaviKumar, A.; Puranik, V.G.; Zinjarde, S.S. 4-Phenyl Quinoline Derivatives as Potential Serotonin Receptor Ligands with Antiproliferative Activity. *European Journal of Medicinal Chemistry* **2017**, *136*, 246-258. https://doi.org/10.1016/j.ejmech.2017.05.002.
18. Borsoi, A.F.; Alice, L.M.; Sperotto, N.; Ramos, A.S.; Abbadi, B.L.; Hopf, F.S.M.; Dadda, A.D.; Rambo, R.S.; Silva, R.B.M.; Paz, J.D.; Pissinate, K.; Muniz, M.N.; Neves, C.E.; Galina, L.; González, L.C.; Perelló, M.A.; Czeczot, A.D.; Leyser, M.; de Oliveira, S.D.; Lock, G.D.; de Araújo, B.V.; Costa, T.D.; Bizarro, C.V.; Basso, L.A.; Machado, P. Antitubercular Activity of Novel

2-(Quinoline-4-Yloxy) Acetamides with Improved Drug-Like Properties. *ACS Medicinal Chemistry Letters* **2022**, *13(8)*, 1337-1344. https://doi.org/10.1021/acsmedchemlett.2c00254.

19. Marella, A.; Tanwar, O.P.; Saha, R.; Ali, M.R.; Srivastava, S.; Akhter, M.; Shaquiquzzaman, M.; Alam, M.M. Quinoline: A Versatile Heterocyclic. *Saudi Pharmaceutical Journal* **2013**, *21(1)*, 1-12. https://doi.org/10.1016/j.jsps.2012.03.002.
20. Patel, A.; Patel, S.; Mehta, M.; Patel, Y.; Patel, R.; Shah, D.; Patel, D.; Shaha, U.; Patel, M.; Patel, S.; Solanki, N.; Bambharoliya, T.; Patel, S.; Nagani, A.; Patel, H.; Vaghasiya, J.; Shah, H.; Prajapati, B.; Rathod, M.; Bhimani, B.; Patel, R.; Bhavsar, V.; Rakholiya, B.; Patel, M.; Patel, P. A review on Synthetic Investigation for Quinoline- Recent Green Approaches. *Green Chemistry Letters and Reviews 15*(2), 337–372. https://doi.org/10.1080/17518253.2022.2064194.
21. Shaker, B.; Ahmad, S.; Lee, J.; Jung, C.; Na, D. In Silico Methods and Tools for Drug Discovery. *Computers in Biology and Medicine* **2021**, *137*, 104851. https://doi.org/10.1080/17518253.2022.2064194.
22. Stefaniu, A.; Pintilie, L. Molecular Descriptors and Properties of Organic Molecules. Symmetry (Group Theory) Mathematical Treatment in Chemistry **2018**, *7*, 161-176. http://dx.doi.org/10.5772/intechopen.72840.
23. Shahidha, R.; Al-Saadi, A.A.; Muthu, S. Vibrational Spectroscopic Studies, Normal Co-Ordinate Analysis, First Order Hyperpolarizability, HOMO–LUMO Of Midodrine by Using Density Functional Methods. *Spectrochimica Acta Part A: Molecular And Biomolecular Spectroscopy* **2015**, *134*, 127-142. https://doi.org/10.1016/j.saa.2014.06.033.
24. Miar, M.; Shiroudi, A.; Pourshamsian, K.; Oliaey, A.R.; Hatamjafari, F. Theoretical Investigations on The HOMO–LUMO Gap and Global Reactivity Descriptor Studies, Natural Bond Orbital, and Nucleus-Independent Chemical Shifts Analyses of 3-Phenylbenzo [D] Thiazole-2 (3 H)-Imine and its Para-Substituted Derivatives: Solvent and Substituent Effects. *Journal of Chemical Research* **2021**, *45(1-2)*, 147-158. https://doi.org/10.1177/1747519820932091.
25. Zhang, B.; Li, X.; Zhang, L.; Peng, C.; Duan, Y.; Yu, J.; Wang, L.; Yang, K.; Liu, F.; Jiang, R.; Yang, X.; You, T.; Liu, X.; Yang, X.; Bai, F.; Liu, H.; Liu, X.; Luke, W. Guddat, Haitao Yang. Structure of Mpro from SARS-CoV-2 and Discovery of its Inhibitors. *Nature* **2020**, *582(7811)*, 289-293. https://doi.org/10.1038/s41586-020-2223-y.
26. SwissDock - The Online Docking Web Server of the Swiss Institute of Bioinformatics–Docking. **2023**. http://www.swissdock.ch/docking.
27. Stanzione, F.; Giangreco, I.; Cole, J.C. Use of Molecular Docking Computational Tools in Drug Discovery. *Progress in Medicinal Chemistry* **2021**, *60*, 273-343. https://doi.org/10.1016/bs.pmch.2021.01.004.
28. Chem3D 17.0 User Guide, **2017**, pp. 1–335. https://library.columbia.edu/content/dam/libraryweb/locations/dsc/Software%20Subpages/Chem3D_17_manual.pdf.
29. Amudha, G.; Santhakumari, R.; Chandrika, D.; Mugeshini, S.; Rajeswari, N.; Sagadevan, S. Synthesis, Growth, DFT, and HOMO-LUMO Studies on Pyrazolemethoxy Benzaldehyde Single Crystals. *Chinese Journal of Physics* **2022**, *76*, 44-58. https://doi.org/10.1016/j.cjph.2021.10.038.
30. Qader, S.W.; Suvitha, A.; Ozdemir, M.; Benjamin, I.; Ram, A.S.; Akem, M.U.; Frank, A.Z.; Eluwa. E.C. Investigating the Physicochemical Properties and Pharmacokinetics of Curcumin Employing Density Functional Theory and Gastric Protection. *Chemical Physics Impact* **2022**, *5*, 100130. https://doi.org/10.1016/j.chphi.2022.100130.
31. Golea, L.; Chebaki, R.; Laabassi, M.; Mosset, P. Synthesis, Characterization of Some Substituted Quinolines Derivatives: DFT, Computational, in Silico ADME, Molecular Docking and Biological Activities. *Chemical Data Collections* **2023**, *43*, 100977. https://doi.org/10.1016/j.cdc.2022.100977.
32. Sertbakan, T.R. Structure, Spectroscopic and Quantum Chemical Investigations of 4-Amino-2-Methyl-8-(Trifluoromethyl) Quinoline. *Celal Bayar University Journal of Science* **2017**, *13*, 851-861. https://doi.org/10.18466/cbayarfbe.339858.

33. Noureddine, O.; Issaoui, N.; Gatfaoui, S.; Al-Dossary, O.; Marouani, H. Quantum Chemical Calculations, Spectroscopic Properties and Molecular Docking Studies of a Novel Piperazine Derivative. *Journal of King Saud University-Science* **2021**, *33(2)*, 101283. https://doi.org/10.1016/j.jksus.2020.101283.
34. Stefaniu, A.; Pintilie, L. Molecular Descriptors and Properties of Organic Molecules. *Symmetry (Group Theory) and Mathematical Treatment in Chemistry*. *IntechOpen* **2018**, 161-176. http://dx.doi.org/10.5772/intechopen.72840.
35. GBD 2017 Risk Factor Collaborators. Global, Regional, and National Comparative Risk Assessment of 84 Behavioural, Environmental and Occupational, and Metabolic Risks or Clusters of Risks for 195 Countries and Territories, 1990-2017: A Systematic Analysis for the Global Burden of Disease Study 2017. *Lancet (London,England)* **2018**, *392(10159)*, 1923-1994. https://doi.org/10.1136/bmj-2021-068208.