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Modification and Characterization of Some New Levofloxacin Heterocyclic Derivatives as COX-2 Enzyme Inhibitors and Evaluate Their Efficacy Pharmacokinetics by Molecular Docking and the Swiss ADME Studies

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Abstract

In order to predict anti-inflammatory activity against (COX-2) and expect their anticancer potential, new 1,2,4-triazole-5-thiol, Oxadiazole, and Imide derivatives were modified. Physical characteristics, ^{1}H-NMR, ^{13}C-NMR, FT-IR spectroscopy, and other methods were used to characterize and identify the produced compounds. The newly created compounds (1-10) were based in part on the well-known anti-inflammatory medication levofloxacin. The Swiss ADME server was used to perform computational techniques, such as ADME studies, in order to forecast the pharmacokinetics of the novel drugs. To assess the selectivity of created compounds towards the COX-2 enzyme, the results showed that all compounds met the Lipinski rule of five compounds (1-10). Higher PLP fitness values than the reference compound are predicted by docking studies for ligand interactions with COX-2 protein to bind with amino acids in the active pocket (Levofloxacin). The polarity and lipophilicity report for tiny compounds have been predicted using a boiled egg. Predictions linked with each brain disorder as well as diet for the same chemical and physical properties and their direct translation in the design of the medication molecule have also been made.

Keywords: Boiled egg , COX-2 enzyme , Oxadiazole , Triazole-5-thiole , Swiss ADME studies.

Introduction

Recent medical research shows that NSAID (Non-steroidal anti-inflammatory drug) are also neuroprotective drugs and that long-term usage of NSAID lowers the risk of developing Alzheimer's disease. Additionally, research has indicated that the identification of NSAID derivatives is promising to have anticancer action, levofloxacin is a fluoroquinolone antibiotic that has been used to treat a variety of conditions, including allergies, prostatitis, and urinary tract infections. Levofloxacin acts as a DNA synthesis inhibitor in bacterial cells, inhibiting the bacterial type II topoisomerases DNA gyrase and topoisomerase IV. This kills bacteria quickly while safeguarding human DNA, according to studies. Levofloxacin functions as a bactericide, and Topoisomerase IV is required to separate DNA that is replicated (doubled) prior to bacterial cell division[1,2]. Heterocyclic compounds are one of the most important families of organic chemicals used in

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various biological disciplines because of their activity in various diseases [3]. It has been used to create pharmaceuticals that are anticancer, anti-fungal, anti-viral, antioxidants, anti-microbial, and antibacterial[4,5] . In the development of novel energetic molecules. Recent years have seen a lot of interest in nitrogen-rich heterocyclic compounds based on 1,3-diazole[6], 1,2-Diazole[7], pairs of tautomer in the 1,2,3-triazoles and 1,2,4-triazoles [8], tetrazoles[9], and 1,3,4-Oxadiazole[10]. Triazole frameworks have frequently been chosen because of their increased nitrogen content, wide distribution, and high energy of formation as prospective building blocks for the structure of nitrogen-rich heterocyclic molecules[11]. Thus showing high biological activity against influenza, and anti-neurogenic, anticancer activity, and anti-HIV activity [12]. The abbreviation (ADME) [13] is used in pharmacology to describe how an organism's physiology breaks down pharmacological compounds after consumption is excretion, absorption, distribution, and metabolism. The efficacy of the medication, tissue exposure, and ensuing drug-like activity are influenced by all four variables (absorption). Before a substance can be absorbed by target cells, it must first be delivered into the bloodstream, often through mucosal surfaces such as the gastrointestinal tract (intestinal absorption). The amount of drug absorption [13,14] after oral administration is reduced by a variety of conditions, including poor solubility of the compound, timing of gastric emptying, length of intestinal transit, chemical instability in the stomach, and inability to enter the intestinal wall. Therefore, drugs that are poorly absorbed should not be taken orally. Instead, it must be given intravenously or by inhalation, (distribution) [13,14]. After entering the systemic circulation, compounds can be distributed to muscles and organs after being transported to the site of effector, which is frequently the bloodstream, (excretion)[13.14]. The compounds and their constituent "drugs" must be expelled from the body by excretion, typically in the form of urine produced by the kidneys or food waste from the GIT system.

Materials and Methods

Chemical and Instrument:

• Melting points of all achieved products were measured in open glass capillaries by SMP10 digital apparatus , was performed by University of Baghdad , College of Science/ Department of Chemistry.

• The chemical compounds were identified by ^{1}H-NMR and ^{13}C-NMR spectra were recorded in University of Basra , BRUKER

• The pharmaceutical raw material (levofloxacin) was brought from the General Company for Pharmaceutical Industries, Samarra Iraq.

• The pharmacological efficacy was measured in the central laboratory of the University of Al-Nahrain, College of Pharmacy.

Synthesis of Acid Chloride Compound 1

Levofloxacin (0.5gm,1.3 mmol) was taken with (0.5ml) of thionyl chloride in the presence of dry benzene (15 ml) and was refluxed for 4 hrs (depending on TLC results, using ethyl acetate : petroleum ether ; 8:2) evaporated the solvent and washed with Diethyl ether [15] . The products were collected as crystals. Physiochemical properties as shown in Table 1.

Synthesis of Carbonyl Isothiocyanate Compound 2

Ammonium thiocyanate (0.06gm,7.9mmol) was added to compound (1) (0.3gm,7.9 mmol) in a round bottom flask with 15 mL of MeOH stirring for 6 hrs (the reaction was monitored by TLC , using Hexane ; acetone 4:4) the precipitate was filtered, washed with water to give the final product[15]. Physiochemical properties are shown in Table 1.

Synthesis of Acid Hydrazide Compound 3

In a round bottom flask, 10 mL of methanol as a solvent, compound (1) (0.5 g, 1.3 mmol) was dissolved. An excess of hydrazine hydrate was then added to the reaction mixture, which was then refluxed for 8 hrs (the reaction was monitored by

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TLC , using petroleum ether ; chloroform 3:3) The result was filtered and washed with Diethyl ether to get rid of any excess of reactants the final product[16] .Physiochemical properties are shown in Table 1.

Synthesis of 1,2,4-triazole-5-thiol Derivatives Compound 4-6

A mixture of isothiocyanate Levofloxacin (0.3gm,7mmol) and phenyl hydrazine, Hydrazine hydrate and 4-nitro phenyl hydrazine (7 mmol) in (10ml) dioxane. The mixture of reaction was refluxed for 12 hrs. TLC was used to check the reaction completion using petroleum ether; chloroform 3:3, the solvent was then evaporated, and washed with Diethyl ether to give the final product[15]. Physiochemical properties are shown in Table 1.

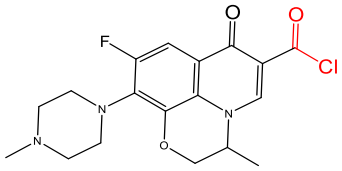
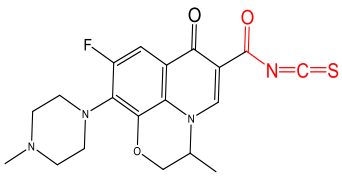
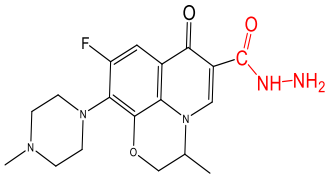
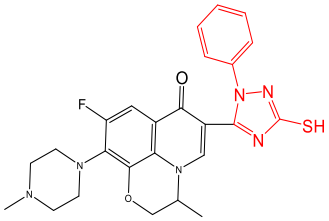
Synthesis of Imide Derivatives Compound 7,8

A mixture of Amic acid (3.7 mmol) in acetic anhydride (10 mL) and sodium acetate (3.7 mmol) was heated for 2 hrs (depending on TLC results, using ethyl acetate: petroleum ether; 4:2). The mixture was cooled for about 1 hrs at room temperature, then poured on ice water (5 mL), filtered out, and washed with Diethyl ether to give the final product[17,18] .Physiochemical properties are shown in Table 1.

Synthesis of 1,3,4-Oxadiazole Derivatives Compound 9,10

Derivatives of (4-methyl benzohydrazide, 2-aminopropanehydrazide) (8 mmol), levofloxacin (8 mmol), and $POCl_3$ (3 mL) were dissolved in THF (10 ml) and refluxed for 18 hrs and the progress of the reaction was monitored by TLC (n-hexane; ETAC: 7:3). The reaction mixture was cooled and poured into beaker, neutralized by Na_2CO_3 solution (10%). The resulting solid was washed with water to give the final product[19]. Physiochemical properties as shown in Table 1.

Table 1. Scheme showing some physical properties of chemical compounds (1-10).

Comp No.	structure	Molecular formula	M.wt (g/mol)	m.p (°C)	Color rf	Yield %
1		$C_{18}H_{19}O_3ClFN_3$	379	236-238	Yellow 0.5	76
2		$C_{19}H_{19}O_3FN_4S$	402	250-252	White 0.7	73
3		$C_{18}H_{22}O_3FN_5$	375	273-275	Green 0.6	62
4		$C_{25}H_{25}O_2FN_6S$	492	198-200	Red 0.6	68

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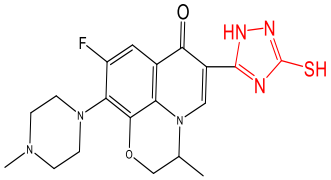
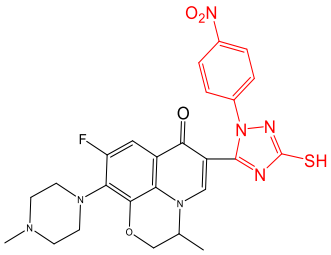
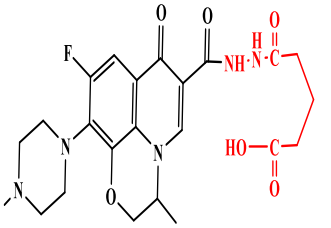
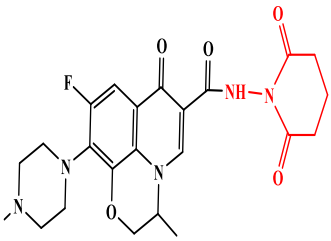
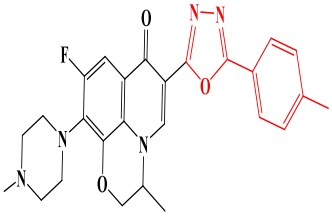
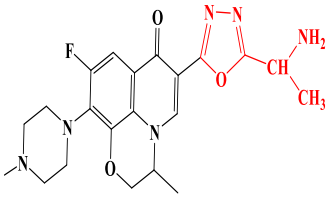
5		$C_{19}H_{21}O_2FN_6S$	416	216-218	Green 0.7	72
6		$C_{25}H_{24}O_4FN_7S$	537	295-297	Light grey 0.6	70
7		$C_{23}H_{28}N_6O_6F$	489	216-218	Yellow 0.6	69
8		$C_{23}H_{26}N_5O_5F$	471	298-300	Gray 0.5	60
9		$C_{26}H_{26}FN_5O_3$	475	228-230	Orange 0.5	66
10		$C_{21}H_{25}N_6O_3F$	428	238-240	Orange 0.7	65

Results and Discussion

The synthetic series for preparation of new substituted triazole, 1,3,4-Oxadiazole and Imide as in Scheme (1) compound (1) was prepared by reaction of Levofloxacin with thionyl chloride in benzene as solvent. the FTIR spectrum indicated the presence of a ν(C=O) at 1768cm^{-1}; ν (C-H) Aliph at 2933cm^{-1}, ν (C-O) at 1294cm^{-1} and ν(C=C cyclic) at 1620cm^{-1} appeared, as listed in Table 2. The ^{1}H-NMR spectrum showed compound (3) a doublet signal at δ= 1.39 ppm due to (-CH-CH_3) protons, a singlet signal at δ= 2.51 ppm due to (-N-CH_3 cyclic) and appeared triplet signal at δ= 3-4 ppm due to (t,2H, N-CH_2CH_2-N), singlet signal for amine at δ= 4.90, singlet signal for aromatic at δ= 8.74 spectrum data were shown listed in Table 3. , compound (3) was a reaction with ammonium thiocyanate. FTIR spectra data showed absorption at ν (2038cm-^{1}) for

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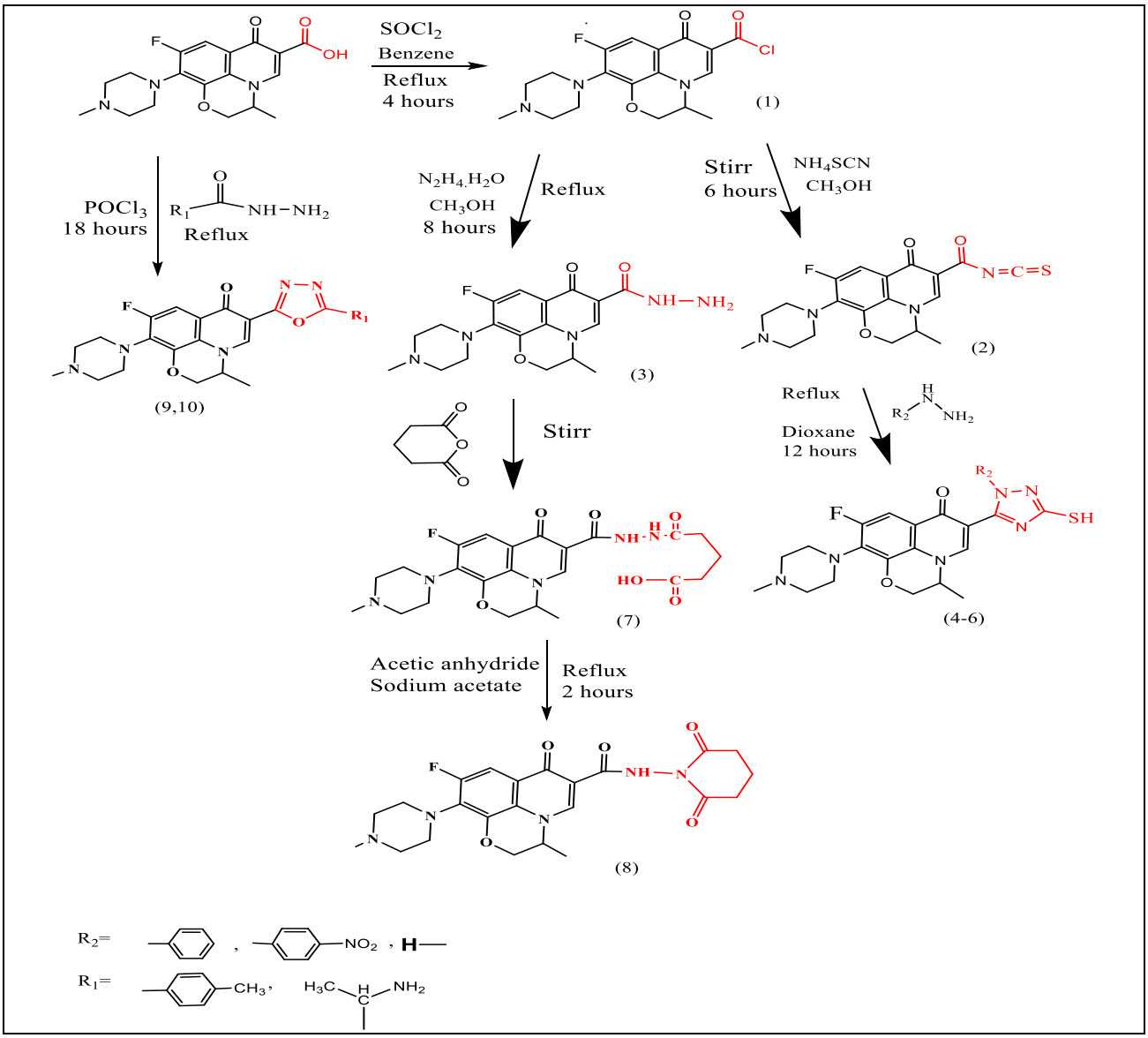
(N=C=S) and ring closer reaction to produce 1,2,4-triazole-5-thiole with (hydrazine hydrate, phenyl hydrazine and 4-nitro phenyl hydrazine) respectively Scheme-1. FTIR spectral data showed absorption at 3197-3103 cm^{-1} for ν (-NH), absorption bands of ν(N=C=S) at 2038 cm^{-1}, absorption bands at 1706-1700 cm^{-1} for ν(C=O). ^{1}H-NMR spectra data in the DMSO-d_6 as solvent for the compounds as shown in Table 3, Figs 15, 17, 19 and 21. ^{13}C-NMR spectrum data of these compounds are listed in Table 4, Figs 16, 18, 20 and 22.



Scheme 1. Scheme showing the reaction of chemical compounds (1-10)

Table 2. The FT-IR spectral data (Cm^{-1}) Of all prepared compounds (1-10)

Comp. No.	υ (NH)	υ (C-H) Ar.	υ (C-H) aliph.	υ (C=O)	υ (C=N)	υ (C=C)	Others
1	_	3041	2933	1768 1718	_	1620 1590	(C-O) 1294
2	_	3043	2989	1706	_	1622 1548	(2038) isothiocyanate
3	3176	3047	2974	1704	_	1622	

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				1683		1575	(NH_2) 3290,3280
4	3197	3047	2979	1701	1654	1620 1575	(2038) isothiocyanate
5	3103	3070	2877	1706	1647	1620 1575	(1332) -NO_2 (Sym.) (1512)- NO_2 (asym)
6	3197	3020	2986	1701	1654	1620 1575	
7	3178	3045	2875	1701 1681		1591 1568	2960-3244 (COOH)
8	3174	3080	2977	1701 1683	_	1639 1556	
9	_	3180	2987	1703	1645	1622 1556	
10	_	3166	2979	1703	1654 1668	1560	 (NH_2) 3270,3310

Table 3. Compounds were characterized by ^{1}H-NMR

Comp. No.	Chemical shift
3	1.39 (d,3H, C**H**$_3$-CH) ; 2.51 (s,3H, C**H**$_3$-N) ; 3-4 (t,2H, N-C**H**$_2$C**H**$_2$-N) ; 4.90 (s,2H,-N**H**$_2$) ; 8.74 (1H, Ar-**H**) ; 8.91. (1H, s, CO-C**H**=C) ; 10.61 (1H , s , CO-N**H**)
4	1.45 (s,3H, C**H**$_3$-N) ; 2.50 (d,3H, C**H**$_3$-CH) ; 2.73-2.89 (t,2H, N-C**H**$_2$-C**H**$_2$-N) ; 4.39-4.96 (2H, d, CH_2-O) ; 7.12-8.07 (m ,- Ar-6**H**) ; 9.01 (1H, s, -C**H**=) ; 15.12 (1H, s, -S**H**)
6	1.45 (3H, d, C**H**$_3$-CH) ; 2.12 (3H, s, C**H**$_3$-N) ; 3.35 (2H, t, N-C**H**$_2$-C**H**$_2$-N) ; 4.39 (2H, d, CH_2-O) ; 7.60-8.86 (m, Ar-5**H**) ; 9.00υ (1H, s, -C**H**=) ; 15.00 (1H , s , -S**H**)
8	1.42-1.62 (10H, m, CH.Aliph.); 2.21 (s,3H, C**H**$_3$-N) ; 3.23 (2H,t, N-C**H**$_2$-C**H**$_2$-N) ;4.42_4.89 (2H, d, CH_2O) ; 8.74 (1H,s, Ar-**H**) ; 9.73 (1H ,s, -CH=C) ; 10.61 (1H ,s, -N**H**)
9	1.18-1.44 (3H, s, C**H**$_3$-N) and (3H, d, C**H**$_3$-CH) ; 3.11-3.61 (2H, t, N-C**H**$_2$-C**H**$_2$-N) ; 4.00-4.61 (2H, d, CH_2-O) ; 7.36-7.59 (m,5H, Ar-**H**); 8.87 (s ,1H, CO-C**H**=C)

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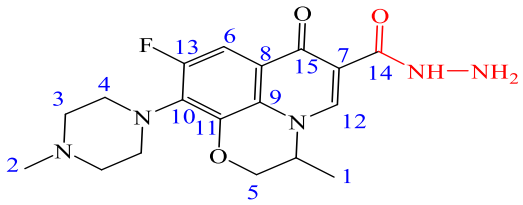
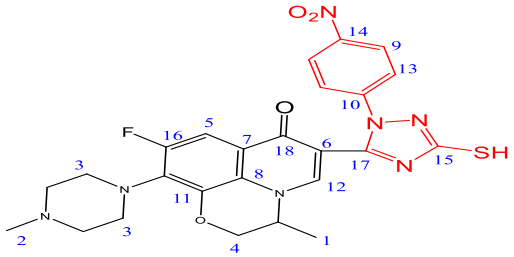
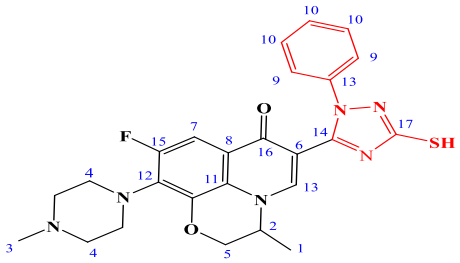
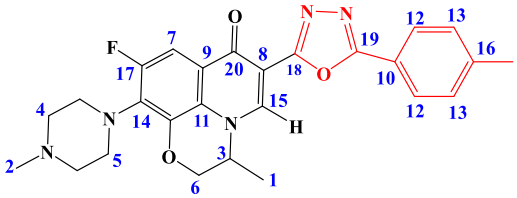
Table 4. Compounds were characterized by ^{13}C-NMR

Comp.	Chemical shift
	C_1/18.42 C_2/40.35 C_3/51.75 C_4/55.75 C_5/68.75 C_6/103.79 C_7/107.28 C_8/120.92 C_9/125.22 C_{10}/130.99 C_{11}/141.06 C_{12}/146.58 C_{13}/157.00 C_{14}/176.85 C_{15}/166.44
	. C_1/18.41 C_2/53.79 C_3/55.31 C_4/68.75 C_5/103.5 C_6/111.39 C_7/123.22 C_8/125.17 C_9/127.9 C_{10}/130.09 C_{11}/138.19 C_{12}/146.09 C_{13}/152.00 C_{14}/149.5 C_{15}/154.6 C_{16}/157.08 C_{17}/161.4 C_{18}/176
	C_1/17.76 C_2/25.60 C_3/39.54 C_4/42.93 , 47.73 C_5/68.79 C_6/107.35 $C_{7,8,11,12}$/121.24-130.83 $C_{9,10,13}$/138.07-150.07 C_{14}/146.97 C_{15}/152.21 C_{16}/166.43 C_{17}/175.00
	C_1/17.21 C_2/42.75 C_3/47.51 C_4/53.48 C_5/55.31 C_6/68.77 C_7/107.29 C_8/108.11 C_9/122.47 C_{10}/124.69 C_{11}/125.21 C_{12}/129.53 C_{13}/130.37 C_{14}/140.99 C_{15}/141.05 C_{16}/145.99 C_{17}/146.75 C_{18}/163.74 C_{19}/166.41 C_{20}/174.07

Computational Technique

The computational approach used in this study is described. The molecular docking experiments for the compounds were carried out using a fully licensed CCDC GOLD Suite (v. 5.7.3). The CCDC visualizer program was used to create the protein, ligands, hydrogen-bonding interactions, brief contacts, and bond length estimates (v. 1.10.3). The pharmacokinetic profile of the synthesized compounds, also known as ADME, or adsorption, distribution, metabolism, and excretion, may be predicted using the Swiss ADME website[20, 21].

- Measuring Drug Likeness

Swiss ADME was used to predict the physicochemical properties of ligands.

-System Preparation

The crystal structure of proteins was retrieved from the protein data bank (PDB)

-Binding Energy Calculations (PLP Fitness)

Hermes was used to calculate the PLP fitness for all docked ligands.

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Molecular Docking

"Genetic docking of flexibility molecules into protein binding sites" is based on genetic optimization for ligand docking. GOLD has received extensive validation and demonstrated great rendering for posture prediction, as well as outstanding outcomes for virtual screening. It's offered as a component of the GOLD Suite. Protein-energy minimization and ligand transfer will correct deformed geometries by releasing internal constraints. When the geometry is fixed following energy minimization, a minimum level of energy has been attained. With the GOLD Suite software, docking studies were carried out to examine the molecular interactions between the synthesized compounds and the protein target's active binding site to forecast the compounds binding energies and selectivity for Cyclooxygenase -1 and Cyclooxygenase-2 (The substrate-binding site is located from Arg117 to near Asp506. (COX-2) has a larger binding cavity (22%) compared with (COX-1). The two enzymes share a sharp 60% homology of amino acids, however the respective conformations of subclass binding sites and active regions are slightly different. (COX-2) has a larger and more flexible sub layer than (COX-1) (COX-2) has a larger surface area at the site where the inhibition binds and this structural difference between (COX-1 and COX-2), all of the produced ligands had excellent docking results with COX-2[20-22] as shown in Figs 1-5, Table 5.

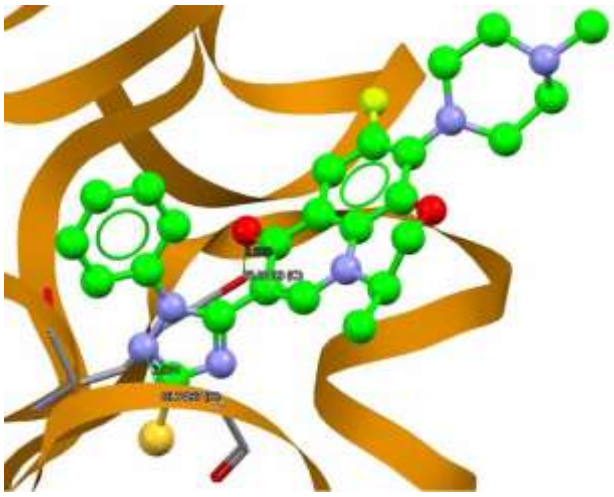

Figure 1. the Interaction between comp. (4) and GLU433 , GLY457 ,GLU433, GLY457

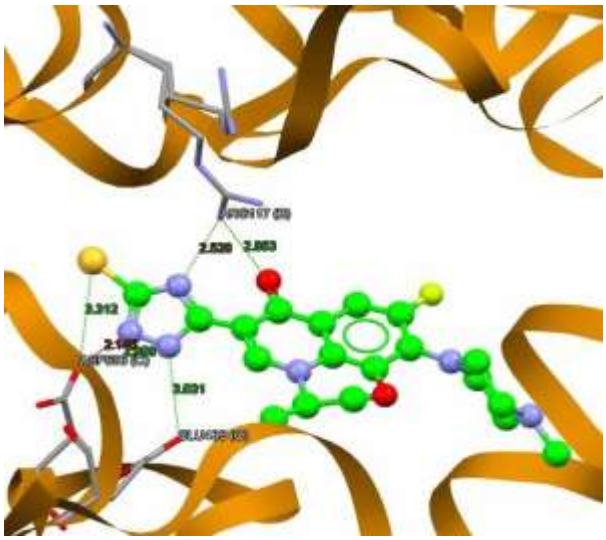

Figure 2. the Interaction between comp. (5) and GLU433 , ASP506 , ARG117

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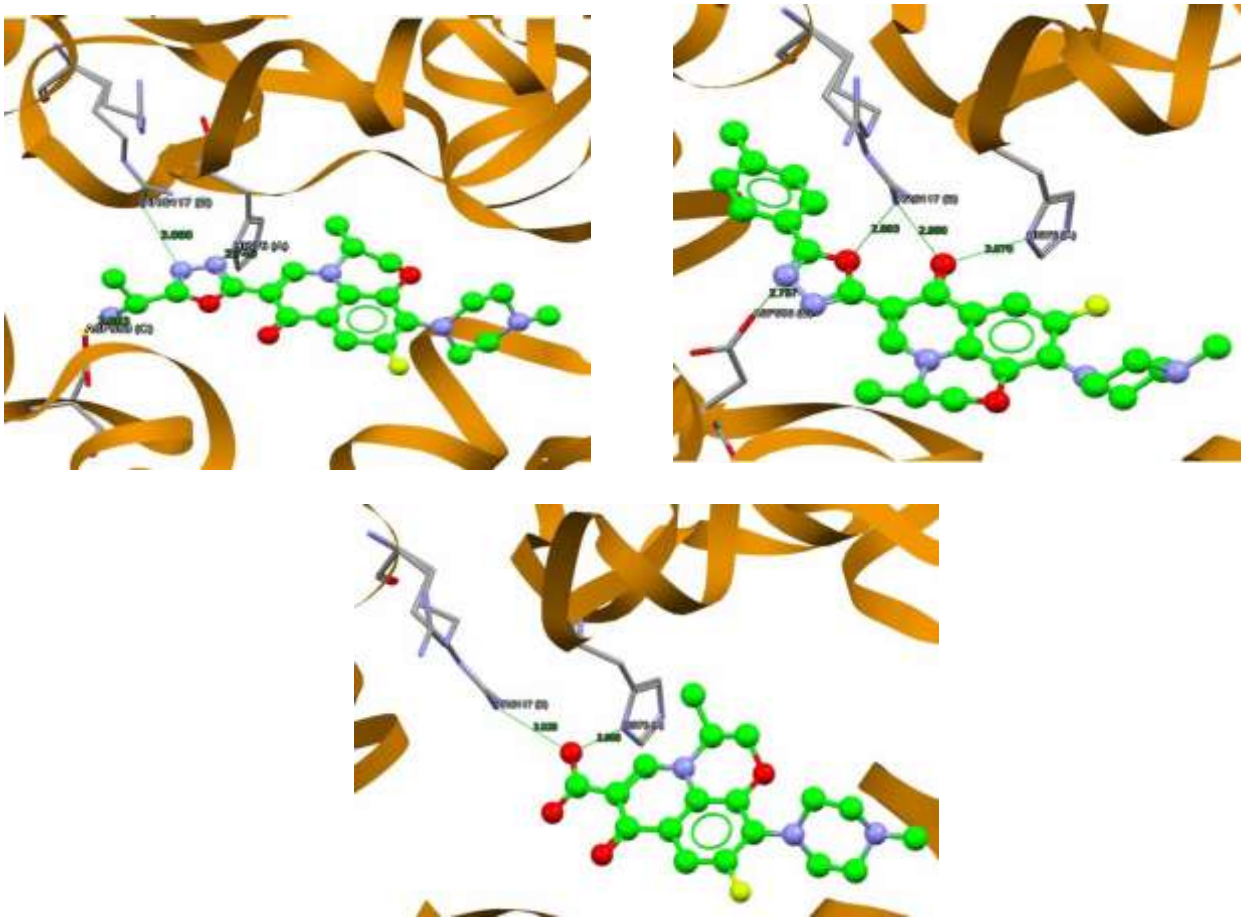

Figure 3-5. the Interaction between Levofloxacin and HIS76, ARG117, ASP508,506

Table 5. The binding energies for Levofloxacin derivatives and Reference Levofloxacin docking with Cyclooxygenase-2

Comp.	(PLP Fitness) Binding energy COX-2	No. of Amino acids in H-bonding	Amino acids	Length of bonding
4	63.94	2	GLU433	2.629
			GLY457	3.074
5	53.15	3	GLU433	3.031
			ASP506	3.312
				2.956
				2.145
			ARG117	2.853
				2.520
9	76.21	3	ASP506	2.757
			ARG117	2.893
				2.850
			HIS76	3.070
10	65.59	3	ASP508	2.883
			HIS76	2.715
			ARG117	3.080
Derivative imide	58.55	1	ARG117	2.957
Levofloxacin	45.54	2	ARG117	3.028
			HIS76	2.805

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Swiss ADME Studies

The characteristics of the compounds created by the (ADME) server were explained based on the (ADME) results. The Swiss company is used to test candidate pharmaceuticals for the highest likelihood of safety and to exclude potentially dangerous vehicles. During the subsequent phases of medication development, we assessed each generated molecule in a certain way (absorption, distribution, metabolism, and excretion). The results that appeared are:

-(Lipinski's rule) regarding oral drug administration must have the ability to give ≤5 or gain ≤10 hydrogen bonds and a molecular weight ≤500 and log P <5 to be taken orally.

- The topological polar surface area (TPSA)[21] because of its very important characteristic associated with drug bioavailability. that adsorbed particles (A° 140> TPSA). Our findings revealed that all compounds had TPSA <140Å ranging.

- The bioavailability of all compounds is (0.55), indicating that all ligands may enter the systemic circulation.

- The GI absorption score evaluates how well a molecule is absorbed from the intestine after being administered orally. If the outcome was favorable, there might be great absorption. That is according to the study, all substances had high GI absorption rates, which indicated that they would be effectively absorbed from the intestine[21, 22].As shown in the Figs. 6-9, Table 6. below.

Table 6. Studies efficacy Pharmacokinetics by using Swiss ADME

Comp.	H-bond acceptors	H-bond donors	TPSA A^2	Synthetic accessibility	Bioavailability score	GI absorption	Lipinski	Water Solubility
4	6	0	107.22	4.38	0.55	High	Yes 0:Violation	Moderately soluble
5	6	1	118.08	3.97	0.55	High	Yes 0:Violation	soluble
10	8	1	102.65	4.69	0.55	High	Yes 0:Violation	soluble
9	7	0	76.63	4.60	0.55	High	Yes 0:Violation	Moderately soluble
8	7	1	104.19	4.25	0.55	High	Yes 0:Violation	soluble

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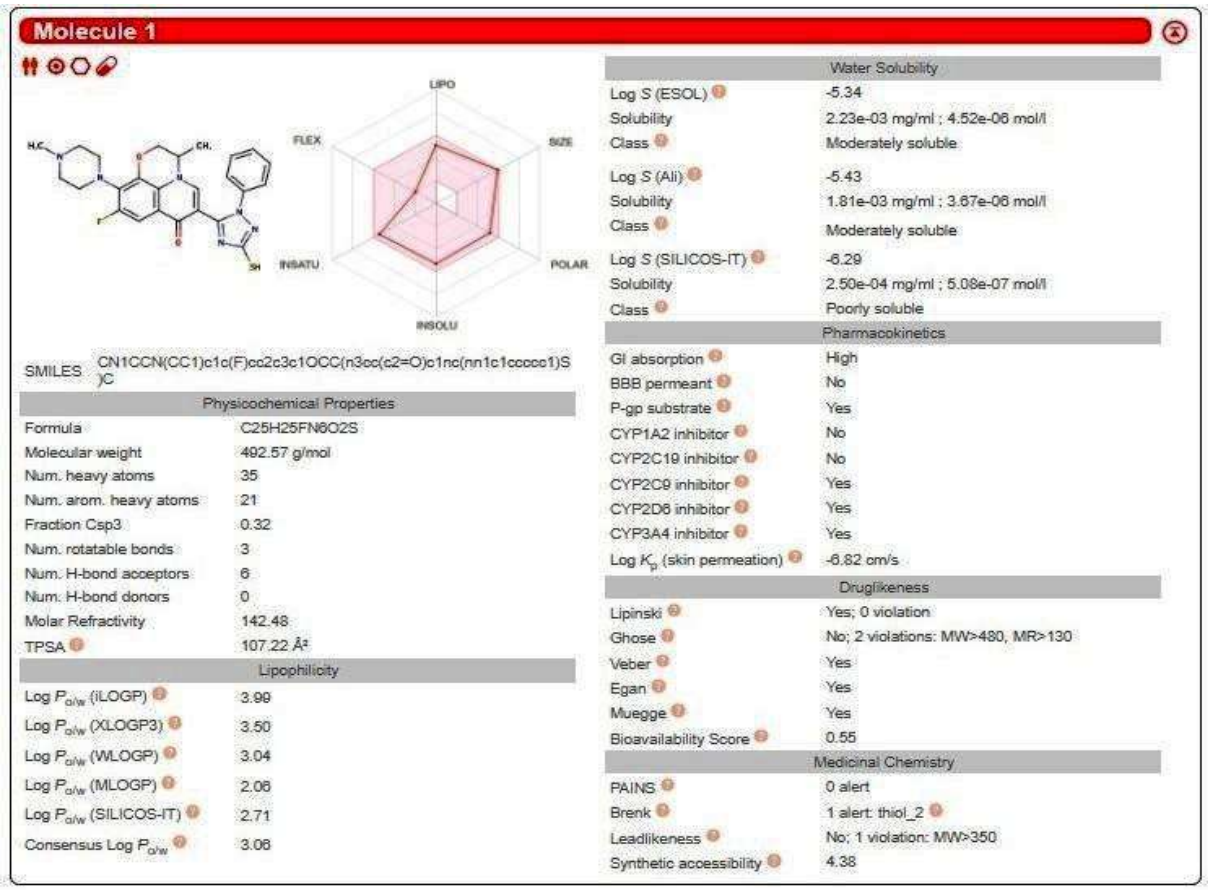

Figure 6. Efficacy Pharmacokinetics of compound (4) by using Swiss ADME

Figure 7. Efficacy Pharmacokinetics of compound (5) by using Swiss ADME

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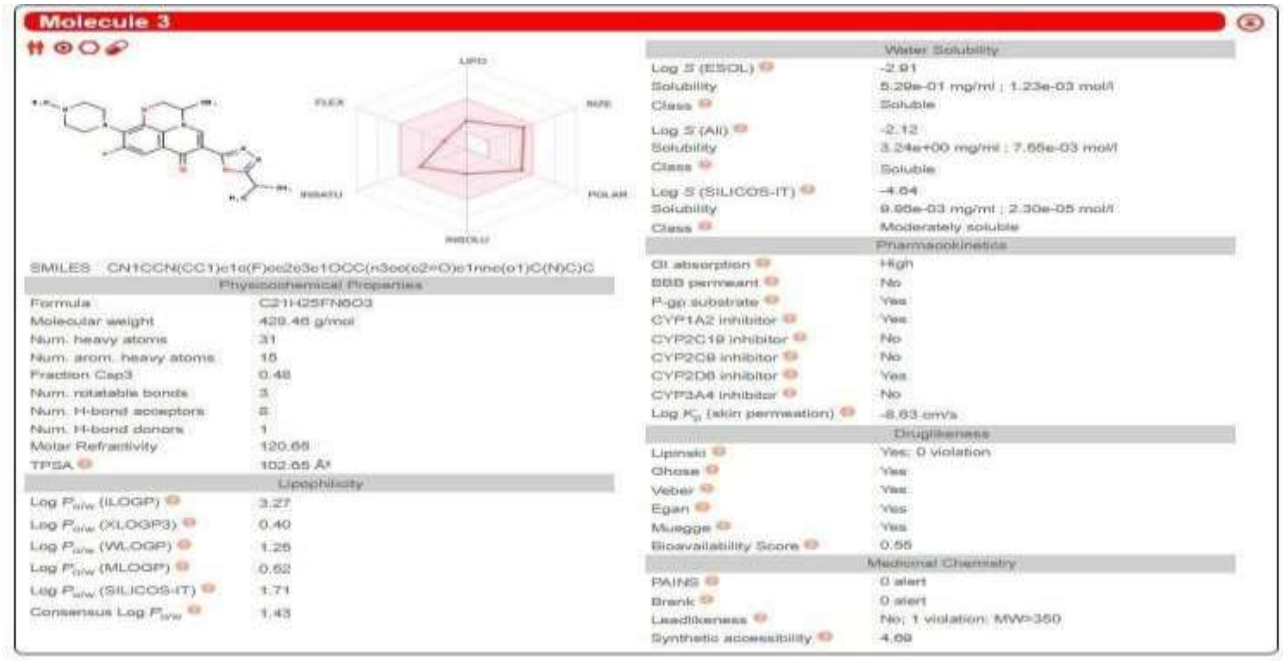

Figure 8. Efficacy Pharmacokinetics of compound (10) by using Swiss ADME

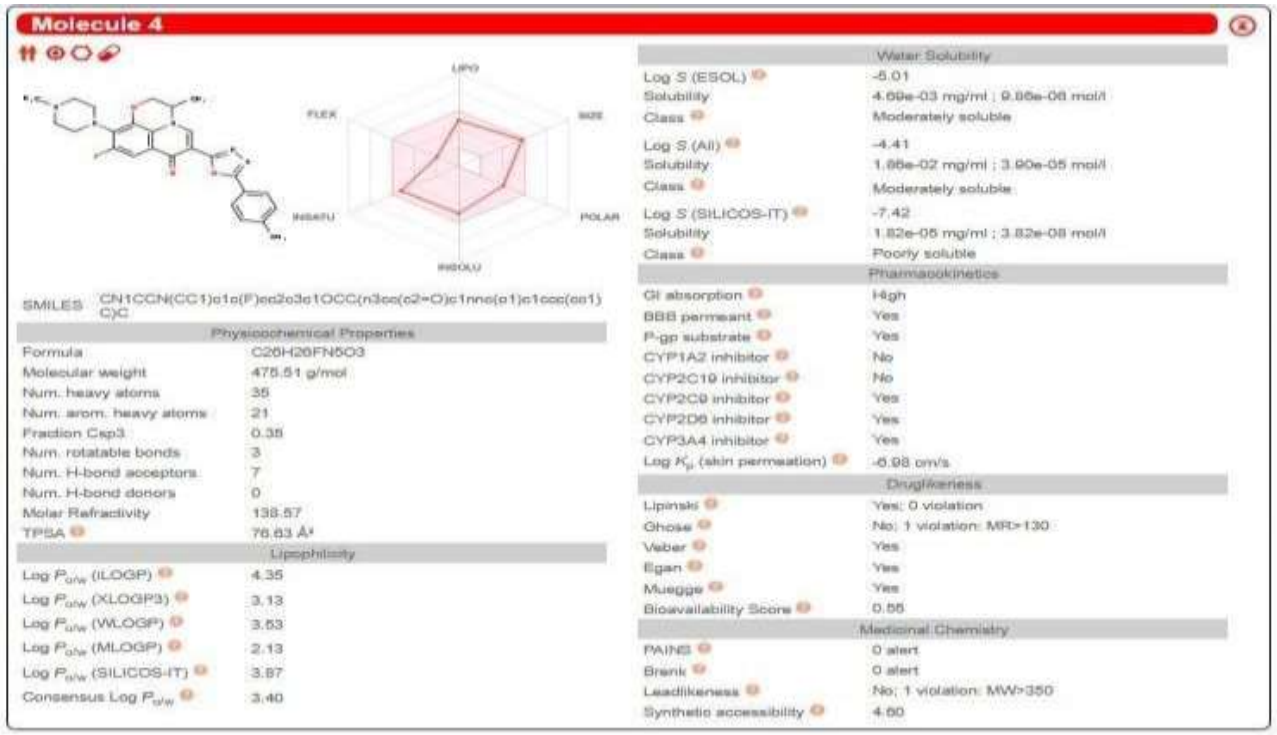

Figure 9. Efficacy Pharmacokinetics of compound (9) by using Swiss ADME

BOILED-Egg

Many of the failures in drug development are calculated for poor pharmacokinetics and bioavailability. Intestinal absorption and access to the brain are two drug behaviors critical for phase estimation of different drug discovery processes. It suggests a brain or gut penetration method.

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-Oval shape (yellow): the molecule is expected to pass exclusively through the blood-brain barriers.[23]

- Oval shape (white): the molecule is expected to be exclusively absorbed by GIT.

-(PGP+): the blue dots are for molecules that are expected to be released from the central nervous system by (p-glycoprotein).

-(PGP-): the red dots are for molecules that are not expected to be released from the CNS system by (p-glycoprotein) [23] as shown in Figs. 11-14.

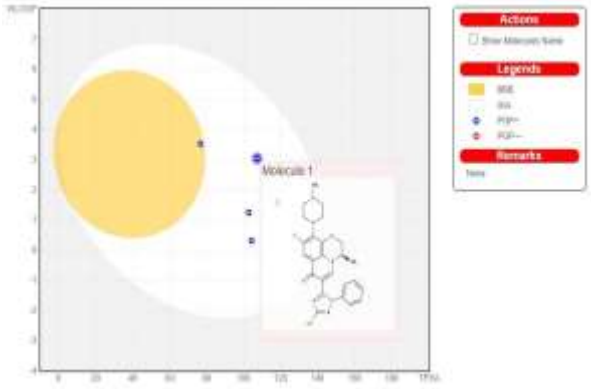

Figure 11. BOILED EGG-of compound (4)

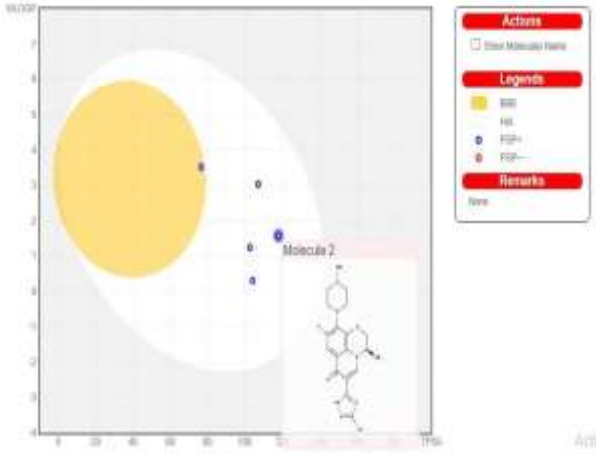

Figure 12. BOILED EGG-of compound (5)

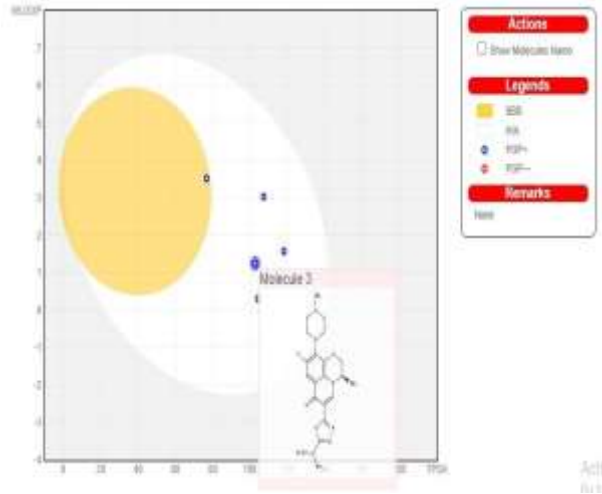

Figure 13. BOILED EGG-of compound (10)

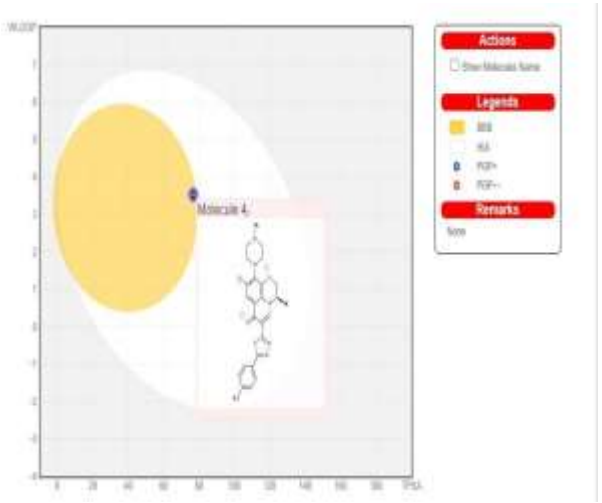

Figure 14. BOILED EGG-of compound (9)

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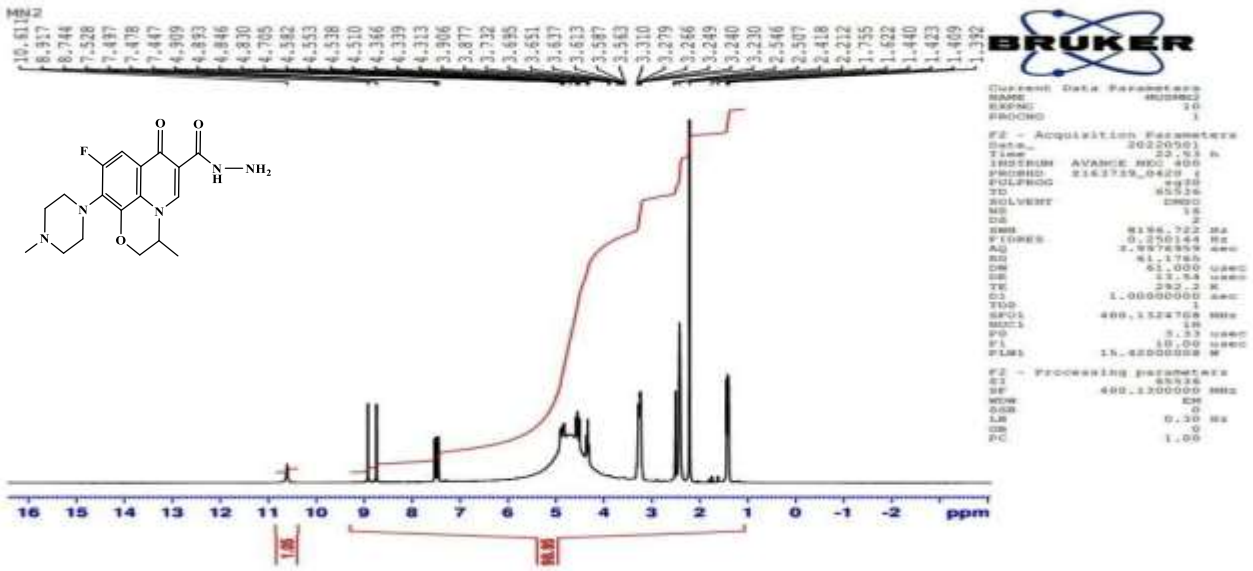

Figure 15. ^{1}H-NMR spectrum of compound (3)

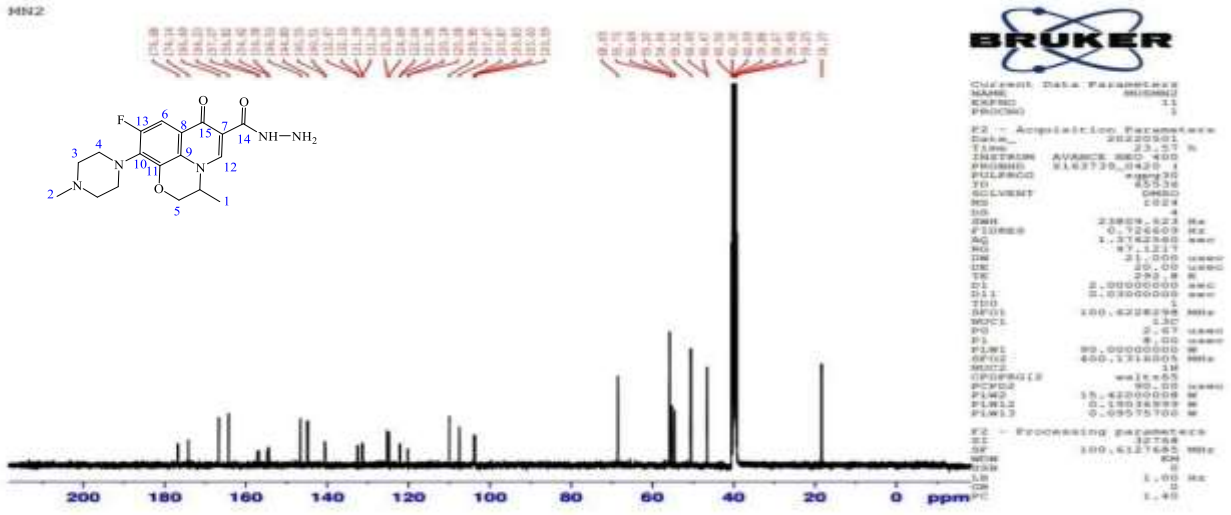

Figure 16. ^{13}C-NMR spectrum of compound (3)

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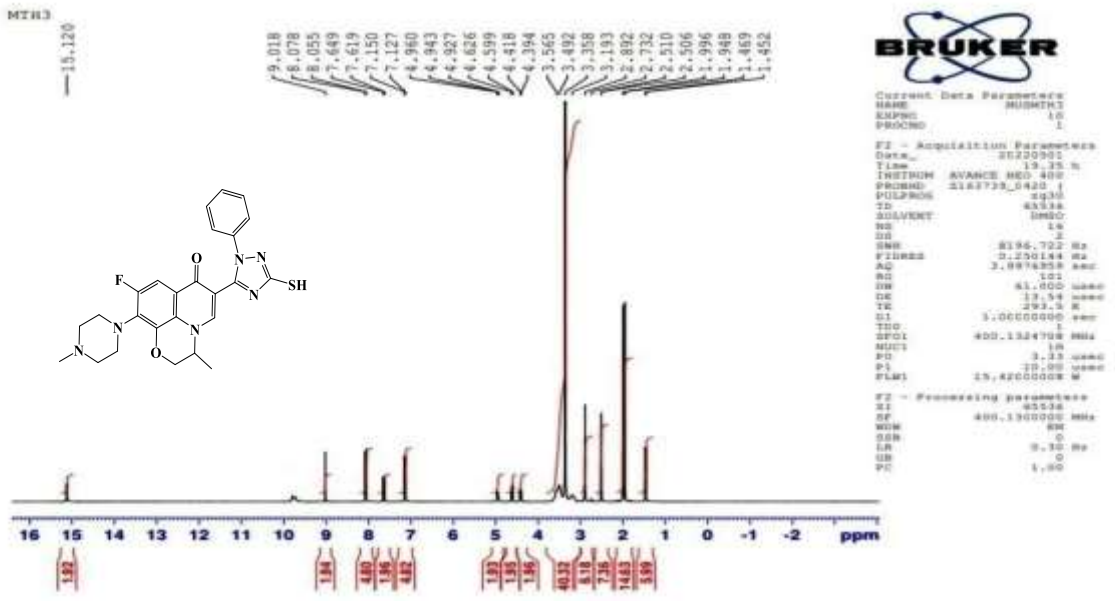

Figure 17. ^{1}H-NMR spectrum of compound (4)

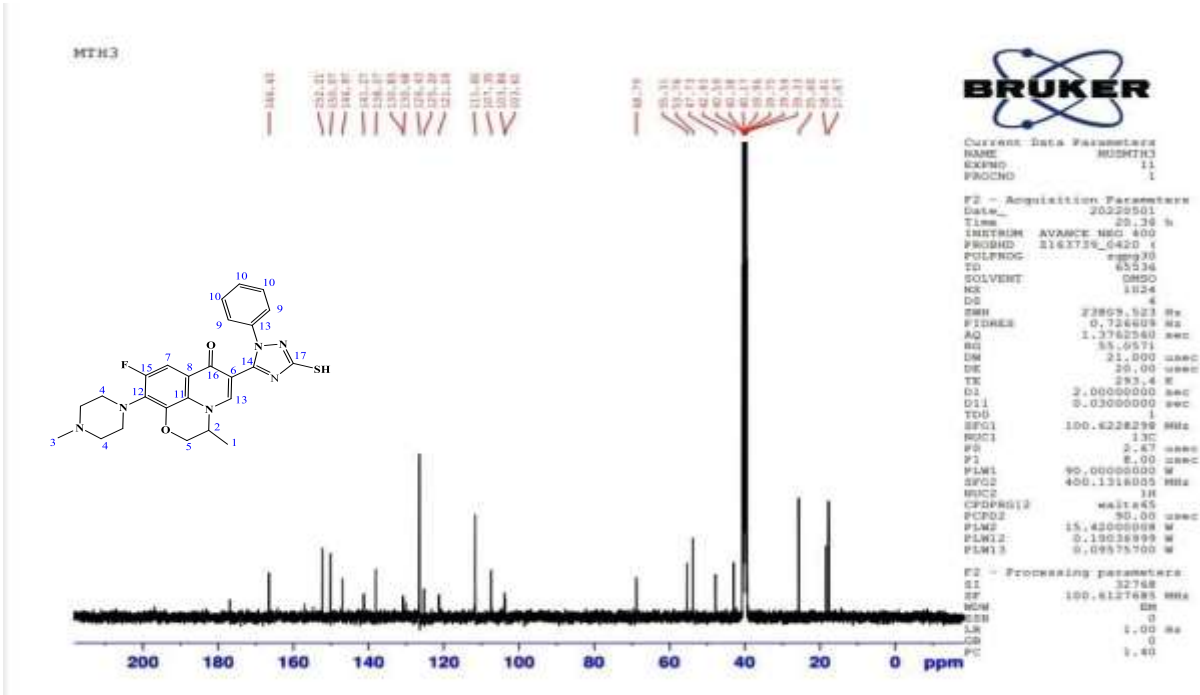

Figure 18. ^{13}C-NMR spectrum of compound (4)

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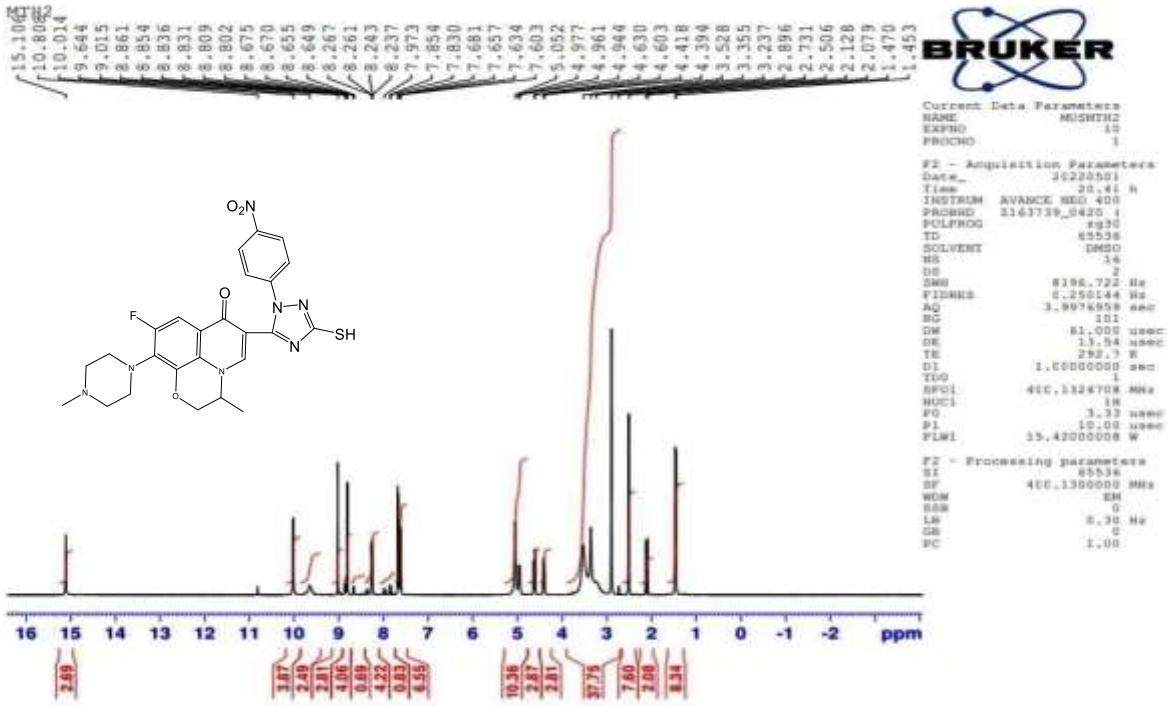

Figure 19. ^{1}H-NMR spectrum of compound (6)

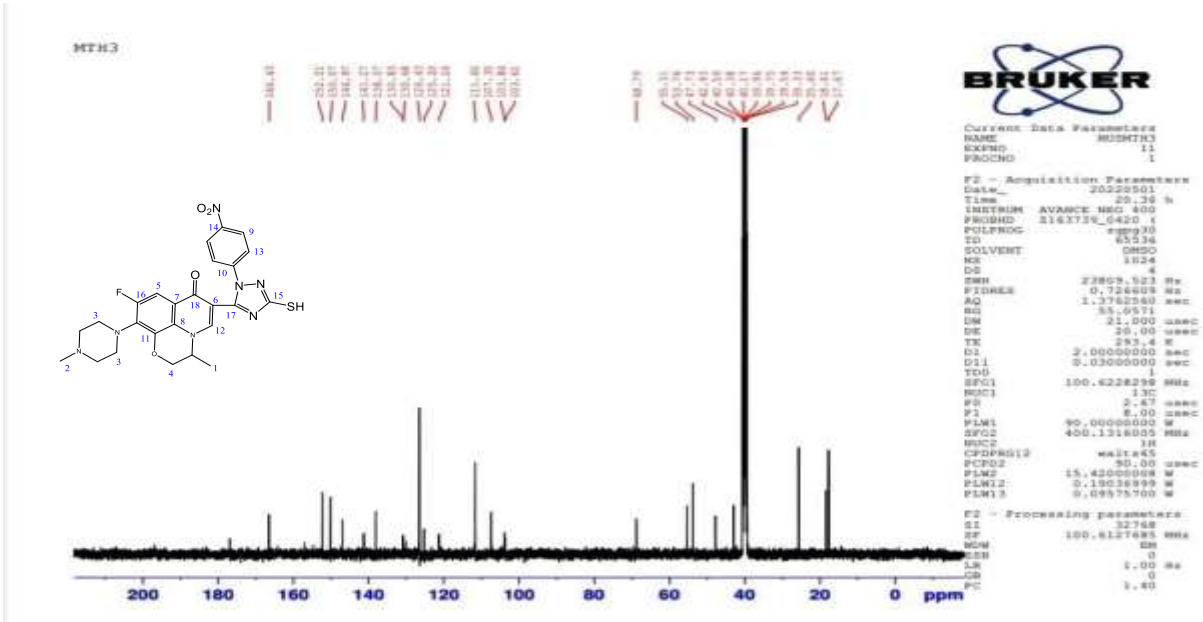

Figure 20. ^{13}C-NMR spectrum of compound (6)

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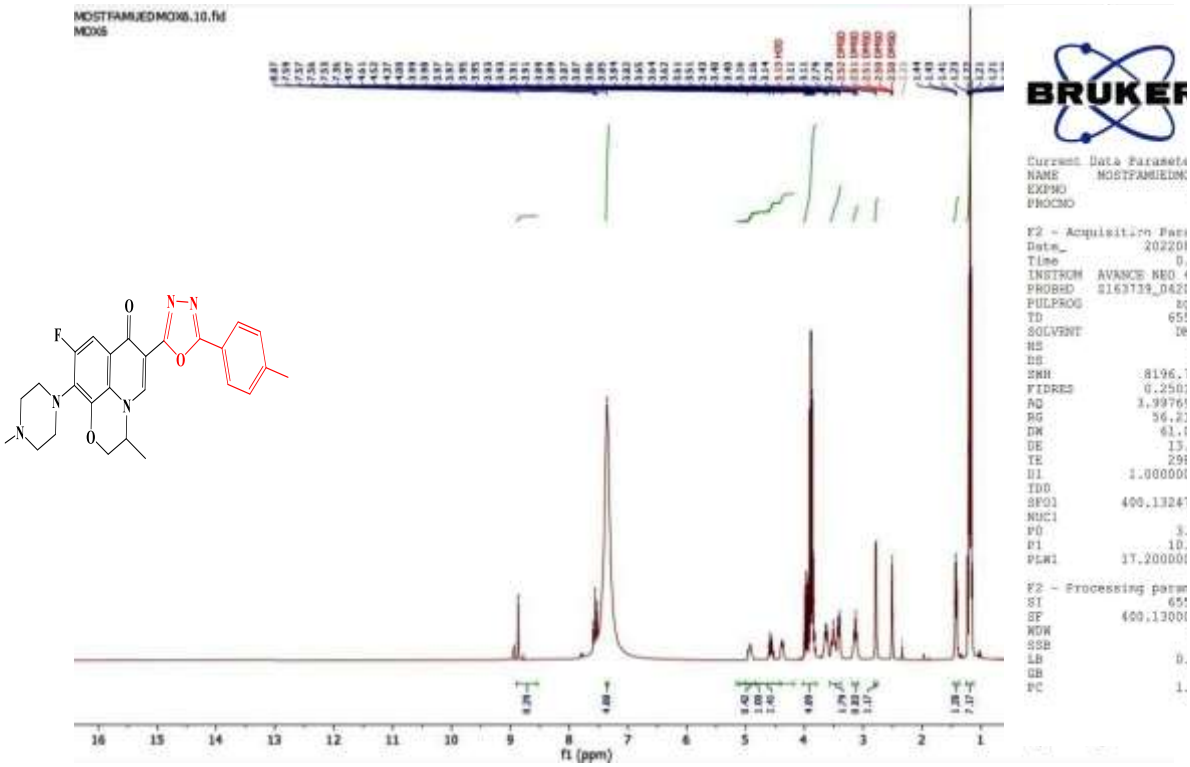

Figure 21. ^{1}H-NMR spectrum of compound (9)

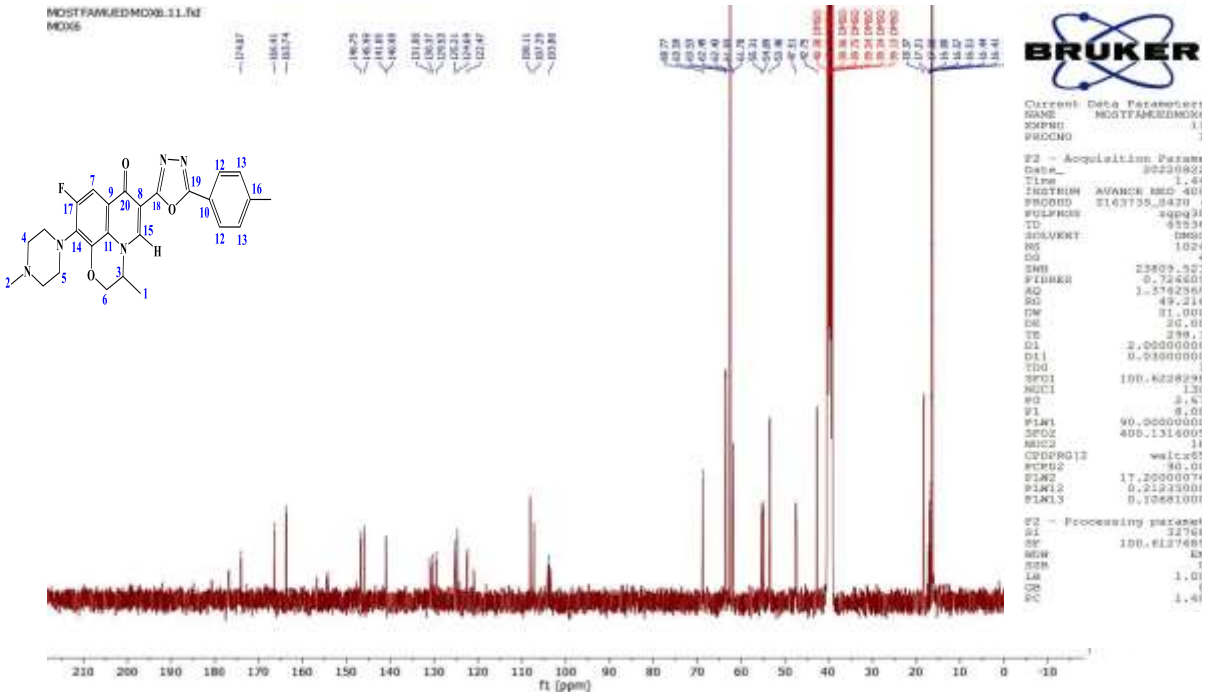

Figure 22. ^{13}C-NMR spectrum of compound (9)

Conclusion

The assessment of the compounds by cyclooxygenase-2 (Although the two enzymes' respective conformations of the active regions and substrate binding sites are slightly different, they have a sharp homology in amino acids. A larger and more flexible sub layer is present in (COX-2) than (COX-1) Because (COX-2) has a higher surface area at the region where the inhibition

binds, the creation of a selective (COX-2) inhibitor was made possible by the structural difference between (COX-1 and COX-2). suggests that Triazole, 1,3,4-Oxadiazole, and Imide were added to levofloxacin. According to the ADME investigation, molecules (M1–M5) and all synthetic compounds were absorbed by the GIT and met the Lipinski criterion. A complete consistency between the in vivo compound study and the Docking study was reported. According to the preliminary study on anti-inflammatory effectiveness, certain chemicals have a greater anti-inflammatory effect than all other substances combined. Greater anti-inflammatory effect than any other substance.

Acknowledgment

We want to express our gratitude to Asst. Prof. Yasser M. Kadhim in the College of Pharmacy for his help in preforming pharmacokinetics and Swiss ADME study of the prepared compound.

Authors' Declaration

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are ours. Furthermore, any Figures and images, that are not ours, have been included with the necessary permission for re-publication, which is attached to the manuscript.
- Ethical Clearance: The project was approved by the local ethical committee in University of Baghdad.

Authors' Contribution Statement

The idea was proposed by M. M. The work and application was made by both M. M. and M. I. K . As for the interpretation of the spectral identification, pharmacokinetics and molecular docking, they were done in cooperation of both of the authors.

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تحوير وتشخيص بعض مشتقات الليفوفلوكساسين الحلقية غير المتجانسة كمثبطات إنزيم COX-2 وتقييم فاعليتها الحركية الدوائية عن طريق الالتحام الجزيئي ودراسات ADME السويسرية.

مصطفى مؤيد اربيع، منى اسماعيل خلف

قسم الكيمياء، كلية العلوم، جامعة بغداد، بغداد، العراق.

الخلاصة

من أجل التنبؤ بالنشاط المضاد للالتهابات ضد انزيمات (COX-2) وتوقع إمكاناتها المضادة للسرطان ، حضرت مشتقات جديدة 1،2،4-تريازول-5-ثايول ، أوكسادايازول وإيمايد. تم استخدام الخصائص الفيزيائية ، H^1-NMR، C^{13}-NMR ، التحليل الطيفي FT-IR ، وطرق أخرى لتوصيف وتحديد المركبات المنتجة. استندت المركبات التي تم إنشاؤها حديثًا (1-10) جزئيًا إلى الأدوية المعروفة المضادة للالتهابات الليفوفلوكساسين. تم استخدام برنامج دراسة ADMET السويسري لإجراء تقنيات حسابية المختص في علم الادوية والعقاقير ويصف كيفية تعامل جسم الكائن الحي مع المركبات الصيدلانية بعد تناولها وكذلك التنبؤ بالحركة الدوائية للعقاقير الجديدة و لتقييم انتقائية المركبات التي تم تحضيرها اتجاه إنزيم COX-2 أظهرت النتائج أن جميع المركبات تتوافق مع قاعدة Lipinski الصيدلانية للمركبات المحضرة. درست قيم طاقة الارتباط PLP أعلى من المركب المرجعي من خلال دراسات الالتحام الجزيئي لتفاعلات الترابط مع بروتين COX-2 للارتباط بالأحماض الأمينية في الدواء الاساسي (Levofloxacin). وكذلك تم التنبؤ عن تحسس الشحمية واستقطاب الجزيئات الصغيرة من خلال نموذج البيضة المسلوقة التي تقترح طريقة تغلغل الدماغ والامعاء بالإضافة الى النظام الغذائي لنفس الخصائص الكيميائية والفيزيائية وترجمتها المباشرة في تصميم جزيئة الدواء.

الكلمات المفتاحية: البيضة المسلوقة , مثبطات أنزيمات الاكسدة الحلقية 2 , أوكسادايازول , تريازول-5-ثيازول , دراسات ADME السويسرية.