COMPUTATIONAL INVESTIGATION OF NORFLOXACIN DERIVATIVES PROPERTIES RELATED TO THEIR BIOLOGICAL ACTIVITY

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Abstract: Background: Fluoroquinolones have great efficacy, broad spectrum of activity, used for treatment of several infections, due to miss use and uncontrolled use of antibacterial agents, lead to emergence of bacterial resistance. Therefore new fluoroquinolones derivatives were synthesized and their biological activities were studied according to their some computational properties. **Aim**: To predict the antibacterial activity of newly synthesized norfloxacin derivatives depending on their computational investigated properties. **Material and method**: Seven norfloxacin derivatives have been designed; their physical properties have been investigated using quantum chemistry computational methods. **Results**: There were six descriptions (one electronic, three physicochemical and two geometric) have highly compatible with Norfloxacin derivative activity, can be used to predicts of their activity by using QSAR equation of Norfloxacin derivatives.

$$pMIC = 0.0795 + 6.12237\times10^{-3}(\eta) - 2.347\times10^{-3}(B.P) - 65.378\times10^{-3}(\log P) + 0.752(\mathrm{MR}) + 6..000995\times10^{-3}\times(\mathrm{NI\text{-}C\text{-}NAA}) - 3.92216\times10^{-3}(\mathrm{NI\text{-}C\text{-}SA})$$

In the above equation, we take the following notations for simplicity:
MR: Molecular Refractivity
NI: N Imine
NAA: N Amine angle
SA: S angle

Conclusion: QSAR would lead to robust equation and predictive models are capable of making accurate and reliable calculations for a new Norfloxacinanalog

Keywords: QSARs, DFT, Molecular Properties, GAMESS, Norfloxacin, Antibacterial resistant.

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INTRODUCTION

Fluoroquinolones are a group of antimicrobial agents used worldwide as they have great efficacy, broad spectrum of activity, and safety [1]. They are used for treatment of several infections as urinary tract infection [2], respiratory tract infection [3], and skin infection [4]. Norfloxacin is one of the second generation fluoroquinolones [5], which act through inhibition of topoisomerase II or gyrase enzyme in gram negative bacteria, while it inhibits topoisomerase IV in gram positive bacteria [6]. In addition to its antibacterial action, it has anti-inflammatory effect through its ability to reduce the cytokines level and white blood cells aggregation [7]. Due to miss use and uncontrolled use of antibacterial agents, lead to emergence of bacterial resistance, therefore, novel antibacterial agents or modification of the per-existing agents is necessary to overcome the bacterial resistance [8].

Quantitative Structure Activity Relation-Ship (QSAR)
The modern QSAR began in the early 1960s, however, as long ago as 1816 scientists were making predictions about physical and chemical properties. The first investigations into the correlation of biological activities with physicochemical properties such as molecular weight and aqueous solubility began in 1841. Throughout the 20th century QSAR progressed, though there were many lean years [9-10]. In 1962 came the seminal work of Corwin Hansch and co-workers, predicts biological activities $\log(\mathrm{I/C}) = 0.94\log(P) + 0.87$, initially that interest lay largely within medicinal chemistry and drug design [11].

METHODOLOGY

Computational Methods
A series of Norfloxacin derivatives tested for their activities were selected for the present study and the program of Windows Chem SW was adopted for molecular modeling studies. The molecules were generated and energy minimization was carried out by using Molecular Modeling Program, all calculations are carried out by General Atomic and Molecular Electronic Structure System (GAMESS) software [12-14]. After minimized energy, physicochemical properties were calculated for all studied molecules and the results are shown in table (2-1).

Selected Norfloxacin derivatives [15]
Norfloxacin is one of the second generation fluoroquinolones, it act through inhibition of bacterial topoisomerase enzyme by that prevent bacterial DNA replication, leading to bactericidal effect. Due to the uncontrolled use and miss use of the fluoroquinolones lead to the emergence of bacterial resistance so; it became necessary to synthesize of new derivative to overcome bacterial resistance. It was found that the incorporation of bulk chemical group at carbon 7 of the piperazine ring lead to reduction in the affinity toward the bacterial efflux pump, which considered as one of the major routs of bacterial resistance. Depending on this background, six norfloxacin derivatives were synthesized through incorporation of triazole derivatives at C-7 piperazine ring.

Table 2-1: Activity of Norfloxacin Derivatives

Compound	IUPAC name	MIC (mcg/ml)
III	7-(4-(2-aminothiazol-4-yl) piperazin-1-yl)-1-ethyl-6 fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid	6.8
IVa	(E)-1-ethyl-6-fluoro-7-(4-(2-((4 hydroxybenzylidene)amino)thiazol-4-yl)piperazin-1-yl)-4-oxo-1, 4-dihydroquinoline-3-carboxylic acid	8.4
IVb	(E)-1-ethyl-6-fluoro-7-(4-(2-((4-methoxybenzylidene)amino)thiazol-4-yl)piperazin-1-yl)-4-oxo-1, 4-dihydroquinoline-3-carboxylic acid	8.6
IVc	(E)-7-(4-(2-((4-(dimethylamino)benzylidene)amino)thiazol-4-yl)piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid	8.8
IVd	(E)-7-(4-(2-((4-chlorobenzylidene)amino)thiazol-4-yl)piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid	8.7
IVe	(E)-7-(4-(2-((4-bromobenzylidene)amino)thiazol-4-yl)piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid	9.4
IVf	(E)-1-ethyl-6-fluoro-7-(4-(2-((4-methylbenzylidene)amino)thiazol-4-yl)piperazin-1-yl)-4-oxo-1, 4-dihydroquinoline-3-carboxylic acid	8.3

Results

Computer Calculations: The calculated description of properties for Norfloxacin was: Geometric structures, electronic structures and physiochemical properties as shown in table (1).

Table (1-a): Norfloxacin Derivatives Calculated Descriptors by GAMSS Program

Compound	MIC (µg/ml)or(ppm)	pMIC	HOMO=-IP(ev)	LUMO=-Aev	Ƞ=LUMO-HOMO (ev)	µ=(HOMO+LUMO)/2 (ev)	$\omega=\mu^2/2\eta$ (ev)	more(+) ev charge atom	more(-) ev charge atom	Kinetic Energy (Kcal/Mol)	Dipole (Debye)	Potential Energy (Kcal/Mol)	Boiling Point (k)	ΔH_f(kJ/mol)
III	68	-1.8325	-7.201	-2.509	4.692	-4.855	2.512	0.781	-0.777	1074381.56	11.643	-2155836.23	870.618	-203.15
IVf	83	-1.9191	-8.544	-2.765	5.779	-5.654	2.766	0.622476	-0.834338	1266193.	11.141	-2541501.1	954.743	-223.06
IVa	84	-1.9243	-8.533	-2.474	6.059	-5.5035	2.4995	0.6702	-0.8683	1288636.293	10.597	-2586343.4	977.98	-368.26
IVb	86	-1.9345	-8.541	-2.711	5.83	-5.626	2.715	0.53165	-0.7657	1326017.805	12.5887	-2655334.03	966.797	-355.28
IVd	87	-1.9395	-8.48	-2.14	6.34	-5.31	2.224	0.700449	-0.855592	1528154.594	7.956949	-3065937.453	961.839	-218.16
IVc	88	-1.9445	-8.552	-2.489	6.063	-5.5205	2,524	0.735647	-0.874515	1325225.816	13.40779	-2659546.432	977.625	-176.17

IVe	94	-1.9731	-8.567	-2.53	6.037	-5.5485	2.5498	0.703771	-0.838836	2853455.51		-5711347.338	973.845	-176.09
	dependent variable variation	R^2	0.942	0.011	0.916	0.711	0.113	0.135	0.27	0.41	0.056	0.41	0.867	0.00001
		Slope	0.074	-0.02	-0.069	0.118	0.00001	0.199	0.53	-5.00E-08	0.005	2.00E-08	-0.001	-2E-06

Table (1-b): Norfloxacin Derivatives Calculated Descriptors by GAMSS Program

Compound	**MIC (µg/ml) or(ppm)**	**Log P**	**Accessible Area (Å^2)**	**Molecular Area (Å^2)**	**Solvent Excluded Volume (Å^3)**	**Number of HBond Acceptors**	**Number of HBond Donors**	**Mol Refractivity**	**Partition Coefficient**	**Entropy cal/(mol K)**	**Log S**	**PKa , Atom : 13**	**Balaban Index**	**Molecular Topological Index**
III	68	3.45	642.57	349.302	318.129	8	2	10.867	2.174	154.964	-5.3543	2.628	849776	15852
IVf	83	5.522	836.47	465.716	429.147	8	2	14.561	0.637	0	-7.2316	2.6281	2557793	36739
IVa	84	4.645	818.129	454.988	419.511	9	3	14.25	0.372	0	-6.80543	2.628	2557793	35867
IVb	86	4.908	853.622	473.427	434.998	9	2	14.714	0.4825	0	-6.9248	2.62809	293891	39391
IVd	87	5.593	830.973	462.337	427.497	8	2	14.5882	0.85146	0	-9.999	0	255779	35431
IVc	88	5.319	880.878	493.371	456.36	9	2	15.3931	0.821958	0	-9.999	0	3350863	43371
IVe	94	5.863	838.67	467.34	432.682	8	2	14.8738	1.0015	0	-7.67904	2.62809	255779	35431
	dependent variable variation R^2	0.833	0.831	0.834	0.846	0.05	0.00001	0.884	0.798	0	0.934	0	0.928	0.938
	slope	-0.0491	0.00001	-0.00001	-0.00001	-0.018	-0.00001	-0.027	0.057	0	0.057	0	-5.00E-08	-4.00E-06

Table (1-c): Norfloxacin Derivatives Calculated Descriptors by GAMSS Program

Compound	MIC (µg/ml) or(ppm)	Sum Of Degrees	Sum Of Valence Degrees	Topological Diameter	Total Connectivity	Total Valence Connectivity	Wiener Index	C(4)-C(5)-C(6)	O(14)Carbonyl pyridine charge	F charge	C(8)-C(7)-F(15)	S charge	N(26)-C(25)-N(29)	N(23)-C(22)-S(21)
III	68	64	106.667	15	3.03E-05	3.06E-08	2315	119.525	-0.565	-0.282	120.501	0.439017	125.397	119.927
IVf	83	82	128.667	21	1.26E-06	6.93E-10	5117	119.437	-0.552	-0.28	120.99	0.282965	118.082	108.501
IVa	84	82	132.667	21	1.26E+06	3.10E-10	5117	119.496	-0.558	-0.286	120.956	0.310204	117.874	108.955
IVb	86	84	134.667	22	8.93E-07	2.83E-10	5589	120.284	-0.457513	-0.348074	120.312	0.245263	114.889	110.778
IVd	87	82	128.4444	21	1.26E-06	7.86E-10	5117	119.584	-0.555447	-0.280954	121.091	0.309275	117.853	108.933
IVc	88	86	134.6667	22	7.29E-07	3.10E-10	6063	119.476	-0.56852	-0.284456	121.063	0.362421	117.895	108.988
IVe	94	82	128.667	21	1.26E-06	6.93E-10	5117	119.343	-0.55994	-0.28197	116.466	0.355084	119.088	108.656
	dependent variable variation R^2	0.972	0.929	0.812	0.00001	0.838	0.957	0.216	0.019	0.012	0.041	0.295	0.857	0.898
	slope	-0.005	-0.003	-0.016	-3.00E-10	4.00E+06	-3.00E-05	0.271	-155	0.2	-0.26	0.379	0.011	0.008

Prediction of Most Dependence Properties-Activity

From 38 descriptions there were six highly dependence of properties-activity as shown in figures (1-2) and table (2).

Table (2): Best Regression Properties to Activity of Norfloxacin

Compound	P MIC	Ƞ S=-0.069 R^2=0.961	B.P (k) S=-0.001 R^2=0.867	LogP S=-0.049 R^2=0.833	Refractivity S=-0.027 R^2=0.884	N Imine–C–N amine S=0.011 R^2=0.857	N Imine–C-S S=0.008 R^2=0.898
III	-1.8325	4.692	870.618	3.45	10.867	125.397	119.927
Ivf	-1.9191	5.779	954.743	5.522	14.561	118.082	108.501
Iva	-1.9243	6.059	977.98	4.645	14.25	117.874	108.955
Ivb	-1.9345	5.83	966.797	4.908	14.714	114.889	110.778
Ivd	-1.9395	6.34	961.839	5.593	14.5882	117.853	108.933
Ivc	-1.9445	6.063	977.625	5.319	15.3931	117.895	108.988
Ive	-1.9731	6.037	973.845	5.863	14.8738	119.088	108.656

Ƞ: hardness, S: slope, R2: regression

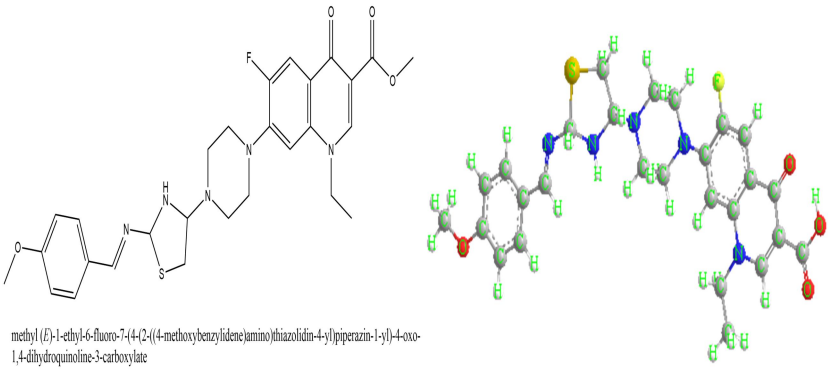
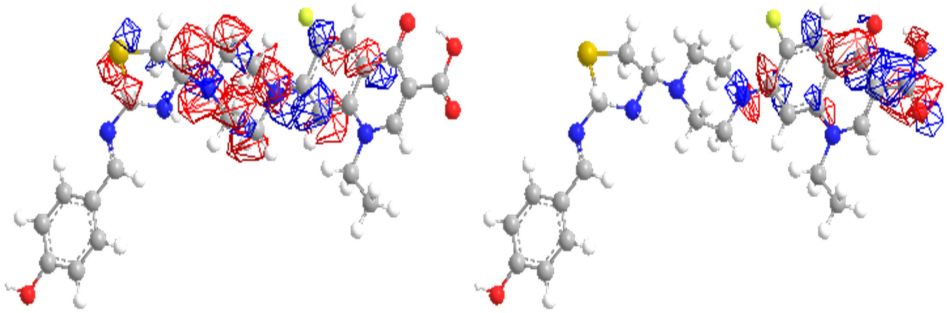


Figure 1: 2D and 3D Molecular Structure of IVb Analog



HOMO LUMO

Figure 2: Electronic Structure HOMO and LUMO of Iva Analog

MATHEMATICAL CALCULATION

By using the general equation of QSAR is: [16-17]

$pMIC = a_0+\sum a_iX_i$

Where Xi: is p_i * slope with activity

p_i: any property

So the general equation:

$pMIC = a_0+a_1s_1p_1+a_2s_2p_2+a_3s_3p_3+a_4s_4p_4+a_5s_5p_5+a_6s_6p_6+\ldots..$

For Norfloxacin analogs pMIC were:

III- a_0-0.323748a_1-0.870618a_2-0.16905a_3-0.293409a_4+1.379367a_5+1.298902a_6=-1.8325

Ivf- a_0-0.398751a_1-0.954743a_2-0.270578a_3-0.393147a_4+1.298902a_5+0.868008a_6=-1.9191

Iva- a_0-0.418071a_1-0.97798a_2-0.228046a_3-0.38475a_4+1.296614a_5+0.87164a_6=-1.9243

Ivb- a_0-0.40227a_1-0.966797a_2-0.240492a_3-0.3938814a_4+1.263779a_5+0.886224a_6=-1.9345

Ivd- a_0-0.43746a_1-0.961839a_2-0.274057a_3-0.3938814a_4+1.296383a_5+0.871464a_6=-1.9395

Ivc- a_0-0.4188347a_1-0.977625a_2-0.260631a_3-0.4156137a_4+1.296845a_5+0.871904a_6=-1.9445

Ive- a_0-0.416553a_1-0.973845a_2-0.287287a_3-0.4015926a_4+1.309968a_5+0.869248a_6=-1.9731

The solution of these 7 equations by using Microsoft office excels give:

a_0	0.079512
a_1	-0.08873
a_2	2.347319
a_3	1.334238
a_4	-0.72507
a_5	0.545545
a_6	-0.49027

So theoretical activity for Norfloxacin analogs according to general equation of QSAR;

pMIC=0.079512+0.00612237 (Η)–0.002347319 (B.P) – 0.065377662 (LogP)+0.75207(molecular refractivity)+0.006000995(N Imine – C –Namine angle) – 0.00392216 (NImine –C-S angle)

Now for following compounds theoretical pMIC will be;

pMIC (III) = 0.079512-0.08873*-0.323748+2.347319*-0.870618+1.334238*-0.16905-0.72507*-0.293409+0.545545*1.379367-0.49027*1.298902 =-1.832500182

pMIC (Ivf) = 0.079512-0.08873*-0.398751+2.347319*-0.954743+1.334238*-0.270578-0.72507*-0.393147+0.545545*1.298902-0.49027*0.8680086=-1.9191003145

pMIC (Iva) = 0.079512-0.08873*-0.418071+2.347319*-0.97798+1.334238*-0.228046-0.72507*-0.38475+0.545545*1.296614-0.49027*0.87164 =-1.924291085

pMIC (Ivb) = 0.079512-0.08873*-0.40227+2.347319*-0.966797+1.334238*-0.240492-0.72507*-0.3938814+0.545545*1.263779-0.49027*0.886224 =-1.934500085

pMIC (Ivd) = 0.079512-0.08873*-0.43746+2.347319*-0.961839+1.334238*-0.274057-0.72507*-0.3938814+0.545545*1.296383-0.49027*0.871464 =-1.939500851

pMIC (Ivc) = 0.079512-0.08873*-0.4188347+2.347319*-0.977625+1.334238*-0.260631-0.72507*-0.4156137+0.545545*1.296845-0.49027*0.871904 =-1.944500085

pMIC (Ive) = 0.079512-0.08873*-0.416553+2.347319*-0.973845+1.334238*-0.287287-0.72507*-0.4015926+0.545545*1.309968-0.49027*0.869248 =-1.973100085

DISCUSSION

Calculation on table (1) founds the relation-ship between each property with analog activity and slope of this relation-ship. The positive (+ev) and negative (-ev) proportionality;

two of them geometric properties {N Imine -C-N amine angle (+ev) and N Imine -C-S} angle (+ev), figure (3) and one electronic structure property $\Delta_{LUMO-HOMO}$ (Ƞ)(-ev) figure (2)and three physicochemical properties {B.p., (-ev), log P, (-ev) and refractivity of molecules, (-ev)} have the best regression (dependent variable variation) selected of R^2 more than 0.83 as shown in Table (3)

Table 3: Practical and Theoretical Norfloxacin Activity

Compound	III	Ivf	Iva	Ivb	Ivd	Ivc	Ive
practical activity	-1.8325	-1.9191	-1.9243	-1.9345	-1.9395	-1.9445	-1.9731
theoretical activity	-1.832500182	-1.919100314 5	-1.924291085	-1.934500085	-1.939500851	-1.944500085	-1.973100085

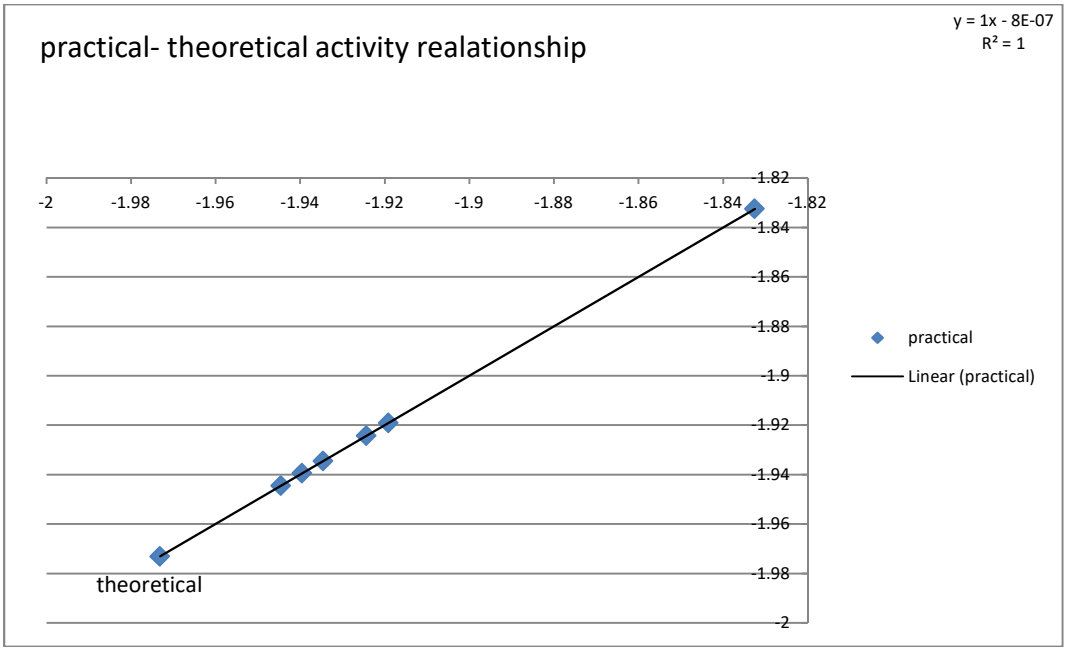


Figure 3: Theoretical and practical Norfloxacin MIC

From table (1) and figure (1) proving that best calculation and predicting of activities and QSAR because the calculated (theoretical) values of activities applicable to practical (experimental) values, So it is excellent method to predicting of novel compound activity.

CONCLUSIONS

QSAR equations in turn are used to predict the activity of new Norfloxacin analog derivatives. Since QSAR produces predictive models derived from application of statistical tools, which correlating with a biological activity included the desirable therapeutic effect with descriptors of molecular structure or properties. In general, the good quality of QSAR equation depends on many factors such as; quality of input data, selection of descriptors and a statistical methods for validation of model. Ultimately, QSAR would lead to robust equation and predictive models are capable of making accurate and reliable calculations for a new Norfloxacinanalog.

Ethical approval: The research involves a computerized study and not involved any in vitro or in vivo experiments, so; not required approval from the ethical committee.

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Conflict of interest: N/A

Informed Consent: the study occurred on animals with the aid of computer software

REFERENCES

i. Stacey, LP, Danielle, SK, Dylan, OP, Ciera, FN, Benjamin, ML, Rebecca, et al. (2021). Fluoroquinolones Antibiotics Exhibit Low Antiviral Activity against SARS-CoV-2 and MERS-CoV. *Viruses*. 13: 8.

ii. Gupta, V, Pal, K, Bhagat, A, Goel, A, Chander, J. (2020). Quinolones Susceptibility in Salmonella Isolates Based on Minimum Inhibitory Concentration Determination. *Journal of Laboratory Physicians*. 12: 4.

iii. APrisnyi, A, Moiseeva, AA, Skvortsov, VN, Yurin, DV. (2021). the comparative analysis of the influence of fluorochinoloneson the blood leucogram of chickens. *AGRITECH-IV.OP Conf. Series: Earth and Environmental Science*. (2021); 677: 042022

iv. Freeman, MZ, Cannizzaro, DN, Naughton, LF, Bove, C. (2021). Fluoroquinolones-Associated Disability: It Is Not All in Your Head. *Neuro Sci*. 2: 235-253.

v. Nagshetty, K, Manjula, NG, Math, GC, Mohan, AS, Shivannavar, CT, Gaddad, SM. (2021). Resistance to Fluoroquinolones and Other Antimicrobials. *Culture-Positive Salmonellatyphi Isolates in Gulbarga, South India. Advances in Microbiology*. 11: 16-26.

vi. Lemaitre, F, Fily, F, Foulquier, JB, Revest, M, Jullien, V, et al. (2021). Development of a dosing-adjustment tool for fluoroquinolones in osteoarticular infections: The Fluo-pop study. *Biomedicine and Pharmacotherapy, Elsevier Masson*. 142: 112053.

vii. Naser, NH. (2018). Design, synthesis and hydrolysis study of gatifloxacin-NSAIDs as mutual prodrugs. *Asian Journal of Chemistry*. 30(1): 195-200.

viii. Ganduh, S. H., Aljeboree, A. M., Mahdi, M. A., & Jasim, L. S. (2021). Spectrophotometric Determination of Metoclopramide-HCl in the standard raw and it compared with pharmaceuticals. *Journal of Pharmaceutical Negative Results*, 12(2), 44-48.

ix. Dearden, JC. (2016). the History and Development of Quantitative Structure-Activity, Relationships (QSARs). *International Journal of Quantitative Structure-Property Relationships*. 1(1): 1-43

x. Paola, Gr, Amatica, University of Insubria, Varese, Italy. (2020). Principles of QSAR Modeling. *International Journal of Quantitative Structure-Property Relationship.* 5(3): 1-37

xi. Hansch, CA. (1969). Quantitative approach to biochemical structure activity relationships. *Accol/llts of Chemical Research*. 2(8): 232-239, doi: 1O.10211a1'50020a002

xii. Omar, N. S., Xinxin, L., Jiayi, X., & Hussain, S. G. (2021). Serum Level of Cytokine IL-30 in Psoriatic Patients and Correlation With Disease Severity. *Journal of Population Therapeutics and Clinical Pharmacology*, 28(01).

xiii. Dupuis, M, Watts, JD, Villar, HO, Hurst, JGB. (1989). the general atomic and molecular electronic structure system Hondo: *Version 7.0. Computer Physics Communications*. 52 (3): 415-425

xiv. Hatem, OA, Suhail, FSA, Juda, AM. (2016). Determination of physicochemical and geometrical, properties of some carvedilol derivatives. *Asian Journal of Pharmaceutical and Clinical Research*. 9(4): 330-336

xv. Ajjah, NT, Naser, NH, Alard, AAA, Diwan, MF. (2020). Design, Synthesis, Docking Study and Preliminary Pharmacological Assessment of New Norfloxacin Analogues Having Triazole Nucleus. *Journal of Biochemical Technology*. 11(3): 58-67.

xvi. Hatem, OA, Suhail, FSA, Juda, AM. (2016). Computational and Polar graphic study on Drug-Receptor Interaction for Atenolol. *Int. J. Pharm. Sci. Rev. Res*. 38(1): 263-270

xvii. Suhail, FSA. (2016). Computational Chemistry Calculation on Stavudine (D4T) and Its Derivatives Activity to predict a new compound with best drug potency. *Journal of Computational Methods in Molecular Design.* 6(3): 1-7