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Research Article

COVID-19 Drug Design Based on the Active Core of Well-known Anti-malarial: A computational Approaches

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ABSTRACT

Background and aims: The present work aimed to design eight molecules based on 7-chloroquinoline unit that has a potential to treat Coronavirus disease (COVID-19).

Results: The AB3 molecule recorded Log P using HyperChem software at 4.18, EHOMO/LUMO gap at 8.195 eV, total energy at -76645.750 Kcal/mol, binding energy at -3979.363 Kcal/mol and dipole moment at 4.87 D. The AI3 recorded Log P at 4.60, EHOMO/LUMO gap at 7.512 eV total energy at -72557.745 Kcal/mol binding energy at -3827.571 Kcal/mol and dipole moment at 3.22 D. Surprisingly the both candidate molecules (AB3 and AI3) reported results very closed to chloroquine. For clarity, the total energy, binding energy, dipole moment, Log P and HOMO/LUMO energy gap for well-known anti-malarial and hottest candidate for COVID19 treatment (chloroquine) calculated to be -76970.9 Kcal/mol, -4788.21 Kcal/mol, 4.10 D, 4.27 and 8.13 respectively. According to calculate results of HOMO/LUMO gap and other related parameters, the AB3, AI3 and chloroquine seems have same stability and reactivity. Studying the molecules in silico to predict physicochemical, pharmacokinetic, ADMET and drug-likeness properties.

Conclusion: AB3 and AI3 calculated results confirmed that both compounds similar to those of chloroquine have provided a potential future drug for anti-malarial and COVID19.

KEYWORDS: Covid-19; 7-chloroquinoline; Computational chemistry; ADMET; Chloroquine

INTRODUCTION

Designing a new molecule with specific medical purposes need to be considered precisely [1]. Nowadays, there is an essential need for design, synthesis, development and screening of molecules potentially used as COVID19 therapies, a disease causing severe acute respiratory complications and its morbidity and mortality rates are still rising around the world [2-5].

Researchers recently reported two types of drug Remdesivir and Chloroquine phosphate, with their potential to inhibit of coronavirus-19 progression [5]. Moreover, anti-malarial drugs such as chloroquine (CQ) and hydroxychloroquine (HCQ) has attracted a considerable interest because of their potentially beneficial pharmacological properties against the respiratory disease caused by the SARS-CoV-2 virus. Both of CQ and HCQ consist of 7-chloroquine units as active biological unit, which is

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considered as a vital molecule in living organisms as an important secondary metabolite with the subsequent chemotherapeutic implications [6]. Furthermore, the pharmacokinetic and toxicity properties 7-chloroquine unit is easy to control through the structural modifications [7]. Besides, the hybridization of quinolone with N-heterocyclic compounds such as quinolone-triazoles produces compounds with high application in pharmacology suitable in vivo conditions [8-10].

Accordingly, computation methods were developed to predict the chemical and human pharmacokinetic properties. Computational chemistry one of the most important methods for predication of chemical and biological characterization [11]. Although many software have been used in computational chemistry, HyperChem is considered among the most useful software to calculate the electronic parameters as well as the quantitative structure-activity relationship (QSAR)[12,13].

QSAR studies can be used to estimate the common biological properties of compounds [14,15]. QSAR not only promote help of the acceptable design of new bioactive molecules such as pharmaceuticals [15], but also promote a more profound understanding of the physicochemical and biophysical processes underlying biological activity and drugs recovery [16,17]. However, a concern still remains in the drug discovery due to insufficient information about ADME (absorption, distribution, metabolism, excretion) properties. Thus, since clinical trial for drug development projects require more information about MADE properties, it is a wise practice to introduce ADME tests at the early stage of drug discovery [18]. Consequently, development of computational methods to obtain ADME properties required in an economical manner in terms of time and cost. In this regard, computation methods were developed to predict the human pharmacokinetic properties using different tools [19]. Presently in silico ADME, many models have been established to be faster, simpler, and more cost effective than transitional investigational procedures [20].

In the present research, we have used HyperChem software (version 8) [12] and SwissADME tools [20] to describe some properties to estimate the reactivity and biological activities of candidate compounds, and compare their calculated values with well-known antimalarial drug and candidate as COVID19 therapies. Moreover, we are showcasing some of our molecules categories which are helpful in working as antiviral therapies of covid-19 and can be suggested as essential compounds to aid the researchers.

Study design and framework

We have built the candidate drugs based on combination of two units reported previously as antimalarial therapies: 7-chloroquinoline [23-26] and N-heterocyclic rings such as triazoles [9,10]. The framework of the compounds presented in (Figure 1 and Figure 2). The main difference between two compounds (ABn and AIn) (i) the movement of the moieties of fused N-heterocyclic system which may plays an important role in drugs functionality or may enhanced the designed molecule to do its function properly; (ii) the symmetrical distribution of pi-electrons between two units; (iii) increase the delocalization of π-electrons which was reported to increase the stability of molecules [27] as well as one of the most important non-covalent interaction in biological system [28,29].

RESULTS AND DISCUSSION

Computational Parameters

The computational predication in silico of candidate drugs was performed in order to obtain relative results of lipophilicity Log P, molecular weight, polar surface area, number of hydrogen bonding donor and acceptors, number of rotary bonds and solubility in water, drug-likeness profile, pharmacokinetic profile of molecules. For clarity, compounds that have higher molecular weight, higher lipophilicity and lower solubility are less drug-like [29-31]. Further, we have been Appling PM3-geometry optimization using semi-empirical methods. Notably, the used methods were the most common and popular computation protocols in the field of chemiinformatics [32].

FRONTIER MOLECULAR ORBITAL (FMO)

HOMO/LUMO and Chemical reactivity

The molecular stability and reactivity can be measured based on the EHOMO/ELUMO gap where; molecule with high HUMO-LUMO gap have a low stability so it has a low reactivity for chemical[22]. Additionally, most of reactivity descriptors such as electrophilicity (ω), the chemical potential (μ), electronegativity (χ), hardness (η) and softness (S) can be determined using some relationship with HOMO and LUMO energy orbital. The ionization energy (I) and electron affinity (A) can be determined using –EHOMO and –ELUMO values respectively [33]. However, we use AB3 and AI3 data here as an illustration; compounds AB3 and AI3 reordered HOMO-LUMO gap at 8.158 eV and 7.512 eV respectively; which reflect that the AI3 more active and has stability higher than AB3. In term of comparison with chloroquine: the energy gap of AI3 and chloroquine, the two molecules reported values closed to each other which reflect that the both molecules have same stability and reactivity. Notably, the AB3 reported values similar to those of chloroquine especially in energy gap. The calculate values of ΔE for AB3 and Chloroquine is 8.15 eV and 8.13 eV which revealed that the stability and reactivity of both molecules is same. However, direct relationship between polarizability, hardness and stability of molecules. The minimum polarizability and minimum hardness indicate the more stable [33]. Additionally, the polarization of molecules usually effected by the energy gap; molecules with low energy gap tend to be easy to polarize [22]. In this regard; we can observe that AI3 recorded polarization at 34.82, Softness (S) at 0.266 and Hardness (η) at 3.756. The AB3 registered polarization at 35.95, S at 4.079 and η at 0.122, which is confirmed the relationship between the energy gap, polarization, Hardness and Softness of molecules[33]. In term of comparison; the calculated values ΔE, S, η and polarization of chloroquine agreed with those of AB3 and AI3 (see table 1,2 for clarity).

	AB1	AB2	AB3	AB4	Reference

EHOMO(eV)	-8.897	-9.031	-9.407	-9.058	-8.921
ELOMO(eV)	-1.088	-1.105	-1.249	-1.252	-0.787
Energy gap(eV)	7.809	7.926	8.158	7.806	8.134
I	8.897	9.031	9.407	9.058	8.921
A	1.088	1.105	1.249	1.252	0.787
μ	-4.992	-3.963	-5.328	-3.903	-4.854
η	3.904	3.963	4.079	4.164	4.067
S	0.128	0.126	0.122	0.128	0.122
χ	4.99	3.963	5.328	3.903	4.854
ω	97.3	62.24	3.48	59.46	95.82

Table 1: The electronic parameters (eV) of ABn compounds.

	AI1	AI2-	AI3	AI4	AI5
EHOMO(eV)	-9.019	-9.169	-8.871	-8.748	-9.119
ELOMO(eV)	-1.495	-1.519	-1.359	-1.335	-1.43
E.gap(eV)	7.524	7.65	7.512	7.413	7.689
I	9.019	9.169	8.871	8.748	9.119
A	1.495	1.519	1.359	1.335	1.43
μ	-5.257	-5.344	-5.115	-5.041	5.275
η	3.762	3.825	3.756	3.7065	3.8445
S	0.265	0.261	0.266	0.269	0.26
χ	5.257	5.344	5.115	5.041	5.275
ω	51.983	54.617	49.138	47.094	53.49

Table 2: The electronic parameters (eV) and some related parameters of candidate AIn compounds.

The relation between FMO and Carcinogenicity

The difference between energy of HOMO and HOMO-1 molecular orbital (ΔH) plays an important role in determined molecular carcinogenicity (Table 3). Recently, the HOMO and LOMO-1 energy level of the candidate molecules was calculated and reported as classification factor of molecular carcinogenicity. Lowest value of ΔH recorded for AB3 which is 0.095 eV and the highest values reported for AI4; 0.681 eV. According to Barone et al. study the candidate compound AI4 classified as carcinogenic whereas AB3 non-carcinogenic.

	EHOMO	EHOMO-1	ΔH
AB1	-8.897	-9.363	0.466
AB2	-9.031	-9.352	0.321
AB3	-9.407	-9.502	0.095
AB4	-9.058	-9.5	0.442
AI1	-9.019	-9.566	0.547
AI2	-9.169	-9.659	0.49
AI3	-8.871	-9.512	0.641
AI4	-8.748	-9.429	0.681
AI5	-9.119	-9.412	0.293

Table 3: The calculated FMO; ΔH (HOMO-HOMO-1) of candidate compounds.

Thermo-physical parameters

The thermo-physical parameters: total energy, binding energy, and dipole moment of AB3 observed at -76645.750 kcal/mol, -3979.363 kcal/mol and 4.868 D respectively. The AI3 recorded Total energy at -72557.745 kcal/mol, Binding energy at -3827.571 kcal/mol and Dipole moment at 3.221 D. Notably, the chloroquine recorded values at -76970.900 Kcal/mol, -4788.241 Kcal/mol and 4.097 D for Total energy, Binding energy and Diploe moment respectively. In regard of binding energy, the both molecules recorded values very closed to the chloroquine binding energy (Tables 4,5)

	AB1	AB3	AB3	AB4	CQ*
Total energy	-75356.2	-76007.5	-76645.8	-75996.5	-76970.9
Binding energy	-4226.22	-4109.3	-3979.36	-4098.28	-4788.24
Dipole moment	2.748	2.173	4.868	3.429	4.097

Table 4: Calculated Thermo-physical parameters of ABn compounds. *CQ= chloroquine.

	AI1	AI2-	AI3	AI4	AI5
Total energy	-72545.2	-73194.3	-72557.7	-71906.4	-82971.8
Binding energy	-3815.02	-3695.98	-3827.57	-3944.43	-4725.56

Dipole moment	2.825	4.509	3.221	1.909	2.626

Table 5: Calculated Thermo-physical parameters of AIn molecules.

The Log P as QSAR Parameters

The QSAR parameters provides the statistical data of biological and pharmacokinetics by which these molecules are considered as a new drug or bioactive molecule. However, the calculated QSAR properties of ABn (n = 1,2,3,4) and chloroquine were listed in Table 6 whereas for AIn compounds (n = 1,2,3,4,5) listed in Table 7. The Log P values of ABn molecules arranged from 4.18 to 5.08. The AIn compounds calculated to be 4.53 for AI1, 4.09 for AI2, AI3 at 4.60, AI4 at 5.05 and AI5 at 3.40. The two closed values observed closed to chloroquine was achieved by AB3 and AI3 which reflects that AB3 tend to be at highest non-polar phase [22].

	AB1	AB2	AB3	AB4	QC*
Polarizability	37.37	36.66	35.95	36.66	38.14
Reactivity	92.42	89.86	89.72	92.28	96.39
Log P	5.08	4.63	4.18	4.63	4.27

Table 6: QSAR parameters of candidate molecules class ABn.*CQ= Chloroquine.

	AI1	AI2	AI3	AI4	AI5
Polarizability	34.82	34.12	34.82	35.53	37.43
Reactivity	87.45	84.89	85.36	87.92	95.05
Log P	4.53	4.09	4.6	5.05	3.41

Table 7: QSAR parameters of candidate AIn molecules.

Physicochemical, pharmacokinetic, medicinal chemistry and drug-likeness prediction

The pharmacological activity of new medicinal molecules needs to be studied using structure activity-relationship techniques moreover some physio-chemical parameters need to be studied as well [22]. Based on the gold standards and earlier published research on various oral bioavailability rules, hundred drugs were evaluated together with some marketed anticancer drugs against the key parameters of physicochemical properties, that is, lipophilicity, log P, MW, TPSA, HBD, HBA, nRot, and aqueous solubility (log S)[7]. The computed molecular properties of Lipinski's rule of five were calculated using SwissADME web [20] and are shown in Table 8-10.

Compounds	Mwta	MLogPb	nHBAc	nHBDd	nRot	TPSA	Ali logs	MR
Rule	<500	<4.15	<10	<5	0	≤140	≤10	≤155
AB1	299.37	3.83	2	0	3	30.71	-4.47	93.68
AB2	320.78	3.35	3	0	3	43.6	-3.94	91.52
AB3	321.76	2.65	4	0	3	56.49	-3.65	98.31
AB4	320.78	3.62	3	0	3	43.6	-4.45	91.52
AI1	306.75	3.57	3	0	2	43.6	-4.52	87.11
AI2	307.74	2.82	4	0	2	56.49	-3.72	84.9
AI3	306.75	3.24	3	0	2	43.6	-4.01	87.11
AI4	305.75	4	2	0	2	30.71	-4.81	89.31
AI5	343.85	3.52	4	0	7	46.84	-4.34	98.37
QC	319.87	4.15	2	1	8	28.16	-4.95	97.41

Table 8: Computed Lipinski`s rule of five of candidate moleculesn.*All of violations from Lipinski's Rule for compounds recorded zero.

Compounds	PAINS Alert	Brenk alert	Lead likeness	Synthetic accessibility
AB1	0	0	No	2.51
AB2	0	0	yes	2.53
AB3	0	0	yes	2.81
AB4	0	0	No	2.64
AI1	0	0	No	2.69
AI2	0	0	yes	2.87
AI3	0	0	yes	2.49
AI4	0	0	No	2.33
AI5	0	0	No	3.04
CQ	0	0	No	2.76

Table 9: Computed medicinal chemistry properties of the compounds.

Compounds	GI absorption	BBB perment	Pgp Substrate	CYP2D6 Inhibitor	CYP3A4 Inhibition
AB1	High	Yes	Yes	Yes	Yes
AB2	High	Yes	Yes	Yes	Yes
AB3	High	Yes	No	Yes	Yes
AB4	High	Yes	Yes	Yes	Yes
AI1	High	Yes	No	No	Yes
AI2	High	Yes	No	Yes	Yes
AI3	High	Yes	Yes	Yes	Yes
AI4	High	Yes	Yes	Yes	Yes
AI5	High	Yes	No	Yes	Yes
CQ	High	Yes	No	Yes	Yes

Table 10: Shows the results related to the pharmacokinetic profile and toxicity data analyzed by the SwissADME Online software: (GI: gastro-intestinal absorption, BBB: blood brain barrier, CYP: Cytochromes, P-gp: P-glycoprotein.

Molecular weight (Mwt)

The analyzed candidate molecules showed molecular weight (Mwt) with acceptable variability by all in silico filters provided by the software (Table 8).

The MLogP and TPSA

Hydrophilic nature molecules are connected to poor permeability, which means low absorption [35,36]. The M Log P value of AB1-AB4 varies from 2.65-3.83 and AI1−AI5 molecules varies from 2.4 to 5.3 (Table8). Notably, there were no significant differences in the MLogP values among the candidate compounds and calculated chloroquine which reflects lipophilic nature and poorly soluble in nonpolar solvents. Eventhough availability of Log P values within the range reflect that probability of a compounds to be considered as drug-Like [37]. However, the SwissADME LogP values assumes to be represented real condition as its calculation based on five different algorithms [20]. TPSA values observed within range (≤140 $Å^2$) [7].

The violations and Hydrogen bonding

Notably, the violations from Lipinski's Rule reveals that all of the derivatives recorded zero violation suggests that the compounds ABn and AIn can be subjected for further preclinical trials [31]. However, the ability of molecules to accept or donate protons H+ can be determined using physicochemical characteristic as well as great importance obtained with respect to the acid-base character of the molecule [38]. According to Lipinski et al. [39] the molecules with higher hydrogen bonding either accepter or donor have the most favorable ADME/Tox profile (Table 8). In term of comparison of Physicochemical Properties of candidate molecules with well-known antimalarial drug(chloroquine); our analysis of Mwt, MLogP, HBA, HBD, nRot, TPSA, ALiLogS and MR shown compounds fall within the accepted range and showed better results [20].

ADMET and drug-likeness evaluation

Drug-likeness is very important in screening drug candidates at the earlier stage of drug discovery and development [20,31,40]. Therefore, the designed molecules were evaluated of their

ADME profile including drug-likeness and several other parameters using SwissADME [20,41]. However, drug candidates should possess favorable ADME properties and ideally non-toxic. According to most the criteria of drug-likenss in SwissADME [20] module provided in SIB (Swiss Institute of Bioinformatics) webserver (https://www.sib.swiss), candidate molecules were considered pass all of them, thus may classified as drug-like compounds (Table 9).

Pharmacokinetic and drug toxicity analysis

The analysis predicts that the molecules ABn and AIn show high GI absorption Table 10, with nearly 100% of the molecules also exhibiting BBB penetration, and 70% are predicted as the non-substrates of P-gp (PGP). The AB3, AI1, AI2, AI5 molecules are P-gp substrates. Notably, most of molecules that included triazole shows P-gp substrates. The toxicity end points consist of the inhibition of cytochrome P450 (CYPS) monooxygenese enzymes [42]. Skin sensitization, LD50 (lethal rat acute toxicity), AMES toxicity, hepatotoxicity and inhibition of hERG-K+ channel effects are determined for evaluation drug-drug interaction (DDIs) [43]. All of candidate molecules were evaluated as inhibitor of CYP3A4 whereas 90% show inhibition against CYP2D6.

CONCLUSION

Molecular of triazole/pyrazole hybrid framework containing quinoline and N-heterocyclic rings may use as treatment for different types of disease. Here we conclude that AB3 as hybridized triazole-molecules can serve as antiviral therapies of covid-19 and can be an essential compound to aid the researchers as they record electronic properties as closed as chloroquine which nowadays expect to be the best treatment of coronvirus19. Moreover, the electronic orbitals reveal that the molecule classified as non-carcinogenic. In silico results allow us to conclude that AB3 molecule is predicted to be a potential future drug candidate, especially via oral administration, due to its relevant Drug-likeness profile, bioavailability, excellent liposolubility and adequate pharmacokinetics. We expect that these investigations will be supportive for designing a new and effective inhibitor against malarial and COVID19 disease.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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REFERENCES

1. Sugerman, P.B., Satterwhite, K., Bigby, M. Autocytotoxic T-cell clones in lichen planus. Dermatol B.R.2000;142(3):449–456.
2. Wang J, "Fast Identification of Possible Drug Treatment of Coronavirus Disease -19 (COVID-19) Through Computational Drug Repurposing Study," Chem.J. Inf. Model., 2020.
3. Zhang L. et al., "Crystal structure of SARS-CoV-2 main protease provides a basis for design of improved a-ketoamide inhibitors," Science (80-.), 2020.
4. Dai.W, et al., "Structure-based design of antiviral drug candidates targeting the SARS-CoV-2 main protease," Science (80-.), 2020.
5. Wang.M et al., "Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro," Cell Res., 2020, vol. 30, no. 3, pp. 269–271.
6. Chung.P.Y, et al., "Recent advances in research of natural and synthetic bioactive quinolines," Future Medicinal Chemistry. 2015.
7. Zafar.F et al., "Physicochemical and Pharmacokinetic Analysis of Anacardic Acid Derivatives," 2020.
8. Ma.N Wang.Y, Zhao.B.X, W. C. Ye, and Jiang.S, "The application of click chemistry in the synthesis of agents with anticancer activity," Drug Des. Devel. Ther.,2015 vol. 9, pp. 1585–1599.
9. Agalave.S.G, Maujan.S.R, and Pore.V.S, "Click chemistry: 1,2,3-triazoles as pharmacophores," Chem. - An Asian J. 2011., vol. 6, no. 10, pp. 2696–2718,
10. Dheer.D, Singh.V0, and Shankar.R, "Medicinal attributes of 1,2,3-triazoles: Current developments.," Bioorg. Chem., Apr. 2017 vol. 71, pp. 30–54,.
11. W. Bray and G. Relativity, "Covid-19 Drug Design via Quantum Mechanical Principles Leads to a New Corona-SARS Anti- Viral Candidate 2-Phosphono-Benzoic-Acid," no. April, 2020.
12. H. oem Software, "No Title HyperChem Professional 8.0, (Molecular modeling system) Hypercube." 2010.
13. Coleman.W.F and Arumainayagam.C.R, "HyperChem 5 (by Hypercube, Inc.)," J. Chem. Educ., 1998.
14. Schwardt.O, B. Cutting, H. Kolb, and B. Ernst, "Drug Discovery Today," in Frontiers in Medicinal Chemistry – 2012, (Volume 2).
15. Leelananda.S.P and Lindert.S, "Computational methods in drug discovery," Beilstein Journal of Organic Chemistry. 2016.
16. Hu.J.Y and Aizawa.T, "Quantitative structure-activity relationships for estrogen receptor binding affinity of phenolic chemicals," Water Res., 2003.
17. Mayer.J.M and Van.H de Waterbeemd, "Development of quantitative structure-pharmacokinetic relationships," Environ. Health Perspect., 1985.
18. Gleeson.M.P, A. Hersey, Montanari.D, and Overington.J, "Probing the links between in vitro potency, ADMET and physicochemical parameters," Nat. Rev. Drug Discov., 2011.
19. Al Omar .A.A.H, Jaafari.S.D, K. A. Al-Sou'od, and Badwan.A.A, Moxifloxacin Hydrochloride, May. 2014,vol. 39, no..
20. Daina.A, Michielin.O, and Zoete.V, "SwissADME: A free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules," Sci. Rep., 2017.
21. "Najar.A.M, Ruwida M.K. Omar , Eman Bobtaina, Computational, Pharmacological Evaluation and Comparative Similarity Against Chloroquine for Some New Designed Hybridized Molecules and Their Potential Use as Antiviral Against COVID-19 and Malaria, 2020 su."
22. Mousa.M.N and Al-rubaie.L, "Synthesis and Assessment of Anti-inflammatory Activity of a Chlorosubstituted Chalcone Derivatives and using the Semi-empirical Methods to Measure the Linked Physicochemical Parameters," no. January, 2016.
23. Salomone.S and T. Godfraind, "Drugs that reverse chloroquine resistance in malaria.," Trends Pharmacol. Sci., 1990,vol. 11, no. 12, pp. 475–476, Dec.
24. Veignie.E and Moreau.S, "The mode of action of chloroquine. Non-weak base properties of 4-aminoquinolines and antimalarial effects on strains of Plasmodium," Ann. Trop. Med. Parasitol., 1991.

25. de Vries.P.J, Oosterhuis.B, and van Boxtel.C.J, "Single-Dose Pharmacokinetics of Chloroquine and its Main Metabolite in Healthy Volunteers," Drug Investig., 1994.
26. Wetsteyn.J, De Vries.P, Oosterhuis.B, and Van Boxtel.C, "The pharmacokinetics of three multiple dose regimens of chloroquine: implications for malaria chemoprophylaxis.," Br. J. Clin. Pharmacol., 1995.
27. Najar,A.M, Tidmarsh.I.S, Adams.H, and Ward.M.D, "Cubes, squares, and books: A simple transition metal/bridging ligand combination can lead to a surprising range of structural types with the same metal/ligand proportions," Inorg. Chem., 2009, vol. 48, no. 24, pp. 11871–11881,
28. Najar.A.M, Tidmarsh.I.S, Adams.H, and Ward.M.D, "Cubes, squares, and books: A simple transition metal/bridging ligand combination can lead to a surprising range of structural types with the same metal/ligand proportions," Inorg. Chem., 2009.
29. Lipinski.A.C, F. Lombardo, Dominy.B.W, and Feeney.P.J, "Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings.," Adv. Drug Deliv. Rev., 3–26, Mar. 2001, vol. 46, no. 1–3, pp.
30. Huuskonen.J, "Estimation of aqueous solubility for a diverse set of organic compounds based on molecular topology.," J. Chem. Inf. Comput. Sci., May 2000, vol. 40, no. 3, pp. 773–777,.
31. Lipinski.C.A, "Drug-like properties and the causes of poor solubility and poor permeability.," J. Pharmacol. Toxicol. Methods, 2000 ,vol. 44, no. 1, pp. 235–249,.
32. Pandey.A.V, Bisht.H, Babbarwa.V.K, Srivastava.J, Pandey.K.C, and Chauhan.V.S, "Mechanism of malarial haem detoxification inhibition by chloroquine," Biochem. J., 2001.
33. Islam.M.J, Sarker.N, and Kumer.A, "The evaluation and comparison of thermo-physical, chemical and biological properties of palladium (II) complexes on binuclear diamine ligands with different anions using the DFT method," Int. J. Adv. Biol. Biomed. Res., 2019,vol. 7, no. 4, pp. 315–334.
34. Barone.P.M.V.B, Camilo.A, and Galvão.D.S, "Theoretical approach to identify carcinogenic activity of polycyclic aromatic hydrocarbons," Phys. Rev. Lett., 1996.
35. van de Waterbeemd.H, Smith.D.A, and Jones.B.C, "Lipophilicity in PK design: Methyl, ethyl, futile," J. Comput. Aided. Mol. Des., 2001.
36. Pliška.V, Testa.B, and van de Waterbeemd.H, Lipophilicity in Drug Action and Toxicology. 2008.
37. Waring.M.J, "Lipophilicity in drug discovery.," Expert Opin. Drug Discov., Mar. 2010, vol. 5, no. 3, pp. 235–248,
38. "Avdeef A. Absorption and drug development: solubility, permeability, and charge state. 2nd ed. Hoboken: John Wiley & Sons; 2012."
39. Lipinski.C.A, Lombardo.F, Dominy.B.W, and Feeney.P.J, "Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings," Advanced Drug Delivery Reviews. 1997.
40. Sliwoski.G, Kothiwale.S, Meiler.J, and Lowe.E.W, "Computational methods in drug discovery," Pharmacological Reviews. 2014.
41. S. Ekins, Computer Applications in Pharmaceutical Research and Development. 2006.
42. "Khojasteh, S. C.; Wong, H.; Hop, C. E. C. A. Pharmacokinetics. Drug Metabolism and Pharmacokinetics Quick Guide; Springer, 2011; p 1."
43. A. P. Li and M. Jurima-Romet, "Applications of primary human hepatocytes in the evaluation of pharmacokinetic drug-drug interactions: Evaluation of model drugs terfenadine and rifampin," in Cell Biology and Toxicology, 1997.