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Structural Modification of Ibuprofen as new NSAIDs via DFT, Molecular Docking and Pharmacokinetics Studies

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Abstract
Inflammations generate uneasiness. Multiple drug resistance imposes restrictions on the effectiveness of most existing drugs which necessitates either novel drug design or systematic derivatization of existing ones. This study adopts quantum mechanical and molecular docking approach to model and explore twenty derivatives of ibuprofen as potential non-steroidal anti-inflammatory drug candidates in order to improve and update existing NSAIDs database, and alleviate global multiple drug resistance challenge taking ibuprofen as the standard. Optimization and calculation of the drug-like quantum chemical parameters of the compounds were conducted at DFT/B3LYP/6-31G* level of theory. Binding affinity, interaction and inhibition of the potential drug-candidates with human cyclooxygenase (COX-2) receptor were investigated using molecular docking studies. Pharmacokinetic properties were studied. The drug candidates interact effectively and spontaneously with the COX-2 receptor via hydrogen bonding and π-π stacking with greater binding affinity than ibuprofen except compounds 5 and 18. The energy gap, global hardness and softness, and chemical potential of the derivatives suggest that they are kinetically unstable, more chemically reactive than the parent drug and are effective electron donors. The docking studies show that compound 7 (3-(4-(3,3,3-trifluoro-2-methylpropyl)phenyl)butan-2-one) displays remarkably high binding affinity to the amino acid residues, ASN382 and HIS207, via H-bonding and π-π stacking interactions, respectively. From the pharmacokinetic studies, all the derivatives are not substrates to permeability glycoprotein (suggesting reduced therapeutic failure), not efficiently permeable to skin, can be absorbed by human intestine and can cross the blood brain barrier. Some derivatives are potential CYP1A2, CYP2D6 and CYP3A4 inhibitors. All the ibuprofen derivatives exhibit comparable drug-likeness with standard.
Keywords: Non-steroidal anti-inflammation drugs; COX-2 inhibitors; Ibuprofen; Density functional theory; Molecular docking; Pharmacokinetics properties.

I. INTRODUCTION

Non-steroidal anti-inflammation drugs (NSAIDs) are a drug category that reduces fever, pain, headache, stiffness and inflammation [1,2]. They are mostly used to treat acute and chronic conditions where pain and inflammation occur [1,3]. NSAIDs work effectively by blocking the cyclooxygenase (COX-1 and COX-2) enzymes, which is responsible for the synthesis of prostaglandin via arachidonic acid pathway, thereby reduces the synthesis of prostaglandin in the body [3-5]. Ibuprofen, a propionic acid derivative, is a class of NSAIDs that is widely used as an anti-inflammatory [6] and analgesic [7] agent. It can also be used in the treatment of cancer [8]. Some common side effects of ibuprofen are aggravated asthma, nausea, indigestion and abdominal pain, constipation or diarrhea [2,9]. Drug discovery and development is a time consuming and expensive process. Modifying existing drugs provides an easy way to rapidly develop novel drugs with improved activity and overcome problems like resistance and allergies associated with existing ones. Structural modification is an alteration of a known lead compound by introducing some substituents into its architecture.

Computer aided drug design (CADD) is a contemporary way of developing new therapeutic lead compounds. It is cost-effective, time saving, helps in understanding experimental findings and probes into the mechanism and atomistic details of molecules and receptors. Density Functional Theory (DFT) is a popular quantum chemical method employed to investigate molecular properties [10-13]. Molecular docking helps to predict the interaction of molecules (ligand) in the active site of the enzyme (receptor) [14,15]. It is also used to identify different binding modes in a protein binding site [16,17]. Investigating the pharmacokinetics helps in predicting the effect, fate and safety of a compound after administration in human body. Recent investigations have been conducted on anti-inflammatory and pharmacological properties of ibuprofen and some of its derivatives using DFT and molecular docking approaches. Careful modification of the propionic acid, aryl and/or the isobutyl moieties of ibuprofen have been found to improve the anti-inflammatory, hepatotoxic and molecular properties of the drug candidates [18,19].

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In this study, ibuprofen and its modified analogues were investigated for their pharmacological activities via density functional theory, molecular docking and pharmacokinetics studies. The physico-chemical properties of these compounds were calculated via DFT method, the molecules were docked into the active site of human cyclooxygenase-2 receptor, 5F1A.

II. METHODOLOGY

2.1. DFT calculations

The structures of the molecules (table 1, Figure 2) were optimized using DFT method with hybrid Becke three-parameter Lee, Yang and Parr (B3LYP) correlation [20] and a 6-31G* basis having initially searched for the molecules' most stable conformers via molecular mechanics force field, all with Spartan 14 computational chemistry software on an intel (R) computer with 2.60GHz, 6.00 GB RAM. Molecular parameters such as energies of the frontier molecular orbitals, that is, the highest occupied molecular orbital (E_{HOMO}) and lowest unoccupied molecular orbital (E_{LUMO}) were computed at this level of theory. Energy band gap, ΔE (eq. 1), chemical hardness, η (eq. 2), chemical softness, δ (eq. 3) and chemical potential, C_P (eq. 4) were calculated from E_{HOMO} and E_{LUMO}. Lipophilicity (Log P), polar surface area (PSA), polarizability, hydrogen bond donor (HBD) and hydrogen bond acceptor (HBA) were also computed.

$$\Delta E = E_{LUMO} - E_{HOMO} \quad (1)$$

$$\eta = \frac{\Delta E}{2} \quad (2)$$

$$\delta = \frac{1}{\eta} \quad (3)$$

$$C_P = \frac{E_{HOMO} + E_{LUMO}}{2} \quad (4)$$

2.2. Molecular docking study

2.2.1. Protein preparation

The crystallized three-dimensional structure of salicylate bounded human cyclooxygenase-2 receptor, an oxidoreductase inhibitor in *Homo sapiens* (PDB ID: 5F1A; resolution 2.38 Å) was downloaded in pdb format from protein data bank [21] (figure 1). It was prepared with Schrodinger Suite 2017-1 interface using protein preparation wizard [22]. The protein was prepared by removing interfering ligand, assigning bond order and charges, deleting water molecules and removing all heteroatom. Furthermore, tautomeric states were generated at pH 7.0 ± 2 using Epik [23] and the protein energy minimization was carried out using OPLS3 force field [24].

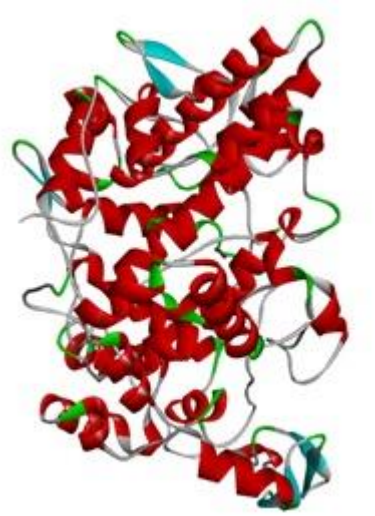

Figure 1: 3D Crystal Structure of Receptor, 5F1A

2.2.2. Ligands preparation

The optimized structures were imported and prepared using ligprep module in Schrodinger Suite 2017-1 via OPLS3 force field. The generation of possible ionization and tautomeric states were achieved using Epik at pH of 7.0 ± 2

2.2.3. Molecular docking and visualization

Molecular docking was done to predict the interaction, binding affinity and to understand the mechanism of COX-2 inhibition by newly modeled molecules. The prepared ligands were dock into the active site (x = 29.99, y = 34.57, z = 238.89) of prepared human prostaglandin synthase protein (5F1A) via glide docking [25] in Schrodinger Suite 2017-1. The interaction and visualization diagrams were viewed via ligand interaction tools.

2.3 Computational Pharmacokinetics

SwissADME [26], an online web tool used in predicting the pharmacokinetics and drug likeness of small compound was employed in testing the drug-likeness of the newly modeled molecules and ibuprofen. The chemical structure of each molecule was input in SMILES (simplified molecular-input line-entry system) format to generate their pharmacokinetics properties.

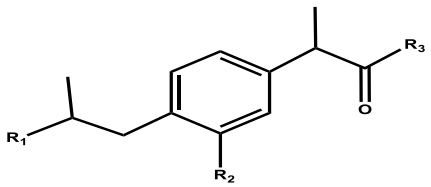

Figure 2: Structure of Ibuprofen Derivatives

Table 1: Chemical structures of ibuprofen and its modified derivatives

Compounds	R_1	R_2	R_3
Ibuprofen	CH_3	H	OH
1	CH_3	H	NH_2
2	CH_3	H	OCH_3
3	CH_3	H	CH_2OH
4	CH_3	H	CH_2NH_2
5	CF_3	H	OH
6	CH_2OH	H	CH_3
7	CF_3	H	CH_3
8	F	OCH_3	OH
9	CH_3	NH_2	OH
10	$NHCOCH_3$	H	CH_3
11	OCH_3	H	NH_2
12	OCH_3	H	CH_3
13	CH_3	COOH	CH_3
14	CH_3	H	CH_2CH_3
15	CH_3	OH	CH_2CH_3
16	CH_3	$NHCOCH_3$	CH_2CH_3
17	CH_3	CF_3	OH
18	CH_3	H	OCH_2CH_3
19	CH_3	F	OH
20	CH_3	H	CH_2F

III. RESULTS AND DISCUSSION

3.1. DFT results

3.1.1. Frontier Molecular Orbital

The molecular descriptors obtained such as the E_{HOMO}, E_{LUMO}, band gap, chemical hardness, chemical softness and other descriptors are tabulated in Table 2 and Table 3. These descriptors were used to predict the reactivity of ibuprofen and its modified derivatives. The energies of the FMOs (table 2) are important in determining the electronic structure of a compound. They are used to study the chemical reactivity, stability and transfer of electron in a molecule. The E_{HOMO} is related to the ionization energy which represents the area with rich electron density, indicating the ability to donate electron to nearby molecule. The higher the E_{HOMO} of a molecule, the greater its potential to donate an electron. E_{LUMO} represents the electron affinity, the area with lowest electron density, indicating the ability to accept electron from nearby molecule. The lower the E_{LUMO} of a molecule, the more it is capable of accepting electron. Hence, higher E_{HOMO} and lower E_{LUMO} are responsible for high chemical reactivity, low stability and the ease with which the electron flow in a molecule would be [27-29]. The E_{HOMO} for all the compounds range from -5.42 eV to -6.76 eV. With the exception of compounds 3, 5, 17 and 19, other derivatives display higher E_{HOMO} than ibuprofen which suggests their great electron donating potential. Furthermore, the significant destabilization of the HOMO of compound 9 relative to ibuprofen implies the higher electron donating ability of the former which, consequently, indicates its better interaction with the electrophilic center of the cyclooxygenase-2 receptor. Also, the E_{LUMO} values for all compounds vary between -0.7 eV and -0.08 eV. The notable relative stabilization of the lowest-energy vacant molecular orbital of compound 13 contributes majorly to its low band gap (enhanced kinetic instability and chemical reactivity) and its susceptibility to nucleophilic interactions with the active sites of COX-2 receptor. The energy band gap, ΔE, is the difference between E_{HOMO} and E_{LUMO}. This gives an insight about the stability of a molecule. Lower band gap energy signifies lower stability and high reactivity of molecule while higher band gap energy signifies high stability and low reactivity [30]. All the modified compounds have lower band gap than ibuprofen (6.14 eV) except for compounds 5 and 18. This implies that almost all the modified compounds are less stable and more reactive toward the receptor than ibuprofen. Compound 13 has the lowest band gap of 4.85 eV. Interestingly, attachment of a carboxylic acid group at R2 position possibly destabilizes the energy gap and improves the chemical reactivity of the potential drug candidate.

3.1.2. Global reactivity descriptors

Global reactivity descriptors (table 2) were calculated to gain a deep understanding of the stability and the reactivity of ibuprofen and its modified derivatives towards the target receptor. Chemical hardness and softness are related to chemical stability of molecule where higher chemical hardness and lower chemical softness translate to higher stability and lower reactivity [30]. The hardness and softness computed for all the studied compounds range from 2.43 eV to 3.08 eV and 0.33 eV to 0.41 eV respectively. All the studied compound, except compounds 5 and 18, possess lower hardness and higher softness than ibuprofen, with compound 13 being the most reactive of them all. The modified compounds are therefore less stable and more reactive than ibuprofen. Furthermore, the electronegativity values calculated for all the compounds are higher than ibuprofen with compound 13 having the highest electronegativity indicating that all the compounds can attract electron easily than ibuprofen.

3.1.3. HOMO map, LUMO map and Molecular electrostatic potential analysis

The optimized structures, HOMO, LUMO and electrostatic potential maps of ibuprofen and its twenty derivatives are shown in Figures 3a to 3e, S1-S16. The HOMO and LUMO of the potential drug candidates are essentially delocalized over the molecular structure. This implies that the compounds possess electron-donating and electron-deficient regions and are susceptible to electrophilic and nucleophilic attack. The uneven distribution of charges on the molecules is also

corroborated by the electrostatic potential map (Figures 3a to 3e, S1-S16).

The electrostatic potential surface map enables visualization, analysis of charge distribution and also displays the area of nucleophilic and electrophilic region in a molecule [31]. The negative electrostatic potential (ESP) represented by red color shows the sites that are prone to electrophilic attacks. Positive region represented by blue color shows the site for nucleophilic attacks. The surface potential energies for all compound range from -205.309 kJ/mol to -142.988 kJ/mol for low energy region and the high energy region range from 79.720 kJ/mol to 258.876 kJ/mol.

Generally, the carbonyl groups and the phenyl ring are mapped red (and yellow) indicating their susceptibility to electrophilic attack while the alkyl groups are essentially subject to nucleophilic invasion. Compounds 5, 8, 9, 17 and 19 have COOH at similar position with ibuprofen. The carboxylic oxygen atoms of these compounds display negative ESP and could be possible sites of electrophilic addition. The replacement of hydroxylic part of the carboxylic acid with electron-rich NH_2 in compounds 1 and 11 converts the amino end to a Lewis-acid center that is subject to nucleophilic attack. Furthermore, systematic substitution of the carboxylic OH with alkyl (6,7,10,12,13,14,15 and 16), alkoxy (compounds 2 and 18), alcohol (compound 3), alkylamine (compound 4) and alkyl halide (compound 20) moieties imposes asymmetric charge distribution and creates nucleophilic and electrophilic sites for effective interaction with the COX-2 inhibitor's active sites. Subsequent derivatization of R1 and R2 groups generates more binding sites.

Table 2: Chemical Parameters obtained from ibuprofen and its modified derivatives *via* DFT at the B3LYP/6-31G* Level

Compounds	E_{HOMO} (eV)	E_{LUMO} (eV)	ΔE (eV)	η (eV)	δ (eV^{-1})	χ (eV)	C_P (eV)
1	-6.32	-0.22	6.10	3.05	0.327	3.27	-3.27
2	-6.30	-0.21	6.09	3.05	0.328	3.26	-3.26
3	-6.49	-0.91	5.58	2.79	0.358	3.70	-3.70
4	-6.14	-0.64	5.50	2.75	0.363	3.39	-3.39
5	-6.64	-0.48	6.16	3.08	0.325	3.56	-3.56
6	-6.18	-0.50	5.68	2.84	0.352	3.34	-3.34
7	-6.34	-0.64	5.70	2.85	0.351	3.49	-3.49
8	-5.87	-0.24	5.63	2.82	0.355	3.06	-3.06
9	-5.42	-0.08	5.34	2.67	0.375	2.75	-2.75
10	-6.36	-0.70	5.66	2.83	0.353	3.53	-3.53
11	-6.27	-0.14	6.13	3.07	0.326	3.21	-3.21
12	-6.20	-0.52	5.68	2.84	0.352	3.36	-3.36
13	-6.30	-1.45	4.85	2.43	0.412	3.88	-3.88
14	-6.21	-0.51	5.70	2.85	0.351	3.36	-3.36
15	-5.90	-0.54	5.36	2.68	0.373	3.22	-3.22
16	-5.91	-0.49	5.42	2.71	0.369	3.22	-3.22
17	-6.76	-0.76	6.00	3.00	0.333	3.76	-3.76
18	-6.29	-0.14	6.15	3.08	0.325	3.22	-3.22
19	-6.44	-0.45	5.99	2.99	0.334	3.45	-3.45
20	-6.31	-0.87	5.44	2.72	0.368	3.59	-3.59
Ibuprofen	-6.37	-0.23	6.14	3.07	0.326	3.30	-3.30

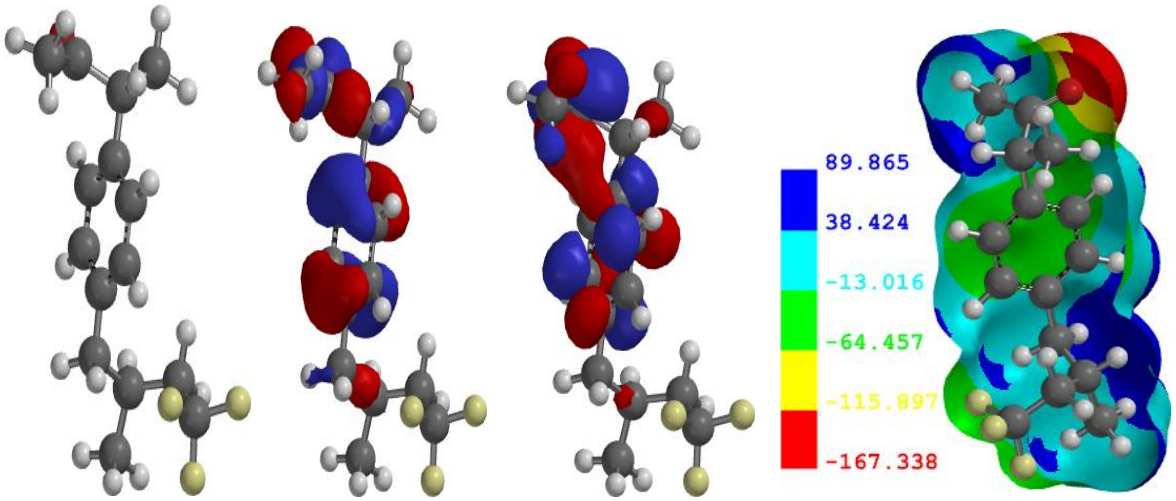

Figure 3a: Compound 7

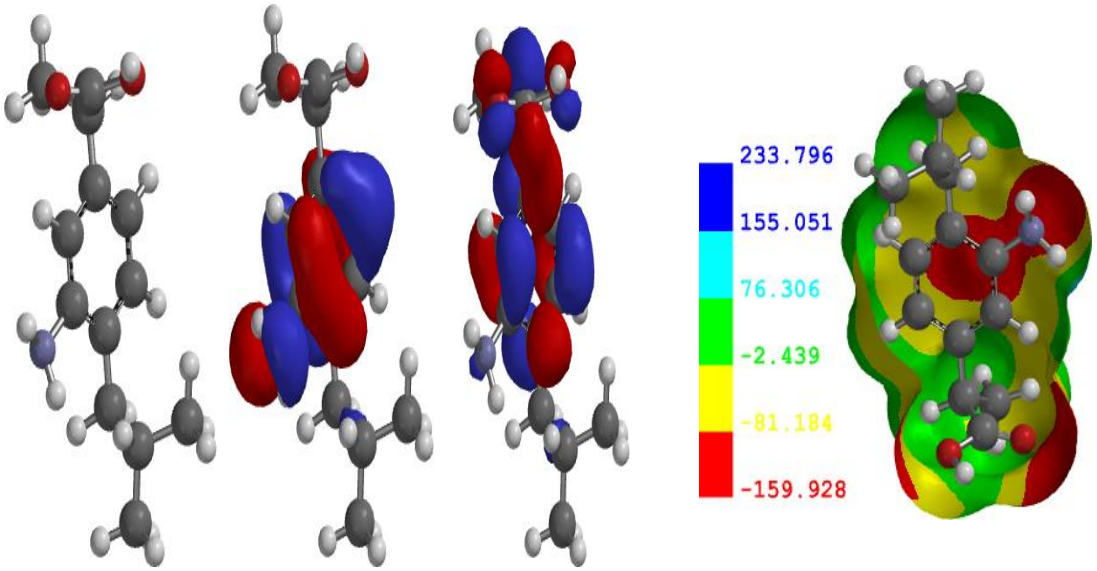

Figure 3b: Compound 9

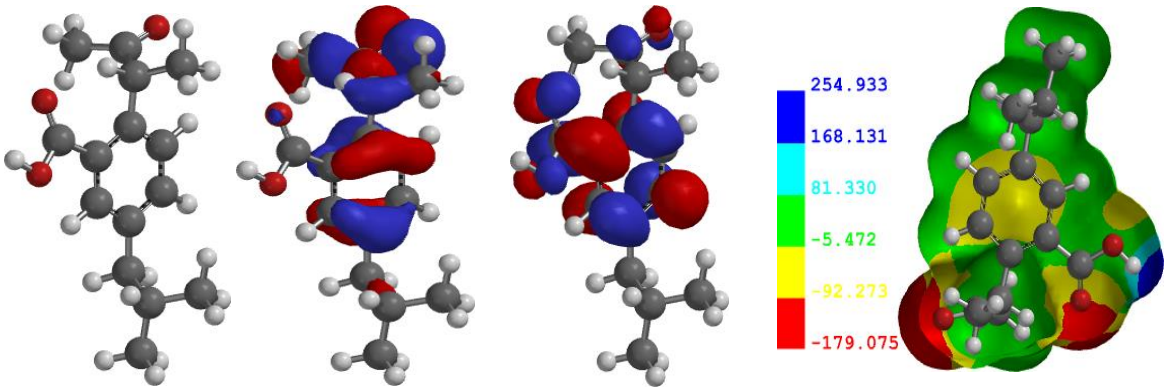

Figure 3c: Compound 13

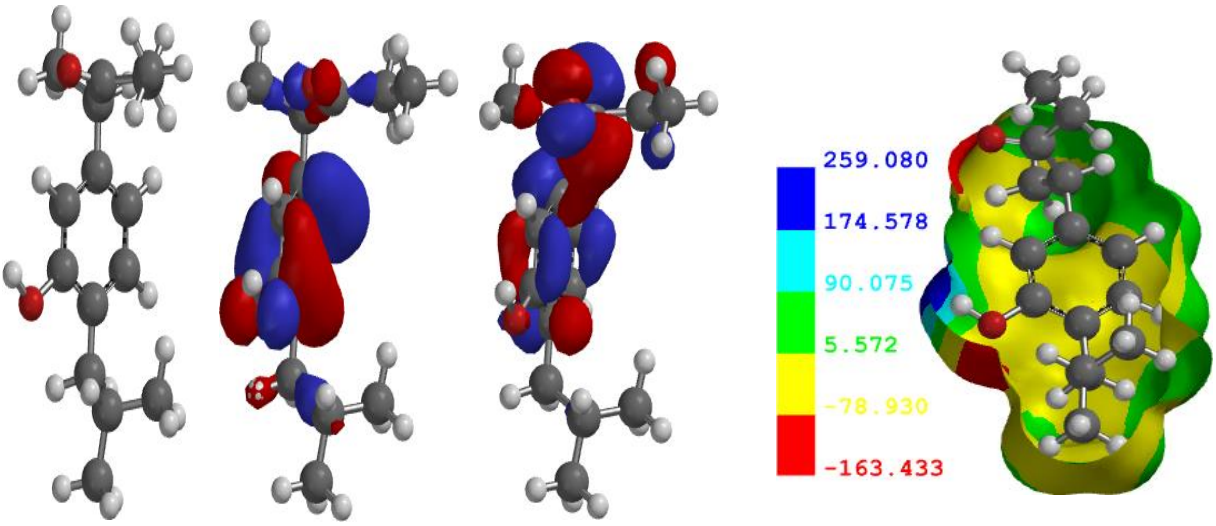

Figure 3d: Compound 15

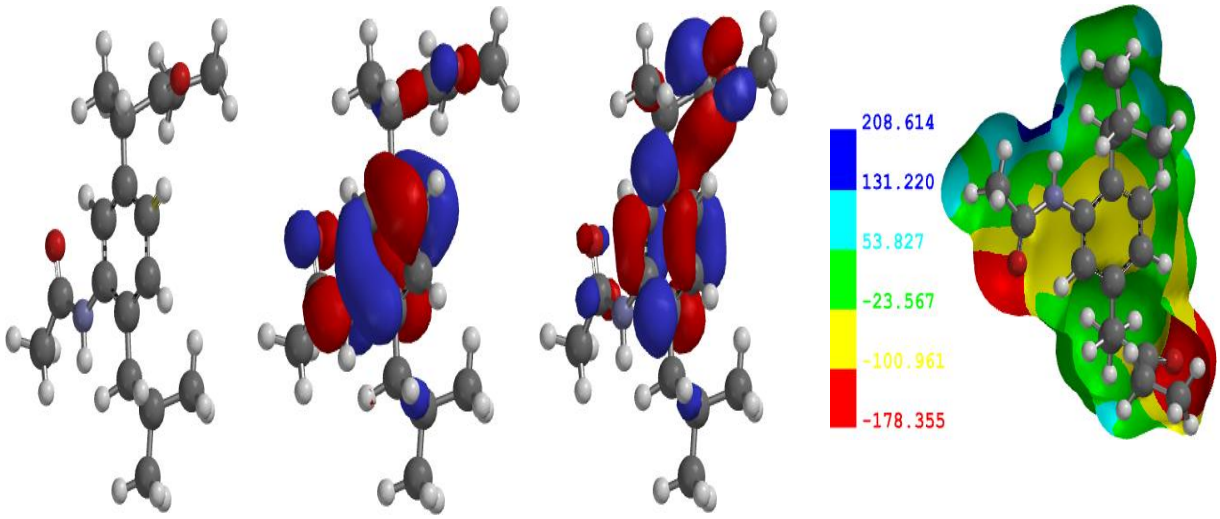

Figure 3e: Compound 16

Other vital molecular descriptors computed (Table3) are molecular weight (MW), polarizability, partition coefficient (log P), hydrogen bond donor (HBD), hydrogen bond acceptor (HBA) and polar surface area (PSA)**.** These properties are important properties used in predicting drug likeness of a biologically active compound. The Lipinski rule of five (RO5) predicts that for a small molecule to be an orally active drug, it should possess the following properties: molecular mass should be less than 500, logP, value should be less than or equal to 5, HBD should not be greater than 5 and HBA should be less than 10 (14) [32]. Violation of two or more of these properties indicate that the biologically active compound is not orally active. As can be seen in Table 3, all the modified compounds obey the Lipinski rule. This is indicative that all the modified compounds and ibuprofen are bioavailable. In addition, PSA is widely used for the potential of biological active compound to permeate cells. PSA not greater than 140 A^2 and PSA not greater than 90 A^2 is required for a compound to permeate cell membrane and blood brain barrier, respectively [33]. The PSA of all the modified compounds range from 14.416 A^2 to 57.167 A^2, showing that all the compound can permeate both cell membrane and can also penetrate blood brain barrier.

Table 3: Chemical Parameters Obtained for ibuprofen and its modified derivatives *via* DFT at the B3LYP/6-31G* Level

Compounds	MW	Log P	PSA (A^2)	Polarizability	HBD	HBA
Ibuprofen	206.285	3.75	34.551	59.14	1	1
1	205.301	3.10	38.290	59.41	1	2
2	220.312	4.02	20.125	60.82	0	1
3	220.312	3.52	32.057	60.77	1	2
4	219.328	3.18	39.748	61.10	0	2
5	260.255	4.12	34.564	60.26	1	1
6	220.312	3.13	34.047	60.77	1	2
7	272.310	4.97	14.416	62.76	0	1
8	240.274	2.71	40.443	60.36	1	2
9	221.300	2.95	57.167	60.14	2	2
10	247.338	2.19	38.524	62.94	1	3
11	235.327	2.33	45.198	61.64	1	3
12	234.339	3.49	21.261	62.41	0	2
13	248.322	3.82	46.345	62.57	1	2
14	218.340	4.92	13.877	61.66	0	1
15	234.339	4.53	32.595	62.31	1	2
16	275.392	3.82	34.692	65.86	1	3
17	274.282	4.67	34.561	61.72	1	1
18	234.339	4.35	20.619	62.30	0	1
19	224.275	3.91	34.539	59.54	1	1
20	222.303	4.27	14.449	60.61	0	1

3.2. Molecular docking studies

Molecular docking of ibuprofen and its modified derivatives with the target protein, salicylate bounded human cyclooxygenase-2 was performed (Table 4). Amongst all the modified derivatives, compounds 7, 16, 11 and 17 had higher docking score of -7.203 kcal/mol, -7.030 kcal/mol, -6.976 kcal/mol and -6.876 kcal/mol than ibuprofen and other derivatives. Compound 7 showed conventional hydrogen bonding with ASN382 amino acid residue from its carbonyl group and the delocalized electron in the benzene ring of the compound form a π-π stacking with HIS207 amino acid residue from its amine group as shown in (figure 4a). Also, compound 16 (figure 4c) showed conventional hydrogen bonding interaction with HIE388 amino acid residue from its amine group, and the delocalized electron in benzene ring exhibited π-π stack interaction with THR385 amino acid residue. Compound 11 (figure 4b) also exhibited hydrogen bonding interaction with PHE210 and ASN386 amino acid residue from its carbonyl and amine group and also showed π-π stacking with HIS207 and HIS386 amino acid residue. Compound 17 (figure 4d) showed hydrogen bonding interaction with HIS207 amino acid from its carbonyl and π-π stacking also occurred between the delocalized electron in benzene ring and HIS207, HIE388 amino acid residue. Similar interaction of drug candidates or NSAIDS with these amino acid residues of 5F1A has been reported in literature [34-37]. All compounds have higher binding affinity than ibuprofen (-5.846 kcal/mol) except compounds 18 (-5.583 kcal/mol) and 20 (-5.816 kcal/mol) which showed lower binding affinity than ibuprofen. The negative values of the binding affinity suggest the spontaneity of the interaction of the ibuprofen derivatives with the COX-2 receptor. Also, similar interaction mechanisms are observed between compounds 7, 11, 16, 17 and ibuprofen. The interactions of other compounds and ibuprofen are presented in figures S17-S33.

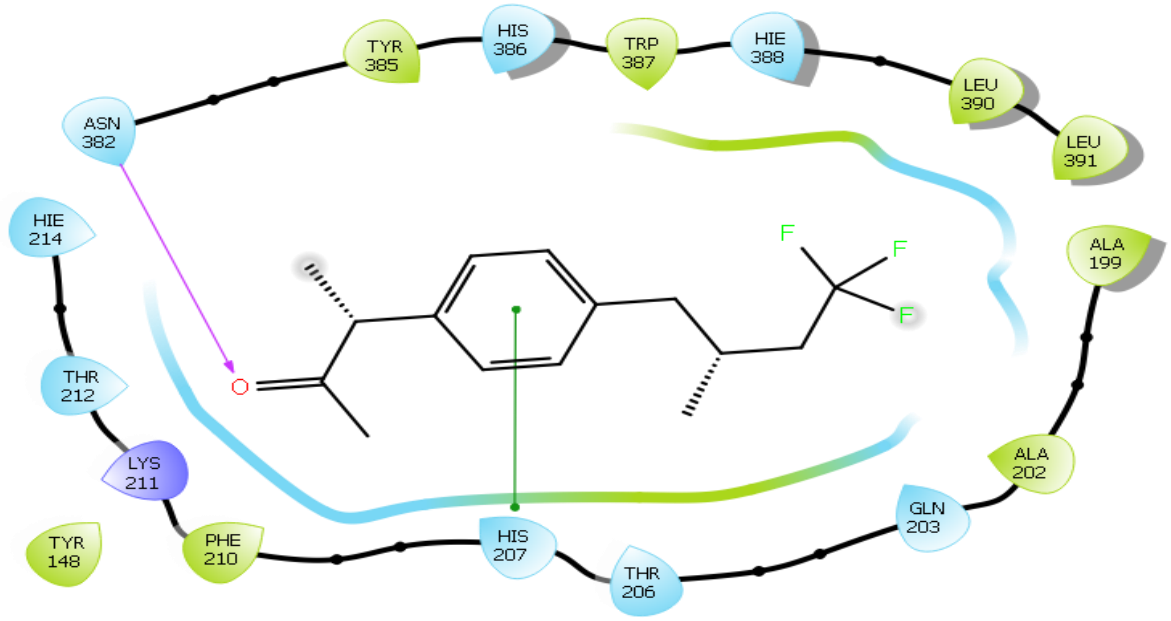

Figure 4a: Compound 7 with 5F1A

Table 4: Binding affinity and interaction type between the compounds and the receptor

Compounds	Binding affinity (kcal/mol)	Amino acid	Interaction
1	-6.914	ASN382, PHE210, HIS386, HIS207	Conventional hydrogen bond, π-π stacking
2	-5.95	HIE388, HIS207	Conventional hydrogen bond, π-π stacking
3	-6.607	ASN386	Conventional hydrogen bond
4	-6.47	HIS386, HIE388	Conventional hydrogen bond
5	-6.798	HIE388	Conventional hydrogen bond
6	-6.533	THR212, PHE210, HIS207, HIS386	Conventional hydrogen bond, π-π stacking
7	-7.203	ASN382. HIS207	Conventional hydrogen bond, π-π stacking
8	-6.531	GLN203, HIE388	Conventional hydrogen bond, π-π stacking
9	-6.639	HIS207, HIE388, THR385	Conventional hydrogen bond, π-π stacking
10	-6.58	ASN386	Conventional hydrogen bond
11	-6.976	PHE210, ASN386, HIS207, HIS386	Conventional hydrogen bond, π-π stacking
12	-6.154	HIS207, HIE388	Conventional hydrogen bond, π-π stacking
13	-6.555	HIE388, HIS207	Conventional hydrogen bond, π-π stacking
14	-6.034	HIS207	π-π stacking
15	-6.545	HIS207, ASN382	Conventional hydrogen bond, π-π stacking
16	-7.03	HIE388, THR385	Conventional hydrogen bond, π-π stacking
17	-6.876	HIS207, HIE388,	Conventional hydrogen bond, π-π stacking
18	-5.583	HIS207	π-π stacking
19	-5.977	HIE388, HIS207	Conventional hydrogen bond, π-π stacking
20	-5.816	ASN382, HIS207, HIS386	Conventional hydrogen bond, π-π stacking
ibuprofen	-5.846	HIE388, HIS207	Conventional hydrogen bond, π-π stacking

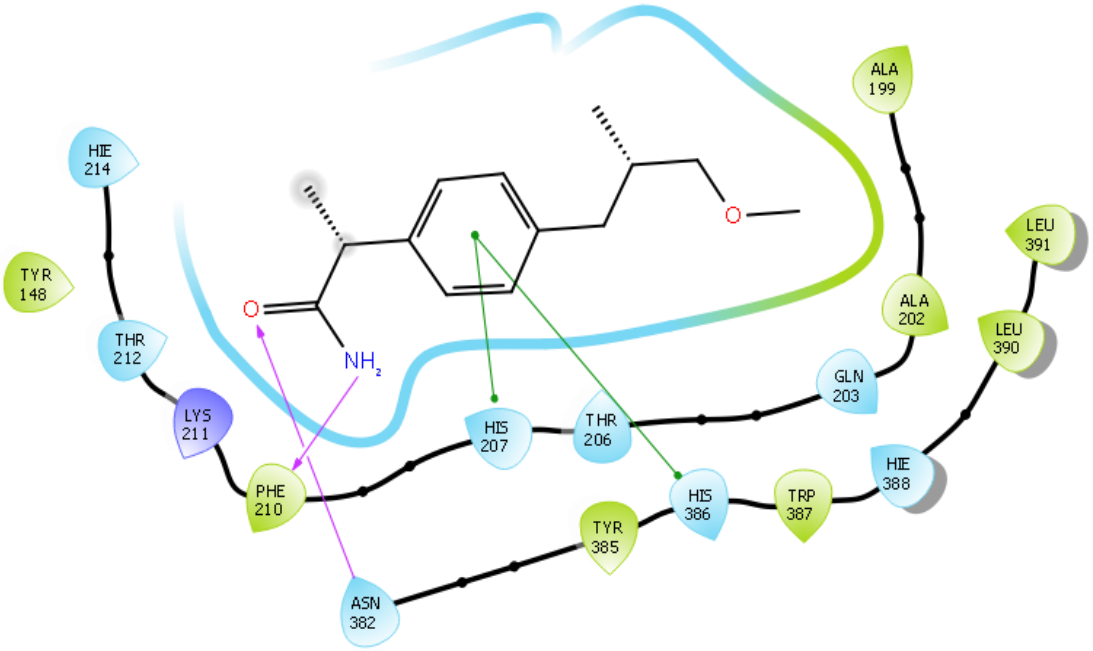

Figure 4b: Compound 11 with 5F1A

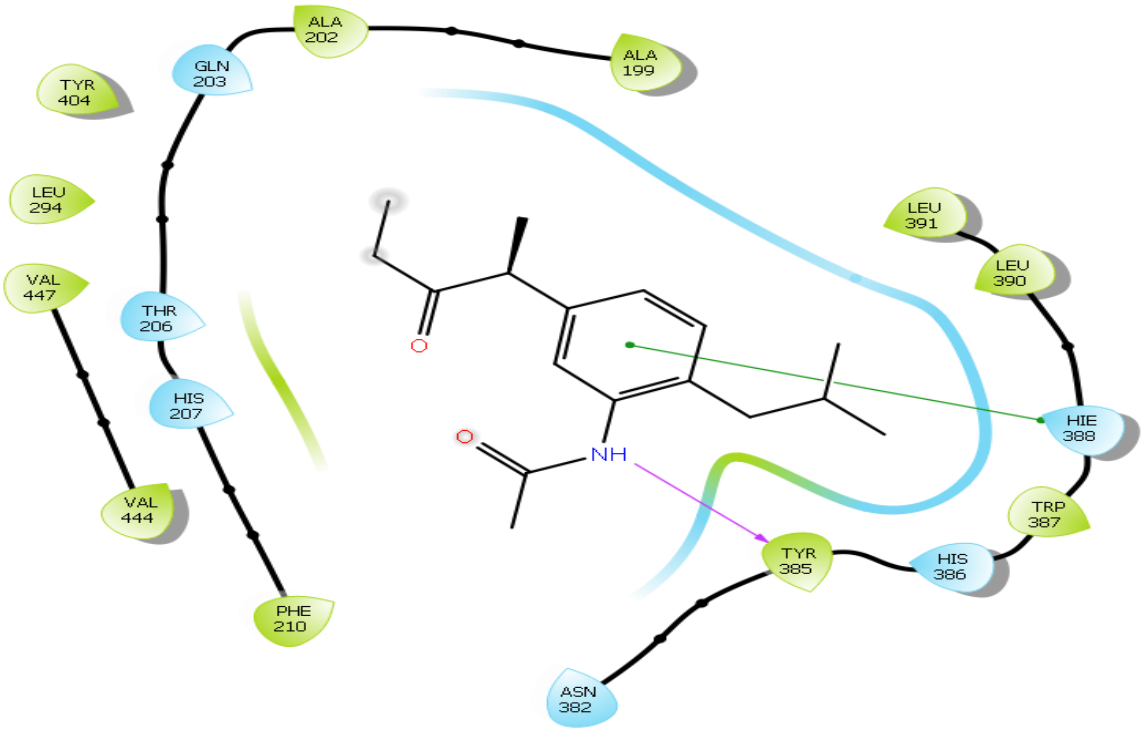

Figure 4c: Compound 16 with 5F1A

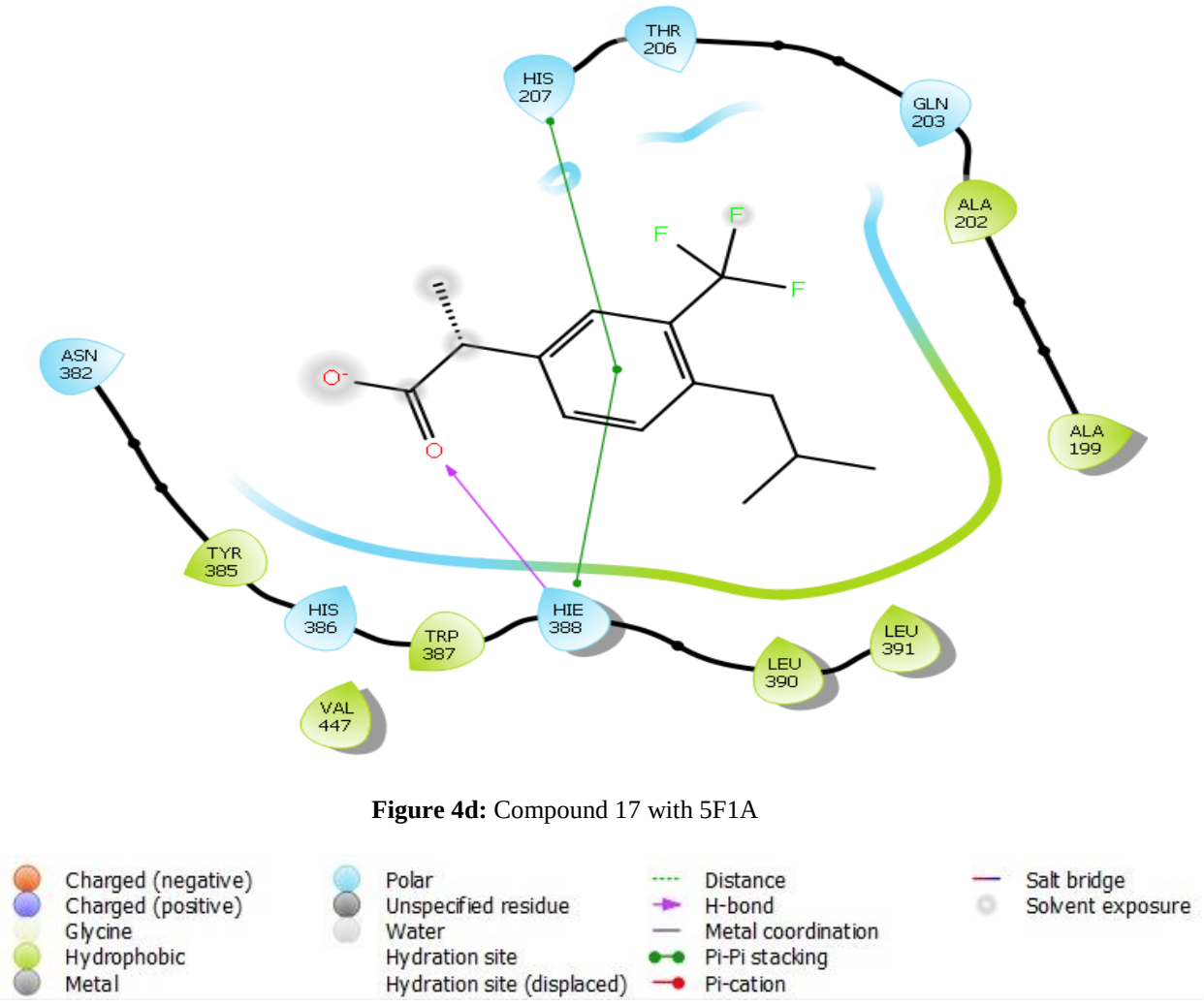

Figure 4d: Compound 17 with 5F1A

3.3. Pharmacokinetics studies

Many setbacks during drug development are related to poor pharmacokinetics. Therefore, monitoring the pharmacokinetic properties at early stage of drug discovery and development reduces the pharmacokinetics related problems. Pharmacokinetics properties which include GI absorption, BBB permeant, P-gp substrate, cytochrome P (CYP) 450 isoforms inhibitor and skin permeation (logKp) were computed as shown in Table 5. The pharmacokinetics properties showed that all the modified compounds could be absorbed by human intestine. Cerebrospinal fluid barrier and Blood brain barrier (BBB) are the main interface separating the central nervous system and blood circulation. BBB permeation is a crucial property in drug development and discovery. BBB permeation predicts if a compound will cross over the BBB and exert its therapeutic effects on the brain [38]. The BBB permeation result showed that all the modified compounds have the ability to cross the BBB. Permeability glycoprotein (P-gp) is an important protein of the cell membrane that convey drug away from cell membrane and cytoplasm which leads to further metabolism and clearance of the molecule thereby enhancing the therapeutic failure due to the reduction in drug concentration [38]. The results showed that none of the compounds is a substrate for P-gp. Cytochrome P_{450} play a crucial role in drug metabolism and clearance in the liver, and some of the isoforms are CYP1A2, CYP2C19, CYP2C9, CYP2D6 and CYP3A4. It is used in checking the drug-drug interaction which might have been caused by the inhibition of Cytochrome P_{450} isoforms and results to failure in co-administered drug metabolism thereby accumulating to toxic level [39]. Some of the compounds inhibited CYP2D6 and CYP3A4 isoform. Furthermore, the skin permeate (log *K*p) is also a vital property in the pharmaceutical company to determine the danger of compounds in case there is accidental contact with skin. The more negative the log *K*p, the less skin permeate is the molecule [40]. All the compounds are poorly permeable to skin.

Table 5: Some selected pharmacokinetics properties of the compounds

Compound	GI absorption	BBB permeant	P-gp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	Log Kp(cm/s)
Ibuprofen	High	Yes	No	No	No	No	No	No	-5.07
1	High	Yes	No	No	No	No	No	No	-5.53
2	High	Yes	No	No	No	No	No	No	-4.92
3	High	Yes	No	No	No	No	Yes	No	-5.48
4	High	Yes	No	No	No	No	Yes	No	-5.56
5	High	Yes	No	No	No	No	No	No	-4.99
6	High	Yes	No	No	No	No	Yes	No	-5.88
7	High	Yes	No	No	No	No	No	Yes	-4.67
8	High	Yes	No	No	No	No	No	No	-5.66
9	High	Yes	No	No	No	No	No	No	-5.61
10	High	Yes	No	Yes	No	No	No	No	-6.30
11	High	Yes	No	No	No	No	No	No	-6.17
12	High	Yes	No	No	No	No	Yes	No	-5.59
13	High	Yes	No	No	No	No	No	No	-5.52
14	High	Yes	No	No	No	No	Yes	No	-4.66
15	High	Yes	No	No	No	No	Yes	No	-5.02
16	High	Yes	No	No	No	No	Yes	Yes	-5.60
17	High	Yes	No	No	No	No	No	No	-4.83
18	High	Yes	No	No	No	No	Yes	No	-4.75
19	High	Yes	No	No	No	No	No	No	-4.74
20	High	Yes	No	No	No	No	Yes	No	-4.76

IV. CONCLUSIONS

Drug likeness, physico-chemical and pharmacokinetic properties of twenty derivatives of a non-steroidal anti-inflammatory drug (ibuprofen) have been investigated using computational approach. The compounds are capable of nucleophilic and electrophilic interactions with the active sites of the cyclooxygenase-2 receptor with comparable chemical reactivity with the standard. The reactivity indices suggest that compound 13 exhibits exceptional reactivity. The compounds exhibit comparable affinity for and intermolecular interactions with the COX-2 receptor as that of the ibuprofen (standard) which may be attributed to the asymmetrical charge distribution in their molecular geometry. They are adequately lipophilic, could permeate the cell membrane and blood brain barrier, and inhibit some isoforms of Cytochrome P_{450} (CYP2D6, CYP3A4 and CYP1A2). These suggest their effective anti-inflammatory potentials. Compound 10 displayed a preferential interaction with CYP1A2 inhibitor. The interaction of the potential drug candidates with active sites of the 5F1A receptor is majorly through the heteroatoms and π-electron system. The π-electron rich imidazole ring of His207 possibly contributes significantly to the π-π stacking interactions with aromatic center of ibuprofen derivatives. The poor skin permeability of the drug candidates suggests gradual assimilation of the active ingredient for effective epicutaneous topical anti-inflammatory or analgesic actions.

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DECLARATION OF COMPETING INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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