International Journal of Scientific Research and Management (IJSRM)
||Volume||06||Issue||09||Pages||C-2018-12-19||2018||
Website: www.ijsrm.in ISSN (e): 2321-3418
Index Copernicus value (2015): 57.47, (2016):93.67, DOI: 10.18535/ijsrm/v6i9.c01

Physiochemical, molecular docking, and pharmacokinetic studies of Naproxen and its modified derivatives based on DFT

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Abstract:
Naproxen (N) is a member of nonsteroidal anti-inflammation drug and widely used as an analgesic, antipyretic, and anti-inflammation agent. In this investigation, the inherent stability and biochemical interaction of Naproxen and its related molecules have been studied. Density functional theory (DFT) with B3LYP/ 6-31G (d, p) has been employed to optimize the structures. Frontier molecular orbital features (HOMO-LUMO gap, hardness, softness), dipole moment, electrostatic potential and thermodynamic properties (electronic energy, enthalpy, Gibb's free energy) of these optimized drugs are investigated. Molecular docking has been performed against prostaglandin H2 (PGH2) synthase protein 5F19 to search the binding affinity and mode(s) of all compounds. It is found that, all compounds are thermodynamically stable; some of them are chemically more reactive and show better binding affinity than the parent drug. ADMET calculations predict the improved pharmacokinetic properties of all compounds. Finally, this study can be helpful for the design of new analgesic, antipyretic drug.

Keywords: Naproxen, Density functional theory, Molecular docking, Pharmacokinetics

1. Introduction

Naproxen is a nonsteroidal anti-inflammatory drug (NSAID) having naphthalene backbone has been widely used as anti-inflammatory drug with regarding analgesic and antipyretic activities [1], [2]. It can inhibit the prostaglandin synthesis by blocking cyclooxygenase (COX) [3]. It has some demerits depending on the type and nature of unusual physical condition and on the limit of dose. Overdose and long term dose can cause of gastrointestinal [4] and cardiovascular diseases [5], [6]. It has *in vivo* selectivity upon human cyclooxygenase (COX) enzyme through inhibition of COX-2 whereas inhibition of COX-1 underwent unwanted occurrence on gastrointestinaltract causes ulceration and perforation of the mucosa layer [7]. COX selectivity depends upon dose differentiation as well as concentration of drug. Each of the substituent groups is important for site selective localization on COX [8]. Properly substitution on methoxy site, leading the direction of selectivity towards COX-2 relative to Naproxen [2]. In order to investigate selectivity upon COX-2-COX-1, focusing on rational derivatization could be the alternative strategy with regarding computational array. Apart from that, naproxen also a potent source of pharmaceutical water pollutant since of their extensive uses [9]. Further, pharmaceuticals discharges in to the sewage water and human excreta expose ecotoxicological effects. Moreover, naproxen under certain conditions underwent photo degradation show photoxicity *in vivo* [10]. Recently, it has been seen the trait of modifying drugs using halogens and alkyl group play important role in improving drug performance. Drug modification is another alternative way to search better agent, which can increase the selective action of drug and reduce the side effect [11].

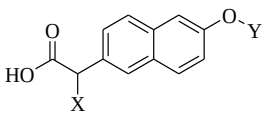
In this study, attempts have been taken to optimize some modified derivatives of Naproxen to investigate their biochemical behaviour on the basis of quantum mechanical approach. The free energy, electronic energy, enthalpy, dipole moment, electrostatic potential, HOMO-LUMO gap,

hardness, softness, and atomic partial charge have been calculated. Molecular docking and nonbonding calculation have been performed to understand the binding affinity, mode(s) and interaction between drugs and the amino acid residues of human prostaglandin synthase protein (5F19). Some of the analogues show better thermal stability, chemical reactivity, binding affinity, nonbonding interactions, and improved pharmacokinetics properties than the parent drug, which can promote more potential analgesic activity.

2. Methods and Computational Details

2.1. Optimization of ligands using DFT

Quantum mechanical (QM) methods has greater attention on calculation of thermodynamic properties, molecular orbital features, dipole moment, atomic partial charge, molecular electrostatic potential and as well as interpretation of different types of interactions [12]. Initial geometry of Naproxen (N) was taken from the online structure database named ChemSpider [13]. Molecular geometry optimization and further modification of all drugs carried out using Gaussian 09 program [14]. All the drugs were optimized using density functional theory (DFT) employing Becke's (B) [15] three-parameter hybrid model, Lee, Yang and Parr's (LYP) correlation functional [16] under Pople's 6-31G (d, p) basis set which has amply been proven to give very good ground state geometries [17]. Initial optimization of all compounds was performed in the gas phase. Dipole moment, electronic energy, enthalpy, free energy, electrostatic potential and atomic partial charge are calculated for all the compounds.



Name	X	Y
N	$-CH_3$	$-CH_3$
N1	$-OCH_3$	$-CH_3$
N2	$-OCH_2CH_3$	$-CH_3$
N3	$-CF_3$	$-CH_3$
N4	$-OCH_3$	-H
N5	$-CH_3$	$-CH_2CH_3$
N6	$-CH_3$	-H
N7	-F	$-CH_3$

Fig.1 Chemical structures of Naproxen (N) and its modified analogues

Frontier molecular orbital features HOMO (highest occupied molecular orbital), LUMO (lowest unoccupied molecular orbital) were calculated at the same level of theory. For each of the drugs, hardness (η), and softness (S), were calculated from the energies of frontier HOMO and LUMO as reported [18] considering Parr and Pearson interpretation [19]-[20] of DFT and Koopmans theorem [21] on the correlation of ionization potential (*I*) and electron affinities (*E*) with HOMO and LUMO energy (*ε*). Hardness (η), and softness (S) are calculated by using the following equations;

$$\eta = [\varepsilon LUMO - \varepsilon HOMO]/2; \quad S = 1/\eta$$

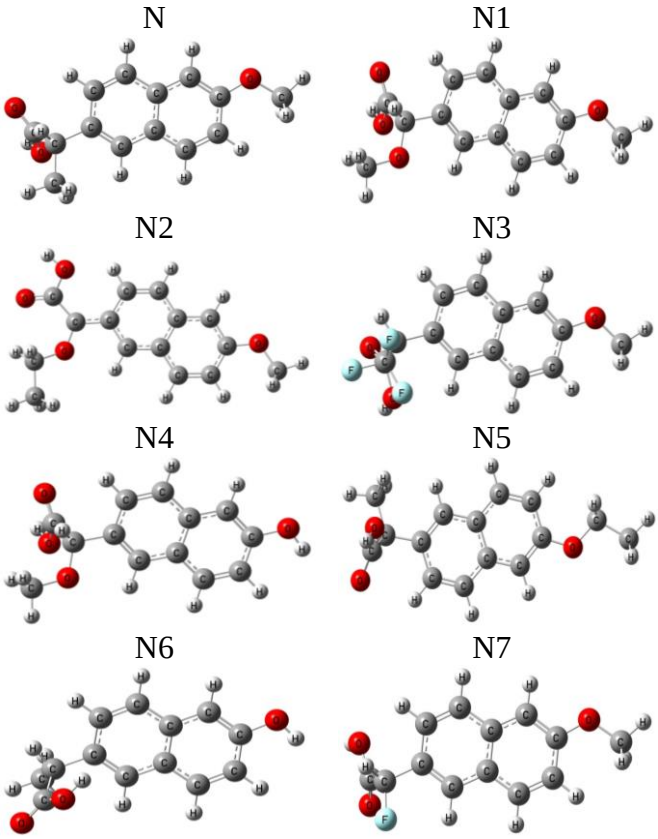


Fig. 2 Most stable optimized structure of all compounds. Optimized with B3LYP/6-31g (d, p)

2.2. Molecular Docking Simulation, Analysis, and Visualization

Three dimensional crystal structure of aspirin acetylated human cyclooxygenase-2 (PDB ID: 5F19) was retrieved in PDB format from online protein data bank (PDB) [22]. All hetero atoms and water molecules were eliminated using PyMol (version 1.3) software packages [23] . Energy minimization of the protein implemented by Swiss-Pdb viewer software (version 4.1.0) [24]. Than optimized drugs were subjected for molecular docking study against human prostaglandin synthase protein (5F19)

In computer aided drug design, binding affinity and mode(s) of ligand with target protein can predict by molecular docking simulation [25], [26]. Finally, molecular docking simulation was performed by

PyRx software (version 0.8) [27] considering the protein as macromolecule and the drug as ligand. In this analysis, rigid docking was performed where, all rotatable bonds were converted into non-rotatable with the center grid box size 64.8642, 73.2984, and 57.9414 Å along x, y and z directions respectively. After docking, both the protein and ligand structures were saved in .pdbqt format required by Accelrys Discovery Studio (version 4.1) to analyze and visualize the docking result and search the interactions between ligands and amino acid residues of receptor protein [28].

2.3. ADMET Analysis

Absorption, metabolism and carcinogenicity of Naproxen and its derivatives were predicted by utilizing AdmetSAR online database [29]. SDF (Structure Data File) and SMILES (simplified molecular-input line-entry system) strings were used throughout the generation process.

3. Results and Discussion

3.1. Thermodynamic Properties

Simple and rational modifications of molecular structure significantly influence the structural properties including free energy, enthalpy, dipole moment, and electrostatic potential. Spontaneity of a reaction and stability of a product can be predicted from Gibb's free energy, enthalpy, and electronic energy [30]. Free energy is a significant criterion to represent the interaction of binding partners, where negative value favourable for spontaneous binding and interaction. Greater negative values predict better thermodynamic properties. The free energy of N is -767.43 Hartree, where N3 shows the highest negative value -998.88 Hartree. The addition of trifluoromethyl group, influence the free energy as well as polarity.With increasing the negative value from N to N3, hence suggesting energetically and configurationally more stable.

In drug design, improved dipole moment can enhance hydrogen bond and non-bonded interactions in drug receptor complexes, which keep an important role to increase binding affinity. Elevated level of dipole moment also improves the polar nature of a molecule [31]. The dipole moment of N is 3.18 Debye, where N6 (4.71 Debye) shows the highest value (Table 1). Therefore, for N6 with increased dipole moment resulted in increased binding affinity against 5F19.

Table 1 Stoichiometry, molecular weight, electronic energy (*E*), enthalpy (*H*), Gibb's free energy (*G*) in Hartree, dipole moment (μ) in Debye of Naproxen and its modified derivatives

Name	M.F	*E*	*H*	*G*	*μ*
N	$C_{14}H_{14}O_3$	-767.37	-767.36	-767.43	3.18
N1	$C_{14}H_{14}O_4$	-842.56	-842.56	-842.62	2.29
N2	$C_{15}H_{15}O_4$	-881.23	-881.23	-881.30	2.83
N3	$C_{14}H_{11}F_3O_3$	-998.10	-998.10	-998.88	3.74
N4	$C_{13}H_{12}O_4$	-803.28	-803.28	-803.34	2.47
N5	$C_{15}H_{16}O_3$	-806.66	-806.66	-806.72	3.21
N6	$C_{13}H_{12}O_3$	-728.09	-728.08	-728.14	4.71
N7	$C_{13}H_{11}FO_3$	-827.31	-827.31	-827.37	2.57

3.2. Frontier Molecular Orbital Analysis

The HOMO and LUMO energies, gap, hardness, softness, chemical potential, electronegativity and electrophilic index of all drugs are presented in **Table 2**. The electronic absorption relates to the transition from the ground to the first excited state and mainly described by one electron excitation from HOMO to LUMO [32]. From frontier molecular orbital theory, energies of HOMO and LUMO play an important role in chemical reactivity. The HOMO-LUMO gap is related to the chemical hardness, softness, chemical potential and electrophilic index of a molecule [18]-[33]. Large HOMO-LUMO gap is responsible for high kinetic stability and low chemical reactivity. On the other hand, small HOMO-LUMO gap is important for low chemical stability, because addition of electrons to a high-lying LUMO and/or removal of electrons from a low-lying HOMO is energetically favourable in any potential reaction. HOMO-LUMO gap as well as hardness, and softness were calculated for all the drugs (**Table 2**). In current analysis, N shows the HOMO-LUMO gap (3.04 eV), where N2 shows lowest energy gap with highest softness (0.97 eV), which may contribute to show higher chemical activity and polarizibility than others.

Table 2 Energy (eV) of HOMO, LUMO, Gap, hardness and softness of all compounds

Name	*ε*HOMO	*ε*LUMO	Gap	Hardness	Softness
N	-8.28	-5.24	3.04	1.52	0.66
N1	-8.26	-5.28	2.98	1.49	0.67
N2	-8.45	-6.40	2.05	1.02	0.97
N3	-8.26	-5.30	2.96	1.48	0.67
N4	-5.51	-0.96	4.55	2.27	0.44
N5	-8.26	-5.28	2.98	1.49	0.67
N6	-5.88	-1.41	4.47	2.24	0.45
N7	-5.59	-1.13	4.46	2.23	0.45

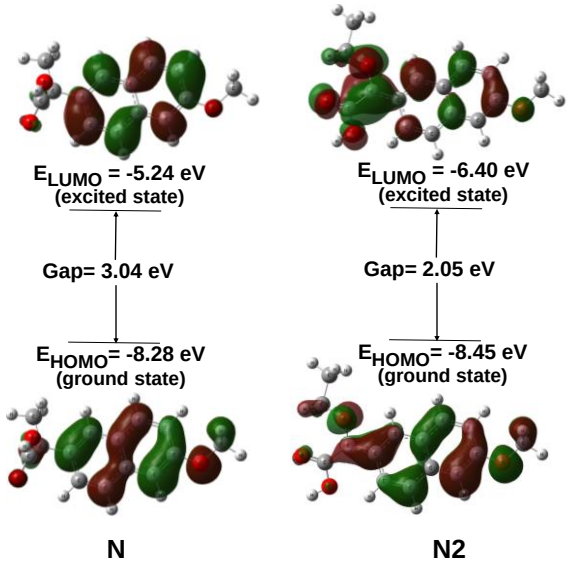


Fig. 3 Frontier molecular orbital and related energy of Naproxen (N) and N2

3.3. Molecular Electrostatic Potential Analysis

Electrostatic potential (ESP) was calculated to forecast the reactive sites for electrophilic and nucleophilic attack of all optimized structures. It also helps to interpret biological recognition process and hydrogen bonding interaction [34]. Red colour represent maximum negative area which favourable site for electrophilic attack , blue colour indicate the maximum positive area which favourable site for nucleophilic attack and green colour represent zero potential area. ESP displays molecular size, shape as well as positive, negative and neutral electrostatic potential regions simultaneously in terms of colour grading. From ESP map, region having the negative potential are over electronegative atom (oxygen atoms) and having positive potential are over hydrogen atoms. Here, the maximum negative potentiality of **N2** molecule is -0.3782 a.u. (deepest red) for oxygen atoms and the highest positive region localized on the hydrogen atoms of **N6** have value +0.2017a.u. (deepest blue, **Fig. 4**)

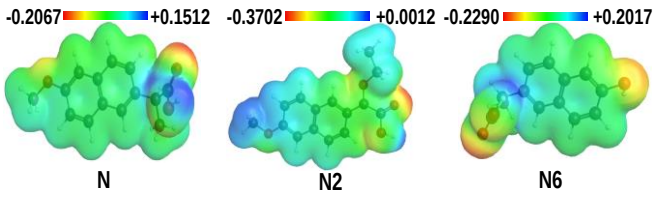


Fig.4 Molecular electrostatic potential map of Naproxen (N), N2, and N6

3.4. Binding Affinity and Interactions of Naproxen and its Analogues with 5F19

Binding properties of all compounds as prostaglandin inhibitor investigated by molecular docking calculation by PyRx software. Binding affinities and ligand-protein interactions are summarized in Table 3. Greater negative values of binding affinity indicate stronger binding between drugs and the receptor protein. Strong hydrogen bonding is the most significant contributing factor in increasing binding affinity of drugs with the receptor. Non-covalent interactions such as hydrogen bond, halogen bond and hydrophobic interaction are involved in the binding of examined drugs. Among various factors, hydrogen bonding is the one which can affect selectivity of nucleotide incorporation by a DNA polymerase. Recently, it is mentioned that, hydrogen bond of <2.3 Å are able to increase the binding affinity by several magnitude [35] and halogen bonds have almost similar importance as hydrogen bond in chemical and biological system [36]. The binding affinity of Naproxen is -9.2 kcal/mol where, N3, N5, N6, and N7 have considerably increased to -9.4, -9.5, -9.5, and -9.4 kcal/mol respectively. Decreased binding affinity found in case of N1 (-9.1 kcal/mol), N2 (-8.9 kcal/mol) and N4 (-8.8 kcal/mol). Significant hydrogen and halogen bonding observed in N3, not only contributes in increasing binding affinity but also increase binding speciality.

Except conventional Hydrogen bonds some weak intermolecular interactions such as CH/π, OH/π, CH/O are observed for all derivatives. In derivative N6, CH/π is mostly driven by leucine and valine also small interaction happen between derivative N6 and tyrosine due to -CH_3 group at X position with that π electron of tyrosine. On the other hand, in N3 apart from leucine interactions, phenylalanine interactions also observed in multiple cases, this is owing to -CF_3 group at X-position and -CH_3 group at Y-position to that with phenyl alanine and so on. Also within shorter intermolecular distance, small interaction observed for alanine due to CH/π interaction between -CH_3 group of alanine and π-electron of naphthalene moiety. Shorter intermolecular distance of alanine revealing that smaller the size more possibilities of approaching together. From molecular docking analysis, the major and common residues of PGH2 active site like Leu531, Gly526, Phe529, and Val349 form different significant interactions with the ligands. Another important residue Gly526, which form Amide-pi stacked with prostaglandin inhibitor. In addition, Leu531 form most important conventional hydrogen bond in almost every compound. In N3, Phe209

form a Pi-pi stacked interaction and some halogen bonds are observed.

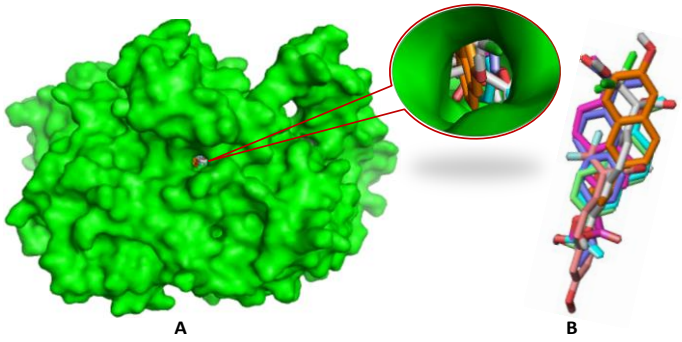


Fig. 5 (A) Docked conformation of all structures at inhibition bounding site of 5F19 (B). Superimposed view of all compounds after rigid docking

Table 3 Binding energy (kcal/mol) and nonbonding interaction of Naproxen derivatives

Name	Binding energy	Residues in contact	Interaction types	Distance (Å)
N	-9.2	Leu531	H	2.84842
		Leu531	H	2.64688
		Gly533	H	2.94241
		Leu534	H	2.40083
		Phe529	H	1.91775
		Met522	C	2.68760
		Phe529	PA	3.96656
		Gly526	Aps	4.76856
		Gly526	Aps	3.77674
		Phe205	Pal	4.58970
		Phe209	Pal	4.82294
		Phe381	Pal	5.13270
		Val349	Pal	5.23448
		Ala527	Pal	4.92957
N1	-9.1	Leu531	H	2.07685
		Phe529	C	2.66983
		Phe529	C	2.95925
		Gly526	Aps	4.15831
		Gly526	Aps	4.53980
		Val349	Pal	4.99488
		Ala527	Pal	5.05337
		Val349	Pal	4.11982
		Ala527	Pal	3.63944
		Leu531	Pal	5.26761
N2	-8.9	Arg44	C	2.18583
		Cys47	H	3.05240
		Leu152	A	5.15650
		Val46	Pal	5.27430
		Cys47	Pal	5.35972
		Pro153	Pal	3.98289
		Cys36	Pal	4.69579
		Cys47	Pal	4.32385
		Pro153	Pal	4.61961
N3	-9.4	Leu531	H	2.77127
		Leu531	H	2.77968
		Ala527	C	1.98639
		Gly526	X	3.43868
		Ala527	X	2.91731
		Phe529	X	3.58353
		Leu531	PC	4.52429
		Phe209	PPS	5.12545
		Leu534	Pal	4.51457
N4	-8.8	Leu534	Pal	4.38603
		Phe529	H	2.51967
		Val523	C	2.29382
		Met522	C	2.59234
		Gly526	Aps	4.48303
		Gly526	Aps	4.31877
		Val349	Pal	5.11530
N5	-9.5	Val349	H	2.42553
		Ser353	C	2.51326
		Phe529	PA	4.47861
		Val523	A	3.80360
		Leu534	A	4.06916
		Phe205	Pal	4.82581
		Phe209	Pal	4.95764
		Val349	Pal	4.00498
		Ala527	Pal	3.98747
		Leu531	Pal	5.25001
		Val349	Pal	4.77254
N6	-9.5	Leu531	H	2.84166
		Leu531	H	1.99440
		Gly526	H	2.78840
		Val344	A	5.39467
		Val349	A	4.88298
		Tyr348	Pal	4.85973
		Val349	Pal	5.03362
		Leu352	Pal	4.95907
		Val349	Pal	4.93668
		Leu352	Pal	4.20127
		Val523	Pal	5.14017
N7	-9.4	Leu531	H	2.60980
		Phe529	H	2.81740
		Met522	C	2.69700
		Leu531	PC	3.04018
		Phe529	PA	3.92486
		Phe529	PA	4.90272
		Gly526	Aps	3.75493
		Val349	Pal	5.29136
		Ala527	Pal	4.98871

H=Conventional hydrogen bond, C= Carbon hydrogen bond, A= Alkyl, PA= Pi-anion, PC= Pi-cation, Pal= Pi-alkyl, PPS= Pi-pi stacked, Aps= Amide-pi stacked, X= Halogen bond

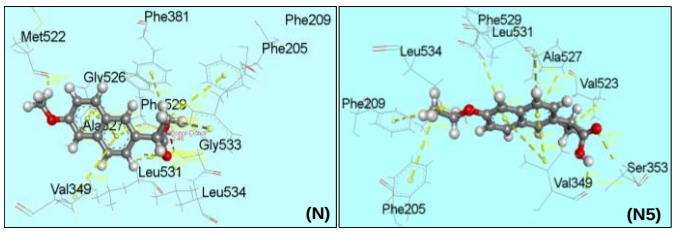


Fig.6 Nonbonding interactions Naproxen (N) and N5 with 5F19 generated by Discovery Studio

3.5. ADMET Analysis

From AdmetSAR calculation (Table 4), all the drugs exhibit positive result for blood brain barrier (BBB) criteria, predicting that can pass through the BBB and non-carcinogenic in nature. N, N1, and N3 show II category acute oral toxicity (AOT) and the remaining molecules show III category acute oral toxicity. So, all the compounds (except N1 and N3)

are relatively harmless than Naproxen (N) for oral administration. All drugs are P-glycoprotein non-inhibitor, where inhibition can interrupt the absorption, permeability and retention of the drugs [37]. Moreover, most of the analogues show improved human intestinal absorption (HIA) value than N. However, all the drugs show weak inhibitory feature for human ether-a-go-go-related gene (hERG) which can lead to long QT syndrome [38], so further more study of this aspect is necessary.

Table 4 Selected pharmacokinetic parameters of Naproxen and its derivatives (Probability values related to each of the parameters are given in the parenthesis)

Name	BBB	HIA	PGI	hERG	Carcinogen	AOT
N	+ (0.69)	+ (0.99)	NI(0.87)	WI (0.96)	NC(0.87)	II
N1	+ (0.64)	+ (0.98)	NI(0.80)	WI (0.98)	NC (0.89)	II
N2	+ (0.60)	+ (0.98)	NI(0.78)	WI (0.98)	NC (0.88)	III
N3	+ (0.87)	+ (1.00)	NI(0.88)	WI (0.97)	NC (0.84)	II
N4	+(0.63)	+(0.97)	NI(0.89)	WI (0.98)	NC (0.92)	III
N5	+ (0.74)	+ (1.00)	NI(0.79)	WI (0.96)	NC (0.78)	III
N6	+ (0.55)	+ (0.99)	NI(0.97)	WI (0.95)	NC (0.86)	III
N7	+ (0.83)	+ (1.00)	NI(0.88)	WI (0.97)	NC (0.85)	III

PGI= P-glycoprotein inhibitor, *NI*=Non-inhibitor, *NC*= Non-carcinogenic, *WI*= Weak -inhibitor

4. Conclusion

Based on current studies, seven analogues of Naproxen have been studied for the exploring of molecular interaction and binding affinity with prostaglandin H2 (PGH2) synthase protein 5F19. From quantum calculation, all the compounds are thermally stable and most of the analogues show lower HOMO-LUMO gap and higher softness than parent drug (**N**). From molecular docking result, strong binding affinity is found for N5-5F19, and N6-5F19complexes with significant interactions. Pharmacokinetic result predicts all drugs are non-carcinogenic and most of them (N2, N5, N6, and N7) relatively harmless than Naproxen for oral administration. Considering present investigation, N3, N5, N6, and N7 can be potent new possible candidate for better performance.

Acknowledgement We are thankful to Amrin Ahsan, Department of Chemistry, University of Chittagong, for her support during optimization.

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