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Molecular docking for rationalizing the use of linkers in polymer drug conjugates design for pegylated anti-inflammatory drug delivery

Vinay Sagar Verma
Shri Shankaracharya Technical Campus, Faculty of Pharmaceutical Sciences, Junwani, Bhilai-490020, C.G., India | Rungta College of Pharmaceutical Sciences and Research, Kohka, Bhilai, Durg, C.G., India. 490023
Email: vinaysagarverma@gmail.com

Aditya Mishra
Shri Shankaracharya Technical Campus, Faculty of Pharmaceutical Sciences, Junwani, Bhilai-490020, C.G., India
Email: aditya38298@gmail.com

Hemant Ramchandra Badwaik
Shri Shankaracharya Institute of Pharmaceutical Sciences and Research, Junwani, Bhilai-490020, C.G., India
Email: hemantrbadwaik@gmail.com

Amit Alexander
NIPER, Department of Pharmaceuticals, Ministry of Chemical and Fertilizers, Guwahati-781101, Assam, India
Email: dramitalexander@gmail.com

Ajazuddin
Rungta College of Pharmaceutical Sciences and Research, Kohka, Bhilai, Durg, C.G., India. 490023
*Corresponding author email: write2ajaz@gmail.com

***Abstract*---**A smart linker is a crucial element throughout the creation of polymer-drug conjugates. It binds different portions or subunits altogether and may be freed by a suitable trigger, resulting in localized drug distribution and enhanced bioavailability. PEG (Polyethylene Glycol) linkers can be synthesized chemically by specifically adding functionalized groups with chemical reactivity at certain structural ends of PEG. Because they may integrate a diverse range of groups, PEG linkers are frequently utilized in molecular biology experiments due to increased water solubility, excellent biocompatibility, and non-immunogenicity. In present work, we have included various linkers

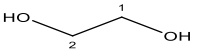
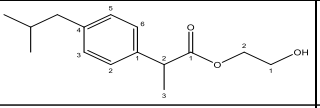
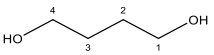
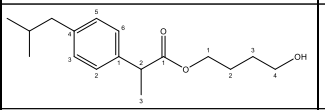
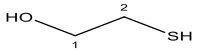
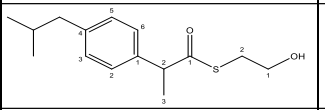
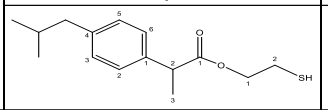
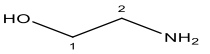
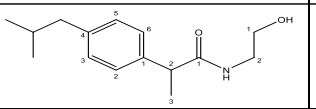
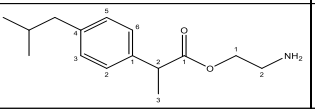
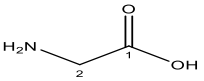
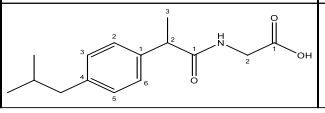
which are incorporated in design of PDC's (polymer drug conjugates) of pegylated NSAIDs (nonsteroidal anti-inflammatory drugs) through PEGylation. The main focus was to investigate the pharmacodynamic changes brought about by these linker's conjugated to model drug Ibuprofen (IB1-IB7). The tools used for the analysis are Argus Lab 4.0 for molecular docking and pkCMS as ADMET prediction tool. The outcome of this work was, establishment of a method for choosing suitable linker for designing PDC's for various NSAIDs and other bioactive agents.

***Keywords*---**ibuprofen, anti-inflammatory, arthritis, rheumatoid arthritis, osteoarthritis.

Introduction

Linkers play versatile role in the development and functioning of polymer-drug conjugates, they act as targeting entity(Chang et al., 2016), solubility enhancer(Chang et al., 2016; Ofokansi et al., 2016), Linking ability provider(Theodosis-Nobelos et al., 2020) and releasability definer.(Lawrence et al., 2016; Taghizadeh et al., 2015; Tedeschini et al., 2021) Various linkers have been utilized in the development of polymer drug conjugates (PDC's) of Ibuprofen, here we have constricted to those linkers which have been employed in the conjugation of polyethylene glycol to Ibuprofen to form respective PDC's.(Bharti et al., 2018; Davaran et al., 2006; Hassani Najafabadi et al., 2014; Mumuni et al., 2014) The group of linkers which have been employed and reported in this work are hydroxy ethyl ester (HEE), hydroxy ethyl thioester (HET), and hydroxy ethyl amide (HEA)(Davaran et al., 2006; Kemisetti & Manda, 2018; Mattheolabakis et al., 2014) **Error! Not a valid bookmark self-reference.**.

Table 1
Linkers and the respective derivatives of Ibuprofen along with their codes

Sr. No.	Group	Linker	Structure	Ibuprofen Derivatives with Respective Linkers	Code
1	HEE	Ethylene glycol			**IB4**
		Butane-1,4-diol			**IB6**
2	HET	2-mercapto-ethanol			**IB3**
					**IB7**
3	HEA	Ethanolamine			**IB1**
					**IB2**
		Glycine			**IB5**

In this research work we have mainly focused on the effect of linkers on pharmacodynamics of the Ibuprofen, i.e., does the linker incorporated in PDC's has enhanced or declined the affectivity of the drug. Ibuprofen is the drug of choice because it is a non-cox selective NSAID (non-steroidal anti-inflammatory drugs) with high risk of peptic ulcer development as side effect.(Rainsford, 2009) Ibuprofen is a drug which has been explored for treatment of various diseased conditions like, Anti-inflammatory(Mumuni et al., 2014)Cancer (Zhao et al., 2016), cystic fibrosis (Konstan et al., 2003), RhoA inhibition in neurons (Dill et al., 2010), and migraine (Evers et al., 2006), etc. Along with this various researcher are working on developing suitable derivative of Ibuprofen or they are trying to work on the prodrug development for the same.(Davaran et al., 2006; Mattheolabakis et al., 2014) Here in this research, we have envisaged the effect of linkers on the pharmacological activity of Ibuprofen while retaining the prodrug form and after being released in its native form. For such an analysis we have made use of in-silico method by employing Argus Lab 4.0 (molecular docking software), Pymol 2.5 and BIOVIA Discovery Studio Visualizer (For 2D and 3D pose visualization). Their ADMET analysis has been also done in similar manner using pkCSM online software.

Materials and Methods

Materials

ChemBio Draw 18.1, Argus Lab 4.0, Pymol 2.5, BIOVIA Discovery Studio Visualizer and pkCSM online software.

Methods

Design of prodrugs with linkers

With the help of literature various linkers have been identified and their derivatives have been designed using ChemBio Draw 18.1 software with ACS structure template settings. All the structures occurrence, were confirmed for their possibility of being synthesized via suitable literatures.(Davaran et al., 2006; Kemisetti & Manda, 2018; Mattheolabakis et al., 2014; Narayanan et al., 2013; Zhao et al., 2016) the various structures of prodrug under current investigation have been listed in Linkers play versatile role in the development and functioning of polymer-drug conjugates, they act as targeting entity(Chang et al., 2016), solubility enhancer(Chang et al., 2016; Ofokansi et al., 2016), Linking ability provider(Theodosis-Nobelos et al., 2020) and releasability definer.(Lawrence et al., 2016; Taghizadeh et al., 2015; Tedeschini et al., 2021) Various linkers have been utilized in the development of polymer drug conjugates (PDC's) of Ibuprofen, here we have constricted to those linkers which have been employed in the conjugation of polyethylene glycol to Ibuprofen to form respective PDC's.(Bharti et al., 2018; Davaran et al., 2006; Hassani Najafabadi et al., 2014; Mumuni et al., 2014) The group of linkers which have been employed and reported in this work are hydroxy ethyl ester (HEE), hydroxy ethyl thioester (HET), and hydroxy ethyl amide (HEA)(Davaran et al., 2006; Kemisetti & Manda, 2018; Mattheolabakis et al., 2014) **Error! Not a valid bookmark self-reference.**.

. Along with those native form of Ibuprofen and a standard molecule celecoxib structure has also been included foe the purpose of comparative analysis of the outcomes (Figure 1).

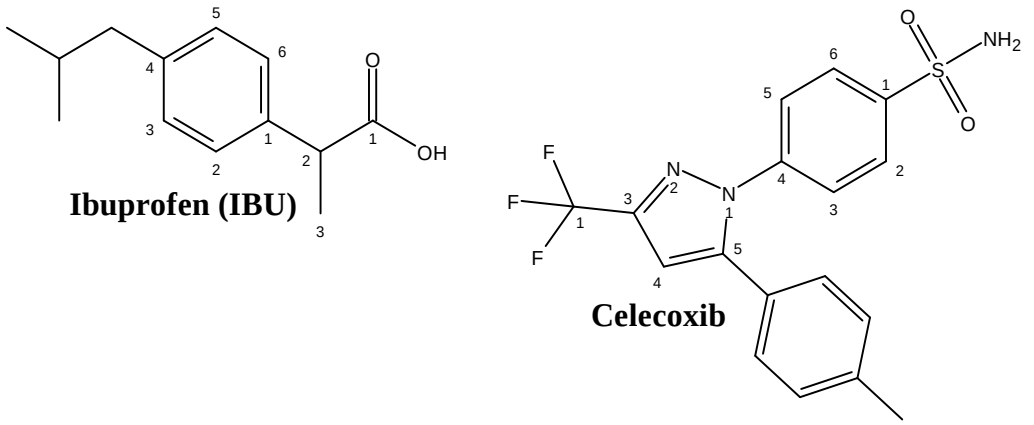


Figure 1.Structure of Ibuprofen and Celecoxib

3D Model Preparation of Above designed Prodrugs

All the structures of standard, reference and derived molecules were converted from 2D to 3D form after the structures were optimized by running MMFF (Merck Molecular Force Field) operation by which the ligands reach the state of lowest possible free energy for better binding. These 3d structures were saved in the .pdb file format for molecular docking in further steps.

Target preparation for molecular Docking

The .pdb file of the selected target protein structures were downloaded from RCSB data base. For our research we have chosen Human Cyclooxygenase-2 (PDB ID: 5f19)(Lucido et al., 2016), human cyclooxygenase (hCOX)-1 (PDB ID: 6y3c)(Miciaccia et al., 2021) and human 5-lipoxygenase (PDB ID: 3o8y)(Gilbert et al., 2011); as the targeting sites for molecular docking study. The protein structure was derived through X-Ray diffraction method and had the resolution of 2.04 Å, 3.36 Å and 2.39 Å respectively. Further the proteins were processed by removing water molecules and all misc. residues and filled with hydrogen to fill the voids.

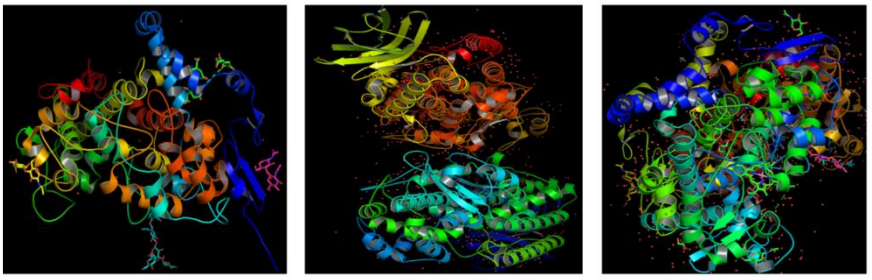


Figure 2.Structure of Target protein structures of hCOX 2, 5Lox and hCOX 1 as obtained from RCSB data Base visualized through Pymol 2.5.

Molecular docking of Prodrugs

Molecular docking of the prepared ligands with selected proteins were done using Argus lab version 4.0.1. The docking results obtained show us docking score G (free energy) and amino acids which were involved in creation of hydrogen bond between ligand and target protein. (Ahirwar et al., 2018; Dewangan et al., 2018) By the means of these parameters, we interpret the binding efficiency and affinity of prepared ligand.

Visualization of Docked Prodrugs

Interaction between ligands and protein were visualized in both 2D and 3D models using BIOVIA Discovery Studio Visualizer. (Dewangan et al., 2021; Kamdi et al., 2021; Verma et al., 2022) The 2D diagram of ligand interaction shows us various kind of forces acting on the ligand molecule including hydrogen bonds,

Vander wall forces, steric hindrance etc and the 3D pose shows us the position and spatial arrangement of ligand molecule and binding site. Few of such ligand binding site amino acid interactions were also captured and visualized via Pymol 2.5 software (Academic Licenced).

ADMET analysis of Prodrugs

All the structures of standard, reference and derived molecules were converted from 2D to respective SMILE forms and were copied and pasted in respective tab of pkCMS. After that, the selection of prediction mode for pharmacokinetic properties the ADMET tab was clicked and the results were obtained in few minutes of run time.(Pires et al., 2015; Han et al., 2019; Pratama, Poerwono and Siswodiharjo, 2020)

Results and Discussions

Molecular docking of Prodrugs

The designed structures are obtained as the result of linkers reported in literature used in PEGylation of drugs for developing respective PDC's; by conjugating them in all possible manner. Thus, we have attained 7 derived structures (IB1-IB7) from 5 different linkers of choice (Linkers play versatile role in the development and functioning of polymer-drug conjugates, they act as targeting entity(Chang et al., 2016), solubility enhancer(Chang et al., 2016; Ofokansi et al., 2016), Linking ability provider(Theodosis-Nobelos et al., 2020) and releasability definer.(Lawrence et al., 2016; Taghizadeh et al., 2015; Tedeschini et al., 2021) Various linkers have been utilized in the development of polymer drug conjugates (PDC's) of Ibuprofen, here we have constricted to those linkers which have been employed in the conjugation of polyethylene glycol to Ibuprofen to form respective PDC's.(Bharti et al., 2018; Davaran et al., 2006; Hassani Najafabadi et al., 2014; Mumuni et al., 2014) The group of linkers which have been employed and reported in this work are hydroxy ethyl ester (HEE), hydroxy ethyl thioester (HET), and hydroxy ethyl amide (HEA)(Davaran et al., 2006; Kemisetti & Manda, 2018; Mattheolabakis et al., 2014) **Error! Not a valid bookmark self-reference.**.

). These linker derived molecules or prodrugs were sketched in in 2d using Chemdraw 18.1, which were converted to 3D by making use of Chem 3D and the file was saved in .pdb format. These obtained structures were saved as ligands for docking and the protein structures obtained from RCSB protein data base (viz. 5f19, 3o8y & 6y3c) were saved as binding site. While, running molecular docking analysis using Argus lab 4.0 software the parameters set has been enlisted in the **Error! Not a valid bookmark self-reference.**. After completion of the docking analysis the results were tabulated in:
On the basis of docking score's comparison, we have observed that IB6 has the highest affinity score: in hCOX 2: -13.745 kcal/mol(**Error! Not a valid bookmark self-reference.**), in h5 LOX: -11.334 kcal/mol (Table *4*) and in COX 1: 13.650 kcal/mol (Table *5*), among other derivatives. In comparison with the celecoxib (a selective COX 2 inhibitor) and Ibuprofen (a nonselective COX inhibitor), we have observed that it has higher binding affinity for hCOX 2 (5f19) (i.e., -10.327 kcal/mol and -12.728 kcal/mol respectively) (Table *3*). Whereas, IB6 has same

docking site as that of Ibuprofen (IBU), when the amino acid residues were compared of their respective binding sites (Figure 3). Other linker derived prodrug having higher affinity then IBU (12.728 kcal/mol) and celecoxib are IB7 (13.219 kcal/mol) and IB3 (13.170 kcal/mol) (Table *3*). Thus, we have obtained better prodrugs which has higher pharmacological activity by itself and the resultant release of IBU from IB6 will again synergise the pain suppression effect. This feature, further emphasises the suitability of selecting 1,4-butanediol as linker for preparing PDC of Ibuprofen.

When these linker derived prodrugs (i.e., IB1-IB7) were brought into docking analysis with h5LOX (3o8y); we observed again that IB6 was leading here too, with docking score of -11.334 kcal/mol in comparison to IBU (-10.598 kcal/mol) and celecoxib (-8.389 kcal/mol) (Table *4*). Thus, this results also showed an aggregable result for the researchers working in designing of dual acting anti-inflammatory agents (i.e., acting on both COX 2 and 5 LOX).(Charlier and Michaux, 2003; Goossens, Pommery and Pierre Henichart, 2007; Shaaban et al., 2020) -10.598 kcal/mol score of docking, supports the pharmacological activity of Ibuprofen against 5 LOX; resulting in its satisfactory inhibition. Whereas the amino acid residues of the derivatives of Ibuprofen obtained by conjugating the linkers share the similar residues as that of native Ibuprofen (see Table 4 and Figure 4). This result validates the pharmacology of these derivative too. Since the derivatives are showing greater binding affinity in comparison to Ibuprofen (-10.598 kcal/mol), their activity in terms of pharmacology will be definitely higher than it. The molecules showing increased docking score are IB6 (11.334 kcal/mol), IB3 (-11.185 kcal/mol), IB1 (-11.088 kcal/mol), IB4 (10.969 kcal/mol), IB5 (-10.846 kcal/mol), and IB7 (-10.683 kcal/mol). Only IB2 (-10.045 kcal/mol) and celecoxib (-8.389 kcal/mol) showed lesser score than that of Ibuprofen. The binding affinity data obtained in Table 3 and Table 4 strongly support and validate that these derivatives of ibuprofen and ibuprofen itself; possesses dual activity ability and can be employed for treatment of inflammation of different types by acting via these mechanisms. This dual acting ability may prove to be very helpful in the field of clinical practices where long-term anti-inflammatory therapy is needed like neuroinflammation, rheumatoid arthritis, Cancer related inflammations, etc.

Table 3
Molecular docking data of Ibuprofen derivatives with hCOX 2 (5f19) (5f19), **Error! Reference source not found.** (3o8y), and **Error! Reference source not found.**

Table 1
Grid dimension details for all the docking studies done using Argus Lab 4.0

Dimension Details	5F19 Grid	3O8Y Grid	6Y3C Grid
Grid min (x, y, z)	-7.47717, 11.0471, 9.56232	-25.7851, 15.5787, -26.8086	-66.7564, -81.618, -27.9242
Grid max (x, y, z)	52.5228, 71.0471, 69.5623	34.2149, 75.5787, 33.1914	-6.7564, -21.618, 32.0758

Grid dimensions	151 x 151 x 151	151 x 151 x 151	151 x 151 x 151

On the basis of docking score's comparison, we have observed that IB6 has the highest affinity score: in hCOX 2: -13.745 kcal/mol(**Error! Not a valid bookmark self-reference.**), in h5 LOX: -11.334 kcal/mol (**Error! Reference source not found.**) and in COX 1: 13.650 kcal/mol (**Error! Reference source not found.**), among other derivatives. In comparison with the celecoxib (a selective COX 2 inhibitor) and Ibuprofen (a nonselective COX inhibitor), we have observed that it has higher binding affinity for hCOX 2 (5f19) (i.e., -10.327 kcal/mol and -12.728 kcal/mol respectively) (**Error! Not a valid bookmark self-reference.**). Whereas, IB6 has same docking site as that of Ibuprofen (IBU), when the amino acid residues were compared of their respective binding sites (
Figure 3). Other linker derived prodrug having higher affinity then IBU (12.728 kcal/mol) and celecoxib are IB7 (13.219 kcal/mol) and IB3 (13.170 kcal/mol) (**Error! Not a valid bookmark self-reference.**). Thus, we have obtained better prodrugs which has higher pharmacological activity by itself and the resultant release of IBU from IB6 will again synergise the pain suppression effect. This feature, further emphasises the suitability of selecting 1,4-butanediol as linker for preparing PDC of Ibuprofen.

When these linker derived prodrugs (i.e., IB1-IB7) were brought into docking analysis with h5LOX (3o8y); we observed again that IB6 was leading here too, with docking score of -11.334 kcal/mol in comparison to IBU (-10.598 kcal/mol) and celecoxib (-8.389 kcal/mol) (**Error! Reference source not found.**). Thus, this results also showed an aggregable result for the researchers working in designing of dual acting anti-inflammatory agents (i.e., acting on both COX 2 and 5 LOX).(Charlier and Michaux, 2003; Goossens, Pommery and Pierre Henichart, 2007; Shaaban et al., 2020) -10.598 kcal/mol score of docking, supports the pharmacological activity of Ibuprofen against 5 LOX; resulting in its satisfactory inhibition. Whereas the amino acid residues of the derivatives of Ibuprofen obtained by conjugating the linkers share the similar residues as that of native Ibuprofen (see At last, the inherent side effect of the NSAIDs is being ulcerogenic in nature. This side effect also needs to be kept in scanner of the pharmacological activity investigations. So, for determining this affect also of derivatives of Ibuprofen also needed to be done, because ibuprofen has been reported of being quite active in causing peptic ulcers. Thus, for investigating this property of ibuprofen's linker derived prodrug; they have been docked with hCOX 1 (6Y3C). The docking scores of this docking analysis (see ADMET analysis **of Prodrugs**

ADMET analysis of any novel chemical entity entitled for being a drug for clinical application is extremely essential. Since the absorption, distribution, metabolism, excretion and toxicity are the structure dependent properties, their structure-based Insilco predictions can satisfactorily pave its path of them being practically possible to exist. Thus, to do so here on the basis of the structures their ADMET predictions have been generated by the use of pkCMS an online tool. This tools in total generates data of 6 different categories, namely Molecular properties, absorption, distribution, metabolism, excretion and toxicity predictions. Therapeutic approaches have typically consisted of small molecules that adhere to the Lipinski's rule of five (i.e., a molecule with a molecular mass less than 500 Da, no more than 5 hydrogen bond donors, no more than 10 hydrogen bond

acceptors, and an octanol-water partition coefficient log P not greater than 5) and meet the other criteria as well. (Goodwin et al., 2017)

Table 4) showed that, derivative IB6 (-13.650 kcal/mol), IB1 (-12.750 kcal/mol), IB3 (-12.510 kcal/mol), IB7 (-12.490 kcal/mol), IB4 (-12.390 kcal/mol), and IB2 (-12.010 kcal/mol) were highly ulcerogenic in accordance with Ibuprofen (-11.79 kcal/mol). Whereas IB5 (-11.180 kcal/mol) and celecoxib (-9.660 kcal/mol) were less ulcerogenic then ibuprofen. Thus, these derivatives of ibuprofen could prove to be severely harmful to the patients/consumers if administered orally in their naive form.

Table 3 and Figure 4). This result validates the pharmacology of these derivative too. Since the derivatives are showing greater binding affinity in comparison to Ibuprofen (-10.598 kcal/mol), their activity in terms of pharmacology will be definitely higher than it. The molecules showing increased docking score are IB6 (11.334 kcal/mol), IB3 (-11.185 kcal/mol), IB1 (-11.088 kcal/mol), IB4 (10.969 kcal/mol), IB5 (-10.846 kcal/mol), and IB7 (-10.683 kcal/mol). Only IB2 (-10.045 kcal/mol) and celecoxib (-8.389 kcal/mol) showed lesser score than that of Ibuprofen. The binding affinity data obtained in **Error! Not a valid bookmark self-reference.** and At last, the inherent side effect of the NSAIDs is being ulcerogenic in nature. This side effect also needs to be kept in scanner of the pharmacological activity investigations. So, for determining this affect also of derivatives of Ibuprofen also needed to be done, because ibuprofen has been reported of being quite active in causing peptic ulcers. Thus, for investigating this property of ibuprofen's linker derived prodrug; they have been docked with hCOX 1 (6Y3C). The docking scores of this docking analysis (see ADMET analysis **of Prodrugs**

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Table 3 strongly support and validate that these derivatives of ibuprofen and ibuprofen itself; possesses dual activity ability and can be employed for treatment of inflammation of different types by acting via these mechanisms. This dual acting ability may prove to be very helpful in the field of clinical practices where long-term anti-inflammatory therapy is needed like neuroinflammation, rheumatoid arthritis, Cancer related inflammations, etc.

Table 2
Molecular docking data of Ibuprofen derivatives with hCOX 2 (5f19)

Code	Amino Acid of Binding Site	Docking Score	Hydrogen Bond Details
celecoxib	1078 ALA ALPHA HELIX, 671 ARG COIL, 643 ILE ALPHA HELIX, 663 ILE ALPHA HELIX, 644 LEU COIL, 910 LEU COIL,1082 LEU COIL, 908 PHE COIL, 635 PRO COIL, 670 SER COIL, 904 SER ALPHA HELIX, 651 TRP COIL, 666 TYR ALPHA HELIX, 906 TYR COIL, 640 VAL ALPHA HELIX, 667 VAL ALPHA HELIX,900 VAL ALPHA HELIX	-10.327	13984 O-906TYR 2.61
IB1	929 ALA BETA STRAND, 927 ARG BETA, 926 ASN BETA, 778 GLY COIL, 1084 GLY COIL, 675 ILE COIL, 928 ILE BETA, 903 LEU ALPHA HELIX, 1082 LEU COIL, 1085 LEU COIL, 1083 LYS COIL, 756 PHE ALPHA HELIX, 760 PHE COIL, 761 PHE COIL, 932 PHE ALPHA HELIX, 1080 PHE COIL, 757THR COIL, 899 TYR ALPHA HELIX, 936 TYR COIL, 779 VAL COIL, 895 VAL ALPHA HELIX, 900 VAL APHA HELIX	-12.136	14358 O-927ARG 2.87 14378 O-926ASN 2.89
IB2	120 ARG ALPHA HELIX, 112 ILE COIL, 93 LEU COIL, 359 LEU BETA STRAND, 531 LEU COIL, 113 MET ALPHA HELIX, 357 PHE BETA STRAND, 100 TRP COIL, 115 TYR ALPHA HELIX, 355 TYR COIL, 89 VAL ALPHA HELIX, 116 VAL COIL, 349 VAL ALPHA HELIX	-12.096	1384 N-120ARG 2.73 1381 N-120ARG 2.99
IB3	929 ALA ALPHA HELIX,927 ARG BETA STRAND, 926 ASN BETA, 778GLY COIL, 1084 GLY COIL, 928ILE BETA STRAND, 903 LEU ALPHA HELIX, 1082 LEU COIL, 1085 LEU COIL, 752 PHE ALPHA HELIX, 756 PHE ALPHA, 7610 PHE COIL, 761 PHE COIL, 932 PHE ALPHA HELIX, 1080 PHE COIL, 700 THR COIL, 757 THR COIL, 899 TYR ALPHA, 936 TYR COIL, 779 VAL COIL, 895 VAL ALPHA HELIX, 900 VAL ALPHA HELIX	-13.170	14358 O-927ARG 2.89 14398 N-929ALA 2.30 14348 N-926ASN 2.49
IB4	929 ALA BETA STRAND, 1078 ALA ALPHA HELIX, 927 ARG BETA STRAND, 926 ASN BETA STRAND, 778 GLY COIL, 1077 GLY	-11.427	14348 N-926ASN 2.77

	ALPHA HELIX, 1084 GLY COIL, 896 ILE ALPHA HELIX, 928 ILE BETA STRAND, 1082 LEU COIL, 760 PHE COIL, 932 PHE ALPHA, 1080 PHE COIL, 757 THR COIL, 899 TYR ALPHA HELIX, 936 TYR ALPHA HELIX, 779 VAL COIL, 895 VAL ALPHA, 900 VAL ALPHA		14358 O-927ARG 2.89
IB5	1078 ALA ALPHA, 926 ASN BETA STRAND, 778 GLY COIL, 1077 GLY ALPHA HELIX, 1087 GLY COIL, 777 HIS COIL, 928 ILE BETA STRAND, 1082 LEU COIL, 1085 LEU COIL, 756 PHE ALPHA HELIX, 760 PHE ALPHA, 932 PHE ALPHA, 1080 PHE COIL, 757 THR COIL, 899 TYR ALPHA, 936 TYR COIL, 779 VAL COIL, 895 VAL ALPHA HELIX, 900 VAL ALPHA HELIX	-12.343	14511 O-936TYR 2.42 16834N-1082LEU 2.73
IB6	929 ALA BETA STRAND, 927 ARG BETA STRAND, 926 ASN BETA, 778 GLY COIL, 1084 GLY COIL, 777HIS COIL, 675 ILE COIL, 928 ILE BETA STRAND, 1082 LEU COIL, 1085 LEU COIL, 1083 LYS COIL, 756 PHE ALPHA, 760 PHE COIL, 761 PHE COIL, 932 PHE ALPHA, 1080 PHE COIL, 700 THR BETA STRAND, 757 THR COIL, 899 TYR ALPHA, 936 TYR ALPHA, 779 VAL COIL, 895 VAL ALPHA, 900 VAL ALPHA	-13.745	14358 O-927ARG 2.89 1438 N-926ASN 2.30
IB7	929 ALA BETA STRAND, 927 ARG BETA, 926 ASN BETA, 778 GLY COIL, 1084 GLY COIL, 896 ILE ALPHA HELIX, 928 ILE BETA STRAND, 1085 LEU COIL, 1083 LYS COIL, 752 PHE ALPHA, 756 PHE ALPHA, 760 PHECOIL, 761 PHE COIL, 932 PHE ALPHA HELIX, 1080 PHE COIL, 757 THR COIL, 899 TYR ALPHA, 936 TYR COIL, 779 VAL COIL, 895 VAL ALPHA, 900 VAL ALPHA	-13.219	14348 N-926ASN 2.52
IBU	926 ASN BETA STRAND, 778 GLY COIL, 1084 GLY COIL, 928 ILE BETA STRAND, 1082 LEU COIL, 1085 LEU COIL, 756 PHE COIL, 760 PHE COIL, 761 PHE COIL, 932 PHE ALPHA HELIX, 1080 PHE COIL, 757 THR COIL, 899 TYR COIL, 936 TYR COIL, 779 VAL COIL, 895 VAL ALPHA HELIX, 900 VAL ALPHA HELIX	-12.728	14348 N-926ASN 2.54

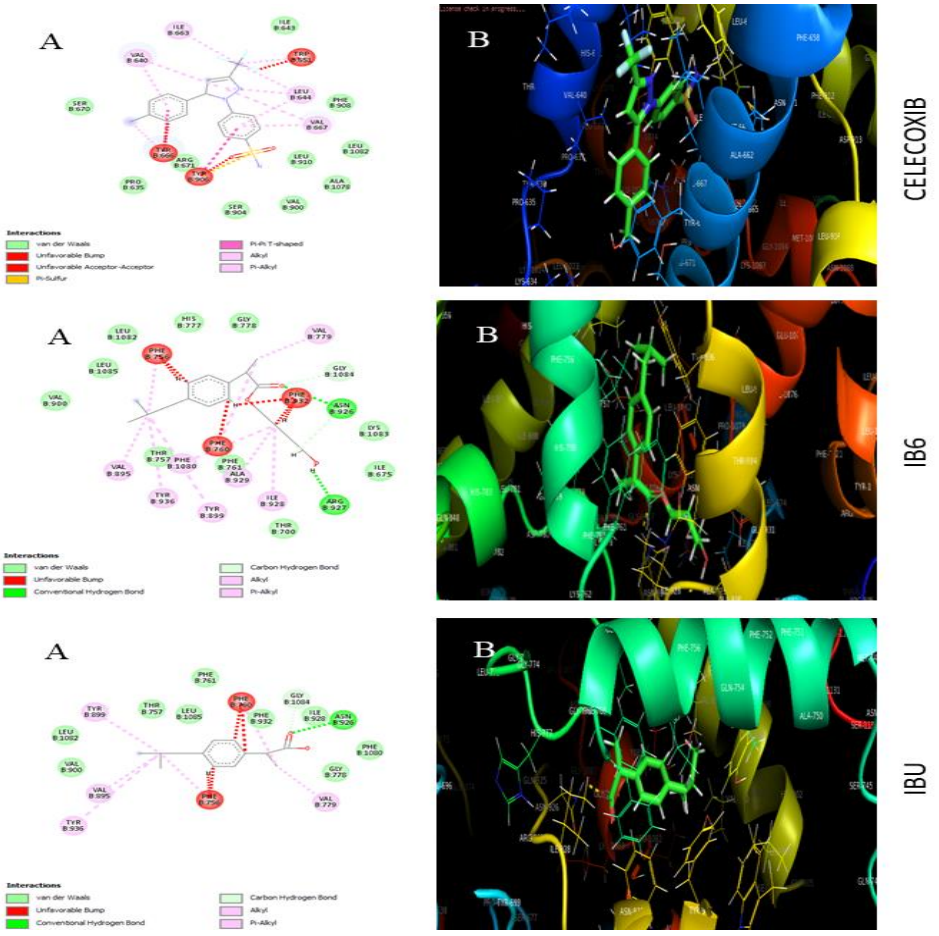

Figure 3.A) 2D pose model. B) 3D pose model, of docked structures of Celecoxib, IB 6, and IBU with hCOX 2 (5F19)

At last, the inherent side effect of the NSAIDs is being ulcerogenic in nature. This side effect also needs to be kept in scanner of the pharmacological activity investigations. So, for determining this affect also of derivatives of Ibuprofen also needed to be done, because ibuprofen has been reported of being quite active in causing peptic ulcers. Thus, for investigating this property of ibuprofen's linker derived prodrug; they have been docked with hCOX 1 (6Y3C). The docking scores of this docking analysis (see ADMET analysis **of Prodrugs**

ADMET analysis of any novel chemical entity entitled for being a drug for clinical application is extremely essential. Since the absorption, distribution, metabolism, excretion and toxicity are the structure dependent properties, their structure-based Insilco predictions can satisfactorily pave its path of them being practically possible to exist. Thus, to do so here on the basis of the structures their ADMET predictions have been generated by the use of pkCMS an online tool. This tools in total generates data of 6 different categories, namely Molecular properties, absorption, distribution, metabolism, excretion and toxicity predictions.

Therapeutic approaches have typically consisted of small molecules that adhere to the Lipinski's rule of five (i.e., a molecule with a molecular mass less than 500 Da, no more than 5 hydrogen bond donors, no more than 10 hydrogen bond acceptors, and an octanol-water partition coefficient log P not greater than 5) and meet the other criteria as well. (Goodwin et al., 2017)

Table 4) showed that, derivative IB6 (-13.650 kcal/mol), IB1 (-12.750 kcal/mol), IB3 (-12.510 kcal/mol), IB7 (-12.490 kcal/mol), IB4 (-12.390 kcal/mol), and IB2 (-12.010 kcal/mol) were highly ulcerogenic in accordance with Ibuprofen (-11.79 kcal/mol). Whereas IB5 (-11.180 kcal/mol) and celecoxib (-9.660 kcal/mol) were less ulcerogenic then ibuprofen. Thus, these derivatives of ibuprofen could prove to be severely harmful to the patients/consumers if administered orally in their naive form.

Table 3
Molecular docking data of Ibuprofen derivatives with 5LOX (3o8y)

CODE	AMINO ACID	Docking Score	Amino acids
celecoxib	411 ARG COIL, 148 ASN COIL, 416 CYS COIL, 413 GLN ALPHA HELIX, 146 GLU BETA STRAND, 412 ALPHA HELIX, 417 GLU COIL, 430 GLY COIL, 432 HIS ALPHA HELIX, 415 ILE COIL, 158 LYS COIL, 145 MET BETA STRAND, 147 TRP COIL, 433 VAL ALPHA HELIX	-8.389	2425 O-147TRP 2.462 7013 N-432HIS 2.714
IB1	203 GLN alpha helix, 207 HIS coil, 388 HIS coil, 444 ILE coil, 295 LEU coil, 408 LEU coil, 391 MET coil, 200 PHE coil, 395 PHE beta strand, 407 PHE coil, 403 SER coil, 404 TYR coil, 447 VAL alpha helix	-11.088	5938 O-364THR 2.899 6795 O-415ILE 2.899 7013 N-432HIS 2.749
IB2	527 ALA alpha helix, 375 ASN beta strand, 227 GLY coil, 526 GLY alpha helix, 533 GLY coil, 226 HIS coil, 377 ILE beta strand, 352 LEU alpha helix, 534 LEU coil, 205 PHE coil, 209 PHE coil, 210 PHE coil, 381 PHE coil, 518 PHE coil, 529 PHE alpha helix, 530 SER alpha helix, 206 THR coil, 387 TRP COIL, 348 TYR alpha helix, 385 TYR coil, 228 VAL coil, 344 VAL alpha helix, 349 VAL alpha helix.	-10.045	9711 N-604VAL 2.622 6944 O-425ASN 2.977
IB3	199 ALA coil, 203 GLN alpha helix, 388 HIS coil, 444 ILE coil, 295 LEU coil, 390 LEU coil, 408 LEU coil, 391 MET coil, 200 PHE coil, 395 PHE beta strand, 407 PHE coil, 399 PRO coil, 387 TRP coil, 404 TYR coil, 447 VAL alpha helix	-11.185	5986 N-367HIS 2.999 5938 O-364THR 2.903 5919 O-363GLN 2.899
IB4	199 ALA coil, 203 GLN alpha helix, 388 HIS	-	5986 N-367HIS

	coil, 444 ILE coil, 295 LEU coil, 408 LEU coil, 391 MET coil, 200 PHE coil, 395 PHE beta strand, 407 PHE coil, 403 SER coil, 404 TYR coil, 447 VAL alpha helix	10.969	2.999 5938 O-364THR 2.460
IB5	120 ARG alpha helix, 90 HIS coil, 93 LEU coil, 112 LEU alpha helix, 115 LEU alpha helix, 357 LEU beta strand, 359 LEU beta strand, 113 MET alpha helix, 89 THR coil, 355 TYR coil, 116 VAL alpha helix, 119 VAL alpha helix	-10.846	7561 N-467TYR 2.956 5215 N-320ILE 2.90 7547 N-466PRO 2.999
IB6	199 ALA coil, 202 ALA alpha helix, 203 GLN alpha helix, 386 HIS coil, 388 HIS coil, 444 ILE coil, 295 LEU coil, 390 LEU coil, 408 LEU coil, 391 MET coil, 200 PHE coil, 395 PHE beta strand	-11.334	5938 O-364THR 2.898 5986 N-367HIS 2.777
IB7	424 ALA COIL, 603 ALA alpha helix, 425 ASN COIL, 363 GLN alpha helix, 386 HIS alpha helix, 432 HIS alpha helix, 600 HIS alpha helix, 415 ILE COIL, 673 ILE, 368 LEU alpha helix, 414 LEU alpha helix, 420 LEU COIL, 607 LEU COIL, 423 LYS COIL, 177 PHE alpha helix, 421 PHE COIL, 364 THR alpha helix, 599 TRP alpha helix, 181 TYR alpha helix	-10.683	5986 N-367HIS 2.998
IBU	410 ALA alpha helix, 603 ALA alpha helix, 411 ARG COIL, 407 ASN alpha helix, 425 ASN COIL, 363 GLN alpha helix, 372 HIS alpha helix, 415 ILE COIL, 368 LEU alpha helix, 414 LEU alpha helix, 607 LEU COIL, 177 PHE alpha helix, 421 PHE COIL, 181 TYR ALPHA HELIX	-10.598	6079 N-372HIS 2.693

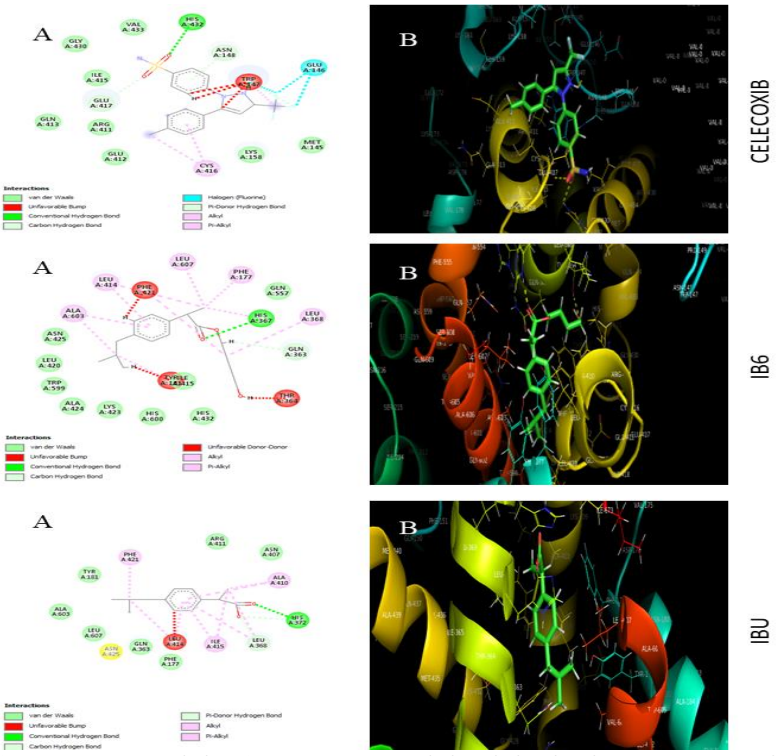

Figure 4.A) 2D pose model. B) 3D pose model, of docked structures of Celecoxib, IB6, and IBU with h5 LOX (3O8Y).

ADMET analysis of Prodrugs

ADMET analysis of any novel chemical entity entitled for being a drug for clinical application is extremely essential. Since the absorption, distribution, metabolism, excretion and toxicity are the structure dependent properties, their structure-based Insilco predictions can satisfactorily pave its path of them being practically possible to exist. Thus, to do so here on the basis of the structures their ADMET predictions have been generated by the use of pkCMS an online tool. This tools in total generates data of 6 different categories, namely Molecular properties, absorption, distribution, metabolism, excretion and toxicity predictions. Therapeutic approaches have typically consisted of small molecules that adhere to the Lipinski's rule of five (i.e., a molecule with a molecular mass less than 500 Da, no more than 5 hydrogen bond donors, no more than 10 hydrogen bond acceptors, and an octanol-water partition coefficient log P not greater than 5) and meet the other criteria as well. (Goodwin et al., 2017)

Table 4
Molecular docking data of Ibuprofen derivatives with hCOX 1 (6y3c)

CODE	AMINO ACID	Docking Score	Hydrogen bonds
celecoxib	405 GLU COIL, 442 HIS COIL, 443 HIS COIL, 446 HIS COIL, 444 ILE COIL, 295 LEU COIL, 408 LEU COIL,	-9.66	6692N-443HIS 2.76

	391 MET COIL, 395 PHE BETA STRATED, 407 PHE COIL, 392 PRO COIL, 404 TYR COIL, 447 VAL ALPHA HELIX		
IB1	203 GLN ALPHA, 207 HIS COIL, 388 HIS COIL, 444 ILE COIL, 295 LEU COIL, 408 LEU COIL, 391 MET COIL, 200 PHE COIL, 395 PHE BETA STRATED, 407 PHE COIL, 403 SER COIL, 404 TYR COIL, 447 VAL ALPHA	-12.75	2820N-203GLU 2.33
IB2	527 ALA ALPHA HELIX, 375 ASN BETA STRANED, 227 GLY COIL, 526 GLY ALPHA, 533 GLY COIL, 226 HIS COIL, 377 ILE BETA STRAND, 352 LEUALPHA, 534 LEU COIL, 205 PHE COIL, 209 PHE COIL, 210 PHE COIL, 381 PHE COIL, 518 PHE COIL, 529 PHE COIL, 530 SER ALPHA, 206 THR COIL, 387 TRP COIL, 348 TYR ALPHA, 385 TYR COIL, 228 VAL COIL, 344 VAL ALPHA HELIX, 349 VAL ALPHA	-12.01	8092O-530SER 2.52 5791O-385TYR 2.89
IB3	199 ALA COIL, 203 GLN ALPHA, 388 HIS COIL, 444 ILE COIL, 295 LEU COIL, 390 LEU COIL, 408 LEU COIL, 391 MET COIL, 200 PHE COIL, 395 PHE BETA STRAND, 407 PHE COIL, 389 PRO COIL, 387 TRP COIL, 404 TYR COIL, 447 VAL ALPHA HELIX	-12.51	5848N-388HIS 2.86 5821O-387TRP 2.36
IB4	199 ALA COIL, 203 GLN ALPHA, 388 HIS COIL, 444 ILE COIL, 295 LEU COIL, 408 LEU COIL, 391 MET COIL, 200 PHE COIL, 395 PHE BETA STRAND, 407 PHE COIL, 403 SER COIL, 404 TYR COIL, 447 VAL ALPHA	-12.39	5848N-388HIS- 2.60 2820N-203GLN- 2.68
IB5	120 ARG ALPHA, 90 HIS COIL, 93 LEU COIL, 112 LEU ALPHA, 115 LEU ALPHA, 357 LEU BETA STRAND, 359 LEU COIL, 113 MET ALPHA, 89 THR COIL, 355 TYR COIL, 116 VAL ALPHA, 119 VAL ALPHA	-11.18	1480N-120ARG- 2.99 1477N-120ARG 2.23 1477N-120ARG 2.98
IB6	199 ALA COIL, 202 ALA ALPHA HELIX, 203 GLN ALPHA, 386 HIS COIL, 388 HIS COIL, 44 ILE COIL, 295 LEU COIL, 390 LEU COIL, 408 LEU COIL, 391 MET COIL, 200 PHE COIL, 395 PHE BETA STRAND, 407 PHE COIL, 387 TRP COIL, 387 TYR COIL, 404 TYR COIL, 447 VAL ALPHA	-13.65	2820N-203GLN 2.46 5848N-388HIS 2.77 5783O-385TYR 2.87 5818N-387TRP 2.99
IB7	527 ALA ALPHA HELIX, 375 ASN	-12.49	8092O-530SER

	BETA STRAND, 227 GLY COIL, 526 GLY ALPHA, 533 GLY COIL, 226 HIS COIL, 377 ILE BETA STRAND, 352 LEU ALPHA, 534 LEU COIL, 201 PHE ALPHA, 205 PHE COIL, 209 PHE COIL, 210 PHE COIL, 38 PHE COIL, 518 PHE COIL, 529 PHE COIL, 550 PHE ALPHA, 530 SER ALPHA, 206 THR COIL, 387 TRP COIL, 348 TYR ALPHA, 228 VAL COIL, 344 VAL ALPHA, 349 VAL ALPHA		2.89 5791O-385TYR 2.49
IBU	375 ASN BETA STRAND, 227 GLY COIL, 533 GLY COIL, 377 ILE BETA STRAND, 352 LEU ALPHA, 534 LEU COIL, 201 PHE ALPHA, 205 PHE COIL, 209 PHE COIL, 381 PHE COIL, 529 PHE ALPHA, 530 SER ALPHA, 206 THR COIL, 387 TRP COIL, 385 TYRCOIL, 228 VAL COIL, 344 VAL ALPHA, 349 VAL ALPHA	-11.79	5618N-375ASN 2.81

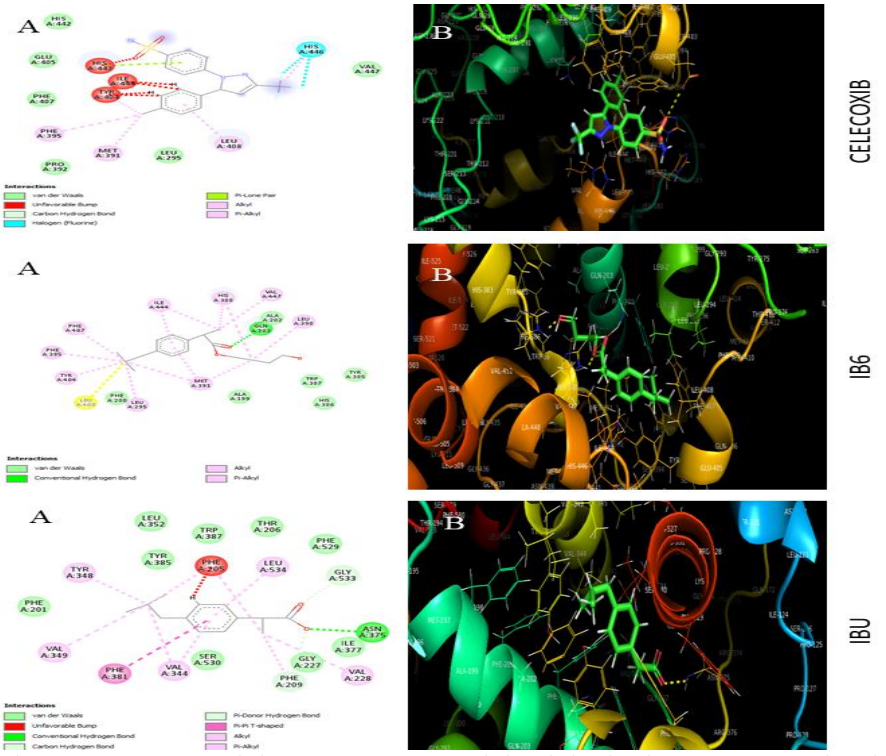

Figure 5. A) 2D pose model. B) 3D pose model, of docked structures of Celecoxib, IB6, and IBU with hCOX 1 (6Y3C)

So, from the molecular properties data in **Error! Not a valid bookmark self-reference.** we can state that all the molecules are in accordance with the

lipinski's rule. The molecules having LogP in the range of aqueous solubility whereas the ones which are above that are poorly soluble in water. Thus, we can say from the LogP data that IB1, IB2, IB4 and IB5 are aqueous soluble whereas IB3, IB6 and IB7 are in order of decreasing aqueous solubility. Molecular weight, number of acceptors and donors of all the molecules i.e standard and derived ones, are within the limit of Lipinski's rule. The surface area parameter also governs the molecular fit into the pocket of receptors binding site; in comparison with the celecoxib's surface area (taking it as the largest size of molecule that can fit in the respective pocket of target receptor) rest all molecules have their surface area within the range. Therefore, all the derived molecules can easily fit into the target's binding site pocket. Thus, on the basis of above discussion, we can say that IB1, IB2, IB4 and IB5 can be administered orally (similar like ibuprofen and celecoxib); whereas in case of IB3, IB6 and IB7, suitable delivery system development/selection will be needed.

Table 5
Molecular properties of selected derivatives as per pkCMS

Sr. No.	Name of Compound	Molecules Properties					
		Mol. Wt.	LogP	Rotable Bonds	Acceptors	Donors	Surface Area
1	celecoxib	381.379	3.51392	3	4	1	147.48
2	IB 1	249.354	2.0971	6	2	2	109.222
3	IB 2	249.354	2.4905	6	3	1	109.331
4	IB3	266.406	3.2407	6	3	1	133.795
5	IB4	250	2.5241	6	3	1	108.785
6	IB5	263.337	2.1894	6	2	2	113.383
7	IB6	278.392	3.3043	8	3	1	121.515
8	IB7	266.406	3.4616	6	3	1	115.146
9	IB U	206.285	3.0732	4	1	1	90.942

The data in The distribution prediction data in Table 7, VDss value of IB5 and IBU is less than -0.15 it has low tissue distribution and IB2, IB3, IB5 and IB7 has values higher than 0.45 they have higher tissue distribution. Thus, molecule celecoxib, IB1, IB4, and IB6 are the most suitable ones for showing better bioavailability. Taking celecoxib and IBU as reference point for fraction unbound parameter, IB6 reported very less value. This suggests it being in more bound state and making it less available for cellular absorption. Thereby making it an entity, requiring novel delivery system's aid for enhancing its absorption. Since IB7 has value more than 0.3 in BBB permeability parameter it can readily cross

it, whereas others are not suitable for such permeation. IB6 is the first one, the next 3 members following it are IB4, IB3 and IB7 high permeation ability through CNS by having values greater than -2. Celecoxib, IB1, IB2 and IB5 the ones lacking such ability due to values less than -3.

By the metabolism predictions (as per data in All the molecules except celecoxib will not be excreted through kidneys on the basis of data in Table 8. Total clearance value of IB6 (1.485 log ml/min/kg) is very high thus making it the only individual having higher bioavailability due to its slower total clearance rate.

Table 9
Metabolism prediction of the derived molecules using pkCMS

Name of Compound	Model Name								
	AMES toxicity (Yes/No)	Max. tolerated dose (human) (log mg/kg/day)	hERG I inhibitor (Yes/No)	hERG II inhibitor (Yes/No)	Oral Rat Acute Toxicity (LD50) (mol/kg)	Oral Rat Chronic Toxicity (LOAEL) (log mg/kg_bw/day)	Hepatotoxicity (Yes/No)	Skin Sensitisation (Yes/No)	T. Pyrifo is toxici (log µg/L)
celecoxib	NO	0.163	NO	NO	2.29	1.197	YES	NO	0.429
IB1	NO	0.676	NO	NO	2.284	2.002	NO	YES	1.427
IB2	NO	0.38	NO	NO	2.396	2.08	NO	YES	1.181
IB3	NO	0.813	NO	NO	2.44	2.094	NO	YES	2.416
IB4	NO	0.937	NO	NO	2.235	2.111	NO	NO	1.862
IB5	NO	0.036	NO	NO	2.324	1.922	YES	NO	0.836
IB6	NO	0.976	NO	NO	2.165	2.341	NO	YES	2.303
IB7	NO	0.719	NO	NO	2.493	2.137	NO	YES	2.549
IBU	NO	0.727	NO	NO	2.324	2.51	NO	YES	0.303

) it has been found that except ibuprofen all other molecules will have problem in their metabolism due to their action on various test models. Though, IB4 and IB5 seems to get metabolised because they are hindering only one factor. To follow them will be IB6, IB2 and IB1 with effect on 2 parameters; rest all will face metabolism related issues. All the compounds are non-mutagenic as per the AMES toxicity data in Table 9. On the basis of same table, all the test molecules and standards are non-cardiotoxic by virtue of non-inhibition of hERG I & II channels. Max tolerated dose of IB5 being very less (0.036 log mg/kg/day) strikes out the possibility of it to come in pharmaceutical and clinical use. Whereas, IB6 and IB4 have the highest dose in same category. The dose required for causing acute and chronic oral toxicity for IB6 is best among all others (due to highest chronic toxicity dose and second position in acute toxicity dose). Thus, making it the most suitable entity to be promoted for pharmaceutical and clinical applications. The other one's following it are IB7, IB3 and IB2.

Table 6 states about the features, determining the absorption predictions of the designed derivatives of ibuprofen from conjugation of linkers. Here again the water solubility parameter has been listed, which follows the same trend as discussed above. The Caco2 permeability defines the permeation ability of the test molecule into the intestinal epithelial cells, which is found to be very low of all the derived molecules. Intestinal absorption of Ibuprofen was higher in comparison to other derived molecules and celecoxib. In terms of skin permeabilityIB1, IB5 and

IB6 are suitable for developing transdermal delivery. All the molecules under p-glycoprotein I & II inhibition analysis showed non-responsiveness. The distribution prediction data in Table 7, VDss value of IB5 and IBU is less than -0.15 it has low tissue distribution and IB2, IB3, IB5 and IB7 has values higher than 0.45 they have higher tissue distribution. Thus, molecule celecoxib, IB1, IB4, and IB6 are the most suitable ones for showing better bioavailability. Taking celecoxib and IBU as reference point for fraction unbound parameter, IB6 reported very less value. This suggests it being in more bound state and making it less available for cellular absorption. Thereby making it an entity, requiring novel delivery system's aid for enhancing its absorption. Since IB7 has value more than 0.3 in BBB permeability parameter it can readily cross it, whereas others are not suitable for such permeation. IB6 is the first one, the next 3 members following it are IB4, IB3 and IB7 high permeation ability through CNS by having values greater than -2. Celecoxib, IB1, IB2 and IB5 the ones lacking such ability due to values less than -3.

By the metabolism predictions (as per data in All the molecules except celecoxib will not be excreted through kidneys on the basis of data in Table 8. Total clearance value of IB6 (1.485 log ml/min/kg) is very high thus making it the only individual having higher bioavailability due to its slower total clearance rate.

Table 9

Metabolism prediction of the derived molecules using pkCMS

Name of Compound	Model Name								
	AMES toxicity (Yes/No)	Max. tolerated dose (human) (log mg/kg/day)	hERG I inhibitor (Yes/No)	hERG II inhibitor (Yes/No)	Oral Rat Acute Toxicity (LD50) (mol/kg)	Oral Rat Chronic Toxicity (LOAEL) (log mg/kg_bw/day)	Hepatotoxicity (Yes/No)	Skin Sensitisation (Yes/No)	T. Pyrifo is toxici (log µg/L)
celecoxib	NO	0.163	NO	NO	2.29	1.197	YES	NO	0.429
IB1	NO	0.676	NO	NO	2.284	2.002	NO	YES	1.427
IB2	NO	0.38	NO	NO	2.396	2.08	NO	YES	1.181
IB3	NO	0.813	NO	NO	2.44	2.094	NO	YES	2.416
IB4	NO	0.937	NO	NO	2.235	2.111	NO	NO	1.862
IB5	NO	0.036	NO	NO	2.324	1.922	YES	NO	0.836
IB6	NO	0.976	NO	NO	2.165	2.341	NO	YES	2.303
IB7	NO	0.719	NO	NO	2.493	2.137	NO	YES	2.549
IBU	NO	0.727	NO	NO	2.324	2.51	NO	YES	0.303

) it has been found that except ibuprofen all other molecules will have problem in their metabolism due to their action on various test models. Though, IB4 and IB5 seems to get metabolised because they are hindering only one factor. To follow them will be IB6, IB2 and IB1 with effect on 2 parameters; rest all will face metabolism related issues. All the compounds are non-mutagenic as per the AMES toxicity data in Table 9. On the basis of same table, all the test molecules and standards are non-cardiotoxic by virtue of non-inhibition of hERG I & II channels. Max tolerated dose of IB5 being very less (0.036 log mg/kg/day) strikes out the possibility of it to come in pharmaceutical and clinical use. Whereas, IB6 and IB4 have the highest dose in same category. The dose required for causing acute and chronic oral toxicity for IB6 is best among all others (due to highest

chronic toxicity dose and second position in acute toxicity dose). Thus, making it the most suitable entity to be promoted for pharmaceutical and clinical applications. The other one's following it are IB7, IB3 and IB2.

Table 6
Absorption prediction of the derived molecules using pkCMS

Name of Compound	Model Name						
	Water Solubility (log mol/L)	Caco2 permeability (Log Papp in 10^{-6} cm/s)	Intestinal absorption (human) % absorbed	Skin Permeability (Log Kp)	P-glycoprotein substrate (Yes/No)	P-glycoprotein I Inhibitor (Yes/No)	P-glycoprotein II Inhibitor (Yes/No)
celecoxib	-3.61	1.067	93.126	-2.755	YES	NO	YES
IB1	-3.136	1.262	93.784	-2.671	YES	NO	NO
IB2	-2.81	1.314	94.295	-2.315	YES	NO	NO
IB3	-4.025	1.652	93.761	-2.12	NO	NO	NO
IB4	-3.214	1.322	94.127	-2.479	NO	NO	NO
IB5	-2.758	0.837	92.936	-2.666	YES	NO	NO
IB6	-4.151	1.461	93.97	-2.508	NO	NO	NO
IB7	-4.366	1.423	93.093	-2.232	YES	NO	NO
IBU	-3.578	1.477	95.679	-2.159	NO	NO	NO

Table 7
Distribution prediction of the derived molecules using pkCMS.

Name of Compound	Model Name						
	CYP2D6 substrate (Yes/No)	CYP3A4 substrate (Yes/No)	CYP1A2 inhibitor (Yes/No)	CYP2C19 inhibitor (Yes/No)	CYP2C9 inhibitor (Yes/No)	CYP2D6 inhibitor (Yes/No)	CYP3A4 inhibitor (Yes/No)
celecoxib	NO	YES	YES	YES	YES	NO	NO
IB1	NO	YES	YES	NO	NO	NO	NO
IB2	NO	YES	YES	NO	NO	YES	NO
IB3	NO	YES	YES	YES	NO	NO	NO
IB4	NO	NO	YES	NO	NO	NO	NO
IB5	NO	YES	NO	NO	NO	NO	NO
IB6	NO	YES	NO	YES	NO	NO	NO
IB7	NO	YES	YES	YES	NO	NO	NO
IBU	NO	NO	NO	NO	NO	NO	NO

All the molecules except celecoxib will not be excreted through kidneys on the basis of data in Table 8. Total clearance value of IB6 (1.485 log ml/min/kg) is very high thus making it the only individual having higher bioavailability due to its slower total clearance rate.

Table 9
Metabolism prediction of the derived molecules using pkCMS

Name of Compound	Model Name								
	AMES toxicity (Yes/No)	Max. tolerated dose (human) (log mg/kg/day)	hERG I inhibitor (Yes/No)	hERG II inhibitor (Yes/No)	Oral Rat Acute Toxicity (LD50) (mol/kg)	Oral Rat Chronic Toxicity (LOAEL) (log mg/kg_bw/day)	Hepatotoxicity (Yes/No)	Skin Sensitisation (Yes/No)	T. Pyrifo is toxici (log µg/L)
celecoxib	NO	0.163	NO	NO	2.29	1.197	YES	NO	0.429
IB1	NO	0.676	NO	NO	2.284	2.002	NO	YES	1.427
IB2	NO	0.38	NO	NO	2.396	2.08	NO	YES	1.181
IB3	NO	0.813	NO	NO	2.44	2.094	NO	YES	2.416
IB4	NO	0.937	NO	NO	2.235	2.111	NO	NO	1.862
IB5	NO	0.036	NO	NO	2.324	1.922	YES	NO	0.836
IB6	NO	0.976	NO	NO	2.165	2.341	NO	YES	2.303
IB7	NO	0.719	NO	NO	2.493	2.137	NO	YES	2.549
IBU	NO	0.727	NO	NO	2.324	2.51	NO	YES	0.303

Table 8
Excretion prediction of the derived molecules using pkCMS

Name of Compound	Model Name	
	Total Clearance (log ml/min/kg)	Renal OCT2 Substra (Yes/No)
celecoxib	0.471	YES
IB1	0.378	NO
IB2	0.847	NO
IB3	0.357	NO
IB4	0.368	NO
IB5	0.309	NO
IB6	1.485	NO
IB7	0.166	NO
IBU	0.294	NO

Table 9
Toxicity prediction of the derived molecules using pkCMS

Conclusion

Name of Compound	Model Name			
	VDss (human) (logL/kg)	Fraction unbound (human) (Fu)	BBB permeability (log BB)	CNS permeability (log PS)
celecoxib	0.095	0.125	-0.952	-2.086
IB1	0.395	0.202	0.094	-2.522
IB2	0.96	0.259	-0.209	-2.414
IB3	0.569	0.103	0.163	-1.642
IB4	0.335	0.176	0.162	-1.781
IB5	-0.533	0.164	-0.305	-2.648
IB6	0.38	0.084	-0.259	-1.792
IB7	0.479	0.102	0.532	-1.618
IBU	-0.825	0.148	0.282	-1.519

The molecular docking has defined the pharmacodynamics of the test molecules (i.e., linker derived analogues of Ibuprofen viz. IB1-IB7) on the basis of Docking score, hydrogen bonds and Similar amino acid residues. On the basis of which the molecule IB6 was found to be best results in all parameters selected. Along with that, it has dual action ability on similar basis of results for COX 2 and 5 LOX receptor. But its high affinity for COX 1 is a problem of concern, which is making it highly ulcerogenic. The ADMET data obtained through pkCSM also suggested that IB6 has high permeability, low aqueous solubility, moderate tissue distribution, high CNS permeation, high bioavailability, higher T half-life than IBU, low chronic and acute toxicity. Thus, making it most suitable molecule for the treatment of inflammation caused by various condition except its application in brain due to lack of BBB permeability.

It is suitable for use in treatment of neuroinflammations also. Since it has high permeability, low aqueous solubility and moderate tissue distribution features; it becomes most suitable entity to be delivered via polymer drug conjugation using polyethylene glycol (PEG) as polymer of choice. Hence, the conjugation with PEG (PEGylation) of IB6 will be best delivery system. Because it will help in overcoming its drawbacks, thereby making it best molecule for the treatment of inflammatory disease of various types (namely: osteo & rheumatoid arthritis, neuro and other tissue inflammations). This work will promote the researchers to think and explore in similar direction. This will lead us to using previously available drugs in more efficient manner only by choosing suitable linker while design PDC's through PEGylation.

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