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Molecular docking of Ibuprofen and its derivatives with novel cancer targets: Implication of anticancer therapy for novel targets

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Research

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ABSTRACT

Epidemiological and clinical studies suggest that the nonsteroidal anti-inflammatory drug (NSAID)-Ibuprofen's anti-carcinogenic property is attributable due to its capacity to inhibit the cyclooxygenase (COX) enzyme (both the isoforms-COX1 and COX-2), inhibit proliferation and induce apoptotic cell death. However, the precise molecular mechanism for the anti-cancer activity of Ibuprofen is still not fully understood. As the COX-dependent mechanisms were already established now the COX-independent mechanisms are targeted along with newly synthesized Ibuprofen derivatives to develop safer and more efficacious drugs for cancer chemoprevention. Here, the interactions of Ibuprofen and its derivatives (Carboxy-Ibuprofen, Hydroxy-Ibuprofen and Methyl ester Ibuprofen) with LDH-A, Survivin, Glucocorticoid Receptor and Androgen receptor were analysed by PatchDock and YASARA (Yet Another Scientific Artificial Reality Application).The docking ability of the drug with the targets were based on the analysis of dissociation constant (Kd), geometric shape complementary score (GSC score), approximate interference area (AI area) and binding energy along with analysis of drug likeness parameters of Ibuprofen and its derivatives. The outcome of this study sheds light on the efficacy drug derivatives and identifying novel target molecule for cancer chemoprevention which can be further used for in vivo studies.

Keywords: Ibuprofen, NSAIDs, *In-silico*, Drug derivatives, Molecular docking, Drug likeness, Molecular targets, Cancer therapeutics;

1. INTRODUCTION

Ibuprofen is the nonsteroidal anti-inflammatory drug (NSAID) class that is used for treating pain, fever and inflammation. Prior epidemiological and clinical studies have suggested effectiveness of long-term and regular use of Ibuprofen in treatment and risk reduction for 7-10 malignancies along with the four major types of cancer: colon, breast, lung, and prostate (Harris et al.,2005;Thun et al.,2002;Janssen et al.,2006;Bittoni et al.,2017).The anti-carcinogenic property is attributable due to its capacity to inhibit the cyclooxygenase (COX) enzyme (both the isoforms-COX1 and COX-2), inhibit proliferation and induce apoptotic cell death (Giardiello et al.,1995; Thun et al.,2002; Leidgens et al.,2015). However, the chemopreventive efficacy may also be exerted due to their COX-independent mechanism of action where they act on the non COX targets, showing different cellular effects (Gurpinar et al., 2013). Novel Ibuprofen derivatives can be synthesized by different modifications of Ibuprofen that would have better/similar significant effect and lesser side effects than the parent Ibuprofen in their chemopreventive efficacy (Ouyang et al., 2013). In silico molecular docking with physicochemical properties and drug likeness parameters can be used for computer-aided drug designing and the newly synthesized Ibuprofen derivatives. These can be used in model in vivo studies, for identifying and characterizing alternate therapeutic (molecular) targets and elucidation of additional biochemical process leading to the development of safer and more efficacious drugs for cancer chemoprevention, also saving valuable time, money and resources.

The COX-dependent mechanism is well established so now in this study, COX- independent mechanisms are being targeted along with newly synthesized Ibuprofen derivatives to develop safer and more efficacious drugs for cancer chemo-prevention. Here, Ibuprofen(IBP) (2-(4-Isobutylphenyl) propanoic acid) and its derivatives - Carboxy-IBP, Hydroxy-IBP(2-Hydroxy-Ibuprofen) and IBP methyl ester are considered for its chemopreventive effect on the COX- independent targets-LDH-A, Survivin, Glucocorticoid Receptor (GR) and Androgen Receptor (AR). As metabolites of IBP, Carboxy-IBP is dicarboxylic acid, i.e. IBP in which one of the methyl groups in the isobutyl portion has been converted to the corresponding carboxylic acid, 2-Hydroxyibuprofen is a hydroxy monocarboxylic acid, i.e. IBP in which the methine proton on the isobutyl group has been replaced by a hydroxy group and Methyl 2-(4-isobutylphenyl) i.e. IBP methyl ester propanoate is the methyl ester of IBP.

Lactate dehydrogenase A (LDH-A) executes the final step of aerobic glycolysis that has been reported to be involved in the tumor progression. Studies show abnormal expression of LDHA has been observed in many human cancers, such as pancreatic cancer (Shi et al., 2014), hepatocellular carcinoma (Sheng et al., 2012), breast cancer (Zhao et al., 2009) and prostate cancer (Xian et al., 2015). Inhibition of LDHA reduced cell malignant transformation and remarkably delayed tumor formation, indicating that the underlying role of LDH-A in tumor initiation or maintenance, thus revealing the oncogenic role of LDHA in prostate cancer which also suggest that LDHA might be a potential therapeutic target in anticancer therapy (Di Stefano et al., 2016).

Survivin is a member of the inhibitor of apoptosis protein (IAP) that blocks apoptotic pathways by inhibition of caspase and pro-caspase molecules (Ambrosini et al.,1997; Tamm et al., 1998) .It is a tumor antigen and overexpressed in human cancers, giving rise to peptides eliciting spontaneous CD8+ and CD4+ responses. Survivin has the dual function of blockade of apoptosis and regulation of cell division (Friedrichs et al., 2006; Dohi et al., 2004; Margulis et al., 2007). IBP treat shows a gradual decrease in expression of surviving in a time-dependent manner, thus due to its direct association with tumor survival, it is regarded as an ideal target structure for anti-cancer therapy (Greenspan et al., 2011).

Various studies show that Glucocorticoid Receptor (GR) functional activity appears to be highly context-dependent (Conzen S. D., 2017). GR is a predominately cytoplasmic protein whose ligand-binding conformation is maintained by its chaperoning partners in a large multi- protein complex. It is able to shuttle between the nucleus and the cytoplasm and can help or inhibit the expression of specific genes via different mechanisms-transactivation, which promotes the transcription of glucocorticoid responsive element (GRE)-driven genes (e.g. GILZ), and trans repression, via which GR inhibits the expression of genes mediated by transcription factors such as NF-κB and AP-1(Hache et al.,1999; Vandevyver et al.,2012; Sundahl et al.,2016; Ratmanet al.,2013; Clarisseet al.,2018).With detailed knowledge of GR signaling it has been a target for prostate, breast

and various other cancers for therapy (Bakker et al.,2017; Kachet al.,2015).

Androgen receptor (AR) is a steroid receptor transcriptional factor for testosterone and dihydro-testosterone, which consists of four main domains, the N-terminal domain, DNA-binding domain, hinge region, and ligand -binding domain (Fujita et al., 2019). AR plays pivotal roles in prostate cancer and prostate cancer therapy. The inhibition of AR activity through mechanisms in addition to androgen ablation, such as modulation of signal transduction pathways, may delay prostate cancer progression thus making it a potent target for therapy (Miyamoto et al., 2008; Huret al., 2004).

2. MATERIALS AND METHODS

Based on proper review literature the 3D structures of the target receptors and ligands were retrieved from Protein Data Bank (https://www.rcsb.org/) and PubChem (https://pubchem.ncbi.nlm.nih.gov/) databases, respectively. The 3D structure of the target proteins was validated thorough BLAST (https://blast.ncbi.nlm.nih.gov/Blast.cgi) , RAMPAGE (http://mordred.bioc.cam.ac.uk/~rapper/rampage.php), ResProx (http://www.resprox.ca/) , ERRAT (https://servicesn.mbi.ucla.edu/ERRAT/) and PDBSum (http://www.ebi.ac.uk/thornton-srv/databases/cgi-bin/pdbsum/) server and VADAR 1.8 (http://vadar.wishartlab.com/). The Active binding sites were identified by MetaPocket (https://projects.biotec.tu-dresden.de/metapocket/) server. Docking was performed by PatchDock (https://bioinfo3d.cs.tau.ac.il/PatchDock/php.php) server and YASARA (http://www.yasara.org/macros.htm) tool, whereas docking complexes were visualized and edited by Discovery Studio 3.5 (http://accelrys.com/products/collaborative-science/biovia- discovery- studio/visualization- download.php) . The druglikeness was analyzed through Lipinski (http://www.scfbio-iitd.res.in/software/drugdesign/lipinski.jsp) filter, SwissADME (http://www.swissadme.ch/), admetSAR (http://lmmd.ecust.edu.cn/admetsar1/predict/) and FAF-Drugs4 (http://fafdrugs4.mti.univ-paris-diderot.fr/) .The methodology is depicted in a flow chart in *Fig 1*.

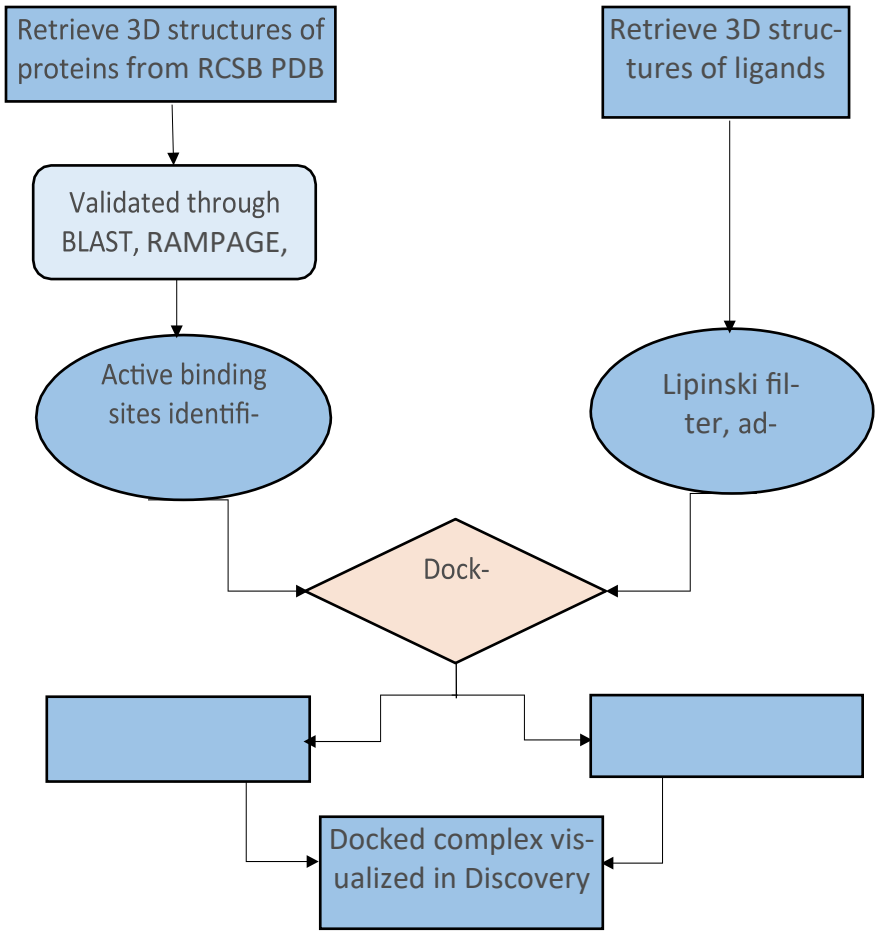


Fig 1. Flow chart depicting schematic methodology of in silico analysis.

2.1.Retrieval of target receptor structures

Protein Data Bank (https://www.rcsb.org/) was used for retrieving the structure of target receptors LDH-A (PDB:4ZVV, DOI:10.2210/pdb4ZVV/pdb), Survivin (PDB:3UEC, DOI: 10.2210/pdb3UEC/pdb), Glucocorticoid Receptor (GR) (PDB:4UDD, DOI:10.2210/pdb4UDD/pdb) and Androgen Receptor (AR) (PDB:3L3X, DOI:10.2210/pdb3L3X/pdb) in cancer in *Homo sapiens*, which are recognized as targets of Ibuprofen and its derivatives- Carboxy-Ibuprofen, Hydroxy - Ibuprofen and Ibuprofen methyl ester. The criteria for selection of the structures were based on PDB advance BLAST, RAMPAGE, ResProx, ERRAT and PDBsum analysis. The structures used in this study were those displaying the maximum score and query cover in BLAST as the first criteria of selection.

2.2. Retrieval of ligand structures

The structures of Ibuprofen (CID: 3672, https://pubchem.ncbi.nlm.nih.gov/compound/3672) and its derivatives-Carboxy-Ibuprofen (CID: 10444113, https://pubchem.ncbi.nlm.nih.gov/compound/10444113), 2-Hydroxy-Ibuprofen (Hydroxy-IBP) (CID: 10443535,https://pubchem.ncbi.nlm.nih.gov/compound/10443535) and Ibuprofen methyl ester (CID: 109101,https://pubchem.ncbi.nlm.nih.gov/compound/109101) were retrieved from the PubChem (https://pubchem.ncbi.nlm.nih.gov/) database. These structures were further used for docking calculation. The selected 3D structure of the ligands was retrieved from PubChem Compound database in SDF format followed by conversion in the PDB format and optimization using Discovery Studio 3.5 visualizer.

2.3.Active binding site prediction

Prior to the docking analysis, the active binding site prediction of LDH- A (PDB:4ZVV), Survivin (PDB:3UEC), Glucocorticoid Receptor (GR) (PDB:4UDD) and Androgen Receptor (PDB:3L3X) were carried out by MetaPocket 2.0 (https://projects.biotec.tu-dresden.de/metapocket/) server, retrieving top 3 major binding pockets for analysis of active binding residues and comparison of the docking results.

2.4.Docking analysis

PatchDock (https://bioinfo3d.cs.tau.ac.il/PatchDock/php.php) server, a geometry based molecular docking algorithm, was used for docking analysis of IBP and its derivatives to target receptors. The PDB files of the ligand and receptors were uploaded to PatchDock server for docking analysis, keeping the cluster RMSD at default value of 4.0 and protein- small ligand complex type as the analysis parameters. Analysis on PatchDock server yielded results for the geometric shape complementarity score (GSC score) and approximate interface area (AI area). Additional docking tool YASARA (http://www.yasara.org/macros.htm) (Yet Another Scientific Artificial Reality Application), an AutoDock based tool for molecular docking and virtual screening was used for analyzing dissociation constant (Kd) and binding energy of the docked complexes. The more binding energy of a ligand during a molecular dynamic simulation indicates a better binding (Yadav et al., 2017).

2.5.Analysis of drug likeness of IBP, Carboxy-IBP, Hydroxy-IBP and IBP methyl ester

The drug likeness prediction of IBP, Carboxy-IBP, Hydroxy-IBP and IBP methyl ester was carried out by the Lipinski filter (http://www.scfbio-iitd.res.in/software/drugdesign/lipinski.jsp) , according to the Lipinski Rule of 5 , an orally active drug should comply to a minimum of four of the five laid down criteria for druglikeness namely: molecular mass, cLogP, hydrogen donor and acceptor and molar refractive index . SwissADME (http://www.swissadme.ch/) computed the physicochemical descriptor, predicted the ADME properties, pharmacokinetic parameters, druglike nature and medicinal chemistry friendliness. Along with that ad-(http://lmmd.ecust.edu.cn/admetsar1/predict/) was used to analyze the properties of ligand with respect to prediction of adsorption, distribution, metabolism, excretion and toxicity (ADMET), which is reported as an useful tool in drug discovery. This tool was utilized for predicting important descriptors of drug likeness. FAFDrugs4(http://fafdrugs4.mti.univ-paris-diderot.fr/) was used to predict additional ADMET properties of IBP and its derivatives, which assist in filtering studies for selection of good drug candidates for drug development projects. The SDF (Structure Data Format) file of the IBP and its derivatives were downloaded from PubChem Database to calculate ADME properties using default parameters.

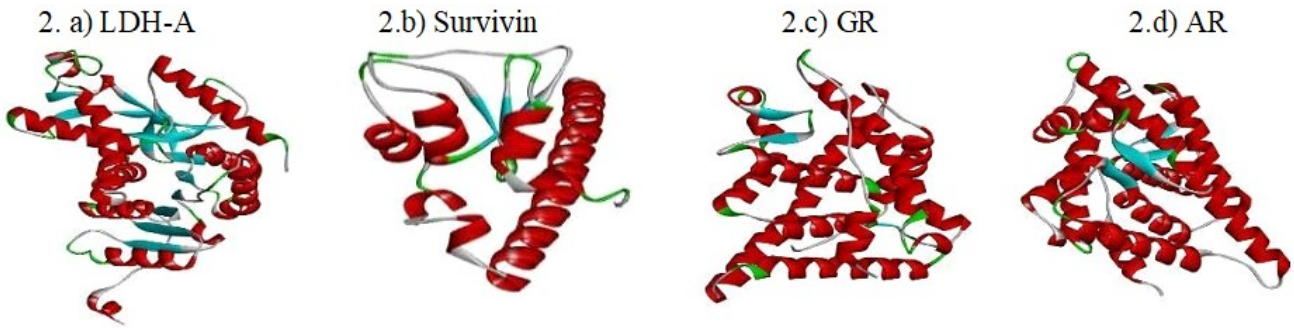


Fig. 2*.a)-d)* 3D structures of retrieved receptors. Structures of LDH-A, Survivin, Glucocorticoid Receptor and Androgen Receptor retrieved from the PDB data bank.

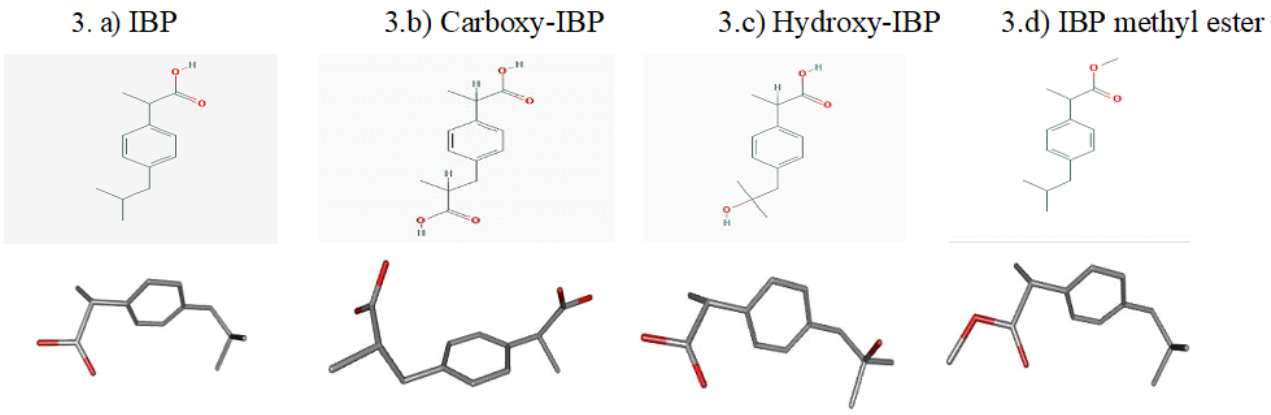


Fig. 3.a)-d) 2D structures and 3D Conformers of IBP and its derivatives-Carboxy-IBP, Hydroxy-IBP and IBP methyl ester from the PubChem compound database.

3. RESULTS & DISCUSSION

3.1.Retrieval of the 3-D structure of the target receptors and ligands

The structural details of target receptors LDH-A (PDB: 4ZVV), Survivin (PDB: 3UEC), Glucocorticoid Receptor (PDB: 4UDD) and Androgen Receptor (PDB: 3L3X) were obtained from the PDB data bank are presented in *Fig 2.a)-2.d)*. The structures of Ibuprofen (CID: 3672) and its derivatives- Carboxy-Ibuprofen (CID: 10444113), 2-Hydroxy-Ibuprofen (Hydroxy-IBP) (CID: 10443535) and Ibuprofen methyl ester (CID: 109101) were retrieved from the PubChem database as presented in *Fig. 3.a)-3.d).*

3.2. Docking analysis of IBP and its derivatives

The results of the docking analysis with PatchDock server and YASARA, which are reported to be highly used and reliable tools for molecular docking analysis are presented in *Fig. 4.a)-4.e)* and the docking calculation depicting the ligand name, receptor name, reported active site, predicted/ prominent active sites from MetaPocket 2.0 up to 3 number of pockets were determined, contacting receptor residues from YASARA and their common residues are shown in *Table 1*.

Table 1. Docking calculations depicting the ligand name, receptor name, reported active site, contacting receptor residues and their common residues.

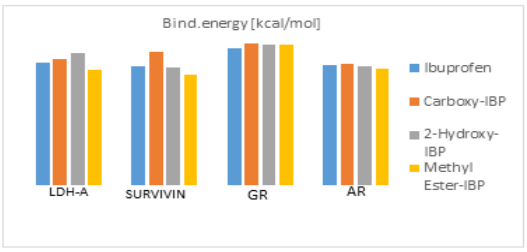
Ligand Name	Receptor Name	Reported Active Site Residues	Predicted Active Site	Contacting receptor residues	Common Residues
IBUPROFEN (CID: 3672)	LDH-A (PDB ID:4ZVV)	Gly^{28},Ala^{29},Val^{30},Asp^{51}, Val^{52},Ile^{53},Thr^{94},Ala^{95}, Gly^{96},Arg^{98},Ile^{115},Val^{135}, Asn^{137},Trp^{147},Pro^{153}, Lys^{154},Leu^{164},Asp^{165}, Arg^{168},Arg^{170},His^{185}, His^{192},Gly^{193},Asp^{194}, Ala^{237},Tyr^{238},Ile^{241}, Gly^{245},Thr^{247},Ile^{251}	**Binding Site Id: 1** Ser^{160},Gly^{161},Leu^{164},His^{192},Ile^{251},Val^{135},Val^{139},Asp^{165}, Val^{25},Gly^{26},Val^{50},Asp^{51},Val^{52},Tyr^{82},Ile^{119},Lys^{80}, Val^{30}, Asn^{137},Ser^{136},Ala^{95},Phe^{118},Ile^{115},Thr^{247},Thr^{94},Arg^{168},Val^{27} ,Gly^{28},Ala^{29},Gly^{31},Ser^{248},Gly^{96},Gly^{193} Val^{233},Ser^{196},Pro^{138} ,Asp^{140},Glu^{191},Leu^{322} ,Ala^{237},Val^{234},Asp^{194},Ile^{141},Asn^{114}, Ile^{53},Lys^{56} ,Tyr^{246},Ser^{236},Asn^{112},$Ilea^{241}$,Ala^{97},Ser^{195} Thr^{321} ,Arg^{98},Val^{240} ,Tyr^{238} ,Ile^{325},Gly^{245} ,Leu^{108},Val^{109} ,Arg^{105} Gln^{99},Glu^{239},Ser^{104},Asn^{107},Lys^{242},Glu^{103},Gln^{100},Ser^{318}, Leu^{106},Glu^{328},Gly^{324},Asp^{320} **Binding Site Id: 2** Trp^{249},Ala^{250},Leu^{253},Ala^{167},Leu^{164},Arg^{168},Ser^{236}, Ala^{237}, Val^{240},Tyr^{171},Leu^{172},Lys^{41},Asp^{257},Glu^{260},Lys^{244}, Thr^{247}, Ser^{248},Arg^{170},Pro^{181},Leu^{182},Asn^{163},Val^{269} ,His^{270}, Pro^{271}, Trp^{187},Ser^{254},Ser^{166},Gly^{186},His^{185} ,His^{180},Arg^{268}, Asp^{165}, Ile^{251},Val^{233},Gln^{232},Glu^{239},Glu^{235}	Ar- g^{168},Tyr^{171},Leu^{172}, Ser^{236},Val^{240},Lys^{244} , Thr^{247},Ser^{248},Trp^{249} , Ala^{250},Ile^{251}	**Binding Site Id: 1** Arg^{168},Thr^{247},Ile^{251} **Binding Site Id: 2** Arg^{168},Thr^{247},Ile^{251}
	SURVIVIN (PDB ID:3UEC)	Phe^{13},Leu^{14} ,Lys^{15},Asp^{16}, Ar- g^{18},Gly^{30},Glu^{40},Glu^{51} , Leu^{54},Cys^{57},Cys^{60},Lys^{62}, Glu^{63},Leu^{64},Glu^{65},Gly^{66}, Trp^{67},Asp^{70},Asp^{71},Glu^{76},His^{77},His^{80},Cys^{84}, Phe^{86},Val^{89},Gln^{92},Glu^{94},Glu^{95},Thr^{97},Gly^{99}, Glu^{107},Lys^{120},Glu^{123}, Ala^{128},Val^{131},Arg^{132}, Ala^{139},Asp^{142}	**Binding Site Id: 1** Phe^{13},Phe^{86},Val^{89},Phe^{93},Leu^{96},Leu^{104},Phe^{59},Lys^{91} ,Ar- g^{18},Leu^{14},Gln^{92},Glu^{94},Lys^{90},Lys^{15},Leu^{87},Ser^{88},Glu^{40},Ala^{85},Ala^{41},Glu^{95},Lys^{78},Asp^{16},Ile^{74},His^{17},Ile^{19} **Binding Site Id: 2** Lys^{62},Lys^{115},Asn^{118},Lys^{122},Cys^{60},Ala^{114},Asn^{111},Ser^{81},Gln^{56},Phe^{61},Glu^{63},Asn^{119},His^{80},Leu^{64},Leu^{54}, Glu^{51},Glu^{65}	Leu^{6},Trp^{10},Phe^{93}, Glu^{94},Glu^{95},Leu^{96}, Thr^{97},Leu^{98},Phe^{101}	**Binding Site Id: 1** Glu^{94},Glu^{95} **Binding Site Id: 2** No Match
	GLUCOCORTI-COIDS (PDB ID:4UDD)	Glu^{540},Pro^{541},Met^{560}, Leu^{563},Asn^{564},Gly^{567}, Gln^{570},Trp^{577},Met^{604}, Trp^{610},Arg^{611},Tyr^{640}, Asp^{641},Gln^{642},His^{645}, Met^{646},Tyr^{648},Tyr^{660}, Lys^{667},Met^{691},Lys^{695} Val^{702},Ser^{708},Trp^{712}, Phe^{715},Glu^{727},Asn^{731}	**Binding Site Id: 1** Asn^{564},Trp^{600},Met^{601},Cys^{736},Phe^{749},Leu^{753},Leu^{563} ,Gly^{567},Thr^{739},Leu^{732},Tyr^{735},Met^{604},Gln^{570},Phe^{623}, Met^{560},Ala^{605}, Met^{646},Ile^{747},Gln^{642},Leu^{608},Leu^{566},Arg^{611},Cys^{643}, Met^{639},Ile^{559},Ile^{629},Asp^{641},Asn^{731},Lys^{644},His^{645},Asn^{734},Gln^{738},Glu^{730},Met^{745},Thr^{556},Leu^{733},Thr^{562}, Met^{565},Leu^{603},Ala^{607},Trp^{557} **Binding Site Id: 2** Ala^{574},Trp^{577},Leu^{603},Met^{604},Pro^{541},Ala^{573},Gln^{570}, Lys^{667}, Ar- g^{569},Glu^{540},Ile^{539},Leu^{544},Ala^{607},Glu^{542},Tyr^{663},Arg^{611}, Val^{543},Phe^{623},Trp^{610},Tyr^{660},Leu^{664},Glu^{537},Arg^{614},	Leu^{563} ,Asn^{564},Leu^{566}, Gly^{567},Gln^{570},Trp^{600},Met^{601},Met^{604},Leu^{608}, Ar- g^{611},Phe^{623},Leu^{732}, Tyr^{735},Cys^{736},Thr^{739},Phe^{749},Leu^{753}	**Binding Site Id: 1** Leu^{563},Asn^{564},Gly^{567}, Gln^{570},Met^{604},Arg^{611},Tyr^{735},Cys^{736},Thr^{739},Phe^{749} **Binding Site Id: 2** Gln^{570},Met^{604},Arg^{611}
	ANDROGEN (PDB ID:3L3X)	Leu^{704},Asn^{705},Gln^{711}, Met^{745},Met^{749},Arg^{752}, Thr^{877}	**Binding Site Id: 1** Asn^{705},Trp^{741},Met^{742},Thr^{877},Phe^{891},Met^{895},Ile^{899}, Leu^{704}, Pro^{892},Met^{780},Gln^{783},Cys^{784},Met^{787},Leu^{873},Phe^{764}, Gln^{711} Met^{745},Val^{746},Met^{749},Gly^{708},Leu^{707},Phe^{876},Leu^{701}, Leu^{880}, Phe^{770} **Binding Site Id: 2** Val^{684},Val^{685},Arg^{752},Tyr^{763},Ala^{765},Pro^{766},Gly^{683},Phe^{764}, Val^{715},Leu^{744},Met^{745},Ala^{748},Lys^{808},Pro^{682},Gln^{711}, His^{714}, Met^{749},Asn^{756},Trp^{718},Glu^{678},Glu^{681},Leu^{805},Trp^{751}, Phe^{804}, Pro^{801},Leu^{677},Cys^{686},Leu^{707},Thr^{755}	Glu^{793},Trp^{796},Leu^{797}, Ar- g^{854},Arg^{855},Gln^{858}, Lys^{861},Leu^{862},Ser^{865}	**Binding Site Id: 1** No Match **Binding Site Id: 2** No Match

CARBOXY-IBUPROFEN (CID:10444113)	LDH-A (PDB ID:4ZVV)	Gly^{28},Ala^{29},Val^{30},Asp^{51}, Val^{52},Ile^{53},Thr^{94},Ala^{95},Gly^{96},Arg^{98},Ile^{115} Val^{135},Asn^{137},Trp^{147}, Pro^{153},Lys^{154},Leu^{164}, Asp^{165},Arg^{168},Arg^{170} ,His^{185},His^{192},Gly^{193}, Asp^{194},Ala^{237},Tyr^{238}, Ile^{241}, Gly^{245},Thr^{247},Ile^{251}	**Binding Site Id: 1** Ser^{160},Gly^{161},Leu^{164},His^{192},Ile^{251},Val^{135},Val^{139}, Asp^{165}, Val^{25},Gly^{26},Val^{50},Asp^{51},Val^{52},Tyr^{82},Ile^{119},Lys^{80} ,Val^{30}, Asn^{137},Ser^{136},Ala^{95},Phe^{118},Ile^{115},Thr^{247},Thr^{94},Arg^{168},Val^{27} ,Gly^{28},Ala^{29},Gly^{31},Ser^{248},Gly^{96},Gly^{193},Val^{233},Ser^{196},Pro^{138} ,Asp^{140},Glu^{191},Leu^{322} ,Ala^{237},Val^{234},Asp^{194},Ile^{141},Asn^{114} Ile^{53},Lys^{56} ,Tyr^{246},Ser^{236},Asn^{112},Ilea^{241},Ala^{97},Ser^{195},Thr^{321} ,Arg^{98},Val^{240} ,Tyr^{238} ,Ile^{325},Gly^{245} ,Leu^{108},Val^{109},Arg^{105}, Gln^{99},Glu^{239},Ser^{104},Asn^{107},Lys^{242},Glu^{103},Gln^{100}, Ser^{318}, Leu^{106},Glu^{328},Gly^{324},Asp^{320} **Binding Site Id: 2** Trp^{249},Ala^{250},Leu^{253},Ala^{167},Leu^{164},Arg^{168},Ser^{236} ,Ala^{237}, Val^{240},Tyr^{171},Leu^{172},Lys^{41},Asp^{257},Glu^{260},Lys^{244}, Thr^{247}, Ser^{248},Arg^{170},Pro^{181},Leu^{182},Asn^{163},Val^{269} ,His^{270} ,Pro^{271}, Trp^{187} ,Ser^{254},Ser^{166},Gly^{186},His^{185} ,His^{180},Arg^{268}, Asp^{165}, Ile^{251},Val^{233},Gln^{232},Glu^{239},Glu^{235}	Leu^{164},Ala^{167},Arg^{168}, Tyr^{171},Val^{240},Lys^{244}, Thr^{247},Ser^{248},Trp^{249}, Ala^{250},Ile^{251}	**Binding Site ID: 1** Leu^{164},Arg^{168},Thr^{247},Ile^{251} **Binding Site ID: 2** Leu^{164},Arg^{168},Thr^{247},Ile^{251}
	SURVIVIN (PDB ID:3UEC)	Phe^{13},Leu^{14},Lys^{15},Asp^{16},Arg^{18},Gly^{30},Glu^{40},Glu^{51},Leu^{54},Cys^{57}, Cys^{60},Lys^{62} ,Glu^{63},Leu^{64},Glu^{65},Gly^{66},Trp^{67},Asp^{70},Asp^{71},Glu^{76}, His^{77},His^{80},Cys^{84},Phe^{86},Val^{89},Gln^{92},Glu^{94} ,Glu^{95},Thr^{97},Gly^{99},Glu^{107},Lys^{120},Glu^{123},Ala^{128},Val^{131},Arg^{132},Ala^{139},Asp^{142}	**Binding Site Id: 1** Phe^{13},Phe^{86},Val^{89},Phe^{93},Leu^{96},Leu^{104},Phe^{59},Lys^{91},Arg^{18},Leu^{14},Gln^{92},Glu^{94},Lys^{90},Lys^{15},Leu^{87},Ser^{88},Glu^{40},Ala^{85},Ala^{41},Glu^{95},Lys^{78},Asp^{16},Ile^{74},His^{17},Ile^{19} **Binding Site Id: 2** Lys^{62},Lys^{115},Asn^{118},Lys^{122},Cys^{60},Ala^{114},Asn^{111}, Ser^{81},Gln^{56},Phe^{61},Glu^{63},Asn^{119},His^{80},Leu^{64} ,Leu^{54},Glu^{51},Glu^{65}	Phe^{13},Leu^{14},Lys^{15}, Arg^{18},Glu^{40},Ala^{41},Ile^{74}, Phe^{86},Leu^{87},Val^{89}, Lys^{90} Lys^{91},Gln^{92},Phe^{93}, Leu^{96}	**Binding Site Id: 1** Phe^{13},Leu^{14},Lys^{15}, Arg^{18},Glu^{40},Phe^{86},Val^{89},Gln^{92} **Binding Site Id: 2** No Match
	GLUCOCORTICOIDS (PDB ID:4UDD)	Glu^{540},Pro^{541},Met^{560} Leu^{563},Asn^{564},Gly^{567}, Gln^{570},Trp^{577},Met^{604}, Trp^{610},Arg^{611},Tyr^{640}, Asp^{641},Gln^{642} His^{645},Met^{646},Tyr^{648} Tyr^{660},Lys^{667},Met^{691}, Lys^{695},Val^{702},Ser^{708}, Trp^{712},Phe^{715},Glu^{727}, Asn^{731},Tyr^{735},Cys^{736}, Gln^{738},Thr^{739},Met^{745}, Ile^{747},Phe^{749} Gln^{776},Lys^{777}	**Binding Site Id: 1** Asn^{564},Trp^{600},Met^{601},Cys^{736},Phe^{749},Leu^{753},Leu^{563},Gly^{567},Thr^{739},Leu^{732},Tyr^{735},Met^{604},Gln^{570},Phe^{623},Met^{560},Ala^{605}, Met^{646},Ile^{747},Gln^{642},Leu^{608},Leu^{566},Arg^{611},Cys^{643} ,Met^{639},Ile^{559},Ile^{629},Asp^{641},Asn^{731},Lys^{644},His^{645}, Asn^{734},Gln^{738},Glu^{730},Met^{745},Thr^{556},Leu^{733},Thr^{562},Met^{565},Leu^{603},Ala^{607},Trp^{557} **Binding Site Id: 2** Ala^{574},Trp^{577},Leu^{603},Met^{604},Pro^{541},Ala^{573},Gln^{570} ,Lys^{667}, Arg^{569},Glu^{540},Ile^{539},Leu^{544},Ala^{607},Glu^{542},Tyr^{663},Arg^{611}, Val^{543},Phe^{623},Trp^{610},Tyr^{660},Leu^{664},Glu^{537},Arg^{614} ,Lys^{576}, Ala^{580},Val^{538},Ile^{572},Ala^{624},Leu^{566},Tyr^{345}	Met^{560},Leu^{563},Asn^{564},Leu^{566},Gly^{567},Gln^{570},Trp^{600},Met^{601}, Met^{604},Ala^{605},Leu^{608},Arg^{611},Phe^{623},Met^{646},Tyr^{735},Cys^{736}, Phe^{749}	**Binding Site Id: 1** Met^{560},Leu^{563},Asn^{564},Gly^{567},Gln^{570}, Met^{604},Arg^{611},Met^{646},Tyr^{735},Cys^{736},Phe^{749} **Binding Site Id: 2** Gln^{570},Met^{604},Arg^{611}
	ANDROGEN (PDB ID:3L3X)	Leu^{704},Asn^{705},Gln^{711}, Met^{745},Met^{749},Arg^{752} ,Thr^{877}	**Binding Site Id: 1** Asn^{705},Trp^{741},Met^{742},Thr^{877},Phe^{891},Met^{895},Ile^{899}, Leu^{704}, Pro^{892},Met^{780},Gln^{783},Cys^{784},Met^{787},Leu^{873},Phe^{764},Gln^{711}, Met^{745},Val^{746},Met^{749},Gly^{708},Leu^{707},Phe^{876},Leu^{701},Leu^{880}, Phe^{770} **Binding Site Id: 2** Val^{684},Val^{685},Arg^{752},Tyr^{763},Ala^{765},Pro^{766},Gly^{683}, Phe^{764}, Val^{715},Leu^{744},Met^{745},Ala^{748},Lys^{808},Pro^{682},Gln^{711} ,His^{714}, Met^{749},Asn^{756},Trp^{718},Glu^{678},Glu^{681},Leu^{805},Trp^{751},Phe^{804}, Pro^{801},Leu^{677},Cys^{686},Leu^{707},Thr^{755}	Glu^{793},Trp^{796},Leu^{797}, Arg^{854},Arg^{855},Gln^{858}, Lys^{861},Leu^{862},Ser^{865}	**Binding Site Id: 1** No Match **Binding Site Id: 2** No Match

2-HYDROXY-IBUPROFEN (CID:10443535)	LDH-A (PDB ID:4ZVV)	Gly^{28},Ala^{29},Val^{30},Asp^{51},Val^{52},Ile^{53},Thr^{94},Ala^{95},Gly^{96},Arg^{98},Ile^{115},Val^{135},Asn^{137},Trp^{147},Pro^{153},Lys^{154},Leu^{164},Asp^{165},Arg^{168},Arg^{170},His^{185},His^{192},Gly^{193},Asp^{194},Ala^{237},Tyr^{238},Ile241,Gly^{245},Thr^{247},Ile^{251}	**Binding Site Id: 1** Ser^{160},Gly^{161},Leu^{164},His^{192},Ile^{251},Val^{135},Val^{139},Asp^{165}, Val^{25},Gly^{26},Val^{50},Asp^{51},Val^{52},Tyr^{82},Ile^{119},Lys^{80},Val^{30} Asn^{137},Ser^{136},Ala^{95},Phe^{118},Ile^{115},Thr^{247},Thr^{94},Arg^{168},Val^{27} ,Gly^{28},Ala^{29},Gly^{31},Ser^{248},Gly^{96},Gly^{193},Val^{233},Ser^{196},Pro^{138} ,Asp^{140},Glu^{191},Leu^{322},Ala^{237},Val^{234},Asp^{194},Ile^{141},Asn^{114}, Ile^{53},Lys^{56} ,Tyr^{246},Ser^{236},Asn^{112},Ilea^{241},Ala^{97},Ser^{195},Thr^{321} ,Arg^{98},Val^{240},Tyr^{238},Ile^{325},Gly^{245},Leu^{108},Val^{109},Arg^{105} Gln^{99},Glu^{239},Ser^{104},Asn^{107},Lys^{242},Glu^{103},Gln^{100},Ser^{318}, Leu^{106},Glu^{328},Gly^{324},Asp^{320} **Binding Site Id: 2** Trp^{249},Ala^{250},Leu^{253},Ala^{167},Leu^{164},Arg^{168},Ser^{236},Ala^{237}, Val^{240},Tyr^{171},Leu^{172},Lys^{41},Asp^{257},Glu^{260},Lys^{244},Thr^{247}, Ser^{248},Arg^{170},Pro^{181},Leu^{182},Asn^{163},Val^{269} ,His^{270},Pro^{271}, Trp^{187} ,Ser^{254},Ser^{166},Gly^{186},His^{185} ,His^{180},Arg^{268},Asp^{165}, Ile^{251},Val^{233},Gln^{232},Glu^{239},Glu^{235}	Arg^{168},Tyr^{171},Leu^{172},Ser^{236},Val^{240},Lys^{244}, Thr^{247},Ser^{248},Trp^{249}, Ala^{250},Ile^{251}	**Binding Site Id: 1** Arg^{168},Thr^{247},Ile^{251} **Binding Site Id: 2** Arg^{168},Thr^{247},Ile^{251}
	SURVIVIN (PDB ID:3UEC)	Phe^{13},Leu^{14},Lys^{15},Asp^{16},Arg^{18},Gly^{30},Glu^{40},Glu^{51},Leu^{54},Cys^{57},Cys^{60},Lys^{62},Glu^{63},Leu^{64},Glu^{65},Gly^{66},Trp^{67},Asp^{70},Asp^{71},Glu^{76},His^{77},His^{80},Cys^{84},Phe^{86},Val^{89},Gln^{92},Glu^{94},Glu^{95},Thr^{97},Gly^{99},Glu^{107},Lys^{120},Glu^{123},Ala^{128},Val^{131},Arg^{132},Ala^{139},Asp^{142}	**Binding Site Id: 1** Phe^{13},Phe^{86},Val^{89},Phe^{93},Leu^{96},Leu^{104},Phe^{59},Lys^{91},Arg^{18},Leu^{14},Gln^{92},Glu^{94},Lys^{90},Lys^{15},Leu^{87},Ser^{88},Glu^{40},Ala^{85},Ala^{41},Glu^{95},Lys^{78},Asp^{16},Ile^{74},His^{17},Ile^{19} **Binding Site Id: 2** Lys^{62},Lys^{115},Asn^{118},Lys^{122},Cys^{60},Ala^{114},Asn^{111},Ser^{81},Gln^{56},Phe^{61},Glu^{63},Asn^{119},His^{80},Leu^{64} ,Leu^{54},Glu^{51},Glu^{65}	Leu^{6} ,Pro^{7},Trp^{10},Phe^{93} ,Glu^{94},Leu^{96},Thr^{97}, Leu^{98} ,Phe^{101}	**Binding Site Id: 1** Glu^{94} **Binding Site Id: 2** No Match
	GLUCOCORTICOIDS (PDB ID:4UDD)	Glu^{540},Pro^{541},Met^{560},Leu^{563},Asn^{564},Gly^{567},Gln^{570},Trp^{577},Met^{604},Trp^{610},Arg^{611},Tyr^{640},Asp^{641},Gln^{642},His^{645},Met^{646},Tyr^{648},Tyr^{660},Lys^{667},Met^{691},Lys^{695},Val^{702} ,Ser^{708},Trp^{712},Phe^{715},Glu^{727},Asn^{731},Tyr^{735},Cys^{736},Gln^{738},Thr^{739},Met^{745},Ile^{747},Phe^{749},Gln^{776},Lys^{777}	**Binding Site Id: 1** Asn^{564},Trp^{600},Met^{601},Cys^{736},Phe^{749},Leu^{753},Leu^{563},Gly^{567},Thr^{739},Leu^{732},Tyr^{735},Met^{604},Gln^{570},Phe^{623},Met^{560},Ala^{605}, Met^{646},Ile^{747},Gln^{642},Leu^{608},Leu^{566},Arg^{611},Cys^{643},Met^{639},Ile^{559},Ile^{629},Asp^{641},Asn^{731},Lys^{644},His^{645} Asn^{734},Gln^{738},Glu^{730},Met^{745},Thr^{556},Leu^{733},Thr^{562},Met^{565},Leu^{603},Ala^{607},Trp^{557} **Binding Site Id: 2** Ala^{574},Trp^{577},Leu^{603},Met^{604},Pro^{541},Ala^{573},Gln^{570},Lys^{667}, Arg^{569},Glu^{540},Ile^{539},Leu^{544},Ala^{607},Glu^{542},Tyr^{663},Arg^{611}, Val^{543},Phe^{623},Trp^{610},Tyr^{660},Leu^{664},Glu^{537},Arg^{614},Lys^{576}, Ala^{580},Val^{538},Ile^{572},Ala^{624},Leu^{566},Tyr^{545}	Met^{560},Leu^{563},Asn^{564}, Leu^{566},Gly^{567},Gln^{570},Trp^{600},Met^{604},Leu^{608},Arg^{611},Phe^{623}, Tyr^{735},Thr^{739},Ile^{747}, Phe^{749},Leu^{753}	**Binding Site Id: 1** Met^{560},Leu^{563},Asn^{564},Gly^{567},Gln^{570}, Met^{604},Arg^{611},Tyr^{735},Thr^{739},Ile^{747},Phe^{749} **Binding Site Id: 2** Gln^{570},Met^{604},Arg^{611}
	ANDROGEN (PDB ID:3L3X)	Leu^{704},Asn^{705},Gln^{711},Met^{745},Met^{749},Arg^{752},Thr^{877}	**Binding Site Id: 1** Asn^{705},Trp^{741},Met^{742},Thr^{877},Phe^{891},Met^{895},Ile^{899},Leu^{704}, Pro^{892},Met^{780},Gln^{783},Cys^{784},Met^{787},Leu^{873},Phe^{764},Gln^{711}, Met^{745},Val^{746},Met^{749},Gly^{708},Leu^{707},Phe^{876},Leu^{701},Leu^{880}, Phe^{770} **Binding Site Id: 2** Val^{684},Val^{685},Arg^{752},Tyr^{763},Ala^{765},Pro^{766},Gly^{683},Phe^{764}, Val^{715},Leu^{744},Met^{745},Ala^{748},Lys^{808},Pro^{682},Gln^{711},His^{714}, Met^{749},Asn^{756},Trp^{718},Glu^{678},Glu^{681},Leu^{805},Trp^{751},Phe^{804}, Pro^{801},Leu^{677},Cys^{686},Leu^{707},Thr^{755}	Glu^{793},Trp^{796},Leu^{797}, Gln^{858},Lys^{861},Leu^{862}, Ser^{865}	**Binding Site Id: 1** No Match **Binding Site Id: 2** No Match

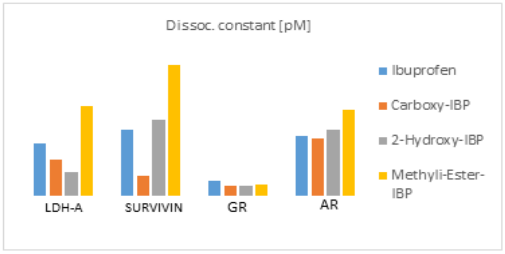
IBUPROFEN METHYL ESTER (CID: 109101)	LDH-A (PDB ID:4ZVV)	Gly^{28},Ala^{29},Val^{30},Asp^{51},Val^{52},Ile^{53},Thr^{94},Ala^{95},Gly^{96},Arg^{98},Ile^{115},Val^{135},Asn^{137},Trp^{147},Pro^{153},Lys^{154},Leu^{164},Asp^{165},Arg^{168},Arg^{170},His^{185},His^{192},Gly^{193},Asp^{194},Ala^{237},Tyr^{238},Ile^{241},Gly^{245},Thr^{247},Ile^{251}	**Binding Site Id: 1** Ser^{160},Gly^{161},Leu^{164},His^{192},Ile^{251},Val^{135},Val^{139},Asp^{165}, Val^{25},Gly^{26},Val^{50},Asp^{51},Val^{52},Tyr^{82},Ile^{119},Lys^{80}, Val^{30}, Asn^{137},Ser^{136},Ala^{95},Phe^{118},Ile^{115},Thr^{247},Thr^{94},Arg^{168},Val^{27} ,Gly^{28},Ala^{29},Gly^{31},Ser^{248},Gly^{96},Gly^{193},Val^{233},Ser^{196},Pro^{138} ,Asp^{140},Glu^{191},Leu^{322} ,Ala^{237},Val^{234},Asp^{194},Ile^{141},Asn^{114}, Ile^{53},Lys^{56} ,Tyr^{246},Ser^{236},Asn^{112},Ilea^{241},Ala^{97},Ser^{195},Thr^{321} ,Arg^{98},Val^{240} ,Tyr^{238} ,Ile^{325},Gly^{245} ,Leu^{108},Val^{109},Arg^{105}, Gln^{99},Glu^{239},Ser^{104},Asn^{107},Lys^{242},Glu^{103},Gln^{100},Ser^{318}, Leu^{106},Glu^{328},Gly^{324},Asp^{320} **Binding Site Id: 2** Trp^{249},Ala^{250},Leu^{253},Ala^{167},Leu^{164},Arg^{168},Ser^{236},Ala^{237}, Val^{240},Tyr^{171},Leu^{172},Lys^{41},Asp^{257},Glu^{260},Lys^{244},Thr^{247}, Ser^{248},Arg^{170},Pro^{181},Leu^{182},Asn^{163},Val^{269} ,His^{270} ,Pro^{271}, Trp^{187},Ser^{254},Ser^{166},Gly^{186},His^{185} ,His^{180},Arg^{268},Asp^{165}, Ile^{251},Val^{233},Gln^{232},Glu^{239},Glu^{235}	Val^{30},Thr^{94},Ala^{95},Gly^{96},Ala^{97},Leu^{108},Asn^{112}, Val^{135},Ser^{136},Asn^{137}, Leu^{164},His^{192},Thr^{247}, Ile^{251}	**Binding Site Id: 1** Val^{30},Thr^{94},Ala^{95},Gly^{96},Val^{135},Asn^{137},Leu^{164},His^{192},Thr^{247},Ile^{251} **Binding Site Id: 2** Leu^{164},Thr^{247},Ile^{251}
	SURVIVIN (PDB ID:3UEC)	Phe^{13},Leu^{14},Lys^{15},Asp^{16},Arg^{18},Gly^{30},Glu^{40},Glu^{51},Leu^{54},Cys^{57},Cys^{60},Lys^{62},Glu^{63},Leu^{64},Glu^{65},Gly^{66},Trp^{67},Asp^{70},Asp^{71},Glu^{76},His^{77},His^{80},Cys^{84},Phe^{86},Val^{89},Gln^{92},Glu^{94},Glu^{95},Thr^{97},Gly^{99},Glu^{107},Lys^{120},Glu^{123},Ala^{128},Val^{131},Arg^{132},Ala^{139},Asp^{142}	**Binding Site Id: 1** Phe^{13},Phe^{86},Val^{89},Phe^{93},Leu^{96},Leu^{104},Phe^{59},Lys^{91},Arg^{18},Leu^{14},Gln^{92},Glu^{94},Lys^{90},Lys^{15},Leu^{87},Ser^{88},Glu^{40},Ala^{85},Ala^{41},Glu^{95},Lys^{78},Asp^{16},Ile^{74},His^{17},Ile^{19} **Binding Site Id: 2** Lys^{62},Lys^{115},Asn^{118},Lys^{122},Cys^{60},Ala^{114},Asn^{111},Ser^{81},Gln^{56},Phe^{61},Glu^{63},Asn^{119},His^{80},Leu^{64} ,Leu^{54},Glu^{51},Glu^{65}	Phe^{59} ,Ala^{85} ,Ser^{88},Val^{89},Lys^{90},Lys^{91},Leu^{96},Glu^{100},Lys^{103},Leu^{104}, Glu^{107}	**Binding Site Id: 1** Val^{89} **Binding Site Id: 2** No Match
	GLUCOCORTICOIDS (PDB ID:4UDD)	Glu^{540},Pro^{541},Met^{560},Leu^{563},Asn^{564},Gly^{567},Gln^{570},Trp^{577},Met^{604},Trp^{610},Arg^{611},Tyr^{640},Asp^{641},Gln^{642},His^{645},Met^{646},Tyr^{648},Tyr^{660},Lys^{667},Met^{691},Lys^{695},Val^{702},Ser^{708},Trp^{712},Phe^{715},Glu^{727},Asn^{731},Tyr^{735},Cys^{736},Gln^{738},Thr^{739},Met^{745},Ile^{747},Phe^{749},Gln^{776},Lys^{777}	**Binding Site Id: 1** Asn^{564},Trp^{600},Met^{601},Cys^{736},Phe^{749},Leu^{753},Leu^{563},Gly^{567},Thr^{739},Leu^{732},Tyr^{735},Met^{604},Gln^{570},Phe^{623},Met^{560},Ala^{605}, Met^{646},Ile^{747},Gln^{642},Leu^{608},Leu^{566},Arg^{611},Cys^{643},Met^{639},Ile^{559},Ile^{629},Asp^{641},Asn^{731},Lys^{644},His^{645},Asn^{734},Gln^{738},Glu^{730},Met^{745},Thr^{556},Leu^{733},Thr^{562},Met^{565},Leu^{603},Ala^{607},Trp^{557} **Binding Site Id: 2** Ala^{574},Trp^{577},Leu^{603},Met^{604},Pro^{541},Ala^{573},Gln^{570},Lys^{667}, Arg^{569},Glu^{540},Ile^{539},Leu^{544},Ala^{607},Glu^{542},Tyr^{663},Arg^{611}, Val^{543},Phe^{623},Trp^{610},Tyr^{660},Leu^{664},Glu^{537},Arg^{614},Lys^{576}, Ala^{580},Val^{538},Ile^{572},Ala^{624},Leu^{566},Tyr^{545}	Thr^{556},Ile^{559},Met^{560},Leu^{563},Asn^{564},Met^{601},Phe^{623},Ile^{629},Met^{639},Gln^{642},Cys^{643},Met^{646},Leu^{732},Tyr^{735},Cys^{736},Thr^{739},Phe^{749}	**Binding Site Id: 1** Met^{560},Leu^{563},Asn^{564},Gln^{642},Met^{646},Tyr^{735},Cys^{736},Thr^{739},Phe^{749} **Binding Site Id: 2** No Match
	ANDROGEN (PDB ID:3L3X)	Leu^{704},Asn^{705},Gln^{711} Met^{745},Met^{749},Arg^{752} Thr^{877}	**Binding Site Id: 1** Asn^{705},Trp^{741},Met^{742},Thr^{877},Phe^{891},Met^{895},Ile^{899},Leu^{704}, Pro^{892},Met^{780},Gln^{783},Cys^{784},Met^{787},Leu^{873},Phe^{764},Gln^{711}, Met^{745},Val^{746},Met^{749},Gly^{708},Leu^{707},Phe^{876},Leu^{701},Leu^{880}, Phe^{770} **Binding Site Id: 2** Val^{684},Val^{685},Arg^{752},Tyr^{763},Ala^{765},Pro^{766},Gly^{683},Phe^{764}, Val^{715},Leu^{744},Met^{745},Ala^{748},Lys^{808},Pro^{682},Gln^{711},His^{714}, Met^{749},Asn^{756},Trp^{718},Glu^{678},Glu^{681},Leu^{805},Trp^{751},Phe^{804}, Pro^{801},Leu^{677},Cys^{686},Leu^{707},Thr^{755}	Glu^{793},Trp^{796},Leu^{797}, Arg^{854},Gln^{858},Lys^{861}, Leu^{862},Ser^{865}	**Binding Site Id: 1** No Match **Binding Site Id: 2** No Match

4.a)



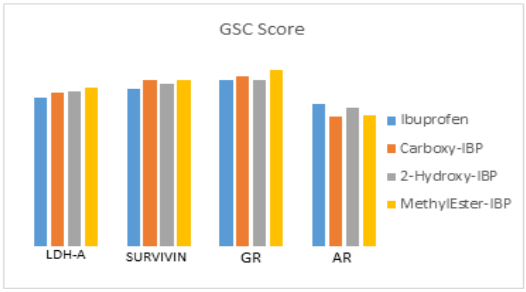
Bind.energy [kcal/mol]	IBP	Carboxy-IBP	2-Hydroxy-IBP	Methyl Ester-IBP
LDH-A	5.912	6.13	6.383	5.591
SURVIVIN	5.776	6.485	5.695	5.372
GR	6.646	6.884	6.839	6.824
AR	5.837	5.852	5.773	5.615

4.b)



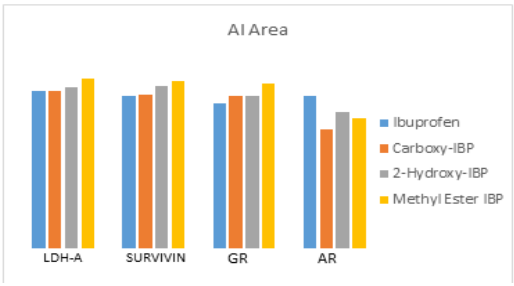
Dissoc. constant [pM]	IBP	Carboxy-IBP	2-Hydroxy-IBP	Methyl Ester-IBP
LDH-A	46392368	32110748	20950720	79752200
SURVIVIN	58362764	17637294	66912868	115417536
GLUCOCORTICOIDS GR	13440561	8994170	9703905	9952717
AR	52652896	51336604	58659032	76586184

4.c)



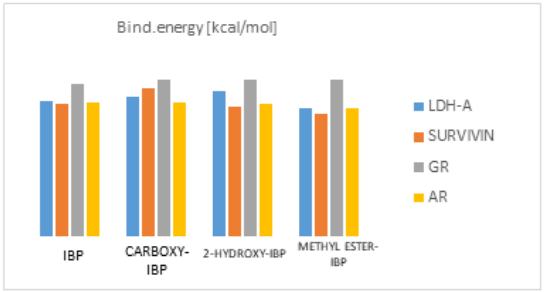
GSC Score	IBP	Carboxy-IBP	2-Hydroxy-IBP	Methyl Ester-IBP
LDH-A	3626	3744	3784	3852
SURVIVIN	3844	4054	3960	4060
GLUCOCORTICOIDS GR	4040	4146	4060	4300
AR	3464	3174	3376	3188

4.d)



AI Area	IBP	Carboxy-IBP	2-Hydroxy-IBP	Methyl Ester-IBP
LDH-A	446.4	448.4	459.1	483.5
SURVIVIN	432.7	436.4	463.1	474.6
GR	411.5	432.9	434	467.2
AR	432.2	338.7	387.6	368.9

4.e)



	LDH-A	SURVIVIN	GR	AR
IBP	5.912	5.776	6.646	5.837
C-IBP	6.13	6.485	6.884	5.852
2H-IBP	6.383	5.695	6.839	5.773
ME-IBP	5.591	5.372	6.824	5.615

Fig. 4*.a)-4.e)* Drug-receptor docking analysis results with PatchDock and YASARA

Table 2. Results obtained from RAMPAGE statistics, ResProx, ERRAT, and PDBSum Server

Parameters	**LDH-A**	**Survivin**	**GR**	**AR**
Resolution ((Å)	2.2	2.18	1.8	1.55
RAMPAGE-Number of residues in favoured region (~98.0% expected)	98.2%	98.5%	98.8%	98.8%
RAMPAGE-Number of residues in allowed region (~2.0% expected)	1.8%	98.5%	1.2%	1.2%
RAMPAGE-Number of residues in outlier region	0%	0%	0.0%	0.0%
ResProx-GOOD(0-1.5),MIDDLE(1.5-2.5), BAD (>2.5)	2.159	1.918	1.526	2.075
ERRAT AT >91	97.4684	98.4615	100	96.281
PDBSum-Most favoured regions	92.8%	92.6%	94.3%	95.2%
PDBSum-Additional allowed regions	7.2%	7.4%	5.7%	4.8%
PDBSum-Generously allowed regions	0%	0%	0.0%	0.0%
PDBSum-Disallowed regions	0%	0%	0.0%	0.0%

Table 3. Results obtained from VADAR analysis

	Mean H-bond distance		**Mean H-bond energy**		**Residue with H-bonds**		**Helix**	**Beta**	**Coil**	**Turn**
Protein Name	**Observed**	**Expected**	**Observed**	**Expected**	**Observed**	**Expected**				
LDH-A	2.2 sd=0.3	2.2 sd=0.4	-1.7 sd=0.9	-2.0 sd=0.8	262 (79%)	248 (75%)	142 (42%)	67 (20%)	122(36%)	88 (26%)
Survivin	2.2 sd=0.4	2.2 sd=0.4	-1.8 sd=1.0	-2.0 sd=0.8	112 (81%)	103 (75%)	69 (50%)	16 (11%)	53 (38%)	40 (28%)
GR	2.2 sd=0.3	2.2 sd=0.4	-1.7 sd=1.0	-2.0 sd=0.8	211 (84%)	186 (75%)	170 (68%)	14 (5%)	65 (26%)	44 (17%)
AR	2.2 sd=0.4	2.2 sd=0.4	-1.7 sd=1.0	-2.0 sd=0.8	218 (87%)	187 (75%)	170 (68%)	14 (5%)	66 (26%)	32 (12%)

Table 4. Results obtained from Lipinski filter

Parameters	**IBP**	**Carboxy-IBP**	**Hydroxy-IBP**	**IBP methyl ester**
Molecular mass less than 500 Dalton	205	234	221	220
High lipophilicity (expressed as LogP less than 5)	1.7385	-0.5315	0.8534	3.1615
Hydrogen bond donors(Lessthan5)	0	0	1	0
Hydrogen bond acceptors(Lessthan10)	2	4	3	2
Molar refractivity should be between 40-130	58.405987	57.738991	59.865788	65.414986

Table 5. Results obtained from admetSAR

Parameters	IBP	Carboxy-IBP	Hydroxy-IBP	IBP methyl ester
Blood-Brain Barrier	BBB+	BBB+	BBB+	BBB+
Human Intestinal Absorption	HIA+	HIA+	HIA+	HIA+
Caco-2 Permeability	Caco2+	Caco2+	Caco2+	Caco2+
P-glycoprotein Substrate	Non-substrate	Non-substrate	Non-substrate	Non-substrate
AMES Toxicity	Non AMES toxic	Non AMES toxic	Non AMES toxic	Non AMES toxic
Carcinogens	Carcinogens	Non-carcinogens	Non-carcinogens	Carcinogens
Acute Oral Toxicity	III	III	III	III
Rat Acute Toxicity	2.3092LD50,mol/kg	2.0465 LD50,mol/kg	1.8844LD50,mol/kg	1.9786LD50,mol/kg
CYP450 Substrate & Inhibitor	Non-substrate, Non-inhibitor	Non-substrate, Non-inhibitor	Non-substrate, Non-inhibitor	Non-substrate, Non-inhibitor
hERG	Weak inhibitor	Weak inhibitor	Weak inhibitor	Weak inhibitor

Table 6. Results obtained from FAFDrugs4

Parameters	IBP	Carboxy-IBP	Hydroxy-IBP	IBP methyl ester
Veber Rule	Good	Good	Good	Good
Egan Rule	Good	Good	Good	Good
Solubility (mg/l)	6613.10	18409.52	15552.37	7082.91
n_LipinskiViolations	0	0	0	0
Rotatable Bonds	4	5	4	5
Rigid Bonds	7	8	7	7
n_carbon	13	13	13	14
ratioH/C	0.15	0.31	0.23	0.14
NumCharges	1	2	1	0
logP	3.89	2.29	2.50	3.87
tPSA	40.13	80.26	60.36	26.3
State	Accepted	Accepted	Accepted	Accepted

Table 7. Results obtained from SwissADME

Parameters	IBP	Carboxy-IBP	Hydroxy-IBP	IBP methyl ester
SMILES	CC(Cc1ccc(cc1)[C@H](C(=O)O)C)C	OC(=O)C(Cc1ccc(cc1)C(C(=O)O)C)C	CC(c1ccc(cc1)CC(O)(C)C)C(=O)O	COC(=O)C(c1ccc(cc1)CC(C)C)C
Formula	C13H18O2	C13H16O4	C13H18O3	C14H20O2
Molecular weight	206.28 g/mol	236.26 g/mol	222.28 g/mol	220.31 g/mol
Num. heavy atoms	15	17	16	16
Consensus Log $P_{o/w}$	3.01	2.01	2.11	3.44
Lipinski	Yes; 0 violation	Yes; 0 violation	Yes; 0 violation	Yes; 0 violation
Bioavailability Score	0.56	0.56	0.56	0.55
PAINS	0 alert	0 alert	0 alert	0 alert
Brenk	0 alert	0 alert	0 alert	0 alert
Leadlikeness	No; 1 violation: MW<250	No; 1 violation: MW<250	No; 1 violation: MW<250	No; 2 violations: MW<250, XLOGP3>3.5
Synthetic accessibility	1.92	2.31	1.95	2.16

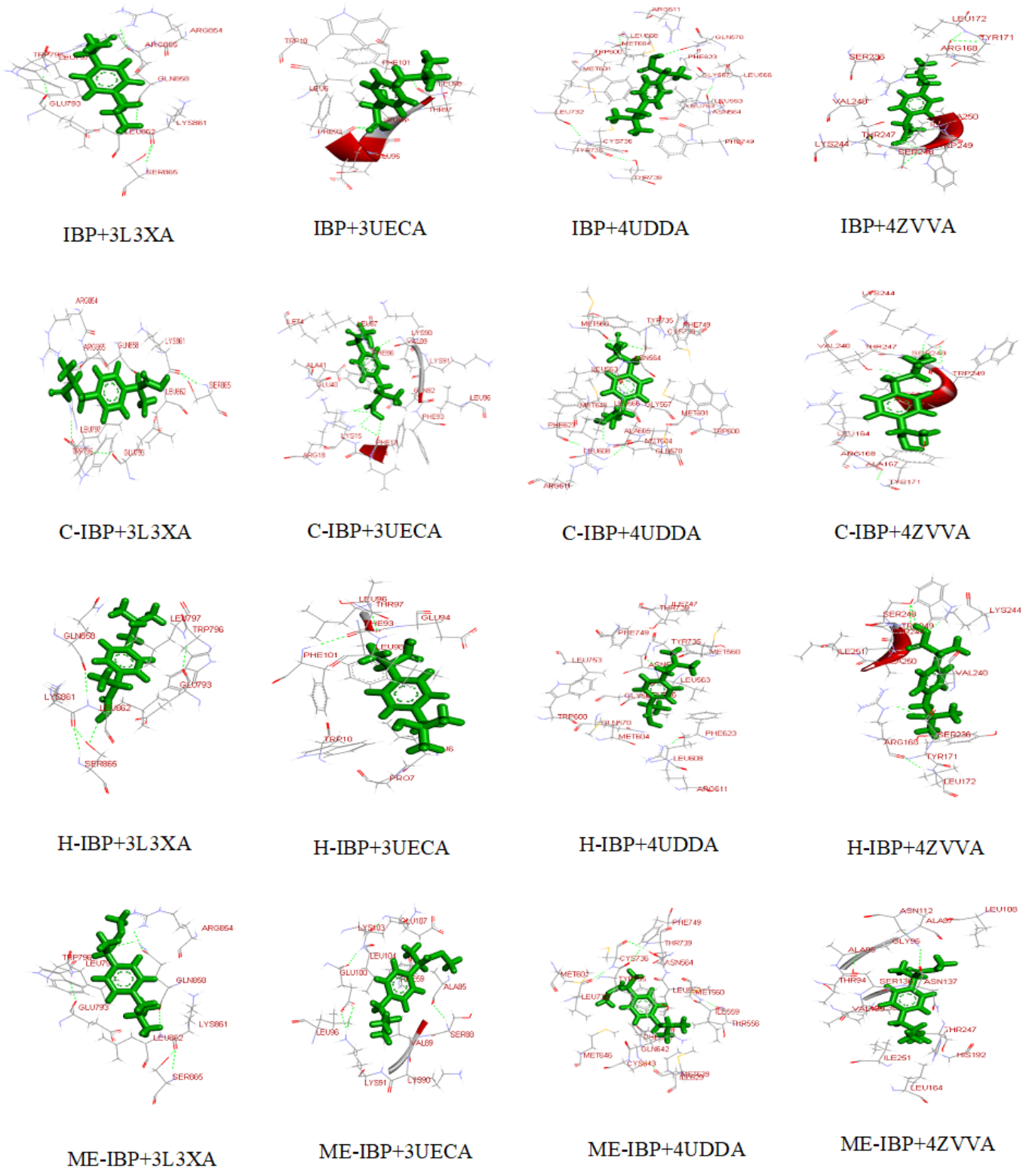


Fig 5. Visualization of docked complexes. The figure shows 3-D models of docked complexes as visualized by Discovery Studio 3.5, showing interactions of IBP and its derivatives with the target receptors.

The docking analysis result to PatchDock server and YASARA software are shown in *Fig. 4.a)-e)* which are reported to be highly reliable tools for molecular docking studies (Krieger et al., 2014). The docking analysis was based on the vital parameters of molecular docking indicating the strength of molecular interactions (Yadav et al., 2017). *Fig 4.a)* and *4.b)* shows a graphical representation of the Binding energy (in kcal/mol) and Dissociation constant (in pM) respectively between IBP and its derivatives and the receptor molecules using YASARA software. *Fig 4.c)* and *4.d)* is a graphical representation of GSC Score and AI Area respectively between IBP and its derivatives and the receptor molecules using PatchDock server. The docked complexes are visualized by Discovery Studio 3.5 and are shown in *Fig 5*. The optimum docking and better binding is indicated by the lower value of Dissociation constant and more positive values of Binding energy and higher values of GSC Score and AI Area (Rocheleau et al., 2016; Pandey et al., 2019).From the observed values Glucocorticoids Receptor (GR) shows the minimum value in dissociation constant (Kd) and higher value of binding energy, GSC Score and AI Area with all the ligands when all the receptor-ligand interaction is compared *Fig 4.e)*. And among the drugs the Ibuprofen derivatives- Carboxy IBP and 2-Hydroxy IBP shows the best result with minimum value in dissociation constant (Kd) and higher value of binding energy, GSC Score and AI Area.

The *Table 2.* represents the results from RAMPAGE statistics, ResProx, ERRAT and PDBSum server showing all the receptor within the acceptable range. *Table 3.*shows the VADAR analysis with the hydrogen bond statistics. *Table 4.*shows zero Lipinski violation for all the ligands and *Table 6.*and *Table 7.*shows the FAFDrugs4 and SwissADME results respectively. *Table 5.*shows the admetSAR properties where Carboxy-IBP and 2-Hydroxy-IBP are non-carcinogenic and rest all the parameters are within the range.

4. CONCLUSION

Based on all the docking calculations and druglikeness analysis finally it can be concluded that Ibuprofen derivatives- Carboxy IBP and 2-Hydroxy IBP shows the best result with minimum value in dissociation constant (Kd) and higher value of binding energy, GSC Score and AI Area and among all the targets Glucocorticoids Receptor (GR) shows the best result with lowest dissociation constant and highest binding energy, GSC Score and AI Score which can be summarized and understood from the graphical representations in Fig. 4.a)-d).GR shows the best docking interaction with Ibuprofen derivatives Carboxy-Ibuprofen and 2-Hydroxy-Ibuprofen, which are non-carcinogenic, better and more efficacious than the parent drug Ibuprofen itself. Glucocorticoids Receptor (GR) can be considered a novel receptor for the Ibuprofen derivatives. Ibuprofen derivatives Carboxy IBP and 2-Hydroxy IBP are more efficacious from the observations can be used for cancer therapeutics like breast, lung and can be utilized for further research.

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