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A Review

Computational modeling for predicting the drug metabolism: A novel approach for developing new drugs and to predict drug interactions

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Drug metabolism (DM) plays the crucial role in the drug therapy and research as it influences the pharmacokinetics (PK), Pharmacodynamic (PD) of the drug, decides the drug's efficacy and safety and drug interactions (DDIs). An exogenous compound includes the drugs, toxins and other foreign materials undergoes metabolism. The current review represents the computational approaches to predict the drug metabolism in human. This explains the metabolism related aspects for a drug molecule related to the type of enzyme that metabolise, binding sites on the substrate, metabolites formation process and drug-drug interactions. As the usage of multiple drugs containing regimens is increased, the identification and prediction of drug interactions is gaining importance in the personalized medication. The present review also exemplified using a case study by using the propionic derivatives drugs metabolism prediction by using *in silico* software's Bio Transformer 3 and AutoDock vina against enzymes Cytochrome P 450 and transferase enzymes. The binding score obtained for the above molecules and enzymes guiding safer and more effective drug design. Finally, based on the study concluded that every drug had their individual enzyme and metabolism process even though they are structurally similar.

Keywords: Computational tools, Drug metabolism, Drug discovery, Drug – drug interactions

Introduction

Drug metabolism (DM) is one of the complex processes that symbolises the drug response, toxicity and its pharmacological activity[1]. The major site for this process is liver where several enzymatic transformations are occurred, it's depend up on the several factors like health, age, sex, and hereditary aspects[2]. Drug metabolic stability and intrinsic clearance is assessed by *in vivo* and *in vitro* studies such as microsomal studies that are costly, tedious, time consuming process and lacking of complete information on the full spectrum of process and interactions[3]. For the absolute prediction, visualization, simulation of drug metabolism and its interactions for a ligand, various computational approaches are available which includes QSAR, PBPK, molecular modelling and machine learning algorithms[4]. Through this *in silico* approach the cons in the traditional approaches are rectified along with procuring of faster insights involved in the enzyme-substrate specificity, binding affinities and interaction approaches can be easily predicted. Despite of the scientific advancements there are so many challenges such as low experimental data, multiple enzymatic molecules and sites, difficulty in predicting metabolism of large and novel compounds. Major reason for this problem is lacking of usage and selection of accurate computational tools that represent the pathway of metabolism and interactions of various structurally different drugs[5]. One more drawback for this method was lacking on focusing of drug interactions with the isolated enzymes with incomplete structure reactivity limits, network interactions and dynamic related issues and multi tissue nature [6, 7]. To overcome this problem the computational tools must explore the methodologies that can effectively identify the drug metabolism based drug – drug interactions[8,9]. As per the data the following steps can provide the accurate information regarding the interactions.

1. Revise the foundational principles of drug metabolism and the enzymes related to the drug metabolism commonly.
2. Selection of computational strategies used for predicting drug metabolism including both ligand and structure based modeling, QM/MM simulations.

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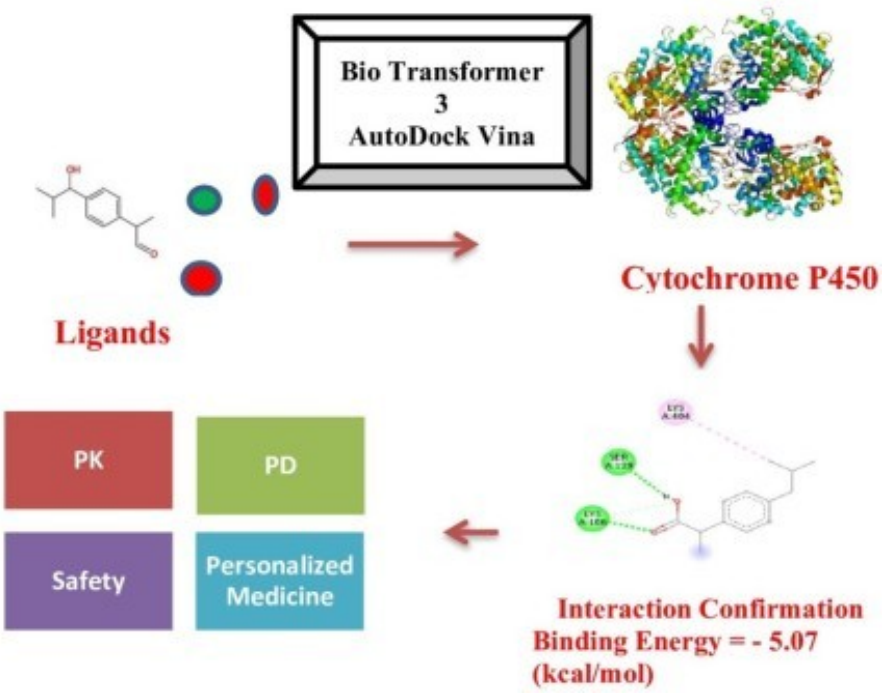


Graphical abstract

3. Identification of potential metabolites through machine learning approaches.
4. Docking prediction to obtain the binding energies between the ligand and substrate molecules based on the preferred metabolic pathways.

The liver is central to metabolism, and by applying relevant metabolic rate equations, one can compute metabolic concentrations over time. Given that metabolic enzymes are saturable, the Michaelis-Menten kinetic model is frequently used to describe drug metabolism[10].

$$-\frac{\mathrm{dC}}{dt} = Vmax\ \frac{C}{k_m} + C$$

–dC/dt = rate at which drug concentration decreases over time,

V_{max} = theoretical peak rate of the process, and

K_m = Michaelis constant.

The rate of increase of metabolite amount with time dA_m/dt is computed with following equation.

$$d\frac{A_m}{d_t} = V_{max}\frac{C_L}{k_m} + C_L$$

C_L = The concentration of parent compound in the liver.

The change in molar amount of parent compound in the liver dA_L/dt is computed with the following equation.

$$\frac{\mathrm{dA_L}}{\mathrm{dt}} = \mathrm{Q_L}(\mathrm{C_{Af}} - \mathrm{C_{LV}}) - \frac{\mathrm{dA_m}}{\mathrm{dt}}$$

Q_L is the arterial blood flow into the liver.

$C_{A,f}$ is the unbound arterial blood concentration

C_{LV} is the unbound blood concentration leaving the liver.

Methods to study DM

The key factors to be considered in various *in vitro* and *in vivo* methods employed to study the DM is furnished in following (Fig. 1)[11].

Predicting DM by Computation

The scope and limitations of computation in DM studies is furnished in following (Table 1)[12].

Computational techniques and combined strategies for forecasting drug metabolism are categorized into specific ("local") and comprehensive ("global") tools[13]. Specific models focus on particular metabolic enzymes or reactions, while global models are designed for broader applicability across various biological systems, accommodating any metabolic enzyme and transformation processes involving a wide range of small organic compounds.

Successful prediction of drug metabolism relies on several key components:

Experimental data

Computational works are built on experimental data obtained under controlled conditions. This

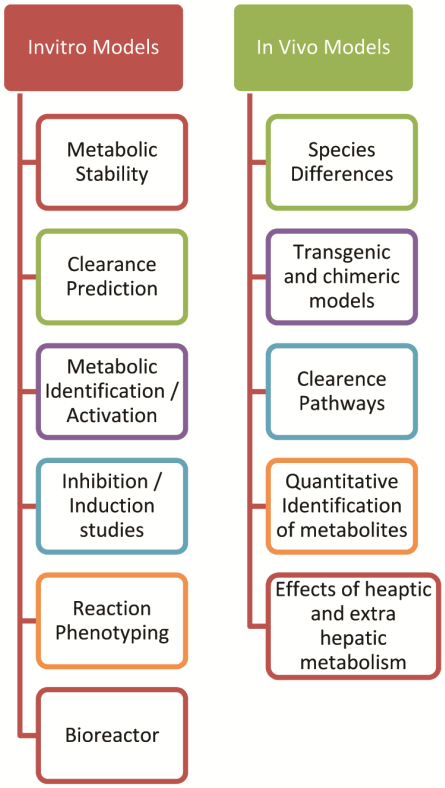


Fig. 1—Methods to study drug metabolism

Table 1—Scope and limitations of computation in drug metabolism

Scope	Limitations
Analysis of binding accuracy of ligands and enzymes	Ranking of metabolites accurately was difficult.
Usefull to identify unstable intermediate reactions at short lifetimes.	Cast of mechanism based inhibitors are difficult task.
Prediction of metabolic sites with adequate accuracy.	High false positive rates are occurred.
Able to produce large number of metabolites.	Expensive
Ligand binding affinity and inhibitory activity prediction can be possible.	Prediction of mechanism based inhibitors is highly challenged.

data, including bioactivities, can be analyzed using QSAR methods, which are progressed from machine learning approaches. The interpretation of data must contain quality, variability and devoid of errors.

Expert knowledge

Researchers have sought to create rule sets derived from expert insights to build reasoning engines for predicting metabolite structures. Knowledge-based approaches, like Meteor21, analyse molecules for specific target fragments to predict metabolic sites and products[14].

Physicochemical properties

Calculated physicochemical properties, including water solubility, log P (octanol/ water), and log D, serve as valuable predictors for ranking and filtering metabolites in drug metabolism studies.

Target Structure

This section provides the interaction between the ligands and receptor sites. The result can be expressed as docking of the ligand with the specific site on the target protein. This can be characterized as molecular interaction fields (MIFs), which can be calculated through the energies and the binding features are characterized by hydrogen bonds and hydrophobic areas.

Target flexibility

Molecular dynamic simulations are very powerful tools for predicting the interaction between protein – ligand that represent the structure, function, specificity and mechanism established between the enzymes and target molecule.

Reactivity

QM methods establishes the crucial factor reactivity and suitable for the examination at the electronic level. QM/MM techniques have an essential while studying enzyme reactions, leveraging the complementary strengths of MD simulations and QM methods.

Metabolic networks – Systems biology

A thorough understanding and prediction of factors such as (i) drug concentrations and distribution, (ii) metabolic vulnerabilities (Sites of Metabolism), (iii) the chemical structures of metabolites, (iv) interactions with pharmacologically and toxicologically significant biomolecules, (v) reaction rates, and (vi) the positioning of enzymes and cofactors within tissues are necessary to estimate biological effects accurately[15-16].

Categories of metabolic prediction

Different categories of metabolic prediction are categorized in (Fig. 2).

Computational tools used for predicting drug metabolism

The computational tools used for prediction of drug metabolism are presented in the following (Fig. 3).

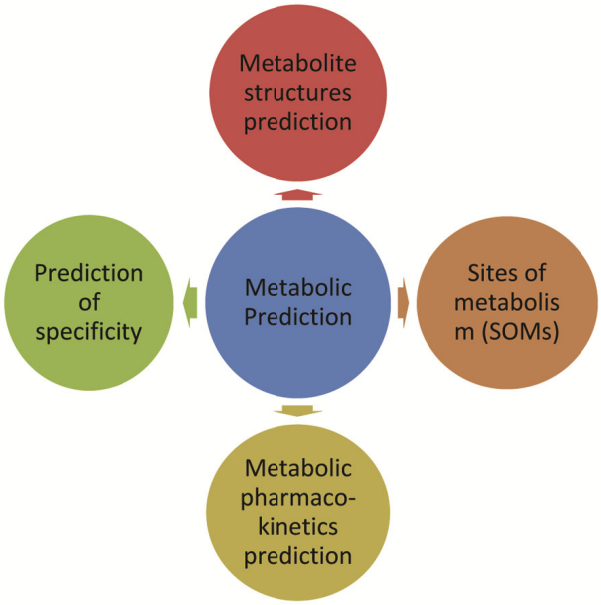


Fig. 2 — Categories of metabolic prediction

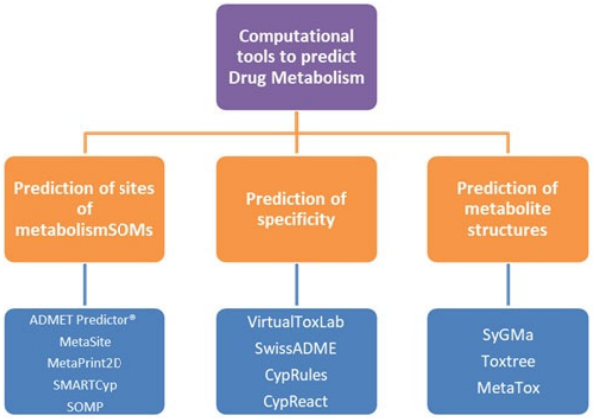


Fig. 3 —Predict drug metabolism through computational tools

Bio Transformer is a freely accessible software package that utilizes a machine learning and knowledge-based approach for precise, swift, and extensive *in silico* predictions of metabolism and compound identification in human tissues (such as liver tissue), the human gut, and environmental contexts (including soil and water microbiota) through its metabolism prediction tool. Query molecules must only contain carbon (C), hydrogen (H), nitrogen (N), oxygen (O), sulfur (S), phosphorus (P), or halogens[17].

In step I, Metabolic transformations can be chosen from several options, including Phase I (CYP450) transformations, enzyme commission (EC) based transformations, Phase II transformations, transformations by human gut microbes, environmental microbial transformations, and various combinations of human and human gut microbial transformations, as well as custom multi-step and abiotic transformations[18].

In the second step, users must input the drug for which they want to predict metabolism either in SMILES format or by uploading the drug's structure as an SDF file. The third step involves selecting the number of reaction iterations to calculate, typically ranging from one to three. After submitting the data, the results can be downloaded in JSON, SDF, or CSV file formats[19, 20].

Past Studies on drug metabolism prediction

Random Forests and Support Vector Machines models of machine learning have become popular choices for quicker inference in drug metabolism studies[21-22]. Researchers have also utilized Graph Convolutional Neural Networks to gain knowledge how molecules interact with enzymes[23-24].These machine learning models can predict reaction outcomes and provide valuable information about reaction mechanisms[25-27].

Methods for studying drug interactions

Drug – Drug interactions in humans are studied by using pharmacokinetic studies includes comparing substrate concentrations which interactions with drug or not[28]. The choice of study design is influenced by factors related to both the drug substrate and the interacting drug, including (i) whether the use is acute or chronic, (ii) safety considerations, (iii) the pharmacokinetic and pharmacodynamic characteristics of both medicaments, and (iv) assessment of enzyme inhibition or induction[29-32]. The dosing of both the inhibiting/inducing drugs and the drug substrates should reflect their clinical usage[33]. Generally, three methods are distinguished: (i) *in vitro* and *in vivo* experimental approaches, (ii) patient-centered processes (such as social network analysis and review of medical records)[34-35] and (iii) *in silico* computational predictive techniques[36].

Past Studies on predicting metabolic drug-drug interactions (DDIs)

Experimental and patient-oriented methods tend to be labour-intensive and costly; in contrast, computational approaches offer a robust alternative for predicting DDIs[37]. Gottlieb *et al.* studied about 37,212 interactions related to cytochrome and 18,601 non-CYP-related DDIs through the computational approaches[38]. Vilar *et al.* studied not only with the

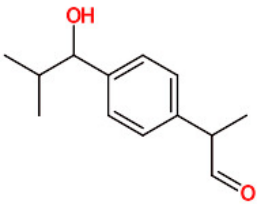
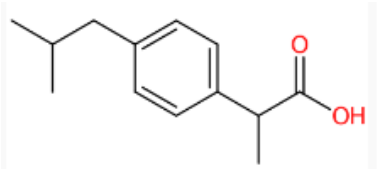
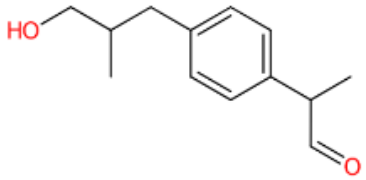
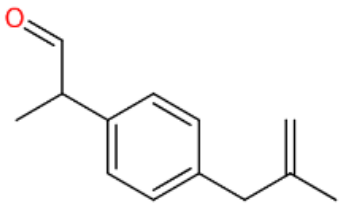
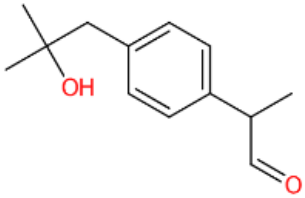
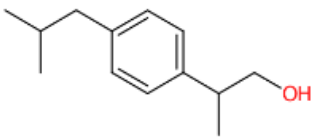
interactions and also shows the similarities in side effects based on the selected enzyme and structurally similar drugs which mentioned the data about 928 drugs and 9,454 interactions, predicting 430,128 possible DDIs by utilizing 2D/3D molecular structures[39].

Illustration

The mentioned case study shows the prediction of Ibuprofen metabolism through the computational approach by using Bio Transformer 3 software. When the software was explored firstly choose Human multistep transformation option after submitting the ibuprofen structure in smiles format. Then customize in to various steps one after another which contains the choosing of enzyme type then go further steps to undergo the second phase of metabolism process and endothelial cell (EC)based metabolism of given drug. Finally step IV choosing of the region where with the number of iterations set to one. Finally various metabolites of Ibuprofen are identified and presented in (Table 2).

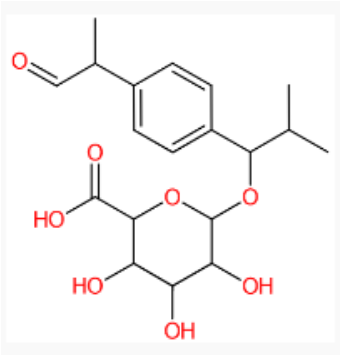
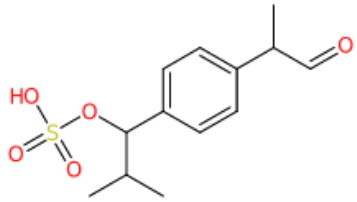
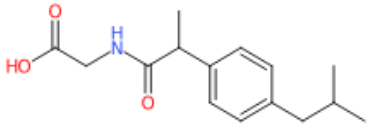
The above table represents the various biotransformation process and yield diverse range of metabolites after processing of Phase – I, Phase – II, EC

Table 2 —Metabolites of Ibuprofen predicted by Biotransformer 3.0

Predicted result	Reaction type	Reaction information
	Hydroxylation of non-terminal aliphatic carbon near an aromatic ring and from CyProduct	Cytochrome P450 1A2
	Aldehyde oxidation and from CyProduct	Cytochrome P450 1A2
	Hydroxylation of terminal methyl and from CyProduct	Cytochrome P450 1A2
	Terminal desaturation	Cytochrome P450 1A2
	Hydroxylation of penultimate aliphatic tertiary carbon and from CyProduct	Cytochrome P450 2A6
	Reduction of aldehyde to alcohol	Cytochrome P450 3A4

(*Contd.*)

Table 2 —Metabolites of Ibuprofen predicted by Biotransformer 3.0 (*Contd.*)

Predicted result	Reaction type	Reaction information
	Alkyl OH glucuronidation	UDP-glucuronosyl transferase
	Sulfation of secondary alcohol	Alcohol sulfo transferase
	Glycine conjugation	Glycine N Acyl transferase

based and microbial based metabolism. The reactions of all the phases are mentioned below.

Phase I Metabolism – Cytochrome P450-Mediated Reactions

- Hydroxylation of non-terminal aliphatic carbon (CYP1A2)
- Terminal methyl hydroxylation (CYP1A2)
- Terminal desaturation (CYP1A2)
- Penultimate aliphatic carbon hydroxylation (CYP2A6)
- Aldehyde oxidation and aldehyde reduction (CYP1A2 and CYP3A4 respectively)

The results of the first phase of metabolism predicted by the software states that CYP2C9, CYP2C8, and CYP3A4 plays a key role in the metabolism of ibuprofen through hydroxylation. It also stated that CYP1A2 and CYP2A6 had showed the metabolism which is not significant but vary with physiological and ailmentary conditions.

Phase II Metabolism – Conjugation Reactions included

- O-glucuronidation (UDP-glucuronosyltransferase)
- Alkyl-OH-glucuronidation
- Sulfation (Alcohol sulfotransferase)
- Glycine conjugation (Glycine N-acyltransferase)

As the Phase – II reactions involved in the elimination of drug by enhancing water solubility and facilitate the excretion from the body through various routes. It also very significant in determining the pharmacological activity and toxicity related aspects. As per the data obtained from the Bio Transformation 3 glucuronidation mostly through UGT2B7 is important for its elimination.

As there a inter individual metabolic activity which can differ from one person to another due to difference in the enzyme expression for sulfation and glucuronidation can affect the metabolism of ibuprofen and this implies the importance of computational approaches in the personalized medication.

Some of the previous computational and experimental reports are:

- Marchant *et al.* studied the common and rare metabolites by using the Bio Transformer software along with Metaprint 2D of various drug molecules which emphasises the phase – I & Phase – II reaction pathways[41].
- Djoumbou-Feunang *et al.* also studied predictions regarding the metabolism of ibuprofen using *in silico* studies[42].

Molecular docking studies predict drug metabolism

For the prediction of basic metabolic mechanism requires docking studies which will be very significant to identify various enzymes involved in the

metabolism. The present case study summarises the binding affinity between propionic acid and cytochrome P 450 1A2 derivatives with computational studies.

Steps involved in docking studies are mentioned below:

1. **Ligand preparation:** The first step was to procure the canonical SMILES based on the chemical structure of ligand. The SMILES were inserted in the Chimera software and saved in the PDB format.
2. **Protein preparation:** The target protein structures of 3D crystal were downloaded from protein data bank in PDB format. Structural changes based on standard procedures were made to macromolecules.
3. **Grid generation:** Depending upon the ligand and receptor binding sites residues grid box was organised. The dimensions were adjusted in the cubic box of grid in which the drug and receptor was organised inside and saved in PDB format.
4. **Docking: Generation of PDBQT, GPF, DPF, and LPF:** By using AutoDock Vina molecular docking analysis was done to identify the binding energies for receptor. All the PDB files was converted into PDBQT for both ligand and receptors. By using the AutoDock Vina interface and command prompt the PDBQT files generate Grid Parameter Files (GPF), Docking Parameter Files (DPF) and Log Parameter Files (LPF) was created and saved for further use.

b. **Analyzing the files in AutoDock:** After completion of the command prompt the docking files for ligand and receptor were used to find the maximum number of probable confirmations. Each confirmation includes binding affinity, electrostatic and hydrogen bonding data.

5. **Visualization:** For the visualization process Biovia Discovery studio was employed to obtain the 2D/ 3D structures of the generated confirmations[43].

The performed docking studies of propionic acid derivatives with Cytochrome P450 1A2 (2HI4) and UDP-glucuronosyl transferase were displayed in the (Table 3 and Table 4).

The key insights were derived from the molecular docking studies conducted on various propionic acid derivatives with Cytochrome P450 1A2 (CYP1A2) and UDP-glucuronosyl transferase (UGT1A3) showcased the potential metabolic interactions. Binding energy, reflects the affinity between a drug and a target enzyme and provides valuable information regarding the metabolic transformation and its pathways.

Table 3 —Binding energies observed for propionic acid derivatives and Cytochrome 4501A2 and UDP-glucuronosyl transferase

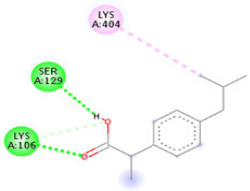
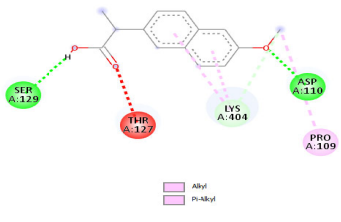
S. No	Drug name	Binding energy	Conformation
1.	Ibuprofen	-5.07	
2.	Naproxen	-6.1	

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Table 3 —Binding energies observed for propionic acid derivatives and Cytochrome 4501A2 and UDP-glucuronosyl transferase

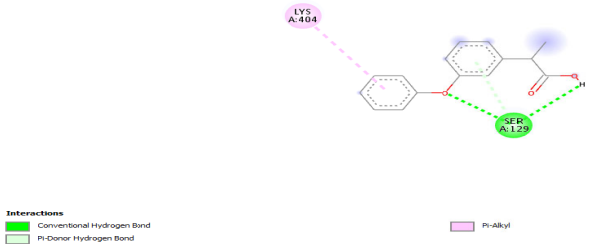
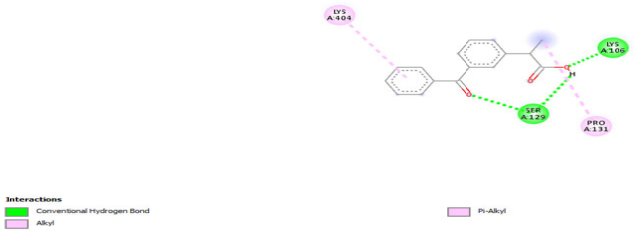
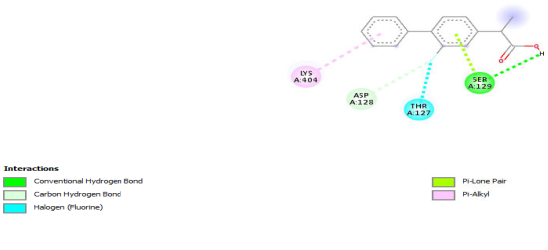
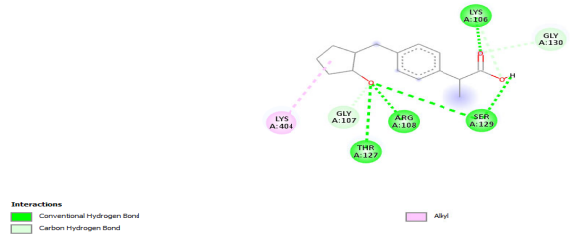
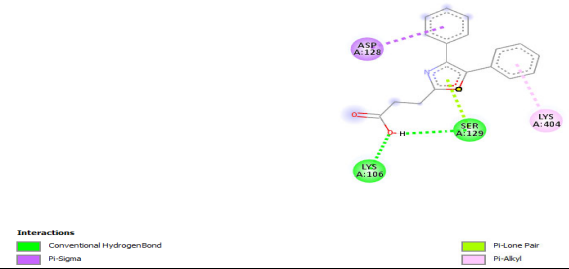
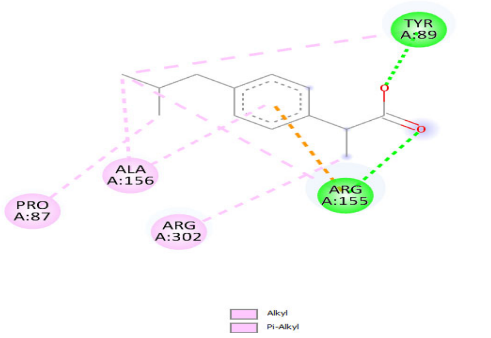
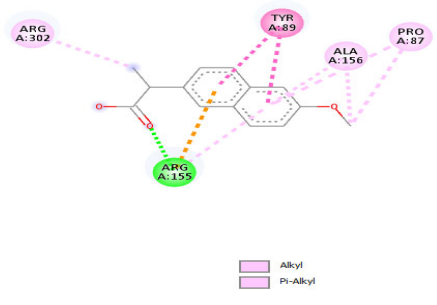
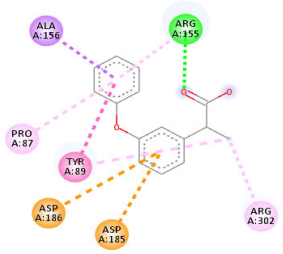
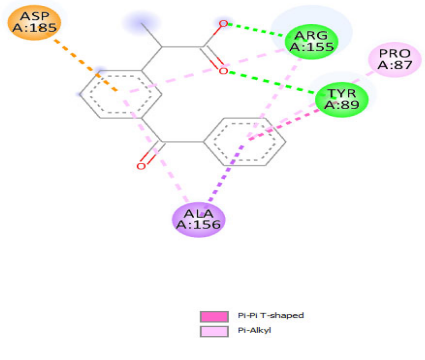
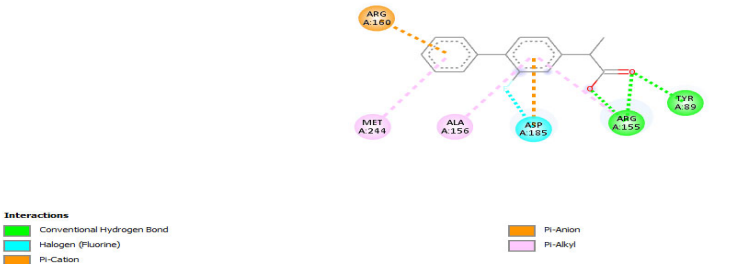
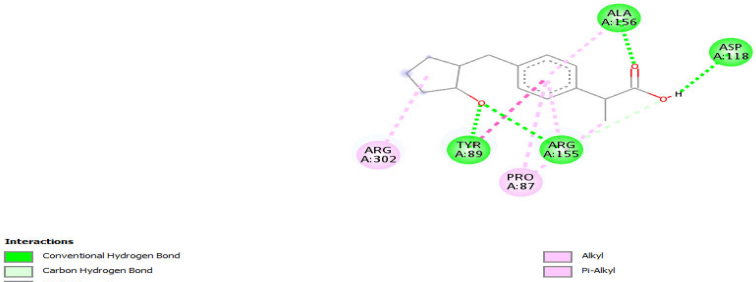
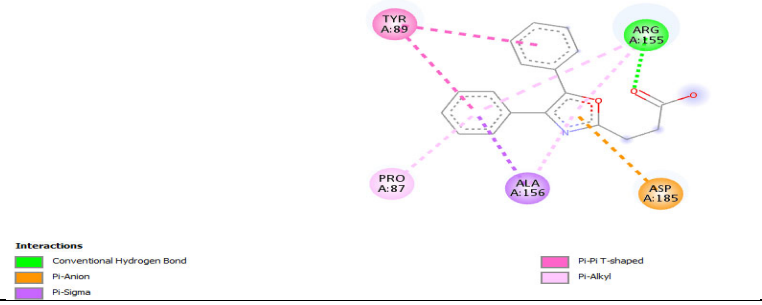
S. No	Drug name	Binding energy	Conformation
3.	Fenoprofen	-5.97	
4.	Ketoprofen	-6.4	
5.	Flurbiprofen	-6.12	
6.	Loxoprofen	-6.47	
7.	oxaprozin	-6.39	

Table 4 —Observed binding energies in between propionic acid derivatives and UDP-glucuronosyl transferase (UGT1A3)

S. No	Drug	Binding energy	2D conformation
1.	Ibuprofen	-6.32	
2.	Naproxen	-5.62	
3.	Fenoprofen	-6.67	
4.	Ketoprofen	-6.48	

(*Contd.*)

Table 4 — Observed binding energies in between propionic acid derivatives and UDP-glucuronosyl transferase (UGT1A3) (*Contd.*)

S. No	Drug	Binding energy	2D conformation
5.	Flurbiprofen	-5.49	
6.	Loxoprofen	-6.7	
7.	oxaprozin	-5.99	

The following interpretations are noticed from the observed docking studies:

The highest binding affinity towards CYP1A2 was shown for these drugs Loxoprofen (-6.47 kcal/mol), Ketoprofen (-6.4 kcal/mol), and Oxaprozin (-6.39 kcal/mol) whereas Ibuprofen (-5.07 kcal/mol) displayed the weakest binding affinity.

- As the Loxoprofen and Ketoprofen, are having stronger affinities, towards the CYP1A2 showcase that these are likely to be metabolized more extensively.
- The Ibuprofen showed weaker affinity for the enzyme CYP1A2 and it was majorly metabolised by CYP2C9.

The results revealed that propionic acid NSAIDs exhibit different metabolism profiles depending on substituent groups and stereochemistry.

- For example Naproxen, has moderate binding (-6.1 kcal/mol) undergoes demethylation and hydroxylation through CYP1A2 and CYP3A4 represents the above condition.

According to the data obtained from Table 4, binding affinities for the UGT1A3 are mentioned below.

- Loxoprofen (-6.7 kcal/mol) and Fenoprofen (-6.67) showed the highest affinity.
- Flurbiprofen (-5.49) and Naproxen (-5.62) exhibited the lowest affinities.

Phase II glucuronidation reactions are essential for increasing water solubility and aiding in drug excretion.

- The strong interaction of Fenoprofen and Loxoprofen with UGT1A3 implies efficient glucuronidation, potentially leading to faster elimination or reduced duration of action.
- Conversely, Naproxen and Flurbiprofen, with weaker affinities, may undergo slower glucuronidation, contributing to a longer half-life.
- Glucuronidation with UGT2B7 and UGT1A3 is a major metabolic pathway for NSAIDs, responsible for forming acyl-glucuronides, doesn't exhibit any pharmacological activity instead they can produce toxicity.
- Prior work by Kiang *et al*. demonstrated inter-individual and inter-species variability in glucuronidation, supporting the need for such computational screening tools.[43]

Conclusion

Overall, the case study's findings support the ability of computational prediction tools such as BioTransformer3.0 to mimic important ibuprofen metabolic changes, providing a quick, scalable, and non-invasive substitute for experimental assays. The coverage and depth of predicted metabolites, particularly the inclusion of Phase II conjugates, validate the usefulness of these tools in preclinical drug metabolism studies, despite small differences in enzyme attribution (e.g., CYP1A2 instead of CYP2C9). These results encourage their continued incorporation into drug development processes, particularly for metabolite profiling, toxicity risk assessment, and early DDI detection. The docking results demonstrate the metabolic heterogeneity among NSAIDs containing propionic acid and emphasize the value of computational methods for initial metabolic evaluation. They complement experimental research and are in line with current pharmacokinetic knowledge by offering an affordable method of predicting enzyme-substrate interactions. In both clinical and research contexts, these insights are crucial for improving drug design, dosage schedules, and safety profiles. The concept of compound-specific metabolic profiles is supported by the differential affinities of certain enzymes, such as CYP1A2 and UGT1A3.

These findings reinforce the importance of early *in silico* profiling in drug development to:

- Predict metabolic liabilities
- Identify potential drug-drug interaction risks
- Prioritize candidates for further *in vitro/in vivo* validation

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Conflict of interest

All authors declare no conflict of interest.

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