# Chapter X
# AI-based Platforms for Drug Discovery: Current Tools and Human-Centered Design Strategies

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**Abstract** This chapter presents an overview of ten selected Artificial Intelligence (AI)-driven web platforms designed to support the early stages of the drug discovery process. Its primary aim is to serve as both a practical guide and a critical review for potential users of such platforms, including those without cheminformatics or programming expertise. Additionally, we underline the limitations of these platforms and explore potential enhancements through Human-Centered Design (HCD) strategies to help improve both existing and future web-based platforms for optimal use.

**Keywords** Web-platforms, Bioactivity/toxicology Prediction, Generative models, Usability, Human-centered design.

Artificial Intelligence (AI)-driven methods and tools are playing an increasingly crucial role in accelerating the early phases of the Drug Discovery process, thanks to the growing availability of freely accessible repositories containing bioactivity and toxicity data. The integration of AI has created new and alternative pathways that promise to reduce both time and resources required for developing novel therapeutics. A key advantage of machine-driven hypothesis generation is its ability to design new compounds based on multiple pharmacokinetic (Absorption, Distribution, Metabolism, Excretion, and Toxicity; ADMET) and pharmacodynamic (selectivity, bioactivity) criteria simultaneously, including potential off-target and side effects (Schneider, 2018). These approaches enable a more comprehensive evaluation of compounds during the early stages of drug development, even before chemical synthesis occurs.

To ensure broad applicability of AI-based models within the scientific community, it is increasingly common for them to be made directly accessible to the public through intuitive and user-friendly web platforms. While current platforms are designed for users with varying levels of expertise in the field, to ensure intuitive and accessible interaction, they are predominantly developed by researchers with a medicinal chemistry background, particularly in cheminformatics. True advancements of these web-based platforms in this field necessitate the collaboration between medicinal chemistry and computer science, specifically through the integration of the Human-Computer Interaction (HCI) principles. To create systems that place users at the core of the process, Human-Centered Design (HCD) should be integrated to create solutions that effectively address users' needs, preferences, and behaviors while ensuring a positive experience. Regrettably, HCD concepts continue to be largely undervalued by researchers creating web platforms for drug discovery.

The aim of this chapter is to take a first step in bridging this gap by offering an in-depth analysis of AI-based platforms designed to assist experts in the early phases of drug discovery, while also emphasizing the significance of HCI basis. A selection of web-based platforms will be presented providing a practical and useful guide for potential users, including those without cheminformatics or programming skills. At the same time, AI platforms' limitations will be displayed, along with suggestions for improvements, particularly in terms of usability (cf. Designing Usable AI-Based Strategies). Finally, we will consider a practical example; a critical review of a platform, based on HCI methods will be provided, demonstrating how usability can be enhanced to facilitate and make the interaction process more effective.

## 1.1 AI-Based Platforms for Drug Discovery: selected examples

In this section, we will present ten cheminformatics platforms available on the web and realized to support researchers involved in the early phases of the drug discovery process. The input required by these tools is generally represented by a two-dimensional (2D) structure or a Simplified Molecular Input Line Entry System (SMILES; Weininger, 1988) representation of one or more molecules, provided by the user.

Considering their aim and the nature of the tasks they address, these platforms can be classified as either predictive or generative. The former are designed to predict chemical-physical, pharmacological, or toxicological properties of molecules based on Quantitative Structure-Activity Relationship (QSAR) models trained for prediction. Notably, when query compounds significantly differ from the chemicals used to train a QSAR model, the reliability of predictions is compromised. To ensure confidence in predictions, an Applicability Domain (AD) is often defined. The AD outlines the chemical space covered by the model, specifying the range within which predictions can be considered reliable (Gadaleta *et al.*, 2016). On the other hand, generative platforms go beyond prediction, using more advanced Machine Learning (ML) methods, called Deep Learning (DL), with algorithms such as Recurrent Neural Networks (RNN), to automatically design new molecules with specific desired characteristics (Gupta *et al.*, 2018). They could be used to *i)* generate novel, potentially bioactive compounds, *ii)* generate molecules that explore a new chemical space, and *iii)* optimize existing molecules to improve their physicochemical properties (Lamanna *et al.*, 2023). Notably, some cheminformatics platforms integrate both predictive and generative functionalities, enabling simultaneous molecular property estimation and *de novo* molecule design.

Based on a predefined set of key features, we analyze a selection of platforms that were conceived for virtual screening, binding affinity prediction, ADMET profiling, and automatic design of novel drug-like compounds. More specifically, for each platform we examine, a technical sheet specifying certain characteristics will be provided. Firstly, the platform name will be presented including the specific version (when available), followed by general information such as the year of development and the research group behind its creation. The field *Category* will specify whether the platform is predictive or generative, detailing the type of prediction it performs. This may include tasks such as the prediction of toxicological or pharmacological activity, affinity, selectivity, ADMET properties, target fishing, bioactivity profiling, or de novo design. The *Endpoint* section will offer a detailed explanation of the platform's final aim, clarifying its intended application. Meanwhile, *Background and Significance* will feature the specific objectives and relevance of the platform for the scientific community, providing insights into its importance, particularly concerning specific protein targets. The technical aspects will be covered in *Technical information*, where the computational methods and models employed by the platform will be described. Additionally, if the *AD* is considered within the platform, it will be explicitly stated. Furthermore, *Access* will specify whether the platform is publicly available, whether registration is required, and will include a link to the webpage. The nature

of the data input will be detailed in the *Input* section, explaining both the type and modality of the required information. Similarly, the *Output* section will outline the type and format of the results provided, accompanied by a visual representation (Figure). Information about updates and engagement with the scientific community will be covered in *Community and updates*, where the year and publication of any available updates will be recorded. For user assistance, the *Technical support* section will list available resources such as contact forms, or direct contact addresses. Finally, *Further information* will include supplementary details that may be useful for users, such as guidelines, instructions, and estimated processing time, whenever these details are provided.

### 1.1.1 PRED-hERG (5.0)

Developed in 2014 (Braga *et al.*, 2014, 2015) by the Laboratory for Molecular Modeling and Drug Design (LabMol, http://insightai.labmol.com.br/), which was established at the Faculty of Pharmacy of the Federal University of Goiás in Brasil.

*Category*: Predictive – classification and regression prediction of toxicological activity.

*Endpoint:* The platform performs binary and multiclass classification of chemicals that may induce cardiotoxicity by blocking the human Ether-à-go-go Related Gene (hERG) channel (Taglialatela *et al.*, 1998). The compounds are categorized as strong blockers, moderate/weak blockers, and non-blockers. Through a regression model, it also provides a prediction of the $pIC_{50}$ resulting from the hERG-related block.

*Background and Significance*: hERG is a transmembrane potassium channel involved in the regulation of cardiac action potential. Binding of structurally diverse drugs can cause hERG blockage induced cardiotoxicity associated with ventricular arrhythmia and, in extreme cases, sudden death (Taglialatela *et al.*, 1998; Cavalluzzi *et al.*, 2020).

*Technical information*: The tool includes two classification models, namely binary and multiclass, and a regression model. All the three tasks (binary, multiclass and regression) are integrated into a weighted consensus prediction. The platform was trained on 14,364 chemicals with hERG data extracted from ChEMBL database (Gaulton *et al.*, 2012).

*AD*: The reliability of the prediction, based on the AD of the model, is reported in the platform output. Specifically, it indicates whether the input molecule falls within the AD, considering a similarity threshold of 30%.

*Access*: The platform is freely accessible at http://predherg.labmol.com.br/ and no registration is required.

*Input*: The user can either draw the 2D chemical structure of the query using the drawing tool Ketcher (Version 2.10.0; Karulin and Kozhevnikov, 2011) provided in the app or paste the compound's SMILES string directly. For batch evaluations, a csv or sdf file, containing the SMILES of multiple compounds, can be uploaded. Once the compounds have been drawn or uploaded, the evaluation process begins by clicking the button ‘Predict’. When the analysis is complete, the app displays the results.

*Output*: PRED-hERG provides *i)* a classificatory and multiclass prediction of hERG blockage, with an associated percentage of confiability score, *ii*) a regression prediction, with the $pIC_{50}$ value estimation, *iii*) the reliability assessment of the predictions, based on the AD of the model, *iv*) a probability map , highlighting the contribution of specific chemical fragments to each prediction, and *v*) a prediction based on the consensus of the binary, multiclass and regression models, to better assist the decision-making process of the user. An example of the platform output is available in Figure 1. The user can also launch an eXplainable AI (XAI) analysis, enabling the visualization of SHapley Additive exPlanations (SHAP) values (Lundberg and Lee, 2017) to better understand the contribution of individual features to binary classification.

*Community and updates*: The platform does not include user communication features. It has been updated in 2018 (Alves, Braga and Andrade, 2018) and 2024 (Sanches *et al.*, 2024).

*Technical support*: The platform includes a 'GET IN TOUCH' button which allows users to contact the research group by completing a form to report any issues they encounter.
*Further information*: The platform provides detailed instructions to guide users through the input process, ensuring ease of use even for those with limited technical expertise. However, it does not allow customizing settings or parameters. Once processing is completed, the system supplies the outcomes in a few seconds. The output is presented in a clear and structured manner, with a well-organized interface that facilitates interpretation and navigation.

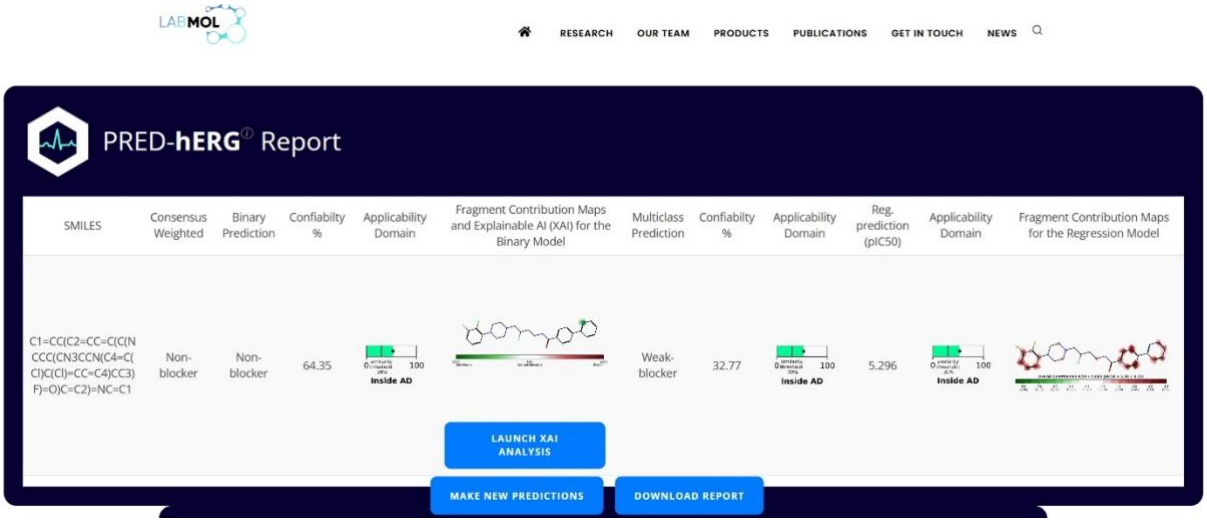



**Figure 1.** Screenshot of the output reported by the PRED-hERG web platform (http://predherg.labmol.com.br/; Braga *et al.*, 2014, 2015) using as input SMILES:
`C1C=CN=C(C2C=CC(C(=O)NCCC(F)CN3CCN(C4C=CC=C(Cl)C=4Cl)CC3)=CC=2)C=1`

### 1.1.2 PRED-SKIN (3.0)

Developed in 2017 (Alves *et al.*, 2016; Braga *et al.*, 2017) by LabMol at the Faculty of Pharmacy of the Federal University of Goiás, Brasil.
*Category*: Predictive – classification prediction of toxicological activity.
*Endpoint:* The platform performs a binary classification of chemicals based on their skin sensitization potential, categorizing compounds as sensitizer/non-sensitizer.
*Background and Significance*: Skin sensitization is an immunological response to certain chemicals that can manifest as an inflammatory skin reaction, mediated by delayed-type T cells causing allergic contact dermatitis (Kimber *et al.*, 2002).
*Technical information*: The tool employs five QSAR models built for different skin sensitization assays, including the Direct Peptide Reactivity Assay (DPRA, *in chemico;* OECD, 2024), Local Lymph Node Assay (LLNA, *in vivo;* OECD, 2010), KeratinoSens (Casati *et al.*, 2014), and the human Cell Line Activation Test (h-CLAT, *in vitro;* EU, 2009) and human assays. Additionally, a Bayesian model is provided as a consensus classifier integrating predictions from all the other models.
*AD*: In the platform output, an indication of whether the compound is inside or outside the AD for each prediction model is provided.
*Access*: The platform is freely accessible at http://predskin.labmol.com.br/ and no registration is required.
*Input*: The user has two options for inputting its query molecule, they can either draw its 2D structure using the JSME canvas applet (Bienfait and Ertl, 2013) or directly enter a SMILES string into the designated text field. Subsequently, the user can click the red 'Predict Skin Sensitization' button to launch the prediction and obtain the results.
*Output*: The results are displayed as a table showing the predicted skin sensitization potential. The predictions are based on an *in silico* integrated approach employing two models with non-animal data,

namely the *Molecular initiating event* and the *Cellular response.* Moreover, two *in vivo* models are being used; specifically, one built on LLNA (*Tissue/Organ response)*, and one built on human data (*Organism response)*. The predictions made by these models serve as inputs for the Bayesian model, which, ultimately, generates a final ensemble prediction for the skin sensitization response in humans (Figure 2). Alongside the predictions and their confiability, the platform assesses the compliance of the input molecule with the AD and generates maps highlighting the predicted fragment contributions to the overall response.

*Community and updates*: User communication features are not included. It has been updated in 2018 (Alves *et al.*, 2018) and 2021 (Borba *et al.*, 2021).

*Technical support*: A 'GET IN TOUCH' button which allows the user to contact the research group is available.

*Further information*: The platform provides step-by-step instructions to guide users through the input process. Once processing is complete, the system delivers results within seconds. However, the platform does not allow customization of settings or parameters. While the output is presented in a structured format within a well-organized interface, the results page is densely packed with text-based information. This can reduce intuitiveness and increase the time required to locate and fully comprehend the output data.

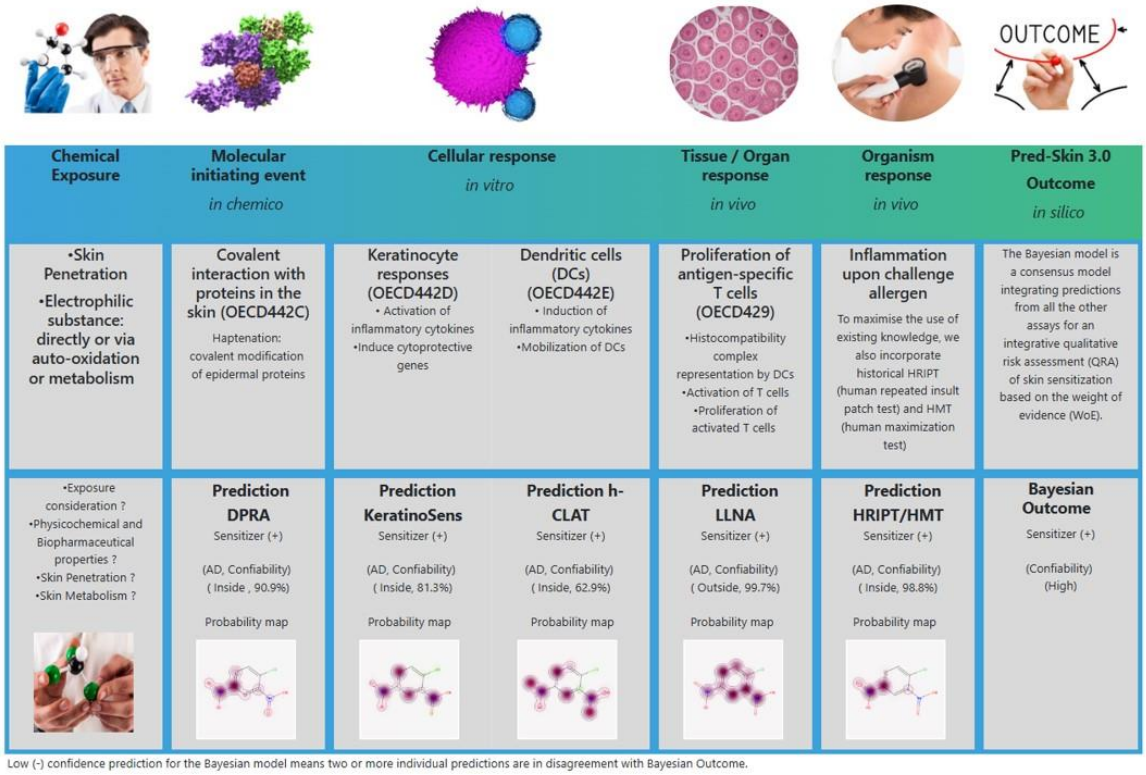



**Figure 2.** Screenshot of the output reported by the PRED-SKIN web platform (http://predskin.labmol.com.br/; (Alves *et al.*, 2016; Braga *et al.*, 2017) using as input SMILES: `C1=CC(=CC(=C1C)N+[O-])N+[O-]`

### 1.1.3 CYTO-SAFE

Developed in December of 2024 (Feitosa *et al.*, 2024) by LabMol at the Faculty of Pharmacy of the Federal University of Goiás, Brasil.

*Category*: Predictive – classification prediction of toxicological activity.

*Endpoint*: The platform performs binary classification of chemicals based on their cytotoxic potential, categorizing compounds as toxic/non-toxic.

*Background and Significance*: Cytotoxicity is the ability of a chemical to cause damage on cellular health, often causing cell death (Khalef *et al.*, 2024). Assessing the cytotoxic potential of molecular structures can help prioritize low-risk compounds for further validation in the early stages of the drug discovery process.
*Technical information*: The platform utilizes two QSAR models based on a PubChem dataset of approximately 90,000 compounds, evaluated against two cell lines, 3T3 and HEK-293.
*AD*: It is considered by the platform and reported in the output specifying a similarity threshold of 10%.
*Access*: The platform is freely accessible at http://cytosafe.labmol.com.br/ and no registration is required.
*Input*: The user can draw the 2D chemical structure of the query using the drawing tool Ketcher (Version 2.10.0) provided in the app. Alternatively, it is possible to paste the compound's SMILES string directly into the drawing tool. For batch evaluations, a csv or sdf file containing the SMILES of multiple compounds can be uploaded. Once the compound(s) have been drawn or uploaded, by clicking the button 'Predict' the evaluation process begins. When the analysis is complete, the platform displays the results.
*Output*: The output includes a binary toxicity prediction for each cell line (toxic/non-toxic), along with a confidence percentage, and the AD assessment for the input molecule. Additionally, users can initiate an XAI analysis via a dedicated button, enabling the visualization of molecular diagrams and heatmaps and the identification of specific molecular regions that contribute to either 'cytotoxic' (red) or 'non-cytotoxic' (green) outcomes (Figure 3).
*Community and updates*: The platform does not include user communication features and has not yet received updates.
*Technical support*: The platform includes a 'GET IN TOUCH' button in the top-right section, which allows users to complete a form to report any issues they encounter.
*Further information*: The platform provides detailed instructions to guide users through the input process. Once processing is complete, the system delivers results within seconds. However, the platform does not support customization of settings or parameters. The output is presented in a clear and structured manner, with a well-organized interface that facilitates interpretation and navigation. Publications for more information are not yet available, as the dedicated section currently displays the message 'Will be available soon'.

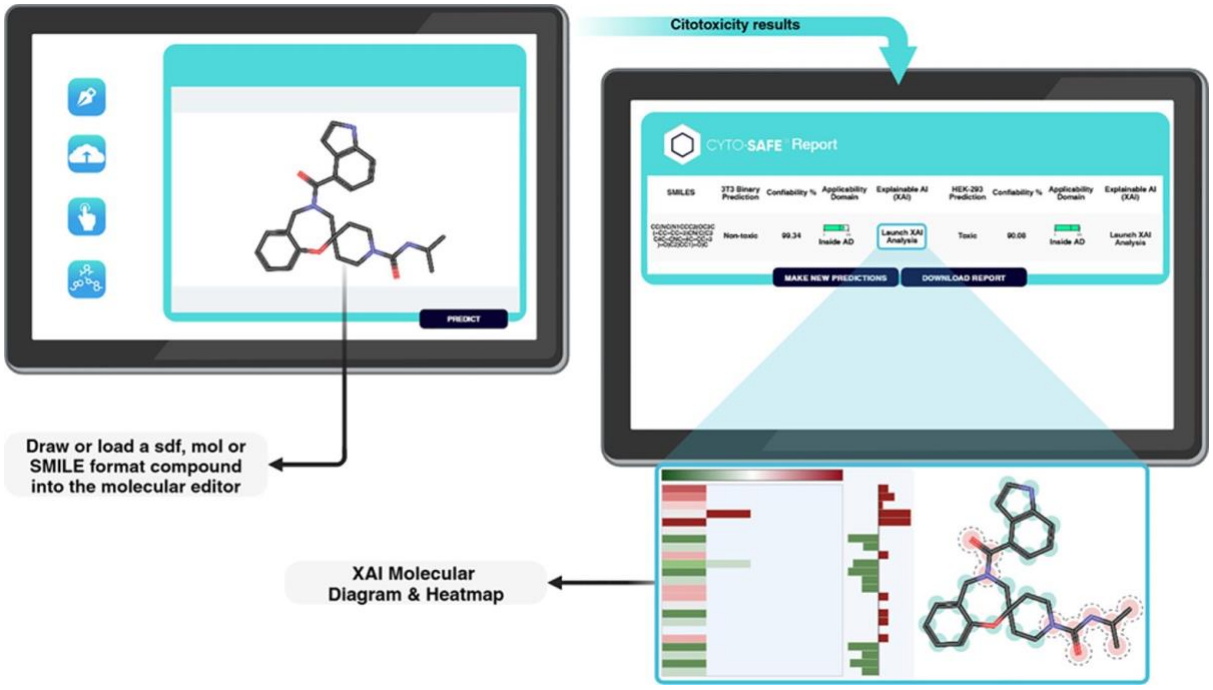



**Figure 3.** General scheme of usage, outcome and XAI of Cyto-Safe web app (http://cytosafe.labmol.com.br/). Figure taken from Feitosa *et al.*, 2024 (https://creativecommons.org/licenses/by/4.0/).

### 1.1.4 AMALPHI

Developed in 2024 (Lomuscio *et al.*, 2024) by our research group as a result of the on-going collaboration between the Institute of Crystallography, National Research Council (IC-CNR) and the Department of Pharmacy-Pharmaceutical Sciences, University of the Studies of Bari "Aldo Moro".

*Category*: Predictive – classification prediction of toxicological activity.

*Endpoint*: The platform performs binary classification of chemicals based on their Phospholipidosis (PLD) potential, categorizing compounds as either PLD inducers or non-inducers.

*Background and Significance*: PLD is a side effect associated with prolonged exposure to drug-like compounds, predominantly Cationic Amphiphilic Drugs (CADs), characterized by the accumulation of phospholipids in cells, particularly within lysosomes, of different organs, including liver and kidneys (Lüllmann *et al.*, 1975).

*Technical information*: The tool relies on a Balanced Random Forest (BRF) algorithm used to build a classifier whose training was based on high-quality chemical collection comprising 545 curated small molecules extracted from ChEMBL v30.

*AD*: A binary output (yes/no) on prediction reliability, based on AD, is included.

*Access*: The platform is freely accessible for academic users at https://www.ba.ic.cnr.it/softwareic/amalphiportal/ and requires user registration with an email address.

*Input*: The user has two options for inputting its query molecule, they can either draw its 2D structure using the JSME canvas applet or directly enter a SMILES string into the designated text field. Additionally, for virtual screening applications, the user can upload a text file containing a list of SMILES strings by selecting the 'Massive' button.

*Output*: AMALPHI predicts the potential of each compound to act as a PLD inducer. Results are displayed as 'YES' if the BRF model predicts the compound to induce PLD, and 'NO' if it does not. The prediction is provided along with a confidence level (Figure 4). The user can download the results as a csv file, and a link to download the predictions is also sent to the user's registered email address.

Moreover, the platform 'History' page keeps a complete record of all user executions, including the uploaded input SMILES files and their corresponding outputs, ensuring easy access to past analyses.
*Community and updates*: The platform does not include user communication features and has not yet received updates.
*Technical support*: The platform offers technical support through a section accessible by clicking the 'Contact' button. Here, the user can complete a form to report any issues they encounter.
*Further information*: The platform provides the output in a few seconds with a well-organized interface. Settings or parameters customization are not provided.

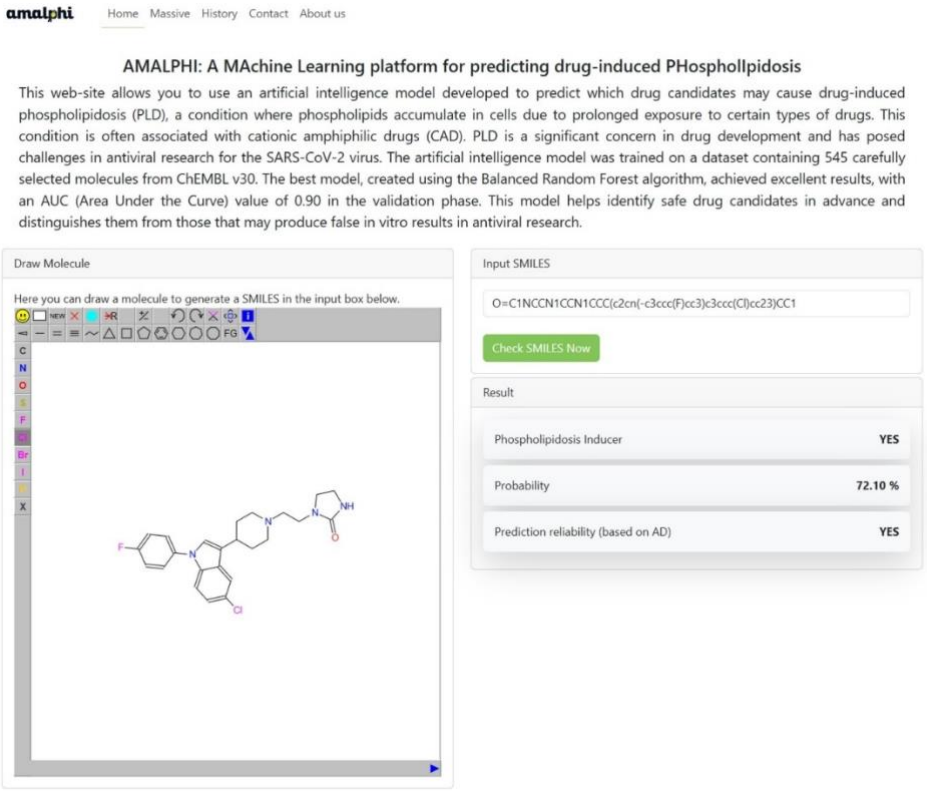



**Figure 4.** Screenshot of the output page returned by the AMALPHI web platform (https://www.ba.ic.cnr.it/softwareic/amalphiportal/). Figure taken from Lomuscio *et al.*, 2024 (https://creativecommons.org/licenses/by-nc-nd/4.0/).

### 1.1.5 SIGMAP

Developed in 2024 (Lomuscio *et al.*, 2025) by our research group as a result of the ongoing collaboration between the IC-CNR, the Department of Computer Science and the Department of Pharmacy-Pharmaceutical Sciences, University of the Studies of Bari "Aldo Moro".
*Category*: Predictive – classification prediction of pharmacological affinity.
*Endpoint*: The platform performs binary classification of chemicals based on their affinity potential for Sigma-1 Receptor, categorizing compounds as high affinity S1R ligands (yes/no).
*Background and Significance*: S1R is involved in the pathological processes of neurodegenerative diseases, (Couly, Yasui and Su, 2023) cancer progression (Fallica *et al.*, 2021), and viral infections, including COVID-19 (Gordon *et al.*, 2020; Abatematteo *et al.*, 2023). Hence, developing S1R modulators is considered a valuable therapeutic approach for addressing these diverse medical conditions.
*Technical information*: The system uses an ML-based model employing the support vector machine algorithm, trained on a curated dataset of high-quality bioactivity data. The dataset consists of 2,967 chemicals extracted from ChEMBL v33 and experimentally tested as potential S1R modulators.

*AD*: The platform includes a binary output (yes/no) for the prediction reliability, based on AD.
*Access*: SIGMAP is freely accessible for academic users at https://www.ba.ic.cnr.it/softwareic/sigmap/ and requires user registration with an email address.
*Input*: The user has two options for inputting its query molecule: they can either draw its 2D structure using the JSME canvas applet or directly enter a SMILES string into the designated text field. Additionally, the user can upload a txt file containing a list of SMILES strings by selecting the 'Massive' button.
*Output*: If the model identifies a molecule as S1R high-affinity binder, the result is shown as 'YES'. If low or no affinity is predicted, it is displayed as 'NO'. For predictions of high affinity, the system also provides a confidence level. When a unique query molecule is entered, SIGMAP offers additional insights through SHAP and Contrastive Explanation-based analyses (Jacovi *et al.*, 2021), aiding in the interpretation of the results (Figure 5). Through the Contrastive Explanation, SIGMAP can also generate 10 structural analogs of the input molecule providing the user with both similar (predicted as the input molecule) and dissimilar (counterfactual) examples. Similar examples can strengthen the classifier robustness by validating the model stability within the chemical prediction space. Additionally, counterfactual examples make the analysis actionable by bringing out small structural modifications that would alter the model prediction (Wellawatte *et al.*, 2023). This analysis is achieved using a generative model named (Alberga *et al.*, 2024) *DeLA-DrugSelf,* with which SIGMAP is integrated.
*Community and updates*: The platform does not include user communication features and has not yet received updates.
*Technical support*: The platform offers technical support through a section accessible by clicking the 'Contact' button. Here, the user can complete a form to report any issues they encounter.
*Further information*: The platform provides the output within minutes with a structured manner, facilitating interpretation. However, the platform does not support customization of settings or parameters.

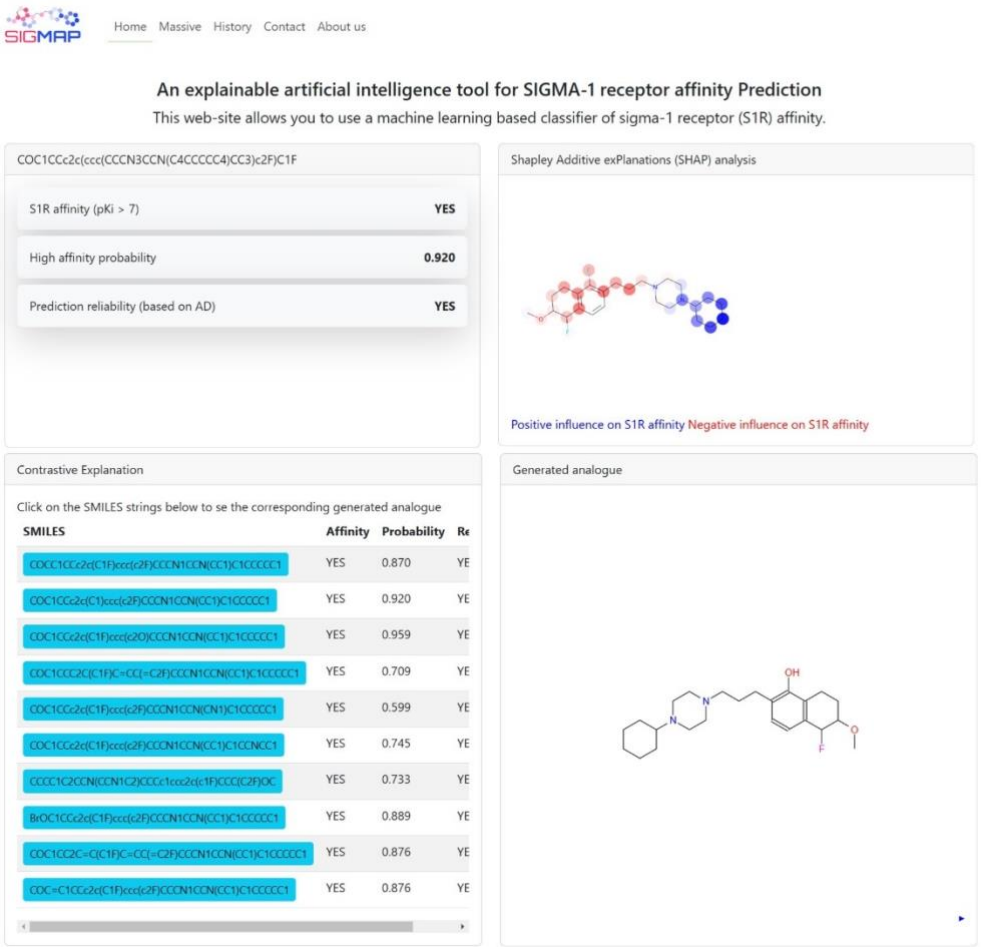



**Figure 5.** Screenshot of the output page returned by the SIGMAP web platform (https://www.ba.ic.cnr.it/softwareic/sigmap/). Figure taken from Lomuscio *et al.*, 2025 (https://creativecommons.org/licenses/by/3.0/).

### 1.1.6 ALPACA

Developed in 2023 (Delre *et al.*, 2023) by our research group as a result of the on-going collaboration between IC-CNR and the Department of Pharmacy-Pharmaceutical Sciences, University of the Studies of Bari "Aldo Moro".

*Category*: Predictive – classification prediction of pharmacological affinity and selectivity.

*Endpoint*: The platform performs binary classification of chemicals based on their potential affinity for Cannabinoid Receptor 1 (CB1R) and Cannabinoid Receptor 2 (CB2R) and prediction of their CB2R selectivity.

*Background and Significance*: CB1R and CB2R are involved in several disorders linked to inflammation (Turcotte *et al.*, 2016), such as neurodegenerative diseases, cancer and neuropathic pain. CB2R is overexpressed in inflammatory state, suggesting that developing selective CB2R agents may be an effective strategy for treating neuroinflammation, while avoiding the psychotropic side effects associated with CB1R stimulation in the central nervous system (Komorowska-Müller and Schmöle, 2020; Tanaka, Sackett and Zhang, 2020).

*Technical information*: The tool uses multiple random forest-based models, trained on three different curated datasets, comprising 3,514 (for CB2R affinity models), 3,846 (for CB1R affinity models), and 2,183 (for CB2R/CB1R selectivity model) chemicals extracted from ChEMBL v30.

*AD*: The platform evaluates the input molecule and provides a binary output indicating whether it falls within or outside the AD.
*Access*: ALPACA is freely accessible for academic users at https://www.ba.ic.cnr.it/softwareic/alpaca/ and requires user registration with an email address.
*Input*: The user has two options for inputting its query molecule: they can either draw its 2D structure using the JSME canvas applet or directly enter a SMILES string into the designated text field. Additionally, the user can upload a txt file containing a list of SMILES strings by selecting the 'Massive' button.
*Output*: The tool predicts the affinity of the query molecule for CB2R and CB1R. For CB2R, affinity is evaluated based on pKi thresholds of 6.5 and 7, while for CB1R, the thresholds are set at pKi 5.5 and 6. If the predicted affinity exceeds the respective threshold, the result is displayed as 'YES'; otherwise, it appears as 'NO' (Figure 6). If the query molecule is predicted to bind both CB2R and CB1R above their respective thresholds, a tertiary classifier further evaluates CB2R/CB1R selectivity. The user can download the results as a csv file, and a link is also sent to the registered email address. Additionally, the 'History' page maintains a record of all user submissions, including input SMILES and corresponding outputs.
*Community and updates*: The platform does not include user communication features and has not yet received updates.
*Technical support*: The platform offers technical support through a section accessible by clicking the 'Contact' button. Here, the user can complete a form to report any issues they encounter.
*Further information*: ALPACA generates the output within seconds and presents it through a well-structured interface for easy navigation. However, it does not support customization of parameters.

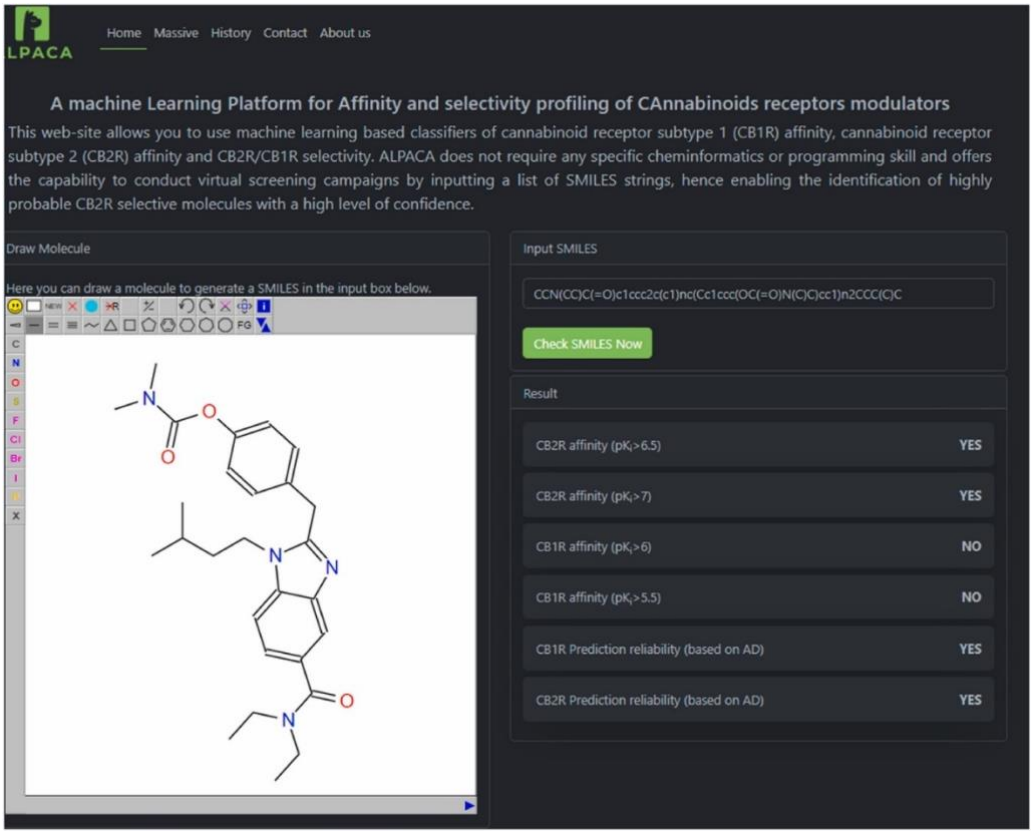



**Figure 6.** Example of the output page returned by the ALPACA web platform (https://www.ba.ic.cnr.it/softwareic/alpaca/). Figure taken from Delre *et al.*, 2023 (https://creativecommons.org/licenses/by/4.0/).

### 1.1.7 PLATO (r35)

Developed in 2022 (Ciriaco *et al.*, 2022) by the Department of Pharmacy-Pharmaceutical Sciences and the Department of Chemistry of University of the Studies of Bari "Aldo Moro".

*Category*: Predictive – classification and regression prediction for target fishing and bioactivity profiling.

*Endpoint*: The platform performs classification and regression prediction of affinity on 6,297 different targets.

*Background and significance:* In-silico target fishing can be used to predict potential side-effects of a given compound, identify putative drug polypharmacology and facilitate drug repositioning.

*Technical information*: PLATO is based on two multi-fingerprint similarity-based predictive approaches designed for target fishing (based on classification models) and bioactivity profiling (based on regression models; Montaruli *et al.*, 2019; Ciriaco *et al.*, 2021), specifically employing the Multifingerprint Similarity Search Algorithm (Mussel) (Alberga *et al.*, 2019). The models use a set of 634,116 compounds with experimental bioactivity data for 6,297 protein targets, retrieved from ChEMBL v35 (Zdrazil *et al.*, 2024).

*AD*: This platform does not consider an AD and hence does not provide an AD evaluation.

*Access*: The platform is freely accessible for academic users at http://plato.uniba.it/plato/; no registration is required.

*Input*: The query molecule is entered either as SMILES or by using the JSME sketcher for opening, importing or modifying a molecular structure. The user can then choose the output format as well as the prediction method, which can be 'Target fishing' or 'Bioactivity profiling'. The 'Get a response' button is used to launch the prediction. A batch evaluation is not possible.

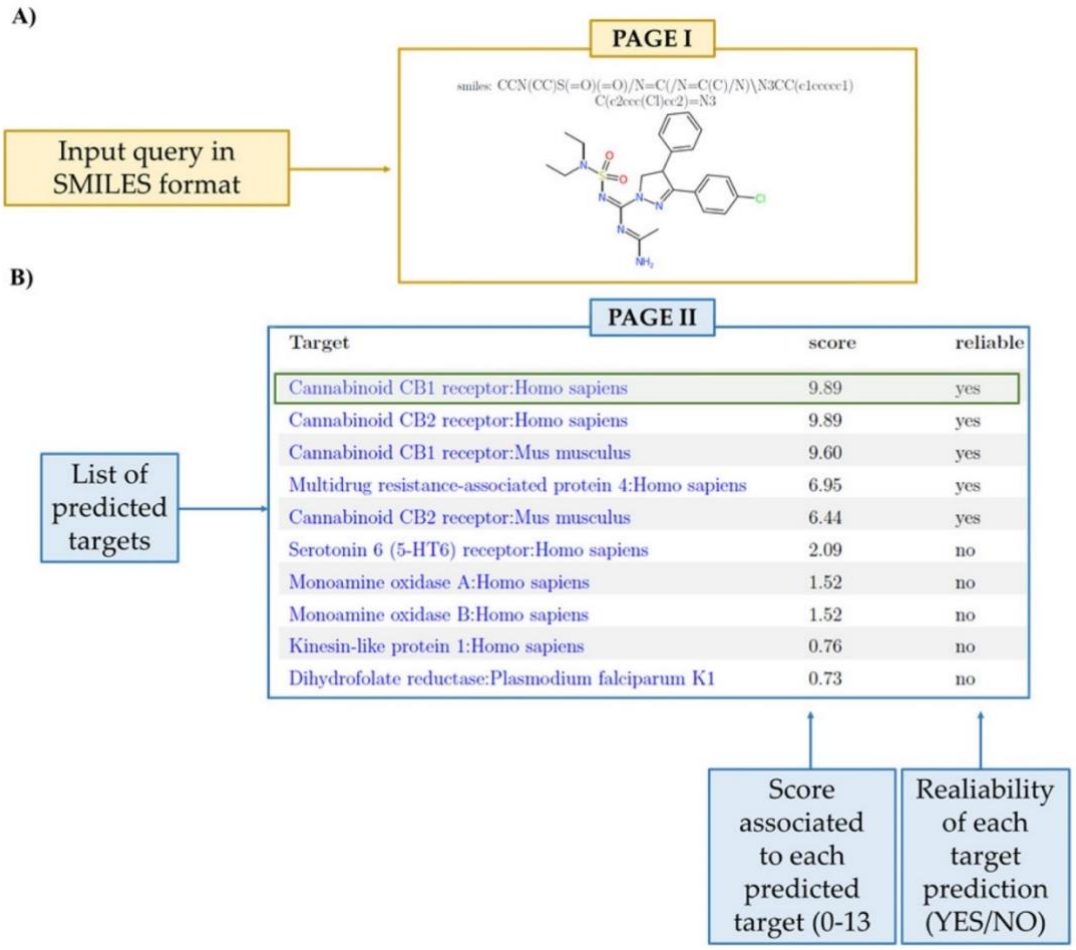
*Output*: A downloadable pdf output is returned. In the first page, the type of prediction (target fishing or bioactivity profiling), the query chemical structure and SMILES notation are reported (Figure 7). The following pages contain the prediction reports. The report of the quantitative bioactivity profiling algorithm contains the target name, the score, on a scale 0-13 of the protein drug target ranking and the 'reliable' column expressing the probability to detect a target with a degree of accuracy according to a similarity threshold. The quantitative bioactivity profiling report includes the target name, the predicted activity values expressed as $IC_{50}$, $K_i$ or $EC_{50}$, and the variance for the best predicted activity type.

*Community and updates*: The platform does not include user communication features. However, it received multiple updates, aligning with each new release of the ChEMBL database (Davies *et al.*, 2015; Gaulton *et al.*, 2017; Mendez *et al.*, 2019).

*Technical support*: The platform provides users with a mail address for technical support, but no form to report potential issues is available.

*Further information*: The platform offers a downloadable user guide and generates the output within 2 to 20 seconds, as stated in a message that appears after the prediction process is submitted.

Once processing is complete, the output is delivered differently from other platforms. Instead of displaying a webpage, the results are provided directly to the user as a pdf or json file.




| Target | score | reliable |
|---|---|---|
| Cannabinoid CB1 receptor:Homo sapiens | 9.89 | yes |
| Cannabinoid CB2 receptor:Homo sapiens | 9.89 | yes |
| Cannabinoid CB1 receptor:Mus musculus | 9.60 | yes |
| Multidrug resistance-associated protein 4:Homo sapiens | 6.95 | yes |
| Cannabinoid CB2 receptor:Mus musculus | 6.44 | yes |
| Serotonin 6 (5-HT6) receptor:Homo sapiens | 2.09 | no |
| Monoamine oxidase A:Homo sapiens | 1.52 | no |
| Monoamine oxidase B:Homo sapiens | 1.52 | no |
| Kinesin-like protein 1:Homo sapiens | 0.76 | no |
| Dihydrofolate reductase:Plasmodium falciparum K1 | 0.73 | no |

**Figure 7.** Example of the target fishing output page returned by the PLATO web platform (http://plato.uniba.it/) including A) the SMILES query and the B) table of the predicted protein targets. Figure adapted from Ciriaco *et al.*, 2022 (https://www.mdpi.com/openaccess).

### *1.1.8* SwissADME

Developed in 2017 (Daina, Michielin and Zoete, 2017), SwissADME is an example of application within *SwissDrugDesign*, a project whose goal is to create a comprehensive web-based *in silico* drug design environment freely available to researchers worldwide. The platform, providing a diverse set of tools that covers all aspects of Computer-Aided Drug Design, has been developed by the Molecular Modelling group (MMG) of the Swiss Institute of Bioinformatic (SIB) with the support of the Swiss National Science Foundation, for the scientific developments, and of the SIB, for the creation and maintenance of its web-based tools.

SwissDrugDesign includes seven applications for multiple objectives, including the prediction of molecular interactions between a target protein and a small molecule, hit identification and lead optimization, target fishing and Absorption, Distribution, Metabolism, Excretion (ADME) properties prediction.

*Category*: Predictive – classification and regression prediction of ADME properties.

*Endpoint*: The platform performs classification and regression prediction of physicochemical properties, lipophilicity, water solubility, pharmacokinetics, drug-likeness and medicinal chemistry friendliness.

*Background and Significance*: These properties and parameters influence the ADME of a molecule. Assessing ADME properties is crucial in drug development to identify compounds with high biological activity and minimal toxicity, increasing their likelihood of successful clinical translation.

*Technical information*: The platform integrates multiple computational methods to provide a comprehensive assessment of the pharmacokinetics profile of small molecules. Open-source algorithms are at the base of some of these methods, ensuring the freedom for the global scientific community to use the results without requiring further permission. Additionally, it offers models specifically developed and tested by the MMG of SIB. Whenever possible, the platform provides multiple predictions for the same property, making possible a consensus-based evaluation of the results. The physicochemical properties, such as molecular weight, molar refractivity and polar surface area, are computed through the OpenBabel API (O'Boyle *et al.*, 2011). For lipophilicity prediction, four established methods, along with an in-house approach (iLOGP; Daina, Michielin and Zoete, 2014), are implemented to calculate the logP. A consensus value is then provided based on the predictions from all five methods. Three methods, ESOL model (Delaney, 2004), Ali (Ali *et al.*, 2012) and SILICOS-IT (www.silicos-it.be/software.html) are implemented to predict the water solubility. Most of the models used for pharmacokinetic prediction are machine-learning binary classifiers based on the support vector machine algorithm. Passive Gastro-Intestinal Absorption (HIA) and Blood-Brain Barrier (BBB) permeation are assessed using the BOILED-Egg classification model (Daina and Zoete, 2016).
The *drug-likeness* prediction is based on six rule-based filters, including the Lipinski rule-of-five (Lipinski, 2004) and the Abbot Bioavailability Score (Martin, 2005).
*AD*: This platform does not consider an AD and hence does not provide an AD evaluation.
*Access*: SwissADME is freely accessible at http://www.swissadme.ch/ and no registration is required.
*Input*: The input area features a molecular sketcher powered by ChemAxon's Marvin JS (Cherinka *et al.*, 2019), enabling users to import chemical structures from files or external databases, as well as draw and edit 2D structures before adding them to a molecule list. This list, located on the right side of the submission page, serves as the actual input for computation. It can be edited as text, enabling the user to type or paste SMILES. Each entry in the list corresponds to a single molecule, represented by its SMILES notation and, optionally, a name, separated by a space.
*Output*: The output panels, one for each molecule submitted, are loaded immediately after calculation completion on the same web page (Figure 8). The 2D chemical structure and the corresponding canonical SMILES are reported below the title, indicating which molecule the prediction refers to. Additionally, a bioavailability radar plot is displayed, offering a quick assessment of drug-likeness based on six physicochemical properties: lipophilicity, size, polarity, solubility, flexibility, and saturation. Then, the various models and the corresponding data are grouped in different sections of output panel ('Physicochemical Properties', 'Lipophilicity', 'Pharmacokinetics', 'Druglikeness' and 'Medicinal Chemistry'). Additional information and references appear as pop-ups when hovering over the red question mark icons next to certain entries or over the bioavailability radar plot. SwissADME output data can be exported in two ways. An option is to download a csv file, via the red icon below the SMILES list, or to copy the values to the clipboard using the adjacent red icon, allowing pasting into any text or spreadsheet application. A graphical output is also available; once all calculations are completed, the 'Show BOILED-Egg' red button appears below the sketcher, allowing users to visualize the results on the same page. The BOILED-Egg model provides an intuitive prediction of passive HIA and BBB penetration, based on the molecule's position in the WLOGP-versus-TPSA referential. The white region indicates a high probability of passive absorption in the gastrointestinal tract, while the yellow region suggests a high likelihood of brain penetration. Finally, points are blue for predicted PGP+ and red for PGP−.
*Community and updates*: The platform does not include user communication features. As stated in the 'For information' section, the platform received updates in look and feel while keeping the underlying technologies and parameters unchanged. As a result, the updated web tool delivers the same results as the previous version.

*Technical support*: The platform offers technical support through a section accessible by clicking the 'Contact' button. Here, the user can complete a form to report any issues they encounter.
*Further information*: The platform provides detailed instructions to guide the user through the input process. The guide is available by clicking the 'Help' button in the navigation bar. Additionally, clicking the 'Fill with an example' button provides the user with four sample SMILES, two of which are accompanied by the corresponding molecule names, offering an example of how the input should be entered. Once processing is completed, the output is provided almost immediately in a clear and structured manner, with a well-organized interface that facilitates interpretation. The platform does not allow customizing settings or parameters.

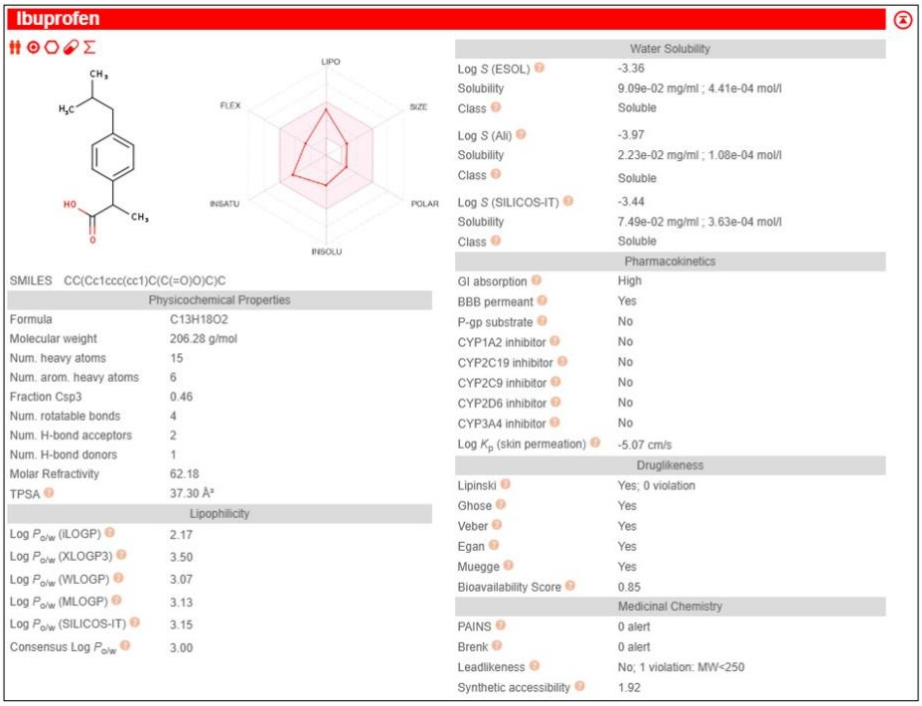



**Figure 8.** Screenshot of the output reported by the SwissADME web platform (http://www.swissadme.ch/; Daina, Michielin and Zoete, 2017) using the following string as input: `CC(C)CC1=CC=C(C=C1)C(C)C(=O)O Ibuprofen`

### 1.1.9 DELA-DRUGSELF

Developed in 2024 (Alberga *et al.*, 2024) by our research group as a result of the on-going collaboration between the IC-CNR, the Department of Pharmacy-Pharmaceutical Sciences of University of the Studies of Bari "Aldo Moro" and the Institute of Biomolecular Chemistry of CNR of Pozzuoli.
*Category*: Generative.
*Endpoint*: The platform performs automatic generation of drug-like analogues.
*Background and Significance*: The automatic generation of analogues supports medicinal chemists in designing derivatives of molecules already available in their laboratories, making them strong candidates for easy and cost-effective synthesis. The resulting libraries serve as valuable starting points for virtual screening procedures.
*Technical information*: The model consists of an R-NN composed of two layers of Long Short-Term Memory (LSTM) units. LSTM architecture is exploited in two generative approaches, namely Sampling from Scratch and Sampling with Mutations.
The Training Set of *DeLA-DrugSelf* was prepared starting from the entire ChEMBL v28 database and consists of 1,092,285 compounds.

While preserving the overall architecture of its predecessor, DeLA-Drug (Creanza *et al.*, 2022), an R-NN model with two layers of LSTM cells, DeLA-DrugSelf introduces significant advancements. The most notable improvement is the adoption of SELF-referencing Embedded Strings (SELFIES) as a molecular representation. Furthermore, it expands generation capabilities by allowing not only token substitutions but also insertions and deletions, thereby enhancing molecular diversity and design flexibility.

*AD*: Generative models are neither definable nor usable, as opposed to predictive models.

*Access*: The platform is freely available at https://www.ba.ic.cnr.it/softwareic/delaself/ and requires user registration with an email address.

*Input*: The user has two options for inputting its query molecule: they can either draw its 2D structure using the JSME canvas applet or directly enter a SMILES string into the designated text field. Additionally, JSME enables the direct import of mol or sdf files into the system. The user can customize the tool based on their preferences by adjusting parameters such as the number of desired compounds (ranging from 10 to 100, with a default of 10) and the number of mutations (ranging from 1 to 5, with a default of 1). Notably, when a query molecule is inserted, the web portal calculates its Quantitative Estimate of Drug-likeness (QED) score. If this score falls below a predefined threshold (<0.35), a warning is displayed, allowing the user to decide whether to proceed with analogues generation. Once the process is complete, the outcomes are displayed.

*Output*: The platform provides an interactive list of SELFIES, converted into SMILES format for simplicity, where the Synthetic Accessibility (SA) values do not exceed a one-unit difference compared to the query molecule (Figure 9). The user can navigate this list in various ways. The generated compounds are ranked based on their QED score, SA value, and Tanimoto similarity to the query, allowing for an intuitive and structured exploration. Additionally, the user has the option to download the ranked list in SMILES (txt or smi format) or sdf files, making it easy to analyze the results offline. For a more detailed inspection, the 2D structures of the generated compounds are readily accessible within the JSME editor by simply clicking on the corresponding SMILES string. Moreover, if requested, the platform can predict whether the generated compounds may interact with specific cytochrome P450 isoforms, including CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4. These predictions are performed using the software CypReact (Tian *et al.*, 2018), providing valuable insights into potential metabolic interactions.

Once the process is complete, the system sends download links for the generated data to the user's registered email. Additionally, a 'History' page keeps track of all user executions, recording details such as the input SMILES and the corresponding generated output, ensuring easy access to past results.

*Community and updates*: The platform does not include user communication features and has not yet received updates.

*Technical support*: The platform offers technical support through a section accessible by clicking the 'Contact' button. Here, the user can complete a form to report any issues they encounter.

*Further information*: The platform provides the output in a few seconds with a well-organized interface. Additionally, it allows customizing some parameters such as 'The maximum number of generated compounds' and 'Number of mutations'.

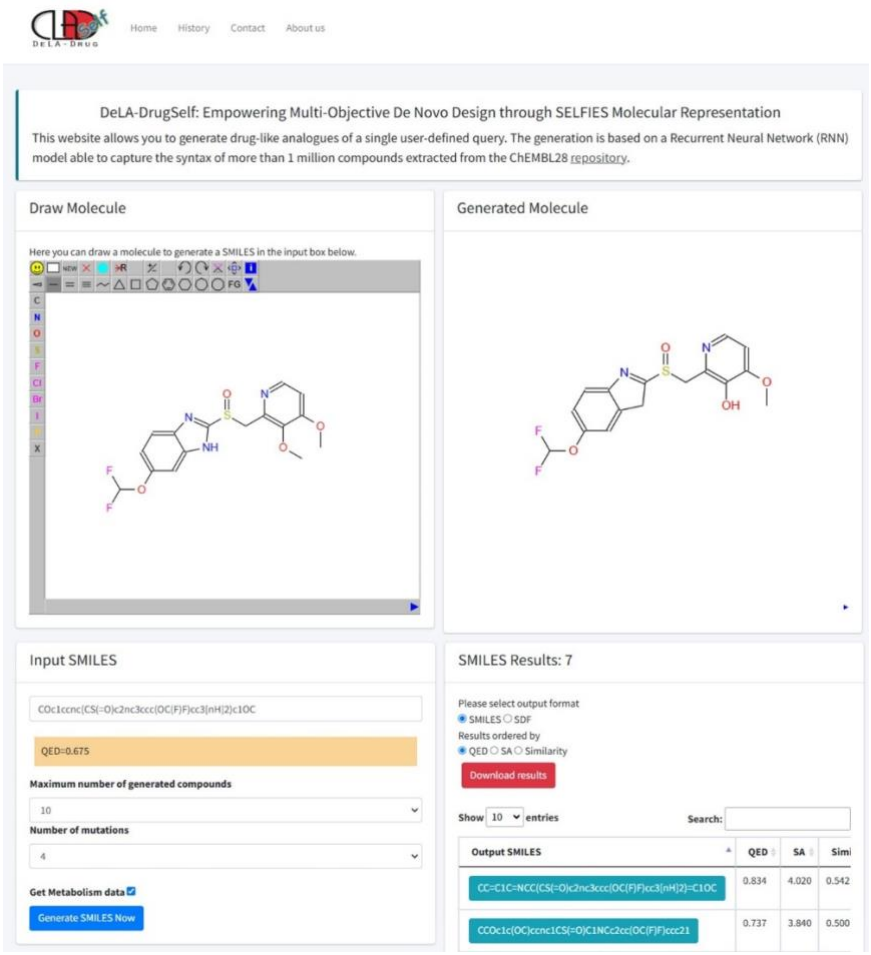



**Figure 9.** Example of the output page returned by the DeLA-DrugSelf web platform (https://www.ba.ic.cnr.it/softwareic/delaself/). Figure taken from Alberga *et al.*, 2024 (https://creativecommons.org/licenses/by/4.0/).

### 1.1.10 **Deep-PK**

Developed in 2024 (Myung, de Sá and Ascher, 2024) by Biosig Lab, located at St Lucia Campus in Brisbane.

*Category*: Predictive - classification and regression prediction of ADMET properties - and generative.

*Endpoint*: The platform performs classification and regression prediction of 73 endpoints - including 64 ADMET and 9 general physicochemical properties - and generation of drug-like analogues.

*Background and Significance*: Evaluating ADMET and general physicochemical properties is essential for identifying compounds with high biological activity and low toxicity. Examining these properties supports molecular optimization ensuring favorable pharmacokinetic and safety profiles. Moreover, the automated generation of analogues helps medicinal chemists by facilitating the design of new derivatives based on already available molecules.

*Technical information*: The platform incorporates multiple DL models based on Graph Neural Networks, specifically using D-MPNN of Chemprop (Yang *et al.*, 2019), including 49 models designed for binary classification and 24 for regression tasks. Chemprop (Heid *et al.*, 2024) was also utilized to identify key molecular substructures influencing predictions, offering insights into which molecular sites should be retained, modified, or removed.

For the optimization process in Deep-PK, the MultI-constraint MOlecule Sampling (MIMOSA) method (Fu *et al.*, 2021) was implemented, enabling the generation of up to 100 molecular variants from a given query structure by adding, replacing, or removing substructures. Moreover, a pre-trained model was

employed to optimize the QED, ensuring the refinement of generated compounds based on drug-likeness criteria.

*AD*: Deep-PK includes binary indicators for regression tasks, specifying whether the input molecule falls or not within the AD.

*Access*: The platform is freely accessible at https://biosig.lab.uq.edu.au/deeppk/ and no registration is required.

*Input*: Deep-PK supports different types of input. The user can provide a single molecule as a SMILES string or upload a file containing multiple compounds. Specifically, the platform accepts SMILES files and sdf files, each capable of containing up to 2,000 molecular structures. Additionally, the user can input a molecule by drawing its structure using the JSME canvas applet, from which the corresponding SMILES representation is automatically generated.

*Output*: The platform shows four key prediction outputs, each presented on a dedicated page (Figure 10). First, the 'Predictions' page displays the predicted pharmacokinetic, toxicity, and general molecular properties when all selected models have completed their analyses. Second, the 'Focus' page provides a detailed overview of the molecule, including its structure, SMILES representation, and predicted properties. Third, the 'Analysis' page allows for a deeper exploration of the molecules whose ADMET properties were predicted. The user can examine general properties, drug-likeness scores, and the importance of specific molecular substructures in the predictions. Additionally, this page features radar plots that visually represent different aspects of drug-likeness. Lastly, the 'Optimization' page is dedicated to refining the given query molecule to improve its pharmacokinetic and toxicity properties. The user can download the results from both the 'Prediction' and 'Optimization' pages as csv files, while the data from the 'Analysis' page is provided in a zip file.

*Community and updates*: The platform lacks user communication features and has not yet been updated.

*Technical support*: The platform offers technical support through a dedicated section accessible by clicking the 'Contact' button and selecting 'Deep-PK' in the 'Subject' field. The user can then write a message and send it by clicking the 'Send' button.

*Further information*: The platform provides detailed instructions available by clicking the 'Help' button in the navigation bar. The 'Theory' button offers detailed insights into all target predictions, including their description, interpretation, and assay type. The user can also download this information as a pdf file for offline reference. Deep-PK requires up to 15 minutes to predict all 73 properties of a single molecule. Optimizing a molecule, generating and predicting 100 analogues requires approximately 20 minutes. Once processing is completed, the output is provided with a well-organized interface.

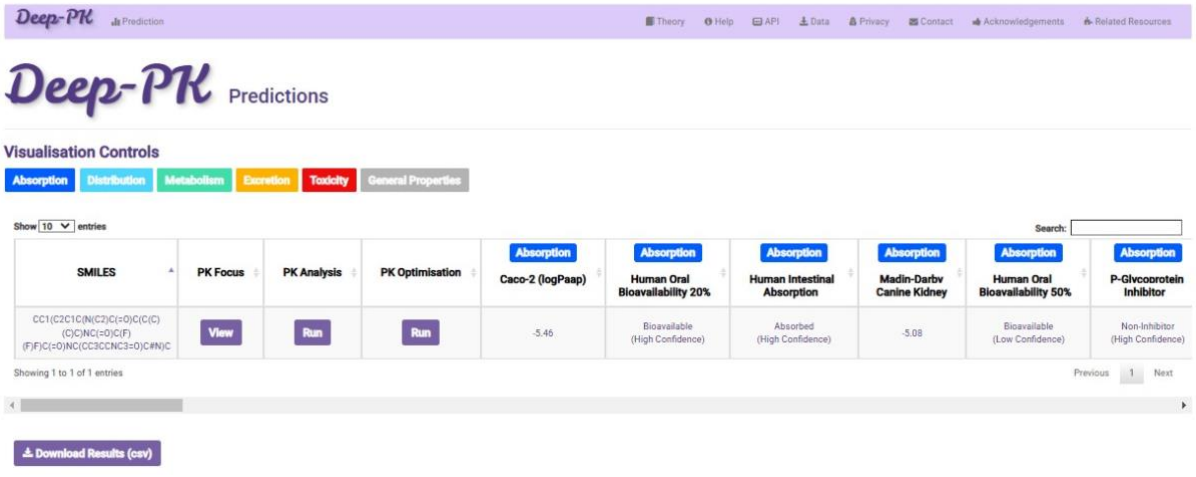



**Figure 10.** Screenshot of the 'Predictions' output page reported by the Deep-PK web platform (https://biosig.lab.uq.edu.au/deeppk/; Myung, de Sá and Ascher, 2024) using as string SMILES: `CC1(C2C1C(N(C2)C(=O)C(C(C)(C)C)NC(=O)C(F)(F)F)C(=O)NC(CC3CCNC3=O)C#N)C`

A comprehensive overview of all the web platforms presented is provided in Table 1.

**Table 1**. Comparative overview of the platforms discussed in this chapter. Each entry is characterized by category (Predictive and/or Generative), endpoint and relative reference.

| Name | Category | Endpoint | References |
|---|---|---|---|
| PRED-hERG (5.0) | Predictive | hERG-related cardiotoxicity | Braga *et al.*, 2015<br>Alves, Braga and Andrade, 2018 |
| PRED-SKIN (3.0) | Predictive | Skin sensitization potential | Braga *et al.*, 2017<br>Borba *et al.*, 2021 |
| CYTO-SAFE | Predictive | Cytotoxic potential | Feitosa *et al.*, 2024 |
| AMALPHI | Predictive | Phospholipidosis potential | Lomuscio *et al.*, 2024 |
| SIGMAP | Predictive | Affinity potential for Sigma-1 Receptor | Lomuscio *et al.*, 2025 |
| ALPACA | Predictive | Affinity potential for Cannabinoid receptors | Delre *et al.*, 2023 |
| PLATO (r35) | Predictive | Target fishing | Ciriaco *et al.*, 2022 |
| SwissADME | Predictive | ADME properties | Daina, Michielin and Zoete, 2017 |
| DeLA-DrugSelf | Generative | Drug-like analogues generation | Alberga *et al.*, 2024 |
| Deep-PK | Predictive and generative | ADMET properties / drug-like analogues generation | Myung, de Sá and Ascher, 2024 |

## 1.2 Human-Centered Design Strategies

AI-based web platforms have the potential to reshape the drug discovery process. These tools, however, are predominantly developed by researchers with a medicinal chemistry background, particularly in cheminformatics. We do believe that for a true advancement in the field, a closer collaboration between medicinal chemists and computer scientists specializing in HCI is highly desirable. Specifically, the HCD is the iterative design approach that places human needs, preferences, and behaviors at the core of the design and development process and focuses on understanding users' contexts, goals, and expectations by actively involving them throughout the design cycle (ISO, 2019) (Figure 11). Employing HCD increases the overall quality of software systems (Ardito *et al.*, 2014) and, in particular, of their *usability,* which is defined in the ISO standard 9241:11 as *"the extent to which a system, product, or service can be used by specified users to achieve specified goals with effectiveness, efficiency, and satisfaction in a specified context of use"* (ISO, 2018). HCD ensures that AI platforms are functional, useful, usable, and aligned with their values and constraints, prioritizing the needs and goals of users (Desolda *et al.*, 2024).

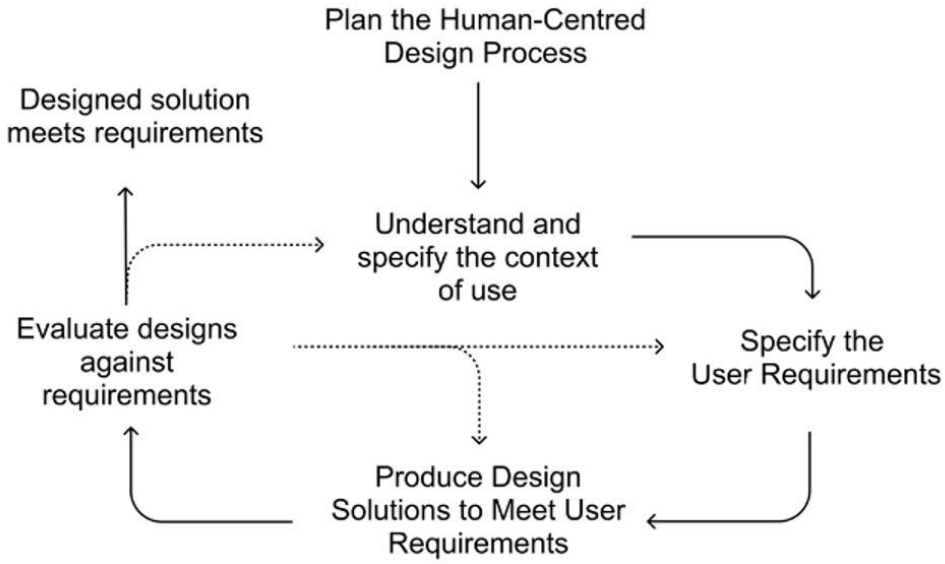



**Figure 11.** The HCD model, as defined in the International Organization for Standardization (ISO, 2019).

Building on the core principles of HCI, recent scientific literature introduces Human-Centered Artificial Intelligence (HCAI), as a specialization of HCI, to guide the creation of AI systems (Shneiderman, 2022). HCAI systems are designed, developed, and evaluated involving users in the process; in this way, it is possible to improve the performance of the platforms and to increase the satisfaction of the users (Desolda *et al.*, 2024).

## 1.3 Designing Usable AI-Based Tools for Drug Discovery

Designing HCAI systems is a multidisciplinary effort. Besides the two pillars of HCI and AI, other disciplines converge to provide techniques and methodologies. Particularly, ML, XAI, Software Engineering, and Ethics also contribute to HCAI (Desolda *et al.*, 2024). The same principles can be applied when designing usable HCAI systems for drug discovery. More specifically, in the context of HCAI, the HCD approach is fundamental when an interaction between users and system is expected. As such, two main phases are required to create HCAI systems: the actual *design* phase and the *evaluation* of the designed solution. This process for the HCAI systems requires methodologies that prioritize usability as the main principle, while ensuring ethical alignment, adaptability (*i.e.;* the ability of a system to be customized by the user (Fischer, 2023)), and adaptivity (*i.e.;* the ability of a system to automatically change its behavior in response to usage patterns (Fischer, 2023)). For simplicity, throughout the rest of this section, we will provide an overview of useful techniques to design and evaluate usable AI-based systems. If the reader is interested in exploring how researchers deal with ethical issues, transparency of the decision-making process, and other AI-related issues, we suggest reading the following books and reviews (Nam, Jung and Lee, 2022; Shneiderman, 2022; Desolda *et al.*, 2024).

The absence of a strong focus on usability may limit the adoption of even the most advanced AI systems, as users may struggle to use them effectively, efficiently, and with satisfaction. As previously proved by studies surveying users, a well-designed, usable interface can mitigate ambiguity, thereby reducing the risk of misinterpretation (Esposito, Desolda and Lanzilotti, 2024). HCD strategies, often overlooked by developers of AI-based platforms, play a crucial role in ensuring that these

cheminformatics platforms are truly effective. The development of an HCAI system is inherently an iterative process, where design and evaluation phases alternate in a continuous cycle. However, this process can be applied to existing systems, which require improving and refining the product via a re-design phase, as well. This way, evaluation strategies that identify potential issues and guide future updates can be implemented. The following sections will focus on useful techniques (heavily adopted in HCI) to design and evaluate *usable* software products. We will especially focus on techniques and strategies that are considered useful for AI-based systems and may guide the further development of tools for drug discovery.

### 1.3.1 Designing for Usability

As mentioned above (cf. Human-Centered Design Strategies) one of the cornerstones of HCD is the iterative design process, which enables designers to incorporate users' feedback. However, it is recommended to involve users prior to the final stages of development. Early engagement of users in the design phase fosters solutions that better align with their needs and expertise. Certain well-established techniques have been specifically developed for this purpose in the HCI community. These techniques are reported below.

**Rapid prototyping** is extremely useful for obtaining quick user feedback. It consists in the creation of *prototypes*, i.e., simplified drawings which represent the interface of a system (Rogers, Sharp and Preece, 2023). This method allows designers to freely explore ideas without allocating excessive time and resources to them, thereby facilitating the adoption of users' feedback thanks to the low costs of edits.

**Participatory Design** is an approach that actively involves users in the design process ensuring that their perspectives and expertise shape the system's development (Rogers, Sharp and Preece, 2023). Leveraging rapid prototyping, designers can quickly explore ideas and get feedback from users, which in turn can support the designers by sharing their needs and requirements. This approach enables the rapid exploration of potentially innovative solutions while ensuring alignment with users' real-world experiences.

**Value-Sensitive Design** is an approach to design that recognizes the importance of the social, cultural, and moral environments in which software operates (Friedman and Hendry, 2019). It incorporates ethical considerations and human values into design choices. Value-sensitive design is especially useful for AI-based systems, especially for highly regulated fields, such as drug discovery. It is important to note that the values are elicited by discussing them with the end-users, and it is not possible to pre-define target values as 'universal truths' during the design phase.

In the context of AI-based systems for drug discovery, end-users often have a different background compared to those who designed and developed such tools (e.g., experimental vs. computational medicinal chemists). This gap must therefore be considered since the developers' understanding of the end-users' needs may not be sufficient to create *usable* software. It is, therefore, imperative that design solutions are systematically evaluated to ensure their usability.

### 1.3.2 Evaluating Usability of AI-Based Systems

Evaluating the usability of a system involves various approaches. Two main classes of evaluation techniques can be adopted: i) inspections exclusively by usability experts and ii) usability studies involving end-users (Rogers, Sharp and Preece, 2023). It is important to note that neither technique should be preferred over the other, since they reveal a complementary set of errors, particularly when inspections emphasize higher-level issues that may limit the users' interaction with the system (Nielsen, 2010).

i) **Inspections** do not require the presence of the system's end-user during the evaluation process since it is performed. The experts detect usability issues and verify the compliance system with standards. One of the most well-known methods to perform inspections is *Heuristic Evaluation* in which researchers are guided by a set of usability principles, called heuristics, to evaluate their adherence of User-Interface (UI) elements to them (Rogers, Sharp and Preece, 2023). A commonly used set of heuristics are the so-called Nielsen's heuristics (Nielsen, 1994).

ii) **Usability Studies** require user participation. They may be conducted in controlled environments (i.e. usability laboratories). However, the currently used techniques prefer informal settings, where the users are directly observed while interacting with the system. This technique provides information on task efficiency, error rates, and user satisfaction. Furthermore, implementing the *thinking aloud* protocol, it also provides insights into the users' mental model of their tasks (Rogers, Sharp and Preece, 2023).

## 1.4 How to Improve Usability of AI-Based Tools for Drug Discovery: An Example

This section focuses on how the inspection technique can support the evaluation phase of HCD. The ten heuristics developed by Jakob Nielsen are one of the core instruments to inspect and assess systems without involving real end-users (Nielsen, 1994). The heuristics are presented and described below:

1. **Visibility of system status**: the design should consistently inform users about system status by providing timely and appropriate feedback.
2. **Match between system and the real world**: the design should use the users' language, incorporating familiar words, phrases, and concepts instead of internal jargon. It should adhere to real-world conventions, presenting information in a natural and logical order.
3. **User control and freedom**: users are prone to errors and should have clearly marked "emergency exits" that allow them to undo unwanted actions quickly and effortlessly.
4. **Consistency and standards**: users should not be left uncertain about whether different words, situations, or actions have the same meaning.
5. **Error prevention**: the design should either eliminate error-prone conditions or detect them and provide users with a confirmation option before they proceed.
6. **Recognition rather than recall**: reduce the user's cognitive load by making elements, actions, and options visible. Users should not need to recall information from one part of the interface to another, but it should be available when necessary.
7. **Flexibility and efficiency of use**: shortcuts can enhance efficiency for expert users, allowing the design to accommodate both novice and experienced users, possibly remaining hidden for beginners.
8. **Aesthetic and minimalist design**: a system's interface should present only relevant information, avoiding unnecessary or extraneous content. Irrelevant elements can create confusion and hinder usability; thus, they must not be highlighted.
9. **Help users recognize, diagnose, and recover from errors**: error messages should be written in clear, simple language, enabling the user to identify the issue and offering constructive solutions.
10. **Help and documentation**: although it is ideal for the system to be intuitive enough to require no additional explanation, documentation should be available to assist users in completing their tasks.

These ten heuristics were used to propose new design solutions for an AI-based platform for drug discovery described and illustrated in the following.

### 1.4.1 Towards a More Usable AI-Based Platform for Drug Discovery

In this section, we provide a simple example of how HCI methods may improve a platform without requiring extensive resources. We considered SIGMAP as an example of AI-based platform for drug discovery. We inspected the platform based on Nielsen's heuristics, (cf. How to Improve Usability of AI-Based Tools for Drug Discovery: An Example) and herein propose possible solutions to the weaknesses that could negatively impact its usability. This step represents a preliminary phase aimed to identify major issues that need to be solved before we conduct a user study.

One of the main activities of SIGMAP is to predict the affinity of potential drug candidates for S1R.

The section in which this output is shown is currently labeled with the SMILES corresponding to the input molecule. To ensure that the platform aligns better with the *Match between the system and the real-world* heuristic, it can be renamed 'Affinity Prediction' instead.

Another modification that could further enhance the platform's compliance with this heuristic is making it available in multiple languages. Although this rule is generally applied to the optimization of systems, scientific platforms, such as SIGMAP, are often available exclusively in English. Indeed, the scientific community adopts English as *lingua franca.* Since language limitations could still hinder usability and adoption, providing multilingual support would make the platform more inclusive and allow a broader range of users to interact with it more intuitively.

To foster *User Control and Freedom*, 'Cancel Prediction' buttons can be added to the loading page. This would ensure that users are enabled to revert their actions if needed. Currently, when an input is being processed, the UI remains active, possibly causing its involuntary interruption. To minimize errors the interface should be kept noninteractive during this time, as suggested by *Error Prevention.*

Another change that can positively impact SIGMAP's usability consists of revising the structure of the navigation bars and footers. The navigation bar should be modified to ensure its fixed position at the top of each page allowing users to always access the basic functions of the systems, avoiding confusion and frustration. Additionally, the footer uselessly takes up excessive space on the UI and should therefore be redesigned to better align with the heuristic *Aesthetic and Minimalist Design*. Finally, the visibility and clarity of the loading process bar should be improved to comply with the *Visibility of system status* heuristic. At the moment a throbber is shown while the system is loading, but no information on the status of the system is provided (i.e., percentage of completion). Similar changes should be implemented for other visual clues to ensure that users can distinguish them from the rest of the UI, such as enhancing contrast with their visual context.

The changes presented in this section –resulting from an evaluation which is in no way exhaustive– aim to solve issues that can generate negative feelings in users that impact the interaction process and the accomplishment of the task. To address these issues, we recommend adding new elements to the UI or modifying the structure of those that can be improved. Indeed, such high-level issues might interfere with users' feedback during a subsequent user study of the platform, hindering the recognition of deeper obstacles in the interaction (Nielsen, 2010). Therefore, the heuristic rules considered in our preliminary analysis elucidate flaws and weaknesses of SIGMAP that negatively impact the usability of the platform, highlighting the areas in which it can be improved prior to a user study.

## 1.5 Conclusions: Towards a Symbiosis Between Humans and AI Platforms for Drug Discovery

In this chapter, we analyzed in detail a selection of AI-driven web-based platforms developed to support medicinal chemists working on early stages of the drug discovery process. These platforms are often created by cheminformatics experts, whose background does not necessarily match the one of the end-users, such as experimental medicinal chemists. Additionally, platform design and development are seldom assisted by the intervention of computer scientists specialized in HCD. We propose that a multidisciplinary collaboration between experts in the creation of systems ensures that the end-users are placed at the core of the process resulting in *usable* platforms.

The selected web applications herein reported represent a subset of open-source models which are ideated to accelerate the drug discovery pipeline. We overviewed the platforms describing key aspects of their interface and their functional interaction (*Input*, *Output*, *Technical support*). Then, we identified strengths and weaknesses of the platforms from a cheminformatic point of view. However, a systematic improvement of UI requires computer scientists' expertise, implementing heuristic principles, as well as supervised user studies. This synergy can promote a productive 'partnership' where human expertise and intuition complement the efficiency and scalability of AI (Desolda *et al.*, 2024). By considering the end-users' feedback, AI platforms can be adapted and refined. This reciprocal relationship defines the concept of human-AI symbiosis (Grigsby, 2018), a vision where humans and AI systems work together combining the strengths and compensating for limitations in tackling complex challenges of modern drug discovery.

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