Perturbation-Theory Machine Learning (PTML) Multilabel Model of the ChEMBL Dataset of Preclinical Assays for Antisarcoma Compounds

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ABSTRACT: Sarcomas are a group of malignant neoplasms of connective tissue with a different etiology than carcinomas. The efforts to discover new drugs with antisarcoma activity have generated large datasets of multiple preclinical assays with different experimental conditions. For instance, the ChEMBL database contains outcomes of 37,919 different antisarcoma assays with 34,955 different chemical compounds. Furthermore, the experimental conditions reported in this dataset include 157 types of biological activity parameters, 36 drug targets, 43 cell lines, and 17 assay organisms. Considering this information, we propose combining perturbation theory (PT) principles with machine learning (ML) to develop a PTML model to predict antisarcoma compounds. PTML models use one function of reference that measures the probability of a drug being active under certain conditions (protein, cell line, organism, etc.). In this paper, we used a linear discriminant analysis and neural network to train and compare PT and non-PT models. All the explored models have an accuracy of 89.19−95.25% for training and 89.22−95.46% in validation sets. PTML-based strategies have similar accuracy but generate simpler models. Therefore, they may become a versatile tool for predicting antisarcoma compounds.

INTRODUCTION
Sarcomas are a group of malignant neoplasms of connective tissue. Although their prevalence is much lower than carcinomas, the number of cases is increasing according to the World Health Organization. At the molecular level, their behavior differs from carcinomas, presenting a more varied and complex etiology. This high etiological complexity possibly stems from their mesenchymal origin, which makes it difficult to propose new therapeutic targets for the respective treatment. Representative anticancer compounds tend to have high cytotoxicity and low cellular specificity. This leads to a decreased efficiency within the treatment and a low remission rate of the disease. However, a description of new molecular markers and the constant performance of drug preclinical assays have generated large amounts of data. This data, if adequately rationalized, may lead in turn to the design of more selective drugs, which takes into account specific drivers based on pathogenic signaling pathways. For instance, the Chemical Database of the European Molecular Biology Laboratory (ChEMBL) contains experimental outcomes for >37,900 different preclinical assays of antisarcoma drug candidates. These assays cover a large and structurally heterogeneous series of >34,900 different chemical compounds. Furthermore, the preclinical assays have been carried out on very different experimental conditions. These experimental conditions include up to 155 different types of biological activity parameters, 36 protein targets, 43 cell lines, and 17 assay organisms. Overall, this forms a large and complex dataset susceptible to analysis so as to extract useful knowledge for drug discovery.

In this context, we can use computational techniques to explore this experimental dataset due to the evident difficulties to analyze it manually. Specifically, cheminformatics methodologies have succeeded in the discovery of new drug candidates effective in the wet-lab. However, many models developed thus far are applied only to carcinomas and/or are focused on homologous series of compounds with one target or a single cell line. In recent years, several studies have focused on applying these methodologies to the study of new types of antisarcoma drugs, mainly on cell lines. However, almost all the models reported have a narrow domain of application because they focus on only one set of conditions, for instance,
Table 1. PTML Model Results

| condition symbol | condition name | formula operator information |
|------------------|----------------|------------------------------|
| c0                | activity type | f(vij)calc = IF(AND(vij > cutoff(c0), d(c0) = 1), 1, IF (AND (vij < cutoff(c0), d(c0) = -1), 0)) |
| c0                |                | observed classification of the outcome vij in the assay with conditions c0 |
| c0, c1, c2, c3    | all conditions | DΔD (cij)ref = (ΔLOGP(cij)) |
| c0, c1, c2, c3    | all conditions | DΔD (cij)pred = 0 |
| c0, c1, c2, c3    | all conditions | DΔD (cij)pred = 1 |

Table 2. Variables Used to Fit the PTML Model

| condition symbol | condition name | symbol | operator formula | operator information |
|------------------|----------------|--------|-----------------|---------------------|
| c0                | activity type | f(vij)calc = IF(AND(vij > cutoff(c0), d(c0) = 1), 1, IF (AND (vij < cutoff(c0), d(c0) = -1), 0)) |
| c0                |                | f(vij)calc | observed classification of the outcome vij in the assay with conditions c0 |
| c0, c1, c2, c3    | all conditions | ΔLOGP, · (ΔLOGP(cij)) |
| c0, c1, c2, c3    | all conditions | PSA, · (PSA(cij)) |

“Sn, sensitivity (%); Sp, specificity (%); Ac, accuracy (%).

PTML models begin with one function of reference that measures the probability of a drug to be active under certain conditions (protein, cell line, organism, etc.). Next, PTML models use PT operators (PTOs) to account for the perturbations (deviations) of the input variables of this drug with respect to a population of drugs assayed under the same conditions. ML algorithms are used to establish the relationship between the inputs and the output variable. In cancer research, Speck-Planche et al. and other researchers have developed PTML-like models for different types of cancers (with an emphasis on carcinomas) such as bladder, prostate, brain, and breast cancers. In addition, Bediaga et al. developed a PTML algorithm for predicting anticancer compounds using data for multiple types of carcinomas at the same time. Speck-Planche et al. also recently developed the first PTML-like model for the prediction of anticancer compounds using a spectral moment approach.

In any case, there are no reports of other PTML-like models for anticancer compounds. In this study, we carried out a comprehensive compilation, curation, and preprocessing of the ChEMBL dataset for preclinical assays of anticancer compounds. After that, we developed the first PTML model able to fit this complex dataset with >37,900 assays and >34,900 compounds. To the best of our knowledge, the study outperforms all previous efforts in terms of simplicity of the model and number of cases, compounds, and cell lines considered.

RESULTS AND DISCUSSION

PTML Antisarcoma Compound Model. The statistical parameters for the PTML model showed a high specificity (Sp) and sensitivity (Sn) for the training series (95.63 and 79.64, respectively). In addition, similar values were obtained for Sp (95.79) and Sn (81.62) in the validation sets. Furthermore, the p-level obtained from the chi-square (χ² = 16848.08) was <0.05, indicating that the model is able to perform a statistically significant separation of both classes. It is also interesting to observe the high overall accuracy (Ac) obtained in both sets: over 94% (Table 1). These results suggest that the generated model performs a statistically significant classification of antisarcoma compounds; hence, it can be considered useful for classification models with application in medicinal chemistry. The full list of biological activities (c0) in the ChEMBL dataset of antisarcoma preclinical experimental assays is shown in Table S1.

The resulting PTML—linear discriminant analysis (LDA) model showed the following formula

\[ f(vij)_{\text{calc}} = -11.8545 + 34.8028 \cdot f(vij)_{\text{ref}} + 0.37 \cdot D_1 - 0.0128 \cdot D_2 - 0.3616 \cdot [D_1 - (D_2(cij))] + 0.0191 \cdot [D_2 - (D_2(cij))] \]

\[ n = 34955, \chi^2 = 16848.08, p < 0.001 \] (1)

The PTML-LDA model was initiated by using as an input the values the function of reference \( f(vij)_{\text{ref}} \) for each compound and by adding the effect of perturbations within the system. These perturbation effects refer to the PTOs ΔDk(cij). In eq 1, “i” and “j” are the assay and condition, respectively. Additional coefficients and terms are described in Table 2.

The parameters ALOGP and PSA are widely used in medicinal chemistry because they are related to the lipophilicity of drugs and, consequently, to their capacity to pass through biological membranes or interact with protein
anticancer drugs. As shown in Table 3, most applications have previously applied to the study of multiple preclinical assays of subtypes.51 In addition, PTML-like models have been tested values as we did (>90%).51 All these PTML-like models are carcinomas simultaneously and obtained similar Sn and Sp demonstrated the application of a PTML on several types of etc.

### Table 3. Comparison to Other PTML Models of Anticancer Compounds

| cancer type  | PT          | ML     | NV | cases   | Sn(%) | Sp(%) | ref   |
|--------------|-------------|--------|----|---------|-------|-------|-------|
| MSS sarcoma  | MMA         | LDA    | 3  | 37,919  | ~80   | >90   | this work |
| MSS carcinoma | MA         | LDA    | >10| 3017    | >90   | >90   | 52    |
| bladder      | MA          | LDA    | >10| 664     | >90   | >90   | 44    |
| brain        | MA          | ANN (RBF) | 10 | 1236    | ~90   | >90   | 45    |
| breast       | MA          | LDA    | >10| 2272    | >85   | >90   | 47    |
| colorectal   | MA          | LDA    | >10| 1651    | >90   | >90   | 46    |
| prostate     | MA          | LDA    | >10| 1668    | >85   | >90   | 49    |
| MCS bladder  | MMA         | LDA    | >10| 116,934 | >70   | ~90   | 51    |
| MCS breast   | MMA         | LDA    | 3  | 116,934 | >70   | >90   | 51    |
| MCS colorectal | MMA       | ANN    | 4  | 116,934 | >80   | >80   | 51    |

aMSS, multiple sarcoma subtypes; MCS, multiple carcinoma subtypes. bPT operators used in PTML models: MMA, multicondition moving average; MA, moving average. cML method used for the PTML models: LDA, linear discriminant analysis; ANN, artificial neural networks; RBF, radial basis function; LNN, linear neural networks; E-ANN (RBF), ensemble of artificial neural networks based on the RBF architecture. dNV, number of input variables. eNumber of preclinical assays. fApproximate values for training series.

### Table 4. Di erent Scores Calculated for the Selected Biological Activities (c0)

| activity parameter for \( v(c0) \) (unit) | \( n(c0) \) | \( \langle v(c0) \rangle \) | \( d(c0) \) | cutoff (c0) | \( n(f(v(c0)) = 1) \) | \( p(f(v(c0)) = 1/c0) \) |
|-------------------------------------------|-------------|----------------|--------|------------|----------------|----------------|
| potency (nM)                               | 31,581      | 19669.199      | 1      | 100        | 149            | 0.005          |
| IC0 (nM)                                   | 1808        | 228362.82      | 1      | 100        | 177            | 0.098          |
| inhibition (%)                             | 690         | 39.186507      | 1      | 50         | 225            | 0.326          |
| CCo (nM)                                   | 450         | 134445.04      | 1      | 100        | 4              | 0.009          |
| activity (%)                               | 404         | 52.416163      | 1      | 50         | 208            | 0.515          |
| EC10 (nM)                                  | 379         | 63578.521      | 1      | 100        | 44             | 0.116          |
| TG1 (%)                                    | 202         | 43.915842      | 1      | 50         | 102            | 0.505          |
| T/C                                        | 173         | 26.556832      | 1      | 50         | 28             | 0.162          |
| IC50 (\( \mu \)g mL\(^{-1}\))             | 167         | 64.429402      | 1      | 60         | 118            | 0.707          |
| T/C (%                                     | 144         | 156.92153      | 1      | 50         | 123            | 0.854          |
| GI10 (nM)                                  | 113         | 66515.131      | 1      | 60         | 13             | 0.115          |
| EC10 (\( \mu \)g mL\(^{-1}\))             | 90          | 60.733562      | 1      | 60         | 57             | 0.633          |

ah\( n(c0) \), total compounds with experimental values. b\( \langle v(c0) \rangle \), average calculated of each c0 biological activity. c\( d(c0) \), desirability value (1, −1) assigned to each c0. d\( n(f(v(c0)) = 1) \), total number of biologically active compounds observed within each c0 according to the experimental values \( v(c0) \) reported for the parameters j. e\( p(f(v(c0)) = 1/c0) \), probability of a desired biological activity within the conditions c0.

hydrophobic pockets.53–56 The PTML algorithm has been previously applied to the study of multiple preclinical assays of anticancer drugs. As shown in Table 3, most applications have been directed toward the most prevalent carcinomas among the global population. For instance, Speck-Planche et al. reported PTML-like models for bladder,44 colorectal,46 breast, prostate9 cancers and for multiple carcinoma subtypes.51 In addition, PTML-like models have been tested in antibiotic tumor agents.55 Interestingly, Bediaga et al. demonstrated the application of a PTML on several types of carcinomas simultaneously and obtained similar Sn and Sp values as we did (>90%).51 All these PTML-like models are able to account for changes in target proteins, cellular lines, organisms, etc. However, they are specific models for carcinomas, not for sarcomas.

It is worth noting that to the best of our knowledge, Speck-Planche et al.52 seem to be the only researchers to have reported a previous PTML-like model for sarcomas thus far. In their study, the prediction model in external validation resulted in Ac (90.78) and Sp (90.65) values that were lower than what was obtained in our model (Ac = 94.98 and Sp = 95.79). However, our PTML algorithm showed a lower sensitivity in external validation data (81.62%) than the model obtained by Speck-Planche et al. (91.74%). Even when our model had a much lower number of variables and used a stricter cut-off definition for activity class (i.e., IC50 = 0.1 \( \mu \)M instead 1 \( \mu \)M), these aspects alone cannot explain the sensitivity reduction.

The generated PTML-LDA model (eq 1) has important characteristics that allow it to be used within research focused on drug discovery. One of the main advantages of our model is the considerable reduction of input variables for the construction of the algorithm through the inclusion of PTOs. This reduction allowed us to work on datasets with a large amount of information, to define cut-off values, and to calculate the probability of belonging to a class, whether this was a prediction for active compounds (1) or inactive compounds (0). In this way, the Sn or Sp values of the model can be adjusted according to the delimited cut-offs. An ideal prediction model has a reasonable trade-off between Sn and Sp. This means that a high sensitivity is achieved by accepting a relatively low Sp and, conversely, a high Sp is reached by compromising Sn. Sp is synonymous with a true-negative rate, which is related to the false-positive rate,30 so a high specificity in a prediction model for drug discovery implies that it is unlikely to get a positive result in a drug that does not have a desired biological activity. Thus, a positive
outcome in a specific model is quite informative in a drug discovery scenario. On the other hand, a main attribute is the possible combination of several experimental conditions for the prediction of new compounds. In this sense, Speck-Planche et al. used around 3000 interactions derived from 14 cell lines and only considered IC50 assays for their model. However, we modeled 37,919 interactions cases comprising 36 protein targets, 43 cell lines, and 17 assay organisms. We also included several different assay types (Table 4). The modeling task we have is more complex not only because of the increment in the chemical diversity but also the wide type of heterogeneity in the interactions (i.e., target types and organisms). The two models cannot be compared in this scenario and our reduction in the ability to detect the true-positive cases (Sn) could be a consequence of this data complexity and also the modeling strategy.

PTML Cut-Off Scanning Study. As mentioned above, the cut-off implemented in the model is a rigorous value that, at the experimental level, is important if one desires to increase effectiveness in the process of discovering antisarcoma drugs. A restricted value promotes high certainty in the prediction of active compounds (1). When looking at these results, our prediction algorithm not only takes into account several experimental conditions but also restricts the prediction of compounds to those that have true biological activity.

PTML vs ML Model Comparison. Most multitasking or multilabel ML methods are useful for predicting multiple categorical outputs for the same set of input continuous variables. However, our problem was a little different: we had to develop an ML model with only two possible outputs, for the same set of input variables. That meant that our model was not multitasking for a single case with a set of input variables containing multiple continuous variables plus multiple categorical input variables. However, we had multiple combinations of input categorical variables or levels for the same set of input continuous variables. Hence, our model was multilabel in the input categorical variables for the same set of input continuous variables. To illustrate this fact, we developed here a comparison of our PTML-LDA model vs classic ML using multiple labeling categorical variables. As seen in Figure 2A, the performance of our PTML-LDA model compared to a classic ML-LDA demonstrates similar values based on Sp, Sn, and Ac. Similarly, when developing neural networks (NN), the results of PTML-NN (Figure 2B) and ML-NN (Figure 2C) are quite similar. One of the advantages of our PTML model is the inclusion of PTOs, which greatly reduces the number of variables to generate the algorithm. Thus, although the statistics of all the models generated are quite similar, the PTML methodology allows for the reduction of variables from 164 variables in classic ML methods to only 5 in the PTML model. All the PTML and non-PTML model results are described in Table S2.
Previous studies have considered a wide variety and quantity of molecular descriptors in PTML models. For example, for sarcoma modeling, Speck-Planche et al.\textsuperscript{52} used 423 descriptors followed by a feature selection strategy. Similarly, 289 descriptors were used in a PTML model on breast cancer.\textsuperscript{47} We used this approach as a strategy to compare the performance of PTML model vs classic ML techniques including new molecular descriptors (Figure 2A). In this ML study, we included 12 BCUT molecular descriptors ($D_i$, with $k > 2$) as an input, which were not used in the previous model, and 162 categorical (dummy) variables ($C_j$). These $C_j$ have been used to label the multiple conditions of the assays $c_i$ (organisms, proteins, cell lines, etc.). One must remember that $D_1 = \text{ALOGP}$ and $D_2 = \text{PSA}$. The new molecular descriptors were $D_3, D_4, \ldots, D_{14}$. The expansion of the variables together with the ML strategies yielded good results but did not outperform what was obtained for the PTML-LDA anti-sarcoma model (as seen in Figure 2A and Table S2) and the number of variables increased to 174 input variables in total. This suggests that by adding different molecular descriptors and probably feature selection strategies, acceptable models for drug discovery can be built. However, our PTML-LDA model based on $D_1$ and $D_2$ is a simpler yet effective model.
Multiple-Condition Averages in the PTML Antisarcoma Model. In total, we found 83 possible combinations of multiple conditions for all the included sarcoma assays. As shown in Table S, the $n_j(c_i)$ with the highest number of entries corresponded to tests on human cell lines and on cell lines in *Mus musculus*. The multicondition moving averages (MMAs) used here, $\langle D_1(c_i) \rangle$ and $\langle D_2(c_i) \rangle$, vary significantly across all combinations. However, the anticancer compounds observed for the human osteosarcoma cell lines U2OS, HOS, SAOS-2, MG-63, and 143B and for the fibrosarcoma cell line HT-1080 were in a range of $\langle D_1(c_i) \rangle$ of 1.2–3.7. A similar range was observed in compounds tested in *M. musculus* ($\langle D_1(c_i) \rangle = 1–3$). Interestingly, when comparing these values with the variation of $\langle D_2(c_i) \rangle$, tests on virus lines, such as Moloney murine sarcoma virus and Woolly monkey sarcoma virus, had higher means (between 140 and 205). Since the ALOGP coefficient is a measure widely used in drug discovery to assess the degree of absorption, distribution in the body, penetration across biological membranes, metabolism, and excretion, this range identified in our results is an important space for the prediction of antisarcoma drugs. Likewise, the range of PSA evidenced in viral line assays may be a better space for this coefficient if it is desired to predict new compounds in these experimental conditions. This may be interesting when defining the validation of a certain antisarcoma compound. Thus, if a compound is significantly predicted in an experimental animal or human cell lines, then it will be possible to propose validations at the preclinical level or in clinical trials, respectively.

**How to Use the PTML Model in Practice.** The model is capable of scoring the activity of a single compound under different assay conditions. To predict a new compound, first, we have to substitute the expected values of function of reference $f(v_j)_\text{ref} = p(f(v_j) = 1)_\text{ref}$ in the model. As
aforementioned, this is the probability of the compound being active for a given biological activity parameter \( (c_0) \) (see Table 2). Next, we need to substitute into the equation the values of molecular descriptors \( D_1 = \text{ALOGP} \) and \( D_2 = \text{PSA} \) of the compound (chemical structure), calculated with the same algorithm used in the ChEMBL dataset. Last, we have to substitute into the equation the average values (expected values) of the molecular descriptors \( \langle D_k(c_j) \rangle \) for the specific subset of conditions of the assay \( c_j \) we want to predict. In Table S, we show some selected values of these averages with >25 assays reported. It can be noted that the most populated assays in *Homo sapiens* in the dataset were those in *in vitro* assays that targeted the protein O75874 (IDHI) and that targeted the cell line U2OS. Upon inspecting Table S, we can see that \( \langle D_k(c_j) \rangle \) values change for different subsets of conditions \( c_j \). Consequently, when we substitute the different \( \langle D_k(c_j) \rangle \) values into the model for the same compound, we can calculate different scores \( f(v_{ij}) \text{calc} \) of biological activity of the same compound under multiple assay conditions. The full list of the values of \( \langle D_k(c_j) \rangle \) appears in Table S3.

## CONCLUSIONS

In this research work, we generated a PTML-LDA model constructed with antisarcoma assays obtained from ChEMBL and a heterogeneous set of different cell lines, organisms, and targets. As far as we know, this constitutes the first time that this kind of model was tested for sarcoma comprising 34,955 chemical compounds and 37,919 assays. The PTML-LDA model was compared with classic ML approaches like the neural network and also with non-PT consideration. The rate of true positives and true negatives is similar when comparing PTML-LDA to other prediction models. PTML-LDA reduces the amount of input variables (ALOGP and PSA) needed, thus increasing the simplicity and interpretability of the model.

## METHODS

ChEMBL Data Curation and Preprocessing. In total, we downloaded >370,000 outcomes for preclinical assays of antisarcoma drug candidates from the ChEMBL database. The keywords (fields) used for the search were as follows: Sarcoma (Assay) and also keywords for more relevant cell osteosarcoma lines MG-63, U2O2, HOS, SAOS-2, and 143B. After that, we carried out a data fusion of the datasets obtained into one single raw dataset. The working dataset was curated by eliminating all duplicated entries. We also eliminated all cases with missing values of biological activity \( (v_{ij}) \) and/or molecular descriptors. The molecular descriptors used were the same as those precalculated by the ChEMBL database where \( D_1 = \log P \) and \( D_2 = \text{PSA} \). The final dataset obtained after curation contained 37,919 cases comprising 36 protein targets, 43 cell lines, and 17 assay organisms (Table S1). For comparison and exploration with other models, we additionally computed 12 BCUT molecular descriptors with ChemAxon (http://www.chemaxon.com). The classical unweighted Burden descriptors as well as those weighted by charge and hydrogen bond properties were calculated. The lowest and the three highest eigenvalues were used for descriptor calculation.

To train the model, we split this dataset into two data subsets: training and validation series. We performed a random, stratified, and representative selection of training/validation cases. To accomplish this task, we sorted the cases by \( n_j \) (from highest to lowest) as well as by assay conditions: biological activity, protein accession, cell line, and assay organism (alphabetically from A to Z). After this, we selected every fourth case (1 out of 4) to form a training subset (75% of cases) and validation subset (25% of cases). The result of each experimental assay is the value obtained from the quantification of each biological activity and named \( v_{ij} \). Each experimental assay was discretized based on the desirability \( d(c_j) \). This variable was defined as 1 when the result of the desired biological activity depended on an increased value of \( v_{ij} \) and -1 when the desired biological activity depended on a lower value of \( v_{ij} \). Thus, the discretized value \( f(v_{ij}) \text{obs} \) was calculated as follows: \( f(v_{ij}) \text{obs} = 1 \) when \( v_{ij} > \text{cut-off} \) and \( d(c_j) = 1 \). The function \( f(v_{ij}) \text{obs} = 1 \) when \( v_{ij} < \text{cut-off} \) and \( d(c_j) = -1 \); otherwise, \( f(v_{ij}) \text{obs} = 0 \). The value \( f(v_{ij}) \text{obs} = 1 \) refers to a strong effect of the compound over the target. Since \( d(c_j) \) has a direct relationship with \( f(v_{ij}) \text{obs} \) we applied a rational cut-off for each \( c_j \) which will be discussed later. Briefly, the cut-off for properties related to drug concentrations and described in nM (potency, IC₅₀, CC₅₀, EC₅₀, GL₅₀, etc.) was set at 100. For properties described in % (inhibition, activity, TGI, among others), the cut-off was set at 50. Last, to calculate the probability of these expected values, we evaluated the relationship between the total number of the observed cases \( n(f(v_{ij}) = 1) \text{obs} \) within the level of biological activity desired for the condition \( c_j \) and the total number of compounds \( n_j \) that were described in that same condition. In this sense, we have that \( p(f(v_{ij}) = 1) = n(f(v_{ij}) = 1) \text{obs}/n_j \).

**PTML Linear Model.** The multicondition moving averages (MMAs) are PTOs similar to Box-Jenkins moving average operators. However, MMAs are PTOs accounting for perturbations (changes) in multiple conditions \( c_j \) at the same time, while MA quantities changes in only one condition. By using linear discriminant analysis (LDA), we obtained a PTML-LDA equation as follows:

\[
\Delta D_k(c_j) = a_0 + a_1 f(v_{ij})_{\text{calc}} + \sum_{k=1}^{k_{\text{max}}} a_{kj} D_k + \sum_{k=1}^{k_{\text{max}}} a_{kj}' D_k
\]

The model generates an output score \( f(v_{ij}) \text{calc} \) that refers to a score function for a biological activity \( v_{ij} \) under the assay conditions \( c_j \). The LDA algorithm includes the Mahalanobis’ distance metric, which makes it possible to infer predictive values through a probability calculation \( p(f(v_{ij}) = 1) \text{pred} \). For the variable selection, we detected specific perturbations within the conditions \( c_j \) that will be adjusted to anticancer properties through a forward-stepwise strategy. Such conditions as \( c_1 \) = protein accession, \( c_2 \) = cell line, and \( c_3 \) = assay organism were significant, so we took them into consideration in our model. Through \( p(f(v_{ij}) = 1) \text{pred} \), we predicted the activity of each compound by applying the function \( f(v_{ij})_{\text{pred}} \text{calc} = 1 \) when \( p(f(v_{ij}) = 1) \text{pred} > 0.5 \) or \( f(v_{ij})_{\text{pred}} = 0 \). For comparison, we also used a strategy that is not based on perturbation theory. In this sense, besides the molecular descriptors, we added conditions \( c_4 \) and \( c_5 \) as a separate set of categorical variables. A total of 237 variables were needed to represent all conditions. Filtering using the variance of each
variable leads to a total of 162 variables, including ALOGP and PSA. The evaluation of the discriminant model was calculated from Wilks’ lambda ($\Lambda$) as follows

$$\Lambda = 1 + \frac{1}{\text{df}} \frac{\sum(Z_1 - Z_2)^2}{\sum(Z_1^2 - Z_2^2)}$$

where $\Lambda$ is chi-square distributed for $\text{df} = (k - 1)$, $k$ is equal to the number of parameters estimated, and $\lambda$ is the number of correctly classified inactive compounds.

For ML, besides LDA, we also used neural networks (NN) with different architectures. STATISTICA software was used in both cases. The final networks obtained were multilayer perceptron (MLP), linear neural network (LNN), and radial basis function network (RBF). All these ML strategies were applied with perturbation and nonperturbation theory. The predicted 1 or 0 values were used to determine the specificity or true-negative rate (Sp), sensitivity or true-positive rate (Sn), and accuracy (Ac) when compared to the observed values. Thus, when $f(v_{ij}) = f(v_{ij})_{obs}$, the cases were determined to be correct.

The metrics to evaluate the performance of all the prediction models were Ac, Sn, and Sp using the following formulae:

$$\text{Ac} = \frac{\text{number of correctly classified compounds}}{\text{total number of compounds}}$$

$$\text{Sn} = \frac{\text{number of correctly classified active compounds}}{\text{total number of active compounds}}$$

$$\text{Sp} = \frac{\text{number of correctly classified inactive compounds}}{\text{total number of inactive compounds}}$$

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.0c03356.

CheMBL dataset of antisarcoma preclinical experimental assays for the PTML model; results of the analyzed models for sarcoma biological activities; all the multiple-condition averages for all sarcoma assays (XLSX)

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A.C.-A. and A.L.-C. contributed equally to the study.

### Notes

The authors declare no competing financial interest.

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