Predicting Drug Sensitivity of Cancer Cell Lines to BET Inhibitor OTX015 Using Machine Learning Approaches

Gizem Tutkun , Muharrem Okan Cakir , G Hossein Ashrafi , Mustafa Ozdogan , Ugur Bilge *

Posted Date: 28 March 2025

doi: 10.20944/preprints202503.2146.v1

Keywords: Machine Learning; IC_{50} Prediction; Bromodomain Inhibitors; OTX015; Cancer Cell Lines; Support Vector Machine; Gene Expression; R Programming; Personalized Medicine

Article

Predicting Drug Sensitivity of Cancer Cell Lines to BET Inhibitor OTX015 Using Machine Learning Approaches

Gizem Tutkun [1], Muharem Okan Cakir [2], G Hossein Ashrafi [2], Mustafa Ozdogan [3] and Ugur Bilge [4,*]

[1] Department of Medical of Biotechnology, Institute of Health Sciences, Akdeniz University, 07058 Antalya, Turkey
[2] School of Life Sciences, Pharmacy and Chemistry, Kingston University London, London KT1 2EE, UK
[3] Division of Medical Oncology, Memorial Hospital, 07025 Antalya, Turkey
[4] Department of Biostatistic and Medical Informatics, Faculty of Medicine, Akdeniz University, 07058 Antalya, Turkey
* Correspondence: ubilge@akdeniz.edu.tr

Abstract: Bromodomain and Extra-Terminal (BET) proteins are crucial epigenetic regulators involved in transcriptional processes linked to cancer progression. Inhibiting these proteins has emerged as a promising therapeutic strategy, with OTX015, a potent BET inhibitor, showing promising efficacy against various cancer types. However, accurately predicting drug sensitivity across cancer cell lines remains a challenge. In this study, we present a machine learning-based approach to predict the half-maximal inhibitory concentration (IC_{50}) of OTX015 across various cancer cell lines using their gene expression profiles. By employing regression-based machine learning models, including Support Vector Machine (SVM), K-Nearest Neighbor (KNN), Extreme Gradient Boosting (XGB), Elastic Net (EN), and Neural Networks (NNET), we aimed to optimize prediction accuracy. The dataset was divided into subsets containing 10, 25, 50, 75, and 100 genes based on their correlation with IC_{50} values, enabling a comprehensive evaluation of model performance across different data dimensions. The SVM model consistently demonstrated the best performance, achieving the lowest Mean Absolute Error (MAE) scores across all datasets, thereby proving most effective for predicting IC_{50} values. This approach highlights the potential of integrating machine learning algorithms with gene expression data to enhance drug discovery and personalized medicine, particularly in the context of cancer research. Future work should focus on expanding datasets, optimizing feature selection, and evaluating additional machine learning approaches to improve prediction reliability and generalizability.

Keywords: Machine Learning; IC_{50} Prediction; Bromodomain Inhibitors; OTX015; Cancer Cell Lines; Support Vector Machine; Gene Expression; R Programming; Personalized Medicine

1. Introduction

Cancer remains a major global public health concern, ranking as the second leading cause of death worldwide. Projections indicate a dramatic increase in cancer cases by 2050, attributed to population growth, aging, and lifestyle factors [1]. However, advancements in early detection, treatment, and supportive care have significantly improved survival rates, with approximately 70% of cancer patients surviving at least five years after diagnosis, and 11% surviving for 25 years or more [2]. Despite progress in traditional treatments such as radiotherapy, surgery, and chemotherapy,

 doi:10.20944/preprints202503.2146.v1

advanced biotechnological approaches, including gene therapy, stem cell therapy, epigenetic-based therapies, and precision medicine, are increasingly recognized for their potential in cancer diagnosis and treatment [3].

The Bromodomain and Extra-Terminal (BET) protein family, particularly BRD2, BRD3, BRD4, and BRDT, plays a central role in transcriptional regulation and chromatin remodeling by recognizing acetylated histones. Overactivation of BET proteins is implicated in various cancers, including hematologic malignancies, neuroblastomas, breast cancer, and prostate cancer [4,5]. BET inhibitors (BETi) like OTX015, JQ1, and I-BET762 have demonstrated significant efficacy in preclinical and clinical studies by downregulating oncogenic transcription factors such as MYC, BCL-2, and E2F [6,7].

Machine learning (ML) has emerged as a powerful tool to accelerate drug discovery and precision medicine. Supervised learning, in particular, offers a promising approach for predicting drug responses by recognizing patterns within complex biological data [8,9]. The use of programming languages such as R, alongside comprehensive repositories like Bioconductor, facilitates the development of robust models to predict drug efficacy based on genomic data [10].

In this study, we aimed to develop predictive models for estimating the half-maximal inhibitory concentration (IC_{50}) of OTX015 across various cancer cell lines, leveraging gene expression profiles and regression-based ML techniques. Among the models tested, the Support Vector Machine (SVM) consistently achieved the lowest Mean Absolute Error (MAE), outperforming other models across multiple datasets. These findings suggest that ML models, particularly SVM, hold great potential for enhancing drug discovery and personalized medicine. Future research should focus on refining these models, expanding datasets, and integrating diverse machine learning approaches to improve prediction accuracy.

2. Results

This study employed five regression-based machine learning models to predict the half-maximal inhibitory concentration (IC_{50}) values of the compound OTX015 across various cancer cell lines. The selected models were Elastic Net (EN), K-Nearest Neighbor (KNN), Neural Networks (NNET), Support Vector Machine (SVM), and Extreme Gradient Boosting (XGB). The prediction performances of these models were assessed based on their Mean Absolute Error (MAE) scores, which serve as a key metric for evaluating prediction accuracy.

2.1. The Impact of Data Dimensions on Model Performance

To investigate the impact of data dimensionality on model performance, the main dataset was divided into five subsets. Each subset contained a different number of genes, specifically 10, 25, 50, 75, and 100, selected based on their correlation with IC_{50} values. This approach allowed for the evaluation of whether increasing or decreasing the number of genes influences the performance of prediction models. Table 1 presents the MAE scores achieved by each model across different data dimensions.

The performance of the OTX015 compound across different data dimensions is shown in Table 1.

Table 1. The MAE scores of OTX015 compound across different data dimensions and models based on the number of genes. The lowest MAE score and the dataset yielding this score are highlighted in bold.

Data	EN	KNN	NNET	SVM	XGB
Data of 10	1,357	1,625	1,491	1,143	1,593
Data of 25	0,52	0,618	0,558	0,434	0,687
Data of 50	1,04	1,174	1,167	0,855	1,307
Data of 75	0,55	0,673	0,722	0,464	0,672
Data of 100	0,281	0,355	0,491	**0,254**	0,352

 doi:10.20944/preprints202503.2146.v1

The SVM model consistently demonstrated the best performance across all datasets, achieving the lowest MAE scores. This suggests that the SVM model is particularly suitable for predicting IC_{50} values, even when the number of genes varies.

2.2. Evaluation of Error Dimensions of Models

Although MAE scores provide a general assessment of model performance, it is important to examine the distribution of errors across different cancer cell lines to ensure robustness. Individual errors for each model across all data groups are depicted in Figure 1.

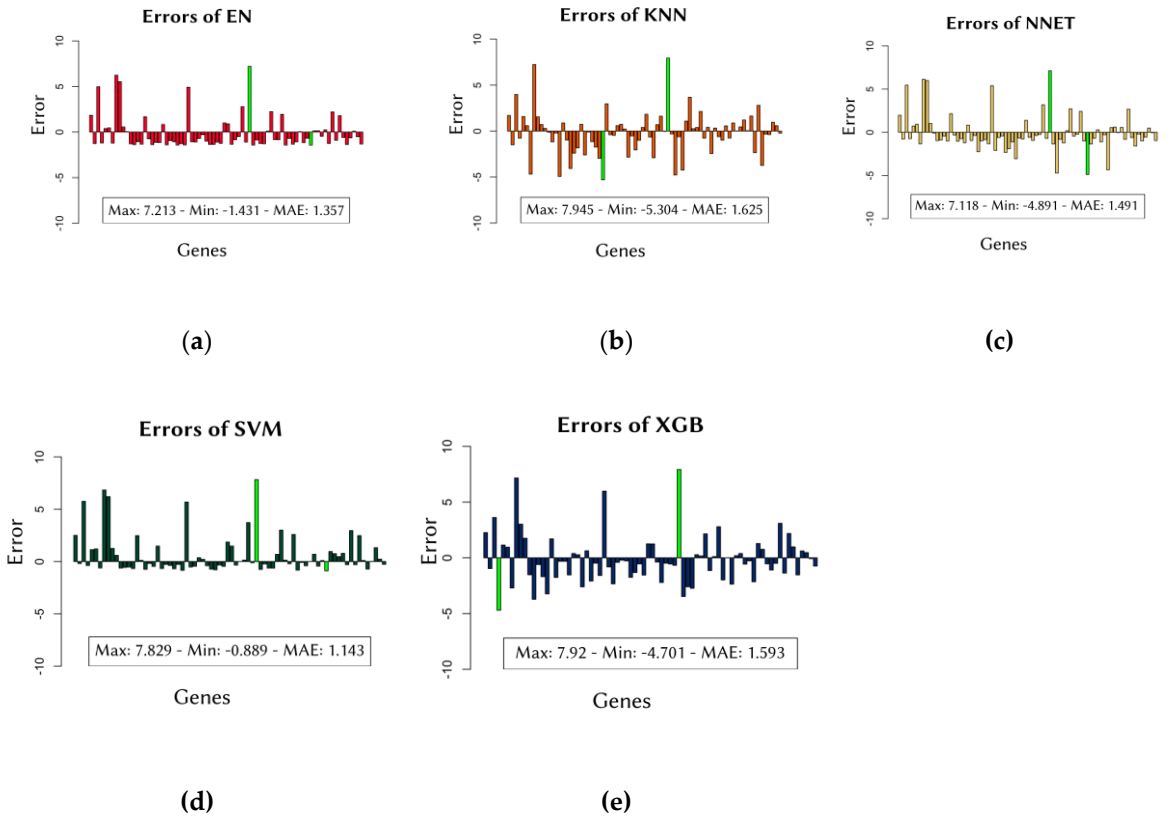


Figure 1. Errors made by the models in predicting IC_{50} values for each cell line in the Data of 10. The light green bars represent the highest and lowest errors. (a) EN, (b) KNN, (c) NNET, (d) SVM, and (e) XGB models show individual errors.

Additionally, examining the frequency of errors allows for the identification of models that produce low-degree errors more frequently than high-degree errors. As illustrated in Figure 2, the SVM model showed the highest concentration of errors close to zero, indicating consistent predictive accuracy. This analysis confirms that the SVM model is particularly effective in minimizing prediction errors across various cell lines.

 doi:10.20944/preprints202503.2146.v1

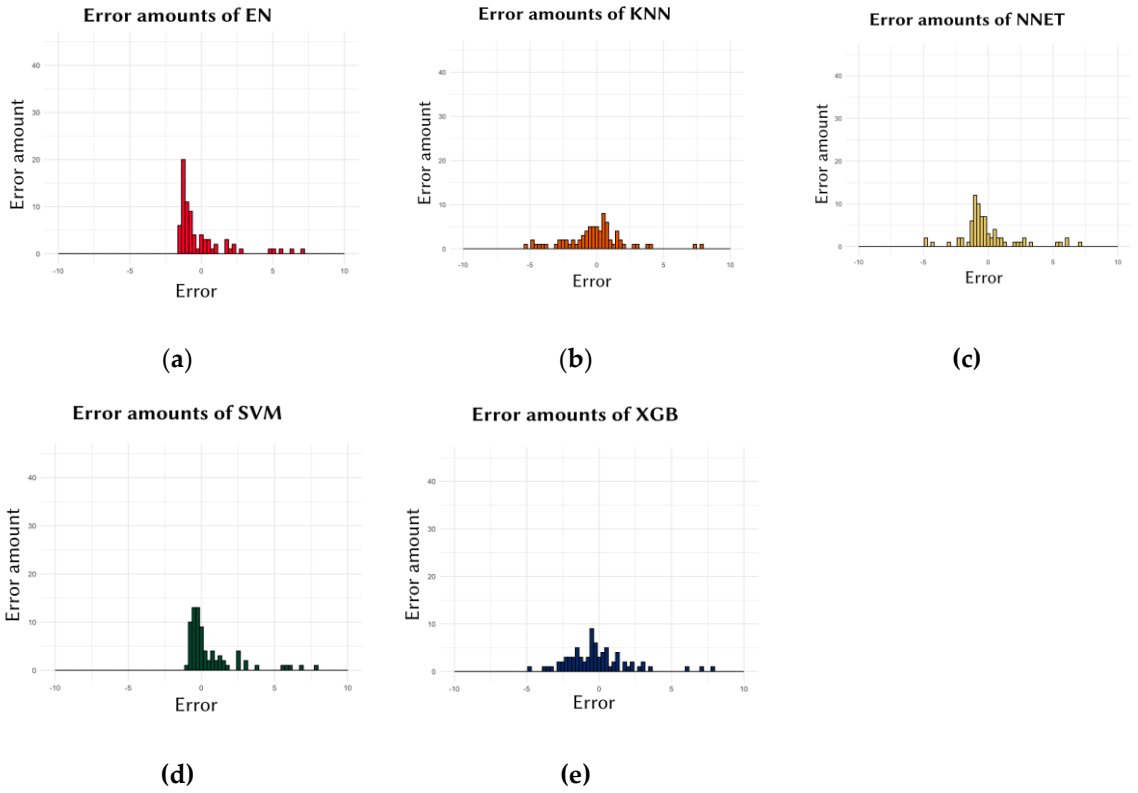
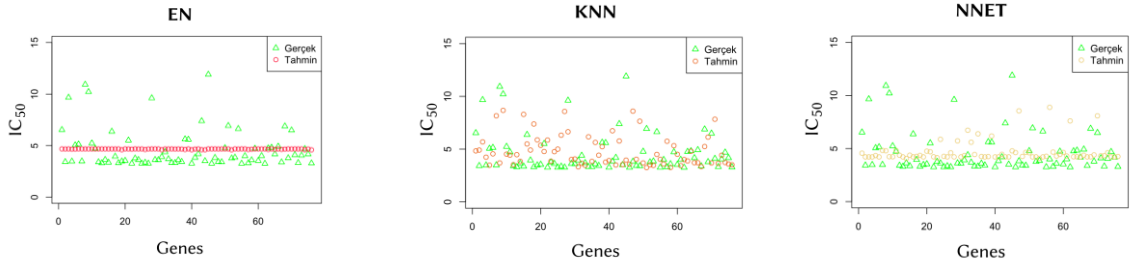


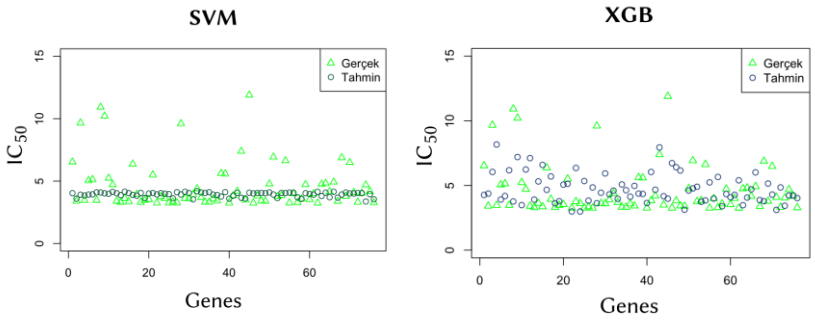
Figure 2. Frequency of errors made by the models in the Data of 10. The X-axis represents the error magnitude, while the Y-axis indicates the frequency of these errors. (a) EN, (b) KNN, (c) NNET, (d) SVM, and (e) XGB models show the frequency of errors.

2.3. Comparison of Predicted and Actual IC_{50} Values

To further evaluate model performance, predicted IC_{50} values were compared with actual values. The comparison graphs in Figure 3 illustrate the ability of each model to generalize predictions from training data. The results show that the SVM model is capable of producing predictions that closely align with actual values, demonstrating its generalization capability.



 doi:10.20944/preprints202503.2146.v1



(d) **(e)**

Figure 3. Comparison of the predicted IC_{50} values (colored circles) and the actual IC_{50} values (light green triangles) for the models in the Data of 10. The X-axis represents the index numbers of the cell lines in the dataset, while the Y-axis represents the IC_{50} values. (a) EN, (b) KNN, (c) NNET, (d) SVM, and (e) XGB models show the performance of the models.

2.4. Performance of the SVM Model in Single Cell Line Predictions

Given the superior performance of the SVM model, additional evaluations were conducted to assess its predictive accuracy for individual cell lines. Each cell line in the validation set of the Data of 10 was considered as a single sample, and predictions were generated accordingly. The results for 76 cell lines are presented in Table 2.

Table 2. Single cell line performance of the SVM model.

Patient	Predicted IC_{50}	Real IC_{50}	Error
Patient 1	4,03	6,528	-2,498
Patient 2	3,604	3,413	0,191
Patient 3	3,909	9,664	-5,755
Patient 4	3,843	3,464	0,379
Patient 5	3,918	5,052	-1,134
Patient 6	3,935	5,136	-1,201
Patient 7	4,091	3,476	0,615
Patient 8	4,085	10,923	-6,838
Patient 9	4,014	10,214	-6,2
Patient 10	3,985	5,233	-1,248
Patient 11	4,131	4,716	-0,585
Patient 12	4,022	3,397	0,625
Patient 13	3,871	3,302	0,569
Patient 14	4,149	3,626	0,523
Patient 15	4,036	3,359	0,677
Patient 16	3,891	6,366	-2,475
Patient 17	3,83	3,939	-0,109
Patient 18	4,052	3,307	0,745
Patient 19	3,651	3,469	0,182
Patient 20	3,998	3,535	0,463
Patient 21	4,038	5,51	-1,472
Patient 22	3,931	3,259	0,672
Patient 23	4,03	3,755	0,275
Patient 24	3,986	3,614	0,372
Patient 25	3,953	3,26	0,693
Patient 26	3,625	3,351	0,274

 doi:10.20944/preprints202503.2146.v1

Patient 27	4,108	3,264	0,844
Patient 28	3,923	9,608	-5,685
Patient 29	4,144	3,622	0,522
Patient 30	4,046	3,597	0,449
Patient 31	3,542	3,907	-0,365
Patient 32	4,184	4,389	-0,205
Patient 33	4,085	3,69	0,395
Patient 34	4,052	3,326	0,726
Patient 35	4,107	3,318	0,789
Patient 36	3,915	3,586	0,329
Patient 37	3,882	3,424	0,458
Patient 38	3,763	5,623	-1,86
Patient 39	4,115	5,589	-1,474
Patient 40	3,598	3,261	0,337
Patient 41	3,835	3,833	0,002
Patient 42	4,058	4,19	-0,132
Patient 43	3,67	7,39	-3,72
Patient 44	3,616	3,499	0,117
Patient 45	4,068	11,897	**-7,829**
Patient 46	4,011	3,256	0,755
Patient 47	4,045	3,818	0,227
Patient 48	4,051	3,425	0,626
Patient 49	4,029	3,399	0,63
Patient 50	4,088	4,773	-0,685
Patient 51	3,923	6,924	-3,001
Patient 52	3,636	3,761	-0,125
Patient 53	4,05	3,844	0,206
Patient 54	4,044	6,627	-2,583
Patient 55	4,08	3,257	0,823
Patient 56	4,073	3,991	0,082
Patient 57	3,699	3,298	0,401
Patient 58	3,579	3,582	-0,003
Patient 59	4,028	4,722	-0,694
Patient 60	3,961	3,524	0,437
Patient 61	3,911	4,002	-0,091
Patient 62	4,14	3,251	**0,889**
Patient 63	3,803	4,755	-0,952
Patient 64	4,075	4,819	-0,744
Patient 65	3,705	4,166	-0,461
Patient 66	4,142	4,921	-0,779
Patient 67	3,679	3,382	0,297
Patient 68	3,922	6,88	-2,958
Patient 69	4,084	3,784	0,3
Patient 70	4,006	6,483	-2,477
Patient 71	4,001	4,095	-0,094
Patient 72	4,04	3,319	0,721
Patient 73	4,033	4,043	-0,01
Patient 74	3,37	4,689	-1,319
Patient 75	3,943	4,166	-0,223
Patient 76	3,548	3,283	0,265
Mean Absolute Error (MAE)			1,143

 doi:10.20944/preprints202503.2146.v1

The SVM model exhibited a low average error rate (MAE = 1.143), highlighting its robust performance even when applied to single cell lines. This finding demonstrates the suitability of the SVM model for predicting drug sensitivity on an individual cell line basis, enhancing its potential application in personalized medicine.

3. Discussion

The findings of this study highlight the efficacy of machine learning models, particularly the Support Vector Machine (SVM), in predicting the half-maximal inhibitory concentration (IC_{50}) of the compound OTX015 in various cancer cell lines. The use of gene expression profiles for prediction aligns well with current trends in precision medicine, where genomic data is utilized to tailor therapeutic approaches for individual patients [11,12].

The performance of the models across different data dimensions demonstrated that increasing the number of genes included in the dataset generally improved prediction accuracy, as reflected by lower Mean Absolute Error (MAE) scores. However, the improvement was not strictly linear, indicating that certain subsets of genes may provide more relevant information for predicting IC_{50} values than others. This observation is consistent with the idea that the quality of features is more important than their quantity, a key concept in feature selection and model optimization [13,14].

The comparison of individual errors and error distributions across models showed that the SVM model consistently outperformed other models, achieving the lowest average errors and exhibiting a high concentration of errors near zero. This suggests that the SVM model is robust in minimizing prediction errors across various cell lines. Additionally, the strong performance of the Elastic Net model, which incorporates both L1 and L2 regularization, indicates that hybrid methods may also hold promise for enhancing prediction accuracy [15,16].

A critical observation in this study is the performance of the SVM model when applied to single cell line predictions. Despite training on a general dataset, the SVM model demonstrated strong predictive capabilities for individual cell lines, further supporting its suitability for personalized medicine applications. This finding is particularly significant, as personalized predictions can guide experimental studies towards prioritizing high-potential compounds and optimizing therapeutic strategies.

The results of this study are in agreement with previous research efforts aimed at developing predictive models for drug sensitivity using genomic data. For instance, Chiu et al. (2019) successfully applied neural networks and random forests to predict drug efficacy based on mutation and expression profiles of cancer cells [17]. Similarly, Su et al. (2019) demonstrated the potential of deep forest models to predict drug sensitivity from gene expression data [18]. Furthermore, Ding et al. (2019) highlighted the value of integrating machine learning algorithms with omics data to improve prediction accuracy and therapeutic efficacy [19].

Despite the promising results, certain limitations must be acknowledged. First, this study focused exclusively on predicting IC_{50} values for a single compound, OTX015. While this approach allowed for a detailed evaluation of prediction models, it limits the generalizability of the findings to other BET inhibitors or unrelated drug classes. Expanding the analysis to include additional compounds would provide a more comprehensive evaluation of model performance. Second, the training datasets used in this study were derived from existing literature, which may lack diversity in terms of cancer cell lines, experimental conditions, and data quality. The reliance on publicly available datasets could introduce biases that may not accurately reflect real-world scenarios. Addressing this limitation would require integrating more diverse datasets, including those generated from patient-derived samples and primary tumor cells. Third, while the models demonstrated strong predictive capabilities on existing data, their performance on real-world patient-derived samples remains unexplored. Testing the models against clinical datasets or organoid models derived from patient tissues would be essential to validate their practical applicability in precision medicine. Finally, the current study utilized gene expression data as the sole feature set for prediction. Integrating other omics data types, such as proteomics, metabolomics, and epigenomics,

 doi:10.20944/preprints202503.2146.v1

could enhance prediction robustness by providing a more comprehensive representation of the molecular mechanisms influencing drug sensitivity.

Overall, the results of this study emphasize that the SVM model is the most appropriate choice among the models evaluated, due to its superior generalization capability and ability to provide consistent predictions across diverse datasets. Future research should focus on expanding the dataset to include additional cell lines and drugs, optimizing feature selection processes, and integrating various machine learning approaches to enhance prediction robustness.Moreover, the integration of biological pathway information and transcriptomic profiles could provide additional insights into the molecular mechanisms underlying drug sensitivity, further enhancing the applicability of machine learning models in precision oncology.

The findings of this study contribute to the growing body of research advocating the use of machine learning for predicting potential drug candidates and optimizing cancer treatment strategies. Continued efforts to refine predictive models and incorporate additional datasets will be essential to advance personalized medicine and improve therapeutic outcomes for cancer patients.

4. Materials and Methods

In this study, five different regression-based machine learning models were developed using the R programming language and R Studio to predict the IC_{50} values of the bromodomain inhibitor OTX015 in cancer cell lines:

- **IC_{50} Values:** The IC_{50} values of OTX015 in cancer cell lines were obtained from the CancerRxGene (https://www.cancerrxgene.org/) data source. This data provides a crucial measure of the impact of OTX015 on cancer cell lines.
- **Gene Expression Data:** The gene expression levels of cancer cells were obtained from the Sanger Institute's Cancer Cell Lines Project (https://cancer.sanger.ac.uk/cell_lines) data source. These data allow for a detailed examination of the gene expression profile in cancer cells.

4.1. Comparison of Predicted and Actual IC_{50} Values

The collected IC_{50} values and gene expression data underwent a series of preprocessing steps before being used for model training, testing, and validation. The preprocessing was conducted using the R programming language, employing various statistical and machine learning packages. The following steps were performed:

1. **Data Integration:** IC_{50} values and gene expression data were merged based on cancer cell lines. This step helped determine in which cancer cells IC_{50} values were determined for the OTX015 compound and in which cells gene expression levels were measured.
2. **Data Processing:** Missing data were checked, and any incomplete data were removed from the dataset. Following the literature (Table 1), cell lines with IC_{50} values of 200 μM or higher were considered inactive and were excluded from the dataset [20].
3. **Feature Engineering:** To determine the features used for model development, feature engineering was performed on the gene expression data. Only significant gene expression levels were selected. Each gene in the dataset was subjected to Pearson correlation with the IC_{50} value. The relationships were ranked from highest to lowest based on the absolute value of the correlation, irrespective of whether the correlation was positive or negative. Genes with significant correlations to IC_{50} values were selected in sets of 10, 25, 50, 75, and 100 to evaluate the impact of data dimensions on the models, resulting in five different new datasets.
4. **Data Scaling:** Rescaling the data often improves model performance by reducing error rates, depending on the nature of the problem, data, and models. Therefore, rescaling was applied to all five models used in this study. This contributed to better model performance and lower error rates.
5. **Creation of Training, Testing, and Validation Data:** To evaluate the model's performance on a dataset it had not seen before, the dataset was randomly split before model training. 80% of the data (314 samples) was used for training and testing, and 20% (76 samples) was used for

 doi:10.20944/preprints202503.2146.v1

validation. The validation data set was reserved for assessing the model's performance and was not used during the training or optimization stages. Cross-validation was performed using the training data. In cross-validation, the value of k was set to 5, creating five different training and testing sets during model training.

4.2. Model Training, Utilization, and Evaluation

In this study, five different regression-based machine learning models were implemented using the R programming language and relevant libraries to predict the IC_{50} values of the bromodomain inhibitor OTX015 in cancer cell lines based on gene expression profiles. Each model was developed using its respective R package, leveraging their built-in functions for model training and evaluation. The selected models, along with their corresponding R libraries, are as follows:

1. K-Nearest Neighbor (KNN) – implemented using the kknn package
2. Extreme Gradient Boosting (XGB) – implemented using the xgboost package
3. Elastic Net (EN) – implemented using the glmnet package
4. Neural Networks (NNET) – implemented using the nnet package
5. Support Vector Machine (SVM) – implemented using the e1071 package

These five regression models were trained separately using the same dataset and their performances were compared using the same validation set. Model training and evaluation were conducted in R Studio, utilizing the caret package for workflow standardization, hyperparameter tuning, and cross-validation.

During model training, hyperparameter optimization was performed for key parameters influencing model performance, ensuring that each model was fine-tuned for optimal accuracy. The optimal hyperparameters were determined based on the Mean Absolute Error (MAE) calculated using Equation (1)

$$MAE = \frac{1}{n}\sum_{i=1}^{n} |x_i - x| \quad (1)$$

MAE was used to compute the mean of the absolute differences between the predicted and actual values. The parameters with the lowest MAE scores were selected as the optimal hyperparameters to maximize model performance. The models were then retrained with these optimal parameters and the same training set, and these retrained models were considered the best-performing models.

After optimization, the performance of the best models was evaluated using the validation set, which comprised 20% of the initial data that was not used during training. The MAE score was used for this evaluation. The MAE scores facilitated the comparison of model performances across different data sizes as well as among the five different machine learning models. The MAE scores obtained by the models on the validation sets are presented in Table 2. The entire workflow is illustrated in Figure 4.

 doi:10.20944/preprints202503.2146.v1

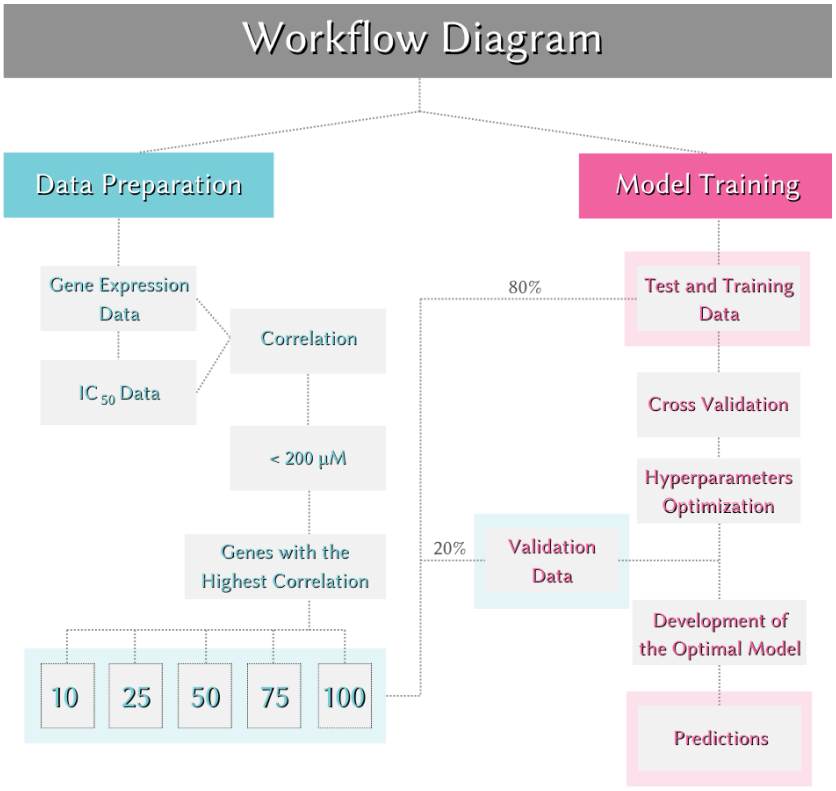


Figure 4. This is the workflow diagram of the study.

5. Conclusions

This study demonstrated that the Support Vector Machine (SVM) model provides the most accurate predictions of IC_{50} values for the BET inhibitor OTX015 in cancer cell lines compared to other models. Its strong performance across varying gene expression datasets highlights its potential for drug discovery and personalized oncology.However, the study's limitations include its focus on a single drug, reliance on literature-derived datasets, and lack of validation with real-world patient-derived samples. Future research should include diverse datasets, integrate additional omics data, and validate predictions using clinical and organoid-based systems. The SVM model's reliable performance makes it a promising tool for drug response prediction, contributing to the advancement of precision oncology and improving therapeutic strategies.

Author Contributions: Con-ceptualization, Uğur Bilge, M. Okan Çakır, Mustafa Özdoğan and Gizem Tutkun; methodology, Uğur Bilge and Gizem Tutkun; software, Gizem Tutkun.; validation, Uğur Bilge; formal analysis, M. Okan Çakır; investigation, Uğur Bilge and M.Okan Çakır.; resources, Gizem Tutkun; data curation, Uğur Bilge; writing—original draft preparation, Gizem Tutkun.; writing—review and editing, M.Okan Çakır and Mustafa Özdoğan; visualization, Gizem Tutkun; supervision and project administration, Uğur Bilge. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

BET	Bromodomain and Extra-Terminal
BETi	BET inhibitors
ML	Machine Learning
SVM	Support Vector Machine
KNN	K-Nearest Neighbor

 doi:10.20944/preprints202503.2146.v1

XGB	Extreme Gradient Boosting
EN	Elastic Net
NNET	Neural Networks
MAE	Mean Absolute Error
IC_{50}	Half-maximal Inhibitory Concentration

References

1. Siegel, R.L.; Miller, K.D.; Fuchs, H.E.; Jemal, A. Cancer Statistics, 2021. *CA Cancer J Clin* 2021, *71*, 7–33, doi:10.3322/caac.21654.
2. Tonorezos, E.; Devasia, T.; Mariotto, A.B.; Mollica, M.A.; Gallicchio, L.; Green, P.; Doose, M.; Brick, R.; Streck, B.; Reed, C.; et al. Prevalence of Cancer Survivors in the United States. *JNCI: Journal of the National Cancer Institute* 2024, doi:10.1093/jnci/djae135.
3. Kaur, R.; Bhardwaj, A.; Gupta, S. Cancer Treatment Therapies: Traditional to Modern Approaches to Combat Cancers. *Mol Biol Rep* 2023, *50*, 9663–9676.
4. Pérez-Salvia, M.; Esteller, M. Bromodomain Inhibitors and Cancer Therapy: From Structures to Applications. *Epigenetics* 2017, *12*, 323–339.
5. Filippakopoulos, P.; Knapp, S. Targeting Bromodomains: Epigenetic Readers of Lysine Acetylation. *Nat Rev Drug Discov* 2014, *13*, 337–356.
6. Shu, S.; Polyak, K. BET Bromodomain Proteins as Cancer Therapeutic Targets. In Proceedings of the Cold Spring Harbor symposia on quantitative biology; Cold Spring Harbor Laboratory Press, 2016; Vol. 81, pp. 123–129.
7. Boyson, S.P.; Gao, C.; Quinn, K.; Boyd, J.; Paculova, H.; Frietze, S.; Glass, K.C. Functional Roles of Bromodomain Proteins in Cancer. *Cancers (Basel)* 2021, *13*, 3606.
8. Greener, J.G.; Kandathil, S.M.; Moffat, L.; Jones, D.T. A Guide to Machine Learning for Biologists. *Nat Rev Mol Cell Biol* 2022, *23*, 40–55, doi:10.1038/s41580-021-00407-0.
9. Yang, J.; Li, A.; Li, Y.; Guo, X.; Wang, M. A Novel Approach for Drug Response Prediction in Cancer Cell Lines via Network Representation Learning. *Bioinformatics* 2019, *35*, 1527–1535, doi:10.1093/bioinformatics/bty848.
10. Giorgi, F.M.; Ceraolo, C.; Mercatelli, D. The R Language: An Engine for Bioinformatics and Data Science. *Life* 2022, *12*, 648, doi:10.3390/life12050648.
11. Adam, G.; Rampášek, L.; Safikhani, Z.; Smirnov, P.; Haibe-Kains, B.; Goldenberg, A. Machine Learning Approaches to Drug Response Prediction: Challenges and Recent Progress. *NPJ Precis Oncol* 2020, *4*, 19, doi:10.1038/s41698-020-0122-1.
12. Firoozbakht, F.; Yousefi, B.; Schwikowski, B. An Overview of Machine Learning Methods for Monotherapy Drug Response Prediction. *Brief Bioinform* 2022, *23*, bbab408.
13. L'heureux, A.; Grolinger, K.; Elyamany, H.F.; Capretz, M.A.M. Machine Learning with Big Data: Challenges and Approaches. *Ieee Access* 2017, *5*, 7776–7797.
14. Osisanwo, F.Y.; Akinsola, J.E.T.; Awodele, O.; Hinmikaiye, J.O.; Olakanmi, O.; Akinjobi, J. Supervised Machine Learning Algorithms: Classification and Comparison. *International Journal of Computer Trends and Technology (IJCTT)* 2017, *48*, 128–138.
15. Roy, A.; Chakraborty, S. Support Vector Machine in Structural Reliability Analysis: A Review. *Reliab Eng Syst Saf* 2023, *233*, 109126, doi:10.1016/j.ress.2023.109126.
16. Hans, C. Elastic Net Regression Modeling With the Orthant Normal Prior. *J Am Stat Assoc* 2011, *106*, 1383–1393, doi:10.1198/jasa.2011.tm09241.
17. Chiu, Y.-C.; Chen, H.-I.H.; Zhang, T.; Zhang, S.; Gorthi, A.; Wang, L.-J.; Huang, Y.; Chen, Y. Predicting Drug Response of Tumors from Integrated Genomic Profiles by Deep Neural Networks. *BMC Med Genomics* 2019, *12*, 143–155.
18. Su, R.; Liu, X.; Wei, L.; Zou, Q. Deep-Resp-Forest: A Deep Forest Model to Predict Anti-Cancer Drug Response. *Methods* 2019, *166*, 91–102.

 doi:10.20944/preprints202503.2146.v1

19. Ding, M.Q.; Chen, L.; Cooper, G.F.; Young, J.D.; Lu, X. Precision Oncology beyond Targeted Therapy: Combining Omics Data with Machine Learning Matches the Majority of Cancer Cells to Effective Therapeutics. *Molecular Cancer Research* 2018, *16*, 269–278, doi:10.1158/1541-7786.MCR-17-0378.
20. Indrayanto, G.; Putra, G.S.; Suhud, F. Validation of In-Vitro Bioassay Methods: Application in Herbal Drug Research. In; 2021; pp. 273–307.