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DrugSK: A Stacked Ensemble Learning Framework for Predicting Drug Combinations of Multiple Diseases

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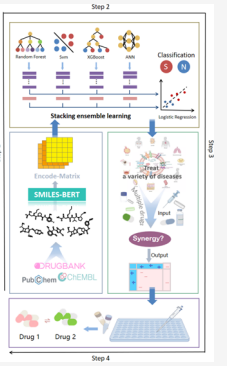
ABSTRACT: Combination therapy is an important direction of continuous exploration in the field of medicine, with the core goals of improving treatment efficacy, reducing adverse reactions, and optimizing clinical outcomes. Machine learning technology holds great promise in improving the prediction of drug synergy combinations. However, most studies focus on single disease-oriented collaborative predictive models or involve excessive feature categories, making it challenging to predict the majority of new drugs. To address these challenges, the DrugSK comprehensive model was developed, which utilizes SMILES-BERT to extract structural information from 3492 drugs and trains on reactions from 48,756 drug combinations. DrugSK is an integrated learning model capable of predicting interactions among various drug categories. First, the primary learner is trained from the initial data set. Random forest, support vector machine, and XGboost model are selected as primary learners and logistic regression as secondary learners. A new data set is then "generated" to train level 2 learners, which can be thought of as a prediction for each model. Finally, the results are filtered using logistic regression. Furthermore, the combination of the new antibacterial drug Drafloxacin with other antibacterial agents was tested. The synergistic effect of Drafloxacin and Isavuconazonium in the fight against *Candida albicans* has been confirmed, providing enlightenment for the clinical treatment of skin infection. DrugSK's prediction is accurate in practical application and can also predict the probability of the outcome. In addition, the tendency of Drafloxacin and antifungal drugs to be synergistic was found. The development of DrugSK will provide a new blueprint for predicting drug combination synergies.



1. INTRODUCTION

In the realm of pharmacotherapy, elucidating the intricate domain of drug synergies stands as a critical yet complex pursuit. Positive interactions between drugs, known as synergies, can not only amplify therapeutic effects but also reduce adverse reactions and toxicity.[1,2] Hence, comprehending and prognosticating the mechanisms governing drug synergistic actions hold pivotal significance.

Traditional medical research has historically focused on independently assessing and studying the efficacy of individual drugs.[3] However, with an ever-deepening understanding of disease physiology and molecular underpinnings, there is increasing evidence that interventions utilizing combinations of multiple drugs could yield more effective disease management.[4] The potency of combination therapy lies in its ability to concurrently target distinct biomarkers, pathways, or molecular targets, thereby orchestrating a comprehensive modulation of disease-related biological processes.[5]

However, experimentally exploring synergistic drug combinations is not only time-consuming but also financially taxing. Thus, the urgent need for efficient and economical drug combination screening has prompted the emergence of machine learning (ML) techniques. Over the last few decades, conventional computational methodologies, including kinetic models,[6,7] systems biology approaches,[8] biological networks, and mathematical frameworks,[9,10] were often constrained by prior knowledge and deemed suitable only for smaller data sets. However, the surge in drug-related data has propelled ML methods to the forefront, offering robust predictive capabilities.[11] As a potent data analysis tool, machine learning paves novel avenues for understanding and predicting the synergistic effects of drugs.[12]

Artificial intelligence (AI) methods have been applied in a variety of fields, such as using ML to calculate features computed from primary sequences[13] and combining efficient radial basis function networks and important amino acids to predict G-proteins via guanosine triphosphate binding sites in transporters.[14] Currently, although ML techniques are widely used in related research in the field of medicine, most research tends to revolve around predictive models in the field of cancer treatment.[12,15] For instance, Kuenzi et al. developed an interpretable deep learning model, DrugCell, specifically for human cancer cell predictions.[16] Preto et al. utilized various

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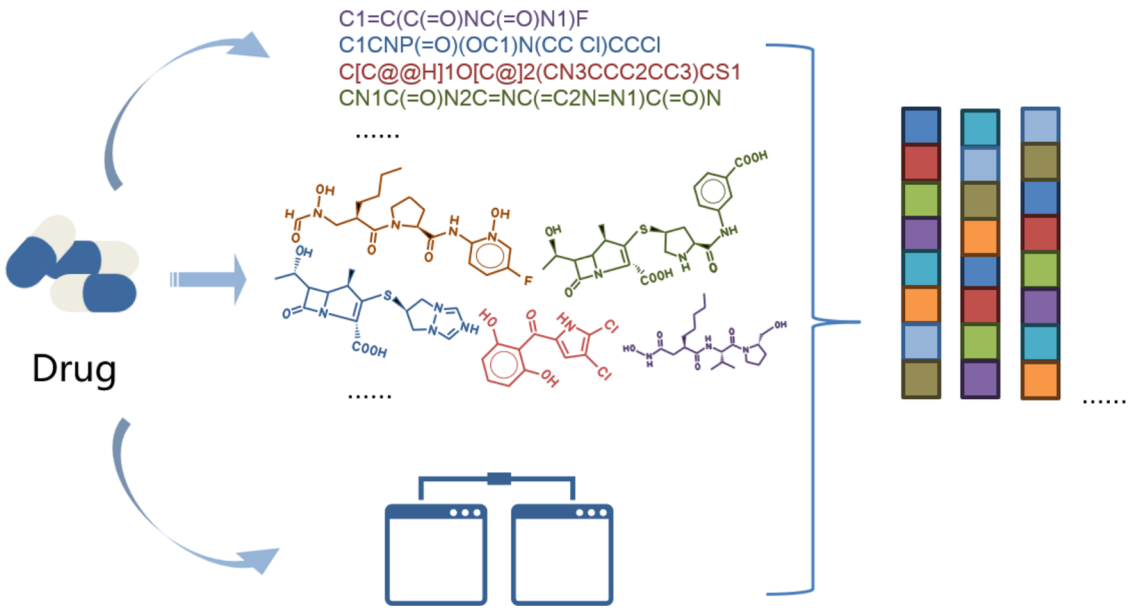

Figure 1. Mapping molecule to feature vector (fingerprint with different methods).

scoring methods to forecast the synergistic effects of anticancer drugs.[17] Sun's research group proposed a deep tensor factorization (DTF) algorithm to predict the synergistic effects of anticancer drugs.[18] However, there remains a paucity of models capable of predicting drugs for other disease categories or forecasting interactions among all drug categories. Moreover, most models are trained with an abundance of feature categories, such as Li et al., who modeled with five categories of features: drug targets, drug structures, drug gene expression, drug indications, and drug modules,[19] and Lin et al., who modeled with four categories of features: drug structures, drug physicochemical properties, drug-gene expression profiles, and drug cell lines.[20] Sidorov et al. considered comprehensive information, including fingerprints, MACCS keys, ISIDA/SIRMS fragments, and physicochemical properties.[21] Li et al. manually designed 18 features encompassing drug chemical structures, drug target networks, and drug genomics similarities.[22] While these approaches might augment model performance, they pose hindrances in predictions for drugs lacking certain feature data. Moreover, most new drugs might lack comprehensive and relevant data, heightening the difficulty of predicting drug interactions for novel medications. Presently, most models evaluate performance solely based on model evaluation metrics or external validation sets, with limited experimental validation of results. For example, Yang et al. developed a framework for predicting injectable drug combinations based on heterogeneous information and deep learning, verifying only a portion of the results without experimental validation.[23] El Khili et al. constructed a multitask deep learning model for predicting synergy scores of drug combinations and predicted synergy scores for 133,722 new drugs against CCL combinations but solely providing results without validation.[24] There is an urgent need for a comprehensive model that is reliable, authentic, and capable of predicting interactions among multiple drug categories.

To address the challenges in predicting drug interactions for novel medications, this study aims to develop a machine learning approach using a more streamlined set of drug feature data specifically tailored to predict interactions among all drug categories. Leveraging the SMILES-BERT natural language processing model, structural information was extracted from 3492 drug structures and the model was trained on reactions of 48,756 drug combinations. A stacked ensemble learning model was constructed to be capable of predicting the interactions between various types of drugs. In addition, the combination of Delafloxacin, a newly marketed antibacterial drug, with other antibacterial and antibacterial drugs was tested and validated by a checkerboard experiment.[25] DrugSK's predictions are accurate in practical applications and can also forecast result probabilities. Through an in-depth understanding of drug synergies, it is intended to contribute to personalized therapy and enhance precision medicine, enhancing the efficacy and safety of drug therapy.

Using the proposed methodology, specific drug combinations involving Delafloxacin were predicted and several candidate drug combinations were obtained. In this process, the experiment demonstrated that Isavuconazonium and Delafloxacin can synergically act against *Candida albicans* and this discovery is expected to provide new therapeutic options for the clinical treatment of a variety of skin diseases caused by *C. albicans*. Drafloxacin was also observed to have a tendency to interact with antifungal drugs, a finding that is expected to provide clinicians with a wider range of treatment options and provide new insights into the field of drug trials.

2. RESULTS

DrugSK represents an integrated learning model capable of predicting interactions across various classes of drugs. 48,757 drug combination data were collected to train the model. The best model achieved an area under the receiver operating characteristic (ROC) curve (AUC) of 0.81 and an accuracy of 0.76. Leveraging this model, we have conducted predictions for interactions across diverse drug classes, including the synergy between chronic obstructive pulmonary disease (COPD) and lung cancer therapies. Furthermore, we tested combinations involving the newly marketed antibiotic Delafloxacin with other antibacterial drugs, validated through checkerboard experiments. Our observations confirmed the synergistic interaction between Delafloxacin and Isavuconazonium, validating the accuracy and reliability of our model. Addition-

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J. Chem. Inf. Model. 2024, 64, 5317−5327

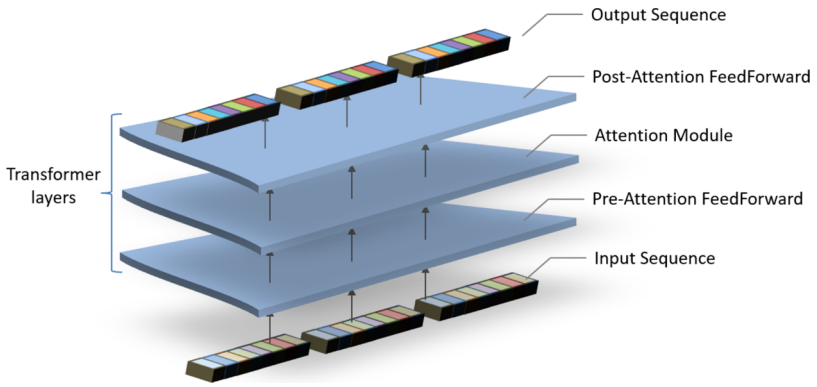

Figure 2. Structure of the Transformer layer.

ally, we identified a pattern wherein Delafloxacin tends to interact prominently with antifungal medications.

2.1. Data Collection and Processing. Data on 48,757 drug combinations and their SMILES were collected from multiple databases. Then, SMILES drug information was transformed by the SMILES-BERT method. The approach focuses on embedding molecules into continuous feature spaces for further tasks. Since molecules have different representations, these methods can be divided into three categories based on the input representation format used: sequence-based, graph-based, and manual feature engineering methods (Figure 1).

Conventional molecular fingerprints like PubChem fingerprints and MACCS fingerprints are known to describe specific parts of a molecule's structure rather than computing fundamental properties.[26,27] And traditional molecular fingerprints necessitate intensive manual feature engineering and domain expertise, and typically contain limited information to encompass all of the intrinsic details within molecules. Moreover, these fingerprints are highly task-dependent and may lack universality for other attribute prediction tasks.[28]

However, SMILES-BERT is improved based on the BERT model in natural language processing. Pretraining on SMILES representation of chemical molecules can better learn the feature representation of molecules.[29] SMILES-BERT consists of an attention-mechanism-based Transformer layer that pretrains large-scale unlabeled data with a masked SMILES recovery task and then fine-tunes the pretrained model to different molecular property prediction tasks (Figure 2). The proposed method has been evaluated on several molecular property prediction tasks and achieved good performance, which can provide better feature representation for molecular property prediction tasks. The approach focuses on embedding molecules into continuous feature spaces for further tasks.

Molecular structures significantly influence the reactivity, polarity, phase, color, magnetism, and bioactivity of chemical substances. To validate the efficacy of information extraction by SMILES-BERT from SMILES representations, common drug features such as molecular fingerprints, physicochemical properties of drugs, drug ATC codes, and drug targets were collected for comparative analysis with the constructed model. Accuracy, precision, recall rate, F1 score, and AUC were used as evaluation indicators, as shown in Figure 3. The results indicated that SMILES-BERT had superior performance in extracting information from SMILES strings compared to other common features, demonstrating its capability to thoroughly extract drug-related information embedded within SMILES representations.

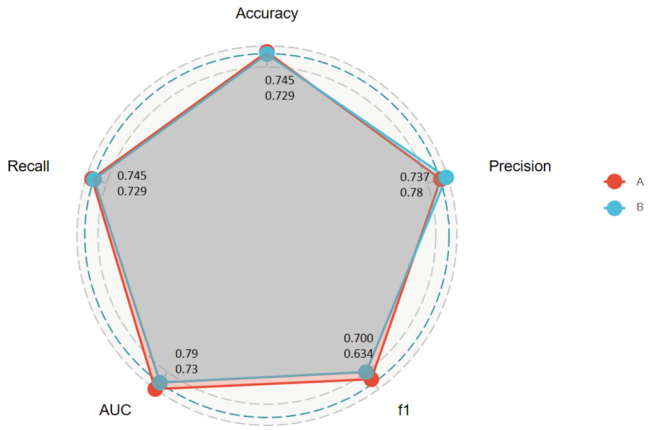

Figure 3. Comparison of SMILES-BERT processing data and multifeature data training model evaluation results. (1) A is the model constructed using the data extracted from SMILES-BERT. B is the model constructed using common drug features such as molecular fingerprints, physicochemical properties of drugs, drug ATC codes, and drug targets. (2) The metrics included accuracy, precision, recall, F1 score, and AUC. The results show that SMILES-BERT has comparable or higher performance in extracting information from SMILES.

2.2. Model Design and Performance Evaluation. In recent years, stacking methods have been widely used in many fields, such as using stacking methods to predict causes of death, classification of diabetes, and identification of bioactive small molecule protein targets.[30−32] In the field of drug combination prediction, building the DrugSK integrated model is a complex and innovative approach that we have adopted in our research. Instead of relying on a single model, we fused multiple highly complex machine learning algorithms altogether to build a powerful and efficient ensemble learning model. The construction of the model goes far beyond simply averaging the predictions of individual models. Our approach involves the latest techniques and theories in the field of deep learning and ensemble learning. Through a carefully designed approach to overlay and fusion, different models learn from and complement each other to achieve higher levels of performance. In this study, diverse information was extracted by various models from the data. Due to the presence of noise in the data, different models excel in different features while exhibiting shortcomings in others. To integrate their strengths and circumvent their weaknesses, the DrugSK ensemble model

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J. Chem. Inf. Model. 2024, 64, 5317−5327

is designed. It incorporates different algorithms such as support vector machine (SVM) and random forest (RF), among others. The stacking method is used to integrate the models together, so that different models can learn different features of the data, and the result of stacking and fusion can perform better and learn from each other. The innovation involves combining artificial neural network (ANN), RF, SVM, eXtreme Gradient Boosting (XGBoost), and logistic regression (LR) models to build a composite ensemble learning model. To avoid overfitting, models were trained across 5-fold cross-validation, ensuring training on different folds of data. Each model generated a 5-fold prediction, consolidating all predictions from the first layer models into the training set for the secondary learner. The results from each test set in the *K*-fold became the training set for the secondary learner. Finally, the prepartitioned test set was used for evaluation (Figure 4), where the best model achieved an AUC of 0.81 and an accuracy of 0.76.

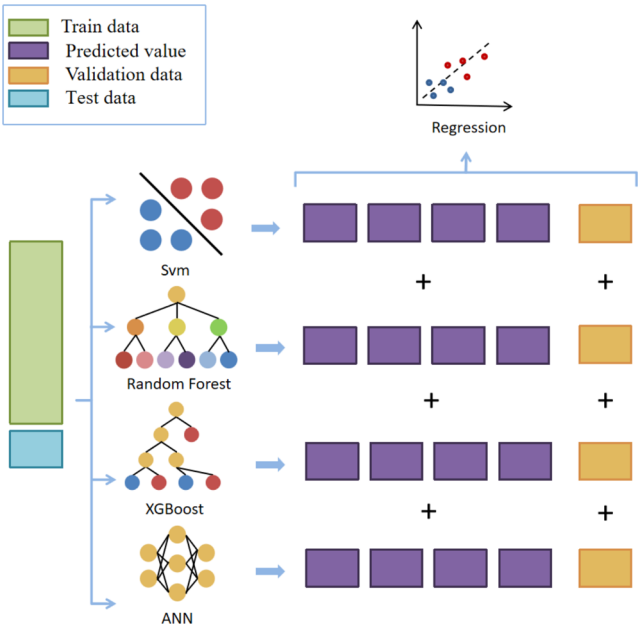

Figure 4. Each round of cross-validation comprises two stages. 1. The primary learner is initially trained on the original data set using RF, SVM, XGBoost, and ANN models as primary learners and logistic regression as a secondary learner. 2. Subsequently, "generating" a new data set for training the secondary learner, representing the first layer of predictions by various models and the second layer involving logistic regression for result refinement.

ROC curves for four independent ML algorithms are plotted and compared to an ensemble learner on the validation set for analysis (Figure 5). 95% confidence interval (95% CI) for the performance metrics was derived by Bootstrapping 10,000 times. CI is an estimated range of parameter values in a statistical inference that has a 95% probability of containing the true parameter values. The AUROC for RF, SVM, XGB, ANN, and LR were 0.793 ([CI] 0.787−0.799), 0.770 (0.760−0.783), 0.783 (0.769−0.793), 0.753 (0.740−0.766), and 0.753 (0.742−0.767).

The final DrugSK model integrates all four basic ML algorithms. When testing on a validation set, 95% CI of AUC, accuracy, precision, F1, and recall were 0.796 (0.7787−0.810), 0.746 (0.745−0.750), 0.741 (0.740−0.742), 0.738 (0.737−0.740), and 0.746 (0.745−0.747). Accuracy, precision, F1, recall, and AUC scores of other baseline models are shown in Table 1.

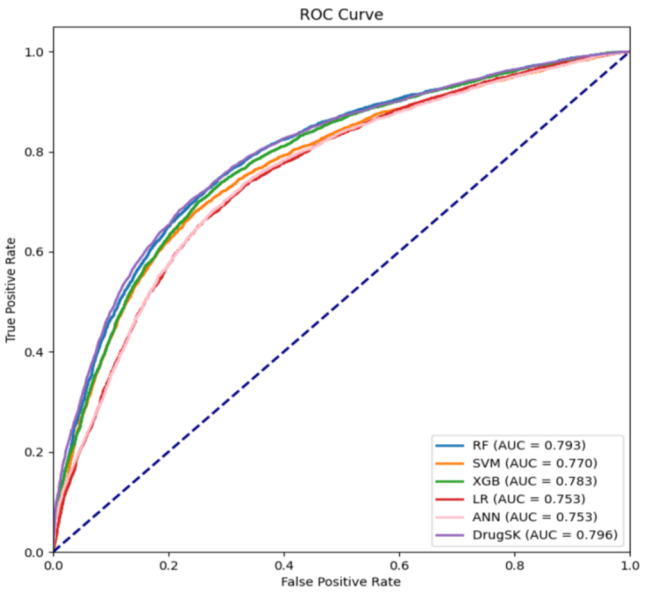

Figure 5. Working characteristic curves of four basic learners and DrugSK model. RF, Random forest; SVM, support vector machine; XGB, extreme gradient lift; LR, logistic regression.

2.3. Prediction Result Output. COPD might represent different aspects of the same condition, sharing underlying susceptibilities. Mutations could result in cancer, while excessive damage to cells and proteins could lead to COPD.[33,34] Given the close relationship between lung cancer and COPD, drug combinations used to treat both diseases are predicted in the hope of slowing the progression and mortality of these interrelated diseases. We collected data on 9 first-line and second-line drugs for LC and 21 first-line and second-line drugs for COPD from the *Diagnosis and Treatment Guidelines for Chronic Obstructive Pulmonary Disease* (2021 edition) and the *Clinical Diagnosis and Treatment Guidelines for Lung Cancer of the Chinese Cancer Society* (2021 edition). The prediction results are outlined in Figure 6 and Table 2 (detailed results are in the Supporting Information).

Three pairs, Terbutaline and Irinotecan, Azithromycin and Irinotecan, and Fluticasone furoate and Docetaxel, have been confirmed to interact according to databases such as Drugbank, PubChem, and Therapeutic Target Database (TTD), which validates the accuracy of the model to some extent.

With a deep understanding of the mechanisms of inflammatory diseases,[35] there is increasing evidence that the inflammatory response can be more comprehensively regulated by the proper combination of anti-inflammatory drugs.[36−38] The advantage of this combination therapy is that it acts simultaneously on different inflammatory pathways or molecular targets. More significant efficacy can be achieved through drug combinations, which is expected to provide a new strategy for clinical treatment.[39] Synergistic combinations of anti-inflammatory drugs are therefore predicted, hopefully providing the basis for more effective treatment regimens and personalized medicine. Data on 306 anti-inflammatory drugs were collected in the PubChem database, and the information was extracted using SMILES-BERT technology. The drug information was arranged and combined to form a feature

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J. Chem. Inf. Model. 2024, 64, 5317−5327

Table 1. DrugSK Model Performance with Other Machine Learning Machines on Validation Sets

	accuracy	precision	F1	recall	AUC
DrugSK	0.747 (0.745−0.755)	0.741 (0.740−0.742)	0.738 (0.737−0.740)	0.746 (0.745−0.747)	0.796 (0.787−0.810)
RF	0.748 (0.738−0.756)	0.715 (0.703−0.730)	0.623 (0.610−0.634)	0.551 (0.550−0.572)	0.793 (0.786−0.811)
SVM	0.735 (0.721−0.745)	0.686 (0.663−0.690)	0.609 (0.602−0.626)	0.548 (0.531−0.559)	0.770 (0.760−0.783)
XGB	0.737 (0.731−0.747)	0.692 (0.678−0.704)	0.608 (0.589−0.618)	0.542 (0.534−0.557)	0.783 (0.769−0.793)
ANN	0.721 (0.702−0.734)	0.627 (0.618−0.642)	0.610 (0.598−0.621)	0.594 (0.582−0.616)	0.753 (0.740−0.766)
LR	0.711 (0.701−0.724)	0.657 (0.639−0.664)	0.558 (0.545−0.568)	0.484 (0.478−0.495)	0.753 (0.742−0.767)

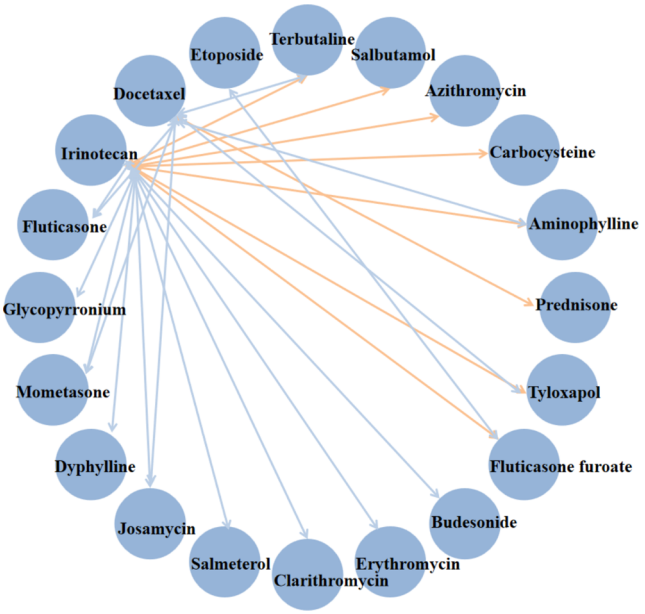

Figure 6. Predicted synergistic effects of combined use of lung cancer drugs and COPD drugs. The two-wire connection indicates that the two drugs will have a synergistic effect. The orange arrow represents a high probability of synergistic interaction between the two drugs, and the blue arrow represents a low probability of synergistic interaction between the two drugs.

Table 2. Prediction Results and Probability of Synergistic Combination of Lung Cancer Drugs and COPD Drugs

drug 1	drug 2	probability
Terbutaline	Irinotecan	0.764568002
Salbutamol	Irinotecan	0.714793931
Azithromycin	Irinotecan	0.712845042
Carbocysteine	Irinotecan	0.712386443
Aminophylline	Irinotecan	0.703541425
Fluticasone furoate	Docetaxel	0.701440888
Tyloxapol	Irinotecan	0.701078405
Fluticasone furoate	Irinotecan	0.700599915
Tyloxapol	Docetaxel	0.699641106
Budesonide	Irinotecan	0.695368814
Erythromycin	Irinotecan	0.694869729
Clarithromycin	Irinotecan	0.694030251
Salmeterol	Irinotecan	0.693080828
Josamycin	Irinotecan	0.685982183
Dyphylline	Irinotecan	0.683785611
Mometasone	Irinotecan	0.680056614
Glycopyrronium	Irinotecan	0.677606574
Fluticasone furoate	Etoposide	0.671530141
Fluticasone	Irinotecan	0.671019582
Josamycin	Docetaxel	0.664241145
Terbutaline	Docetaxel	0.661671832
Aminophylline	Docetaxel	0.659645141
Mometasone	Docetaxel	0.658664335
Fluticasone	Docetaxel	0.657482873

matrix of 22,656 samples and 1536 features, which served as a predictive data set for anti-inflammatory drug synergies. The forecast results are shown in Figure 7 and Table 3 (detailed results are in Supporting Information, Document 1).

Three of the above-predicted results can be confirmed in Drugbank, PubChem, TTD, and other databases for interaction (including Dersalazine and Flunisolide, Dersalazine and Fluprednisolone, and Dersalazine and Betamethasone). The result also proves the accuracy and comprehensiveness of the model.

Delafloxacin, approved by the US FDA on June 19, 2017, is a novel fluoroquinolone broad-spectrum antibiotic co-developed by Japan's Wakunaga Pharmaceutical Company and the US-based Melinta Corporation. It demonstrates potent antibacterial activity against a wide range of pathogens causing skin diseases or respiratory infections.[40] However, since the drug has just been introduced to the market, clinical studies on its interactions are very limited. Hence, this drug was chosen to be studied. Information on commonly prescribed antimicrobial drugs was retrieved from the PubChem database to predict the drug pairing with Delafloxacin. The predicted synergistic effects are listed in Figure 8 and Table 4 (detailed results are in Supporting Information, Document 1).

2.4. Experimental Verification. To ensure model accuracy, Isavuconazonium and Delafloxacin, identified as synergistic in Table 4, underwent experimental validation. Conversely, the nonsynergistic combination of Drafloxacin and Dierythromycin was selected for negative validation.[41] The checkerboard method was chosen for this experimental verification. The checkerboard test is a commonly used experimental design method to evaluate the effects of different drug combinations on antimicrobial efficacy. In this experiment, different drug combinations are applied to bacterial strains or clinical isolates to compare their inhibitory effects on bacterial growth.[42] In this study, the checkerboard method was used to evaluate the interaction between the antimicrobial agents Drafloxacin and the antifungal agents Isavuconazonium and Dirithromycin. The minimum inhibitory concentration (MIC) of individual drugs was measured by a double dilution method at different concentration ranges (4−2048 μg/mL for Drafloxacin, 0.25−128 μg/mL for Isavuconazonium, and 0.25−128 μg/mL for Dirithromycin). The drug to be tested was diluted continuously in a 96-well plate with a certain amount of liquid medium. Then a certain amount of tested bacteria solution was added to each tube (the concentration was 10^6 CFU/mL). After the 96-well plate was cultured at 37 °C for 24 h, bacterial growth was observed. Compared with the blank control, the MIC of the drug was determined to be the lowest concentration where the medium was clear and no

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J. Chem. Inf. Model. 2024, 64, 5317−5327

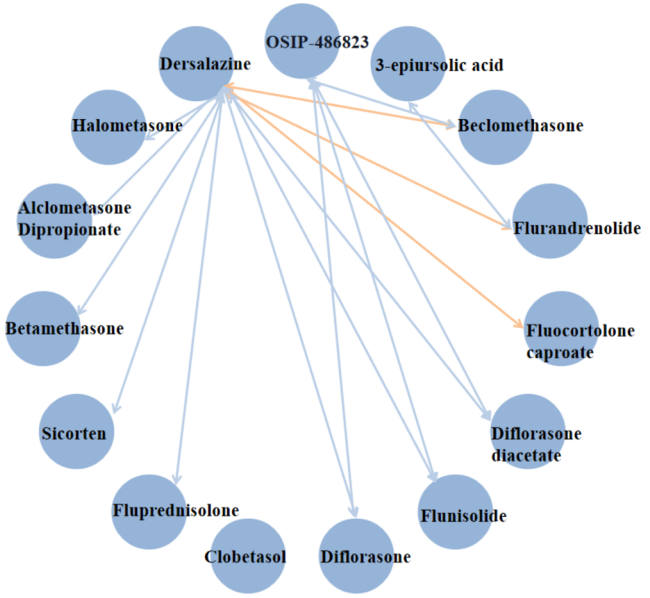

Figure 7. Predicted synergistic effects of combined use of anti-inflammatory drugs. The two-wire connection indicates that the two drugs will have a synergistic effect. The orange arrow represents a high probability of synergistic interaction between the two drugs, and the blue arrow represents a low probability of synergistic interaction between the two drugs.

Table 3. Prediction Results and Probability of Synergistic Combination of Anti-inflammatory Drugs

drug 1	drug 2	probability
Dersalazine	Beclomethasone	0.712663404
Dersalazine	Flurandrenolide	0.709540085
Dersalazine	Fluocortolone caproate	0.701600043
Dersalazine	Diflorasone diacetate	0.699956921
Dersalazine	Flunisolide	0.698724689
Dersalazine	Diflorasone	0.691893205
OSIP-486823	Beclomethasone	0.69002581
Dersalazine	Fluprednisolone	0.689311566
3-Epiursolic acid	Flurandrenolide	0.687852824
OSIP-486823	Diflorasone	0.685582465
OSIP-486824	Diflorasone diacetate	0.685079472
OSIP-486825	Flunisolide	0.682527034
Dersalazine	Clobetasol	0.680700661
Dersalazine	Sicorten	0.680159264
Dersalazine	Betamethasone	0.680113989
Dersalazine	Alclometasone dipropionate	0.679481336
Dersalazine	Halometasone	0.679370616

bacterial growth was observed by the naked eye, and the MIC was recorded. Then the MIC of the combination drug was measured by the double dilution method according to the different concentration ranges of 0.25−128 μg/m for Isavuconazonium combined with Drafloxacin (4−2048 μg/mL). Based on the experimental results, the synergistic index of drug combinations to judge the type of interaction between drugs was calculated as follows: The fractional inhibition concentration (FIC) of each drug was calculated by dividing the MIC or minimum effective concentration (MEC) of the drug by the MIC or MEC of the individual drug.[43,44] All readings were taken after incubation at 37 °C for 24 h. The out-of-range MIC was converted to the next higher dilution for calculation (e.g., >32 = 64 μg/mL). Calculation of FIC index:

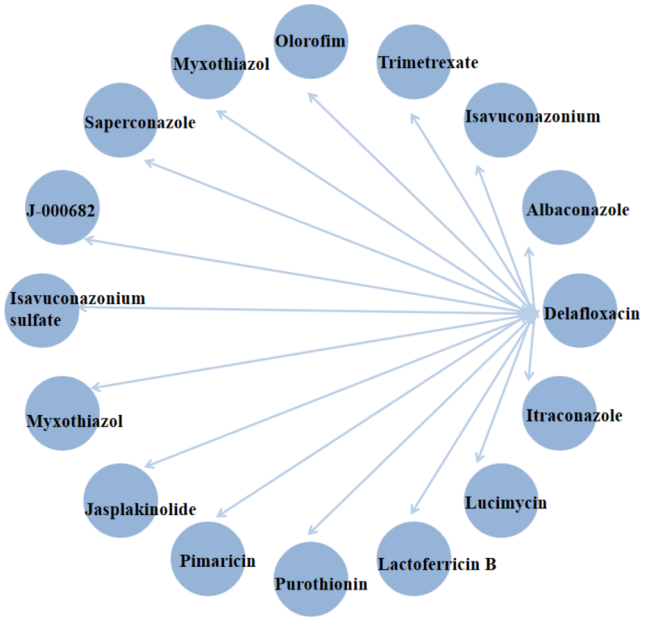

Figure 8. Predicted synergistic effects of combined use of Drafloxacin and other antimicrobials. The two-wire connection indicates that the two drugs will have a synergistic effect.

Table 4. Prediction Results and Probability of Synergistic Combination of Drafloxacin and Antimicrobials

drug 1	drug 2	probability
Albaconazole	Delafloxacin	0.690257316
Isavuconazonium		0.680533832
Trimetrexate		0.68048028
Isavuconazonium sulfate		0.673941811
Isavuconazonium chloride		0.667300115
Olorofim		0.660515082
Saperconazole		0.645611553
J-000682		0.645177806
Myxothiazol		0.631060709
Filipin		0.637709535
Jasplakinolide		0.634483486
Pimaricin		0.632873542
Myxothiazol		0.631060709
Purothionin		0.6288659
Lactoferricin B		0.628274954
Lucimycin		0.628253762
Itraconazole		0.628274954

FIC index = MIC (Group A combined)/MIC (Group A single-use) + MIC (Group B combined)/MIC (group B single-use). The FIC index method is the standard method to evaluate the interaction of two drugs[45] (FIC ≤ 0.5 represents synergistic action, FIC > 4 antagonistic action, 0.5 < FIC ≤ 4 no interaction).[46]

The MIC ranges (geometric mean) of individual drugs against *C. albicans* were as follows: Isavuconazonium, 128 μg/mL; Dirithromycin, 128 μg/mL; and Drafloxacin, > 2048 μg/mL. The MIC ranges for combination therapy against *C. albicans* were as follows: Isavuconazonium and Drafloxacin combination, 64 μg/mL; Dirithromycin and Drafloxacin combination, >256 μg/mL (Table 5).

A synergistic effect of Delafloxacin and Isavuconazonium against *C. albicans* was observed, while no interaction was observed between Delafloxacin and Dirithromycin. The

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J. Chem. Inf. Model. 2024, 64, 5317−5327

Table 5. In Vitro Combination MIC and FIC of Drafloxacin with Isavuconazonium and Dirithromycin against *C. albicans*[a]

combination	individual MIC (μg/mL)	combined MIC (μg/mL)	FIC
Delafloxacin + Isavu conazonium	4096/128	64	0.258 (s)
Delafloxacin + Dirith romycin	4096/128	512	2.060 (−)

[a]Interpretation of FIC values: FIC ≤ 0.5, synergy (S); 0.5 < FIC ≤ 4, no difference (−).

mixture was incubated at 37 °C for 24 h in a culture chamber. Additionally, absorbance values of each well in the 96-well plate used for the checkerboard assay were measured at 530 nm using a SYNERGY multifunctional microplate reader to determine the concentration of *C. albicans* liquid cultures. The measurements were repeated three times and averaged. Comparative absorbance values for individual drugs and their combinations are displayed in Figures 9 and 10.

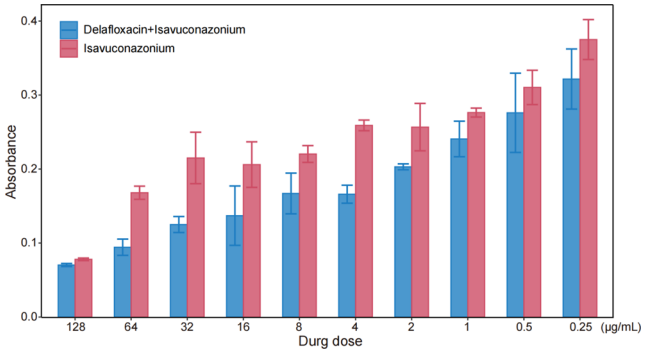

Figure 9. Comparative chart of *C. albicans*' absorbance values at 530 nm when using Isavuconazonium alone and in combination with Delafloxacin at the same dosage. Combining Delafloxacin and Isavuconazonium (blue) against Isavuconazonium (red) against *C. albicans* at different doses.

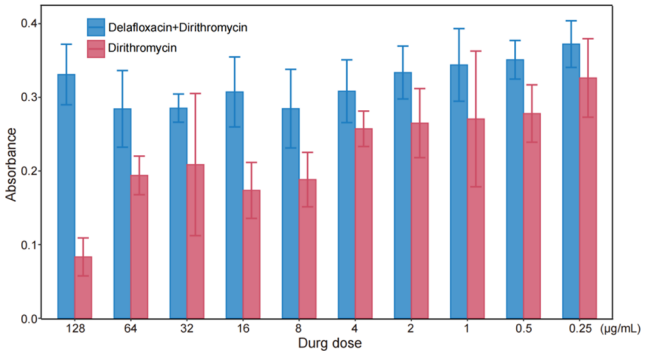

Figure 10. Comparative chart of *C. albicans*' absorbance values at 530 nm when using Dirithromycin alone and in combination with Delafloxacin at the same dosage. Combining Delafloxacin and Dirithromycin (blue) against Dirithromycin (red) for combating *C. albicans* at different doses.

In the figures, smaller absorbance values indicate stronger antimicrobial activity. It was observed that the combination of Delafloxacin and Isavuconazonium at the same dosage exhibited significantly stronger efficacy against *C. albicans* compared to Isavuconazonium alone. Conversely, the combination of Delafloxacin and Dirithromycin at the same dosage showed significantly weaker efficacy against *C. albicans* compared to Dirithromycin alone.

3. DISCUSSION

In this study, we explored an ensemble model harnessing the advantages of combining multiple models to address challenges in predicting interactions for certain drugs lacking comprehensive feature data or where most new drug-related data might be incomplete. We achieved precise predictions through singular structural features, advancing predictive modeling to save time and costs in clinical trials while promoting collaborative drug therapies, a crucial facet of precision medicine. Incorporating experimental validation postmodel prediction with mechanistic explanations enables experimentalists or clinicians to participate in inferring biological functions. For instance, we observed a synergistic interaction between the novel drug Delafloxacin and multiple antifungal drugs. This human-in-the-loop reasoning and subsequent experiments substantially enhance accountability and trust in machine learning model predictions. In contrast, traditional predictive modeling merely generates model outputs (drug responses) without further insights to establish trust in the process. A lot of time and money can be reduced through the simulation of the model. However, the accuracy and reliability of prediction results are still difficult problems in today's computing field, which leads to certain limitations of calculation models. Therefore, it is very necessary to add relevant experiments to verify the computational prediction research.

DrugSK, a flexible model, is suitable for studying interactions among all types of chemical drugs with limited related data information. If employed in a clinical setting, DrugSK's recommendations could be provided to physician-scientists who consider recommended combinations based on additional biological knowledge not explicitly used in the modeling, such as potential toxicities and specific case-related information. Ultimately, the decision-making power for treatment lies with the doctors and patients after careful consideration of all relevant information. This demand for human accountability is not exclusive to drug response predictions but is a core principle for high-risk applications in machine learning.[47]

DrugSK amalgamates the strengths of different models. Combining predictions from multiple models reduces the bias of individual models, resulting in more robust and stable predictions. It potentially mitigates overfitting risks, enhancing overall predictive performance. Furthermore, by using the predictions of multiple models as feature inputs to a metamodel, DrugSK amalgamates the advantages of multiple models, thereby enhancing the model's generalizability. The model is suitable for drug combination therapy for many diseases. It includes a variety of diseases and states in the disease process that need to be treated with chemical drugs. The model can be used to predict drug combinations for oral, injectable, and topical chemicals and to provide some guidance for the prediction of chemical and molecular drug interaction.

Future work might involve constructing models for three-drug combinations. This integration can be achieved by collecting and processing data on currently known three-drug combination therapies to predict novel three-drug combinations. Utilizing deep learning models to enhance predictive performance could involve integrating additional information levels via new visible or conventional neural network branches.

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J. Chem. Inf. Model. 2024, 64, 5317−5327

Delafloxacin and Isavuconazonium were found to have synergistic effects on *C. albicans*. To our knowledge, this study represents the first investigation of this combination against *C. albicans*. In addition, this study showed that Drafloxacin and antifungal drugs are prone to positive interaction. Many nonantifungal drugs exhibit activity against fungal pathogens and might synergize with antifungal drugs. Our findings support some previous research, as prior studies have explored similar aspects.[48] For example, Venturini et al. evaluated the sensitivity of 20 clinical isolates of Aspergillus to classic antifungal drugs and nonantifungal agents.[49] Fiori et al. discovered that the effective synergy of Doxycycline and Fluconazole against *C. albicans* is mediated by interfering with iron homeostasis.[48] Shi et al. also found in vitro interactions between antifungal and antibacterial agents.[50] Rodrigues et al. found that antifungal−antibacterial combination therapy could counteract Candida-Copper Green Pseudomonas biofilms.[51] Numerous studies are exploring the underlying mechanisms. It is hoped that the proposed model can provide researchers with insights and discoveries, leading to further exploration of the mechanisms and patterns, thereby contributing to medical advancements.

By constructing a versatile model capable of predicting various interactions and integrating the profound understanding of drug synergy among researchers across fields, it is expected to facilitate contributions to the development of personalized therapy and precision medicine, ultimately improving the efficacy and safety of drug treatments.

4. CONCLUSIONS

In this study, an integrated learning model called DrugSK is introduced, designed to predict interactions between different classes of drugs. Leveraging a data set comprising 48,757 drug combination instances, we trained our model to discern patterns indicative of drug synergies and interactions. Our best-performing model achieved notable performance metrics, including an AUC of 0.81 and an accuracy of 0.76. Through the application of DrugSK, we successfully predicted interactions spanning various drug classes. Notably, our model identified synergistic effects between treatments for chronic obstructive pulmonary disease (COPD) and lung cancer, as well as interactions among anti-inflammatory agents. Additionally, we conducted experimental validation, employing checkerboard assays to confirm predictions involving the newly introduced antibiotic, Delafloxacin, in combination with other antibacterial agents. Our findings affirmed the predicted synergistic interaction between Delafloxacin and Isavuconazonium, underscoring the precision and robustness of our model. Furthermore, our investigation unveiled a recurring trend wherein Delafloxacin exhibited notable interactions with antifungal medications, indicating potential avenues for further exploration in drug combination therapies.

In summary, our study underscores the efficacy of DrugSK in predicting complex drug interactions across diverse therapeutic domains. The validated interactions and identified patterns offer valuable insights for drug development and personalized treatment strategies, highlighting the potential of integrated learning approaches in advancing pharmacological research and clinical practice.

5. METHODS

5.1. Data Acquisition and Processing. *5.1.1. Drug Synergy Data.* Drug combination-related data was obtained from the DrugCombDB database (http://drugcombdb.denglab.org/main). DrugCombDB serves as a comprehensive repository, encompassing various sources of drug combinations, including high-throughput screening analyses, external databases, and PubMed literature. Comprising 6,891,566 experimental data points across 2887 unique drugs and 124 human cancer cell lines, DrugCombDB provides quantitative dose−response and drug combination concentration information. 48,757 drug combination data were collected for follow-up training.

5.1.2. Drug Features. SMILES (Simplified Molecular Input Line Entry System) of Drugs was retrieved and collected from PubChem, DrugBank, and ChEMBL databases. SMILES represents chemical structures through a string notation, enabling a text-based expression for molecules and chemical reactions. These SMILES strings, employed for chemical structure representation, were processed using the SMILES-BERT method in natural language processing models. This extraction facilitated the acquisition of advanced molecular representations to enable predictive tasks concerning relationships between molecules.

5.2. Model Design Research. *5.2.1. Model Design and Training.* Training on the data set involved training and utilizing multiple models for prediction to generate multiple sets of predictions or meta-features. These models were employed to predict the test data, yielding hyper-features. Subsequently, a new model was trained to map these hyper-features to ground-truth values. Initially, primary learners were trained from the initial data set, followed by the creation of a new data set for training secondary learners. RF, support vector machine, and XGBoost models were used as primary learners, and logistic regression as the secondary learner. This approach essentially constitutes the first layer of predictions by individual models and the second layer involving logistic regression for result refinement.

5.2.2. SMILES-BERT Methods for Extracting Features. SMILES is a method used to represent the structure of chemical molecules, which focuses on accurately expressing the structural information of molecules. It can accurately describe the composition of a molecule, including information such as atoms, bonds, and rings. In addition, it can also represent special information about chemical properties, such as chirality and isomers. Because of its concise and accurate nature, SMILES strings can be easily parsed and converted by computer programs into three-dimensional structural information for molecules. SMILES strings have a wide range of applications in computer programs and databases, where they can be used for large-scale molecular analysis and processing, allowing researchers to process and analyze molecular data more efficiently. SMILES strings can also be used for visualization and editing of molecular structures, providing researchers with tools to intuitively understand and analyze molecular structures.[52−54]

The Converter Bidirectional encoder (BERT) is a pretrained deep learning model proposed by Google in 2018. It is based on Transformer (referring to a deep learning architecture proposed by Vaswani et al.[55]). Transformer revolutionizes natural language processing tasks by enabling state-of-the-art performance in a variety of applications such as machine

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J. Chem. Inf. Model. 2024, 64, 5317−5327

translation, text generation, and language understanding. It is an architecture for learning common language representations from large-scale text corpora through unsupervised learning.[56] Unlike traditional natural language processing models, BERT adopts a bidirectional strategy in the pretraining phase; that is, all words in the context are considered at the same time to better understand the context. The pretraining process of BERT mainly consists of two tasks: mask language model (MLM) and next sentence prediction (NSP). In the MLM task, the model needs to predict randomly masked words in the input text; in the NSP task, the model needs to determine whether two input texts are consecutive. With pretrained BERT models, it can be easily fine-tuned to accommodate a variety of natural language processing tasks, such as text classification, named entity recognition, text generation, and more. BERT achieved excellent performance on a number of natural language processing tasks and became one of the important milestones in the field of natural language processing.[56] The SMILES-BERT method is used to extract high-level representations of chemical molecules so that subsequent models can learn and understand the relationships between molecules for predictive tasks.

5.3. Model Evaluation Metrics. 5-fold cross-validation was used to evaluate the model. To prevent data bias, the process repeats 1,000 samples and takes the average performance as the final result. Two common binary classification metrics, namely accuracy and AUC, were employed to evaluate the model. In addition, other machine learning metrics were combined: F1 scores, recall rates, and accuracy. These three metrics were calculated based on the quantities of true positive (TP), false positive (FP), true negative (TN), and false negative (FN) using the following formulas:

$$\text{Accuracy} = \frac{TP + TN}{TP + TN + FP + FN} \quad (1)$$

$$\text{Recall} = \frac{TP}{TP + FN} \quad (2)$$

$$\text{Precision} = \frac{TP}{TP + FP} \quad (3)$$

$$F1 = 2 \times \frac{\text{precision} \times \text{recall}}{\text{precision} + \text{recall}} \quad (4)$$

5.4. Discovery and Experimental Verification of the Synergistic Mechanism. In order to ensure the accuracy and authenticity of the model prediction, Isavuconazonium and Delafloxacin, identified as synergistic drug combinations in Table 4, were selected for experimental verification. Cultivation of *C. albicans* was performed in Sabouraud glucose liquid medium. A small amount of *C. albicans* nutrient agar slant culture was inoculated into 5 mL liquid medium, sealed with a membrane, and incubated at 37 °C, 120 rpm, until reaching the logarithmic growth phase. The resulting 10^6 CFU/mL bacterial solution was used for subsequent experiments.

Working solutions were prepared in culture media according to Clinical and Laboratory Standards Institute (CLSI) guidelines for each drug.[57] Considering *C. albicans* as a fungus, Drafloxacin[25] and Dirithromycin as antibacterial drugs,[58] and Isavuconazonium as an antifungal drug,[59,60] the concentration range was set as follows: Drafloxacin ranged from 4 to 2048 μg/mL, Isavuconazonium from 0.25 to 128 μg/mL, and Dirithromycin from 0.25 to 128 μg/mL.

Meanwhile, in the nonsynergistic drug combination, Drafloxacin and Dierythromycin were selected for negative validation. The MIC of individual drugs and drug combinations was measured using the 2-fold dilution method. Each drug was serially diluted in liquid medium in a 96-well plate, followed by inoculation with bacterial strains (concentration: 10^6 CFU/mL). After incubating the plates at 37 °C for 24 h, bacterial growth was observed. The lowest concentration with clear medium and no visible bacterial growth was determined as the MIC.[42]

The microdilution checkerboard assay was employed to evaluate the interaction between the antibacterial drug Delafloxacin and the antifungal drugs Isavuconazonium and Dirithromycin.[42] The FIC was calculated by dividing the MIC or MEC of the combination by the MIC or MEC of each drug alone.[43,44] All readings were taken after incubation at 37 °C for 24 h. MICs beyond the measurement range were converted to the next higher dilution for calculations (e.g., >32 = 64 μg/mL).

■ ASSOCIATED CONTENT

Data Availability Statement

Training data can be obtained in the Supporting Information for Publication and prediction data can be obtained at https://github.com/csq474747/DrugSK_data; https://github.com/csq474747/DRAKSK/tree/main.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jcim.4c00296.

Training data and detailed results (ZIP)

The predicted synergistic effects (XLSX)

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J. Chem. Inf. Model. 2024, 64, 5317−5327

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Notes

The authors declare no competing financial interest.

Ethics approval and consent to participate This study is based on public data sets and does not include new data that require ethical approval and consent.

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