JCIM JOURNAL OF CHEMICAL INFORMATION AND MODELING

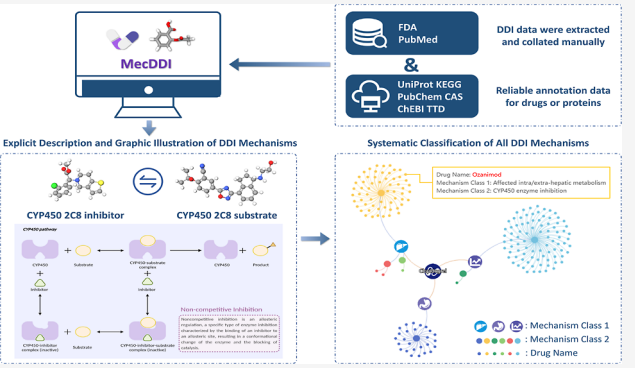
pubs.acs.org/jcim Article

MecDDI: Clarified Drug−Drug Interaction Mechanism Facilitating Rational Drug Use and Potential Drug−Drug Interaction Prediction

Wei Hu, Wei Zhang, Ying Zhou, Yongchao Luo, Xiuna Sun, Huimin Xu, Shuiyang Shi, Teng Li, Yichao Xu, Qianqian Yang, Yunqing Qiu, Feng Zhu,* and Haibin Dai*

Cite This: *J. Chem. Inf. Model.* 2023, 63, 1626−1636 Read Online

ABSTRACT: Drug−drug interactions (DDIs) are a major concern in clinical practice and have been recognized as one of the key threats to public health. To address such a critical threat, many studies have been conducted to clarify the mechanism underlying each DDI, based on which alternative therapeutic strategies are successfully proposed. Moreover, artificial intelligence-based models for predicting DDIs, especially multilabel classification models, are highly dependent on a reliable DDI data set with clear mechanistic information. These successes highlight the imminent necessity to have a platform providing mechanistic clarifications for a large number of existing DDIs. However, no such platform is available yet. In this study, a platform entitled "MecDDI" was therefore introduced to systematically clarify the mechanisms underlying the existing DDIs. This platform is unique in (a) clarifying the mechanisms underlying over 1,78,000 DDIs by explicit descriptions and graphic illustrations and (b) providing a systematic classification for all collected DDIs based on the clarified mechanisms. Due to the long-lasting threats of DDIs to public health, MecDDI could offer medical scientists a clear clarification of DDI mechanisms, support healthcare professionals to identify alternative therapeutics, and prepare data for algorithm scientists to predict new DDIs. MecDDI is now expected as an indispensable complement to the available pharmaceutical platforms and is freely accessible at: https://idrblab.org/mecddi/.



INTRODUCTION

Drug−drug interactions (DDIs) are a major concern in clinical practice and have been recognized as one of the key threats to public health.[1−5] To address such a critical threat, many studies have been conducted to clarify the mechanisms underlying each DDI,[6−9] and alternative therapeutic strategies are subsequently proposed.[10−13] Taking the antihypertensive medication amlodipine as an example, it is frequently co-administered with cholesterol-lowering drugs[14] and results in a significant DDI with a commonly prescribed anti-dyslipidemia drug simvastatin by inhibiting its metabolizing enzyme CYP3A4.[15] To overcome the DDI, another drug rosuvastatin (which is not a substrate of CYP3A4) is proposed as the alternative to simvastatin in the co-medication.[16] In other words, the successful discovery of a new therapeutic strategy to avoid undesired clinical DDI is highly dependent on the mechanistic clarification (especially at the molecular level) for each DDI,[17−20] which has been widely and successfully adopted in the clinical practice.[21−24]

However, current clarifications of the mechanisms for existing DDIs are far from comprehensive, which makes it very difficult to cope with treatment failure and adverse drug reactions induced by DDIs.[25−30] Various DDI mechanisms have therefore been revealed, which can be classified into two types: pharmacokinetic (PK) and pharmacodynamic (PD) DDIs.[31−37] Particularly, the PK DDIs (as illustrated in Figure 1) indicate the alterations of one drug's ADME (absorption, distribution, metabolism, and elimination) profile by another,[31−33] and the PD DDIs (as shown in Figure 2) arise when the pharmacological effect of one drug is affected by that of another.[34] These newly revealed mechanistic data, on the one hand, are key to extending our understanding of the occurrence of a specific DDI and inspiring the identification of new therapeutic strategies.[38−42] On the other hand, with the extensive application of computational techniques [especially, artificial intelligence (AI)] to DDI-related research,[43−46] such mechanistic data have become even precious for researchers in the fields of pharmacoinformatics, bioinformatics, and clinical

Received: December 29, 2022
Published: February 20, 2023

https://doi.org/10.1021/acs.jcim.2c01656
J. Chem. Inf. Model. 2023, 63, 1626−1636

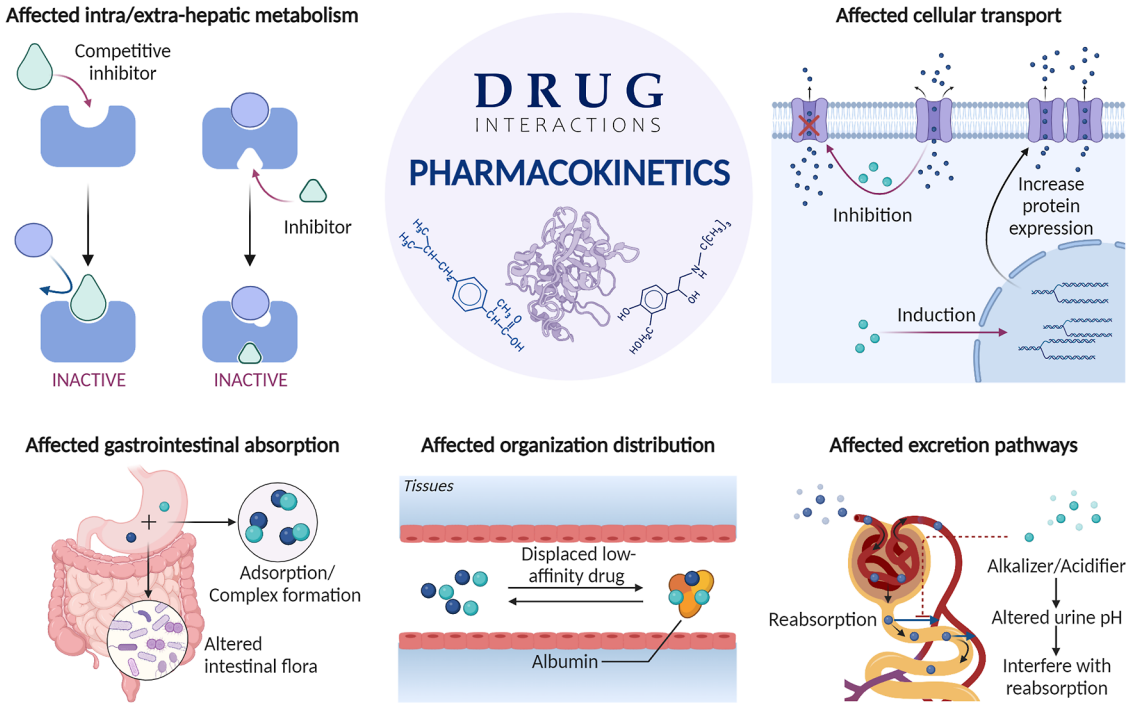


Figure 1. PK type of DDIs, which indicate the alterations of one drug's ADME profile by another. PK DDIs could be categorized into five subclasses, which include affected intra/extra-hepatic metabolism, cellular transport, gastrointestinal absorption, organization distribution, and excretion pathways.

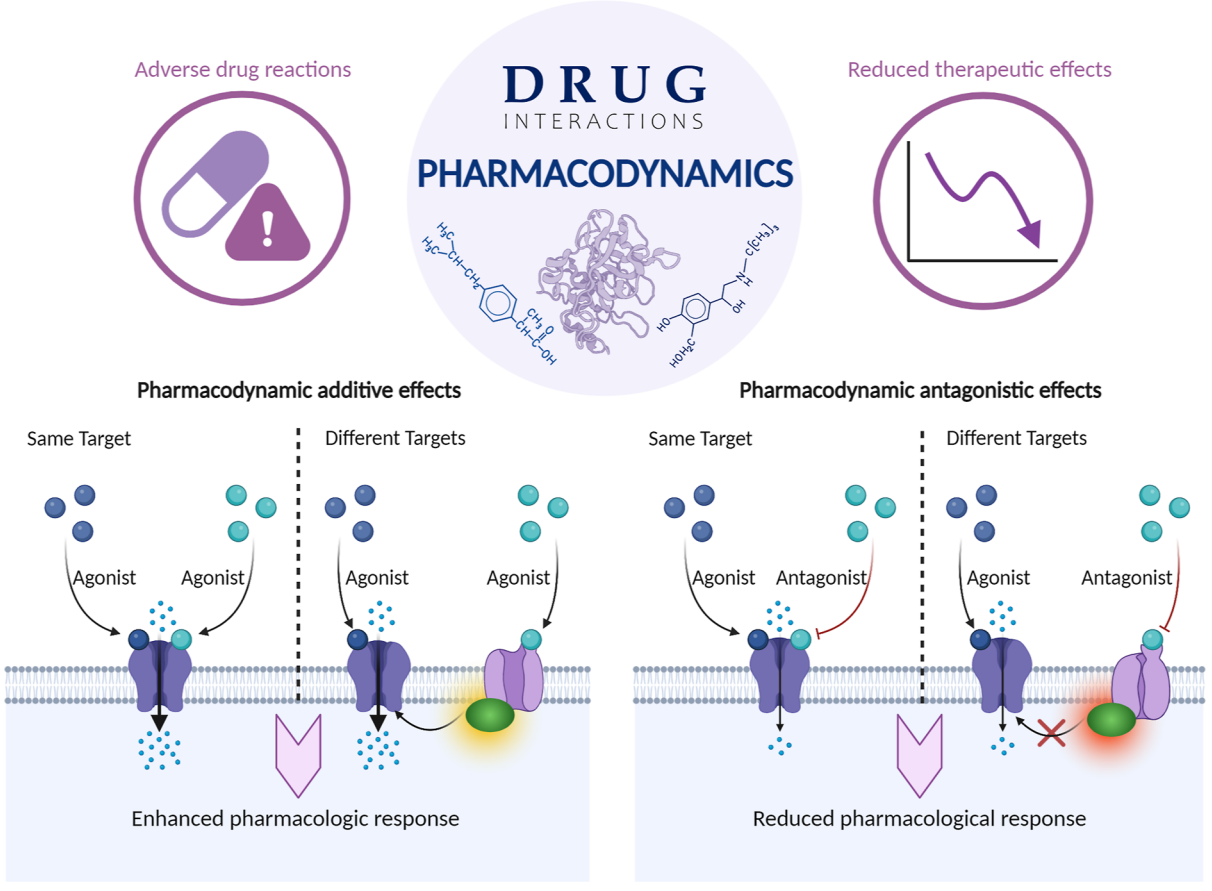


Figure 2. PD type of DDIs, which denote how the pharmacological effect of one drug is affected by that of another. PD DDIs could be grouped into two subclasses, which include the PD additive and antagonistic effects.

https://doi.org/10.1021/acs.jcim.2c01656
J. Chem. Inf. Model. 2023, 63, 1626−1636

practice.[47−53] Therefore, a knowledge base providing mechanistic clarifications for a large number of existing DDIs (both PK and PD) is highly required.

So far, several databases have been constructed to provide DDI-relevant information, which have become popular data resources for current pharmaceutical studies.[54−63] Some of them contain DDI information as part of a broader collection of biological and pharmacological data (such as DrugBank,[54] TTD,[55] SuperDRUG2,[56] Transformer,[57] and SuperCYPsPred[58]), and some others focus on providing the clinical phenomena and outcomes of DDIs (such as DDInter,[59] Drugs.com,[60] and Liverpool drug interaction[61]). Particularly, DDInter, the newly-constructed DDI database, provides a wealth of DDI information. These databases have attracted broad interest from the research community and accumulated a huge number of visits and citations in the past few years.[54−63] However, none of the databases provides explicit clarifications on the molecular mechanism underlying a comprehensive list of existing DDIs (both PK and PD).

In this study, a platform named "MecDDI" was therefore introduced to systematically clarify the mechanisms underlying DDIs. To the best of our knowledge, this platform is unique in (a) clarifying the mechanisms underlying >1,78,000 DDIs by explicit descriptions and graphic illustrations and (b) providing a systematic classification for all collected DDIs based on their clarified mechanisms. Due to the long-lasting threats of DDIs to public health, this database could provide medical scientists with a clear clarification of the mechanism underlying all existing DDIs, support healthcare professionals in the identification of alternative therapeutic strategies, and prepare valuable big data for algorithm scientists to predict potential DDIs. All in all, MecDDI is expected to be applied as an indispensable complement to the available pharmaceutical databases and is now freely accessible by all users at https://idrblab.org/mecddi/.

MATERIALS AND METHODS

Data Collection, Curation, and Processing. DDI data were collected based on the following procedure. First, >2000 approved drugs were collected from the official site of the U.S. FDA and several well-established databases (such as DrugBank[54] and TTD[55]). Second, based on these drugs, a large amount of DDI data was obtained from the corresponding drug labels provided by the FDA website and the scientific literature retrieved from PubMed, which brought the number of raw DDI data to nearly 2,00,000. Third, further systematic reviews were conducted to extract the mechanism information underlying each identified DDI, and other important information (such as clinical consequence and management recommendation) was also collected during literature reviews. In total, 1,78,406 DDIs with mechanism information were generated during this process. Of these DDIs, 1,56,445 and 1,00,609 DDIs were manually extracted from the drug interactions section of drug labels and scientific literature, respectively (78,648 DDI data were reported in both FDA labels and scientific literature). The mechanism of DDI was analyzed and identified by a professional team of clinical pharmacists and further classified according to the specific aspects of PK or PD that affect the drug. Finally, the severity of each DDI was reviewed and categorized into different levels: major, moderate, and minor.[64] As defined in the previous publication,[64] "major" indicates that the corresponding DDI is life-threatening or requires medical intervention for reducing serious adverse outcomes, which should be avoided in clinical practice; "moderate" denotes that the studied DDI exacerbates the condition of patients, which asks for a modulation in the dosage/usage of current therapy; "minor" refers to that the studied DDI limits the clinical outcome but does not require modulation in therapy.

Online Platform Implementation. The MecDDI is programmed using PHP and deployed on the Apache HTTP Server and the Ubuntu operating system. All data in MecDDI is stored and managed with MySQL v15.1 for easy custom database searching. The web user interface is developed in JavaScript, HTML5, and CSS. To enhance the experience of user interaction, the visualization of dynamic data is implemented with ECharts v5.3.3, including the generation of sunburst graphs and relationship graphs for each drug. Furthermore, MecDDI has been tested on different browsers, such as Google Chrome, Mozilla Firefox, Safari, and Internet Explorer 10/later, to ensure that all data is searchable. The web interface is available online at https://idrblab.org/mecddi/.

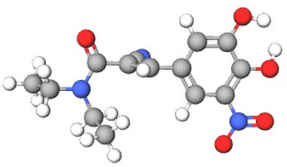
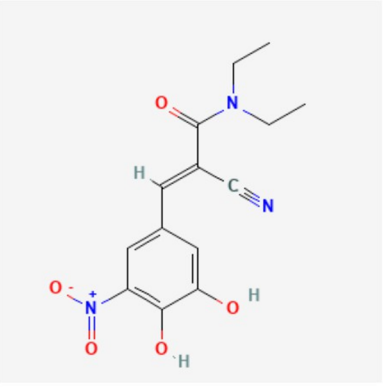
RESULTS AND DISCUSSION

Data Summary and Analysis of MecDDI. In MecDDI, a total of 1,78,406 DDIs with experimentally/clinically clarified mechanisms, covering 1922 approved drugs, were manually documented based on systematic literature reviews. Drug-type information was obtained from TTD[55] and DrugBank.[54] 1673 of the drugs were small-molecule drugs, accounting for approximately 87% of all drugs, followed by protein/peptide and antibody drugs (including monoclonal and polyclonal antibodies) with 91 and 90%, respectively. The approved disease indications for these drugs were linked to International Classification of Diseases (ICD)-11 codes. To understand the disease-specific DDIs, a statistical analysis was performed to determine the average number of DDIs caused by the drugs included in the different ICD codes. Drugs for neoplasms (285 drugs), mental, behavioral, or neurodevelopmental disorders (120 drugs), and diseases of the nervous system (136 drugs) involved more DDIs, with an average number of DDIs per drug of 406, 337, and 237, respectively. In MecDDI, 47.2% of drugs were able to interact with ≥100 drugs, with the drug that caused the most DDIs being ozanimod, which interacted with 679 drugs. The main mechanisms that ozanimod (a sphingosine 1-phosphate receptor modulator used to treat multiple sclerosis and inflammatory bowel disease)-triggered DDIs include (1) an increased risk of ventricular arrhythmias in patients receiving concomitant drugs with the same adverse effects or prolonged QT interval due to its risk of bradycardia and atrioventricular block and (2) may increase the risk of unexpected additive immunosuppressive effects when co-administered with antineoplastic, immunosuppressive, or other immunomodulatory therapies. Such mechanistic data were clearly described and systematically categorized in the MecDDI and further provided risk severity levels and recommendations for action for the DDI by which medical professionals can gain insight and effectively manage the DDI.

Comprehensive List of DDIs for the Studied Drugs. Drugs are frequently reported to be able to interact with multiple co-administered agents.[65−68] Particularly, with the rapidly accumulating number of aging people, there is a significant increase in the incidence of multiple acute/chronic diseases, which greatly promotes the administration of combinatorial therapies and a subsequent threat of DDIs.[69−76] Therefore, a comprehensive collection of all drugs that interact with the studied drugs is of great importance to the prevention of

https://doi.org/10.1021/acs.jcim.2c01656
J. Chem. Inf. Model. 2023, 63, 1626−1636

Drug General Information (ID: D0575)

Drug Name	Entacapone
Drug Type	Small molecule
Drug Synonymous	Comtan; Comtess; Entacapona; Entacaponum; Novartis brand of entacapone; Orion brand of entacapone; KB475572; OR 611; COM-998; Comtan (TN); Entacapona [INN-Spanish]; Entacapone [USAN:INN]; Entacaponum [INN-Latin]; OR-611; Stalevo (TN); Entacapone (JAN/USAN/INN); N,N-diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl) acrylamide; (2E)-2-cyano-3 Click to Show/Hide
Disease Class	8A00: Parkinsonism
Therapeutic Class	Antiparkinson Agents
Structure	 
	3D Structure / 2D Structure

Full list of drugs interacting with Entacapone

Affected gastrointestinal absorption	
Complex formation	Drug Num: 6
Affected intra/extra-hepatic metabolism	
CYP450 enzyme inhibition	Drug Num: 1
Non-CYP450 enzyme inhibition	Drug Num: 10
Pharmacodynamic additive effects	
Additive CNS depression effects	Drug Num: 50
Additive dopaminergic effects	Drug Num: 2

Drug ID	Drug Name	Formula	Pubchem ID	Severity Level	Interaction Detail	REF
D1492	Solriamfetol	C10H14N2O2	10130337	Moderate	Inter Info	
D0998	Memantine	C12H21N	4054	Minor	Inter Info	

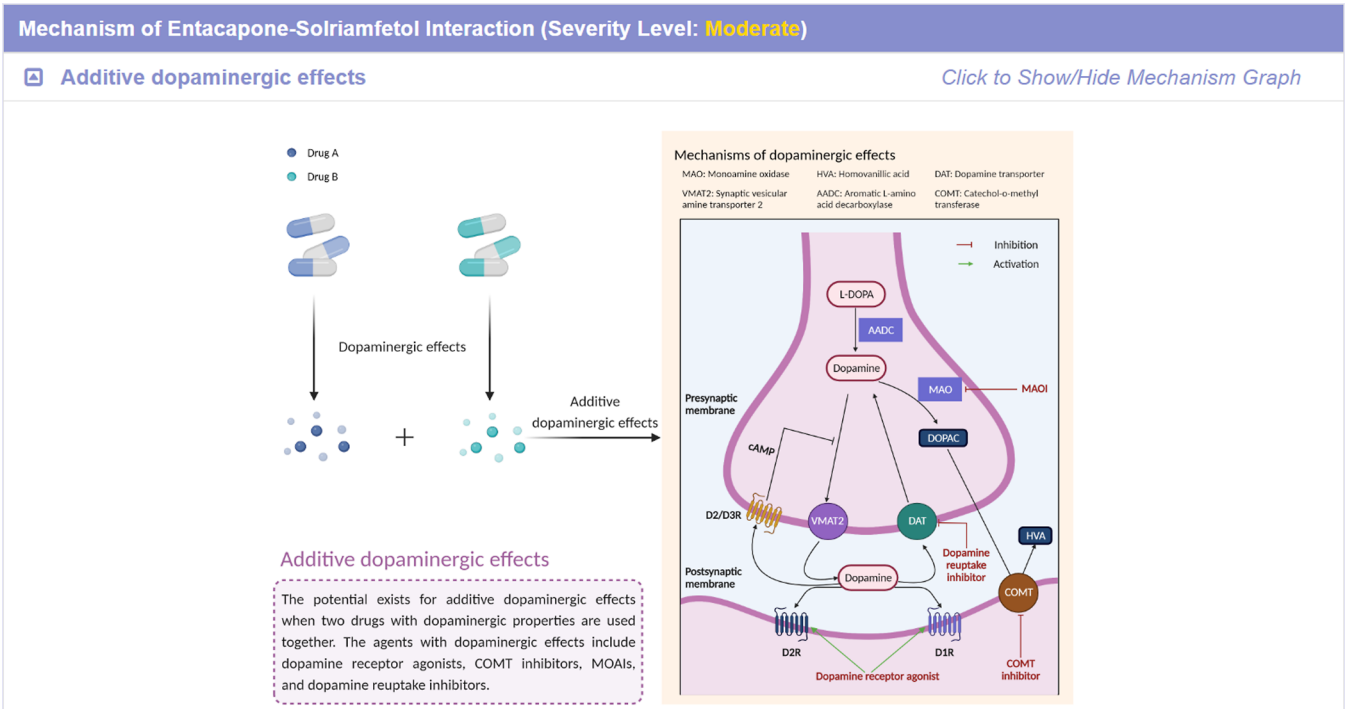
Additive hypotensive effects	Drug Num: 34
Pharmacodynamic antagonistic effects	
Antagonize the effect of dopaminergic agents	Drug Num: 35

Figure 3. Typical drug page providing the general information of a drug together with the list of DDIs of this drug. In the upper part, the general data of the drug are provided, which include drug name, drug type, synonyms, indications, therapeutic class, 2D/3D molecular structures, and so on. In the lower part, various drugs interacting with the studied drug are further categorized based on the classification system (class, subclass, and leaf-class) constructed in and adopted by this study. Detailed description on each DDI could be accessed by clicking the "Inter Info" button.

potential DDIs, and such full lists of DDIs for each drug were provided in MecDDI. In Figure 3, the drug page that describes the general information of a drug together with the list of DDIs for this drug is provided. Taking the drug entacapone as an example, the general data of this drug is provided in the upper part of Figure 3, including drug name, drug type, synonym, disease indications, therapeutic class, 3D and 2D molecular structures, formula, InChI, InChIKey, SMILES, as well as the external link to the existing databases: PubChem,[77] CAS, ChEBI,[78] TTD,[55] VARIDT,[79] and INTEDE.[80] Moreover, a list of drugs interacting with entacapone is described in the lower part of Figure 3. The molecular information on these drugs (such as formula and compound ID) and the severity level of the DDI are also provided. Users can click on the "Inter Info" button to jump to a new page explicitly describing a particular DDI.

Explicit Clarification of the DDI Mechanisms. The mechanisms underlying a particular DDI provide an effective way to identify and avoid its potential harm.[81−83] The explanation of the molecular mechanism for these DDIs provides a solid foundation for clinicians to deeply understand

https://doi.org/10.1021/acs.jcim.2c01656
J. Chem. Inf. Model. 2023, 63, 1626−1636



Drug Name	Entacapone	Solriamfetol
Mechanism	Dopaminergic effects Catechol-O-methyl-transferase Inhibitor	Dopaminergic effects Dopamine transporter Inhibitor
Key Mechanism Factor 1	Factor Name	Catechol-O-methyl-transferase Structure Sequence
	Gene Name	COMT
	Uniprot ID	COMT_HUMAN
	KEGG Pathway	hsa:1312
	Protein Family	Class I-like SAM-binding methyltransferase superfamily
	Protein Function	Catalyzes the O-methylation, and thereby the inactivation, of catecholamine neurotransmitters and catechol hormones. Also shortens the biological half-lives of certain neuroactive drugs, like L-DOPA, alpha-methyl DOPA and isoproterenol.
Key Mechanism Factor 2	Factor Name	Dopamine transporter Structure Sequence
	Gene Name	SLC6A3
	Uniprot ID	SC6A3_HUMAN
	KEGG Pathway	hsa:6531
	Protein Family	Sodium:neurotransmitter symporter (SNF) (TC 2.A.22) family
	Protein Function	Amine transporter (PubMed:1406597, PubMed:8302271, PubMed:15505207). Terminates the action of dopamine by its high affinity sodium-dependent reuptake into presynaptic terminals (By similarity). Regulator of light-dependent retinal hyaloid vessel regression, do Click to Show/Hide
Mechanism Description	• Additive dopaminergic effects by the combination of Entacapone and Solriamfetol	

Figure 4. Typical page of the DDI mechanism demonstrated by explicit description and a graphic illustration. Graphical illustration of each mechanism is depicted according to the DDI mechanism category. The mechanism underlying a DDI and the different roles played by two drugs in this DDI are provided. The biological functions of the molecules playing essential roles in the DDI are also described. The structures and sequences of these essential molecules could be accessed by clicking the button in the dark blue background. The summary of the mechanism underlying each DDI is depicted for each DDI.

how DDI is developed and discover effective alternative therapies.[83−86] In this study, MecDDI is thus developed to clarify the mechanisms underlying >1,78,000 DDIs by explicit descriptions and graphic illustrations.

Explicit Description and Graphic Illustration of DDI Mechanisms. Clarification of the mechanisms underlying each DDI was provided in the MecDDI database. Taking the interaction between entacapone and solriamfetol as an example

https://doi.org/10.1021/acs.jcim.2c01656
J. Chem. Inf. Model. 2023, 63, 1626−1636

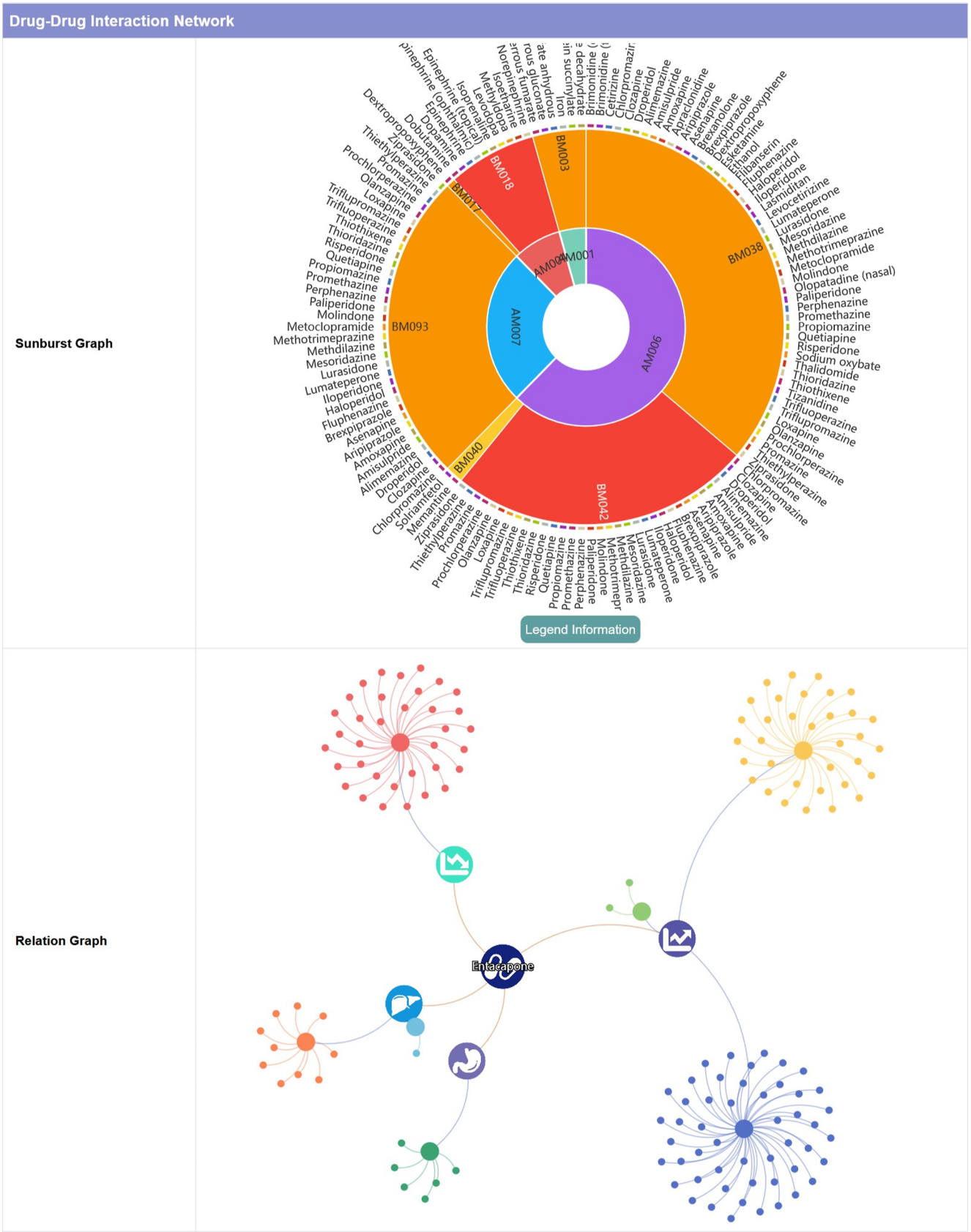


Figure 5. Hierarchical visualization of the DDI classification system (class, subclass, and leaf-class) for a particular drug constructed and adopted in this study. Two interactive plots including sunburst and relationship graphs based on this classification system are provided.

(as shown in Figure 4), first, the corresponding mechanism of this DDI is described, and the different roles played by two drugs in this DDI are specified based on a comprehensive literature review. Then, the biological functions of any molecules playing

https://doi.org/10.1021/acs.jcim.2c01656
J. Chem. Inf. Model. 2023, 63, 1626−1636

essential roles in the mechanisms of this DDI are explicitly described in the online DDI page, which include protein name, gene name, UniProt ID, KEGG ID, protein family, protein function, etc. In the meantime, both structures and sequences of these essential molecules are collected and provided via clicking "Structure" and "Sequence" buttons on a dark blue background (shown in Figure 4). Finally, a summary of the mechanism underlying each DDI is explicitly provided. Notably, if more than one mechanism is involved in the DDI, all mechanisms would be displayed on the interactions page. Moreover, a graphical illustration of each mechanism is depicted according to the DDI mechanism category. As shown in the upper section of Figure 4, the interaction pattern of the DDI generated through the same class of mechanisms is described, which was created using BioRender.com.

Systematic Classification of All DDI Mechanisms. The mechanisms underlying DDIs were found to be extremely diverse.[87−89] Therefore, it was highly demanded to have a systematic classification of the existing interaction mechanisms. In MecDDI, a well-established classification system based on PK and PD was adopted.[90,91] For each of the well-established classifications, further classifications (subclasses) were systematically constructed for all DDI mechanisms in the study.

Classification System Constructed and Adopted in MecDDI. The mechanisms of DDIs provided in MecDDI were first classified based on the well-established PK and PD systems.[90,91] As illustrated in Figure 1, the PK DDIs[92−94] were further grouped into five subclasses, which included affected intra/extra-hepatic metabolism, cellular transport, gastrointestinal absorption, organization distribution, and excretion pathways. Moreover, the PD DDIs,[34,95] as illustrated in Figure 2, could also be further grouped into two subclasses, which included the PD additive and PD antagonistic effects.

All seven subclasses of mechanisms were further divided into 109 leaf-classes. For example, based on various metabolic enzymes and mechanisms of action, the effects on intra/extra-hepatic metabolism could be divided into the inhibition of CYP450 enzyme, the induction of UGTs, and so on; the cellular transport could be divided into the inhibition of transporters, the induction of transporters, and so on; and the PD additive effects could be divided into additive cholinergic effects, additive dopaminergic effects, and so on.

Online Description of a Drug's DDIs by the Classification System. As shown in the lower section of Figure 3, a list of drugs that were reported to interact with the studied drug was systematically categorized using the classification system (class, subclass, and leaf-class) constructed in this study. Taking the drug entacapone as an example, a total of four subclasses were identified and adopted to classify all drugs in the interaction list into four groups. Moreover, the mechanism could be further divided to seven leaf-classes, such as the CYP450 enzyme inhibition, non-CYP450 enzyme inhibition, and so on. To intuitively describe the distribution of mechanisms and the correlation of all DDIs for a studied drug, two interactive plots based on the classification system were constructed. As shown in Figure 5, a sunburst graph and a relationship graph were drawn. In the sunburst graph, the subclass and the leaf-class of the mechanism for all DDIs were represented from inside to outside, respectively. The detailed description on the mechanisms can be found by clicking the "Legend Information" button. In a relationship graph, the first node denoted the studied drug, and the secondary and tertiary nodes represented the subclasses and leaf-classes, respectively. The interacting drugs belonging to each mechanism class were given as leaf nodes. Users can hover the mouse on the node to obtain detailed data of the mechanisms and drugs.

Rational Drug Use and Potential DDI Prediction. *Mechanisms of DDI to Facilitate Rational Drug Use.* In order to reduce the risk of harm from a DDI caused by the coadministration of two drugs that are necessary to treat diseases, it is crucial to find a safe alternative drug. Explicit mechanisms for DDI were provided in MecDDI, which can effectively avoid potential DDIs and facilitate the selection of alternative drugs. Taking imatinib and warfarin as an example, imatinib is effective in treating myeloid leukemia, while warfarin is effective in preventing and treating venous thrombosis in oncology patients. Both of the drugs are necessary for patients with leukemia.[96,97] By querying MecDDI, a serious potential DDI between imatinib and warfarin was found; the underlying mechanism was due to imatinib inhibition of CYP450 2C9 affecting warfarin metabolism. If imatinib must be used to treat leukemia, drugs with the same pharmacological effects but not metabolized by CYP450 2C9 (rivaroxaban, apixaban, edoxaban, betrixaban, low-molecular heparin, and unfractionated heparin) could be substituted for warfarin as candidates to reduce the potential harms.[96] However, in MecDDI, imatinib has a moderate risk of DDI with rivaroxaban or apixaban, with a mechanism via inhibition of CYP450 3A4, and no existing DDI was found with the remaining drug candidates. Therefore, edoxaban, betrixaban, low-molecular heparin, and unfractionated heparin may be suitable alternatives to warfarin when coadministered with imatinib.

Potential of MecDDI in DDI Prediction. In recent years, with the extensive application of AI, AI-based methods have proven to be able to infer potential DDIs quickly and economically.[98−101] As well as the construction of excellent algorithms, the performance of AI models largely depends on reliable data sets. Furthermore, AI researchers are not satisfied with just binary DDI prediction (whether two drugs interact or not), an increasing number of studies are focusing on multi-type DDI prediction (how two or more drugs interact with each other),[44,102−104] which is more meaningful and useful for studying the hidden mechanisms behind combination drug use or adverse reactions. Thus, one reliable knowledge base that provides mechanistic clarification and classification for the large number of available DDIs is highly required. In MecDDI, 1,78,406 DDIs with experimentally/clinically defined mechanisms are provided, covering 1922 approved drugs, and the mechanisms involved in these DDIs have been systematically classified. Therefore, in the field of DDI prediction, the newly developed MecDDI platform in this study should be considered as a comprehensive, first-hand knowledge base to meet the urgent needs of the relevant research community.

Standardization, Access, and Retrieval of Data. In order to make MecDDI data easily accessible and analyzable for all readers, the collected raw data were carefully cleaned and then systematically standardized. Standardization of drug names was realized by referencing to the available databases, such as TTD[55] and PubChem.[77] All disease indications were standardized by the latest version of the ICD-11 officially released by WHO.[105] Various types of data in MecDDI were fully cross-linked to a variety of well-established databases. All data on drugs and DDIs can be viewed, accessed, and downloaded online, and the MecDDI database is now freely accessible by all users without any login requirement at: https://idrblab.org/mecddi/.

https://doi.org/10.1021/acs.jcim.2c01656
J. Chem. Inf. Model. 2023, 63, 1626−1636

Despite the time and effort spent to ensure that the most comprehensive DDI information is collected, new DDIs and mechanisms of DDIs continue to be reported. New DDIs are critical to avoid potential clinical adverse events, and mechanistic information is important to guide rational drug use. Therefore, we will continue to update MecDDI quarterly to keep the data in MecDDI up to date.

CONCLUSIONS

DDIs have become a key threat to public health, and inadequate knowledge of the mechanisms underlying the existing DDIs significantly limits their clinical management. In this study, a new platform was developed to clarify the mechanisms underlying 1,78,406 DDIs by explicit descriptions and graphic illustrations and provide systematic classification for all newly collected DDIs using their clarified mechanisms. Due to the long-lasting threats of DDI to public health, MecDDI could give medical scientists a clear clarification of the mechanism underlying all existing DDIs, support healthcare professionals in the identification of alternative therapeutic strategies, and prepare valuable big data for algorithm scientists to predict potential DDIs.

DATA AVAILABILITY

MecDDI is freely accessible by all users without any login requirement at https://idrblab.org/mecddi/, and all data in MecDDI can be downloaded online.

AUTHOR INFORMATION

Corresponding Authors

Feng Zhu − *Department of Pharmacy, Center of Clinical Pharmacology, The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310009, China; College of Pharmaceutical Sciences, Zhejiang University, Hangzhou 310058, China; Innovation Institute for Artificial Intelligence in Medicine of Zhejiang University, Alibaba-Zhejiang University Joint Research Center of Future Digital Healthcare, Hangzhou 330110, China;* orcid.org/0000-0001-8069-0053; Email: zhufeng@zju.edu.cn

Haibin Dai − *Department of Pharmacy, Center of Clinical Pharmacology, The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310009, China; Clinical Pharmacy Research Center, Zhejiang University School of Medicine, Hangzhou 310009, China;* Email: haibindai@zju.edu.cn

Authors

Wei Hu − *Department of Pharmacy, Center of Clinical Pharmacology, The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310009, China*

Wei Zhang − *College of Pharmaceutical Sciences, Zhejiang University, Hangzhou 310058, China; Innovation Institute for Artificial Intelligence in Medicine of Zhejiang University, Alibaba-Zhejiang University Joint Research Center of Future Digital Healthcare, Hangzhou 330110, China*

Ying Zhou − *State Key Laboratory for Diagnosis and Treatment of Infectious Disease, Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, Zhejiang Provincial Key Laboratory for Drug Clinical Research and Evaluation, The First Affiliated Hospital, Zhejiang University, Hangzhou 310000, China*

Yongchao Luo − *College of Pharmaceutical Sciences, Zhejiang University, Hangzhou 310058, China; Innovation Institute for Artificial Intelligence in Medicine of Zhejiang University, Alibaba-Zhejiang University Joint Research Center of Future Digital Healthcare, Hangzhou 330110, China;* orcid.org/0000-0002-4140-5392

Xiuna Sun − *College of Pharmaceutical Sciences, Zhejiang University, Hangzhou 310058, China; Innovation Institute for Artificial Intelligence in Medicine of Zhejiang University, Alibaba-Zhejiang University Joint Research Center of Future Digital Healthcare, Hangzhou 330110, China*

Huimin Xu − *Department of Pharmacy, Center of Clinical Pharmacology, The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310009, China*

Shuiyang Shi − *College of Pharmaceutical Sciences, Zhejiang University, Hangzhou 310058, China; Innovation Institute for Artificial Intelligence in Medicine of Zhejiang University, Alibaba-Zhejiang University Joint Research Center of Future Digital Healthcare, Hangzhou 330110, China*

Teng Li − *Department of Pharmacy, Center of Clinical Pharmacology, The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310009, China*

Yichao Xu − *Department of Pharmacy, Center of Clinical Pharmacology, The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310009, China*

Qianqian Yang − *Department of Pharmacy, Affiliated Hangzhou First Peoples Hospital, Zhejiang University School of Medicine, Hangzhou 310006, China; Clinical Pharmacy Research Center, Zhejiang University School of Medicine, Hangzhou 310009, China*

Yunqing Qiu − *State Key Laboratory for Diagnosis and Treatment of Infectious Disease, Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, Zhejiang Provincial Key Laboratory for Drug Clinical Research and Evaluation, The First Affiliated Hospital, Zhejiang University, Hangzhou 310000, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.jcim.2c01656

Author Contributions

W.H., W.Z., and Y.Z. contributed equally to this work as co-first authors.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was funded by Natural Science Foundation of Zhejiang Province (LR21H300001); National Natural Science Foundation of China (U1909208 & 81872798); Leading Talent of "Ten Thousand Plan" of the National High-Level Talents Special Support Plan of China; Fundamental Research Fund of Central University (2018QNA7023); Key R&D Program of Zhejiang Province (2020C03010); Chinese "Double Top-Class" Universities (181201*194232101); Westlake Laboratory (Westlake Laboratory of Life Science & Biomedicine); Alibaba-Zhejiang University Joint Research Center of Future Digital Healthcare; Alibaba Cloud; and Information Tech Center of Zhejiang University.

REFERENCES

(1) Sennesael, A. L.; Henrard, S.; Spinewine, A. Drug interactions with non-vitamin k oral anticoagulants. *JAMA* **2018**, *319*, 829.

(2) Hoel, R. W.; Giddings Connolly, R. M.; Takahashi, P. Y. Polypharmacy management in older patients. *Mayo Clin. Proc.* **2021**, *96*, 242−256.
(3) Brüggemann, R. J.; Verheggen, R.; Boerrigter, E.; Stanzani, M.; Verweij, P. E.; Blijlevens, N. M. A.; Lewis, R. E. Management of drug-drug interactions of targeted therapies for haematological malignancies and triazole antifungal drugs. *Lancet Haematol.* **2022**, *9*, e58−e72.
(4) Zerah, L.; Henrard, S.; Wilting, I.; O'Mahony, D.; Rodondi, N.; Dalleur, O.; Dalton, K.; Knol, W.; Haschke, M.; Spinewine, A. Prevalence of drug-drug interactions in older people before and after hospital admission: analysis from the OPERAM trial. *BMC Geriatr.* **2021**, *21*, 571.
(5) Ye, Q.; Hsieh, C. Y.; Yang, Z.; Kang, Y.; Chen, J.; Cao, D.; He, S.; Hou, T. A unified drug-target interaction prediction framework based on knowledge graph and recommendation system. *Nat. Commun.* **2021**, *12*, 6775.
(6) Ye, H.; Wu, J.; Liang, Z.; Zhang, Y.; Huang, Z. Protein S-nitrosation: biochemistry, identification, molecular mechanisms, and therapeutic applications. *J. Med. Chem.* **2022**, *65*, 5902−5925.
(7) Wu, Z.; Lei, T.; Shen, C.; Wang, Z.; Cao, D.; Hou, T. ADMET Evaluation in Drug Discovery. 19. Reliable Prediction of Human Cytochrome P450 Inhibition Using Artificial Intelligence Approaches. *J. Chem. Inf. Model.* **2019**, *59*, 4587−4601.
(8) Stader, F.; Battegay, M.; Marzolini, C. Physiologically-Based Pharmacokinetic Modeling to Support the Clinical Management of Drug-Drug Interactions With Bictegravir. *Clin. Pharmacol. Ther.* **2021**, *110*, 1231−1239.
(9) Zhu, S.; Noviello, C. M.; Teng, J.; Walsh, R. M., Jr.; Kim, J. J.; Hibbs, R. E. Structure of a human synaptic GABAA receptor. *Nature* **2018**, *559*, 67−72.
(10) Li, Y.; Meng, Q.; Yang, M.; Liu, D.; Hou, X.; Tang, L.; Wang, X.; Lyu, Y.; Chen, X.; Liu, K.; Yu, A. M.; Zuo, Z.; Bi, H. Current trends in drug metabolism and pharmacokinetics. *Acta Pharm. Sin. B* **2019**, *9*, 1113−1144.
(11) Nigam, S. K. What do drug transporters really do? *Nat. Rev. Drug Discov.* **2015**, *14*, 29−44.
(12) Dou, L.; Yang, F.; Xu, L.; Zou, Q. A comprehensive review of the imbalance classification of protein post-translational modifications. *Briefings Bioinf.* **2021**, *22*, bbab089.
(13) Ding, Y.; Tang, J.; Guo, F.; Zou, Q. Identification of drug-target interactions via multiple kernel-based triple collaborative matrix factorization. *Briefings Bioinf.* **2022**, *23*, bbab582.
(14) Rockers, P. C.; Laing, R. O.; Ashigbie, P. G.; Onyango, M. A.; Mukiira, C. K.; Wirtz, V. J. Effect of Novartis access on availability and price of non-communicable disease medicines in Kenya: a cluster-randomised controlled trial. *Lancet Global Health* **2019**, *7*, e492−e502.
(15) Wu, P.; Nelson, S. D.; Zhao, J.; Stone, C. A., Jr.; Feng, Q.; Chen, Q.; Larson, E. A.; Li, B.; Cox, N. J.; Stein, C. M.; Phillips, E. J.; Roden, D. M.; Denny, J. C.; Wei, W. Q. DDIWAS: High-throughput electronic health record-based screening of drug-drug interactions. *J. Am. Med. Inf. Assoc.* **2021**, *28*, 1421−1430.
(16) Seong, S. J.; Ohk, B.; Kang, W. Y.; Gwon, M. R.; Kim, B. K.; Cho, S.; Yang, D. H.; Lee, H. W.; Yoon, Y. R. Pharmacokinetic Drug Interactions Between Amlodipine, Valsartan, and Rosuvastatin in Healthy Volunteers. *Adv. Ther.* **2019**, *36*, 1642−1656.
(17) Wiebe, S. T.; Huennemeyer, A.; Kadus, W.; Goettel, M.; Jambrecina, A.; Schultz, A.; Vinisko, R.; Schlieker, L.; Herich, L.; Mikus, G. Midazolam microdosing applied in early clinical development for drug-drug interaction assessment. *Br. J. Clin. Pharmacol.* **2021**, *87*, 178−188.
(18) Mikus, G.; Foerster, K. I.; Schaumaeker, M.; Lehmann, M. L.; Burhenne, J.; Haefeli, W. E. Microdosed cocktail of three oral factor Xa inhibitors to evaluate drug-drug interactions with potential perpetrator drugs. *Clin. Pharmacokinet.* **2019**, *58*, 1155−1163.
(19) Sun, T.; Lv, T.; Wu, J.; Zhu, M.; Fei, Y.; Zhu, J.; Zhang, Y.; Huang, Z. General strategy for integrated bioorthogonal prodrugs: Pt(II)-triggered depropargylation enables controllable drug activation in vivo. *J. Med. Chem.* **2020**, *63*, 13899−13912.
(20) Gu, X.; Huang, Z.; Ren, Z.; Tang, X.; Xue, R.; Luo, X.; Peng, S.; Peng, H.; Lu, B.; Tian, J.; Zhang, Y. Potent inhibition of nitric oxide-releasing bifendate derivatives against drug-resistant K562/A02 cells in vitro and in vivo. *J. Med. Chem.* **2017**, *60*, 928−940.
(21) Jones, N. S.; Yoshida, K.; Salphati, L.; Kenny, J. R.; Durk, M. R.; Chinn, L. W. Complex DDI by fenebrutinib and the use of transporter endogenous biomarkers to elucidate the mechanism of DDI. *Clin. Pharmacol. Ther.* **2020**, *107*, 269−277.
(22) Foerster, K. I.; Hermann, S.; Mikus, G.; Haefeli, W. E. Drug-drug interactions with direct oral anticoagulants. *Clin. Pharmacokinet.* **2020**, *59*, 967−980.
(23) Elmeliegy, M.; Vourvahis, M.; Guo, C.; Wang, D. D. Effect of P-glycoprotein (P-gp) inducers on exposure of P-gp substrates: review of clinical drug-drug interaction studies. *Clin. Pharmacokinet.* **2020**, *59*, 699−714.
(24) Unger, M. S.; Mudunuru, J.; Schwab, M.; Hopf, C.; Drewes, G.; Nies, A. T.; Zamek-Gliszczynski, M. J.; Reinhard, F. B. M. Clinically relevant OATP2B1 inhibitors in marketed drug space. *Mol. Pharm.* **2020**, *17*, 488−498.
(25) Crescioli, G.; Brilli, V.; Lanzi, C.; Burgalassi, A.; Ieri, A.; Bonaiuti, R.; Romano, E.; Innocenti, R.; Mannaioni, G.; Vannacci, A.; Lombardi, N. A.-O. Adverse drug reactions in SARS-CoV-2 hospitalised patients: a case-series with a focus on drug-drug interactions. *Intern. Emerg. Med.* **2021**, *16*, 697−710.
(26) Roden, D. M. A current understanding of drug-induced QT prolongation and its implications for anticancer therapy. *Cardiovasc. Res.* **2019**, *115*, 895−903.
(27) Kontsioti, E.; Maskell, S.; Dutta, B.; Pirmohamed, M. A reference set of clinically relevant adverse drug-drug interactions. *Sci. Data* **2022**, *9*, 72.
(28) Ismail, M.; Khan, S.; Khan, F.; Noor, S.; Sajid, H.; Yar, S.; Rasheed, I. Prevalence and significance of potential drug-drug interactions among cancer patients receiving chemotherapy. *BMC Cancer* **2020**, *20*, 335.
(29) Sun, F.; Wang, Y.; Luo, X.; Ma, Z.; Xu, Y.; Zhang, X.; Lv, T.; Zhang, Y.; Wang, M.; Huang, Z.; Zhang, J. Anti-CD24 antibody-nitric oxide conjugate selectively and potently suppresses hepatic carcinoma. *Cancer Res.* **2019**, *79*, 3395−3405.
(30) Zou, Y.; Zhao, D.; Yan, C.; Ji, Y.; Liu, J.; Xu, J.; Lai, Y.; Tian, J.; Zhang, Y.; Huang, Z. Novel ligustrazine-based analogs of piperlongumine potently suppress proliferation and metastasis of colorectal cancer cells in vitro and in vivo. *J. Med. Chem.* **2018**, *61*, 1821−1832.
(31) Salerno, S. N.; Edginton, A.; Gerhart, J. G.; Laughon, M. M.; Ambalavanan, N.; Sokol, G. M.; Hornik, C. D.; Stewart, D.; Mills, M.; Martz, K.; Gonzalez, D.; Benjamin, D. K., Jr.; Hornik, C.; Zimmerman, K.; Kennel, P.; Beci, R.; Hornik, C. D.; Kearns, G. L.; Laughon, M.; Paul, I. M.; Sullivan, J.; Wade, K.; Delmore, P.; Kennedy, E.; Taylor-Zapata, P.; Lee, J.; Anand, R.; Sharma, G.; Simone, G.; Kaneshige, K.; Taylor, L.; Green, T.; Lurie, R. H.; Ambalavanan, N.; McNair, T. E.; Phillips, V.; Atz, A.; Choudhary, K. J.; Sokol, G. M.; Gunn, S.; Herron, D.; Smiley, L.; Hornik, C. D.; Michael Cotten, C.; Andrews, L.; Stewart, D.; Sullivan, J.; Michael, A.; Mundakel, G.; Limbu, S.; Poindexter, B.; Wuertz, S. Physiologically-Based Pharmacokinetic Modeling Characterizes the CYP3A-Mediated Drug-Drug Interaction Between Fluconazole and Sildenafil in Infants. *Clin. Pharmacol. Ther.* **2021**, *109*, 253−262.
(32) Ziesenitz, V. C.; Mikus, G. Methodological Considerations on CYP 2D6 Phenoconversion Due to Drug-Drug Interaction. *Clin. Pharmacol. Ther.* **2019**, *105*, 1076.
(33) Rohr, B. S.; Mikus, G. Proposal of a Safe and Effective Study Design for CYP3A-Mediated Drug-Drug Interactions. *J. Clin. Pharmacol.* **2020**, *60*, 1294−1303.
(34) Niu, J.; Straubinger, R. M.; Mager, D. E. Pharmacodynamic drug-drug interactions. *Clin. Pharmacol. Ther.* **2019**, *105*, 1395−1406.
(35) Bloomingdale, P.; Meregalli, C.; Pollard, K.; Canta, A.; Chiorazzi, A.; Fumagalli, G.; Monza, L.; Pozzi, E.; Alberti, P.; Ballarini, E.; Oggioni, N.; Carlson, L.; Liu, W.; Ghandili, M.; Ignatowski, T. A.; Lee, K. P.; Moore, M. J.; Cavaletti, G.; Mager, D. E. Systems pharmacology

https://doi.org/10.1021/acs.jcim.2c01656
J. Chem. Inf. Model. 2023, 63, 1626−1636

modeling identifies a novel treatment strategy for bortezomib-induced neuropathic pain. *Front. Pharmacol.* **2021**, *12*, 817236.
(36) Nakada, T.; Mager, D. E. Systems model identifies baseline cytokine concentrations as potential predictors of rheumatoid arthritis inflammatory response to biologics. *Br. J. Pharmacol.* **2022**, *179*, 4063−4077.
(37) Niu, J.; Nguyen, V. A.; Ghasemi, M.; Chen, T.; Mager, D. E. Cluster gauss-newton and CellNOpt parameter estimation in a small protein signaling network of vorinostat and bortezomib pharmacodynamics. *AAPS J.* **2021**, *23*, 110.
(38) Ailabouni, N. J.; Marcum, Z. A.; Schmader, K. E.; Gray, S. L. Medication use quality and safety in older adults: 2019 update. *J. Am. Geriatr. Soc.* **2021**, *69*, 336−341.
(39) Supuran, C. T. An update on drug interaction considerations in the therapeutic use of carbonic anhydrase inhibitors. *Expert Opin. Drug Metab. Toxicol.* **2020**, *16*, 297−307.
(40) Fravel, M. A.; Ernst, M. Drug Interactions with antihypertensives. *Curr. Hypertens. Rep.* **2021**, *23*, 14.
(41) Song, Y.; Zhu, S.; Zhang, N.; Cheng, L. Blood circulating miRNA pairs as a robust signature for early detection of esophageal cancer. *Front. Oncol.* **2021**, *11*, 723779.
(42) Mikus, G. Probes and cocktails for drug-drug interaction evaluation: the future is microdosing? *Clin. Pharmacol. Ther.* **2019**, *105*, 1335−1337.
(43) Feng, Y. Y.; Yu, H.; Feng, Y. H.; Shi, J. Y. Directed graph attention networks for predicting asymmetric drug-drug interactions. *Briefings Bioinf.* **2022**, *23*, bbac151.
(44) Yu, Y.; Huang, K.; Zhang, C.; Glass, L. M.; Sun, J.; Xiao, C. SumGNN: multi-typed drug interaction prediction via efficient knowledge graph summarization. *Bioinformatics* **2021**, *37*, 2988−2995.
(45) Wu, Q.; Zheng, X.; Leung, K. S.; Wong, M. H.; Tsui, S. K.; Cheng, L. meGPS: a multi-omics signature for hepatocellular carcinoma detection integrating methylome and transcriptome data. *Bioinformatics* **2022**, *38*, 3513−3522.
(46) Bloomingdale, P.; Mager, D. E. Machine learning models for the prediction of chemotherapy-induced peripheral neuropathy. *Pharmaceut. Res.* **2019**, *36*, 35.
(47) Wang, J.; Hsieh, C.; Wang, M.; Wang, X.; Wu, Z.; Jiang, D.; Liao, D.; Zhang, X.; Yang, T.; He, Q.; Cao, D.; Chen, X.; Hou, T. Multi-constraint molecular generation based on conditional transformer, knowledge distillation and reinforcement learning. *Nat. Mach. Intell.* **2021**, *3*, 914−922.
(48) Lin, S.; Wang, Y.; Zhang, L.; Chu, Y.; Liu, Y.; Fang, Y.; Jiang, M.; Wang, Q.; Zhao, B.; Xiong, Y.; Wei, D. Q. MDF-SA-DDI: predicting drug-drug interaction events based on multi-source drug fusion, multi-source feature fusion and transformer self-attention mechanism. *Briefings Bioinf.* **2022**, *23*, bbab421.
(49) Deng, Y.; Qiu, Y.; Xu, X.; Liu, S.; Zhang, Z.; Zhu, S.; Zhang, W. META-DDIE: predicting drug-drug interaction events with few-shot learning. *Briefings Bioinf.* **2022**, *23*, bbab514.
(50) Cheng, Y.; Gong, Y.; Liu, Y.; Song, B.; Zou, Q. Molecular design in drug discovery: a comprehensive review of deep generative models. *Briefings Bioinf.* **2021**, *22*, bbab344.
(51) Khanal, J.; Tayara, H.; Zou, Q.; To Chong, K. DeepCap-Kcr: accurate identification and investigation of protein lysine crotonylation sites based on capsule network. *Briefings Bioinf.* **2022**, *23*, bbab492.
(52) Wang, R.; Zheng, X.; Wang, J.; Wan, S.; Song, F.; Wong, M. H.; Leung, K. S.; Cheng, L. Improving bulk RNA-seq classification by transferring gene signature from single cells in acute myeloid leukemia. *Briefings Bioinf.* **2022**, *23*, bbac002.
(53) Li, H.; Zheng, X.; Gao, J.; Leung, K. S.; Wong, M. H.; Yang, S.; Liu, Y.; Dong, M.; Bai, H.; Ye, X.; Cheng, L. Whole transcriptome analysis reveals non-coding RNA's competing endogenous gene pairs as novel form of motifs in serous ovarian cancer. *Comput. Biol. Med.* **2022**, *148*, 105881.
(54) Wishart, D. S.; Feunang, Y. D.; Guo, A. C.; Lo, E. J.; Marcu, A.; Grant, J. R.; Sajed, T.; Johnson, D.; Li, C.; Sayeeda, Z.; Assempour, N.; Iynkkaran, I.; Liu, Y.; Maciejewski, A.; Gale, N.; Wilson, A.; Chin, L.; Cummings, R.; Le, D.; Pon, A.; Knox, C.; Wilson, M. DrugBank 5.0: a major update to the DrugBank database for 2018. *Nucleic Acids Res.* **2018**, *46*, D1074−D1082.
(55) Zhou, Y.; Zhang, Y.; Lian, X.; Li, F.; Wang, C.; Zhu, F.; Qiu, Y.; Chen, Y. Therapeutic target database update 2022: facilitating drug discovery with enriched comparative data of targeted agents. *Nucleic Acids Res.* **2022**, *50*, D1398−D1407.
(56) Siramshetty, V. B.; Eckert, O. A.; Gohlke, B. O.; Goede, A.; Chen, Q.; Devarakonda, P.; Preissner, S.; Preissner, R. SuperDRUG2: a one stop resource for approved/marketed drugs. *Nucleic Acids Res.* **2018**, *46*, D1137−D1143.
(57) Hoffmann, M. F.; Preissner, S. C.; Nickel, J.; Dunkel, M.; Preissner, R.; Preissner, S. The Transformer database: biotransformation of xenobiotics. *Nucleic Acids Res.* **2014**, *42*, D1113−D1117.
(58) Banerjee, P.; Dunkel, M.; Kemmler, E.; Preissner, R. SuperCYPsPred-a web server for the prediction of cytochrome activity. *Nucleic Acids Res.* **2020**, *48*, W580−W585.
(59) Xiong, G.; Yang, Z.; Yi, J.; Wang, N.; Wang, L.; Zhu, H.; Wu, C.; Lu, A.; Chen, X.; Liu, S.; Hou, T.; Cao, D. DDInter: an online drug-drug interaction database towards improving clinical decision-making and patient safety. *Nucleic Acids Res.* **2022**, *50*, D1200−D1207.
(60) Mello, A.; Melo, K. R.; Sousa, A.; Rolim Neto, P. J.; Silva, R. Product indiscriminate use of vitamin risks: a review. *Crit. Rev. Food Sci. Nutr.* **2020**, *60*, 2067−2082.
(61) Marzolini, C.; Kuritzkes, D. R.; Marra, F.; Boyle, A.; Gibbons, S.; Flexner, C.; Pozniak, A.; Boffito, M.; Waters, L.; Burger, D.; Back, D.; Khoo, S. Prescribing nirmatrelvir-ritonavir: how to recognize and manage drug-drug interactions. *Ann. Intern. Med.* **2022**, *175*, 744−746.
(62) Liu, H.; Zhang, W.; Zou, B.; Wang, J.; Deng, Y.; Deng, L. DrugCombDB: a comprehensive database of drug combinations toward the discovery of combinatorial therapy. *Nucleic Acids Res.* **2020**, *48*, D871−D881.
(63) Chen, X.; Ren, B.; Chen, M.; Liu, M. X.; Ren, W.; Wang, Q. X.; Zhang, L. X.; Yan, G. Y. ASDCD: antifungal synergistic drug combination database. *PLoS One* **2014**, *9*, No. e86499.
(64) Hochheiser, H.; Jing, X.; Garcia, E. A.; Ayvaz, S.; Sahay, R.; Dumontier, M.; Banda, J. M.; Beyan, O.; Brochhausen, M.; Draper, E.; Habiel, S.; Hassanzadeh, O.; Herrero-Zazo, M.; Hocum, B.; Horn, J.; LeBaron, B.; Malone, D. C.; Nytrø, O.; Reese, T.; Romagnoli, K.; Schneider, J.; Zhang, L. Y.; Boyce, R. D. A minimal information model for potential drug-drug interactions. *Front. Pharmacol.* **2020**, *11*, 608068.
(65) Patel, P.; Leeder, J. S.; Piquette-Miller, M.; Dupuis, L. L. Aprepitant and fosaprepitant drug interactions: a systematic review. *Br. J. Clin. Pharmacol.* **2017**, *83*, 2148−2162.
(66) Bates, E. R.; Lau, W. C.; Angiolillo, D. J. Clopidogrel-drug interactions. *J. Am. Coll. Cardiol.* **2011**, *57*, 1251−1263.
(67) Engell, A. E.; Svendsen, A. L. O.; Lind, B. S.; Stage, T. B.; Hellfritzsch, M.; Pottegård, A. Drug-drug interactions between vitamin K antagonists and statins: a systematic review. *Eur. J. Clin. Pharmacol.* **2021**, *77*, 1435−1441.
(68) Damkier, P.; Lassen, D.; Christensen, M. M. H.; Madsen, K. G.; Hellfritzsch, M.; Pottegård, A. Interaction between warfarin and cannabis. *Basic Clin. Pharmacol. Toxicol.* **2019**, *124*, 28−31.
(69) Agergaard, K.; Mau-Sørensen, M.; Stage, T. B.; Jørgensen, T. L.; Hassel, R. E.; Steffensen, K. D.; Pedersen, J. W.; Milo, M.; Poulsen, S. H.; Pottegård, A.; Hallas, J.; Brøsen, K.; Bergmann, T. K. Clopidogrel-paclitaxel drug-drug interaction: a pharmacoepidemiologic study. *Clin. Pharmacol. Ther.* **2017**, *102*, 547−553.
(70) Jensen, L.; Monnat, S. M.; Green, J. J.; Hunter, L. M.; Sliwinski, M. J. Rural population health and aging: toward a multilevel and multidimensional research agenda for the 2020s. *Am. J. Publ. Health* **2020**, *110*, 1328−1331.
(71) Zhi, K.; Chen, Y.; Huang, J. China's challenge in promoting older migrants' health and wellbeing: a productive ageing perspective. *BMJ* **2021**, *375*, n2874.
(72) Hellfritzsch, M.; Lund, L. C.; Ennis, Z.; Stage, T.; Damkier, P.; Bliddal, M.; Jensen, P. B.; Henriksen, D.; Ernst, M. T.; Olesen, M.; Broe, A.; Kristensen, K. B.; Hallas, J.; Pottegård, A. Ischemic stroke and systemic embolism in warfarin users with atrial fibrillation or heart valve

https://doi.org/10.1021/acs.jcim.2c01656
J. Chem. Inf. Model. 2023, 63, 1626−1636

replacement exposed to dicloxacillin or flucloxacillin. *Clin. Pharmacol. Ther.* **2020**, *107*, 607−616.
(73) Brown, D. G.; Wobst, H. J. A decade of FDA-approved drugs (2010-2019): trends and future directions. *J. Med. Chem.* **2021**, *64*, 2312−2338.
(74) Henderson, L. M.; Steinbronn, C. E.; Yu, J.; Yeung, C. K.; Ragueneau-Majlessi, I. Analysis of drug-drug interaction labeling language and clinical recommendations for newly approved drugs evaluated with digoxin, midazolam, and s-warfarin. *Clin. Therapeut.* **2021**, *43*, 2032−2039.
(75) Wastesson, J. W.; Morin, L.; Tan, E. C. K.; Johnell, K. An update on the clinical consequences of polypharmacy in older adults: a narrative review. *Expet Opin. Drug Saf.* **2018**, *17*, 1185−1196.
(76) Jiang, H.; Lin, Y.; Ren, W.; Fang, Z.; Liu, Y.; Tan, X.; Lv, X.; Zhang, N. Adverse drug reactions and correlations with drug-drug interactions: A retrospective study of reports from 2011 to 2020. *Front. Pharmacol.* **2022**, *13*, 923939.
(77) Kim, S.; Chen, J.; Cheng, T.; Gindulyte, A.; He, J.; He, S.; Li, Q.; Shoemaker, B. A.; Thiessen, P. A.; Yu, B.; Zaslavsky, L.; Zhang, J.; Bolton, E. E. PubChem 2019 update: improved access to chemical data. *Nucleic Acids Res.* **2019**, *47*, D1102−D1109.
(78) Hastings, J.; Owen, G.; Dekker, A.; Ennis, M.; Kale, N.; Muthukrishnan, V.; Turner, S.; Swainston, N.; Mendes, P.; Steinbeck, C. ChEBI in 2016: improved services and an expanding collection of metabolites. *Nucleic Acids Res.* **2016**, *44*, D1214−D1219.
(79) Fu, T.; Li, F.; Zhang, Y.; Yin, J.; Qiu, W.; Li, X.; Liu, X.; Xin, W.; Wang, C.; Yu, L.; Gao, J.; Zheng, Q.; Zeng, S.; Zhu, F. VARIDT 2.0: structural variability of drug transporter. *Nucleic Acids Res.* **2022**, *50*, D1417−D1431.
(80) Yin, J.; Li, F.; Zhou, Y.; Mou, M.; Lu, Y.; Chen, K.; Xue, J.; Luo, Y.; Fu, J.; He, X.; Gao, J.; Zeng, S.; Yu, L.; Zhu, F. INTEDE: interactome of drug-metabolizing enzymes. *Nucleic Acids Res.* **2021**, *49*, D1233−D1243.
(81) Deng, J.; Zhu, X.; Chen, Z.; Fan, C. H.; Kwan, H. S.; Wong, C. H.; Shek, K. Y.; Zuo, Z.; Lam, T. N. A review of food-drug interactions on oral drug absorption. *Drugs* **2017**, *77*, 1833−1855.
(82) Sudsakorn, S.; Bahadduri, P.; Fretland, J.; Lu, C. 2020 FDA Drug-drug Interaction Guidance: A Comparison Analysis and Action Plan by Pharmaceutical Industrial Scientists. *Curr. Drug Metab.* **20202020**, *21*, 403−426.
(83) Tsoukalas, N.; Brito-Dellan, N.; Font, C.; Butler, T.; Rojas-Hernandez, C. M.; Butler, T.; Escalante, C.; Group, M. H. S. Complexity and clinical significance of drug-drug interactions (DDIs) in oncology: challenging issues in the care of patients regarding cancer-associated thrombosis (CAT). *Support. Care Cancer* **2022**, *30*, 8559−8573.
(84) Allahgholi, M.; Rahmani, H.; Javdani, D.; Weiss, G.; Módos, D. ADDI: Recommending alternatives for drug-drug interactions with negative health effects. *Comput. Biol. Med.* **2020**, *125*, 103969.
(85) Wiggins, B. S.; Saseen, J. J.; Pagell, R. L.; Reed, B. N.; Sneed, K.; Kostis, J. B.; Lanfear, D.; Virani, S.; Morris, P. B. Recommendations for management of clinically significant drug-drug interactions with statins and select agents used in patients with cardiovascular disease: a scientific statement from the american heart association. *Circulation* **2016**, *134*, e468−e495.
(86) Bahar, M. A.; Kamp, J.; Borgsteede, S. D.; Hak, E.; Wilffert, B. The impact of CYP2D6 mediated drug-drug interaction: a systematic review on a combination of metoprolol and paroxetine/fluoxetine. *Br. J. Clin. Pharmacol.* **2018**, *84*, 2704−2715.
(87) Fogli, S.; Del Re, M.; Curigliano, G.; van Schaik, R. H.; Lancellotti, P.; Danesi, R. Drug-drug interactions in breast cancer patients treated with CDK4/6 inhibitors. *Cancer Treat Rev.* **2019**, *74*, 21−28.
(88) Stefanovic, S.; Jankovic, S. M.; Novakovic, M.; Milosavljevic, M.; Folic, M. Pharmacodynamics and common drug-drug interactions of the third-generation antiepileptic drugs. *Expet Opin. Drug Metabol. Toxicol.* **2018**, *14*, 153−159.
(89) Pan, D.; Quan, L.; Jin, Z.; Chen, T.; Wang, X.; Xie, J.; Wu, T.; Lyu, Q. Multisource Attention-Mechanism-Based Encoder-Decoder Model for Predicting Drug-Drug Interaction Events. *J. Chem. Inf. Model.* **2022**, *62*, 6258−6270.
(90) van Hasselt, J. G. C.; Iyengar, R. Systems Pharmacology: Defining the Interactions of Drug Combinations. *Annu. Rev. Pharmacol. Toxicol.* **2019**, *59*, 21−40.
(91) Aronson, J. K. Classifying drug interactions. *Br. J. Clin. Pharmacol.* **2004**, *58*, 343−344.
(92) Lu, C.; Di, L. In vitro and in vivo methods to assess pharmacokinetic drug- drug interactions in drug discovery and development. *Biopharm. Drug Dispos.* **2020**, *41*, 3−31.
(93) Peng, Y.; Cheng, Z.; Xie, F. Evaluation of pharmacokinetic drug-drug interactions: a review of the mechanisms, in vitro and in silico approaches. *Metabolites* **2021**, *11*, 75.
(94) Yu, J.; Wang, Y.; Ragueneau-Majlessi, I. Pharmacokinetic Drug-Drug Interactions with Drugs Approved by the US Food and Drug Administration in 2020: Mechanistic Understanding and Clinical Recommendations. *Drug Metab. Dispos.* **2022**, *50*, 1−7.
(95) Chou, T. C. Theoretical basis, experimental design, and computerized simulation of synergism and antagonism in drug combination studies. *Pharmacol. Rev.* **2006**, *58*, 621−681.
(96) Key, N. S.; Khorana, A. A.; Kuderer, N. M.; Bohlke, K.; Lee, A. Y. Y.; Arcelus, J. I.; Wong, S. L.; Balaban, E. P.; Flowers, C. R.; Francis, C. W.; Gates, L. E.; Kakkar, A. K.; Levine, M. N.; Liebman, H. A.; Tempero, M. A.; Lyman, G. H.; Falanga, A. Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: ASCO Clinical Practice Guideline Update. *J. Clin. Oncol.* **2020**, *38*, 496−520.
(97) Wang, T. F. Drug-drug interactions: Implications for anti-coagulation, with focus in patients with cancer. *Thromb. Res.* **2022**, *213*, S66−S71.
(98) Jang, H. Y.; Song, J.; Kim, J. H.; Lee, H.; Kim, I. W.; Moon, B.; Oh, J. M. Machine learning-based quantitative prediction of drug exposure in drug-drug interactions using drug label information. *NPJ Digit. Med.* **2022**, *5*, 88.
(99) Ferdousi, R.; Safdari, R.; Omidi, Y. Computational prediction of drug-drug interactions based on drugs functional similarities. *J. Biomed. Inf.* **2017**, *70*, 54−64.
(100) Li, Z.; Zhu, S.; Shao, B.; Zeng, X.; Wang, T.; Liu, T. Y. DSN-DDI: an accurate and generalized framework for drug-drug interaction prediction by dual-view representation learning. *Briefings Bioinf.* **2023**, *24*, bbac597.
(101) He, C.; Liu, Y.; Li, H.; Zhang, H.; Mao, Y.; Qin, X.; Liu, L.; Zhang, X. Multi-type feature fusion based on graph neural network for drug-drug interaction prediction. *BMC Bioinf.* **2022**, *23*, 224.
(102) Yu, H.; Zhao, S.; Shi, J. STNN-DDI: a Substructure-aware Tensor Neural Network to predict Drug-Drug Interactions. *Briefings Bioinf.* **2022**, *23*, bbac209.
(103) Deng, Y.; Xu, X.; Qiu, Y.; Xia, J.; Zhang, W.; Liu, S. A multimodal deep learning framework for predicting drug-drug interaction events. *Bioinformatics* **2020**, *36*, 4316−4322.
(104) Ryu, J. Y.; Kim, H. U.; Lee, S. Y. Deep learning improves prediction of drug-drug and drug-food interactions. *Proc. Natl. Acad. Sci. U. S. A.* **2018**, *115*, E4304−E4311.
(105) Lancet, T. ICD-11: a brave attempt at classifying a new world. *Lancet* **2018**, *391*, 2476.

https://doi.org/10.1021/acs.jcim.2c01656
J. Chem. Inf. Model. 2023, 63, 1626−1636