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SHORT COMMUNICATION

PREDICTION OF POTENTIAL ADVERSE DRUG REACTIONS UTILIZING HIGHLY SPECIFIC STRUCTURAL FRAGMENTS

P.I. Savosina*, D.A. Filimonov, D.S. Druzhilovskiy

Institute of Biomedical Chemistry,
10 Pogodinskaya str., Moscow, 119121 Russia; *e-mail: polina.savosina@ibmc.msk.ru

The use of *in silico* approaches to assess potential adverse reactions of new pharmaceutical substances reduces the risks, financial and time costs, associated with drug development. Using our previously developed method for identifying chemical motifs associated with certain types of undesirable biological activity, we have evaluated the off-target toxicity of clinically investigated pharmaceutical substances that would help to evaluate the potential risks of further research and use in clinical practice. For this purpose, we have created highly specific structural fragments for epidermal growth factor receptor and dipeptidyl peptidase 4 inhibitors, which are two molecular targets associated with a wide range of adverse reactions. A search for compounds containing these fragments was performed among 12,070 entries with information on clinical trials in the PubChem database. We have shown that five compounds entering phase I and II trials may have an unfavorable benefit-risk ratio due to the potential inhibition of at least one of the analyzed enzymes. Incorporating such analytical frameworks into early drug discovery and preclinical assessment could substantially reduce overall development costs and timelines, facilitating the introduction of safer and more cost-effective therapeutic agents.

Keywords: *in silico* studies; undesirable molecular targets; "*off-target*" toxicity; structural fragments; adverse drug reaction

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INTRODUCTION

Adverse reactions (ARs) arising from the use of pharmaceuticals represent a global pharmacotherapeutic problem. They can create additional burden on the healthcare system and increase risks for all participants in the drug management system, from patients to pharmaceutical companies [1, 2]. Significant reduction of the risk probability and the increase of the safety of new pharmacotherapeutic agents is possible through preliminary preclinical evaluation of the active pharmaceutical ingredient (API) under development. Such evaluation will enable the filtering of unsafe compounds that exhibit potential off-target toxicity due to the interaction of the API with multiple non-therapeutic and undesirable targets [3, 4].

Off-target toxicity analysis is traditionally performed through numerous *in vitro* experiments, which is costly and time-consuming. To reduce these costs, *in silico* approaches are becoming increasingly popular, enabling preliminary screening of potentially unsafe compounds before experimental testing [5].

Among the undesirable targets associated with the development of a wide range of ARs and included in the research kits of many pharmaceutical companies are the epidermal growth factor receptor (EGFR) and dipeptidyl peptidase 4 (DPP4) [6]. Inhibition of EGFR is accompanied by dermatological ARs (itching, dry skin, acneiform rash, paronychia, hair and nail changes), which significantly reduce the quality of life of patients [7]. Blockade of the DPP4 action can decrease the degradation rate of endogenous peptides, chemokines, and cytokines (bradykinin, substance P, stromal growth factor-1, etc.), which, in turn, can cause the development of serious allergic reactions (e.g., angioedema) [8] or arthralgia [9].

We previously developed a method for *in silico* assessment of compound interactions with undesirable targets which consists of identification of fragments highly specific for a particular type of biological activity in the structural formulas of the analyzed molecules [10]. Using this method it is possible to identify potential adverse reactions that could terminate the development of a new API. In the present study, the developed method was applied to a number of pharmaceutical substances in various stages of clinical trials, with the aim of predicting the potential risks of taking these substances based on an assessment of interactions with two undesirable targets: EGFR and DPP4.

MATERIALS AND METHODS

Data on pharmaceutical substances studied at various stages of clinical trials were obtained from the PubChem database [11] and contained

12,070 structural formulas of compounds for which information on the performance of clinical trials was submitted in one of three registries (Table 1): ClinicalTrials.gov (US registry), EudraCT (clinical trials database of the European Union countries), and NIPH Clinical Trials Search of Japan (a joint registry of clinical trials of three Japanese research centers). Among the analyzed structures, 5,198 have been previously approved for medical use, studied with the aim of their repositioning. Information on the performance of phase I, phase II, phase III, and phase 4 clinical trials was submitted for 6,787, 8,047, 5,373, and 3,668 PubChem records, respectively. We also found information about early phase I studies, also known as phase 0, for 1,249 compounds in the dataset. For 5,300 structures, information about the stage of the trials was not provided. It is important to note that a single compound may be at different stages of study in several clinical trials across different nosologies.

Using a previously described method [10] for assessing the contribution of each atom of a compound to its biological activity, we constructed structural fragments highly specific for EGFR and DPP4 inhibitors (Fig. 1). As positive controls, we have added the structures of two APIs, whose approval for medical use has been revoked to the analyzed dataset: mobocertinib [12], which blocks EGFR, and saxagliptin [13], inhibiting DPP4 activity.

RESULTS AND DISCUSSION

Our search resulted in identification of 18 pharmaceutical substances (not related to repurposed approved drugs) whose structural formulas contained the required highly specific fragments. One compound was found using a fragment characteristic of DPP4 inhibitors. Seventeen of the identified structures contained a fragment specific for EGFR inhibitors. Based on data presented in PubChem, EGFR is the therapeutic target for 13 of these compounds. This indicates that our previously developed method [10] can be used to assess not only undesired activity but also the pharmacotherapeutic potential of the studied compounds.

Table 1. The number of drug compounds in the different phases of clinical trials submitted to the three registries according to PubChem data

Registry name	Number of drug compounds*						
	Phase 0	Phase I	Phase II	Phase III	Phase IV	Phase not determined	Total
ClinicalTrials.gov	1213	6338	6413	4164	2691	3429	9787
EudraCT	0	1164	4502	3282	2299	84	5872
NIPH Clinical Trials Search of Japan	0	173	396	251	256	1873	1951

* One compound may be studied in several clinical trials conducted at different phases.

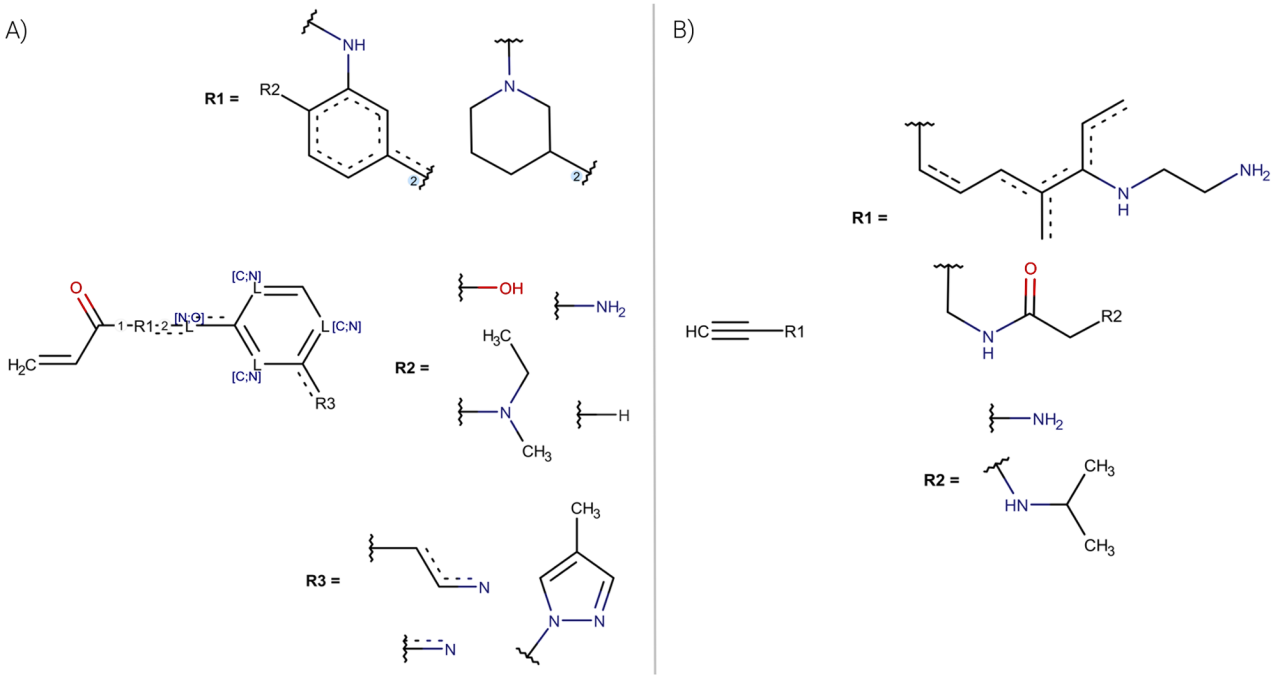
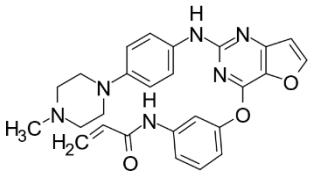
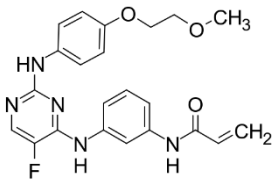
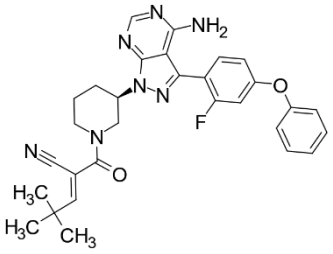
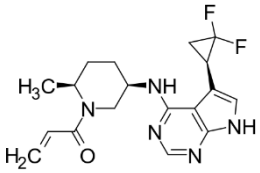
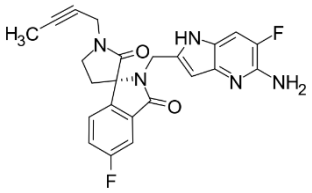
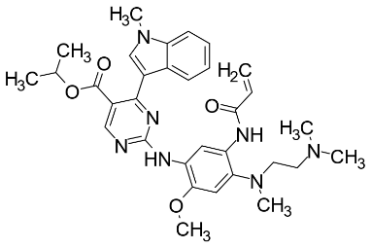
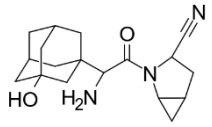


Figure 1. The designed highly specific structural fragments for: **A**) EGFR inhibitors, **B**) DPP4 inhibitors.

Table 2. Structural formulas and brief characteristics for potential inhibitors under clinical trials

#	Structure	PubChem identifier or API name	Target associated with the recognized fragment	Studied or approved for treatment	Maximal phase of trials
1		56644522	EGFR	Rheumatoid arthritis	Phase II
2		59174488	EGFR	Lymphoma / Leukemia; Rheumatoid arthritis	Phase I; Phase II
3		73438222	EGFR	Atopic dermatitis	Phase II
4		146343907	EGFR	Atopic dermatitis	Phase II
5		167507156	DPP4	Solid tumors; Hematological malignancies	Phase I–II
6		mobocertinib	EGFR	Non-small cell lung cancer	Revoked
7		saxagliptin	DPP4	Diabetes mellitus type 2	Revoked

Since the goal of this study was to evaluate off-target toxicity, further analysis was focused on the five identified compounds (Table 2); their primary mechanisms of action in the treatment of the diseases studied in clinical trials were not mediated by EGFR or DPP4. Currently no data on experimental testing of the identified compounds against the two analyzed targets are available in PubChem. Mobocertinib and saxagliptin, added as controls to the analyzed structures, were also detected using the fragments we constructed.

The four identified compounds (**1**–**4**) can potentially inhibit EGFR. Since this type of tyrosine kinase receptor is a therapeutic target in the treatment of a number of malignancies (particularly non-small cell lung cancer), it is important to note that these compounds are studied not only as antineoplastic agents (compound **2**) but also as immunosuppressants.

Compounds **1** and **2** are being developed for the treatment of rheumatoid arthritis. Although some authors (e.g., [14]) report the potential of EGFR inhibitors for the treatment of autoimmune arthropathies, there are currently no drugs with a similar mechanism of action approved for this pathological condition [15]. In this context, we believe that the EGFR may be considered an undesirable target for molecules **1** and **2**. Given the wide range of EGFR-associated adverse reactions that may negatively impact the benefit-risk ratio, we suggest that the development of these drugs will be discontinued or their use will be limited to a specific patient population failing standard therapies.

Compounds **3** and **4** are being studied for the treatment of atopic dermatitis. The presence of fragments highly specific for EGFR inhibitors in the structural formulas of these molecules, identified through our analysis, suggests that the development of compounds **3** and **4** may be discontinued due to the emergence of dermatological ARs or disease worsening.

Compound **5**, considered as a drug candidate for the treatment of various malignancies, can inhibit DPP4. According to existing *in vivo* data, inhibition of this enzyme correlates with stimulation of primary tumor growth and activation of metastatic processes [16]. It should be noted that in 2016, the US Food and Drug Administration issued a warning that DPP4 inhibitors caused severe joint pain, which could lead to patient disability [17]. Therefore, further development of compound **5** as an antitumor agent will likely be discontinued.

CONCLUSIONS

Thus, the results of our analysis suggest that further study of the five studied pharmaceutical substances will likely be suspended due to their potential interaction with at least one undesirable target associated with the development of adverse reactions that alter the benefit/risk ratio. Conducting such analysis at the preclinical stages of the drug research and development process would avoid the study of drugs unsafe for these pharmacotherapeutic areas and reduce the overall financial and time costs of development, as well as potential risks to patients and the healthcare system. It should be emphasized that this study has several limitations, primarily related to the need for experimental confirmation of the theoretical conclusions.

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COMPLIANCE WITH ETHICAL STANDARDS

This article does not contain any research involving humans or the use of animals as objects.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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ПРОГНОЗ ПОТЕНЦИАЛЬНЫХ НЕЖЕЛАТЕЛЬНЫХ ЛЕКАРСТВЕННЫХ РЕАКЦИЙ С ИСПОЛЬЗОВАНИЕМ ВЫСОКОСПЕЦИФИЧНЫХ СТРУКТУРНЫХ ФРАГМЕНТОВ

П.И. Савосина*, Д.А. Филимонов, Д.С. Дружиловский

Научно-исследовательский институт биомедицинской химии имени В.Н. Ореховича,
112191, Москва, Погодинская ул., 10; *эл. почта: polina.savosina@ibmc.msk.ru

Использование *in silico* подходов для оценки потенциальных нежелательных реакций новых фармацевтических субстанций позволяет уменьшить риски, а также финансовые и временные затраты, связанные с разработкой лекарственных средств. С помощью разработанного нами ранее метода выявления химических мотивов, ассоциированных с определёнными типами нежелательной биологической активности, мы оценили "*off-target*" токсичность клинически исследуемых фармацевтических субстанций, чтобы оценить потенциальные риски их дальнейшего исследования и использования в клинической практике. Для этого созданы структурные фрагменты, высокоспецифичные для ингибиторов рецептора эпидермального фактора роста и дипептидилпептидазы 4 — двух молекулярных мишеней, ассоциированных с широким спектром нежелательных реакций. Проведён поиск соединений, содержащих созданные фрагменты, среди 12070 записей базы данных PubChem, содержащих информацию о проведении клинических испытаний. Показано, что пять соединений, исследуемых в фазах I и II, могут обладать неблагоприятным соотношением "польза-риск", возникающим из-за потенциального ингибирования одного из двух анализируемых ферментов. Применение подобных аналитических стратегий на ранних доклинических этапах разработки может значительно снизить совокупные финансовые и временные затраты, способствуя ускоренному выводу на рынок более безопасных и доступных лекарственных средств.

Полный текст статьи на русском языке доступен на сайте журнала (http://pbmc.ibmc.msk.ru).

Ключевые слова: *in silico* исследования; нежелательные молекулярные мишени; "*off-target*" токсичность; структурные фрагменты; нежелательные реакции

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