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Evaluation of Pheniramine Hydrogen Maleate in the Context of Drug Repositioning: Could an Innocent Histaminic be a Novel Hope?

Esra TANYEL AKÇİT[*1,2,4], Ece ŞİMŞEK[1,3,4]

[1]*Akdeniz University Tuberculosis Research Center, Antalya, Turkey, esratanyel@akdeniz.edu.tr*
[2]*Akdeniz University Vocational School of Health Services, Antalya, Turkey,*
[3]*Akdeniz University, Faculty of Health Sciences, Department of Nutrition and Dietetics, Antalya, Turkey.*
[4]*Department of Medical Biotechnology, Akdeniz University Institute of Health Sciences, Antalya, Turkey.*

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ABSTRACT

Objective: Antihistamines are excellent candidates for drug repositioning in cancer treatment as they are safe drugs that are well tolerated and have minimal side effects. We aimed to demonstrate the effects of Pheniramine Hydrogen Maleate (FHM) on non-small cell lung carcinoma (NSCLC) in the context of drug repositioning.

Method: The similarity of FHM to other cancer drugs in the context of drug repositioning in NSCLC treatment was investigated with the web server DrugCentral2023.org. The possible apoptotic effects of the drug and the interaction between FasLR and FHM in the extrinsic pathway were evaluated in silico.

Findings: FHM, which has very low toxicity, is similar to cancer drugs in the context of drug repositioning. According to the analysis of molecular docking results, there are three different chemical interactions.

Conclusion: It is thought that the possible effects of FHM, which has very low toxicity, will lead to new in vitro and in vivo studies in the context of drug repositioning.

1. Introduction

Pheniramine Hydrogen Maleate is an antihistamine that binds to H1 receptors and has vasodilating properties. Although it has low side effects, it is easily accessible and inexpensive [1-3]. Therefore, it is the most widely used class. The aim of our study is to reveal the anti-cancer potential of FHM, an H1 receptor antagonist that is frequently used in allergy treatment within the scope of drug repositioning, through in silico analyses. The main aim of drug repositioning is to determine whether drugs with known side effects and metabolic profiles can be used in the treatment of different diseases [4-6].

When considered in terms of cancer, many different drugs are evaluated within the scope of repositioning. As a result of literature research, it has been determined that some anti-allergic drugs have anti-cancer potential [4]. However, to date, the effect of pheniramine hydrogen maleate on lung cancer has never been investigated.

Lung cancer is the second most common cancer and the leading cause of cancer-related deaths [7]. The majority (80%) of lung cancer cases belong to the non-small cell lung carcinoma (NSCLC) subtype. NSCLC is highly resistant to treatment due to its heterogeneity and plasticity of cancer stem cells [4, 7, 8].

Therefore, in our study, within the scope of drug repositioning to treat NSCLC, the similarity rate of pheniramine hydrogen maleate to existing chemotherapeutics was determined by the L1000 gene profile similarity analysis in the Drug Central 2023 web server. DrugCentral.org is an online resource that provides comprehensive information about medications and their interactions. DrugCentral.org contains a database of more than 20,000 drugs that can be searched by name, chemical structure, or target [9-11]. The RMSD value, which is frequently used to detect drug similarities within the scope of drug repositioning, must be below 1. In this way, it is aimed to reveal potential new drugs that can be studied in this field by creating tables containing drugs with RMSD values below 1. Using this database, 13216 drugs similar to FHM were tabulated, and among these drugs, 213 drugs were determined to be similar to anticancer drugs. DrugCentral.org is updated regularly to reflect the latest research and regulatory information.

In the other stage of our in silico study, the interaction of the drug with the FasL Receptor, one of the death receptors in the extrinsic pathway of apoptosis, was investigated by the molecular docking method. It has been shown that pheniramine hydrogen maleate can initiate exogenous apoptosis signaling within the cell by changing the three-dimensional conformation of the protein.

2. Material And Method

2.1 DrugCentral 2023

The similarities of pheniramine hydrogen maleate to other chemotherapeutics were determined by L1000 gene profile similarity analysis on the Drug Central 2023 web server [11].

Scanning on the DrugCentral.org website:

Using the search section at the top of the home page, our drug was searched by chemical structure or target. DrugCard page has been opened for pheniramine maleate. The DrugCard page provides important information about the drug, including its mechanism of action, pharmacology, indications, and approved formulations. Related publications and external resource links are also available. The potential drug-target interaction database will be used for pheniramine maleate, and the drug-drug interaction section was used to evaluate potential drug interactions. In this analysis, RMSD (Root Mean Square Deviation) values were used to determine the similarity value of the drug. Drugs with RMSD values below 1 and anticancer drugs among them were identified and tables were prepared [9, 11].

In the Pheniramine Maleate similarity analysis, 13106 drugs with RMSD (Root Mean Square Deviation) value below 1 were tabulated. Among these, those with RMSD values closest to 1 (213 drugs) were selected. The diseases for which 213 drugs were used were investigated and a table was created. Using this table, another data table was created containing anticancer drugs with a high similarity rate to pheniramine hydrogen maleate (RMSD value closest to 1).

2.2 Determination of the interaction between Fas Ligand Receptor and Pheniramine maleate by molecular docking method

2.2.1 Preparation of Ligand Structure

The molecular structure of pheniramine maleate, whose effect will be investigated within the scope of the thesis project, was accessed from PubChem. (Fig. 1) [1, 12]

The ligand was subjected to energy minimization to ensure that it was in the appropriate starting position before docking.

1. mmff94, one of the Force Field calculation methods, was used.

2. Conjugate Gradients was used for the optimization algorithm.

2.2.2 Preparation of Receptor Protein for Molecular Docking

The molecular structure of the receptor protein (Fas ligand receptor) whose possible interaction with pheniramine maleate will be investigated was obtained from the Protein Data Bank database. (Fig. 2) [13].

After downloading the Fas ligand receptor protein from the Protein Data Bank with the relevant PDB code, it was prepared in the Chimera 1.17.1 program before the docking study [14].

These stages are:

1. Purification of protein from heteroatoms and water molecules,

2. Adding hydrogen atoms since hydrogen atoms are missing in the PDB files,

3. Calculation of the net charge of atoms using the AM1-BCC algorithm.

3. RESULTS

The similarities of pheniramine hydrogen maleate to other chemotherapeutics were determined by L1000 gene profile similarity analysis on the Drug Central 2023 web server. In the Pheniramine Maleate similarity analysis, 13106 drugs with RMSD (Root Mean Square Deviation) value below 1 were tabulated. Among these, those with RMSD values closest to 1 (213 drugs) were selected. The diseases for which 213 drugs were used were investigated and a table was created. (Table1, Table 2) Using this table, another data table was created containing anticancer drugs with a high similarity rate to pheniramine hydrogen maleate (RMSD value closest to 1).

Among the objectives of the project are;
1. Is Pheniramine Maleate similar to other drugs used today?

2. In what other diseases might this similarity be potential for use in terms of drug repositioning?

The answers to the questions were reached with the results of Table 1 and Table 2. Based on the results obtained in Table 2, in order to investigate the usability of pheniramine hydrogen maleate in the treatment of lung cancer, its interaction with FasL Receptor, one of the death receptors in the extrinsic pathway of apoptosis, was demonstrated in silico by molecular docking method.

Fig. 1 PubChem ID: 4761.

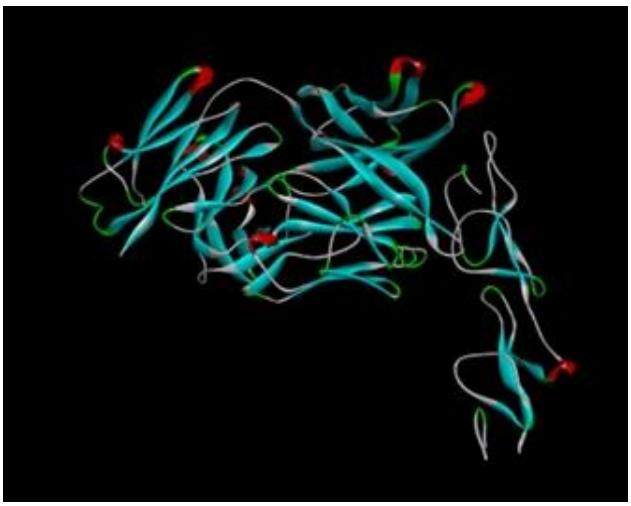

Fig. 2 Fas ligand receptor three-dimensional structure, PDB code: 1DDF

3.1 Ligand/Protein Molecular Docking Study

Fas ligand receptor and pheniramine hydrogen maleate interaction in the extrinsic pathway of apoptosis. It was done using AutoDock Vina software. The best binding position was selected and recorded according to binding affinity (kcal/mol). The interaction between Fas ligand receptor andpheniramine maleate was analyzed and visualized in the BIOVIA Discovery Studio Visualizer program. The relationship between Fas ligand receptor and pheniramine maleate is best illustrated in two different figures, Fig. 3 and Fig. 4.

The interaction between Fas ligand receptor and pheniramine maleate was analyzed by selecting the docking pose with the best binding affinity (-6.2 kcal/mol) from 10 different binding poses. According to the analysis of molecular docking results, there are three different chemical interactions. These are van der Waals, pi-alkyl and hydrogen bonds. It binds to the 3rd active site of Phenirmanin's receptor protein. This may initiate an exogenous apoptosis signal within the cell by changing the three-dimensional conformation of the protein.

4. DISCUSSION

In our study, the similarities of Pheniramine maleate with other drugs were investigated for the first time in silico within the scope of drug repositioning. There is no such data in the literature. While there is no research on lung cancer of Pheniramine Maleate, an anti-allergic drug, in the literature, the effect of chlorpheniramine on breast and colon cancers has been investigated [15]. No study investigating its effect has been found. In addition, the interaction of Pheniramine maleate, which we have shown can lead cancer cells to death via the apoptosis pathway, with the FasL Receptor, which is involved in the extrinsic pathway of apoptosis, were also evaluated in silico. There are no in silico studies on this interaction, and our study is quite unique in these aspects. Lung cancer treatment is based on surgical interventions, radiotherapy, chemotherapy and immunotherapy. NSCLC, which accounts for 80% of lung cancers, is highly resistant to treatments. Combination treatments cause numerous side effects, such as cytotoxicity, cognitive difficulties, nerve damage and osteoporosis, and also increase the risk of other cancers in patients.

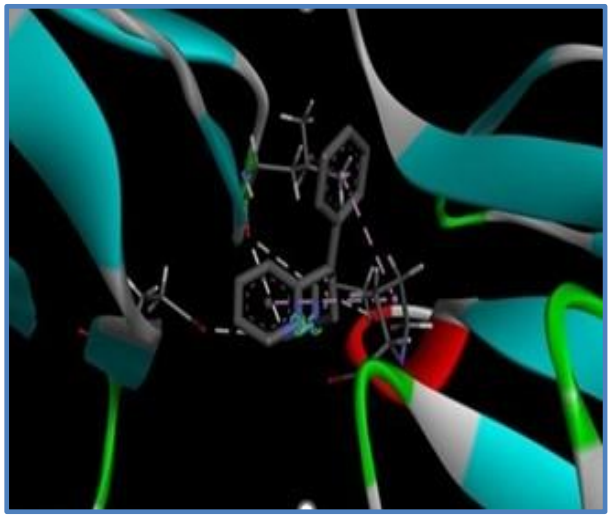

Fig. 3 Interaction between Fas ligand receptor and pheniramine maleate I

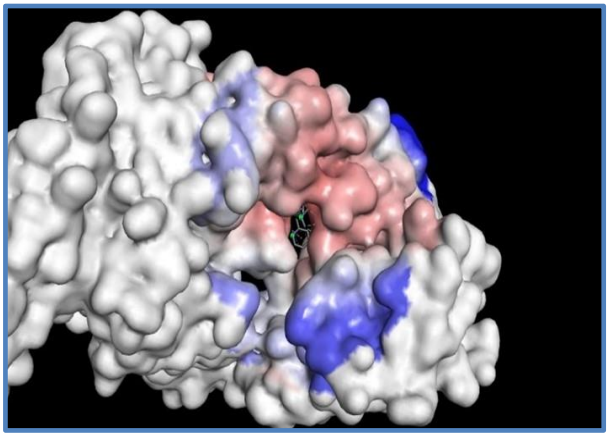

Fig. 4 Interaction between Fas ligand receptor and pheniramine maleate II.

5 CONCLUSION

Within the scope of drug repositioning, the use of low-toxicity, low-cost, and highly accessible antihistamines for new purposes outside their original indication opens the way for a new investigational drug to be submitted for use in a much shorter time than the application process. Pheniramine hydrogen maleate, which is easily and cheaply accessible and has low toxicity, may provide treatment options with low cost and side effects. There may be a possibility of synergistic or additive effects and increased treatment success as a result of combined use with chemotherapy drugs or future modern immunotherapeutic agents.

Declaration

Author Contribution: Conceive– E.Ş.; Design– E.Ş.; Supervision- E.Ş.; Experimental Performance, Data Collection and Processing– E.T.A.; Analysis and Interpretation– E.T.A.; Literature Review– E.T.A.; Writer– E.T.A.; Critical Review– E.Ş.

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Orcid-ID

Esra TANYEL AKÇİT https://orcid.org/0000-0003-0561-7440

Ece ŞİMŞEK https://orcid.org/0000-0002-7642-6601

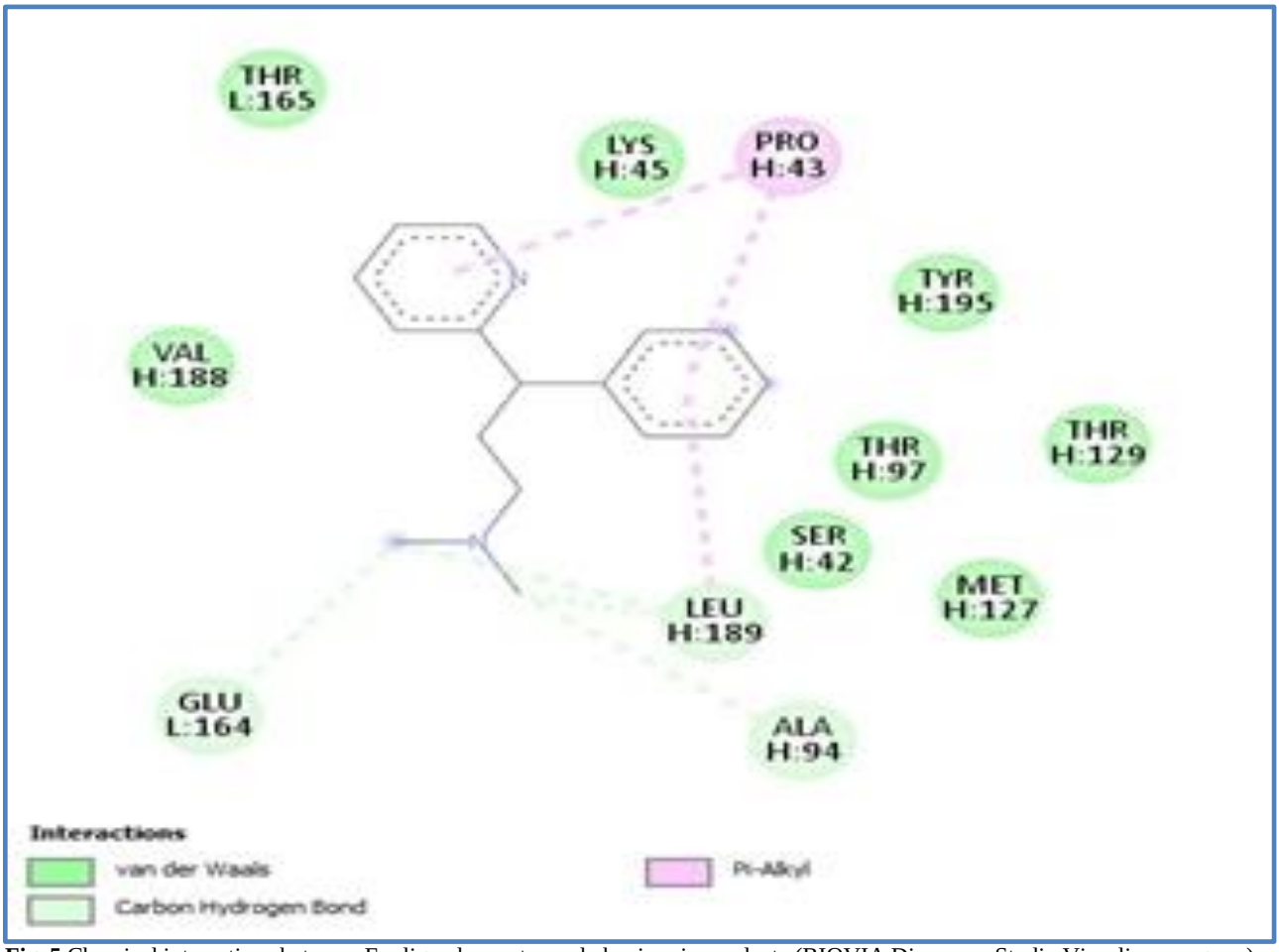

Fig. 5 Chemical interactions between Fas ligand receptor and pheniramine maleate (BIOVIA Discovery Studio Visualizer program).

Table 1. Pheniramine Maleate similarity analysis, 13106 drugs with RMSD (Root Mean Square Deviation) value below 1 were tabulated.

Drug1	Drug2	cell_id	RMSD <1	DİSEASE
pheniramine	acadesine	HT29 (human colorectal adenocarcinoma cell line)	0,963820319911241	Cardiac
pheniramine	acamprosate	HT29 (human colorectal adenocarcinoma cell line)	0,927763556326971	Alcoholism treatment
pheniramine	acepromazine	SKB (human breast cancer cell line)	0,912244052705288	anti psychotic(on cat and dogs)
pheniramine	acitretin	SKB (human breast cancer cell line)	0,935392590859814	Psoriasis
pheniramine	amantadine	PHH (Primary human hepatosite cell line)	0,919565417535444	Parkinson's disease
pheniramine	amantadine	SKB (human breast cancer cell line)	0,98390182399772	Parkinson's disease
pheniramine	diflorasone	HT29 (human colorectal adenocarcinoma cell line)	0,928400543748483	Eczema treatment (gel)
pheniramine	diflorasone	SKB (human breast cancer cell line)	0,854344834400255	Eczema treatment (gel)
pheniramine	cyproterone	HT29 (human colorectal adenocarcinoma cell line)	0,961224752426759	Prostate cancer
pheniramine	cyproterone	SKB (human breast cancer cell line)	0,900562581599442	Prostate cancer
pheniramine	amoxapine	SKB (human breast cancer cell line)	0,932055562818658	Anti-depressant
pheniramine	amperozide	SKB (human breast cancer cell line)	0,994456614878384	Anti-depressant
pheniramine	anagrelide	SKB (human breast cancer cell line)	0,934602804256589	Thrombocytosis treatment
pheniramine	aprepitant	SKB (human breast cancer cell line)	0,991255193146871	nausea and vomiting treatment due to chemotherapy
pheniramine	Beclometasone dipropionate	SKB (human breast cancer cell line)	0,980565284797261	Hay fever
pheniramine	diphenidol	SKB (human breast cancer cell line)	0,897905309954721	Vertigo
pheniramine	bifemelane	SKB (human breast cancer cell line)	0,939117095673908	Glaucoma treatment
pheniramine	brinzolamide	A375 (human melanoma cellline)	0,959551444298766	Glaucoma treatment

pheniramine	bromhexine	SKB (human breast cancer cell line)	0,991947340660171	Bronchitis
pheniramine	brompheniramine	SKB (human breast cancer cell line)	0,996529680895028	Antihistamine drug
pheniramine	budesonide	SKB (human breast cancer cell line)	0,909933932596511	Asthma disease treatment
pheniramine	calcifediol	HT29 (human colorectal adenocarcinoma cell line)	0,994322335121046	Rickets disease treatment
pheniramine	calcifediol	PHH (Primary human hepatosite)	0,876293080582817	Rickets disease treatment
pheniramine	Potassium canrenoate	SKB (human breast cancer cell line)	0,955251082472298	Antimineralocorticoids
pheniramine	captopril	A375 (human melanoma cellline)	0,886417925672091	Hypertension disease treatment
pheniramine	carprofen	SKB (human breast cancer cell line)	0,906949067976907	NSAID (Non steroidal anti-inflammatory drug)
pheniramine	cefixime	SKB (human breast cancer cell line)	0,966544252165879	Antibiotics
pheniramine	chlortalidone	ASC (Human adipose derived mesenchymal stromal cells)	0,974087572625822	Hypertension disease treatment
pheniramine	cianidanol	NPC (*nasopharyngeal carcinoma*)	0,972246070999782	Antioxidants
pheniramine	cyclacillin	A375 (human melanoma cellline)	0,973674196593785	Antibiotics
pheniramine	cyclacillin	NPC (*nasopharyngeal carcinoma*)	0,980211021926477	Antibiotics
pheniramine	cinalukast	A375 (human melanoma cellline)	0,987137263278188	Antitussive
pheniramine	clomipramine	SKB (human breast cancer cell line)	0,944843969470393	Anti-depressant
pheniramine	cortisoneacetate	HT29 (human colorectal adenocarcinoma cell line)	0,952629738019276	Allergy, asthma disease treatment
pheniramine	dantrolene	SKB (human breast cancer cell line)	0,961694546089914	Myorelaxant
pheniramine	decitabine	SKB (human breast cancer cell line)	0,824388778512362	Acute myeloblastic leukemia
pheniramine	dexbrompheniramine	HT29 (human colorectal adenocarcinoma cell line)	0,962935749451523	Antihistamine drug
pheniramine	dexrazoxane	SKB (human breast cancer cell line)	0,973439584870013	Cardiomyopathy
pheniramine	dibenzepin	PHH (Primary human hepatosite)	0,994323349986455	Anti-depressant
pheniramine	dibenzepin	SKB (human breast cancer cell line)	0,970925122651809	Anti-depressant
pheniramine	dienestrol	NPC (*nasopharyngeal carcinoma*)	0,993490398859377	Vajinitis treatment (gel)
pheniramine	diethylcarbamazine	SKB (human breast cancer cell line)	0,97905880221001	Antihelminthic
pheniramine	diethylstilbestrol	PHH (Primary human hepatosite)	0,954088664878072	Breast cancer treatment
pheniramine	diflunisal	PHH (Primary human hepatosite)	0,946912364238691	NSAID (Non steroidal anti-inflammatory drug)
pheniramine	dihydroergotamine	SKB (human breast cancer cell line)	0,956674799754249	Migraine treatment
pheniramine	hydroquinidine	NPC (*nasopharyngeal carcinoma*)	0,981238730501147	Antiarryhthmic
pheniramine	diloxanidefuroate	SKB (human breast cancer cell line)	0,964687340986471	Amebiasis treatment
pheniramine	dipyridamole	SKB (human breast cancer cell line)	0,999599075609962	PD3 (phosphodiesterase enzyme) inhibitör
pheniramine	domperidone	SKB (human breast cancer cell line)	0,957526753397385	nausea and vomiting treatment, dophamine antagonist
pheniramine	doxylamine	PHH (Primary human hepatosite)	0,966713112827767	Antihistamine drug
pheniramine	enalapril	SKB (human breast cancer cell line)	0,907207445741154	Hypertension disease treatment
pheniramine	entecavir	SKB (human breast cancer cell line)	0,852163797553335	Antiviral
pheniramine	epirizole	SKB (human breast cancer cell line)	0,987419609839175	NSAID (Non steroidal anti-inflammatory drug)
pheniramine	ergometrine	PHH (Primary human hepatosite)	0,979266901243717	Uterotonic
pheniramine	erlotinib	PHH (Primary human hepatosite)	0,966347817686741	EGFR (epidermal growth factor inhibitor) inhibitor for lung cancer
pheniramine	erlotinib	SKB (human breast cancer cell line)	0,922057332235376	EGFR (epidermal growth factor inhibitor) inhibitor for lung cancer
pheniramine	erythromycin	PHH (Primary human hepatosite)	0,996806011393324	Antibiotics
pheniramine	etamivan	SKB (human breast cancer cell line)	0,950501200016335	Respiratory stimulant
pheniramine	etomidate	SKB (human breast cancer cell line)	0,954867344651868	General anesthetic
pheniramine	febuxostat	ASC (Human adipose derived mesenchymal stromal cells)	0,979989472968449	Gut Disease

pheniramine	febuxostat	SKB (human breast cancer cell line)	0,968198361233013	Gut Disease
pheniramine	fenbufen	SKB (human breast cancer cell line)	0,979471609305622	NSAID (Non steroidal anti-inflammatory drug)
pheniramine	fenoldopam	SKB (human breast cancer cell line)	0,971526038810391	Hypertension disease treatment
pheniramine	flavoxate	PHH (Primary human hepatosite)	0,941709441749173	Urinary tract infection, anticholinerjic
pheniramine	fluconazole	SKB (human breast cancer cell line)	0,90931588372935	Antifungal
pheniramine	fluocinonide	A375 (human melanoma cell line)	0,970214814657418	Antibiotics (gel)
pheniramine	flupentixol	ASC (Human adipose derived mesenchymal stromal cells)	0,967512940326787	Antipsychotic
pheniramine	gamolenicacid	HT29 (human colorectal adenocarcinoma cell line)	0,896028074764903	Auto-immune disease treatment
pheniramine	gamolenicacid	PHH (Primary human hepatosite)	0,949876928683009	Auto-immun disease treatment
pheniramine	glipizide	SKB (human breast cancer cell line)	0,993939354182189	Antidiabetics
pheniramine	gliquidone	SKB (human breast cancer cell line)	0,969939818724588	Antidiabetics
pheniramine	glibenclamide	SKB (human breast cancer cell line)	0,998334871172216	Antidiabetics
pheniramine	hexylcaine	ASC (Human adipose derived mesenchymal stromal cells)	0,997423302922626	Lokal anesthetic agent
pheniramine	hexylcaine	HT29 (human colorectal adenocarcinoma cell line)	0,935798589173157	Lokal anesthetic agent
pheniramine	hexylcaine	SKB (human breast cancer cell line)	0,842783926422538	Lokal anesthetic agent
pheniramine	hydralazine	A375 (human melanoma cell line)	0,983348122603697	Hypertension disease treatment
pheniramine	hydralazine	SKB	0,997445267591434	Hypertension disease treatment
pheniramine	iloprost	SKB (human breast cancer cell line)	0,997366548333309	Kardiyoloji
pheniramine	imatinib	SKB (human breast cancer cell line)	0,932353932569442	Chronic myeloid leukemia(KML) and gastro intestinal stromal tumor (GIST) treatment
pheniramine	iobenguane	A375 (human melanoma cell line)	0,995168852141928	Radiopharmaceutical agent used for the diagnosis of primary and metastatic pheochromocytoma or neuroblastoma.
pheniramine	adipiodone	HT29 (human colorectal adenocarcinoma cell line)	0,988090300164754	Radiocontrast
pheniramine	ipratropium	SKB (human breast cancer cell line)	0,978095420238455	Anticholinerjic
pheniramine	iproniazid	HT29 (human colorectal adenocarcinoma cell line)	0,911598831565507	Tuberculosis treatment/anti-depressant
pheniramine	isocarboxazid	A375 (human melanoma cell line)	0,997211682818826	Anti-depressant
pheniramine	ketoprofen	SKB (human breast cancer cell line)	0,946536689957589	NSAID (Non steroidal anti-inflammatory drug)
pheniramine	ketotifen	SKB (human breast cancer cell line)	0,912647962522652	Allergic conjunctivitis, rhinitis
pheniramine	lamotrigine	SKB (human breast cancer cell line)	0,89197430077901	Epilepsy
pheniramine	lidocaine	SKB (human breast cancer cell line)	0,967208764926106	Lokal anesthetic
pheniramine	lopinavir	PHH (Primary human hepatosite)	0,991393330440707	Antiviral
pheniramine	lovastatin	PHH (Primary human hepatosite)	0,994144534687665	Hyperlipidemia treatment
pheniramine	mebendazole	SKB (human breast cancer cell line)	0,926734211677001	Antihelminthic
pheniramine	mebeverine	SKB (human breast cancer cell line)	0,921458509000701	Anti-spasmodic
pheniramine	mefenamicacid	HT29 (human colorectal adenocarcinoma cell line)	0,907266798121157	NSAID (Non steroidal anti-inflammatory drug)
pheniramine	meptazinol	SKB (human breast cancer cell line)	0,94476827084766	Opioid analgesic
pheniramine	mesna	HT29 (human colorectal adenocarcinoma cell line)	0,976233790208727	Akrolein toxicity prevention (Anti-hemorrhagic effect)
pheniramine	methocarbamol	SKB (human breast cancer cell line)	0,958910757955399	Myorelaxant
pheniramine	levomepromazine	HT29 (human colorectal adenocarcinoma cell line)	0,98059807406431	Antipsychotic
pheniramine	levomepromazine	SKB (human breast cancer cell line)	0,981824510022927	Antipsychotic
pheniramine	naltrexone	PHH (Primary human hepatosite)	0,969804436585295	Opioid antagonist
pheniramine	metoclopramide	SKB (human breast cancer cell line)	0,962152903420139	Anti-emetic
pheniramine	metolazone	PHH (Primary human hepatosite)	0,962514977521194	Hypertension treatment
pheniramine	metolazone	SKB (human breast cancer cell line)	0,979298602893975	Hypertension treatment

pheniramine	milrinone	SKB (human breast cancer cell line)	0,8836609002174	Heart failure treatment, pulmonary vasodilator
pheniramine	minoxidil	SKB (human breast cancer cell line)	0,816867388315864	Vasodilator, Alopesia treatment
pheniramine	moexipril	PHH	0,94573538440688	Hypertension disease treatment
pheniramine	mofezolac	HT29 (human colorectal adenocarcinoma cell line)	0,997052769910245	NSAID (Non steroidal anti-inflammatory drug)
pheniramine	mofezolac	SKB humanbreastcancer ***cellline)***	0,914468679672862	NSAID (Non steroidal anti-inflammatory drug)
pheniramine	moxifloxacin	PHH (Primary human hepatosite)	0,999587205270273	Antibiotics
pheniramine	moxifloxacin	SKB (human breast cancer cell line)	0,954019775379673	Antibiotics
pheniramine	moxonidine	SKB (human breast cancer cell line)	0,983359877894116	Hypertension disease treatment
pheniramine	Mycophenolate mofetil	SKB (human breast cancer cell line)	0,950387907741471	inhibitor of inosine monophosphate dehydrogenase (IMPDH) after transplantation treatment
pheniramine	naftifine	SKB (human breast cancer cell line)	0,987692662489018	Antifungal
pheniramine	nalbuphine	PHH (Primary human hepatosite)	0,875766304028576	Opioid analgesic
pheniramine	nemonapride	SKB (human breast cancer cell line)	0,942583147444197	Antipsychotic
pheniramine	niflumicacid	A375	0,895126888407559	Used for joint and muscular pain. İnhibitor of cyclooxygenase-2
pheniramine	nilutamide	SKB (human breast cancer cell line)	0,86488631461131	Non steroid antiandrogen (NSAA), prostat disease treatment
pheniramine	nitrendipine	PHH (Primary human hepatosite)	0,947690501957742	Hypertension disease treatment
pheniramine	nitrendipine	SKB (human breast cancer cell line)	0,917105345645007	Hypertension disease treatment
pheniramine	Nomegestrol acetate	PHH (Primary human hepatosite)	0,950452389475907	Progestine, hormonal treatment
pheniramine	Nomegestrol acetate	SKB (human breast cancer cell line)	0,985197092066234	Progestine, hormonal treatment
pheniramine	nomifensine	A375 (human melanoma cellline)	0,928891356276715	Anti-depressant
pheniramine	norepinephrine	A375 (human melanoma cellline)	0,985324787454125	Cathecolamine, cardiac stimulant
pheniramine	norethisterone	PHH (Primary human hepatosite)	0,905094839971219	Progestine, hormonal treatment
pheniramine	nortriptyline	SKB (human breast cancer cell line)	0,903872260164674	Anti-depressant
pheniramine	Olmesartan medoxomil	PHH (Primary human hepatosite)	0,950455891150867	Hypertension disease treatment
pheniramine	oxyphenonium	HT29 (human colorectal adenocarcinoma cell line)	0,948708611694995	Hypertension disease treatment
pheniramine	ozagrel	ASC (Human adipose-derivedmesenchymalstromalcells)	0,993342554841721	Hypertension disease treatment
pheniramine	ozagrel	SKB (human breast cancer cell line)	0,976720103586533	Hypertension disease treatment
pheniramine	papaverine	SKB (human breast cancer cell line)	0,953040640746795	Opioid alcholoid, vasodilatator
pheniramine	pargyline	HT29 (human colorectal adenocarcinoma cell line)	0,900649910138837	MAO (Monoamineoxidase inhibitör), Hypertension disease treatment, Anticancer
pheniramine	pargyline	SKB (human breast cancer cell line)	0,88342428381051	MAO (Monoamineoxidase inhibitör), Hypertension disease treatment, Anticancer
pheniramine	benzylpenicillin	SKB (human breast cancer cell line)	0,940169175391692	Antibiotics
pheniramine	pergolide	SKB (human breast cancer cell line)	0,97588395021652	Parkinson disease, dopamin receptor agonist
pheniramine	perindopril	SKB (human breast cancer cell line)	0,922491975339191	Hypertension disease treatment, ACE inhibitör
pheniramine	phenolphthalein	SKB (human breast cancer cell line)	0,966322038068337	Acide-base indicator
pheniramine	phenprobamate	A375 (human melanoma cellline)	0,950996083518006	Myorelaxant
pheniramine	phenylbutazone	HEPG2 (human hepatoblastoma ***cell line)***	0,974397102080652	NSAID (Non steroidal anti-inflammatory drug)
pheniramine	phenylbutazone	SKB (human breast cancer cell line)	0,900022770891639	NSAID (Non steroidal anti-inflammatory drug)
pheniramine	pioglitazone	SKB (human breast cancer cell line)	0,978342101617962	Antidiabetics
pheniramine	piretanide	SKB (human breast cancer cell line)	0,916992694591943	Diuretic effect, Hypertension disease treatment
pheniramine	piroxicam	SKB (human breast cancer cell line)	0,949802226782579	NSAID (Non steroidal anti-inflammatory drug)
pheniramine	pivmecillinam	SKB (human breast cancer cell line)	0,998252771242736	Antibiotics
pheniramine	prilocaine	A375	0,921165913406514	Lokal anesthetic agent

pheniramine	procarbazine	SKB (human breast cancer cell line)	0,931628315534727	Chemotherapeutic
pheniramine	prochlorperazine	SKB (human breast cancer cell line)	0,906408408125889	Antipsychotic, antiemetic
pheniramine	progesterone	SKB (human breast cancer cell line)	0,91098672858592	Steroidal hormone
pheniramine	proguanil	SKB (human breast cancer cell line)	0,985823154486065	Malariasis treatment
pheniramine	propantheline	A375 (human melanoma cellline)	0,974593046772754	Anticholinergic
pheniramine	proparacaine	SKB (human breast cancer cell line)	0,937930945126989	Tophical anesthetics
pheniramine	raltegravir	SKB (human breast cancer cell line)	0,888740761037932	Antiretroviral drug
pheniramine	ranolazine	SKB (human breast cancer cell line)	0,885081872597479	Angina pectoris treatment
pheniramine	rescinnamine	A375 (human melanoma cellline)	0,952159296370914	Hypertension disease treatment, ACE inhibitör
pheniramine	retinol acetate	ASC (human adipose-derivedmesenchymalstromalcells)	0,985965500220748	Vitamine A derivate
pheniramine	rifabutin	SKB (human breast cancer cell line)	0,923281260298338	Antibiotics
pheniramine	rifampicin	ASC (human adipose-derivedmesenchymalstromalcells)	0,971424727082056	Antibiotics
Pheniramine	rifampicin	SKB (human breast cancer cell line)	0,991059882089887	Antibiotics
Pheniramine	rilmenidine	PHH (Primary human hepatosite)	0,967647781542643	Hypertension disease treatment
Pheniramine	rilmenidine	SKB (human breast cancer cell line)	0,974224601677978	Hypertension disease treatment
Pheniramine	riluzole	SKB (human breast cancer cell line)	0,860077379201122	Nöroprotektif, amiyotrofik lateral skleroz tedavisi
Pheniramine	spectinomycin	A375 (human melanoma cellline)	0,834226045288244	Antibiotics
pheniramine	spectinomycin	HT29 (human colorectal adenocarcinoma cell line)	0,944716979341433	Antibiotics
pheniramine	succimer	SKB (human breast cancer cell line)	0,914330091307863	Heavy metal chelator Poisoning treatment
pheniramine	talipexole	SKB (human breast cancer cell line)	0,855880497423026	Dopamine receptor agonist, Parkinson disease treatment
pheniramine	telmisartan	SKB (human breast cancer cell line)	0,902737749394558	Hypertension disease treatment, Angiotensine II receptor antagonisti
pheniramine	tenoxicam	SKB (human breast cancer cell line)	0,996678151592948	NSAID (Non steroidal anti-inflammatory drug)
pheniramine	terguride	PHH (Primary human hepatosite)	0,990477375989701	Dopamin receptor agonisti, Parkinson tedavisi
pheniramine	tetracycline	A375 (human melanoma cellline)	0,886034186955506	Antibiotics
pheniramine	tetracycline	HT29 (human colorectal adenocarcinoma cell line)	0,893970375781807	Antibiotics
pheniramine	sapropterin	HT29 (human colorectal adenocarcinoma cell line)	0,998777953648322	Phenylketonuria treatment
pheniramine	thalidomide	SKB (human breast cancer cell line)	0,976814262800346	İmmunsupressive
pheniramine	tolazamide	PHH (Primary human hepatosite)	0,923098791656448	Antidiabetics
pheniramine	tolazamide	SKB (human breast cancer cell line)	0,847738721291961	Antidiabetics
pheniramine	tolmetin	SKB (human breast cancer cell line)	0,864255689768057	NSAID (Non steroidal anti-inflammatory drug)
pheniramine	tranilast	SKB (human breast cancer cell line)	0,972245563110113	Antihistamine drug, antiallerjik
pheniramine	trazodone	SKB (human breast cancer cell line)	0,952650602003599	Anti-depressant
pheniramine	triamterene	SKB (human breast cancer cell line)	0,995624012478616	Hypertension disease treatment, diuretic effect
pheniramine	Trimetho benzamide	SKB (human breast cancer cell line)	0,999728247468265	Antiemetics
pheniramine	tropisetron	SKB (human breast cancer cell line)	0,929858582160402	Antiemetics, Serotonin reuptake inhibitör
pheniramine	vardenafil	SKB (human breast cancer cell line)	0,920174005295001	PDE5 inhibitor, sexual disfunction treatment
pheniramine	vecuronium	SKB (human breast cancer cell line)	0,89642544075679	Neuromusculer blocker, general anesthesia
pheniramine	venlafaxine	SKB (human breast cancer cell line)	0,944348252938032	Anti-depressant, Serotonin reuptake inhibitor
pheniramine	phytomenadione	A375 (human melanoma cellline)	0,935114152182444	Vitamine K1
pheniramine	warfarin	SKB (human breast cancer cell line)	0,832744974715946	Anti-coagulants, cardiac diseases
pheniramine	zoxazolamine	SKB (human breast cancer cell line)	0,976555056243225	Myorelaxant, Antisphasmodic
pheniramine	zuclopenthixol	ASC (human adipose derived mesenchymal stromal cells)	0,970537072949127	Antipsychotics
pheniramine	teicoplanin	HT29 (human colorectal adenocarcinoma cell line)	0,985325861585251	Antibiotics

pheniramine	cholicacid	SKB (human breast cancer cell line)	0,992381238251878	Bile acides
pheniramine	dantron	SKB (human breast cancer cell line)	0,998364403353832	Genotoxic, oral cavity diseases
pheniramine	diiodotyrosine	SKB (human breast cancer cell line)	0,875173210321952	Tiroid gland diseases
pheniramine	dioxybenzone	PHH (Primary human hepatosite)	0,920199723543189	UV barrier (Suntan cream)
pheniramine	lenalidomide	SKB (human breast cancer cell line)	0,936848453378204	Multiple myeloma treatment
pheniramine	meclocycline	HT29 (human colorectal adenocarcinoma cell line)	0,994333858192347	Antibiotics
pheniramine	meclocycline	SKB (human breast cancer cell line)	0,967476950417854	Antibiotics
pheniramine	naphazoline	PHH (Primary human hepatosite)	0,980823018194509	Decongestant
pheniramine	pentetrazol	SKB (human breast cancer cell line)	0,964381114638805	Proton pump inhibitör, Stomach ulcer treatment
pheniramine	roquinimex	SKB (human breast cancer cell line)	0,966532671328956	İmmune stimulant
pheniramine	tamibarotene	SKB (human breast cancer cell line)	0,991850851444739	Acute premyelocytic leukemia treatment
pheniramine	vincamine	SKB (human breast cancer cell line)	0,99155846055223	Cancer, Alzheimer disease etc treatment
pheniramine	benidipine	A375 (human melanoma cellline)	0,977100467118912	Hypertension disease Calcium channel blocker
pheniramine	oxantel	NPC (*nasopharyngeal carcinoma*)	0,985526564405556	Anti helminthic, Parasitosis treatment
pheniramine	oxantel	SKB (human breast cancer cell line)	0,973512812164931	Anti helminthic, Parasitosis treatment
pheniramine	pazopanib	SKB (human breast cancer cell line)	0,976252300056045	Chemotherapeutic, proteaz kinase inhibitör
pheniramine	rivaroxaban	SKB (human breast cancer cell line)	0,96671721059777	Anti trombotics, prevents blood clots
pheniramine	vemurafenib	SKB (human breast cancer cell line)	0,981854185931702	Melanoma disease treatment, B-RAF enzyme inhibitor
pheniramine	doconexent	ASC (human adipose derived mesenchymal stromal cells)	0,991912143721403	Omega 3 fatty acide
pheniramine	chenodiol	SKB (human breast cancer cell line)	0,990016034750319	Antilithic, bile acid
pheniramine	diethyltoluamide	SKB (human breast cancer cell line)	0,941318472034739	Anti-insecticide
pheniramine	fenbendazole	SKB (human breast cancer cell line)	0,950988778604334	Parasitosis treatment
pheniramine	Clocortolone pivalate	A375 (human melanoma cell line)	0,954420613754358	Corticosteroid
pheniramine	polydatin	A375 (human melanoma cell line)	0,954565468591877	Antioxidants
pheniramine	polydatin	HT29 (human colorectal adenocarcinoma cell line)	0,881759894444649	Antioxidants
pheniramine	alfadoloneacetate	SKB (human breast cancer cell line)	0,907881009355645	General Anesthesic agent

Table 2. Anticancer drugs with a high similarity rate to pheniramine hydrogen maleate (RMSD value closest to 1).

Drug1	Drug2	cell_id	RMSD <1	DISEASE
Feniramin	siproteron	HT29 (human colorectal adenocarcinoma cell line)	0,961224752426759	Prostat cancer
Feniramin	aprepitant	SKB (human breast cancer *cell line)*	0,991255193146871	Nausea and vomiting treatment due to chemotherapy
Feniramin	decitabine	SKB (human breast cancer *cell line)*	0,824388778512362	Acute myeloblastic leukemia
Feniramin	diethylstilbestrol	PHH (Primary human hepatosite)	0,954088664878072	Breast Cancer
Feniramin	erlotinib	PHH (Primary human hepatosite)	0,966347817686741	Lung cancer
feniramin	imatinib	SKB (human breast cancer *cell line)*	0,932353932569442	Chronic myeloid leukemia(KML) and gastro intestinal stromal tumor (GIST) treatment
feniramin	iobenguane	A375 (human melanoma cell line)	0,995168852141928	Adrenal gland and tyroid gland diseases treatment
feniramin	lenalidomide	SKB (human breast cancer *cell line)*	0,936848453378204	Multiple myeloma treatment
feniramin	tamibarotene	SKB (human breast cancer *cell line)*	0,991850851444739	Acute promyelositic leukemia treatment
feniramin	vincamine	SKB (human breast cancer *cell line)*	0,99155846055223	Cancer, Alzheimer disease etc. treatment
feniramin	vemurafenib	SKB (human breast cancer *cell line)*	0,981854185931702	Melanoma treatment, B-RAF enzyme inhibitor

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