ORIJINAL MƏQALƏ AÇIQ GİRİŞ (OPEN ACCESS)

IN SILICO STUDY TAURINE DEHYDROGENASE INHIBITOR ACTIVITY OF SOME ARYL-HYDRASONES OF α-KETOAETHERS

Konul F. Huseynguliyeva[1], Kamala K. Badalova[1], Abel M. Maharramov[2], Namiq Q. Shikhaliyev[4], Ayten M. Qajar[2], Khatira A. Garazadeh[2], Sahira R.Mammadova[3], Zunaira Akram[5], Abdur Rauf[6]

Abstract

Computer-Aided Drug Design has changed the drug development process by improving the pharmacodynamics, pharmacokinetics, and possible side effects. This study uses in silico techniques to assess the biological, pharmacokinetic and toxicological, properties of eight α-ketoether derivatives, including both Z- and E-isomers, synthesized through the solvolysis reaction of dichlorodiazadienes in methanol. This study provides a thorough in silico assessment of these derivatives using programs like SwissADME for physicochemical parameters, ProTox II for toxicity analysis, and PassOnline for biological activity predictions. Among the compounds studied, derivatives 5 (Z-isomer) and 6 (E-isomer) showed significant taurine dehydrogenase inhibitory activity, with a predicted activity value (Pa) of 0.694, indicating strong potential for further development. Moreover, toxicity estimations indicate that these compounds are most likely safe and unlikely to cause liver or cancer issues. According to pharmacokinetics, these derivatives are well-absorbed and are likely to cross the blood-brain barrier (BBB), which makes them strong candidates for neurological problems. In conclusion, the computational findings suggest that derivatives 5 and 6 could be employed in drug development by targeting taurine dehydrogenase because of their high effectiveness and safety.

Key words: In silico, PassOnline, SwissADME, Swiss TargetPrediction, ProTox-II, arylhydrozones of α-ketoesters

INTRODUCTION

Finding new therapeutic substances takes a complex process that includes laboratory research, clinical studies, and their use in medical care. Nonetheless, traditional drug development can take a long time, is costly, and often does not turn out as expected [[1], [2]]. Computational methods have allowed CADD to play an important role in drug discovery, as it speeds up the process of finding drugs that might be effective. By implementing new computational approaches, Computer-Aided Drug Design (CADD) has an important role in modern drug discovery by making it

© ATUJ and The Author(s) 2026. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to theoriginal author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of thislicence, visit http://creativecommons.org/licenses/by/4.0/.

easier to choose promising compounds [[3], [4]]. With help from CADD methods, including,virtual screening, and predictive modelling, researchers look into the biological impact, toxicity, and drug effects of compounds before starting any tests, helping to reduce the costs and time needed for drug development [[5], [6]].

Potentially a class of eight different therapeutic compounds known as α-ketoether derivatives (Table 1), have been discovered after the solvolysis reaction of dichlorodiazadienes in methanol (Figure 1). These compounds, including both Z- and E-isomers, exhibit diverse biological activities, making them suitable candidates for in-depth investigation in drug design [7].

Yazışma üçün əlaqə:
Konul F. Huseynguliyeva1, Kamala K. Badalova1, Abel M. Maharramov2, Namiq Q. Shikhaliyev4, Ayten M. Qajar2, Khatira A. Garazadeh2, Sahira R.Mammadova3, Zunaira Akram5, Abdur Rauf6
1Azerbaijan Medical University, Department of Pharmaceutical toxicology and chemistry, Baku, Azerbaijan
2Baku State University, Department of Organic Chemistry, Baku, Azerbaijan
3Azerbaijan Medical University, Department of Radiology, Baku, Azerbaijan
4Baku Engineering University, Department of Chemical Engineering, Baku, Azerbaijan
5Department of Pharmacology, Faculty of Pharmaceutical Sciences, Baqai Medical University, Karachi, Pakistan
6Department of Chemistry, University of Swabi, Swabi, Anbar, Khyber Pakhtunkhwa, Pakistan
Email: kamala.badalova@mail.ru

Each newly created chemical compound must serve the well-being of people by identifying its potential area of application in the future. Often, these applications involve using chemicals for humans, as they are part of chemical or pharmaceutical industries, or for analyzing and synthesizing things, including drugs. The safety of new chemicals is always the main concern in any discipline [[8], [9]]. If the compounds do not possess hazardous properties, their possible toxicity to the human body must be explored. Following the results, their toxicity class must be determined by using the Hodge and Sterner scale [10]. Industrial production of compounds with low toxicity is permitted.

Historically, scientists checked the possible harm of new chemicals by analyzing their impact on laboratory animals. Nevertheless, the introduction of REACH (Registration, Evaluation and Authorization of Chemicals) has resulted in greater use of methods conducted outside of living organisms to address both morality issues and high costs linked to animal experiments [[11], [12]]. Testing of large chemical quantities (≥10 tons) is prescribed by these new measures, and *in vitro* studies are needed to assess any dangers to human health [13].

Substances with few toxins and strong biological activities may be considered useful for health treatment in humans. The process, called drug design, is used to develop biologically active chemicals into usable medicines. Using traditional ways to discover new drugs often takes time and costs a lot of money. As a

consequence, virtual screening, which forms part of the *in silico* approach, is now widely used [14]. Thanks to these methods, it is possible to recognise drug candidates faster and more accurately while saving time and costs [5]. One important part of bioinformatics is Computer-Aided Drug Design (CADD), which combines biology, computer skills, and statistics. With the help of algorithms and modelling, it can show how ligands attach to bigger protein molecules, giving useful information about their efficacy and effectiveness in medicine.

The first discovery of taurine happened in 1827 when it was found in a bull's bile (the term Taurus was inspired by the bull). Taurine is not found in the group of amino acids contained in protein. It is well known that taurine (2-aminoethanesulfonic acid) is one of the ‘‘semi-essential’’ amino acids, as it consists of an amino plus sulphur framework and is mainly produced in the liver and kidneys from cysteine and methionine. Taurine can be seen in the retina, brain and spinal cord, heart, and placenta and has numerous functions in the body. Taurine protects organs from damage inflicted by inflammation and oxidative stress in model experiments. Taurine regulates processes like endoplasmic reticulum stress, Ca^{2+} levels, and activity of neurons in the body at the molecular level. Taurine influences different functions in cells, such as metabolizing energy, controlling gene activity, adjusting fluid levels, managing protein quality, and linking bile acids to other molecules. Notably, research has revealed that taurine may provide positive effects in the treatment of nervous system-related problems such as neurodegenerative disorders, stroke, epilepsy, diabetic nerve damage, and other neurological problems [[15], [16]].

Among its functions, taurine, in the brain, affects neurons' activity, moderates memory abilities, manages aggression, and helps protect against alcohol. According to Jang *et al.* in 2017, giving taurine orally at a dose of 1000 milligrams per kilogram of body weight each day can help improve memory and reverse brain changes seen in severe cognitive dementia caused by Alzheimer's disease [17].

As revealed by Columbia University Irving Medical Center investigators in recent studies, a lack of taurine might be a reason for aging. Studies done on mice, monkeys, and humans have shown that with age, the body's taurine levels decrease[18]. Taurine dehydrogenase breaks down taurine with the formation of sulfa-acetylaldehyde, ammonia, and acceptors of electrons.

The purpose of this study is to investigate eight derivatives in terms of their toxicology, biology, and pharmacokinetics, by considering their potential to function as taurine dehydrogenase inhibitors. Taurine, which is an amino acid with sulphur, is needed for multiple body activities [[19], [20], such as neurotransmission modulation [21], maintaining cell balance [22] and shielding the body from stress caused by reactive oxygen species [[15], [22]]. Having low taurine can result in several neurological issues, so taurine dehydrogenase and other relevant

enzymes could be considered as possible treatments [15].

Despite knowing much about taurine and α-ketoether derivatives, there is very little insight found in chemical literature on their use as taurine dehydrogenase inhibitors. This study aims to resolve this issue by checking if these compounds can inhibit taurine dehydrogenase, an important enzyme needed for taurine metabolism. By analyzing the chemical, biological, and pharmacokinetic features of these derivatives, we intend to pick out good candidates for medicines that address neurological conditions related to taurine.

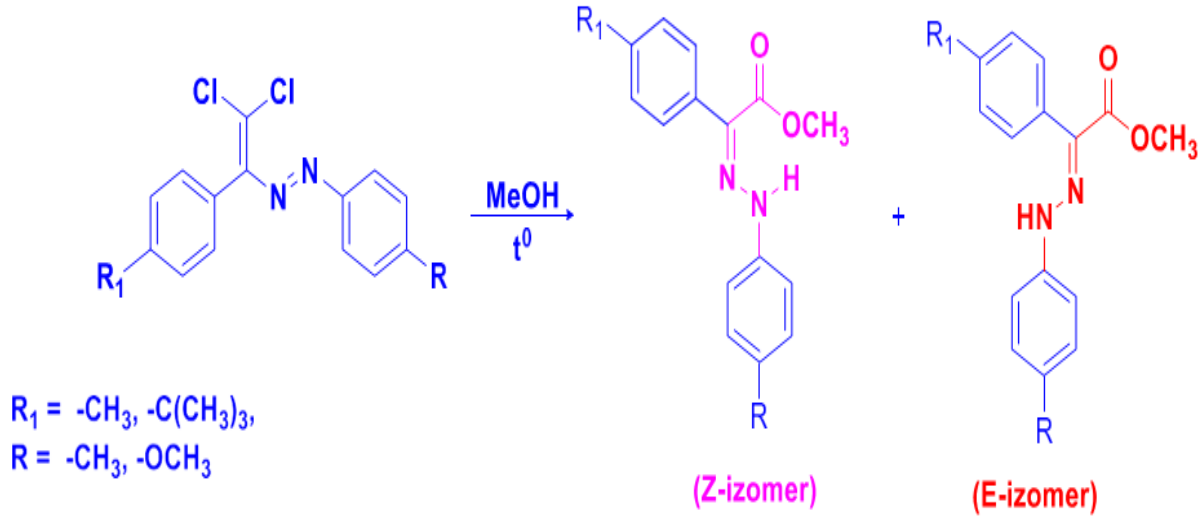
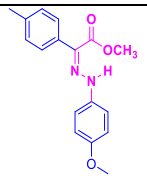
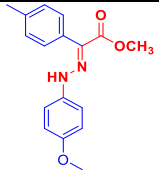
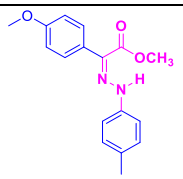
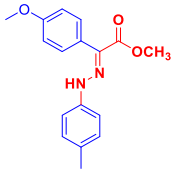
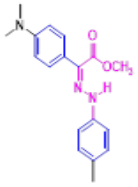
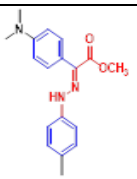
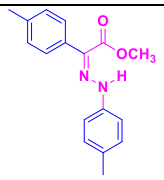
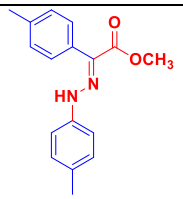


Figure 1: The Solvolysis Reaction of Dichlorodiazadienes in Methanol is Represented by this Scheme That Forms Both the Z- and E-Isomers of α-Ketoether Derivatives.

Table 1: α-Ketoether Derivatives: Nomenclature and Structural Details of Z- and E-Isomers

No	R/R1	NAME	STRUCTURE
I	OCH3/CH3	methyl (Z)-2-(2-(4-methoxyphenyl)hydrazineylidene)-2-(p-tolyl) acetate	
II	OCH3/CH3	methyl (E)-2-(2-(4-methoxyphenyl)hydrazineylidene)-2-(p-tolyl) acetate	

III	CH3/OCH3	methyl (Z)-2-(4-methoxyphenyl)-2-(2-(p tolyl)hydrazineylidene) acetate	
IV	CH3/OCH3	methyl (E)-2-(4-methoxyphenyl)-2-(2-(p-tolyl)hydrazineylidene)acetate	
V	CH3/N(CH3)3	methyl (Z)-2-(4-dimethylamino)phenyl)-2-(2-(p-tolyl)hydrazineylide-ne)acetate	
VI	CH3/N(CH3)3	methyl (E)-2-(4-dimethylamino)phenyl)-2-(2-(p-tolyl)hydrazineylidene)acetate	
VII	CH3 / CH3	methyl (Z)-2-(p-tolyl)-2-(2-(p tolyl)hydrazineylidene)acetate	
VIII	CH3 / CH3	methyl (E)-2-(p-tolyl)-2-(2-(p-tolyl)hydrazineylidene)acetate	

METHODOLOGY

In Silico Predictions of Toxicity and Biological Activity

The toxicity and biological activity for the eight α-ketoether derivatives (KEA), Z- and E-forms both, were studied using the PassOnline program (http://www.way2drug.com/passonline/). Using PassOnline, scientists can observe structure-activity relations and find out the possible biological activities of up to 45,000 chemicals. The estimates for each class are given in terms of the probability of an observation being active (Pa) or inactive (Pi), both of these ranging from zero to one. A higher Pa value and lower Pi value indicate a higher likelihood of detecting activity in the experiment.

Canonical SMILES Generation

Using the PassOnline software, the canonical SMILES (Simplified Molecular-Input Line-Entry System) for each of the α-ketoether derivatives have been generated.

Physicochemical and Pharmacokinetic Properties

The physicochemical properties and pharmacokinetic ADME (Absorption, Distribution, Metabolism, and Excretion) studies of the α-ketoether derivatives were performed using the SwissADME program (http://www.swissadme.ch/) and Swiss Target Prediction program (http://www.swisstargetprediction.ch/) [23]. The SwissADME software provided valuable information regarding molecular properties such as solubility, lipophilicity, and other essential characteristics. The Swiss Target Prediction tool was used to predict the potential biological targets for each compound.

Toxicity Prediction

To predict the toxicity of compounds 5 and 6, ProTox II (https://tox-new.charite.de) was used to find the probability of these compounds having any of the following effects: hepatotoxicity, carcinogenicity, and organ-related toxicities [24].

It should be noted that earlier studies were conducted with the creation of pyrazine substitutes to predict the activities of taurine inhibitors with the Pass program [25].

RESULTS

Canonical SMILES

With PassOnline software, the standard SMILES all the α-ketoether have been determined and summarized in Table 2.

Table 2: Molecule formula and canonical SMILES

No.	Molecule	Canonical SMILES
I	C17H18N2O3	COC(=O)C(=N/N(C)C1=CC=C(OC)C=C1)\C1=CC=C(C)C=C1
II	C17H18N2O3	COC(=O)C(=N\NC1=CC=C(OC)C=C1)\C1=CC=C(C)C=C1
III	C17H18N2O3	[H]N(\N=C(/C(=O)OC)C1=CC=C(OC)C=C1)C1=CC=C(C)C=C1
IV	C17H18N2O3	COC(=O)C(=N\NC1=CC=C(C)C=C1)\C1=CC=C(OC)C=C1
V	C18H21N3O2	[H]N(\N=C(/C(=O)OC)C1=CC=C(C=C1)N(C)C)C1=CC=C(C)C=C1
VI	C18H21N3O2	COC(=O)C(=N\NC1=CC=C(C)C=C1)\C1=CC=C(C=C1)N(C)C
VII	C17H18N2O2	[H]N(\N=C(/C(=O)OC)C1=CC=C(C)C=C1)C1=CC=C(C)C=C1
VIII	C17H18N2O2	COC(=O)C(=N\NC1=CC=C(C)C=C1)\C1=CC=C(C)C=C1

Pharmacokinetic Predictions (ADME)

Pharmacokinetic properties, including ADME, are key determinants in evaluating the drug-likeness of chemical compounds. In this study, we used SwissADME software to estimate the pharmacokinetic traits and physicochemical properties of eight α-ketoether derivatives. Such predictions are crucial because they help us know how compounds will interact with the body and what risks they may carry.

Physicochemical Descriptors and Pharmacokinetic Properties

The SwissADME tool provides vital information, including the Molar Refractivity (MR) for each compound, as well as Total Polar Surface Area (TPSA), Log P (lipophilicity), and solubility predictions. These predictions are used to decide if a compound is likely to be well absorbed, distributed through the body, and generally available. Table 3 estimates the Molar Refractivity, Total Polar Surface Area, and Log P values for all eight α-Ketoether derivatives.

Table 3: Predictions of Molar Refractivity, Total Polar Surface Area and Log P Values for Various α-Ketoether Derivatives

Mol	Formula	MR	MW g,mol	TPSA	iLOGP	XLOGP3	WLOGP	MLOGP
I	$C_{17}H_{18}N_2O_3$	86,28	298,34	59,92 A^2	2,93	4,70	2,80	2,60
II	$C_{17}H_{18}N_2O_3$	86,28	298,34	59.92 A^2	3,01	4,70	2,80	2,60
III	$C_{17}H_{18}N_2O_3$	86,28	298,34	59,92 A^2	2,88	4,70	2,80	2,60
IV	$C_{17}H_{18}N_2O_3$	86,28	298,34	59,92 A^2	3,17	4,70	2,80	2,60
V	$C_{18}H_{21}N_3O_2$	93,99	311,38	53,93 A^2	2,96	4,85	2,86	2,84
VI	$C_{18}H_{21}N_3O_2$	93,99	311,38	53,93 A^2	3,07	4,85	2,86	2,84
VII	$C_{17}H_{18}N_2O_2$	84,75	282,34	50,69 A^2	2,91	5,09	3,10	3,17
VIII	$C_{17}H_{18}N_2O_2$	84,75	282,34	50,69 A^2	3,03	5,09	3,10	3,17

Solubility Predictions

Solubility is a critical factor in determining whether a compound can be absorbed by the body. The SwissADME software also predicts solubility in various environments, using ESOL and Ali Solubility methods. Table 4 presents the predicted solubility for each compound

.

Table 4: Solubility Predictions for Various α-Ketoether Derivatives

Molecule	Silicos-IT Log P	Consensus Log P	ESOL Log S	ESOL Solubility (mq/ml)	ESOL Solubility (mol/l)	Ali Log S	Ali Solubility (mq/ml)	Ali Solubility (mol/l)
I	3,27	3,26	4,66	6,55e-03	2,20e-05	-5,69	6,14e-04	2,06e-06
II	3,27	3,28	4,66	6,55e-03	2,20e-05	-5,69	6,14e-04	2,06e-06
III	3,27	3,25	4,66	6,55e-03	2,20e-05	-5,69	6,14e-04	2,06e-06
IV	3,27	3,31	4,66	6,55e-03	2,20e-05	-5,69	6,14e-04	2,06e-06
V	2,90	3,28	4,82	4,76e-03	1,53e-05	-5,72	5,98e04	1,92e-06
VI	2,90	3,30	4,82	4,76e-03	1,53e-05	-5,72	5,98e04	1,92e-06
VII	3,73	3,60	4,89	3,64e-03	1,29e-05	-5,90	3,57e-04	1,27e-06
VIII	3,73	3,62	4,89	3,64e-03	1,29e-05	-5,90	3,57e-04	1,27e-06

Gastrointestinal Absorption, Blood-Brain Barrier Permeability, and Metabolism

Pharmacokinetics was investigated further by considering the absorption through the GI tract, passage through the BBB, and how each compound is metabolized. These values explain how absorption will progress, whether the compound may penetrate the blood-brain barrier, and if metabolism could occur. All these compounds have high GI absorption, which means they are likely to be absorbed well in the gut. Additionally, all the tested derivatives are expected to cross the BBB, so they could help treat nervous system diseases (Table 5).

Table 5: Gastro Intestinal Absorption, Blood Brain Barrier Permeability and Metabolism of Various α-Ketoether Derivatives

Molecule	GI Absorption	BBB permeant	Pgp substrate	CYP1A2 inhibitor	CYP2C19 Inhibitor	CYP2C9 Inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor
I	High	Yes	No	Yes	Yes	No	No	No
II	High	Yes	No	Yes	Yes	No	No	No
III	High	Yes	No	Yes	Yes	No	No	No
IV	High	Yes	No	Yes	Yes	No	No	No
V	High	Yes	No	Yes	Yes	Yes	No	No

VI	High	Yes	No	Yes	Yes	Yes	No	No
VII	High	Yes	No	Yes	Yes	No	No	No
VIII	High	Yes	No	Yes	Yes	No	No	No

Bioavailability, Lipinski Rule, Veber Rule, and Ghose Rule Predictions

The bioavailability score**,** Lipinski's Rule of Five, and Veber and Ghose's rules were used to predict whether the compounds possess desirable characteristics for oral drug administration.

Bioavailability Score: All derivatives are thought to have a moderate likelihood of getting into the bloodstream because their bioavailability score is 0.55. Having a high score usually reflects that the drug can be absorbed more effectively (Table 6).

Lipinski's Rule of Five: Lipinski's Rule considers a few molecular attributes (such as weight, the ability to take part in hydrogen bonding, and Log P) when evaluating the compounds. In all cases, the XLOGP3 of these drugs is more than 3.5, which suggests that their ability to travel through and be absorbed by the body may be restricted. Nevertheless, these necessary features are still met by these compounds since they do not have any violations in the number of hydrogen bond donors and acceptors (Table 6).

Veber and Ghose Rules**:** According to the Veber Rule (which underlines factors such as rotatable bonds and polarity on the surface) and the Ghose Rule (which pays attention to molecular size and polarity), these derivatives fall within the desired ranges for drugs that can be taken by mouth. While a few of the derivatives have a violation for XLOGP3 exceeding 3.5, their overall molecular characteristics indicate they can still be orally absorbed well (Table 6).

Synthetic Accessibility**:** The fact that all compounds are marked as having "Yes" for synthetic accessibility allows us to assume that they are suited for effective drug development (Table 6).

PAINS Alerts: PAINS alerts are the same for all compounds, as they often have building blocks that tend to bind with multiple partners and could make it hard for the molecules to be used as effective drugs (Table 6).

Table 6: Bioavailability Score, Lipinski Rule, Veber Rule, Ghose Rule predictions for Various α-Ketoether Derivatives

Mole-cule	**Bioavailability Score**	**PAINS #alerts**	**Brenk #alerts**	**Leadlikeness #violations**	**Synthetic Accessibility**	**Lipinski #violations**	**Ghose #violations**	**Veber #violations**
I	0,55	0 alert	1 alert: imine_1	No; 1 violation: XLOGP3>3,5	2,73	Yes; 0 violation	Yes	Yes

II	0,55	0 alert	1 alert: imine_1	No; 1 violation: XLOGP3>3,5	2,73	Yes; 0 violation	Yes	Yes
III	0,55	0 alert	1 alert: imine_1	No; 1 violation: XLOGP3>3,5	2,73	Yes; 0 violation	Yes	Yes
IV	0,55	0 alert	1 alert: imine_1	No; 1 violation: XLOGP3>3,5	2,73	Yes; 0 violation	Yes	Yes
V	0,55	0 alert	1 alert: imine_1	No; 1 violation: XLOGP3>3,5	2,92	Yes; 0 violation	Yes	Yes
VI	0,55	0 alert	1 alert: imine_1	No; 1 violation: XLOGP3>3,5	2,92	Yes; 0 violation	Yes	Yes
VII	0,55	0 alert	1 alert: imine_1	No; 1 violation: XLOGP3>3,5	2,77	Yes; 0 violation	Yes	Yes
VIII	0,55	0 alert	1 alert: imine_1	No; 1 violation: XLOGP3>3,5	2,77	Yes; 0 violation	Yes	Yes

Biological Activity and Toxicity Predictions

Using the PassOnline program, the researchers focused on evaluating the α-ketoether derivatives as potential inhibitors of Taurine Dehydrogenase (TDH). The program also calculated toxicity values for each compound (LD50 and toxicity class), an important factor used to determine their safety.

The results, summarized in Table 7, indicate that while all compounds show varying levels of TDH inhibition (Pa values), the KEA 5 and 6 isomers exhibited the highest inhibitory activity, with a Pa value of 0.694, which corresponds to approximately **7**0% inhibitory activity. This makes them the most promising candidates for further drug development targeting taurine dehydrogenase inhibition.

Table 7: Results of Taurine Dehydrogenase Inhibitor Activity (Pa – Pi) and Toxicity

Molecule	Taurine dehydrogenase inhibitor	Number of rotable bonds (NRB)	Predictted LD50 mg,kg	Predicted Toxicity class	Average similarity %	Prediction accuracy %
I	0,495	6	900	4	57,14	67,38
II	0,495	6	900	4	57,14	67,38
III	0,495	6	1500	4	60,56	68,07
IV	0,495	6	1500	4	60.56	68.07
V	0,694	6	3000	5	56,67	67,38
VI	0,694	6	3000	5	56,67	67,38
VII	0,521	5	1800	4	56,68	67,38
VIII	0,521	5	1800	4	56,68	67,38

According to the obtained results, the toxicities of KEA 5 and 6 isomers, which exhibit superior taurine dehydrogenase inhibitory activity, were investigatedusing the ProTox-II program (Table 8).

Table 8: Results of investigation of molecules V and VI by ProTox – II (Prediction of Toxicity)

Molecule Target	**V**		**VI**	
	Prediction	**Probability**	**Prediction**	**Probability**
Hepatotoxicity	Active	0,52	Active	0,52
Carcinogenicity	Active	0,54	Active	0,54
İmmunotoxicity	İnactive	0,97	İnactive	0,97
Mutagenicity	Active	0,74	Active	0,74
Citotoxicity	İnactive	0,68	İnactive	0,68
Aryl hydrocarbon Receptor (AhR)	Active	0,76	Active	0,76
Androgen Receptor (AR)	İnactive	0,72	İnactive	0,72
Androgen Receptor Ligand Binding Domain (AR-LBD)	İnactive	0,91	İnactive	0,91
Aromatase	İnactive	0,89	İnactive	0,89
Estrogen Receptor Alpha (ER)	İnactive	0,50	İnactive	0,50
Estrogen Receptor Ligand Binding Domain (ER-LBD)	İnactive	0,93	İnactive	0,93
Peroxisome Proliferator Activated Receptor	İnactive	0,96	İnactive	0,96

Gamma (PPAR-Gamma)				
Nuclear Factor (erythroid-derived 2)-like2/antioxidant responsive element (nrf2/ARE)	İnactive	0,63	İnactive	0,63
Heat shock factor response element (HSE)	İnactive	0,63	İnactive	0,63
Mitochondrial Membrane Potential (MMP)	Active	0,60	Active	0,60
Phosphoprotein (Tumor Supressor) p53	İnactive	0,84	İnactive	0,84
ATPase family AAA domain-containing protein 5 (ATAD5)	Active	0,58	Active	0,58

DISCUSSION

Concerning their possible taurine dehydrogenase enzyme inhibitors, this research provides an extensive in silico study on eight α-ketoether derivatives analyzing their biological, pharmacokinetic, and toxicological profiles. To assess the efficacy of these compounds as potential taurine dehydrogenase drugs, predicted toxicity of compounds, and performed ADME profiling.

Using the SwissADME tool, pharmacokinetic forecasts were produced that showed all derivatives had great ability to pass the blood-brain barrier (BBB) and strong gastrointestinal absorption (GI). Given that both qualities are essential for chemicals meant to target the nervous system [23], this makes them excellent candidates for the treatment of neurological conditions. Furthermore predicted to be metabolized by several cytochrome P450 (CYP) enzymes, the molecules' possible efficient body processing is supported [6].

Toxicity predictions, employing ProTox II, showed Derivatives V and VI to be very promising, with low levels of toxicity and low risks for hepatotoxicity and carcinogenicity. This is a significant discovery in the drug development process, as it implies that these compounds will have fewer possibilities of inducing serious adverse effects, a key consideration when deciding on a compound for therapeutic purposes. The immunotoxicity and cytotoxicity predictions were also positive, suggesting that such derivatives would be safer than conventional drugs, which are usually associated with high toxicity levels [11]. Nonetheless, more in vivo experiments should be conducted to confirm these predictions and determine the safety of the compounds in actual biological systems [13].

PassOnline was utilized to explore the activity of the compounds, confirming that V and VI gave the greatest taurine dehydrogenase inhibition with a Pa value of 0.694. Because these substances block inhibitory activity strongly, they are especially valuable for treating neurological disorders since taurine protects the brain and supports its function. Some neurological issues, particularly Alzheimer's disease, are connected to a lack of taurine, which makes taurine dehydrogenase inhibitors an interesting option for treatment [[15], [18]].

This study increases medical experts' knowledge about using taurine-focused drugs, encouraging them to create new drugs that control taurine levels. As scientists previously found, taurine is important for the brain and taurine dehydrogenase inhibitors have potential medicinal effects. Besides, the practice ADME predictions shows new ways used in drug discovery nowadays. Thanks to these tools, scientists can predict the success, risks, and how drugs will move in the body even before they are fully developed, which hastens the process and reduces expenses [[1, [5]].

To conclude, the research found that certain α-ketoether derivatives have strong activity against taurine dehydrogenase, a good pharmacokinetic profile, and a low risk of toxicity. Specifically, V and VI derivatives appear to have the potential to be used as drugs that target taurine dehydrogenase for neurological therapy. These findings indicate that using *in silico* methods is important in drug discovery since they help identify the most promising drugs without spending too much time or money.

CONCLUSIONS

Based on *in silico* or CADD predictions, toxicological properties, biological activities, physicochemical properties and pharmacokinetic ADME parameters of 8 derivatives, including Z- and E-isomers of α-ketoethers aryl hydrozos (KEA) from the solvolysis reaction of dichlorodiazadienes in methanol, were virtuallyinvestigated. *In silico* predictions of compounds used the PassOnline program, physicochemical properties and pharmacokinetic ADME predictions were studied using SwissADME and Swiss TargetPrediction, and toxicity indicators were studied using ProTox II programs. It was determined that KEA 5 – methyl (Z)-2-(4-dimethylamino)phenyl)-2-(2-(p-tolyl)hydrazineyldene) acetate and 6 – methyl (E)- 2-(4-dimethylamino)phenyl)-2-(2-(p-tolyl) hydrazineylidene acetate chemicalcompounds demonstrate more TDH inhibitory activity (Pa – 0.694).

According to Lipinski's "rule of five" (Ro5), the obtained indicators for the investigated chemical compounds yield positive results. Thus, n-octanol/water partition coefficient: logP ≤ 5, the molecular weight: MW ≤ 500 g/mol, the numberof hydrogen bond acceptors: HBA ≤ 10, the number of hydrogen bond donors: HBD ≤ 5, a number of rotatable bonds: NRB ≤ 10.

Authorship contribution

Konul F. Huseynguliyeva, Kamala K. Badalova: experimental, analysis, and design of the study. Abel M. Maharramov, Namiq Q. Shikhaliyev, Ayten M. Qajar,

Khatira A. Garazadeh, Resources and methodology. Zunaira Akram, Abdur Rauf: Software and methodology. Supervision, Methodology.

REFERENCES

1. S. Sinha, D. Vohora, Drug discovery and development: An overview, Pharm. Med. Transl. Clin. Res., (2018), pp. 19–32, https://doi.org/10.1016/B978-0-12-802103-3.00002-8

2. S.M. Paul, D.S. Mytelka, C.T. Dunwiddie, C.C. Persinger, B.H. Munos, S.R. Lindborg, A.L. Schacht, How to improve R&D productivity: The pharmaceutical industry's grand challenge, Nat. Rev. Drug Discov., 9 (3) (2010), pp. 203–214, https://doi.org/10.1038/nrd3078

3. S.K. Niazi, Z. Mariam, Computer-aided drug design and drug discovery: A prospective analysis, Pharmaceuticals, 17 (1) (2023), pp. 22, https://doi.org/10.3390/ph17010022

4. V.T. Sabe, T. Ntombela, L.A. Jhamba, G.E. Maguire, T. Govender, T. Naicker, H.G. Kruger, Current trends in computer-aided drug design: A review, Eur. J. Med. Chem., 224 (2021), pp. 113705, https://doi.org/10.1016/j.ejmech.2021.113705

5. P. Gupta, A. Chanana, Y.R. Kulkarni, A. Narayan, O. Shanker, B. Mahato, D. Singh, A. Patel, U. Havelikar, R.P. Singh, H.S. Chawra, Computer-aided Drug Design: Innovation and its Application in Reshaping Modern Medicine, Curr. Artif. Intell., (2024), https://doi.org/10.2174/22139885096662 31221100633

6. K. Singh, B. Bhushan, B. Singh, Advances in drug discovery and design using computer-aided molecular modeling, Curr. Comput.-Aided Drug Des., 20 (5) (2024), pp. 697–710, https://doi.org/10.2174/15734099196662 31009103047

7. N.G. Shikhaliyev, A.M. Maharramov, G.T. Suleymanova, A.A. Babazade, V.G. Nenajdenko, V.N. Khrustalev, A.S. Novikov, A.G. Tskhovrebov, Arylhydrazones of α-keto esters via methanolysis of dichlorodiazabutadienes, Mendeleev Commun., 31 (5) (2021), pp. 677–679, https://doi.org/10.1016/j.mencom.2021.09.010

8. M.D. Eastgate, M.A. Schmidt, K.R. Fandrick, On the design of complex drug candidate syntheses in the pharmaceutical industry, Nat. Rev. Chem., 1 (2) (2017), pp. 0016, https://doi.org/10.1038/s41570-016-0016

9. P.W. Erhardt, Medicinal chemistry in the new millennium. A glance into the future, Pure Appl. Chem., 74 (5) (2002), pp. 703–785, https://doi.org/10.1351/pac20027405070 3

10. H.C. Hodge, J.H. Sterner, Tabulation of toxicity classes, Am. Ind. Hyg. Assoc. Q., 10 (4) (1949), pp. 93–96, https://doi.org/10.1080/00968204909344 352

11. B.E. Erickson, US FDA seeks to slash animal testing, Chem. Eng. News, (2022).

12. B.E. Erickson, US EPA struggles to replace animal tests for pesticide toxicity, Chem. Eng. News, 97 (20) (2019), pp. 24–25.

13. W. Lilienblum, W. Dekant, H. Foth, T.

Gebel, J.G. Hengstler, R. Kahl, P.J. Kramer, H. Schweinfurth, K.M. Wollin, Alternative methods to safety studies in experimental animals: Role in the risk assessment of chemicals under the new European Chemicals Legislation (REACH), Arch. Toxicol., 82 (2008), pp. 211–236, https://doi.org/10.1007/s00204-008-0300-4

14. E.A. Garayev, K.F. Huseynguliyeva, S.A. Pashayeva, K.M. Yagubov, Application of computer programs in drug design, Modern Achievements of Azerbaijani Medicine, (1) (2023), pp. 166–174.

15. M. Jakaria, S. Azam, M.E. Haque, S.H. Jo, M.S. Uddin, I.S. Kim, D.K. Choi, Taurine and its analogs in neurological disorders: Focus on therapeutic potential and molecular mechanisms, Redox Biol., 24 (2019), pp. 101223, https://doi.org/10.1016/j.redox.2019.101223

16. J.A. Yeon, S.J. Kim, Neuroprotective effect of taurine against oxidative stress-induced damages in neuronal cells, Korean J. Appl. Pharmacol., 18 (1) (2010), pp. 24–31.

17. H. Jang, S. Lee, S.L. Choi, H.Y. Kim, S. Baek, Y. Kim, Taurine directly binds to oligomeric amyloid-β and recovers cognitive deficits in Alzheimer model mice, Taurine 10, Springer, (2017), pp. 233–241, https://doi.org/10.1007/978-94-024-1079-2_22

18. P. Singh, K. Gollapalli, S. Mangiola, D. Schranner, M.A. Yusuf, M. Chamoli, S.L. Shi, B. Lopes Bastos, T. Nair, A. Riermeier, E.M. Vayndorf, Taurine deficiency as a driver of aging, Science, 380 (6649) (2023), pp. 621–628, https://doi.org/10.1126/science.abn9257

19. J.T. Brosnan, M.E. Brosnan, The sulfur-containing amino acids: an overview, J. Nutr., 136 (6) (2006), pp. 1636S–1640S.

20. N. Rais, A. Ved, M. Shadab, R. Ahmad, M. Shahid, Taurine, a non-proteinous essential amino acid for human body systems: An overview, Arab Gulf J. Sci. Res., 41 (1) (2023), pp. 48–66, https://doi.org/10.1108/AGJSR-05-2023-0054

21. Y. Yachou, A. El Idrissi, Taurine role in neuroprotection, Nat. Mol. Neuroprotect. Neurotox., Acad. Press, (2024), pp. 677–696, https://doi.org/10.1016/B978-0-443-15259-3.00037-2

22. L. Wang, Z. Xie, M. Wu, Y. Chen, X. Wang, X. Li, F. Liu, The role of taurine through endoplasmic reticulum in physiology and pathology, Biochem. Pharmacol., (2024), pp. 116386, https://doi.org/10.1016/j.bcp.2024.116386

23. A. Rauf, Z. Akram, M. Naveed, N. AlMasoud, T.S. Alomar, M. Saleem, A. Waheed, G. Ribaudo, Studies on the inhibition of ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1) by a flavonoid from Pistacia chinensis, Chem., 5 (4) (2023), pp. 2094–2103, https://doi.org/10.3390/chemistry5040137

24. A. Rauf, M.U. Khan, Z. Akram, C.A. Shabbir, Y.S. al-Awthan, O.S. Bahattab, A.A.H. Mujawah, H.A. Hemeg, M. Iriti, Lipoxygenase inhibitory potential of secondary metabolites from Pistacia integerrima: In vitro and in silico studies, Tradit. Med. Res., 10 (2025), pp. 52, https://doi.org/10.53388/TMR202402250

01
25. T.S. Kapralova, O.M. Lavrova, M.F. Pistsov, A.A. Ermolaeva, E.Yu. Tovkaleva, Potential biological activity of complexes based on substituted pyrazines, Issled. Molodykh Uchenykh, (2019), pp. 7–10.

BƏZİ α-KETOEFİRLƏRİN ARİL-HİDRAZONLARININ TAURİN DEHİDROGENAZA İNHİBİTOR AKTİVLİYİNİN İN SİLİCO TƏDQİQİ

Könül F. Hüseynquliyeva[1], Kəmalə K. Bədəlova[1], Abel M. Məhərrəmov[2], Namik K. Şıxəliyev[4], Aytən M. Qacar[2], Xatirə A. Qarazadə[2], Sahirə R. Məmmədova[3], Zunayra Əkrəm[5], Əbdür Rauf[6]

[1]Azərbaycan Tibb Universiteti, Əczaçılıq Toksikologiyası və Kimyası Kafedrası, Bakı, Azərbaycan

[2]Bakı Dövlət Universiteti, Üzvi Kimya Kafedrası, Bakı, Azərbaycan

[3]Azərbaycan Tibb Universiteti, Radiologiya Kafedrası, Bakı, Azərbaycan

[4]Bakı Mühəndislik Universiteti, Kimya Mühəndisliyi Kafedrası, Bakı, Azərbaycan

[5]Farmakologiya Kafedrası, Əczaçılıq Elmləri Fakültəsi, Bakai Tibb Universiteti, Karaçi, Pakistan

[6]Kimya Kafedrası, Swabi Universiteti, Swabi, Ənbar, Xayber Paxtunxva, Pakistan

Email: kamala.badalova@mail.ru

Xülasə

Kompüter əsaslı dərman dizaynı CADD proqramları (Computer-Aided Drug Design) farmakodinamik, farmakokinetik xüsusiyyətlərin yaxşılaşdırılması və mümkün əlavə təsirlərin azaldılması yolu ilə yeni dərman molekullarının yaradılması prosesini əhəmiyyətli dərəcədə dəyişdirmişdir. Bu tədqiqatda, dixlordiazadienlərin metanolda solvoliz reaksiyası vasitəsilə sintez edilən həm Z-, həm də E-izomerləri daxil olmaqla, səkkiz α-ketoefir törəməsinin bioloji, farmakokinetik və toksikoloji xüsusiyyətləri *in silico* metodlardan istifadə etməklə qiymətləndirilmişdir. Törəmələrin hərtərəfli *in silico* qiymətləndirilməsi fiziki-kimyəvi parametrlər üçün SwissADME, toksiklik analizi üçün ProTox II və bioloji aktivliyin proqnozlaşdırılması üçün PASS Online proqramları vasitəsilə aparılmışdır. Tədqiq olunan birləşmələr arasında 5-ci törəmə (Z-izomer) və 6-cı törəmə (E-izomer) taurin dehidrogenazaya qarşı əhəmiyyətli inhibitor aktivlik göstərmiş, proqnozlaşdırılan aktivlik göstəricisi (Pa) 0,694 olmuşdur ki, bu da onların gələcək inkişaf üçün yüksək potensiala malik olduğunu göstərir. Bundan əlavə, toksiklik qiymətləndirmələri bu birləşmələrin böyük ehtimalla təhlükəsiz olduğunu və qaraciyər toksikliyi və ya kanserogen təsir yaratma ehtimalının aşağı olduğunu göstərir. Farmakokinetik göstəricilərə əsasən, bu törəmələr yaxşı sorulur və qan-beyin baryerini (BBB) keçə bilirlər ki, bu da onları nevroloji xəstəliklərin müalicəsi üçün perspektivli namizədlər edir. Nəticə olaraq, hesablama üsulları ilə əldə olunan nəticələr göstərir ki, 5 və 6-cı törəmələr yüksək effektivlik və təhlükəsizlik xüsusiyyətlərinə görə taurin dehidrogenazanı hədəfləyən dərmanların hazırlanmasında istifadə oluna bilər.

Açar sözlər: In silico, PassOnline, SwissADME, Swiss TargetPrediction, ProTox-II, α-ketoefirlərin arilhidrozonları

İN SİLİCO ИССЛЕДОВАНИЕ ИНГИБИРУЮЩЕЙ АКТИВНОСТИ ТАУРИНДЕГИДРОГЕНАЗЫ НЕКОТОРЫХ АРИЛГИДРАЗОНОВ А-КЕТОЭФИРОВ

Конул Ф. Хусейнгулиева[1], Камала К. Бадалова[1], Абель М. Махаррамов[2], Намик К. Шихалиев[4], Айтен М. Каджар[2], Хатира А. Гаразаде[2], Сахира Р.Мамедова[3], Зунайра Акрам[5], Абдур Рауф[6]

[1]Азербайджанский Медицинский Университет, Кафедра Фармацевтической Токсикологии и Химии, Баку, Азербайджан

[2]Бакинский Государственный Университет, Кафедра Органической Химии

[3]Азербайджанский Медицинский Университет, Кафедра Радиологии

[4]Бакинский Инженерный Университет, Кафедра Химической Инженерии

[5] Кафедра Фармакологии, Факультет Фармацевтических Наук, Медицинский Университет Бакаи, Карачи, Пакистан

[6] Кафедра Химии, Университет Сваби, Сваби, Анбар, Хайбер-Пахтунхва, Пакистан

Email: kamala.badalova@mail.ru

Резюме

Компьютерное проектирование лекарственных препаратов CADD (Computer-Aided Drug Design) изменило процесс разработки лекарств, улучшив фармакодинамику, фармакокинетику и снизив вероятность побочных эффектов. В данном исследовании используются методы in silico для оценки биологических, фармакокинетических и токсикологических свойств восьми производных α-кетоэфиров, включая как Z-, так и E-изомеры, синтезированных в результате реакции сольволиза дихлордиазадиенов в метаноле. В исследовании представлена тщательная оценка этих производных с использованием таких программ, как SwissADME для физико-химических параметров, ProTox II для анализа токсичности и PassOnline для прогнозирования биологической активности. Среди изученных соединений производные 5 (Z-изомер) и 6 (E-изомер) показали значительную ингибирующую активность в отношении тауриндегидрогеназы с прогнозируемым значением активности (Pa) 0,694, что указывает на высокий потенциал для дальнейшей разработки. Более того, оценки токсичности показывают, что эти соединения, скорее всего, безопасны и вряд ли вызовут проблемы с печенью или раком. Согласно фармакокинетическим данным, эти производные хорошо абсорбируются и, вероятно, преодолевают гематоэнцефалический барьер (ГЭБ), что делает их перспективными кандидатами для лечения неврологических заболеваний. В заключение, результаты вычислительных исследований показывают, что производные 5 и 6 могут быть использованы в разработке лекарственных препаратов путем воздействия на тауриндегидрогеназу благодаря их высокой эффективности и безопасности.

Ключевые слова: In silico, PassOnline, SwissADME, Swiss TargetPrediction, ProTox-II, арилгидрозоны α-кетоэфиров