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PREDICTION OF BIOLOGICAL ACTIVITY BY MEANS OF SYNTHESIS AND QSAR MODEL OF PHENYLHYDRAZONE BASED ON METHYL 4-FORMYLBENZOATE

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Abstract. In the submitted article, on the basis of methyl 4-formylbenzoate, the corresponding phenylhydrazones were synthesized and their structure was confirmed by NMR. A computer simulation was carried out to assess the possible toxicological risks, antiviral, antibacterial, antifungal activities and antiretroviral activities of the compounds, taking into account the high biological activity of phenylhydrazones, in particular the benzoate group. Five online computer programs were used for this: Gusar (Acute Rat Toxicity), PASS Online (AntiVir-Pred), PASS Online (AntiBac-Pred), PASS Online (AntiFun-Pred), PASS Online (AntiHiv-Pred). The predictions of toxicity and antiviral, antibacterial, antifungal activations and antiretroviral activity using the mentioned programs are based on computer learning based on the structural similarity of molecules, widespread character traits and predetermined real (in vitro and in vivo) models, resulting in predicted biological activity of existing and virtual compounds. The results obtained are satisfactory and may provide information about the existence of the biological activity of the compounds mentioned

Keywords: *Phenylhydrazones, Acute Rat Toxicity, AntiVir-Pred, AntiBac-Pred, AntiFun-Pred, AntiHiv-Pred.*

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1. Introduction

Hydrazones, which are included in the class of organic compounds, are derived from carbonyl compounds and are divided into N-unsubstituted R1R2C = NNH2 and N-substituted R1R2C = NNHR (Al-Kahraman *et al*., 2012; Tan *et al*., 2018; El-Azab *et al*., 2016; Mauger & Mignani, 2005; Januario *et al*., 2018; Mlostoń *et al*., 2016). Phenylhydrazones synthesized by us are polyfunctional compounds and if we look at the structure, the carbon atom contained in the compound shows both nucleophilic and electrophilic properties, but is also involved in isomerization and adjacent to the same carbon atom-H is involved in functionalization. Nitrogen atoms show nucleophilic

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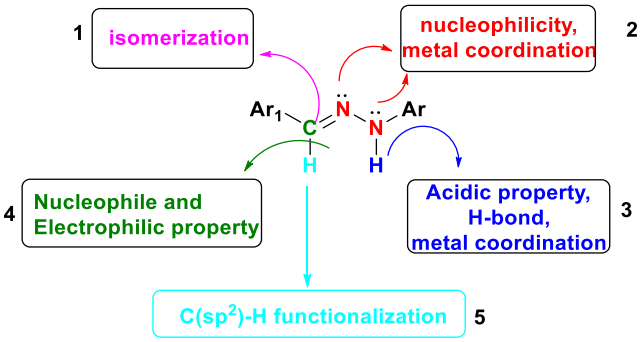
properties, but are also involved in metal coordination. The H atom of the imin group indicates an acidic property, forms an H bond and participates in metal coordination (Corey *et al*., 1976, Kitaev & Buzykin, 1974). What has been said can be shown schematically as follows.



The substituted hydrogen atoms of azomethine groups in hydrazones are used as intermediates for the synthesis of a number of important compounds. For example, iproniazide and isocarboxazide derived from CONHN =CH reductation of hydrazide-hydrazones are used as anti-tuberculosis drugs (Singh *et al*., 1992). Phenylhydrazones are frequently referred to by chemists as extremely useful compounds for the synthesis of heterocyclic compounds with biological and pharmacological properties. Therefore, synthetics have synthesized this type of hydrazone as a key unit in recent years and studied its microbial properties (Shakdofa *et al*., 2014). As we mentioned, hydrazones enter metal coordination due to nitrogen atoms and hydrogen of the imine group, so that some of the obtained compounds are used in medicine as antitumor drugs (Mo *et al*., 2018).

The main feature that distinguishes the synthesized hydrazones from others (Nenajdenko *et al*., 2020; 2021; Maharramov *et al*., 2018; Shikhaliyev *et al*., 2021a; 2021b) is the retention of a benzoate group, which, as we know, is used against yeasts, fungi and bacteria in an acidic environment. As we know, Sodium benzoate is used in the food system (Chipley, 2020). So, it is used as a substitute for antibiotics in animal feed. At the same time, antibacterial properties of Mg(II), Ca(II), Cu(II) and Zn(II) benzoates (Borawska *et al*., 2009) and their complex compounds (Krajníková *et al*., 2015; Mohanapriya *et al*., 2016) activities have been studied.

The basic concepts in molecular modeling and computational chemistry are the target and drug molecule, which is called a drug molecule that has certain physiological functions in the human body and in the case of injury or destruction, when it interacts with any part of the target, the response to which leads to pathological processes. Insilico research plays an increasingly important role in understanding how drug receptors work and their impact on the human body and in assisting the researcher in the design of new medicines (Marshall, 1987; Hassan *et al*., 2016; Macalino *et al*., 2015; Surabhi & Singh, 2018). At the same time, their application makes it possible to save time and prevent additional (sometimes inappropriate) laboratory work from being carried out. During the investigation of the biological activity of the drug in drug design through computer modeling techniques, researchers - computer aided drug design CADD (Computer Aided Drug Design) (Marshall, 1987; Hassan *et al*., 2016; Macalino *et al*., 2015; Surabhi & Singh, 2018), molecular dynamics (MD) (Torres *et al*., 2019), rational drug design

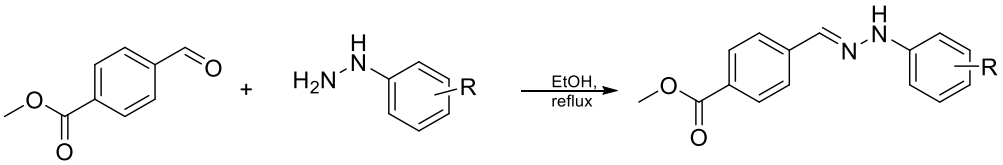
(Mandal *et al*., 2009; Mavromoustakos *et al*., 2011; Rognan, 2007; Gane & Dean, 2020), molecular docking (Molecular Docking) (Torres *et al*., 2019), quantitative structure activity relationship - programs such as QSAR (Quantitative Structure-Activity Relationship) (Verma *et al*., 2010; Veerasamy *et al*., 2011; Lagin *et al*., 2011; Poroikov *et al*., 2019). The main database used for these programs is PubChem, which is based on millions of chemical compounds tested in biological assays (Kim *et al*., 2019; 2016; Wang *et al*., 2009; Li *et al*., 2010).

The QSAR model is used in this article. As we know, the QSAR method correlates biological activity with structure. Thus, the selected descriptors are associated with the biological activity of the corresponding compound through a mathematical model. The QSAR model can be useful in the design of new classes of compounds by benchmarking the compounds included in the PubChem database (Tropsha, 2010). Through this model, we are able to pronounce beforehand about Acute mouse toxicity, antiviral, antibacterial, antifungal and antiHiv activities of the compounds we synthesize. Five online computer programs were used by us for this: Gusar (Acute Rat Toxicity) (Veerasamy *et al*., 2011), PASS Online (AntiVir-Pred) (dos Santos *et al*., 2022), PASS Online (AntiBac-Pred) (Pogodin *et al*., 2019), PASS Online (AntiFun-Pred) (Zaidi *et al*., 2024), PASS Online (AntiHiv-Pred) (Stolbov *et al*., 2020; Kaku *et al*., 2020; Rosa *et al*., 2014).

2. Materials and Methods

The syntheses of compounds were carried out at the Organic Chemistry Department of Baku State University (Baku, Azerbaijan). Unless stated otherwise, all the reagents used in this study were obtained from the commercial sources (Aldrich, TCI-Europe, Strem, ABCR). NMR spectra were recorded on a Bruker Avance 300 (1H: 300 MHz, Karlsruhe, Germany); chemical shifts (δ) are given in ppm relative to TMS, coupling constants (J) in Hz. The solvent signals were used as references ($CDCl_3$ δH = 7.26 ppm, δC = 77.16 ppm). Predicting the biological activities of synthesized corresponding phenylhydrazone derivatives is available for free on the QSAR model from the website https://www.way2drug.com/.

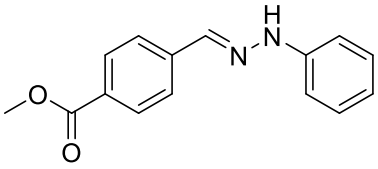
Taking into account that corresponding hydrazines, as well as compounds containing benzoat groups, show high biological activity, we have synthesized the following phenylhydrazones.



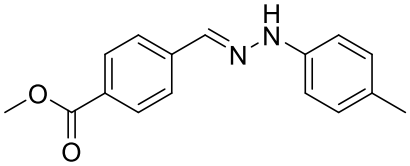
R=H (1), 4-CH_3 (2), 4-OCH_3 (3), 3,4$(CH_3)_2$ (4), 3-F (5), 4-Br (6), 4-I (7)

2.1. Synthetic Part

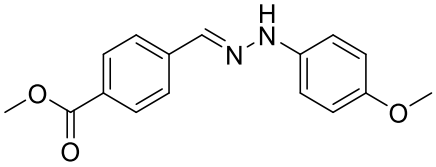
Schiff bases 1-7 were synthesized according to the reported method (Maharramov *et al*., 2018). A mixture of methyl 4-formylbenzoate (10.2 mmol), CH3COONa (0.82 g) and a corresponding phenylhydrazines (10 mmol) were refluxed with stirring in ethanol (50-100 mL) for 2-5 h. The reaction mixture was cooled to room temperature and water (50-100 mL) was added to give a precipitate of crude product, which was filtered off, washed with diluted ethanol (1:3 with water) and dried in vacuo.



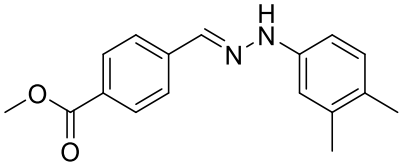
I. **methyl (E)-4-((2-phenylhydrazineylidene)methyl)benzoate.** Yellow solid (yield 90%, 229 mg), mp 138 °C, Anal. Calcd for $C_{15}H_{14}N_2O_2$ (M=254.28). ^{1}H NMR (300 MHz, DMSO-d6) δ 10.64 (s, 1H, -NH), 7.94 (d, *J* = 8.3 Hz, 2H, arom), 7.88 (s, 1H, -CH), 7.74 (d, *J* = 8.2 Hz, 2H, arom), 7.24 (t, *J* = 7.7 Hz, 2H, arom), 7.10 (d, *J* = 8.0 Hz, 2H, arom), 6.79 (t, *J* = 7.0 Hz, 1H, arom), 3.83 (s, 3H, -OCH_3). ^{13}C NMR (75 MHz, DMSO) δ 166.5, 145.1, 140.9, 135.2, 130.0, 129.6, 128.6, 125.9, 119.9, 112.6, 52.5, 40.5. Smile notation COC(=O)C1=CC=C(\C=N\NC2=CC=CC=C2)C=C1



II. **methyl (E)-4-((2-(p-tolyl)hydrazineylidene)methyl)benzoate.** Yellow solid (yiled 83%, 222 mg), mp 107 °C. Anal. Calcd for $C_{16}H_{16}N_2O_2$ (M=268.31). ^{1}H NMR (300 MHz, DMSO-d6) δ 10.66 (s, 1H, -NH), 8.04-7.98 (m, 2H,), 7.40-7.36 (m, 2H, arom), 7.21-717 (m, 2H, arom), 7.21-7.18 (m, 2H, arom), 6.12-7.07 (m, 3H, arom, -CH), 3.83 (s, 3H, -OCH_3). 2.30 (s, 3H, -CH_3). ^{13}C NMR (75 MHz, DMSO) δ 20.3, 50.2, 115.5, 128.4, 128.9, 129.4, 130.9, 131.9, 134.0, 141.4, 142.8, 166.6 Smile notation COC(=O)C1=CC=C(\C=N\NC2=CC=C(C)C=C2)C=C1

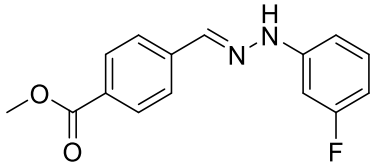


III. **methyl (E)-4-((2-(4-methoxyphenyl)hydrazineylidene)methyl)benzoate.** Yellow solid (yield 68%, 235mg), mp 142 °C. Anal. Calcd for $C_{16}H_{16}N_2O_3$ (M=284.31). ^{1}H NMR (300 MHz, DMSO-d6) δ 10.46 (s, 1H, -NH), 7.93 (d, *J* = 8.0 Hz, 2H, arom), 7.81 (s, 1H, -CH), 7.71 (d, *J* = 8.0 Hz, 2H, arom), 7.04 (d, *J* = 8.4 Hz, 2H, arom), 6.85 (d, *J* = 8.2 Hz, 2H, arom), 3.83 (s, 3H, -OCH_3), 3.70 (s, 3H, -CH_3). ^{13}C NMR (75 MHz, DMSO) δ 153.4, 141.1, 139.1, 134.0, 130.0, 128.2, 125.6, 115.1, 113.7, 55.7, 52.5, 40.5. Smile notation COC(=O)C1=CC=C(\C=N\NC2=CC=C(OC)C=C2)C=C1

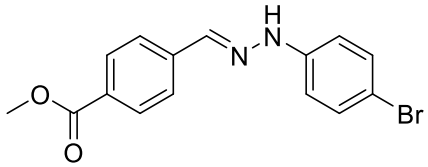


IV. **methyl (E)-4-((2-(3,4-dimethylphenyl)hydrazineylidene)methyl)benzoate.** Yellow solid (yield 86%, 242mg), mp 108 °C. Anal. Calcd for $C_{17}H_{18}N_2O_2$ (M=282.34). ^{1}H NMR (300 MHz, DMSO-d6) δ 10.48 (s, 1H, -NH), 7.93 (d, *J* = 8.1 Hz, 2H, arom), 7.83 (s, 1H, -CH), 7.72 (d, *J* = 8.2 Hz, 2H, arom), 6.99 (d, *J* = 8.1 Hz, 1H, arom), 6.91 (s, 1H, arom), 6.83 (d, *J* = 8.0 Hz, 1H, arom), 3.84 (s, 3H, -

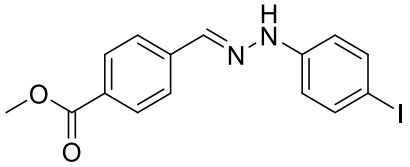
OCH_3), 2.18 (s, 3H, -CH_3), 2.12 (s, 3H, -CH_3). ^{13}C NMR (75 MHz, DMSO) δ 166.5, 143.1, 141.1, 137.2, 134.3, 130.5, 130.0, 128.3, 127.4, 125.7, 114.0, 110.2, 52.5, 40.5, 20.2, 19.0. Smile notation COC(=O)C1=CC=C(\C=N\NC2=CC(C)=C(C)C=C2)C=C1



V. **methyl (E)-4-((2-(3-fluorophenyl)hydrazineylidene)methyl)benzoate.** Yellow solid (yield 77 %, 209 mg), mp 114 °C. Anal. Calcd for $C_{15}H_{13}FN_2O_2$ (M= 272.09). ^{1}H NMR (300 MHz, DMSO-d6) δ 10.74 (d, *J* = 58.1 Hz, 1H, NH), 7.98 - 7.85 (m, 3H, arom, -CH), 7.81 – 7.70 (m, 2H, arom), 7.09 (d, *J* = 6.8 Hz, 2H, arom), 6.88 (t, *J* = 10.4 Hz, 1H, arom), 3.84 (s, 3H, -OCH_3). ^{13}C NMR (75 MHz, DMSO) δ 166.5, 141.8, 140.8, 140.4, 136.6, 135.3, 130.0, 129.0, 128.6, 126.2, 116.3, 113.6, 108.8, 52.5. Smile notation COC(=O)C1=CC=C(\C=N\NC2=CC(F)=CC=C2)C=C1



VI. **methyl (E)-4-((2-(4-bromophenyl)hydrazineylidene)methyl)benzoate.** Yellow solid (yield 87%, 288mg), mp 122°C. Anal. Calcd for $C_{15}H_{13}BrN_2O_2$ (M=332.18). ^{1}H NMR (300 MHz, DMSO-d6) δ 10.85 – 10.74 (m, 1H, -NH), 7.99 – 7.88 (m, 3H, arom, -CH), 7.76 (d, *J* = 7.8 Hz, 2H, arom), 7.38 (d, *J* = 8.1 Hz, 2H, arom), 7.06 (d, *J* = 8.0 Hz, 2H, arom), 3.84 (s, 3H, -OCH_3). ^{13}C NMR (75 MHz, DMSO) δ 166.4, 144.5, 140.6, 136.2, 132.2, 130.0, 128.8, 126.1, 114.6, 110.7, 52.5, 40.7. Smile notation COC(=O)C1=CC=C(\C=N\NC2=CC=C(Br)C=C2)C=C1



VII. **methyl (E)-4-((2-(4-iodophenyl)hydrazineylidene)methyl)benzoate.** Yellow solid (yield 92%, 350mg), mp 131 °C. Anal. Calcd for $C_{15}H_{13}IN_2O_2$ (M=380.18). ^{1}H NMR (300 MHz, DMSO-d6) δ 10.76 (s, 1H, -NH), 7.94 (d, *J* = 8.3 Hz, 2H, arom), 7.88 (s, 1H, -CH), 7.75 (d, *J* = 8.3 Hz, 2H, arom), 7.53 (d, *J* = 8.5 Hz, 2H, arom), 6.94 (d, *J* = 8.6 Hz, 2H, arom), 3.84 (s, 3H, -OCH_3). ^{13}C NMR (75 MHz, DMSO) δ 166.4, 138.0, 136.3, 135.6, 130.0, 128.9, 126.1, 124.4, 115.2, 52.5, 40.5. Smile notation COC(=O)C1=CC=C(\C=N\NC2=CC=C(I)C=C2)C=C1

NMR interpretation

At 300 MHz ,in the ^{1}H NMR spectrum of compounds in DMSO-d_6 solvent, signals of N-H and -CH=N-protons resonated in singlet form at 10.46-10.85 and 7.81-7.88 parts per million (ppm), respectively. All aromatic (6.79-7.99) and aliphatic -CH_3 and -$(CH_3)_2$, -OCH_3) protons were observed in the expected areas. In the 13C NMR spectra of corresponding phenylhydrazones (compounds 1-7) all carbon atoms were also found at expected regions.

3. Results and Discussion

3.1. Acute Mouse Toxicity Prediction

In humans and rodents, chemical toxicity (toxicity) can be associated with many dangerous biological effects, such as gene damage, carcinogenicity or fatal diseases. It is important to assess the degree of toxicity (toxicity) of all commercial chemicals, especially high-volume compounds (HPV)1, as well as drugs or pharmaceuticals or candidates for use as drugs, because these compounds can directly affect human health. Many Quantitative Structure Activity Relationship (QSAR) models have been developed to address this problem. One of the main goals of modern chemistry is to determine the relationship between the structures and properties of compounds. It should be noted that the number of synthesized organic compounds is increasing dramatically, therefore prior quantification of specific properties based on physicochemical parameters of compounds before new compounds are synthesized is one of the urgent issues. It first began with the idea of scientists looking for a quantitative relationship between the structure and properties of compounds and expressing this in the form of mathematical equations. Currently, QSAR is used as an indicator (descriptor) of chemical structures (Veerasamy *et al*., 2011).

As a descriptor - any parameter that characterizes an organic compound (molecule mass, number of atoms (hybridized), bonds or clusters, molecule size, atomic charge, etc.) can be used. During calculus by means of QSAR, steric, topological specificity, electronic effects, lipophilicity of the structure, such as descriptor, are usually taken. Thus, at the expense of structure descriptors, QSAR determines the persistence of the molecule-bioformal, ionization or polynomial of the compound at the expense of electron effluents and the solubility in fats on the basis of lipophilicity. As a result of these records, QSAR estimates that the drug may cross different types of biological barriers and tissue membranes.

Through the QSAR model we have used, it is possible to predict the toxicity and biological activity of substances in 21 indicators. One of the indicators mentioned is Acute Mouse Toxicity (Acute Rat Toxicity), which gives an overview of the LD50 indicator in white mice with 4 types of intestinal, intravenous, abdominal internal, subcutaneous tract (Veerasamy *et al*., 2011).

Rodents refer to experiments on mice and rats. Due to the large number of such tests in the literature, QSAR models were developed based on these tests. It uses a database based on the SYMYX MDL Toxicity Database, which combines data on the high toxicity of ~10,000 chemical compounds to rats. By acute toxicity, we mean the negative effects observed after a single exposure of the body to the substance and by LD 50 value, we mean the dose that causes the death of half (50%) of the rodents within a day. Based on the log10 representation of LD 50 values (mmol/kg) for rats as toxicity peaks: mg/kg is understood as the ratio of the substance per kilogram of body weight to milligrams of substance. If the LD 50 value is above 0.5 log10, these compounds are excluded from the system for further analysis.

Pearson's coefficient was calculated as a measure of pairwise similarities of chemical compounds. According to these calculations, the 3 nearest neighbor compounds in the training set of the proposed compound are found. The common similarities of our compound with the 3 similar compounds found during the evaluation of the AD-compound application area are used and based on this we can say whether the Synthesized

compound falls into the AD of the given models or not. If the given indicators are highly similar, we write in the form of AD.

The SMILES (Simplified Molecular Input Line Entry System) was used as input for various computer models. SMILES strings were obtained from http://www.swissadme.ch/.

At the same time, toxicity classes are given in the program, which in turn are determined according to the Global Harmonized Classification System of Chemical Substances Labeling (UNECE- 2019): the classes and their degree of harm are listed below. Class 1-More harmful (LD50 ≤ 5), Class 2-harmful (5 < LD50 ≤ 50), Class 3-Less harmful (50 < LD50 ≤ 300, Class 4- relatively harmful (300 < LD50 ≤ 2000), Class 5-Practically harmless (2000 < LD50 ≤ 5000), Class 6-means harmless (LD50 > 5000).

Table 1. Characteristic Values Predictions of Rat Ld50 Qsar Models

Compounds	Rat IP LD50 Log10(mmol/kg)	Rat IV LD50 log10(mmol/kg)	Rat Oral LD50 log10(mmol/kg)	Rat SC LD50 log10(mmol/kg)
1	0,308 in AD	-0,260 in AD	0,913 in AD	0,681 in AD
2	0,216 in AD	-0,390 in AD	0,728 in AD	0,789 out of AD
3	0,200 in AD	-0,411 in AD	0,621 in AD	0,793 in AD
4	0,469 in AD	-0,461 in AD	0,727 in AD	0,536 in AD
5	0,229 in AD	-0,327 in AD	0,762 in AD	0,548 in AD
6	0,178 in AD	-0,405 in AD	0,738 in AD	0,889 in AD
7	0,163 in AD	0,004 in AD	0,801 in AD	0,682 out of AD

Routes of internal administration are summarized in the tables as follows: IP - intraperitoneal route, IV- intravenous route, Oral - Oral route, SC - subcutaneous route.

Considering all the above, the Acute Rat Toxicity properties were calculated based on the QSAR model of phenylhydrazones containing the benzoate group and the following results were obtained (Table 1).

As can be seen from the table, intraperitoneal and intravenous indicators for oral administration of all phenylhydrazones are below 0.5 log10. Oral and subcutaneous intake is higher than 0.5 log10, so it is removed from the system at a later stage. The following table shows the ratio of the given milligrams of synthesized phenylhydrazones per kilogram of body weight of rats (Table 2).

Table 2. Ratio of the given milligrams compounds per kilogram of body weight of rats

Compounds	Rat IP LD50 (mg/kg)	Rat IV LD50 (mg/kg)	Rat Oral LD50 (mg/kg)	Rat SC LD50 (mg/kg)
1	516,300 in AD	139,700 in AD	2080,000 in AD	1219,000 in AD
2	441,500 in AD	109,400 in AD	1433,000 in AD	1649,000 out of AD
3	450,600 in AD	110,300 in AD	1188,000 in AD	1766,000 in AD
4	831,900 in AD	97,690 in AD	1507,000 in AD	970,500 in AD
5	460,900 in AD	128,200 in AD	1575,000 in AD	962,000 in AD
6	501,500 in AD	131,100 in AD	1822,000 in AD	2582,000 in AD
7	553,400 in AD	383,300 in AD	2404,000 in AD	1829,000 out of AD

In the given tables, compounds 2 and 7 show out of AD administration by the subcutaneous route, which means that their similarity to the compounds in the system base was not detected by this route. The Acute Rodent Toxicity Classification of Chemical Compounds is reflected in the table below (Table 3).

Table 3. Acute Rodent Toxicity Classification of Chemical Compounds by OECD

Compounds	Rat IP LD50 Classification	Rat IV LD50 Classification	Rat Oral LD50 Classification	Rat SC LD50 Classification
1	Class 5 in AD	Class 4 in AD	Class 5 in AD	Class 5 in AD
2	Class 4 in AD	Class 4 in AD	Class 4 in AD	Class 5 out of AD
3	Class 4 in AD	Class 4 in AD	Class 4 in AD	Class 5 in AD
4	Class 5 in AD	Class 4 in AD	Class 4 in AD	Class 4 in AD
5	Class 4 in AD	Class 4 in AD	Class 4 in AD	Class 4 in AD
6	Class 5 in AD	Class 4 in AD	Class 4 in AD	Non Toxic in AD
7	Class 5 in AD	Class 5 in AD	Class 5 in AD	Class 5 out of AD

As can be seen from the table, compounds are considered relatively harmful to practically harmless. Only compound 2 and 7 are believed to be safe when taken by the intradermal route.

Thus, the indicators given to us by the Acute Rat Toxicity program show how toxic the synthesized compounds are and what category of harm they fall into.

3.2. A Predicted Inhibitor Against Viral Proteins

The concept of virus is one of the main global problems of the modern world. Recent times are one of the biggest examples of this in the pandemics that have occurred in humanity. For example, more than 6 million people have died during the Covid19 pandemic, which shows how important vaccines are to save lives. However, even though emerging vaccines reduce the risks of diseases, they are not fully effective and for this reason, computer programs are used to get higher results with less time and money. As we have already mentioned, it is possible to pre-predict how active a compound with suspected antiviral activity is through computer programs and as a result, get more results with less experience. One of the programs used by researchers is the AntiVir-Pred (dos Santos *et al*., 2022) method on the Way2Drug website, where we have reported predicted inhibitors against viral proteins for 7 phenylhydrazones synthesized on the basis of ethoxy benzaldehyde.

It should be noted that the protein target for Dengue virus type 2 is Genome polyprotein, DNA polymerase for Vaccinia virus (strain Western Reserve) (VACV) (Vacciniavirus (strainWR)), 3C-likeprotease for Infectious bronchitis virus, Genome polyprotein for Coxsackievirus B3 (strain Nancy), SARS coronavirus 3C-like proteinase for SARS coronavirus, Dengue virus type 2(strain Thailand/16681/1984) (DENV-2) for Dengue virus type 2 NS3 protein, Human immunodeficiency virus type 2 integrase, Severe acute respiratory syndrome coronavirus 2 for Replicase polyprotein 1ab, Hepatitis C virus genotype 1b(isolate BK) (HCV) for Genome polyprotein, Hepatitis C virus type 3(isolate NZL1) (HCV) for Genome polyprotein (Table 4).

Table 4. Predicted inhibitors against viral proteins

Compounds / **Virus**	1	2	3	4	5	6	7
Dengue virus type 2	0.7460	0.7351	0.7965	0.7661	0.5342	0.7984	0.5679
Vaccinia virus (strain Western Reserve) (VACV) (Vaccinia virus (strainWR))	0.2475	0.2749	0.2365	0.2498	-	0.3205	-
Infectious bronchitis virus	0.1712	0.1685	0.2133	0.1569	0.1030	0.2361	0.0079
Coxsackievirus B3 (strain Nancy)	0.1383	0.1256	0.1271	0.1085	0.1739	0.1386	0.0871
SARS coronavirus	0.0257	-	0.0123	-	-	0.0334	0.1403
Dengue virus type 2 (strain Thailand/16681/1984)(DENV-2)	0.0178	0.0033	0.0288	-	-	-	-
Human immunodeficiency virus 2	0.0112	0.0746	-	0.0362	0.0530	-	-
Severe acute respiratory syndrome coronavirus 2	-	-	-	-	-	0.0738	0.2200
Hepatitis C virus genotype 1b (isolate BK) (HCV)	-	-	-	-	-	0.0275	0.0079
Hepatitis C virus genotype 3a (isolate NZL1) (HCV)	-	-	-	-	-	0.0009	-

According to the given data, the highest result is Genome polyprotein (0.7460-0.5679), which indicates a protein target that can have an effect against Dengue virus type 2. The weakest result also shows against Genome polyprotein, which shows 6 compounds (0.009) against Hepatitis C virus genotype 3a (isolate NZL1) (HCV). As a result, in the future, phenylhydrazones synthesized on the basis of ethoxy benzaldehyde can be considered as a vaccine against Dengue virus type 2.

3.3. Antibacterial Activity Prediction

AntiBac-Pred (Pogodin *et al*., 2019) allows the researcher to predict the fact that a chemical compound can inhibit the growth of one or more of 353 bacteria at a concentration below 10,000 nM. A value is given for the synthesized compounds, which indicates its activity. That is, the name of the chemical compounds indicates the difference between the probability of inhibiting the growth of the listed bacteria. The higher the value, the more likely the prediction is correct. The same study was conducted for 7 phenylhydrazones synthesized on the basis of ethoxy benzaldehyde and the obtained results are reflected in the table below (Table 5).

Table 5. Predicted inhibitors against bacteria

Compounds / **Bacteria**	1	2	3	4	5	6	7
Mycobacterium tuberculosis	0.2698	0.2411	0.2446	0.2659	0.2601	0.2359	0.0923
Yersinia pestis	0.1412	0.2685	0.2154	0.1091		0.3701	
Mycobacterium phlei	0.1266	0.1203	0.1163	0.0956	0.1136	0.1052	0.0252
RESISTANT Helicobacter pylori	0.1062	0.0700	0.1287	0.0386	0.0419		
Kocuria rhizophila	0.0890	0.0500	0.1913	0.0165		0.2562	

RESISTANT Mycobacterium phlei	0.0583	0.0627	0.0575	0.0551	0.0187	0.0421	0.1309
Staphylococcus saprophyticus	0.0460		0.0272		0.0906	0.1532	
RESISTANT Mycobacterium fortuitum	0.0297	0.0042	0.0494		0.0355		
Salmonella enterica subsp. Enterica	0.0276						
Listonella anguillarum	0.0200	0.0334	0.0145	0.0133		0.0213	
Nocardia nova	0.0162						
Staphylococcus aureus subsp. aureus RN4220	0.0150	0.0052	0.0198			0.0573	
Streptococcus suis	0.0130						
RESISTANT Mycobacterium tuberculosis H37Rv	0.0058			0.0008	0.0375	0.0868	0.0012
Mycobacterium scrofulaceum	0.0028					0.0250	
Neisseria gonorrhoeae		0.0282				0.0233	
Pseudomonas fluorescens		0.0153	0.0481			0.0850	
RESISTANT Bacillus cereus		0.0077					
RESISTANT Prevotella intermedia				0.0269			
Dialister micraerophilus				0.0194			
Bacillus sphaericus					0.0552		
RESISTANT Salmonella typhi					0.0069		
RESISTANT Staphylococcus aureus subsp. aureus MW2						0.2240	
Mycobacterium mageritense						0.1443	
RESISTANT Mycobacterium avium						0.0687	
Streptococcus mutans						0.0355	0.0982
Mycobacterium gordonae						0.0227	
Staphylococcus haemolyticus						0.0046	
Staphylococcus warneri							0.4728
Mycobacterium tuberculosis H37Ra							0.0340
RESISTANT Bacillus subtilis							0.0193

As can be seen from the Table 5, the highest result was 1 compound for Mycobacterium tuberculosis and 6 compounds for Yersinia pestis bacteria, which allows us to predict how these compounds will be important in the fight against bacteria in the future.

3.4. Antifungal Activity Prediction

By means of the AntiFun program (PASS Online (AntiFun-Pred)) (Zaidi *et al*., 2024), it is possible to predict whether the growth of one or more of the 38 fungi can be inhibited at a concentration below 5000 nM. A value is given for the synthesized compounds, which indicates its activity. That is, the name of the chemical compounds indicates the difference between the probability of inhibiting the growth of the listed bacteria. The higher the value, the more likely the prediction is correct. The same study was carried out for 7 phenylhydrazones synthesized on the basis of ethoxy benzaldehyde and the obtained results are reflected in the table below.

Table 6. Predicted inhibitors fungus

Compounds / **Name**	1	2	3	4	5	6	7
Galactomyces geotrichum	0.1645	0.1674	0.1620	0.1718	0.1430	0.1357	0.1357
Epidermophyton floccosum	0.1180	0.0040	0.1393	-	0.1136		
Microsporum canis	0.0674	0.0642	0.0762	-	0.0710	0.1303	
Trichophyton mentagrophytes						0.1533	
Candida Albicans							0.0565

The following table lists Galactomyces geotrichum (modern name Galactomyces candidus) fungus, the Epidermophyton floccosum fungus that causes nails and skin infection, Microsporum canis fungus that infects the upper dead layers of pets and humans, Trichophyton mentagrophytes fungus that causes haircuts, Candida Albicans fungus that causes respiratory, gastrointestinal and female genital infections (Table 6).

The highest result, as can be seen from the table, was 4 combinations of Galactomyces against the fungus geotrichum, which allows us to tell you in advance how important this combination will be in the fight against fungi in the future.

3.5. Prediction of antiretroviral activity and treatment of HIV-related comorbids

The HIV/AIDS pandemic was first observed in the early 1980s. The virus known as human immunodeficiency virus (HIV-1) was caused by a new type of retrovirus. According to the data provided by the WHO-World Health Organization, 38 million people have been infected with this virus and 33 million people have died from this disease. To prevent this, scientists have applied to a number of scientific fields. Through intense efforts by many experts in retrovirology, medicinal chemistry, enzymology, computational modeling and structural biology, a number of antiretroviral drugs have been developed to target several different stages of the viral life cycle, cell attachment and entry and viral activity. However, unfortunately, the existing drugs did not provide complete treatment, showed serious side effects and caused the emergence of resistant strains. For this reason, synthetics initially turn to computer programs, one of which is

the QUSAR model. Both the effects of the compound on HIV-1 targets were obtained with QUSAR models and the biological activities related to the treatment of HIV-related diseases were obtained with the PASS computer program. AntiHIV-Pred (Stolbov *et al*., 2020; Kaku *et al*., 2020; Rosa *et al*., 2014) examines the prediction of antiretroviral activity and treatment implications for HIV-related comorbidities. Comorbid - the simultaneous presence of two or more diseases or medical conditions in one patient. The main goal of these studies is to focus on HIV-1 PR (Protease HIV-1), which is a valuable target for antiretroviral drugs. At the same time, there are targets such as Reverse transcriptase (HIV-1), Integrase (HIV-1), REV (HIV-1), TAT (HIV-1), which were quickly recognized as potential targets for the synthesis of antiretroviral drugs.

AntiHIV-Pred was investigated for phenylhydrazones synthesized on the basis of ethoxy benzaldehyde and the results are reflected in the table below (Table 7).

Table 7. HIV Comorbidities Spectrum of Activity

Compound	Target	Value	Probability	Application Domain
1.	Protease (HIV-1)	pIC50	3.545	not in AD
2.	Protease (HIV-1)	pIC50	4.231	not in AD
3.	Protease (HIV-1)	pIC50	4.245	not in AD
4.	Protease (HIV-1)	pIC50	4.709	not in AD
5.	Protease (HIV-1)	pIC50	4.352	not in AD
6.	Protease (HIV-1)	pIC50	2.91	not in AD
7.	Protease (HIV-1)	pIC50	3.882	not in AD

Compound	Target	Value	Probability	Application Domain
1.	Reverse transcriptase (HIV-1)	pIC50	5.644	not in AD
2.	Reverse transcriptase (HIV-1)	pIC50	6.745	not in AD
3.	Reverse transcriptase (HIV-1)	pIC50	6.393	not in AD
4.	Reverse transcriptase (HIV-1)	pIC50	6.769	not in AD
5.	Reverse transcriptase (HIV-1)	pIC50	6.179	not in AD
6.	Reverse transcriptase (HIV-1)	pIC50	5.406	not in AD
7.	Reverse transcriptase (HIV-1)	pIC50	5.764	not in AD

Compound	Target	Value	Probability	Application Domain
1.	Integrase (HIV-1)	pIC50	4.19	not in AD
2.	Integrase (HIV-1)	pIC50	4.682	not in AD
3.	Integrase (HIV-1)	pIC50	4.823	not in AD
4.	Integrase (HIV-1)	pIC50	4.422	not in AD
5.	Integrase (HIV-1)	pIC50	5.071	not in AD
6.	Integrase (HIV-1)	pIC50	4.464	not in AD
7.	Integrase (HIV-1)	pIC50	4.515	not in AD

Compound	Target	Value	Probability	Application Domain
1.	REV (HIV-1)	pIC50	4.871	not in AD
2.	REV (HIV-1)	pIC50	4.924	not in AD
3.	REV (HIV-1)	pIC50	4.731	not in AD
4.	REV (HIV-1)	pIC50	4.89	not in AD
5.	REV (HIV-1)	pIC50	4.645	not in AD
6.	REV (HIV-1)	pIC50	4.866	not in AD
7.	REV (HIV-1)	pIC50	4.737	not in AD

Compound	Target	Value	Probability	Application Domain
1.	TAT (HIV-1)	pIC50	inactive	not in AD
2.	TAT (HIV-1)	pIC50	inactive	not in AD
3.	TAT (HIV-1)	pIC50	active	not in AD
4.	TAT (HIV-1)	pIC50	inactive	not in AD
5.	TAT (HIV-1)	pIC50	inactive	not in AD
6.	TAT (HIV-1)	pIC50	active	not in AD
7.	TAT (HIV-1)	pIC50	active	not in AD

Compound	combination	Pa	Pi
1.	Preneoplastic conditions treatment	0.693	0.007
2.	Preneoplastic conditions treatment	0.608	0.016
3.	Preneoplastic conditions treatment	0.715	0.005
4.	Preneoplastic conditions treatment	0.578	0.021
5.	Preneoplastic conditions treatment	0.513	0.037
6.	Preneoplastic conditions treatment	0.551	0.027
7.	Preneoplastic conditions treatment	0.551	0.027

If we interpret the table given above as follows, in AD - the combination falls within the scope of application of models, out of AD - it is outside the scope of application of complex models. As can be seen from the tables, synthesized phenyl hydrazones are not in the field of application for all targets. At the same time, it indicates the probability of Pa being active and the probability of Pi being inactive. If Pa>Pi, it means that the combinations are likely to be useful for the treatment of HIV-related comorbidities. Consequently, our respective compounds may be used for the treatment of preneoplastic conditions. pIC50 = -log(IC50). The IC50 represents the concentration of a compound required for 50% inhibition-the larger the pIC50 value, the more potent the compound. And the highest result shows for reverse transcriptase (HIV-1) (5.406-6.745). It is also known from the results in the table that 7 phenylhydrazone synthesized on the basis of ethoxy benzaldehyde can be used for the treatment of comorbid diseases.

3. Conclusion

Possible toxicological risks, antiviral, antibacterial, antifungal activities and antiretroviral activities of the corresponding phenylhydrazones synthesized by us through five online computer programs - GUSAR (Acute Rat Toxicity), PASS Online (AntiVir-Pred), PASS Online (AntiBac-Pred), PASS Online (AntiFun-Pred), PASS Online (AntiHiv-Pred) were evaluated and the obtained results show that the compounds can be recommended as effective drugs in the treatment of a number of diseases.

References

Al-Kahraman, Y.M., Yasinzai, M. & Singh, G.S. (2012). Evaluation of some classical hydrazones of ketones and 1, 2-diketones as antileishmanial, antibacterial and antifungal agents. *Archives of Pharmacal Research*, 35, 1009-1013. https://doi.org/10.1007/s12272-012-0608-7

Borawska, M.H., Koczoń, P., Piekut, J., Świsłocka, R. & Lewandowski, W. (2009). Vibrational spectra and antimicrobial activity of selected bivalent cation benzoates. *Journal of Molecular Structure, 919*(1-3), 284-289. https://doi.org/10.1016/j.molstruc.2008.09.018

Chipley, J.R. (2020). Sodium benzoate and benzoic acid. In *Antimicrobials in Food*, 41-88. CRC Press.

Corey, E.J., Enders, D. (1976). Synthetic routes to polyfunctional molecules via metallated N, N-dimethylhydrazones. *Tetrahedron Letters*, *17*(1), 11-14. https://doi.org/10.1016/S0040-4039(00)71309-8

dos Santos, A.F., Ortiz, M.M., Montagner, G.E., Schultz, J.V., Gomes, P., da Silva, I.Z. & Fagan, S.B. (2022). In-Silico study of antivirals and non-antivirals for the treatment of SARS-COV-2. *Disciplinarum Scientia| Naturais e Tecnológicas*, *23*(2), 57-83. https://doi.org/10.37779/nt.v23i2.4200

El-Azab, A.S., Ghabbour, H.A., El-Husseiny, W.M., Maarouf, A.R., Mohamed, M.A. & Abdel-Aziz, A.A.M. (2016). Lewis acid-promoted direct synthesis of N-unsubstituted hydrazones via the reaction of hydrazine with acetophenone and isatin derivatives. *Russian Journal of General Chemistry*, 86, 2837-2844. https://doi.org/10.1134/S1070363216120471

Gane, P.J., Dean, P.M. (2000). Recent advances in structure-based rational drug design. *Current Opinion in Structural Biology*, *10*(4), 401-404. https://doi.org/10.1016/S0959-440X(00)00105-6

Hassan Baig, M., Ahmad, K., Roy, S., Mohammad Ashraf, J., Adil, M., Haris Siddiqui, M. & Choi, I. (2016). Computer aided drug design: success and limitations. *Current Pharmaceutical Design*, *22*(5), 572-581.

Januario, J.P., De Souza, T.B., Lavorato, S.N., Maiolini, T.C., Domingos, O.S., Baldim, J.L. & Dos Santos, M.H. (2018). Design and synthesis of new benzophenone derivatives with in vivo anti-inflammatory activity through dual inhibition of edema and neutrophil recruitment. *Molecules*, *23*(8), 1859. https://doi.org/10.3390/molecules23081859

Kaku, Y., Kuwata, T., Gorny, M.K. & Matsushita, S. (2020). Prediction of contact residues in anti-HIV neutralizing antibody by deep learning. *Japanese Journal of Infectious Diseases*, *73*(3), 235-241. https://doi.org/10.7883/yoken.JJID.2019.496

Kim, S., Chen, J., Cheng, T., Gindulyte, A., He, J., He, S. & Bolton, E.E. (2019). PubChem 2019 update: improved access to chemical data. *Nucleic Acids Research*, *47*(D1), D1102-D1109. https://doi.org/10.1093/nar/gky1033

Kim, S., Thiessen, P.A., Bolton, E.E., Chen, J., Fu, G., Gindulyte, A. & Bryant, S.H. (2016). PubChem substance and compound databases. *Nucleic Acids Research*, *44*(D1), D1202-D1213. https://doi.org/10.1093/nar/gkv951

Kitaev, Yu.P., Buzykin, B.I. (1974). *Hydrazones*. Moscow, 415. (In Russian).

Krajníková, A., Rotaru, A., Győryová, K., Homzová, K., Manolea, H. O., Kovářová, J. & Hudecová, D. (2015). Thermal behaviour and antimicrobial assay of some new zinc (II) 2-aminobenzoate complex compounds with bioactive ligands. *Journal of Thermal Analysis and Calorimetry*, 120, 73-83. https://doi.org/10.1007/s10973-010-1161-6

Lagunin, A., Zakharov, A., Filimonov, D. & Poroikov, V. (2011). QSAR modelling of rat acute toxicity on the basis of PASS prediction. *Molecular Informatics*, *30*(2-3), 241-250. https://doi.org/10.1002/minf.201000151

Li, Q., Cheng, T., Wang, Y. & Bryant, S.H. (2010). PubChem as a public resource for drug discovery. *Drug Discovery Today*, *15*(23-24), 1052-1057. https://doi.org/10.1016/j.drudis.2010.10.003

Macalino, S.J.Y., Gosu, V., Hong, S. & Choi, S. (2015). Role of computer-aided drug design in modern drug discovery. *Archives of Pharmacal Research*, 38, 1686-1701. https://doi.org/10.1007/s12272-015-0640-5

Maharramov, A.M., Shikhaliyev, N.Q., Suleymanova, G.T., Gurbanov, A.V., Babayeva, G.V., Mammadova, G.Z. & Pombeiro, A.J. (2018). Pnicogen, halogen and hydrogen bonds in (E)-1-(2, 2-dichloro-1-(2-nitrophenyl) vinyl)-2-(para-substituted phenyl)-diazenes. *Dyes and Pigments*, 159, 135-141. https://doi.org/10.1016/j.dyepig.2018.06.022

Mandal, S., Mandal, S.K. (2009). Rational drug design. *European Journal of Pharmacology*, *625*(1-3), 90-100. https://doi.org/10.1016/j.ejphar.2009.06.065

Marshall, G.R. (1987). Computer-aided drug design. *Annual Review of Pharmacology and Toxicology*, *27(*1), 193-213. doi.org/10.1146/annurev.pa.27.040187.001205

Mauger, C., Mignani, G. (2005). The Synthesis of important pharmaceutical building blocks by palladium-catalyzed coupling reaction: Access to various Arylhydrazines. *Advanced Synthesis & Catalysis*, *347*(6), 773-782. https://doi.org/10.1002/adsc.200404392

Mavromoustakos, T., Durdagi, S., Koukoulitsa, C., Simcic, M., G. Papadopoulos, M., Hodoscek, M. & Golic Grdadolnik, S. (2011). Strategies in the rational drug design. *Current Medicinal Chemistry, 18*(17), 2517-2530. https://doi.org/10.2174/092986711795933731

Mlostoń, G., Urbaniak, K., Utecht, G., Lentz, D. & Jasiński, M. (2016). Trifluoromethylated 2, 3-dihydro-1, 3, 4-thiadiazoles via the regioselective [3+ 2]-cycloadditions of fluorinated nitrile imines with aryl, hetaryl and ferrocenyl thioketones. *Journal of Fluorine Chemistry*, 192, 147-154. https://doi.org/10.1016/j.jfluchem.2016.10.018

Mo, Q., Deng, J., Liu, Y., Huang, G., Li, Z., Yu, P. & Yang, F. (2018). Mixed-ligand Cu (II) hydrazone complexes designed to enhance anticancer activity. *European Journal of Medicinal Chemistry*, 156, 368-380. https://doi.org/10.1016/j.ejmech.2018.07.022

Mohanapriya, S., Muthukumaran, M. & Vairam, S. (2016). Synthesis, characterization, thermal behavior and antimicrobial activity of 3-methyl benzoate complexes of transition metal with hydrazine. *Bulletin of the Chemical Society of Ethiopia*, *30*(2), 241-252. https://doi.org/10.4314/bcse.v30i2.8

Nenajdenko, V.G., Shikhaliyev, N.G., Maharramov, A.M., Atakishiyeva, G.T., Niyazova, A.A., Mammadova, N.A. & Tskhovrebov, A.G. (2022). Structural organization of dibromodiazadienes in the crystal and identification of Br··· O halogen bonding involving the nitro group. *Molecules*, *27*(16), 5110. https://doi.org/10.3390/molecules27165110

Nenajdenko, V.G., Shikhaliyev, N.G., Maharramov, A.M., Bagirova, K.N., Suleymanova, G.T., Novikov, A.S. & Tskhovrebov, A.G. (2020). Halogenated diazabutadiene dyes: Synthesis, structures, supramolecular features and theoretical studies. *Molecules*, *25*(21), 5013. https://doi.org/10.3390/molecules25215013

Pogodin, P.V., Lagunin, A.A., Rudik, A.V., Druzhilovskiy, D.S., Filimonov, D.A. & Poroikov, V.V. (2019). AntiBac-Pred: A web application for predicting antibacterial activity of chemical compounds. *Journal of Chemical Information and Modeling*, *59*(11), 4513-4518. https://doi.org/10.1021/acs.jcim.9b00436

Poroikov, V.V., Filimonov, D.A., Gloriozova, T.A., Lagunin, A.A., Druzhilovskiy, D.S., Rudik, A.V. & Pogodin, P.V. (2019). Computer-aided prediction of biological activity spectra for organic compounds: The possibilities and limitations. *Russian Chemical Bulletin*, 68, 2143-2154. https://doi.org/10.1007/s11172-019-2683-0

Rognan, D. (2007). Chemogenomic approaches to rational drug design. *British Journal of Pharmacology*, *152*(1), 38-52. https://doi.org/10.1038/sj.bjp.0707308

Rosa, R.S., Santos, R.H., Brito, Á.Y. & Guimarães, K.S. (2014). Insights on prediction of patients' response to anti-HIV therapies through machine learning. In *2014 International Joint Conference on Neural Networks (IJCNN)*, 3697-3704. https://doi.org/10.1109/IJCNN.2014.6889659

Shakdofa, M.M., Shtaiwi, M.H., Morsy, N. & Abdel-rassel, T. (2014). Metal complexes of hydrazones and their biological, analytical and catalytic applications: A review. *Main Group Chemistry*, *13*(3), 187-218. https://doi.org/10.3233/MGC-140133

Shikhaliyev, N.G., Maharramov, A.M., Bagirova, K.N., Suleymanova, G.T., Tsyrenova, B.D., Nenajdenko, V.G. & Tskhovrebov, A.G. (2021a). Supramolecular organic frameworks derived from bromoaryl-substituted dichlorodiazabutadienes via Cl··· Br halogen bonding. *Mendeleev Communications*, *31*(2), 191-193. https://doi.org/10.1016/j.mencom.2021.03.015

Shikhaliyev, N.G., Maharramov, A.M., Suleymanova, G.T., Babayeva, G.V., Mammadova, G.Z., Shikhaliyeva, I.M. & Nenajdenko, V.G. (2021b). Halogen-bonding in 3-nitrobenzaldehyde-derived dichlorodiazadienes. *Organic Chemistry*, 65-74. https://doi.org/10.24820/ark.5550190.p011.403

Singh, V., Srivastava, V.K., Palit, G. & Shanker, K. (1992). Coumarin congeners as antidepressants. *Arzneimittel-forschung*, *42*(8), 993-996.

Stolbov, L., Druzhilovskiy, D., Rudik, A., Filimonov, D., Poroikov, V. & Nicklaus, M. (2020). AntiHIV-Pred: Web-resource for in silico prediction of anti-HIV/AIDS activity. *Bioinformatics, 36*(3), 978-979. https://doi.org/10.1093/bioinformatics/btz638

Surabhi, S., Singh, B.K. (2018). Computer aided drug design: An overview. *Journal of Drug Delivery and Therapeutics, 8*(5), 504-509. https://doi.org/10.22270/jddt.v8i5.1894

Tan, X.J., Wang, D., Lei, X.G. & Chen, J.P. (2018). Theoretical insight into the disordered structure of (Z)-2-[(E)-(4-methoxybenzylidene) hydrazinylidene]-1, 2-diphenylethanone: the role of noncovalent interactions. *Acta Crystallographica Section C: Structural Chemistry, 74*(9), 1058-1067. https://doi.org/10.1107/S2053229618009762

Torres, P.H., Sodero, A.C., Jofily, P. & Silva-Jr, F.P. (2019). Key topics in molecular docking for drug design. *International Journal of Molecular Sciences, 20*(18), 4574. https://doi.org/10.3390/ijms20184574

Tropsha, A. (2010). Best practices for QSAR model development, validation and exploitation. *Molecular Informatics, 29*(6-7), 476-488. https://doi.org/10.1002/minf.201000061

Veerasamy, R., Rajak, H., Jain, A., Sivadasan, S., Varghese, C.P. & Agrawal, R.K. (2011). Validation of QSAR models-strategies and importance. *International Journal of Drug Design and Discovery, 2*(3), 511-519.

Verma, J., Khedkar, V.M. & Coutinho, E.C. (2010). 3D-QSAR in drug design-a review. *Current Topics in Medicinal Chemistry, 10*(1), 95-115. https://doi.org/10.2174/156802610790232260

Wang, Y., Xiao, J., Suzek, T.O., Zhang, J., Wang, J. & Bryant, S.H. (2009). PubChem: A public information system for analyzing bioactivities of small molecules. *Nucleic acids research, 37*(suppl_2), W623-W633. https://doi.org/10.1093/nar/gkp456

Zaidi, Z., Sharma, G., Sahaya Shibu, B., Khan, M.A., Moin, S. & Sundararajan, G. (2024). In silco prediction of pharmacological properties of the 2-(4-allylpiperazin-1-yl)-1-(1-(4-nitrophenyl)-1h-tetrazol-5-yl) ethanone. *African Journal of Biological Sciences, 6*(Si4), 2522-2540. https://doi.org/10.48047/AFJBS.6.Si4.2024.2522-2540