Acta Scientiarum
http://periodicos.uem.br/ojs/acta
ISSN on-line: 1807-8664
Doi: 10.4025/actascitechnol.v47i1.70639

Potential biological targets prediction and adme profiling of methyl group containing phenyl hydrazones

Gulnar Tofiq Atakishiyeva[1*], Ayten Muzeffer Qajar[1], Gulnara Vali Babayeva[1,2], Nazrin Rafael Zeynalli[1], Nigar Eyvaz Ahmadova[1] and Namiq Qurbet Shikhaliyev[1]

[1]Organic Chemistry Department, Baku State University, Z. Khalilov str. 23, AZ 1148, Baku, Azerbaijan, [2]Department of Analytical and Organic Chemistry, Azerbaijan State Pedagogical University, Baku, Azerbaijan. *Author for correspondence. E-mail: Gulnar.suleymanova.911@gmail.com

ABSTRACT. Hydrazones characterized by the azomethine group (NHN=CH-) are recognized for their potent antimicrobial properties. Concurrently, compounds featuring a methyl group are utilized in the treatment of bacterial infections in humans and animals. Taking all this into account, Swiss ADME and Swiss Targeted Prediction software was used to study biological targets of the synthesized compounds and to create their ADME profiles. New biological targets for phenylhydrazones include Mapping of Bioavailability Radar of substances, ADME Profiling, Egan BOILED EGG, Lipinski Drug ability (ROF) criteria and biological activities based on the obtained results. Thus, obtained results allow us to say that synthesized phenylhydrazones are able to show biological activity.

Keywords: Mapping of bioavailability radar of Phenylhydrazones; biological activities; BOILED-Egg; *ADME* profiling; lipinski drug ability criteria.

Received on December 12, 2023.
Accepted on February 28, 2024.

Introduction

Hydrazones, compounds with -NHN=CH- group, have a number of applications used in the fields of medicinal chemistry for synthesizing biologically active substances (Vicini et al., 2002; Loncle et al., 2004; Savini et al., 2004; Cocco et al., 2006.; Masunari & Tavares, 2007; Vicini et al., 2009), dye industry (Raue et al., 1991), complex compounds (Rollas & Güniz Küçükgüzel, 2007) and so on. The main reason for the wide application area is connected with the structure of hydrazones, which leads to the compounds having electrophilic and nucleophilic properties. As a result of such structural features, hydrazones have demonstrated activities against cancer, worms, depression, fungus, inflammation, swelling, and convulsions (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; Negi et al., 2012; Narang et al., 2012). Various investigations demonstrate that hydrazones containing methyl and tert-butyl groups can be considered as compounds with the expected biological activities.

Meanwhile, we know that the synthesis of new medications is an actual issue. As much actual as this process is it requires effort, time and financial ability. In order to decreas financial issues and increase efficiency, various programs with the ability to predict the biological properties of synthesised compounds are used. The significance of the programs is highlighted by the following example. Exploratory studies, which were conducted on approximately 10,000-30,000 substances, extend approximately a decade and cost up to several billion dollars. Compounds with successful results are directed to preclinical studies, during which their number was reduced to 250. Then, selected the best 5 substances participated in the clinical studies (Dharampreet et al., 2020). This example shows clearly the importance of special programs predicting biological properties.

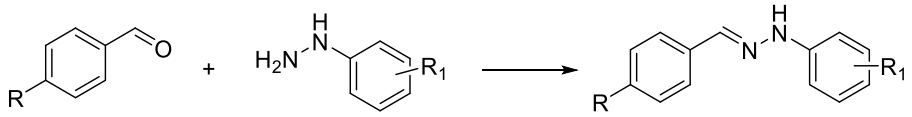
Considering the above-mentioned, the calculating of physicochemical descriptors of synthesized hydrazones by Swiss Targeted Prediction and Swiss ADME softwares, as well as determining absorption, distribution, metabolism, and excretion- ADME parameters, drug design-like nature, drug chemistry compatibility, and related pharmacokinetic properties (Ballester & Richards, 2007; Willett, 2011; Armstrong et al., 2010; Liu et al., 2011; Armstrong et al., 2011; Pérez-Nueno et al., 2012; Sastry et al., 2011) were performed.

Based on obtained results, we are able to predict that the methyl group containing phenyl hydrazones may show biological activity and may be used as medicinal substances in the future.

Material and methods

Unless stated otherwise, all the reagents used in this study were obtained from 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 (DMSO-d6 δH = 2.50ppm, δC = 39.52pp). Predicting the biological targets of synthesized hydrazone derivatives is available for free on the SwissADME software from the website http://www.swissadme.ch .

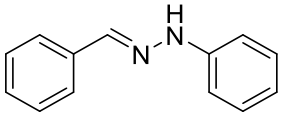
Taking into account that hydrazones, as well as compounds containing methyl groups, show high biological activity, we have synthesized the following phenylhydrazones.



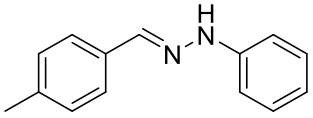
R=H, R_1=H (1), R=CH_3, R_1=H (2)
R=CH_3, R_1=CH_3 (3), R=CH_3, R_1= 3,5$(CH_3)_2$ (4)
R=$C(CH_3)_3$, R_1=H (5), R=$C(CH_3)_3$, R_1=CH_3 (6)
R=$C(CH_3)_3$, R_1= 3,4$(CH_3)_2$ (7)

Synthetic part

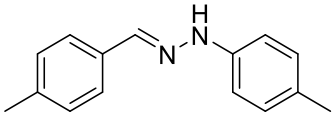
Schiff bases 1–7 were synthesized according to the reported method (Qacar et al., 2020, Nenajdenko et al., 2017, Maharramov et al., 2018, Nenajdenko et al., 2023). A mixture of (2-nitrophenyl) hydrazine hydrochloride (10.2 mmol), CH3COONa (0.82 g) and a corresponding aldehyde (10 mmol) were refluxed with stirring in ethanol (50-100 mL) for 2-5h. 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 (E)-1-benzylidene-2-phenylhydrazine. White solid (yield 92%, 181 mg), mp 122°C, Anal. Calcd for C13H12N2 (M=196.25). ^{1}H NMR (300 MHz, DMSO-d6) δ 6,8-7.7 (m, 10 H, arom), 7,9 (s, 1H, -CH), 10,3 (s, 1H, -NH), ^{13}C NMR (75 MHz, DMSO) δ 112,4, 119,3 , 1126,1 , 128,3, 129,1, 136,3, 136,9, 137,1, 145,8

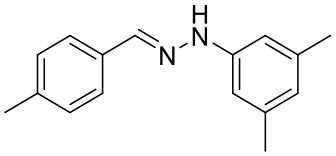


II (E)-1-(4-methylbenzylidene)-2-(p-tolyl)hydrazine. White solid (yiled 82%, 184 mg), mp 111°C. Anal. Calcd for C14H14N2 (M=210.28). ^{1}H NMR (300 MHz, DMSO-d6) δ 10.27 (s, 1H, -NH), 7.84 (s, 1H, -CH), 7.54 (d, *J* = 7.4 Hz, 2H, arom), 7.20 (d, *J* = 7.2 Hz, 3H, arom), 7.07 (d, *J* = 7.5 Hz, 2H, arom), 6.73 (t, *J* = 7.4 Hz, 1H, arom), 2.31 (s, 3H, -CH_3). ^{13}C NMR (75 MHz, DMSO) δ 21.3, 112.3, 118.9, 126.0, 129.5, 129.7, 133.5, 137.0, 137.8, 145.8

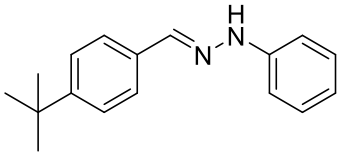


III (E)-1-(4-methylbenzylidene)-2-(p-tolyl)hydrazine. White solid (yield 57%, 128 mg), mp 122°C. Anal. Calcd for C15H16N2 (M=224.31). ^{1}H NMR (300 MHz, DMSO-d6) δ 10.15 (s, 1H, -NH), 7.80 (s, 1H, -CH), 7.52 (d, *J* = 7.4 Hz,

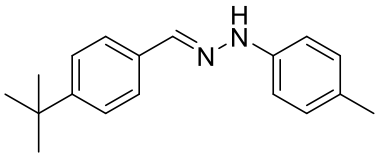
2H, arom), 7.18 (d, *J* = 7.4 Hz, 2H, arom), 7.00 (q, *J* = 7.8 Hz, 4H, arom), 2.30 (s, 3H, -CH_3), 2.21 (s, 3H, -CH_3). ^{13}C NMR (75 MHz, DMSO) δ 20.7, 21.3, 112.3, 125.9, 127.4, 129.6, 129.9, 133.6, 136.3, 137.6, 143.6.



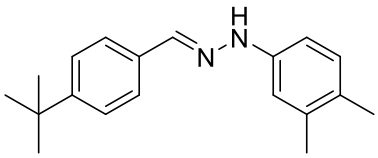
IV (E)-1-(3,5-dimethylphenyl)-2-(4-methylbenzylidene)hydrazine. White solid (yield 57%, 136 mg), mp 122°C. Anal. Calcd for C16H18N2 (M=238.33). ^{1}H NMR (300 MHz, DMSO-d6) δ 9.82 (s, 1H, NH), 7.73 (s, 1H, CH), 7.45 (d, *J* = 8.7 Hz, 2H, arom), 6.99 (d, *J* = 8.2 Hz, 2H, arom), 6.91 (d, *J* = 8.3 Hz, 2H, arom), 6.72 (d, *J* = 8.7 Hz, 2H, arom), 2.93 (s, 6H, -CH_3), 2.20 (s, 3H, -CH_3). ^{13}C NMR (75 MHz, DMSO) δ 20.6, 40.4, 112.1, 112.5, 124.2, 126.7, 127.1, 129.8, 137.5, 144.0, 150.6.



V (E)-1-(4-(tert-butyl)benzylidene)-2-phenylhydrazine. White solid (yield 57%, 144 mg), mp 122°C. Anal. Calcd for C17H20N2 (M=252.36). ^{1}H NMR (300 MHz, DMSO-d6) δ 10.24 (s, 1H, -NH), 7.83 (s, 1H, -CH), 7.55 (d, *J* = 8.1 Hz, 2H, arom), 7.43 – 7.36 (m, 2H, arom), 7.20 (t, *J* = 7.7 Hz, 2H, arom), 7.04 (d, *J* = 8.0 Hz, 2H, arom), 6.73 (t, *J* = 5.7 Hz, 1H, arom), 1.27 (s, 9H, -$C(CH_3)_3$). ^{13}C NMR (75 MHz, DMSO) δ 31.4. 111.7, 112.3, 119.0, 125.8, 129.5, 133.4, 137.0, 145.7, 151.0, 152.9.



VI (E)-1-(4-(tert-butyl)benzylidene)-2-(p-tolyl)hydrazine. White solid (yield 57%, 152 mg), mp 122°C. Anal. Calcd for C18H22N2 (M=266.39). ^{1}H NMR (300 MHz, DMSO-d6) δ 10.11 (s, 1H, -NH), 7.79 (s, 1H, CH), 7.53 (d, *J* = 7.4 Hz, 2H, arom), 7.38 (d, *J* = 7.2 Hz, 2H, arom), 7.01 (d, *J* = 7.5 Hz, 2H, arom), 6.94 (d, *J* = 7.4 Hz, 2H, arom), 2.19 (s, 3H, -CH_3), 1.26 (s, 9H, -$C(CH_3)_3$). ^{13}C NMR (75 MHz, DMSO) δ 20.6, 31.4, 112.3, 125.7, 125.8, 126.4, 127.6, 130.0, 133.5, 136.3, 143.5, 150.6, 150.8.



VII (E)-1-(4-(tert-butyl)benzylidene)-2-(3,4-dimethylphenyl)hydrazine. White solid (yield 57%, 160 mg), mp 122°C. Anal. Calcd for C19H24N2 (M=280.42). ^{1}H NMR (300 MHz, DMSO-d6) δ ^{1}H NMR (300 MHz, DMSO-d6) δ 10.06 (s, 1H, NH), 7.79 (s, 1H, CH), 7.46 (dd, *J* = 46.5, 8.4 Hz, 4H, arom), 7.08 – 6.59 (m, 3H, arom), 2.17 (s, 3H, -CH_3), 2.12 (s, 3H, -CH_3), 1.28 (s, 9H, -$C(CH_3)_3$). ^{13}C NMR (75 MHz, DMSO) δ 19.0, 20.2, 31.5, 34.8, 109.8, 113.7, 125.7, 125.8, 126.4, 130.4, 133.7, 136.1, 137.0, 143.7, 150.7.

Result and discussion

NMR interpretation

Corresponding phenylhydrazones were synthesized in ethanol through the condensation reaction of benzaldehyde derivatives in CH_3COONa medium at a temperature of 78 degrees. 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 10.11–10.3 and 7.79–7.9 parts per million (ppm), respectively. All aromatic (6.8-7.7) and aliphatic –CH_3 and –$(CH_3)_2$, -$C(CH_3)_3$) protons were observed in the expected areas.

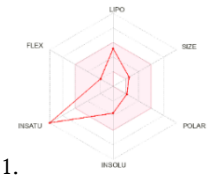
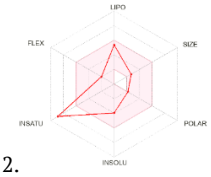
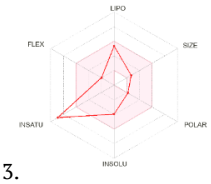
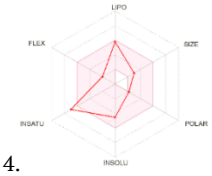
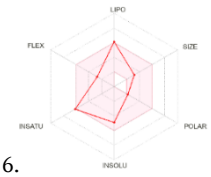
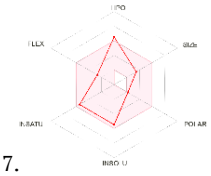
Potential biological targets prediction and ADME profiling

The investigation of new biological targets and ADME properties of phenylhydrazones is considered by means of Swiss ADME and Swiss Targeted Prediction software. New biological targets for phenylhydrazones include Mapping of Bioavailability Radar of substances, ADME Profiling, Egan BOILED EGG, Lipinski Drug ability (ROF) criteria and biological activities

Mapping of bioavailability radar of phenylhydrazones

Firstly, the pharmacokinetic properties of the synthesized phenylhydrazones were studied. Lipophilicity, volume, polarity, insolubility, insaturation and elasticity of compounds are studied by means of the Swiss ADME program (Pastewska et al., 2021, Atakishiyeva et al., 2023, Yousuf et al., 2022). For the six descriptors mentioned below (INSATU, SIZE, INSOLU, FLEX, LIPO, POLAR), red lines are situated in the pink zone, which means that the compounds show good bioavailability properties in the body (Table 1).

Table 1. Activity indicators of hydrazones.

Bioavailability radar	Lipophilicity	Volume	Polarity	Insolubility	Insaturation	Elasticity
 1.	Situated in the pink zone	Situated in the pink zone	Situated in the pink zone	Situated in the pink zone	Situated clearly out of the pink zone	Situated in the pink zone
 2.	Situated in the pink zone	Situated in the pink zone	Situated in the pink zone	Situated in the pink zone	Situated out of the pink zone	Situated in the pink zone
 3.	Situated in the pink zone	Situated in the pink zone	Situated in the pink zone	Situated in the pink zone	Situated out of the pink zone	Situated in the pink zone
 4.	Isn't situated in the pink zone	Situated in the pink zone	Situated in the pink zone	Situated in the pink zone	Situated out of the pink zone	Situated in the pink zone
 5.	Situated in the pink zone	Situated in the pink zone	Situated in the pink zone	Situated in the pink zone	Situated in the pink zone	Situated in the pink zone
 6.	Situated in the pink zone	Situated in the pink zone	Situated in the pink zone	Situated in the pink zone	Situated in the pink zone	Situated in the pink zone
 7.	Situated slightly out of the pink zone	Situated in the pink zone	Situated in the pink zone	Situated in the pink zone	Situated in the pink zone	Situated in the pink zone

From the results obtained by means of the program, it was determined that the insaturation in the radar of the bioavailability of hydrazone, which does not contain any substitution group, has sharply deviated from the pink zone. This sharp deviation decreases with increasing number of methyl groups in the compound.

In the compound (E)-1-(3,5-dimethylphenyl)-2-(4-methylbenzylidene)hydrazine, that is, in the hydrazone containing tret-butyl group, all properties are located in the pink zone. Increasing the number of methyl groups in the compound caused a change in the lipophilic property. Thus, in compound 7 a slight deviation of the lipophilic property was observed.

Generally, as the number of methyl groups in the hydrazones increases, indicators show increasingly good bioavailability radar properties for INSATU, SIZE, INSOLU, FLEX, LIPO, POLAR identifiers.

Biological activities

The similarity of hydrazones, which are supposed to be biologically active, to some enzymes and proteins is compared by means of the Swiss Targeted Prediction program (Figure 1). Thus, screenings are performed to find similar molecules between synthesized phenylhydrazones and other active compounds known to be on trial of the approximately 4,000 proteins. (Daina et al., 2019). In the following table demonstrated this biological activities diagram.

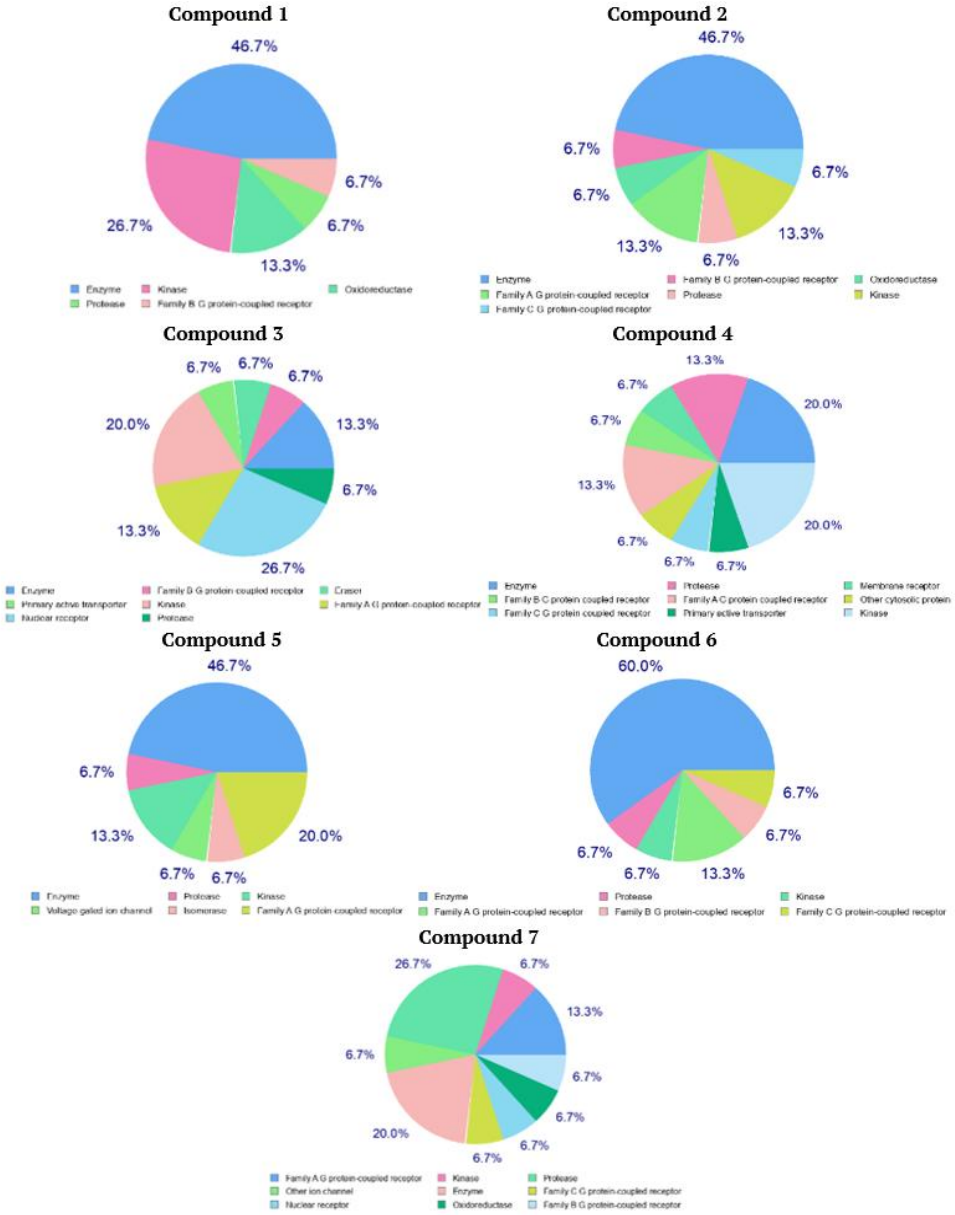


Figure 1. Biological activities of compounds.

Compounds 1, 2, 4, 5 and 6 are predicted to be enzyme inhibitors predominantly, whereas compound 7 is predicted to be a protease inhibitor. Compound 3 is predicted to be a nuclear receptor inhibitor. At the same time, compound 4 is a family of CG protein-coupled receptor.

Egan boiled egg, pi charts of biological activities

Brain or Gut permeability method (Egan BOILED-Egg) was also used by means of SWISS ADME prediction program. The method - Brain or Gut permeability refers to a computer software that gives accurate predictions calculating the polarity and lipophilicity properties for small organic molecules. The principle of operation is as below.

WLOGP and TPSA characterize the total area of the polar surface, and the relationship between them is shown as a graph. These graphs are presented as a white ellipse and a yellow ellipse, which is similar to egg white and yolk. If the compounds are passively absorbed in the gastrointestinal tract they are situated in the white ellipse, if the compounds enter central nervous system despite BBB (meaning Blood-brain barrier) and have high chance of being absorbed they are situated in the yellow ellipse as dots. Compounds with lack of BBB permeability or good absorption are situated in the grey zone.

As for the color of the dots, blue dot compounds are actively absorbed from the gastrointestinal lumen or brain, which allows us to say that they will be substrates of P-glycoprotein (PGP+) , while red dot means the exact opposite (Figure 2).

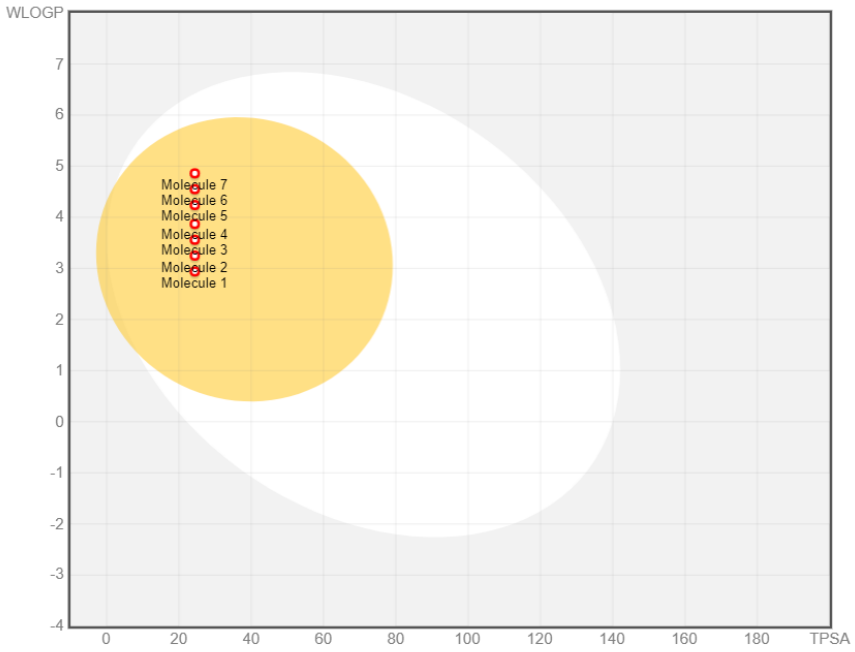


Figure 2. biological activities of phenylhydrazone using Brain or Gut permeability method.

It bears mentioning that all of the 7 compounds were observed as red dots in the white ellipse, so we can say that they enter the central nerve system, but they are non-substrates of P-glycoprotein (PGP-).

ADME Profiling by using Swiss ADME

With additional data from the program, it is possible to do the pharmacokinetic calculation of P-glycoprotein and cytochrome P450 protein. It should be noted that, pharmacokinetics studies the movement trajectory of medicines in the human organism. Cytochromes P450 (also written as P450s or CYPs) refers to a family of enzymes. Thus, their main function is to oxidize protein steroids, and fatty acids in mammals, they are crucial in the synthesis and decomposition of some hormones. From the results of the program, it was determined that all the compounds have good GI absorption and good BBB permeability.

All compounds other than compound 1 showed inhibition against CYP2D6, but compound 5 showed inhibition against CYP2C9. Compounds 2-6 showed inhibition against CYP1A2. As a result, the gastrointestinal absorption of compounds is good. In addition, blood-brain barrier permeability is excellent (Table 2).

Table 2. Pharmacokinetic property of the compounds.

Substance	GI absorption	BB Bermeant	P-gp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor
1	High	+	-	-	+	-	-	-
2	High	+	-	+	+	-	+	-
3	High	+	-	+	+	-	+	-
4	High	+	-	+	+	-	+	-
5	High	+	-	+	+	+	+	-
6	High	+	-	+	+	-	+	-
7.	High	+	-	-	+	-	+	-

Lipinski Drug ability criteria- ROF

Lipinski's five rules- ROF, also known as Pfizer's five rules, are utilized to determine the similarity between drugs and compounds that are drug candidates. These rules are used in order to determine whether the compounds that are assumed to have pharmacological activity show necessary physical and chemical properties.

Since it is impossible to test so many chemical compounds, i.e., ligands, drug-like properties of substances are investigated.

For this purpose, Lipinski's five rules are used. This rule was proposed by Christopher Lipinski in 1997 to characterize the pharmacological and biological activity of a chemical compound (Lipinski et al., 2012). The principle often applies to oral tablets. According to this principle, in order for a substance to be similar to a drug, it must have the following properties:

- The number of hydrogen bond donors (OH and / or NH) should not exceed 5
- The total number of hydrogen bond acceptors (nitrogen and/or oxygen atoms) should not exceed 10
- Molecular weight should be less than 500 Da (Dalton);
- Lipophilicity should not exceed 5 (log P < 5 in octanol/water medium) and
- Must not have excessive conformational mobility (no more than 10 rotators).

The following table shows the physico-chemical properties of the compounds, from which it can be seen that they comply with Lipinski's 5 rules (Table 3).

Table 3. Physico-chemical property of compounds.

Given data	1	2	3	4	5	6	7
Molecular weight g $mole^{-1}$	196.25	210.27	224.30	238.33	252.35	266.38	280.41
Number of heavy atoms	15	16	17	18	19	20	21
Number of aromatic heavy atoms	12	12	12	12	12	12	12
Fraction Csp3	0.00	0.07	0.13	0.19	0.24	0.28	0.32
Number rotatable bonds	3	3	3	3	4	4	4
Number of H-bond acceptors	1	1	1	1	1	1	1
Number of H-bond donors	1	1	1	1	1	1	1
Molar Refractivity	63.92	68.89	73.85	78.82	83.19	88.16	93.12
TPSA	24.39 Å²	24.39 Å²	24.39 Å²	24.39 Å²	24.39 Å²	24.39 Å²	24.39 Å²
Log Po/w(iLOGP)	2.28	2.44	2.69	2.96	3	3.25	3.44

Conclusıon

If we consider the data obtained by means of the Swiss ADME and Swiss Targeted Prediction program, it is possible to determine that all synthesized phenylhydrazones will demonstrate biological activity. However, it can also be noted that as a result of the increase in the number of methyl groups in the composition of the compounds, the elimination of deviations in 6 indicators (INSATU, SIZE, INSOLU, FLEX, LIPO, POLAR) in the bioavailability radar, and the biological activities of the synthesized phenylhydrazones are more similar to enzymes. has been done. Based on these results, we can predict that the synthesized phenylhydrazones may show biological activity and may be used as medicinal substances in the future.

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

Armstrong, M. S., Finn, P. W., Morris, G. M., & Richards, W. G. (2011). Improving the accuracy of ultrafast ligand-based screening: incorporating lipophilicity into ElectroShape as an extra dimension. *Journal of Computer-aided Molecular Design*, *25*, 785-790. https://doi.org/10.1007/s10822-011-9463-8

Armstrong, M. S., Morris, G. M., Finn, P. W., Sharma, R., Moretti, L., Cooper, R. I., & Richards, W. G. (2010). ElectroShape: fast molecular similarity calculations incorporating shape, chirality and electrostatics. *Journal of Computer-aided Molecular Design*, *24*, 789-801. https://doi.org/10.1007/s10822-010-9374-0

Atakishiyeva, G. T., Qajar, A. M., Babayeva, G. V., Mukhtarova, S. H., Zeynalli, N. R., Ahmedova, N. E., & Shikhaliyev, N. Q. (2023), Biological New Targets Prediction & ADME Profiling Of 1, 1-Dichlordiazodienes On The Basis Of O-Nitrobenzoic Aldehyde, New Materials. *Compounds and Applications*, *7*(2), 84-92

Ballester, P. J., & Richards, W. G. (2007). Ultrafast shape recognition to search compound databases for similar molecular shapes. *Journal of Computational Chemistry*, *28*(10), 1711-1723. https://doi.org/10.1002/jcc.20681

Cocco, M. T., Congiu, C., Lilliu, V., & Onnis, V. (2006). Synthesis and in vitro antitumoral activity of new hydrazinopyrimidine-5-carbonitrile derivatives. *Bioorganic and Medicinal Chemistry*, *14*(2), 366-372. https://doi.org/10.1016/j.bmc.2005.08.012

Daina, A., Michielin, O., & Zoete, V. (2019). SwissTargetPrediction: updated data and new features for efficient prediction of protein targets of small molecules. *Nucleic Acids Research*, *47*(W1), W357-W364. https://doi.org/10.1093/nar/gkz382

Dharampreet, S., Ramanjeet, K., Patil, R. K., & Patil, H. C. (2020). A review on: Computer Aided Drug Design. *JETIR*, *7*(3) 1165-1176.

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

Januario, J. P., De Souza, T. B., Lavorato, S. N., Maiolini, T. C., Domingos, O. S., Baldim, J. L., Folquitto, L. R. S., Soares, M. G., Chagas-Paula, D. A., Dias, D. F., & 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

Qacar, A. M., Əbdülov, M. S., İbrahimova, Ş. A., Süleymanova, G. T., Babayeva, G. V., Şıxaliyev, N. Q., & Məhərrəmov, A. M. (2020). 4-Metil benzaldehid əsasinda dixlordiazabutadienlərin sintezi. *Pedaqoji Universitetin Xəbərləri*, *C68*(N1), 39-47

Lipinski, C. A., Lombardo, F., Dominy, B. W., & Feeney, P. J. (2012). Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Advanced Drug Delivery Reviews*, *64*, 4-17. https://doi.org/10.1016/S0169-409X(96)00423-1

Liu, X., Jiang, H., & Li, H. (2011). SHAFTS: a hybrid approach for 3D molecular similarity calculation. 1. Method and assessment of virtual screening. *Journal of Chemical Information and Modeling*, *51*(9), 2372-2385. https://doi.org/10.1021/ci200060s

Loncle, C., Brunel, J. M., Vidal, N., Dherbomez, M., & Letourneux, Y. (2004). Synthesis and antifungal activity of cholesterol-hydrazone derivatives. *European Journal of Medicinal Chemistry*, *39*(12), 1067-1071. https://doi.org/10.1016/j.ejmech.2004.07.005

Maharramov, A. M., Shikhaliyev, N. Q., Suleymanova, G. T., Gurbanov, A. V., Babayeva, G. V., Mammadova, G. Z., Zubkov, F. I., Nenajdenko, V. G., Mahmudov, K. T., & Pombeiro, A. J. L. (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

Yousuf, M., Rafi, S., Ishrat, U., Shafiga, A., Dashdamirova, G., Leyla, V., & Iqbal, H. (2022). Potential Biological Targets Prediction, *ADME* Profiling, and Molecular Docking Studies of Novel Steroidal Products from *Cunninghamella blakesleana*. *Medicinal Chemistry*, *18*(2), 288-305. https://doi.org/10.2174/1573406417666210608143128.

Masunari, A., & Tavares, L. C. (2007). A new class of nifuroxazide analogues: synthesis of 5-nitrothiophene derivatives with antimicrobial activity against multidrug-resistant Staphylococcus aureus. *Bioorganic and Medicinal Chemistry*, *15*(12), 4229-4236. https://doi.org/10.1016/j.bmc.2007.03.068

Mauger, C., & Mignani, G. (2005). The Synthesis of Important Pharmaceutical Building Blocks by Palladium-Catalyzed Coupling Reaction: Access to Various Arylhydrazines. *Advanced Synthesis and Catalysis*, *347*(6), 773-782. https://doi.org/10.1002/adsc.200404392

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*(A), 147-154. https://doi.org/10.1016/j.jfluchem.2016.10.018

Narang, R., Narasimhan, B., & Sharma, S. (2012). A review on biological activities and chemical synthesis of hydrazide derivatives. *Current Medicinal Chemistry*, *19*(4), 569-612. https://doi.org/10.2174/092986712798918789

Nenajdenko, V. G., Shastin, A. V., Gorbachev, V. M., Shorunov, S. V., Muzalevskiy, V. M., Lukianova, A. I., Dorovatovskii, P. V., & Khrustalev, V. N. (2017). Copper-Catalyzed Transformation of Hydrazones into Halogenated Azabutadienes, Versatile Building Blocks for Organic Synthesis. *ACS Catalysis*, *7*(1), 205-209. https://doi.org/10.1021/acscatal.6b03196

Nenajdenko, V. G., Kazakova, A. A., Novikov, A. S., Shikhaliyev, N. G., Maharramov, A. M., Qajar, A. M., Atakishiyeva, G. T., Niyazova, A. A., Khrustalev, V. N., Shastin, A. V., & Tskhovrebov, A. G. (2023). Copper-Catalyzed Reaction of N-Monosubstituted Hydrazones with CBr4: Unexpected Fragmentation and Mechanistic Study. *Catalysts*, *13*(8), 1194. https://doi.org/10.3390/catal13081194

Pastewska, M., Bednarczyk-Cwynar, B., Kovačević, S., Buławska, N., Ulenberg, S., Georgiev, P., Kapica, H., Kawczak, P., Bączek, T., Sawicki, W., & Ciura, K. (2021). Multivariate assessment of anticancer oleanane triterpenoids lipophilicity. *Journal of Chromatography A*, *1656*, 462552. https://doi.org/10.1016/j.chroma.2021.462552

Pérez-Nueno, V. I., Venkatraman, V., Mavridis, L., & Ritchie, D. W. (2012). Detecting drug promiscuity using Gaussian ensemble screening. *Journal of Chemical Information and Modeling*, *52*(8), 1948-1961. https://doi.org/10.1021/ci3000979

Raue, R., Brack, A., & Lange, K. H. (1991). Salt-free Synthesis of Azo and Hydrazone Dyes Under CO2 Pressure. *Angewandte Chemie International Edition in English*, *30*(12), 1643-1644. https://doi.org/10.1002/anie.199116431

Rollas, S., & Güniz Küçükgüzel, Ş. (2007). Biological activities of hydrazone derivatives. *Molecules*, *12*(8), 1910-1939.

Sastry, G. M., Dixon, S. L., & Sherman, W. (2011). Rapid shape-based ligand alignment and virtual screening method based on atom/feature-pair similarities and volume overlap scoring. *Journal of Chemical Information and Modeling*, *51*(10), 2455-2466. https://doi.org/10.1021/ci2002704

Savini, L., Chiasserini, L., Travagli, V., Pellerano, C., Novellino, E., Cosentino, S., & Pisano, M. B. (2004). New α-(N)-heterocyclichydrazones: evaluation of anticancer, anti-HIV and antimicrobial activity. *European Journal of Medicinal Chemistry*, *39*(2), 113-122. https://doi.org/10.1016/j.ejmech.2003.09.012

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

Vicini, P., Incerti, M., La Colla, P., & Loddo, R. (2009). Anti-HIV evaluation of benzo [d] isothiazole hydrazones. *European Journal of Medicinal Chemistry*, *44*(4), 1801-1807. https://doi.org/10.1016/j.ejmech.2008.05.030

Vicini, P., Zani, F., Cozzini, P., & Doytchinova, I. (2002). Hydrazones of 1, 2-benzisothiazole hydrazides: synthesis, antimicrobial activity and QSAR investigations. *European Journal of Medicinal Chemistry*, *37*(7), 553-564. https://doi.org/10.1016/S0223-5234(02)01378-8

Willett, P. (2011). Similarity searching using 2D structural fingerprints. *Chemoinformatics and Computational Chemical Biology*, 133-158. https://doi.org/10.1007/978-1-60761-839-3_5