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PREDICTION OF INTERACTIONS (SMP) AND SITES OF INTERACTIONS (SOMP) ON BIOLOGICAL TARGETS (Z)-N,N-DIMETHYL-2-(PERFLUOROPHENYL) - 2-(2-PHENYLHYDRAZINEYLIDENE) ACETAMIDE USING THE PASS PROGRAM

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Abstract. Using the resources of the Prediction of Activity Spectra for Substances (PASS) program and Crystal Explorer 17.5 (analysis of the surface of Hirschfeld and double graphs of fingerprint prints), predicted and analyzed interactions obtained (Z)-N,N,-dimethyl-2-(perfluorphenyl)-2-(phenldiazenyl) acetamide with biological targets.

Keywords: *computer prediction of SMP and SOMP, PASS program, perfluorophenyl derivatives, dimethylamino derivatives.*

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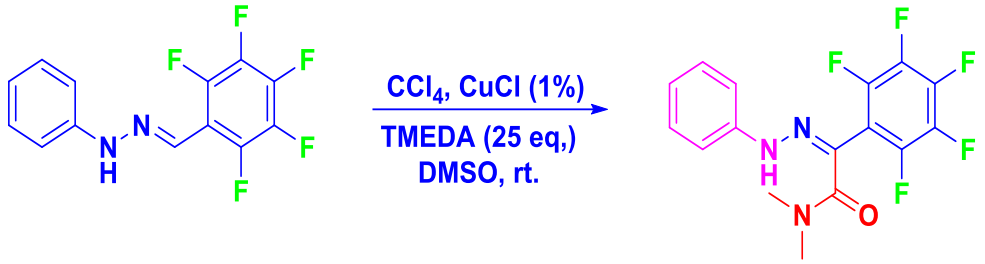
1. Introduction

It's known that the high technologies are being introduced into our daily life, starting from everyday life and of course affecting our professional activities. Engaged in organic synthesis, we purposefully, and sometimes accidentally, synthesize again and again new compounds, and then we naturally show interest in terms of studying them as physiologically active substances and the mechanism of their effects (from the point of view of a chemist), which require a lot of time and resources, which of course we are limited, given the pace of development today. There is also an ethical point in this. Taking into account our beliefs, namely in matters of the environment, the problems of a civil attitude towards animals (in preclinical studies) and under the frequent high cost of starting materials, and therefore the impossibility of obtaining a product in large quantities (as was the case before), the duration of the study of physiological activity, etc. (sometimes in vain) encourage us to "technologize" the process of research (screening) and resort to alternative (technologically advanced) methods. In this article, we used the resources of the PASS program - a program for predicting the spectrum of activity of a synthesized compound (Prediction of Activity Spectra for Substances) (http://www.way2drug.com/PASSonline) and Crystal Explorer 17.5 (analysis of the Hirschfeld surface and 2D fingerprint plots).

2. Discussions and Results

By means of a tandem reaction, under the conditions of a catalytic olefination reaction, we obtained (Z)-N,N-dimethyl-2-(perfluorophenyl)-2-(2-phenylhydrazineylidene)acetamide. The structure of the compound was established by

NMR and X-ray (Atioğlu, 2021a,b,c). For this compound, was carried out primary analysis of physiological activity (prediction of acute toxicity in rats) (Askerova, 2021).



(Z)-N,N-dimethyl-2-(perfluorophenyl)-2-(2-phenylhydrazineylidene)acetamide

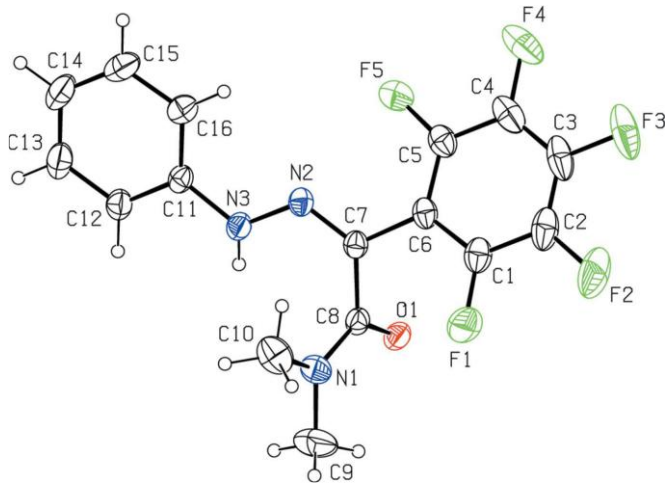


Figure 1. Structure of (Z)-N,N-dimethyl-2-(perfluorophenyl)-2-(2-phenylhydrazineylidene) acetamide

Colourless crystals of the compound were obtained by slow evaporation of a dichloromethane solution (69%); m.p. 405 K. Analysis calculated for $C_{16}H_{12}F_5N_3O$: C 53.79, H 3.39, N 11.76; found: C 53.73, H 3.36, N 11.71%. ^{1}H NMR (300MHz, $CDCl_3$) 3.04 (6H, NMe_2), 6.50–7.33 (5H, Ar). ^{13}C NMR (75MHz, $CDCl_3$) 33.58, 108.97, 116.87, 120.75, 124.11, 124.76, 140.95, 146.33, 149.87, 150.91, 155.21.

Analysis of the structure of the synthesized compound (theoretically) shows that a strong electron-acceptor pentaphenyl group (-J), carbonyl group (-J, -M), a group of nitrogen atoms exert their influence and, as a consequence, we assume that in our compound hydrogen atoms are in methyl, amino groups will have proton activity and tend to form hydrogen bonds. The second phenyl group, in view of the presence of the aforementioned strong acceptor fragments, will act as an electron donor and hydrogen atoms in distant positions (meta- and para-) will most likely also have proton activity. Thus, it can be assumed that the system will be more a proton donor for the formation of hydrogen bonds.

The question what kind of interactions play a key role in the interaction of synthetic substances with biotargets and in the formation of protein complexes - van der Waals interactions, salt bridges, hydrogen bonds, is the most important issue in understanding their physiological activity. And although this question is raised in most

studies, there is no definitive answer. The answer to this question should not only shed light on the mechanism of protein recognition, but also make it possible to create a basis for the design of efficiently binding ligands when creating new drug forms (Anashkina, 2008).

In the context of drug development, hydrogen bonds have received little attention so far, mainly because they are considered weak compared to other non-covalent interactions such as OH ⋯ O hydrogen bonds, π / π interactions, and van der Waals interactions (Salonen, 2009; Salonen, 2012; Bissantz, 2010; Nittinger, 2017). Non-covalent interactions such as heteroatom-hydrogen bonds XH ⋯ Y (X = O or N; Y = O, N or halogen) and π / π interactions play a decisive role in the formation of protein-ligand complexes (Zhou, 2012; Böhm, 1996; Ma, 1997; Salonen, 2011; Atioglu, 2021a,b,c; Atioglu, 2021). Such interactions are manifested between proteins and their ligands in many protein complexes registered in the Protein Data Bank (PDB). Accordingly, these interactions should always be taken into account when developing ligands for target proteins (Bissantz, 2010).

Today, 95,000 protein ligand structures are now available in the PDB, and this provides a strong foundation for new large-scale statistical analyzes. On the basis of these results, the geometry of the interaction is derived for the formation of computational models, and in all likelihood these observations will be used in the development of new chemical structures for biological applications (Nittinger , 2017).

We used a freely available web server based on the PASS technology (prediction of substance activity spectra) (http://www.way2drug.com/PASSonline) and MNA descriptors: to predict the specificity of the substrate / metabolite (Rudik, 2015) and predict the sites of metabolism (SOM) based on the structural formula of chemicals. Biological activity spectra are predicted for a given compound using structure-activity ratios calculated from data for all other compounds. The result of the prediction is compared with the known experimental data for the test compound. The procedure is repeated for all compounds from the PASS training sample;

SMP - predicts interactions with 18 isoforms of cytochrome P450 and UGT: CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, UGT1A10, UGT1A1, UGT2B7, UGT1A7, UGT2B15, UGT1AGT1A1, UGT2B15, UGT1AGT1A1A, UGT2B15, UGT1AGT1A1A

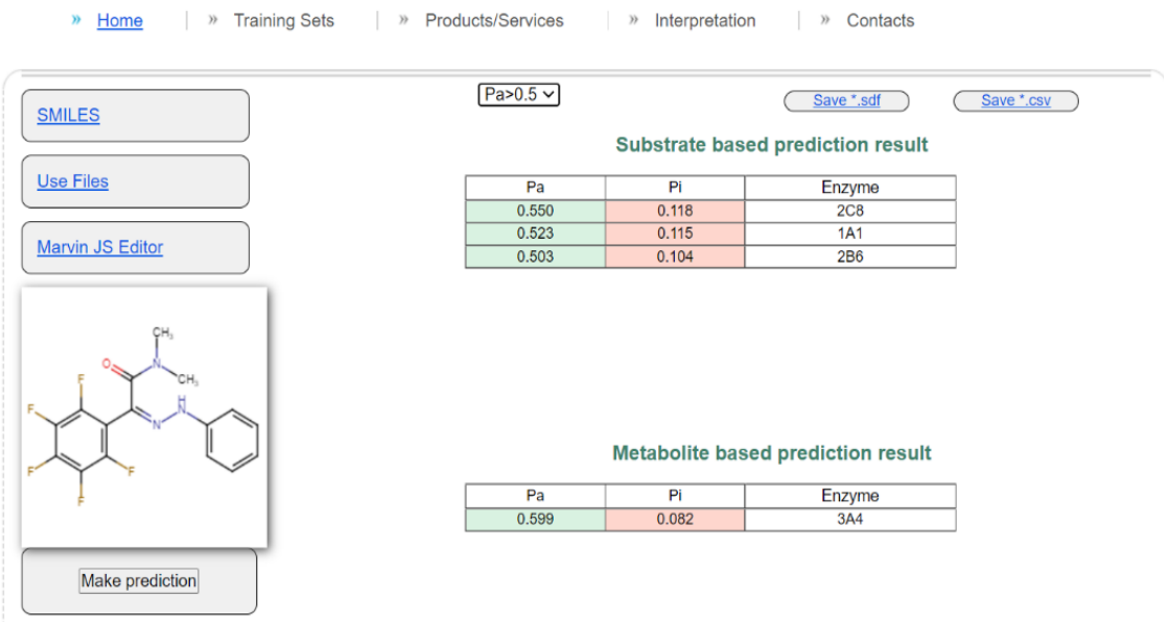
Pa (probability "to be active") estimates the probability that the test compound belongs to the subclass of active substances (resembles the molecular structures that are most typical in the subset of "active substances" in the PASS training set).

Pi (probability of "being inactive") estimates the probability that the test compound belongs to the subclass of inactive compounds (resembles the molecular structures that are most typical in the subset of "inactive" in the PASS training set).

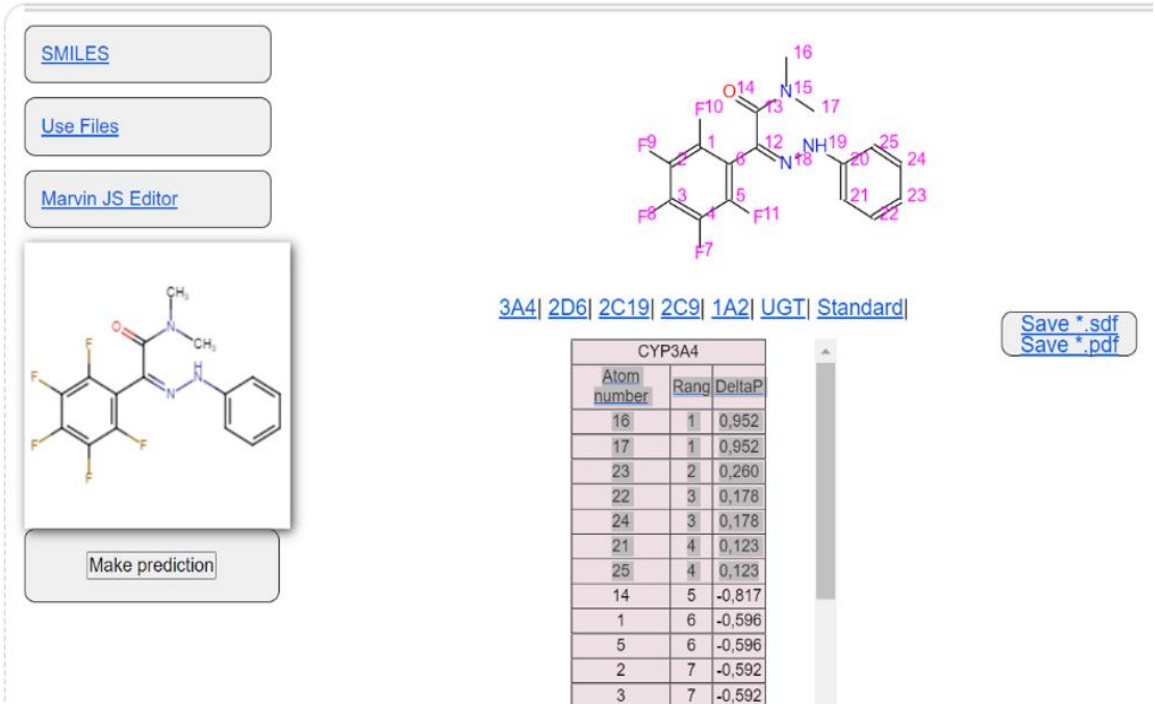
Only activities with Pa> Pi are considered possible for a specific compound.

SOMP is a web service for in silico metabolic site prediction .

Prediction of sites of metabolism of medicinal compounds for cytochrome P450 (five main human): CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. Glucuronization sites were also included in the training set.



Prediction is based on PASS technology (prediction of substance activity spectra) (http://www.way2drug.com/PASSonline) and LMNA descriptors.



The atoms in the compounds are arranged according to the delta P =(Pt -Pf).

P_t is the probability that labeled atom in the SoLA is the SOM of the appropriate enzyme.

P_f is the probability that the labeled atom in SoLA is not the SOM of the appropriate enzyme.

For each non-hydrogen atom in the molecular structure that was sent to the prediction, ΔP was calculated, and the atoms are arranged in decreasing order of ΔP. As

the data in the table show, atoms 16 and 17 are in the first position. Atom 22 - in position 2 and atoms 22 and 24 - in position 3. The forecast is given for non-hydrogen hydrogen atoms, prompts us to think that the type of interactions arising between the synthesized compound and biological objects is possible by the type of hydrogen interactions, and this is also in the algorithm of the previously stated assumptions.

3. Conclusion

An indirect evidence of our assumptions is the study of the Hirschfeld surface and two-dimensional plots of "fingerprints" (fingerprint plots).

Data processing for (Z) -N, N-dimethyl-2- (perfluorophenyl) -2- (2-phenylhydrazinylidine) acetamide using the Crystal Explorer 17.5 software showed that the molecules in the crystal are linked in pairs NH ... O by hydrogen bonds, the resulting dimers are linked by hydrogen CH… O bonds and aromatic π···π stacking interactions. Analysis of the three-dimensional Hirschfeld surface showed that hydrogen interactions H9C… F1, H16… F2, F3… H10C, H3N… O1, N3-H3N… O1 and C14-H14… O1 play a key role in molecular packing.

Established that the percentage contributions to the Hirschfeld surfaces from various interatomic contacts are: FH / HF (41.1%), HH (21.8%), CH / HC (9.7%) CC (7.1%) and OH / HO (7.1%). Other types of contacts, including NH / HN, NC / CN, and NN contacts, make up less than 5.4% of the Hirschfeld surface map and seem to have minimal directional influence on crystal formation, and the system as a whole is a proton (hydrogen atom) donor. Analysis of two-dimensional plots of "fingerprints" indicates the fact that this compound is in the blue zone and is more a proton donor (Atioğlu, 2021a,b,c). That is, when interacting with biological objects (enzymatic systems), and it is certainly possible (based on SMP and SOMP), it is hydrogen bonds that will play a key role.

These results convinced us once again that the SOMP web server has a reasonable prediction accuracy and can be used to study drug metabolism and confirm our assumptions regarding the role of hydrogen bonds in physiological effects on biological objects.

Acknowledgment

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References

Anashkina, A.A. (2008). Steric selectivity of protein-protein and protein-nucleic acid contacts. Doctor of Sciences Thesis, Lomonosov Moscow State University.

Askerova, U.F. (2021). Prediction of Acute Toxicity of (Z) -N, N-Dimethyl-2- (perfluorophenyl) -2- (2- phenylhydrazinylidine)acetamide for Rats using the GUSAR Program. *The Pharmaceutical and Chemical Journal, 8*(5), 63-66.

Atioğlu, Z., Akkurt, M., Askerova, U.F., Mukhtarova, S.H., Askerov, R.K., & Mlowe, S. (2021a). Crystal structure and Hirshfeld surface analysis of (3Z)-7-methoxy-3-(2-phenylhydrazinylidene)-1-benzofuran-2 (3H)-one. *Acta Crystallographica Section E: Crystallographic Communications, 77*(9). https:// doi.org/10.1107/S2056989021007891

Atioğlu, Z., Akkurt, M., Shikhaliyev, N.Q., Askerova, U.F., Mukhtarova, S.H., Askerov, R.K., & Bhattarai, A. (2021b). Crystal structure and Hirshfeld surface analysis of 3-[2-(3, 5-dimethylphenyl) hydrazinylidene] benzofuran-2 (3H)-one. *Acta Crystallographica Section E: Crystallographic Communications*, *77*(12).

Atioğlu, Z., Akkurt, M., Shikhaliyev, N.Q., Askerova, U.F., Niyazova, A.A., & Mlowe, S. (2021c). Crystal structure and Hirshfeld surface analysis of (2Z)-N, N-dimethyl-2-(pentafluorophenyl)-2-(2-phenylhydrazin-1-ylidene) acetamide. *Acta Crystallographica Section E: Crystallographic Communications*, *77*(8), 829-833.

Bissantz, C., Kuhn, B., & Stahl, M. (2010). A medicinal chemist's guide to molecular interactions. *Journal of Medicinal Chemistry*, *53*(14), 5061-5084.

Böhm, H.J., Klebe, G. (1996). What can we learn from molecular recognition in protein–ligand complexes for the design of new drugs?. *Angewandte Chemie International Edition in English*, *35*(22), 2588-2614. https://doi.org/10.1002/anie.199625881

Ma, J.C., Dougherty, D.A. (1997). The cation− π interaction. *Chemical Reviews*, *97*(5), 1303-1324. https://doi.org/10.1021/cr9603744

Nittinger, E., Inhester, T., Bietz, S., Meyder, A., Schomburg, K.T., Lange, G., ... & Rarey, M. (2017). Large-scale analysis of hydrogen bond interaction patterns in protein–ligand interfaces. *Journal of Medicinal Chemistry*, *60*(10), 4245-4257.

Salonen, L.M., Bucher, C., Banner, D.W., Haap, W., Mary, J.L., Benz, J., ... & Diederich, F. (2009). Cation–π interactions at the active site of factor Xa: dramatic enhancement upon stepwise N-alkylation of ammonium ions. *Angewandte Chemie International Edition*, *48*(4), 811-814. https://doi.org/10.1002/anie.200804695

Salonen, L.M., Ellermann, M., & Diederich, F. (2011). Aromatic rings in chemical and biological recognition: energetics and structures. *Angewandte Chemie International Edition*, *50*(21), 4808-4842. https://doi.org/10.1002/anie.201007560

Salonen, L.M., Holland, M.C., Kaib, P.S., Haap, W., Benz, J., Mary, J.L., ... & Diederich, F. (2012). Molecular recognition at the active site of factor Xa: cation–π interactions, stacking on planar peptide surfaces, and replacement of structural water. *Chemistry – A European Journal*, *18*(1), 213-222. https://doi.org/10.1002/chem.201102571

Zhou, P., Huang, J., & Tian, F. (2012). Specific noncovalent interactions at protein-ligand interface: implications for rational drug design. *Current Medicinal Chemistry*, *19*(2), 226-238. https://doi.org/10.2174/092986712803414150