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Quantitative prediction of counter attack profiles for (Z) -N, N-dimethyl-2- (perfluorophenyl) -2- (2-phenylhydrazinylidine) acetamide using the GUSAR program

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Abstract

There are a sufficient number of theories about the nature of physiological effect, such us receptor, neural, biochemical, physicochemical to quantum. All of them are true, because nature is a much more complex system than we can imagine. In this article we try to open the curtain on the nature physiological activity in the framework of synthesized by us - (Z) -N, N-dimethyl-2- (perfluorophenyl) -2- (2-phenylhydrazinylidine) acetamide, using the modern capabilities of computer programs.

Keywords: computer prediction of counter attack profiles, GUSAR program, perfluorophenyl derivatives, dimethylamino derivatives

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1. Introduction

What is physiological activity by the chemist's point? It is the ability to interact with a biological target. What is a biological target? A polymolecular system that has a certain structure and composition, depending on which they can enter certain interactions (reactions) with chemical compounds. Thus, the assessment of possible interactions between chemical compounds and proteins is an important task in the process of studying the physiological activity of substances. One of the possible ways to solve this problem is using QSAR models to predict the endpoints of counteraction. GUSAR software was developed to create QSAR/QSPR models on the basis of the appropriate training sets represented as SD file contained data about chemical structures and endpoint in quantitative terms. Three nearest neighbours from the training set are calculated for each test chemical compound using a similarity value. The average similarity of three nearest neighbours is used for assessment of the applicability domain (AD) of the model.

2. Methods.

Quantitative prediction of counter attack profiles for chemical compounds

Data on the chemical structure and quantitative endpoints (IC_{50}, or concentration of half-maximal inhibition is an indicator of the effectiveness of a ligand in inhibiting biochemical or biological interactions. IC_{50} is a quantitative indicator that shows how much ligand-inhibitor is needed to inhibit a biological process by 50%. Ki is a constant inhibition, a coefficient characterizing the affinity of a ligand for a cellular receptor or another protein or DNA and an activation constant- Kact) for approximately 4000 chemical compounds

interacting with 18 antibodies to proteins (13 receptors, 2 enzymes and 3 carriers) were collected from various literature sources [1]. Each set was randomly divided into training and test sets in a ratio of 80% to 20%, respectively. The test suites were used for external validation of the QSAR models generated from the training suites. The prediction coverage for all test sets exceeded 95%, and for half of the test sets it was 100%. The prediction accuracy for the 32 endpoints, based on external test sets, was typically in the range of R^2_{test} = 0.6–0.9; three sets of tests had lower test R 2 values, namely 0.55-0.6. The proposed approach showed reasonable prediction accuracy for 91% of antibody endpoints and high coverage for all external test sets [2]. Based on the created models, a freely available online service was developed for in silico prediction of 32 endpoints of counteraction: http://www.pharmaexpert.ru/GUSAR/antitargets.html.

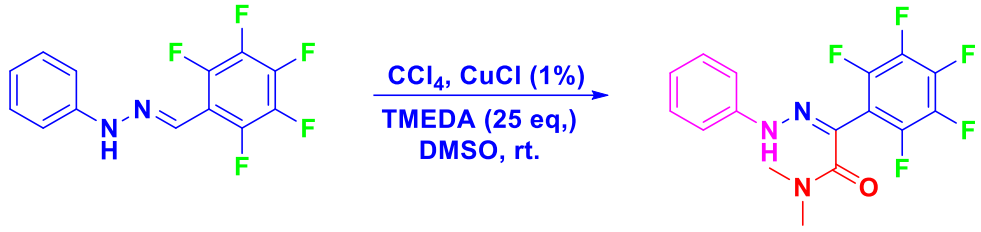
Activity Name	End-point	Number of compounds Training set / Test set	Number of models	R2 training set	Q2 training set	R2 test set	Coverage, %
5-hydroxytryptamine 1B receptor antagonist	IC_{50}	297 / 74	8	0.83	0.79	0.67	100.0
5-hydroxytryptamine 1B receptor antagonist	$\mathbf{K_i}$	266 / 66	7	0.73	0.66	0.72	100.0
5-hydroxytryptamine 2A receptor antagonist	IC_{50}	555 / 143	13	0.83	0.78	0.71	98.6
5-hydroxytryptamine 2A receptor antagonist	$\mathbf{K_i}$	1010 / 252	13	0.72	0.65	0.59	99.6
5-hydroxytryptamine 2C receptor antagonist	IC_{50}	128 / 32	18	0.77	0.73	0.58	100.0
5-hydroxytryptamine 2C receptor antagonist	$\mathbf{K_i}$	487 / 121	14	0.74	0.66	0.62	99.2
alpha1a adrenergic receptor antagonist	IC_{50}	438 / 111	16	0.79	0.73	0.72	98.2
alpha1a adrenergic receptor antagonist	$\mathbf{K_i}$	1366 / 344	5	0.83	0.79	0.80	97.0
alpha1b adrenergic receptor antagonist	$\mathbf{K_i}$	410 / 102	17	0.73	0.66	0.63	100.0
alpha-2A adrenergic receptor antagonist	IC_{50}	109 / 27	16	0.88	0.84	0.75	100.0
alpha-2A adrenergic receptor antagonist	$\mathbf{K_i}$	525 / 131	17	0.84	0.79	0.77	99.2
amine oxidase [flavin-containing] A inhibitor	IC_{50}	286 / 71	9	0.80	0.75	0.72	100.0
amine oxidase [flavin-containing] A inhibitor	$\mathbf{K_i}$	60 / 15	5	0.73	0.62	0.64	100.0
androgen receptor antagonist	IC_{50}	116 / 29	8	0.79	0.73	0.67	100.0
carbonic anhydrase II activator	K_{act}	104 / 26	20	0.92	0.90	0.91	100.0
carbonic anhydrase I activator	K_{act}	108 / 27	12	0.98	0.97	0.93	100.0
carbonic anhydrase I inhibitor	$\mathbf{K_i}$	935 / 234	11	0.91	0.86	0.86	98.3
carbonic anhydrase II inhibitor	IC_{50}	866 / 217	7	0.87	0.79	0.76	98.6
d(1A) dopamine receptor antagonist	IC_{50}	126 / 31	11	0.76	0.72	0.80	100.0
d(1A) dopamine receptor antagonist	$\mathbf{K_i}$	291 / 73	10	0.72	0.66	0.57	100.0
d3 dopamine receptor antagonist	$\mathbf{K_i}$	822 / 206	9	0.73	0.66	0.62	98.0
delta-type opioid receptor antagonist	$\mathbf{K_i}$	1044 / 261	16	0.75	0.70	0.65	98.5
estrogen receptor antagonist	IC_{50}	402 / 100	4	0.66	0.61	0.70	97.0
estrogen receptor antagonist	$\mathbf{K_i}$	255 / 68	13	0.76	0.71	0.70	100.0
kappa-type opioid receptor antagonist	$\mathbf{K_i}$	884 / 221	7	0.74	0.67	0.65	100.0
mu-type opioid receptor antagonist	IC_{50}	545 / 136	7	0.67	0.61	0.70	97.8
mu-type opioid receptor antagonist	$\mathbf{K_i}$	1354 / 338	4	0.69	0.62	0.60	96.7
sodium- and chloride-dependent GABA transporter 1 antagonist	IC_{50}	75 / 19	10	0.9	0.86	0.89	100.0
sodium-dependent dopamine transporter antagonist	IC_{50}	920 / 230	5	0.7	0.65	0.67	98.3
sodium-dependent dopamine transporter antagonist	$\mathbf{K_i}$	655 / 164	7	0.77	0.69	0.64	100.0
sodium-dependent serotonin transporter antagonist	IC_{50}	796 / 199	7	0.8	0.75	0.69	97.5
sodium-dependent serotonin transporter antagonist	$\mathbf{K_i}$	823 / 206	2	0.72	0.65	0.61	95.6

Table1. Quantitative prediction of antitarget interaction profiles for chemical compounds

3. Results and discussions.

Quantitative prediction of counter attack profiles for (Z)-N, N-dimethyl-2-(perfluorophenyl)-2-(2-phenylhydrazinylidene) acetamide.

For the first time, by means of a tandem reaction, under the conditions of a catalytic olefination reaction, we have synthesized (Z)-N, N-dimethyl-2-(perfluorophenyl)-2-(2-phenyldiazenyl) acetamide.



a)

a) (Z)-N, N-dimethyl-2-(perfluorophenyl)-2-(2- phenyldiazenyl) acetamide

The structural features of this compound [3] have been studied.

In order to investigate possible interactions between (Z)-N, N-dimethyl-2-(perfluorophenyl)-2-(2- phenyldiazenyl) acetamide and antibody proteins, we used QSAR models to predict counteraction endpoints. Table 2 shows the quantitative prediction data of the counter attack profiles for (Z)-N, N-dimethyl-2-(perfluorophenyl)-2-(2-phenylhydrazinylidine) acetamide.

In medicine, have developed and used compounds that change the activity of enzymes in order to regulate the rate of metabolic reactions and reduce the synthesis of certain substances in the body are actively developed and used (antagonists, inhibitors, activators and inactivators, etc.).

An antagonist (receptor antagonist) in biochemistry and pharmacology is a subtype of ligands for cellular receptors. A ligand with receptor antagonist properties is a ligand that blocks, reduces or prevents the physiological effects caused by the binding of an agonist (including an endogenous agonist) to a receptor. At the same time, he himself is not obliged (although he can) to produce any physiological effects due to his binding to the receptor (and according to the strict definition, which implies and includes only neutral antagonists, he should not even produce any physiological effects by itself [4]. Suppression of enzyme activity is usually called inhibition, but this is not always correct. An inhibitor is a substance that causes a specific decrease in enzyme activity [5]. Enzyme activators are substances that increase the rate of an enzymatic reaction [6].

Activity	Prediction Value, -Log10(Value), Mole	Applicability Domain
5-hydroxytryptamine 1B receptor antagonist IC_{50}	6,698	Out of AD
5-hydroxytryptamine 1B receptor antagonist K_i	6,205	In AD
5-hydroxytryptamine 2A receptor antagonist IC_{50}	7,425	Out of AD
5-hydroxytryptamine 2A receptor antagonist K_i	6,824	Out of AD
5-hydroxytryptamine 2C receptor antagonist IC_{50}	6,862	In AD
5-hydroxytryptamine 2C receptor antagonist K_i	7,849	In AD
alpha1a adrenergic receptor antagonist IC_{50}	5,708	Out of AD
alpha1a adrenergic receptor antagonist K_i	5,584	Out of AD
alpha1b adrenergic receptor antagonist K_i	5,965	Out of AD
Alpha-2A adrenergic receptor antagonist IC_{50}	4,770	In AD
Alpha-2A adrenergic receptor antagonist K_i	5,627	In AD
amine oxidase [flavin-containing] A inhibitor IC_{50}	5,677	In AD

amine oxidase [flavin-containing] A inhibitor K_i	5,455	In AD
androgen receptor antagonist IC_{50}	5,578	In AD
carbonic anhydrase I activator K_{act}	7,495	In AD
carbonic anhydrase I inhibitor K_i	6,469	In AD
Carbonic anhydrase 2 activator K_{act}	7,537	In AD
carbonic anhydrase II inhibitor K_i	7,689	In AD
D(1A) dopamine receptor antagonist IC_{50}	5,300	In AD
D(1A) dopamine receptor antagonist K_i	6,054	In AD
D3 dopamine receptor antagonist K_i	6,214	Out of AD
delta-type opioid receptor antagonist K_i	6,358	Out of AD
estrogen receptor antagonist IC_{50}	4,985	In AD
estrogen receptor antagonist K_i	5,391	In AD
kappa-type opioid receptor antagonist K_i	6,127	Out of AD
mu-type opioid receptor antagonist IC_{50}	5,508	Out of AD
mu-type opioid receptor antagonist K_i	7,001	Out of AD
sodium- and chloride-dependent GABA transporter 1 antagonist IC_{50}	4,606	In AD
sodium-dependent dopamine transporter antagonist IC_{50}	6,337	Out of AD
sodium-dependent dopamine transporter antagonist K_i	5,704	In AD
sodium-dependent serotonin transporter antagonist IC_{50}	5,509	In AD
sodium-dependent serotonin transporter antagonist K_i	6,379	Out of AD

Table 2. Quantitative prediction of antitarget interaction profiles for (Z)-N, N-dimethyl-2-(perfluorophenyl)-2-(2-phenylhydrazinylidene) acetamide.

*in AD - compound falls in the applicability domain of the model
*out of AD - compound is out of the applicability domain of the model

The total number of antitarget(s): 7

Analysis of Table 2 demonstrates that for a given compound, seven counteractions fall within the scope of the model. For (Z) -N, N-dimethyl-2- (perfluorophenyl) -2- (2-phenylhydrazinylidine) acetamide, based on the GUSAR program, it is predicted:

1. It is a 5-hydroxytryptamine receptor antagonist. 5-HT antagonists are a subtype of serotonin receptors, these are many chemical substances and drugs, in particular, some beta-blockers, some typical and atypical antipsychotics, some anti-migraine [7-12].
2. The second important effect is an antagonist of alpha-2A adrenergic receptors. It is known that direct antagonists of presynaptic alpha-2-adrenergic receptors mianserin and mirtazapine are widely used as antidepressants [13].
3. The next is the androgen receptor antagonist. Androgen receptor antagonists are often used in the treatment of diseases caused by excess androgens, such as prostate cancer. Compounds that are full or partial antagonists of androgen receptors are called antiandrogens. Complete AR antagonists are, for example, the non-steroidal compounds hydroxyflutamide, nilutamide, and bicalutamide [14-17].
4. Dopamine receptor antagonist. Compounds with similar effects are known as anti-dopaminergic and are a type of drug that blocks dopamine receptors. Most antipsychotics are dopamine antagonists, and as such they have found use in the treatment of schizophrenia, bipolar disorder, and stimulant psychosis [18].
5. Estrogen receptor antagonists. Most often, these are drugs that block estrogen receptors. Estrogen receptor antagonists are commonly used in breast cancer therapy, as androgen receptor antagonists are used in prostate cancer therapy as shown by Harvison et al [26]].

Antiestrogens, also known as estrogen antagonists or estrogen blockers, are a class of drugs that prevent estrogens such as estradiol from mediating their biological effects in the body [20-24].

6. Further, an inhibitor of the enzyme amine oxidase (flavin-containing). Monoamine oxidase inhibitors are biologically active substances that can inhibit the enzyme monoamine oxidase contained in nerve endings, preventing this enzyme from destroying various monoamines (serotonin, norepinephrine, dopamine, phenylethylamine, tryptamines, octopamine) and thereby increasing their concentration in the synaptic cleft. For this reason, for medical purposes, these substances are used mainly as antidepressants, as well as in the treatment of parkinsonism and narcolepsy [25].
7. Activator and inhibitor of carbonic anhydrase. This enzyme is known as a substance that acts as a catalyst in living organisms to help speed up chemical reactions as shown by Harvison et al [26]. Carbonic anhydrase is one of the important enzymes found in erythrocytes, gastric mucosa, pancreatic cells, and even in the renal tubules [27]. The main role of carbonic anhydrase in the human body is to catalyze the conversion of carbon dioxide to carbonic acid and vice versa. However, it can also help with the transport of CO_2 in the blood, which in turn promotes respiration. It may even participate in the formation of hydrochloric acid in the stomach as shown by Harvison et al [26]. Thus, the role of carbonic anhydrase depends on where it is located in the body. Carbonic anhydrase inhibitors (CAI), used both systemically and topically, effectively reduce intraocular pressure. Unlike systemic CAI, 2% dorozolamide and 1% brinzolamide, penetrating deep into the tissues of the eye, do not lead to systemic effects, and therefore these drugs are widely used in the treatment of glaucoma [28].

4. Conclusion

The results show that seven antitargets are predicted for (Z) -N, N-dimethyl-2-(perfluorophenyl) -2- (2-phenylhydrazinylidine) acetamide. It once again confirms the fact that QSAR models can be successfully used to filter chemical compounds using the correction value estimated by taking an average of three chemicals values from the training set that the most similar to the chemical under prediction. Thus, without spending quite a lot of time and resources on preclinical studies, can be to conduct an initial screening of the synthesized compound in order to increase the efficiency of the search for drugs with the desired pharmacological effects.

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