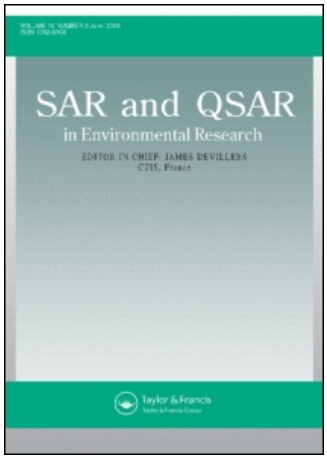

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Computer-aided prediction of QT-prolongation

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Computer-aided prediction of QT-prolongation[1]

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Drug-induced cardiac arrhythmia is acknowledged as a serious obstacle in successful development of new drugs. Several methods for *in silico* prediction of acquired long QT syndrome (LQTS) caused by the pharmacological blockade of human hERG K^+ channels are discussed in literature. We propose to use the computer program PASS, which estimates the probabilities of about 3000 biological activities, not only for prediction of hERG blockade and QT-prolongation but also for the analysis of indirect mechanisms of these actions. After addition in the PASS training set of 163 compounds with data on QT-Prolongation and re-training, it was shown that accuracy of prediction was 87.1% and 81.8% for hERG blockade and QT-prolongation, respectively. Using computer program PharmaExpert we found that in the predicted biological activity spectra there was a certain correlation between the hERG blockade and some other molecular mechanisms of action. Possible role of 1-phosphatidylinositol-4-phospate 5-kinase, dimethylargininase and progesterone 11 alpha-monooxygenase inhibition in hERG blockade was discussed.

Keywords: QT interval prolongation; hERG channels blockade; PASS; PharmaExpert; 1-phosphatidylinositol-4-phospate inhibitors; dimethylargininase inhibitors

1. Introduction

Long QT syndrome (LQTS) is defined as a prolongation of QT interval on electrocardiogram. This is a severe abnormality leading to the high risk of a sudden cardiac death [1]. LQTS appears as a consequence of delayed repolarization of myocardium, which may occur due to the necrosis of some cardiomyocytes or pharmacological blockade of hERG potassium channels. Some other mechanisms are discussed in literature [2].

The inherited and acquired forms of LQTS have been described to date [3]. Acquired form is usually caused by class I and class III antiarrhythmics, fluoroquinolone antibiotics, antipsychotics, and some other drugs. A few drugs including astemizole, sertindole, terfenadine, cisapride, greparfloxacin have been withdrawn from the market due to the reports of a sudden cardiac death [3, 4].

Several *in vitro, in vivo* and *in silico* approaches are currently used for evaluation of LQTS [5]. Computer-aided predictions require only structural formula as input data and,

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therefore, they can be applied to virtual chemical libraries for filtering out potentially dangerous compounds prior to chemical synthesis.

A variety of methods for *in silico* predictions of LQTS has been published in literature during the past years, most of which are based on the analysis of hERG blockade [3, 6–21]. The earlier works were examined in reviews [4, 22–25] and also in the later publications. Therefore, instead of consideration of the proposed methods [3, 6–21] in detail, some general problems that may influence the accuracy of prediction are discussed here.

Target-based approaches to hERG blockade's prediction (see, e.g., [11, 13, 14]) are typically based on homology modelling of hERG channels using crystal structures of KcsA or MthK channels [25]. Docking of low energy conformers of drug-like compounds to the inner cavity of the constructed 3D hERG channel models allow to obtain some qualitative description of channel-drug interactions. Therefore, as concluded by Sangunietti and Mitcheson [25], these models are rather descriptive than predictive.

The majority of ligand-based methods are constructed on the relatively small training sets of hERG blockers, including from one-two dozens to about 100 compounds. Since this information is collected from publications, the compounds were tested in different laboratories using slightly different experimental protocols.

For example, in a recent publication [15], 99 compounds representing a structurally diverse training set were tested on hERG blockade in six different cell types. In such case the quantitative values may vary significantly: e.g., according to Sierstad and Agrafiotis [17], IC_{50} values for sildenafil taken from three different publications equalled 100, 31.6 and 3.16 μM, respectively. Despite the inconsistency of the IC_{50} values used for analysis of QSARs, Ekins *et al.* [15] concluded that they obtained Q(SAR) models that can be used for prediction of hERG blockade.

In the paper by Sierstad and Agrafiotis [17] in house developed training set, including 439 compounds studied on hERG blockade under the same conditions, was used for QSAR analysis by neural network models in conjunction with several feature selection methods. The authors [17] concluded that the final model showed good predictive abilities being validated *versus* an external test set of literature compounds. Unfortunately, the proprietary training set used in publication [17] is not available for other researchers (at least, no publication was found in correspondence with the reference [20] cited in Sierstad and Agrafiotis [17] as being "In press").

The purpose of this study was to estimate the possibilities of computer program PASS [26–29] application for predicting QT-Prolongation and hERG blockade. Since PASS training set includes the information about structure and biological activity collected from literature, PASS algorithm is robust enough to overcome the incompleteness/inconsistency of data [30]. Moreover, PASS estimates the probability for about 3000 kinds of biological activity and, therefore, it was interesting to analyse whether PASS predictions could be used for identification of indirect mechanisms of hERG blockade and QT-Prolongation.

2. Methods

2.1 *Computer program PASS*

PASS (Prediction of Activity Spectra for Substances) is designed as a tool for evaluation of general "biological potential" of the organic molecule being studied [26–29]. In PASS biological activities are described qualitatively ("active" or "inactive"), and the Multilevel Neighbourhoods of Atoms (MNA) descriptors are used for chemical structure

representation [28]. PASS estimations of biological activity spectra for new compounds are based on the SARBase, which accumulated the results of the structure-activity relationships obtained during the training procedure. PASS training set currently includes about 120,000 substances, which were thoroughly selected from literature. These molecules are presented by the completely determined simply connected 2D structural formulae of uncharged molecules. User can explore the existing SARBase, provided with PASS, or create its own SARBase using its own training set(s).

The predicted activity spectrum in PASS is presented by the rank-order list of activities with probabilities "to be active" *Pa* and "to be inactive" *Pi*. If the compound under prediction has the equivalent structure in the PASS SAR Base (the substances are considered equivalent if they have the same MNA descriptors set), this structure is "excluded" from the SARBase during the prediction with all associated information about its biological activities. The estimation of prediction accuracy is based on the Independent Accuracy of Prediction (IAP) criterion [28] calculated in leave-one-out cross-validation (LOO-CV) procedure.

2.2 *QT-Prolongation training set*

To re-train PASS for prediction of QT-prolongation and hERG blockade, a set with 163 compounds was collected, for which such information was available [31–42]. This set was highly diverse both in structural and biological spaces (Table 1).

Compounds, with $IC_{50} \leq 10\,\mu M$ (hERG blockade) were considered as "active"; with $IC_{50} > 10\,\mu M$ – as "inactive". If the information about IC_{50} for hERG blockade was not available, but in several publications it was mentioned that the compound causes both hERG blockade and QT-prolongation, such compound was considered as "active".

For those compounds, which cause the QT-Prolongation but do not cause the direct hERG blockade, it was reasonable to suggest the existence of other mechanisms for QT-Prolongation. This corresponds to some cases described in literature [43, 44].

Information about all 163 compounds was stored in ISIS Base [45]. The data included ID number, name, structural formula, international nonproprietary name and IC_{50} values (if available). Data on structures and activities exported from ISIS Base as SDF file were used for PASS re-training.

2.3 *Analysis and interpretation of PASS predictions*

To analyse the PASS prediction results, computer program PharmaExpert was applied. PharmaExpert is a program which interprets PASS predictions taking into account known mechanism-effects and effect-mechanism relationships. It provides a flexible mechanism for selection of compounds with desirable but without unwanted kinds of biological activity in libraries of chemical compounds. It calculates the statistics of different kinds of activity for a particular set of compounds. PharmaExpert knowledgebase includes information about 5188 mechanisms of action, 537 pharmacotherapeutical effects and 5747 types of relationships between them.

PharmaExpert is considered in details elsewhere [46], and its application to the analysis of PASS predictions for the QT-prolongation set is described below.

Database Brenda, available via the Internet [47] was used as a source of information about the enzymes, which appeared in the statistics calculated by PharmaExpert.

Table 1. List of compounds included into the QT-prolongation training set.

Pharmacotherapeutical classes	*Name of drugs*
Analgesic drugs (9) and its metabolite (1)	Articaine*, Buprenorphine, Cocaethylene, Cocaine*, Codeine, Fentanyl, Levomethadyl, Lidocaine*, Meperidine*, Methadone
Antiarrythmic drugs (17)	Almokalant, Ambasilide, Amiodarone, Azimilide, Bepridil, Disopyramide*, Dofetilide, E-4031, Flecainide, Ibutilide, Lidoflazine, Nifekalant, Procainamide, Propafenone, Quinidine, Sotalol, Terikalant
Antibiotics and antiprotozoal, including macrolide-like antibiotics (24)	Ampicillin, Azythromycin (macrolide-like), Ciprofloxacin*, Clarithromycin (macrolide-like), Cloroquine, Doxepin, Erythromycin (macrolide-like), Gatifloxacin, Gemifloxacin (macrolide-like), Grepafloxacin, Halofantrine, Hydroquinidine, Josamycin(macrolide-like), Levofloxacin*, Mefloquine, Moxifloxacin*, Pentamidine, Primaquine, Pyrimethamine, Sparfloxacin*, Spiramycin (macrolide-like), Telithromycin(macrolide-like), Trimetoprim*, Verapamil
Antyhypertensive drugs (7)	Carvedilol*, Isradipine, Losartan, Mibefradil, Nicardipine, Nifedipine*, Vincamine
Antihystaminic drugs (15) and its metabolite (1)	Astemizole, Carebastine*, Cetirizine, Chlorphenamine, Clemastine, Desloratadine, Desmethylastemizole, Diphenhydramine, Ebastine*, Hydroxyzine, Levocetrizine, Loratadine, Mizolastine, Norclozapine, Tecastemizole, Terfenadine
Antiviral agents (5)	Foscarnet, Lopinavir*, Nelfinavir, Ritonavir, Saquinavir
Diuretics (2)	Indapamide, Spironolactone*
Psychotropic agents (38) and its metabolites (3)	Amisulpride, Amitriptyline*, Amoxapine, Budipine, Caffeine, Chlorpromazine, Clomipramine, Clozapine, Clozapine N-oxide*, Desipramine, Dextropropoxyphene, Domperidone, Doxepin, Droperidol, Felbamate, Fluoxetine*, Fluphenazine, Fluvoxamine, Haloperidol, Imipramine, Mesoridazine, Nicotine*, Norclozapine, Norpropoxyphene, Olanzapine, Paliperidone, Paroxetine, Phenobarbital, Phenytoin*, Pimozide, Pyrilamine, Quetiapine, Risperidone, Sertindole, Sertraline, Sulpiride, Thioridazine, Tiapride, Trazodone, Venlafaxine, Ziprasidone
Other agents (42)	Alosetron, Amsacrine,Bisindolylmaleimide I, Brl 32872, Chromanol-293B, Clotrimazole, Dolasetron, Doxazosin, Emd 60263, Erythromyclamine, Fenmetozol*, Fosphenytoin, Glibenclamide, Glyceryl-nonivamide, Granisetron, Isoproterenol, Ketoconazole, L-365260, Lubeluzole, Lumefantrine, Mdl 74156, Methylecgonidine*, Moexipril, Naratriptan, Octreotide, Perhexiline, Pirenzepine, Prazosin, Probucol, Salbutamol, Salmeterol, Sibutramine*, Sildenafil, Sumatriptan, Tamoxifen, Terazosin*, Terodiline, Tizanidine, Vardenafil, Veratridine, Vesnarinone, Vinpocetine, Zolmitriptan

Note: *Inactive compounds.

Only predictions associated with the human enzymes were considered as possible mechanisms for QT-Prolongation.

3. Results and discussion

After the addition of 163 compounds with data on QT-Prolongation to the SARBase in the current version of PASS and re-training of the program, the following results were obtained: Mean accuracy of prediction in LOO-CV for the whole training set was 81.8% for the activity ''QT interval prolongation'', and 87.1% for the activity ''HERG-channel antagonist''. The number of active compounds was 130 and 75 for the QT interval prolongation and HERG-channel antagonists, respectively.

SDF files with the results of PASS prediction for the QT-prolongation training set were used as input data in PharmaExpert. Since all these compounds were considered as ''equivalent'' (see paragraph 2.1), the appropriate exclusion procedure was performed during the prediction.

For further analysis 75 substances were selected, which might prolong QT interval with reasonable probability (Pa $>$ 0.5). Statistics for all activities, which were predicted with Pa $>$ 0.5 for more than 40% of compounds from this sub-set, calculated by PharmaExpert statistics is presented in Table 2.

Some activities presented in the Table 2 are related to bacteria and protozoa but not to the human cells, including: Cyclohexylamine oxidase inhibitor, methanol dehydrogenase inhibitor, farnesol dehydrogenase inhibitor, 2-haloacid dehalogenase inhibitor, fructose 5-dehydrogenase inhibitor and Methylamine-glutamate *N*-methyltransferase inhibitor. The activity ficain inhibitor is specific to plants and trimethylamine-oxide aldolase inhibitor is specific for fishes. Therefore, all these (non-human) activities were considered as irrelevant and excluded from the further analysis.

Activity hERG channel antagonist may be regarded as a mechanism for QT interval prolongation, which, on the other hand, is a mechanism for torsades des pointes. So, the hierarchy at the molecular, cellular, organ/tissue and organism levels is used as the basis for activity-activity relationships. All three activities related to the cardiac arrhythmia are observed in Table 2.

Forty chemicals from this sub-set inhibit dimethylargininase (dimethylarginine dimethylaminohydrolase, DDAH). DDAH is an enzyme that catalyses the metabolism of asymmetric dimethylarginine (ADMA), an endogenous inhibitor of nitric oxide synthase (NOS). NO is a messenger involved in many biological processes. NO is responsible for endothelium derived tonic relaxation of blood vessels by stimulating soluble guanylate cyclase and increasing cGMP in smooth muscle cells [48]. Thus, the inhibition of endogenous NOS by increased level of ADMA may lead to ischemia of cardiomyocytes. QT interval prolongation may occur, in this case, due to acidosis and decreasing the hERG current amplitude [49].

It is interesting, that 34 molecules, having dimethylargininase inhibitor activity are used for myocardial ischemia treatment. Perhaps, the ischemia treatment by these compounds is based on some other mechanisms of action.

Another important source of NO in the vasodilatation system is NOergic neurons. The NO from endothelium and NOergic neurons may be related to certain pathological conditions. For example, some blood vessels, especially in the heart, lung and brain, seriously damage the surrounding tissue when ischemia reperfusion occurs in conjunction

Table 2. Fragment of statistics, computed for compounds, which might cause QT-prolongation with Pa > 0.5.

No	*Number**	*Types of Activity*
1	**74**	**QT interval prolongation**
2	63	Cerebrovascular disorde treatment
3	60	Adrenaline release inhibitor
4	**54**	**HERG channel antagonist**
5	49	CYP2D19 substrate
6	49	Antianoxic
7	**48**	**Torsades de pointes**
8	47	Antinephrotoxic
9	45	Methanol dehydrogenase inhibitor
10	45	Farnesol dehydrogenase inhibitor
11	44	2-Hydroxyquinoline 8-monooxygenase inhibitor
12	44	Gene expression inhibitor
13	44	Gluconate 2-dehydrogenase (acceptor) inhibitor
14	43	Myocardial ischemia treatment
15	42	Methylamine-glutamate *N*-methyltransferase inhibitor
16	42	MCP 1 antagonist
17	41	Aldehyde oxidase inhibitor
18	41	Hydrolase inhibitor
19	40	Electron-transferring-flavoprotein dehydrogenase inhibitor
20	**40**	**Dimethylargininase inhibitor**
21	40	Hyperglycemic
22	40	Microsomal triglyceride transfer protein inhibitor
23	**39**	**Progesterone 11 alpha-monooxygenase inhibitor**
24	38	5 Hydroxytryptamine uptake stimulant
25	38	Oxytocin agonist
26	37	Quinine 3-monooxygenase inhibitor
27	37	*N*-formylmethionyl-peptidase inhibitor
28	36	Horrilysin inhibitor
29	36	2-Haloacid dehalogenase inhibitor
30	36	27-Hydroxycholesterol 7alpha-monooxygenase inhibitor
31	35	Coronary insufficiency treatment
32	35	Chondroitin 4-sulfotransferase inhibitor
33	35	2-Hydroxyquinoline 5,6-dioxygenase inhibitor
34	35	Ficain inhibitor
35	35	Fructose 5-dehydrogenase inhibitor
36	34	Antiviral (Rhinovirus)
37	34	CXC chemokine receptor antagonist
38	34	Antineoplastic (ovarian cancer)
39	33	Appetite stimulant
40	33	Antieczematic atopic
41	33	Psychotropic
42	33	Transactivator transcription protein inhibitor
43	33	Antineurotoxic
44	33	Systemic lupus erythematosus treatment
45	32	Acylglycerol kinase inhibitor
46	32	Antischizophrenic
47	32	Vascular (periferal) disease treatment
48	32	Spermidine dehydrogenase inhibitor
49	**32**	**1-Phosphatidylinositol-4-phosphate 5-kinase inhibitor**
50	32	2-Hydroxymuconate-semialdehyde hydrolase inhibitor
51	31	Arylmalonate decarboxylase inhibitor
52	31	4-Hydroxyproline epimerase inhibitor

(*Continued*)

Table 2. Continued.

No	*Number**	*Types of Activity*
53	31	Trimethylamine-oxide aldolase inhibitor
54	31	Formaldehyde transketolase inhibitor
55	31	Steroid-transporting ATPase inhibitor
56	31	Antineoplastic (renal cancer)
57	31	Poly(beta-D-mannuronate) lyase inhibitor
58	31	Taurine dehydrogenase inhibitor
59	31	Na+-transporting two-sector ATPase inhibitor
60	31	Alkane 1-monooxygenase inhibitor
61	30	8-Hydroxyquercitin 8-*O*-methyltransferase inhibitor
62	30	Dopamine D4 agonist
63	30	Ferroxidase inhibitor
64	30	Exoribonuclease II inhibitor
65	30	CC chemokine 2 receptor antagonist
66	30	Cardioprotectant

Notes: *Number = number of compounds for which a particular activity was predicted with Pa > 50%.
Activities related to the QT interval prolongation are marked in bold.

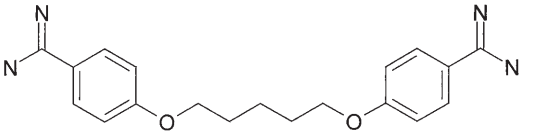
with accelerated NO production [50]. Although it is believed that NO is related to the tissue damage, it has not been determined why excess NO concentrations is produced. Probably, increased level of NO is produced in response to high level of ADMA in blood in conditions of DDAH inhibition. In this case, substances, which inhibit dimethylargininase, also might cause serious cardiotoxic effect.

Twenty-nine compounds from this sub-set inhibit 1-phosphatidylinositol-4-phosphate 5-kinase, involved in synthesis of phosphatidyl-inositol phosphate. It was shown experimentally that phosphatidyl-inositol phosphate (PIP2) participates in hERG channels regulation [51]. Mechanisms of activation are not clear enough, but different assumptions exist. Thyrotropine-releasing hormone (TRH) can modulate the hERG-type rapid delayed potassium channel. TRH modifies the current kinetics of hERG channel co-expressed in *Xenopus* oocytes with the TRH receptor, whose activity is regulated via the protein kinase C pathway and depends on the PIP2 concentration in the membrane [52]. There are data about acceleration of Ikr-channel activation by PIP2. Thus, inhibition of phosphatidylinositol-4-phosphate 5-kinase leads to decrease of PIP2 concentration in plasma resulting to reduction of hERG currents.

The fact that calcium may participate in endoplasmatic reticulum protein synthesis and modification has been reported [53]. In this case, the second messenger PIP2 modulated calcium concentration in plasma, and activates hERG protein synthesis.

Activity «hERG channel antagonist» is not present in activity spectra of seven substances, which can inhibit 1-phosphatidylinositol-4-phosphate 5-kinase. One may be suggest, that 1-phosphatidylinositol-4-phosphate 5-kinase inhibition is the indirect mechanism of QT interval prolongation.

There are some suggestions about dispersion of QT interval in men and women and it is concerned with concentration of estrogen and progesterone in blood. Moreover, it is not known if the risk of drug-induced torsades de pointes varies during the menstrual cycle. It is also can be suggested that progesterone has direct or indirect mechanism for cardiac repolarizing currents [54]. In case of reduction of cardiac currents by progesterone,



0.664 0.232 1-Phosphatidylinositol-4-phosphate 5-kinase inhibitor
0.527 0.351 Dimethylargininase inhibitor
0.074 0.446 HERG channel antagonist

Figure 1. Structural formula of pentamidine with PASS prediction of biological activities related to QT-prolongation.

the influence of Progesterone 11 alpha-monooxygenase inhibitor on QT interval duration is obvious. However, the action of progesterone on repolarization is not investigated enough to date.

4. Conclusions

It was shown that PASS was able to predict QT-Prolongation and hERG blockade with reasonable accuracy (81.8% and 87.1%, respectively). Such accuracy of prediction is comparable for the quality of other methods discussed in literature [3–21].

Moreover, using PASS predictions for some compounds probable mechanisms of QT-prolongation, other than the hERG blockade, can be identified. For example, pentamidine is known as a compound that causes QT-prolongation, but does not block hERG K^+ channel. PASS prediction for pentamidine demonstrates, that it is not predicted as hERG blocker, but is predicted as 1-phosphatidylinositol-4-phosphate 5-kinase inhibitor and dimethylargininase inhibitor (Figure 1).

Thus, inhibition of 1-phosphatidylinositol-4-phosphate 5-kinase and dimethylargininase can be considered as probable indirect mechanisms of hERG inhibition and QT-prolongation.

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