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Computational investigations of hERG channel blockers: New insights and current predictive models $\stackrel{\frown}{\approx}$ 2

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ABSTRACT

Identification of potential human Ether-a-go-go Related-Gene (hERG) potassium channel blockers is an essential 17 Available online xxxx 8 part of the drug development and drug safety process in pharmaceutical industries or academic drug discovery 18 9 Keywords. centers, as they may lead to drug-induced QT prolongation, arrhythmia and Torsade de Pointes. Recent reports 19 10 hERG also suggest starting to address such issues at the hit selection stage. 2011 TdP In order to prioritize molecules during the early drug discovery phase and to reduce the risk of drug attrition due 21 12Arrhythmia to cardiotoxicity during pre-clinical and clinical stages, computational approaches have been developed to pre- 22 OSAR 13 dict the potential hERG blockage of new drug candidates. 23 14 Computational approaches In this review, we will describe the current in silico methods developed and applied to predict and to understand 24 Ligand-based 15the mechanism of actions of hERG blockers, including ligand-based and structure-based approaches. We then 25 Structure based, Polymorphism 03 discuss ongoing research on other ion channels and hERG polymorphism susceptible to be involved in LQTS 26 and how systemic approaches can help in the drug safety decision. 27© 2015 Elsevier B.V. All rights reserved. 2830 31 Contents $\frac{34}{33}$ 3 3 3 3 4

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1. Introduction

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Voltage-dependent ion channels give in part rise to the shape and duration of the cellular action potential and this electrical activity of

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http://dx.doi.org/10.1016/j.addr.2015.03.003 0169-409X/© 2015 Elsevier B.V. All rights reserved. the heart is commonly recorded using electrocardiography (ECG) 52 approaches. These recent years, a particular channel was extensively in- 53 vestigated as it was found to play a major role in both cardiac electro- 54 physiology and drug safety [1]. This protein is encoded by the human 55 ether-a-go-go related gene (hERG), which produces the pore-forming 56 subunit of a delayed rectifier voltage gated K⁺ channel. The family 57 name "ether-a-go-go" was coined in 1969 [2] and was intended as ref- 58 erence to how the legs of mutant flies shake under ether anesthesia 59 like the go-go dancers of the 1960s [3]. During drug development, 60 there are in fact several types of cardiovascular toxicity that have to 61 be considered, but admittedly, promiscuous block of cardiac hERG 62

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channels by a variety of structurally different low molecular weight 63 64 drugs represents a major therapeutic challenge with profound impacts on human health. It is indeed known that genetic disorders and drugs 65 66 that affect ion channels in the heart can change ECG parameters such as the QT-interval. A special cardiovascular safety concern is commonly 67 referred to as QT interval prolongation (Fig. 1). QT interval (which 68 69 represents the time from the depolarization to the repolarization of 70the ventricules) prolongation can cause Torsade de Pointes (TdP), a 71ventricular tachyarrhythmias. If this episode resolves spontaneously 72and rapidly, it can trigger syncope and in extreme situations can progress to ventricular fibrillation and sudden death [4,5]. 73

These last years, it was found that many drugs belonging to different 74 chemical and therapeutic groups, such as antiarrhythmics, anti-75histamines, antifungals, antipsychotics or antitussives, have the poten-76 tial for QT prolongation and may cause TdP while being relatively po-77 tent inhibitors of hERG. For instance terfenadine (Antihistamine), 78 astemizole (Antihistamine), and cisapride (Serotonin receptor agonist) 79 80 were all approved for human use and were withdrawn from the market as they had safety issues, inducing QT interval prolongations and ar-81 rhythmias. Along the same line, vardenafil (Anti-anginal/vasodilator) 82 83 and ziprasidone (*psychiatric drug*) were approved but with cautionary labeling as they can affect the ECG (see sites such as the Internet Drug 84 85 Index: http://www.rxlist.com or the list of "OTDrugs" at: https:// www.crediblemeds.org or at: http://www.sads.org.uk/) [6]. 86

As a result of these observations and because of the unjustified risk 87 of sudden cardiac death, regulatory agencies started to be concerned 88 by the potential risk of Long QT Syndrome (LQTS) caused by drugs 89 90 and more specifically, given our present understanding of the problem, 91 by hERG (although in theory many other events could cause LQTS and 92 LQTS are not always associated with cardiac toxicity). A first guideline 93 (the regulatory basis for safety pharmacology studies is defined by the international conference on harmonization (ICH) guidelines, e.g., the 9495non clinical guideline S7B) was adopted in 2005 that required from the pharmaceutical companies to identify drugs with QT liability. A sec-96 ond guideline was compiled in parallel (the clinical guideline ICH E14). 97 There, the FDA required for almost all new low molecular weight 98 99 drugs to be assessed in a "thorough QT" clinical study [7] to determine if the drug prolongs the heart-rate-corrected QT interval (QTc). 100

Additionally, the harmonization for drug labeling was also requested. 101 With these guidelines, it is believed that improving the efficiency and 102 effectiveness of medical product development could be advanced 103 most rapidly by combined analysis of clinical and preclinical data from 104 previous marketing applications. For example, the FDA reviewed >250 105 thorough QT study reports, of which ~20% have been positive for QT 106 prolongation [8]. Consequently, many drugs had to be withdrawn 107 from the market [9]. 108

As mentioned above and directly related to these guidelines, several 109 studies have shown that the blockage of the delayed rectifier current 110 during the inward rectification (lkr) was a primary factor in acquired- 111 LQTS. Such deregulation of the voltage dependent K^+ ion channel is 112 mediated by the human ether-a-go-go related gene (hERG), a key 113 component of the IKr [4,10]. Seventy-eight Kv channel family have 114 been reported so far [11] and although hERG (defined also as KCNH2 115 and Kv11.1) is expressed in a wide array of tissues, its physiological 116 function is best characterized in cardiac cells where it plays a critical 117 role in the repolarization of the cardiac action potential [2]. Globally, 118 during the plateau phase, there is reduced K⁺ permeability whereas 119 the K⁺ channel remains open during the repolarization phase [12]. 120 Because of the importance of this channel on human health, functional 121 assays measuring drug-induced blockage of hERG current started to be 122 developed and are now routinely used [13,14]. All major pharmaceuti- 123 cal companies have to monitor the potential risk of LOTS induced by 124 new drugs during each stage of the drug discovery process [15]. To as- 125 sess the hERG channel blockage induced by a drug, electrophysiological 126 experiments (i.e., patch clamp) were the preferred techniques. The 127 drawback is that such studies are expensive and time consuming. Sim- 128 pler, faster and more "high-throughput", binding assays can also be 129 used but there are concerns about the physiological relevance of such 130 experiments. Of importance is that all these experiments allow to devel- 131 op databases that should ultimately help to design theoretical models to 132 rapidly flag new molecules as being potential hERG binders [16]. Overall 133 and independently of the assay used, it is in general very difficult to 134 derive guidelines for chemical synthesis from analysis of such experi-135 mental data [17]. In the meantime, in order to improve our knowledge 136 over the mechanisms of blockage and possibly facilitate drug develop- 137 ment, structural biology investigations and/or mutagenesis studies in 138



Fig. 1. Schema of a normal electrocardiogram (on the left) versus a prolongation of the QT interval (on the right).

combination with various homology models of the channel were carried
out such as to propose likely poses for the drug blockers into the channel
and give new ideas for compound optimizations [18]. Ligand-based
models were also established such as to suggest key chemical features
to avoid during the design of a new drug and where chemical modifications could be introduced in the molecules to reduce binding to the
channel [19].

There are however many difficulties with hERG studies and drug 146 147 development strategies. For instance, the relationship between 148 hERG block and clinical QTc (corrected QT) prolongation is still unclear 149and some drugs that inhibit hERG (verapamil) do not trigger TdP (and 150vice versa). While all typical TdP are high-potency hERG blockers, not all hERG blockers cause TdP. For example, both verapamil and 151152ranolazine are hERG blockers and prolong QT, but appear not to be proarrhythmic, because of the effects on calcium (verapamil) or late 153sodium (ranolazine) currents [20]. Indeed, systemic approach studies 154suggest the involvement of others proteins and others mechanisms in 155 TdP [21]. Some insights start to be provided about the underlying com-156plexity of such cardiac toxicity problem, stressing the fact that hERG 157liability does not necessarily translate into TdP risk in humans. Along 158the same line, estimates are that 40-70% of the new molecular entities 159developed as potential therapeutic agents test positive when assayed 160 161 for hERG blocking liability [22]. These molecules are then abandoned 162while their true torsadogenic potential is unknown. To some extent, these problems could be acceptable if TdP risk could be clearly elicited 163in clinical trials. However, drug induced TdP from non-antiarrhythmic 164drugs is a relatively rare event and may not be detected even in clinical 165166 trials of several thousands of patients, underlying further the challenges ahead. 167

Because hERG assays and QT animal studies are expensive and time 168 169 consuming specially in the early stages of drug discovery, when numer-170ous molecules would need to be assessed, or else because assay results 171could be misleading, numerous in silico models have been developed over the years to assist decision making (see a list of free in silico tools 172and databases at www.vls3d.com, [23]). With this review, we will pres-173ent the new insights and current predictive in silico models developed 174 for hERG and the new investigations based on systemic approaches re-175176lated to the acquired-LQTS.

177 2. Diagnosis of QT-interval prolongation and harmonization of the 178 data for *in silico* predictions

Numerous issues have been reported on the prediction of drugs 179that induced LOTS, notably drug-metabolism, drug solubility, the vari-180 ability of the concentration of inhibition depending upon the experi-181 mental methods used and the relation between different clinical 182183 observations and QT-interval prolongation [24]. In this review, we will highlight several key points that should be taken into account by drug 184 designers in order to develop novel and more accurate algorithms and 185protocols. 186

187 2.1. Detection of QT prolongation at the clinical level

One of the most critical issues in the development of predictive and
 accurate models is the acquisition of reliable data, not only at the molec ular level, but also at the clinical level. Such harmonization is often
 discussed by the different agencies.

In 2005, based on close to 300,000 case reports of suspected adverse
drug reactions for 52 proarrhythmic drugs, De Bruin et al. reported a
significant association between the hERG blockage of drugs and ventricular arrhythmias and sudden death. Interestingly, these reports on
drug-induced Torsades de Pointes concerned more often women
(68%) [25].

Recently, Kesselheim et al. conducted a study comparing prescription information (i.e., drug labels) approved by the FDA and by the European, Canadian and Australian regulatory authorities. They found that significantly fewer adverse drug reactions were listed in the UK 201 label compared with the US label and concluded that the international 202 variations in the presentation of safety data in the drug label could 203 have important implications for patient safety [26]. In addition, substan-204 tial differences on safety information exist for several therapeutic clas-205 ses, notably the cardiovascular system [27]. 206

Warnier et al. did a comparison of the QT interval prolongation label-207 ing for newly approved drugs [28] and concluded that only a moderate 208 agreement in the semantic use of the phrase QT-prolonging properties 209 of a drug in US and EU could be found, although the expected clinical de-210 cisions were more consensual. For example, one product (asenapine) 211 had no QT-prolonging properties according to the EU label, whereas 212 this drug possibly prolongs the QT interval according to the semantics 213 in the US label. So, differences in QT labeling language can result in mis-214 communication of safety information and also in the development of 215 TQT models [29]. 216

2.2. Harmonization of the in vitro approaches for in silico prediction 217

The problem of harmonization is also present at the preclinical level, 218 where different *in vitro* approaches for the determination of hERG bind-219 ing are applied, such as whole-cell patch clamp electrophysiological as-220 says, fluorescence-based assays, radioligand binding assays or rubidium221 flux, on different mammalian cell lines i.e., HEK (Human Embryonic Kid-222 ney cells), CHO (Chinese Hamster Ovary cells), COS (*Cercopithecus*223 *aethiops* cells) and neuroblastoma, or non mammalian cell lines such as XO (*Xenopus laevis* oocytes) [30,31]. For example a measured IC₅₀225 of 100-fold difference has been determined for loratidine in the function of the cell lines used (100 µM in HEK and lower than 1 µM in XO cells, 227 respectively) [32,33].

Moreno-Galindo studied the impact of the whole-cell patch-clamp 229 configuration on the pharmacological assessment of the hERG channel 230 and estimated that a potential source of error could be related to the 231 conventional whole-cell configuration of the patch-clamp technique 232 (at least on HEK-293 cells). It may have an impact on conclusions regarding the mechanism of inhibition. [34]. However, since the primary 234 goal of pharmaceutical industry is to determine the hERG-blocking potency of drugs (IC₅₀), this technique is still recommended for regulatory 235 submissions. 237

3. Ligand-based approaches

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As the majority of the in vitro experiments to assess drug-induced 239 LOTS are associated to the hERG blockage, understandably in silico ap- 240 proaches (and more specifically ligand-based approaches) started to 241 be developed as they are known to be relatively efficient in dealing 242 with this type of data. Interestingly, whereas the first in silico model 243 was based on fifteen molecules [35], the most recent one which is 244 also available online is based on more than 4980 diverse molecules col- 245 lected from several sources [36]. Other groups, essentially in the private 246 sector, have published models with even larger private datasets, as 247 indeed most pharmaceutical companies have their own source of data 248 [37,38]. Recently, experimental data obtained from a primary screen 249 using electrophysiology approaches performed on more than 300,000 250 structurally diverse compounds were stored in a large database [39]. 251 Although these data can be visualized for a specific query compound, 252 the database is not available to the scientific community for building 253 predictive hERG model. Overall, close to 70 hERG models have been re- 254 ported in the literature using various molecular descriptors in combina- 255 tion with diverse machine learning methods and showing a large panel 256 of performance (Table 1). Comments about some of these models have 257 been reported previously [40,41]. 258

A majority of the models are classifiers and only a few regression 259 models on a small subset of compounds have been reported [42]. This 260 can be explained by the analysis of the hERG content inside the ChEMBL 261 database, one of the largest repositories of bioactive compounds, on 262

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t1.1 Table 1

t1.2 hERG models reported in the literature.

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119 Dubs et al. [137] Q33 Recursive partition Acc. = 905 121 Sun H, [138] [177] Q9 Recursive partitionSOM R2 = 0.87, c = 0.8	t1.18	Coi et al. [135]	82	Codessa-QSAR	R2 = 0.82
1.30 Ends et al. [137] 99 Recursive partition(SOM) R2 = 0.83, sec = 0.57. 1.21 Genp et al. [138] 1977 Naives Bayes classifier acc = 76. 1.22 Genp et al. [130] 90 Fragment-base4-Q5R R2 = 0.91 1.25 Varing et al. [140] 194 Page et al. [150] R2 = 0.91 1.25 Varing et al. [140] 194 Page et al. [150] R2 = 0.97 1.26 Gravaphan et al. [171] 853 Patimaceophone-SVM R2 = 0.97 1.27 Gravaphan et al. [143] 123 Outcomove at al. [142] R2 = 0.57 1.29 Rife et al. [143] 132 Synd acc = 757 1.29 Rife et al. [143] 132 Synd acc = 67-742 1.29 Rife et al. [143] 132 Synd acc = 67-742 1.29 Rife et al. [143] 132 Synd acc = 67-742 1.21 Jact et al. [143] 132 Synd acc = 67-742 1.21 Jact et al. [143] 133 Synd acc = 67-742 1.21 Jact et al. [143] 133 Synd ac	t1.19	Dubus et al. [136]	203	Recursive partition	acc = 96%
1.11 Sun H, [13] 1979 Nate Baye classifier $ac = 0.87_{x}$ 123 Gopp et al. [13] 339 Decision tree $ac = 75_{x}$ 123 Song et al. [13] 194 Pinamochone-LackAR $R2 = 0.91$ 124 Kong et al. [14] 194 Pinamochone-SWM $R2 = 0.91$ 125 Loreng [14] 765 Pinamochone-SWM $R2 = 0.97$ 126 Loreng [14] 765 Pinamochone-SWM $R2 = 0.97$ 127 Goragehan et al. [142] 137 Gaussian processes $R2 = 0.81$ 128 Inter al. [146] 491 SVM $ac = 943$ 120 Inter al. [147] 133 Binary (CoAR) $R2 = 0.90$ 121 Intardo et al. [143] 132 Dio-CoAR $R2 = 0.81$ 123 Intar (146] 133 Binary (CoAR) $ac = 0.83$ 124 Thai et al. [147] 285 Counter propagation NN $ac = 0.83$ 123 Intardo et al. [148] 275 Symidarity-based classifier $ac = 0.87$ 123 Nike et al. [148] 284 Coutard al. (ac al. 148) <th>t1.20</th> <th>Ekins et al. [137]</th> <th>99</th> <th>Recursive partition/SOM</th> <th>R2 = 0.83; acc = 95%</th>	t1.20	Ekins et al. [137]	99	Recursive partition/SOM	R2 = 0.83; acc = 95%
1:22 Gepp et al. [139] 339 Decision tree $acc = 756$. 1:32 Song et al. [43] 194 194 Planmacophore/Volume $acc = 756$. 1:31 Aronov et al. [43] 194 194 Planmacophore/Volume $acc = 758.225$. 1:31 Aronov et al. [43] 194 195 Planmacophore/Volume $acc = 758.225$. 1:32 Goreanov et al. [43] 133 Planmacophore/Volume $acc = 67.935$. $R2 = 0.031$. 1:30 It et al. [46] 401 SVM $acc = 94%$. $acc = 54%$. 1:31 Inanobe et al. [142] 32 30-CSAR $R2 = 0.90$. $acc = 67.735$. 1:32 Ija et al. [144] 1043 SVM $acc = 67.736$. $acc = 57.736$. 1:33 Inanobe et al. [147] 333 Context properiod cacofferer $acc = 0.57.738$. 1:34 That et al. [149] 676 Biasr egression-CGAR RXE = 0.00 1:35 Inaster al. [151] 250 SVM-context real systs $acc = 0.57.388$. 1:35 Inaster al. [151] 250 SVM-context real systs $acc = 0.51.388$. <t< th=""><th>t1.21</th><th>Sun H. [138]</th><th>1979</th><th>Naives Bayes classifier</th><th>acc = 0.87%</th></t<>	t1.21	Sun H. [138]	1979	Naives Bayes classifier	acc = 0.87%
121 30 ang et al. [16] 90 Fragment-based-40AA $k2$ = 0.91 123 Anone et al. [16] 194-519 Lagistic regression acc = 78.423. 125 Waring et al. [140] 788 Lagistic regression acc = 76.93. 126 Obresanova et al. [142] 197 Gaussian procession R2 = 0.63.1 128 Obresanova et al. [142] 197 Gaussian procession R2 = 0.63.1 129 Lie et al. [164] 491 SWM acc = 87.4 120 Lie et al. [144] 104.3 SWM acc = 94.4 121 Inanobe et al. [143] 32 3D-GSAR acc = 67.7.4% 121 Inanobe et al. [144] 104.3 SVM acc = 87.2 122 Jai et al. [144] 104.3 SUM acc = 62.88%. 123 Thair et al. [147] 28.5 Counter propagation NN acc = 87.2 124 Nuisu et al. [148] 27.2 StMinarty-based classifier acc = 62.88%. 124 Holda et al. [151] 68 22-0.05AR R2 = 0.81 125 Holda et al. [152] 77 StM	t1.22	Gepp et al. [139]	339	Decision tree	acc = 76%
1.21 Avalue ℓ al. [43] 194-519 Plantacophole Volum $\Delta c = 78 + 2.5$ 128 Long [141] 25 Plantacophole SVM R2 = 0.07 129 Long [141] 25 Plantacophole SVM R2 = 0.07 129 Leng [141] 25 Plantacophole SVM R2 = 0.07 129 Fibre 41 [156] 163 PVAS programs $\Delta c = 94\%$ 129 Ibre 14 [164] 163 SVM $\Delta c = 94\%$ 121 Iard 1, [46] 401 SVM $\Delta c = 94\%$ 121 Iard 1, [144] 1043 SVM $\Delta c = 62.83\%$ 123 Iard 1, [144] 1043 SVM $\Delta c = 62.84\%$ 124 Tobi et al. [145] 83 KNNS VM-SOM $\Delta c = 62.84\%$ 125 Tobi et al. [146] 313 Binary (26A*) $\Delta c = 0.03$ 126 Nisku et al. [148] 252 SVM-fuster analysis $A c = 0.83$ 128 Parinet al. [146] 676 Bas regression-QSAR R2 = 0.93 129 Emondri et al. [150] 31 Amond-QSAR $A c = 0.83 - 0.94$ 12	t1.23	Song et al. [63]	90	Fragment-based-QSAR	R2 = 0.91
1.35 Varing et al. [140] Abs3 Lognitic Tegression $dcc = 0.04$ 1.27 Gravghan et al. [171] 8332 Online D-optimal design QsQR $acc = 67.33$; 1.28 Optezanov et al. [142] 117 Caussian processes $bl = -0.05$ 1.28 Interest al. [160] 161 Phymoconsesses $bl = -0.05$ 1.29 Interest al. [161] 122 3D-QSAR $bl = -0.05$ 1.29 Interest al. [161] 133 Binary QSAR $acc = 0.774$; 1.20 Interest et al. [164] 313 Binary QSAR $acc = 0.05$ 1.30 Nisture et al. [164] 255 Constremographics $acc = 0.87$. 1.31 Nisture et al. [164] 265 Constremographics $acc = 0.87$. 1.31 Nisture et al. [164] 265 Constremographics $acc = 0.87$. 1.32 Nisture et al. [164] 264 LDA-SVM $acc = 0.87$. 1.33 Binary QSAR $acc = 0.87$. $acc = 0.91$. $acc = 0.87$. 1.34 Large et al. [163] 2664 LDA-SVM $acc = 0.91$. 1.34 Boror	t1.24	Aronov et al. [45]	194-519	Pharmacophore/voting	acc = 78-82%
Liss Long [14] 25 Platimic oparity All $Z = 0.3^{\prime}$ 1.25 Gavgin et al. [37] B333 Onion D-optimal design-dSAR $acc = 0.73 sc$ 1.25 Obream over al. [142] 137 Cassim processed $Bc = 0.7$ 1.25 Obream over al. [143] 137 Cassim processed $Bc = 0.7$ 1.26 Obream over al. [144] 1043 SVM $acc = 0.44$ 1.21 In et al. [144] 1043 SVM $acc = 0.47$ 1.30 Chekmarev et al. [145] 83 NNN-SVM-SOM $acc = 6.7.47$ 1.35 Thair et al. [147] 285 Counter propagation N $acc = 0.7.47$ 1.35 Nissies et al. [148] 275 Similarity based Classifier $acc = 0.7.47$ 1.36 Nissies et al. [149] 676 Bas regression-QSAR $acc = 0.7.42$ 1.37 Nissies et al. [150] 31 Almond-QSAR $acc = 0.9.04$ 1.38 Hasen et al. [151] 250 4D fingerprint-QSAR $acc = 0.9.04$ 1.38 Garg et al. [151] 3	t1.25	waring et al. [140]	/685	Logistic regression	acc = 70%
Late Observation (x on z_{1}^{A}) Observation (x on $z_{1}^{A})$ Observation (x on $z_{1}^{A})$ </th <th>τ1.20 +1.97</th> <th>Leong [141] Cayaghan et al [27]</th> <th>20 ددەە</th> <th>Onion D-ontimal design OSAP</th> <th>$K_2 = 0.97$</th>	τ1.20 +1.97	Leong [141] Cayaghan et al [27]	20 ددەە	Onion D-ontimal design OSAP	$K_2 = 0.97$
Lass Optication et al. [142] 1.12 Catassam Dicksed $A = 0.5$ Pile et al. [45] 163 PNS program acc = 0.7 13 Let al. [46] 491 SNA acc = 0.7 13 Let al. [46] 491 SNA acc = 0.7 141 Dia et al. [141] 12 SNA acc = 0.7 142 Ipart al. [144] 13 SNA acc = 0.7 143 Thai et al. [147] 255 Counter program NN acc = 0.7 143 Nision et al. [148] 275 Similarity based Classifier acc = 0.8 143 Nision et al. [149] 676 Bassen et al. [148] acc = 0.8 143 Nision et al. [149] 676 Bassen et al. [148] acc = 0.8 143 Issim et al. [141] 20 31 Almone-QSAR R2 = 0.93 143 Doddrarddre et al. [48] 264 D.575 Similarity based Classifier acc = 0.89-0.94 144 Dordgrave et al. [151] 166 NN acc = 0.92-0.94 <tr< th=""><th>41.00</th><th>Obrozapova et al [142]</th><th>127</th><th>Caussian processos</th><th>ACC = 07-55% P2 = 0.91</th></tr<>	41.00	Obrozapova et al [142]	127	Caussian processos	ACC = 07-55% P2 = 0.91
Index tar, [a] Index tar, [a] <thindex [a]<="" tar,="" th=""> Index t</thindex>	+1.20	Filz et al [56]	163	DASS program	$R_2 = 0.01$
111 121 124	+1.20	Liet al [46]	491	SVM	acc = 94%
112 [] ja et al. [] [14] 1043 SVM cc = 943 112 Chelmarvet al. [145] 83 KNN-SVM-SOM acc = 67.74% 113 Thai et al. [146] 133 Binary OSA acc = 67.74% 113 Thai et al. [146] 235 Contruer prongation NN acc = 0.93 113 Nisius et al. [148] 275 Similarly-based classifier acc = 0.93 1147 Nisius et al. [149] 676 Biar regression QSAR RME = 0.60 1149 Doddardott al. [150] 31 Antomed QSAR RME = 0.60 1149 Doddardott al. [161] 250 4D fine-print QSAR acc = 0.93 1141 Boddardott al. [151] 68 2D QSAR R2 = 0.83 1143 Boray et al. [153] 166 NN-LLR Q2 = 0.83 1144 Boray et al. [153] 166 NN-LLR Q2 = 0.81 115 Ordiner Set al. [155] 166 NN-LLR Q2 = 0.81 115 Maine Set al. [155] 166 NN-LLR Q2 = 0.81 116 Maine Set al. [155] 166 NN-LLR Q2 = 0.81 <th>+1 31</th> <th>Inanobe et al [143]</th> <th>32</th> <th>3D-OSAR</th> <th>$R_2 = 0.90$</th>	+1 31	Inanobe et al [143]	32	3D-OSAR	$R_2 = 0.90$
133 Chelmarve et al. [146] 33 KNN-SVA-SOM acc = 67-248 134 Thai et al. [146] 313 Binary QSAR acc = 62-888 135 Thai et al. [147] 285 Counter propagation NN acc = 675 136 Nisus et al. [148] 232 Similarity-based classifier acc = 675 138 Hansen et al. [148] 232 SiMi-cluster analysis acc = 635 138 Hansen et al. [148] 232 SiMi-cluster analysis acc = 639 149 Doddaredity et al. [150] 31 Almond-QSAR R2 = 0.03 141 Suet et al. [151] 264 LDA-SVM acc = 6.93 141 Suet et al. [151] 264 DA-SVM acc = 6.93 142 Hidak et al. [152] 37 SOM NA acc = 0.93 142 Hidak et al. [153] 68 DA-SAR R2 = 0.43 R1 143 Beronoliti Stat. [153] 166 NN-LL R2 = 0.48 R2 = 0.48 143 Beronoliti Stat. [155] 157 NN R2 = 0.52 R2 = 0.52 144 Borcourty Et al. [1	t1.32	lia et al [144]	1043	SVM	acc = 94%
11.31 Thai et al. [146] 313 Binary QSNF acc = 0.23 11.35 Thai et al. [147] 285 Counter propagation NN acc = 0.93 11.36 Nisus et al. [148] 275 Similarity-based classifier acc = 0.85 11.37 Nisus et al. [148] 232 SVM-Custer analysis acc = 0.85 11.37 Nisus et al. [149] 676 Bias regression-QSAR RMSE = 0.60 11.39 Ermondi et al. [150] 31 Almond-QSAR R2 = 0.93 11.40 Doddarddy et al. [151] 250 4D fingerprint-QSAR R2 = 0.94 11.41 Borsey et al. [154] 25 Hologram (DSAR R2 = 0.34 11.41 Borsey et al. [154] 25 Hologram (DSAR R2 = 0.34 11.42 Othine Set al. [155] 166 KNN-LLR Q2 = 0.81 11.43 Care et al. [157] 3916 NN R2 = 0.34 11.44 Fortu Let al. [157] 3916 NR R2 = 0.53 11.45 Obiol-Pardo et al. [96] 400 PLS, SVR R2 = 0.53 11.44 Fortu Let al. [157] 3916 NN	t1.33	Chekmarev et al. [145]	83	KNN-SVM-SOM	acc = 67-74%
1.35 Thai et al. [147] 285 Courter propagation NN acc = 0.93 1.30 Nisus et al. [148] 275 Similarity-based classifier acc = 0.85 1.37 Nisus et al. [149] 676 Bias regression-QSAR RDS = 0.60 1.38 Hansen et al. [150] 31 Altono QSAR R2 = 0.93 1.40 Doddaredby et al. [151] 250 4D fingerprint-QSAR acc = 0.87 + 0.03 1.41 Greg et al. [153] 68 2D-QSAR R2 = 0.93 1.42 Hidska et al. [152] 37 SOM NA 1.43 Greg et al. [153] 68 2D-QSAR R2 = 0.93 1.44 Boresy et al. [154] 259 Hologram QSAR R2 = 0.94 1.45 Offeine Set al. [38] 50963 NN NS se = 0.66; Sp = 0.33 1.45 Churtur Se et al. [156] 113 P15, SVR R2 = 0.34 1.44 Karpet Cet al. [156] 113 P15, SVR R2 = 0.52 1.45 Robinson R et al. [159] 157 NN R2 = 0.52 1.46 Robinson R et al. [159] 157 NN	t1.34	Thai et al. [146]	313	Binary OSAR	acc = 82-88%
1.36 Nisius et al. [148] 275 Similafity Desci classifier acc = 87% 1.37 Nisus et al. [149] 676 Bias regresion-QSAR RMSE = 0.60 1.38 Hansen et al. [150] 31 Almond-QSAR RZ = 0.93 1.40 Dddareddy et al. [48] 2644 LDA-SVM acc = 0.89.0.94 1.41 Sue et al. [151] 250 4D fingerprint-QSAR acc = 0.93 1.41 Sue et al. [152] 37 SOM NA 1.43 Garg et al. [153] 68 2D-QSAR RZ = 0.03 1.44 Borsey et al. [154] 25 Hologram QSAR RZ = 0.84 1.45 O'Brien Set et al. [155] 166 KNN-LIR Q2 = 0.81 1.44 Forsey et al. [154] 131 PLS, SVR RZ = 0.52 1.46 Outrin Set et al. [157] 3916 NB acc = 0.53 1.47 Krauner C et al. [157] 3916 NB acc = 0.53 1.48 Fenu L et al. [157] 3916 NB acc = 0.53 1.44 Fenu L et al. [161] 293 NM, RF Acc = 0.72-0.90	t1.35	Thai et al. [147]	285	Counter propagation NN	acc = 0.93
1.47 Nisus et al. [149] 222 SVM-Custer analysis acc = 0.85 1.48 Hasen et al. [149] 676 Bias regression-QSAR RNSE 0.60 1.49 Doddareddy et al. [151] 250 4D ingerprint-QSAR R2 = 0.93 1.40 Doddareddy et al. [152] 37 SOM Acc = 0.91 1.42 Hidak et al. [153] 68 2D-QSAR R2 = 0.83 1.44 Boros yet al. [153] 68 2D-QSAR R2 = 0.84 1.45 Othern SE et al. [138] S9963 NN See 0.86; Sp = 0.83 1.44 Kramer Cet al. [155] 166 KNN-LIR Q2 = 0.81 1.45 Othern SE et al. [155] 166 KNN-LIR Q2 = 0.81 1.44 Kramer Cet al. [156] 113 KPISS R2 = 0.52 1.45 OtherArdor et al. [166] 400 PIS R2 = 0.94 1.45 Sinha N. et al. [159] 157 NN R2 = 0.92 1.46 Robinson R. et al. [151] 293 NR, FF Acc = 0.82-0.93 1.45 Sinha N. et al. [162] 2214 SVM Acc = 0.73-0.90	t1.36	Nisius et al. [148]	275	Similarity-based classifier	acc = 87%
1.1.8.Hansen et al. [149]676Bis regression-QSARRMSE = 0.601.3.9Ernondi et al. [150]31Almond-QSARR2 = 0.931.4.0Doddareddy et al. [48]2644LDA-SVMacc = 0.89-0.941.4.1Suet al. [151]2504D fingerprint-QSARacc = 0.911.4.2Hidaka et al. [152]37SOMNA1.4.3Garg et al. [153]682D-QSARR2 = 0.931.4.4Grocy et al. [154]25Hologram QSARR2 = 0.941.4.5O'Brien Se et al. [154]25Hologram QSARR2 = 0.941.4.6Cuttori Se et al. [155]166KNN-LLRQ2 = 0.811.4.6Cuttori Se et al. [155]113PLS, SVRR2 = 0.321.4.8Fenu Let al. [157]3916NBacc = 0.531.4.9Obiol-Pardo et al. [96]400PLSR2 = 0.521.5.0Robinson R. et al. [158]368SVM, RFMCC = 0.10-0.831.5.10Robinson R. et al. [160]529KNNR2 = 0.591.5.3Sinha N. et al. [161]293NB RFAcc = 0.82-0.961.5.4Sum Let al. [162]2214SVMAcc = 0.73-0.901.5.5Hordson M. RefAll et al. [163]242DDA, PLS1.5.6Karl Se tal. [163]242DDA, PLSR2 = 0.811.5.7Tan Y, et al. [164]113HeuristicR2 = 0.911.5.8Karl Se tal. [163]242DDA, PLSR2 = 0.52-0.661.5.6Karl	t1.37	Nisius et al. [148]	232	SVM-cluster analysis	acc = 0.85
L30 Ermondi et al. [150] 31 Almode/SAR $R2 = 0.93$ L40 Doddarddy et al. [151] 250 40 fingeprint-QSAR acc = 0.91 L41 Su et al. [151] 37 50M NA L42 Hidak et al. [152] 37 50M NA L44 Borosy et al. [154] 25 Holgram QSAR R2 = 0.83 L44 Borosy et al. [154] 25 Holgram QSAR R2 = 0.83 L45 O'Brien Set al. [38] 58963 NN See 0.85; Sp = 0.83 L46 Gunturi SB et al. [155] 166 KNN-LIR Q2 = 0.81 L47 Krame Cet al. [156] 113 PLS, SVR R2 = 0.52 L40 Obiol-Pardo et al. [166] 400 PLS R2 = 0.52 L50 Bohinson R. et al. [159] 157 NN R2 = 0.52 L51 Sinha N. et al. [156] 113 PLS R2 = 0.52 L51 Sinha N. et al. [157] 293 NR FF R2 = 0.52 L52 Du-Cury Let al. [161] 293 NR KF R2 = 0.55 0.66 L53 Kim JF, et al. [162	t1.38	Hansen et al. [149]	676	Bias regression-QSAR	RMSE = 0.60
14.0 Doddareddy et al. [45] 264 DA SYM acc = 0.89-0.94 14.4 Suet al. [151] 250 Ab fingerprint-QSAR acc = 0.91 14.4 Suet al. [152] 37 SOM NA 14.3 Garg et al. [153] 68 2D-QSAR R2 = 0.83 14.4 Forosy et al. [154] 25 Hologram QSAR R2 = 0.94 14.4 Forosy et al. [155] 166 kNN-LR Q2 = 0.81 14.4 Forosy et al. [157] 131 PLS, SVR R2 = 0.84 14.4 Foru Let al. [157] 3916 NB acc = 0.53 14.4 Foru Let al. [157] 3916 NB acc = 0.52 15.0 Robins R. et al. [158] 366 SVM, RF MC = 0.10-0.83 15.1 Sinha N. et al. [159] 157 NN R2 = 0.52 15.0 Robins R. et al. [161] 293 NB, RF Acc = 0.37-0.03 15.1 Sinha N. et al. [161] 293 NB, NF Acc = 0.37-0.90 15.3 Kin JH. et al. [161] 293 NB, NF Acc = 0.53-0.60 15.4 Su	t1.39	Ermondi et al. [150]	31	Almond-QSAR	R2 = 0.93
11.41 Suet al, [151] 250 40 fingerprint-QSAR acc = 0.51 11.42 Hidka et al, [152] 37 SOM NA 11.43 Garg et al, [154] 25 Hologram QSAR R2 = 0.83 11.44 Borosy et al, [155] 166 kNN-LLR Q2 = 0.81 11.45 Obrien SE et al, [155] 166 kNN-LLR Q2 = 0.81 11.44 Kramer C et al, [156] 113 PLS, SVR R2 = 0.82 11.44 Kramer C et al, [156] 113 PLS, SVR R2 = 0.81 11.44 Kramer C et al, [156] 3916 NB acc = 0.52 11.40 ObioInson R, et al, [159] 157 NN R2 = 0.62 11.51 Sinha N, et al, [161] 293 NB, RF Acc = 0.32-0.96 11.52 Du-Cuy L et al, [161] 293 NA, NPLSDA Acc = 0.37-0.90 11.54 Sinha L et al, [162] 2214 SVM R2 = 0.63 11.55 Broccatelli F et al, [24] 803 CA-HNN, PLSDA Acc = 0.73-0.90 11.55 Broccatelli F et al, [24] 804 CA-HNR R2 = 0.91	t1.40	Doddareddy et al. [48]	2644	LDA-SVM	acc = 0.89-0.94
1.12 Hidak at al. [152] 37 SOM NA 1.14 Garget al. [153] 68 2D-QSAR R2 = 0.83 1.14 Borosy et al. [154] 25 Hologram QSAR R2 = 0.84 1.14 Borns Set al. [155] 166 kNN-LLR Q2 = 0.81 1.14 Kramer C et al. [156] 113 PLS, SVR R2 = 0.84 1.14 Kramer C et al. [156] 106 NB acc = 0.53 1.148 Fenu L et al. [157] 3916 NB acc = 0.53 1.148 Fenu L et al. [158] 366 SVM, RF R2 = 0.31 1.150 Ninson R. et al. [159] 157 NN R2 = 0.32 1.51 Sinha N. et al. [160] 293 NB, RF Acc = 0.32-0.96 1.54 SubH. et al. [161] 293 NB, RF Acc = 0.32-0.96 1.54 SubH. et al. [161] 293 NB, RF Acc = 0.32-0.96 1.55 Brocatelli F. et al. [161] 294 DA, PLS A Acc = 0.32-0.96 1.54 Su BH. et al. [162] 204 DA, PLS A Acc = 0.32-0.96 1.55 Brocatelli F. et al. [164] 113 Heuristic R2 = 0.91 1.56 Kar S. et al. [163] 242 DA, PLS A <td< th=""><th>t1.41</th><th>Su et al. [151]</th><th>250</th><th>4D fingerprint-QSAR</th><th>acc = 0.91</th></td<>	t1.41	Su et al. [151]	250	4D fingerprint-QSAR	acc = 0.91
1.1.3 Garg et al. [153] 68 2D-QSAR R2 = 0.83 11.4 Boroy et al. [154] 25 Holgram QSAR R2 = 0.94 11.45 O'Brien Ste tal. [185] 166 KNN-LIR Q2 = 0.81 11.47 Kamer C et al. [156] 113 PLS, SVR R2 = 0.84 11.48 Fenu LA et al. [157] 3916 NB acc = 0.53 11.40 Obinson R. et al. [158] 368 SVM, RF MCC = 0.10-0.83 11.51 Sinha N. et al. [159] 157 NN R2 = 0.52 11.50 Du-Cuny L et al. [160] 529 kNN R2 = 0.73 11.51 Sinha N. et al. [151] 203 NB, RF Acc = 0.82-0.96 11.53 Sinda N. et al. [162] 2214 SVM Acc = 0.73-0.50 11.55 Broccatelli F. et al. [24] 803 GA-kNN, PLSDA Acc = 0.73-0.50 11.55 Broccatelli F. et al. [41] 113 Heuristic R2 = 0.91 11.56 Kar S. et al. [163] 424 UAA, PLS Score al. [164] R57 = 0.65.0.66 11.56 Kar S. et al. [165] 806 NB, RP<	t1.42	Hidaka et al. [152]	37	SOM	NA
1.14. Borosy et al. [154] 2.5 Hologram (SAR) $KZ = 0.94$ 14.45 OBrin SE et al. [13] \$5963 NN Se = 0.86; Sp = 0.83 14.46 Cunturi SB et al. [157] 166 KNN-LIR Q2 = 0.81 14.47 Kramer C et al. [156] 113 PLS, SVR R2 = 0.84 14.48 Fenu LA et al. [157] 3916 NB acc = 0.53 14.49 Obiol-Pardo et al. [96] 400 PLS NN R2 = 0.84 14.49 Obiol-Pardo et al. [96] 400 PLS R2 = 0.62 R2 = 0.52 11.50 Sinha N. et al. [159] 157 NN R2 = 0.73 R2 = 0.59 11.51 Sinha N. et al. [161] 293 NB, RF Acc = 0.32-0.96 R2 = 0.51 11.54 Su BH, et al. [161] 293 NB, RF Acc = 0.73-0.90 R2 = 0.76-0.97 11.55 Brocatelli F, et al. [24] 803 CA-kNN, PLSDA Acc = 0.76-0.97 R1 11.55 Brocatelli F, et al. [24] 113 Heuristic R2 = 0.91 R1 11.56 Warg S, et al. [165] 106 NB <td< th=""><th>t1.43</th><th>Garg et al. [153]</th><th>68</th><th>2D-QSAR</th><th>R2 = 0.83</th></td<>	t1.43	Garg et al. [153]	68	2D-QSAR	R2 = 0.83
1.4.6Online Set al. [35]363903NNSet = 0.66, 5p = 0.831.4.6Gunturi Set al. [155]166KNN-LIRQ2 = 0.811.4.7Kramer C et al. [156]113PLS, SVRR2 = 0.841.4.8Fenu LA et al. [157]3916NBacc = 0.531.4.9Obiol-Pardo et al. [96]400PLSR2 = 0.731.1.9Obiol-Pardo et al. [96]400PLSR2 = 0.731.1.5Knh N, et al. [158]368SVM, RFMCC = 0.10-0.831.1.5Knh N, et al. [159]157NNR2 = 0.731.1.5Lin M, et al. [161]293NB, RFAcc = 0.82-0.961.1.5Knh M, et al. [162]2214SVMAcc = 0.73-0.901.1.5Knh S, et al. [163]242LDA, PLSR2 = 0.511.1.6Kar, S. et al. [163]242LDA, PLSR2 = 0.911.1.5Ikh Age, Set al. [166]1686NB, KNN, PWMSE = 0.55-0.661.1.6Vang Z, et al. [166]1686NB, KNN, PWMSE = 0.55-0.661.1.6Vang Z, et al. [166]1686NB, KNN, PWMQ2 = 0.56-0.891.1.6Coortowski P, [43]3721RFAUC = 0.66-0.891.1.6Kargui F, et al. [29]98VariousRMS = 0.86-1.171.1.6Rogui F, et al. [168]25MLRQ2 = 0.71-0.871.1.6Rogui F, et al. [169]1889Stochastic QSAR samplerBalanced Acc = 0.661.1.6Rodurowski P, [43]3721RFAUC = 0.68-0.39 <th>t1.44</th> <th>Borosy et al. [154]</th> <th>25</th> <th>Hologram QSAR</th> <th>K2 = 0.94</th>	t1.44	Borosy et al. [154]	25	Hologram QSAR	K2 = 0.94
11-40 Contain 156 et al. [155] 105 NN+LIK Q2 = 0.51 11-47 Kramer Cet al. [156] 113 PLS, SVR R2 = 0.84 11-40 Koin-Pardo et al. [156] 400 PLS R2 = 0.52 11-50 Robinson R et al. [159] 157 NN R2 = 0.52 11-50 Sinha N. et al. [159] 157 NN R2 = 0.51 11-50 Ucruy L et al. [160] 529 KNN R2 = 0.51 11-51 Su BH, et al. [161] 293 NB, RF Acc = 0.82-0.96 11-55 Brocatelli F, et al. [24] 803 CA-kNN, PLSDA Acc = 0.76-0.97 11-55 Brocatelli F, et al. [164] 113 Heuristic R2 = 0.91 11-56 Kar S, et al. [165] 806 NB, RP Acc = 0.85-0.89 11-57 Tan Y, et al. [164] 113 Heuristic R2 = 0.91 11-58 ItoSa (F, et al. [24] 803 CA-kNN, PLSDA Q2 = 0.56-0.69 11-59 106 NB, RP Acc = 0.85-0.89 R1.58 11-58 ItoSa (F, et al. [165] 806 NB, KNB, PVM Q2 = 0.56-0.69	t1.45	Cupturi SP et al. [155]	58903	ININ I-NIN LLD	Se = 0.86; Sp = 0.83
11.44 Fent LA et al. [157] 3916 NB acc = 0.53 11.45 Fent LA et al. [157] 3916 NB acc = 0.53 11.46 Mobiol-Pardo et al. [96] 400 PLS R2 = 0.52 11.50 Sinha N. et al. [159] 157 NN R2 = 0.73 11.51 Sinha N. et al. [161] 293 NB, RF R2 = 0.73 11.52 Du-Curny Let al. [162] 2214 SVM Acc = 0.73-0.90 11.55 Brocatelli F. et al. [162] 2214 SVM Acc = 0.73-0.90 11.55 Brocatelli F. et al. [163] 242 LDA, PLS R2 = 0.91 11.56 Kar S. et al. [163] 242 LDA, PLS R2 = 0.91 11.58 Wang S. et al. [164] 113 Heuristic R2 = 0.91 11.58 Wang S. et al. [165] 806 NB, RNP Acc = 0.85-0.89 11.69 11686 NB, KNB, PWM SE = 0.55-0.66 R16 11.61 158 S04 RF AUC = 0.66-0.89 11.60 1686 NB, KNB, PWM SE = 0.55-0.66 R16 11.60	t1.40	Guilluri SB et al. [155]	100		$Q_2 = 0.81$
11.49Obiol-Pardo et al. [96]400PLSRC = 0.6311.49Obiol-Pardo et al. [96]400PLSMC = 0.10-0.8311.50Robinson R. et al. [158]368SVM, RFMC = 0.10-0.8311.51Sinha N. et al. [159]157NNR2 = 0.5911.52Du-Cuny L. et al. [160]529kNNR2 = 0.5911.53Sinha N. et al. [161]293NB, RFAcc = 0.82-0.9611.54Su BH. et al. [162]2214SVMAcc = 0.73-0.9011.55Broccatelli F. et al. [24]803GA-kNN, PLSDAAcc = 0.76-0.9711.56Broccatelli F. et al. [164]113HeuristicR2 = 0.5911.57Tan, Y. et al. [164]113HeuristicR2 = 0.51-0.6611.58[Wang S. et al. [165]806NB, RPAcc = 0.85-0.8911.59[Wang Z. et al. [166]1686NB, KNB, PWMSE = 0.55-0.6611.60Pourbasheer et al. [167]45MLR, SVMQ2 = 0.56-0.6911.61Codrowski P. [43]694RFAUC = 0.66-0.6611.62Codrowski P. [43]694RFQ2 = 0.71-0.8711.64Moorthy N. et al. [169]1889Stochastic QSAR samplerBalanced Acc = 0.6611.65Regult V. et al. [169]1889Stochastic QSAR samplerBalanced Acc = 0.6611.66Ruggiu F. et al. [170]34NBAcc = 0.63-0.9311.66Stom M. Et al. [171]2644NBAcc = 0.63-0.9311.66Shen M. Et al. [172	11.47 +1.48	Fenu I A et al [157]	3916	NB	$R_2 = 0.84$
River and Statistical State Acce 0.010-0.83 River and State State State MCC 0.10-0.83 River and State State State State NN R2 0.73 River and State State State State R2 0.73 R2 0.73 River and State State State State R2 0.73 R2 0.59 River and State State State State R2 0.59 R2 0.59 R2 0.59 R2 0.59 R2 0.59 R2 0.59 R2 0.50 R2 0.50 0.60 R2 0.50 0.60 R2 0.51 0.60 R2 0.51 0.60 R2 0.51 0.60 R1 R2 0.51 0.60 <t< th=""><th>t1 49</th><th>Obiol-Pardo et al [96]</th><th>400</th><th>PLS</th><th>$R_2 = 0.53$</th></t<>	t1 49	Obiol-Pardo et al [96]	400	PLS	$R_2 = 0.53$
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11.53 Kim JH, et al. [161] 293 NB, RF Acc = 0.82-0.96 11.54 Su BH, et al. [162] 2214 SVM Acc = 0.73-0.90 11.55 Brocatelli F, et al. [24] 803 GA-kNN, PLSDA Acc = 0.73-0.90 11.56 Kar S, et al. [163] 242 LDA, PLS R2pred = 0.53-0.60 11.57 Tan Y, et al. [164] 113 Heuristic R2 = 0.91 11.58 [Wang S, et al. [166] 1686 NB, KNB, PVM SE = 0.55-0.66 11.59 [Wang Z, et al. [166] 1686 NB, KNB, PVM SE = 0.55-0.66 11.60 Pourbasheer et al. [167] 45 MLR, SVM Q2 = 0.56-0.89 11.61 Czodrowski P. [43] 3721 RF AUC = 0.66 11.62 Czodrowski P. [43] 694 RF Q2 = 0.71-0.87 11.64 Moorthy N, et al. [168] 59 GA-MLR Q2 = 0.87 11.64 Moorthy N, et al. [169] 1889 Stochastic QSAR sampler Balanced Accc = 0.66 11.65 Polak S. et al. [29] 94 NB Acc = 0.62 11.66 Ruggiu F. et al. [170] 34	t1.52	Du-Cuny L, et al. [160]	529	kNN	R2 = 0.59
t1.54 Su BH. et al. [162] 2214 SVM Acc = 0.73-0.90 t1.55 Broccatelli F. et al. [24] 803 GA-kNN, PLSDA Acc = 0.76-0.97 t1.56 Kar S. et al. [163] 242 LDA, PLS R2pred = 0.53-0.60 t1.57 Tan Y. et al. [164] 113 Heuristic R2 = 0.91 t1.58 [Wang S. et al. [165] 806 NB, RP Acc = 0.85-0.89 t1.59 [Wang Z. et al. [166] 1686 NB, KNP, PVM SE = 0.55-0.66 t1.60 Pourbasheer et al. [167] 45 MLR, SVM Q2 = 0.56-0.89 t1.61 Czodrowski P. [43] 3721 RF AUC = 0.66 t1.62 Czodrowski P. [43] 694 RF AUC = 0.66 t1.63 Coi A. et al. [85] 59 GA-MLR Q2 = 0.87 t1.64 Moorthy N. et al. [168] 25 MLR Q2 = 0.71-0.87 t1.64 Moorthy N. et al. [169] 1889 Stochastic QSAR sampler Balanced Acc = 0.62 t1.65 Polak S. et al. [170] 34 NB Acc = 0.83-0.91 t1.64 Liu L et al. [171] 2644 NB <th>t1.53</th> <th>Kim JH. et al. [161]</th> <th>293</th> <th>NB, RF</th> <th>Acc = 0.82-0.96</th>	t1.53	Kim JH. et al. [161]	293	NB, RF	Acc = 0.82-0.96
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t1.57 Tan Y, et al. [164] 113 Heuristic R2 = 0.91 t1.58 [Wang S, et al. [165] 806 NB, RP Acc = 0.85-0.89 t1.59 [Wang Z, et al. [166] 1686 NB, KNB, PWM SE = 0.55-0.66 t1.60 Pourbasheer et al. [167] 45 MLR, SVM Q2 = 0.56-0.89 t1.61 Czodrowski P. [43] 3721 RF AUC = 0.66 t1.62 Czodrowski P. [43] 59 GA-MLR Q2 = 0.70 t1.64 Moorthy N, et al. [168] 25 MLR Q2 = 0.71-0.87 t1.65 Polak S, et al. [29] 98 Various RMSE = 0.86-1.17 t1.66 Ruggiu F, et al. [179] 34 NB Acc = 0.62 t1.67 Mirams GR, et al. [171] 2644 NB Acc = 0.62 t1.69 Shen MY, Et al. [172] 1668 SVM Acc = 0.63-0.91 t1.69 Shen MY, Et al. [172] 1668 SVM Acc = 0.68-0.81 t1.70 Braga RC, et al. [36] 4980 SVM, RF, GBM, TreeBag Acc = 0.68 - 0.81 t1.71 Kireeva N, et al. [173] 242 SVM-GTIM	t1.56	Kar S. et al. [163]	242	LDA, PLS	R2pred = 0.53-0.60
t1.58 [Wang S. et al. [165] 806 NB, RP Acc = 0.85-0.89 t1.59 [Wang Z. et al. [166] 1686 NB, KNB, PWM SE = 0.55-0.66 t1.60 Pourbasheer et al. [167] 45 MLR, SVM Q2 = 0.56-0.89 t1.61 Czodrowski P. [43] 3721 RF AUC = 0.66 t1.62 Czodrowski P. [43] 694 RF AUC = 0.56-0.66 t1.63 Coi A. et al. [85] 59 GA-MLR Q2 = 0.87 t1.64 Moorthy N. et al. [168] 25 MLR Q2 = 0.71-0.87 t1.64 Moorthy N. et al. [169] 1889 Stochastic QSAR sampler Balanced Acc = 0.66 t1.67 Mirams GR. et al. [170] 34 NB Acc = 0.87-0.99 t1.69 Shen MY. Et al. [171] 2644 NB Acc = 0.87 t1.69 Shen MY. Et al. [172] 1668 SVM Acc = 0.83-0.93 t1.70 Braga RC. et al. [36] 4980 SVM, RF, GBM, TreeBag Acc = 0.83-0.93 t1.70 Braga RC. et al. [173] 242 SVM-GTM Acc = 0.63-0.93 t1.71 Kireeva N. et al. [173] 242	t1.57	Tan Y. et al. [164]	113	Heuristic	R2 = 0.91
t1.59 [Wang Z, et al. [166] 1686 NB, KNB, PWM SE = 0.55-0.66 t1.60 Pourbasheer et al. [167] 45 MLR, SVM Q2 = 0.56-0.89 t1.61 Czodrowski P. [43] 3721 RF AUC = 0.66 t1.62 Czodrowski P. [43] 694 RF AUC = 0.56-0.66 t1.63 Coi A, et al. [85] 59 GA-MLR Q2 = 0.87 t1.64 Moorthy N, et al. [168] 25 MLR Q2 = 0.71-0.87 t1.65 Polak S, et al. [29] 98 Various RMSE = 0.86-1.17 t1.66 Ruggiu F, et al. [169] 1889 Stochastic QSAR sampler Balanced Acc = 0.62 t1.67 Mirams GR, et al. [170] 34 NB Acc = 0.58-0.91 t1.69 Shen MY, Et al. [171] 2644 NB Acc = 0.62 t1.70 Braga RC, et al. [36] 4980 SVM Acc = 0.837 t1.71 Krieeva N, et al. [173] 242 SVM-GTM Acc = 0.68 - 0.80 t1.72 Yu P, et al. [174] 806 CPAR, CMAR, CBA F-score = 0.60-0.78 t1.73 Kratz K.M. et al. [175] 37 P	t1.58	[Wang S. et al. [165]	806	NB, RP	Acc = 0.85 - 0.89
t1.60 Pourbasheer et al. [167] 45 MLR, SVM Q2 = 0.56 - 0.89 t1.61 Czodrowski P. [43] 3721 RF AUC = 0.66 t1.62 Czodrowski P. [43] 694 RF AUC = 0.56 - 0.69 t1.63 Coi A. et al. [85] 59 GA-MLR Q2 = 0.87 t1.64 Moorthy N. et al. [168] 25 MLR Q2 = 0.71 - 0.87 t1.65 Polak S. et al. [29] 98 Various RMSE = 0.86 - 1.17 t1.66 Ruggiu F. et al. [169] 1889 Stochastic QSAR sampler Balanced Acc = 0.62 t1.64 Mirams GR. et al. [170] 34 NB Acc = 0.58 - 0.91 t1.69 Shen MY. Et al. [171] 2644 NB Acc = 0.62 t1.69 Shen MY. Et al. [172] 1668 SVM Acc = 0.87 t1.70 Braga RC. et al. [36] 4980 SVM, RF, GBM, TreeBag Acc = 0.68 - 0.80 t1.71 Kireeva N. et al. [173] 242 SVM-CTM Acc = 0.68 = 0.80 t1.72 Yu P. et al. [174] 806 CPAR, CMAR, CBA F-score = 0.60-0.78 t1.73 Kratz K.M. et al. [175] <t< th=""><th>t1.59</th><th>[Wang Z. et al. [166]</th><th>1686</th><th>NB, KNB, PWM</th><th>SE = 0.55 - 0.66</th></t<>	t1.59	[Wang Z. et al. [166]	1686	NB, KNB, PWM	SE = 0.55 - 0.66
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	t1.74	Kratz K.M. et al. [175]	37	Pharmacophore model	AUC = 0.89

which the measurements show a large deviation between the different
assays [43]. Such deviation can be reasonably covered with the transformation of the measurement into class.

Based on these models, several structure activity relationships were 266 revealed such as the presence of key features including two hydropho-267 bic features and one hydrogen bond acceptor (preferably a charged 268

nitrogen) [44,45]. It has been shown that removing carbons and/or 269 270changing the electronic environment around the basic nitrogen can result in a reduction in hERG inhibition [46,47]. In addition, transforma-271272tions that add a hydroxyl group reduce hERG inhibition [36]. Some bioisosteric replacements have resulted in dramatic changes in activity. 273Replacement of a furane ring by a tetrazole ring resulted in a substantial 274alteration in hERG binding, changing the compound from a blocker to 275non-blocker. Modification of chlorine to the hydroxyl group or the ni-276277trile group in an aromatic ring changes an hERG blocker to a non-278blocker compound [36]. Using the maximum common substructure 279search to learn about the structural features specific to hERG blockers, 280Doddareddy et al. found that the three major factors contributing to 281the hERG blockage are a positively charged nitrogen atom, high lipophi-282licity and the absence of negatively charged oxygen atom [48]. It was also confirmed later on by Sherhod et al. based on an emerging pattern 283 mining method. In addition to the known pharmacophores for hERG 284 channel inhibition, other features were characterized like compounds 285 with a quinolinol group that were found to be hERG blockers [49]. It 286should also be mentioned here that some authors suggest that for the 287prediction of primary targets, the benefit of using 3D over 2D similarity 288search appears small while for the prediction of off-targets, like in the 289case of hERG, the added benefit of using 3D similarity seems to be 290291large [50,51].

Many hERG models have been developed by software companies 292but are not always easy to evaluate and to compare. On the other 293hand, some tools (essentially from academic groups) are freely available 294to predict the hERG activity. We can mention Pred-HERG (http:// 295296 labmol.farmacia.ufg.br/predherg), Tox-Comp.Net (http://www.toxcomp.net/), and ACD-/I-Lab (https://ilab.acdlabs.com/iLab2/index. 297php). Not specifically associated to hERG, but with the possibility to pro-298vide also interesting output on hERG inhibition, are the use of large 299300 chemogenomics databases such as ChEMBL [52], PubChem [53] and 301 ChemProt [54] where it is possible to carry out some search by chemical similarity. Target prediction web services such as the SEA search tool 302 [55], PASS [56], Swiss Target Prediction [57], HitPick [58], SuperPred 303 [59], and admetSAR [60] can also be considered for hERG prediction. 304

305 Overall, with these tools it is now possible to estimate the risk for a 306 compound to be an hERG inhibitor and which features contribute to that. For example, we performed a search on three known drugs acting 307 on hERG (terfenadine, astemizole and cisapride) and 2 molecules 308 (vardenafil, ziprasidone) with a warning for QT prolongation on their 309 prescription label. Looking for instance in ChemProt, all of them have 310 been reported with an activity on hERG i.e., terfenadine ($pIC_{50exp} =$ 311 6.67 [61]), astemizole (pIC_{50exp} = 8.04 [62]), cisapride (pIC_{50exp} = 312 7.57 [63]), vardenafil ($pIC_{50exp} = 4.89$ [64]), and ziprasidone 313 $((pIC_{50exp} = 6.92 [65]))$. We then analyzed each compound with the 314315Stardrop package (Optibrium). The Stardrop model for hERG prediction is built on a dataset of about 200 molecules with patch-clamp IC₅₀ 316 values for inhibition of hERG K⁺ channels expressed in mammalian 317 cells. The model returns pIC₅₀ values and some additional information 318 such as the distance of the predicted compound from the chemical 319320 space of the training set such as to partially assess the reliability of the 321 results. An interesting feature of this package is the "glowing molecule" mode that displays the results of a computational model rendered as a 322heat map to highlight the regions of the molecule that are responsible 323324for the activity in the model with red indicating structural features 325that have a positive effect and the cooler blue color a negative effect on the model. In our easy test case (as some of the molecules were cer-326 tainly present in the training of the statistical model), red areas are 327 zones that are predicted to increase hERG activity and could be impor-328 tant to modify in order to produce optimized compounds. The pIC_{50} 329330 values obtained for our 5 test compounds were 6.7 for terfenadine, 8.2 for astemizole, 5.8 for cisapride, 5.8 for vardenafil and 6.6 for 331 ziprasidone. Because hERG activity is only one endpoint, we also com-332 puted with the FAF-Drugs2 server [66] some other properties like the 333 334 Lipinski rule of 5 [67] and the Pfizer's 3/75 rule [68] (the rule is agnostic with regard to the details of the mechanism of toxicity and states that 335 there is a six fold reduction in toxicity *in vivo* (24-fold for bases) when 336 the compound's log $P \le 3$ and PSA ≥ 75 Å²) to look at the molecules 337 from another angle. Terfenadine has one violation to the R05 (due a 338 predicted log *P* higher than 5) and falls it the read area (risky zone) of 339 the 3/75 rule. Astemizole passes the R05 but not the 3/75, cisapride 340 passes the R05 and is close to the 3/75 threshold, vardenafil passes the 341 RO5 and the 3/75 rule, while ziprasidone passes the R05 and is really 342 border line with regard to the 3/75 rule (Fig. 2). 343

Finally we should notice that natural products start to be screened 344 on hERG and some of them show potential risk for inducing LQTS 345 [69–71]. Integration of such information into hERG models should 346 help to develop new and more accurate *in silico* prediction packages. 347

4. Structure-based approaches

Four identical α -subunits form the hERG K⁺ channel and each 349 unit accommodates six α -helical transmembrane segments defined as 350 S1–S6. The voltage sensor domain (VSD) is embedded by segments 351 S1–S4. The movement of the gating is governed by the positively 352 charged Lys and Arg in the S4 helix and enables the pore domain to 353 open and to close in response to changes in membrane potential. 354 Segments S5–S6 form the pore domain allowing the K⁺ ions to cross 355 the membrane. A lengthy S5-P linker that contains an amphipathic 356 helix (the turret helix) and a selectivity filter loop are also present in 357 these segments. Finally, the N-terminal domain, consisting of the Per-358 Arnt-Sim (PAS) domain, and the C-terminal domain, which is composed 359 of a cyclic nucleotide-binding domain, are located on the intracellular 360 side of the membrane [72] (Fig. 3).

All structure-based studies are performed on homology models as 362 hERG has not yet been crystallized. The structural models are essentially 363 based on bacterial K⁺ channels KscA (close form) [73], KvaP [74], MthK 364 [75], Kir2.2 [76] and mammalian channel Kv1.2 [77], although the se- 365 quence identity is relatively low. A variety of homology models of the 366 open, partially open or closed forms of hERG in combination to docking 367 (rigid and flexible), and molecular dynamics described primarily 368 conformational change differences in the S6 helices. For example, an 369 atomistic hERG model generated by long supercomputer molecular 370 dynamics simulations has developed and used to predict drug 371 cardiotoxicity [78]. In the closed state the S6 helices are smooth, creat- 372 ing a point of constriction below the central cavity [17]. The residue 373 G648 is conserved all over the potassium channel members and seems 374 to act as a hinge point in the bending of the S6 helix. The conformational 375 change produced in S6 allows the K⁺ ions to get access to the central 376 cavity and could act as a selectivity filter [72,78]. Beside this amino 377 acid, three other residues (Y652, F656 and V659), facing inward to- 378 wards the pore domain, play an important role in drug binding [79, 379 80]. Additional residues such as T623, S624 and V625, located at the 380 base of the selectivity and W563, F559 and F551 facing outward to- 381 wards the voltage sensor, contribute to the differences in activation 382 and inactivation properties of hERG [81,82]. Models of the hERG 383 potassium channel and of the drug-binding cavity (surrounding by the 384 S6 segments) are depicted in Fig. 4. 385

The movement of S4 in hERG has also been studied to explain the 386 gating properties. Elliott et al. [82] suggested that the extent of S4 move-387 ment in hERG is large and similar to other Kv channels. This movement 388 is coupled to the opening of channel gates located at the intracellular 389 aspect of the channel via the S4–S5 linker, leading to K⁺ efflux [83]. 390

Since most hERG-blocking drugs access the pore cavity from the in- 391 tracellular side of the membrane when the channel opens in response to 392 membrane depolarization, open state pore models are likely to best represent the arrangements of key amino side chains that are productive 394 for drug binding. More specifically, the open state MthK structure was 395 recently suggested to be the best template to model binding of many 396 drugs [84]. 397

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Fig. 2. On the left, structural features, which are responsible for the hERG activity based on the Stardrop model, are represented. The red areas indicate features that have a positive effect and the color blue a negative effect on the model. On the right, the Lipinski and Pfizer's 3/75 rules were computed with FAF-Drugs2 and represented in a 2D map. When the studied compound (the blue dot) is on the red area, it means that one of the rules is violated. For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.

Combinations of structure- and ligand- based approaches to study
 the different binding modes were also investigated. Coi et al. built four
 3D models representing different conformational states of hERG K⁺



Fig. 3. Schema of the hERG potassium channel.

channel and carried out molecular docking-based molecular descriptors 401 to develop QSAR models [85]. However, molecules can block hERG in 402 other sites and thus docking studies need to be performed cautiously. 403 For example fluvoxamine and doxepin blocked the channel indepen- 404 dently of mutations around Y652 and F656. Similarly, peptides block 405 in the entrance of K^+ channels [61]. An interesting perspective of 406 structure-based approaches is to combine them with hERG polymor- 407 phism and drug response variation data. Some clinical studies have re- 408 ported a higher risk of LQTS induced by drugs in patients having 409 genetic variations in hERG and we could imagine that structure-based 410 approach could provide new structural basis for the development of 411 safer drugs [86–94]. For example, Du et al. estimated the activity of 412 the ranolazine drug (an antianginal) on hERG and concluded the 413 N588K mutation is unlikely to be effective in patients with short QT syn- 414 drome. Using docking simulations, the study indicated that the large 415 size of ranozaline favors interactions with the hERG pore [18]. 416

Interestingly, allosteric modulation of the hERG K⁺ channel started 417 to be studied as an alternative way of interaction. For example, com- 418 pound A-935142 has recently been stated to possess a binding site re- 419 sponsible for hERG current enhancement, which is different from the 420 pore binding site of the traditional hERG blockers [95,96]. Similarly Yu 421 et al. [97] demonstrated that LUF6200 is an allosteric inhibitor. The 422 binding sites of several peptide blockers like saxitoxin and BeKm-1 are 423 located in the extracellular parts of the hERG K⁺ channel [98,99]. Multi- 424 ple binding sites for these diverse compounds on the hERG K⁺ channel 425 imply a plausible allosteric modulation among them. They might allo- 426 sterically increase (allosteric inhibitors/negative allosteric modulators) 427 or decrease (allosteric enhancers/positive allosteric modulators) the 428 dissociation rates of typical hERG blockers and thus mediate a greater 429 (or poorer) safety profile for some drugs. Dynamic simulation studies 430 could be performed and help in deciphering the allosteric modulation 431 of some of these compounds. 432

5. Systemic approaches

5.1. Multiple ion channels

The role of hERG in the ventricular repolarization is of critical impor-435 tance, however, it is widely accepted that the complexity of the events 436 involved in TdP makes the cardiac safety assessment, based only on 437 hERG, a high risk of producing either false positive or negative results. 438 In fact, drug effects on multiple ionic currents may modulate or mask 439 the effects of hERG blockade [100,101]. For example, two drugs 440 displaying low hERG safety margins yet not demonstrating convincing 441 QTc prolongation are eltrombopag (used to treat low blood platelet 442 counts) and lamotrigine (anticonvulsant). Based solely on hERG potency 443

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Fig. 4. 3D models of the hERG potassium channel. A) 3D representation of the tetrameric hERG potassium channel based on the full-length Shaker potassium channel Kv1.2. B) Dimeric representation of segments S5–S6. Residues involved in most of the drug interactions are depicted in sticks. Each magenta sphere represents a potassium ion. For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.

and therapeutic plasma exposures, both drugs would likely have been
 categorized as having high risks for QTc prolongation and subject to un warranted attrition [21].

A hypothesis is that by blocking the inward current, through calcium
or sodium channel, the torsadogenic effect of outward current, by hERG
potassium channel, is also blocked. This is the case for example of fluoxetine (antidepressants) and verapamil (treatment of hypertension,
cardiac arrhythmia) that have been shown to block opposing currents
(repolarizing (outward) hERG current vs. depolarizing (inward)
calcium current) [102,103]. However, it seems that the calcium or

sodium channel block needs to occur at the same concentration or at a 454 lower concentration than the hERG potassium channel block. For exam-455 ple, bepridil, a calcium channel blocker, was removed from the market 456 in the United States because of TdP. It was shown that bepridil blocks 457 hERG potassium channels at a concentration lower than the one 458 required to block calcium channels, which could explain the acquired-459 LQTS [8]. Similarly, alfuzosin, which is used for benign prostatic hyper-460 plasia, was shown to mildly prolong the QT interval although it does 461 not block hERG. The drug seems to increase the late sodium current 462 during the cardiac action potential (hNav1.5) and thus extend the QT 463 interval [8].

Based on these observations, recent studies suggest that considering 465 multiple ion channels provides better cardiotoxicity predictions [104]. 466 Obio-Pardo et al. developed a combination of docking simulations on 467 two potassium channels, hERG and KCNQ1, and 3D-QSAR for predicting 468 how the tested compound will block the potassium currents IKr and IKs. 469 As methods based solely on hERG provide a limited picture of the drug 470 effects on the ventricular repolarization, such combination approaches 471 outperform the classic hERG-based models [105]. Multiple QSAR 472 models have also been implemented in a cardiac safety simulator, 473 enabling the *in vitro-in vivo* extrapolation of the drug's proarrhythmic 474 effect and ECG simulation [106]. Therefore, other ions channels that 475 are modulated by drugs and involved in acquired LQTS and TdP are 476 now investigated in combination with hERG [7].

The recent introduction of the IonWorks plate-based device has ren- 478 dered the multiple ion channel electrophysiological assays popular 479 [107]. To better interpret the integrated drug effect on various ion chan- 480 nels, computational models to predict drug-induced changes in the 481 action of potential (AP) have been developed [108,109]. In these 482 approaches, potency data are directly integrated within the model by 483 reducing conductance in accordance with measured concentration-ef- 484 fect (C–E) curves. So, the modulation of other ion channels is considered 485 in this approach and leads to a better estimation of the cardiac risk as- 486 sessments. For example Davies et al. have developed a comprehensive 487 model that predicts AP modulation of ventricular midmiocardial cells 488 based on a panel of five ion channels and corresponding C-E curve 489 data [110]. Similarly, Kramer et al. measured the concentration- 490 responses of hERG, Nav1.5 and Cav1.2 currents for 32 torsadogenic 491 and 23 non-torsadogenic drugs from several therapeutic classes in an 492 automated gigaseal patch clamp instrument and developed a logistic re- 493 gression model that predicted more accurately the torsadogenic poten- 494 tial than models based on hERG effects alone [111]. 495

Overall, the multiple ion channel effects (MICE) approach is believed 496 to be more robust than IKr assay alone at evaluating the proarrhythmic 497 risk of new drugs, with fewer false-positive results. 498

5.2. hERG trafficking inhibition

Recent findings indicated that chronic treatment with various drugs 500 not only inhibits hERG channels but also decreases hERG channel 501 expression in the plasma membrane of cardiomyocytes, which has 502 become another concern in safety pharmacology [112,113]. 503

Understanding of drug-induced hERG trafficking inhibition may provide new strategies for predicting drug-induced QT prolongation and 505 lethal cardiac arrhythmia in pharmaceutical drug development. 506 For example Ficker et al. [114] demonstrated that arsenic trioxide 507 ("antineoplastic" or "cytotoxic" molecule) did not show any direct inbibitory effect on hERG channel activity but disrupted the hERG traffick-509 ing by reducing the formation of the hERG-chaperone (Hsp90 and 510 Hsp70). Similarly the antibiotic geldanamycin inhibits the formation of the hERG–Hsp90 complex that accelerates hERG channel degradation [115]. Pentamadine, an antiprotozoal agent does not directly inhibit 513 hERG current but binds to hERG protein in a folding intermediate transport from the ER [113,116]. Interestingly, its inhibitory effect is reversed in the presence of pharmacological chaperones, astemizole and 517

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dofetilide, suggesting that pentamidine and pharmacological chaper-518 ones compete for the same binding site within the hERG channel, 519 although the precise mechanism of action of pentamidine has not 520521been elucidated. Probucol, a cholesterol-lowering drug, accelerates the degradation of mature hERG channels from the cell membrane through 522accelerated caveolin-1 turnover [117]. Wible et al. estimated that 523around 40% of hERG blockers carry the additional risk of inhibiting 524hERG trafficking [118]. 525

526 5.3. Transcriptional profiles

Drugs may share similar and undesirable side effects despite being un-527related chemical structures or having different primary mechanisms-of-528529action (MOA). Exploring similarities in drug-induced transcriptional effects and combining with additional publicly available annotations 530for LQT side effect enable to identify clusters of drugs with similar 531 expression profiles annotated for channel inhibitors. Babcock et al. 532[119] performed such analysis combining the drug-induced transcrip-533tional effects from the Connectivity Map (cMap), a collection of 534Affymetrix[™] microarray profiles generated by treating three indepen-535dent lineages of cancer cell lines with small molecule drugs [120], and 536the hERG inhibitors annotated using a database of experimental mea-537538surements (hERGcentral) and clinical indications [39]. This analysis showed that structurally diverse hERG inhibitors mediate similar 539 physiological effects revealed by transcriptional response profiles. 540Furthermore, evaluation of enriched gene ontology (GO) annotations 541among genes up and down regulated indicated positive effects on choles-542543terol biosynthesis (GO:0006695), isoprenoid biosynthesis (GO:0008299), and the unfolded protein response (GO:0030968), and negative effects 544on cell cycle checkpoint (GO:0000075), S phase of mitotic cell cycle 545(GO:000084), and DNA replication (GO:0006260) although the phys-546547iological correlation between hERG block and these processes remains to be investigated. 548

549 6. Conclusion

Assessing the ability of all new drugs to cause TdP before reaching 550the market is required from the regulatory agencies and the current 551 approaches focus exclusively on QT prolongation and hERG inhibition. 552An impressive number of *in silico* studies have been performed to 553understand the mechanism of drug-hERG blockage and to predict in 554555advance the torsadegenic risk of new potential drugs. However, although these models provided structural key features in the interac-556tion with hERG, safe compounds can be predicted as hERG blockers or 557even worse the algorithms can fail to detect toxic compounds [121]. 558Furthermore with such models, some hERG blockers, like fluoxetine or 559560verapamil would probably not be accepted on the market based solely on hERG study. Indeed, it is widely accepted that hERG represents 561only one of the multiple ionic currents involved in the mechanism of 562ventricular repolarization and the modulation of these channels by 563drugs may mask the effect of hERG blockage. These observations have 564565created recent interests in testing entire panels of cardiac ion channels 566rather than just hERG. Drugs start to be screened on multiple ion channel assays and some *in silico* models start to investigate the combination 567of the outcome from these assays. 568

hERG polymorphisms are believed to have a large contribution in 569570the acquisition of LQTS and numerous studies showed the impact of several mutations in the variation of hERG blockage by drugs. However, 571these results come essentially from in vitro studies and only few clinical 572studies and on a small cohort of people have been reported. Clearly, 573pharmacogenomic studies on hERG potassium channel in association 574with computational structure-based approaches can provide new in-575sights on TdP and would be of interest for the development of personal-576ized medicines. 577

578 Finally, chronic effects of drugs are not detected in conventional car-579 diac safety screening. As some therapies are based on a long-term exposure to drugs, such analysis is of large interest. Recently, the use 580 of induced pluripotent stem cell (iPSC)-derived human cardiomyocytes 581 has been proposed to functionally assess chronic drug effects on the ac-582 tion potential duration and cell excitability in cardiac tissue [122,123]. 583 This technology is believed to create new opportunities for cardiovascu-584 lar research by providing platforms to study the mechanisms of disease 585 pathogenesis that could lead to new therapies or reveal drug sensitivi-586 ties and has been recommended for adoption in the revised ICH guide-587 lines in the near future [124]. 588

Overall, the field of LQTS is tremendously active and the develop- 589 ment of future *in silico* methods more sensitive and more accurate to 590 predict TdP is ongoing. With the application of new and higher throughput assays, new data will be available and exploitable for a broader 592 understanding of the molecular pharmacology of acquired LQTS. 593

Uncited reference			

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