Reviewer's report

Title: tox-database.net - data describing the chemicals triggered in vitro cardiac ionic channels inhibition

Version: 2 Date: 24 May 2012

Reviewer number: 3

Reviewer's report:

The availability of easily exploitable databases on drug toxicity of chemicals is of paramount importance in a safety perspective, for academics, researchers, and drug companies. Therefore, the contribution of the authors is commendable as covers an area, which is currently overlooked, i.e., the effect on ion currents other than hERG/Ikr, namely INa and ICa. The database is new and use an easy interface, which can be fully used after subscription.

However, I have some concerns requiring clarification before the paper is accepted.

Major Compulsory Revisions
- The inclusion of INa and ICa currents is the most important aspect of the database, which, in my opinion, should be emphasized in more details. Specifically, INa and ICa should be explicitly mentioned in the background and clearly represent the core of the aim. In this context, the objective of the paper should be immediately reported in the background section, after major initiatives have been described.
- It is not clear to me what is the difference between figure 3 and 4. Likewise, it is also difficult to find difference between figure 5 and 6. It should be considered to merge these figures in the appropriate way.
- In the “Abstract”, “Background” and “Intended use” sections, it should be actually emphasized the specific concept of arrhythmogenicity, torsadogenicity (the risk of torsade de pointes occurrence), QT liability instead of the general term “cardiotoxicity”. This safety aspect was responsible in the past decade of several drug withdrawals and currently represent a regulatory issue in drug development.
- The authors state at the end of “Data collection” that in some instances, it was not always possible to collect the planned full set of information. This aspect requires clarification. For instance, in several cases, when an IC50 is not provided in the publication, this could be due to the fact that the drug has only a minimal effect on the channel. In these cases, it is often reported at least the concentration causing a specific percentage of the inhibition capacity. Is this information recorded in the database?
- The author also reinforce this aspect after Table 2. Could you please clarify with some examples what is meant with the published information was questioned at
the verification stage?
- Figure 7 is redundant and could be omitted, as the main objective of the database is to show all available information on ion currents. Figure 8 is clear, complete and best representative of the intended use.
- In the “Conclusions and further development plans”, the authors express the plan to increase the number of ionic currents by including for example Ito and Ik1. Although this aspect is important, it is still premature to include these current. To the best of my knowledge, the inhibitory effect on these currents is proposed in the literature to be antiarrhythmic rather than pro-arrhythmic. This clarification should be addressed. Ikur is another channel that could be considered, provided the aforementioned clarification.
- In the “Intended use”, the authors correctly report that there are hERG inhibitors that do not cause TdP and vice versa, due to the multichannel activity that may amplify or reduce the torsadogenic effect. Relevant reference should be quoted with some examples. Moreover, further specification may be warranted. Indeed, while drugs acting on calcium channels usually counterbalance the arrhythmogenic potential of hERG blockade (e.g., verapamil), it is possible, by contrast, that drugs acting on sodium channel could amplify the pro-arrhythmic risk.

Minor Essential Revisions
Please provide a legend for the acronyms presented in Table 1 (e.g., SIDS, which I suppose to indicate Sudden Instant Death Syndrome).
Please provide a legend in Table 1. What exactly “+” and “-” indicate?
I suggest to fully and clearly write some of the acronyms for non-expert reader

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.