Subject: Re: non-toxic Build Evolutionary Library
Posted by juliocoll on Mon, 28 Aug 2023 10:12:31 GMT
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Dear Thomas,
Thanks to Norwid awardeness of the toxicity risk criteria option to the old DW updates at the end of the "Build Evolutionary Library"(EL) Add Criterion, I am experimenting with different protein/ligand pairs by adding it to my usual DW docking score, molecular weight and logP criteria that I called "evolutionary dockings".
I focus my comments now to preliminary results predicted with one model previously described for the ratVKORC1 protein/brodifacoum ligand complex (Coll, 2023 vs2 https://chemrxiv.org/engage/chemrxiv/article-details/64c8ddd 1ce23211b20ee37e3).

1) PRELIMINARY EXPERIMENTS
I first made some preliminary experiments with different ± toxicity risk values. The EL version was the most recent Windows update of 10/08/2023 which included the toxicity risk in an e9 of 47 CPU provided with 64Gb of RAM. Additional criteria included, DW docking score to the VKORC1/brodifacoum complex (Coll, 2023vs2) weight x4, molecular weight <400 x2, logP <3 x1 and ± toxicity risk values x4. Other running variables were: cycle: automatic, total run count=1, compounds per cycle=128, compounds survive a cycle =16 , Create compounds like=Approved drugs. Results in Table and graphic:

1) Numbers of raw children. There were similar numbers of randomly generated raw children (13033-15827) for toxic risks 0, 0.3, 1 and 2. The lowest numbers were those obtained at the highest toxic risk=4. Maximal fitting to the set criteria were very similar for all cases (>0.89). Maximal docking affinities of the nontoxi-macro children were all higher than 114 DW docking-score unitless. Norwid Behrnd discovered that the number of raw children divided by the number of cycles was nearly constant ~100 (now confirmed in 6 other protein/ligand models). Norwid sugested that "there seems to be a compensation by DW, it keeps generating new molecules until enough spots per generation are allocated". It remains unclear whether or how that is accomplished by EL.

2) Numbers of fitted children. The numbers of raw children fitting the targeted criteria were between 1393 and 2691, except for those that were lower at the maximal toxic risk=4 (977).

3) Numbers after nontoxi-macro. The percentages of children fitting all the criteria which remained toxic (nontoxi-macro) as detected by the NorwidJulio's macro after EL, were minimal at risks 0.01, 0.1, 0.3, and 1 (100% may be expected if the criteria were not a preference). It looks like the risk option=0 doesn’t work as expected. Is that because is a prefernce or because trouble interpreting the "<"=0 risk?. Surprisingly, the toxic risk option =4 did not generated any nontoxic-macro children (?).

4) Main conclusions: With the above mentioned model and criteria, the toxic risk value =1 generated the highest number of nontoxi-macro children (2330). An ~ 2.6 fold higher than that obtained without using any toxic risk criteria (893). The recently introduced toxicity risk criteria seem to perform as expected during individual molecular docking evolution (confirmed in 6 differn protein/ligand published pairs). The final/manual Norwith/julio's macro serves to detect any toxic "survivors" that may remain after the EL with toxicity risk criteria. Their residual presence may be

explained because the toxicity risk criteria is a preference rather than a threshold.
These are preliminary results because i) only one protein/ligand model was analysed, b) stochastic variations may be expected when more than 1 run would be applied, and c) all the EL criteria are defined at DW as preferences rather than as thresholds.

File Attachments

1) Thomas Tables Agosto tocxicityRisks.docx, downloaded 256 times