
Assessment of PYRX and autodock vina software for the design of new anticancer inhibitors by virtual screening and bioassay

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The Research and Development of new drugs is a very expensive venture costing over \$1.24 billion lasting over 14years¹. Virtual screening is one of the new strategies applied to improve speed and accuracy of the drug discovery process so as to considerable reduce costs and increase new drug development success rates².

The aim of this study was to assess PyRx and AutoDock Vina for the design of new anti-cancer drugs using Virtual Screening and MTT bioassay. Virtual screening was done for over 27,000 ligands on the ZINC³ and SWEETLEAD databases using FGF-2 as the target. Aberrant release of FGF-2 (bFGF) is implicated in; enhancement of solid tumor angiogenesis, rapid cell proliferation and facilitation of metastasis and resistance to various anti-cancer medications⁴.

Two of the best high ranked ligands, Clofarabine and 7, 8-Dihydro-L-biopterin were tested for activity on Molt-4 and K562 Leukaemia cell lines that were stimulated with FGF-2 (4ng/ml) at drug doses of 50,100,200 and 500ug using 5 days incubation MTT assay . Two-way ANOVA and non-linear regression analysis was done on bioassay results using Graphpad Prism 6.

Multiple binding sites were realised on FGF-2 with most of the highest ranked ligands binding away from the target Heparin-FGF-2 low affinity binding site. Clofarabine inhibited both Molt-4 and K562 cells proliferation (IC₅₀: 0.24, 0.094 mg/ml respectively), while 7, 8-Dihydro-L-biopterin increased proliferation of Molt-4 Cell and reduced K562 cell proliferation substantially (P<0.001) but with no significant difference at the various doses. Clofarabine IC₅₀ values increased substantially compared to 0.00091ug/ml and 0.0138 ug/ml values reported for non-FGF-2 stimulated K562 and Molt-4 cells respectively, suggesting that it lacks anti-FGFs activity and possibly increased FGF-2 activity induces resistance to Clofarabine.

In this study, PyRx and AutoDock Vina software lacked desired accuracy to predict anticancer activity of the ligands screened. Future works should investigate further; the other binding sites observed, interactions between FGF-2 and 7, 8-Dihydro-L-biopterin, the role of FGF-2 in resistance to clofarabine and involve a larger sample of ligands and at varying concentrations of FGF-2.

References

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