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# Diversity Oriented Privileged Structures as Drug Molecules

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The Exploration of privileged structures in drug discovery is a rapid emerging theme in Medicinal Chemistry. Privileged structures/substructures, is a single molecule frame work able to provide ligands for diverse receptors. Privileged structures represented as ideal source of lead compounds. These structures must display key physicochemical characteristics that facilitate their ability to bind with multiple receptors. The main objective was to design inhibitors for Dihydrofolate Reductase (DHFR) and Thymidylate Synthase (TS) enzymes. The blocking of the enzymatic activity is a key element in the treatment of many diseases including cancer, bacterial, protozoal and also opportunistic infections associated with AIDS like Pneumonia and Toxoplasmosis. Our computationally designed privileged structures having characteristic requirements like low Molecular weight, cyclic structure in scaffolds, since they provide molecular rigidity, allowing less entropy to be lost upon binding to the receptors and also providing better bioavailability. In addition to the above characteristics of privileged structures medicinal chemist favorite suite of descriptors like rotatable bonds, polar surface area and Lipinski's drug like characteristics have been applied. The designed molecules along with existing ligands with known activity, when docked into the multiple receptors of DHFR (1OHJ, 1MVS, 1S3V, 1KMS, 1KMV, 1DHF, 1MVT, 3GHC and 3GHW) extracted from protein data bank have shown greater binding affinity with these receptors. In order to further evaluate these results homology modeling of bovine and rat liver DHFR were established based on the template structures of mouse DHFR (PDB entry 1FZJ and 3D80) respectively using MODELLER 8v2 program. These results were assessed as reliable structures by PROCHECK, Verify 3D and PROSA 2003. These structurally diverse ligands were docked into the active site of modeled 3D structures of rat liver, bovine and also into the template structure of mouse DHFR using Glide 4.0 to identify important protein ligand interactions. Interestingly all these molecules showed greater affinity towards the active site showing 7-9 hydrogen bond interactions. When docked into the active site of pneumocystis carnii (1DYR) and modeled bifunctional protein Toxoplasma gondii (Tg) having 610 amino acids. Tg model was generated taking the modeled TS having 290 amino acids that was build using 1HVY template and DHFR having 248 amino acids was modeled using 1J3K and 2BL9 as templates. The linker region between these two proteins consisting of 72 amino acids was modeled using 1ON3 as a template. This bifunctional protein modeled by this process was very much refined compared to the conventional modeling scenario. The docking results were impressing by showing designed molecules to be top ranked compared to the existing molecules. Several classical and non- classical inhibitors of Thymidylate synthase with wide range of inhibition constants were taken and QSAR model was generated using multiple linear regression (MLR) method, this gave a good predictive model with $r^2$ = 0.959 and $r^2_{loo}$ = 0.871 with leave-one-out method with cross validation $r^2_{cv}$ = 0.587. All the existing and designed molecules were docked into the TS (Human and E.coli) active site and existing molecules showed maximum 1-2 hydrogen bond interactions. The designed molecules had 6-8 hydrogen bonds with the active site. In the current docking studies on multiple receptors with 75 diverse structures, it is established that the designed molecules showed better binding affinity in terms of estimated dock scores. Hence, suggesting that these diversity oriented privileged molecules can be considered as most potent anti cancer agents.