High throughput virtual screening of cyclooxygenase-2 by using database

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ABSTRACT

COX-2 is a type of Non-steroidal mitigating drug (NSAID) that legitimately targets COX-2, a protein liable for irritation and torment. Selectivity for COX-2 decreases the danger of peptic ulceration and is the fundamental component of celecoxib, rofecoxib and different individuals from this medication class. COX-2 selectivity doesn't appear to influence other antagonistic impacts of NSAIDs (most prominently an expanded danger of renal disappointment), and a few outcomes have excited the doubt that there may be an expansion in danger for cardiovascular failure, apoplexy and stroke by a relative increment in thromboxane. The target of this investigation is to screen drug-like compounds from Zinc database and to predict the potency and activity by using Virtual Screening and Molecular Docking Study. The scope of the study extends to predict the feasibility of the compounds for Drug development. Hence, this examination expresses the significance of little particle libraries and their utilization to upgrade drug revelation measure earlier amalgamation. This way to deal with screen original mixes as COX-2 inhibitors from ZINC information base relies upon different boundaries, for example, Lipinski’s standard of 5, pharmacophoric bunches appended on the ligand, size of the dataset and compound libraries among others. Additional, exertion can be stretched out to consider the receptor-ligand associations tentatively, and assessment of their organic action would help in planning mixes dependent on simulated screening strategies.

INTRODUCTION

Cyclooxygenase (COX) is a catalyst that is liable for the development of significant organic go-betweens called prostanooids, containing prostaglandins, prostacyclin and thromboxane. Pharmacological restraint of COX can give help from the side effects of aggravation and torment. Non-steroidal mitigating drugs, for example, anti-inflammatory medicine and ibuprofen, apply their belongings concluded hindrance of COX [1]. The name "prostaglandin synthase (PHS)" and "prostaglandin endoperoxide synthetase (PES)" are as yet used to allude to COX.

COX-2 particular inhibitor is a type of Non-steroidal mitigating drug (NSAID) that legitimately targets COX-2, a protein liable for irritation and torment. Selectivity for COX-2 decreases the danger of peptic ulceration and is the primary element of celecoxib, rofecoxib and different individuals from this medication class [1-3]. COX-2 selectivity doesn't appear to influence other unfriendly impacts of NSAIDs (most eminently an expanded danger of renal dis-
appointment), and a few outcomes have excited the doubt that there may be an expansion in danger for respiratory failure, apoplexy and stroke by a relative increment in thromboxane. Rofecoxib (regularly known as Vioxx) was removed from the market in 2004, given these worries \[^2\].

Early COX-2 hindering medications, for example, Celebrex and Vioxx, were presented in 1999 and quickly turned into the most often endorsed new medications in the United States. COX-2 Inhibitors as a treatment for neuroblastomas in future \[^4\].

Virtual screening is a computational strategy utilized in medication configuration research. It includes the fast appraisal of vast libraries of substance structures to direct the choice of likely medication applicants \[^3\]. Advances in atomic demonstrating, combinatorial science and sub-atomic science have profoundly changed the way to deal with drug revelation in the drug business, and Virtual Screening is a result of exploration in these zones \[^5\–8\].

**MATERIALS AND METHODS**

**Hardware environment**

**System configuration**
- Pentium 4 - 3.20 GHz
- 512 MB of RAM
- 40 GB Hard Disk Drive
- 1 MB cache
- 1.44” Floppy Disk Drive
- 17” Color Monitor
- 128 MB AGP Card

**Softwares**

- Operating System : LINUX EL – 5.0, Dos
- Virtual Screening Software: Argus lab
- Molecular Docking : AutoDock version-3.0
- Visualization Tool : PyMOL
- Conversion Tool : CORINA.
- Databases : PDB and PubChem

**PyMOL** \[^5\]

PyMOL is an open-source, client supported, atomic representation framework made by Warren Lyford DeLano and marketed by DeLano Scientific LLC, which is a private programming organization committed to making helpful apparatuses that generally converted available to logical and instructive groups \[^4\, 9–11\]. It is appropriate for delivering top-notch 3D pictures of little particles and organic macromolecules, for example, proteins. PyMOL is one of only a handful not many open source exemplification devices reachable for use in rudimentary science. The ‘Py’ part of the product’s name mentions to the way that it broadens, and is extensible by, the Python Programming Language \[^12\].

**METHODOLOGY**

**Preparation of ligand** \[^4\]

At first, the hydrogens were added to all the particles in the ligand and guaranteed that their valences were finished. This was finished utilizing this sub-atomic demonstrating bundle (ADT). It was ensured that the iota types were right before, including hydrogens \[^7\]. Contingent upon whether emotional or unbiased amides and carboxylates are wanted, the PH was indicated naturally.

Next, halfway nuclear responsibilities were relegated to the ligand atom. MOPAC or AMPAC was utilized to produce fractional nuclear custodies for the ligand. These customers were inscribed in ‘pdbq’ design, which had similar segments as a Brookhaven PDB design, yet with an additional section of fractional nuclear charge \[^6\].

**Autodock**

Consecutively AutoDock Once the network maps have been set up via AutoGrid and the docking boundary document, or ‘dpf’, is equipped, the client is organized to run an AutoDock work \[^9\].

The docking consequences were seen exploiting “get-docked”, a PDB arranged document was made. It was designated "lig.macro.dlg.pdb" and will comprise all the cropped compliances produce via AutoDock in the "lig.macro.dlg" record.

**RESULTS & DISCUSSION**

The X-ray structure of COX-2, PDB ID: 6COX was selected as the template from pdb. The drug-like compounds from Zinc database were selected and submitted to virtual screening.

**Molecular Docking [Figures 1 and 2 ] \[^8\]**

Virtual screening approaches are routinely and broadly used to diminished expense and season of medication revelation. It has been exhibited that the methodology used in this investigation is fruitful in discovering two novel COX-2 inhibitors from the ZINC information base. ZINC03832518, ZINC03782818 specifically, demonstrated high restricting liking with an Argus lab dock score of -10.6204 kcal/mol, -9.91631 kcal/mol against 6COX respectively showed in fig1 and fig2. The
ligand was docked deeply within the binding pocket region forming interactions with ZINC03832518 {GLN (192) at 2.95 Å, LEU (352) at 2.92 Å, MET (522) at 2.40 Å, SER (530) at 2.59 Å, SER (530) at 2.90 Å, GLY (526) at 3.21 Å, TYR (385) at 3.54 Å and TYR (385) at 2.62 Å} and ZINC03782818 {LEU (224) at 3.15 Å, ARG (376) at 3.03 Å, LEU (224) at 3.23 Å, LEU (224) at 2.62 Å, and ASN (375) at 3.91 Å} respectively. [12–14].

From the Virtual Screening interpretation, we confirm that the Drugs have shown best docking score (kcal/mol) from Argus lab the ZINC03832518 (-10.6204) and ZINC03782818 (-9.91631) were submitted to AutoDock to observe the interactions [[15]].

CONCLUSION

Hence, this examination expresses the significance of little particle libraries and their utilization to upgrade drug revelation measure earlier amalgamation. This way to deal with screen original mixes as COX-2 inhibitors from ZINC information base relies upon different boundaries, for example, Lipinski’s standard of 5, pharmacophoric bunches appended on the ligand, size of the dataset and compound libraries among others. Additional, exertion can be stretched out to consider the receptor-ligand associations tentatively, and assessment of their organic action would help in planning mixes dependent on simulated screening strategies.

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Conflict of Interest

The authors declare that they have no conflict of interest for this study.

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