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B.Sc. Thesis Summary

Novel Anti-Epileptic Drug Design Targeting the Brain Capillary Leakage Pathway; An *in silico* Approach

[1]*Atul Kaushik*, [2]*Heaven Alazar Abu*, [3]*Issayas Yosief Tsegay*, [4]*Jordana G/Hiwet G/Michael*, [5]*Lwam Semereab Habtesion and* [6]*Yosan Fitsum G/Michael*
[1]*Supervisor (0000-0002-6984-8865) and* [2,3,4,6]*Student*
[1,2,3,4,5,6]*Unit of Pharmacy, Department of Medical Sciences,*
Orotta College of Medicine and Health Sciences, Asmara, Eritrea

Background and Objective: Cytosolic phospholipase A2 (cPLA2), an important isoform of PLA2 that mediates the release of arachidonic acid, plays a role in the pathogenesis of Epileptic seizures through mediation of brain capillary leakage. The expression and activation of cPLA2 are significantly higher in epilepsy. Novel strategies are needed to substantially reverse the effect of cPLA2 activation. To identify a new lead molecule that can serve as a baseline for developing a new drug for refractory epilepsy.

Methodology: In this research project, *in silico* approach was used to identify lead compounds to be developed into marketable drugs with further SAR studies. While 164 compounds with potential cPLA2 inhibitory activity, including phytochemicals from the plant *Centella asiatica*, were selected and downloaded from the PubChem database. These compounds were docked against a 3D model of the enzyme cPLA2 using the CLC Drug Discovery Workbench. Those with docking scores higher than that of the known inhibitor ATK were chosen to be screened using PreADMET server. The compound with the most favorable ADME, drug-likeness and toxicity profile was chosen for the next phase of drug development i.e., SAR studies.

Results: A total of 164 compounds were screened for their docking affinity using CLC drug discovery Workbench. Of those, 23 compounds were found to have higher docking results than the known inhibitor ATK. Those 23 compounds underwent PreADMET screening and the compound with PubChem CID 9826222 and IUPAC name 2-[2-[4-(5-phenylpentylsulfanyl) phenoxy] acetyl]-1, 3-benzoxazole-5-carboxylic acid with a very high docking score of -62.74, was chosen for its favorable ADME, drug-likeness and toxicity profiles.

Conclusion: The identified potential drug candidate can serve as a lead compound for further SAR modifications as well as *in vitro* and *in vivo* studies.

KEYWORDS
Epilepsy, cPLA2, drug discovery, molecular docking simulation, virtual screening

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KEY CONTRIBUTIONS

- The identified compound showed a very good docking score of -62.74 which is even higher than that of the known cPLA2 inhibitor arachidonyl trifluoromethyl ketone (ATK) (with PubChem CID 5280436) which showed a docking score of -61.7
- The compound is non-mutagenic, non-carcinogenic in both mouse and rats and a low risk hERG inhibitor which is superior to that of ATK (non-mutagenic but carcinogenic in both rodents and a medium hERG inhibition)
- We recommend considering the compound with PubChem CID 9826222 and IUPAC name 2-[2-[4-(5-phenylpentylsulfanyl) phenoxy] acetyl]-1, 3-benzoxazole-5-carboxylic acid for further SAR modification as well as *in vitro* and *in vivo* studies

FUTURE DIRECTIONS

There is an imminent need for the development of a novel AED to tackle the ever increasing cases of refractory epilepsy. The above mentioned theories regarding the leaky BBB and the role of cPLA2 in epileptogenesis make the enzyme cPLA2 an excellent target for therapeutic intervention of refractory epilepsy.

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DECLARATION LETTER

Subject: Declaration of Intent to Publish Thesis Summary in Science Digest

Dear Editor,
I, Atul Kaushik, hereby declare on behalf of all the authors involved in the research, that we have reached a unanimous agreement to publish the summary of our thesis, titled "Novel Anti-Epileptic Drug Design Targeting the Brain Capillary Leakage Pathway; An *in silico* Approach", in Science Digest.

This research was conducted at the [Pharmaceutical chemistry, Medical Sciences, Orotta College of Medicine and Health Sciences, Eritrea], under the supervision of [Atul Kaushik], during the academic year 2022. The study represents the culmination of [Heaven, Yosan, Luwam, Jordana and Isayas]'s [B.Sc.] research project and we are excited to share the key findings with the global scientific community through the esteemed platform of Science Digest.

This declaration confirms that all co-authors have been made aware of and have consented to the publication of the thesis summary in Science Digest. Furthermore, we affirm the accuracy and completeness of the information provided in the submission.

Thank you for considering our work for publication.

Sincerely,

Atul Kaushik
Heaven Alazar Abu
Issayas Yosief Tsegay
Jordana G/Hiwet G/Michael
Lwam Semereab Habtesion
Yosan Fitsum G/Michael