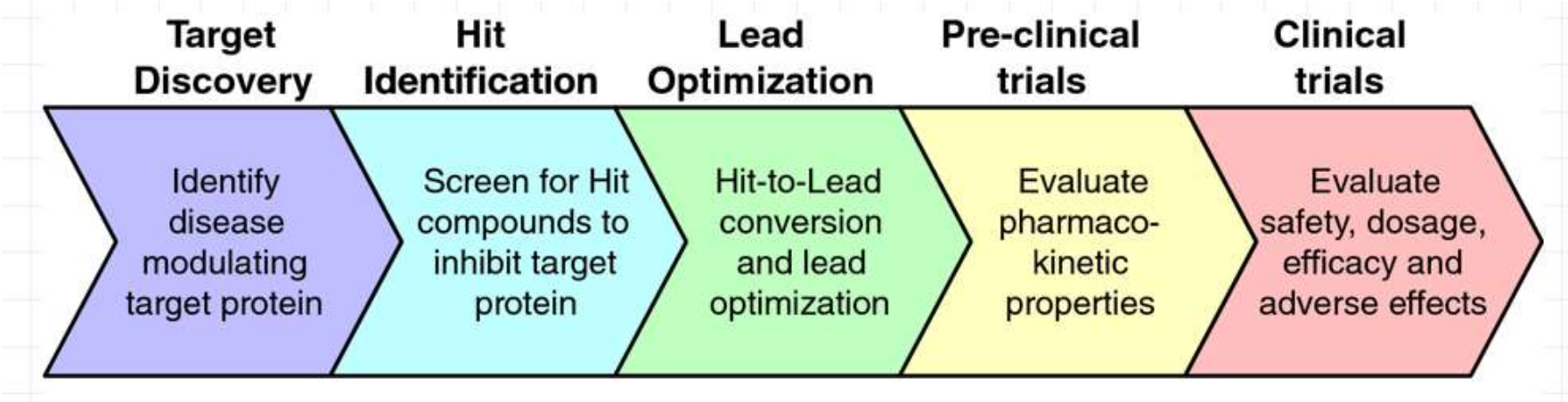
Damilola Bodun [1,*] and Damilola Omoboyowa [1]

[1] Department of Biochemistry, Adekunle Ajasin Univerisity, Akungba-Akoko

* Corresponding author: dbodun56@gmail.com

Graphical Abstract

Lead Optimization of Top compounds targeting Eg5



Cancer remains a paramount global health challenge with multifaceted mechanisms driving its proliferation. One pivotal target in this complex landscape is the Mitotic kinesin Eg5, a key player during cell division. Inhibiting this protein holds immense potential to combat cancer effectively. Building on a recent breakthrough, our study aims to enhance the inhibitory efficacy against Eg5 by optimizing a promising novel compound identified in our previous research, which has shown superior inhibitory properties compared to a standard treatment. As we progress through the drug discovery funnel, our focus shifts to lead optimization. We seek to elevate the binding affinity of the lead compound while simultaneously enhancing its Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) properties. This optimization phase is critical for ensuring the compound's therapeutic efficacy, safety, and potential for clinical translation. Our proposed research aligns with the urgent need for innovative cancer treatments and addresses a vital aspect of drug development. By refining the lead compound's molecular interactions and ADMET profile, we endeavor to contribute to the advancement of targeted cancer therapy, potentially bringing us closer to a transformative solution in the battle against cancer.

Keywords: Lead Optimization; Medicinal Chemistry; QSAR

Introduction

MITOTIC KINESIN EG5

Mitotic Kinesin Eg5 is an enzyme that plays a crucial role in the process of cell division by separating chromosomes and moving them to opposite poles of the cell.

Cancer cells often display rapid and abnormal cell proliferation, making them potential targets for drugs that activate the spindle checkpoint

Introduction

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QSAR-based virtual screening of traditional Chinese medicine for the identification of mitotic kinesin Eg5 inhibitors

Damilola S. Bodun [a,*], Damilola A. Omoboyowa [a], Olaposi I. Omotuyi [b], Ezekiel A. Olugbogi [a], Toheeb A. Balogun [c], Chiamaka J. Ezeh [d], Emmanuel S. Omirin [a]

[a] Department of Biochemistry, Adekunle Ajasin University, Akungba-Akoko, Ondo State, Nigeria
[b] Department of Pharmacology and Toxicology, College of Pharmacy, Afe Babalola University, Ado Ekiti, Nigeria
[c] Department of Biological Sciences, University of California, San Diego, San Diego, CA, United States
[d] Department of Biochemistry, Micheal Okpara University of Agriculture, Umudike, Abia State, Nigeria

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ABSTRACT

Cell division is a crucial process for the growth and development of all living organisms. Unfortunately, uncontrolled cell division and growth is a hallmark of cancer, leading to the formation of tumors. The Human Eg5 protein, also known as the mitotic kinesin Eg5, plays a vital role in the regulation of cell division and its dysfunction has been linked to cancer development. This study aimed to identify new inhibitors of the Human Eg5 protein. Over 2000 Traditional Chinese Medicine (TCM) compounds were screened through a combination of virtual and structure-based screening methods. The top five compounds (Compounds 1–5) showed improved binding affinity to Human Eg5 compared to the standard drug Monastrol, as demonstrated by docking and MMGBSA scores, as well as interactions with key amino acids GLY 116 and GLY 118. The potential absorption and bioactivity of these compounds were also predicted through ADMET properties and a QSAR model, respectively, and showed improved results compared to the standard. Further quantum mechanics docking confirmed the better binding affinity of the lead compound, Compound 1. Our findings highlight Compound 1–5 as promising hits for inhibiting Human Eg5 and the need for experimental validation of their potential in treating cancer.

Figure 1: Snapshot of the previous study

Introduction

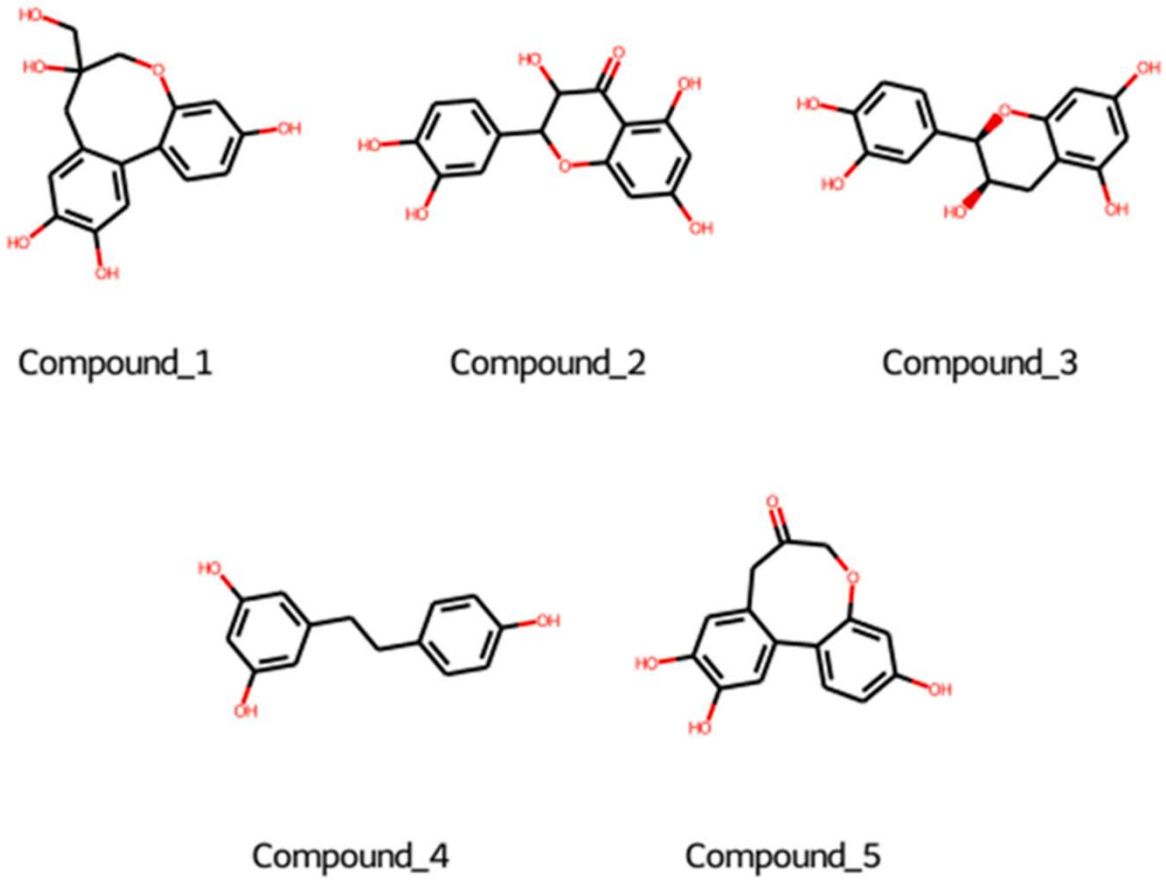


Figure 2: Top compounds from the Prior Study.

Materials and Methods

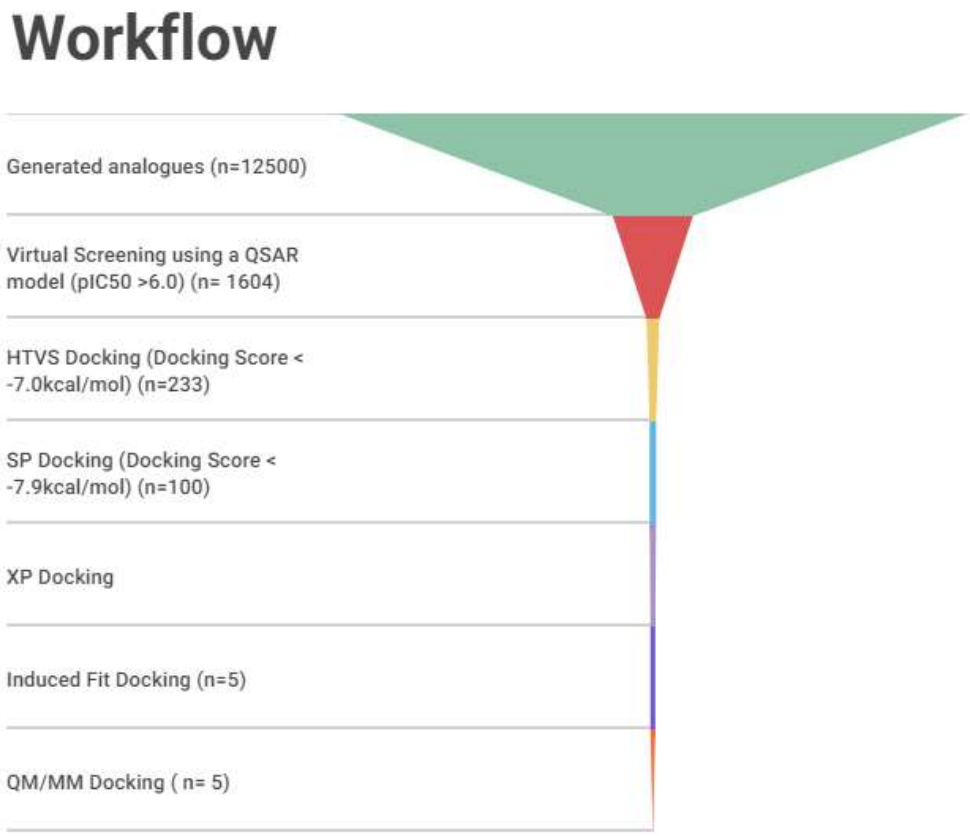
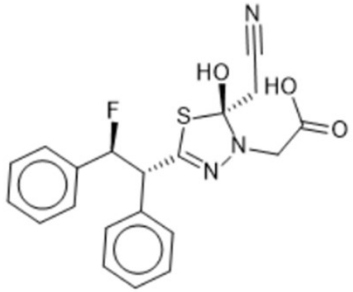


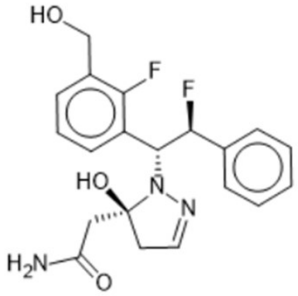
Figure 3 : Workflow of this study.

- Using a Deep learning platform, we generated 12500 analogues of the top 5 compounds from the prior study (Figure 2)
- The generated analogues had a better binding affinity compared to the co-crystallized ligand.
- The better binding affinity were confirmed using free energy calculations (MM-GBSA), Induced fit docking and Quantum based Docking (Table 2-4).
- Also a detailed QSAR model was built using the list of ChembL inhibitors. The model predicted the better inhibitory potential of the compounds compound to the standard (Table 1).

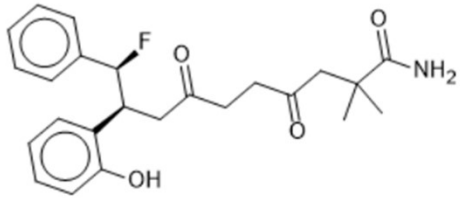
Results and Discussion



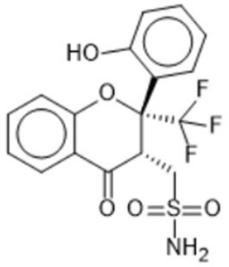
Compound 9794



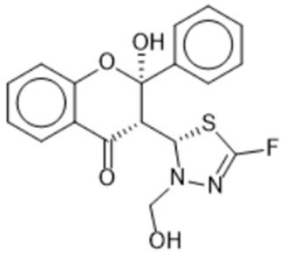
Compound 8592



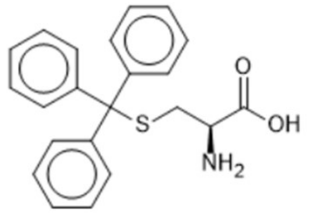
Compound 9786



Compound 2744



Compound 3246



Co-crystallized Ligand
(Reference Ligand)

Figure 4: Top compounds from this study compared to the co-crystallized ligand (Reference Ligand).

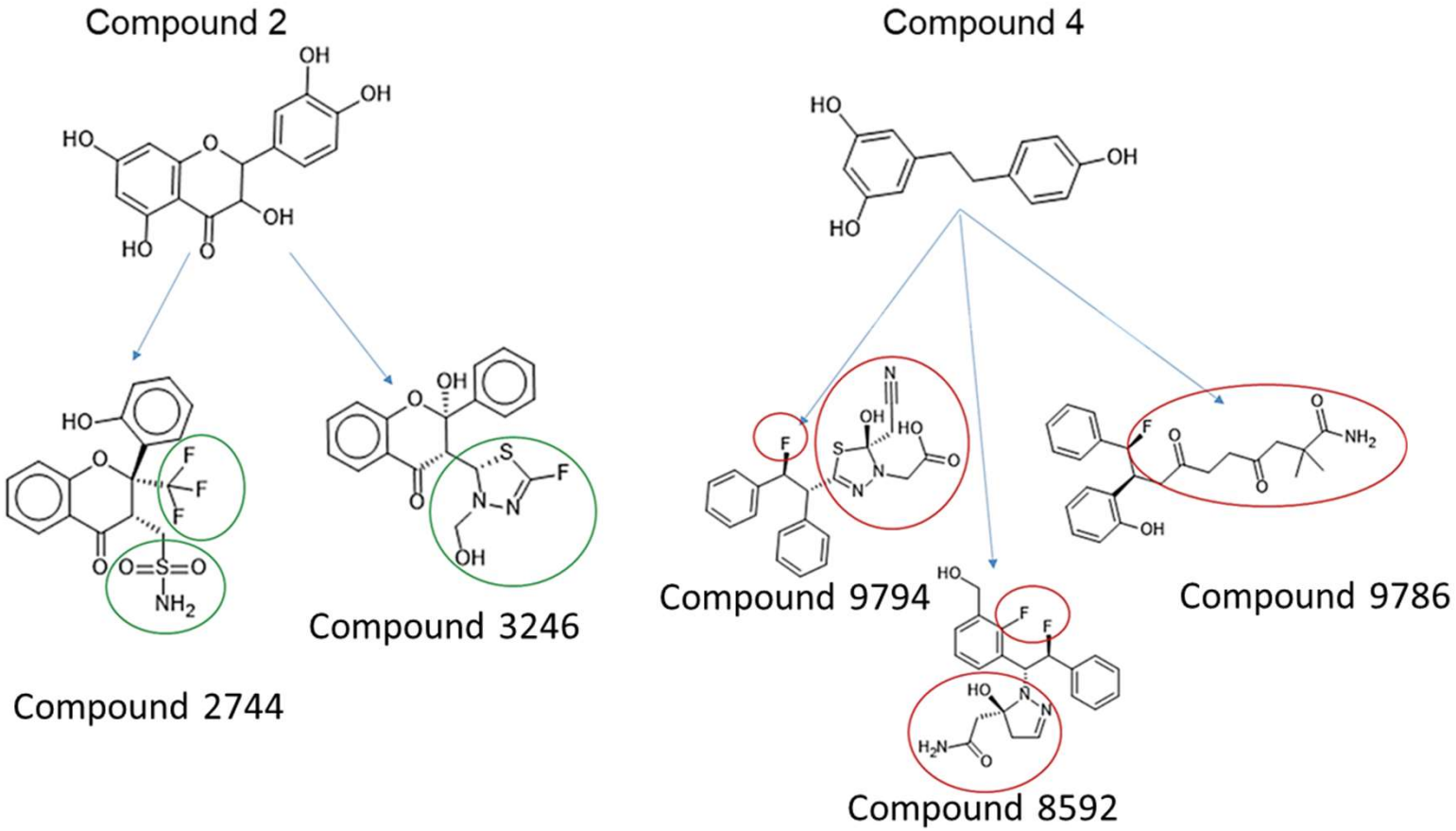


Figure 5: Optimized part of the analogues

Table 1: Top compounds and their predicted pIC50 values

Compound	Pred Y
Compound 9794	6.267
Compound 8592	6.298
Compound 9786	6.080
Compound 2744	6.056
Compound 3246	6.248
Co-crystallized Ligand (Standard)	5.893

Table 2: Docking and MMGBSA scores of the top compounds

Compound	XP docking	MMGBSA
Compound 9794	-8.559	-66.9
Compound 8592	-8.557	-59.44
Compound 9786	-8.517	-56.76
Compound 2744	-8.356	-60.1
Compound 3246	-8.354	-59.3
Co-crystallized Ligand (Standard)	-8.323	-76.98

Table 3: Docking and IFD scores of the top compounds after Induced fit docking

Compound	Docking score	IFD score
Compound 9794	-8.529	-717.4
Compound 8592	-7.948	-716.93
Compound 9786	-9.15	-721.33
Compound 2744	-8.799	-719.78
Compound 3246	-8.094	-717.07
Co-crystallized Ligand (Standard)	-8.821	-718.16

Table 4: Docking and Glide eModel scores of top compounds after Quantum based docking .

Compound	Docking score	Glide eModel
Compound 9794	-8.678	-70.735
Compound 8592	-9.268	-58.405
Compound 9786	-9.15	-76.568
Compound 2744	-8.279	-63.953
Compound 3246	-8.327	-55.717
Co-crystallized Ligand (Standard)	-9.017	-87.309

Conclusions

The results of this study confirms the better binding affinity of the optimized analogues compared to the co-crystallized ligand after Rigid docking, Induced Fit Docking and Quantum based docking. However a more detailed calculation which involves MD simulation will be done. Also these compounds should be tested for both *in vitro* and *in vivo* test for their efficacy.

Acknowledgments