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Design of Novel Protein Kinase Inhibitors Using the Naturally Occurring Staurosporine Scaffold as a Lead

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Abstract

Staurosporine is a naturally occurring alkaloid isolated which inhibits the protein kinases class of enzymes inducing apoptosis and thus having potential anti-tumour activity. Recent studies showed that staurosporine had high affinity for the protein kinase C receptor, however lacked selectivity resulting in a wide adverse effect profile. Thus, this study targets the protein kinase C receptor for the development of novel structures capable of its inhibition using staurosporine as template molecule. This study has yielded two molecular cohorts, one from each approach. These were filtered for Lipinski Rule compliance and segregated into families of pharmacophoric similarity and ranked in order of affinity. The affinities of the optimal molecules exceeded that of stautosporine, and these molecules will be proposed for further study.

Introduction

Protein kinase C (PKc) inhibitors are important anticancer drugs[1,2]. The alkaloid staurosporine isolated from *Streptomyces staurosporeus*[3] has recognised PKc inhibitory ability[4] and will be used as a template for the design of clinically useful high affinity PKc inhibitors.

Methods and Materials

Method 1: *de novo* Drug Design

- Pdb crystallographic deposition 1STC[5] was used as a template.
- 2D topology map (Figure 1) describing the critical interactions forged between staurosporine and the PKc receptor were generated and used to guide the modeling of seed structures.
- The designed seed fragments (n = 4) were planted into this restricted pharmacophoric space, and novel molecular growth driven using the GROW module of LigBuilder® v.1.2[8] was carried out.

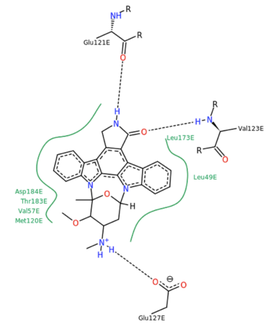


Figure 1: Interactions formed between staurosporine and the LBP of the PKc

Method 2: Virtual Screening

- An average pharmacophore (Figure 2), was used to query the molecular data base ZINCPharmer® [9].
- This process identified small molecules present on this database which were morphologically, 3 dimensionally, and electronically similar to the query.
- A protomol was modeled.
- The Lipinski Rule compliant molecules that were identified from ZINCPharmer® [9] during VS were uploaded into the modeled protomol and their affinity quantified.

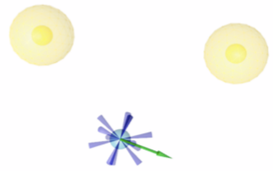


Figure 2: Consensus pharmacophore

Results

Method 1: *de novo* Drug Design

The two best molecules (Figures 3 and 4) generated using this approach were derived from seed 4. They possess the highest ligand binding affinity (*pKd* 10) for the PKc receptor.

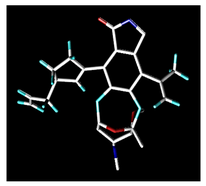


Figure 3: Molecule 1 (left)

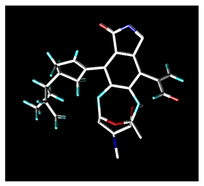


Figure 4: Molecule 22 (right)

Method 2: Virtual Screening

The molecule (Figure 5) with the highest *pKd* of 9.65 was molecule ZINC13554963 and was selected for further optimisation.

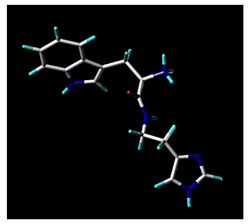


Figure 5: Molecule ZINC13554963

Discussion

This study was valuable in demonstrating that the staurosporine scaffold was suitable for the identification and design of high affinity structures capable of modulating the PKc receptor through two distinct approaches –VS and de novo design. The affinities of the optimal molecules exceeded that of staurosporine, will be proposed for further study.

Conclusions

In conclusion, this study has shown that staurosporine is a useful lead for ligand generation. A library of drug-like molecules with inhibitory activity on PKc was generated. This library is suitable for in vitro testing. This will evaluate whether the enzyme inhibition is replicated in vitro. If this proves true the generated molecules are viable candidates for further drug development as future anticancer drugs.

Future Dirsctions

The enhanced molecular interactions of the high affinity Lipinski Rule compliant molecules will be explained from an atomic perspective, and through Molecular Dynamic simulation studies.

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