# High throughput *in silico* screening for polypharmacological bromodomain 4 and cancer associated kinase inhibitors

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## Introduction

Polypharmacology is an intense subject of research in the development and design of anti-cancer compounds[1].

Drugs that have more than one target can have higher efficacy in the treatment of triple negative breast cancer and can potentially prevent drug resistance from developing[1].

High throughput virtual screening is a cost-effective way of identifying potential hits with a hit rate of up to 0,2%[2]. Bromodomain containing protein 4 (BRD4) is a known dysregulated enzyme in triple negative breast cancer,ogether with other kinases such as aurora kinase A and B, and EGFR[3-4]

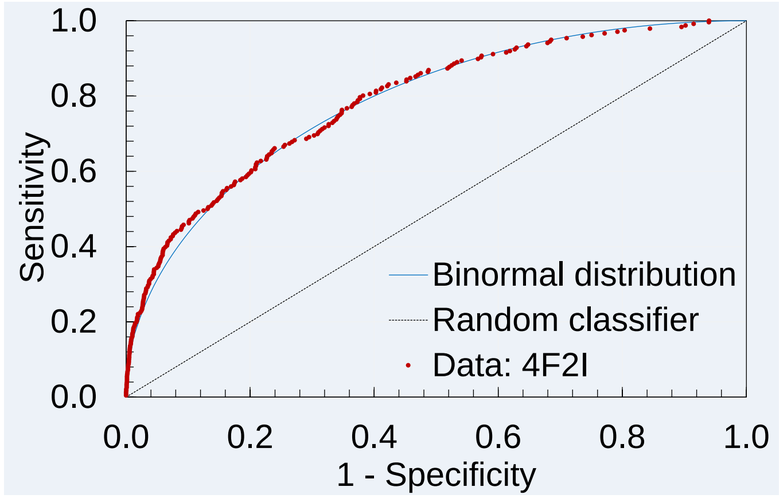


**Fig 1**: ROC curve of one of the BRD4 proteins (4F3I)

## Aim

The aim of this study is to, by means of high throughput virtual screening using the Schrodinger package and the Lengau cluster of the Centre for High Performance computing, identify dual BRD4 and kinase inhibitors (AurkA and B, and EGFR)

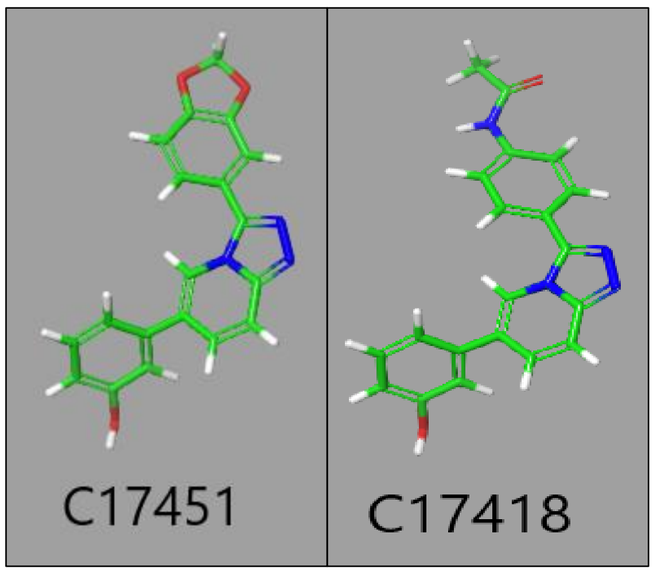


**Fig 2**: Ball and stick models of C17451 and C17418

## Methods

The Biofocus library (20 000 compounds), provided by the CSIR were docked into 14 prepared BRD4 receptors. For this the docking job was created in Maestro (Schrödinger package) and submitted to the Lengau cluster of the HPC. The receptors were chosen because they best distinguished between known ligands and decoy ligands (See ROC curve, Figure 1).

Compounds with a docking score lower than -9,00 (Indicates significant binding activity) were docked into the kinases. The kinase docked ligands with the lowest docking score are being used in the in vitro study

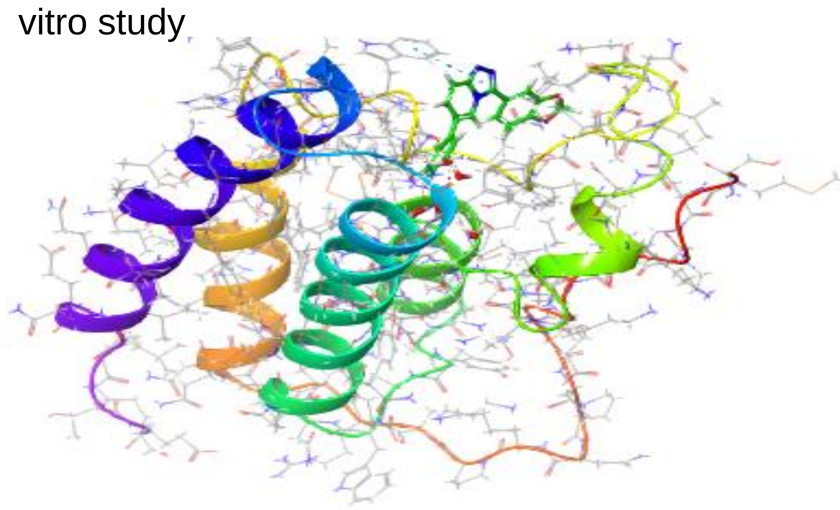

**Fig 3**: C17418 and C17451 (green) docked into the crystal structure of BRD4. Interactions are represented by dashed lines

## Results

The docking of the Biofocus library (Fig 2) into the BRD4 crystal structures produced 80 ligands with a docking score lower than -9. The docking score refers to the mathematical function that predicts the affinity that two molecules will have for each other, -9 and lower being an indication of good binding interactions. These 80 ligands were then docked into AurkA (Fig 3, 4 and 5), AurkB and EGFR crystal structures producing producing a list of 25 compounds (docking score ≤ -9). From this list 10 compounds were chosen based on the lowest combined docking score of BRD4, AurkA, Aurk B and EGFR (Fig 6).

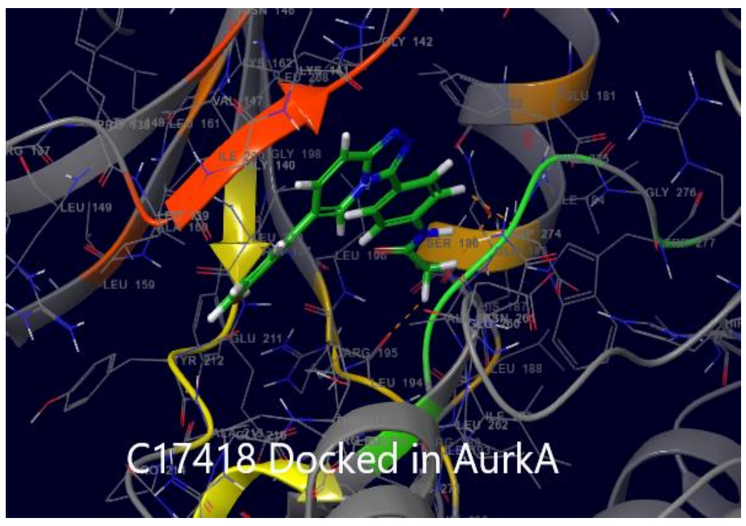


**Fig 4**: Visual representation of the interaction of C15513 with the crystal structure of AurkA, notice the prominent hydrogen bonds

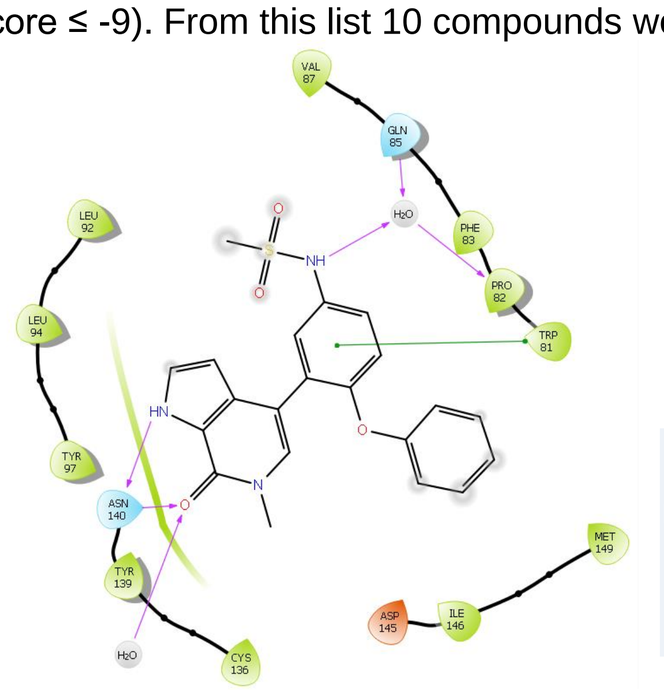


**Fig 5**: C17418 and C17451 docked into crystal structures of AurkA. Interactions are represented by dashed lines.

## Conclusion

In conclusion, 10 potential BRD4/Kinase dual inhibitors were identified. Further in silico experiments will be conducted to identify the molecular dynamics at work. The next phase of research are the in vitro studies of the identified compounds.

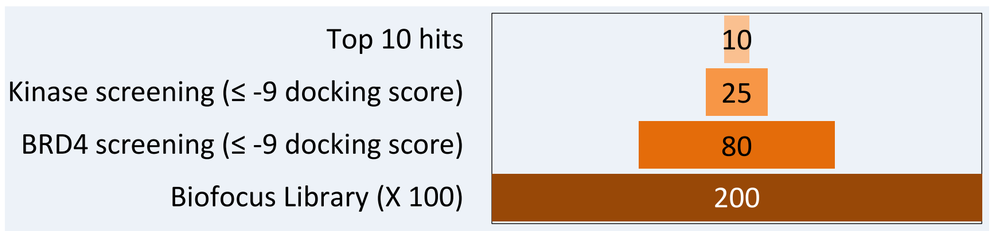


**Fig 6**: Funnel diagram of the elimination strategy employed to filter the library of 20 000 compounds down to 2 hits.

## References

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