

Poster presentation

## Identification of Plk1 type II inhibitors by structure-based virtual screening

S Keppner\*, E Proschak, G Schneider and B Spänkuch

Address: Johann Wolfgang Goethe University, Beilstein Endowed Chair for Cheminformatics, Siesmayerstr. 70, 60323 Frankfurt/Main, Germany

\* Corresponding author

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Protein kinases are targets for drug development [1]. Dysregulation of kinase activity leads to various diseases [2], e.g. cancer, inflammation, diabetes [1]. Human polo-like kinase 1 (Plk1), a serine/threonine kinase, is a cancer-relevant gene and a potential drug target which attracts increasing attention in the field of cancer therapy. Plk1 is a key player in mitosis and modulates entry into mitosis and the spindle checkpoint at the meta-/anaphase transition. Plk1 overexpression is observed in various human tumors, and it is a negative prognostic factor for cancer patients [3].

The same catalytical mechanism and the same co-substrate (ATP) lead to the problem of inhibitor selectivity. A strategy to solve this problem is represented by targeting the inactive conformation of kinases [2]. Kinases undergo conformational changes between active and inactive conformation and thus an additional hydrophobic pocket is created in the inactive conformation where the surrounding amino acids are less conserved [2].

A "homology model" of the inactive conformation of Plk1 was constructed, as the crystal structure in its inactive conformation is unknown. A crystal structure of Aurora A kinase served as template structure. With this homology model a receptor-based pharmacophore search was performed using SYBYL7.3 software. The raw hits were filtered using physico-chemical properties. The resulting hits were docked using Gold3.2 software, and 13 candidates for biological testing were manually selected.

Three compounds of the 13 tested exhibit anti-proliferative effects in HeLa cancer cells. The most potent inhibitor, SBE13, was further tested in various other cancer cell lines of different origins and displayed *EC*<sub>50</sub> values between 12  $\mu$ M and 39  $\mu$ M. Cancer cells incubated with SBE13 showed induction of apoptosis, detected by PARP (Poly-Adenosyl-Ribose-Polymerase) cleavage, caspase 9 activation and DAPI staining of apoptotic nuclei.

### References

1. Thaimattam R, Banerjee R, Miglani R, Iqbal J: **Protein kinase inhibitors: structural insights into selectivity.** *Curr Pharm Des* 2007, **13**:2751-2765.
2. Liu Y, Gray NS: **Rational design of inhibitors that bind to inactive kinase conformations.** *Nat Chem Biol* 2006, **2**:358-364.
3. Strebhardt K, Ullrich A: **Targeting polo-like kinase I for cancer therapy.** *Nat Rev Cancer* 2006, **6**:321-330.