Usage Report for Fiscal Year 2015

**Project Title:**

# Computational structure-based design of protein inhibitors

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## 1. Background and purpose of the project, relationship of the project with other projects

Structure based virtual screening of small molecule compound libraries has been proven as an efficient methodology in drug discovery. Scaffold hopping is a commonly used strategy to discovery new chemical classes of inhibitors from existing ones. We would like to discover novel chemical class of inhibitors for the sumoylation enzyme SUMO E1. These inhibitors may not only provide starting points for drug development but will also be useful chemical probes to further our understanding the biological role of these proteins.

Sumoylation is a post-translational modification that plays an important role in a wide range of cellular processes including chromosome packing and dynamics, DNA replication and repair, genome integrity, signal transduction, nuclear transport, and cell proliferation. The sumoylation pathway has been linked to a significant number of pathogenicities including neurodegenerative diseases and cancer. This makes sumoylation a novel drug target.

## 2. Specific usage status of the system and calculation method

In order to identify new chemical scaffolds with SUMO E1 inhibitory activity, we utilized a weak inhibitors (compound 1) previously reported by us as a template for scaffold hopping. Shape and electrostatic potential matching calculations were used to retrieve compounds endowed with similar chemical features but a different scaffold from the known inhibitor. Namiki shoji small molecular collection containing about 4 million purchasable compounds was used as the screening library. At the outset, shape comparisons were performed using ROCS. EON program was then used to perform electrostatic potential matching calculations on the top ranking 100 compounds from shape similarity.

## 3. Result

As expected the top ranking five compounds belonged to quinazolinyloxy biaryl urea. Other than this scaffold, compound **2** was the top-ranking compound ($6^{th}$ in ranking) with EON ET_Combo score (a combined score for electrostatics and shape overlap) of 1.54 and ROCS TanimotoCombo (which is a combined Tanimoto coefficient for overlap of shape and chemical features) of 1.21 (both in the scale of 0 to 2). As compound **2** shares O-methyl and O-cyclopentyl substituted phenyl urea substructure with compound **1**, significant overlap in shape and electrostatic potential field was observed. Major differences were observed in the other half of the molecule. A thiazole moiety replaced the pyridine ring in compound **2** while the chloro substituted quinozolinyl ring was substituted by a methyl and chloro substituted phenyl ring. The experimental validation of compound **2** using in vitro sumoylation assay revealed moderate SUMO E1 inhibitory activity. Compound **2** inhibited the sumoylation of substrate RanGAP1 in a concentration dependent manner with a half maximal inhibitory

concentration ($IC_{50}$) value of 92.6 μM.

In order to identify thiazole urea scaffold containing compounds with better SUMO E1 inhibitory activity, structurally related compounds were identified by carrying out 2D structural similarity search against Namiki shoji collection of commercially available compounds. Compound **2** was used as a query to retrieve compounds utilizing MACCS structural keys. A Tanimoto coefficient [32] cut-off of 0.7 was used. About 340 structurally similar compounds with thiazole urea scaffold were obtained. After docking analysis and visual inspection, a set of 22 compounds were acquired from commercial vendors for evaluation of SUMO E1 inhibitory activity using an in vitro sumoylation assay. Compound 8 with thiazole urea scaffold inhibited the sumoylation of substrate RanGAP1 in a concentration dependent manner with $IC_{50}$ of 33.2 μM.

We investigated whether the pyridine ring in compound **1** or thiazole core in reported compounds could be replaced by a bioisostere that would display similar properties. In order to obtain compounds with pyrazole ring in place of pyridine or thiazole ring, a substructure search for pyrazole urea scaffold was carried out that revealed 133 compounds in Namiki shoji collection. These compounds were further prioritized using shape and electrostatic matching calculations. Compound **1** was again used as a query to filter pyrazole urea scaffold compounds with similar shape and electrostatic properties. Shape similarity between compound **1** and each molecule in Namiki shoji collection of commercially available compounds was calculated using ROCS program. TanimotoCombo was used to rank-order compounds. All 133 compounds were also evaluated for their similarity in electrostatic potential field with compound **1** using EON program. These compounds were tested for their ability to inhibit the sumoylation of substrate RanGAP1 in the similar manner as the previously tested thiazole urea compounds. Compounds **39** and **41** with pyrazol scaffold were found to be the most potent with $IC_{50}$ values of 13.8 and 30.4 μM respectively.

## 4. Conclusion

We have identified thiazole and pyrazole urea based compounds as moderately potent inhibitors of SUMO E1 protein. These compounds were identified using scaffold hopping and virtual screening approaches. The biological activities of reported compounds were comparable to previously reported compounds. Both classes of inhibitors present broad scope for chemical optimization for better drug-like and pharmacokinetic properties and can be used as starting points for development into more potent SUMO E1 inhibitors with therapeutic potential.

## 5. Schedule and prospect for the future

We plan to optimize the initial hits for sumoylation enzymes SUMO E1 that have been identified by virtual screen and confirmed by biochemical assays. Various computation tools will be used to optimize these initial hits into more potent inhibitors. We also plan to develop new methods to facilitate ligand-based and receptor-based virtual screening.

## 6. If no job was executed, specify the reason.

N/A.

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## Fiscal Year 2015 List of Publications Resulting from the Use of the supercomputer

### [Publication]


1. Kumar, A., Ito, A., Hirohama, M., Yoshida, M., Zhang, K. Y. J. (2016) Identification of new SUMO activating enzyme 1 inhibitors using virtual screening and scaffold hopping. *Bioorg. Med. Chem. Lett.*, **26**, 1218-1223. DOI:10.1016/j.bmcl.2016.01.030.
2. Kumar, A., Zhang, K. Y. J. (2015) Application of Shape Similarity in Pose Selection and Virtual Screening in CSARdock2014 Exercise. *J. Chem. Inf. Model.*, DOI: 10.1021/acs.jcim.5b00279.


### [Oral presentation at an international symposium]

1. The International Chemical Congress of Pacific Basin Societies, Dec. 15-20, 2015, Honolulu, Hawaii, USA. Kam Zhang, "Discovery of small molecule inhibitors targeting the SUMO-SIM interaction using a protein interface consensus approach".
2. 10th Asian Federation for Medicinal Chemistry International Medicinal Chemistry Symposium, Oct. 18-20, 2015, Jeju, Korea. Kam Zhang, "A Rotation-translation Invariant Molecular Descriptor of Partial Charges for Ligand-based Virtual Screening".
3. JCUP-V, June 4-5, 2015, Tokyo, Japan. Ashutosh Kumar and Kam Zhang, "Application of Shape Similarity in Pose Prediction and Virtual Screening".
4. JCUP-V, June 4-5, 2015, Tokyo, Japan. Ashutosh Kumar, Akihiro Ito, Misao Takemoto, Minoru Yoshida and Kam Zhang, "Discovery of Novel SENP Inhibitors Utilizing Structure Based Virtual Screening".