SancaMedChem

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MEETING
ABSTRACTS

THE SÃO CARLOS SPECIAL MEDICINAL CHEMISTRY MEETING

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SancaMedChem - The São Carlos Special Medicinal Chemistry Meeting

November 25th to 27th, 2019

São Carlos Institute of Chemistry (IQSC), University of São Paulo (USP)

São Carlos – SP, Brazil

MEETING ABSTRACTS

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Predicting the $\Delta\Delta G_{bind}$ of halogenated reversible covalent inhibitors of hCatL through computer simulation

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The cysteine protease human Cathepsin L (hCatL) are expressed in different types of cancer, then the inhibition of this enzyme may be important to discovery of novel therapeutics. In this study five nitrile-based inhibitors analogs of the prototypical **Neq0570** were studied. All of them are halogenated reversible covalent inhibitor of hCatL. To describe the halogen bonding interaction in active site of hCatL, we applied an extra point (EP) of charge in the halogen atom to represent the σ-hole. We used molecular dynamics calculation to verify the distance between the halogen atom and the oxygen atom from Gly61. To evaluate the overall relative binding free energy of these inhibitors, we used alchemical free energy calculations of two-state binding model: noncovalent and covalent state. The results show that EP improve the average of halogen bond and the use of free energy perturbation (FEP) can predict the hCatL binding affinities of the compounds with a close agreement with experimental results, as shown in Table 1.

Table 1: Relative binding free energy of hCatL inhibitors, all values in kcal/mol. Note that $\Delta\Delta G_{bind}$ corresponds to the sum of the relative binding free energy of covalent and noncovalent states.

Transformation	Mutation	$\Delta\Delta G_{bind}$ (FEP)	$\Delta\Delta G_{bind}$ (exp)	$\lvert\Delta x^a\rvert$
Neq0570 → 0802	H → F	-0.49	0.22	0.71
Neq0570 → 0710	H → Cl	-1.59	-0.82	0.77
Neq0570 → 0803	H → Br	-1.51	-1.54	0.03
Neq0570 → 0804	H → I	-1.80	-1.99	0.19

[a]Absolute error between the calculated and experimental values

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References

[1] Lameira, J.; Bonatto, V.; Cianni, L.; Rocho, R. F.; Leitão, A.; Montanari, C.A., Physical Chemistry Chemical Physics, **2019**, DOI: 10.1039/C9CP04820K.