Structure activity relationship studies on KasA: aldonamides' affinity to receptor in context of TB drug design

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KasA is a key enzyme involved in the synthesis of mycolic acids. The latter, being the fragments of *M. tuberculosis* cell wall, protect bacteria from the action of acidic environment, thereby allowing them to persist in the human body. Inhibition of this enzyme leads to disruption of the FAS-II system, preventing the build-up of the fatty acid chain [1]. This mechanism underlies the action of few TB drugs, including the legendary isoniazid.

We have studied the series of more than 50 open-chain aldonamides in context of the influence of their relative configuration and functionality on affinity to KasA receptor. The receptor choice (2WGF Transferase: chain A [1]) is based on the comparison of SAR obtained both *in silico* and *in vitro* experiments for free-hydroxy and acylated isonipecotamides synthesized previously [2]. To design open-chain derivatives we have chosen monose derivatives which are structurally and functionally isosteric to isonipecotamides and possessing all possible relative configurations. Structure design includes monose skeleton modification by introduction of the substituted amide and amino groups (both transformations are available from the classical sugar chemistry). The *in silico* study was carried out in [3] by using the semi-empirical PM6 and the MMFF94 geometric optimization techniques for pH=7. To find the energetically optimal conformations for labile open-chain aldonamides we have proceeded every docking for at least 100 runs. L-altro- and D-gluco- configuration-based derivatives showed the highest affinity to receptor. After variation of substituents in amide fragment and replacement of hydroxyl with amino group we have found the highest affinity for N-tert-butyl L-4-deoxy-4-aminoaltrosamide (-10.93 kcal / mol), N-benzyl L-4-deoxy-4-amino-altrosamide (-11.48 kcal / mol) and N-benzyl D-gluconamide (-10.01 kcal / mol), The SAR analysis showed these structures form conformations with the maximum number and the optimal geometry of intramolecular hydrogen bonds, as well as hydrophobic interactions. The latter can be discussed in terms of multiple interactions between N-alkyl substituted amide group and protein hydrophobic side chains (Pro and Ile in protein studied). Based on the data obtained, a pharmacophore was proposed with the L-altro- or D-gluco- configuration, bulky hydrophobic N-substituted amide group and possible amino group at 4^{th} C-Carbon.

References

[1] S.R. Luckner, C.A. Machutta, C. Kisker. Structure (2009) 17 (7):1004.

[2] T.T. Lakhvich, P.U. Zushchyk, A.T. Lakhvich. Advances in medicine and medical sciences: coll. of Belarusian State Medical University (2019) 9:389

[3] Docking Server [http://www.dockingserver.com/web/]