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Determining the most relevant crystal structure to virtually identify type 1 inhibitors of c-Met: Part A

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c-Met is a receptor tyrosine kinase, which plays a crucial role in cell proliferation, migration and angiogenesis. Its dysregulation results in aberrant signalling, resulting in tumor growth and metastasis; an important target in cancer treatment. Multiple crystal structures are available from the protein data bank of c-Met bound to various inhibitors. Since the receptor tyrosine kinases are conformationally flexible receptors, each of these crystal structures represents a distinct conformation suited to accommodate the ligand. For the identification of new ligands as inhibitors of c-Met using computational methods, such a situation presents a challenge, as the use of some crystal structures for docking may result in the identification of false negatives. To address this issue, we have screened the available crystal structures of c-Met; bound to Type 1 inhibitors systematically to identify the most relevant crystal structure which can be used for docking. The procedure involved ascertaining the presence of Type 1 inhibitors in the crystal structure, self-docking to ensure the suitability of docking protocol, cross-docking to establish the ability of that crystal structure to accommodate chemically distinct ligands and followed by judging the ability of the top-ranked crystal structures to identify actives over decoys preferentially. The Enrichment Factors and other statistical parameters such as the number of outranking decoys, Robust Initial Enhancement, ROC, BEDROC and Diversity Enrichment Factor were also calculated and analysed. All the results pointed towards 3ZXZ outperforming in all the tests and thus can be used as the most appropriate crystal structure for virtual screening of Type 1 inhibitors of c-Met.

Keywords: Type 1 inhibitors of c-Met, Self-docking, Cross-docking, Enrichment parameters