

3rd International Conference on Medicinal Chemistry & Computer Aided Drug Designing

December 08-10, 2014 DoubleTree by Hilton Hotel San Francisco Airport, USA

Targeting the dimerization region of the epidermal growth factor receptor through the design of small inhibitory molecules as novel anticancer agents

Marting Zechariah Garba, Hibbs D E, Groundwater P and Grewal T
The University of Sydney, Australia

Post-translational modification of proteins, particularly the reversible protein phosphorylation, is critical to biochemical events, which are mediated by the phosphorylation of residues such as serine, threonine, and tyrosine, often considered under protein kinase superfamily. A dimer or [an] oligomer formation (i.e., dimerization or oligomerization) is cardinal to the effective connection of extracellular events with the intracellular composition of the cell world occurring in all cells, which is then usually followed by an often gazillion of cellular interactions, since most native proteins exist as monomers. The epidermal growth factor receptor family is the archetypal of the protein kinases hence the receptor tyrosine kinase larger family. The family is made of four members (HER1, HER2, HER3, and HER4) that are almost all affianced in different dimerization processes, resulting in either a homodimer or heterodimer, depending on the ligand binding, e.g. epidermal growth factor (EGF). The dimers formed pave way for protein phosphorylation, warranting the adequate communication between the external and internal cell composite through an avalanche of biochemical reactions and pathways, in health and disease. The healthy participation of the EGFR family in ontogeny, morphogenesis, cell proliferation, migration, and differentiation among other cellular outcomes when bound by cognate ligands are well noted. However, the aberrant roles of the family in several diseases, including different cancer types have also been extensively reported. A number of inhibitors to treat such atypical conditions are in circulation such as the receptor tyrosine kinase inhibitors (e.g. Erlotinib and Gefitinib) and several monoclonal antibodies (e.g. Cetuximab, Trastuzumab, and Panitumumab), however, the emergence of resistance and hard-to-manage side effects against these modern therapeutic approaches have reduced their continued consideration. Our knowledge of the role of and mechanisms involved in dimer formation (dimerization process) as a fundamental requirement to proceed with its cellular interactions, has initiated the novel search for small molecule inhibitors that can prevent the 'two dimer arms' coinciding each other in order to prevent this initial mechanism. We have focused on the EGF receptor EGFR complex based on their canonical 2:2 format. The Schrodinger software was utilized to design the potentially active compounds on a ligand-based principle through the high-throughput virtual screening technique. The leads were optimized and bio-evaluated and using the CombiGlide libraries of more potent agents were generated and then assayed by Western Blotting and/or synthesized.

zmar5563@uni.sydney.edu.au