Discovery of new human epidermal growth factor receptor-2 (HER2) inhibitors for potential use as anticancer agents via ligand-based pharmacophore modeling

Abstract

To discover potential antitumor agents directed toward human epidermal growth factor receptor-2HER2/ErbB2 overexpression in cancer, we have explored the pharmacophoric space of 115 HER2/ErbB2 inhibitors. This identified 240 pharmacophores which were subsequently clustered into 20 groups and cluster centers were used as 3D-pharmacophoric descriptors in QSAR analysis with 2D-physicochemical descriptors to select the optimal combination. We were obliged to use ligand efficiency as the response variable because the logarithmic transformation of bioactivities failed to access self-consistent QSAR models. Two binding pharmacophore models emerged in the optimal QSAR equation, suggesting the existence of distinct binding modes accessible to ligands within the HER2/ErbB2 binding pocket. The QSAR equation and its associated pharmacophore models were employed to screen the National Cancer Institute (NCI) and Drug Bank databases to search for new, promising, and structurally diverse HER2 inhibitory leads. Inhibitory activities were tested against HER2-overexpressing SKOV3 Ovarian cancer cell line and MCF-7 which express low levels of HER2. In silico mining identified 80 inhibitors out of which four HER2 selective compounds inhibited the growth of SKOV3 cells with IC50 values < 5 μM and with virtually no effect in MCF-7 cells. These lead compounds are excellent candidates for further optimization.