

2-(2,4,5-Substituted-anilino)pyrimidine Compounds 2 - (2, 4, 5 - SUBSTITUTED -ANILINO) PYRIMIDINE DERIVATIVES AS EGFR MODULATORS USEFUL FOR TREATING CANCER

The present invention relates to certain 2-(2,4,5-substituted-anilino)pyrimidine compounds and pharmaceutically salts thereof which may be useful in the treatment or prevention of a disease or medical condition mediated through certain mutated forms of epidermal growth factor receptor (for example the L858R activating mutant, the Exon19 deletion activating mutant and the T790M resistance mutant). Such compounds and salts thereof may be useful in the treatment or prevention of a number of different cancers. The invention also relates to pharmaceutical compositions comprising said compounds and salts thereof, especially useful polymorphic forms of these compounds and salts, intermediates useful in the manufacture of said compounds and to methods of treatment of diseases mediated by various different forms of EGFR using said compounds and salts thereof.

EGFR is a transmembrane protein tyrosine kinase member of the erbB receptor family. Upon binding of a growth factor ligand such as epidermal growth factor (EGF), the receptor can homo-dimerise with another EGFR molecule or hetero-dimerise with another family member such as erbB2 (HER2), erbB3 (HER3), or erbB4 (HER4).

Homo- and/or hetero-dimerisation of erbB receptors results in the phosphorylation of key tyrosine residues in the intracellular domain and leads to the stimulation of numerous intracellular signal transduction pathways involved in cell proliferation and survival. Deregulation of erbB family signalling promotes proliferation, invasion, metastasis, angiogenesis, and tumour cell survival and has been described in many human cancers, including those of the lung, head and neck and breast.

The erbB family therefore represents a rational target for anticancer drug development and a number of agents targeting EGFR or erbB2 are now clinically available, including gefitinib (IRESSATM), erlotinib (TARCEVATM) and lapatinib (TYKERBTM, TYVERBTM). Detailed reviews of erbB receptor signalling and its involvement in tumourigenesis are provided in *New England Journal of Medicine* (2008) Vol. 358,1160–74 and *Biochemical and Biophysical Research Communications* (2004) Vol. 319, 1–11.

In 2004 it was reported (*Science* [2004] Vol.304, 1497–500 and *New England Journal of Medicine* [2004] Vol. 350, 2129–39) that activating mutations in EGFR correlated with response to gefitinib therapy in non-small-cell lung cancer (NSCLC). The

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