

## New Product Highlights

### GW2974: A novel, dual epidermal growth factor receptor (EGFR)/ErbB-2 protein tyrosine kinase inhibitor

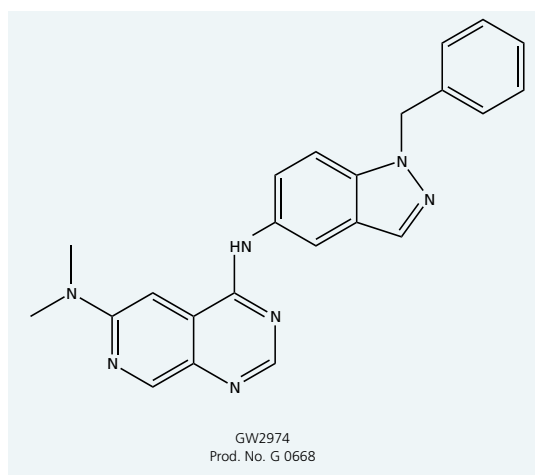
Protein tyrosine kinases (PTKs) are divided into two main classes, receptor PTKs and non-receptor PTKs. Receptor PTKs possess an extra-cellular ligand binding domain and an intra-cellular catalytic domain. Upon ligand binding, the receptor becomes activated, undergoes dimerization and autophosphorylates tyrosine residues outside the catalytic domain via cross-phosphorylation. The autophosphorylation creates phosphotyrosine docking sites for proteins which transduce signals within the cell. Epidermal growth factor receptor (EGFR; Prod. No. **E 3641**) and ErbB-2 are two members of the Type I (ErbB) family of receptor protein tyrosine kinases. Over-expression of both EGFR and ErbB-2, which have similar biochemical and kinetic properties, has been implicated in the development and progression of head and neck, gastric and breast cancers [1]. Therefore, the search for small molecule inhibitors to block Type I receptor protein tyrosine kinase signaling and prevent subsequent tumor growth has proven a focus of research.

Sigma-RBI is pleased to offer the dual EGFR/ErbB-2 protein tyrosine kinase inhibitor GW2974 (Prod. No. **G 0668**). GW2974 blocks the phosphorylation of a peptide substrate by either the EGFR or ErbB-2 kinase domain with  $IC_{50}$  values of 16 nM and 6 nM, respectively [1]. The compound demonstrates greater than 75-fold selectivity in inhibiting cell growth of breast carcinoma (BT474), gastric carcinoma (N87) and head/neck carcinoma (HN5) cell lines versus normal human foreskin fibroblasts (HFF) [1]. In CB-17 SCID mice bearing tumors from the BT474 cell line over-expressing ErbB-2, 95% inhibition of tumor growth was observed after 21 days of treatment with a dose of 30 mg/kg of GW2974 [1]. In CD-1 nude mice

bearing tumors from the HN5 cell line over-expressing EGFR, complete tumor inhibition was obtained utilizing the same dosage regimen [1]. Furthermore, when mice bearing tumors from both BT474 and HN5 cell lines were treated with 30 mg/kg doses of GW2974 for 5 days, phosphorylation of both receptors was inhibited by 90% while no changes in EGFR or ErbB-2 expression levels were observed [1].

Thus, GW2974 provides an exciting tool to study Type I receptor protein tyrosine kinase signaling and may assist in the discovery of additional potential cancer therapeutic agents.

*GW2974 is sold for research purposes under agreement from Glaxo Wellcome Inc. and Glaxo Group Limited.*



#### References

1. Rusnak, D.W., et al., *Cancer Res.*, **61**, 7196-7204 (2001).