

Summary

Chimeric molecules developed (combi-molecules) capable of blocking the tyrosine kinase domains of both Src and epidermal growth factor receptors (EGFR).
Quinazoline moiety (EGFR) and a 7-phenyl-pyrazolopyrimidine (Src)
Synthesis of SB162, SB166 and SB163.
SB163 with longest linker only dual inhibitor
SB163 also inhibits Abl and PDGFR.

Introduction

The non-receptor Src tyrosine kinase and the epidermal growth factor receptor are both involved in tumour metastasis, Inhibitors of both have potential as anti-cancer agents.
Molecular modelling of known EGFR / Src inhibitors.
Quinazoline pharmacophore (EGFR) and purine moiety (Src)
Binding modes used to rationalize design of chimeric structures SB162, SB163 and SB166

Key new finding in this study

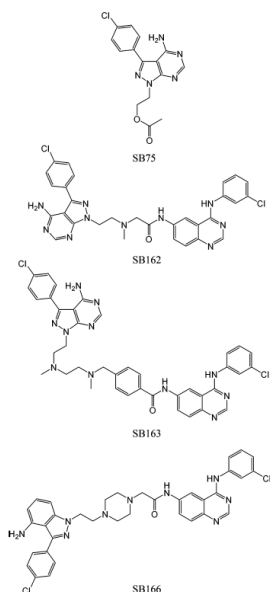
Rational design of inhibitor that specifically interacts with more than one tyrosine kinase implicated in cancer.

Methods

Crystal structures of EGFR PDB complex (PDB code 1M17) and Src complexes (PDB codes 2H8H, 1YOM, 1YOL, 1QCF, 2BDF, 2BDJ) downloaded from PDB
MOE 2007.081 used for molecular modelling and protein alignments
Synthesised compounds tested in tyrosine kinase using purified enzymes.

Results

Purine binding to the Src pocket occurs in two modes; both evaluated by molecular modelling as starting point for dual inhibitors.
Quinazoline groups joined with available linkers to aminopurine group
Molecules synthesised and tested in kinase assays.



SB75 designed as a Src inhibitor for linkage to the substituted quinazolines (IC50 0.9 μ M)
SB163 inhibits EGFR (IC50 = 0.32 μ M) and Src with (IC50 of 2.9 μ M) also induced dose-dependent inhibition of Abl and PDGFR.
SB162 and SB166, (both with short spacers) were inactive.

SB163 is being evaluated further: Saade K., Todorova M., Barchechat S., Williams C., Jean-Claude B. (2008) Identification of a potent anti-invasive molecule through mixed targeting design: a novel approach in drug development against breast cancer. Submitted.

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Key Background References

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