A MIM depicting intramolecular domains, their modifications and molecular interactions:

Activation of src by EGFR
Src has the following domains:
SH3: binds to proline-rich domains
SH2: binds to phosphotyrosine motifs
Pro: proline-rich domain
kinase: tyrosine kinase domain

The SH3 domain binds the Pro domain.
The Src tail region can be phosphorylated at Tyr 527.
The SH2 domain binds to the tyrosine-phosphorylated tail.
The 2 intra-molecular bonds form cooperatively, and fold the Src molecule, hiding the kinase domain and keeping Src in an inactive configuration.
Src binds to plasma membrane through a myristyl group.
Src’s tyrosine kinase domain could phosphorylate various substrates.
Phosphorylation of Tyr416 is required for the kinase to be active.
Activated (phosphorylated) EGFR could phosphorylate Tyr416.
However, access to Tyr416 is blocked by the intra-molecular folding.
SRC activation:
Through one of its phosphotyrosines, activated EGFR recruits p85.

EGFR

Plasma membrane

p85-PI3K
SH3 Pro SH2

Myristyl

Src SH3 SH2 Pro kinase tail

pY416 pY527

Substrates

pY
Pro domain of p85 competes with Pro of Src for binding to SH3 of Src.

If binding is to p85, then this inhibition is relieved.
Phosphotyrosine of EGFR competes with P-Tyr527 of Src for binding to SH2 of Src.
With Tyr527 gone, Src cannot refold and remains active even if it dissociates from the EGFR:p85 complex. Thus multiple Src’s can be activated by a single active EGFR -- *i.e.*, an amplification step.

Kohn, K.W. 2001 Chaos 11:84-97
A dynamic animated map of Src activation by EGFR
(press the arrow keys to follow the interactions)
Summary of src activation
(no need to press any key)