Claims

1. An allosteric inhibitor binding site, derived from the extracellular domain of a tyrosine kinase receptor.

2. An allosteric inhibitor binding site according to claim 1, whereby said binding site is derived from a tyrosine kinase receptor with an Ig domain.

3. An allosteric inhibitor binding site, according to claim 1 or 2, whereby binding of an inhibitor to said binding site induces a biased antagonism.

4. An allosteric inhibitor binding site according to any of the previous claims, whereby said binding site comprises a frustrated domain.

5. An allosteric inhibitor binding site according to any of the previous claims, whereby said tyrosine kinase receptor is the Fibroblast Growth Factor receptor, the Vascular Endothelial Growth Factor Receptor or the Platelet Derived Growth Factor Receptor, or a homolog, paralog or otholog thereof.

6. An allosteric inhibitor binding site according to any of the previous claims, consisting in SEQ ID N° 1:

His Val Glu Lys Asn Gly Ser Lys Tyr Gly Pro Asp Gly Leu Pro Tyr

Leu Lys Val Leu Lys Ala Ala Gly Val Asn Thr Thr Asp Lys Glu Ile

Glu Val Leu Tyr Ile Arg Asn

or a sequence presenting at least 70%, 80%, 90% or 95% of homology with SEQ ID NO.1

7. A frustrated binding site according to claim 4, consisting in SEQ ID NO.2

Leu Lys Ala Ala Gly Val Asn Thr Thr Asp Lys Glu Ile Glu Val Leu Tyr Ile Arg Asn

or a sequence presenting at least 70%, 80%, 90% or 95% of homology with SEQ ID NO.2

8. The use of an allosteric inhibitor binding site according to claim 1-6 to induce a biased antagonism in a tyrosine kinase receptor pathway.

9. The use of an allosteric inhibitor binding site according to claim 1-7 to screen for small compound inhibitors

10. A method for identification of an allosteric inhibitor binding site in the extracellular domain of a tyrosine kinase receptor, comprising the screening of frustrated domains in said extracellular domain.

11. A method for identificationof a small compound allosteric inhibitor binding to an allosteric inhibitor site in the extracellular domain of a tyrosine kinase receptor according to claim 1-7 comprising the comparison of at least two different reporters induced by two different downstream pathways dependent upon the activation/inhibition of said tyrosine kinase receptor.

12. A method for identification of an allosteric inhibitor of a RTK, comprising the steps of:

a) contacting an allosteric binding site of a RTK with a small compound allosteric inhibitor candidate compound

b) measuring the changes in at least two downstream pathways dependent upon the activation/inhibition of said tyrosin kinase receptor.

c) comparing changes in state of at least one reporters for at least two different downstream pathways dependent upon the activation/inhibition of said tyrosin kinase receptor.

wherein an allosteric inhibitor is identified when, in presence of a ligand binding to the ligand binding domain of the receptor, at least one downstream pathway is inhibited whereas at least one other downstream pathway is unaffected.

13. A method for identification of an allosteric inhibitor of a RTK, according to claim 12, wherein the said two different downstream pathways correspond to the ERK1/2 signalling pathway and the PLCγ signalling pathway.14. A compound binding to an allosteric binding site according to any of the claims 1-6, wherein said compound is a small molecule.

Claims

~~14.~~1. The use of an allosteric inhibitor binding site consisting of either SEQ ID NO. 1 or a sequence presenting at least 70%, 80%, 90% or 95% of homology with SEQ ID NO.1, to screen for small compound inhibitors of FGFR, said inhibitors having a molecular weight of less than 1000 D.

~~15.~~2. A method for identification of a putative allosteric inhibitor binding site in the extracellular domain of a FGFR, comprising the screening of frustrated domains in said extracellular domain using a protein secondary structure prediction program or programs, to identify those domains, or fragments thereof, in said extracellular domain that are not unambiguously directed towards one structural conformation.

~~16.~~3. A method according to claim ~~15~~2 wherein said domains, or fragments thereof, are prone to undergo β-sheet to α-helix transitions.

~~17.~~4. A method for identification of a small compound allosteric inhibitor of a RTK binding to an allosteric inhibitor site in the extracellular domain of a tyrosine kinase receptor comprising

- contacting an allosteric binding site of a RTK with the small compound allosteric inhibitor candidate compound, and
- comparing the changes in the state of at least two different reporters induced by two different downstream pathways dependent upon the activation/inhibition of said tyrosine kinase receptor,

wherein said small compound inhibitor has a molecular weight of less than 1000 D.

~~18.~~5. A method according to claim ~~17~~4 wherein an allosteric inhibitor is identified when, in presence of a ligand binding to the ligand binding domain of the receptor, at least one downstream pathway is inhibited whereas at least one other downstream pathway is unaffected.

~~19.~~6. A method according to claim ~~17~~4 or ~~18~~5, wherein the tyrosine kinase is an FGFR.

~~20.~~**7.** A method according to claim ~~19~~6, wherein the FGFR is chosen from one of FGFR-1, FGFR-2, FGFR-3 or FGFR-4.

~~21.~~**8.** A method for identification of an allosteric inhibitor of a RTK, according to any of claims ~~17~~4 to ~~20~~7, wherein the said two different downstream pathways correspond to the ERK1/2 signalling pathway and the PLCγ signalling pathway.