ATP Site Ligands Determine the Assembly State of the Abelson Kinase Regulatory Core via the Activation Loop Conformation

ID 4488528
Author(s) Sonti, Rajesh; Hertel-Hering, Ines; Lamontanara, Allan Joaquim; Hantschel, Oliver; Grzesiek, Stephan
Author(s) at UniBasel Grzesiek, Stephan ; Sonti, Rajesh ; Hertel-Hering, Ines ;
Year 2018
Title ATP Site Ligands Determine the Assembly State of the Abelson Kinase Regulatory Core via the Activation Loop Conformation
Journal Journal of the American Chemical Society
Volume 140
Number 5
Pages / **Article-Number** 1863-1869
Mesh terms Adenosine Triphosphate, chemistry, metabolism; Binding Sites; Ligands; Models, Molecular; Protein Conformation; Proto-Oncogene Proteins c-abl, chemistry, metabolism
The constituent SH3, SH2, and kinase domains of the Abl kinase regulatory core can adopt an assembled (inactive) or a disassembled (active) conformation. We show that this assembly state strictly correlates with the conformation of the kinase activation loop induced by a total of 14 ATP site ligands, comprising all FDA-approved Bcr-Abl inhibiting drugs. The disassembly of the core by certain (type II) ligands can be explained by an induced push on the kinase N-lobe via A- and P-loop toward the SH3 domain. A similar sized P-loop motion is expected during nucleotide binding and release, which would be impeded in the assembled state, in agreement with its strongly reduced kinase activity.
Publisher American Chemical Society
ISSN/ISBN 1520-5126
URL https://pubs.acs.org/doi/10.1021/jacs.7b12430
edoc-URL https://edoc.unibas.ch/67050/
Full Text on edoc Restricted;
Digital Object Identifier DOI 10.1021/jacs.7b12430
PubMed ID http://www.ncbi.nlm.nih.gov/pubmed/29319304
Document type (ISI) Journal Article