Year of publication 2009

Thi My-Nhung Hoang, Bertrand Favier, Annie Valette, Caroline Barette, Chi Hung Nguyen, Laurence Lafanechère, David S Grierson, Stéfan Dimitrov, Annie Molla (2009 Feb 18)

Benzo[e]pyridoindoles, novel inhibitors of the aurora kinases.

Cell cycle (Georgetown, Tex.) : 765-72

Summary

Aurora kinases are serine/threonine protein kinases that are involved in cancer development and are important targets for cancer therapy. By high throughput screening of a chemical library we found that benzo[e]pyridoindole derivatives inhibited Aurora kinase. The most potent compound (compound 1) was found to be an ATP competitive inhibitor, which inhibited in vitro Aurora kinases at the nanomolar range. It prevented, ex vivo, the phosphorylation of Histone H3, induced mitosis exit without chromosome segregation, known phenomena observed upon Aurora B inactivation. This compound was also shown to affect the localization of Aurora B, since in the presence of the inhibitor the enzyme was delocalized on the whole chromosomes and remained associated with the chromatin of newly formed nuclei. In addition, compound 1 inhibited the growth of different cell lines derived from different carcinoma. Its IC(50) for H358 NSCLC (Non Small Cancer Lung Cells), the most sensitive cell line, was 145 nM. Furthermore compound 1 was found to be efficient towards multicellular tumor spheroid growth. It exhibited minimal toxicity in mice while it had some potency towards aggressive NSCLC tumors. Benzo[e]pyridoindoles represent thus a potential new lead for the development of Aurora kinase inhibitors.

Year of publication 2008

Renaud Prudent, Miriam López-Ramos, Virginie Moucadel, Caroline Barette, David Grierson, Liliane Mouawad, Jean-Claude Florent, Laurence Lafanechère, Frédéric Schmidt, Claude Cochet (2008 Aug 5)

Salicylaldehyde derivatives as new protein kinase CK2 inhibitors.

Biochimica et biophysica acta : 1412-20 : DOI : 10.1016/j.bbagen.2008.06.010

Summary

Protein kinase CK2 is a Ser/Thr kinase, with a constitutive activity, that is considered as a promising target for cancer therapy. The currently available CK2 inhibitors lack the potency and the pharmacological properties necessary to be suitable and successful in clinical settings. We report the development of new potent CK2 inhibitors from salicylaldehyde derivatives identified by automated screening of a proprietary small-molecule library. Docking simulations and analysis of the structure-activity relationship for the hits allowed to determine their binding modes on CK2, and to carry out the optimization of their structures. This strategy led to the discovery of potent CK2 inhibitors with novel structures, one of which was able to inhibit CK2 activity in living cells and promote tumor cell death. The essential features required for potent CK2 inhibitory activity of this class of compounds are discussed.

Renaud Prudent, Virginie Moucadel, Miriam López-Ramos, Samia Aci, Beatrice Laudet, Liliane Mouawad, Caroline Barette, Jacques Einhorn, Cathy Einhorn, Jean-Noel Denis, Gilles Bisson, Frédéric Schmidt, Sylvaine Roy, Laurence Lafanechere, Jean-Claude Florent, Claude Cochet (2008 Jun 20)

Expanding the chemical diversity of CK2 inhibitors.

Molecular and cellular biochemistry : 71-85 : DOI : 10.1007/s11010-008-9828-z

Summary

None of the already described CK2 inhibitors did fulfill the requirements for successful clinical settings. In order to find innovative CK2 inhibitors based on new scaffolds, we have performed a high-throughput screening of diverse chemical libraries. We report here the identification and characterization of several classes of new inhibitors. Whereas some share characteristics of previously known CK2 inhibitors, others are chemically unrelated and may represent new opportunities for the development of better CK2 inhibitors. By combining structure-activity relationships with a docking procedure, we were able to determine the binding mode of these inhibitors. Interestingly, beside the identification of several nanomolar ATP-competitive inhibitors, one class of chemical inhibitors displays a non-ATP competitive mode of inhibition, a feature that suggests that CK2 possess distinct druggable binding sites. For the most promising inhibitors, selectivity profiling was performed. We also provide evidence that some chemical compounds are inhibiting CK2 in living cells. Finally, the collected data allowed us to draw the rules about the chemical requirements for CK2 inhibition both in vitro and in a cellular context.

Year of publication 2007

Nadia Bakkour, Yea-Lih Lin, Sophie Maire, Lilia Ayadi, Florence Mahuteau-Betzer, Chi Hung Nguyen, Clément Mettling, Pierre Portales, David Grierson, Benoit Chabot, Philippe Jeanteur, Christiane Branlant, Pierre Corbeau, Jamal Tazi (2007 Oct 31)

Small-molecule inhibition of HIV pre-mRNA splicing as a novel antiretroviral therapy to overcome drug resistance.

PLoS pathogens : 1530-9

Summary

The development of multidrug-resistant viruses compromises antiretroviral therapy efficacy and limits therapeutic options. Therefore, it is an ongoing task to identify new targets for antiretroviral therapy and to develop new drugs. Here, we show that an indole derivative (IDC16) that interferes with exonic splicing enhancer activity of the SR protein splicing factor SF2/ASF suppresses the production of key viral proteins, thereby compromising subsequent synthesis of full-length HIV-1 pre-mRNA and assembly of infectious particles. IDC16 inhibits replication of macrophage- and T cell-tropic laboratory strains, clinical isolates, and strains with high-level resistance to inhibitors of viral protease and reverse transcriptase. Importantly, drug treatment of primary blood cells did not alter splicing profiles of

endogenous genes involved in cell cycle transition and apoptosis. Thus, human splicing factors represent novel and promising drug targets for the development of antiretroviral therapies, particularly for the inhibition of multidrug-resistant viruses.

Sébastien Durand, Nicolas Cougot, Florence Mahuteau-Betzer, Chi-Hung Nguyen, David S Grierson, Edouard Bertrand, Jamal Tazi, Fabrice Lejeune (2007 Sep 26)
Inhibition of nonsense-mediated mRNA decay (NMD) by a new chemical molecule reveals the dynamic of NMD factors in P-bodies.
The Journal of cell biology : 1145-60

Summary

In mammals, nonsense-mediated mRNA decay (NMD) is a quality-control mechanism that degrades mRNA harboring a premature termination codon to prevent the synthesis of truncated proteins. To gain insight into the NMD mechanism, we identified NMD inhibitor 1 (NMDI 1) as a small molecule inhibitor of the NMD pathway. We characterized the mode of action of this compound and demonstrated that it acts upstream of hUPF1. NMDI 1 induced the loss of interactions between hSMG5 and hUPF1 and the stabilization of hyperphosphorylated isoforms of hUPF1. Incubation of cells with NMDI 1 allowed us to demonstrate that NMD factors and mRNAs subject to NMD transit through processing bodies (P-bodies), as is the case in yeast. The results suggest a model in which mRNA and NMD factors are sequentially recruited to P-bodies.

Year of publication 2006

Alexandra Erve, Yasmina Saoudi, Sylvie Thirot, Corinne Guetta-Landras, Jean-Claude Florent, Chi-Hung Nguyen, David S Grierson, Andrei V Popov (2006 Mar 21)
BENA435, a new cell-permeant photoactivated green fluorescent DNA probe.
Nucleic acids research : e43

Summary

N'-(2,8-Dimethoxy-12-methyl-dibenzo [c,h] [1,5] naphthyridin-6-yl)-N,N-dimethyl-propane-1,3-diamine (BENA435) is a new cell-membrane permeant DNA dye with absorption/emission maxima in complex with DNA at 435 and 484 nm. This new reagent is unrelated to known DNA dyes, and shows a distinct preference to bind double-stranded DNA over RNA. Hydrodynamic studies suggest that BENA435 intercalates between the opposite DNA strands. BENA435 fluoresces much stronger when bound to dA/dT rather than dG/dC homopolymers. We evaluated 14 related dibenzonaphthyridine derivatives and found BENA435 to be superior in its in vivo DNA-binding properties. Molecular modelling was used to develop a model of BENA435 intercalation between base pairs of a DNA helix. BENA435 fluorescence in the nuclei of cells increases upon illumination, suggesting photoactivation. BENA435 represents thus the first known cell-permeant photoactivated DNA-binding dye.

Year of publication 2005

Johann Soret, Nadia Bakkour, Sophie Maire, Sébastien Durand, Latifa Zekri, Mathieu Gabut, Weronika Fic, Gilles Divita, Christian Rivalle, Daniel Dauzonne, Chi Hung Nguyen, Philippe Jeanteur, Jamal Tazi (2005 Jun 9)

Selective modification of alternative splicing by indole derivatives that target serine-arginine-rich protein splicing factors.

Proceedings of the National Academy of Sciences of the United States of America : 8764-9

Summary

The prevalence of alternative splicing as a target for alterations leading to human genetic disorders makes it highly relevant for therapy. Here we have used in vitro splicing reactions with different splicing reporter constructs to screen 4,000 chemical compounds for their ability to selectively inhibit spliceosome assembly and splicing. We discovered indole derivatives as potent inhibitors of the splicing reaction. Importantly, compounds of this family specifically inhibit exonic splicing enhancer (ESE)-dependent splicing, because they interact directly and selectively with members of the serine-arginine-rich protein family. Treatment of cells expressing reporter constructs with ESE sequences demonstrated that selected indole derivatives mediate inhibition of ESE usage in vivo and prevent early splicing events required for HIV replication. This discovery opens the exciting possibility of a causal pharmacological treatment of aberrant splicing in human genetic disorders and development of new antiviral therapeutic approaches.