

BIKINS, INNOVATIVE KINASE INHIBITOR LIBRARIES

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PROTEIN KINASE INHIBITORS, AN ATTRACTIVE MARKET

Kinases are a large family of protein that have now become firmly established as a major class of drug targets for the pharmaceutical industry. Inhibition of the kinase function is a potential therapeutic approach for the treatment of cancers, immune-mediated, CNS, metabolic and infectious diseases.¹

Since Imatinib (Gleevec®) in 2001, U.S. FDA has approved about 28 kinases inhibitors, half of which during the last 3 years.² Until now, only a small subset of the kinome has been targeted while the human genome encodes for approximately 518 kinases. Moreover, many of the current inhibitors are built on the same pharmacophore. Therefore, there is an urgent need for new types of scaffolds.

We have developed three innovative kinase inhibitor libraries (BiKin 1-3) based on novel chemotypes.

¹ Cohen and Alessi, *ACS Chem Biol.*, 2013, 8, 96-104,

² Wu et al., *Trends in Pharmacological Sciences*, 2015, in press, doi:10.1016/j.tips.2015.04.005

Global revenue of kinase inhibitors market 2009-2016, \$ Billions

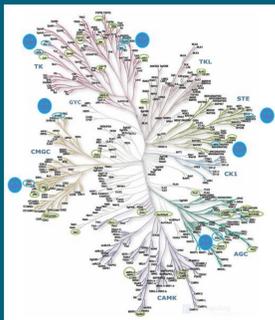
Source: BCC Research, report code BIO053C



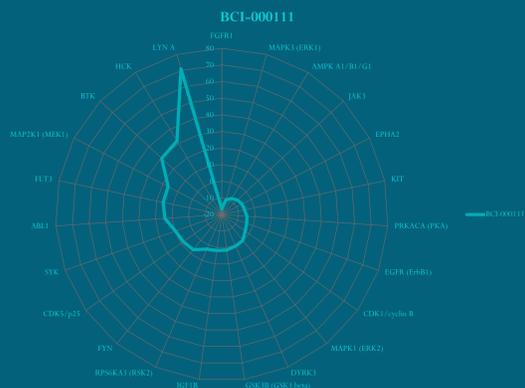
BIKIN 1, A MULTI-TARGET LIBRARY

BiKin 1 compounds are a diverse set of molecules built around a new scaffold. This library explores a large and novel chemical space and satisfies rules for a drug-like compound with low molecular weight and high aqueous solubility.

The screening on a diversified panel of 25 to 48 kinases has revealed interesting and promising results. First, our compounds are actives against a large part of the kinome. Second, the compounds profiling can be modified by only a small chemical modification.



Activity found



BiKin 1 has a real potential to be the starting point of a research program

BIKIN 2, A NEW GENERATION OF FLT3 INHIBITORS

BiKin 2 screening identified a relevant inhibitors series of FLT3 kinase, a validated therapeutic target in Acute Myeloid Leukemia^{3,4} and autoimmune disease⁵.

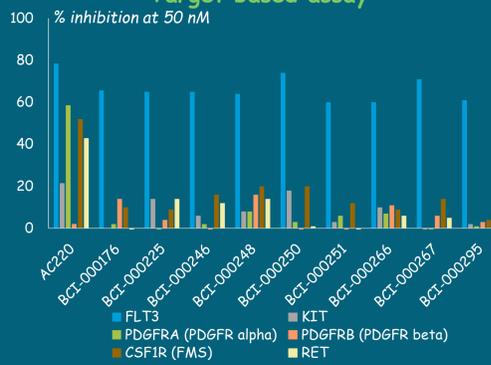
Hit optimization led to highly potent inhibitors of FLT3, showing inhibitory potencies in the low nanomolar range against both wild-type and mutants similar to AC220 (Quizartinib, currently in phase III).

Activity : Inhibition of BiKin 2 compounds against FLT3 wt and mutants



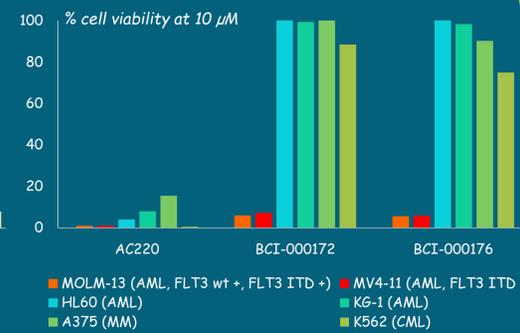
Selectivity of BiKin 2 compounds

Target based assay



Only FLT3 kinase is affected by BCI compounds

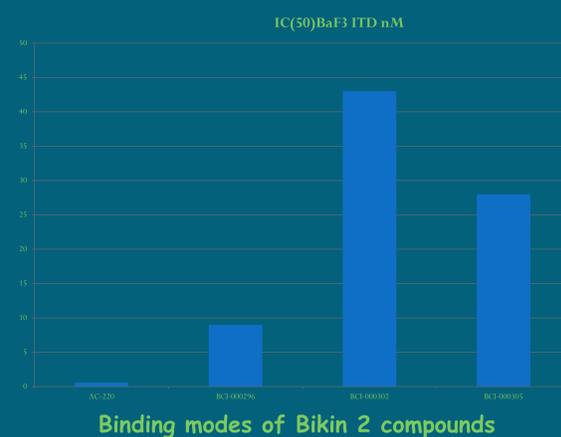
Cell based assay



Only cells expressing FLT3 are affected by BCI compounds

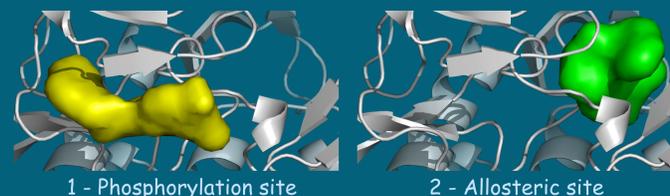
BiKin 2 compounds also show a strong selectivity toward the other related kinases, commonly targeted by the FLT3 inhibitors. Furthermore, contrary to AC220, our compounds exhibit potent and selective activities against human leukemia cell lines overexpressing FLT3 wt and/or FLT3 ITD (MOLM-13 and MV4-11).

IC₅₀ (nM) BaF3 cell expressing FLT3-ITD



Binding modes of BiKin 2 compounds

Our FLT3 inhibitors seem to have a new and unprecedented mode of binding with IC₅₀ values decreasing with the ATP concentration. Molecular modeling and docking studies highlighted two potential binding modes:



³ Wander et al., *Ther Adv Hematol*, 2014, 5, 65-77.

⁴ Grunwald and Lewis, *Int J Hematol*, 2013, 97, 683-694.

⁵ Wartenby et al., *Expert Opin. Investig. Drugs*, 2008, 17, 1685-1692.

BIKINS, POTENT AND SELECTIVE LIBRARIES

We have demonstrated that our first two innovative libraries are effective kinase inhibitors, the third one is currently in development. Our drug-like compounds based on a new chemotype, were also found to be selective with an adjustable profile.

Indeed, small modifications on the scaffold of BiKin 1 enable to reach different targets of the kinome and thus enable to specifically choose the desired kinase. Besides, BiKin 2 is a promising FLT3 inhibitors library with IC₅₀ in the low nanomolar range and selective *in vitro* and *in cellulo* activities.

So if you are interested in our kinase inhibitor libraries, please contact us... We would be pleased to collaborate with you!