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]

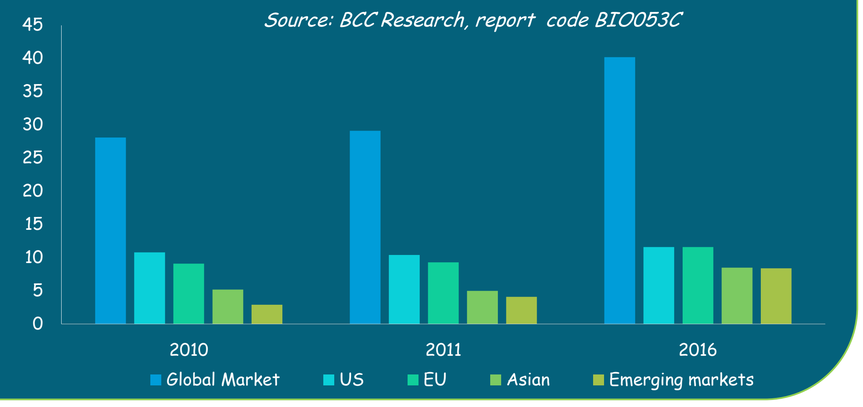
Since Imatinib (Gleevec®) in 2001, U.S. FDA has approved about 28 kinases inhibitors, half of which during the last 3 years.[2] Until now, only a small subset of the kinome has been targeted while the human genome encodes for approximately 518 kinases. Moreover, many of the current inhibitors are built 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

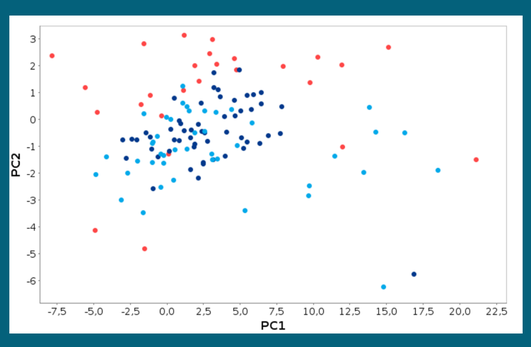
Global revenue of kinase inhibitors market
2009-2016, $ Billions

Source: BCC Research, report code BIO053C



BIKIN 1, A MULTI-TARGET LIBRARY

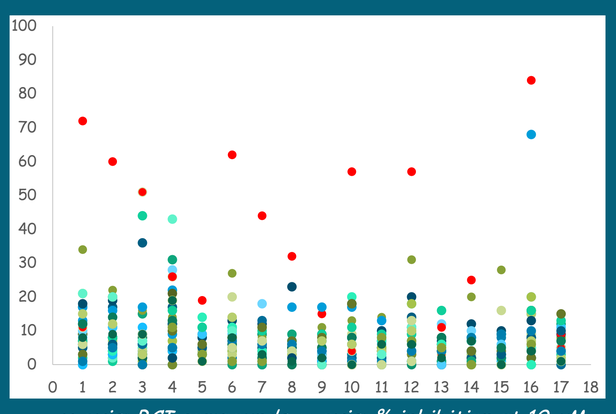
BiKin 1 compounds are a diverse set of molecules built around a new scaffold. This library explores a large and novel chemical space and satisfies rules for a drug-like compound with low molecular weight and high aqueous solubility.

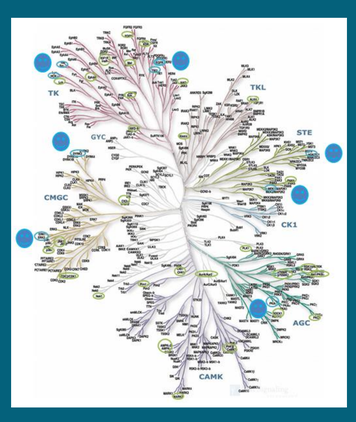


Chemical diversity of BCI compounds

blue dots represent the chemical space of BCI Pharma kinase inhibitors and the red dots the chemical space of approved kinase inhibitors

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.





BiKin 1 compounds profiling kinase activities

Examples of SAR:

BCI compounds	LCK	HGK	SRC	TIE2
BCI-000054	83	64	56	50
BCI-000110	89	15	76	26
BCI-000111	80	14	50	91
BCI-000112	16	3	12	1
BCI-000128	84	13	62	41

% inhibition at 10 µM

All compounds are BCI-000054 analogues

BCI compounds	MEK1	ERK2	ERK1
BCI-000004	59	43	37
BCI-000106	89	75	66
BCI-000107	40	27	26
BCI-000108	73	54	49

% inhibition at 10 µM

All compounds are BCI-000004 stereoisomers

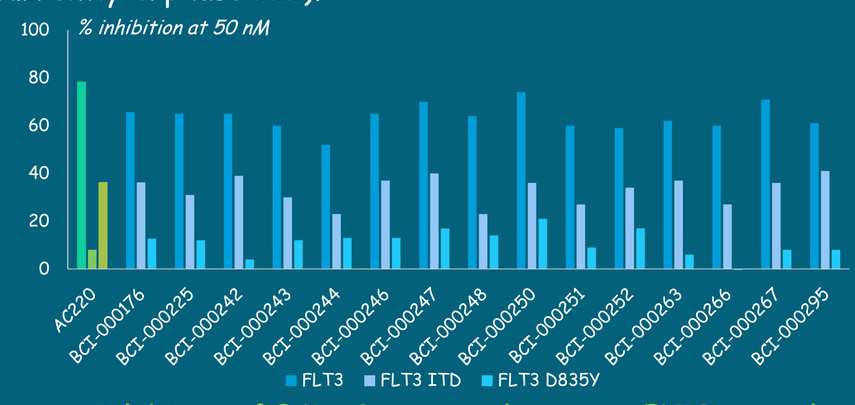
⇨Small modification has a huge impact on the potency and the selectivity

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

BIKIN 2, A NEW GENERATION OF FLT3 INHIBITORS

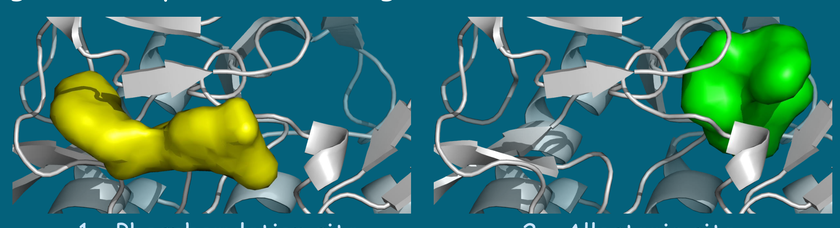
BiKin 2 screening identified a relevant inhibitor series of FLT3 kinase, a validated therapeutic target in Acute Myeloid Leukemia[3,4] and autoimmune disease[5].

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).



Inhibition of BiKin 2 compounds against FLT3 wt and mutants

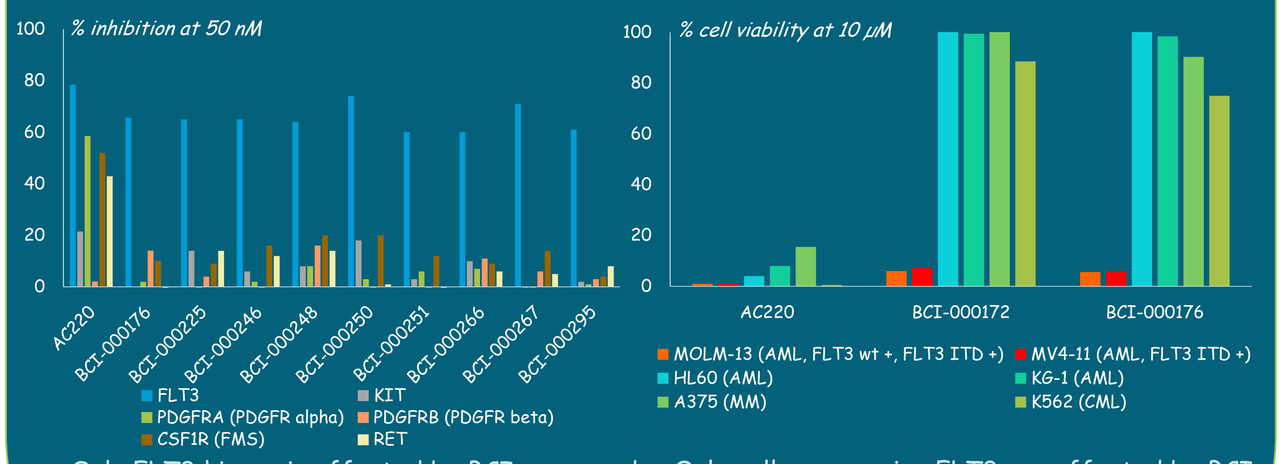
Our FLT3 inhibitors seem to have a new and unprecedented mode of binding with IC50 values decreasing with the ATP concentration. Molecular modeling and docking studies highlighted two potential binding modes:



1 - Phosphorylation site 2 - Allosteric site

Binding modes of BiKin 2 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).



Only FLT3 kinase is affected by BCI compounds Only cells expressing FLT3 are affected by BCI compounds

Selectivity of BiKin 2 compounds

[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!

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