SELECTED OPPORTUNITY IN ONCOLOGY

Novel B-Raf inhibitors devoid of rapid metabolism and of binding to Pregnane X Receptor (BIO18530)

NOVEL B-RAF INHIBITORS DEVOID OF RAPID METABOLISM AND OF BINDING TO PREGNANE X RECEPTOR

Product factsheet

Preclinical

- **Target:** B-Raf sérine/thréonine kinase
- **Application:** Melanoma, lung cancer, colorectal cancer and gastro-intestinal stromal cancer
- **Potential Product** : N-(3-(5-(PYRIMIDIN-4-YL)THIAZOL-4-YL)PHENYL)SULFONAMIDE compounds devoid of rapid metabolism and of binding to Pregnane X Receptor (PXR).
- **Rationale:**

- Mutation B-Raf V600E is found in nearly 15% of all cancers and especially in melanoma, lung cancer, colorectal cancer and gastro-intestinal stromal cancer

- Vemurafenib and Dabrafenib (the two B-RAF marketed inhibitors) strongly activate the PXR

- This behavior explains the rapid metabolization and the accelerated clearance and hence the lack of efficiency. Furthermore, this unwanted PXR activation also impairs its combination with other drug treatments in particular MEK inhibitors

Patent Applications : EP19306579.4 : N-(3-(5-(PYRIMIDIN-4-YL)THIAZOL-4-YL)PHENYL)SULFONAMIDE COMPOUNDS AND THEIR USES.

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Novel B-Raf inhibitors devoid of rapid metabolism and of binding to Pregnane X Receptor

Proof of concept

Preclinical

	IC50 dabrafenib/ IC50 compound BRAF activity	EC50 dabrafenib/ EC50 compound PXR activity
Dabrafenib	**1**	**1**
GL176	0,79	0,067
GL184	**0,53**	**0,0018**
GL191	**0,9**	**0,00042**
GL195	*0,25*	*0,0012*
GL214	0,76	0,43
GL215	**0,69**	**0,0024**
GL222	0,05	0,00045
GL223	0,16	0,0051
GL224	0,5	0,01
GL229	0,007	0,0012

New B-Raf inhibitors with potency as high as Dabrafenib but devoid of any significant activation of PXR. The novel compounds are highly effective in inhibiting the purified enzyme (in mutated and wild-type forms), with activity in the low nanomolar range (1-6 nM). They also showed strong activity on in vitro cell cultures A375. In addition, they showed little or no activation of PXR on a cell-based reporter assay (less than 0.2 % of Dabrafenib activity).

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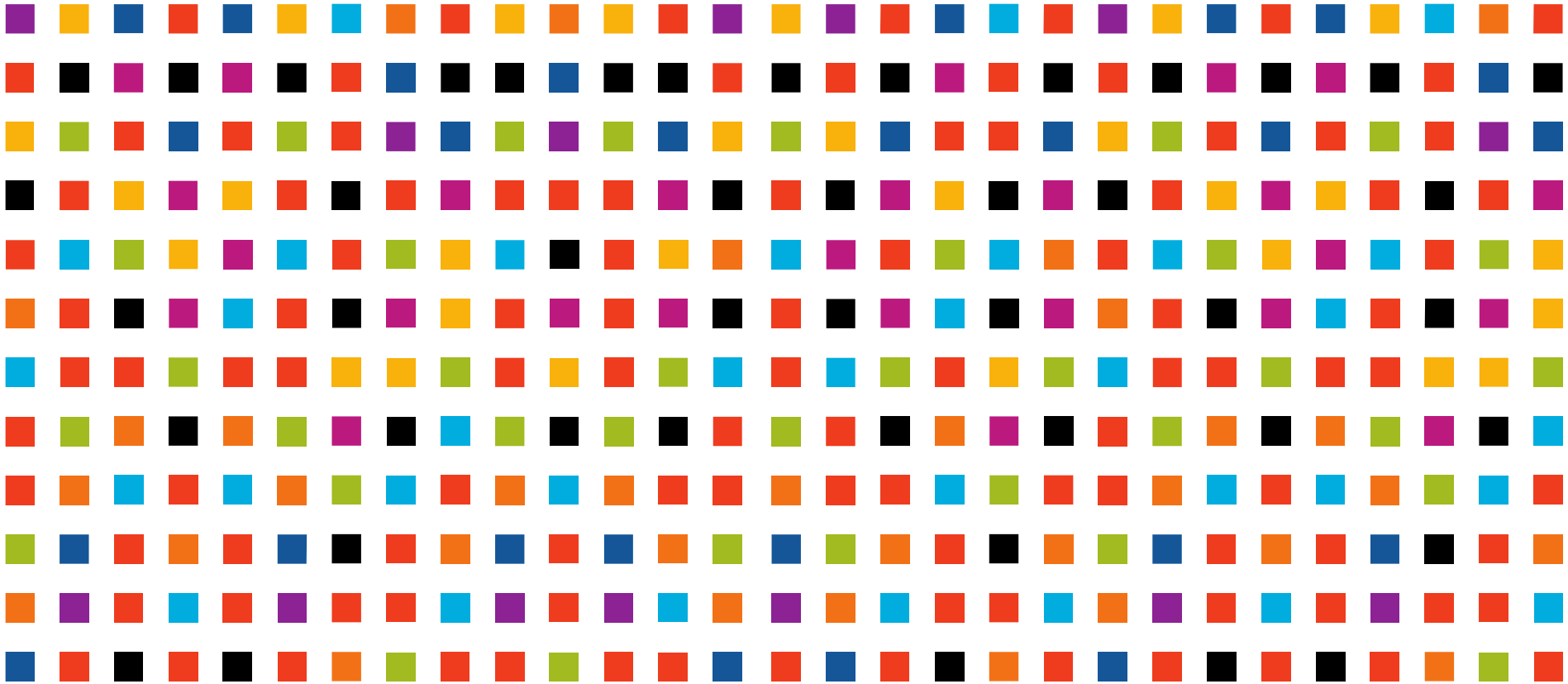

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