Towards a Bioisosteric Alkaest:
application to the bioisosteric modulation of IMD-0354.

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Bio(iso)steric replacement is a powerful tool for the medicinal chemist. Two functional groups should be called isoster if they share similar physico-chemical properties and bioisoster if they have the same biological profile. It could be said that while chemistry rules the isosteric similarity between groups, only the biological target will be able to answer positively to the following bioisosteric hypothesis.

In this study, the implementation of the BA toward the structure of IMD-0354, a potent antiinflammatory agent claimed to selectively inhibit IKKβ, is presented. Ideally starting from IMD-0354 structure, the bioisosteric substitution of the acidic phenolic substructure with a substituted hydroxylated heterocyclic should mimic the phenol role and also generate additional binding opportunities. In the following the characterization of the mechanism of action of IMD-0354 is presented together with the investigation of the activity profile on TKT0001 (structure not shown).

Characterization of the mechanism of action of IMD-0354

1. IMD-0354 potently inhibits the TNFα dependent activation of the canonical NF-κB signaling pathway

2. IMD-0354 does not show inhibitory activity on isolated WT or constitutively active IKKβ

3. IMD-0354 shows only modest inhibitory activity against IKK complex purified from TNFα stimulated Jurkat cells

Bibliography

“Bioisosteric Alkaest”

An universal bioisosteric substitution able to afford always optimized compounds….

The word “alkahest” came directly from the alchemist’s word. It reflects the importance at those times of the search of the universality in properties. As for alchemists, the term “alkahest” when applied to bioisosteric represents a dream for any medicinal chemist: the finding of such bioisosteric universal tool that, avoiding any biological target judgment, when applied to a structure is always able to afford compounds optimized in terms of biological properties.

TAKTIC is a consortium focused on targeting kinases and has been widely used as tool for reach IP value. In this occasion the first results are discussed.

The application of the Bioisosteric Alkaest to the IMD-0354 structure afforded a series of analogues. Inside them, TKT0001 was found to bioisosterically be able to mimic the IMD-0354 profile increasing the activity on Jurkat cells to submicroM.

Conclusions

Although IMD-0354 potently inhibits the TNFα dependent activation of the canonical NF-κB signaling pathway in intact cells, neither isolated IKK nor the trimeric IKK complex appear to be a high affinity target for IMD-0354. Also TKT0001 seems to act in the same way although with higher potency.