MULTITARGET TRIAZOLES: AN INNOVATIVE APPROACH FOR THE TREATMENT OF ALZHEIMER'S DISEASE

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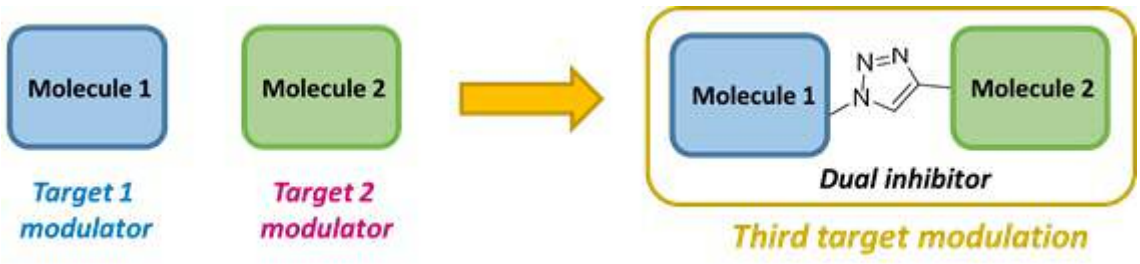
Multitarget drugs are molecular entities that are designed to present more than one biological activity. They are arising as powerful tools to tackle complex diseases including bacterial resistances, cancer or neurodegenerative diseases. Typically, the rational strategies to design multitarget drugs are linkage, fusion and incorporation or merge. Here we present the creation of a multitarget drug combining active fragments in a way that could inhibit an additional third target with the objective to create powerful modulating agents for neurodegenerative diseases. Multitarget compounds are ideally suited for the treatment of these pathologies due to their unknown etiology, multifactorial pathology and lack of efficient treatments. To achieve this aim we have combined fragments that inhibit kinases involved in the main pathomolecular pathways of Alzheimer's disease such as tau aggregation, neuroinflammation and decreased neurogenesis, looking for a third action in BACE1, responsible of β-amyloid production. To synthesize the multitarget compounds we have employed the copper(I)-catalyzed alkyne-azide cycloaddition (CuAAC)[1,2] methodology to obtain the 1,4-disubstituted triazoles. The synthesized triazoles exhibited three inhibitory activities against the desired targets.
Finally, and after the successful results obtained using this methodology, we have started to implement the in situ click chemistry technique[3] to better select the multitarget compounds using BACE1 as a template.



References

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