Identification of a new class of highly selective inhibitors of casein kinase 1

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Recently, we identified potent and highly selective inhibitors of casein kinase 1 (CK1). Individual isoforms of CK1 play pivotal roles in some key cellular signaling pathways. Thus, they have been recently recognized as attractive targets for pharmacological inhibition, especially in the context of the treatment of acute myeloid leukemia (AML)[1,2] and chronic lymphocytic leukemia (CLL).[3] In the preparation of our imidazole-based inhibitors, we typically utilized the van Leusen cyclization.[4] However, some compounds could not be made via this methodology and we had to use alternative approaches., e.g. organocatalyzed construction of the imidazole core.[5] Overall, we prepared and tested >200 compounds, which allowed for thorough mapping of the structure-activity relationship (SAR) around the central azaindole-imidazole pharmacophore, and identification of potent and highly selective inhibitors of CK1 α, δ and ε isoforms. The series of the inhibitors has been patented and served as the basis for establishing of the spin-off company CasInvent Pharma a.s.

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