Synthesis and Evaluation of new 6-Formyl-oxazolo[3,2-a]pyrimidine Derivatives as Potential Src Kinase Inhibitors

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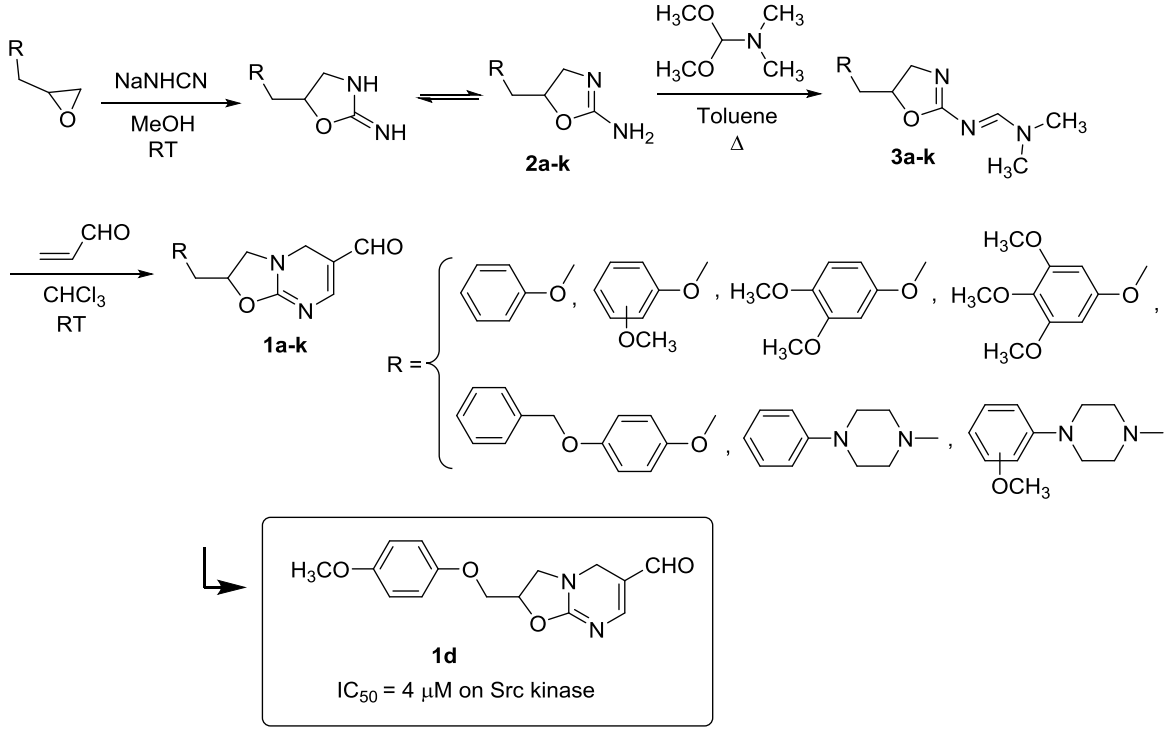
The tyrosine-protein kinase Src, also known as proto-oncogene c-Src or simply c-Src, is a non-receptor tyrosine kinase protein that has been shown to be involved in the regulation of important cellular processes including migration, survival and proliferation. In fact, Src activation has been associated with multiple cancers, such as colon, breast, pancreas, lung, or brain (Roskoski, R. Jr. *Pharmacol. Res.* 2015, *94*, 9-25; Creedon, H., et al., *Crit. Rev. Oncog.* 2012, *17*, 145-159). There are only few Src inhibitors in clinical development, therefore, there is an urgent need to identify new low molecular weight therapeutics able to inhibit Src and, thus, to modulate aberrant pathways leading to malignant transformation of cells (Lu, X.L., et al., *Curr. Med. Chem.* 2012, *19*, 1821-1829). Heterocyclic compounds attracted a lot of attention because of their wide spread biological activities. Thus, we have previously reported the synthesis of biological active heterocyclic derivatives based on the reactivity of the amidine moiety of 2-amino-2-oxazolines **2** with bis-electrophiles (Massip, S., et al., *Bioorg. Med. Chem.* 2006, *14*, 2697-2719).



In a preliminary screening testing our heterocycles library, we have identified a "hit" (compound **1d**) derived from various substituted 6-formyl-oxazolo[3,2-*a*]pyrimidines as a new Src kinase inhibitor (IC_{50} = 4 μM). These original oxazolo[3,2-*a*]pyrimidine derivatives **1a-k** were synthesized through a Diels-Alder cycloaddition of alkylidene derivatives of 2-amino-2-oxazoline (compounds **3a-k**) with acrolein, as an electron-poor dienophile, a reaction previously described by our group (Guillon, J., et al., *Synlett* 2002, *8*, 1249-1252). Versatility given by this reaction allowed us to access a promising family of diversely substituted 6-formyl-oxazolo[3,2-*a*]pyrimidines with inhibitory effect on Src kinase.

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