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

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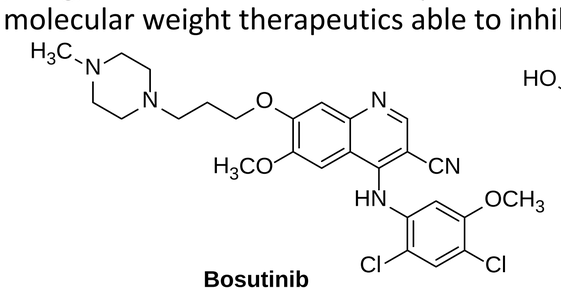
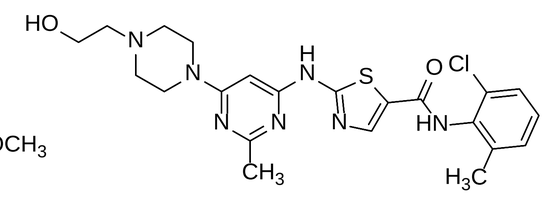
INTRODUCTION

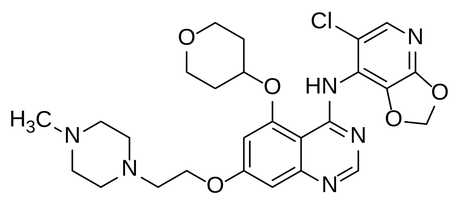
The tyrosine-protein kinase Src, also known as proto-oncogene c-Src or simply c-Src, is a non-receptor tyrosine kinase protein that has been shown to be involved in the regulation of important cellular processes including migration, survival and proliferation. In fact, Src activation has been associated with multiple cancers, such as colon, breast, pancreas, lung, or brain.[1,2] There are only few Src inhibitors in clinical development (Bosutinib, Dasatinib, Saracatinib and KX-01), 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.[3]



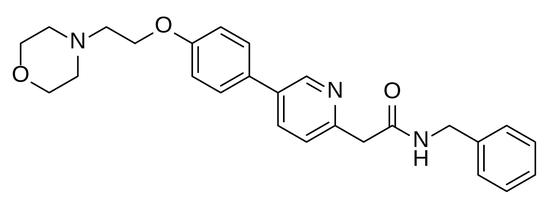
Bosutinib



Dasatinib (BMS-354825)



Saracatinib

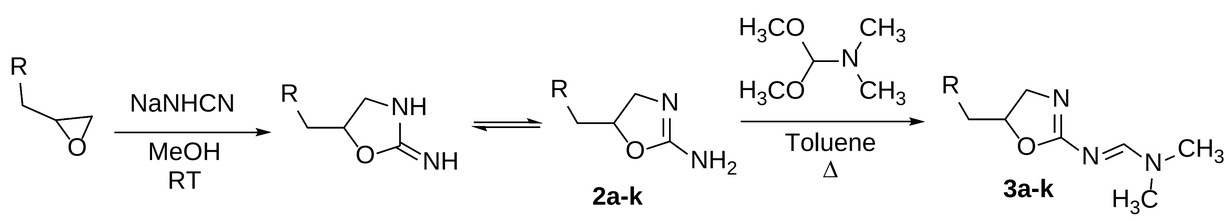


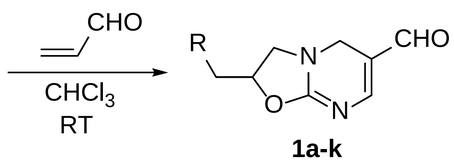
KX-01

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.[4] By following this chemical strategy, we have designed and synthesized a novel series of various substituted 6-formyl-oxazolo[3,2-*a*]pyrimidine derivatives **1a-k** that have been screened in a drug discovery approach in order to identify new chemical entities.

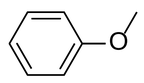
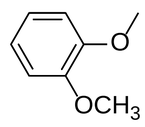
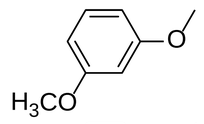
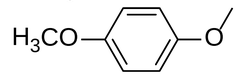
RESULTS & DISCUSSION

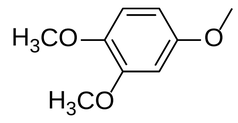
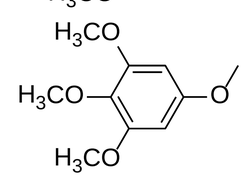
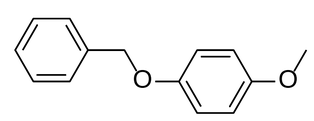
These original oxazolo[3,2-*a*]pyrimidine derivatives **1a-k** were synthesized through a Diels-Alder cycloaddition of alkylidene derivatives of 2-amino-2-oxazoline (compounds **3a-k**) with acrolein, used as an electron-poor dienophile, and followed by spontaneous elimination of dimethylamine.[5] The heterocyclic diazodienes **3a-k** were synthesized according to a general literature method by heating a toluene solution of substituted 2 amino-2-oxazolines **2a-k** and *N*,*N*-dimethylformamide-dimethyl acetal.[6,7] The starting racemic 2-amino-2-oxazolines **2a-k** were easily prepared from the corresponding epoxides.[8,9]

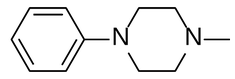
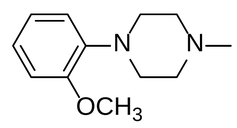
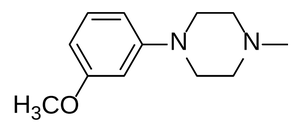
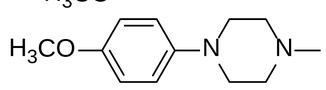




1a-k

	R-
1-3a	
1-3b	
1-3c	
1-3d	

	R-
1-3e	
1-3f	
1-3g	

	R-
1-3h	
1-3i	
1-3j	
1-3k	

These original 6-formyl-oxazolo[3,2-*a*]pyrimidine derivatives **1a-k** were then submitted to a preliminary screening on various biological targets. Therefore, this new series was evaluated on the Src kinase. Among the data, we identified a "hit" (compound **1d**) as a new Src kinase inhibitor with an IC_{50} of 4 µM (Table 1). Unfortunately, all the other derivatives were found inactive toward this target kinase.

Compound	IC_{50} (µM)	Compound	IC_{50} (µM)	Compound	IC_{50} (µM)
1a	> 20	**1e**	> 20	**1i**	> 20
1b	> 20	**1f**	> 20	**1j**	> 20
1c	> 20	**1g**	> 20	**1k**	> 20
1d	4	**1h**	> 20		

Table 1 : IC_{50} Src kinase

CONCLUSION

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. Moreover, this promising Src kinase inhibitor **1d** will be then tested for its antiproliferative activity against various cancer cell lines. Its potency on different isolated enzymes will be also evaluated to determine its specificity. In addition, further studies could be required to know the specific mechanism of action of this new bioactive 6-formyl-oxazolo[3,2-*a*]pyrimidine derivative. These studies are currently under progress.

1) Roskoski, R. Jr. *Pharmacol. Res.* 2015, *94*, 9-25; 2) Creedon, H., et al., *Crit. Rev. Oncog.* 2012, *17*, 145-159; 3) Lu, X.L., et al., *Curr. Med. Chem.* 2012, *19*, 1821-1829; 4) Massip, S., et al., *Bioorg. Med. Chem.* 2006, *14*, 2697-2719; 5) Guillon, J., et al., *Synlett* 2002, *8*, 1249-1252; 6) Sanfilippo, P.J., et al., *J. Med. Chem.* 1988, *31*, 2221-2227; 7) Hirota, T., et al., *J. Heterocyclic Chem.* 1991, *28*, 257-261; 8) Jarry, C., et al., *Ann. Pharm. Fr.* 1985, *43*, 183-188; 9) Jarry, C., et al., *Eur. J. Med. Chem.* 1986, *21*, 138-142.

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