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Synthesis of ALK5 kinase inhibitors based on substituted homoallenyl aldehyde

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ALK5 (Activin-like kinase-5) plays important roles in many pathological states including inflammation, fibrosis, cancer, asthma and cardiovascular diseases. 1-3 Various low molecular weight inhibitors of ALK5 containing different substituted heterocyclic skeletons like imidazole, pyrazole, pyrrolo[1,2-b]pyrazole and pteridine were synthesized and published. 4-5 Our recent work is focused on synthesis of new inhibitors of ALK5 kinases. 6-7 We synthesized a series of 5,5-dimethyl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazoles with various substitution at positions 2, 3 and 4. The most active compound in the set of almost 40 final products showed $IC_{50} = 80$ nM for ALK5. The selectivity for ALK5 in a panel of 50 protein kinases, as well as some experiments in cells (dephosphorylation of SMAD2/3 to nuclei) are discussed. In the literature one can find several ways for the formation of 5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole ring but their synthesis is often complicated and has not always good yield. 8-9 Our experience in application of homoallenyl aldehyde enabled us to find an easier route to those fused heterocyclic compounds. Our approach is depicted at Figure 1.

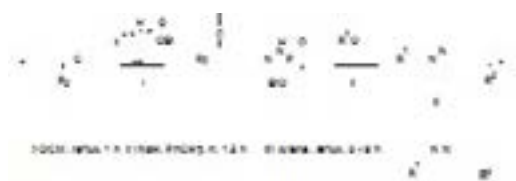


Figure 1 : Application of allenyl aldehyde for formation of fused heterocyclic systems.

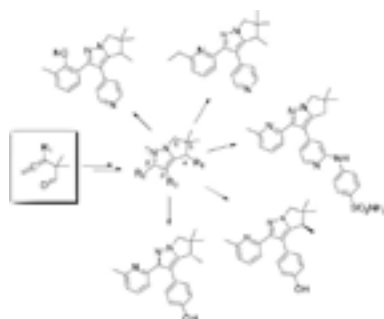


Figure 2 : Schematically depicted synthesis of variously substituted 5,5-dimethyl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazoles synthesized via homoallenyl aldehyde they underwent biological screening.

Biography

Milan Potáček is working in heterocyclic chemistry in the field of pericyclic reactions, their regio and stereoselectivity, especially on 1,3-dipolar cycloadditions and their new intramolecular variation - "criss-cross" cycloadditions with application of allene synthon as a dipolarophile. Following their applications lead to many various products otherwise difficult to preparation. Here presented work was carried out by his doctoral students.

Notes: