Obtainment of 3,4-dihydro-2*H*-1,4-benzoxazine enantiopure analogues for potential biological applications

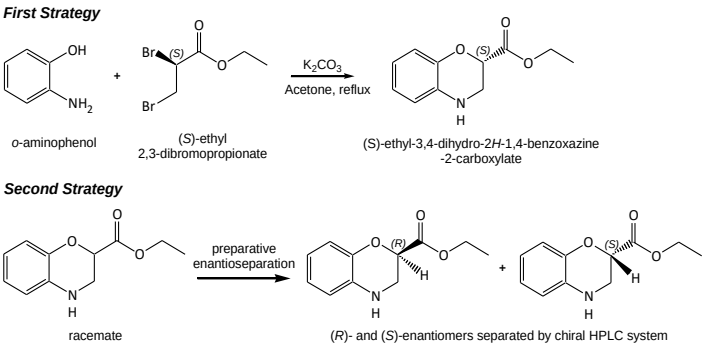
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Abstract

3,4-dihydro-2*H*-1,4-benzoxazine and its derivatives were described as promising candidates for many choices of therapeutic applications. This fascinating class of heterocyclic compounds can exhibit various biological properties such as antibacterial[1], cardiovascular protector[2], anti-hypertensive[3], anti-angiogenesis[4], anti-thrombin[5] or neuroprotective activities[6]. Due to those potential effects, 3,4-dihydro-2*H*-1,4-benzoxazine became an attractive target to develop. However, because of receptor selectivity, chirality now becomes a top subject in chemistry. Within one molecule such as levofloxacin or thalidomide, different chirality may exhibit different pharmacological activities.

As a result, we raised an awareness about the obtainment of 3,4-dihydro-2*H*-1,4-benzoxazine enantiopure analogues but there were not many reports in the literature brought up an effortless procedure to achieve it. Therefore, we are making an effort to design a straightforward way to directly acquire the chiral ethyl 3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate. As our targeted compound could be easily prepared by allowing appropriate aminophenol reacts with ethyl 2,3-dibromopropionate, this reaction always lead to racemic 1,4-benzoxazine as the main product in high yield. Our desire is to attempt chiral (*R*)- or (*S*)-ethyl-2,3-dibromopropionate which had never been described in the literature in order to replace the role of racemic one and (*R*)- or (*S*)-ethyl-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate by two strategies: enantioselective synthesis and preparative enantioseparation of racemate using different chiral stationary phases (CSPs). Once ethyl-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate enantiopure is obtained, it could be easily to introduce as new β-amino acid analogs in peptidic chains by coupling O- and *N*-terminal extremities with different α-amino acids. Finally, studies of the conformational behavior of obtained compounds will be led and their potential biological activities will be examined.

Image



Scheme 1. Strategies for obtainment of chiral 1,4-benzoxazine developed in our project

Publications

References

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5. Sullivan EV, Zahr NM (2008) Neuroinflammation as a neurotoxic mechanism in alcoholism: Commentary on "Increased MCP- 1 and microglia in various regions of human alcoholic brain". Experimental neurology 213:10-17.



Biography

Hong-Ngoc PHAM received her master degree in Drug Development in 2016 from Vietnam-France University (Vietnam). She joined Laboratoire de Chimie Physique Macromoleculaire (LCPM), Université de Lorraine (France) in 2017 as PhD student in Organic Chemistry. Her research focused on the synthesis of heterocycle-based peptidomimetics for different biological applications. She expects to work as a researcher and teaching assisant in university after gaining the PhD diploma.

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