proceedings

MDPI

Extended Abstract

Synthesis of Heterocyclic Fused [1,5]naphthyridines by Intramolecular HDA Reactions †

Concepcion Alonso *, Endika Martin-Encinas, Gloria Rubiales and Francisco Palacios

Department of Organic Chemistry I, Faculty of Pharmacy and Lascaray Research Center, Universidad del País Vasco/Euskal Herriko Unibertsitatea (UPV/EHU), Paseo de la Universidad 7, 01006 Vitoria-Gasteiz, Spain

* Correspondence: concepcion.alonso@ehu.eus

† Presented at the 2nd Molecules Medicinal Chemistry Symposium (MMCS): Facing Novel Challenges in Drug Discovery, Barcelona, Spain, 15–17 May 2019.

Published: 6 September 2019

Keywords: chromeno[4,3-b][1,5]naphthyridines; Topoisomerase I; enzyme inhibition; antiproliferative effect

---

Povarov reaction [1] can be considered as an example of HDA reactions and represents an excellent method for the preparation of nitrogen-containing heterocyclic compounds [2]. When aldimines, derived from aromatic amines and unsaturated functionalized aldehydes, are treated with a Lewis acid, the Povarov reaction takes place intramolecularly [3].

In this work, the synthesis of new families of heterocyclic fused [1,5]naphthyridines is reported. In this way, via an efficient and straightforward intramolecular Povarov reaction catalyzed by boron trifluoride etherate, tetrahydro-6*H*-chromeno[4,3-b][1,5]naphthyridines and tetrahydro-6*H*-quinolino[4,3-b][1,5]naphthyridines are obtained. Dehydrogenation of tetrahydroderivatives with DDQ gives compounds 6*H*-chromeno[4,3-b][1,5]naphthyridine and 6*H*-quinolino[4,3-b][1,5]naphthyridine.

This methodology allows access to novel compounds with biological activity. Based on the success of camptothecin (CPT) and its derivatives as inhibitors of Topoisomerase I (TopI) [4], as well as our results obtained with naphthyridine derivatives [5], we report here that these novel heterocyclic compounds are possible candidates, some of them showing excellent activity as TopI inhibitors. The cytotoxic effect on several cancer and noncancer cell lines was also screened.

References

1. Povarov, L.S. αβ-Unsaturated ethers and their analogues in reactions of diene synthesis. *Russ. Chem. Rev.* **1967**, *36*, 656.
2. Alonso, C.; González, M.; Palacios, F.; Rubiales, G. Study of the hetero-[4+2]-cycloaddition reaction of aldimines and alkynes. Synthesis of 1,5-naphthyridine and isoindolone derivatives. *J. Org. Chem.* **2017**, *82*, 6379–6387.
3. Kouznetsov, V.V. Recent synthetic developments in a powerful imino Diels–Alder reaction (Povarov reaction): Application to the synthesis of N-polyheterocycles and related alkaloids. *Tetrahedron* **2009**, *65*, 2721–2750.
4. Pommier, Y. Topoisomerase I inhibitors: camptothecins and beyond. *Nav. Rev. Cancer* **2006**, *6*, 789–802.
5. Alonso, C.; Fuertes, M.; González, M.; Rubiales, G.; Palacios, F. Synthesis and biological evaluation of indeno[1,5]naphthyridines as topoisomerase I (TopI) inhibitors with antiproliferative activity. *Eur. J. Med. Chem.* **2016**, *115*, 179.