SYNTHESIS OF SPIRO-γ-HYDROXYLACTAM OXINDOLES AS HYBRID PROHIBITIN-2 LIGANDS

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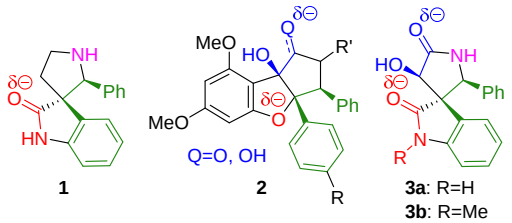
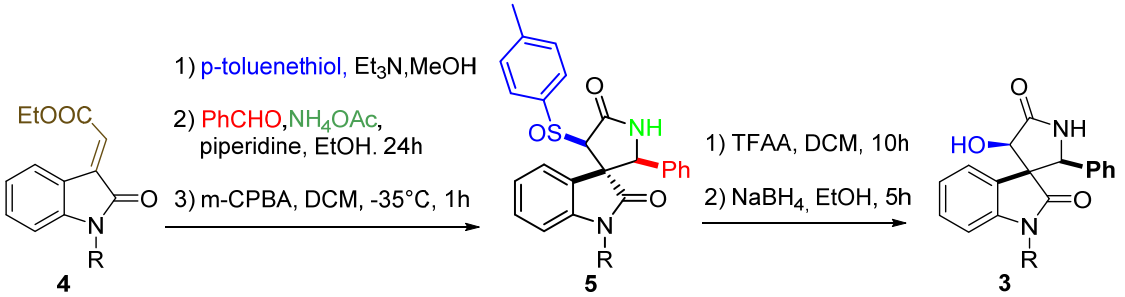
Prohibitins-1 and 2 (PHB1/2) are scaffold proteins that represent emerging targets in oncology [1]. Recently, a new PHB2 ligand, the spiro-oxindole 1, was reported to be cytotoxic in MCF-7 breast cancer cells [2]. This compound displays some structural features with the pharmacophore of flavaglines (2), a group of natural product derivatives that display potent anticancer activities due to their action on PHBs [1].



In the continuation of our medicinal program on PHB ligands [1], we developed the first synthesis of the spiro-oxindoles 3 substituted by a hydroxy and an adjacent lactam that combine the structural features of 1 and 2. These syntheses were achieved in four steps using a one-pot thiol-Michael/Mannich/lactamization [3] and a Pummerer rearrangement coupled to a carbonyl reduction as key steps.



Such hydroxy-spiro-γ-hydroxylactam oxindoles have never been reported yet. Their pharmacological on PHB signaling is currently under investigation and will be reported in due course.

[1] F. Thuaud, N. Ribeiro, C.G. Nebigil, L. Désaubry, *Chem. Biol*., 20: 316-331 (2013).

[2] S. Hati, S. Tripathy, P.K. Dutta, *et al., Sci Rep.*, 6: 32213 (2016).

[3] X. Huang, M. Liu, K. Pham, X. Zhang, W-B Yi, *et al., J. Org. Chem.*, 81: 5362-5369 (2016).