Design, synthesis and pharmacological evaluation of new Rac1 protein inhibitors

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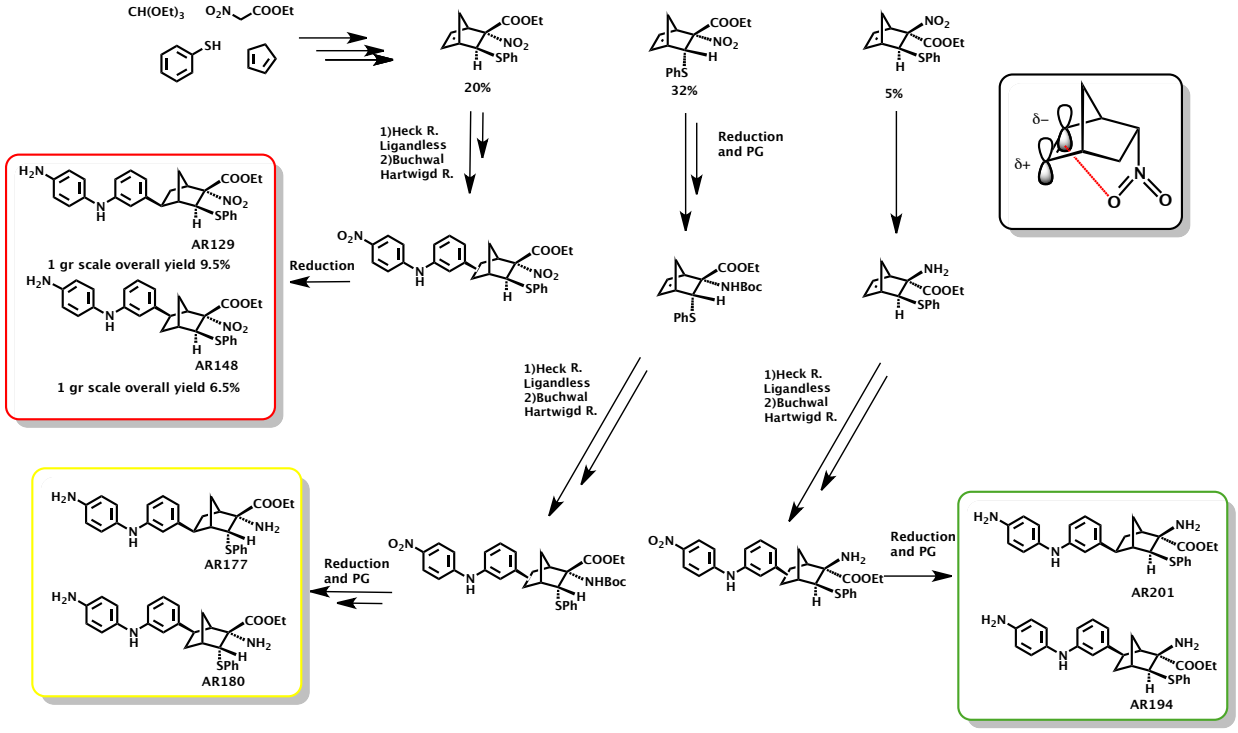
A new class of RAC1-TIAM inhibitors was designed and synthesized from simple and cheap reagents as nitroacetati, thiols, orthoformate and cyclopentadiene. [1] The compounds differ for stereochemistry of the substituents on a norbornanic scaffold. The common synthetic strategy for the compounds AR129, 148, 177, 180, 194, 201 consist in: i) Diels-Alder cycloaddition between the appropriate acrylate and cyclopentadiene; [2] ii) functionalization of the double by Heck-type hydroarylation; iii) Buchwald amination iiii) deprotection steps and reductive manipulations. The synthesis of the compounds AR148 and AR129 was optimized and scale-up to 1 gr. The regiochemistry of Heck-type hydroarylation on norbornen core was object of further investigation on large substrate scope highlighting long-range effect beteween EWG in endo position of C2 or C3 with the p orbital of the double bond. [3] Subsequent developments have shown also the possibility to run the reaction in absenece of phosphine lignads.



1. N. Ferri, A. Corsini, F. Clerici, A. Contini, *J Med. Chem.*, **2009**, *52(14)*, 4087 – 90.
2. A. Ruffoni, A. Contini, M. L. Gelmi, F. Clerici, *Tetrahedron.*, **2012**, *68*, 1951 – 62.
3. A. Ruffoni, A. Casoni, M. L. Gelmi, F. Clerici, *Current Organic Chem.* **2012**, *16*, 2724 – 38