DEVELOPMENT OF A MICROWAVE-ASSISTED PROLINE/Pd CATALYSED MULTICOMPONENT APPROACH FOR THE SYNTHESIS OF POTENTIAL LRRK2 INHIBITORS

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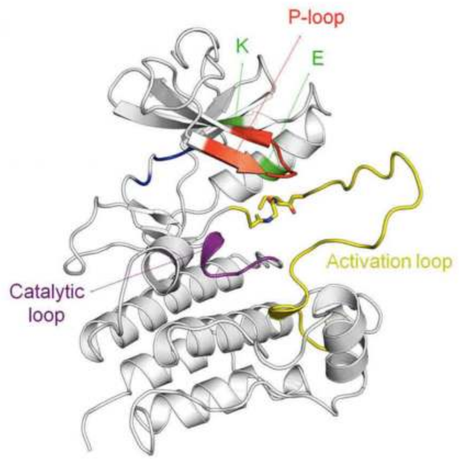
Role of LRRK2 in Parkinson's disease

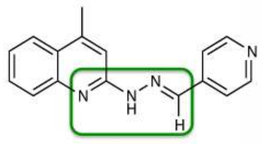
Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by both motor and cognitive dysfunctions. Recently, mutations in the catalytic domain of **leucine-rich repeat kinase 2 (LRRK2)** have been associated with both autosomal-dominantly inherited and late-onset sporadic Parkinson's disease cases[1] and modulation of LRRK2 activity has been proposed as an attractive therapeutic strategy.[2]



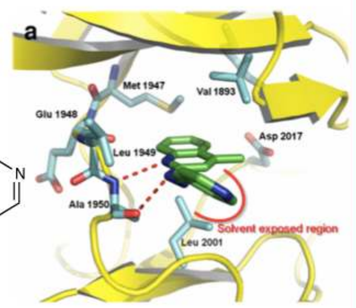
Background

A few (E)-2-(2-Arylidenehydrazinyl)quinolone derivatives have been recently reported as selective LRRK2 inhibitors, targeting the catalytic site (**Hit-1**, IC_{50}= 4.1 μM).[3]

Docking studies highlighted the key role played by the heteroaryl-hydrazone **pharmacophore moiety** (circled in green) for the interaction with the catalytic site of LRRK2.

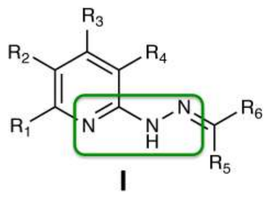


Hit-1



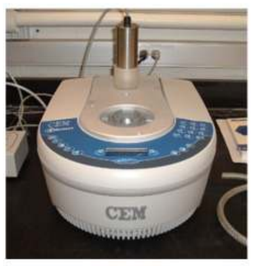
Aim of the work

Development of a **new multicomponent approach** for the synthesis of highly functionalized heteroaryl-hydrazones (general structure **I**) bearing the key pharmacophore moiety.



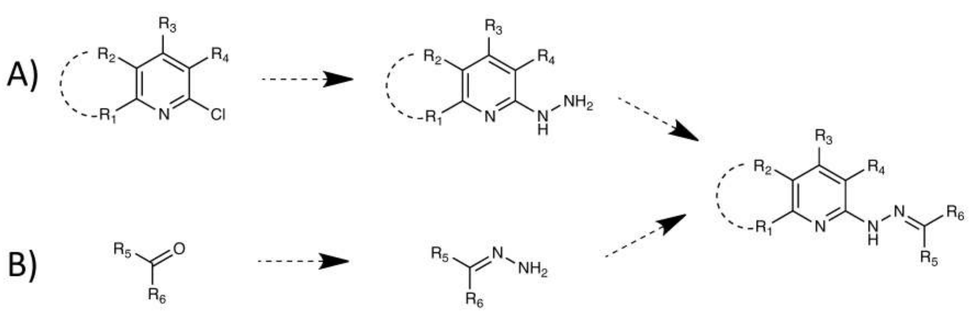
I

- **VERSATILE**, starting from commercially available reagents;
- **QUICK**, combining microwave irradiation, organo- and metal-catalysis;
- **PRACTICAL**, to explore the biologically relevant chemical space around their basic pharmacophore-fragment.



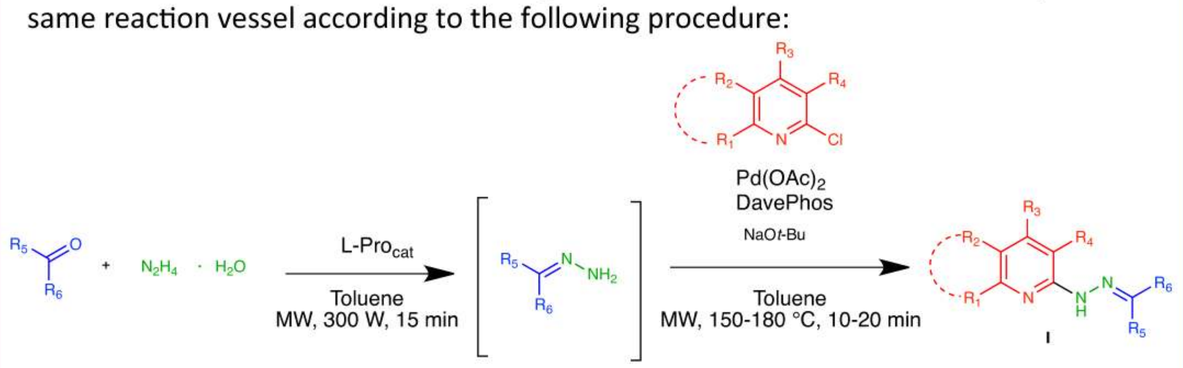
Classical synthesis of heteroaryl-hydrazones

Hydrazone derivatives represent an important class of biologically active compounds. The classical multistep approaches (**A** and the less explored **B**) for the synthesis of substituted heteroaryl-hydrazones require long reaction times and multiple purifications.[4-5]

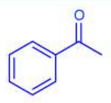
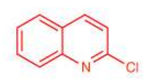
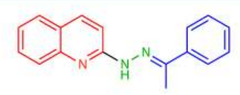
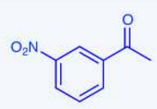
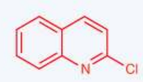
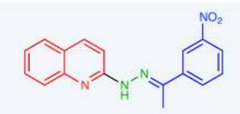
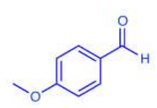
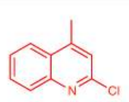
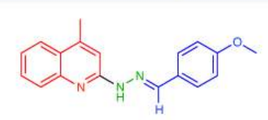
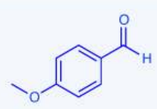
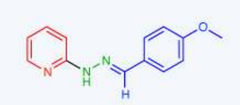
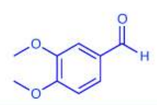
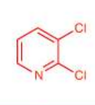
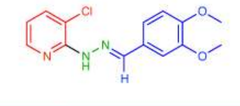
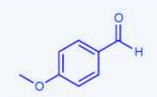
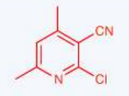
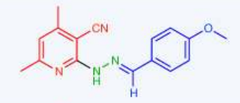
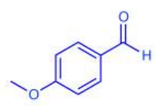
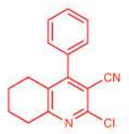
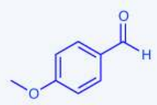
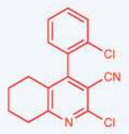
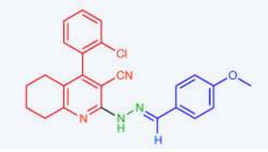


Our optimized one-pot two-step protocol

The best results were obtained dividing the reaction in two consecutive steps, in the same reaction vessel according to the following procedure:



STEP I: MW-assisted conversion of aldehydes or ketones into the corresponding hydrazones, catalysed by L-Proline;
STEP II: MW-assisted Pd-catalysed amination of heteroaryl chlorides.

Entry	Ketone/Aldehyde	Heteroaryl chloride	Product (Yield=30-50%)
1			
2			
3			
4			
5			
6			
7			
8			

Conclusions and future perspectives

We report the development of a **new versatile chemical tool** for the rapid identification of novel LRRK2-targeting scaffolds as potential anti-Parkinson's agents.
Each new compound can be obtained in only 30 minutes with acceptable yields.
The enzymatic screening of the synthesized compounds is ongoing.
The biological results will guide the rational synthesis of improved heteroaryl-hydrazone derivatives.

References

1) Cookson, M. P. *Nat. Rev. Neurosci.* **2010**, *11*, 791-797; 2) Li, J. Q. et al. *Molecular Neurodegeneration* **2014**, *9(47)*, 1-17; 3) Yun, H. et al. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 2953-2957; 4) Won Gi, S. et al. KR 2012019785 ; 5) Calatayud, d. G. et al. *Eur. J. Inorg. Chem*. **2013**, *1*, 80-90; 6) Sleebs, B. E. et al. *J. Med. Chem*. **2013**, *56*, 5514-5540.