NEW MCR APPROACHES FOR THE SYNTHESIS OF PRILIVEGED SCAFFOLD IN THE TREATMENT OF PARKINSON'S DISEASE

Sabrina Tassini,[1] Paolo Vincetti,[1] Anna Brianza,[1] Federica Giagnorio,[1] Nicolò Scalacci,[2,3] Daniele Castagnolo[2] and Marco Radi[1,*]

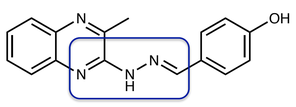
[1]P4T Group, Dipartimento di Farmacia, Università degli Studi di Parma, Viale delle Scienze 27/A, 43124 Parma, Italy. [2]Institute of Pharmaceutical Science, King's College London, 150 Stamford Street SE1 9NH London, United Kingdom. [3]University Newcastle, Department of Applied Sciences, Ellison Building, Ellison Place, NE1 8ST Newcastle upon Tyne, United Kingdom

sabrina.tassini@studenti.unipr.it
http://p4T.farmacia.unipr.it

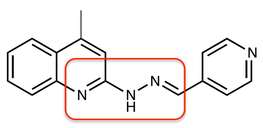
Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by both motor and cognitive dysfunctions.[1] Different pathways are implicated in the development of PD and recently a few compounds demonstrated a promising profile as anti-PD agents:

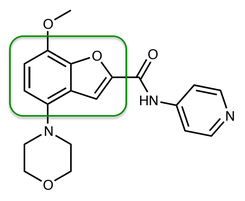
- Benzylidene hydrazinyl-3-methylquinazoline compounds as potent positive allosteric modulators of **metabotropic receptor subtype 4 (mGluR4)**;[2]



- 2-(2-Arylidenehydrazinyl)quinlone derivatives targeting the catalytic domain of **leucine-rich repeat kinase 2 (LRRK2)**;[3]

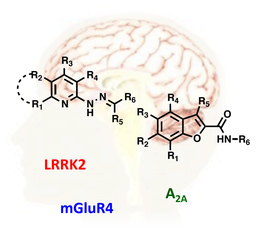


- Benzofuran-2-carboxamide compounds as selective antagonists of **adenosine A_{2A} receptors**.[4]



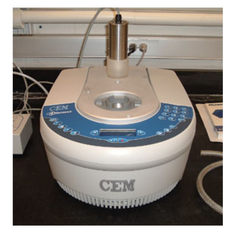
Aim of the work

We decided to develop **new diversity-oriented synthesis around key pharmacophore hydrazone and benzofuran fragments** for the discovery of novel anti-Parkinson's agents.

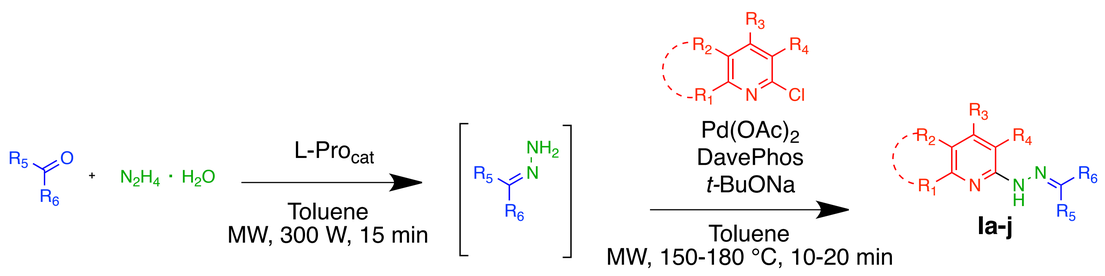


This **pharmacophore fragment decoration approach** could be considered as a good compromise between a target-based and a phenotypic drug discovery approach.

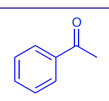
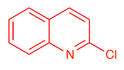
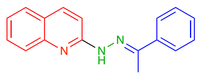
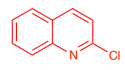
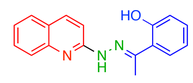
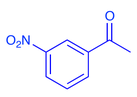
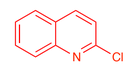
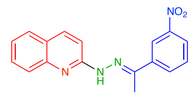
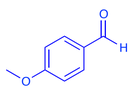
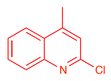
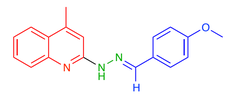
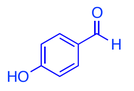
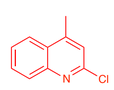
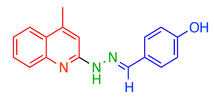
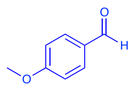
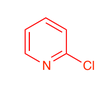
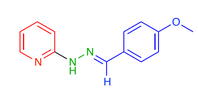
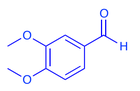
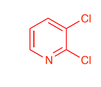
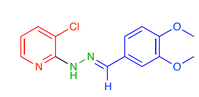
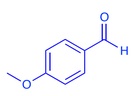
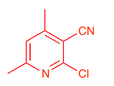
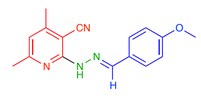
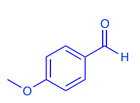
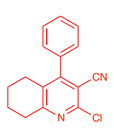
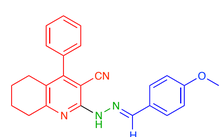
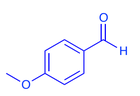
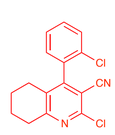
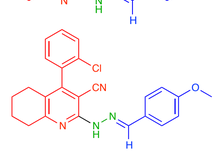
- ✓ **VERSATILE**, starting from commercially available reagents
- ✓ **FASTER than the common procedures**,[5,6] using the microwave irradiation
- ✓ **PRACTICAL**, combining the advantages of multistep protocols (high chemical diversity) and multicomponent reactions (atom- and cost-efficiency).



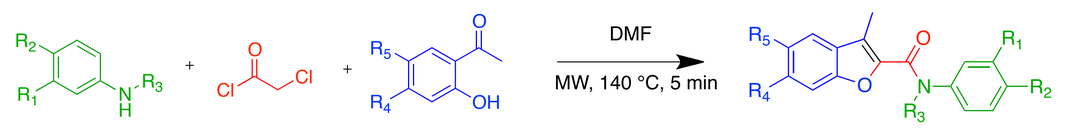
Synthesis of heteroaryl hydrazone derivatives



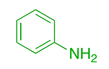
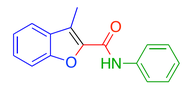
Ist STEP: Proline-catalysed conversion of ketone or aldehyde into the corresponding hydrazone;
IInd STEP: Pd-catalysed amination of the heteroaryl chloride.

Compound	Ketone/Aldehyde	Heteroaryl chloride	Product (Yield=26-49%)
Ia			
Ib			
Ic			
Id			
Ie			
If			
Ig			
Ih			
Ii			
Ij			

Synthesis of benzofuran derivatives



One-pot one-step protocol

Compound	Acetophenone	Aniline	Product (Yield=15-59%)
IIa			
IIb			
IIc			
IId			
IIe			
IIf			
IIg			
IIh			
IIi			
IIj			
IIIk			

Conclusions

We report the development of **new MCR approaches** for the rapid synthesis of highly functionalized **heteroaryl hydrazone and benzofuran derivatives**, that are considered **privileged scaffold in the treatment of Parkinson's disease**.

References

1) J. Jancovic, J Neurol Neurosurg, **2008**, *79*, 368-376; 2) R. Williams et al., *Bioorg. Med. Chem. Lett.*, **2009**, *19*, 962-966; 3) H. Yun et al., *Bioorg. Med. Chem. Lett.*, **2011**, *21*, 2953-2957; 4) R. J. Nevagi et al., *Eur. J. Med. Chem.*, **2015**, *97*, 561-581; 5) B. E. Sleebs et al., *J. Med. Chem.*, **2013**, *56*, 5514-5540; 6) L. De Luca et al., *Curr. Med. Chem.*, **2009**, *16*, 1-20.