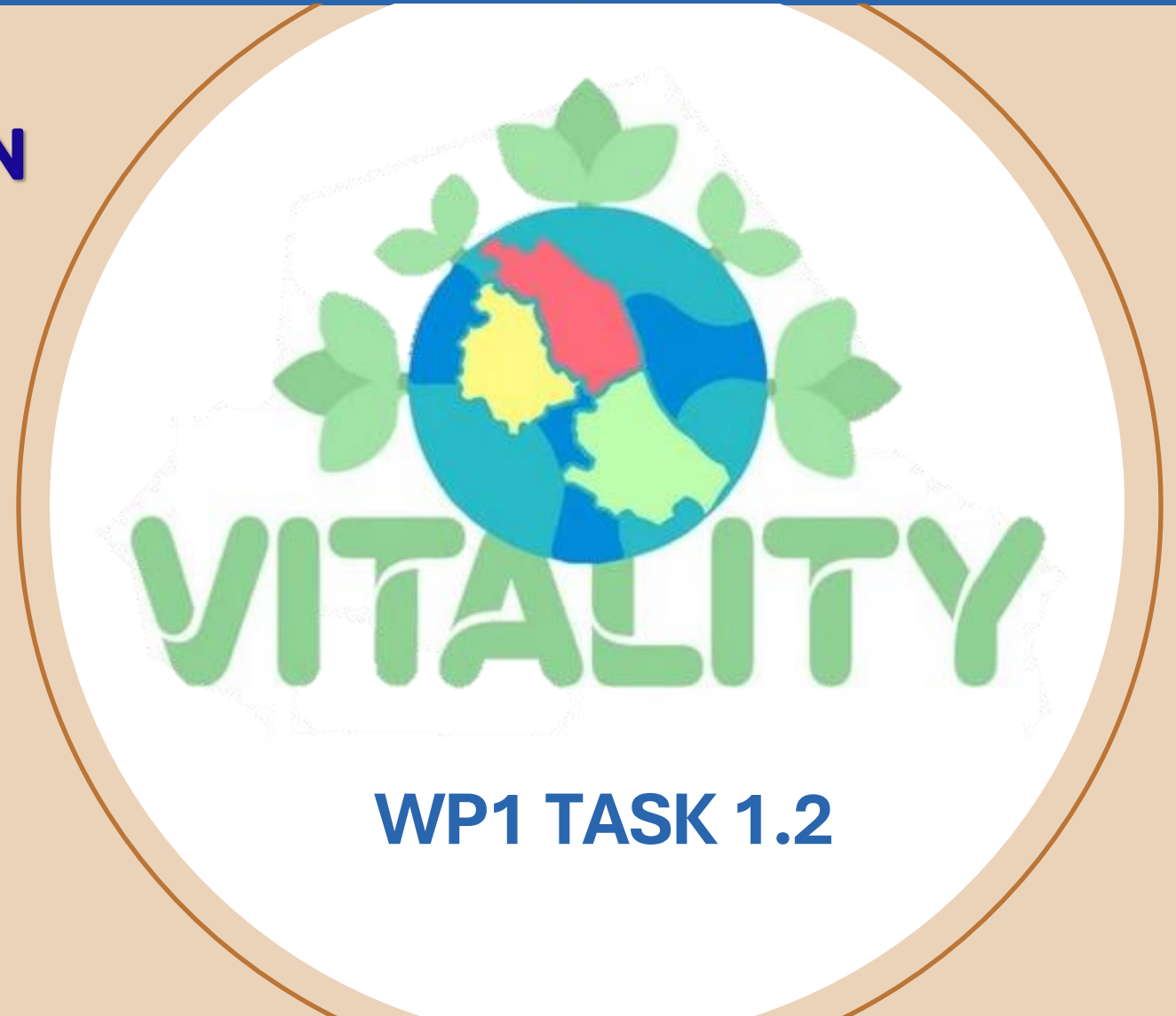




IDENTIFICAZIONE E SINTESI DI UN POTENZIALE MODULATORE MACROCICLICO DR/GSK-3 β PER IL TRATTAMENTO DEL DISTURBO BIPOLARE

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WP1 TASK 1.2



WHAT IS BIPOLAR DISORDER ?

- Bipolar disorder (BD) is **a severe neuropsychiatric condition** in which episodes of mania alternate with depression.
- With an estimated worldwide prevalence up to 4%, BD is one of the **leading causes of disability**.

MANIA/HYPOMANIA

- Extremely high energy
- Grandiose levels of self-esteem
- Loud, rapid speech
- Very little need for sleep
- Engaging in risky behaviors



DEPRESSION

- Feeling of lethargy
- Feeling of worthlessness
- Overwhelming sadness
- Insomnia or sleeping too much
- Thoughts of suicide

TREATMENT OF BIPOLAR IS COMPLEX

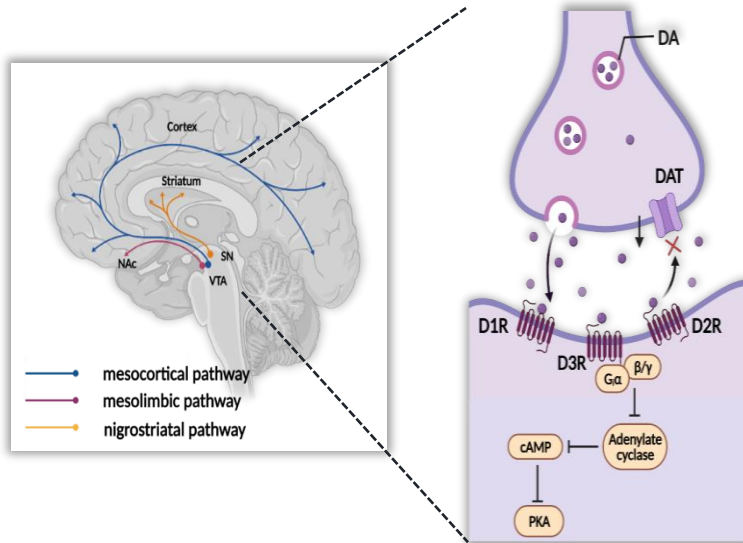
Combination of medication and psychotherapy

- **Mood stabilizers** *treat or prevent mania or hypomania* (e.g., lithium , valproic acid, carbamazepine, lamotrigine)
- **Antipsychotics** *for mania or hypomania or maintenance treatment* (e.g., olanzapine, risperidone, quetiapine, aripiprazole, cariprazine)
- **Antidepressants** *used cautiously in bipolar disorder, typically in combination with a mood stabilizer, to prevent triggering mania* SSRIs (e.g., fluoxetine, sertraline); SNRIs (e.g., venlafaxine)
- ✗ limited efficacy to particular patient subgroups
- ✗ little efficacy in preventing relapse
- ✗ significant side effects

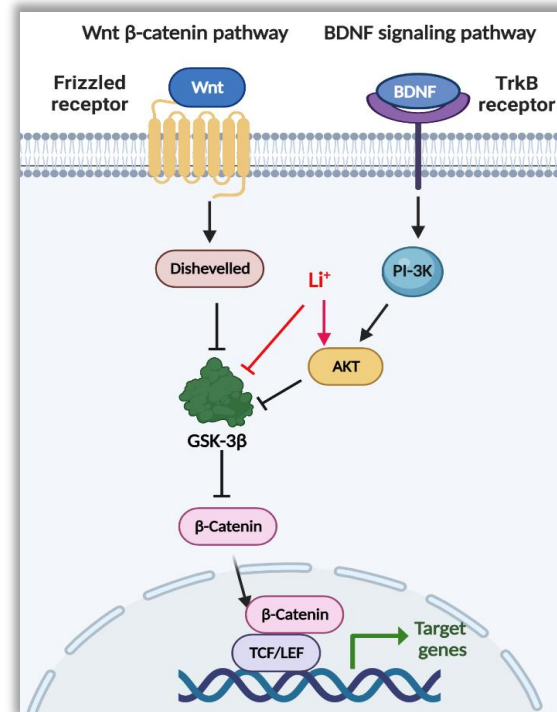


PHATOPHYSIOLOGY OF BIPOLAR DISORDER

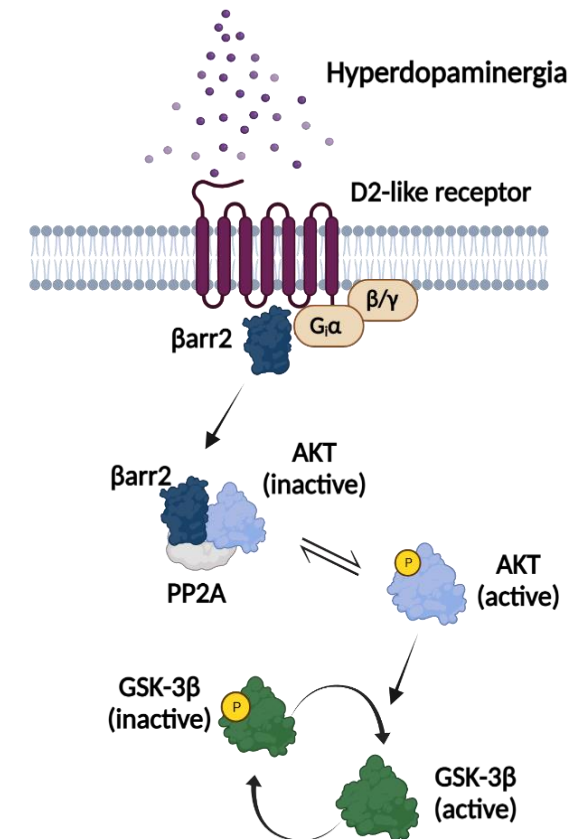
Homeostatic mechanism of dopamine



GSK-3 β dysregulation

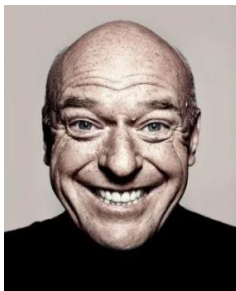
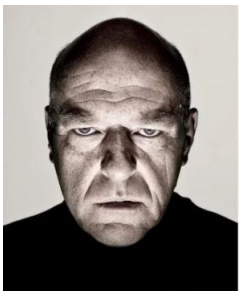


D2R - GSK-3 β cross talk



**DUAL TARGET
DIRECT
LIGANDS**

**DAT
levels**

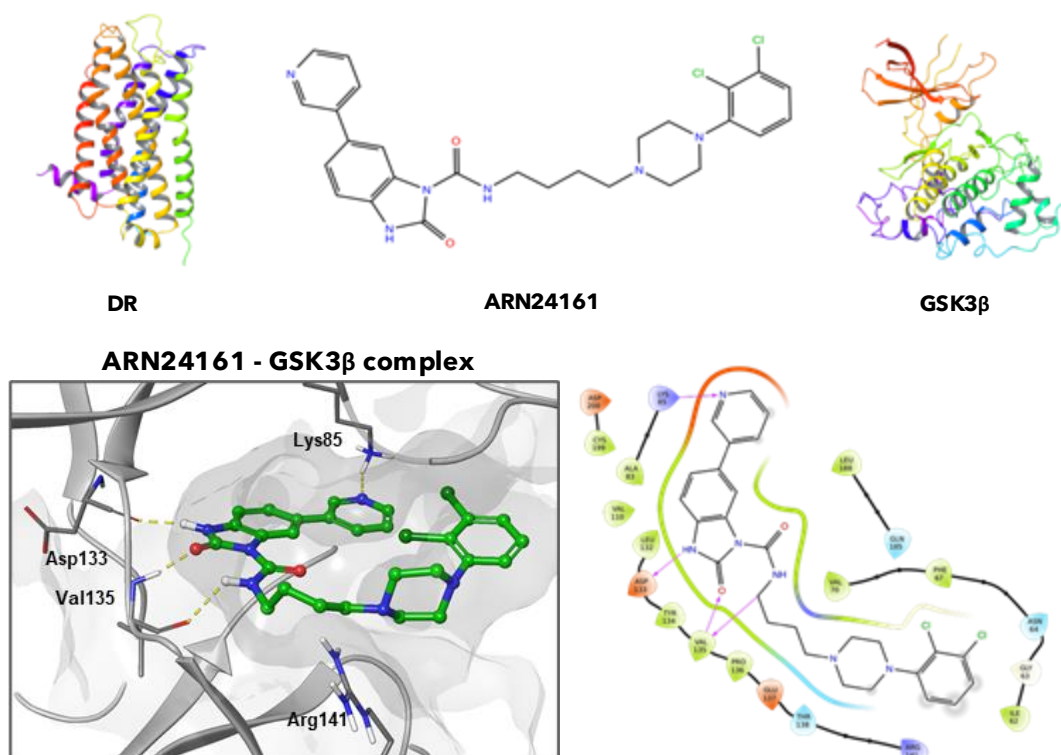


**D2R/D3R
levels**



MACROCYCLE IDENTIFICATION

Previous work



Di martino et al., *ChemMedChem*. **2020**, 15, 949-954



Extraction of Macrocyclic Kinase Inhibitors from ChEMBL

ChEMBL

424 Kinase proteins



100368 Inhibitors
Activity $\leq 10 \mu\text{M}$

702 Macrocyclic
Inhibitors

Preparation of ligands

Schrödinger

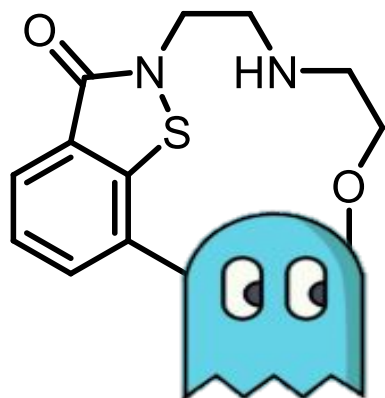
Docking GSK-3 β

Docking DR

Selection of potential dual ligands

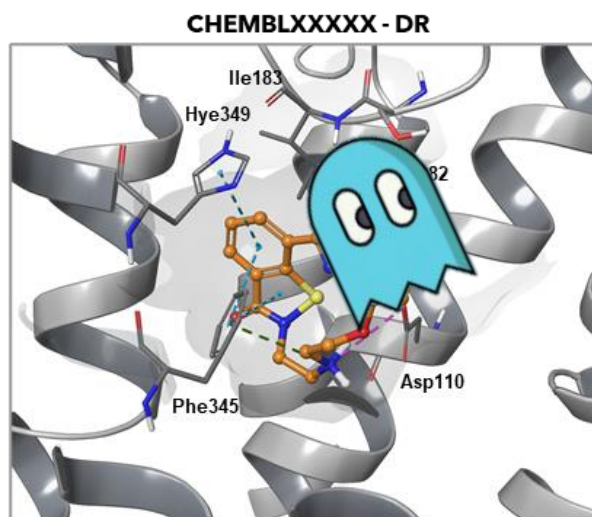
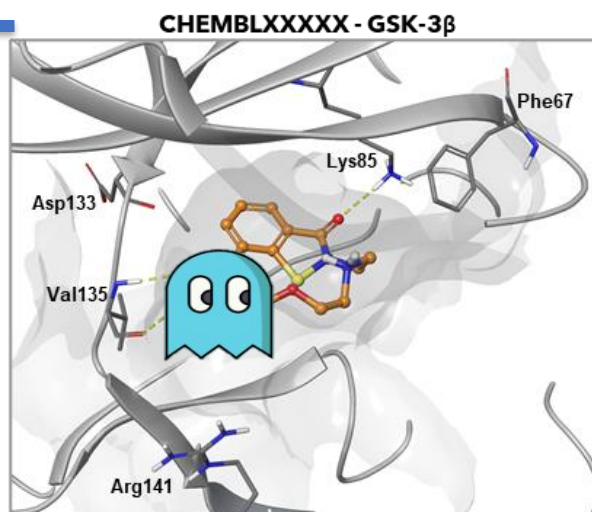


MACROCYCLE IDENTIFICATION

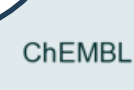


CHEMBLXXXXX

IC_{50} on kinase protein = **6 nM**



Extraction of Macrocyclic Kinase Inhibitors from ChEMBL



424 Kinase proteins



100368 Inhibitors
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702 Macrocyclic
Inhibitors

Preparation of ligands



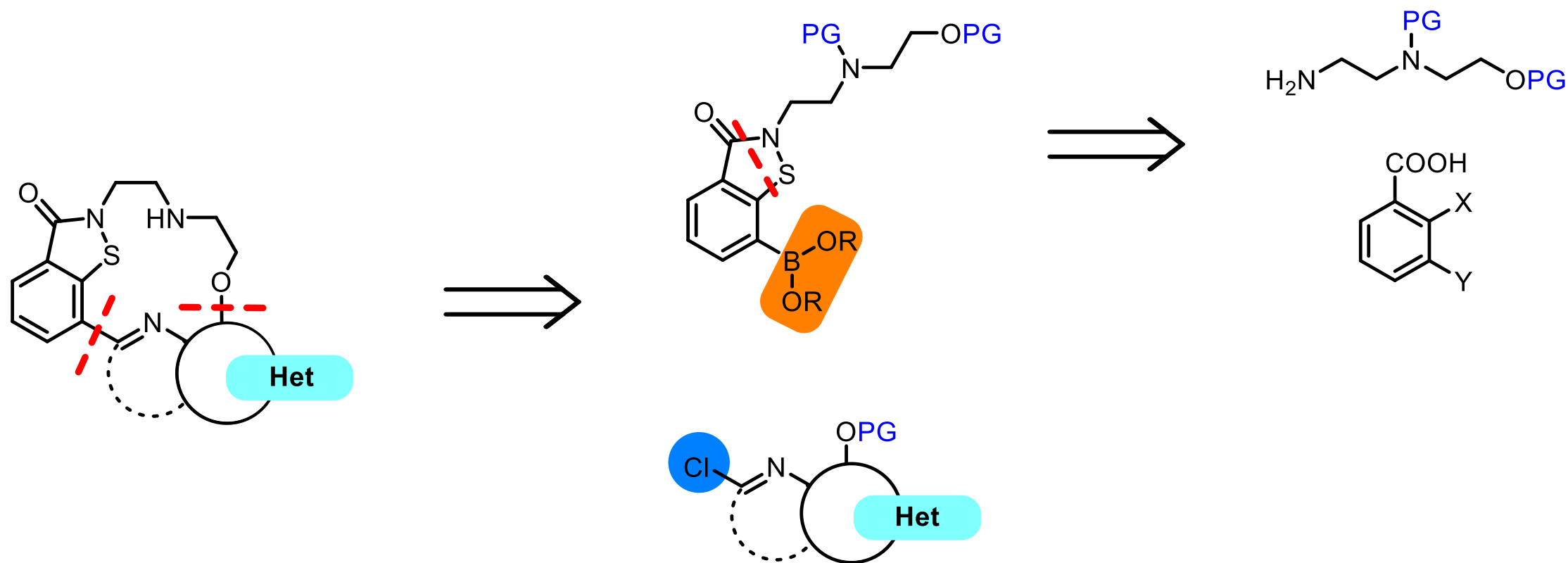
Docking **GSK-3 β**

Docking **DR**

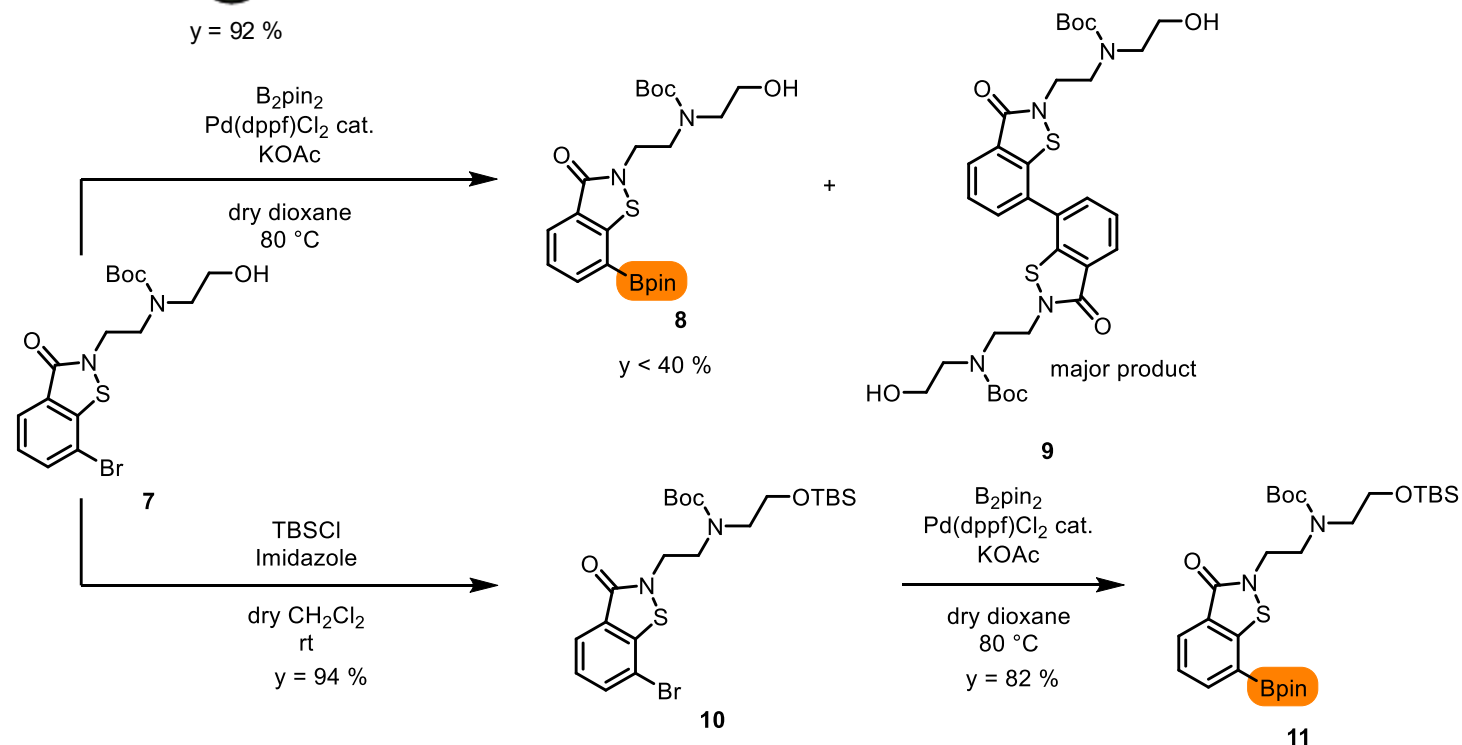
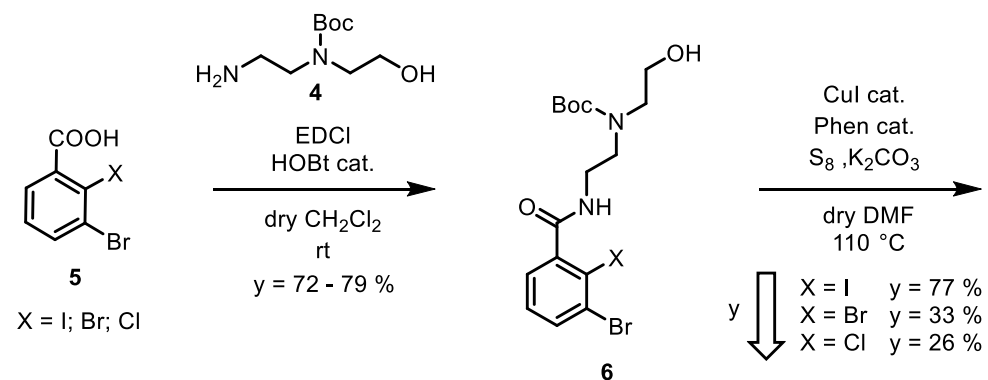
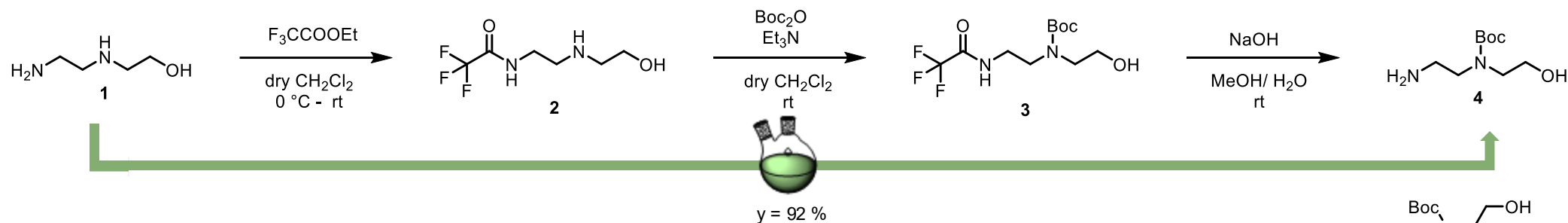
Selection of potential dual ligands



RETROSYNTHESIS

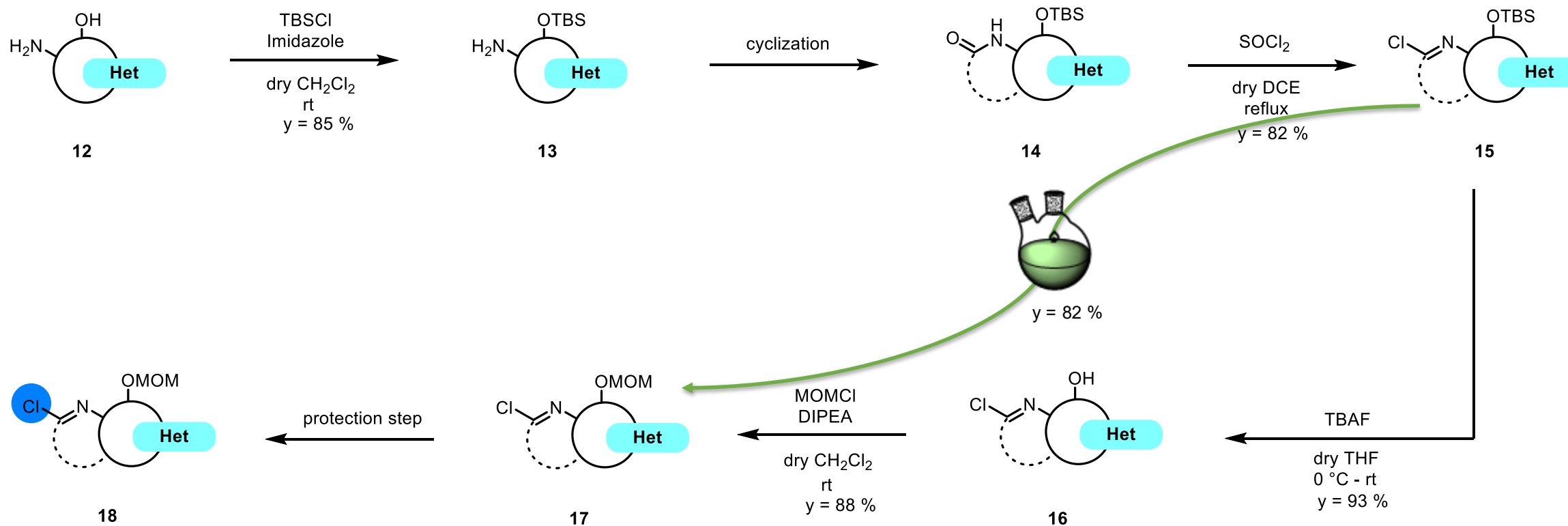


SYNTHESIS - BENZISOTHIAZOLINONE DERIVATIVE



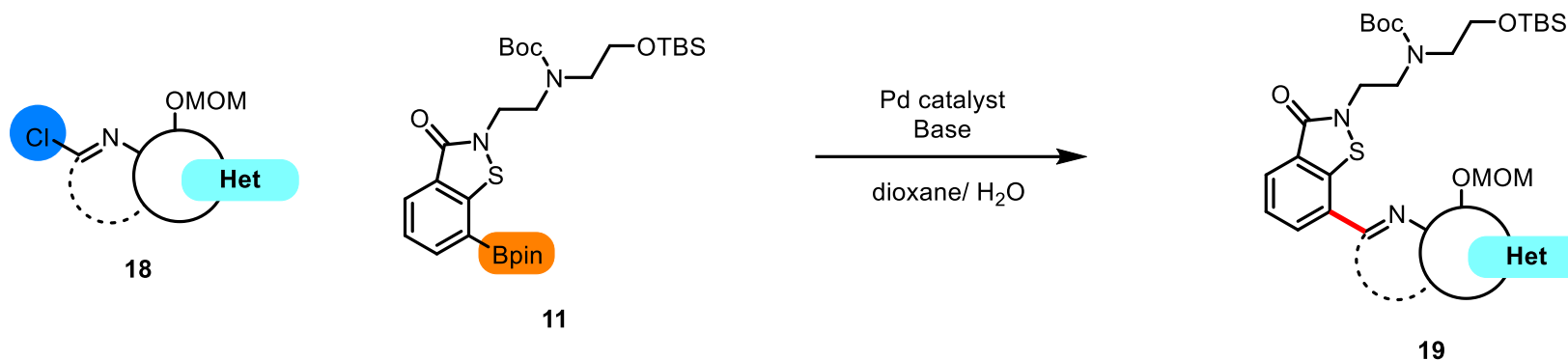


SYNTHESIS - HETEROCYCLE DERIVATIVE





SYNTHESIS - THE KEY STEP - SUZUKI COUPLING



Entry ^a	Pd catalyst ^b	Base ^c	V/v ratio ^d	Yield (%)
1 ^e	PdppfCl ₂	K ₂ CO ₃	3:1	24
2	PdCl ₂ (PPh ₃) ₂	K ₂ CO ₃	3:1	26
3	Pd(PPh ₃) ₄	K ₂ CO ₃	3:1	33
4	Pd(PPh ₃) ₄	Cs ₂ CO ₃	3:1	25
5	Pd(PPh ₃) ₄	K ₂ CO ₃	2:1	20
6	Pd(PPh ₃) ₄	K ₂ CO ₃	4:1	38
7	Pd(PPh₃)₄	K₂CO₃	10:1	52

^a T = 80 °C, ^b catalyst loading 10 mol%, ^c 2 equiv., ^d anhydrous and degassed solvents

^e Thun-Honenstein et al. *ChemMedChem*. **2022**, 17, e202100582



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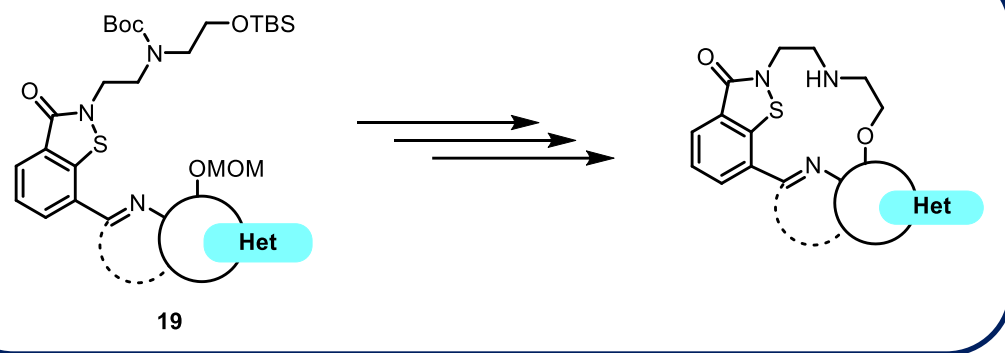


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Italiadomani
PIANO NAZIONALE
DI RIPRESA E RESILIENZA

FUTURE PERSPECTIVE



Binding assay on GSK-3 β (purified enzymes)

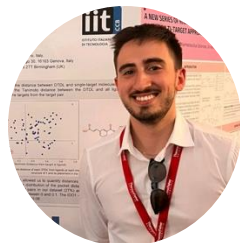


Functional assay on DR



Assessing ADME characterization and PK profile

ACKNOWLEDGMENTS



THANK YOU