

## DUAL MODULATORS OF PHOSPHODIESTERASE (PDE10A) AND SEROTONIN RECEPTOR 5-HT<sub>2A</sub> AS AN ALTERNATIVE APPROACH IN THE DEVELOPMENT OF NEW THERAPY FOR PSYCHIATRIC AND NEURODEGENERATIVE DISEASES

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### Introduction

Atypical neuroleptics, also known as second-generation antipsychotics (SGAs), are used in the treatment of schizophrenia, depression, and anxiety disorders. SGAs are multifunctional ligands that act as 5-HT<sub>2A</sub> and D<sub>2</sub> receptor antagonists and modulate neurotransmitter levels in the brain. Some of them are used off-label in neuropsychiatric symptoms (NPS) accompanying dementia [1]. Individual SGAs may cause several side effects and have varying effects on memory [2], thus in the search for ligands with better effectiveness and safety profile, the dual modulators of phosphodiesterase 10A (PDE10A) and serotonin 5-HT<sub>2A</sub> receptors were designed. PDE10A inhibition produces effects similar to D<sub>2</sub> receptor antagonism in dendritic membranes in medium spiny neurons of the subcortical striatum and has precognitive effects in animal models of cognitive disorders in schizophrenia [3]. Thus, we explored the potential of combining PDE10A inhibition with 5-HTR affinity as a viable strategy for developing ligands effective in neuropsychiatric symptoms (NPS) in dementia.

### Design

The compounds of the Series I (Fig.1) were designed with significant modifications to the Hofmann-La Roche PDE10A modulators from WO2011/0071128 [4].

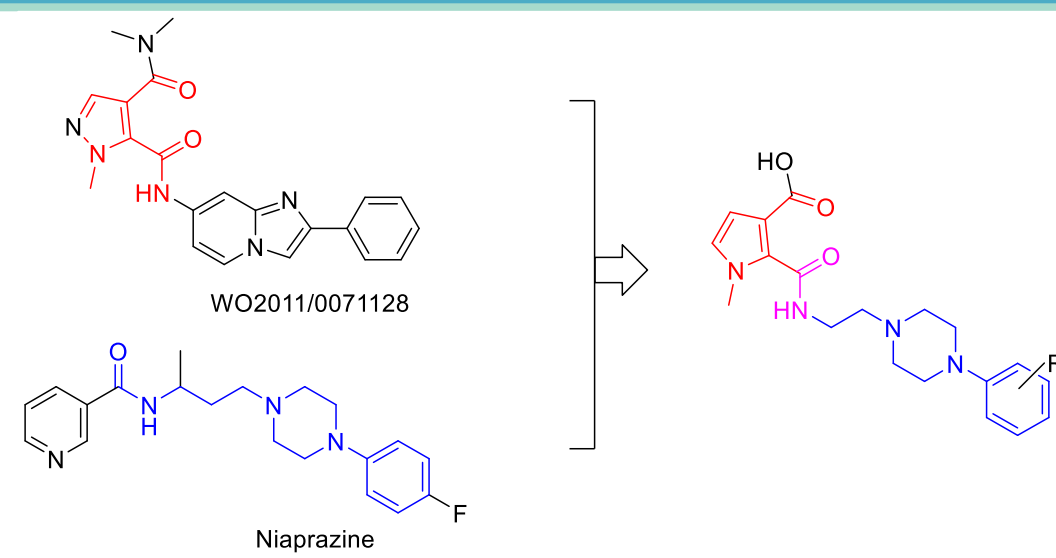


Fig.1 Design of Series I

The Series II was designed based on an isoquinoline fragment of PDE10A inhibitor – papaverine (Fig.2).

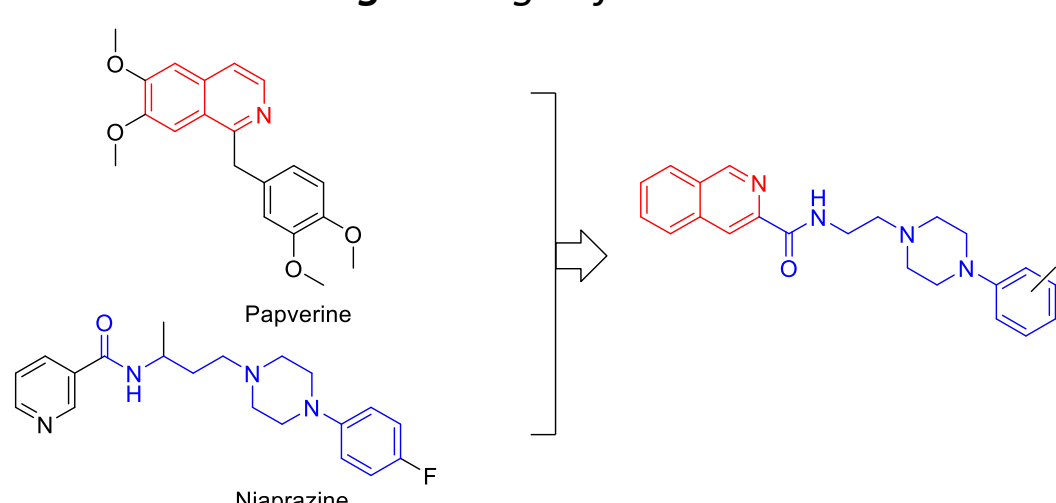


Fig.2 Design of Series II

These modifications, along with the well-known pharmacophore system for 5-HTRs ligands such as long-chain arylpiperazines (LCAPs), form the basis of our research.

### Synthesis

The synthesis of compounds from Series I and II was multi-stage (Fig.5). The first step was a chemical reaction that transformed primary alkyl halides into primary amines, according to the Gabriel method. The second step was the standard procedure of amide coupling with TBTU/DIPEA as an acid group activator.

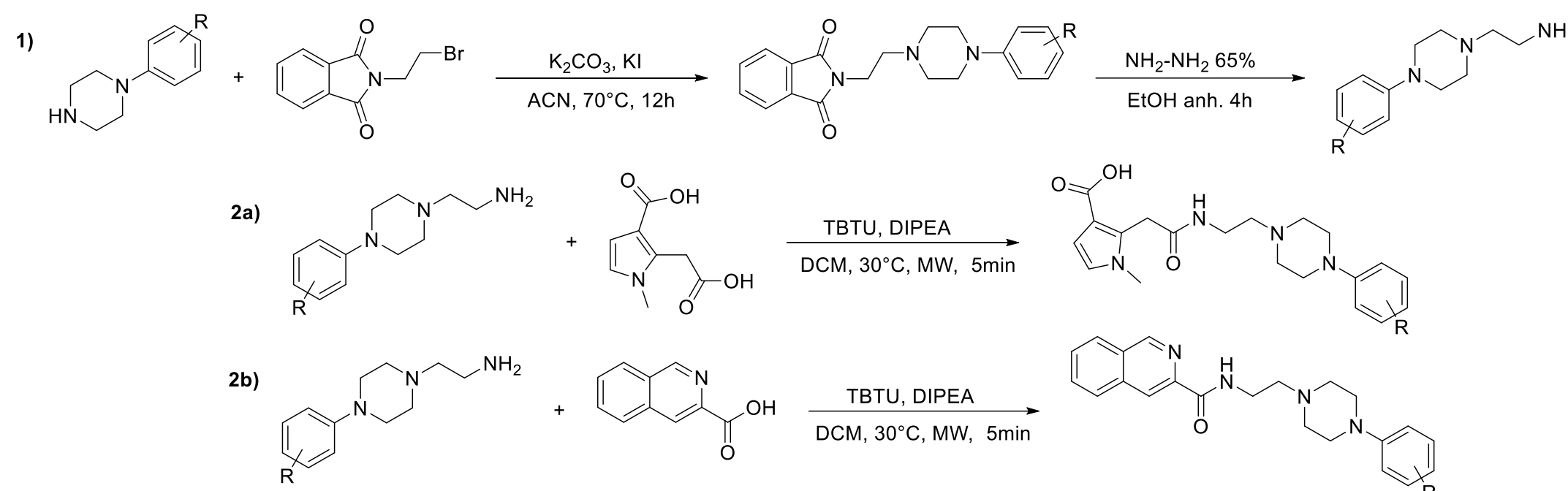


Fig.5 1) Amines synthesis; 2a) Amide coupling of Series I; 2b) Amide coupling of Series II

### Physicochemical properties

**Table 1** Properties calculated SwissADME: LogP - Predicted octanol/water partition coefficient; MW – molecular weight; HBD – hydrogen bond donor; HBA – hydrogen bond acceptor; RB – rotatable bonds; TPSA – total polar surface area

Compound	Lipinski's rule of 5				Veber filter	
	LogP	MW	HBD	HBA	RB	TPSA
AZAB1	0.80	370.4	2	4	8	77.81
AZAB2	1.07	388.4	2	5	8	77.81
AZAB5	0.71	400.5	2	5	9	87.04
AZAB7	1.25	404.9	2	4	8	77.81
AZAB8	1.11	388.4	2	5	8	77.81
AZAB9	1.31	404.9	2	4	8	77.81
AZAB10	0.79	400.5	2	5	9	87.04
AZAB11	2.73	360.5	1	3	6	48.47
AZAB12	2.96	378.4	1	4	6	48.47
AZAB15	2.61	390.5	1	4	7	57.70
AZAB17	3.15	394.9	1	3	6	48.47
AZAB18	2.97	378.5	1	4	6	48.47
AZAB19	3.17	394.9	1	3	6	48.47
AZAB20	2.63	390.5	1	4	7	57.70

### Metabolic stability

**Table 2.** The results expressed as the percentage of the compound that remains after 45 minutes of incubation with mouse liver microsomes (MLM). Verapamil was used as a positive control (30 ± 1% compound remaining after 45 min). Values are means of at least two experiments ± SD.

Compound	MLM stability (%) <sup>a</sup> ± SD
AZAB1	100 ± 5
AZAB2	100 ± 1

The study showed that compounds AZAB1 and AZAB2, which are derivatives from Series I, were metabolically stable.

### Molecular modeling

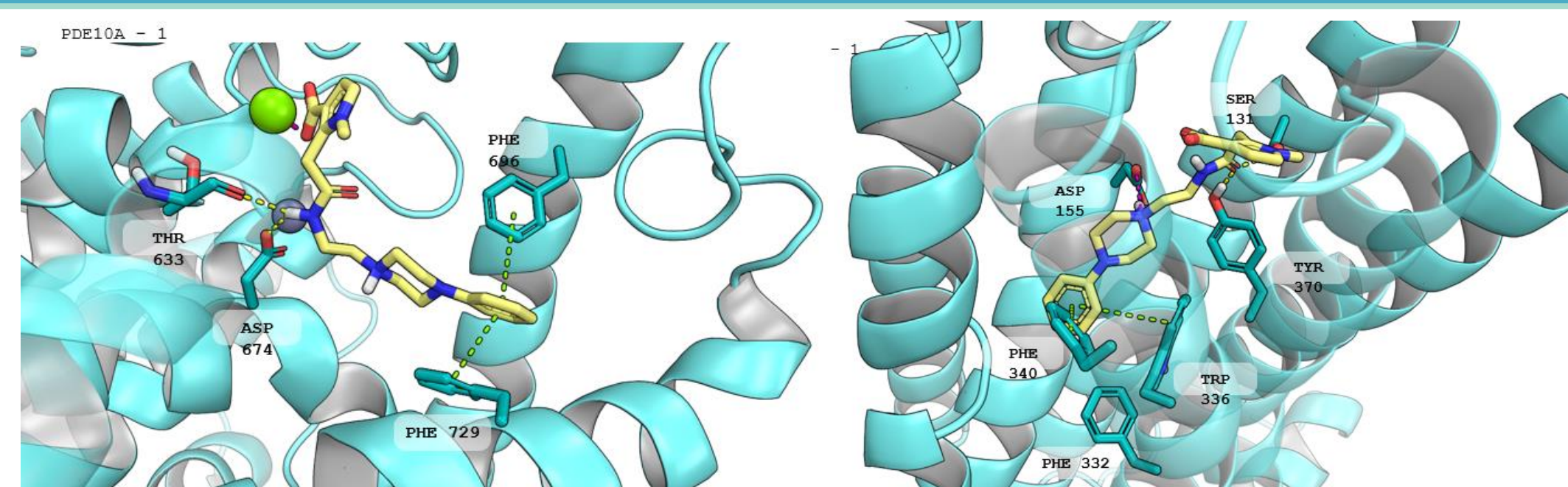


Fig.3 AZAB1 docked to the cristal structure of PDE10A and 5-HT<sub>2A</sub>R

Crucial interactions AZAB1 (derivative from Series I) docked to the crystal structure of PDE10A, were hydrophobic binding. The compound demonstrated also ability to coordinate with Zinc and Magnesium ions. AZAB1 formed a salt bridge with the deprotonated carboxylic group of Asp155 at the 5-HT<sub>2A</sub>R binding site (Fig.3).

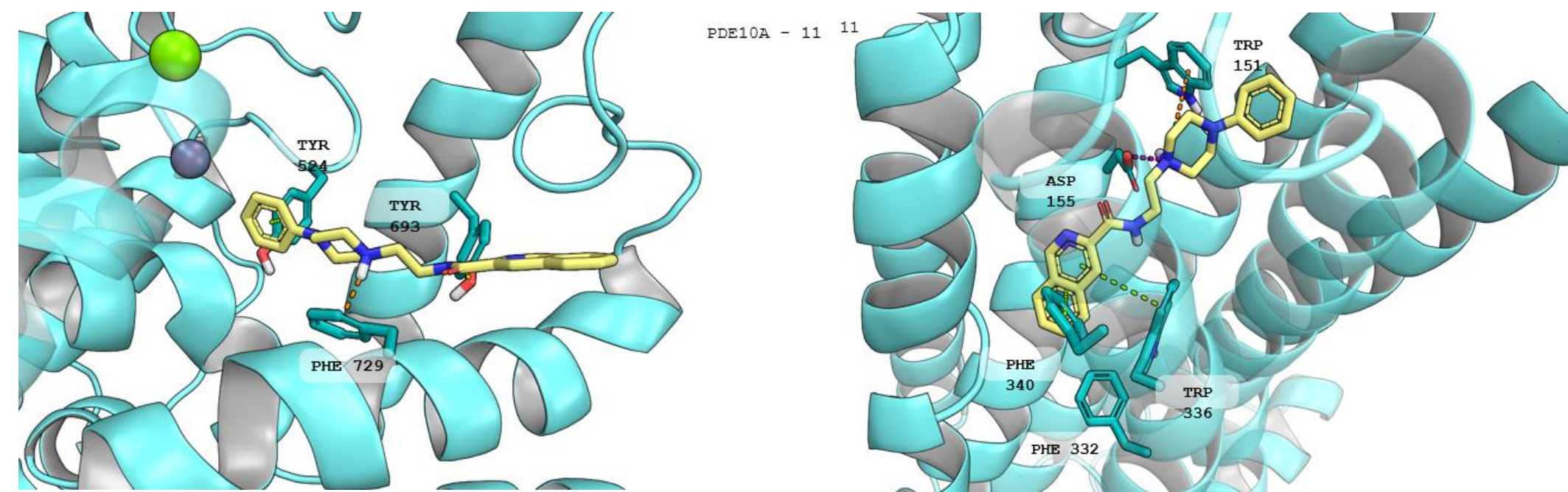


Fig.4 AZAB11 docked to the cristal structure of PDE10A and 5-HT<sub>2A</sub>R

Compared to AZAB1, AZAB11 (a derivative from Series II) were not demonstrate the ability to coordinate with Zinc and Magnesium ions. In the crystal structure of PDE10 and 5-HT<sub>2A</sub>R, AZAB11 bound with hydrogen bonds and indicated π-π/CH-π interactions (Fig.4).

### In vitro studies

The compounds AZAB1 and AZAB2, which are derivatives from Series I, were chosen for initial in vitro studies. They were tested for their PDE10A inhibitory activity using a luminescent assay and compared to the well-known PDE10A inhibitor, papaverine. The compounds exhibited inhibitory activity at a concentration of 10μM (Fig.6). Additionally, functional bioassays conducted in isolated rat aorta showed that compound AZAB2 had an antagonistic effect on 5-HT<sub>2A</sub>, with a pKB of 6.595 ± 0.098 (Fig.7).

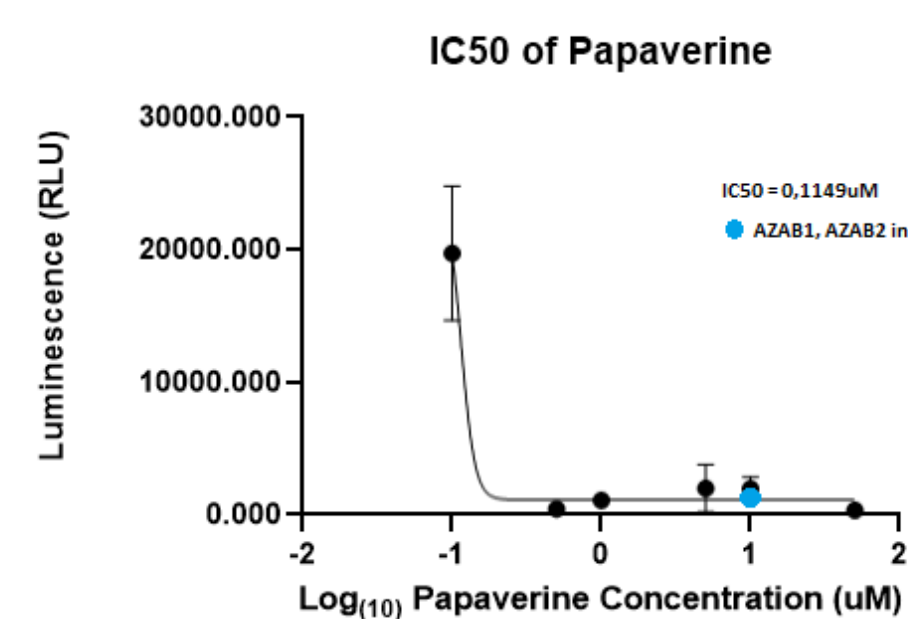


Fig.6 IC<sub>50</sub> curve of papaverine in PDE10A inhibitory activity assay. Results are expressed as luminescence depending on concentration.

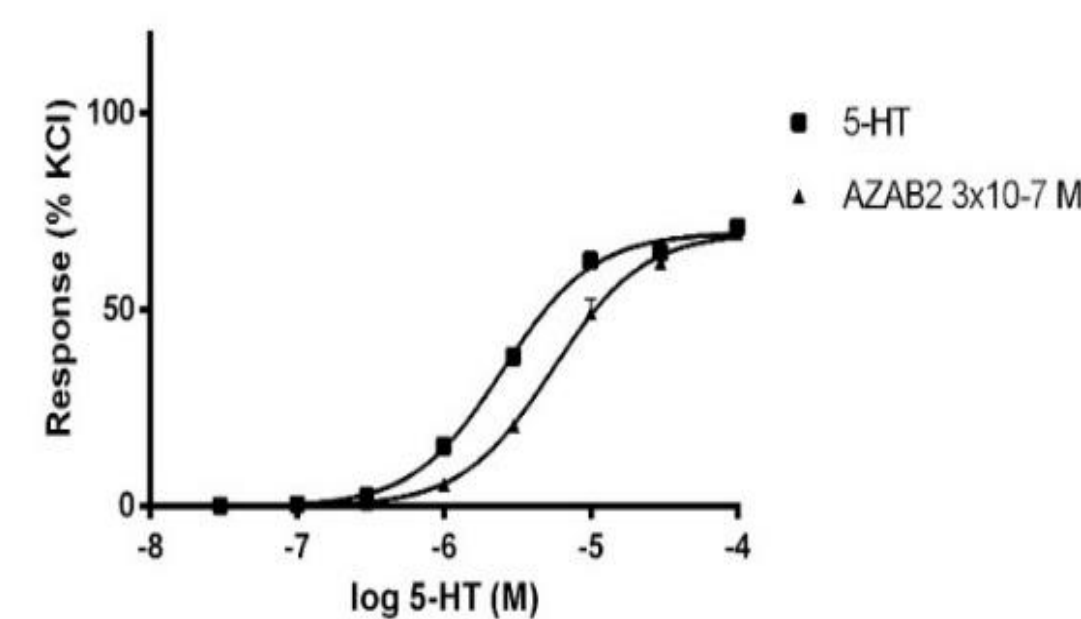


Fig.7 Concentration-response curves to 5-HT in the rat aorta. Results are expressed as a percentage of the maximal response to the KCl depolarizing solution.

### Conclusions

- Two series of compounds were designed and successfully synthesized.
- Compounds have been docked to the crystal structure of PDE10A and 5-HT<sub>2A</sub>R.
- Compounds satisfy Lipinski's rule of 5 and the Veber filter.
- Selected compounds were metabolically stable after 45 min in the MLM test.
- Compounds AZAB1 and AZAB2 in *in vitro* tests were found as PDE10A inhibitors with antagonistic effect on 5-HT<sub>2A</sub>R

### REFERENCES:

- [1] Pless, A. et al. *Front. Neurosci.* **2023**, *17*
- [2] Tampi, Rajesh R. et al. *Ther Adv Chronic Dis*, **2016**, *5*, 229–45
- [3] Zagórska, A. *Expert Opin Ther Pat*, **2020**, *2*, 147-157
- [4] Bachmann. Pde10 modulators. Published online August 30, **2012**

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