C3-FUNCTIONALIZED ANDROSTANE HYDRAZONO-HYDRAZIDES: NEW CANDIDATES FOR AKR1C3 INHIBITION

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AKR1C3 as a drug target

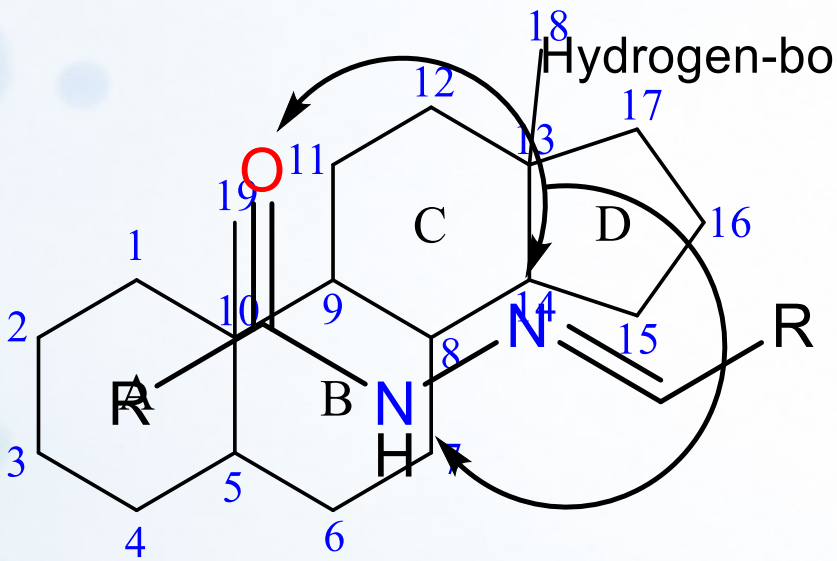


Fig 1. Structure of steroid core.

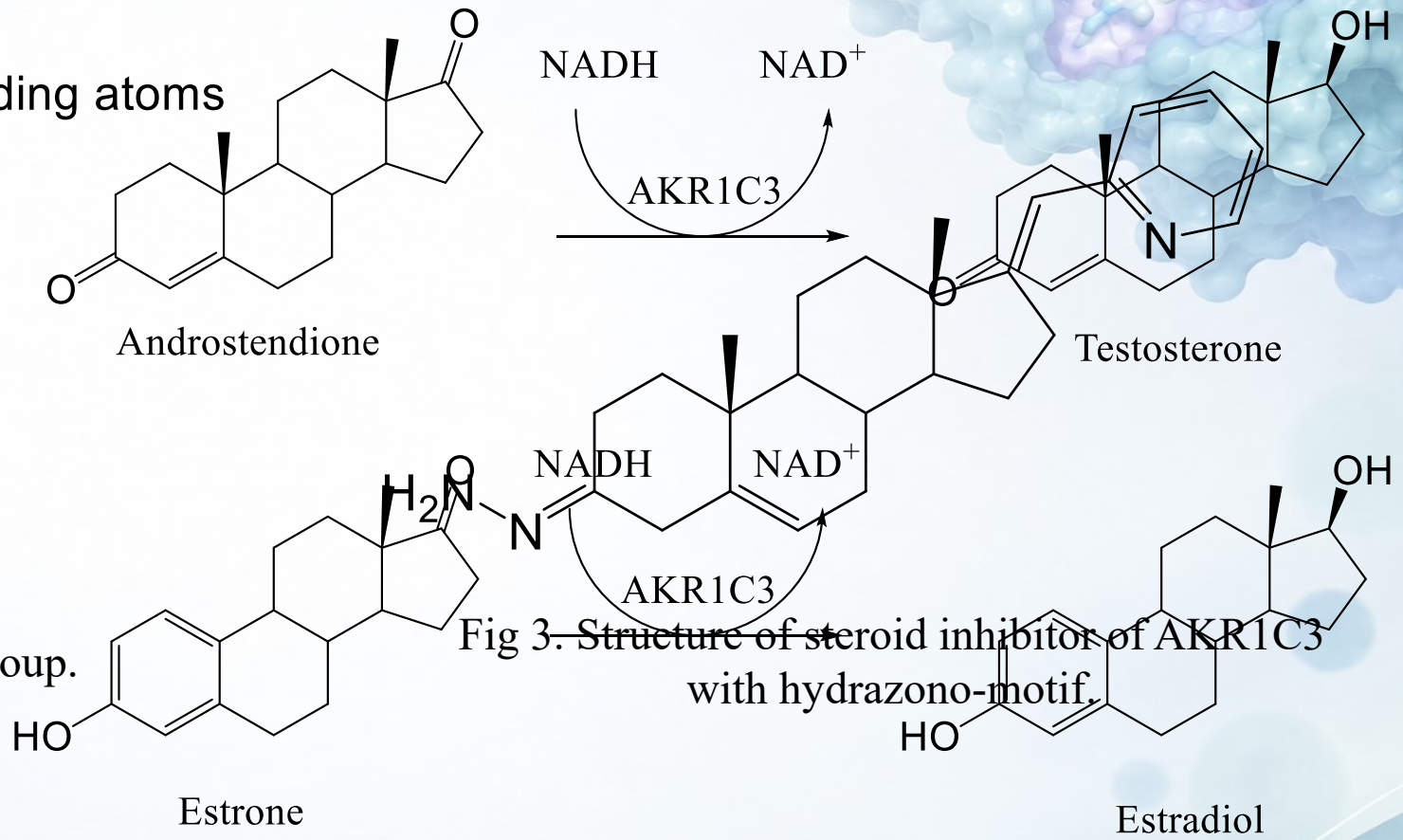
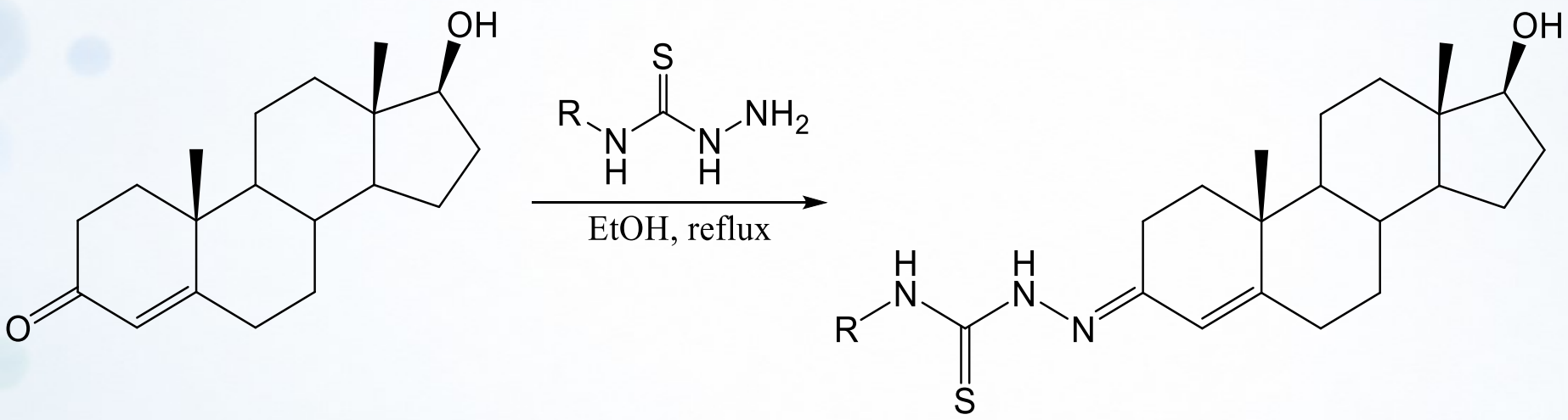


Fig 2. Structure of hydrazono-hydrazode group.

Fig 3. Structure of steroid inhibitor of AKR1C3 with hydrazono-motif.

Scheme 1. Steroid transformations catalyzed by AKR1C3.

Synthesis of new compounds



Testosterone

1 R=NH_2; 10 h, 34%

2 R=Ph; 19.5 h, 84%

Scheme 2. Synthesis of new testosterone hydroazono-hydrazide derivatives.



In silico ADMET prediction

Table 1. Toxic prediction of compounds **1** and **2** using Protox 3.0 online tool.

Clasification	Target	Prediction	
		Compound 1	Compound 2
Organ toxicity	Hepatotoxicity	Weakly inactive	
	Neurotoxicity	Weakly inactive	
	Nephrotoxicity	Weakly inactive	
	Respiratoy toxicity	Active	
	Cardiotoxicity	Weakly inactive	
Toxicity and points	Carcinogenicity	Weakly active	
	Immunotoxicity	Active	
	Mutagenicity	Weakly active	Weakly inactive
	Cytotoxicity	Weakly inactive	Inactive
	Ecotoxicity	Weakly active	

Fig 4. Radars bioavailability of compounds **1** and **2**.

Fig 5. Graphic analysis of intenstinal and brain permeation for compounds **1** and **2** using "BOILED Egg" model.

In vitro biological activity against AKR1C3 and AKR1C4

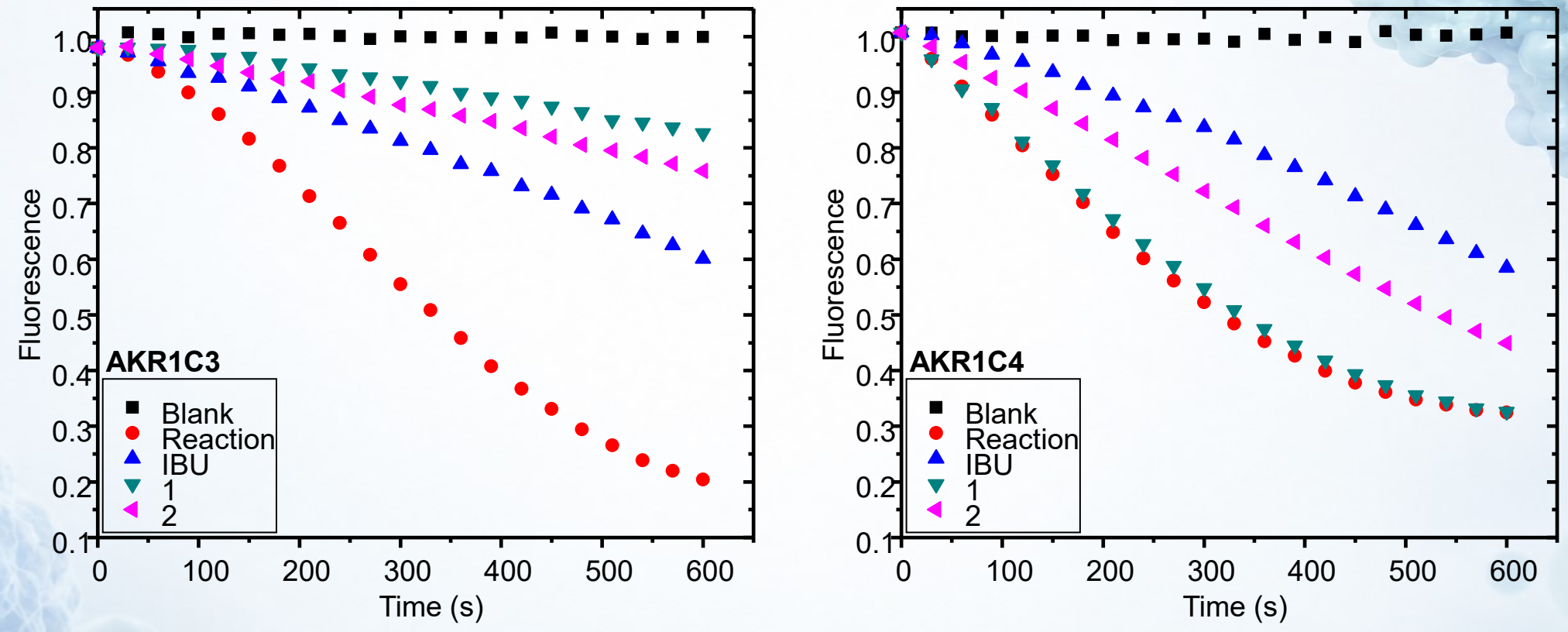


Fig 6. *In vitro* inhibition potential against AKR1C3 and AKR1C4 enzymes.

Docking analysis

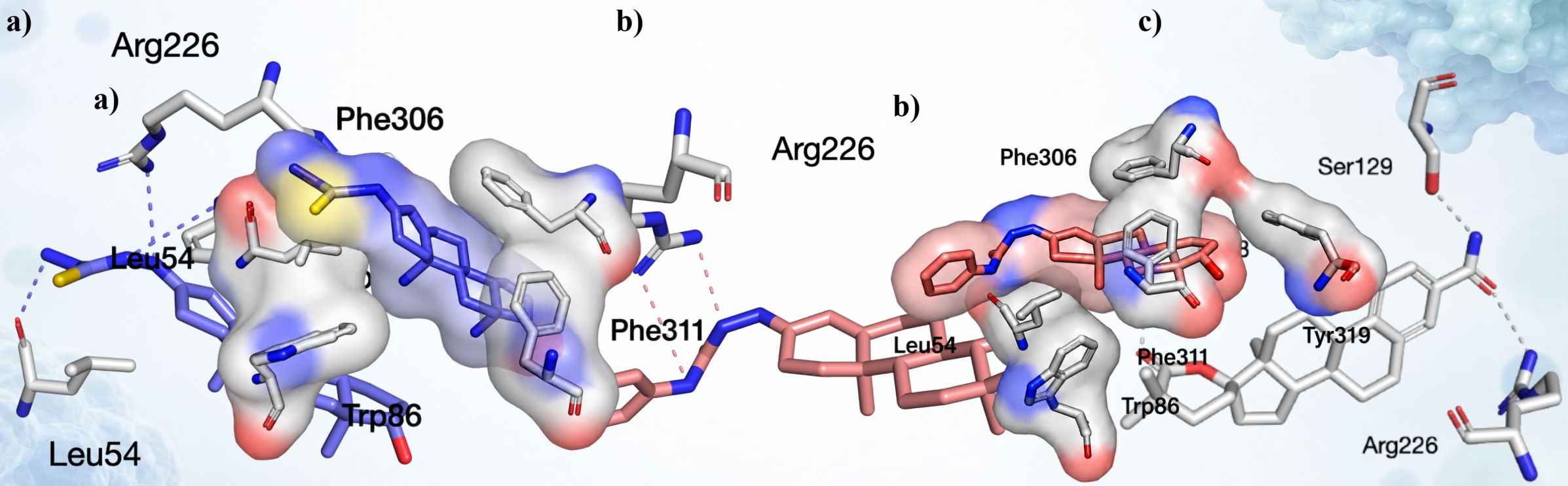


Fig 8. Hidrofobic interactions with AKR1C3 a) compound **1**; b) compound **2**

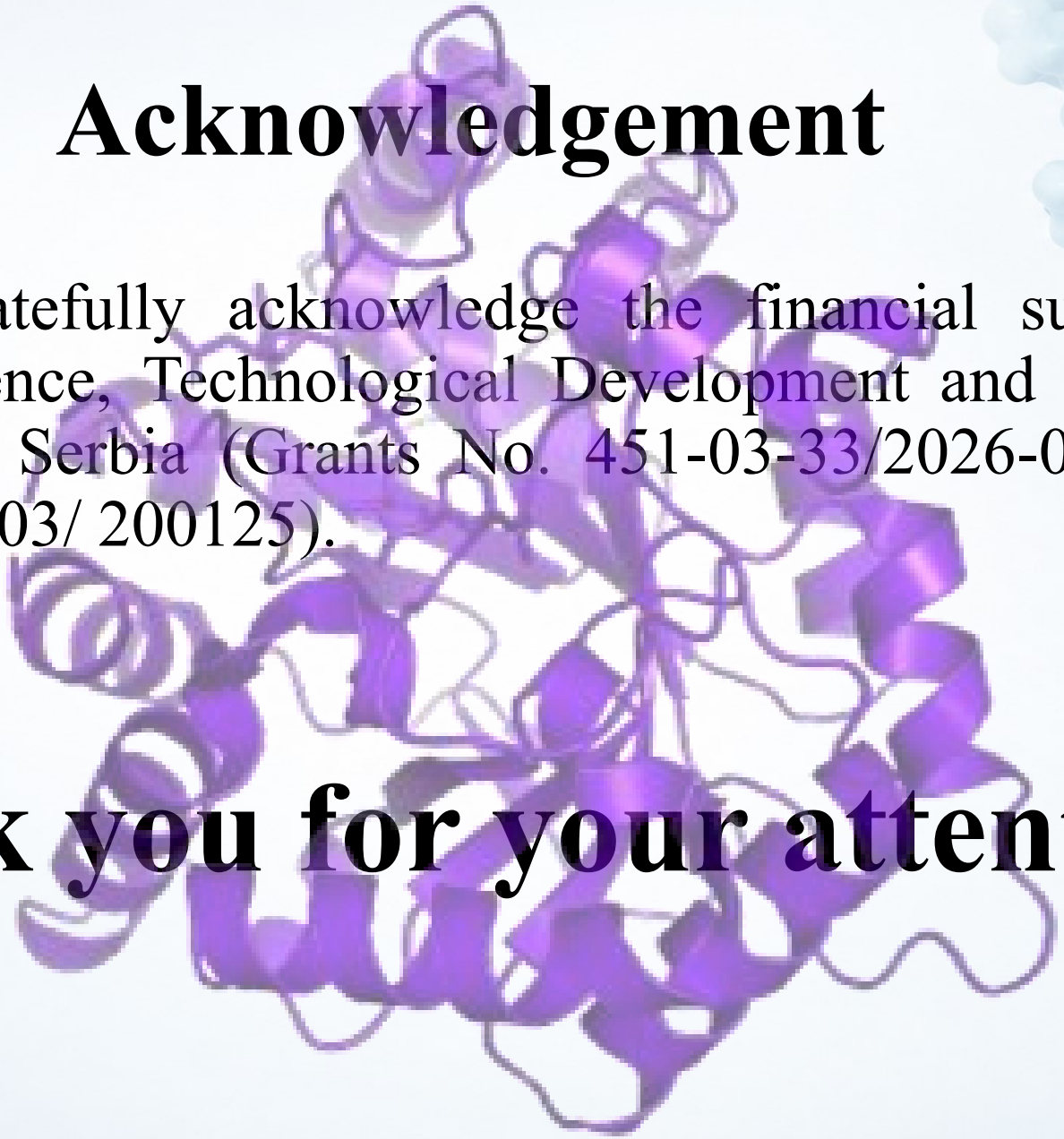
Fig 7. Hidrogen interactions with AKR1C3 a) compound **1** (-9.72 kCal/mol); b) compound **2** (-10.43 kCal/mol); c) control docking (-15.30 kCal/mol).

Conclusion

- Two novel testosterone thiohydrazono-hydrazides were synthesized, both showing selective *in vitro* inhibitory potential against AKR1C3;
- *In silico* predictions indicated gastrointestinal absorption and no blood–brain barrier penetration, alongside potential immunotoxicity and respiratory toxicity;
- Molecular docking revealed key interactions between our compounds and AKR1C3 active site.

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Thank you for your attention