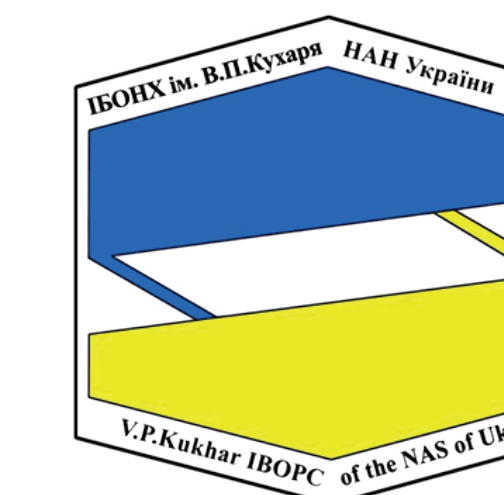
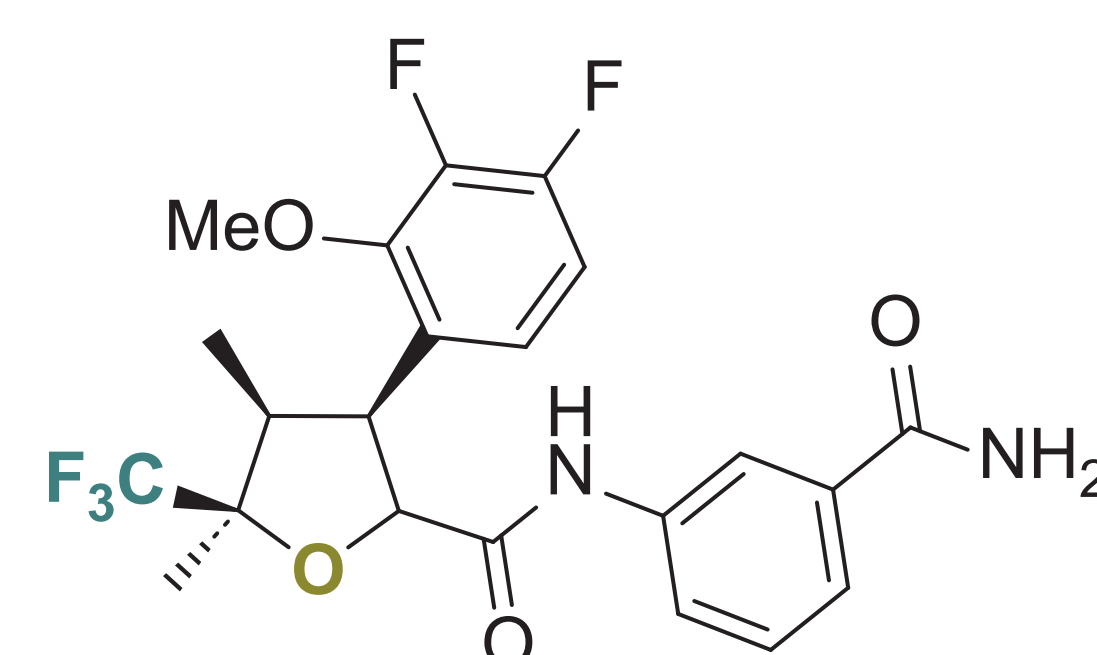


# $\gamma$ -Functionalized $\alpha$ -CF<sub>3</sub>-substituted derivatives of tetrahydrofuran and tetrahydrothiophene: synthesis and physicochemical evaluation



Oleksandr S.Liashuk, Mykhailo Redka, Nazar Dovhaniuk, Ivan Kondratov, Oleksandr Grygorenko

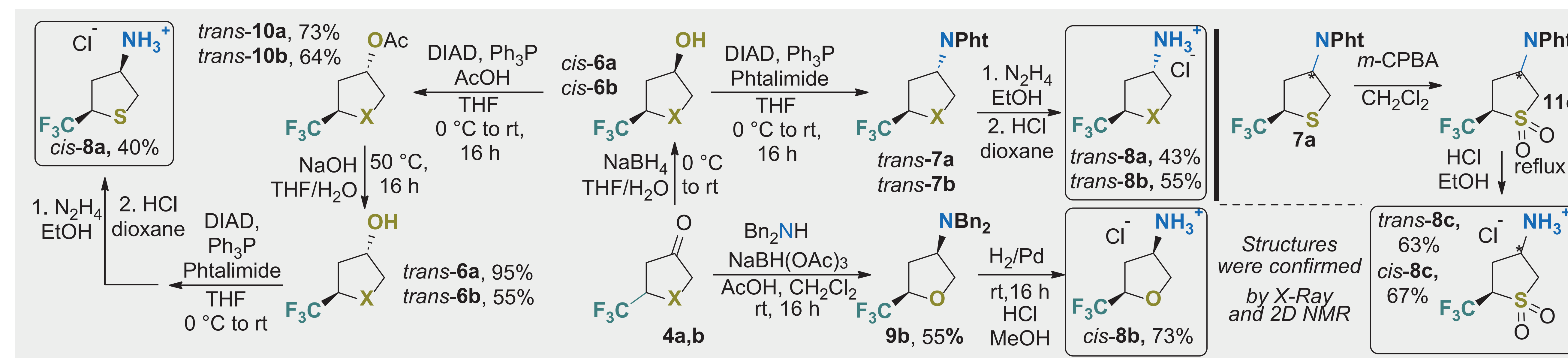
## Concept of the Project



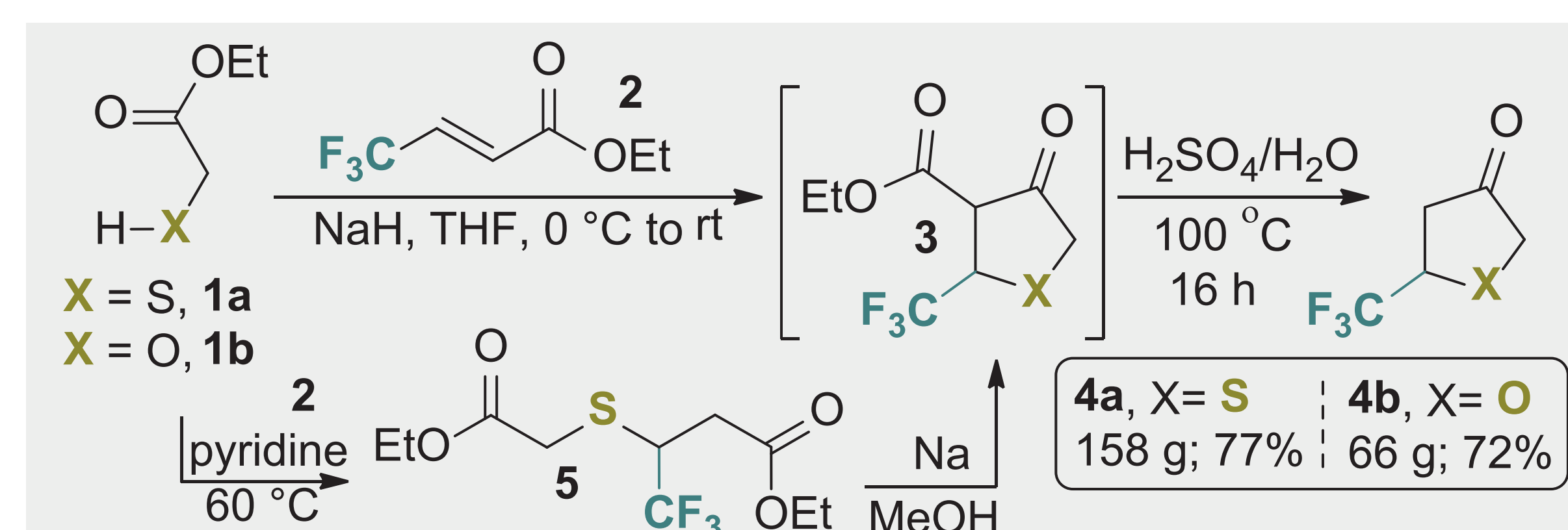
**Suzetrigine (Journavx®)**  
selective inhibitor  
of Na<sub>v</sub>1.8-dependent  
pain-signaling pathways

- Development of the synthetic methodology toward  $\gamma$ -functionalized  $\alpha$ -CF<sub>3</sub>-substituted saturated O and S-heterocycles;
- Evaluation and comparison of the physicochemical properties of O-, S- and SO<sub>2</sub>- heterocycles with or without CF<sub>3</sub> fragment.

## FG transformations



## Key BBs preparation



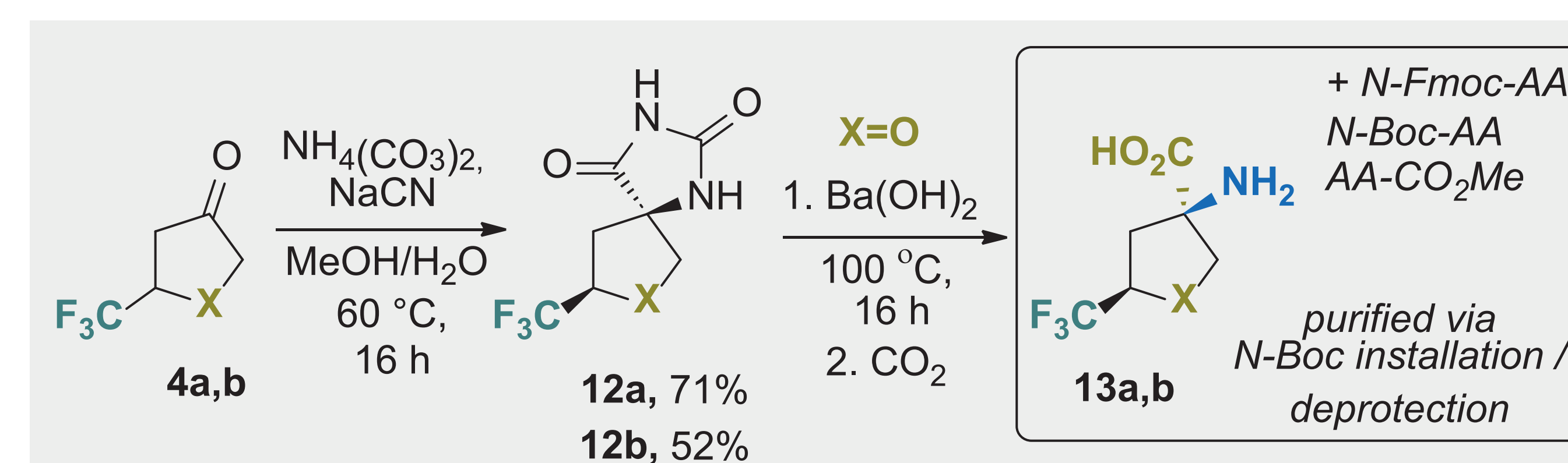
## Conclusions

- ✓ Diastereoselective synthesis of the target amines and aminoacids was achieved;
- ✓ Acidity and lipophilicity was only **slightly** affected by the spatial orientation of the substituents;
- ✓ **Isoelectric** point mainly governed by the **amino** group properties;
- ✓ Acidity and lipophilicity in the discussed scaffolds demonstrated the **downstream** trend in order **S>O>SO<sub>2</sub>**;

## Contact

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## Synthesis of CF<sub>3</sub>-aminoacids



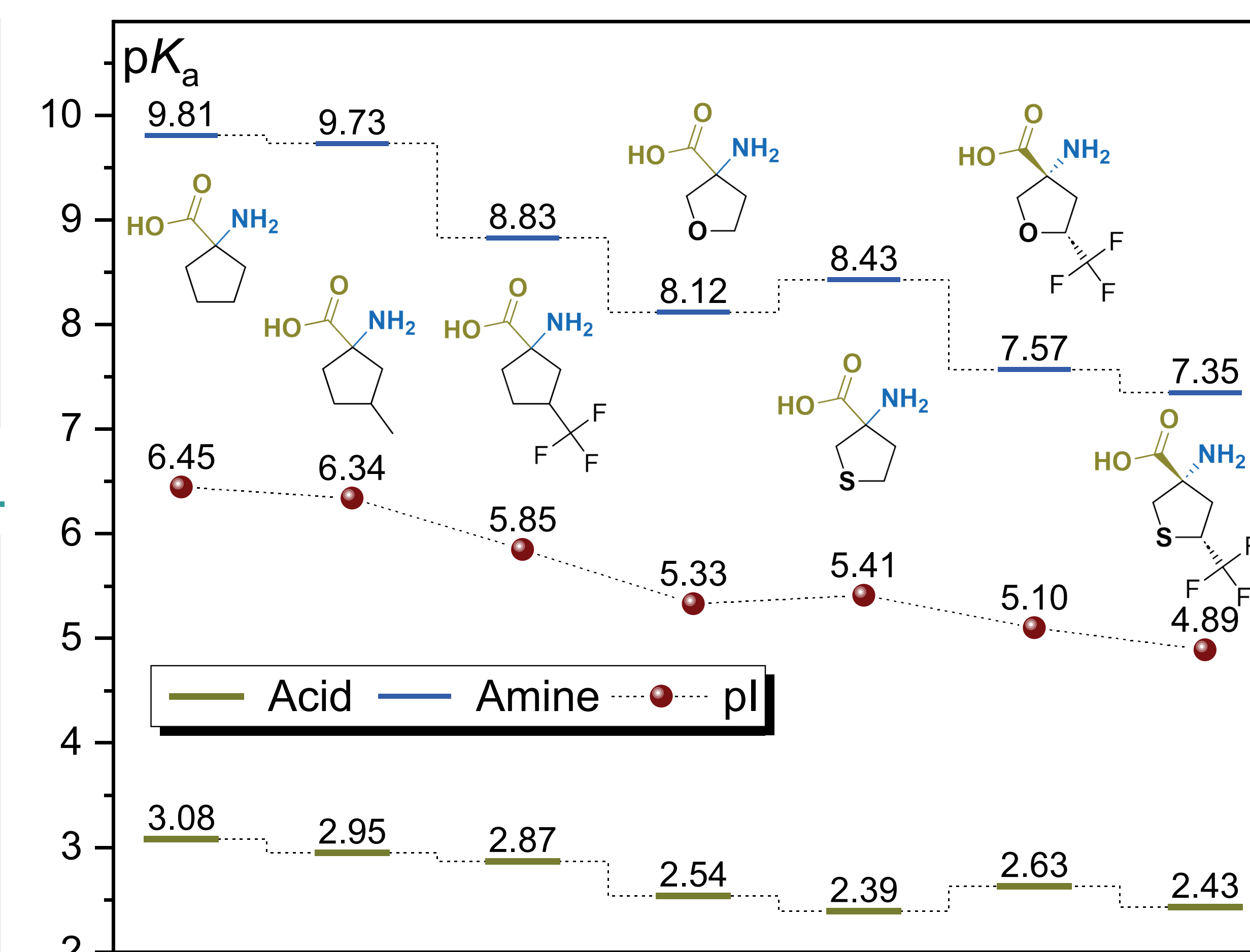
## Physicochemical properties of amines 8a-c

(\* LogP was measured for corresponding benzamide derivatives)

| LogP           | pKa            | LogP           | pKa            | LogP           | pKa            |
|----------------|----------------|----------------|----------------|----------------|----------------|
| cis-8b: 1.86   | cis-8b: 7.58   | cis-8a: 2.82   | cis-8a: 7.60   | cis-8c: 1.57   | cis-8c: 5.82   |
| trans-8b: 2.01 | trans-8b: 7.65 | trans-8a: 2.70 | trans-8a: 7.60 | trans-8c: 1.54 | trans-8c: 5.71 |

✓ Cis- and trans- isomers demonstrated identical **pKa** and **LogP** values

## Physicochemical properties of aminoacids



## Quick summary

**One scaffold** →  
**3 heterocycles** →  
**different ionization**  
**& polarity profiles**

- Diastereoselective access to CF<sub>3</sub>-heterocycles and amino acids.
- Fine-tuning of pKa, LogP, and pI by scaffold and orientation.
- Scope for bioisosteric design and polarity-driven SAR.

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MINISTRY  
OF EDUCATION AND  
SCIENCE OF UKRAINE