

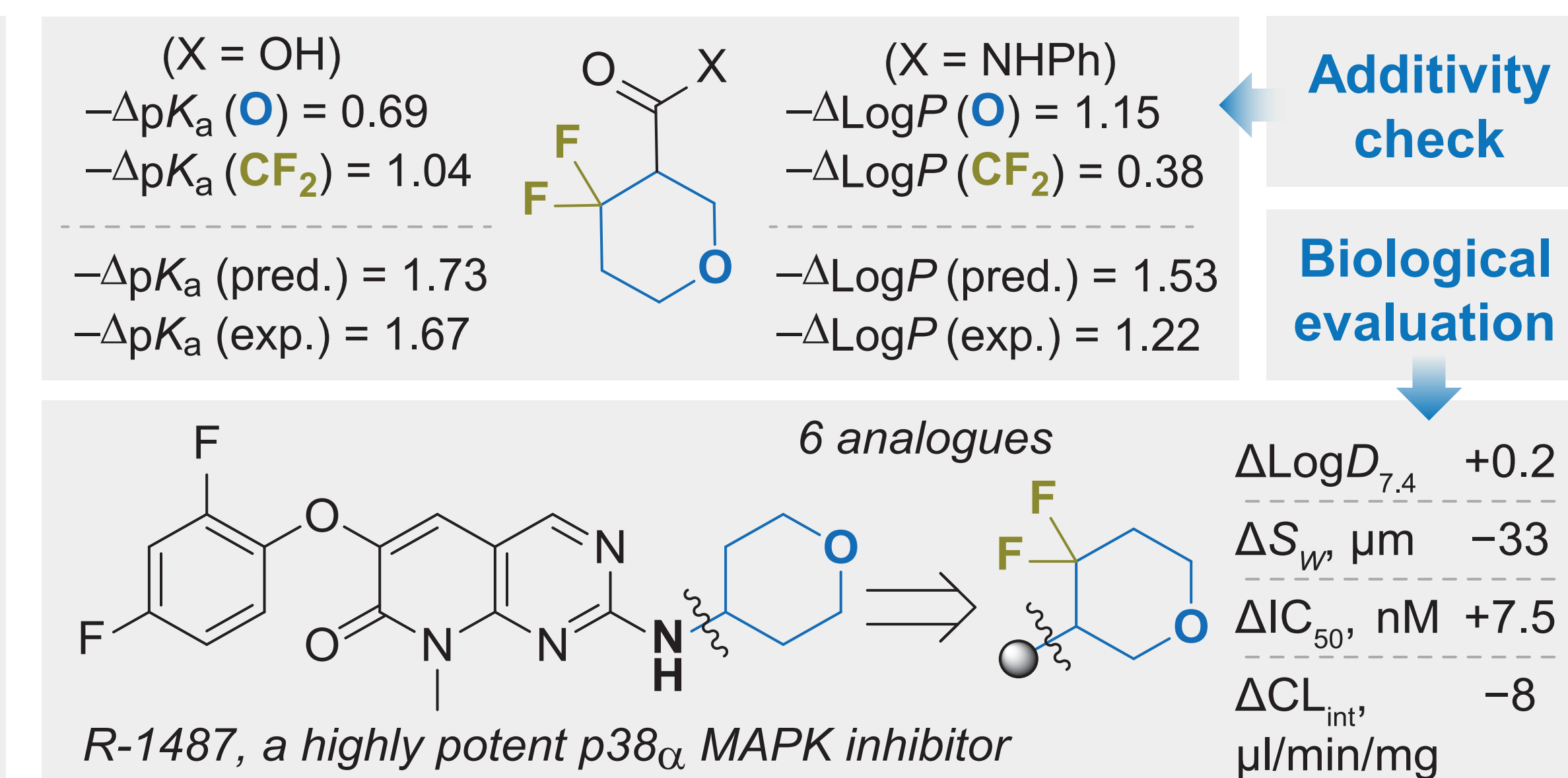
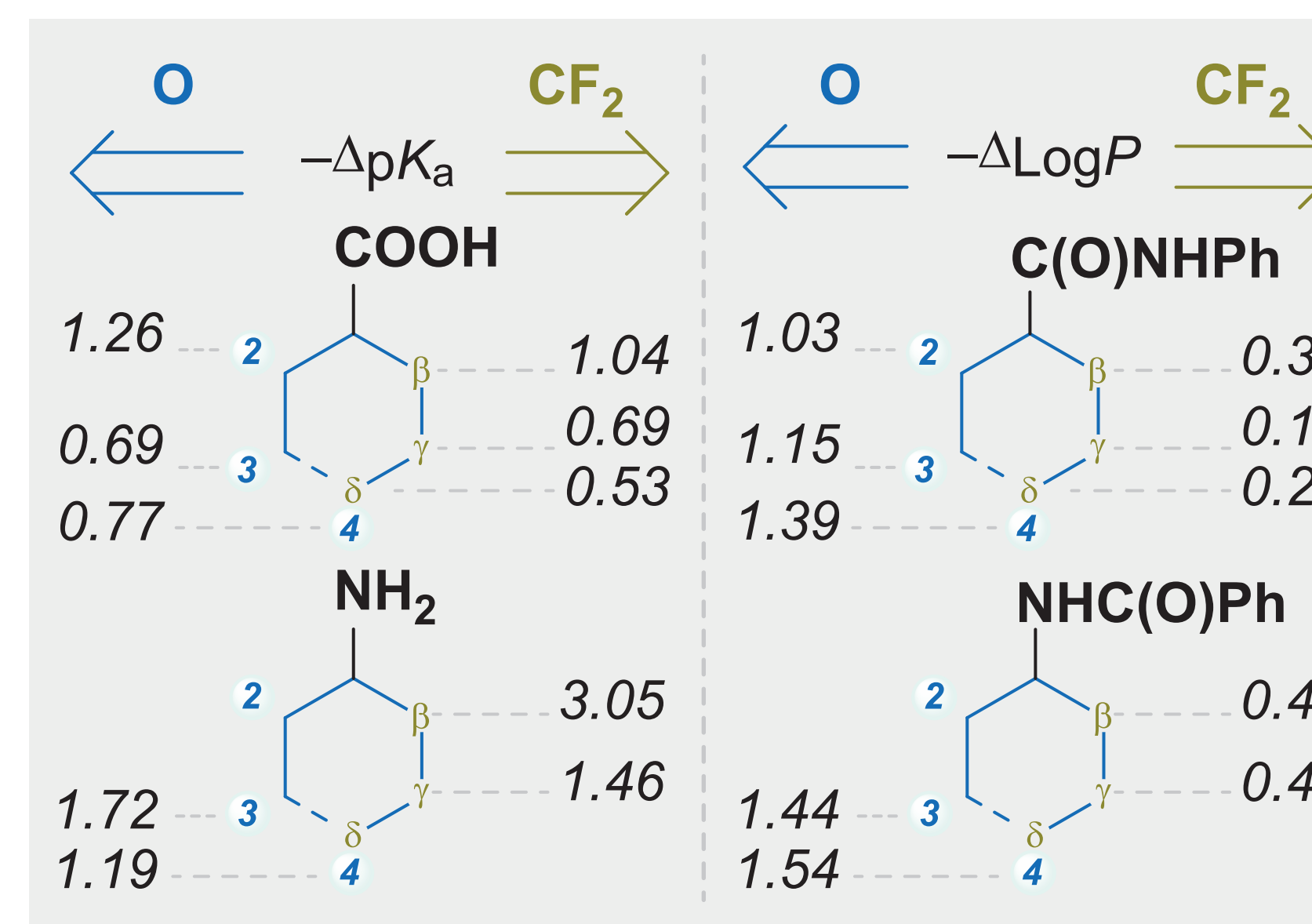
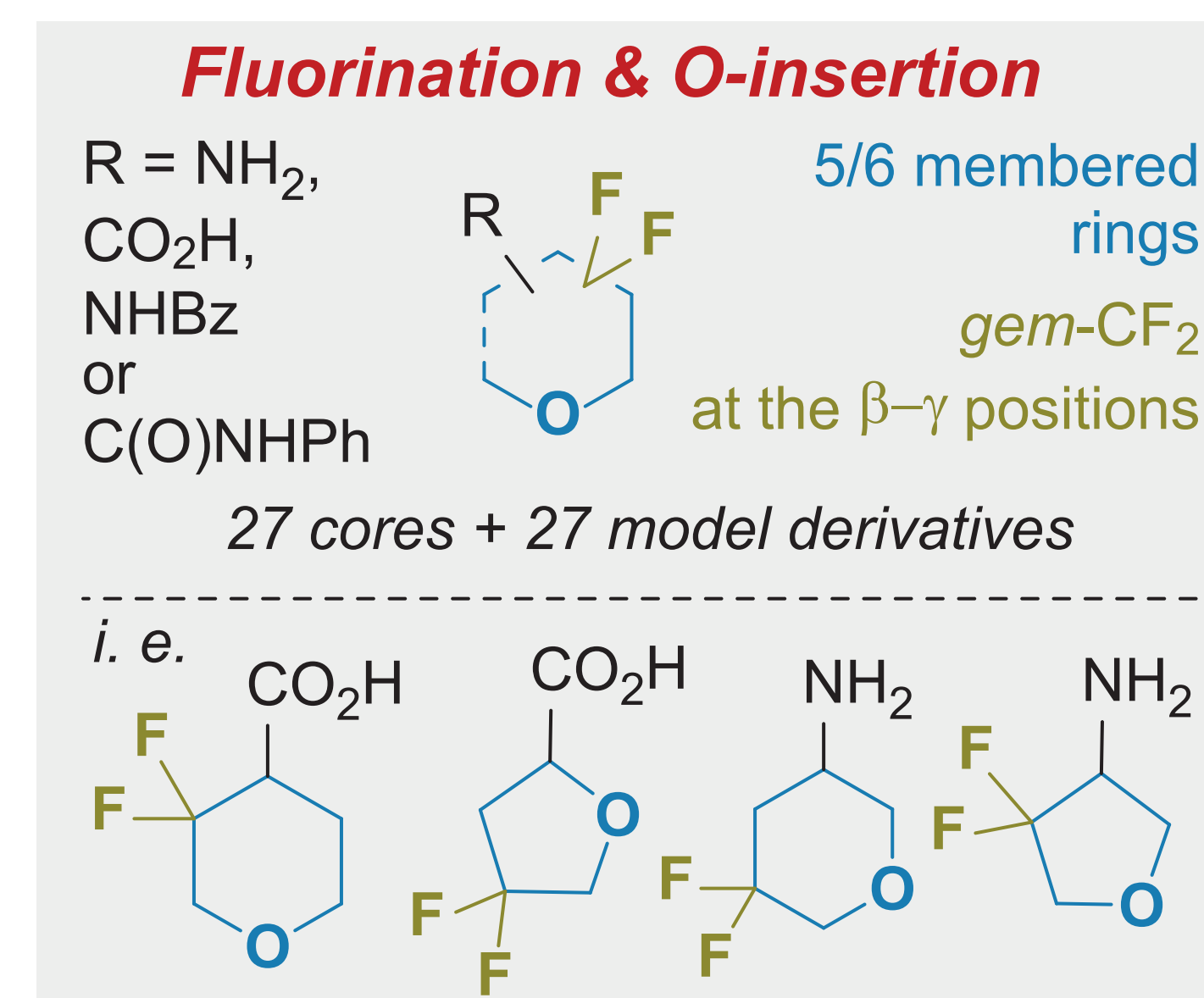
gem-Difluorinated saturated O- and N-heterocycles - the new tools for fine tuning of physicochemical properties



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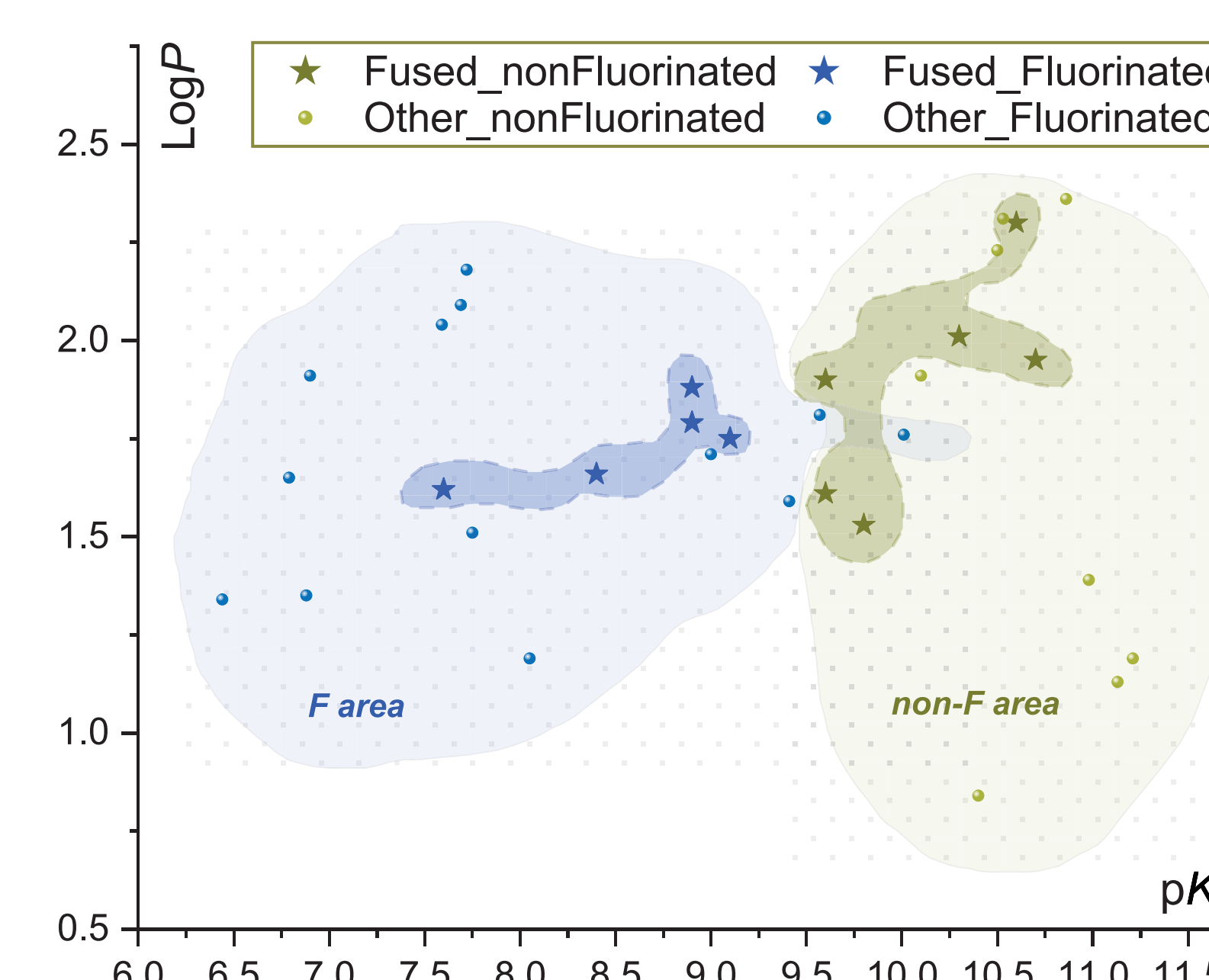
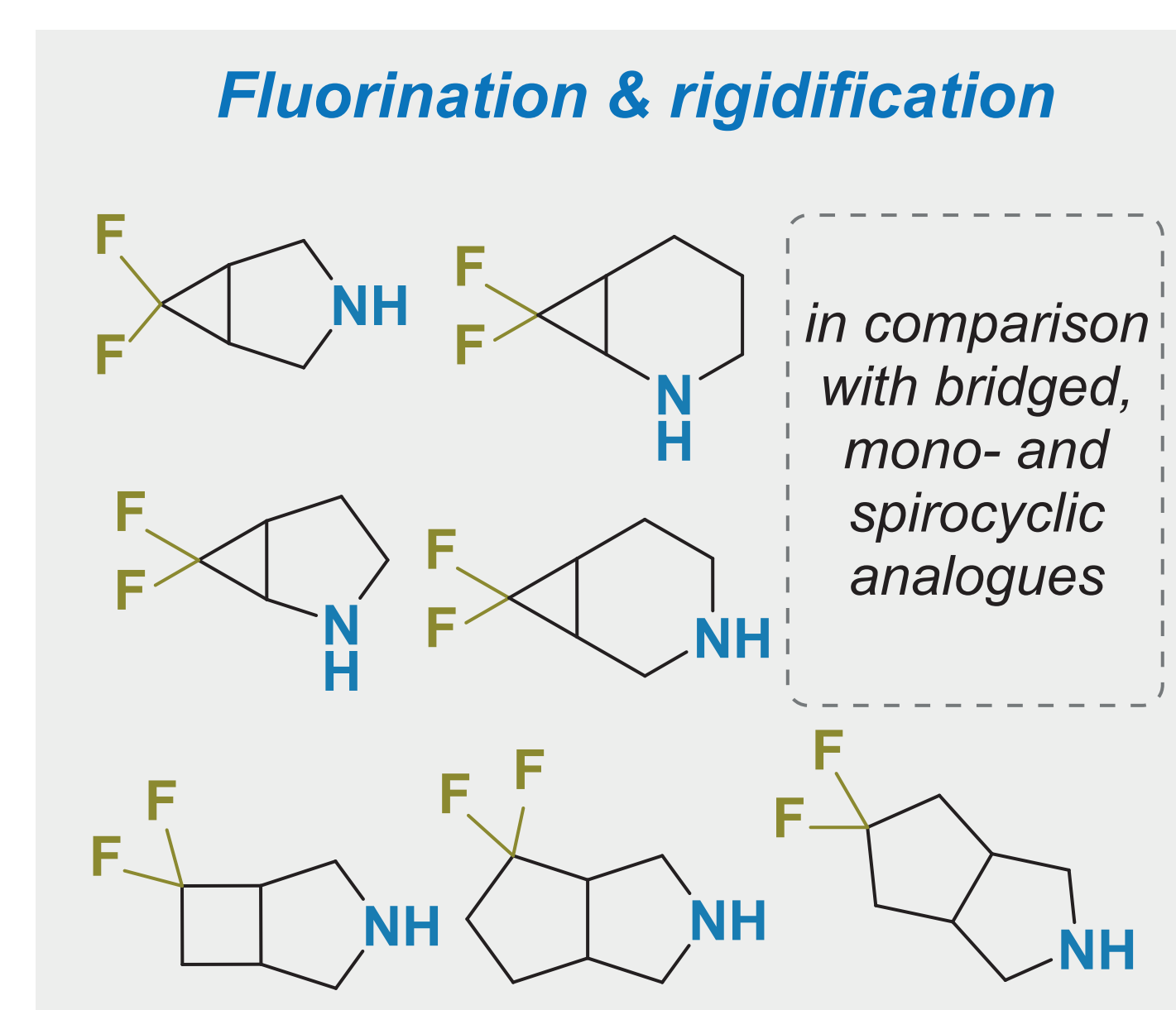
Concept of the Project

- Investigation of the synergistic effects of **fluorination** and **structure rigidification** or **heteroatom addition** on physicochemical properties of simple scaffolds;
- Unveiling the possible regularities between the fluorination pattern and the net fluorination effect;

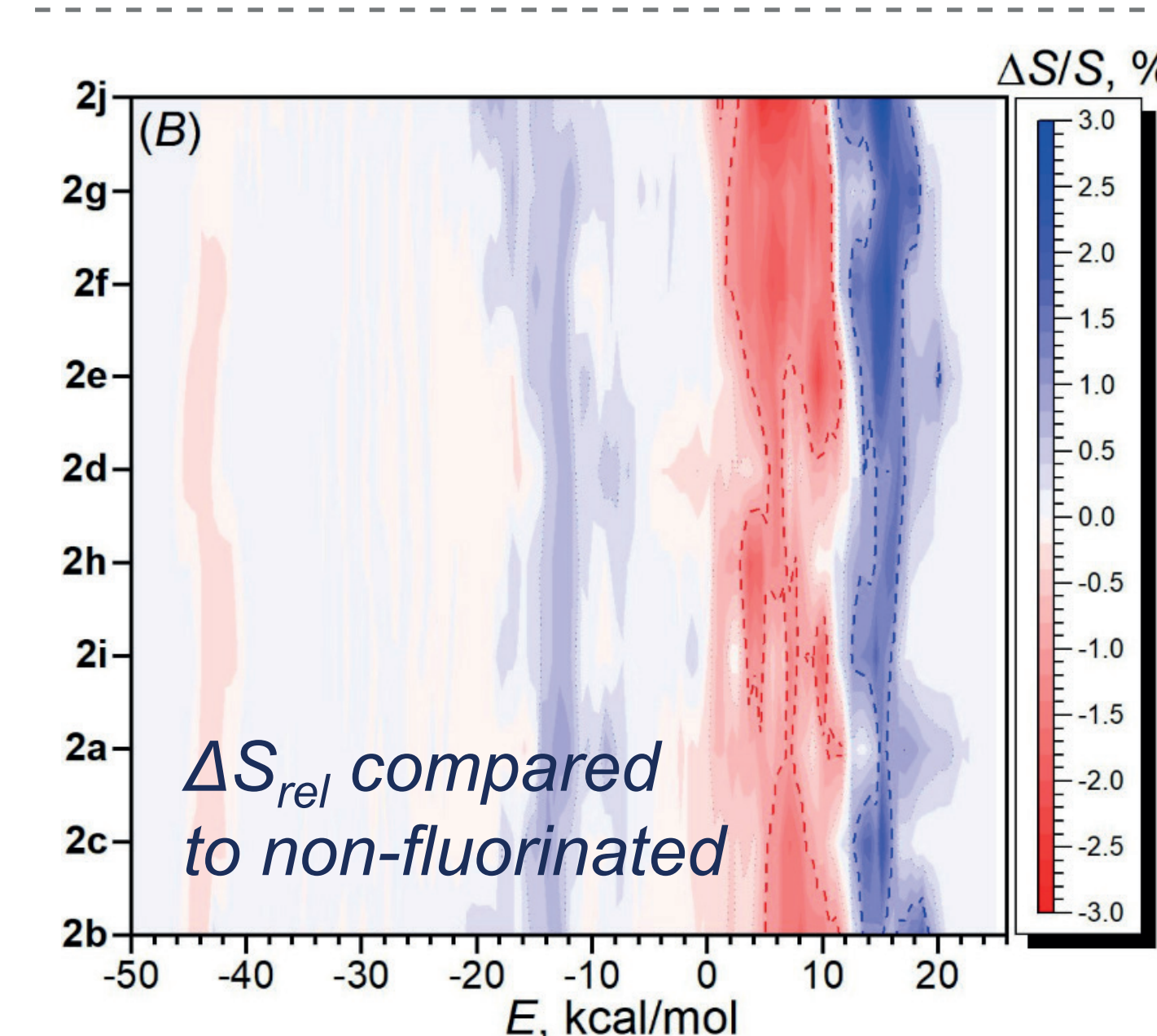
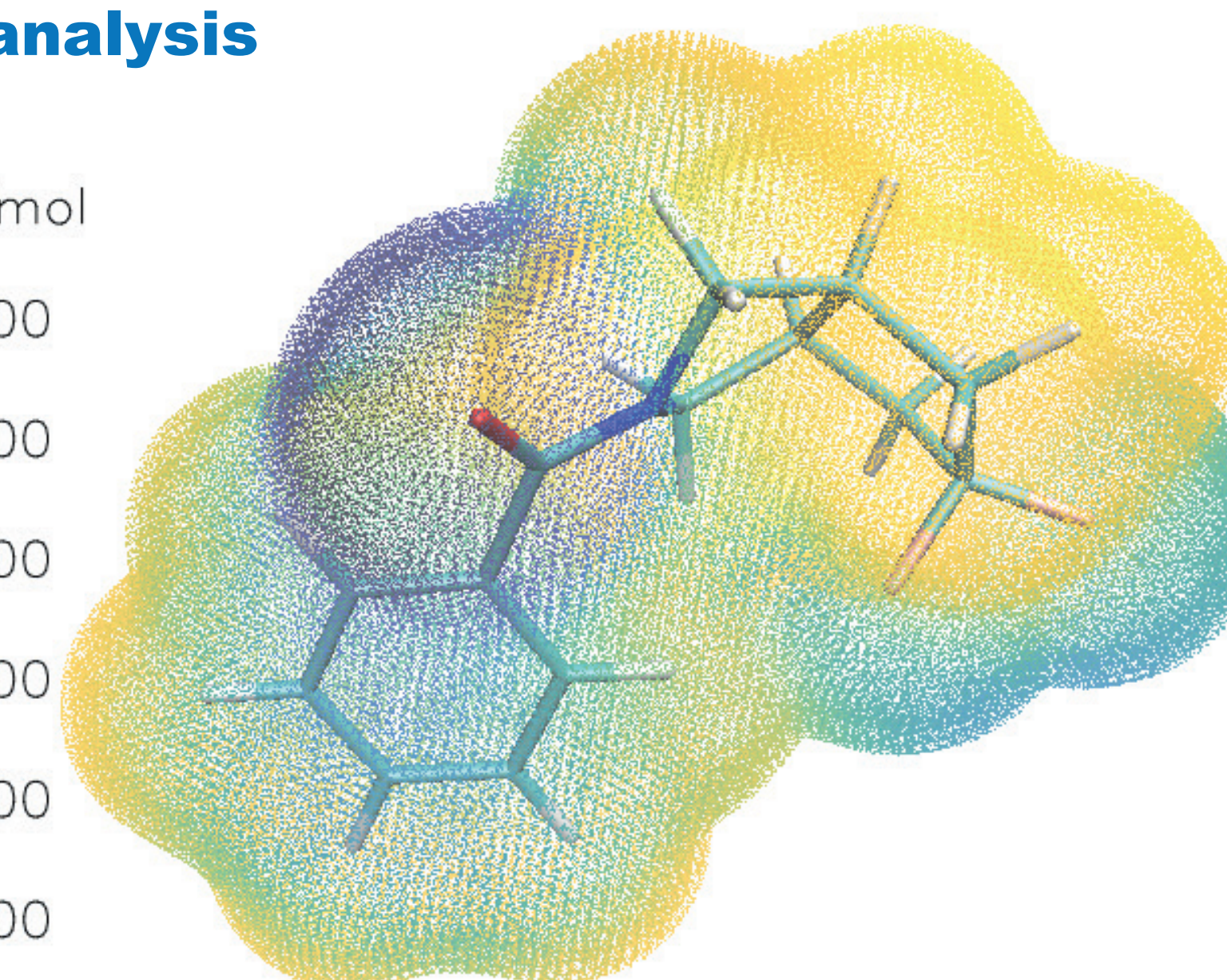
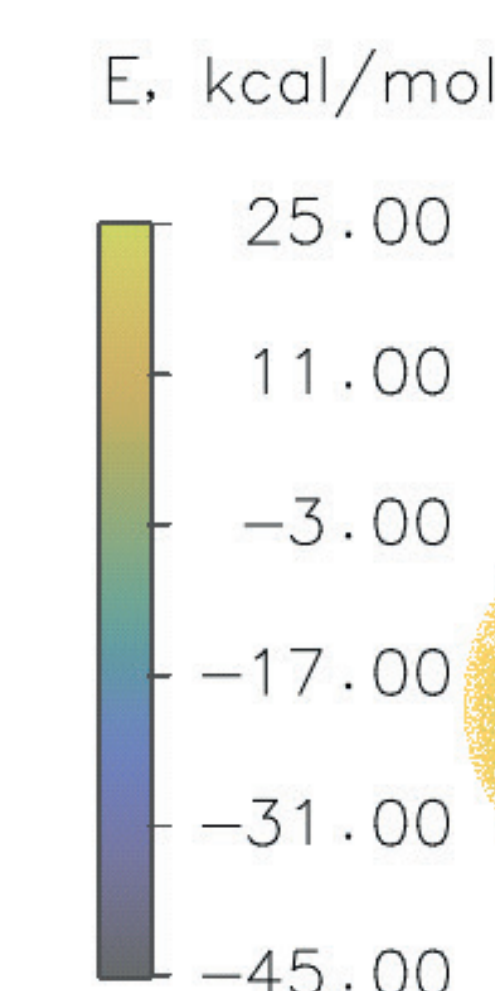


Key Findings of the Project

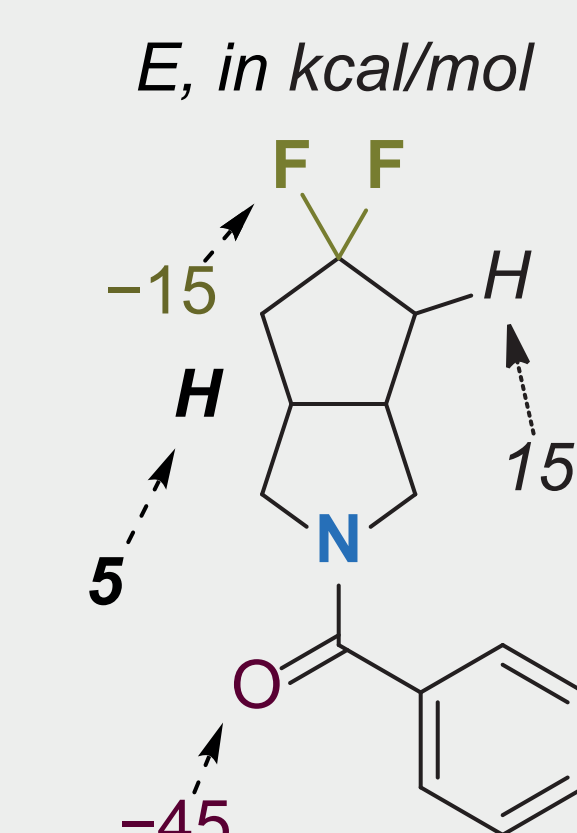
- pK_a** of the ionizable groups is mostly affected by **inductive** effect.
 - Additive** in case of polyfunctionalized molecules;
 - Strictly **dependent on the number of C-C bonds** between heteroatom fragment and functional group;
- LogP** is less predictable and not additive.
 - “Repolarization”** of the amide fragment is **important** for overall result;
 - Fluorine** itself **increases** lipophilicity;
 - Increased** hydrophilicity upon fluorination could be related to **polarization** of the nearby C-H bonds, including hyperconjugation pathway; strongly dependent on the spatial orientation.



MEPS analysis



Polarization shift upon fluorination



Parameter	Cyclopropane derivatives	Higher homologues
ΔLogP/LogP	Mostly positive ^[a]	Negative
“Highly negative” area (E = -45...-40 kcal/mol, corresponds to the oxygen atom)	No correlation	Negative, R ² = 0.94
“Negative” area (E = -20...-5 kcal/mol, corresponds to the fluorine atoms)	No correlation	Negative, R ² = 0.84
“Neutral” area (E = -5...10 kcal/mol, corresponds to non-polarized hydrogen atoms)	Negative, R ² = 0.94	Positive, R ² = 0.91
“Highly positive” area (E = 10...20 kcal/mol, corresponds to polarized hydrogen atoms)	Positive, R ² = 0.92	Negative, R ² = 0.76

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