Easy access to enantiopure aspartic acids featuring conformational lock

Yelyzaveta Zvarych , Oleksandr Kucher , Dmytro Volochnyuk , Serhiy Ryabukhin

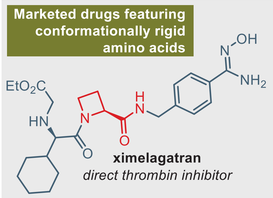
Background of the project

THE 15-YEAR-OLD EQUATION OF CLINICAL SUCCESS

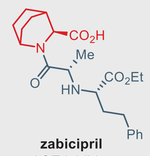
SATURATION + THREE-DIMENSIONALITY + CONFORMATIONAL RESTRICTION

- solubility
- complexity
- receptor/ligand complementarity
- reducing entropy penalty
- well-defined vectorization

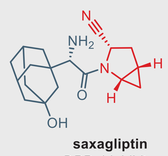
Marketed drugs featuring conformationally rigid amino acids



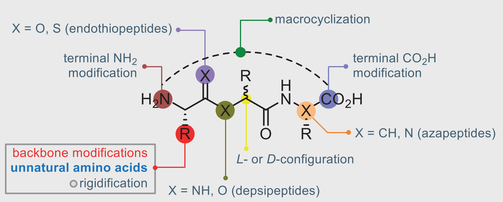
ximelagatran *direct thrombin inhibitor*



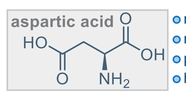
zabicipril *ACE inhibitor*



saxagliptin *DPP-4 inhibitor*



So far, certain amino acid topologies featuring a conformational lock have been overlooked and not sufficiently explored.

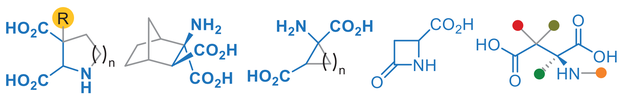


- neurotransmitter (stimulates NMDA receptors)
- metabolite in the urea cycle
- participates in gluconeogenesis
- hydrogen acceptor in a chain of ATP synthase

- **Cyclization** (incorporation of AA into cyclic frameworks)
- **Csp^3 backbone substitution** (introducing side chains)
- **Bridged Structures** (spirocyclic and bicyclic scaffolds)
- **α,β-Dehydro Amino Acids** (introducing a double bond)

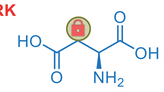
- Improve metabolic stability
- Enhance binding affinity
- Reduce entropic penalties
- protease inhibitors, probes

Possible aspartic acid mimics



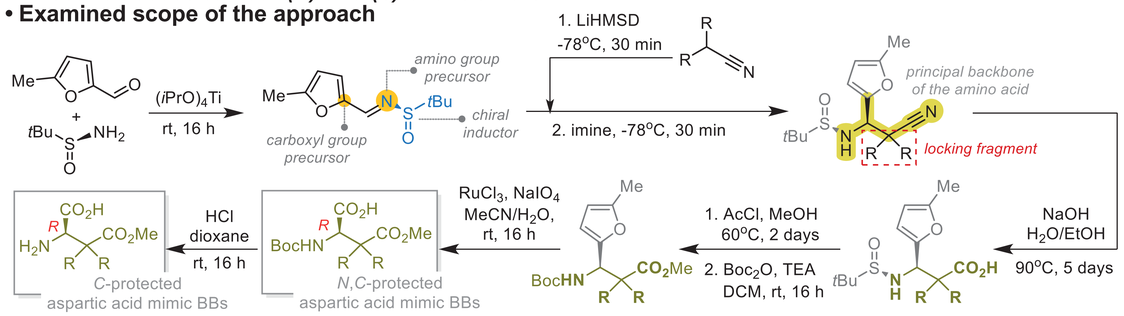
OUTLINE OF THE WORK

asymmetric large scale synthesid of the seldom aspartic acid mimics



Outline of the synthetic results

- **Elegant synthetic decision**
- **Effective access to both *(R)* and *(S)* enantiomers**
- **Examined scope of the approach**

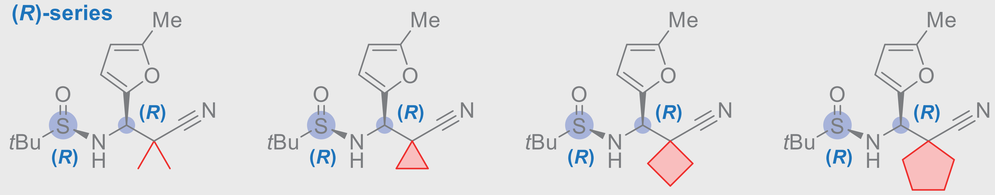


Contact

Serhiy V. Ryabukhin, Prof. Dr. Sci., s.v.ryabukhin@gmail.com
Dmytro M. Volochnyuk, Prof. Dr. Sci., d,volochnyuk@gmail.com

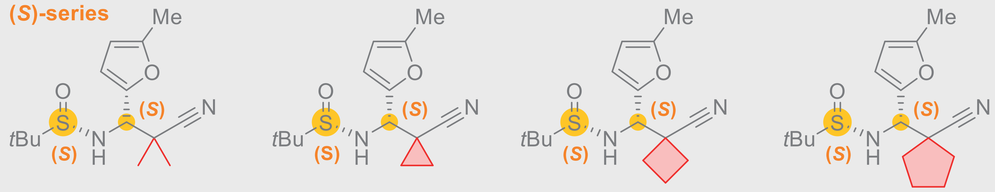
Stereochemical outcome of the addition stage

(*R*)-series



ee1,% = 85.30 **ee2**,% = 97.00 | **ee1**,% = 44.82 **ee2**,% = 98.36 | **ee1**,% = 83.00 **ee2**,% = 93.02 | **ee1**,% = 84.86 **ee2**,% = 98.34

(*S*)-series

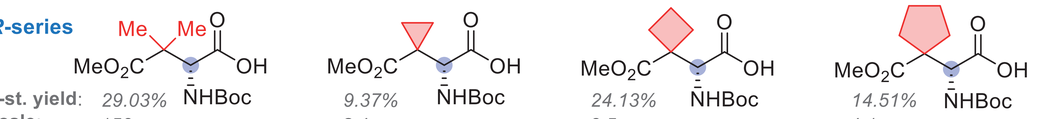


ee1,% = 90.06 **ee2**,% = 99.15 | **ee1**,% = 44.72 **ee2**,% = 97.90 | **ee1**,% = 73.82 **ee2**,% = 93.08 | **ee1**,% = 82.38 **ee2**,% = 98.88

Note: *ee1* – enantiomeric excess after reaction; ***ee2*** – enantiomeric excess after purification

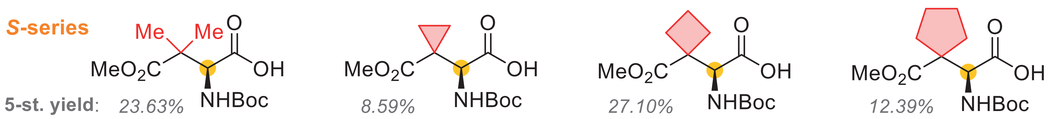
Scope of the synthesized conformationally restricted aspartic acids

(*R*)-series



5-st. yield: *29.03%* | *9.37%* | *24.13%* | *14.51%*
scale: 150 g | 2.4 g | 6.5 g | 4.1 g

(*S*)-series



5-st. yield: *23.63%* | *8.59%* | *27.10%* | *12.39%*
scale: 6.1 g | 2.2 g | 7.3 g | 3.5 g

LIMITATION

Application of the approach to **higher cycloalkane analogs is currently limited by the nitrile hydrolysis step,** which is accompanied by the disassembling of the molecule