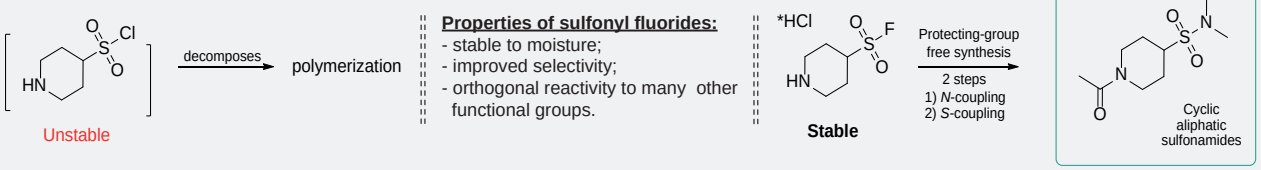
Aminosulfonyl fluorides for drug design

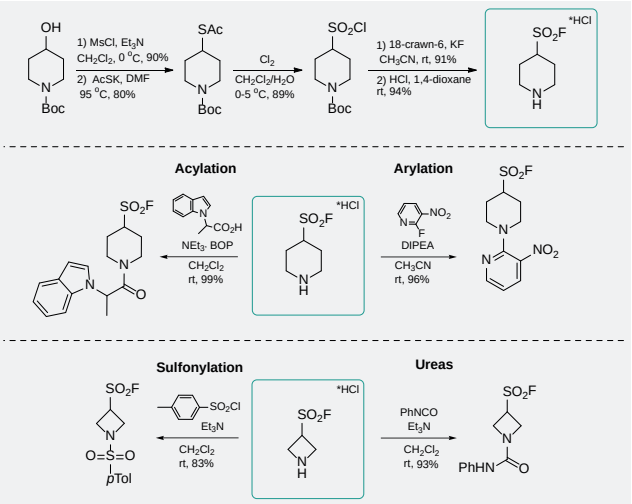
P. Mykhailiuk, S. Zhersh, O. Blahun, I. Sadkova, Y. Moroz, V. Ripenko, A. Tolmachev

Introduction and Aim

Sulfonyl chlorides (-SO_2Cl) are widely used in medicinal chemistry and agrochemistry as precursors to pharmacologically important sulfonamides. Many sulfonyl chlorides are unstable due to SO_2 extrusion and polymerization.[1] More stable sulfonyl fluorides (-SO_2F) in many cases are the only option to synthesize the desired sulfonamides. They are less reactive, so that they might even have free aliphatic amino groups in their structure and can be used for the protecting-group free synthesis of sulfonamides.[2] In the presence of the -SO_2F group, the nitrogen atom can be modified by means of acylation, arylation, and reductive amination, that has a high potential for the synthesis of bioactive compounds. Herein, we aim to design and synthesize novel aminosulfonyl fluorides for drug discovery.



Synthesis

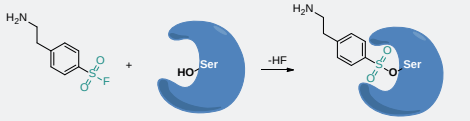


RSO_2F in Chemical Biology

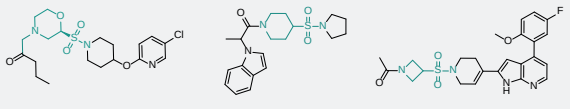
RSO_2F reactive probes in chemical biology

Over 40 approved drugs possess covalent mechanism of action[3] and the interest for discovery of novel entities only tends to increase.[4] High efficiency, selective binding with rare and specific targets, longer duration of action are among their main advantages. The -SO_2F group covalently modifies many protein residues but in a context-specific manner: serine, threonine, tyrosine, lysine, cysteine, and histidine. Thus, sulfonyl fluorides can be uniquely enlisted in chemical probes, covalent inhibitors, or various stages of translational workflow.[5]

Mechanism of action



RSO_2NH_2 in drug discovery

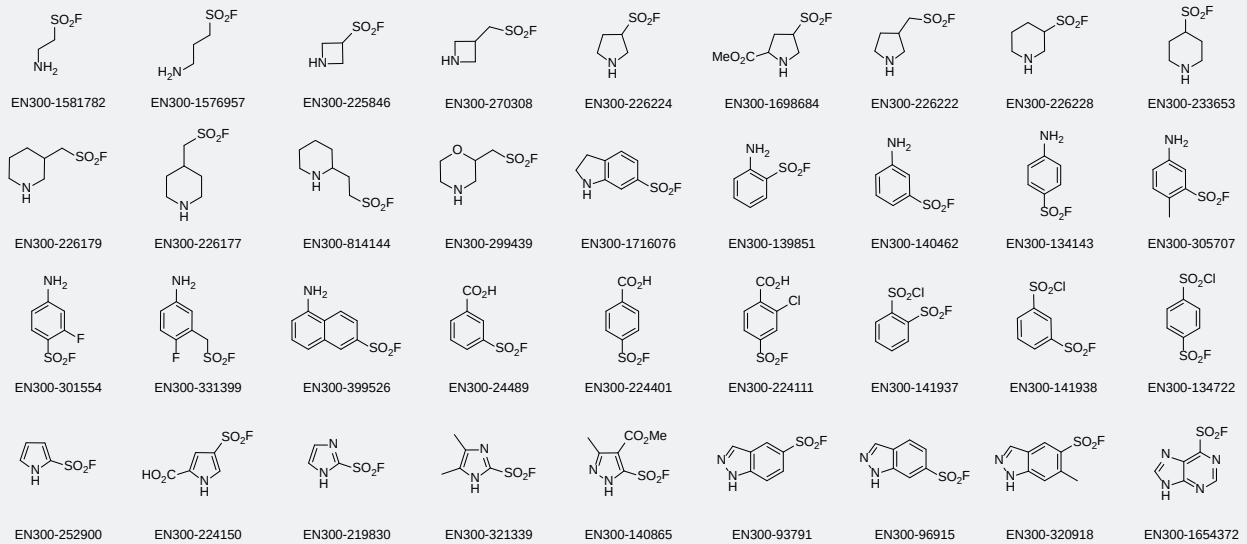


Matrix metalloptotease inhibitor
AstraZeneca, 2006

Ion channel modulator
Vertex Pharm., 2007

CDK9 kinase inhibitor
Abbvie Inc., 2014

Results



Contact

Pavel Mykhailiuk, Dr. Sci., PhD
Pavel.Mykhailiuk@mail.enamine.net, www.mykhailiukchem.org
Enamine Ltd, www.enamine.net
78 Chervonotkatska St, 02094 Kyiv, Ukraine

References

1. S. Zhersh et al. *Synthesis* **2011**, 3669.
2. S. Zhersh et al. *Chem. Eur. J.* **2018** *in press* (DOI: chem.201801140).
3. J. Singh et al. N*at. Rev. Drug Discovery* **2011**, 307.
4. R. Mah et al. *Bioorg. Med. Chem. Lett.* **2014**, 33.
5. A. Narayanan et al. *Chem. Sci.* **2015**, 2650.