Masaryk University

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CZECH REPUBLIC

Chemistry site

BRNO

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Our organic chemistry laboratory focuses on the development of synthetic methods and strategies for preparation of structurally non-trivial small molecules for applications in biomedical research.

THE PEOPLE

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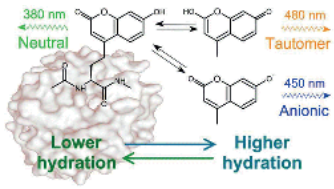
THE PROJECTS

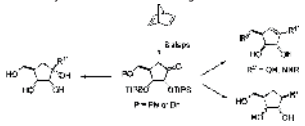
1. Synthesis of new fluorescent probes and unnatural aminoacid for in vivo labelling of proteins and monitoring of their hydration.



Hydration of proteins profoundly affects their functions. We describe a simple and general method for site-specific analysis of protein hydration based on the in vivo incorporation of fluorescent unnatural amino acids and their analysis by steady-state fluorescence spectroscopy. Using this method, we investigate the hydration of functionally important regions of dehalogenases. The experimental results are compared to findings from molecular dynamics simulations.

2. Synthesis of new carbocyclic C-nucleosides.

Carbocyclic C-nucleosides are quite rare. Our route enables flexible preparation of three classes of these nucleoside analogs from common precursors–properly substituted cyclopentanones, which can be prepared racemic (in six steps) or optically pure (in ten steps) from inexpensive norbornadiene. The methodology allows flexible manipulation of individual positions around the cyclopentane ring, namely highly diastereoselective installation of carbo- and heterocyclic substituents at position 1', orthogonal functionalization of position 5', and efficient inversion of stereochemistry at position 2'. Newly prepared carbocyclic C-analog of tubercidine, profiled in MCF7 (breast cancer) and HFF1 (human foreskin fibroblasts) cell cultures, is less potent than tubercidine itself, but more selectively toxic toward the tumorigenic cells.



3. Preparation of potent and selective inhibitors of CHK1 kinase for synthetic lethal treatments in modern oncology.

Treatment options for TP53-mutated lymphoid tumors are very limited. In experimental models, TP53-mutated lymphomas were sensitive to direct inhibition of checkpoint kinase 1 (Chk1), a pivotal regulator of replication. We initially tested the potential of the highly specific Chk1 inhibitor SCH900776 to synergize with nucleoside analogs (NAs) fludarabine, cytarabine and gemcitabine in cell lines derived from B-cell malignancies. In p53-proficient NALM-6 cells, SCH900776 added to NAs enhanced signaling towards Chk1 (pSer317/pSer345), effectively blocked Chk1 activation (Ser296 autophosphorylation), increased replication stress (p53 and γ-H2AX accumulation) and temporarily potentiated apoptosis. In p53-defective MEC-1 cell line representing adverse chronic lymphocytic leukemia (CLL), Chk1 inhibition together with NAs led to enhanced and sustained replication stress and significantly potentiated apoptosis. Altogether, among 17 tested cell lines SCH900776 sensitized four of them to all three NAs. Focusing further on MEC-1 and co-treatment of SCH900776 with fludarabine, we disclosed chromosome pulverization in cells undergoing aberrant mitoses. SCH900776 also increased the effect of fludarabine in a proportion of primary CLL samples treated with pro-proliferative stimuli, including those with TP53 disruption. Finally, we observed a fludarabine potentiation by SCH900776 in a T-cell leukemia 1 (TCL1)-driven mouse model of CLL. Collectively, we have substantiated the significant potential of Chk1 inhibition in B-lymphoid cells.

THE EQUIPMENT

- *in-house 500 MHz NMR*
- *MS-TOF*
- *autopurification LC/MS*
- *semi-prep. chiral HPLC*
- *SciFinder and reaxys . . .*

THE MEDCHEM

- chemical synthesis (wet chemistry, work in inert atmosphere (glovebox))
- microwave chemistry
- high pressure chemistry (up to 200 bar)

associated core facility:
X-ray Diffraction Core Facility

THE OUTPUT

1. Maier, L et al., 2017, J. Org. Chem., DOI: 10.1021/acs.joc.6b02594
2. Hylsová, M. et al., 2016, Eur. J. Med. Chem, DOI: 10.1016/j.ejmech.2016.12.023
3. Amaro, M. et al., 2013, J. Phys. Chem. B, DOI: 10.1021/jp403708c
4. Amaro, M. et al., 2015, J. Am. Chem. Soc., DOI: 10.1021/jacs.5b01681
5. Kováčová, S. et al., 2015, Tetrahedron, DOI: 1016/j.tet.2015.08.005
6. Zemanová, J. et al., 2016, Oncotarget, DOI: 10.18632/oncotarget.11388

15 international (US) patents e.g. WO 2015/165428 A1, WO 2015/192817 A1.

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THE FUTURE

capacity:
2 medium-size medicinal chemistry projects

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