NEW REAGENTS FOR FLUOROMETHYLENE TRANSFER CHEMISTRY

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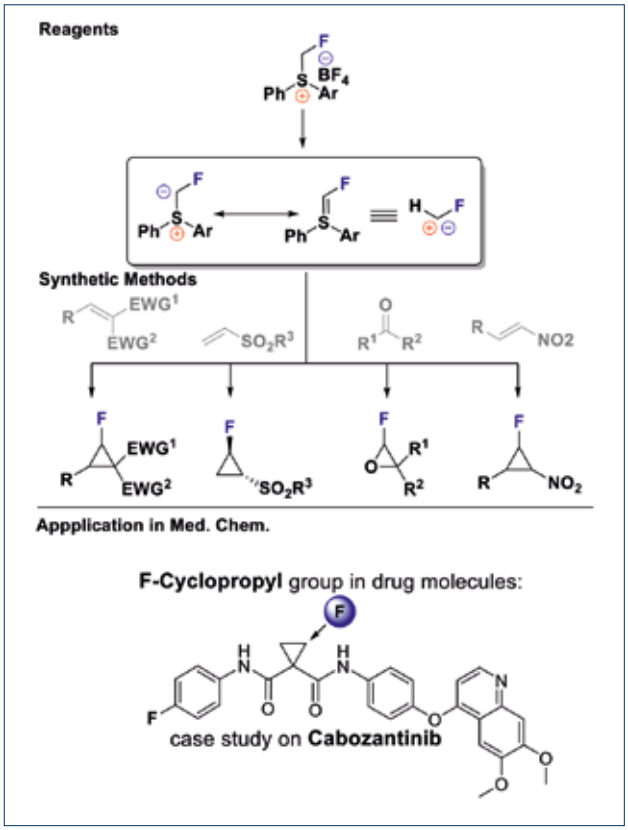
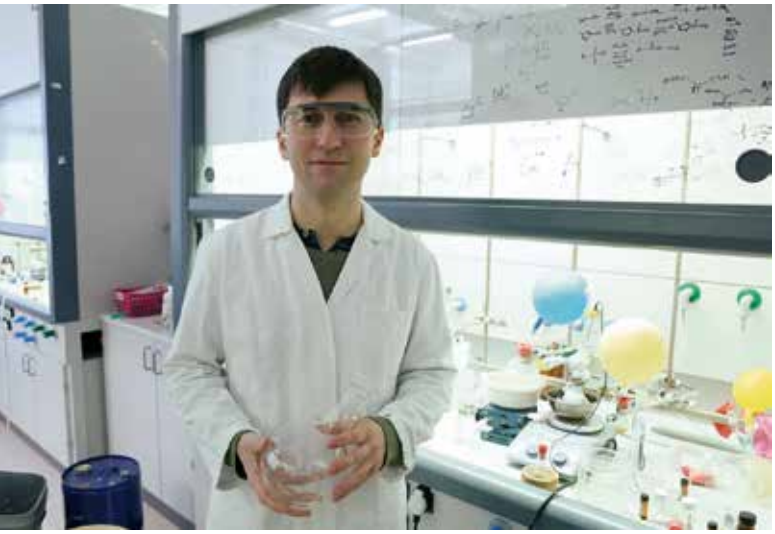
Chemistry is all around us. All visible matter is made of atoms and molecules. The biological processes taking place in a living organism are complex cascades of chemical reactions catalysed by enzymes. Since ancient times, humans have tried to transform matter – smelting ore into metals, converting fat and oils into soap, making fermentation to rise bread and produce beverages. The modern chemical science has not only revealed the molecular bases of all these processes known for millennia but also has created methods and reagents to make new, previously inexistent compounds, to develop drugs against previously incurable diseases as well as specialty materials that make our modern life possible. The same as surgeon needs all kinds of tools, like scalpels, forceps, and scissors, a chemist needs reagents to manipulate molecules. New compounds are created in chemical reactions requiring special reagents dedicated to do a certain task by converting a starting material into a desired product in a predictable manner. Our research group deals with the development of methods and reagents for the synthesis of a special class of chemicals – organofluorine compounds.

Fluorine is an extremely rare element in living organisms. A completely different picture reveals when looking at the chemical structures of known pharmaceutical drugs. Almost 25% of currently available drugs in the market contain at least one fluorine atom in their chemical structure which belongs to a class of organofluorine compounds. Why fluorine is so special in pharmaceuticals? This arises from the unique properties of this element. Due to the small size of a fluorine atom it can often be considered as bioisosteric replacement of very abundant hydrogen atoms in the structures of organic compounds. Also, it forms strong carbon–fluorine bonds, which is a prerequisite to have stable chemical entities. Additionally, it is the most electronegative element in the periodic table, which can significantly alter the electronic landscape of the molecule under investigation, bringing additional interactions with the enzyme of interest. Thus, incorporation of this element can be used to trick naturally occurring enzymes to improve the biological activities or increase the metabolic stability of the potential drug. Replacement of one or several hydrogen atoms in a drug molecule with fluorine substituent is a common practice in medicinal chemistry to alter the biological activity of a compound in the lead optimisation studies. This process in drug discovery is very important, where an initially identified hit compound is chemically modified to improve overall biological properties of the active scaffold and, eventually, the potency of the future therapeutical for the treatment of a disease under investigation. All these unique properties make organofluorine compounds an important class of chemicals with various applications. Therefore, for chemists the development of new techniques and reagents that would allow synthesis of new organofluorine compounds is a task of high priority.



A route of fluoromethylene transfer reagents from a concept and methodology development to a medicinal chemistry relevant compounds

Our research team is involved in the development of new reagents for a transformation that would facilitate the synthesis of previously difficult to access organofluorine compounds. More specifically, our group deals with the development of reagents that can be used for fluoromethylene transfer applications. This is a chemical transformation where one-fluorine-one-carbon-one-hydrogen unit (CHF:) is transferred from the reagent to a target substrate. This is a synthetically very useful approach to access certain classes of monofluorinated compounds, for example, small fluorinated cycles. The current approach to perform such type of chemistry was mostly dealing with fluorohalomethanes or freons as reagents, which are gases or low-boiling liquids possessing ozone depleting properties. In this situation our goal was to find solid, easy-to-use and effective reagents capable to perform the aforementioned transformation. Sulphur ylide chemistry is a well-known approach among chemists, to transfer methylene groups to alkenes or carbonyl compounds. However, in 2018, when our studies begun, there were no reports in literature on the existence of sulphur fluoromethylide species as a reactive intermediates, which we envisioned to be easily accessible from diaryl fluorometyhlsulfonium salts. These salts adored to the expected properties for being good reagents for the purpose – as bench stable compounds with tunable reactivity and crystallinity depending on the substituent. Initially, deuteration experiments showed the first mechanistic evidences suggesting of sulphur fluoromethylide intermediates. This finding was eventually developed into a useful synthetic methodology to access rare organofluorine compounds – monofluorinated epoxides. Further, we were able to show that fluoromethylene transfer from diaryl fluoromethylsulfonium salts can be used as a synthetic strategy for the preparation of various monofluorocyclopropane derivatives offering a good alternative to the existing technologies. Pursuing the research in this area we were able to showcase that our developed synthetic methods can be applied for the synthesis of relevant medicinal chemistry targets. We opted to synthesise the fluoro-analogue of anticancer drug cabozantinb- a c-Met and VEGFR-2 kinese inhibitor, which is used for the treatment of medullary thyroid cancer and renal cell carcinoma. This molecule attracted our attention because its chemical structure contained a cyclopropyl ring, but its fluorocyclopropane analogue was unknown in literature. We anticipated that our methodology would give a straightforward access to such fluoro-analogues. Consequently the diastereoselective synthetic route was developed to access the F-analogues of cabozantinib. In collaboration with our pharmacology colleagues at LIOS, J. Kuka and M. Videja, we have demonstrated that incorporation of fluorocyclopropane moiety in cabozantinib could be an interesting tool for fine-tuning of the properties of biologically active compounds. *In vitro* cytotoxicity studies have shown that one of the stereoisomers of F-cabozantinib displayed better selectivity when compared to the non-fluorinated parent drug. Of course, there is still a long way for this to be developed in real therapeutics, but at this point, we have opened a new perspective for further studies. There is still a lot to do, and our highly dedicated team



Dr. sci. nat. Jānis Veliks in the lab

consisting of very talented students R. Melngaile, A. Kazia, A. Sperga was the key to the success of this project. This was recognised by various awards that these young investigators received for their work on this project.

In conclusion, our investigations have led us from demonstration of proof-of-concept to the development of new reagents and synthetic methodologies, to the application of the method on medicinal chemistry target placing it as an important contribution in the area of fluorine chemistry.

Renāte Melngaile receiving Straumanis and Ieviņš Prize for young researchers in chemistry

Armands Kazia receiving Best Poster Award in the 11th Paul Walden Symposium, Rīga, 2019. From the left: *Dr. chem.* Vilnis Liepiņš, Armands Kazia, Professor *Dr. rer. nat.* Herbert Mayr

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