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Report on the PhD manuscript of mister Marcin DROP

Mister Marcin DROP presents a thesis document entitled "Flow chemistry methods in the search for new 2-arylpyrrole derivatives as 5-HT_6 receptor ligands ".
The 83 pages manuscript starts with an abstract, then a general introduction followed by eight chapters, a conclusion and perspective part and the experimental part. Finally, three publications from this work complete the thesis document.

Chapter 1, a general bibliographic introduction, focuses on green chemistry and continuous flow chemistry, then 5-HT_6 receptors are presented in term of target for drug development, particularly the search for antagonists.

Chapter 2 presents the background and goal of the thesis, which is the search for central nervous system treatment amenable with modern sustainable synthetic methodologies.
Based on all the previous work from the two thesis PI, Prof. Paweł Zajdel and Dr. Frédéric Lamaty, a new scaffold will be worked out from pyrroloquinolines to 2-phenyl-1*H*-pyrroles, with the goal to reach novel selective 5-HT_6 receptor antagonists.

Chapter 3 deals with compounds design, and thus three series of structures are considered from 2-phenyl-1*H*-pyrrole scaffold in order to explore the chemical space.

Chapter 4 details the synthesis of the 3 series of compounds. For series 1, arylsulfonamides derivatives are constructed on 2-phenyl-1*H*-pyrrole-3-carboxamide scaffold. Therefore, after the synthesis of 2-phenyl-1*H*-pyrrole-3-carboxylic acids (detailed in publications 2 and 3 appended to the document), the optimization of RCM in continuous flow for accessing 2,5-dihydro-1*H*-pyrrole-3-carboxylates is reported. The impact of continuous flow chemistry on the reaction time, yields and most of all on the scale-up capacity is clearly perceived. The final series 1 derivatives are then easily obtained in 2 steps.
Then, two sets of series 2 derivatives were obtained distinguished by either a sulfonamido or methylene bridging unit. A last set was accessible thanks to modification of the link between the pyrrole and the piperazine parts.
Finally, series 3 was synthesized using Suzuki-Miyaura cross-coupling reaction for linking the pyrrole and the aryl moieties. Further couplings are then realized (Buchwald-Hartwig, Ullmann) to functionalize the scaffold.

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Chapter 5 is about structure-activity relationship studies done on the different series. Thus, the affinity for the 5-HT_6 receptor is studied, allowing to distinguish the important features for high affinity (detailed in publication 3 in annex). Moreover, the selectivity over off-target receptors was also sought after.

Chapter 6 focused on functional profiling of 5-HT_6 receptor-dependent signaling pathways, thus adenylate cyclase activity was examined on cells expressing 5-HT_6 receptors by TR-FRET (Gs signaling), then CDK5 activation and mTOR pathway were further studied.

Chapter 7 deals with the ADME/Tox and pharmacological studies and chapter 8 with the *in vivo* behavior evaluation.

The last chapter, chapter 9, is about the optimization of the route for 2-phenyl-1*H*-pyrrole-3-carboxamide series, with a one-pot approach for the 2-phenyl-1*H*-pyrrole-3-carboxylate core along with a continuous flow approach for the sulfonylation step. A comparison scheme is finishing this chapter.

The experimental part (and also in the publications appended) gathers the data of the physicochemical characterizations of the numerous synthetic products, their description is done carefully, attested by NMR data, high resolution masses and HPLC results.

All the research activities of mister Marcin DROP have already led to the publication of 3 articles in excellent international journals. The medicinal chemistry work is outstanding in terms of diversity in the chemistry studied, sustainable or catalytic methods used and biological/biochemical evaluations reported.

For all these reasons I am highly positive for the thesis defence of mister Marcin DROP.

For all legal purposes,