CHARLES UNIVERSITY

FACULTY OF PHARMACY IN HRADEC KRALOVE

Department: of Pharmaceutical Chemistry and Pharmaceutical Analysis

Master´s degree program in Pharmacy

Opponent´s review of Master´s thesis

Student´s name: Legae G. B. Kebakuile

Mentor of the thesis: PharmDr. Jan Zitko, Ph.D.

Opponent of the thesis: PharmDr. Marta Kučerová, Ph.D.

Year of the thesis defense: 2018

Title of the thesis:

Creation and analysis of in-house database of pyrazine derivatives with potential antimicrobial activity

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Formal comments: number of pages: 57, number of figures: 25, number of tables: 4, number of references: 60.

Type of work: Experimental work

a) The aim of the thesis is: Fulfilled

b) Language and graphic level: Excellent

c) Processing of the theory: Very good

d) Methods description: Excellent

e) Results description: Excellent

f) Discussion and conclusions: Very good

I recommend Diploma thesis for the recognition as Rigorous thesis ☒.

Opponent´s comments:
The Master´s thesis of Legae Kebakuile is a breakthrough work in our department and possibly also at the faculty, as I have not found this type of work in the theses repository. It describes the creation of a virtual library comprising 623 compounds that have been synthesized by prof. M. Doležal and his team since the year 2000.
In the theoretical part of the thesis, some important parameters and descriptors used in drug design are presented. I miss complete survey of molecular descriptors, but I suppose, that only these were included, that were important for the practical part.
In the experimental part, procedure for setting particular entries into the database is described on example of one compound. Statistics on particular descriptors are provided and compared with drug-likeness and lead-likeness parameters, as well with MycPermCheck parametres, as all of the compounds were intented to be mycobacteria inhibitors.
Regardless the number of my comments, I appreciate student´s work and many hours spent on PC.
Here are my comments on the work:

1. In the thesis, the Czech abstract is missing and also the declaration that the work was not misused for obtaining the same or different academic degree. Both these items should have been included in the thesis.
2. The title of Chapter 3 in the table of contents is not clear and it is missing in the thesis at all.
3. In the last sentence of the chapter Aim of the work: "The resulting database must also be usable in guiding future syntheses", it would be better to use "usable in the future drug design."
4. References are not cited in a uniform style, e.g. ref. 3 versus 6. Some information are missing, e.g. the journal title in the ref. 3. Some information issues are redundant, e.g. it is not necessary to cite the publisher in a journal article reference, e.g. 2.
5. On the page 19, there are some inaccuracies in the definitions: "number of heavy atoms…, number of rotatable bonds…" should be introduced as "the total number of atoms except for hydrogen atoms…, total number of the bonds that are able to freely rotate".
6. On the pages 22 (penultimate line) and 23 (Fig. 5), the units of polar surface area should be indicated.
7. On the page 24, there are wrongly spelled the names of towns.

Questions:
1. Could you elucidate the first sentence of the last paragraph on the page 9?
2. On the pages 13/14 you wrote, that in the PDB database, there are "especially large biomolecules like nucleic acids, obtained via x-ray crystallography and NMR (nuclear magnetic resonance) spectroscopy". Could you tell or show, what types of macromolecules are present in the PDB and their approximately percentage amount and which methods were generally (not for particular type of compounds) used for their 3D-structure determination?
3. Could you define hydrogen bond acceptors and donors in a better way (p. 19.) Does also electronegativity play a role in this type of bonding?
4. Are the terms hydrophobic and lipophilic synonyms in all cases? (p. 19, logP)
5. Could you present definition of "drug" and "lead" from glossary of medicinal chemistry terms of IUPAC. If you compare them with the WHO definitions, which is more understandable for you?
6. In table 1 on the pages 26/27, you mentioned Structural-aided drug design and Virtual screening. How are these terms related?
7. Is there something missing at the end of the first paragraph on the page 29?
8. Was the period for IC80 value estimation (i.e. 24 hours) equal for all bacteria and fungi Pp. 30)?
9. I miss any discussion on the number of rotatable bonds and polar surface area in the set of active and inactive compound.
10. Did you have to solve stereochemistry (isomer determination) in any of the molecules?

The database resulted from this diploma work might be used as an input in molecular modelling studies in future. The advantage is the fact that the compounds are real and they are or they were present at the faculty. Ownership of such databases is usual in pharma industry or in specialized companies and they are often matter of purchase.
I recommend the thesis for defense and I suppose that a short show of the virtual database will be demonstrated to the commission, as the database is attached in the SIS but not included in the thesis.

Evaluation of Master´s thesis: Excellent

Recommendations for the thesis defense: Recommended

In Hradec Kralove September 7th, 2018 ……

Opponent´s signature