

**UNIVERZITA KARLOVA
FARMACEUTICKÁ FAKULTA V HRADCI KRÁLOVÉ**

Katedra Organické a bioorganické chemie

Studijní program: Farmacie

Posudek oponenta diplomové práce

Rok obhajoby: 2022

Autor/ka práce: **Richard Župina**

Vedoucí práce: prof. PharmDr. Vávrová Kateřina, Ph.D.

Konzultant/ka: Dr. Georgios Paraskevopoulos, Ph.D.

Oponent/ka: PharmDr. Lukáš Opálka, Ph.D.

Název práce: **Synthesis of fluorinated serine derivatives and study of their effect on skin barrier function**

Rozsah práce: 61 stran, 42 obrázků, 7 tabulek, 68 citací

Hodnocení práce:

- | | |
|--|-------------|
| a) Odborná úroveň a zpracování teoretické části: | výborná |
| b) Náročnost použitých metod: | výborná |
| c) Zpracování metodické části (přehlednost, srozumitelnost): | velmi dobré |
| d) Kvalita získaných experimentálních dat: | výborná |
| e) Zpracování výsledků (přehlednost, srozumitelnost): | výborné |
| f) Hodnocení výsledků včetně statistické analýzy: | velmi dobré |
| g) Myšlenková úroveň a rozsah diskuse výsledků: | výborná |
| h) Srozumitelnost, výstižnost a adekvátnost závěrů: | výborná |
| i) Splnění cílů práce: | výborné |
| j) Množství a aktuálnost literárních odkazů: | výborné |
| k) Jazyková úroveň (stylistická a gramatická úroveň): | výborná |
| l) Formální úroveň práce (členění textu, grafické zpracování): | výborná |

Doporučuji diplomovou práci k uznání jako práci rigorózní

Případné poznámky k hodnocení:

Diploma thesis written by Richard Župina under a supervision of prof. Katerina Vavrova was focused first on the synthesis of polyfluorinated ceramide analogues and then on determination of their effect to regenerate a damaged skin barrier ex vivo. The synthesis started from protected L-serine which was subsequently modified by an attachment of two lipophylic chains, one of them was polyfluorinated. Non-fluorinated compounds were prepared by the same procedure for comparison. Products were prepared in four reaction steps with reasonable yields and were well characterized. To determine the potential regenerative effect of these compounds, stratum corneum as the uppermost skin layer was first isolated from skin and then damaged by organic solvents. After an application of model compounds, barrier properties were determined by TEWL and flux of a model drug. Unfortunately the results showed that the perfluorinated molecules prepared in this project were less effective in the barrier repairing properties than their non-fluorinated analogues, however the decreased activity of perfluorinated compounds may have been caused by their low solubility.

The diploma thesis is written clearly and consistently, without significant typing errors and with figures clearly explaining both the skin composition and function and the chemical structures of individual compounds. Thesis organization is standard and it contains all required chapters. Chemical syntheses are described in detail and biophysical experiments are in general well characterized.

Dotazy a připomínky:

I have several comments and then several questions:

Comments

- Citations in text represented by a number in brackets are usually written before the punctuation mark
- Page 24 - it would be nice to show some structures of the described pseudoceramides in a separate figure
- Experimental section - when describing results of MS measurements, it is more common to calculate m/z for the same ion as finally found (for example for $(M+H)^+$)
- Melting points are shown sometimes as a range, sometimes as an individual value, this should be unified (ideally in the form of a melting temperature range)
- Page 43 - in HPLC, retention time is a useless value unless a column is specified
- Figure 41 - one of the error bars is cut out

Questions

- Page 14 - you are showing a stratum corneum lipid composition, but when calculated together, it is mostly less than 100%. How could this be explained? Is something missing?
- All products have a chiral center. Was an optical rotation measured?
- Compound C10b - the formula $C_{20}H_{34}NO_3$ already represents a charged molecule. $M+H^+$ ion would then be double charged which would decrease the value to approximately half based on the formula m/z . How is this possible?
- Esterification reaction using EDC and DMAP provided satisfactory yields, but was other esterification method tested as well?
- Yields of some reactions are unexpected or non-consistent. For example how can you explain that the preparation of CF14a provided higher yield than CF10a when CF14a has an extensive fluorination? How many times were the reactions repeated? The yields could also be better commented in the discussion section.
- In biophysical experiments, the products were applied in the mixture of PG/EtOH - is it a solution or a suspension? Do you think buffer could be used to deliver these compounds?
- In the thesis, I haven't found any information about statistical analysis. The data are presented as means with standard deviation or standard error of mean? What method was used to determine a statistical significance?
- Figure 41 - some of the error bars seem quite large. Would it be possible to show individual values in the graph?

hodnocení, práce je: výborná

k obhajobě: doporučuji

V Hradci Králové

8. září 2022

podpis oponenta/ky