

**UNIVERZITA KARLOVA V PRAZE
FARMACEUTICKÁ FAKULTA V HRADCI KRÁLOVÉ**

Katedra farmaceutické chemie a kontroly léčiv

Studijní program: Farmacie

Posudek oponenta diplomové práce

Oponent/ka: **Doc. PharmDr. Miroslav Miletín, Ph.D.**

Rok obhajoby: 2015

Autor/ka práce: **Barančoková Michaela**

Název práce:

Characterisation of Gyrase inhibitors using ITC and enzymatic assay

Rozsah práce: počet stran: 53, počet grafů: 0, počet obrázků: 9,

počet tabulek: 17, počet citací: 42

Práce je: experimentální

- a) Cíl práce je: zcela splněn
- b) Jazyková a grafická úroveň: výborná
- c) Zpracování teoretické části: výborné
- d) Popis metod: velmi dobrý
- e) Prezentace výsledků: velmi dobrá
- f) Diskuse, závěry: výborné
- g) Teoretický či praktický přínos práce: výborný

Případné poznámky k hodnocení:

Barančoková Michaela elaborated her diploma thesis named "Characterisation of Gyrase inhibitors using ITC and enzymatic assay" at University of Ljubljana, Faculty of Pharmacy, Department of Medicinal Chemistry.

The thesis consists of standard chapters. After short Introduction the Theoretical background chapter is included, which outlines basics of DNA structure and topology and describes the problematics and classification of DNA topoisomerases. The main types of topoisomerase inhibitors are described in the end of Theoretical background chapter. Experimental part describes methods used and experiments performed. Results of the thesis are summarized in the following separate part. In the end, short Discussion and Conclusion are placed. Nice and instructive figures are included.

The thesis is elaborated on a very good level with only few formal shortcomings. The topic is highly actual and very interesting. The thesis corresponds in its extend and content to the task as well as to the convention in this type of qualification work.

Dotazy a připomínky:

I have only few following questions and comments:

p. 23: Concerning the side effects of fluoroquinolones.

You mention the phototoxicity - could you explain the mechanism?

Additional information to be discussed with a patient is to avoid some food, drinks or drugs taken together with fluoroquinolones. Which ones and why?

Table 6, 7: The bonds at some substituents are drawn incorrectly.

p. 30: The TFO1 oligonucleotide was probably biotin modified(?), which is a common way to bind oligonucleotides specifically to the avidin. If yes it could be noted. Also the sequence of the TFO would be valuable information, if you know it.

Concerning the Results and Discussion:

Some of the compounds are chiral - were they tested as the pure (S) isomers as drawn or in form of racemates?

Some of the compounds tested are esters and they are generally less active or even inactive (especially against the enzymes in last three columns in the tables). Since the corresponding free acids are much more active the idea arises they could behave in vivo as pro-drugs.

Therefore, the simple conclusions about their lower activity because of bad solubility is not quite correct.

Since you explain the low or no activity of some compounds by their pure solubility: Have you tried to assume the solubility in final media? Have you observed some precipitates after addition of the DMSO solutions into the media?

Many of the compounds are carboxylic acids - have you tried to dissolve them in water as salts?

And one more question to the solubility properties: Have you considered logP values calculation to assume activity relationships?

The thesis is elaborated on a very good level almost without formal shortcomings. The topic is highly actual and very interesting. Despite of the my above notes and comments the thesis fully complies with requirements for such type of work and I recommend it to defence.

Celkové hodnocení: výborně, k obhajobě: doporučuji

V Hradci Králové dne 26.5. 2015

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podpis oponentky / oponenta