UNIVERZITA KARLOVA V PRAZE
FARMACEUTICKÁ FAKULTA V HRADCI KRÁLOVÉ
Katedra farmaceutické chemie a kontroly léčiv
Studijní program: Farmacie

Posudek vedoucího / školitele diplomové práce

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Syntéza funkčních derivátů kyseliny malonové jako základních kamenů pro inhibitory elastasy

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Téma práce si autor/ka **vybrala v rámci programu ERASMUS**.

Práce s literaturou autora/ky byla **výborná**

Jazyková vybavenost autora/ky byla **výborná**

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Hodnocení výsledků v kontextu jiných prací bylo **velmi zodpovědné**

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Grafická a jazyková úprava byla **výborná**

Působení autora/ky na katedře bylo **přínosné**.

Slovní hodnocení, výrazné rysy autora/ky a práce:

Marie Hrušková začala na Katedře farmaceutické chemie a kontroly léčiv pracovat již koncem třetího ročníku. Přestože v polovině čtvrtého ročníku měla již část své původně zadané práce hotovou, rozhodla se prohloubit si své vzdělání a zkušenost pobytem na zahraničním pracovišti. Hodnocení zahraničního školitele je uvedeno na dalších stranách posudku a plně odpovídá schopnostem Marie Hruškové tak, jak se projevily i při její práci na našem pracovišti. Výsledky své práce prezentovala na Studentské vědecké konferenci.

Celkové hodnocení: výborně, k obhajobě: doporučuji

V Hradci Králové dne 23. 5. 2011 ……

podpis

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Referee report concerning the diploma thesis of Marie Hrušková "Synthese von funktionalisierten Malonsäure-Derivaten als Bausteine für Elastase-Inhibitoren"

Marie Hrušková from Domažlice did her diploma work at the University of Bonn, Pharmaceutical Institute, in the field of Pharmaceutical Chemistry. She came as an ERASMUS exchange student from the Univerzita Karlova v Praze / Farmaceutická fakulta v Hradci Králové to our group. It was the aim of the present study to discover a possible synthetic access to azetidine-2,4-diones (malonimides) with a protected amino group (to enhance the peptidic character) and a ethyl group (to interact with the S1 pocket of elastase), both in 3-position. A simplified type of azetidinediones has been reported to possess strong elastase inhibiting properties. Moreira and co-workers (refs 2, 3) have obtained such diethyl-substituted azetidinediones from the reaction of corresponding malonic dichlorides with aromatic amines. Thus, we envisaged a comparable route to prepare the key compound **4** (page 42) and cyclize it with aniline.

Marie Hrušková provides introducing paragraphs to mention the target enzyme (human leukocyte elastase) and the desired inhibitor structure (page 7) to continue with the description of the structure of HLE. With the help of one co-worker of our group, she presented nice pictures of HLE. The first compound to be synthesized (**2**) was isolated after precipitation of the material under low temperature. The new alkylated derivative 3 was purified by column chromatography. Prochiral molecules such as **2** and **3** showed rather unexpected coupling pattern of their ester metylene protons. Although not being chiral, the methylene protons appear as diastereotopic ones. To shed more light on this item, Marie Hrušková has undertaken a literature survey and presented some references with examples for NMR data of prochiral methylene groups. Chapter 2.1 is then finished with some accurately presented NMR spectra. Further spectra can be found in an instructive apendix of the diploma thesis (pages 70 ff).

The hydrolytic cleavage of the malonic ester derivative **3** could be accomplished under basic conditions. Concerns have been raised that product **4** might undergo decarboxylation. Indeed, depending on the temperature applied during workup, the undesired butyric acid derivative **5** was formed as by-product. Marie Hrušková has obtained **5** in the course of an independent synthesis.

Next, optimal conditions for the work-up procedure for **4** were identified. Under such conditions, **4** was free of the impurity **5**, but contains some ethyl acetate. The spectra with colored accentuations (pages 31-38) demonstrate the different product mixtures.

The activation of **4** with oxalyl chloride, followed by reaction with aniline was then investigated (chapter 2.3). We found that under different conditions, the hydantoin **14** was always produced. Its formation was envisaged by a mechanism outlined in Schema 12. The structure of **14** could be unequivocally elucidated based on NMR data as well as the comparison with another type of 5-carbamoyl hydantoins, previously described in our group (A. Ambrozak, PhD thesis; M. Meusel, A. Ambrozak, T. K. Hecker, M. Gütschow; *J. Org. Chem.* 2003). By analyzing several modifications of this reaction, Marie Hrušková could demonstrate that the preparation of the desired azetidinedione is likely impractical. Nevertheless, the newly obtained synthetic entry to a new type of hydantoins shows great promise for future synthetic work, even though first attempts failed to use aliphatic amines in place of aniline.

Marie Hrušková is presenting a high-quality thesis, accurately written and including significant results. She dexterously performed the experiments and was able to discuss the result in an appropriate manner.

I recommend the acceptance of the thesis and grade the work with

mark 1 (very good)

Bonn, 21.05.2011 Prof. Dr. Michael Gütschow