Initial steps on the synthesis of new antimicrobial fumiquinazoline related alkaloids

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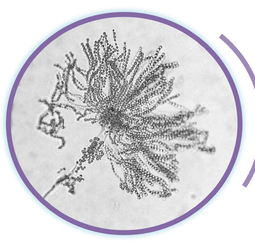
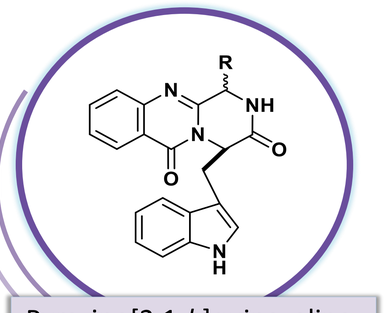


Currently drug resistance is rising to dangerously high levels worldwide and threatening our ability to treat even common infectious diseases [1]. Secondary metabolites, especially alkaloids containing an indole group and structurally related to fumiquinazolines, can be found in both marine and terrestrial secondary metabolites and are of great importance in the area of drug discovery with promising antimicrobial properties [2].

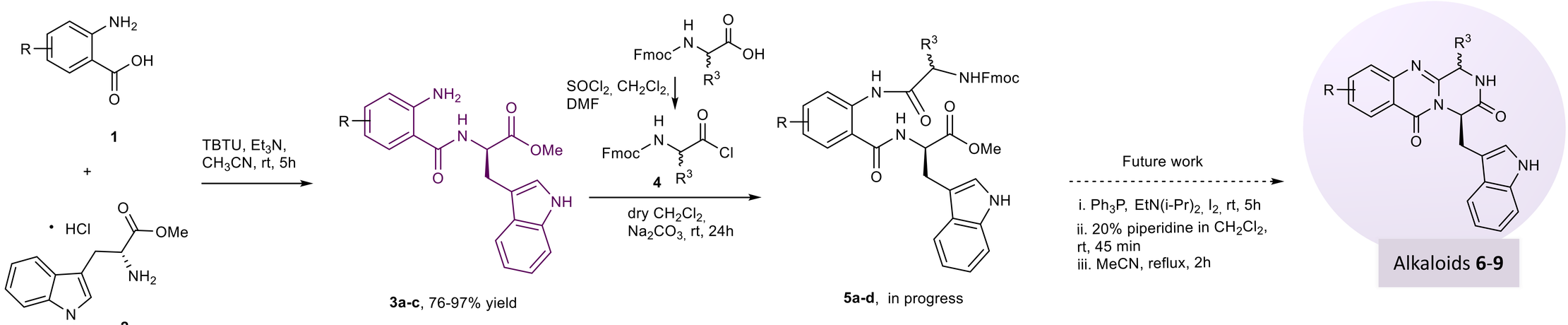


Pyrazino[2,1-*b*]quinazoline-3,6-dione core structure.

This work aims to synthesize alkaloids related to fumiquinazolines, as well as introducing new molecular modifications, in order to improve their properties as antimicrobial agents.

Results

A multi-step synthetic pathway [3] was followed through conjugation of anthranilic acid, D-tryptophan methyl ester hydrochloride and a third amino acid (glycine or alanine).



Structure elucidation

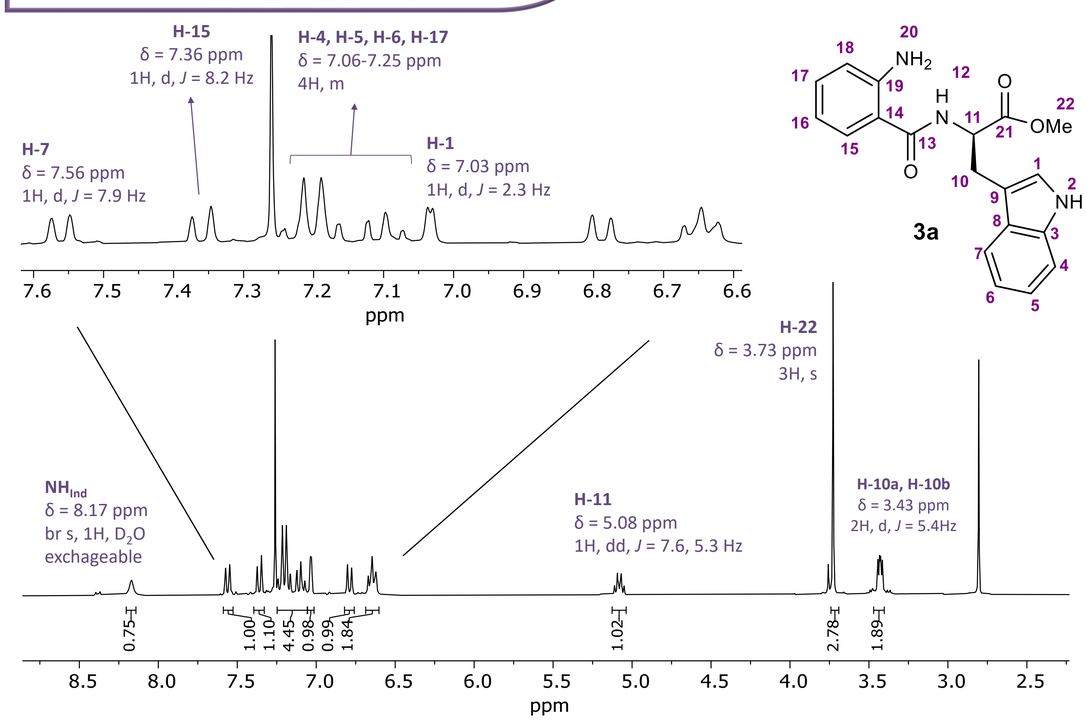


Figure 1. ^{1}H NMR ($CDCl_3$) of *N*-(2-aminobenzoyl)-D-tryptophan methyl ester (**3a**).

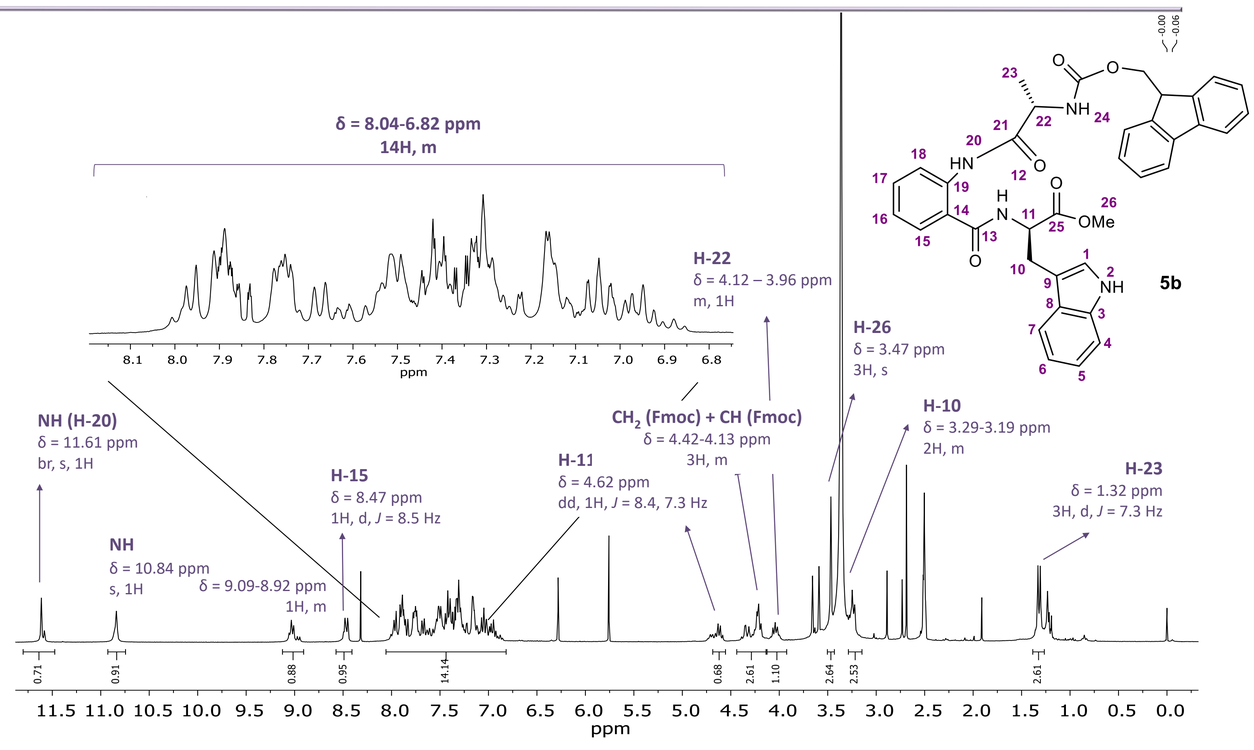


Figure 2. ^{1}H-NMR (DMSO) of methyl (*R*)-2-(2-((*R*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl) amino)propanamido)benzamido)-3-(1*H*-inden-3-yl)propanoate (**5b**).

Conclusions

- Linear dipeptide **3** and tripeptide **5** alkaloid intermediates were synthesized to be further used towards the synthesis of alkaloids **6**-**9**, structurally related to fumiquinazolines.
- Structure elucidation by ^{1}H-NMR spectroscopy indicated that the obtained compounds correspond to the expected structures.
- Future work will involve screening of the new alkaloids for their antibacterial activities.

References

1. Cheng, G. et al. *Frontiers in Microbiology* **2016**, 7, 470; **2.** Resende, D., et al. *Nat. Prod. Rep.*, **2019**, *36*, 7-34; **3.** Wang, H., et al. *J. Org. Chem.* **2000**, *65*, 1022-1030.

Acknowledgments

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