ABSTRACT

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Title of diploma thesis: Synthesis of precursors of 4-quinolones against *Trypanosoma brucei* for ^{18}F-radiolabelling

Human African trypanosomiasis (HAT), also known as sleeping sickness, is a parasitic disease caused by two subspecies of *Trypanosoma brucei (T.b.gambiense* and *T.b.rhodesiense*). This parasite is transmitted by the bite of infected tsetse flies. The sleeping sickness occurs in two clinical stages. The first one is characterized by the multiplication of parasites in the blood and lymphatic system. Very nonspecific symptoms, like fever, swollen lymph nodes, joint pain and headache are present. After a few weeks, a parasite crosses the blood-brain barrier and neurological symptoms like behavior changes, confusion, aggression and disruptions of sleep cycle appear. A coma and death results, if left untreated.

Nowadays, there are only five drugs available for the medical treatment of HAT. Suramin and pentamidine are used for the first stage, melarsoprol and eflornithine in combination with nifurtimox for the second one. Life threatening side-effects and a developing of resistances are the reasons, why new compounds are urgently needed. Since antitrypanosomal activity of quionolones was discovered, a quinolones-type library was synthesized and studied. *In vitro* evaluations and structure-activity relationships analysis showed, that 4-quinolones with a benzylamide function in position 3 and cyclic or acyclic amines in position 7 possessed high antitrypanosomal activity. According to studies, one compound from a library, *N*-benzyl-1-butyl-6-fluoro-7-morpholino-4-oxo-1,4-dihydroquinoline-3-carboxamide (**1**, Figure 1) exhibited promising *in vitro* and *in vivo* activity against *T.b.gambiense* (IC_{50} = 47 nM) and *T.b.rhodesiense* (IC_{50} = 9 nM) together with a low cytotoxicity against macrophages.

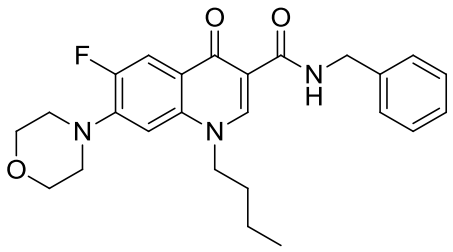

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Figure 1. *N*-benzyl-1-butyl-6-fluoro-7-morpholino-4-oxo-1,4-dihydroquinoline-3-carboxamide

Nevertheless, ^{18}F-radiolabeled compound is needed for *in vivo* testing. Measurements using positron emission tomography-computed tomography would clarify, whether the compound is able to cross blood-brain barrier and thus to be a potential drug against the second stage of HAT. In this study, I focused on the synthesis of precursor of *N*-benzyl-1-butyl-6-fluoro-7-morpholino-4-oxo-1,4-dihydroquinoline-3-carboxamide, which will be used for ^{18}F-radiolabelling.