Thesis Summary

Introduction

Leishmaniasis is a major disease in humans and animals. Leishmaniasis is an infectious disease caused by a parasite of the genus Leishmania from the *Trypanosomatidae* family. Today, many of the common drugs are used to treat the disease are toxic and may not even be able to treatment of the disease. Lack of successful treatment of leishmaniasis can be attributed to the increased resistance of the parasite to chemical drugs. In this study, a series of 1,4-dihydropyridine-3,5-dicarboxylate derivatives were designed and synthesized using the hantzsch reaction. Then, anti-leishmaniasis activity of synthesized derivatives was evaluated agianst amastigote and promastigote forms of *L. major*.

Material and method

In this study, after design, derivatives were synthesized through the Hantzsch reaction. Then, their structural identification and confirmation were performed by ^{1}H-NMR, FT-IR and MS spectroscopy methods. The anti-leishmaniasis effects of the synthesized compounds were evaluated against the forms of amastigote and promastigote forms of *L. major*. Finally, the survival amount of macrophages was assessed.

Results

Overall, compounds 5 (IC_{50} = 2.38 µM) and 4 (IC_{50} = 1.09×10^{-4} nM) showed the highest efficacy among the derivatives against amastigote and promastigote forms, respectively. Also, the toxicity results of these compounds were investigated on macrophages. The results showed that all compounds except compound 4, in 72 h of incubation and exposure to macrophages, had a higher toxicity than the positive control (glucantime).

Discussion and conclusion

Comparing the IC_{50} values of the synthesized compounds with the monstrol compound against the amastigote form, observed that all the compounds had a stronger effect than the monsterol (compound 5 having the best effect and compound 1 having the weakest effect). Also, based on comparing the IC_{50} values of the synthesized compounds with the standard drug amphotericin B against the promastigote form, observed that all the compounds were more active than the amphotericin B (compound 4 was the potent compound). In addition, according to IC_{50} values of the synthesized compounds and the standard drug glucantime against the amastigote form, all compounds showed less activity than glucantime. In general, based on performed comparisons between the activity of compounds in the present study as well as similar previous studies, it can be concluded that one of the factors that may affect the effectiveness of the compounds, is the coexistence of two massive substitutions with high lipophilicity in *meta* and *para*-aromatic ring positions. Also, the presence of methyl substitution with less length and steric hindrance than the ethyl group in 3 and 5 positions of the ester moieties of the dihydropyridine ring is probably one of the better effective factors of the compounds on amastigot phase of *L. major*.

Also, in the study of other compounds, it was found that the presence of substrates with smaller size and lower lipophilicity in meta and para-aromatic ring positions reduce the effect of the compounds on the amastigote form of *L. major*. Also, the presence of hydroxy substitution in the para position and methoxy substitution in the meta-aromatic ring position at the same time, probably due to the formation of intramolecular hydrogen bonds, are among the factors influencing the reduction of the effect of the compounds.

Key words:

Leishmaniasis, Multi-component reaction, dihydropyridine