DOI: 10.20396/revpibic2720192568

Synthesis of novel acyl-hydrazones as potential dual binding ligands for acetylcholinesterase. Biological evaluation and in silico pharmacokinetic profile prediction.

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Abstract

In this work, we have obtained eleven acyl-hydrazones derived from isoniazid, and three from substituted benzhydrazide.The effect of these compounds on acetylcholinesterase (AChE) was evaluated and benzydrazide derivatives were more effective in inhibiting AChE. Among the isoniazid derivatives, those having a benzodioxol or dihydroxyl groups are the most potent. The antioxidant activity was also studied. In silico studies of pharmacokinetic (PK) properties of the synthesized compounds suggests that all of them are able to cross the blood brain barrier (BBB). They are predicted to have high gastrointestinal abosrption (GI).

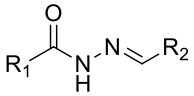
Key words: *Acyl-hydrazones, Acetylcholinesterase, Pharmacokinetic properties.*

Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder, characterized by a progressive loss of cognitive functions[1]. Cholinergic deficit and oxidative stress are, two main hallmarks. Because the limited therapeutic arsenal, drug candidates to treat AD have become attractive. Our group has discovered that acyl-hydrazones derived from 3-carboxy-4-quinolone as potent AChE inhibitors[2]. In order to better understand the structural requirements for this effect, we proposed the synthesis and evaluation of acyl-hydrazones derived from isoniazid and benzydrazide. The ability of these compounds in trapping DPPH radical was also studied. In silico study of some PK properties were conducted.

Results and Discussion

Compounds were prepared by a condensation reaction between a hydrazide and substituted aromatic aldehydes, in MeOH/DMF (Figure 1). Chemical yields range from 28 to 94%. In general, non-isoniazid derivatives have the highest yields.



CCF 1-14

Figure 1. Structures of the synthesized acyl-hydrazones. **1**: R_1=4-Py, R_2=(2,3-diCl)-Ph; **2**: R_1=4-Py, R_2=(3,4-OCH_2O)-Ph; **3**: R_1=4-Py, R_2=(2-F)-Ph; **4**: R_1=4-Py, R_2=(2-NO_2)-Ph; **5**: R_1=4-Py, R_2=(2-NO_2-4,5-di-OCH_3)-Ph; **6**: R_1=4-Py, R_2=(2,3-diOH)-Ph; **7**: R_1=4-Py, R_2 = (4-CF_3)-Ph; **8**: R1= 4-Py, R_2 = 2-thiophenyl; **9**: R_1= 4-Py, R_2 = (3,5-diF)-Ph;**10**: R_1=4-Py, R_2=(2-OH)-Ph; **11**:R_1=4-Py, R_2=(2-Cl)-3-quinolinyl;**12**: R_1=(3,4-OCH_2O)-Ph, R_2=(2,3-diCl)-Ph; **13**: R_1=(4-OCH_3)-Ph, R_2=(2,3-diCl)-Ph;**14**: (2-F)-Ph, R_2=(2-OH)-Ph.

Compounds were characterized by spectroscopic methods (NMR and IR). X-Ray diffraction was performed when a single crystal was obtained, as shown for CCF10 in Figure 2, highlighting the *E*-configuration for the C=N bond.

C=N (*E*-configuration)

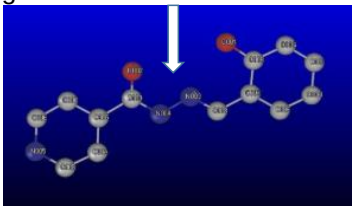


Figure 2. Structure of **CCF10** generated by SHELXTL XT.

AChE activity was evaluated by the colorimetric Ellman's method[3] and the antioxidant effect measurement employed DPPH [4]. Results are depicted in Table 1.

Table 1. Biological evaluation of the acyl-hydrazones.

Compound	AChE inhibition (%)	Antioxidant (%)
CCF2	69	94
CCF6	-	88
CCF9	89	-
CCF12	92	-
CCF13	90	-
Tacrine	93	-
Ascorbic acid	-	88

Among the test-compounds, **CCF9**, **12** and **13** showed high percentual of AChE inhibition. Regarding the antioxidant activity, **CCF2** and **6** exhibited an excellent profile, compared to the positive control.

In respect of PK properties (Swiss ADME)[5], all compounds are predicted to have GI absorption and none of them are P-gp substrates. Among isoniazid derivatives, only **CCF7**, **9** and **11** are BBB permeant, while all benzydrazide ones do. Except for **CCF6**, **9**, **10** and **14**, compounds are CYP inhibitors, being CYP 1A2 the main target.

Conclusions

Acyl-hydrazone **2** acts as AChE inhibitors and antioxidant. The presence of the methylenedioxy moiety seems to be important. However, it is not as effective as acyl-hydrazones derived from 4-quinolone having a methylenedioxy moiety. Molecular docking study between AChE and this acyl-hydrazone was compared to that performed with **2**. In this case, important interactions were missing.

Acknowledgement

PIBIC-CNPq, Fapesp (2018/02879-3), IQ-Unicamp and Prof. Wanda Almeida for her kindness and supervision.

[1] Alzheimer's Association. *Alzheimer's disease facts and figures*. **2019**, *15*, 87; [2] da Silva, G. S.. Figueiró, M.; Tormena, C. F., *et al. J. Enz.Inhib. Med. Chem*., **2016**, 31, 1464; [3] Ellman, G. L., Courtney, K. D., Andres, V. & Featherstone, R. M.. *Biochem. Pharmacol*. **1961**, 7, 27; [4] Brand-Williams, W., Cuvelier, M. E. *Food Sci. Technol.* **1995**, 28**,** 25; [5] Daina, A.; Michelin, O.; Zoete, V. *Sci. Rep*., **2016**, *7*, 42717.