Synthesis and Docking of new (2-(2,5-dimethoxyphenyl)-1H-benzo[d]imidazol-1-yl)(aryl)methanone derivatives designed as novel cannabinoid CB_1 receptor antagonists.

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INTRODUCTION

The endocannabinoid system has been known to mediate a complex array of biological effects. These effects are regulated through at least two distinct G-protein coupled receptors, the CB_1 and CB_2 receptor [1]. Specifically, the antagonists of the CB_1 receptor possess very useful applications, particularly in the obesity treatment such as Rimonabant [2]. In this work we inform the synthesis and docking studies of several (2-(2,5-dimethoxyphenyl)-1*H*-benzo*[d]*imidazol-1-yl)(aryl)methanone as potential CB_1 receptor antagonists.

RESULTS AND DISCUSSION

The first step in the synthetic sequence displayed in figure 1 is a condensation between *o*-phenylenediamines and 2,5-dimethoxybenzaldehyde [3]. This reaction is carry out using ethanol as solvent under reflux conditions during 24 h. The ^{1}H-NMR spectral data analysis for the benzimidazole series shows a signal in the range of 12-13 ppm for the NH group.

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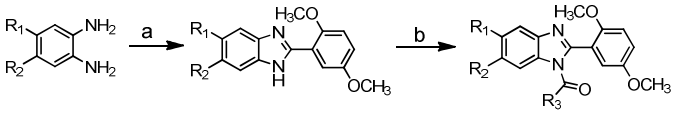
R1	R2	R3	Yield (%)	R1	R2	R3	Yield (%)
H	H	1-naphtyl	38	CH_3	CH_3	1-naphtyl	33
H	H	2-naphtyl	27	CH_3	CH_3	2-naphtyl	18
H	H	4-biphenyl	31	CH3	CH3	4-biphenyl	27
H	H	4-nitrophenyl	67	CH_3	CH_3	4-nitrophenyl	72
H	H	3-nitrophenyl	56	CH_3	CH_3	3-nitrophenyl	65
H	H	4-cianophenyl	62	CH_3	CH_3	4-cianophenyl	48
H	H	3-cianophenyl	58	CH_3	CH_3	3-cianophenyl	51

Table1. Derivatives synthesized and their respective yields



Reagents and conditions: a) 2,5-dimethoxybenzaldehyde, ethanol, reflux, 24 h. b) acyl chlorides, THF, Na_2CO_3, 6 h.

Figure 1. Synthetic route for the target series

Finally, the 2-(2,5-dimethoxyphenyl)-1H-benzimidazoles derivatives were acylated with various commercial acyl chlorides using THF as solvent and base in anhydrous atmosphere. The docking studies suggest, especially for derivatives **A** R_1, R_2=H; R_3=1-naphtyl and **B** R_1, R_2=H; R_3=2-naphtyl, a favorable binding ΔG, compared with the potent selective CB_1 antagonist LY-320135 (Table 2).

Compound	Binding ΔG
A	-18,34 kcal/mol
B	-18,23 kcal/mol
LY-320135	-13,56 kcal/mol

Table 2. ΔG binding values.

CONCLUSION

We synthesized a series of 2-(2,5-dimethoxyphenyl)-1H-benzo[d]imidazol-1-yl)(aryl) methanone. According to docking studies, two of them A and B, would be promising CB_1 cannabinoid receptor antagonists. Biological assays are currently in progress

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