Synthesis and docking of new benzimidazole derivates designed as novel and potent CB_1 cannabinoid ligands.

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INTRODUCTION

Despite the fact that medicinal and cognitive effects of Marijuana (*Cannabis sativa*) have been known for thousands of years, only recent studies provided convincing information on the biological mediation of it effects. Currently, two subtypes of cannabinoid receptor (namely CB_1 and CB_2) have been cloned and pharmacologically characterized. Both CB_1 and CB_2 belong to the G protein-coupled receptor family (GPCRs)[1].

Knowledge of the characteristics of CB_1 binding site has notably increased the interest on the synthesis of new small molecules as potential ligands, significantly less lipophilic and more potent than Δ9-THC[2]. Our interest in developing new cannabinoid ligands is based on the therapeutic opportunities associated to these chemical entities.

RESULTS AND DISCUSSION

The aim of this study is to obtain new cannabinoids ligands, trying to emulate the powerful indole cannabinoid agonist WIN 55,212-2 (see Figure 1) by replacing the indole by the isostere ring benzimidazole.

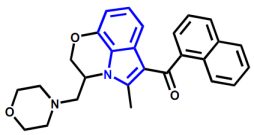

Figure 1: Cannabinoid agonist WIN 55,212-2. Blue bonds represent the heterocycle frame to be replaced.

Benzoimidazole series have been synthesized by oxidative condensation of 1,2-phenylenediamine with commercially available aldehydes. Substitution reactions in the N1 of the benzimidazole were carried out by using acid halides. Figure 2 shows the reaction conditions for the obtaining of heterocycle framework and the substitution of the N1 of the benzimidazole.

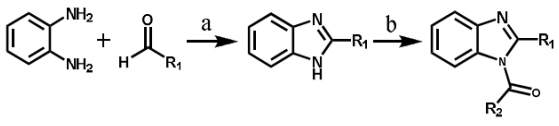

Figure 2: Synthetic secuence to the obtaining of target benzimidazoles. a) Ethanol, reflux. b) acid halides, triethylamine, THF, 6h.

To date twelve benzimidazole derivates have been synthesized, which possess a short chain aliphatic portion in position 2 and an aromatic substitution on the N1. This last substitution will give us valuable information about the contribution of the naphthalene moiety in WIN 55,212-2 to the total energy binding. Therefore, we included this moiety in six compounds meanwhile the other six molecules bear a 4-methoxyphenyl in this position. The series was subjected to experiments and then compared the results with WIN 55,212-2 binding ΔG, which value is – 8.50 kcal/mol. In silico study suggest that all molecules have a similar ability compaired with WIN 55,212-2 to interact into the binding site of the receptor CB_1. Table 1 shows synthesized benzimidazole analogues and their calculated binding ΔG.

R_1	R_2	Yield (%)	Binding ΔG (kcal/mol)
1-Naphtyl	Methyl	78	-6.55
1-Naphtyl	Propyl	66	-5.54
1-Naphtyl	Butyl	51	-5.66
1-Naphtyl	Isospropyl	84	-6.31
1-Naphtyl	2- Methyl propyl	56	-6.71
1-Naphtyl	Cyclopenthyl	81	-6.33
4-Methoxyphenyl	Methyl	33	-5.81
4-Methoxyphenyl	Propyl	24	-5.65
4-Methoxyphenyl	Butyl	21	-5.67
4-Methoxyphenyl	Isospropyl	42	-5.07
4-Methoxyphenyl	2- Methyl propyl	50	-6.40
4-Methoxyphenyl	Cyclopenthyl	28	-8.96

Table 1: ΔG Binding values.

CONCLUSION

The synthesis of a series of benzimidazole derivates structurally referible to WIN 55,212-2 have been afforded. The in silico docking studies predicts a good binding affinity like the agonist indole.

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