Docking and Synthesis of a series of 1-(naphthalen-1-ylmethyl)-2-(pyridin-2-yl)-1*H*-benzo[*d*]imidazole derivatives designed as novel CB_1 cannabinoid ligands.

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INTRODUCTION

The benzimidazole system has been focus of our attention owing to their affinity to CB_2 cannabinoid receptors[1,2,3]. However there are few reports of their CB_1 receptors affinity[4]. A preliminary screening of our library of benzimidazole derivatives yielded the hit compound **C6** (figure1), a potent cannabinoid ligand[5]. This molecule is structurally related to WIN 55212-2, a well know CB_1 receptor agonist[6]. In order to generate new CB_1 ligands with a benzimidazole framework we made a docking study on a CB_1 model, and we identified four possible zones of chemical modification (figure 1). Following this criteria we synthesized a series of 48 molecules which are being currently biologically evaluated (binding assays).

RESULTS AND DISCUSSION

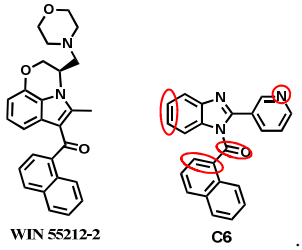
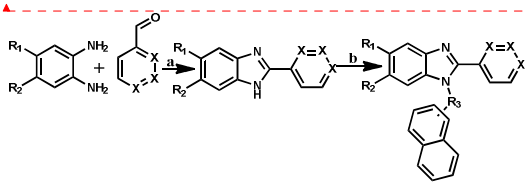


Figure 1. Structures of WIN 55212-2 and C6. In red circles the possible modification areas according the docking study.

The 48 compounds were synthesized with high yields in a two steps sequence (Firure 2). Primarily, a oxidative condensation of the substituted o-phenilenediamine with the respective pyridine carboxaldehide in ethanol in presence of a catalytic amount of CAN and H_2O_2 allows to obtain the benzoimidazoles. In a second step, the benzimidazoles were acylated with 1 or 2- naphtyl chloride or alkylated with 1 or 2 naphtyl bromide to give the target compounds.



Reagents and conditions: a) CAN, H_2O_2, ethanol, reflux 8 h. b) acyl or alkyl chlorides, THF-CH_3CN, NaH, 1Hr.

Figure 2. Synthetic route for the target compounds

In order to determine the affinity of the molecules to the CB_1 receptor, all the compounds are being evaluated in binding assays.

CONCLUSION

We complete the synthesis of a series of novel benzimidazoles structurally related to WIN 55212-2. The biological assays are in progress. Once the Ki will be obtained, a QSAR study is considered in order to direct the synthesis of improved novel molecules.

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REFERENCES

[1]Cichero E, Cesarini S, Mosti L, Fossa P. J Mol Model. 2010;16(9):1481-98

[2]Pagé D, et al. Bioorg Med Chem Lett. 2008;18(13):3695-700

[3]Verbist BM, De Cleyn MA, Surkyn M, Fraiponts E, Aerssens J, Nijsen MJ, Gijsen HJ.Bioorg Med Chem Lett. 2008;18(8):2574-9

[4]PATENT WO/2007/120101

[5] Katherine A. Araya, C. David Pessoa Mahana, Luis G. González. European Journal of Pharmacology 572 (2007) 32–39.

[6]Compton DR, Gold LH, Ward SJ, Balster RL, Martin BR.*Journal of Pharmacology and Experimental Therapeutics*. 1992; 263(3):1118-1126

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