Docking and Synthesis of a series of 1-(naphthalen-1-ylmethyl)-2-(pyridin-2-yl)-1H-benzo[d]imidazole derivatives designed as novel CB1 cannabinoid ligands.

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INTRODUCTION

The benzimidazole system has been a focus of our attention owing to their affinity to CB$_2$ cannabinoid receptors$^{1,2,3}$. However, there are few reports of their CB$_2$ receptors affinity$^4$. A preliminary screening of our library of benzimidazole derivatives yielded the lead compound C6 (Figure 1), a potent cannabinoid ligand$^{4}$. This molecule is structurally related to WIN 55212-2, a well-known CB$_2$ receptor agonist$^5$. In order to generate new CB$_2$ ligands with a benzimidazole framework, we made a docking study on a CB$_2$ 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

The 48 compounds were synthesized with high yields in a two steps sequence (Figure 2). Primarily, a oxidative condensation of the substituted o-phenalenediamine with the respective pyridine carboxaldehyde in ethanol in presence of a catalytic amount of CAN and H$_2$O$_2$ allows to obtain the benzimidazoles. In a second step, the benzimidazoles were acylated with 1 or 2- naphthyl chloride or alkylated with 1 or 2 naphthyl bromide to give the target compounds.

![Figure 1. Structures of WIN 55212-2 and C6. In red circles the possible modification areas according the docking study.](image)

![Figure 2. Synthetic route for the target compounds](image)

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 IC$_{50}$ will be obtained, a QSAR study is considered in order to direct the synthesis of improved novel molecules.

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REFERENCES

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