Design, synthesis, biological evaluation and binding mode modeling of benzimidazole derivatives targeting the cannabinoid receptor type 1

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 A series of N-acyl-2,5-dimethoxyphenyl-1H-benzimidazoles were designed based on a CoMFA model for cannabinoid receptor type 1 (CB1) ligands. Compounds were synthesized and radioligand binding affinity assays were performed. Eight novel benzimidazoles exhibited affinity for the CB1 receptor in the nanomolar range, and the most promising derivative compound 5 displayed a Ki value of 1.2 nM when compared to CP55,940. These results confirm our previously reported QSAR model on benzimidazole derivatives, providing new information for the development of small molecules with high CB1 affinity.