Introduction
Fluorine substitution, which had been merely perceived as a means of increasing the lipophilicity while not adding bulk, later gained a reputation of a complex personality, with effects such as increased metabolic stability due to strength of C-F bond, polar hydrophobicity, changes in acidity/basicity, changing conformation via hyperconjugation or dipole-dipole interaction, being constantly exploited. Even since more and more subtle fluorine effects have been discussed such as the enhancement of halogen bonding via sigma hole enlargement.
A study of fluorinated 3-(1-alkyl-1H-imidazol-5-yl)-1H-indoles which were designed to optimize the halogen bond formation between ligand and the receptor backbone revealed potent and highly drug-like 5-HT₇R agonists: 3-(1-alkyl-1H-imidazol-5-yl)-5-loido-4-fluoro-1H-indoles. Compounds were shown to produce potent anti-nociceptive effects at very low doses in NOR and ASST tests. Both 5-HT₇R agonists were shown to produce potent anti-nociceptive effects in mice model of neuropathic pain.