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Indole-imidazole conjugates as potential nootropics and antinociceptives for the treatment of neuropathic pain

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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 hyperconjungation or dipole-dipole interaction, being constantly exploited. Ever 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-1*H*-imidazol-5-yl)-1*H*-indoles[1] which were designed to optimize the halogen bond formation between ligand and the receptor backbone revealed potent and highly drug-like 5-HT_7R agonists: 3-(1-alkyl-1*H*-imidazol-5-yl)-5-iodo-4-fluoro-1*H*-indoles. Compounds exhibited high selectivity over related CNS targets, high metabolic stability and low toxicity in HEK-293 and HepG2 cell cultures. A rapid absorption to the blood, high blood-brain barrier permeation and a very high peak concentration in the brain were found for compounds AGH-192 and AGH-194 after *i.p., p.o.* and *i.v.* (2.5 mg/kg) administration in mice. AGH-194 was shown to produce procogonitive effects at very low doses in NOR and ASST tests. Both 5-HT_7R agonists were shown to produce potent anti-nociceptive effect in mice model of neuropathic pain.

[1] Hogendorf, A. S.; Hogendorf, A.; Kurczab, R.; Satała, G.; Lenda, T.; Walczak, M.; Latacz, G.; Handzlik, J.; Kieć-Kononowicz, K.; Wierońska, J. M.; et al. Low-basicity 5-HT7 Receptor Agonists Synthesized Using the van Leusen Multicomponent Protocol. *Sci. Rep*. 2017, *7*, article 1444.

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