A NEW INDICATION FOR SOLUBLE EPOXIDE HYDROLASE INHIBITORS: DESIGN, SYNTHESIS AND IN VIVO EVALUATION OF NOVEL UREAS IN A MURINE MODEL OF CHEMOTHERAPY-INDUCED NEUROPATHIC PAIN

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Chemotherapy-induced neuropathic pain (CINP) is a severe side effect of several anticancer agents, such as oxaliplatin, cisplatin, carboplatin and paclitaxel. The prevalence of CIPN is high, is the primary dose-limiting factor of several chemotherapy treatments and can last even after stopping the treatment. Although several analgesics are prescribed to treat painful CIPN, they are either ineffective (NSAIDs) or endowed with severe side effects (narcotics, gabapentinoids). Therefore, there are no current therapies that offer adequate relief for CINP [1].

Soluble epoxide hydrolase inhibitors (sEHI) are a new class of non-opioid analgesics, with a representative compound, EC5026, currently in clinical trials for the management of neuropathic pain [2,3]. In the last few years, our group has designed, synthesized and pharmacologically evaluated novel series of potent benzohomoadamantane-based sEHI and we found that a selected compound presented robust analgesic efficacy in the cyclophosphamide-induced murine model of cystitis, a well-established model of visceral pain [4].

Herein, we report further medicinal chemistry around the abovementioned polycyclic scaffold in order to improve DMPK properties of previous hits. After an extensive *in vitro* screening cascade, molecular modeling, and *in vivo* pharmacokinetics studies, a candidate was evaluated *in vivo* in a murine model of CINP.

CINP was performed by a daily injection of paclitaxel via i.p. (2 mg/kg), for 5 consecutive days. Mice developed neuropathic mechanical allodynia, which peaked on day 10 after the first paclitaxel administration –time when the acute effects of sEHI were tested. Subcutaneous administration of EC5026 (1.25-5 mg/kg) or UB-BJ-01 (2.5-5 mg/kg) completely reversed in a dose dependent manner the sensory hypersensitivity, and this effect was abolished by the administration of MSPPOH (20 mg/kg, s.c.), indicating the selectivity of their antiallodynic effects. Finally, administration of UB-BJ-01 (5 mg/kg, s.c.) 30 min before each paclitaxel injection completely prevented the development of neuropathic allodynia.

[1] Chemotherapy-induced peripheral neuropathy: part 1-current state of knowledge and perspectives for pharmacotherapy. *Pharmacol. Rep.* **2020**, *72*, 486-507.

[2] Movement to the clinic of soluble epoxide hydrolase inhibitor EC5026 as an analgesic for neuropathic pain and for use as a nonaddictive opioid alternative. *J. Med. Chem.* **2021**, *64*, 1856−1872.

[3] Soluble epoxide hydrolase inhibition alleviates chemotherapy induced neuropathic pain. *Front. Pain Res*. **2023**, *3*, 1100524.

[4] Synthesis, *in vitro* profiling, and *in vivo* evaluation of benzohomoadamantane-based ureas for visceral pain: a new indication for soluble epoxide hydrolase inhibitors. *J. Med. Chem.* **2022**, *65*, 13660-13680.