STRUCTURE-ACTIVITY AND HIGH-CONTENT IMAGE ANALYSIS OF NOVEL LOXAPINE DERIVATIVES AGAINST INTRAMACROPHAGIC *SALMONELLA*

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KEYWORDS: Macrophage, Virulence-targeted, Efflux pump

The emergence and spread of multiple-antibiotic-resistant *Salmonella* have been a serious threat worldwide. *Salmonella* can invade into host cells and evade the attacks of host humoral defenses and antibiotics with poor membrane permeation. Thus, a new antibacterial drug with a novel action mechanism against intracellular *Salmonella* is highly needed. Previously, we showed that an antipsychotic drug, loxapine, exhibited potent antibacterial activity against intracellular *Salmonella* Typhimurium in murine RAW264.7 macrophagic cells [1]. To optimize its antibacterial activity, a series of loxapine derivatives were designed and synthesized. The antibacterial activity and cytotoxicity of these compounds were simultaneously evaluated using an image-based high-content assay. The screening identified a new compound SW14 which showed a multifold increase in the antibacterial activity against intracellular *Salmonella* Typhimurium, *Shigella flexneri*, and *Listeria monocytogenes*. Subsequent investigation indicated that loxapine and its derivatives exhibited suppressive activity on bacterial efflux pumps which play an important role in the resistance of *Salmonella* to host innate defense. Together, our data suggested that loxapine might suppress intracellular bacteria through efflux pump inhibition, and SW14 represents a promising scaffold for the development of a new virulence-targeted antibacterial agent against intracellular bacteria.

[1] Yang C.Y., Hsu C.Y., Fang C.S., Shiau C.W., Chen C.S., Chiu H.C*, "Loxapine, an antipsychotic drug, suppresses intracellular multiple-antibiotic-resistant Salmonella enterica serovar Typhimurium in macrophages", *J Microbiol Immunol Infect*. **52(4)**:638-647 (2019)