KL02 Histamine H_3 Receptor Antagonists — From Bench to Bedside

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The identification of histamine H_3 (H_3R) receptors some time ago as an important subpopulation within the four histamine receptor subtypes known revived the interest in histamine research and exposed attractive perspectives for the potential therapeutic exploitation of these new drug targets. Meanwhile novel lead optimizations for histamine H_3 receptor antagonists made their way from an early stage already into the clinics [1]. Whereas in the beginning the main structures have been imidazole-based, the newer developments belong to different non-imidazole structural classes. Useful pharmacological tools with additional physicochemical properties, e.g. fluorescence, or pharmacodynamic profiles, e.g. multiple targeting, can be drawn to limited variations of some pharmacophore blue-prints [2]. Structure-activity relationships, cross-affinities and side effects as well as pharmacokinetic profiling will be discussed on selected promising compound series [3]. The H_3R is a recognised drug target for neuronal diseases, such as cognitive impairment, schizophrenia, sleep-wake disorders, epilepsy and neuropathic pain and a small number of selective H_3R antagonists have already passed some clinical phase II trials. Due to diversity in potential therapeutic applications and in some cases a controversial debate, different indications will be highlighted with the potential and the problems of the test compounds, e.g. sleep-wake disorders, ADHD, epilepsy, cognitive impairment, schizophrenia, obesity and neuropathic pain. Some of the most promising compounds so far are PF-3654746, SAR-110894, JNJ-31001074, SCH-497079, HPP-404 and tiprolisant. First data published on clinical trials phase II (IIb) are presented showing proof of concept of H_3 receptor antagonists in narcolepsy and photo-induced epilepsy [4].

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