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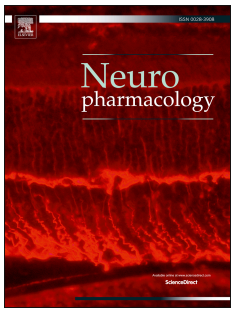

$mGlu_4$ allosteric modulation for treating Parkinson's disease

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$mGlu_4$ allosteric modulation for treating Parkinson's Disease

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Abstract:

2017 is the 200th anniversary of the first published description of Parkinson's disease (PD). Fifty years ago, the clinical benefit of levodopa was first documented, representing the most important advance in the treatment of PD so far. Among the novel targets identified in the last decade, positive allosteric modulators (PAM) of $mGlu_4$ receptors show great promise, with the potential to change the paradigm of the PD treatment approach. $mGlu_4$ PAMs have shown consistent efficacy in various preclinical models of PD, and entered clinical trials for the first time in 2017. This review synthesizes the rationale for $mGlu_4$ PAM development for PD and progress to date, reporting the key achievements from preclinical studies to the first-in-class compound assessment in man.

Keywords: Parkinson's disease; dyskinesia; glutamate; dopamine; $mGlu_4$

Abbreviations: 6-OHDA: 6-hydroxydopamine; **ADX88178:** 4-methyl-N-[5-methyl-4-(1H-pyrazol-4-yl)-1,3-thiazol-2-yl]pyrimidin-2-amine; **AIM:** abnormal involuntary movements; **CODA-RET:** complemented donor acceptor resonance energy transfer; **D1:** dopamine receptor type 1; **D2:** dopamine receptor type 2; **GABA:** gamma-aminobutyric acid; **GPe/i:**