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Rapid communication

EMD 281014, a new selective serotonin 5-HT$_{2A}$ receptor antagonist

Gerd D. Bartoszyk*, Christoph van Amsterdam, Henning Böttcher, Christoph A. Seyfried

Department of CNS Research, Preclinical Research Merck KGaA, 64271 Darmstadt, Germany

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Abstract

The 5-HT$_{2A}$ receptor ligand 7-{4-[2-(4-fluoro-phenyl)-ethyl]-piperazine-1-carbonyl}-1*H*-indole-3-carbonitrile HCl (EMD 281014) selectively binds to human (h) and rat 5-HT$_{2A}$ receptors (IC$_{50}$ values 0.35 and 1 nM, respectively; vs. 1334 nM for h5-HT$_{2C}$) and inhibited 5-HT-stimulated [^{35}S]guanosine 5′-*O*-3-thiotriphosphate (GTPγS)-accumulation in h5-HT$_{2A}$ transfected Chinese hamster ovary cells (IC$_{50}$ 9.3 nM). EMD 281014 counteracted the *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ)-induced decrease of [^{3}H]ketanserin binding in rat frontal cortex (ID$_{50}$ 0.4 mg/kg p.o.) and R-(−)-1-(2,5-dimethoxy-4-iodophenyl)-aminopropane (DOI)-induced head-twitch behaviour in mice (ID$_{50}$ 0.01 mg/kg s.c., 0.06 mg/kg p.o.), demonstrating unique selectivity and efficacy.

Keywords: 5-HT$_{2A}$ receptor antagonist; EMD 281014; M 100907

The search for novel atypical antipsychotics with less extrapyramidal side effects, due to remaining affinity for dopamine receptors, led to the discovery of M 100907 ((*R*)-(+)-(2,3-dimethoxy-phenyl)-{1-[2-(4-fluoro-phenyl)-ethyl]-piperidine-4-yl}-methanol), the first selective 5-HT$_{2A}$ receptor antagonist (Kehne et al., 1996) in clinical development (Offord, 1998). EMD 281014 (7-{4-[2-(4-fluorophenyl)-ethyl]-piperazine-1-carbonyl}-1*H*-indole-3-carbonitrile HCl) was discovered in search for 5-HT$_{2A}$ receptor antagonists with a much higher selectivity for 5-HT$_{2A}$ vs. 5-HT$_{2C}$ receptors. The present studies investigated the in vitro and in vivo profile of EMD 281014 in comparison to M 100907 with respect to the 5-HT$_{2A}$ receptor antagonistic properties.

In common in vitro binding assays (Klockow et al., 1986), EMD 281014 bound with high affinity to human (h) and rat (r) 5-HT$_{2A}$ receptors (IC$_{50}$ values expressed as mean ± S.E.M. from at least three replications: h5-HT$_{2A}$ 0.35 ± 0.08 nM, r5-HT$_{2A}$ 1.0 ± 0.3 nM), showing an about 4000-fold separation from the h5-HT$_{2C}$ receptor (Bonhaus et al., 1995) (IC$_{50}$ 1334 ± 224 nM) compared to M 100907 with a 100-fold separation (h5-HT$_{2A}$ 0.39 ± 0.03 nM, r5-HT$_{2A}$ 0.3 ± 0.1 nM, h5-HT$_{2C}$ 36.0 ± 3.3 nM). For EMD 281014, an affinity of < 1000 nM was only observed for the σ receptor (687 ± 66 nM). IC$_{50}$ values of ≥ 1000 nM were obtained for the α$_1$- and α$_2$-adrenoceptors, 5-HT$_{1A}$, 5-HT$_{2B}$, 5-HT$_7$ and dopamine D1 receptors and serotonin, noradrenaline and dopamine uptake, and IC$_{50}$ values of ≥ 10.000 nM for about 30 other receptors including the 5-HT$_{1B}$, 5-HT$_{1D}$, 5-HT$_3$, 5-HT$_4$, 5-HT$_6$, dopamine D2, D3, D4 and histamine H$_1$ receptors.

In functional in vitro assays for the inhibition of 5-HT-stimulated [^{35}S] guanosine 5′-*O*-3-thiotriphosphate (GTPγS) accumulation in Chinese hamster ovary (CHO) cells transfected with the human 5-HT$_{2A}$ receptor (adapted from Newman-Tancredi et al., 1997), EMD 281014 and M 100907 showed IC$_{50}$ values of 9.3 ± 2.5 (n = 3) and 6.2 ± 1.3 nM (n = 2), respectively.

In the ex vivo model of receptor inactivation by use of the alkylating agent *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) (Kettle et al., 1999), male Wistar rats (WiWu; 190–240 g body weight) were treated with EMD 281014 p.o. 25 h before and with EEDQ (10 mg/kg s.c.) 24 h before decapitation. Triple replications revealed that EMD 281014 antagonized EEDQ-induced decreases in 5-HT$_{2A}$-specific [^{3}H]ketanserin binding in the frontal cortex with an ID$_{50}$ value of 0.4 mg/kg p.o. and completely at 1 mg/kg p.o. without affecting dopaminergic [^{3}H]spiperone binding in the striatum even at 10 mg/kg.

The in vivo 5-HT$_{2A}$ receptor antagonistic properties were assessed in male NMRI mice (SPF; 22–36 g bodyweight) in the model of 1-(2,5-dimethoxy-4-iodophenyl)-aminopro-

* Corresponding author. Tel.: +49-6151-722447; fax: +49-6151-723041.
E-mail address: Gerd.Bartoszyk@merck.de (G.D. Bartoszyk).

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pane (DOI)-induced head-twitch behaviour (Darmani and Gerdes, 1995). EMD 281014 and M 100907, 30 min after application, dose-dependently and at higher dose completely antagonized R-(−)-DOI HCl (3 mg/kg i.p.)-induced head-twitch behaviour in mice. Compared to M 100907, EMD 281014 demonstrated a similar potency and efficacy after subcutaneous administration (ID_{50} values 0.01 mg/kg s.c. for both compounds) but a much improved efficacy after oral administration (ID_{50} 0.06 mg/kg p.o. for EMD 281014 vs. 2 mg/kg p.o. for M 100907). Using equally effective doses, i.e. the lowest doses giving a nearly complete inhibition (>95%) of DOI-induced head-twitch behavior, EMD 281014 had a much longer duration of action (at 0.1 mg/kg s.c., 2 h after application: 100% inhibition, 4 h: 82%, 6 h: 40%; at 0.3 mg/kg p.o. 3 h: 85%, 6 h: 89%) compared to M 100907 (0.1 mg/kg s.c. 2 h: 51%, 4 h: 16%; at 10 mg/kg p.o. 2 h: 90%, 4 h: 57%, 6 h: 8%).

To our knowledge, none of the further clinical trials with M 100907 in schizophrenia have been reported since the first early results (Offord, 1998). However, the low separation between 5-HT_{2A} and 5-HT_{2C} receptors may have contributed to some discouraging findings for M 100907, i.e. the lack of superiority to haloperidol and the bell-shaped dose–response curve. Antagonism at 5-HT_{2C} receptors exacerbates overactive mesolimbic dopaminergic function, as seen in schizophrenia (e.g. Hutson et al., 2000). In comparison to M 100907, EMD 281014 demonstrated a much higher selectivity for 5-HT_{2A} vs. 5-HT_{2C} receptors with 5-HT_{2A} receptor antagonistic properties. In the DOI-induced head-twitch model, EMD 281014 had an improved efficacy after p.o. administration and a longer duration of action. This makes EMD 281014 a candidate for clinical development with an improved profile not only for schizophrenia but also for other indications (e.g. de Angelis, 2002) such as depression and anxiety, learning and memory or sleep disturbances.

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