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Deramciclane improves object recognition in rats: Potential role of NMDA receptors

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ABSTRACT

The cognition-enhancing properties of deramciclane (N,N-dimethyl-2-([(1R,4R,6 S)-1,7,7-trimethyl-6-phenyl-6-bicyclo[2.2.1]heptanyl]oxy)ethanamine) and memantine (3,5-dimethyl-tricyclo[3.3.1.1$_{3,7}$]decylamine-3,5-dimethyladamantan-1-amine) were evaluated in the novel object recognition (OR) test in the rat, while their effect in comparison with other *N*-methyl-D-aspartate (NMDA) receptor blockers such us MK-801 ([+]-5-methyl-10,11-dihydro-5H-dibenzocyclohepten-5,10-imine maleate) and CPP ([+/−]-3-(2-carboxypiperazin-4-yl)propyl-1-phosphonic acid) on NMDA-evoked spreading depression (SD) was investigated in the chicken retina, *in vitro*. In the OR test, pretreatment of rats with either deramciclane (30 mg/kg p.o.) or memantine (10 and 30 mg/kg, p.o.) resulted in preference for the novel object, compared to the familiar one, indicating procognitive activity of the compounds. In the *in vitro* studies memantine (10–30 M), or deramciclane (30–100 M) as well as CPP (0.1–1 M), MK-801 (0.3–1 M), concentration-dependently inhibited NMDA evoked SD. Furthermore, the inhibitory effect of memantine, deramciclane and MK-801 was activity-dependent. These results support the role of NMDA receptors in the procognitive effect of deramciclane.

1. Introduction

The glutamatergic system has been a therapeutic target for decades in diseases in which either hypo- (schizophrenia) or hyper activation (oxidative stress, epilepsy, chronic neurodegenerative disorders) of the excitatory system plays an important role. The balanced function of NMDA receptors is crucial for proper physiological functions including cognitive processes and memory formation. Overexcitation of NMDA type ionotropic glutamate receptors causes degenerative alterations in the neurons, which eventually results in cell death. Strong inhibition, on the contrary, induces cognitive, psychic and motor anomalies (Gunduz-Bruce, 2009; Manahan-Vaughan et al., 2008; Morris et al., 1986; Parada-Turska and Turski, 1990) and hinders synaptic plasticity (Collingridge and Bliss, 1995). The moderate, voltage-dependent NMDA receptor blocking potency of a drug, however, may reduce the risk of adverse effects — as described at memantine, the only clinically approved uncompetitive NMDA receptor antagonist for the treatment of Alzheimer's dementia (Chen et al, 1992; Parsons et al., 1993, 2007; Pietá Dias et al., 2007; Rammes et al., 2008).

(1R,2S,4R)-(−)-2-phenyl-2-(2'-dimethylamino-ethoxy)-1,7,7-trimethyl-bicyclo[2.2.1]heptane (deramciclane) is a potent and specific serotonin 5-HT$_{2A/2C}$ receptor antagonist (Pälvimäki et al., 1998), proved to be anxiolytic in various animal models (Gacsályi et al., 1997) as well as in a placebo-controlled, double blind clinical trial (Naukkarinen et al., 2005). Deramciclane was demonstrated to inhibit [^{3}H]MK-801 binding (Gacsályi et al., 1997) and NMDA-induced [3H]D-aspartate release in rat cerebrocortical homogenates (Kovács et al., 2000). Recently, we have demonstrated that the NMDA blocker activity of deramciclane showed concentration- and activity-dependent characteristics in patch clamp measurements on rat telencephalon neurons and on SD in the chicken retina (Kertész et al., 2005). Moreover, receptor binding profile of deramciclane (EGIS-3886) was determined during preclinical development of the compound. In this process, inhibition of [^{3}H]MK-801 binding by deramciclane was evaluated in a contract study at Orion-Farmos Pharmaceuticals, Espoo, Finland. Deramciclane was found to inhibit [^{3}H]MK-801 binding to rat forebrain membranes with an IC$_{50}$ of 5.7 μM (unpublished data of Vasar E.). These effects resemble that of memantine, and the functional similarities between memantine and deramciclane raised the possibility that deramciclane may also have beneficial effects on cognition and memory.

SD, first described in the cerebral cortex by Leão (1944), is characterized by a transient, slowly propagating wave of depression of electrical activity. SD is accompanied by an intrinsic optical signal that can be observed by unaided eye in the avian retina (Martins-Ferreira and de Oliveira Castro, 1966). Glutamatergic ligands influence the initiation and propagation of SD. Therefore, SD in the retina is a simple functional test to evaluate the capability of a drug to either inhibit (Kapus et al., 2004; Sheardown, 1993) or potentiate (Kertész et al., 2004) the ionotropic glutamatergic system.

The OR task is a widely used paradigm to investigate either phase of recognition memory, namely encoding, consolidation or retrieval in

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rodents (Sargolini et al., 2003; Winters and Bussey, 2005; Winters et al., 2008). The test exploits the spontaneous exploratory behaviour of the experimental animals, therefore drug effect on memory formation can be evaluated without the influence of a stressful situation of any punishment or drive for reward (Dere et al., 2007).

The aim of this study was to evaluate the effect of deramciclane in comparison with different type NMDA receptor blockers, memantine, MK-801 and CPP on NMDA-evoked SD in the chicken retina *in vitro* and the procognitive effect of deramciclane and memantine in the OR test in the rat, to determine whether deramciclane has similar features to memantine which could then imply similar therapeutic potential.

2. Materials and methods

SD experiments were performed on isolated retinas of 5–7-day-old chickens (Shaver Redbrow; Labnyul Ltd., Hungary), as previously described elsewhere (Sheardown, 1993). The animals were decapitated under ether anaesthesia. The eyes were enucleated and cut along the equatorial plane. After removal of the anterior part and the vitreous body, the posterior parts (retinas) were placed in Ringer solution with lowered Mg^{2+} concentration (100 mM NaCl, 3 mM KCl, 1 mM $CaCl_2$, 0.33 mM $MgSO_4$, 30 mM $NaHCO_3$, 1 mM NaH_2PO_4, 10 mM glucose, pH 7.4. Solution was saturated with carbogen (95% O_2 and 5% CO_2), and kept at room temperature (24 °C). After an equilibrium period of 60 min retinas were placed into Ringer solution containing 50 μM NMDA. Latency to the appearance of a slowly increasing grey spot — the initiation of SD was measured. After a 25 minute washout in Ringer solution, retinas were incubated for 20 min in solutions containing the test compounds (NMDA receptor antagonists). Then latency of SD evoked by NMDA was measured again. This procedure (25 min washout plus 20 min incubation with the test compound) was carried out 5 times. Percent inhibition was calculated by comparing latency of SD in the presence and absence (control) of test compounds. A thirty second increase in control latency was considered 100% inhibition of SD. NMDA, (+/−)-3-(2-carboxypiperazin-4-yl)propyl-1-phosphonic acid (CPP) and 1-amino-3,5-dimethyladamantane (memantine) were purchased from Tocris Cookson Ltd. (Bristol, UK). (+)-5-methyl-10,11-dihydro-5H-dibenzo-[*a*,*d*]cyclo-hepten-5,10-imine-maleate (MK-801) was obtained from Sigma-Aldrich (St. Louis, MO). Deramciclane was synthesized at EGIS Pharmaceuticals Plc., Budapest, Hungary. Compounds were first dissolved in DMSO and further diluted with the bathing solution to the final concentrations (DMSO concentration was ≤0.3%). Percent inhibition values were compared and statistically analyzed (ANOVA followed by Tukey HSD test (StatSoft Statistica 8.0). Concentrations of drugs caused 50% inhibition (IC_{50} values) were calculated using sigmoidal curve fitting (GraphPad Prism 3.02).

OR experiments were carried out on male Sprague–Dawley rats (EGIS Plc, Budapest, Hungary) weighing 220–260 g at the start of behavioral testing. Four animals were kept per cage at 25 °C on sawdust bedding, regularly handled for a week before experiment. Free access to food and water, on a 12 h light/dark cycle (light period from 6.00 to 18.00 h). Experiments were performed in the same room where only the experimental animals were kept during the investigations. The test apparatus was a black plexiglas box with sawdust bedding, 70×50×40 cm, indirectly lit with a 50 W halogen lamp. There were no cues visible for the animals around the box except for the desk lamp (above the box, equidistant from the two objects), and the camera (opposite to the desk lamp, equidistant from the two objects). Metal triangular (8.5×5×14 cm) and rectangular prisms (5×5×14 cm) were used as objects to be discriminated. The test procedure was executed as described elsewhere (Ennaceur and Delacour, 1988) with minor modifications. Briefly: on the day before the test day (Day 0) the animals were allowed to explore test apparatus without objects for 150 s. Twenty four hours later (Day 1: sample trial, T1) two identical objects (either two triangular or two rectangular prisms) in the test apparatus were allowed to be explored for altogether 20 s. Exploration time was measured manually by the observer. Animals were considered to explore objects when their noses were toward the objects at a distance of no more than 2 cm while sniffing and/or touching the objects. Climbing or sitting on the objects were not considered as exploration. Retrieval was observed after 24 h (on Day 2: choice trial, T2). A new (*N*) and a familiar (*F*) object was placed in the test box and the animals were placed in the box for 4 min. The location of the new and the familiar object was randomized to reduce the potential effect of place or object preference. The objects were cleaned thoroughly after each trial to prevent animals from meeting olfactory trails. Drugs were administered orally either 60 min before sample trial (T1) (deramciclane and memantine) or immediately after T1, or 60 min before choice trial (T2) (deramciclane). The time spent in exploration of the familiar (*F*) and the new (*N*) object was measured and statistically analyzed (ANOVA followed by Scheffé's test (StatSoft Statistica 8.0) Discrimination index $(F-N)/(F+N)$ was calculated. Animals were tested on Day 2 only if no significant difference in discrimination indexes was measured on Day 1. Rats with low exploratory activity on Day 1 (less than 20 s object exploration up to 5 min) were excluded from further investigation (0–3 animals per group). The care and use of the experimental animals were in accordance with the 86/609/EEC directive. All experimental protocols were approved by the local ethical committee at EGIS Pharmaceuticals Plc.

3. Results

Deramciclane (100 μM) did not influence SD evoked by either AMPA (5 μM) or NMDA (100 μM) when Mg2+-concentration was physiological (1 mM) (data not shown). When Mg^{2+} concentration was lowered to 0.33 mM, NMDA (50 μM) in the chicken retina elicited SD with a latency of 15–20 s. Under these conditions deramciclane, like MK-801, CPP and memantine, inhibited the NMDA-evoked SD in a concentration-dependent manner. Concentrations of drugs caused 50% inhibition (IC_{50}), calculated at the 5th repeated elicitation of SD (225th min of the experiment) are 56.25±2.47 μM, 12.67±0.99 μM, 0.18±0.02 μM, and 0.48±0.04 μM, for deramciclane, memantine, MK-801, and CPP, respectively. The concentration–response curve of the competitive NMDA receptor antagonist CPP (0.1–1 μM) did not change during repeated elicitations of SD. The inhibitory effect of MK-801 (0.3–1 μM), memantine (10–30 μM), or deramciclane (30–100 μM) increased during consecutive elicitations of SD (Fig. 1). The time scale of the inhibitory effect of deramciclane was different from that of the competitive antagonist CPP, and was similar to that of the non-competitive antagonists MK-801 and memantine (Fig. 1).

For OR, no object or place preference was measured at any groups on Day 1 (data not shown). On Day 2, comparison of the times spent with exploration of familiar and new objects showed that animals treated 60 min before T1 with 30 mg/kg p.o. deramciclane explored the new object for longer time than familiar one (Fig. 2A). There was no significant difference in exploration times either in 3 mg/kg or 10 mg/kg deramciclane treated groups. Statistical analysis of discrimination indexes showed significant difference between vehicle-treated and 30 mg/kg deramciclane-treated groups (Fig. 2B). Rats pretreated with memantine (at 10 and 30 mg/kg, but not at 3 mg/kg, po.) spent significantly more time with exploration of the new object, whereas times spent with exploration of the familiar object were similar in all memantine-treated groups (Fig. 3A). Statistical analysis of discrimination indexes revealed significant difference between vehicle-treated and 10 or 30 mg/kg memantine-treated groups (Fig. 3B). Animals treated with the highest dose of deramciclane (30 mg/kg, p.o.) either immediately after T1 or 60 min before T2, spent more time with the exploration of the novel than the familiar object (Table 1). Statistical analysis of discrimination indexes demonstrated significant difference between vehicle-treated and 30 mg/kg deramciclane-treated groups (Table 1).

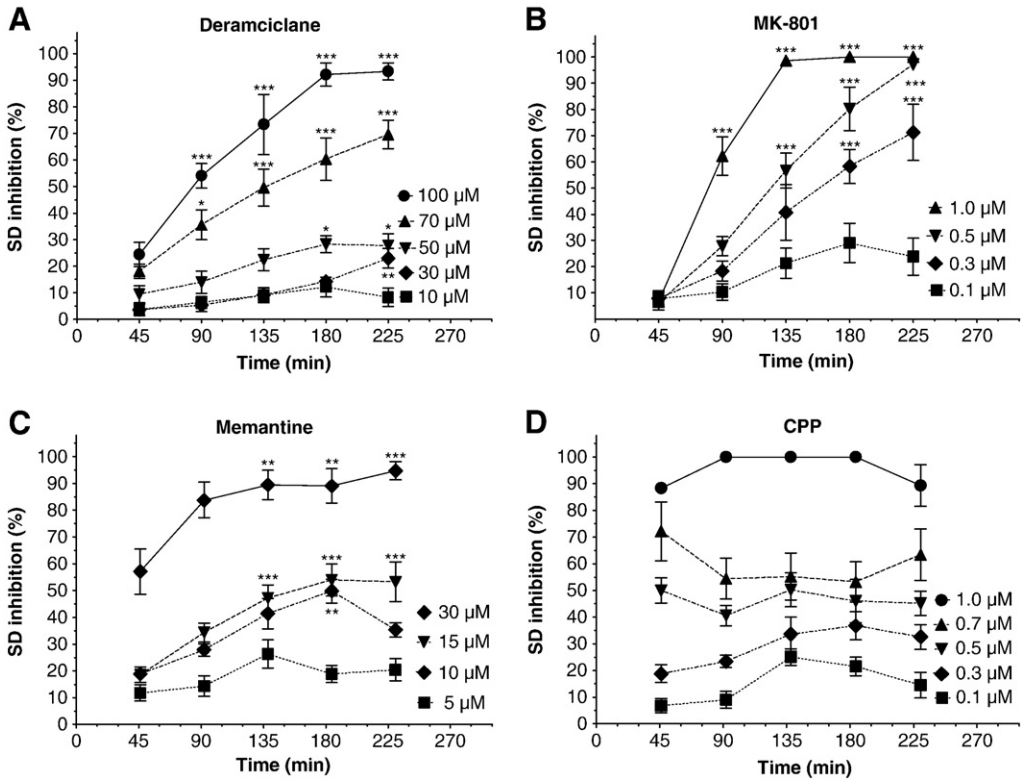

Fig. 1. Activity-dependent change of concentration–response curves during repetitive administrations of deramciclane (A), MK-801 (B), memantine (C), and CPP (D), respectively, in the NMDA-evoked spreading depression (SD) in the isolated chicken retina. Data represent means ± S.E.M. of percent inhibition of SD latency. *: $p<0.05$, **: $p<0.01$ ***: $p<0.001$ compared to the respective percent inhibition measured at 45 min.

4. Discussion

The present study investigated the inhibitory effect of deramciclane on NMDA-induced SD in the chicken retina *in vitro* in comparison with other NMDA receptor blockers, and the procognitive effect of deramciclane compared to that of memantine. SD in the retina can readily be induced by NMDA, and inhibited by NMDA antagonists. NMDA receptor plays central role in initiating SD. AMPA/kainate receptor agonists evoke SD indirectly through NMDA receptors, whereas only NMDA but not AMPA/kainate receptor antagonists inhibit NMDA-evoked SD (Sheardown, 1993). In this paper we demonstrated that deramciclane, in micromolar concentrations, inhibits NMDA-evoked SD in the chicken retina, similarly to other NMDA receptor antagonists tested. The concentration–response curves of the channel-blocker, uncompetitive, NMDA receptor antagonists MK-801 and memantine, as well as that of deramciclane shifted to the left during repetitive administrations of the drugs, showing activity-dependency. In addition, statistical analysis did not demonstrate difference in the extent and characteristics of the activity-dependent changes of the concentration–response curves among MK-801, memantine and deramciclane. The concentration–response curve of the competitive antagonist CPP, however, did not shift to the left when the drug was added in a repetitive manner. It was suggested earlier that deramciclane influences NMDA receptor function similarly to MK-801 (Kovács et al., 2000). Our results are consistent with this finding, and show that deramciclane inhibits NMDA-evoked SD as an open-channel, uncompetitive NMDA receptor antagonist.

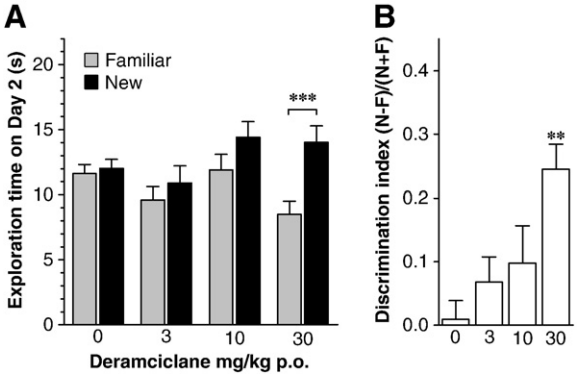

Fig. 2. The effect of pre-sample administration of deramciclane on the novel object recognition in the rat. A: Total exploration times (seconds) measured on Day 2. ***: $p<0.001$ compared respective familiar (F) and new (N) exploration time. B Discrimination indexes $(N-F)/(N+F)$ measured on Day2. **: $p<0.01$ different from control (0); values represent mean ± S.E.M. ($N=11$–14 per group);

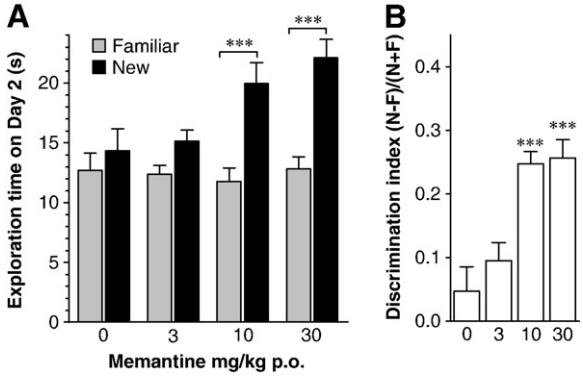

Fig. 3. The effect of pre-sample administration of memantine on the novel object recognition in the rat. A: Total exploration times (seconds) measured on Day 2. ***: $p<0.001$ compared respective familiar (F) and new (N) exploration time. B: Discrimination indexes $(N-F)/(N+F)$ measured on Day2. ***: $p<0.001$ different from control (0); Values represent mean ± S.E.M. ($N=12$ per group);

Table 1
The effect of deramciclane, on the novel object recognition in the rat, administered immediately after sample test (T1) or 60 min before choice test (T2). Values are mean ± S.E.M. (N = 11–14 per group); ***: $p<0.001$ significant difference from the respective familiar exploration time (F); ##: $p<0.01$, ###: $p<0.001$ significant difference from the respective control value.

Treatment	Dose (mg/kg, p.o.)	Exploration time on day 2 (s)		Discrimination index	N
		Familiar (F)	New (N)	$(N-F)/(N+F)$	
Control		10.5 ± 1.2	10.7 ± 1.3	0.01 ± 0.04	13
Deramciclane	3	9.2 ± 1.2	11.3 ± 1.4	0.12 ± 0.05	13
(After T1)	10	8.7 ± 1.3	12.0 ± 1.4	0.18 ± 0.04	12
	30	9.8 ± 1.0	16.7 ± 1.2***	0.28 ± 0.05##	14
Control	0	8.5 ± 1.1	8.7 ± 1.3	−0.01 ± 0.05	13
Deramciclane	3	8.1 ± 0.8	8.5 ± 0.7	0.03 ± 0.05	11
(Before T2)	10	7.8 ± 0.8	10.8 ± 1.2	0.15 ± 0.05	13
	30	6.8 ± 0.8	12.4 ± 1.0***	0.31 ± 0.05###	12

Memantine differs from MK-801 regarding their NMDA receptor affinity, kinetics and voltage dependency (Chen et al., 1992; Gilling et al., 2009), which results in beneficial effect of memantine on cognitive processes. Memantine inhibits tonic, rather than phasic activity of NMDA receptors, similar to the extracellular Mg^{2+}, the physiological, voltage-sensitive blocker of the receptor. Therefore memantine prevents tonic, pathological overexcitation, whereas fails to hinder fast, physiological activation of the NMDA receptor (Parsons et al., 1993).

Since it was first described in rats (Ennaceur and Delacour, 1988) the OR task has become a widely used paradigm to investigate recognition memory in rodents. Longer retention interval (several hours to days) allows for investigating the effect of drug administration in distinct phases of memory formation. A number of studies with NMDA receptor ligands on recognition memory demonstrated that proper function of NMDA receptors was indispensable for memory formation, as NMDA receptor antagonists impair recognition memory encoding and consolidation as well (de Lima et al., 2005; Pitsikas et al., 2008; Puma et al, 1998; Puma and Bizot, 1998; Sargolini et al., 2003; Winters and Bussey, 2005). There are only few reports discussing the role of NMDA receptors specifically on retrieval of recognition memory, and the comparison of their results is difficult because of the various protocol, dose regimen, route and loci of administration and animal species used. The competitive antagonist AP5 infusion into the perirhinal cortex before retention test did not influence OR memory retrieval in rats (Winters and Bussey, 2005). On the contrary, systemic, intraperitoneal injection of MK-801 resulted in an increased neophilic activity in mice (Nilsson et al., 2007). Intraseptal infusion of the NMDA receptor competitive antagonist AP5 at higher dose (8 nmol) impaired memory in an OR task (Puma et al., 1998) whereas at lower dose (2 nmol) improved each phase of OR, even retrieval (Puma and Bizot, 1998). Similarly, data regarding the procognitive effect of memantine on OR do not seem to be obvious. Memantine was found to reduce age and/or oxidative stress-induced memory impairment (Pietá Dias et al., 2007) whereas it did not influence normal memory formation at clinically relevant doses (Réus et al., 2008). It was found, however, that memantine improved memory retrieval in the OR test in the rat, after i.p. administration (Pitsikas and Sakellaridis, 2007). Our results are consistent with these data: memantine (10 and 30 mg/kg) was shown to improve performance of rats in the OR task after p.o. administration. In addition, we found that deramciclane induced similar improvement at the highest dose tested (30 mg/kg, p.o.). The effect of deramciclane on memory retrieval was not different if the compound was administered in different phases of the test, i.e. either immediately after acquisition or before retrieval. Our findings indicate that deramciclane similarly improves either memory encoding or consolidation or retrieval of recognition memory in the OR paradigm.

The absorption and distribution of deramciclane in different brain regions after oral treatment is fast (Magyar et al., 1998). Immediate oral administration of the drug after T1 may result in reaching effective concentrations within the first half an hour, in which period NMDA receptors, at least in the perirhinal cortex, contribute to memory consolidation (Winters and Bussey, 2005). Indeed, preliminary investigations in our laboratory showed that deramciclane increased step-through latency at acquisition as well as at 24 h retention in passive avoidance test in rats (unpublished data). Pharmacokinetic data with lower doses (3 and 10 mg/kg, p.o.) (Klebovich et al., 1998; Nemes et al., 2000) indicated reasonable exposition in rats. Moreover, autoradiography studies in rats (Hazai et al., 1999) showed that deramciclane completely and rapidly penetrates blood-brain barrier. Although exposition following 30 mg/kg dose treatment is not available from the literature, cautious extrapolation of data makes presumable that deramciclane influences NMDA receptor function in the rat brain *in vivo* after oral administration at a dose of 30 mg/kg. Although it needs further investigations, the NMDA receptor blocking potency at higher micromolar range and the uncompetitive characteristics of the antagonist action of deramciclane supposedly contribute to its beneficial action in OR in the rat.

Deramciclane is a well-tolerated and safe compound with anxiolytic properties in humans (Naukkarinen et al., 2005). Our report indicates that it also has procognitive properties in the rat. Although this procognitive potency is somewhat weaker than that of the therapeutic drug memantine, the anxiolytic efficacy of deramciclane along with the clinically proved favourable side effect profile makes the compound an interesting drug candidate. Further investigations on other cognitive models are needed to determine the beneficial effect and the exact mechanism of action of deramciclane on memory and learning, and its potential efficacy in models of Alzheimer's disease.

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