ANXIOLYTIC-LIKE ACTIVITY OF PZ-1433, A NOVEL ARYLSULFONAMIDE DERIVATIVE OF ARYLOXY(PROPYL)PIPERIDINE, IN RODENTS

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Abstract

A novel arylsulfonamide derivative of aryloxy(propyl)piperidine PZ-1433, has been proved to possess a preclinical activity profile appropriate for the treatment of depression and memory impairments. In the present study its pharmacological activity toward anxiety symptoms as well as its anxiolytic properties have been examined in mouse and rat models. PZ-1433 significantly increased the number of punished crossings and decreased the number of buried marbles in two tests conducted in mice. Moreover, PZ-1433 evoked anxiolytic-like activity in "conditional" anxiety paradigm in rats, meaningly increasing the number of accepted shocks in the Vogel conflict drinking test. However, it did not produce a significant anxiolytic-like effect in "unconditional" anxiety model, i.e. the elevated plus-maze test. From these results, it is likely that direct antagonism toward serotonin 5-HT7 receptors may be involved in the anxiolytic action of PZ-1433. However, in vitro detected inhibition of serotonin transporter evoked by PZ-1433, might also contribute to this effect.

Keywords: anxiety, serotonin 5-HT7 receptor, rats, mice

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Introduction

Anxiety disorders are heterogeneous group of illnesses having excessive fear and anxiety as their core features. Furthermore, anxiety disorders often co-occur with other psychiatric and neurodegenerative diseases, like major depressive disorder, bipolar disorder, Alzheimer and Parkinson diseases. Such comorbidity usually leads to more chronic and treatment refractory course of illness and increases the risk of suicide [1–3].

Currently available first-line treatments for anxiety disorders are limited and include selective serotonin reuptake inhibitors (SSRIs), serotonin noradrenaline reuptake inhibitors (SNRIs) and benzodiazepines used as a short-term and/or adjunctive treatment [1]. These drugs cause numerous burdensome side effects; SSRIs and SNRIs induce gastrointestinal and sexual dysfunctions, and benzodiazepines evoke sedation, memory impairments and addiction [4]. Moreover, some reports question the effectiveness of drugs used in anxiety treatment [5–7]. These drawbacks, together with a fact that no mechanistically novel anxiolytic drug was introduced to market over two decades, make that there is an urgent need for more effective and safer antianxiety treatment.

Localization of 5-HT_7 receptors in limbic regions involved in the regulation of anxiety behavior [8] makes these receptors an interesting target for potential anxiolytics. Preclinical studies have shown that 5-HT_7 antagonists exert anxiolytic-like effects in the Vogel conflict drinking and the elevated plus-maze (EPM) tests in rats as well as in the

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four-plate (FPT) and marble burying (MBT) tests in mice [9–12]. Moreover, considerable body of evidence supports a role of the 5-HT_7 receptor in depression [9,11,13–15]. Further, strong data reveal an involvement of 5-HT_7 antagonists in selected aspects of learning, memory as well as their procognitive potential [11,16–20].

PZ-1433 is an arylsulfonamide derivative of (aryloxy)propylpiperidine that acts as a potent 5-HT_7 antagonist (K_i = 32nM) presenting high-to-moderate selectivity over serotonergic 5-HT_{1A}, 5-HT_{2A}, 5-HT_6 and dopaminergic D_2 receptors. Furthermore, it displays a moderate affinity for serotonin transporter (SERT) (79% at 1 μM) and does not bind to norepinephrine and dopamine transporters (<10% at 1 μM). In the previous studies PZ-1433 demonstrated antidepressant-like activity in the forced swim test (FST) in Swiss albino mice with a minimum effective dose (MED) of 0.625 mg/kg and in the tail suspension test (TST) in C57BL/6J mice (MED = 1.25 mg/kg) [15]. In the interaction studies PZ-1433 potentiated antidepressant characteristics of inactive doses of escitalopram and bupropion, but not reboxetine, in the FST in mice. Such results suggest that anti-immobility effects of PZ-1433 observed in the FST are mediated *via* serotonergic and dopaminergic rather than noradrenergic systems [15]. The antidepressant properties of PZ-1433 were confirmed in the FST conducted in Wistar rats (MED = 0.1 mg/kg) (data not published). Furthermore, this compound displayed procognitive properties in novel object recognition test (NORT) in rats with MED of 0.3 mg/kg [15].

Taking into account the coexistence of depression and anxiety disorders, we decided to continue the exploration of PZ-1433' central activity and determine its potential anxiolytic activity in mouse and rat models of anxiety.

Materials and methods

Subject

Male Swiss albino mice weighing 21-23 g upon arrival from a licensed dealer (Staniszewska; Ilkowice, Poland) or CD-1 mice weighing 21-23 g from accredited animal facility Jagiellonian University Medical College (Kraków, Poland) were group-housed for 4 day period in polycarbonate Makrolon type 3 cages (dimensions 26.5×15×42 cm) in an environmentally controlled, experimental room (ambient temperature 21±1 °C; relative humidity 50-60 %; 15-20 air changes; 12:12 light:dark cycle, lights on at 8:00), in groups of 15. Male Wistar rats weighing 205-225 g upon arrival from accredited animal facility Jagiellonian University Medical College (Kraków, Poland) were group-housed for 6 day period in polycarbonate Makrolon type 3 cages (dimensions 26.5×15×42 cm) in an environmentally controlled room (ambient temperature 22±2 °C; relative humidity 50-60%; 15-20 air changes; 12:12 light:dark cycle, lights on at 8:00), in groups of 4. Standard laboratory food (LSM-B) and filtered water were freely available. On the day before experiments the equipment produces "white noise" was turned on for 30 min and mice or rats were weighted exact to 1g. Animals were assigned randomly to treatment groups. All the experiments were performed by two observers unaware of the treatment applied between 9:00 and 14:00 on separate groups of animals. All animals were used only once and were killed immediately after the experiment. All the experimental procedures were approved by the II Local Ethics Commission at the Institute of Pharmacology PAS in Kraków.

Drug treatment

PZ-1433, synthesized by Vittorio Canale Ph.D., was dissolved in distilled water immediately before intraperitoneal (i.p.) administration made 60 min before an experimental

procedure, in a volume of 10 ml/kg (mice) or 2 ml/kg (rats).

Four-plate test (FPT) in Swiss albino mice

The FPT apparatus (BIOSEB, France) consists of a cage (25×18×16 cm) floored by four identical rectangular metal plates (8×11 cm) separated from one another by a gap of 4 mm. The top of the cage is covered by a transparent Perspex lid that prevents escape behavior. The plates are connected to a device that can generate electric shocks. Following a 15-s habituation period, the animal's motivation to explore a novel environment is suppressed by an electric foot shock (0.8 mA, 0.5 s) every time it moves from one plate to another during a 1-min test session. This action is referred to as a 'punished crossing', and is followed by a 3 s shock interval, during which the animal can move across plates without receiving a shock. The number of punished crossings was used as an indication of anxiolytic-like action [21].

Marble burying test (MBT) in CD-1 mice

MBT was carried out on the basis of the procedure described by Broekkamp et al. [22]. Mice were placed individually into plastic cages that were identical to their home cage containing 20 glass marbles (1.5 cm in diameter) evenly spaced on sawdust 5 cm deep, without food and water. After 30 minutes the number of marbles at least 2/3 buried/1/3 uncovered was recorded. The number of marbles left uncovered was used as an indication of anxiolytic-like activity.

Spontaneous locomotor activity in Swiss albino and CD-1 mice

The locomotor activity was recorded with an Opto M3 multichannel activity monitor (MultiDevice Software v.1.3, Columbus Instruments). Swiss albino or CD-1 mice were individually placed in plastic cages (22×12×13 cm) for 30 min habituation period, and then the ambulation were counted from 1 min (Swiss albino mice) or for 30 min (CD-1 mice), that is the time equal to the observation period in the FPT or the MBT, respectively. The cages were cleaned up with 70% ethanol after each mouse.

Vogel conflict drinking test in rats

The testing procedure based on a method described by Vogel et al. [23] was performed using Anxiety Monitoring System "Vogel test" produced by TSE Systems. Apparatus was consisted of a polycarbonate cage (dimensions 26.5×15×42 cm), equipped with a grid floor made from stainless steel bars and a drinking bottle containing tap water. Experimental chambers (two) were connected to PC software by control chassis and a device that generates electric shocks. In this "conditional" model an electric shock as noxious stimulus is applied. The testing procedure consisted of two-day habituation/adaptation and an exact test. On the first day of the experiment, the rats were adapted to the test chamber for 10-min adaptation period during which they had free access to the drinking bottle followed by a 24 h water deprivation period. Afterwards, they were allowed a 30-min free-drinking session in their home cages. This protocol of 24-hour deprivation and adaptation period was repeated on the second day. On the third day animals were place again in the test chamber 60 min after administration of vehicle or PZ-1433 and were given free access to drinking bottle during 5 min. Recording data started immediately after the first lick and every 20 licks rats were punished with an electric shock (0.5 mA, lasting 1 s). The impulses were released *via* the spout of the drinking bottle. The number of shocks received throughout a 5-min experimental session was recorded automatically and was used as an indication of anti-conflict activity.

Hot plate and free-drinking tests in rats

To exclude possible drug-induced changes in shock sensitivity or an increasing influence on thirst drive which can lead to false positive results in the Vogel conflict drinking test, stimulus threshold and water consumption during a free-drinking session were determined in separate groups of rats. In either of those two studies, the rats were manipulated similarly to the Vogel conflict drinking test, including two 24-h water deprivation periods separated by 10-min adaptation session in experimental cages and 30-min of water availability in their home cages. In the free-drinking test, each animal was allowed to freely drink from the drinking bottle and the amount of water (g) consumed during 5 min was recorded for each rat. The pain threshold was evaluated using hot plate test (Commat Ltd, Turkey) in rats [24]. The plate was enclosed with a transparent Plexiglass cylinder (35 cm high) to keep the animal on the heated surface of the plate. The latency to pain reaction (lick a hind paw or jump) when the rat was placed on a hot plate (52.5 ± 0.5 ˚C, 19 cm diameter) was measured. The rat was removed from the plate immediately upon visible pain reaction or if no response occurred within 30 s.

Elevated plus-maze (EPM) test in rats

The testing procedure was based on a method described by Pellow and File [25]. Plus-maze apparatus (an automated device produced by Campden Instruments Ltd., United Kingdom) made of durable, high density, non-porous black plastic, elevated to a height of 50 cm, consisted of two open arms (50×10 cm) and two closed arms (50×10 cm, and 30 cm high walls), arranged so that the two arms of each type were opposite each other. Floor of the plus-maze was made of infrared transparent material what means that there are no visible sensors. Plus-maze apparatus was connected to PC software by control chassis. The experiments were conducted in a darkened room, only the center of the maze was illuminated with low-intensity light (30 lux measured on the maze level). Each rat was gently placed in the center of the plus-maze, facing one of the closed arms, immediately after a 5 min adaptation period in a plastic black box (60×60×35 cm), to increase the overall activity in the EPM. During a 5 min test period, automated Motor Monitor System recorded the number of entries into the closed and open arms and the time spent in either type of the arms. The device counted an effective arm-entry when the four paws of a rat were into any arm. The maze was thoroughly cleaned after each trial. The number of open-arms entries, total time spent in open arms and the percentages of these parameters were used as indications of anxiolytic-like activity.

Exploratory activity measured in the EPM in rats

To assess an influence of the tested compound on general exploratory activity of rats and control possible changes within, total ambulation (the total distance covered by a rat, and ambulation along X and Y axis) and total number of entries (into open and closed arms) was taken during a 5 min test period (i.e. the time equal to the observation period in the EPM test). The experiment was performed using EPM apparatus (details see above).

Statistical analysis

All the data are presented as the mean ± SEM. The statistical significance of the results was evaluated by a one-way ANOVA, followed by Bonferroni's Comparison Test.

Results

FPT in Swiss albino mice

As shown in Fig. 1, PZ-1433 administered at doses of 0.625 and 1.25 mg/kg showed anxi-

olytic-like activity, increasing the number of punished crossings by 52% and 81%, respectively. The lowest dose of PZ-1433 0.325 mg/kg was not active.

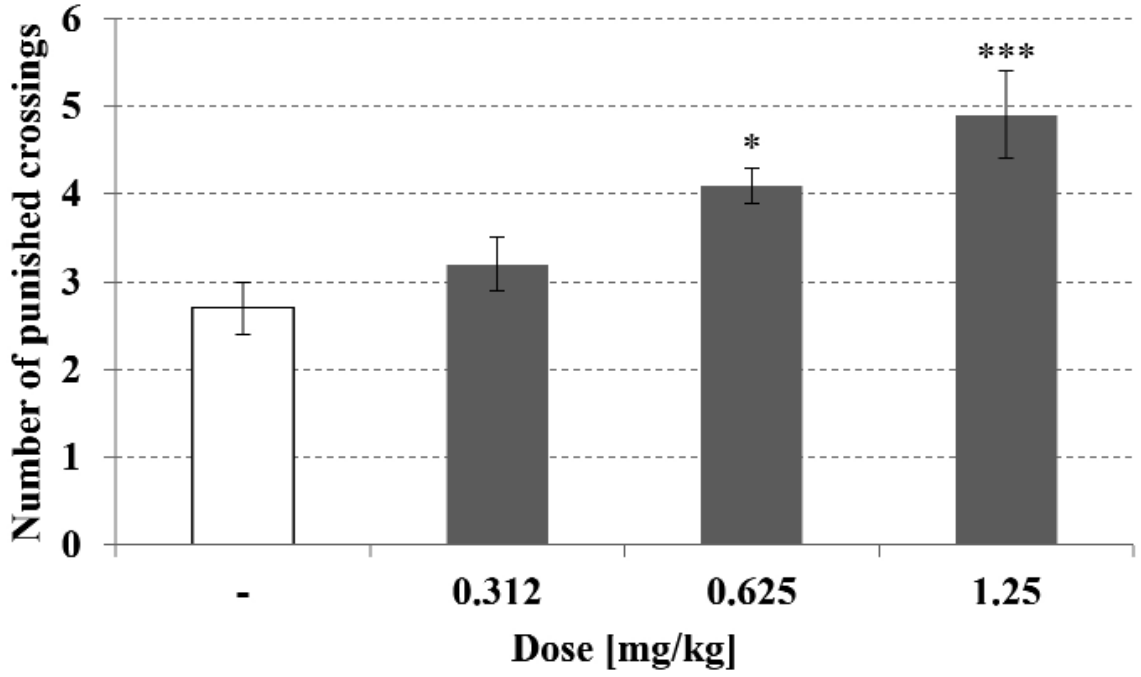

Fig. 1. Effect of PZ-1433 on the number of punished crossings in the FPT in Swiss albino mice
Each bar represents the mean ± SEM for 8-10 mice. One-way ANOVA revealed the significant effect: [F(3,32)=8.400, p<0.001]. *p<0.05, ***p<0.001 vs control group (Bonferroni's test)

Spontaneous locomotor activity in Swiss albino mice

Table 1 shows that PZ-1433 administered at anxiolytic doses did not change locomotor activity of mice measured during 1 min, i.e. at the time equal to the test session in the FPT.

Tab. 1. Effect of PZ-1433 on spontaneous locomotor activity in Swiss albino mice

Treatment	Dose [mg/kg]	Ambulation Mean ± SEM
Control	-	8.8 ± 5.4
PZ-1433	0.625	9.2 ± 2.7
	1.25	32.3 ± 15.2

The results are presented for 6 mice per group. One-way ANOVA revealed no significant effect: [F(2,14)=1.857, ns]

MBT in CD-1 mice

As shown in Fig. 2, PZ-1433 given only at a dose of 0.312 mg/kg significantly reduced the number of buried marbles by 35%, presenting the U-shape mode of action.

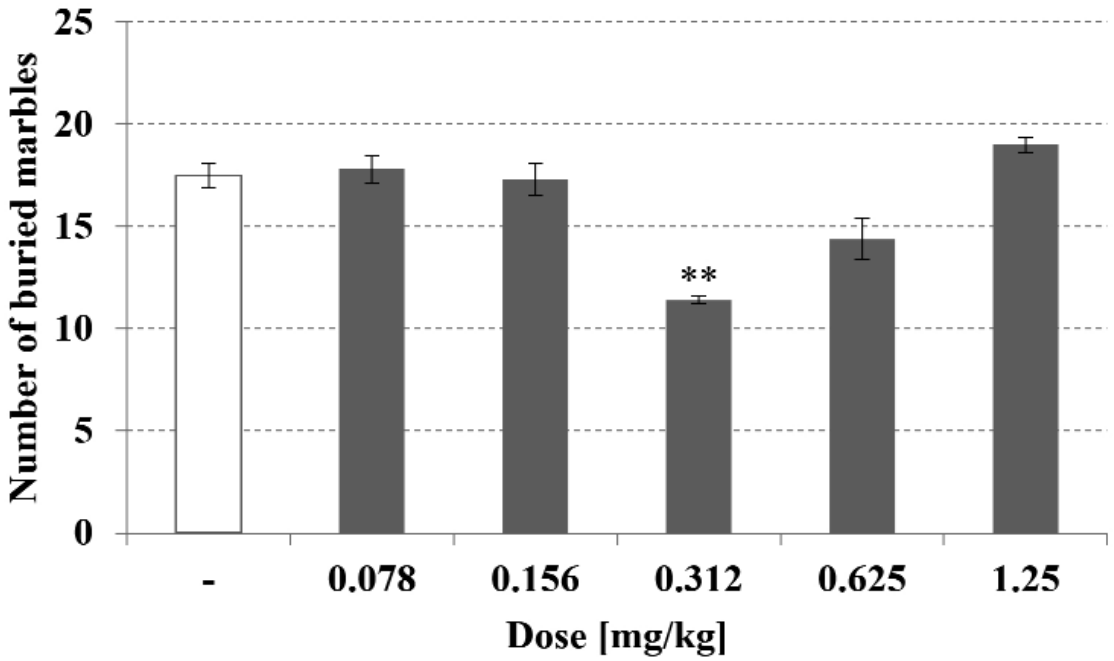

Fig. 2. Effect of PZ-1433 on the number of buried marbles in the MBT in CD-1 mice
Each bar represents the mean ± SEM for 8-10 mice. One-way ANOVA revealed the significant effect: [F(5, 58)=10,591, p<0,0001]. **p<0.01 vs control group (Bonferroni's test)

Spontaneous locomotor activity in CD-1 mice

PZ-1433, administered at an active anxiolytic dose, found in MBT, did not affect locomotor activity measured during 30 min (Tab. 2).

Tab. 2. Effect of PZ-1433 on spontaneous locomotor activity in CD-1 mice

Treatment	Dose [mg/kg]	Ambulation Mean ± SEM
Control	-	882.7 ± 279.5
PZ-1433	0.312	999.2 ± 458.2

The results are presented for 8-10 mice per group. One-way ANOVA revealed no significant effect: [F(1,18)=0.218, ns]

Vogel conflict drinking test in rats

As shown in Fig. 3, PZ-1433 dose-dependently increased the number of accepted shocks; however, a significant effect was observed for a dose of 1 mg/kg only (257% of vehicle-treated group).

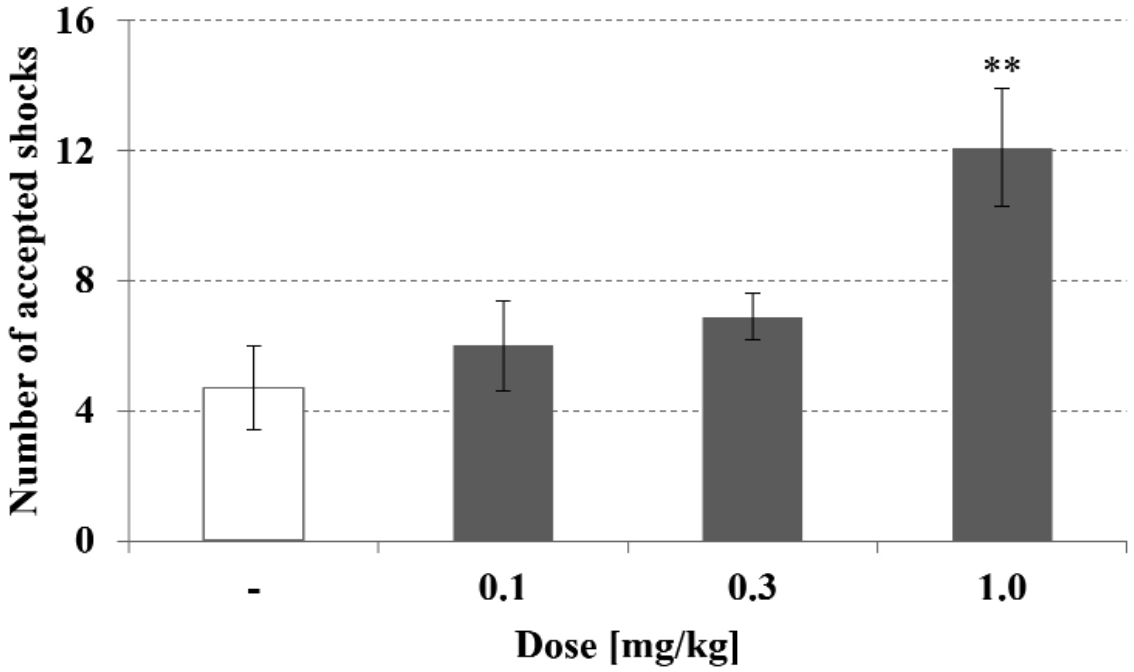

Fig. 3. Effect of PZ-1433 in Vogel conflict drinking test in rats

Each bar represent the mean ± SEM for 7-8 rats. One-way ANOVA revealed the significant effect: [F(3, 24)=5,9491, p<0,01]. **p<0.01 vs control group (Bonferroni's test)

Hot plate and free-drinking tests in rats

PZ-1433 administered at an anti-conflict dose of 1 mg/kg did not influence the time of pain reaction measured in the hot plate test as well as the amount of water consumed by water-deprived rats during 5 min in free-drinking test (Tab. 3).

Tab. 3. Effect of PZ-1433 in the hot plate and free-drinking tests in rats

Treatment	Dose [mg/kg]	Hot plate test time of reaction [s] Mean ± SEM	Free-drinking test Water consumption [g/5 min] Mean ± SEM
Control	-	9.2 ± 0.9	5.3 ± 0.4
PZ-1433	1.0	8.9 ± 0.6	4.4 ± 0.2

The results are presented for 7-8 rats per group. One-way ANOVA revealed no significant effect: time of reaction [F(1, 12)=0,07413, ns] and water consumption [F(1, 13)=0,13119, ns]

EPM test in rats

Table 4 presents the effect of PZ-1433 on time spent in open part of the plus-maze and the number of entries into open arms. The studied compound did not change those parameters in statistically significant manner; however, some increase is noticeable in open arm exploration after administration of PZ-1433 at a dose of 0.3 mg/kg.

Tab. 4. Effect of PZ-1433 in elevated plus-maze test in rats

Treatment	Dose [mg/kg]	Time spent in open arms [s] Mean ± SEM	Percentage of time spent in open arms Mean ± SEM	The number of entries into open arms Mean ± SEM	Percentage of entries into open arms Mean ± SEM
Control	-	47.6 ± 7.7	20.0 ± 3.0	8.6 ± 1.2	30.3 ± 3.1
PZ-1433	0.1	57.1 ± 8.1	23.2 ± 3.6	7.6 ± 1.2	30.9 ± 4.0
	0.3	66.2 ± 9.8	26.7 ± 4.0	10.1 ± 0.9	34.4 ± 3.3
	1.0	56.5 ± 11.9	22.9 ± 5.1	7.7 ± 1.1	33.0 ± 3.6

The results are presented for 7-8 rats per group. One-way ANOVA revealed no significant effect: time spent in the open arms [F(3,25)= 0,65563, ns], percentage of time spent in open arms [F(3,25)=0,48872, ns], number of entries into the open arms [F(3,25)=1,286, ns], percentage of entries into the open arms [F(3,25)= 0,29678, ns]

Exploratory activity measured in the EPM in rats

As demonstrated in Tab. 5 PZ-1433 given at doses of 0.1, 0.3 and 1 mg/kg had no influence on all exploratory parameters measured in EPM in rats.

Tab. 5. Effect of PZ-1433 on total exploratory activity in EPM in rats

Treatment	Dose [mg/kg]	Total entries Mean ± SEM	Total distance [cm] Mean ± SEM	X ambulation Mean ± SEM	Y ambulation Mean ± SEM
Control	-	28.6 ± 3.5	3726.3 ± 270.3	128.6 ± 17.4	78.6 ± 9.4
PZ-1433	0.1	24.9 ± 2.8	4563.4 ± 186.2	169.1 ± 12.5	113.7 ± 9.9
	0.3	30.5 ± 2.5	4412.3 ± 197.2	172.1 ± 13.2	103.4 ± 9.2
	1.0	24.0 ± 2.8	4323.6 ± 207.8	164.4 ± 14.2	91.9 ± 11.8

The results are presented for 7-8 rats per group. One-way ANOVA revealed no significant effect: total entries [F(3,25)=1,1455, ns], total distance [F(3,25)=2,7905, ns], X ambulation [F(3,25)=1,9493, ns], Y ambulation [F(3,25)=2,1874, ns]

Discussion

As part of ongoing studies focused on the development of 5-HT_7 receptor antagonists among arylsulfonamide derivatives of aryloxy(propyl)piperidines, we managed to obtain a promising leading molecule PZ-1433 that acts as a preferential 5-HT_7 receptor antagonist/moderate inhibitor of SERT with significant selectivity over serotonergic 5-HT_{1A}, 5-HT_{2A}, 5-HT_6 and dopaminergic D_2 receptors. This compound was significantly active in tests for antidepressant and pro-cognitive activities in animal models, and was effective even at lower doses than the reference selective 5-HT_7 receptor antagonist SB-269970 [15]. Thus, our present experiments were conducted to broaden the knowledge base of the pharmacological *in vivo* activity of PZ-1433, especially toward its potential action in common rodent models of anxiety. We used different anxiety procedures based on a variety of distinct threatening stimuli. In two independent mouse models, i.e. FPT and MBT, PZ-1433 evoked specific anxiolytic/compulsive-like behavior which did not stem from the increased locomotor activity. It significantly increased the number of punished

crossings in FPT after administration at doses of 0.625 and 1.25 mg/kg and decreased the number of buried marbles at a dose of 0.312 mg/kg. At the same time, its effects observed in rat models, i.e. "conditional" (Vogel conflict drinking test) and "unconditional" (EPM) seem to be task specific. The EPM test is postulated to induce unconditioned fear due to heights and open spaces, which seems to be consistent with panic anxiety [26] whereas the Vogel conflict procedure is of rather broad significance to clinical anxiety, particularly to generalized anxiety disorder [27]. In the Vogel conflict drinking test, PZ-1433 at a dose of 1 mg/kg significantly increased the number of accepted shocks without any influence on pain threshold, thirst, and water intake in water-deprived rats. However, in the EPM, PZ-1433 produced no anxiolytic-like effect measured as activity in open arms. Only the dose of 0.3 mg/kg of the tested compound slightly increased the time spent in open arms, percentage of the time spent in open arms, the number of open-arm entries and the percentage of open-arm entries without affecting the exploratory activity measured in the EPM. Though, it did not reach a statistically significant level. Thus, it appears that PZ-1433 clearly exerts the anxiolytic-like effect in tests incorporating a punishing stimuli in combination with compulsive-like behavior, observed in the MBT. Neurobiological mechanism that mediates anxiolytic-like action of PZ-1433 is not clear. However, given the *in vitro* pharmacological profile of PZ-1433, it seems that 5-HT_7 receptor antagonism is directly involved in the anxiolytic-like effect of this compound. Indeed, it was previously shown that a selective 5-HT_7 receptor antagonist, SB-269970, displayed pronounced anxiolytic-like effects in the same animal models as the ones used for characteristic of PZ-1433 [9,12].

A considerable body of experimental evidence indicates that the 5-HT_7 receptor may be involved in the etiology of mental illnesses including anxiety disorders. Also, recent research has suggested that the antagonists of this receptor may constitute a new class of antidepressant/anxiolytic drugs with a faster therapeutic action than that of the currently used drugs [28,29]. Blockade of 5-HT_7 receptors has been shown to increase the extracellular level of serotonin (5-HT) in the prefrontal cortex (PFC) [30]. These findings are consistent with the hypothesis that 5-HT_7 receptors in the dorsal raphe nucleus (DRN) are not localized on 5-HT cells, but rather on local GABAergic interneurons which modulate the activity of 5-HT projection neurons [31]. Moreover, the blockade of the 5-HT_7 receptor enhances the release and metabolism of 5-HT in the PFC. This effect appears to be mediated by the depolarization and enhanced firing of DRN serotonergic projection neurons, resulting from a decreased inhibitory synaptic input received by the projection cells. The results of Kusek et al. [32] confirm and extend an earlier report [30] showing that blockade of the 5-HT_7 receptor with low doses of SB-269970 (0.625 and 1.25 mg/kg) resulted in an increase in the level of extracellular 5-HT. This result points to the activation of mechanisms which do not allow for an excessive tonic release of 5-HT from cortical terminals. An increase in the level of 5-HT metabolite (5-HIAA) is consistent with an increased level of 5-HT in the ex-

tracellular space. Another study demonstrated that SB-269970 administered at a dose of 10 mg/kg did not increase the extracellular concentration of 5-HT in the rat frontal cortex [33]. A most likely explanation of such a discrepancy is the way of drug administration: intraperitoneal [30,32] *vs*. subcutaneous [33].

Furthermore, 5-HT acting through 5-HT_7 receptors, exerts a complex modulatory influence over glutamate- and GABA-mediated synaptic transmission. Study, conducted by Tokarski et al. [34] provided information regarding the role of 5-HT_7 receptors in the mechanisms which allow 5-HT to simultaneously remodel neuronal activity in a functionally appropriate manner in a wide variety of cell types and excitatory as well as inhibitory circuits in the hippocampus. Findings of Tokarski et al. [34] also suggest that the adaptive effects of citalopram treatment on the function of the hippocampus [35] might, potentially, also involve 5-HT_7 receptor-dependent changes in excitatory and inhibitory transmission. The modulatory influence of 5-HT_7 receptors on GABAergic transmission in the hippocampus may also be relevant for developing new treatments of diseases related with abnormalities of GABAergic inhibition, including anxiety.

In the mechanism of anxiolytic-like activity of PZ-1433 its moderate affinity for SERT cannot be omitted, especially that both mechanisms, i.e. 5-HT_7 antagonism and SERT inhibition, are going in the same direction, that is the increase in 5-HT level in the cleft. SERT inhibition, characteristic of SSRI, also might be responsible for the anxiolytic-like effect of PZ-1433, observed in this studies, since SSRI are currently recommended as first-line treatment of generalized anxiety disorder that is a persistent condition characterized by chronic anxiety, exaggerated worry and tension, mainly comorbid with major depressive disorder. This information is particularly important in the aspect of the anti-anxious effect of PZ-1433 measured in the Vogel conflict drinking test. There are few, if any, animal models sufficiently validated to discriminate among the various subtypes of anxiety disorders. Operant conflict procedures are pharmacologically isomorphic with the human state of generalized anxiety [36]. Among these procedures, as mentioned above, the Vogel test is of significance to generalized anxiety disorder [27]. However, everyone must be aware that drawing definite conclusions about clinical potency of a new compound from animal studies is premature. Animal models of anxiety are certainly useful to find out more about a pharmacological profile of newly developed molecules and biological bases of anxiety disorders. These models provide a lot of information on mechanisms which could be involved in the etiology and physiopathology of anxiety disorders, but are usually not satisfactory when confronted directly with clinical symptoms of disorders [37].

Conclusion

The new derivative PZ-1433, a potent and preferential 5-HT_7 antagonist, produces anxiolytic-like effects in mouse and rat models of anxiety which employed a punished stimuli in combination with compulsive-like behavior. These data together with already proven antidepressant and pro-cognitive properties

of PZ-1433 [15], and its lack of any disruptive impact on locomotor and exploratory activities, support evidence on potential usefulness of 5-HT_7 antagonists in central nervous system disorders such as depression, anxiety and memory impairments. Future research should be directed at clarifying potential therapeutic possibilities of PZ-1433.

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Resumo

Oni malkovris, ke la nova arilsulfonamida derivaĵo de ariloksi (propilo) piperidino PZ-1433 posedas preklinikan aktivecan profilon taŭgan por kuraci depresion kaj disordon de memoro. En la nuna studo ĝia farmakologia aktiveco rilate al la simptomoj de angoro same kiel ĝiaj anksiolitikaj proprañoj estis ekzamenitaj ĉe musoj kaj ratoj. PZ-1433 signife pliiĝis la nombro da punitaj transiroj kaj malpliiĝis la nombro da enterigitaj globetoj en du provoj faritaj en musoj. Plie, PZ-1433 elvokis anksiolitikan efikon en "kondiĉa" paradigma angoro en ratoj, kio signifante pliigis la nombron de akceptitaj śokoj en la Vogel-trinkalkohola testo. Tamen, ĝi ne donis signifan anksiolitikan similecon en "senkondiĉa" angoro-modelo, ekz. la levita kruca labirinta testo. Laŭ ĉi tiuj rezultoj estas verŝajne, ke la rekta kontraŭefiko al serotoninaj 5-HT7-receptoroj povas esti implikita en la anksiolitika efiko de PZ-1433. Tamen, in vitro malkovrita inhibicio de serotonina transportisto elvokita de PZ-1433, povus ankaŭ kontribui al ĉi tiu efiko.

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