ISSN NO: 2770-2936
Date of Publication:07-10-2022

Research of Anticonvulsant Activity of Compound 5-(P-Aminophenyl) - 1,3,4-Oxadiazole-2-Thion

Sanoev Zafar Isomiddinovich., Rashidov Sokhib Zamon ugli., Raximboev Sukhrob Davlatyor ugli., Abdinazarov Ibrokhim Tuychievich., Khamroev Tolmas Tolibovich., Ismailova Dilnoza Safaralievna., Elmuradov Burkhon Juraevich.
Academy of Sciences RUz Institute of Chemistry of Plant Substances, Tashkent, Uzbekistan,
Zafarsano19@mail.ru

Resume. In this presented article, it was presented that 5-(p-Aminophenyl) - 1,3,4-oxadiazole-2-tion (conditionally D-111) at doses of 10, 30 and 60 mg / kg when administered orally to white mice with various analyzers, including strychnine (1.2 mg / kg subcutaneously), and also orally in doses of 10 and 30 mg/kg. the anticonvulsant activity of the substance and the comparative drug carbamazepines was studied using a model of convulsive seizure induced using repeated administration of corazole at a dose of 30 mg/kg.The anticonvulsant effects of the compound D-111, carbamazepine and control groups at various doses were studied. Based on the results obtained, the studied substance demonstrated high anticonvulsant activity in convulsive seizures, mainly on the strychnine convulsion model.

Key words. Epilepsy, corazole kidling, 5-(p-Aminophenyl)-1,3,4- oxadiazole-2-tion, strychnine, acute toxicity

Relevance. Epilepsy is a heterogeneous group of brain diseases that are chronic and characterized by convulsive repeated attacks as well as other disorders of the central nervous system [1, 2]. With epilepsy, recurrent convulsive syndrome is formed in this condition, patients have neurobiological, cognitive, psychological and social consequences. According to the International Antiepileptic League, 6 million people suffer from epilepsy in Western and Central Europe, and about 15 million people are expected to suffer from epilepsy over the next 20 years. It is known that this disease requires long-term treatment, and for this reason it is currently considered a serious medical, social and economic problem. According to international population studies, about 1% of the world's population needs antiepileptic drugs, and this indicator is characterized by high stability and immutability for many decades [3, 4, 5]. Clinical studies show that in 30-40% of patients, treatment of newly diagnosed epilepsy with the help of antiepileptic drugs is ineffective and may develop serous undesirable reactions, and in 30% of individuals, the preservation of convulsive activity is recorded against the background of taking medications [6, 7]. All of the above conditions the ongoing search for new molecules based on natural and synthetic substances in order to ensure an optimal activity–safety ratio in the treatment of the disease [8, 9]. In this regard, in recent years there has been an interesting area for studying the synthesis and biological activity of new oxadiazole derivatives. A number of scientific studies in recent years have shown that heterotyclic compounds that are derivatives of the oxadiazole ring (1,3,4-oxadiazoles) exhibit a variety of biological properties associated with neuropsychological characteristics. Thus, 1,3,4 - oxadiazoles include antimicrobial, antituberculous, anticonvulsant, antidiabetic, antiallergic, antipyretic and other pharmacological activities [10, 11, 12]. The Institute of Plant Chemistry named after Academician S.Yu.Yunusov of the Academy of Sciences of the Republic of Uzbekistan studies psychopharmacological - neuroleptic, antidepressant, psychostimulating and anticonvulsant activity of various biologically active substances [13-20], including psychoactive and anticonvulsant activity of oxidiazole derivatives [21]. This article discusses the results of various biological activity of 5-(p-Aminophenyl)-1,3,4- oxadiazole-2-thion (D-111) derivatives of various oxadiazoles.

The objective of the study is to study the acute toxicity and anticonvulsant activity of 5-(p-aminophenyl)-1,3,4-oxadiazole-2-thion (D-111) oxadiazole derivatives.

Materials and methods: The study of acute toxicity and anticonvulsant activity on a strychnine convulsion model was carried out on white mice weighing 20-22 g, strychnine was administered once at a dose of 1.2

ISSN NO: 2770-2936
Date of Publication:07-10-2022

mg / kg subcutaneously before administration of the studied substance in doses of 10 and 30 mg/kg inside. In this method, anticonvulsant activity was measured by the time of onset and the number of convulsive seizures, as well as the survival rate of animals. For corazole convulsion, mongrel white rats weighing 200-220 g were used, and pharmacological kindling is modeled in studies by repeated injections of corazole in a subthreshold dose, usually 30 mg/kg intraperitoneally [22]. The studied substance was injected internally in doses of 10, 30 va 60 mg / kg in animals an hour before the administration of corazole and was observed for 20 minutes. The assessment of convulsive reactions in animals was determined on a 4-point scale from 0 to 4. When assessing anticonvulsant activity, carbamazepine preparation (200 mg No. 20, JSC "Synthesis" (Russia)) was used as comparisons.

The entire statistical processing of the results was carried out by the tabular method proposed by R.B. Strelkov [23].

Results and their discussion: 1. Study of acute toxicity of compound D – 111. To study the acute toxicity of compound D-111, this substance was initially administered as an aqueous solution, starting from a dose of 1000 mg/kg to a dose of 4000 mg/kg. When the test substance was administered from a dose of 1000 mg / kg to a dose of 3000 mg / kg, motor activity decreased in animals, wool barked, respiration rate was initially shallow and accelerated after 60 minutes, and slowed down after 90 minutes, general weakness and tremor were observed, and death was not observed. At a dose of 3500 mg/kg, in addition to the above symptoms, muscle weakness, a large seizure of seizures were observed, and after 120 minutes, 50% of deaths were observed in animals. During studies at a dose of 3700 mg/kg, mortality was observed in animals by 75%, at a dose of 3900 mg/kg by 90% and at a dose of 4000 mg/kg by 100%. Based on the data obtained as a result of the study, it was found that the average lethal dose of compound D-111 in white mice was LD50 ≈ 3490 mg/kg, and according to the classification of acute toxicity IV, that is, low-toxic substances belong to the class.

2. To study the effect of compound D – 111 on strychnine convulsion models in mice. Compound D - 111 in all studied doses increased the onset time of convulsive seizures to 1.2; 1.28 and 1.7 times, respectively, in relation to the control group, in terms of the number of convulsive seizures at the above doses, convulsive seizures were observed in relation to the control group by 1.5; 2.25 and 4.5 times less, respectively, in terms of animal survival at a dose of 10 mg/kg 100% pal was observed, and at doses of 30 and 60 mg/kg, the ratio to the control group increased by 25 and 50%, respectively. The results obtained are presented in Table 2.

1 – Table.
Anticonvulsant effect compound D-111

№	Substances and groups	Doses per mg/kg	The onset of convulsions	Number of seizures	Fell on %
1.	Control + strychnine 1,2 mg/kg s/c		6,5±0,48*	2,25	100
2.	D-111 + strychnine 1,2 mg/kg s/c	10	7,75±0,24*	1,5	100
		30	8,33±0,12*	1	75
		60	11±0,96*	0,5	50
3.	Carbamazepine + strychnine 1,2 mg/kg s/c	20	4,8±0,24*	0,6	40
		50	6,2±0,72*	0,8	60

Note.*P=0.05 comparison with the control group

Thus, the compound D – 111 only at a dose of 60 mg/ kg had significant anticonvulsant activity compared to carbamazepine, and in all studied doses, the activity is expressed by comparing the control group according to convulsive indicators: the onset and number of seizures, as well as survival. Anticonvulsant activity of compounds in this model may be associated with direct activation of glycine-sensitive receptors and with a joint increase in glycine and gabaergic activity [24]. A statistically significant change in the duration of the latent period of convulsive seizures caused by subcutaneous administration of

ISSN NO: 2770-2936
Date of Publication:07-10-2022

strychnine in animals treated with compound D – 111 indicates that the compound under study has a significant effect on the glycinergic system.

3. Study of the effect of compound D – 111 on the models of corazole convulsion in rats. As can be seen from the table, the substance D – 111 in doses of 10 and 30 mg /kg stopped convulsive reactions less than the control group (see Table 2). The data obtained show that the compound D – 111 did not have an anticonvulsant effect compared to the control

2 – Table.
Anticonvulsant effect compound D-111

№	Substances and groups	Doses per mg/kg	Convulsive reactions by score	Effects per %
1.	Контроль (30 mg/kg corazole i/p.)		10,75 ±0,3*	
2.	D – 111 + 30 mg/kg corazole i/p.	10	18±0,42*	- 40,3
		30	11±0,24*	- 2,3
3.	Carbamazepine + 30 mg/kg corazole i/p.	20	13,5±0,54*	- 20,4
		50	6,25±0,42*	+ 72

Note.*P=0.05 comparison with the control group

In the conducted studies, the D-111 compound did not show anticonvulsant activity in the corazole kidling method. It is known that the anticonvulsant activity of compounds in this model can be directly related to the activation of gabaergic receptors [25]. Based on these data obtained, it can be concluded that the D – 111 compound does not affect gabaergic receptors.

Conclusions. Thus, the compound D – 111 belongs to class IV according to the classification of acute toxicity, that is, to the class of less toxic substances, prolongs the latent period of convulsive seizures and reduces both the number and duration of seizures. In addition, higher doses had a positive effect on the survival of animals compared to groups receiving different doses of carbamazepine, widely used in practice. Studies have shown that the compound D – 111 exhibits significant anticonvulsant activity compared to carbamazepine. But in the method of corazole killing did not show anticonvulsant activity. It can be concluded that the high anticonvulsant activity of the D – 111 compound caused by strychnine is associated with its higher effectiveness in convulsive seizures, actions associated with the centers of the spinal cord.

List of used literature

1. ILAE official report: a practical clinical definition of epilepsy / R.S. Fisher, C. Acevedo, A. Arzimanoglou et al. // Epilepsia. – 2014. – Vol. 55. – P. 475-482.
2. *Гордеева Л.* Сложно, дорого, но возможно: Как сегодня лечат эпилепсию // Лекарственное обозрение. — 05/08/2014. — № 6.
3. Hauser, W.A. First seizure definitions and worldwide incidence and mortality / W.A. Hauser, E. Beghi // Epilepsia. – 2008. – Vol. 49. – P. 8-12.
4. Толмачев, П.А. Сравнительная характеристика заболеваемости эпилепсии в Российской Федерации на примере Кировского, Пензенского и Уляновского центров Приволжского Федерального Округа / П.А. Толмачев, Н.В. Наймушина [и др.] // Евразийское Научное Объединение. - 2017. - Т. 1. - №. 5. - С. 64-66.
5. Fisher, Robert S.; Acevedo, Carlos; Arzimanoglou, Alexis; Bogacz, Alicia; Cross, J. Helen; Elger, Christian E.; Engel, Jerome; Forsgren, Lars; French, Jacqueline A.; Glynn, Mike; Hesdorffer, Dale C.; Lee, B.I.; Mathern, Gary W.; Moshé, Solomon L.; Perucca, Emilio; Scheffer, Ingrid E.; Tomson, Torbjörn; Watanabe, Masako; Wiebe, Samuel (2014). "ILAE Official Report: A practical clinical definition of epilepsy". Epilepsia. Wiley. **55** (4): 475—482. DOI:10.1111/epi.12550. ISSN 0013-9580.

ISSN NO: 2770-2936
Date of Publication:07-10-2022

6. Mattson R.H., Cramer J.A., Collins J.F. et al. Comparison of carbamazepine, phenobarbital, phenytoin, and primidone in partial and secondarily generalized tonic-clonic seizures / // N. Engl. J. Med. – 1985. – Vol. 313. – P. 145-151.
7. Kwan, P. Drug treatment of epilepsy: when does it fail and how to optimize its use / P. Kwan, M.J. Brodie // CNS Spectr. – 2004. – Vol. 9. – P. 110- 119.
8. French J.A., White H.S., Klitgaard H. et al. Development of new treatment approaches for epilepsy: unmet needs and opportunities / // Epilepsia. – 2013. – Vol. 54. – P. 3-12.
9. Wilcox K.S., Dixon-Salazar T., Sills G.J. et al. Issues related to development of new antiseizure treatments / // Epilepsia. – 2013. – Vol. 54. – P. 24-34.
10. Kumar B, Kumar A, Beheraand AK, Raj V (2016) Latest Update on Pharmacological Activities of 1,3,4-Oxadiazole Derivatives. Journal of Cell Science & Therapy (2016) Volume 7, Issue 1 Ther 7:233.
11. Ankit Siwach and Prabhakar Kumar Verma. Therapeutic potential of oxadiazole or furadiazole containing compounds. Siwach and Verma BMC Chemistry (2020) 14:70. Page.2-40. https://doi.org/10.1186/s13065-020-00721-2
12. B. Ramana M, Mothilal M, M. Rao G, M.K. Murthy, Ravi Varala, H. Babu Bollikolla. Strategies to Synthesis of 1,3,4-Oxadiazole Derivatives and Their Biological Activities: A Mini Review. J. Chem. Rev., 2022, 4(3), 255-271. https://doi.org/10.22034/JCR.2022.341351.1170
13. Ю.Р.Мирзаев, Н.В.Турсунова, Х.А.Расулова, З.И. Саноев. Особенности психофармакологической активности суммы фуранохинолиновых алкалоидов из *Haplophyllum perforatum*. XLI Международная научно-практическая конференция «Современная медицина: Актуальные вопросы. 2015, с.103-110.
14. Sanoev Z.I., Mirzaev Yu.R. Pharmacological Activity Of The Possessing New Atypical Neuroleptics 1-Phenyltetrahydroisoquinoline Structure. The American Journal of Medical Sciences and Pharmaceutical Research Published: August 11, 2020 | Pages: 18-26 Doi: https://doi.org/10.37547/TAJMSPR/Volume02Issue08-03
15. Sanoev Z.I., Mirzaev Yu.R. Research of a new atypical neuroleptic 1-(3,4,-methylenedioxyphenyl)-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline on the central nervous system. Annals of the Romanian Society for Cell Biology, 2021,25(2), 2363–2369
16. Sanoev Z.I. Skimmianine - a promising antidepressant among furanoquinoline alkaloids. Journal of Biomedicine and Practice 2020, Special issue -2, pp.751-757
17. Khamroev T.T., Sanoev Z.I., Rakhimboev S.D., Abdinazarov I.T., Rashidov S.Z. Effect of antiarrhythmic substance N – dezacetyllapoconitin on the central nervous system. ISJ Theoretical &Applied Science, 07 (99), 153-157. http://soi.org/1.1/TAS-07-99-31 Doi:https://dx.doi.org/10.15863
18. Sanoev Z.I., Mirzaev Yu.R. Influence of donaxine on physical and psychoemotional state of white mice at single and prolonged administration. «European Journal of Biomedical and Life Sciences» №4, 2016, s. 45-49
19. Sanoev Z.I., Mirzaev Yu.R (2018). On comparative stimulating action on the cns of furanoquinoline alkaloids of skimmianine and amitriptyline //Yeuropean science review № 5–6, May–June, Vienna, p.189-192
20. Sanoev Z.I., Khamroev T.T., Abdinazarov I.T., Sadikov A.Z., Rakhimboev S.D., Ras'hidov S.Z. Study of N-deacetylappaconitine (N-DAL) anticonvulsant action. Oriental Journal of Medicine and Pharmacology. 2022, Vol 2, p. 29-37
21. Rashidov S.Z., Rakhimboev S.D., Sanoev Z.I., Abdinazarov I.T., Khamroev T.T., Ismailova D.S., & Elmuradov B.J. (2022). Study of psychoactive activity potassium salt 5-(o-aminophenyl)-1,3,4-oxadiazole-2-thion (d-361). International Journal of Medical Sciences and Clinical Research, 2(09), 1–5. https://doi.org/10.37547/ijmscr/Volume02Issue09-01
22. Миронов А.Н. Руководство по проведению доклинических исследований лекарственных средств. Част первая. — М.: Гриф и К, 2012. — 944 с.

ISSN NO: 2770-2936
Date of Publication:07-10-2022

23. Стрелков Р.Б. Статистические таблитсе для ускоренной количественной отсенки фармакологического еффекта. Фармакология и токсикология 1986. №4 с.100-104.
24. Khatoon, H. Evaluation of anticonvulsant and neuroprotective effects of camel milk in strychnine-induced seizure model / H. Khatoon, R. Najam, T. Mirza [et al.] // Asian Pacific Journal of Tropical Disease. – 2015. – Т. 5. – №. 10. – С. 817-820.
25. Рыбалченко Т.Л., Штрыгол С.Ю., Георгиянц В.А. Определение спектра противосудорожного действия новых антиконвулсантов – производных 1,2,3-триазола и 1,3,4-оксадиазола. Серия Медицина. Фармация. 2014. № 11 (182). Выпуск 26/1. ст.199-203. УДК: 547.791.6:547.461.3:615.213