



TRYFUZOL - NEW ORIGINAL VETERINARY DRUG

TRİFUZOL - YENİ ÖZGÜN VETERİNER İLAÇ

Inna BUSHUEVA¹, Volodymyr PARCHENKO², Roman SHCHERBYNA^{2*}, Andriy SAFONOV², Andriy KAPLAUSHENKO³, Bogdan GUTYJ⁴, Ivan HARIV⁴

¹Department of the Clinical Pharmacy, Pharmacotherapy and MFE of FPE, Zaporizhzhya State Medical University, Zaporizhzhya, Ukraine

²Department of Toxicological and Inorganic Chemistry, Zaporizhzhya State Medical University, Zaporizhzhya, Ukraine

³Department of Physical and Colloidal Chemistry, Zaporizhzhya State Medical University, Zaporizhzhya, Ukraine

⁴Department of Pharmacology and Toxicology, Lviv National University of Veterinary Medicine and Biotechnologies Named After S. Z. Gzhytskyj, Lviv, Ukraine

SUMMARY

Our team of scientists has explored scientific journals for the recent years. It was found that furan substituted 1,2,4-triazoles are promising for the future studying because of their low toxicity and wide range of activity. Ukrainian publications about the studying physical, chemical and biological properties of furan substituted 1,2,4-triazoles prove their prospects as future drugs.

The aim of the study was to explore existing publications of scientists about various properties studies of the active pharmaceutical ingredient of veterinary drug "Tryfuzol". This work shows the analysis result of the publications about studying the properties of piperidine 2-(5-(furan-2-yl)-4-phenyl-4H-1,2,4-triazole-3-ylthio)acetate – the active pharmaceutical ingredient of new original veterinary drug "Tryfuzol".

First time the molecule of the active ingredient of the drug "Tryfuzol" - piperidine 2-(5-(furan-2-yl)-4-phenyl-4H-1,2,4-triazole-3-ylthio)acetate is mentioned in the PhD (candidate) where the method of synthesis was described, the physical-chemical properties and the acute toxicity were studied, primary pharmacological screening was conducted. At this stage scientists proved prospect for further study of the biological properties of piperidine 2-(5-(furan-2-yl)-4-phenyl-4H-1,2,4-triazole-3-ylthio)acetate. In the work the authors investigated the possibility of qualitative and quantitative determination of compound in 1% and 2,5% solutions and publication is devoted to the developing of quantification methods of piperidine 2-(5-(furan-2-yl)-4-phenyl-

* **Corresponding Author / Sorumlu Yazar:** Roman SHCHERBYNA
e-mail: rscherbyna@gmail.com

4H-1,2,4-triazole-3-ylthio)acetate by non-aqueous potentiometric titration. Interesting results about the determination of possible metabolites of the active pharmaceutical ingredient of the future drug substance show scientists in the following publications.

Keywords: biological properties; furan derivatives of 1,2,4-triazole; Tryfuzol; veterinary drugs

ÖZET

Bilimsel ekibimiz, son yıllardaki incelediği bilimsel yayımlar sonucunda furan ile sübtitüe 1,2,4-triazollerin düşük toksisitesi ve çeşitli aktivitelerinden dolayı gelecek çalışmalar için umut verici olduğunu bulmuştur. Ukrayna'da yayımlanan makalelere göre, furan ile sübtitüe 1,2,4-triazol bileşiğinin fiziksel, kimyasal ve biyolojik özellikleri ile geleceğin ilacı olarak beklentileri karşılayacağını göstermiştir.

Bu çalışmanın amacı, veteriner ilaç olan "Tryfuzol"ün aktif farmasötik içeriğinin çeşitli özellik çalışmaları ile ilgili bilim insanlarının mevcut yayınlarını ortaya çıkarmaktır. Bu çalışma, yeni orijinal veteriner ilaç "Tryfuzol" un farmasötik aktif bileşeni piperidin 2-(5-(furan-2-il)-4-fenil-4H-1,2,4-triazol-3-iltiyo)asetatın incelenen özellikleri ile ilişkili yayınların analiz sonuçlarını göstermektedir.

"Tryfuzol"un aktif bileşen molekülü olan piperidin 2-(5-(furan-2-il)-4-fenil-4H-1,2,4-triazol-3-iltiyo)asetatın sentez metodu, fiziksel-kimyasal özellikleri, akut toksisite çalışmaları ve birincil farmakolojik taramaları ilk kez bir doktora aday çalışmasında bahsedilmiştir. Bu aşamada, bilim adamları, piperidin 2-(5-(furan-2-il)-4-fenil-4H-1,2,4-triazol-3-iltiyo)asetatın biyolojik özelliklerinin ileriki çalışmalara yol gösterici olabileceğini kanıtlamışlardır. Çalışmada, susuz potansiyometrik titrasyon metodu ile piperidin 2-(5-(furan-2-il)-4-fenil-4H-1,2,4-triazol-3-iltiyo)asetatın % 1 ve % 2,5'lik solüsyonlarda bileşiğin nitel ve nicel olarak geliştirilmiş miktar tayin yöntemlerini içeren yayınlar incelenmiştir. Gelecekteki ilaç aktif farmasötik maddesinin olası metabolitlerinin belirlenmesiyle ilgili ilginç sonuçlar, bilim insanları tarafından gösterilecektir.

Anahtar kelimeler: biyolojik özellikler; 1,2,4-triazol furan türevleri; Tryfuzol; veteriner ilaç

INTRODUCTION

Over the past decade it has accumulated a lot of information in the literature about various publications on the prospects of studying physical, chemical and biological properties of furan substituted 1,2,4-triazoles [1,2]. The authors carefully studied the physical and chemical properties. Comparative analysis was conducted of appropriatenesses between the structure of compounds and their biological effects [1]. Soluble substances formed by "chemical symbiosis" of 1,2,4-triazole core and furan fragments deserve individual attention [3,4]. These compounds exhibit different types of biological activities while being practically non-toxic [5].

Long term experience of domestic scientists in studying the properties of furan substituted 1,2,4-triazole proves the great potential of water-soluble compounds in this row [5].

An example of the fact that a row of furan substituted salts possess a spectrum of biological activity is the appearance of new original domestic veterinary drug "Tryfuzol" on market in two dosage forms. Thus, the aim of the study was to codify existing publications of domestic scientists various properties studies of the active pharmaceutical ingredient (API) of veterinary drug "Tryfuzol". Chemical name of API is piperidine 2-(5-(furan-2-yl)-4-phenyl-4H-1,2,4-triazole-3-ylthio)acetate and its molecular structure is shown in the Figure 1.

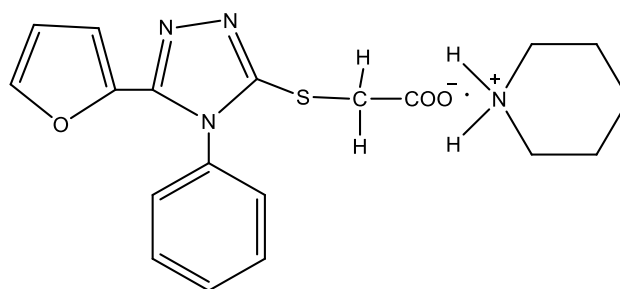


Figure 1. Molecular structure of piperidine 2-(5-(furan-2-yl)-4-phenyl-4*H*-1,2,4-triazole-3-ylthio)acetate

HISTORICAL BACKGROUND

First time the molecule of the active ingredient of the drug "Tryfuzol" - piperidine 2-(5-(furan-2-yl)-4-phenyl-4*H*-1,2,4-triazole-3-ylthio)acetate is mentioned in the PhD (candidate) thesis [1]. The author described method of synthesis, studied the physical-chemical properties of the compound, studied the acute toxicity and conducted primary pharmacological screening. Compatible with other compounds of this class there was established the "structure-activity" dependence for piperidine 2-(5-(furan-2-yl)-4-phenyl-4*H*-1,2,4-triazole-3-ylthio)acetate. Even at this stage the scientists proved promising for further study of the biological properties of piperidine 2-(5-(furan-2-yl)-4-phenyl-4*H*-1,2,4-triazole-3-ylthio)acetate. In the work [2] the authors investigated the possibility of qualitative and quantitative determination of promising compound in 1% and 2,5% solutions. Other publication [3] is devoted to the developing of quantification methods of piperidine 2-(5-(furan-2-yl)-4-phenyl-4*H*-1,2,4-triazole-3-ylthio)acetate by non-aqueous potentiometric titration. Interesting results about the determination of possible metabolites of the active pharmaceutical ingredient of the future drug substance show scientists in the following publications [4].

A further step in a large-scale study of the compound properties in order to implement in the veterinary practice were studies described in PhD (doctoral) dissertation [5]. This work is devoted to a detailed study of harmlessness and specific activity of piperidine 2-(5-(furan-2-yl)-4-phenyl-4*H*-1,2,4-triazole-3-ylthio)acetate - the active ingredient of potential antiviral drug. The author conducted the chemical and technological study of manufacturing the drug "Tryfuzol" which contains piperidine 2-(5-(furan-2-yl)-4-phenyl-4*H*-1,2,4-triazole-3-ylthio)acetate (API), sodium chloride for stabilization and water for injection. The original studies of the antiviral activity of the compound are described in relation to hen embryos viruses and cited by authors in the following work [6]. The results of presented studies indicate that the optimal concentration is 0,01% of piperidine 2-(5-(furan-2-yl)-4-phenyl-4*H*-1,2,4-triazole-3-ylthio)acetate to oppress the reproduction of infectious bronchitis virus and infectious encephalomyelitis virus. This titer of the infectious bronchitis virus decreased at 1,8 log and the virus

encephalomyelitis titer at 1,0 log. There are other interesting works about antiviral action of piperidine 2-(5-(furan-2-yl)-4-phenyl-4*H*-1,2,4-triazole-3-ylthio)acetate [7,8]. A group of researchers demonstrated that this compound is the most effective in inhibition of vesicular stomatitis virus in applying simultaneously with infectioning the cell monolayers by virus when the substance is present in the culture medium for 72 hours [7].

Another group of scientists gives data on neuroprotective activity of piperidine 2-(5-(furan-2-yl)-4-phenyl-4*H*-1,2,4-triazole-3-ylthio)acetate [9]. The researchers argue that in a modeling the acute violation of cerebral circulation it was found increasing of aldehydehydrophenylhydrazone and carboxylhydrophenylhydrazone products of proteins oxidative modification in brain tissues of rats on the 4th day. One of the mechanisms of antioxidative action of piperidine 2-(5-(furan-2-yl)-4-phenyl-4*H*-1,2,4-triazole-3-ylthio)acetate is its positive effect on brain antioxidative system. Thus, after the introduction of this compound it was observed the increase of the main antioxidative enzymes activity [10].

Analyzing the results of biological tests of piperidine 2-(5-(furan-2-yl)-4-phenyl-4*H*-1,2,4-triazole-3-ylthio)acetate made by several groups of researchers it should be focused on what the authors systematized the main pharmacobiochemical characteristics of the compound and conducted the comparative analysis [11]. Another group of scientists studied the antioxidant, hepatoprotective and immunostimulatory activity of piperidine 2-(5-(furan-2-yl)-4-phenyl-4*H*-1,2,4-triazole-3-ylthio)acetate [12]. Scientists claim that the analysis of dynamics in hematological and biochemical parameters indicates that the use of specified compound is provided by intensification of protein and carbohydrate metabolism and stimulates the erythro- and leucopoiesis with hemoglobin level increasing which confirms these types of activity. Ukrainian scientists proved the effectiveness of injecting the solution of piperidine 2-(5-(furan-2-yl)-4-phenyl-4*H*-1,2,4-triazole-3-ylthio)acetate for the course correction in experimental inflammation modeling of the soft tissues that is complicated by purulent infection [13,14,15].

It is known that quail eggs contain a huge amount of vitamins A, P, K, B₁, B₂, iron, cobalt and other trace elements and biologically active compounds. For the obtaining of quality incubation and food quail eggs that matches the national standards it is required the constant zootechnical and veterinary-sanitary control with further optimization of the quail production cycle. An interesting solution of this issue according to scientists is the use of piperidine 2-(5-(furan-2-yl)-4-phenyl-4*H*-1,2,4-triazole-3-ylthio)acetate as a compound for improving the productivity of quails [16].

Other review work confirms the presence of the antioxidant properties in the piperidine 2-(5-(furan-2-yl)-4-phenyl-4*H*-1,2,4-triazole-3-ylthio)acetate [17]. Our studies show higher rates of antioxidant activity of piperidine 2-(5-(furan-2-yl)-4-phenyl-4*H*-1,2,4-triazole-3-ylthio)acetate

according to the results of its impact on clinical status, morphological and biochemical parameters of animal blood «*in vivo*» versus the well-known “Thiotriazolin”.

Topical issue of veterinary medicine today is the possibility of the successful correction of different eye etiologies pathological conditions. The following publications confirm the fact that the use of piperidine 2-(5-(furan-2-yl)-4-phenyl-4*H*-1,2,4-triazole-3-ylthio)acetate for therapeutic purposes has a positive effect on this process [18,19,20]. Analyzing the dynamics of clinical performance in the treatment of catarrhal conjunctivitis the authors prove the efficiency of piperidine 2-(5-(furan-2-yl)-4-phenyl-4*H*-1,2,4-triazole-3-ylthio)acetate [20]. Another work is devoted to the comparison between usage of ointment forms of existing substances "Tryfuzol" and "Lycopene" in the treatment of catarrhal purulent keratoconjunctivitis [21,22].

The next series of works are devoted to the properties studying of the active pharmaceutical ingredient of the drug "Tryfuzol" after its registration as a veterinary drug (Reg. №ПІІ АВ-05486-01-14) [23-25]. Scientists proved efficiency of 1% injectable solution in a pig at a dose of 1 ml per 10 kg of animal [23] and the 1% solution for oral use in poultry at a rate of one liter of 1% solution per a ton of water [24]. There are noteworthy publications on analytical characteristics of piperidine 2-(5-(furan-2-yl)-4-phenyl-4*H*-1,2,4-triazole-3-ylthio)acetate [26]. A group of researchers conducted a quantitative determination of active pharmaceutical ingredient of drug "Tryfuzol" by high performance liquid chromatography [27]. The following work describes the "Tryfuzol" as an effective antiviral agent for the treatment and prevention of diseases [28].

The staff of researchers of the State Scientific-Research Control Institute of Veterinary Medicinal Products and Feed Additives held the determination the therapeutic efficacy and safety of veterinary drug Tryfuzol 1% in adjuvant therapy in dogs babesiosis [29] and researchers from Poltava State Agrarian Academy share their experience in treating wounds in dogs [30] and boars [31] with a new original veterinary drug "Tryfuzol".

CONCLUSION

Analysis of the literature over the past decade about the properties study of piperidine 2-(5-(furan-2-yl)-4-phenyl-4*H*-1,2,4-triazole-3-ylthio)acetate – active pharmaceutical ingredient of new original veterinary drug "Tryfuzol" proves pharmacological effectiveness of the drug and evidence of scholarly interest in a wide range of researchers for further studyings. Thus, the results of the use of “Tryfuzol” in practice indicate its high immunomodulatory activity. High values of antioxidant properties, hepatoprotective properties with pronounced pancreatoprotective effect were also noted. In a special way it should be payed attention to the significant antiviral effect to some strains of viruses. The scientists will continue in future pre-clinical research of Tryfuzol.

REFERENCES

1. Parchenko, V.V. (2006). Synthesis, physico-chemical and biological properties of the 1,2,4-triazole-3-thione derivatives which contain furan core. Dr. med. sci. diss. Kyiv.
2. Parchenko, V.V., Panasenko, O.I., Knysh, Ye.H., Vasyuk, S.O., Tarkhanova, O.O. (2009). Qualitative and quantitative determination piperidine 2-[5-(furan-2-yl)-4-phenyl-1,2,4-triazole-3-ylthio]acetate 1% and 2,5% solutions]. Zaporozhye medical journal, 11(3), 111-113.
3. Parchenko, V.V., Panasenko, O.I., Knysh, Ye.H., Vasyuk, S.O., Tarkhanova, O.O. (2009). Development of methods for the quantitative determination piperidine 2-(5-(furan-2-yl)-4-phenyl-1,2,4-triazole-3-ylthio)acetate as a substance. Ukrainskyi biofarmatsevychnyi zhurnal, 4(4), 44 – 47.
4. Parchenko, V.V., Kaplaushenko, A.G., Panasenko, O.I., Knysh, Ye.H. (2010). The identification of possible metabolites of the certain 1,2,4-triazole S-derivatives. Ukrainskyi biofarmatsevychnyi zhurnal, 5(10), 32–37.
5. Parchenko, V.V. (2014). Synthesis, transformation, physico-chemical and biological properties in the number of 5-furylsubstituted 1,2,4-triazole-3-thiones. Dr. med. sci. diss. Zaporizhzhia.
6. Parchenko, V.V., Panasenko, O.I., Knysh, Ye.H., Izdeps'kyi, V.Y., Il'yina, O.V., Pohorlyuk, A.Yu. (2009). Piperidine 2-[5-(furan-2-yl)-4-phenyl-1,2,4-triazole-3-ylthio]acetate which shows antiviral activity against chicken embryos viruses. Zaporozhskij medicinskij zhurnal, 1, 97-98.
7. Knysh, Ye.H., Parchenko, V.V., Panasenko, O.I., Kaplaushenko, A.H., Kaplaushenko, T.M., Hotsulia, T.S., Parkhomenko, L.I., Izdepskyi, V.Yo., Ilina, O.V., Al Ravashdeh, M., Pohorliuk, A.Yu. (2008). 1,2,4-triazole derivatives that exhibit antiviral activity against viruses chicken embryos. Bul., 20.
8. Knysh, Ye.H., Parchenko, V.V., Panasenko, T.O., Dzublyk I.V., Trohymenko O.P. (2006). Piperidine 2-[5-(furan-2-yl)-2H-1,2,4-triazole-3-ylthio] acetate, which exhibits antiviral activity. Bul. 11.
9. Shcherbyna, R.O., Parchenko, V.V., Pavlov, S.V., Panasenko, O.I., Knysh, E.H., Belenichev, I.F. (2011). Neuroprotective activity of the 1,2,4-triazoleS-derivatives. Zaporozhskij medicinskij zhurnal, 13(1), 94–97.
10. Kaplaushenko, A.H., Parchenko, V.V., Scherbyna, R.O., Panasenko, O.I., Knysh, Ye.H., Belyenichev, I.F., Pavlov, S.V. (2012). The usage of morfoliniy 2-(5-(4-pirydyl)-4-(2-metoxifenil)-1,2,4-triazole-3-iltio) acetate or piperydyniy 2-(5-(furan-2-yl)-4-phenyl-1,2,4-triazole-3-iltio) acetate as neuroprotective agents. Bul., 24.
11. Parchenko, V.V., Parkhomenko, L.I., Izdepskyi, V.Yi., Panasenko, O.I., Knysh, E.H. (2013). Farmacobiocemical characteristics of the piperidine 2-(5-furan-2-yl)-4-phenyl-1,2,4-triazole3-iltioacetate. Zaporozhskij medicinskij zhurnal, 1(76), 39–41.

12. Knysh, Ye.H., Parchenko, V.V., Panasenko, O.I., Kaplaushenko, A.H., Makovik, Yu.V., Kulish, S.N. (2009). 1,2,4-triazole-3-yl acetic acid derivatives that exhibit antioxidant, hepatoprotective and immunostimulatory activity. *Biuletten*, 12.
13. Knysh, Ye.H., Parchenko, V.V., Panasenko, O.I., Izdepskyi, V.Yi. (2010). The injectable solution for inflammatory processes correction. *Bul.*, 11.
14. Parchenko, V.V. (2011). Histological study of the soft tissues in sheep with experimental inflammatory processes in the background of using 5-(furan-2-yl)-1,2,4-triazoles-3-thione derivatives. *Medychna khimiia*, 2(47), 13, 84–89.
15. Slyusar, H.V. (2012). The dynamics of immunological parameters of blood of dogs for different treatments skin and muscle wounds. *Visnyk SumDU. Seriya «Medytsyna»*, 1, 38-42.
16. Knysh, Ye.H., Parchenko, V.V., Panasenko, O.I., Kaplaushenko, A.H., Parhomenko, L.I., Izdepskyi, V.Yi. (2012). Derivatives of 1,2,4-triazoles that stimulate egg quail productivity. *Bul.*, 14.
17. Parchenko, V.V. (2014). Antioxidant activity furanpohidnyh 1,2,4-triazoles-3-thiones. *Problemy viys'kovoyi okhorony zdorovja*, 41, 222-231.
18. Knysh, Ye.H., Panasenko, O.I., Parchenko, V.V., Pohorluk A.Yu. (2016). Eye drops of "Tryfuzol" Declared. *Bul.*, 19.
19. Mel'nychuk, V.V. (2013). Treatment of young cattle for catarrhal conjunctivitis. *Naukovi pratsi PF NUBiP Ukrayiny «KATU». Seriya «Veterynani nauky»*, 155, 195-199.
20. Mel'nychuk, V.V., Kulynych, S.N. (2013). Clinical indicators dynamics in the treatment of large horned cattle young catarrhal conjunctivitis using derivatives of 1,2,4-triazole (substance VPK-108)]. *Uchenye zapysy uchrezhdenyya obrazovanyya «Vytebskaya ordena «Znaka pocheta» hosudarstvennaya akademyia veterynarnoy medytsyny»*, 49 (2), 106-109.
21. Maslikov, S.M. (2012). The effectiveness of ointment forms Tryfuzolu and Lycopene in the treatment of cats suffering from suppurative catarrhal experimental keratoconjunctivitis. *Naukovyy visnyk L'vivs'koho Natsional'noho universytetu veterynarnoyi medytsyny ta biotekhnolohiyi imeni S. Z. Hzhys'koho*, 14 (2), 212-219.
22. Panasenko, O.I., Bushuyeva, I.V., Parchenko, V.V., Knysh, Ye.G., Izdepskyi, V.J., Izdepskyi, A.V., Pohorlyuk, A.Yu. (2016). Tryfuzol as pathogenetic agent in dogs conjunctivitis. *S World*, 45, 73-79.
23. Kyrychko, B.P., Parchenko, V.V. (2016). Aspects of the drug "Tryfuzol" use in pig. *Tvarynnytstvo s'ohodni*, 5, 44-47.
24. Kotsymbas, I.Ya., Avdos'yeva, I.K., Parchenko, V.V., Poloka, D.A., Pohorlyuk, A.Yu. (2016). Current trends of the drug "Tryfuzol" 1% for poultry. *Tvarynnytstvo s'ohodni*, 7, 56-58.

25. Pruhlo, E.S., Pohorlyuk, A.Yu., Parchenko, V.V., Kaplaushenko, A.G., Panasenko, O.I., Knysh, Ye.H. (2016). Antiviral activity of trifuzol for the broiler at poultry farm. *Zaporozhskij medicinskij zhurnal*, 1(94), 77 – 80.
26. Varyns'kyy, B.O., Knysh, Ye.H., Panasenko, O.I., Parchenko, V.V., Kaplaushenko, A.H. (2015). Study of holding a number of potential drug substances 1,2,4-triazole-3-iltioatsetatnyh acids and their salts by HPLC / DMD-MS / *Journal of Organic and Pharmaceutical Chemistry*. 13(4), 68-75.
27. Varynskyi, B.O., Knysh, Ye.G., Parchenko, V.V., Panasenko, O.I. (2015). Quantitative analysis of piperidin-1-ium((5-(2-furyl)-4-phenyl-4H-1,2,4-triazol-3yl)thio)acetate, substance of veterinary drug «Tryfuzol», in poultry meat by LC-DAD-MS. *Aktualni pytannia farmatsevychnoi i medychnoi nauky ta praktyky*, 2(18), 25 – 31.
28. Knysh, Ye.H., Panasenko, O.I., Parchenko, V.V. (2015). Veterinary antiviral drug. *Bul.*, 19.
29. Kotsyumbas, I.YA, Zhyla, M.I., Mykhalyuk, O.V., Kalynovs'ka, L.V. (2015). The study of the therapeutic efficacy and safety of veterinary drug Tryfuzol 1% in adjuvant therapy for babesiosis dogs, *Naukovo-tekhnichnyy byuletyn*, 16(2), 288-292.
30. Slyusar, H.V. (2013). Experience of treatment of wounds in dogs, *Mezhdunarodnyy vestnyk veterynaryy*, 4, 22-26.
31. Kulynych, S.M. (2013). Influence "Tryfuzolu" for the healing of wounds in pislyakastratsiynih hogs, *Visnyk Poltavs'koyi derzhavnoyi ahrarnoyi akademiyi*, 4, 77-80.