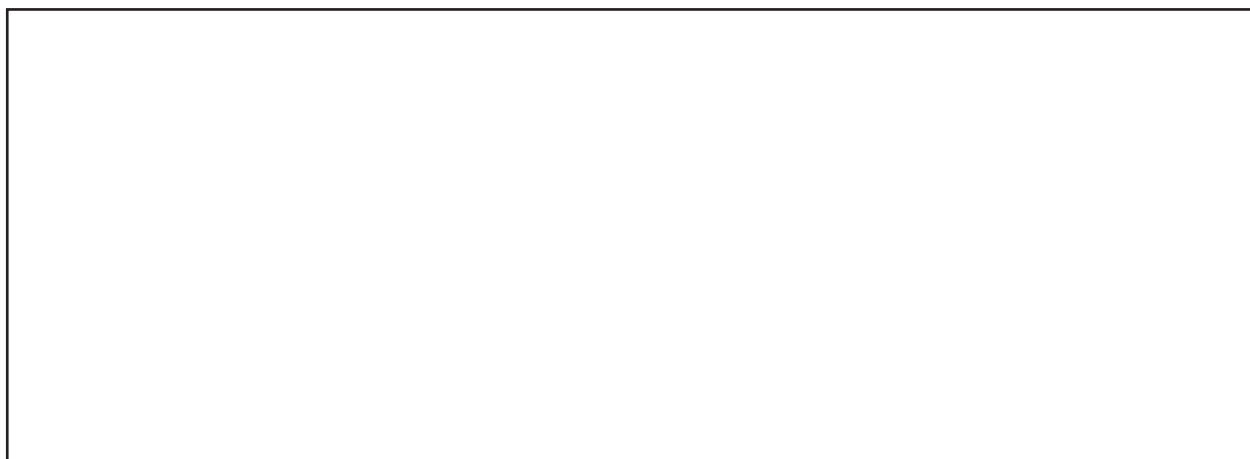




Scheme 1. Synthesis of 2-(E)-cyano(thiazolidin-2-ylidene)thiazoles (6a-d) (derivative from reference No. 7).



Scheme 2. Synthesis of 2-[(E)-(benzo[d]thiazol-2(3H)-ylidene)(cyano)methyl]thiazoles (10a-c) (Bakavoli et al., 2015).

bacterial tested. Just the two derivatives 6d and 10b showed inhibitory effects on *R. equi* and *P. multocida*. The maximum inhibitory effects on *R. equi* and *P. multocida* belonged to derivatives 6d and 10b with MIC of 64 and 32 µg/ml respectively. Ampicillin and neomycin had the maximum and minimum inhibitory effects on *R. equi*, respectively and penicillin and nalidixic acid had the maximum and minimum inhibitory effects on *P. multocida*, respectively. In antibiogram test, the most and the least susceptibility were recorded for *P. multocida* to penicillin with MIC of 0.5 µg/ml and for *B. abortus* to penicillin with MIC of 16 µg/ml (Tables 1 and 2).

Discussion

Thiazole derivatives are novel antibacterial

compounds which promise good replacements for some antibacterial drugs. In the current study, inhibitory effects of eight thiazole derivatives have been assessed on three veterinary bacterial pathogens. Results show that the maximum inhibitory effect against *R. equi* belongs to derivative 6d. The structural study of this derivative shows that this compound includes thiazolidine ring as well as thiazole ring. This thiazolidine ring is similar to that of penicillin family of antibiotics. However, this derivative is expected to affect beta-lactamase producing bacteria due to the lack of a beta-lactam ring (Lv et al., 2009).

Thiazolidines are a novel class of antibacterial agents which include inhibitory effects on a broad-spectrum of gram-positive bacteria, such as streptococci and staphylococci. The inhibitory effect of thiazolidine derivatives on *S.*

Table 1. Bacterial growth inhibitory zone (mm) of the thiazole derivatives and antibiotics on studied bacteria. - absence of inhibition effect.

Derivatives/Drugs	<i>R. equi</i> ATCC 33701	<i>P. multocida</i> ATCC 12948	<i>B. abortus</i> ATCC 23448
6a-c	-	-	-
6d	25.6±0.1	26.3±0.0	-
10a	-	-	-
10b	12.7±0.4	30.1±0.2	-
10c	-	-	-
Gentamicin	25.4±0.3	21.2±0.0	16.3±0.2
Penicillin	27.2±0.5	30.5±0.3	22.1±0.1

Table 2. MICs (µg/ml) of thiazole derivatives and antibiotics on studied bacteria. - absence of inhibition effect.

Derivatives/ Drugs	<i>R. equi</i> ATCC 33701	<i>P. multocida</i> ATCC 12948	<i>B. abortus</i> ATCC 23448
6a-c	-	-	-
6d	64	64	-
10a	-	-	-
10b	256	32	-
10c	-	-	-
Gentamicin	1	8	2
Penicillin	2	0.5	16

faecalis and *S. aureus* has been proven (Majiduddin et al., 2002). Furthermore, the study of derivatives 6a-c has shown that only derivative 6d contains oxygen bonds with thiazole, resulting in the production of oxothiazole. Moreover, this derivative is the only compound within derivatives 6a-d that includes inhibitory effects on *R. equi* and *P. multocida*. Zaky and Yousef have shown that oxothiazole derivatives are able to inhibit the growth of *E. coli* (Patel et al., 2012).

Benzo[d]thiazole derivative 10b had a powerful inhibition on *P. multocida*. The important structure in this compound is benzothiazole. Antibacterial effect on gram-negative bacteria, for example *Escherichia coli* and *Salmonella typhi*, were shown from derivatives which have benzothiazole in their structure (Shirharsha 2006). MICs of thiazole derivatives have demonstrated the ability of these compounds

to significantly inhibit the growth of *Pseudomonas aeruginosa*, *S. aureus*, and *B. subtilis*, compared to penicillin G and kanamycin.

Results have also shown that these derivatives have higher inhibition effects with MICs of 12.5-100 µg/ml. Derivatives within the current study possibly include excited Cl and Br in thiazole ring and, therefore, show intensified inhibitory effects (Venugolpa et al., 2013). In a study by Zaky and Yousef (2011), MIC and inhibition zone of thiazole derivatives on *S. aureus* and *P. aeruginosa* were assessed and showed high antibacterial effects, compared to gentamicin as control (Zaky and Yousef, 2011). Furthermore, high inhibitory effects of thiazole derivatives on bacterial pathogens, such as *Bacillus thuringiensis* and *E. coli*, as well as *S. aureus*, *S. pyogenes*, *Proteus vulgaris* and *Klebsiella pneumonia*, have been studied using growth inhibition zone (Zelisko et al., 2013; Zhang et al., 2013).

In recent studies, inhibition of DNA or enzyme has been proposed as the influential mechanism of thiazole derivatives to inhibit bacteria. The inhibition of one enzyme, ecKA-SIII (or FabH) that is essential for synthesis of fatty acids in gram-negative and gram-positive bacteria, and DNA Gyrase, that is needed to replicate DNA, has been studied. Noting that Quinolone family antibiotics and thiazole derivatives could inhibit subunit A and subunit B of DNA Gyrase enzyme, respectively, has increasingly promised the inhibition of Quinolone-resistant bacteria by thiazole derivatives (Zitouni et al., 2003).

Conclusion: Few studies have been published on antibacterial effects of thiazole derivatives against veterinary bacterial pathogens. In this study, antibacterial effect of thiazole derivatives was proved against *R. equi*, *P. multocida*, and clinical use of these compounds needs in vivo studies for detection therapeutic and toxicity effects of them.

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References

- Adesiyun, A.A., Baird, K., Johnson, A.S. (2011) Antimicrobial resistance, phenotypic characteristics and phage types of *B. abortus* strains isolated from cattle and water buffalo (*Bubalus bubalis*) in Trinidad. *Vet Arch.* 81: 391-404.
- Bakavoli, M., Beyzaei, H., Rahimizadeh, M., Eshghi, H., Takjoo, R. (2009) Regioselective synthesis of new 2-(E)-cyano (thiazolidin-2-ylidene) thiazoles. *Molecules.* 14: 4849-4857.3.
- Bakavoli, M., Beyzaei, H., Rahimizadeh, M., Eshghi, H. (2011) Regioselective synthesis of 2[(E)(benzo[d]thiazol2(3H)ylidene)(cyano)methyl]thiazoles. *Heterocycl Comm.* 17: 151-154.
- Bondock, S., Fadaly, W., Metwally, M.A. (2010) Synthesis and antimicrobial activity of some new thiazole, thiophene and pyrazole derivatives containing benzothiazole moiety. *Eur J Med Chem.* 45: 3692-3701.
- Bondock, S., Naser, T., Ammar, Y.A. (2013) Synthesis of some new 2-(3-pyridyl)-4,5-disubstituted thiazoles as potent antimicrobial agents. *Eur J Med Chem.* 62: 270-279.
- Brvar, M., Perdih, A., Oblak, M., Masic, L.P., Solmajer, T. (2010) In silico discovery of 2-amino-4-(2,4-dihydroxyphenyl) thiazoles as novel inhibitors of DNA gyrase B. *Bioorg Med Chem Lett.* 20: 958-962
- Chementi, F., Bizzarri, B., Bolasco, A., Secci, D., Chimenti, P., Granese, A., Carradori, S., D'Ascenzio, M., Lilli, D., Rivanera, D. (2011) Synthesis and biological evaluation of novel 2,4-disubstituted-1,3-thiazoles anti *Candida* ssp. agents. *Eur J Med Chem.* 46: 378-382.
- Cheng, K., Xue, K.J., Zhu, H.L. (2013) Design, synthesis and antibacterial activity studies of thiazole derivatives as potent eckAS III inhibitors. *Bioorg Med Chem Lett.* 23: 4235-4238.
- Coleman, M., Kuskie K., Liu, M., Chaffin, K., Libal, M., Giguere, S., Bernstein, L., Cohen, N. (2010) In vitro antimicrobial activity of galium maltolate against virulent *Rhodococcus equi*. *Vet Microbiol.* 146: 175-178.
- Helul, M.H.M., Salem, M.A., El-Gaby, M.S.A., Aljahdali, M. (2013) Synthesis and biological evaluation of some novel thiazole compounds as potential anti-inflammatory agents. *Eur J Med Chem.* 65: 517-526.
- Horohov, D.W., Loynachan, A.T., Page, A.E., Hughes, K., Timoney, J.F., Fettingner, M., Hatch, T., Spaulding, J.G., McMichael, J. (2011) The use of streptolysin O (SLO) as an adjunct therapy for *Rhodococcus equi* pneumonia in foals. *Vet Microbiol.* 154: 156-162.
- Jaishree, V., Ramdas, N., Sachin, J., Ramesh, B. (2013) In vitro antioxidant properties of new thiazole derivatives. *J Saudi Chem Soc.* 16: 371-376.
- Juspin, T., Laget, M.L., Terme, T., Azas, N., Vanelle, P. (2010) TDAE-assisted synthesis of new imidazol[2,1-b]thiazole derivatives as anti-infectious agents. *Eur J Med Chem.* 45: 840-845.
- Katsuda, K., Hoshinoo, K., Ueno, Y., Kohmoto, M., Mikami, O. (2013) Virulence genes and antimicrobial susceptibility in *Pasteurella multocida* isolates from calves. *Vet Microbiol.* 167: 737-741.
- Khalil, A., Berghot, M., Gouda, M. (2009) Synthesis and antibacterial activity of some new thiazole and thiophene derivatives. *Eur J Med Chem.* 44: 4434-4440.
- Kofteridis, D.P., Christofaki, M., Mantadakis, E., Maraki, S., Drygiannakis, I., Papadakis, J.A., Samonis, G. (2009) Bacteremic community-acquired pneumonia due to *Pasteurella*

- multocida*. Int J Infect Dis. 13: 81-83.
17. Lv P.C., Wang, K.R., Yang, Y., Mao, W.J., Chen, J., Xiong, J., Zhu, H.L. (2009) Design, synthesis and biological evaluation of novel thiazole derivatives as potent FabH inhibitors. Bioorg Med Chem Lett. 19: 6750-6754.
 18. Majiduddin, F.K., Materon, I.C., Palzkill, T.G. (2002) Molecular analysis of beta-lactamase structure and function. Int J Med Microbiol. 292: 127-137.
 19. Patel, R., Patel, P.K., Kumari, P., Rajani, D.P., Chikhaliya, K.H. (2012) Synthesis of benzimidazolyl-1,3,4-oxadiazol-2ylthio-N-phenyl (benzothiazolyl) acetamides as antibacterial, anti-fungal and antituberculosis agents. Eur J Med Chem. 53: 41-51.
 20. Sriharsha, S.N., Satish, S., Shashikanth, S., Raveesha, K.A. (2006) Design, synthesis antibacterial activity of novel 1,3-thiazolidine pyrimidine nucleoside analogues. Bioorg Med Chem. 14: 7476-7481.
 21. Venugopla, K.N., Krishnappa, M., Nayak, S.K., Subruhmany, B.K., Vaderapura, J.P., Chalanavar, R.K., Gleiser, R.M., Odhav, B. (2013) Synthesis and antimosquito properties of 2,6-substituted benzo[d] thiazole and 2,4-substituted benzo[d]thiazole analogues against anopheles arabiensis. Eur J Med Chem. 65: 295-303.
 22. Zaky, R.R., Yousef, T.A. (2011) Spectral, magnetic, thermal, molecular modelling, ESR studies and antimicrobial activity of (E)-3-(2-(2-hydroxybenzylidene) hydrazinyl)-3-oxo-n (thiazole-2-yl) propanamide complexes. J Mol Struct. 1002: 76-85.
 23. Zelisko, N., Atamanyuk, D., Vasylenko, O., Grellier, P., Lesyk, R. (2013) Synthesis and antitripanosoma activity of new 6,6,7-trisubstituted thiopyranol [2,3-d][1,3] thiazoles. Bioorg Med Chem Lett. 22: 7071-7074.
 24. Zhang, M., Han, X., Liu, H, Tian, M., Ding, C., Song, J., Sun, X., Liu, Z., Yu, S. (2013) Inactivation of the ABC transporter ATPase gene in *Brucella abortus* strain 2308 attenuated the virulence of the bacteria. Vet Microbiol. 164, 322-329.
 25. Zitouni, G.T., Demirayak. S., Ozdemir, A., Kaplancikli, Z.A., Yıldız, M.T. (2003) Synthesis of some 2-[(benzazole-2-yl) thioacetyl amino] thiazole derivatives and their antimicrobial activity and toxicity. Eur J Med Chem. 39: 267-272.

مطالعه اثر ضد باکتریایی مشتقات تiazول روی رودو کو کوس اکوئی، پاستور لا مولتی سیداو بروسلا آبور توس

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چکیده

زمینه مطالعه: رودو کو کوس اکوئی، پاستور لا مولتی سیداو بروسلا آبور توس از مهمترین باکتری‌های پاتوژن دامپزشکی محسوب شده که در سال‌های اخیر مقاومت این باکتری‌ها به آنتی بیوتیک‌های رایج باعث نگرانی‌هایی در صنعت دامپروری شده است. برای کنترل این باکتری‌ها، استفاده از ترکیبات ضد باکتریایی جدیدی چون مشتقات تiazول در دامپزشکی ضروری است. **هدف:** در این مطالعه به بررسی اثر ضد باکتریایی مشتقات جدید تiazول بر روی سه باکتری رودو کو کوس اکوئی، پاستور لا مولتی سیداو بروسلا آبور توس پرداختیم. **روش کار:** پس از حل کردن مشتقات در DMSO، برای بررسی مقایسه اثر ضد باکتریایی، از روش انتشار در دیسک برای اندازه‌گیری قطر هاله مهار رشد و از روش براس میکرودايلوشن برای تعیین حداقل غلظت بازدارندگی رشد (MIC) استفاده شد. **نتایج:** اثر مهار از هیچ کدام از مشتقات روی بروسلا آبور توس مشاهده نشد اما قطر هاله مهار رشد $12/7 \pm 0/4$ mm تا $31/2 \pm 0/2$ و MIC 33 تا 256 $\mu\text{g/ml}$ برای اثر مهار مشتقات روی رودو کو کوس اکوئی و پاستور لا مولتی سیداو ثابت گردید. **نتیجه‌گیری نهایی:** نتایج این تحقیق قدرت مهار مشتقات تiazول را بر روی دو باکتری مهم دامپزشکی (رودو کو کوس اکوئی و پاستور لا مولتی سیداو) اثبات می‌کند.

واژه‌های کلیدی: اثر ضد باکتریایی، بروسلا آبور توس، پاستور لا مولتی سیداو، رودو کو کوس اکوئی، مشتقات تiazول

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