Synthesis Of 2,5-Dimersapto-1,3,4-Thiadiazol Products

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ABSTRACT
Potentially bioactive 2,5-bis derivatives of 1,3,4-thiadazole with alkaloid moieties were synthesized by reaction of 1,3,4-thiadiazol-2,5-dithiol with N-acryloyl-substituted derivatives of the alkaloids anabasine, cytisine, and D-pseudoephedrine. 1,3,4-Thiadiazole-2,5-disulfonic acid was synthesized by oxidation of 2,5-dimercaptoto-1,3,4-thiadiazole, and onium salts of this acid were prepared by its reactions with selected alkaloids and secondaryamines.

KEYWORDS
Synthesis 1,3,4-thiadiazol-2,5-dithiol, alkaloids, N-alkaloid-substituted acrylamides, 1,3,4-Thiadiazole-2,5-disulfonic acid

INTRODUCTION
One of the main tasks of organic chemistry is the synthesis and production of substances with new therapeutic properties. Today, chemists are interested in heterocyclic compounds and their applications in pharmaceuticals and chemistry. 1,3,4-thiadiazole is a common heterocyclic compound containing two nitrogen and sulfur atoms. There are several isomers of 1,3,4-thiadiazole, including 1,2,3-thiadiazole, 1,2,4-
Thiadiazole, 1,2,5-thiadiazole, 1,3,4-thiadiazole [1]. Scheme 1

1,3,4-Thiadiazole was first described in 1882 by Fischer and further developed by Busch and his coworkers. The advent of sulfur drugs and later discovery of mesoionic compounds greatly accelerated the rate of progress in this field[2].

**Scheme 1.** Isomers of thiadiazole.

![Thiadiazole Isomers](image)

Thiadiazole is found in the live form of ditiolvadition tautome in the literature preserved in gold gugut. In fact, the first of the three tautomeric structures recorded in the literature is the most common.

**Scheme 2.** Three tautomer shapes

![Tautomers](image)

1,3,4-thiadiazole derivatives are widely used in medicine, pharmaceuticals and agriculture [1]. New derivatives of 1,3,4-thiadiazole are gaining popularity because they are widely used in various directions [4]. They are used against fungi [5-8], antibacterial [9-12], anti-inflammatory [13-15], analgesic [16-17], anti-amoebiasis [18-19], anti-cancer [20-22], antioxidant [23-26], molluscicidal [27-28], antidiabetic [29], central nervous system (CNS) depressant [30], anticonvulsant [31-32], anti-tuberculosis [33-34], anti-depressant [35], antitumor [36] and others, therefore, this study is important in the synthesis of new derivatives of 2,5-dimersapto-1,3,4-thiadiazole.

1,3,4-thiadiazole derivatives have high potential in agrochemistry as herbicides, fungicides, insecticides [37], pesticides, bactericides and plant growth regulators [1]. Drugs containing 1,3,4-thiadiazole nuclei, such as metazolamide, megazol, acetazolamide, and cefazolins, are known [38,39].
MATERIALS AND METHODS

Experimental

The course of reactions and purity of 2–4 were monitored using TLC on Silufol UV-254 standard plates with elution by propan-2-ol:NH₄OH:H₂O (7:2:1) and detection by iodine vapor. Elemental analyses of all compounds agreed with those calculated. Melting points were determined on a Boetius apparatus. IR spectra in KBr disks were recorded on an Avatar-320 spectrometer; PMR spectra in DMSO-d₆, on a Bruker AC-300 spectrometer at operating frequency 300 MHz relative to TMS internal standard (compound 2,3,4).

The IR spectra of the compounds were recorded on an Avatar-320 spectrometer in KBr pellets and mulls in mineral oil, and the 1H and 13C NMR spectra, on a Mercury-300 spectrometer with a working frequency of 300 MHz, solvent DMSO-d₆. (compound 5-12).

Synthesis of 2,5-dimercapto-1,3,4-thiadiazole (1) [40]:

A mixture of (99%) hydrazine hydrate (5 mL, 0.02 mol) and carbon disulfide (15 mL, 0.02 mol) with dry pyridine (50 mL) was refluxed for (5 h). Then the excess solvent was then distilled off, and the resulting solid was separated out by adding (25 mL) of water and (5 mL) of hydrochloric acid. The mixture was then filtered and the solid was recrystallized from ethanol.

2,5-Bis(1-(anabasin-1-yl)propan-1-on-3-thio)-1,3,4-thiadiazole (2)[41].

A solution of anabasine (1.62 g, 0.01 mol) in benzene was cooled, stirred vigorously in the presence of triethylamine (1.01 g, 0.01 mol), treated dropwise with acryloylchloride (0.91 g, 0.01 mol) over an hour, and stirred at room temperature for 2 h. The resulting precipitate of triethylammoniumhydrochloride was filtered off. The filtrate was cooled, stirred, treated dropwise with a solution of 1,3,4-thiadiazol-
2,5-dithiol (0.75 g, 0.005 mol) in anhydrous EtOH over an hour, and stirred at room temperature for 2 h. The resulting precipitate was filtered off to afford a white powdery compound (1.3 g, 44%), mp 89–90°C (EtOH), Rf 0.82, C28H34N6O2S3. PMR spectrum (300 MHz, DMSO-d6, δ, ppm, J/Hz): 1.81 (4H, m, H-9,9′), 2.08 (4H, m, H-8,8′), 2.50 (4H, m, H-10,10′), 2.81 (4H, t, J14,15 = 6.0, H-14,14′), 3.27 (2H, m, H-7,7′), 3.32 (4H, t, J15,14 = 6.0, H-15,15′), 3.71 (4H, m, H-11,11′), 7.15 (2H, q, H-3,3′), 7.58 (2H, q, H-4,4′), 8.31 (2H, d, H-6,6′), 8.50 (2H, d, H-2,2′).

2,5-Bis(1-(cytisin-1-yl)propan-1-on-3-thio)-1,3,4-thiadiazole (3) [41].

Was synthesized analogously to 1 from cytosine (1.9 g, 0.01 mol) to afford a white powdery compound (2.4 g, 75%), mp 121–122°C (EtOH), Rf 0.53, C30H34N6O4S3. PMR spectrum (300 MHz, DMSO-d6, δ, ppm, J/Hz): 1.92 (4H, m, H-8,8′), 2.81 (4H, t, J14,15 = 6.0, H-14,14′), 2.90 (4H, m, H-9,9′), 3.10 (2H, m, H-7,7′), 3.30 (4H, t, J15,14 = 6.0, H-15,15′), 3.76 (4H, m, H-11,11′), 3.80 (2H, m, Hax-10,10′), 4.36 (2H, m, H-10,10′), 5.98 (2H, dd, H-5,5′), 6.33 (2H, dd, H-3,3′), 7.23 (2H, dd, H-4,4′).

2,5-Bis(1-(D-pseudoephedrin-1-yl)propan-1-on-3-thio)-1,3,4-thiadiazole (4) [41].

Was synthesized analogously to 1 from D-pseudoephedrine (1.65 g, 0.01 mol) to afford an oily compound that was purified by column chromatography over silica gel with elution by benzene:EtOH (2:1), Rf 0.78, C28H36N4O4S3. PMR spectrum (300 MHz, DMSO-d6, δ, ppm, J/Hz): 0.98 (6H, d, 2CH-CH3), 2.48 (2H, m, 2CH-N), 2.65 (6H, s, 2N-CH3), 2.80 (4H, t, J14,15 = 6.0, H-14,14′), 3.40 (4H, t, J15,14 = 6.0, H-15,15′), 4.68 (2H, d, CH=OH), 5.35 (2H, s, 2OH), 6.28, 7.34 (10H, m, 2ArH).

Synthesis of 1,3,4-Thiadiazole-2,5-disulfonic acid(5) [42]:

A 2.5% aqueous solution of 6.32 g (0.04 mol) of KMnO4 was added dropwise with stirring at room temperature over a period of 3 h to an aqueous solution of 1.5 g (0.01 mol) of 2,5-dimercapto-1,3,4-thiadiazole. The mixture was heated with stirring on a water bath until its complete decolorization. The precipitate of manganese dioxide was filtered off, the filtrate was evaporated, and the dry residue was washed with alcohol. 1,3,4-Thiadiazole-2,5-disulfonic acid 4 was recrystallized from ethanol-water, 10:1.

Synthesis of alkaloid- and amine-containing salts of 1,3,4-thiadiazole-2,5-disulfonic acid, (6-12) [42].

An aqueous solution of 0.02 mol of appropriate secondary amine or alkaloid was added dropwise with stirring over a period of 1 h to an aqueous solution of 2.46 g (0.01 mol) of 1,3,4-thiadiazole-2,5-disulfonic acid 6. The mixture was stirred at room temperature for 12 h and left in a vacuum desiccator to remove the solvent. The solid residue was washed with alcohol, filtered off, and recrystallized from ethanol-water, 10:1.
RESULTS AND DISCUSSION

The mechanism for the formation of 2,5-dimercapto-1,3,4-thiadiazole (1) is shown in Scheme 4.

Scheme 4. Reaction mechanism for the preparation of compound 1.


**Table 1:** Elemental analysis and physical properties of prepared compounds 5-12[42].

| №  | Formula               | %Yield | m.p (°C) | Elemental analysis calc. (found) |
|----|-----------------------|--------|----------|---------------------------------|
|    |                       |        |          | %C    | %H    | %N     |
| 5  | C_2H_2N_2O_5S_3       | 98.0   | >350     | 9.67(9.76) | 0.90(0.81) | 11.30(11.38) |
| 6  | C_{12}H_{12}N_4O_8S_3 | 76.9   | >350     | 34.7(34.62) | 5.72(5.77) | 13.35(13.46) |
| 7  | C_{10}H_{20}N_4O_8S_3 | 66.9   | >350     | 28.5(28.57) | 4.64(4.76) | 13.25(13.33) |
The yields of final products 2–4 were 36–75% and depended not so much on the electron-donating properties of the alkaloid moiety in the amide as on the conformational rigidity of the rings in the starting alkaloids that prevented the β-C atom of the double bond from being shielded. Compound 3 was obtained in the highest yield. This was explained by the conformational rigidity of the cytisine rings compared with the conformational flexibility of anabasine and D-pseudoephedrine. Products 2–4 were powdery and oily compounds that were soluble in EtOH and CHCl₃ with heating. Their structures and compositions were proved using IR and PMR spectroscopy and elemental analysis. IR spectra of 2–4 contained absorption bands at 780–730 cm⁻¹ (C–SH), 1060–1040, 1160–1120, 1270–1250 (S–C–S, N=C–S, N–N), and 1460–1390 (N=C) that were identified as absorption bands of the thiadiazole ring [43, 44]. Other functional groups of 2–4 appeared in characteristic regions of the spectrum at 1695–1624 (C=O), 1480–1440 (–CH₂–), and 705–680 (C=S–) [45].

The structure and composition of 5–12 were confirmed by IR, ¹H NMR, and ¹³C NMR spectroscopy, and also by elemental analysis. The IR spectra of all the onium salts synthesized contain characteristic absorption bands of the thiadiazole ring at 680, 730, 1400, and 1500 cm⁻¹, bands in the range 656–649 cm⁻¹ assigned to -SO₃⁻ vibrations, and absorption bands at 3501–3421 cm⁻¹ characteristic of secondary ammonium salts [45].

In the ¹H NMR spectra of 6–12, recorded in DMSO-d₆, protons of the ammonium group appeared as an ill-resolved multiplet centered at 14.6 ppm. The chemical shifts of signals from protons of alkaloid and secondary amine fragments have typical values [46].

In the ¹³C NMR spectrum of 1,3,4-thiadiazole-2,5-disulfonic acid 5, the heterocyclic carbon atom appears as a singlet at 168.0 ppm. In the ¹³C NMR spectrum of piperidinium salt of 1,3,4-thiadiazole-2,5-disulfonic acid 6, the heterocyclic carbon atom appears as a singlet at 158.4 ppm, and carbon atoms of the piperidine fragment give signals at 23.1, 25.5, 26.0, 42.5, and 45.5 ppm [47].

**CONCLUSION**

2,5-dimercapto-1,3,4-thiadiazole derivatives were synthesized. Oxidation of 2,5-dimercapto-1,3,4-thiadiazole with an aqueous solution of KMnO₄ yielded 1,3,4-thiadiazole-2,5-disulfonic acid. Its reactions with selected alkaloids and cyclic secondary amines gave the corresponding salts.
REFERENCES

1. Yang Hu, Cui-Yun Li, Xiao-Ming Wang, Yong-Hua Yang, and Hai-Liang Zhu., 1,3,4-Thiadiazole: Synthesis, Reactions, and Applications in Medicinal, Agricultural, and Materials Chemistry., Chem. Rev. 2014, 114, 10, 5572–5610.

2. Kratika Shrivastava, Suresh Purohit and Sarita Singhal. Studies On Nitrogen And Sulphur Containing Heterocyclic Compound: 1,3,4 – thiadiazole. Asian Journal of Biomedical and Pharmaceutical Sciences 3(21) 2013, 6-23.

3. Jigar K. Mistry, Richard Dawes, Amitava Choudhury, and Michael R. Van De Mark., 5-Mercapto-1,3,4-thiadiazole-2(3H)-thione: Synthesis and Structure of Alkylated Derivatives., 2014 May Journal of Heterocyclic Chemistry 51(3):747–754.

4. Shaker Awad Abdul Hussein and Ammar Abdul Razzak M. Kubba., Synthesis, characterization and antimicrobial activity of new 2,5-disubstituted-1,3,4-thiadiazole derivatives., Der PharmaChemica, 2015, 7(9):250-260.

5. Liu, F., Luo, X.-Q., Song, B.-A., Bhadury, P. S., Yang, S., Jin, L.-H., Hu, D.-Y. Synthesis and antifungal activity of novel sulfoxide derivatives containing trimethoxyphenyl substituted 1,3,4-thiadiazole and 1,3,4-oxadiazole moiety. Bioorganic & Medicinal Chemistry, (2008).16(7), 3632–3640.

6. Chen, C.-J., Song, B.-A., Yang, S., Xu, G.-F., Bhadury, P. S., Jin, L.-H., Chen, Z. Synthesis and antifungal activities of 5-(3,4,5-trimethoxyphenyl)-2-sulfonyl-1,3,4-thiadiazole and 5-(3,4,5-trimethoxyphenyl)-2-sulfonyl-1,3,4-oxadiazole derivatives. Bioorganic & Medicinal Chemistry, (2007)15(12), 3981–3989.

7. Zoumpoulakis, P., Camoutsis, C., Pairas, G., Soković, M., Glamočlija, J., Potamitis, C., & Pitsas, A. Synthesis of novel sulfonamide-1,2,4-triazoles, 1,3,4-thiadiazoles and 1,3,4-oxadiazoles, as potential antibacterial and antifungal agents. Biological evaluation and conformational analysis studies. Bioorganic & Medicinal Chemistry, (2012)20(4).

8. Alwan, W. S., Karpoormath, R., Palkar, M. B., Patel, H. M., Rane, R. A., Shaikh, M. S., ... Misana, K. P. Novel imidazo[2,1-b]-1,3,4-thiadiazoles as promising antifungal agents against clinical isolate of Cryptococcus neoformans. European Journal of Medicinal Chemistry, (2015).95, 514–525.

9. Wu, Q., Cai, H., Yuan, T., Li, S., Gan, X., & Song, B. Novel vanillin derivatives containing a 1,3,4-thiadiazole moiety as potential antibacterial agents. Bioorganic & Medicinal Chemistry Letters, (2020).127113.

10. Chen, J., Yi, C., Wang, S., Wu, S., Li, S., Hu, D., & Song, B. Novel amide derivatives containing 1,3,4-thiadiazole moiety: Design, synthesis, nematocidal and antibacterial activities. Bioorganic & Medicinal Chemistry Letters. 29 (2019) 1203–1210.

11. Li, P., Shi, L., Yang, X., Yang, L., Chen, X.-W., Wu, F., ... Song, B.-A. Design, synthesis, and antibacterial activity against rice bacterial leaf blight and leaf streak of 2,5-substituted-1,3,4-oxadiazole/thiadiazolesulfone derivative. Bioorganic & Medicinal Chemistry Letters, (2014). 24(7), 1677–1680.

12. Li, P., Shi, L., Gao, M.-N., Yang, X., Xue, W., Jin, L.-H., Song, B.-A. Antibacterial activities against rice bacterial leaf blight and tomato bacterial wilt of 2-mercapto-
5-substituted-1,3,4-oxadiazole/thiadiazole derivatives. Bioorganic & Medicinal Chemistry Letters, (2015).25(3), 481–484

13. Ragab, F. A., Helba, H. I., El-Gazzar, M. G., Abou-Seri, S. M., El-Sabbagh, W. A., & El-Hazek, R. M. Anti-inflammatory, analgesic and COX-2 inhibitory activity of novel thiadiazoles in irradiated rats. Journal of Photochemistry and Photobiology B: Biology, (2017).166, 285–300.

14. Omar, Y. M., Abdu-Allah, H. H. M., & Abdel-Moty, S. G. Synthesis, biological evaluation and docking study of 1,3,4-thiadiazole-thiazolidinone hybrids as anti-inflammatory agents with dual inhibition of COX-2 and 15-LOX. Bioorganic Chemistry, (2018), 80, 461–471.

15. Maddila, S., Gorle, S., Sampath, C., & Lavanya, P. Synthesis and anti-inflammatory activity of some new 1,3,4-thiadiazoles containing pyrazole and pyrrole nucleus. Journal of Saudi Chemical Society, (2016).20, S306–S312.

16. Hafez, H. N., Hegab, M. I., Ahmed-Farag, I. S., & El-Gazzar, A. B. A facile regioselective synthesis of novel spiro-thioxanthene and spiro-xanthene-9',2-[1,3,4]thiadiazole derivatives as potential analgesic and anti-inflammatory agents. Bioorganic & Medicinal Chemistry Letters, (2008).18(16), 4538–4543.

17. Salgın-Gökşen, U., Gökhan-Kelekcı, N., Göktas, Ö., Kıyısal, Y., Kılıç, E., İşik, Ş., Özalp, M. 1-Acylthiosemicarbazides, 1,2,4-triazole-5(4H)-thiones, 1,3,4-thiadiazoles and hyrazones containing 5-methyl-2-benzoazolinones: Synthesis, analgesic-anti-inflammatory and antimicrobial activities. Bioorganic & Medicinal Chemistry, (2007).15(17), 5738–5751.

18. Almandil, N. B., Taha, M., Rahim, F., Wadooq, A., Imran, S., Alqahtani, M., Gollapalli, M. Synthesis of novel quinoline-based thiadiazole, evaluation of their antileishmanial potential and molecular docking studies. Bioorganic Chemistry, (2019).85, 109–116.

19. Tahghighi, A., Marznaki, F. R., Kobarfard, F., Dastmalchi, S., Mojarrad, J. S., Razmi, S., ... Foroumadi, A. Synthesis and antileishmanial activity of novel 5-(5-nitrofuran-2-yl)-1,3,4-thiadiazoles with piperazinyl-linked benzamidine substituents. European Journal of Medicinal Chemistry, (2011).46(6), 2602–2608.

20. Wei, M.-X., Feng, L., Li, X.-Q., Zhou, X.-Z., & Shao, Z.-H. Synthesis of new chiral 2,5-disubstituted 1,3,4-thiadiazoles possessing γ-butenolide moiety and preliminary evaluation of in vitro anticancer activity. European Journal of Medicinal Chemistry, (2009).44(8), 3340–3344.

21. Kumar, D., Maruthi Kumar, N., Chang, K.-H., & Shah, K. Synthesis and anticancer activity of 5-(3-indolyl)-1,3,4-thiadiazoles. European Journal of Medicinal Chemistry, (2010).45(10), 4664–4668.

22. Kumar, D., Kumar, N. M., Chang, K.-H., Gupta, R., & Shah, K. Synthesis and in vitro anticancer activity of 3,5-bis(indolyl)-1,2,4-thiadiazoles. Bioorganic & Medicinal Chemistry Letters, (2011) 21(19), 5897–5900.

23. Jakovljević, K., Matić, I. Z., Stanojković, T., Krivokuća, A., Marković, V., Joksović, M. D., Joksović, L. Synthesis, antioxidant and antiproliferative activities of 1,3,4-thiadiazoles derived from phenolic acids. Bioorganic & Medicinal Chemistry Letters, (2017).27(16), 3709–3715.

24. Jakovljević, K., Joksović, M. D., Botta, B., Jovanović, L. S., Avdović, E., Marković, Z., Marković, V. Novel 1,3,4-thiadiazole
conjugates derived from protocatechuic acid: Synthesis, antioxidant activity, and computational and electrochemical studies. Comptes Rendus. (2019). 22 585-598.
25. Djukic, M., Fesatidou, M., Xenikakis, I., Geronikaki, A., Angelova, V. T., Savic, V., Saso, L. In vitro antioxidant activity of thiazolidinone derivatives of 1,3-thiazole and 1,3,4-thiadiazole. Chemico-Biological Interactions, (2018). 286, 119–131.
26. Sauer, A. C., Leal, J. G., Stefanello, S. T., Leite, M. T. B., Souza, M. B., Soares, F. A. A., Dornelles, L. Synthesis and antioxidant properties of organosulfur and organoselenium compounds derived from 5-substituted 1,3,4-oxadiazole/thiadiazole-2-thiols. Tetrahedron Letters, (2017)58(1), 87–91.
27. Fadda, A. A., Abdel-Latif, E., & El-Mekawy, R. E. Synthesis and molluscicidal activity of some new thiophene, thiazole, pyrazole and pyrazole derivatives. European Journal of Medicinal Chemistry, (2009).44(3), 1250–1256.
28. El Shehry, M. F., Abu-Hashem, A. A., & El-Telbani, E. M. Synthesis of 3-((2,4-dichlorophenoxy)methyl)-1,2,4-triazolo(thiazoles and thiazines) as anti-inflammatory and molluscicidal agents. European Journal of Medicinal Chemistry, (2010).45(5), 1906–1911.
29. Lee, J., Lee, S.-H., Seo, H. J., Son, E.-J., Lee, S. H., Jung, M. E., Lee, J. Novel C-aryl glucoside SGLT2 inhibitors as potential antidiabetic agents: 1,3,4-Thiadiazolylmethylphenyl glucoside congeners. Bioorganic & Medicinal Chemistry, (2010)18(6), 2178–2194.
30. Jatav, V., Mishra, P., Kashaw, S., & Stables, J. P. Synthesis and CNS depressant activity of some novel 3-[5-substituted 1,3,4-thiadiazole-2-yl]-2-styryl quinazoline-4(3H)-ones. European Journal of Medicinal Chemistry, (2008). 43(1), 135–141.
31. Harish, K. P., Mohana, K. N., & Mallesha, L. Synthesis of indazole substituted-1,3,4-thiadiazoles and their anticonvulsant activity. Drug Invention Today, (2013)5(2), 92–99.
32. Rajak, H., Behera, C. K., Pawar, R. S., Singour, P. K., & Kharya, M. D. A novel series of 2,5-disubstituted 1,3,4-thiadiazoles as potential anticonvulsant agent. Chinese Chemical Letters, (2010).21(10), 1149–1152.
33. Quintana, C., Klahn, A. H., Artigas, V., Fuentenalba, M., Biot, C., Halloum, I., Arancibia, R. Cyhretrenyl and ferrocenyl 1,3,4-thiadiazole derivatives: Synthesis, characterization, crystal structures and in vitro antitubercular activity. Inorganic Chemistry Communications, (2015). 55, 48–50.
34. Alegaon, S. G., Alagawadi, K. R., Sonkusare, P. V., Chaudhary, S. M., Dadwe, D. H., & Shah, A. S. Novel imidazo[2,1-b][1,3,4]thiadiazole carrying rhodanine-3-acetic acid as potential antitubercular agents. Bioorganic & Medicinal Chemistry Letters, (2012).22(5), 1917–1921.
35. Yusuf, M., Khan, R. A., & Ahmed, B. Syntheses and anti-depressant activity of 5-amino-1, 3, 4-thiadiazole-2-thiol imines and thiobenzyl derivatives. Bioorganic & Medicinal Chemistry, (2008) 16(17), 8029–8034.
36. Zhang, K., Wang, P., Xuan, L.-N., Fu, X.-Y., Jing, F., Li, S., Chen, B.-Q. Synthesis and antitumor activities of novel hybrid molecules containing 1,3,4-oxadiazole and 1,3,4-thiadiazole bearing Schiff base moiety. Bioorganic & Medicinal Chemistry Letters, (2014) 24(22), 5154–5156.
37. Lv, M., Liu, G., Jia, M., & Xu, H. Synthesis of matrinic amide derivatives containing 1,3,4-thiadiazole scaffold as insecticidal/acaricidal agents. Bioorganic Chemistry, (2018), 81, 88–92

38. Gomha, S., Edrees, M., Muhammad, Z., & El-Reedy, A. 5-(Thiophen-2-yl)-1,3,4-thiadiazole derivatives: synthesis, molecular docking and in vitro cytotoxicity evaluation as potential anticancer agents. Drug Design, Development and Therapy, (2018) Volume 12, 1511–1523.

39. Karolina Jasiak, Agnieszka Kudelko, Monika Wróblowska, Anna Biernasiuk, Anna Malm, and Maria Krawczyk. Convenient Synthesis and Biological Activity of Mono and Diacyl 2,5-Dimercapto-1,3,4-thiadiazole Derivatives. Journal of Heterocyclic Chemistry. 2017. 54(6) 3241-3249.

40. Jumat Salimon, Nadia Salih, Emad Yousif, Ayad Hameed and Hibalbraheem. Synthesis, Characterization and Biological Activity of Schiff Bases of 2, 5-Dimercapto-1,3,4-thiadiazole . Australian Journal of Basic and Applied Sciences, 4(7): 2016-2021, 2010

41. T. S. Zhivotova. Reaction of 1,3,4-thiadiazol-2,5-dithiol with n-acryloyl-substituted derivatives of several alkaloids. Chemistry of Natural Compounds, Vol. 45, No. 6, 2009.

42. T. S. Zhivotova, A. M. Gazaliev, O. V. Dryuk, and A. Zh. Seitembetova. Synthesis and Antioxidant Activity of Alkaloid- and Amine-containing Salts of 1,3,4-Thiadiazole-2,5-disulfonic Acid. Russian Journal of Applied Chemistry, 2008, Vol. 81, No. 2, pp. 259-262.

43. T. E. Glotova, A. S. Nakhmanovich, and T. N. Komarova, Khim. Geterotsikl. Soedin., 8, 1144 (1988).

44. A. A. Katritskii, Physicochemical Methods in Chemistry of Heterocyclic Compounds [in Russian], Khimiya, Moscow, 1966, p. 59.

45. L. J. Bellamy, Advances in Infrared Group Frequencies, Methuen, London, 1968.

46. Gazaliev, A.M., Zhurinov, M.Zh., and Fazylov, S.D., Novyebioaktivnyeproizvodnyealkaloi dov(New Bioactive Alkaloid Derivatives), Alma-Ata: Gylym, 1992.

47. Levy, G.C., and Nelson, G.L., Carbon-13 Nuclear Magnetic Resonance for Organic Chemists, New York: Wiley, 1972.