Synthesis and Antibacterial Activity of some Derivatives of 2-Amino-5-Mercapto-1,3,4-Thiadiazole

A. T. AI-Samarraie* , I. A. AI-Masoudi and A. F. Abbas***
***College of Science, University of Basrah, Basrah Iraq**
****College of Veterinary, University of Basrah, Basrah-Iraq.**

Abstract

Reaction of 2-amino-5-mercapto-l,3,4-thiadiazole **5** with different aldehydes **6-11** afforded the corresponding imino derivatives **12-17**. The structures of these products were characterized by their elemental analysis (C.H.N) , ^{1}H NMR and mass spectra. Compound **16** was also characterized by its ^{13}C NMR. The antibacterial screening of **12-17** has been reported.

تحضير ودراسة الفعالية ضد البكتريا لبعض المشتقات 2-امينو-5-ميركبتو-1،3،4-ثايودايزول

علي طه السامرائي* ايمان عبود المسعودي** عباس فاضل عباس*
*قسم الكيمياء - كلية العلوم - جامعة البصرة
**كلية الطب البيطري - جامعة البصرة

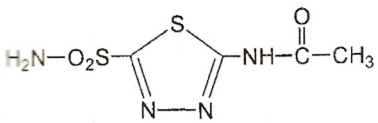
الخلاصة

تمت مفاعلة 2-أمينو-5-مركابتو-1،3،4-ثايادايازول (المركب 5) مع ألديهايدات مختلفة (المركبات 6-11) للحصول على مشتقات الأيمينات المقابلة (المركبات 12-17) . جرى تشخيص المركبات الجديدة بأستخدام التحليل العنصري (C.H.N.) ومطيافية الرنين النووي المغناطيسي للبروتون (^{1}H NMR) ومطيافية الكتلة ، كذلك أستخدم الرنين النووي المغناطيسي للكاربون (^{13}C NMR) في تشخيص المركب 16 . يشتمل البحث أيضاً على المسح الضد بكتيري للمركبات (12-17).

Introduction

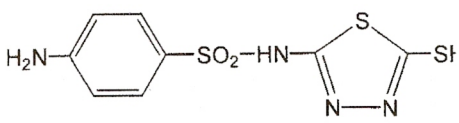
1,3,4-Thiadiazole and its derivatives have become very useful compounds in medicine, agriculture and in many fields of technology. One of the best known drugs based on the thiadiazole molecule is acetazolamide (Acetazola®, **1**) (Aldrich , 1986) , which is a carbonic anhydrase inhibitor, and used in the chemotherapy of glucoma, epilepsy and congestive cardiac failure. Several workers reported the importance of some thiadiazole derivatives as antihypertensive and anticonvulsive agent. It has been reported also that 2-aminothiadiazole attached to the phenyl sulfonyl group (Derwent , 1994) exhibited a potent biological activity like: (Sulfameti®, **2**)

as antimicrobial agent , (Trifuorm®, **3**) as diuretic agent and (Methidath®, **4**) as insecticide. Additionally, some 1,2,4-triazolo-1,3,4-thiadiazole derivatives (Mihele et. al. , 1994) (Al-Younis , 1990)



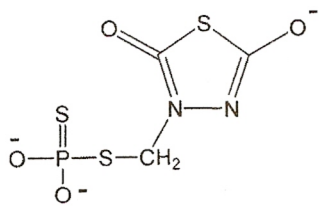
1

(Acetazol : Epilepsy , Gloucoma) Congestive Cardiac-Failure



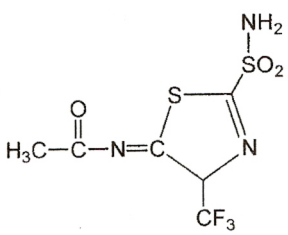
2

(Sulfameti : Urinary-tract Infection)



3

(Methidath : Indsecticides)



4

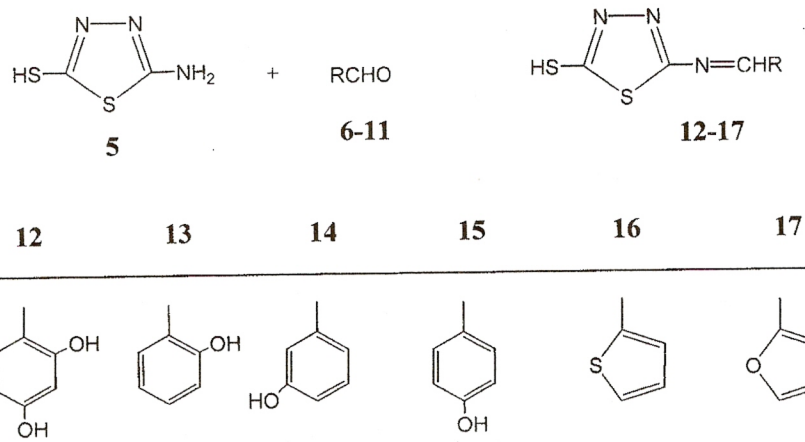
(Trifluorm : Diuretics)

showed remarkable activity against *Escherichia coli, Staphylococcus aureus* and *Candida albicans* as well as effective antifungal agents (Joule and Smith , 1972) (Suman and Bahel , 1979). Recently, thiofunctionalization of some 2-amino-5-mercapto-1,3,4-thiadizole derivatives has been reported (Al-Masoudi et. al , 1993). In 1996, Kornis (Kornis , 1996) has reviewed widely the chemistry of 1,3,4-thiadiazoles including the biological activity of such interesting compounds. Our aim here is to synthesize some schiff's bases of 1,3,4-thiadiazole derivatives and evaluation of their antibacterial activity in comparison to the above known biological active thiadiazole derivatives by studying the structure-activity relationship (SAR).

Results and Discussion

Treatment of the thiadiazole 5 with different aldehydes **6-11** in boiling ethanol gave, after purification from recrystallization or short column of silica gel, the pure imino derivatives **12-17** in 70 - 83% yield, as crystalline compounds (scheme 1). The structures of these products were established from their elemental analysis, mass mcasurmcnts and ^{1}H NMR spectra. All the NMR spectra were characterized by the presence of SH group at ~δ14.0, since the imino proton (H-1') is appreared at ~δ 8.0. The thiophene protons were assigned from their HMQC experiment (Silverstein and Webster , 1998) and 2D NMR spectra. The aromatic protons signals appeared in the region at ~ δ 8.7 - 7.3.

Scheme 1



Biological activity :

The antimicrobial activity of the prepared compounds **12-17** was determined by the agar diffusion method (Perez et. al , 1990). A 0.1% solution of the tested compounds in propylene glycol was used. The microorganisms used were *Staphylococcus aureus, Escherichia coli* and *Ps. aeruginosa.* A 0.1% solution of streptomycin in propylene glycol was used as a standard. Thus, sterile nutrient agar (oxide) was inoculated with the

tested organisms. Three drops of the solution of the tested compounds were separately place in cups (8 mm diameter) cut in the agar medium. The plates were incubated at 37°C for 24 h. The resulting inhibition zones were measured. Under these conditions, the prepared compounds showed slightly or no activity against the above mentioned organisms, except compound **16** exhibited slight activity against S.*aureus* (inhibition zone diameter = 12mm), and against *E. coli* (7 mm), but no activity against *Ps aeruinosa,* whereas the inhibition zones exhibited by streptomycin against the same organisms were 29, 25 and 13 mm respectively. In conclusion with structure-activity relationship (SAR), it has been found that the linkage of the imino group with the thiadiazole backbone will not increase the potency of the new products toward the growth inhibition of the microorganisms, unless in case of the thiophene derivatives which showed interesting biological activity in similar analogues.

Experimental :

General. Melting points are uncorrected. NMR spectra were acquired with a Bruker DRX 600 (^{1}H : 600.13 MHz, ^{13}C : 150.91 MHz) and AC-250 spectrometers. The chemical shifts (δ_{H}, δ_{C}) are referenced to tetramethylsilane (TMS) as internal standard. Spectra were acquired at 300 K.

Preparation of the 2-imino derivatives of 3-mercapto-l,3,4-thiadiazole.

General procedure. A mixture of the aldehyde compound (5.0 mmol) in dry ethanol (50 ml) and the thiadiazole derivative **1** (5.6 mmol) was heated under reflux for 5 h. Then the mixture was evaporated and the residue was purified by recrystallization from ethanol or from short column of silica gel, using chloroform-methanol 4: 1 as eluent.

2-[(2,4-Dibydroxyphenyl-1-yl)-imino]-5-mercapto-l,3,4-thiadiazole (12).

From 2,4-dihydroxybenzaldehyde **6** (0.69 g). Yield: 1.26 g, 83%; m.p.225-228 °C. δ_H ($CDCl_3$): 14.0 (s, 1H, SH); 8.60 (d, 1H, J 5.4 Hz, ArH); 8.10 (5, 1H, H-1', (N=CH)] ; 7.77 (5, 1H, ArH); 7.64, 7.45 (2s, 2H, 2,4-OH); 7.34 (d, 1H, J 5.5 Hz, ArH). Anal. Calc. for $C_9H_7S_2N_3O_2$(253.3): C,42.68 ; H, 2.79 ; N,16.59. Found: C,42.43 ; H,2.70 ; N,16.32. MS: m/z 253 (M^+).

2-[(2-Hydroxyphenyl-1-yl)-imino]-5-mercapto-1,3,4-thiadiazole (13).

From 2-hydroxybenzaldehyde **7** (0.61 g). Yield: 1.05g , 75% , m.p. 229-232 °C. δ_H ($CDCl_3$): 14.2 (s, 1H,SH) ; 8.58-7.31 (m, 7H, ArH, (N=CH), OH). Anal. Calc. for $C_9H_7S_2N_3O$: (237.3) : C, 45.55 ; H, 2.97 ; N, 17.71. Found: C, 45.31 ; H, 2.82 ; N, 17.52 MS: m/z 237 (M+).

2-[(3-Hydroxyphenyl-1-yl)-imino]-5-mercapto-1,3,4-thiadiazole (14).

From 3-hydroxybenzaldehyde **8** (0.61 g). Yield: 1.09g , 78% , m.p. 227-229 °C. δ_H ($CDCl_3$): 14.0 (s, 1H, SH) ; 8.51-7.30 (m, 7H, ArH, (N=CH), OH). Anal. Calc. for $C_9H_7S_2N_3O$: (237.3) : C, 45.55 ; H, 2.97 ; N, 17.71. Found: C, 45.27 ; H, 2.90 ; N, 17.50. MS: m/z 237 (M^+).

2-[(4-Hydroxyphenyl-1-yl)-imino]-5-mercapto-1,3,4-thiadiazole (15).

From 4-hydroxybenzaldehyde **9** (0.61 g). Yield: 1.11g , 80% , m.p. 232-235 °C. δ_H ($CDCl_3$): 14.0 (s, 1H, SH) ; 8.68 (d, 1H, J5.5 Hz, ArH) ; 8.47 (s, 2H, ArH) ; 8.11 (s, 1H, H-P , (N=CH)] ; 7.45 (s, IH, OH) ; 7.34 (d, 1H, J5.5 Hz, ArH). Anal. Calc. for $C_9H_7S_2N_3O$: (237.3) : C, 45.55 ; H, 2.97 ; N, 17.71. Found: C,45.26 ; H, 2.88 ; N, 17.49. MS: m/z 237 (M^+).

5-Mercapto-2-[(thiophen-2-yl)-imino]-1,3,4-thiadiazole (16).

From 2-carboxythiophene **10** (0.56g). Yield: 0.89g, 70%, m.p. 242-246°C. δ_H ($CDCl_3$): 14.42 (s, 1H, SH) ; 8.67 [d, 1H, H-2", J 1.0 Hz, (thiophene)] ; 8.57 [dd, 1H, H-4", J 4.2 Hz, 1.0 Hz, (thiophene)] ; 8.41 8d, 1H, H-5", J 1.0 Hz, (thiophene)] ; 8.00 (s, 1H, H-l', (N=CH)].□C ($CDCl_3$): 179.5 (C-5) ; 162.2 (C-2) ; 154.2 [C-2', (N=CH)] ; 138.8 (C-3") ; 136.4 [(C-2", (thiophene)] ; 128.7 [C-4", (thiophene)] ; 125.4 [C-5", (thiophene)]. Anal. Calc. for $C_7H_5S_3N_3$: (227.33) : C, 36.98 ; H, 2.22 ; N, 18.48. Found: C, 36.71 ; H, 2.17 ; N, 18.17. MS: m/z 228 (MH^+).

2-[(Furan-2-yl)-imino]-5-mercapto-l,3,4-thiadiazole (17).

From 2-carboxyfuran **11** (0.48 g). Yield: 0.83g, 70%, m.p. 238-241 °C. 13.16 (s, 1H, SH) ; 7.82 [s, IH, (N=CH)] ; 7.51 [dd, 1H, $J_{3",4"}$ = 3.5 Hz, $J_{3",5"}$ = 0.9 Hz, H-3", (furyl)] ; 7.35 [dd, 1H, H-4",(furyl)] 6.21 [dd, 1H, H-5", (furyl)]. Anal. Calc. for $C_7H_5S_2N_3O$: (211.3) : C, 39.80 ; H, 2.39 ; N, 19.39. Found: C,39.62 ; H, 2.29 ; N, 19.09. MS: m/z 211 (M^+).

Acknowledgement :

The authors would like to thank Dr. M. Eherman, of faculty of Biology, University of Konstanz, Germany, for the antibacterial screening, Miss A. Friemel for the NMR (COSY, ROSEY, HMQC) experiments, and Mr. Hägele of University of Konstanz for the mass measurments.

References

Aldrich (1986) , "Catalog Handbook of Fine Chemicals" Aldrich chemical company , Inc. USA.

Al-Masoudi, N.A. ; Al-Shaibani, I.S. ; Al-Masoudi, W.A. (1993) , "Thiofunctionalization of some 2-amino-5-mercapto-1,3,4-thiadiazole

derivative" ; Mu'tah Journal for Research and Studies (Jordan) , 8(1) : 21-28.

Al-Younis , Najla Kadhim (1990) , "Synthesis, Spectroscopic and Biological Study of Some Derivatives of 2-amino-5-mercapto-1,3,4-thiadizole" ; M.Sc. thesis , University of Basrah-Collage of Science.

Derwent (1994) "The DERWENT standard drug file of known drug's" Derwent , London.

Mihele, Denisa ; Cristea , Elena ; Zuchi , Gheorghe "Studies on the effects of a new azomethyne : O-hydroxybenzilidine-2-amino-5-R-mercapto-1,3,4-thiadizole on some biochemical constants" ; Farmacia , 42(1-2) : 27-32.

Kornis, G.I. (1996) , "1,3,4-Thiadiazoles in comprehensive heterocyclic Chem. : A review of the lit" ; 1982-1995 , Storr. R.C. Pergamon. Vol.4 P.379.

Joule, J.A. ; Smith, G.F. (1972) "Heterocyclic Chemistry" ; Van Nostrand Reinhold , London.

Perez, C. ; Pauli, M. and Bazerque, P. (1990) , "An antibiotic assay by the agar-well diffusion method" ; J.Actabiologiae , 15 : 113-115.

Silverstein, Robert, M. ; Webster, Francis, X. (1998) , "Spectrometric Identification of Organic Compounds" sixth edition , John Wiley & Sons Inc. , New york.USA.

Suman, S.P. and Bahel , S.C. (1979) , "Synthesis of 2-aryl amino-5-aryl/aryloxy methyl-1,3,4-oxadiazoles, 2--aryl amino-5-aryl aryloxy methyl-1,3,4-thiadiazoles, N_1-aryl/ aryloxy acetyl-3,5-dimethyl pyrazoles and N_1-aryl/aryloxy acetyl-3-methyl-5-pyrazolon as possible fungicides" ; J.Indian Chem. Soc. , Vol. LVI : 374-376.