Synthesis of 1, 2, 4- Triazole Derivatives And Their Biological Activity Study

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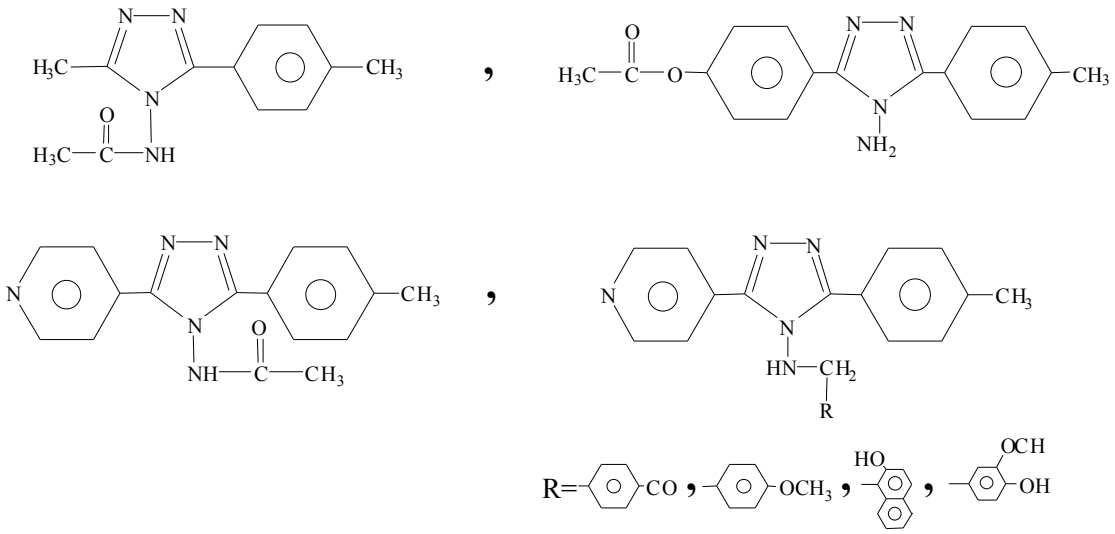
Abstract

This study includes the synthesis of new derivatives of 1, 2, 4- Triazole which are contain Schiff bases derived from 1, 4, 5, 6- tetrahydropyrimidine. The structures of these derivatives were characterized from their melting points, infrared spectroscopy and elemental analysis. These derivatives were tested for inhibition of E-coli and were all found to be active.

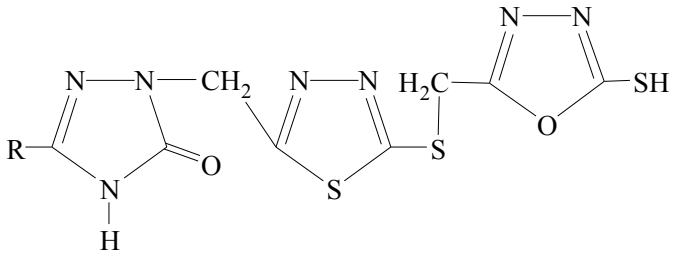
Introductions

The synthesis of 1. 2, 4- triazole derivatives has attracted widespread attention due to their diverse biological activities, including antimicrobial, anti- inflammatory, analgesic, and antitumoral [1-7]. Nurhan et al [8] have prepared some new 1, 2, 4- Triazole derivatives with antimicrobial activity [Figure 1].



[Figure 1]

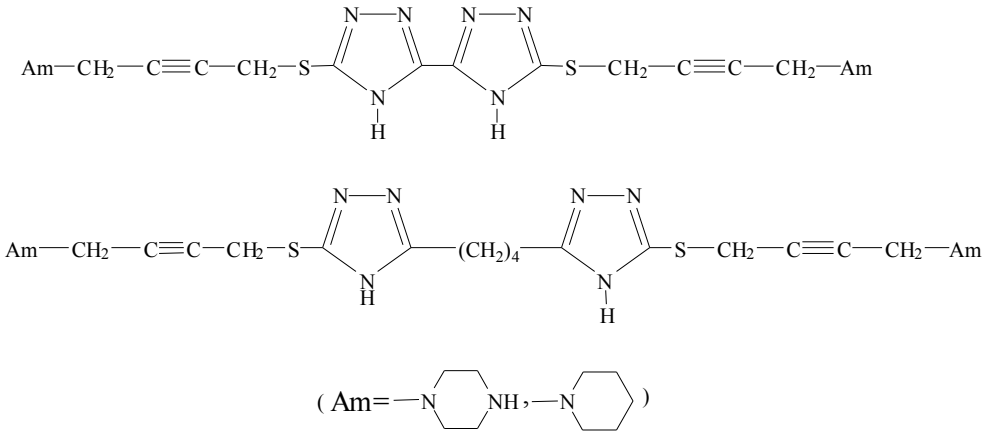
Neslihan [9] has synthesized compounds incorporating both 1, 2, 4- triazole and 1, 3, 4-thiadiazole due to their possible diverse pharmacological properties [Figure 2].



R= - CH_3 , -CH_2 Ph , -Ph

[Figure 2]

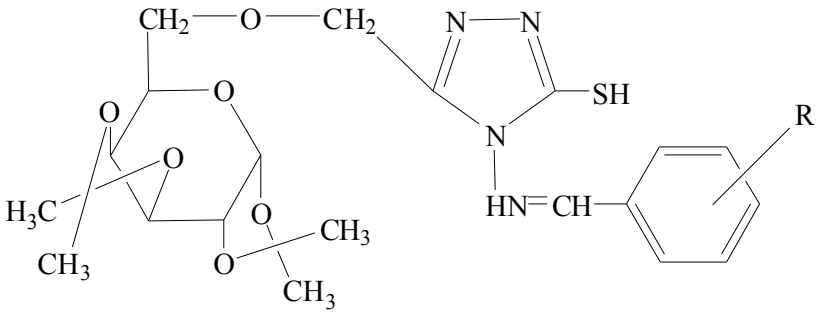
Abeer [10] has synthesized different derivatives of bis- 1, 2, 4-triazole of possible biological activity [Figure 3]



[Figure 3]

Biocidal activity of Schiff bases have also been well established. These have been attributed to the toxophoric C=N linkage in them [11].

Amina [12] has synthesized different heterocyclic compounds derived from D-galactose incorporatoring both 1, 2, 4- trizole and Schiff bases [Figure 4]. These derivatives were tested for inhibition of E-coli and Staphylococcus and were all found to be active.



R= (P-MeC_6H_4,P-$Me_2NC_6H_4$, m-$O_2NC_6H_4$)

[Figure 4]

In this study new derivatives of 1, 2, 4- triazole which are contain schiff bases were synthesized and study their biological activity.

Experimental

Materials

All chemical used were supplied from Riedel- De Haen AG, BDH chemicals, Acros Organics, Janssen chemical, Merk chemicals Fluska AG and Hopkin and Wiliams. Elemental analyzer were carried out by using Carlo Erba / Mod 1106, Infrared spectra were recorded using Shimadzu 408 (KBr disc) and melting points were recorded using Electrothermal melting point apparatus. The biometrials were obtained from Biomerieux Ltd.

Synthbesis of 1, 4, 5, 6- tetrahydropyrimidine-2- thiol. 1

Compound 1 was used as starting material, this derivative was prepared by dissolving1,3- diaminopropane (1 ml) in ethanol (10 ml) and carbon disulphide (2 ml) was added. The mixture was stirred for (15) minutes then refluxed for (3) hrs, the mixture was cooled to room temperature, then the white precipitate was formed filtered and recrystallized from ethanol to give 1.

Synthesis of 3, 4, 5, 6- Tetrahydropyrimidine-2- thioacetic acid. 2

Compound 1 (3g, 25.86 mmol) and sodium hydroxide (1.9, 27.5 mmol) were dissolved in ethanol (25 ml) and refluxed for (2h). A solution of chloroacetic acid (2.44 g, 25.82 mmol) in ethanol (15 ml) was added. The reaction mixture was stirred for (24 hrs). The white precipitate was filtered and recrystallized from ethanol to give 2.

Synthesis of 3, 4, 5, 6- Tetrahydropyrimidine- 2- methylthioacetate. 3

Compound 2 (5g, 28.73 mmol) was dissolved in acetone (100ml) and anhydrous sodium carbonate (3g, 28.3 mmol) was added. The mixture was refluxed for (1h). Dimethylsulphate (3.5 ml) was added and the mixture was further refluxed for (24 hrs). The solvent was removed under pressure and the residue diluted with water and extracted with ethylacetate (2x30 ml). The Organic layer was dried and removed to give 3 as solid.

Compound 3 was recrystallized from ethanol: water (8:2).

Synthesis of 3, 4, 5, 6,-Tetrahydropyrimide- 2- thioacetichydrazide. 4

Compound 3 (3g, 15.95 mmol) and hydrazine hydrate (15 ml) were dissolved in ethanol (25 ml). The reaction mixture was refluxed for (24 hrs). The precipitate which separated on cooling was filtered and recrystallized from ethanol to give 4.

Synthesis of 3, 4, 5, 6- Tetrahydropyrimdine- 2- thiomethylpotassiumxanthate. 5

To a mixture of potassium hydroxide (0.9 g, 16.07 mmol) and compound 4 (3g, 15.95 mmol) in absolute ethanol (25 ml), carbon disulfide (1.5 ml) was added. The reaction mixture was diluted with ethanol (25 ml) and stirred over night at room temperature. It was them diluted with dry ether (30 ml) yielding a pale yellow precipitate which was filtered, washed with ether and dried at room temperature to give the potassium salt 5 in quantitative yield. The product was utilized in the next step without further purification.

Synthesis of 2- [5- Mercapto- 4. Amino-1, 2, 4-triazo-3-yl] thiomethyl-3, 4, 5, 6-tetrahydropyrimdine. 6

The potassium salt 5 (2g, 6.62 mmol) was suspended directly in hydrazine hydrate (98%, 5 ml) and heated under reflux for (3hrs). The mixture was cooling, diluted with water (75 ml) and filtered. The filterate was neutralized with (10 %) HCl The precipitate formed was filtered, dried and recrystallized from ethanol to give 6 as solid.

Synthesis of 2- [Mercapto-4-arylidineimino-1, 2, 4-triazol-3-yl]- thiomethyl-3, 4, 5, 6-tetrahydropyrimdine. (7-11)

General procedure:

A hot ethanolic solution of compound 6 (3g, 12.29 mmol) was mixed with a solution of the selected aldehyde (12.29 mmol) in (25 ml) ethanol.

The resulting mixture was then refluxed for (3 hrs). The product was filtered and recrystallized from ethanol.

Results and Discussion

The Strategy used for the Synthesis new derivatives of 1, 2, 4-triazole was started with derivatve 1 in a series of reactions.

[Scheme 1]. Compound 1 was synthesized from the reaction of 1, 3- diaminopropane with carbon disulphide [13]. The IR spectrum of 1 showed stretching bands at 3220 cm^{-1}, 1050 cm^{-1} and 1625 cm^{-1} for (NH), (C=S) and (C=N) respectively. Tables (1) and (2) showed the characteristic IR absorption bands and physical properties for all new derivatives.

Treatment of compound 1 with chloroacetic acid in basic medium under reflux gave 2. The IR spectrum of compound 2 showed the disapperance of stretching band at 1050 cm^{-1} for thion group with apperance of stretching band at 1660 cm^{-1} for (C=O) group respectively.

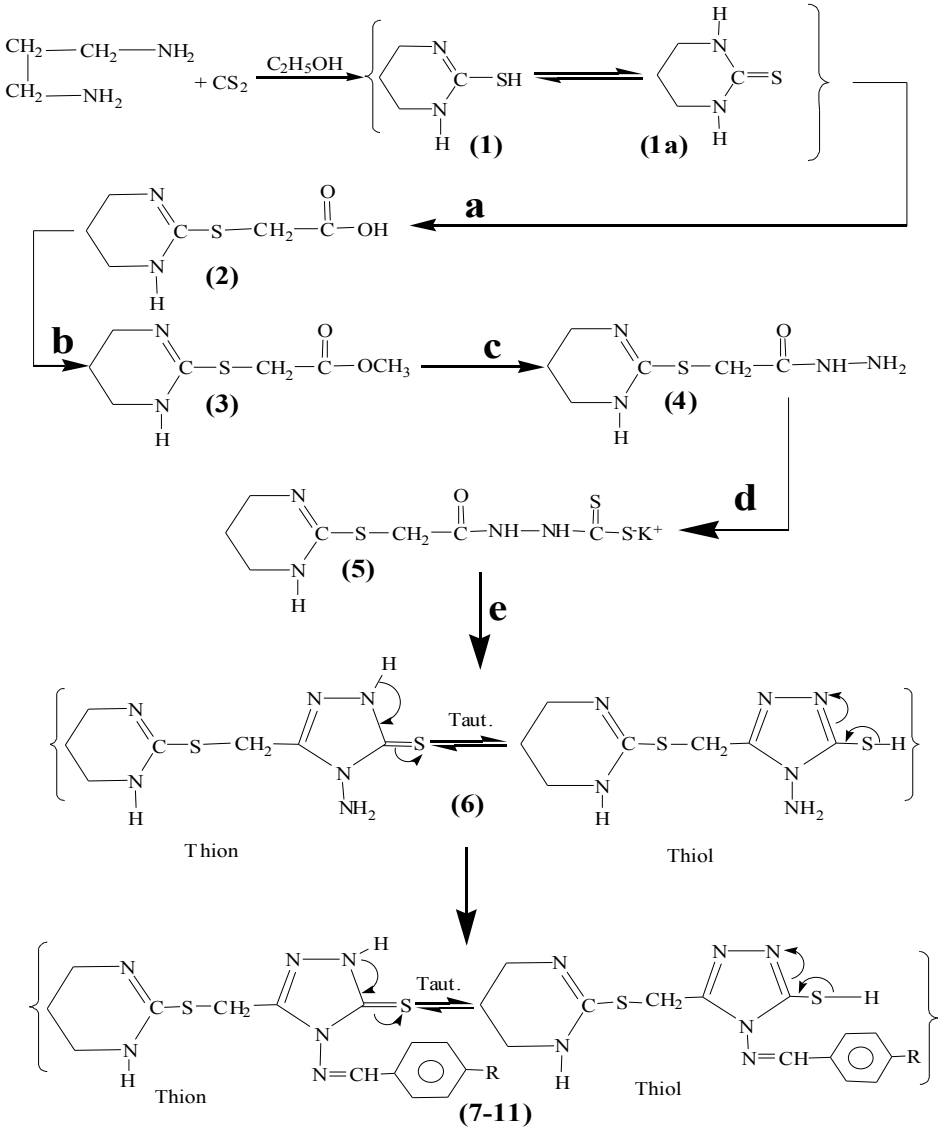
Compound 3 was synthesized by the reaction of compound 2 with dimethylsulphate in aceton. The IR Spectrum of 3 showed the disapperance of stretching broad band of (OH) group at (3200-2300) cm^{-1} with apperance of (C=O) group at 1720 cm^{-1} which is displacement to high frequency. Gatterman method [14] was used for the synthesis of

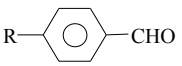
derivative 4. The IR Spectrum of 4 showed the displacement of (C=O) group to low frequency at 1675 cm^{-1} with apperance of stretching band at 3355 cm^{-1} for (NH_2) group. The salt 5 was indicated by its solubility and infrared spectrum which showed multiple (NH) stretching bands at (3300-3100) cm^{-1}, a stretching band at 1640 cm^{-1} due to amide group. The spectrum, also showed absorption at1055 cm^{-1}, 1215 cm^{-1} which is attributed to (C=S) and (N-N) stretching vibrations respectively.

The cyclization of 5 to 6 could be accomplished by the suggested steps [15] in [Scheme 2]. The IR spectrum of compound 6 showed a split broad band at 3360 and 3210 cm^{-1} which was assigned to the asymmetric and symmetric stretching bands of (NH_2 and NH) groups respectively. The IR spectrum also showed a bending band at 1645 cm^{-1} for (NH) group, stretching band at 1595 cm^{-1} for (C=N) endocylic, appearance band at 1496 cm^{-1} due to (-N-C=S) toutomeric [Figure 5]. The compounds 7-11 were synthesized from the reaction of compound 6 with different substituted benzaldehydes in para position. The IR spectra of these derivatives showed the disappearance of stretching bands due to (NH_2) of the triazole and (CO) group of different substituted benzaldehydes with appearance of stretching band in the range (1610- 1650) cm^{-1} attribute to the imine group.

Compound 7-11 exhibited a biological activity against E-coli bacteria. Compound 11 exhibited higher degree of activity than the others Table (3).

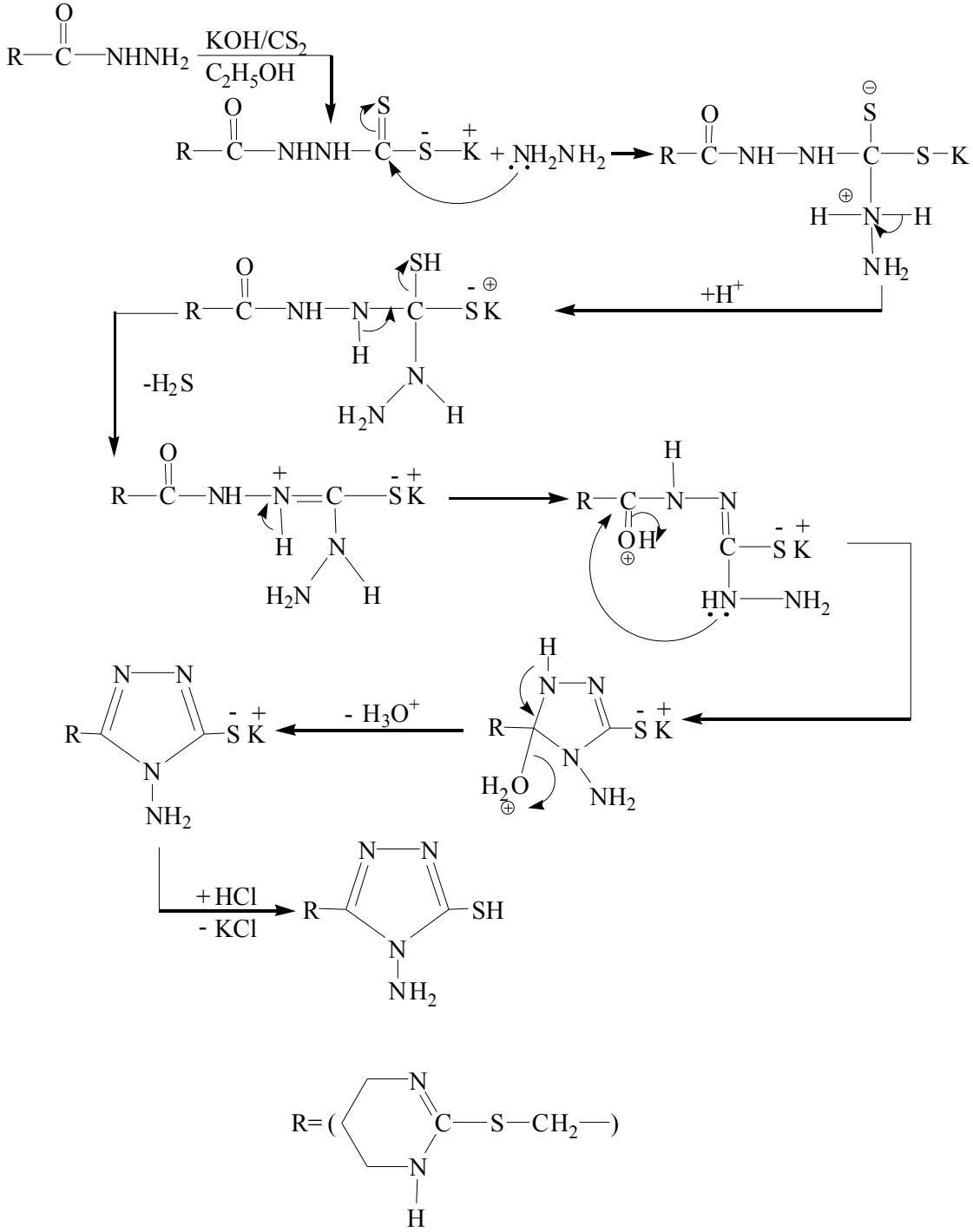
[Scheme 1]



a: $ClCH_2COOH$, NaOH, C_2H_5OH.
b: Na_2CO_3, $(CH_3)_2SO_4$, Acetone.
c: NH_2-NH_2, C_2H_5OH.
d: CS_2, C_2H_5OH, KOH.
e: NH_2-NH_2. H_2O (98%).
f:  , C_2H_5OH

Where R=	H	Me	MeO		CN
Compound No.	7	8	9	10	11

[Scheme 2]



References

1: Neslihan, D.; Ahmet, D.; Sengul, A.and Sancak, K. (2004), "Synthesis and antimicrobial activities of some new 1,2,4-triazolre derivatives", Eur. J. Med. Chem. 39:793-804.

2: Neslihan, D.; Ahmet, D.; Sengul, A., and Elif. C. (2005) "Synthesis and antimicrobial activities of some new [1,2,4] triazolo [3,4-b] [1,3,4] thiadiazines" ARKIVOC (i). 75-91. Antimicrobial activities", ARKIVOC (i), 75- 91.

3: Neslihan, D.; Ahmet, D.and Sengul, A. K. (2005), "Synthesis and biological activity of new 1,2,4-triazol-3-one derivatives", Russian J. Bioorg. Chem. 39: 387- 97.

4: Sabir, H.; Gyoti, S.and Mohd, H. (2008), "Synthesis and antimicrobial activities of 1,2,4-triazole and 1,3,4-thiadiazole derivatives of 5-amino-2-hydroxybenzoic acid", E. J. Chem. 5 (4), 963- 968.

5: Aiyalu, R. and Kalasalingam, A. R. (2009), "Synthesis of some novel triazole derivatives as anti-nociceptive and anti-inflammatory agents", 59: 355- 364.

6: Mudasir, R. B.and Abdul, R. (2009), "Substituted 1,2,4-triazoles and thiazolidinonce from fatty acids: Spectral Charterization and antimicrobial activity", Indian J. Chem., 48 B, 97-102.

7: Malii, R. R.; Somani, R. R.; Toraskar, M. P.; Mali, K. K.and Shirodkar, P. Y. (2009) "Synthesis of some antifungal and Anti-tubercular 1,2,4-triazole analoges", Int. J. Chem Tech Res., 1 (2). 168-173.

8: Nurhan, G.; Mevlut, S.; Elif, C.; Ali, S.and Neslihan, D. (2007), "Synthesis and antimicrobial activity of some new 1,2,4-triazole derivatives", Turk. J. Chem. 31: 335-348.

9: Neslihan, D. (2005) "Synthesis and characterization of new trihetrocyclic compounds consisting of 1,2,4-triazol-3-one, 1,3,4-thiadiazole and 1,3,4-oxadiazole rings", Turk. J. Chem. 29:125-133.

10: Abeer, J. H. (2002), "Synthesis and antimicrobial evolution of some new bis-1,3,4-oxadiazole, bis-1,2,4-triazole and bis-1,3,4-thiadiazole derivatives", M. Sc. Thesis, College of Education/ Ibn Al-Haitham Baghdad University, 29-34.

11: Hodett, E. M. and Dunn, W. D. (1970), "Structure – antitumor activity correlation of some Schiff bases". J. Med. Chem., 13(4):768- 771.

12: Amina, A. F. (2008). "Synthesis of new heterocyclic compounds derived from D-glactose and evolution of their biological activity of these derivatives" Ph. D. Thesis, College of Education/ Ibn Al-Haitham, Baghdad University; 38-47

13: Brown, D. J.and Evans, R. F. (1962), "hydropyrimidines. Part I. 1,4,5,6-Tetrahydropyrimidine and its derivatives", J. Chem. Soc. 527- 533.

14: Gatterman, L.and Weiland, H. (1952), "Laboratory methods of organic chemistry", Macillon Co. P. 135.

15: Hoggarth, E. (1952), "2-benzolyldithiocarbazinic acid and related compounds" J. Chem. Soc., 4811- 4817.

Table (1): Characteristic IR absorption bands of the new derivatives

Compound No.	Infrared data ($\upsilon_{max}cm^{-1}$) (KBr disc)
1	(NH) 3220; (C=S) 1050; (C=N) 1625.
2	(NH) 3215; (OH) (3200-2300); (C=O) 1660; (C=N) 1620.
3	(NH) 3230; (C=O) 1720; (C=N) 1620.
4	(NH_2) 3355; (NH) 3215; (C=O) 1675; (C=N) 1615.
5	Multiple (NH) (3300- 3100); (C=O) amide 1640; (C=N) 1615; (C=S) 1055; (N-N) 1215.
6	(NH_2) 3360; (NH) 3210; (NH) bending (1645); (C=N) 1595; (-N-C=S) 1496; (C=S) 1055.
7	(NH) 3225; (C=S) 1055; (C=N) 1640; (C=C) (1590); (-N-C=S) 1490; (C=C) bending 820.
8	(NH) 3230; (C=S) 1050; (C=N) 1630; (C=C) 1600; (-N-C=S) 1495. (C=C)bending 815.
9	(NH) 3220; (C=S) 1050; (C=N) 1650; (C=C) 1595; (-N-C=S) 1495; (C=C) bending 820.
10	(NH) 3225; (C=S) 1050; (C=N) 1650; (C=C) 1610; (-N-C=S) 1495; (C=C) bending 835.
11	(NH) 3230; (C=S) 1055; (C=N) 1625; (C=C) 1595: (-N-C=S) 1495; (C=C) bending 830.

Table (2): Physical properties for derivatives

Compound No.	Formula	Melting point C°	Elemental analysis calculated (Found)			Yield %
			C%	H%	N%	
1	$C_4H_8N_2S$	210	41.37 (41.22)	6.89 (6.68)	24.13 (23.98)	78
2	$C_6H_{10}N_2O_2S$	172	41.37 (41.05)	5.74 (5.52)	16.09 (15.88)	82
3	$C_7H_{12}N_2O_2S$	188	44.68 (44.8)	6.38 (6.07)	14.59 (14.71)	77
4	$C_6H_{12}N_4OS$	231	38.29 (38)	6.38 (6.11)	29.78 (29.56)	91
6	$C_7H_{12}N_6S_2$	240	34.42 (34.22)	4.91 (4.9)	34.42 (34.61)	65
7	$C_{14}H_{16}N_6S_2$	227	50.60 (50.92)	4.81 (4.53)	25.30 (24.98)	88
8	$C_{15}H_{18}N_6S_2$	235	54.21 (53.99)	5.20 (5.18)	24.27 (24.45)	95
9	$C_{15}H_{18}N_6OS_2$	196	49.72 (49.49)	4.97 (5.11)	23.02 (22.88)	78
10	$C_{16}H_{21}N_7S_2$	218	51.20 (51.00)	5.60 (5.82)	26.13 (26.33)	80
11	$C_{15}H_{15}N_7S_2$	226	50.42 (50.61)	4.20 (3.92)	27.45 (27.54)	96

Table (3): Effect of antimicrobial agents on Escherichia Coli

Compound No.	Effect of new derivatives on the growth of E-coli Bacteria											
	1	0.9	0.8	0.7	0.6	0.5	0.4	0.3	0.2	0.1	0.09	Concentration gm/ml
7	-	-	-	-	-	+						
8	-	-	-	-	-	-	+					
9	-	-	-	-	-	-	-	-	-	+		
10	-	-	-	-	-	-	-	-	+			
11	-	-	-	-	-	-	-	-	-	-	+	
Blank	+											

(-) No growth

(+) Growth

تحضير مشتقات جديدة لـ 4،2،1- ترايزول ذو فعالية بايولوجية محتملة

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الخلاصة

تم في هذا البحث حضرت مشتقات جديدة من مركبات 1، 2، 4- ترايزول تحتوي على قواعد شف. حضر المشتق رقم 1 من مفاعلة المركب 1، 3- ثنائي امين بروبان مع ثنائي كبريتيد الكاربون. استخدم المشتق رقم 1 مادة ابتدائية لتحضير مشتقات 1، 2، 4- ترايزول بعد مروره بسلسلة من التفاعلات وصولا الى المشتق6. ثم مفاعلة المشتق 1 مع حامض كلوريد الخليك في وسط قاعدي ،اذ اعطى المشتق 2 الذي عومل بدوره مع كبريتات ثنائي المثيل، اذ اعطى المشتق 3. المشتق4 حضر من معاملة المشتق 3 مع الهيدرازين بوجود الكحول مذيبا. المشتق 5 حضر من مفاعلة المشتق 4 مع ثنائي كبريتيد الكاربون. عومل ملح الزانثيت 5 مع الهيدرازين ،اذ اعطى المشتق 6 الذي عومل بدوره مع انواع عديدة من الالديهايدات المختارة ليتم الحصول على مشتقات لقواعد شف من 7-11. درست الفعالية البايولوجية للمشتقات من 7-11 ضد بكتريا القولون وكان اكثرها فاعلية هو المشتق 11.