Synthesis And Biological Activity Of Some New Compounds Containing 1,2,4-Triazole And Their Derivatives

تحضير ودراسة الفعالية البايولوجية لبعض المركبات الجديدة ومشتقاتها التي تحتوي على حلقة 1،2،4- ترايزول

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الخلاصة //

حضر المركب [1] 1,2-Ethane-bis-4-oxybenzoic عن طريق تكاثف المركب 2,1 ثنائي برومو أيثان مع بارا هيدروكسي بنزويك اسد وبتفاعل المركب [1] مع الثايونيل كلورايد يتكون المركب [2] 1,2-Ethane-bis-4-oxybenzoyl chlorideويتفاعل الاخير مع الثايوسيكاربازايد يعطي المركب [3] 1,2-Ethane-bis[4-oxybenzoyl-thiosemicarbazide]وتم الحصول على المركب [4] 1,2-Ethane-bis[3-Mercapto-5-phenoxy-1,2,4-triazole]من معاملة المركب [3] مع محلول [4%] من هيدروكسيد الصوديوم. المركبات الجديدة [5 a-d] 1,2-Ethane-bis[3-(substituted thioacyl)-4-(substituted acyl)-5 phenoxy-1,2,4-triazole] و [5e-f] 1,2-Ethane-bis[3-(substituted alkyl thio)-5 phenoxy-1,2,4-triazole]المشتقة من المركب [4] تم تحضيرها وتشخيصها فيزيائياً وطيفياً. وتم دراسة الفعالية الحيوية لها حيث أظهرت أغلب هذه المركبات الفعالية الحيوية تجاه البكتريا المستخدمة بنوعيها بكتريا القولون (G-) والبكتريا المعوية (G-).

Abstract

Condensation of 1,2- dibromo ethane with para hydroxy benzoic acid gave 1,2-Ethane-bis-4-oxybenzoic [1]. This Compound was converted with the thionyl chloride to give 1,2-Ethane-bis-4-oxybenzoyl chloride [2]. Reaction of compound [2] with thiosemicarbizades gave 1,2-Ethane-bis[4-oxybenzoyl-thiosemicarbazide] [3] and opteined 1,2-Ethane-bis[3-mercapto-5-phenoxy-1,2,4-triazole] [4] from treatment compound [3] with NaOH (4%) .The new compounds 1,2-Ethane-bis[3-(substituted thioacyl)-4-(substituted acyl)-5 phenoxy-1,2,4-triazole] [5a-d] and 1,2-Ethane-bis[3-(substituted alkylthio)-5 phenoxy-1,2,4-trizole] [5e-f] derived from compound [4] were synthesized and characterized by physical and spectral data. All the compounds [4], [5a-d] and [5e-f] have been screened for antibacterial activity against Escherichia coli (G-) and Enterobacter (G-). Most of compounds were found to be active antibacterial.

Introduction

1,2,4- triazole and its derivatives represent one of the most biologically active classes of compounds. The derivatives of 1,2,4- triazole exhibited anti – inflammatory (1) antiviral (2) analgesic (3) antimicrobiol (4) anticonvulsant (5) and antidepressant activites (6). Aseries of 1,2,4-derivatives have been patented and extensively employed in agriculture (7). Many workers have reported of organic compounds containing triazole ring (8,9). As well as A.Hussain etal (10) reported many compounds with triazole ring. Further more, Rou'll (11) synthesised and characterization of a novel series of compounds, polymers containing 1,2,4- triazole unit. Many

workers synthesises and studied the antimicrobiol activity of some compounds containing 3- thiol triazole ring (12).

Recently synthesied and characterized of some compounds containing 1,2,4 trizole ring (13,14).

In This work, I report the synthesis of some new compounds containing two hetrocycllic ring [3 substitued- 1,2,4- trizole] and their derivatives through the intramolecular cyclization of disubstituted thiosemicarbazide.

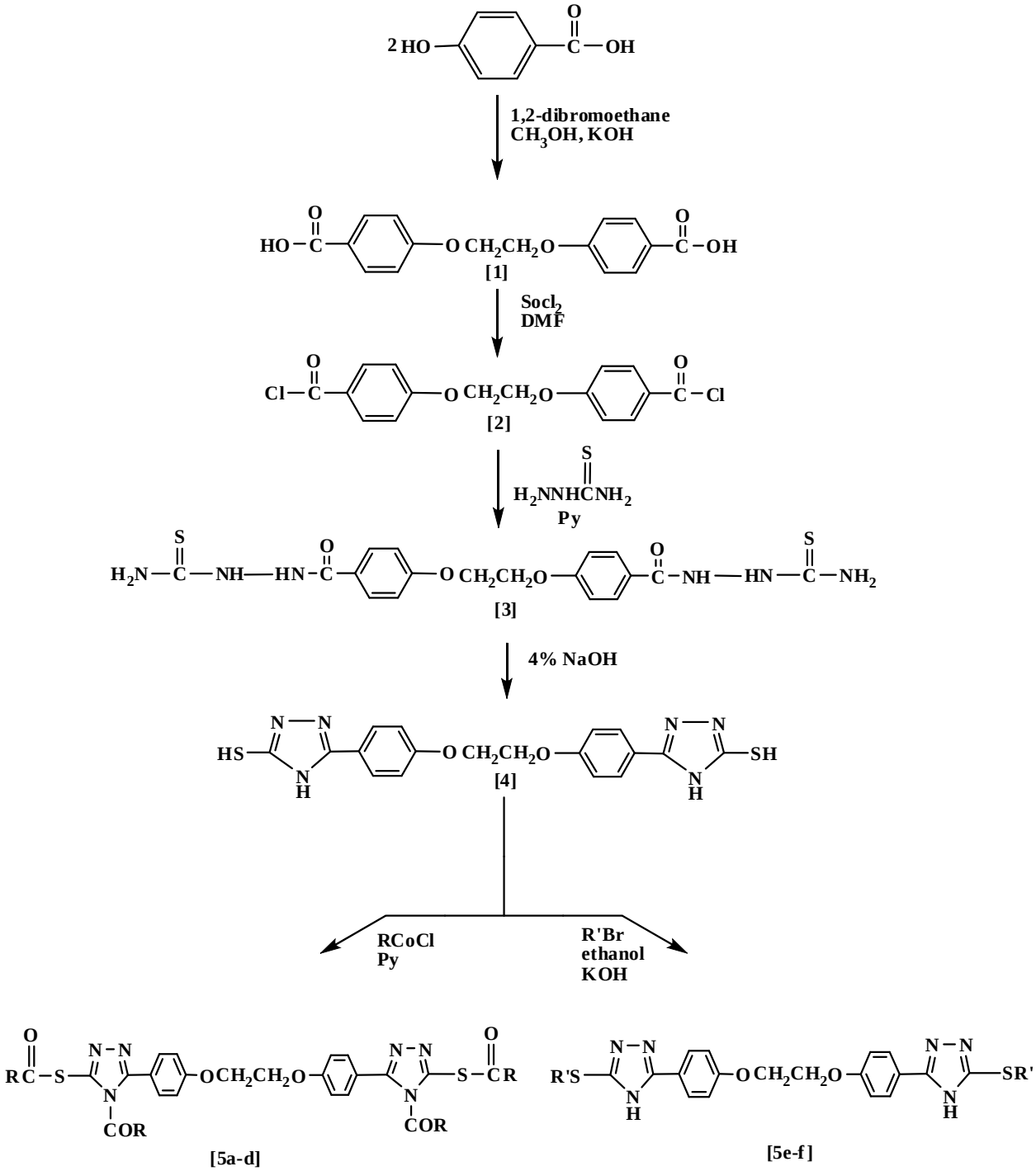
Experimental

Materials: Most of chemicals used were supplied from Fluka and BDH chemicals Co. and used without Further purification.

Techniques: uncorrected melting points were determined by using an Electrothermal melting point apparatus. FTIR spectra were recorded on a 21- Shimadzu spectrophotometer by using potassium bromide disc. UV spectra were performed on CECIL 7200 England spectrophotometer using DMSO as asolvent.

Synthesis

The reaction pathway used to prepare compounds [5a-d] and [5e-f] are shown in scheme (1).



R= ph, p-CH_3oph, p-O_2Nph, m-Iph

R'= $(CH_3)_2CH$ - , n-C_4H_9

Scheme (1)

1,2-Ethane-bis-4-oxybenzoic [1]

4-Hydroxy benzoic acid (11.25 g, 0.10 mol) was dissolved in 75 ml of methanol. After the acid was dissolved, A(0.46 Mol,26.24 g) of potassium hydroxide that dissolved in 20ml of distilled water was added dropwise. The mixture was reflux than a (0.05 mol) of 1, 2- dibromo ethane was added over (2) hours. The reaction mixture was refluxed for 24 hrs. A 50 ml of methanol was removed by evaporation, than a (250 ml) of distilled water was added.A (25 ml) of hexane was added to extract organic impurities. After discarding the organic phase, the aqueousphase was heated to 40°C and neutralized with 20% HCl. Product was collected by filtration and recrystallization from ethanol.

Yield 85%, M.P= 240°C

FTIR (cm^{-1},γ): 1678(C=O), 1168-1300(C-O-C).

1,2-Ethane-bis-4-oxybenzoyl chloride [15][2]

Diacid chloride [2] was prepared by refluxing the dicarboxylic acid [1] with excess of thionyl chloride in presence of 3 drops of DMF, unreacted thionyl was removed under reduced pressure and the diacid chloride was distilled under reduced pressure and Kept under N_2 atmosphere. Yield 98%.

1,2- Ethane-bis [4-oxybenzoyl-thiosemicarbazide] [3]

To astirring solution of thiosemicarbazide (0.91 g, 0.01 mol) in dry pyridine 15 ml, at-5°C. a compound [2] (1.69 g, 0.005 mol) was added dropwise. The stirring was continued for half an hour at-5°C and then overnight at room temperature. The solvent was evaporated. To the residue water 30 ml was added. The precipitate was filtered and recrystallized from ethanol

Yield 85%, M.P= 210°C

FTIR (cm^{-1},γ): 1616 (C=O amid),3471, 3414, 3244 (N-H of CoNH, NH_2), 1180 (C=S).

1,2-Ethane-bis [3-mercapto-5-phenoxy-1,2,4-triazole] [4]

A stirring solution of compound [3] (4.48g, o.o1 mol) and 10 ml 4% aqueous sodium hydroxide solution was refluxed for 4 hours. After that, the mixture was filltered and acidified with dilute hydrochloric acid. The precipitate was filtered and washed several time with water.

Yield 70%, M.P= 270°C

FTIR (cm^{-1},γ): 1635 (C=N), 1234 (C=S), 2357 (S-H), 3448 (N-H)

1,2-Ethane-bis[3-(substitutedthioacyl)-4-(substitutedacyl)-5phenoxy-1,2,4-triazole] [5a-d]

The compound [4] (0.001 mol) was dissolved in 5 ml of dry pyridin. The different acid chloride (0.0022 mol) was added slowly. The mixture was stirred for 3 hrs at room temperature. The reaction mixture was dissolved into 10% HCl, the solid separated than filtered, washed with distilled water and recrystallized from ethanol. The physical properties and UV data of the new synthesized are given in table (1).

[5a] FTIR (cm^{-1},γ): 1786(SC=O), 2831-2881(aliphatic C-H), 1689 (C=N), 1604 (C=C), 860 (p-substituted Benzen ring)

1,2-Ethane-bis[3-(substituted alkyl thio)-5phenoxy-1,2,4-trizole] [5e-f]

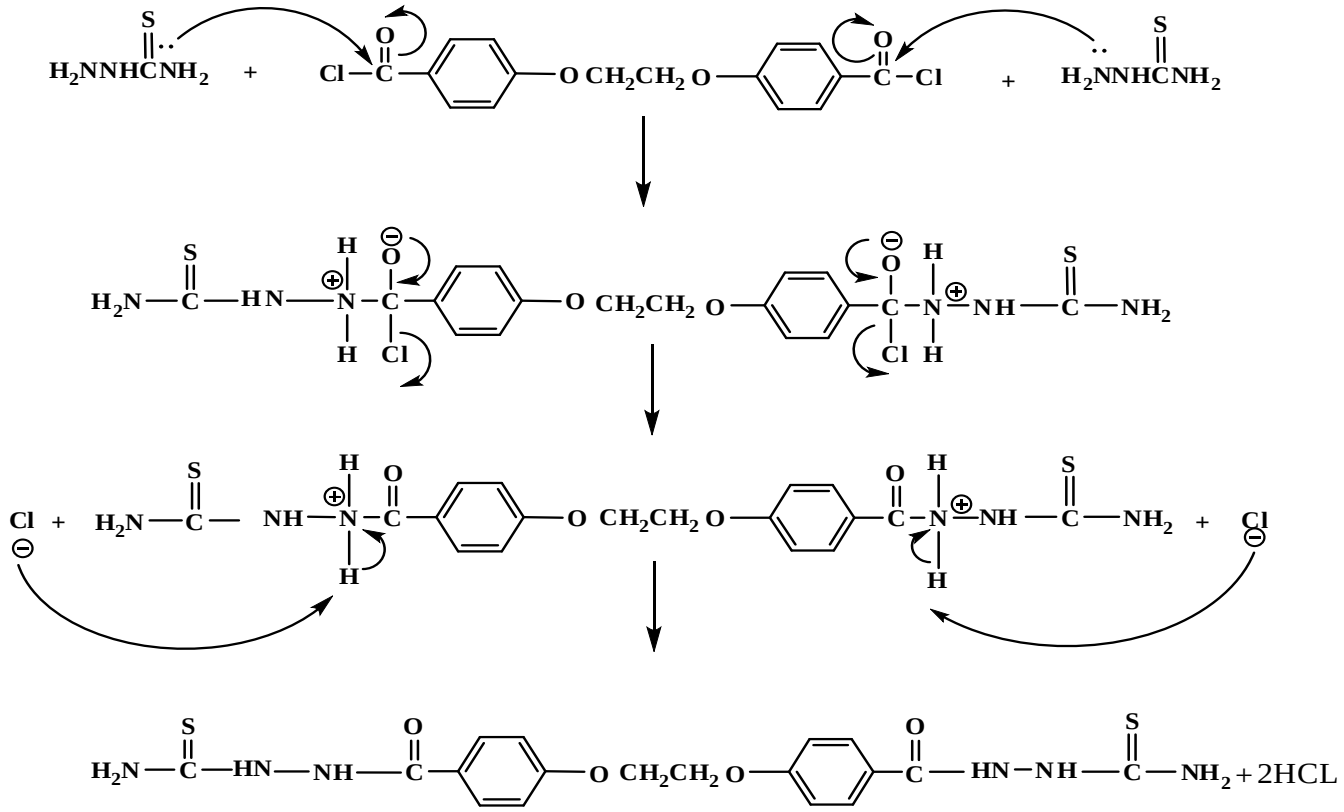
A compound [4] (0.01 mol) and 30 ml of ethanolic alkali (KOH 0.02 mol in 30 ml aqueous EtOH) was refluxed for 15 min and added alkyl halide (0.02 mol). The solution was refluxed for 3hrs.The solvent was evaporated and water was added, the resulting precipitate was collected and recrystallized from ethanol and dried. The physical properties and UV data of the compounds are given in table (1).

[5e] FTIR (cm^{-1},γ): 2854-2924 (aliphatic C-H), 3421(N-H)

Results and Discussion

The compound [1] was prepared by the reaction between p-hydroxy benzoic acid and 1, 2-dibromoethane in alkalimedia. The structure of this compound [1] was studied by FTIR spectroscopy.The FTIR spectrum of this compound,figure (1) showed the disappearance of γ O-H stretching band at 3390 cm^{-1} due to p-hydroxy benzoic acid and appearance the band at 1678 cm^{-1} due to γ C=O stretching of compound [1]. It also showed aband around (1168 – 1300) cm^{-1} due to stretching of the ether group γ (C-O-C).

Treatment the compound [1] with $SoCl_2$ in presence 3 drops from DMF to product compound [2]. The compound [3] was prepared by the reaction of diacid chloride [2] with thiosemicarbazide in 1:2 ratio respectively. The Mechanism of this reaction [16] may be outlined as follows, Scheme (2)

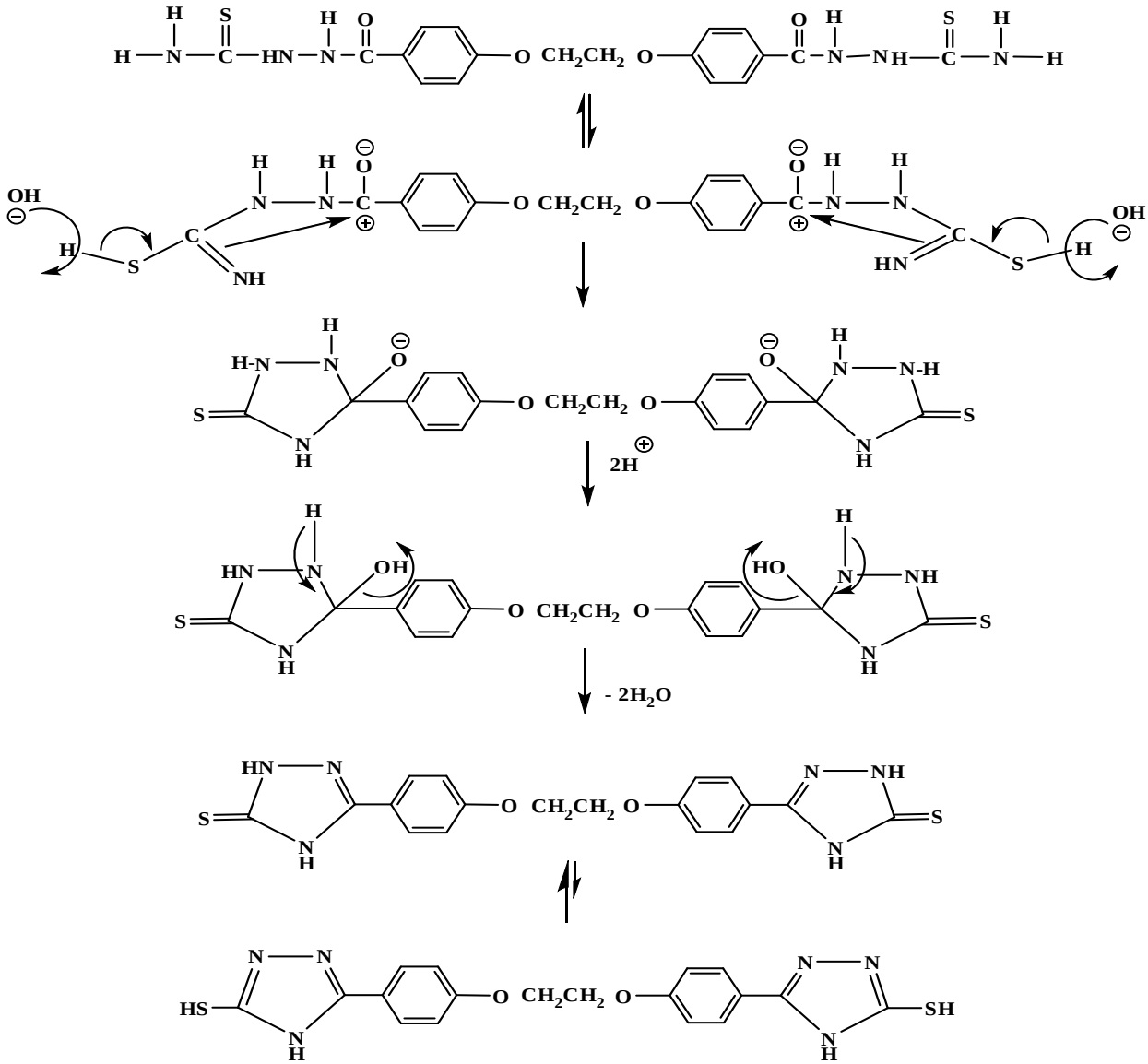


Scheme (2)

The reaction is initiated by nucleophilic attack of the most nucleophilic nitrogen of thiosemicarbazide on the carbonyl carbon of acid chloride via anucleophilic reaction. The structure of this compound [3] was identified by FTIR spectroscopy.

The FTIR spectrum of compound [3], figure (2) showed the following absorption bands γ C=O (amide) stretching at 1616 cm^{-1}, bands in the regions (3471,3414, 3244) cm^{-1} due to γ N-H stretching vibrations of CONH, NH_2 groups respectively. Also the spectrum showed band at 1180 cm^{-1} due to the stretching γ C=S.

To synthesized the corresponding triazole [4], oxidative cyclization of carboxlic acid thiosemicarbazide derivative [3] in the presence of (4%) aqueous sodium hydroxide has been employed. Although, these compounds may exist in twe tautomeric forms [17], thiol and thion according to the position of the mobile hydrogen in the molecule. The mechanism of this reaction [18] may be outlined as follows, Scheme (3).



Scheme (3)

This compound was characterized by FTIR. The FTIR spectrum of compound [4], figure (3) showed the disappearance of absorption band due to γ C=O (amide) stretching of compound [3] together with appearance of a stretching band at 1635 cm^{-1} which is assigned to γ C=N band of triazole moiety. It also shows stretching bands at 1234 cm^{-1} and 2357 cm^{-1} due to γ C=S and γ S-H respectively. which confirmed the tautomerism between thion and thiol forms [17]. The band at 3448 cm^{-1} due to γ N-H band of triazole moiety.

Anew compounds[5a-d] was prepared by the reaction of compound [4] with different acid chloride in dry pyridine. This reaction involue nucleophilic substitution. The product was identified by the melting point, FTIR and U.V spectroscopy. The physical properties and U.V data of the final products were listed in table (1).

The FTIR spectra shows, figure (4) disaberance band at 1234 cm^{-1}, 2357 cm-1 due to γ C=S and γ S-H respectively, which confirmed tautomeris between thion and thiol forms, and disaberance band at 3448 cm^{-1} due to γ N-H band of trizole ring. The spectra shows the following absorption bands at 1786 cm^{-1}due to S C=O of the thioestergroup; 2831-2881 cm^{-1} for aliphatic C-H; 1689 cm^{-1} and 1604 cm^{-1} due to C=N and C=C aromatic stretching; 860 cm^{-1} for p-substituted benzene ring.

The refluxing of compound [4] with iso bromo propane and n-bromo butane in alkaline ethanol yielded corresponding isopropaylthio [5e] and n-butylthio[5f] derivatives of 1,2,4 triazole respectively.

This compounds were identified by melting point, FTIR and U.V spectroscopy. The physical properties and U.V data were listed in table (1).

In each of the synthesized derivatives [5e-f] the absence signals in the region 1234 cm^{-1} and 2357 cm^{-1} in FTIR spectral data, figure (5) established the absence of C=S and S-H respectively and shows the following absorption bands at 2854-2924 cm^{-1} due to aliphatic C-H; 3421 cm^{-1} for N-H. The u.v spectrums of new compounds [5a-d] and [5e-f] showed in figure (6).

Biological Activity

Synthesised [4] , [5a-d] and [5e-f] series of compounds have been screened for their antibacterial activity by agar grawth technique against two type of bacteria Escherichia coli (Gram-negative bacteria) and Enterobacter (Gram-negative bacteria). Each compounds was dissolved in DMSO to give a final concentration of 0.01 mg/ml. The results of the preliminary screening test are listed in table (2).

From the data obtained in table (2), all the compounds [5b,e,f] were found to be highly active against E-coli (G-) and Enterobacter (G-) while the compounds [5a,c] were found to be highly active against E-coli (G-) and inactive against Enterobacter (G-). But the compounds [4] and [5d] were found to be highly active against Enterobacter (G-) and inactive against E-coli (G-).

References

1. a) unanget, P.C.; shurum G.P.; connor, D.T.; Dyer, R.D.; Schrier, D.J.*J*.mod.chem. 1992, 35, 3691 – 3698.
   b) Mullican, M.D.; Wilson, M.W.; connor, D.T.; Kostlan, C.R.; schrier, D.J.; Dyer, R.D. ibid 1993, 36, 1090-1099.
2. Johes, D.H; Slock, R.; squires, S.; Wooldridge, K.R.H. *J*.med. chem. 1965, 8, 676 – 680.

3. Sughen, J.K.; yoloye, T. pharm. Acta Helv. 1978, 58, 64 – 68.
4. a) shams H .Dine, Sh.A.; Hazzaa, A.A.B. pharmaziel 1974, 29, 761 – 768.
   b) cansiz, A.; servi, S.; Koparir, M.; Altintas, M.; Digrak, M.*J*. chem. Soc. Pak. 2001, 23, 237 – 239.
5. Stillings, M.R.; welbourn , A.P.; walter, D.Sc., *J*. med. Chem., 1986, 29, 2280 – 2284.
6. Kane, J.M.; Dudley, M.W.; Sorenseu, S.M.; Miller, F.P. *J*. med. chem. 1988, 3, 1253 – 1258.
7. Vamvakides, A. pharm. Fr. 1990, 48, 154 – 159.
8. R. iq bar; K.zamani and N.H. rama, Tr. *J*. chem. 1996, 20, 295 – 301.
9. K. zamani; K. faghihi; M.R. sangi and J. zolgharnein, Turk.*J*. chem. 2003, 27, 119 – 125.
10. A.H.K. sharba; R.H. AL-Bayati; M.A and N. Rezki, Melecules 2005, 10, 1161 – 1168.
11. I. H. Rou'il, Ph.D., college of education, Ibn AL-Haitham, university of Baghdad 2006.
12. S. baluja; S.chanda; R. chabh adiya; N. kachhadia; R. Nair and A. Sdanki, *J*. Serb. Chem. Soc. 2007, 72(6), 539 – 544.
13. Hussain. S;Sharma.J and Amir.M, *J*. Chem.2008, 5, 963-968.
14. Demirbas.N;Demirbas.A; Ceylan.S; Sahin.D, Turk.*J*.Chem.2008,32,1-8.
15. A. Vogel, "practical organic chem.", Longman Group Ltd., London, 3rd Edition 1974.
16. F. Bentiss and M. Lagrenee, *J*. Heterocyclic .chem., 1999, 36, 1029.
17. M. Dutta and J. Kataky, Ind. *J*. chem., 1996, 6, 59.
18. J. Heihchart; R. Houssin and B. Lablanche, *J*. Herterocyclic. Chem., 1977, 14, 516 – 619.

Table (1): Physical properties and U.V data for compounds [5a-d] and [5e-f]

Comp. No. [5]	Formula	R	Ŕ	M.P °C	Yield %	Color	λ max nm
a	$C_{32}H_{24}N_6O_4S_2$	Ph	-------	95	70	Off white	281
b	$C_{34}H_{30}N_6O_6S_2$	p-CH_3oph	-------	110	90	Off white	280.5
c	$C_{32}H_{22}N_8O_8S_2$	P-O_2Nph	-------	240	80	Brown	280
d	$C_{32}H_{22}N_6O_4S_2I_2$	m-Iph	-------	180	75	Brown	394
e	$C_{24}H_{28}N_6O_2S_2$	-------	$(CH_3)_2CH$-	235	85	Brown	270
f	$C_{26}H_{32}N_6O_2S_2$	-------	n-C_4H_9	162	80	Brown	407

Table (2): Results of biological activity of the compounds [4], [5a-d] and [5e-f]

Comp. No.	E. Coli (G-)	Enterobacter (G-)
4	-------	+++
5a	+++	-------
5b	+++	+++
5c	+++	-------
5d	-------	+++
5e	+++	+++
5f	+++	+++

Highly active = +++ (inhibition > 12mm), Inactive = ------- (inhibition zone <5mm).

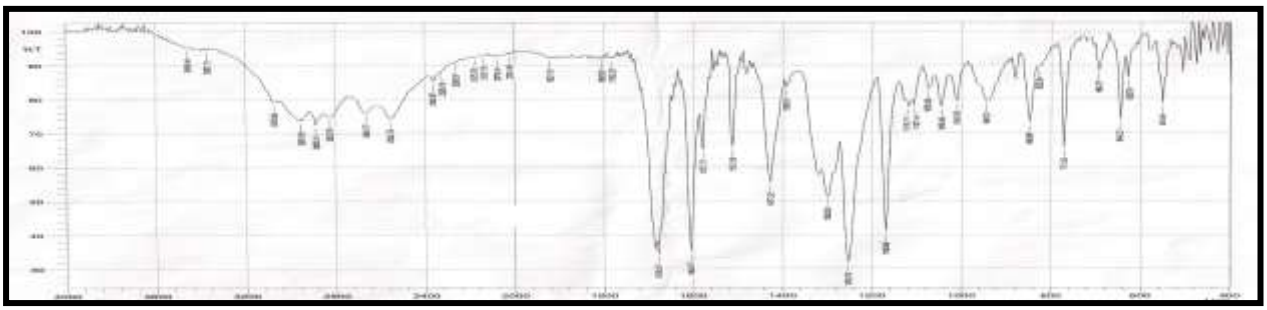


Figure (1): FTIR spectrum of compound [1]

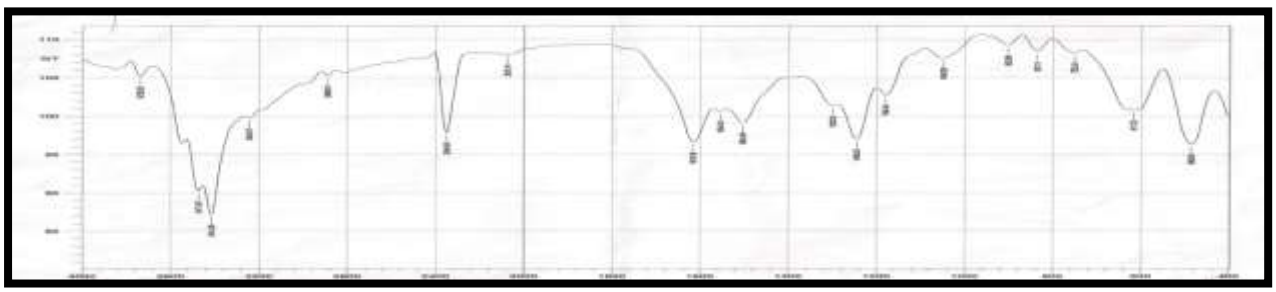


Figure (2): FTIR spectrum of compound [3]

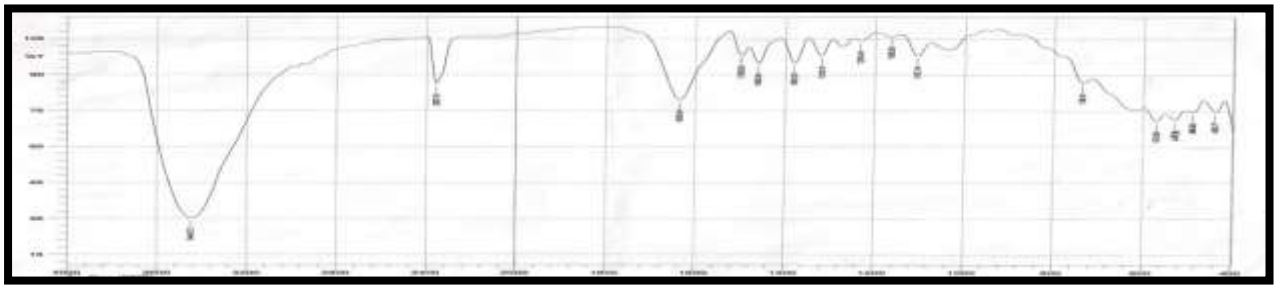


Figure (3): FTIR spectrum of compound [4]

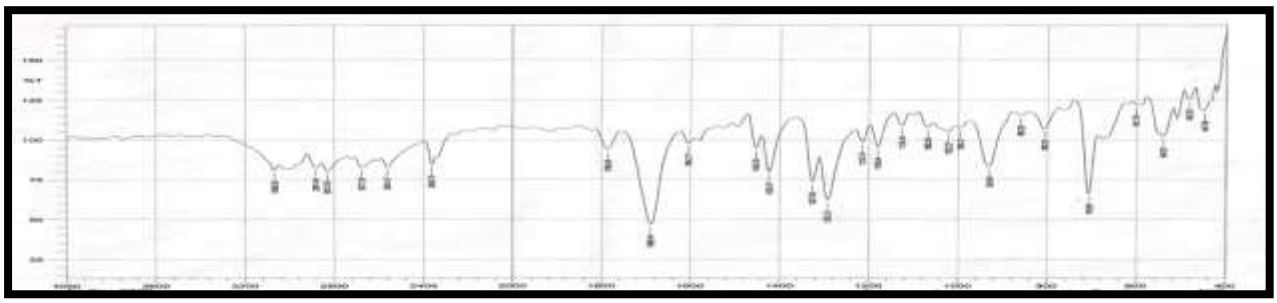


Figure (4): FTIR spectrum of compound [5a]

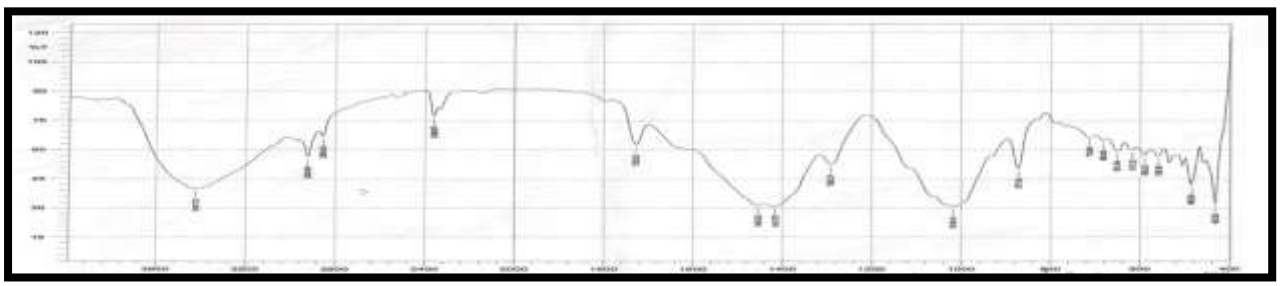


Figure (5): FTIR spectrum of compound [5e]

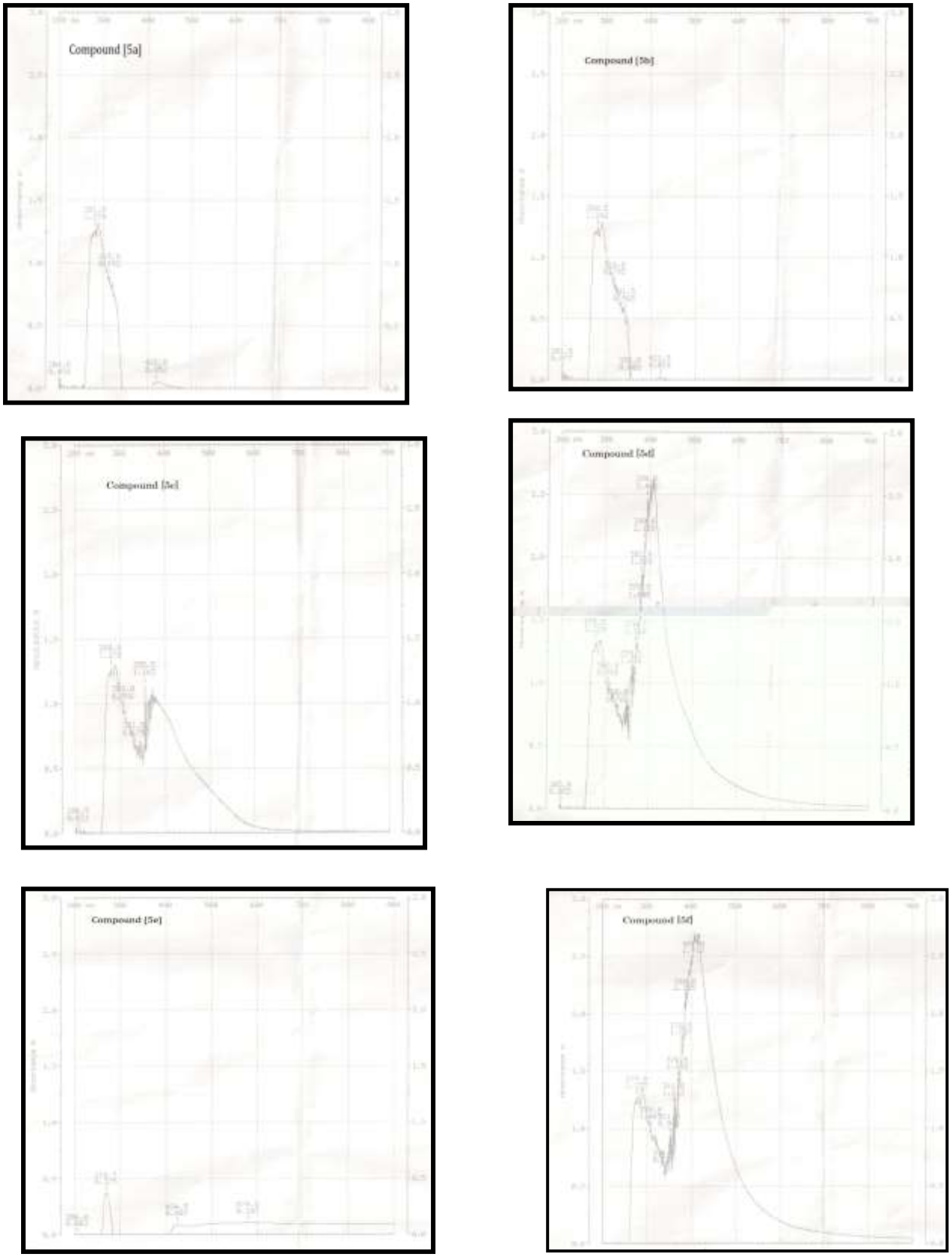


Figure (6): U.V spectrums of compounds [5a-d] and [5e-f]