Synthesis and Biological Active of Some Substituted 1,2,4-Triazoles and Their Fused Ring Derivatives

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Abstract

In this paper demonstrated the synthesis of some fused 1,2,4-triazoles derivatives ; Terphthalic acid condensated with ethanol to obtain diethyl terephthalate (1) in the presence of sulfuric acid as catalyst., the ethyl ester (1) was mixed with hydrazine hydrate is ethyl alcohol to give terephthalohydrazide (2). The hydrazide derivative (2) then reacted with ammonium thiocyanate to give yield 2,2'-terephthaloylbis(hydrazinecarbothioamide) (3). 3,4-diamine-bis – 1,2,4-triazole derivative (4) was obtained by reaction of a compound (3) with hydrazine hydrate. 5,5'-(1,4-phenylene)bis(4H-1,2,4-triazole-3,4-diamine) (4) was reacted with a proper aldehyde to yield Schiff bases derivatives (5,6,7).1-(1H-[1,2,4]triazolo[4,3-b][1,2,4]triazol-5-yl)-4-(3H-[1,2,4]triazolo[4,3-b][1,2,4]triazol-6-yl) benzene derivatives (8,9,10) were yielded by reaction a Schiff bases derivative with glacial acetic acid. The structures of the synthesized compounds were confirmed by physical and spectral methods.

Keywords: Heterocyclic compounds, 1, 2, 4-trazole, fused ring, terephthalic acid.

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تحضير بعض معوضات 1،2،4-ترايازول ومشتقات الحلقية المندمجة منها

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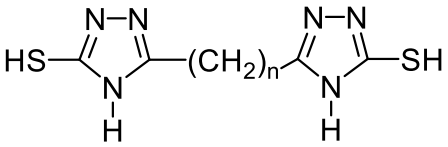
الخلاصة

تم في هذا البحث تحضير عدد من معوضات 1،2،4- ترايازول ذات حلقات غير متجانسة مندمجة. حول حامض التيرفثاليك إلى اثيل استر (1) من خلال تفاعله مع الايثانول المطلق وحامض الكبريتيك المركز كعامل محفز وأعطى تفاعل الاستر (1) مع الهيدرازين المائي في الايثانول هيدرازيد الحامض (2) . تم تفاعل معوض الهيدرازيد (2) مع ثايوسيانات الامونيوم ليعطي ثايوسيميكاربازيد (3). حضر مركب 4،3- ثنائي امينو 4،2،1- ترايازول المعوض (4) من خلال تفاعل الثايوسيميكاربازيد (3) مع الهيدرازين المائي. من تفاعل 5،5(4،1-فنيلين) بس- 4،3- ثنائي امينو -4،2،1- ترايازول مع معوضات البنزلديهايد لتعطي معوضات قواعد شيف . تم حولقة معوضات الهيدرازونات المحضرة إلى مركبات ثنائية الحلقة (10،9،8) باستخدام اوكسي كلوريد الفسفور في الزايلين او باستخدام حامض الخليك الثلجي . شخصت المركبات المحضرة بالطرق الفيزياوية والطيفية .

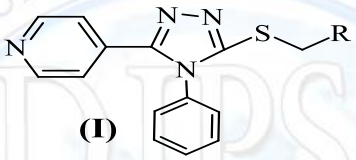
الكلمات المفتاحية : المركبات الحلقية غير المتجانسة ، 4،2،1-ترايازول ، الحلقات المندمجة ، حامض التيرفثاليك.

Introduction

The substituted triazoles are important compounds as drug , antibacterial , anti-fungal , anti-cancer and dyes . 1,2,4- triazole was first synthesized from benzoyl isocyanate and phenyl hydrazine[(1)]. Quanazine 1,2,4- triazole contains three amino groups was synthesized by react trimethyl amino cyanide with hydrazine hydrate[(2)]. Substituted 1,2,4- triazoles have varium biological activities and acts in some comes an a drugs[(3)] , 1,2,4- triazoles have aromatic properties [(4)]and stable against high temperature[(5)]. Bicyclic 1,2,4- triazole compounds were synthesized using ethyl succinate , ethyl glutarate[(6)] and ethyl butyrate[(7)].

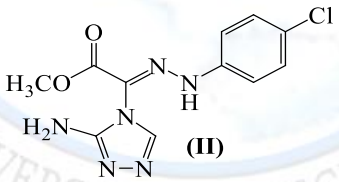


Triazoles substituted show a biological and medical improve [7]. 1,2,4-triazoles derivatives were synthesized from dithiocarbazide salt [8] and substituted thiosemicarbazide[9]. Some new 1,2,4-triazole compounds containing pyridine substituted were synthesized by reduction microwave assistant conditions by multi-step reaction , as compound (I).



(I)

Theoretical calculation of compound (I) was carried out with DFT/B3LYP/6-31G the full geometry optimization was carried out using 6-31G(d,p) basis set and the frontier orbital energy , atomic net charge was discussed[10]. The reaction of hydrazonoyl halide with 3-aminotriazole in tetrahydrofuran / triethyl amine produce methyl-2-[3-amino-4H-1,2,4-triazol-4-yl]-2-[2-(4-chlorophenyl) hydrazone] acetate (II)[11].



(II)

Some antimicrobial 1,2,4-triazole derivative were synthesized from the reaction of ester ethoxycarbonyl hydrazone with primary amine[12].

A fused ring thiadiazole – triazole and triazole – triazole were synthesized as fallows .

Experimental

All chemicals were purchased from Flucka and BDH Chemical Ltd. The melting points were measured on an Electrothermal 9300 Engineering LTD and were uncorrected. IR spectra were recorded on Infrared Spectrophotometer Model Tensor 27, Bruker Co., Germany, using KBr discs.

Synthesis of Diethyl terephthalate[13] (1) :

To terphthalic acid (0.025 mole) in absolute ethanol (50 ml) , concentrated sulfuric acid (5 ml) was added with cooling , the mixture was refluxed for (8 hours) the solvent was evaporated and the residue then neutralized with 20% sodium bicarbonate , the ester was precipitated as white sold , filtered and recrystalized from ethanol – water(1:1) , m.p.(214ºC) , yield (80%).

Synthesis of Terephthalic acid hydrazide[14] (2) :

A mixture of diethyl terphthalate (1) (0.01mole) and hydrazine hydrate 80% (5 ml, 0.1 mole) in ethanol (30 ml) was refluxed for (10-12) hours the solvent was removed under reduced pressure a pale brown crystals was formed , filtered and recrystalized from ethanol . m.p.(283ºC) , yield (86%).

Synthesis of 2,2'-terephthaloylbis(hydrazinecarbothioamide) [15] (3):

A mixture of hydrzide compound (2)(0.01 mole) ammonium thiocyanate (3.04g , 0.02 mole) concentrated hydrochloric acid (5 ml) in abs. ethanol (50 ml) was refluxed for (8 hours) the mixture after cooling was given white precipitate recrystallized from ethanol – water(1:1) , m.p.(132-133ºC) , yield (55%).

Synthesis of 1,4-bis(3,4-diamino-1,2,4-triazol-5-yl) benzene[16] (4):

Thiosemicarbazide (3) (0.8g , 0.0025 mole) was mixed with hydrazine hydrate 80% (10 ml , 0.2 mole) the mixture was refluxed for (2 hours) the precipitate was formed by cooling , filtered , dried and recrystallized from ethanol to give pale green crystals , m.p.(306-307ºC), yield (48%).

Synthesis of Dihydrazone[17] (5-7):

A mixture of compound (4) (0.01 mole) with substituted benzaldehyde (0.04 mole) and conc. hydrochloric acid (0.5ml) in ethanol (25 ml) . the mixture was refluxed for (2) hours , then cooled and the precipitate filtered and recrystallized from ethanol . The Physical Constant and chemical and spectra data of compound are given in table 1 and 3.

Synthesis of substituted 1,4-bis(6-aryl-7-(arylmethyl)-7H-[1,2,4]triazolo[4,3-b][1,2,4]tryazol-3-yl)benzene (8, 9 ,10):

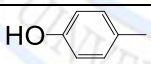
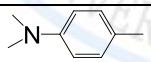
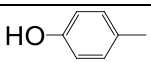
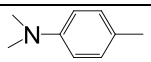
Method A[18]:

Compound (5,6 or 7) was dissolved in dry xylene (50 ml) phosphorus oxychloride (10 ml) was added and the mixture refluxed for (6-8) hours . the solvent was removed under reduced pressure , cold water was added and the precipitate filtered and recrystallized from ether – pet. Ether(3:1) , The Physical Constant and chemical and spectra data of compound are given in table 1 and 3.

Method B[19] **:**

Compound (5,6 or 7) was dissolved in glacial acetic acid (20 ml) and stirring the mixture at 80^{o}C for 2 hr and then added crash ice , filtered and recrystallized from ethanol – water(1:1) , The Physical Constant and chemical and spectra data of compound are given in table 1 and 3.

Table (1): physical data of compounds (5-10)

Comp. no.	Ar	M.P. ^{o}C	Yield %	Color
5		231-233	58	White
6		198-200	62	Yellow
7		285-289	69	Pale yellow
8		186-188	78	Yellow
9		181-182	81	Browne
10		199-202	71	Browne

Theoretical calculation

By use (chem. Office V11) counting Gaussian program is very important and good work advance calculator and give the way for researcher to conduct theoretical and support applied research .

In this paper calculate theoretical some parameter for compound (4-10) by :

1. Draw the figer by (Chem. 3D).
2. Make loser energy by (MM2).
3. Calculate HOMO & LUMO energy .
4. By used equation 1 , 2 , 3 calculate (**η**) hardness , (**μ**) electron chemical potential , (W) Global electrophilcity Index .

$\boldsymbol{\eta} = 1/2\ (E_{LUMO} - E_{HOMO})$ …….(1)

$\boldsymbol{\mu} = 1/2\ (E_{HOMO} + E_{LUMO})$ …….(2)

$\mathbf{W} = \frac{\eta^2}{2\mu}$ …….(3)

Result and Discussion

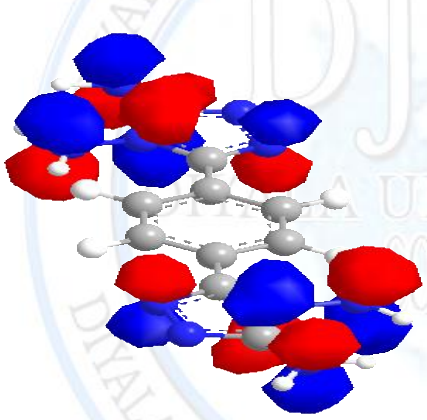
In this paper the synthesis of some substituted fused ring 1,2,4-triazoles is reported . The stricture show the compounds energy for surface and according to calculation of energy of HOMO , highest occupied molecular orbital ; LUMO , lowest unoccupied molecular orbital theory in table(2), that's important factors that affect bioactivity[20] . HOMO has the priority to provide electrons , while LUMO can accept electrons first [20] . The geometry of frame compounds (4-10) is hardly influenced by the introduction of , ether the triazole ring , benzene ring or fuse ring (figure 1) . This also implies that the orbital interaction between the title heterocyclic compound and the aromatic ring or some other side of residue chains of receptors is dominated by π-π or hydrophobic interaction among the frontier molecular orbitals.

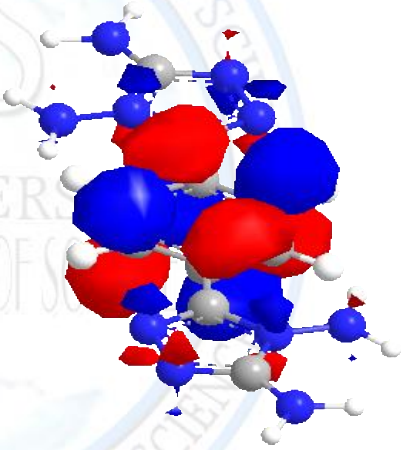
Table 2. Energy of HOMO, highest occupied molecular orbital; LUMO, lowest unoccupied molecular orbital, compounds (4-10) (theory)

Comp.no.	HOMO	LUMO	η	μ	W
4	-6.3773	-1.277	2.5502	-3.8272	2.871807
5	-3.064	-1.547	0.7585	-2.3055	3.503843
6	-2.656	-1.234	0.7110	-1.9450	2.660355
7	-1.759	-1.139	0.3100	-1.4490	2.386453
8	-1.979	-1.220	0.4795	-1.5995	3.370751
9	-1.938	-1.065	0.4365	-1.5015	2.582477
10	-0.343	0.341	0.3420	-0.0010	1.46E-06

Comp.no. HOMO LUMO

4





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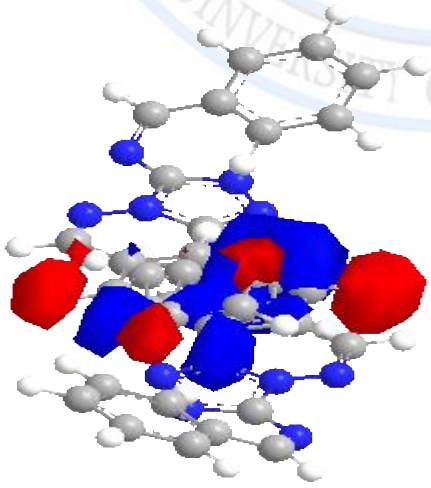

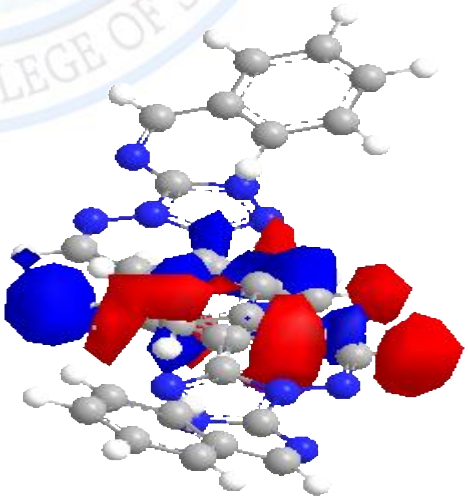

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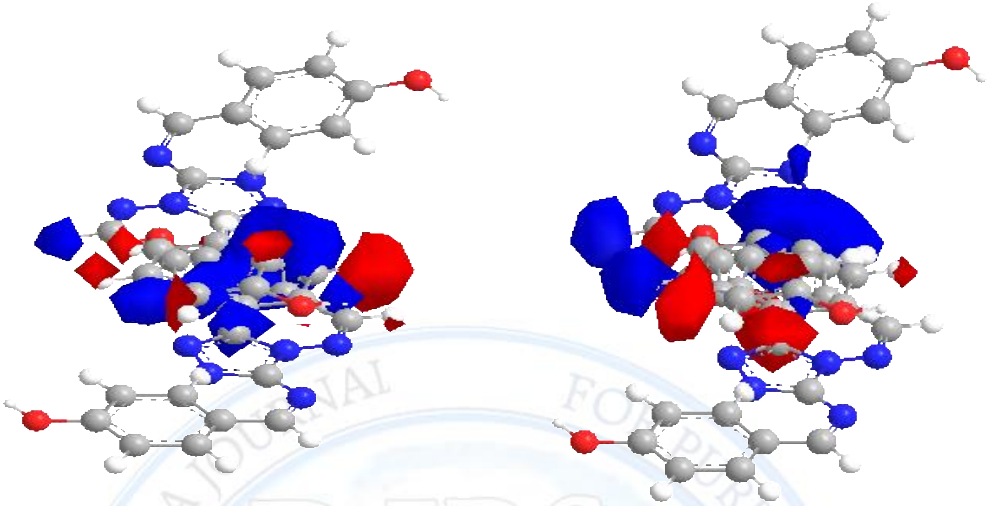

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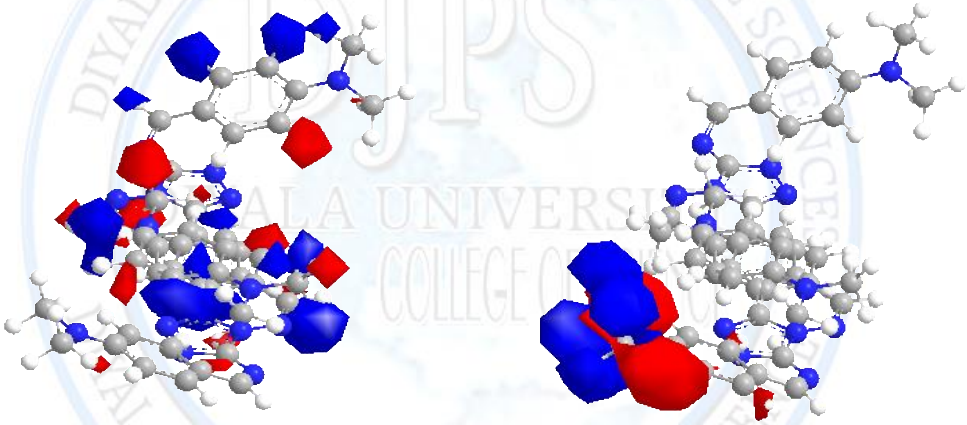

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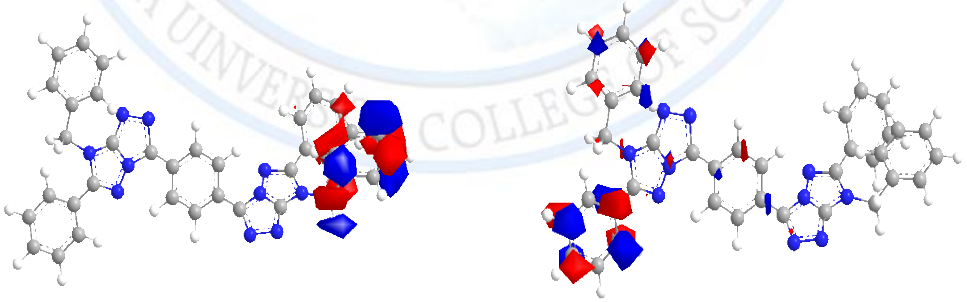


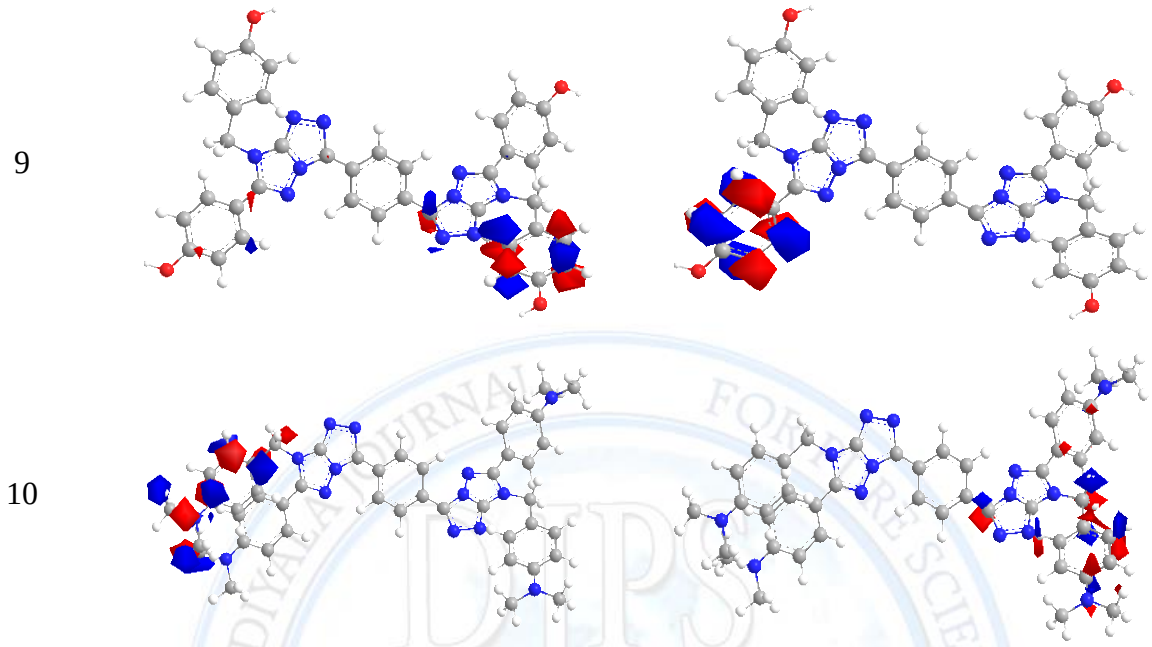


Figure 1. HOMO, highest occupied molecular orbital; LUMO, lowest unoccupied molecular orbital, compounds (4-10)

Note :(Red area mean positive homo energy, blue area mean negative lumo energy)

Homo,Lumo (5,6,7) & (8,9,10)

the energies of HOMO,LUMO values increase with decreasing viability of donor, and increased disability of stereochemistry, the compounds (5,8) that is not substituted in phenyl ring is less values in HOMO,LUMO energy comparing with other compounds synthesis, although the compound (7,10) is set (Dimethyl Amin) larger than the hydroxyl group in compound (6,9), but the electronegativity of an atom of oxygen increases the donor capacity Comparing with the nitrogen atom in the compound (7,10) as Table (2).

Hardness (η) (5, 6, 7) & (8, 9, 10)

Molecular hardness values decrease when there are groups large substituted ring benzene, and then return to its relationship gap energy between Homo and Lumo, where the change of homo , lumo values lead to decrease of deferent energy between the two levels, that is lead to decrease of involve energy to transfer of electron (Excitation energy),that is lead to decrease

of hardness (decrease of molecular hardness of the compound (7,10) comparator with compound(5,8) and (6,9) as Table (2).

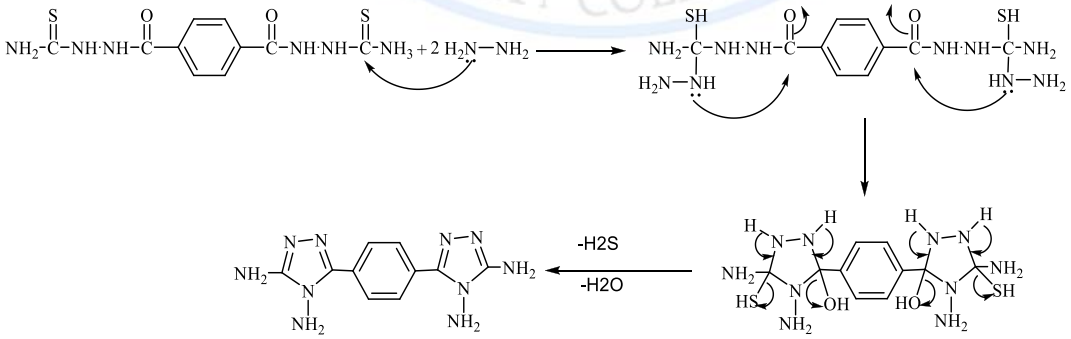
Electron chemical potential (μ) (5, 6, 7) & (8, 9, 10)

Show that increase in electron potential for chemical compounds with decreased susceptibility donor as Table (2).

Global electrophilcity Index (w) (5, 6, 7) & (8, 9, 10)

Show that decreased the value of Global electrophilcity index with the decrease susceptibility Donor ,The increase in electron potential chemical spin Global electrophilcity index is the latest proof of the stability of the prepared compounds as Table (2).

Terephthalic acid was used as starting material which was esterifies to its ethyl ester (1) ester by its reaction with absolute ethanol and concentrated sulfuric acid , the IR spectrum ethyl ester compound (1) show absorption at 1728 cm^{-1} for C=O ester . acid hydrazide prepared by reaction of ethyl ester compound (1) with hydrazine hydrate in ethanol , the C=O absorption for hydrazide at 1642 cm^{-1} , the hydrzide (2) was treated with ammonium thiocyanate and concentrated hydrochloric acid in ethanol to give thiosemicarbazide (3) , the IR spectra show 1674 cm^{-1} C=O and 1244 cm^{-1} C=S , thiosemicarbazide (3) convert to substituted 1,2,4-triazole (4) by treated with hydrazine hydrate in EtOH to give , The mechanism suggest follows[21] :



IR spectra show no absorption for C=O the C=N absorption at 1670 cm^{-1} and C-H aromatic at 3050 cm^{-1} substituted 1,2,4-triazole (4) was treated with substituted benzaldehyde and concentrated hydrochloric acid in ethanol to give hydrazones (5-7) , the IR spectra for compound (5) show absorption at 1686-1661 cm^{-1} for C=N and 3050-3117 cm^{-1} C-H aromatic . the hydrazones (5-7) were treated tow ways the first with phosphorus oxychloride and other with glacial acetic acid to give bicyclic triazoles ring substituted benzene (8-10) , the IR spectra for compound (8) show 1651-1698 cm^{-1} C=N and 3007-3071 cm^{-1} C-H aromatic and no absorption for N-H. Table (2). The structure of the synthesized compounds were confirmed by IR, and physical methods.

Table (3): IR spectra

Comp .no.	IR ύ cm^{-1} , KBr					
	C=O	C=N	-NH	C-H_{alph}	C-H_{arm}	Others
1	1728	--	--	2944	3060	--
2	1642	--	3418	--	3070	--
3	1674	--	3408	--	3080	C=S 1244
4	--	1670	3400,3133	--	3050	--
5	--	1662	--	3011	3074	--
6	--	1666	--	2922	3117	O-H_{phenol} 3445
7	--	1686,1661	--	2926,2871	3050	--
8	--	1651	--	--	3071	--
9	--	1698	--	--	3064	O-H_{phenol} 3422
10	--	1653	--	2924,2853	3007	--

Biological Active

the biological studies of compounds (5,6,7,8,9 &10) were evaluated against *(Eschershia Coli , Staphylococcus Epidermidis , Staphylococcus Areus)* table (4) the results showed that these compounds (5,6,7,8) have a good activity against (*Eschershia Coli* and *Staph Epidermidis*).

Table 4. Biological active compounds (5-10)

Comp.no.	*Staph Epidermidis*	*E. Coil*	*Staph Aureus*
5	14	9	18
6	11	11	21
7	9	15	19
8	16	13	19
9	12	8	17
10	14	13	18
Ciprofloxacin 5mg/disk	-	15	-
Chloramphenicol 30mg/disk	16	14	17

Compounds (7) were tested against *E.coli* shows a good activity against with compare to standard controls, compounds (5, 6, 8, 9, 10) were tested against shows a less activity against *E.coli* with respect to standard controls.

Compounds (5-10) were tested against *Staph Epidermidi* shows a less activity against *Staph Epidermidi* with respect to standard controls.

Compounds (5-10) were tested against *Staph Aureus* shows a good activity against with compare to standard controls.

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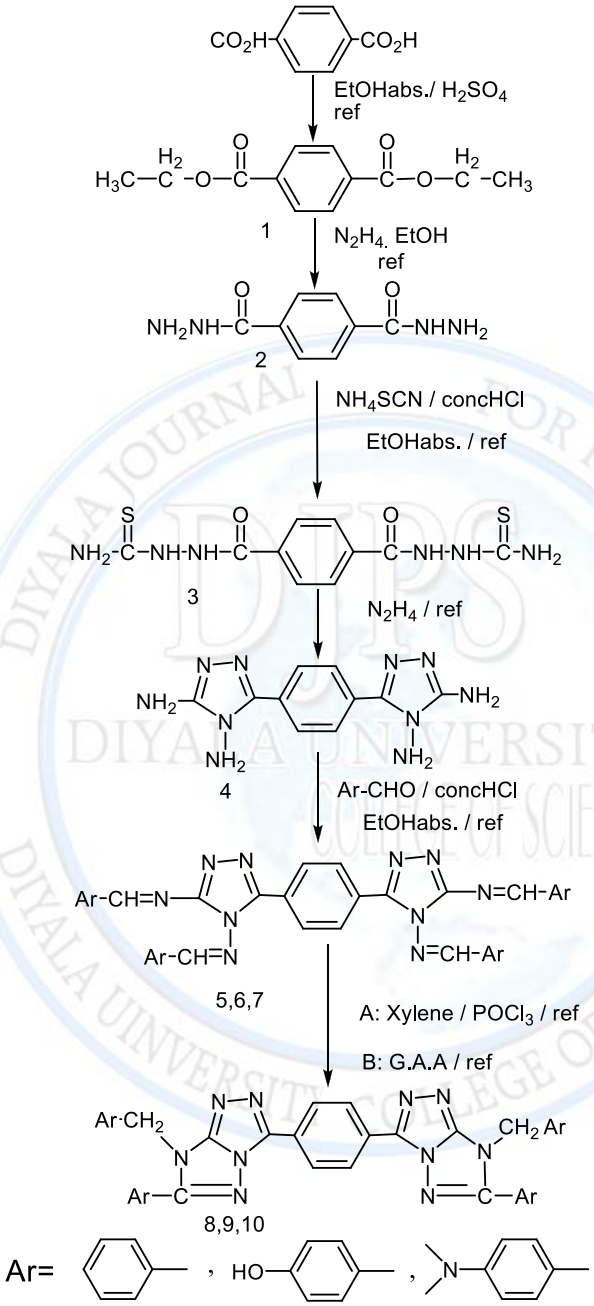

Scheme – 1 –

Conclusion

In conclusion, we have synthesis a simple and efficient method for the synthesis of new triazole fuse ring derivatives and characterized by spectral studies. The newly synthesized compounds (5-10) were evaluated for antibacterial activities. energy for surface calculation of energy of HOMO & LUMO theory . The compounds synthesized have a good activity against

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