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# New Fused Hyterocyclic Compounds: Synthesis of Some 1,4-di[1,2,4-Triazoles[3,4-b]5-phnyl/aryl-1,3,4-thiadiazole] Benzene

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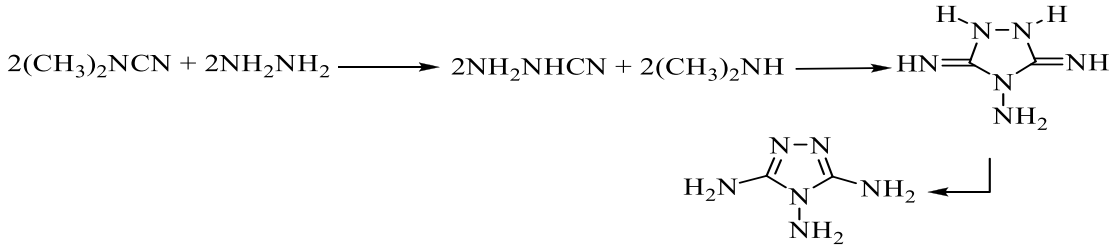
**Abstract:** In this paper the synthesis of some substituted di – 1,2,4-triazoles and it is conversion to multi nuclear heterocyclic compounds ; described Terphthalic acid was esterified to its ethyl ester(1)by its reaction with absolute ethanol , concentrated sulfuric acid , the ethyl ester (1) was treated with hydrazine hydrate is ethanol to give the acid hydrazide (2). the hydrazide (2) then treated with ammonium thiocyanate to give thiosemicarbazide (3) , reaction of thiosemicarbazide (3) with hydrazine hydrate gave 1,4-bis( 3-thiol-4-amino-1,2,4-triazole-5-yl) benzene (4). Compound (4) treatment with three type substituted benzaldehyde gave 1,4-di hydrazones phenyl (5,6 and 7). Cyclization hydrazones compounds (5,6,7) with phosphorous oxychloride in xylene to gave bicyclic system 1,4-bis[1,2,4-triazole[3,4-b]-5-substituted – 1,3,4-thiadiazole] benzene (8,9 and 10) . On the other hand some physical parameters of compounds ( 4 -10 ) under investigation such as the Mullikan charge at the active atoms, HOMO and LUMO energy levels , hardness (η) , electronic chemical potential (μ) and global electrophilicty index (W) were theoretically calculated using ( Gaussian program ). The antibacterial activity some of the synthesis compounds was studied. The structures of the synthesized compounds were confirmed by physical and spectral methods.

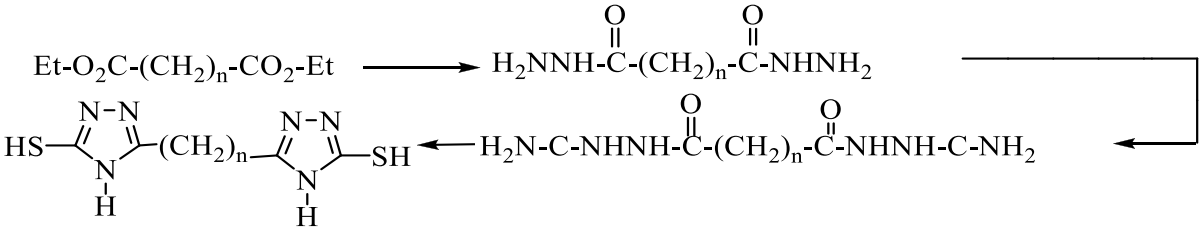
**Keyword:** Hyterocyclic, Triazoles , Thiadiazole, Terphthalic acid

## Introduction

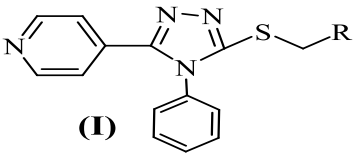
Substituted 1,2,4- triazoles possess various biological activities and acts in some cases as a drugs[(1)] , 1,2,4-triazoles have aromatic properties [(2)]and stable against high temperature[(3)].
1,2,4- triazole was first synthesized from benzoyl isocyanate and phenyl hydrazine[(4)]. Quanazine 1,2,4- triazole contains three amino groups was synthesized as in the fallowing equation is[(5)]:



Bicyclic 1,2,4- triazole compounds were synthesized from ethyl succinate , ethyl glutarate[(6)] and ethyl butyrate[(7)].by conversion to acid hydrazide , the hydrazide was treated with ammonium thiocyanate to give thiosemicarbazide which cyclized to the produd as follows :

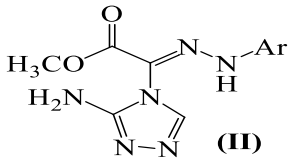


Which show a biological and medical importance [7]. Substituted 1,2,4-triazoles were synthesized from dithiocarbazide salt [8] and substituted thiosemicarbazide[9]. Some novel 1,2,4-triazole compounds containing pyridine moiety were synthesized under microwave assistant conditions by multi-step reaction , as compound (I).



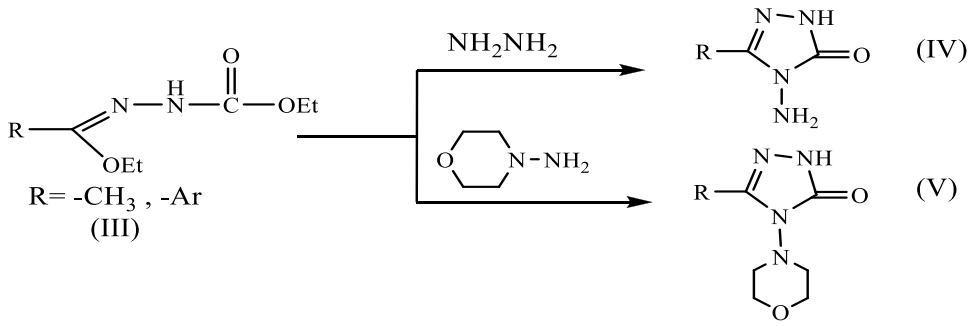
**(I)**

Theoretical calculation of compound (I) was carried out with B3LYP/6-31Gthe 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)**

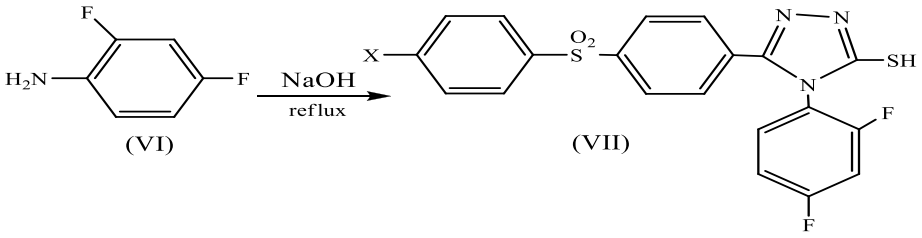
Some antimicrobial 1,2,4-triazole derivative (IV,V) were synthesized from the reaction of ester ethoxycarbonyl hydrazone (III) with primary amine[12].



R= -$CH_3$ , -Ar

(III)

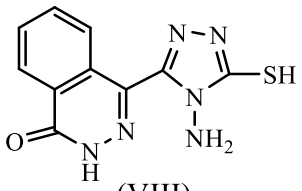
Recently some 1,2,4-triazole compounds (VII) showed good antioxidant activity .this compounds were synthesized by the reaction of hydrzinecarbothioamides (VI) with sodium hydroxide[13].



(VI) (VII)

The azo dyes containing 1,2,4-triazole ring were synthesized and was found that it may exist in three toutomeric frms spcially when para substituted aniline coupling compound was used . 3-ethylthio-5-cyanomethyl-4-phenyl-1,2,4-triazole was treated with diazotiozed aniline derivatives[14].

The synthesis of 4-(4-amino-5-mercapto-4H-1,2,4-triazol-3-yl)phthalazin-1-(2H)-one was achieved (VIII), from the reaction of 4-oxo-3,4-dihydrophthalazine-1-carbohydrazide with potassium hydroxide in ethanol followed by by the addition of carbon disulfide and the mixture than stirred at room temperature to give the potassium salt , its reaction with hydrazine hydrate give final product (VIII)[15].




(VIII)

In this paper the synthesis of fused ring system 1,3,4-thiadiazole - triazole is studied.

## 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. UV spectra were recorded on Shimadzu Double-Beam Spectrophotometer UV-210 A using ethanol as a solvent.

***Synthesis of Diethyl terphthalate (1)[16] :***

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 , m.p.(214$^{o}$C) , yield (80%).

***Synthesis of Terphthalic aced hydrazide (2)[17] :***

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

***Synthesis of Dithiosemicarbazides (3)[18]:***

Hydrazide (2) (0.1 mol) in ethanol absolute was added to a mixture of carbon disulfide (0.15 mole) and potassium hydroxide (0.15 mole) in absolute ethanol (100 ml) the mixture was refluxed for (16 hours) , after the mixture was cooled , dry ether (150 ml) was added the product precipitated , filtered under ruction , the greenish yellow salt m.p.>(310$^{o}$C) , yield (58%)

***Synthesis of 1,4- ( 3-thiol-4-amino-1,2,4-triazole-5-yl) benzene (4)[19]:***

The salt (3) (0.02 mole ) was dissolved hydrazine hydrate (0.04 mole ) and water (2ml) . the mixture was refluxed with stirring for (2 hours) the mixture was cooled , pale green crystals washed with water (100ml) , dried and recrystallized from ethanol to give pale brown crystals , m.p.(211-213$^{o}$C) , yield (62%)

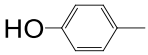
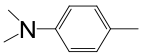
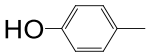
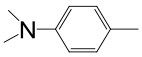
***Synthesis of Hydrazones: 1,4-bis (3-thiol-4-substituted-benzylideneamino) -1,2,4-triazol-5-yl) benzene (5-7)[20]:***

A mixture of (4) (0.01 mole ) substituted benzaldehyde (0.02 mole ) , hydrochloric acid (0.5 ml) in ethanol (25 ml ) was refluxed for ( 2) hours the product was cooled and filtered . tables (1,3).

***Synthesis of 1,4-di[1,2,4-triazole[3,4-b]-5-substituted – 1,3,4-thiadiazole] benzene (8, 9 ,10 )[21]:***

Compound (5,6 or 7) (0.0025 mol) was dissolved in dry xylene (50 ml) phosphorus oxychloride (10 ml) was added and the mixture refluxed for (6-8) hours . the reduced pressure , cold water was added and the precipitate filtered and redrystallized from ether – pet. ether , tables (1,3).

Table 1. Physical data of compounds (5-10)

| Comp. no. | Ar | M.P. °C | Yield % | Color |
|---|---|---|---|---|
| 5 |  | 91 | 74 | Pale yellow |
| 6 |  | 68 | 72 | Pale yellow |
| 7 |  | 79 | 81 | White |
| 8 |  | 139 | 76 | Dark brawn |
| 9 |  | 153 | 64 | Brawn |
| 10 |  | 161 | 83 | Pale brawn |

## 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 .

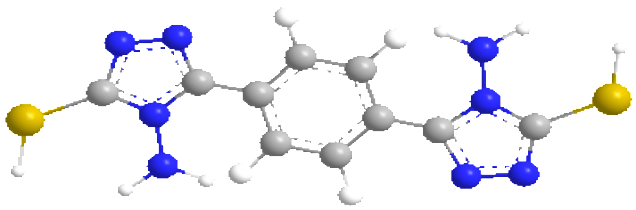
$\eta = 1/2 (E_{LUMO} - E_{HOMO})$ …….(1)

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

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

## Result and Discussion

In this paper the synthesis of some substituted fused ring 1,2,4-triazoles is reported . and draw 3D for compounds (4-10) figure (1):



4

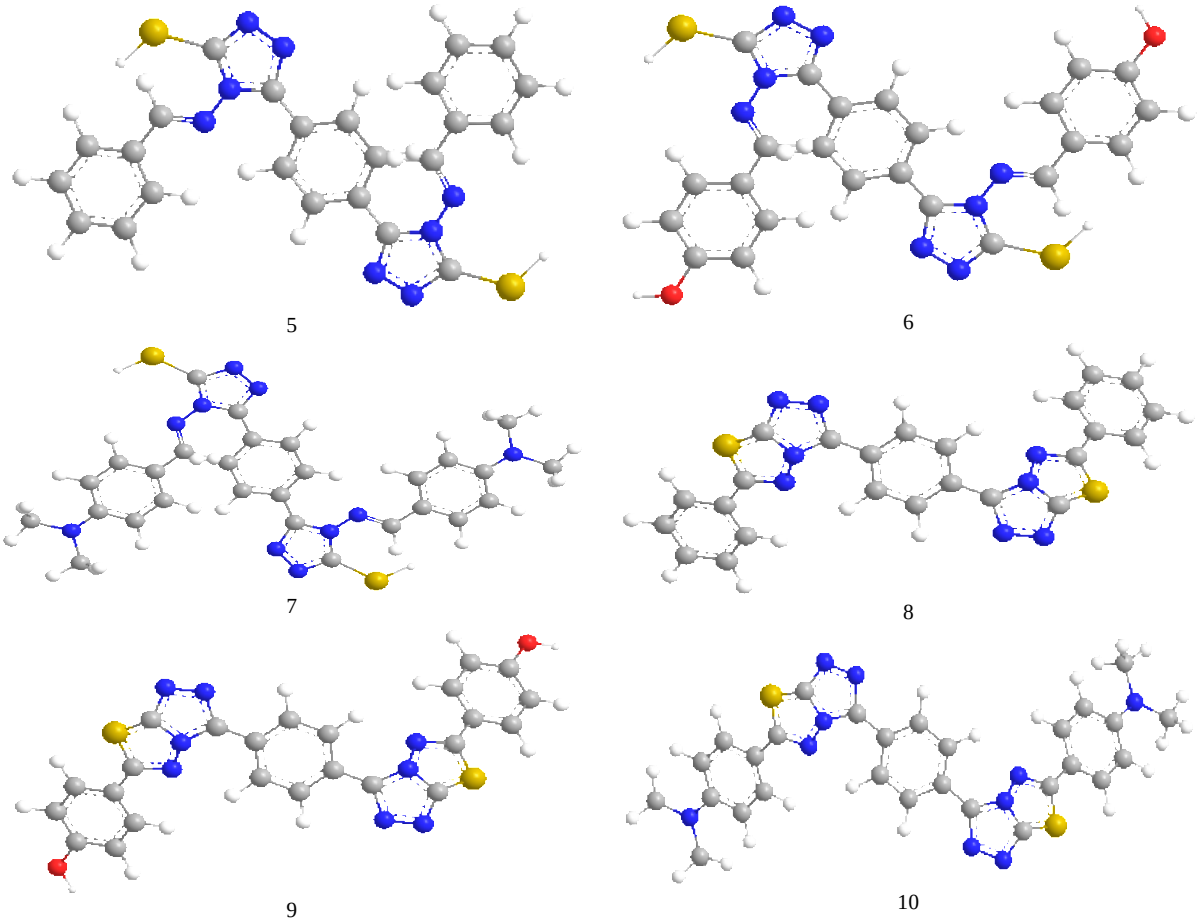



Figure 1. Stricture 3D synthesis compounds (4-10)

The stricture show the compounds is not plan and give idea as state energy for surface and according to calculation of energy of HOMO , highest occupied molecular orbital ; LOML , lowest unoccupied molecular orbital theory in table 3, that's important factors that affect bioactivity . HOMO has the priority to provide electrons , while LOMO can accept electrons first [(22)] . The geometry of frame compounds (4-10) is hardly influenced by the introduction of , ether the triazole ring , benzene ring or fuse ring (figure 2) . 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.

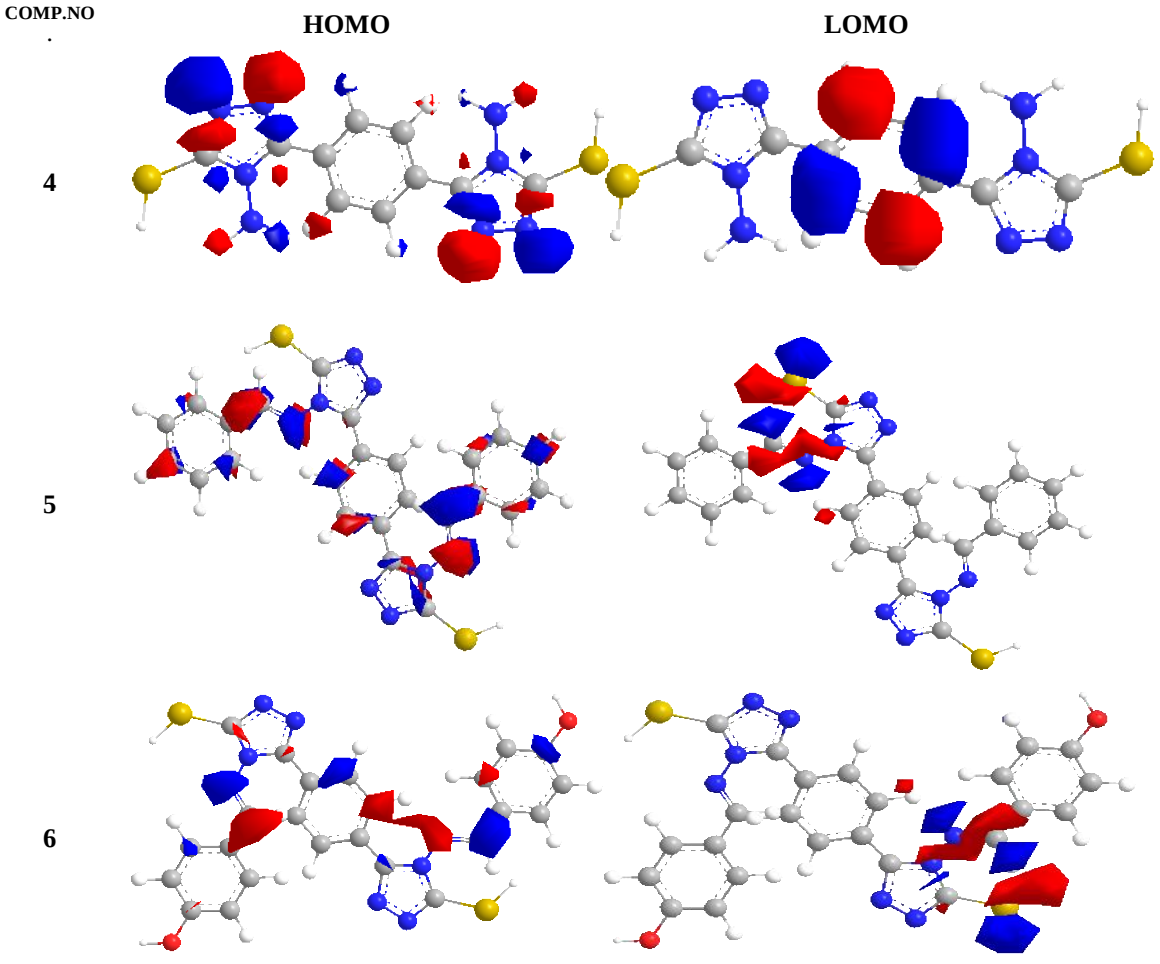
Terephthalic acid was used as starting material which was esterifies to its ethyl ester (1) ester by its reaction with absolute ethanol and concentrated sulfuric acid , the IR spectra of ester show absorption at 1728 $cm^{-1}$ for C=O ester . than converted to acid hydrazide (2) with hydrazine hydrate 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 1718 $cm^{-1}$ C=O and 1275 $cm^{-1}$ C=S , thiosemicarbazide (3) was treated with hydrazine hydrate in ethanol to give substituted 1,2,4-triazole (4) , IR spectra show no absorption for C=O the C=N absorption at 1627 $cm^{-1}$ and C-H aromatic at 3030 $cm^{-1}$ substituted 1,2,4-triazole (4) was treated with substituted benzaldehyde and concentrated hydrochloric acid in ethanol to give hydrazones (5-7) , the NMR spectra compound(5) show sign of multi-at (7.15-8.33)δ back to 14 protons aromatic , single sign at (5.65)δ back to SH group and single sign at (8.9)δ back to N=CH. the IR spectra for compound (5) show absorption at 1669-1620 $cm^{-1}$ for C=N , 3190 $cm^{-1}$ for SH and 3050 $cm^{-1}$ C-H aromatic . the NMR spectra compound(6) show sign of multi-at (7.11-8.19)δ back to 12 protons aromatic , single sign at (5.59)δ back to SH group , single sign at (9.01)δ back to O-H phenol and single sign at (8.82)δ back to N=CH. the NMR spectra compound(7) show sign of multi-at (6.93-8.02)δ back to 12 protons aromatic , single sign at (5.59)δ back to SH group , single sign at (2.4)δ back to tow methylene group substituted on benzene ring and single sign at (8.42)δ back to N=CH. the hydrazones (5-7) were treated with phosphorus oxychloride or with glacial acetic acid to give bicyclic substituted benzene (8-10) , the NMR spectra compound(8) show sign of multi-at (7.57-8.63)δ back to 14 protons aromatic . the IR spectra for compound (8) show 1651 $cm^{-1}$ C=N and 978 , 1166 $cm^{-1}$ C-S-C and and no absorption for S-H. the NMR spectra compound

(9) show sign of multi-at (7.11-8.19)δ back to 12 protons aromatic , and single sign at (8.93)δ back to O-H phenol . the NMR spectra compound (10) show sign of multi-at (6.93-8.02)δ back to 12 protons aromatic and single sign at (2.4)δ back to tow methylene group substituted on benzene ring Table (3).

The vibration analysis showed that the optimized structure was in accordance with the point on the potential minimum energy surface.

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

| **Comp.no.** | $E_{HOMO}$ e.v. | $E_{LOMO}$ e.v. | **H** | **μ** | **W** |
|---|---|---|---|---|---|
| 4 | -6.277 | 0.419 | 3.348 | -2.929 | 1.28121 |
| 5 | -2.141 | -1.231 | 0.455 | -1.686 | 3.12373 |
| 6 | -1.658 | -1.230 | 0.214 | -1.444 | 4.87181 |
| 7 | -1.229 | -0.912 | 0.158 | -1.0705 | 3.62648 |
| 8 | -5.666 | -0.030 | 2.818 | -2.848 | 1.43915 |
| 9 | -5.666 | 0.360 | 3.013 | -2.653 | 1.16800 |
| 10 | -5.665 | 0.429 | 3.039 | -2.618 | 1.12821 |



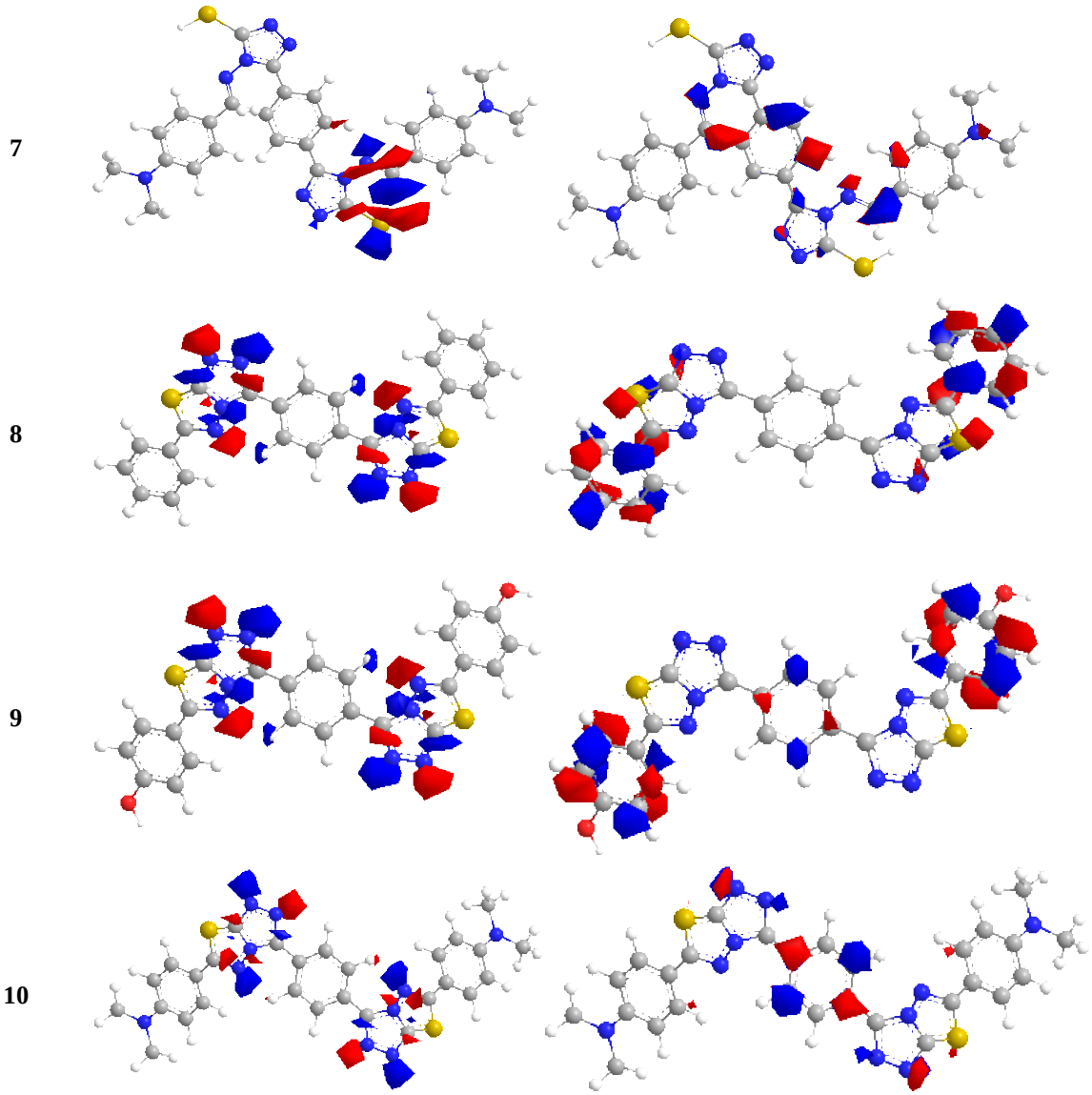



Figure 2. HOMO , highest occupied molecular orbital ; LOML , lowest unoccupied molecular orbital , compounds (4-10)

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 different energy between the tow 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)

comparator with compound(5) and (6) , while the compounds (8-10) show increase values cause the compounds do not contain factional groups only heterocyclic ring 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 increased the value of Global electrophilcity index with the decrease susceptibility Donor with compounds (5-7) the hydrogen atoms in ( N=CH & -SH) well be acidic make compounds behavior electrophilic that's see in W values theoretical calculated . The increase in electron potential chemical spin Global electrophilcity index is the latest proof of the stability of the prepared compounds as Table 2.
compounds (8-10) contains double bonds between (C=N) behavior nuophilic ; that's see in W values theoretical calculated .The structure of the synthesized compounds were confirmed by UV , IR , NMR and physical methods .

Table 3. UV & IR spectra

| Comp. no. | UV | IR ύ $cm^{-1}$ , KBr | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | C=O | C=N | -NH | -SH | C-$H_{alph}$ | C-$H_{arm}$ | Others |
| 1 | 250,324 | 1728 | -- | -- | -- | 2944 | 3060 | -- |
| 2 | 241,342 | 1642 | -- | 3418 | -- | -- | 3070 | -- |
| 3 | 225,318 | 1718 | -- | 3400 | -- | -- | 3030 | C=S 1275 |
| 4 | 234,346 | -- | 1627 | 3406 , 3292 | 3206 | -- | 3030 | -- |
| 5 | 288,390 | -- | 1669 , 1620 | -- | 3190 | 2960 | 3050 | -- |
| 6 | 299,401 | -- | 1656 , 1622 | -- | 3172 | 3000 | 3060 | O-$H_{phenol}$ 3367 |
| 7 | 256,345 | -- | 1670 | -- | 3200 | 2925 | 3050 | -- |
| 8 | 278,377 | -- | 1651 | -- | -- | -- | 3071 | C-S-C 978,1166 |
| 9 | 305,412 | -- | 1698 | -- | -- | -- | 3064 | O-$H_{phenol}$ 3422 C-S-C 993,1159 |
| 10 | 267,349 | -- | 1653 | -- | -- | 2924,2853 | 3007 | C-S-C 1016,1171 |

## 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* ).

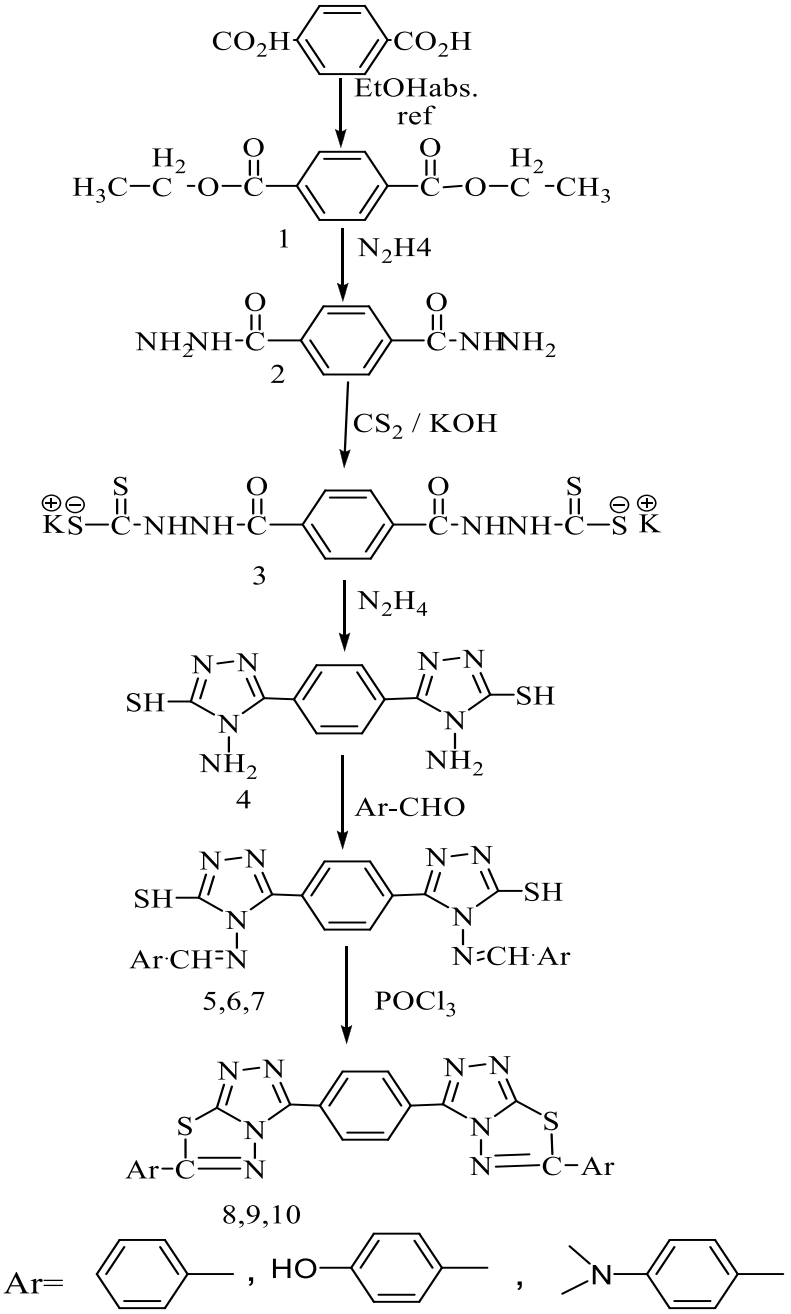
Table 4. Biological active compounds (5-10)

| Compound no. | *Staph Epidermidis* | *E. Coil* | *Staph Aureus* |
|---|---|---|---|
| 5 | 19 | 14 | 17 |
| 6 | 15 | 16 | 11 |
| 7 | 22 | 18 | 9 |
| 8 | 14 | 12 | 18 |
| 9 | 11 | 9 | 15 |
| 10 | 16 | 11 | 14 |
| Ciprofloxacin 5mg/disk | - | 15 | - |
| Chloramphenicol 30mg/disk | 16 | 14 | 17 |

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

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

Compound (8) were tested against *Staph Aureus* shows a good activity against with compare to standard controls , compounds (6,7,9,10) were tested against shows a less activity against *Staph Aureus* with respect to standard controls , compound (5) give same activity standard control with against *Staph Aureus* .Table 3.




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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