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# Preparation of 2-sub stitutedphenyl-3-bis-2,4-(methylphenyl, 4-amino) -s-triazine-6-ylaminobenzoylamino-5-H-4- thiazolidinone Computational Studies of PC Model

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## Abstract

*Thiazolidinones have been shown to have various important therapeutic activities such a antifungal, antibacterial, anticonvulsant, anti-HIV, insecticidal, tuberculostatic and antiviral agents etc. sulfathiazole is an importance bacteriostatic sulfadrug, acetazolamide and methazolamide are power diuretics and all these are thiazole derivatives. Vitamin-$B_1$ (thiamine) is an important thiazole derivative which is used in Beriberi. The reaction of p-toluidine and cyanuric chloride in dioxane gave 2-(4'-methyl phenyl amino) s-triazine (I). The reaction of compound (I) with p- toluidine in dioxane gave bis -2,4-(4'-methyl phenyl amino)-s-triazine (II). The compound (II) was treated with ethyl p-amino benzoate in dioxane gave bis 2,4-(4'-methyl phenyl amino)–s-triazine-6-yl-aminoethylbenzoate (III). The compound (IV) bis-2,4-(4'-methylphenylamino)-s-triazine-6-ylaminobenzoylhydrazone was obtained by reaction of compound (III) with hydrazine hydrate in dioxane. A mixture of compound (IV) and different aromatic aldehydes in dioxane were refluxed which yielded bis-2,4 (4'-methylphenylamino)-s-triazine-6-ylaminobenzoyl substituted benzylhydrazone (V). The compound (V) was refluxed with thioglycolic acid which gave 2-substituted phenyl-3-bis-2,4-(4'-methylphenylamino)-s-triazine-6-ylaminobenzoylamino-5-H-4- thiazolidinone.*

**Keyword:** Thiazole, thiazolidinone, triazine Vitamins,Heterocyclic.

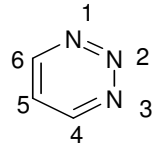
## Introduction

The triazine structure is a heteteocyclic ring, analogous to the six- membered benzene ring but with three carbons replaced by nitrogens. The three isomeric structures of triazine are distinguished from each other by the position of their nitrogen atoms, and are refered to as 1, 2, 3-triazine, 1, 2, 4-triazine and 1,3,5-triazine. Other aromatic nitrogen containing heterocycles are pyridines with 1 nitrogen atom, diazines with 2 nitrogen atoms in the ring and tetrazine with 4 nitrogen atoms. Triazines are weaker bases than pyridine.The three isomers of triazine, with ring numbering.

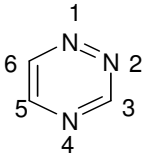
Cyanuric chloride (or) 2,4,6- trichloro-1,3,5-triazine (V) is obtained industrially by the vapour phase polymerization of cyanogens chloride on charcoal and is a valuable dyestuff intermediate. Its chlorine atoms are very reactive and can be displaced readily by nucleophilic reagents,[1-2] for example, hydrolysis with glacial acetic acid, which gives better results than water, which has also been used, yield 2,4,6-trihydroxy 1,3,5-triazine or cyanuric acid (IV). This can also be obtained by the trimerization of hydro cyanic acid or among other products, by heating urea. Cyanuric acid gives cyanuric chloride with phosphorus pentachlroride.

The drug *"paludrine"* also called p*roguanil* (VII), is widely used as an anti-malarial agent. It has, however, been shown that *"Paludrine"* itself has no action on the malaria parasite, but that is converted into the active agent, a triazine (VIII), by the host.

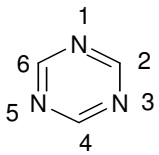
Antibacterial and antifungal disease is very common all over the world. Currently used antimicrobial agents are not effective due to the resistance developed by the microbes. And therefore, it is an ongoing effort to synthesize new antimicrobial agents. Over and above there is no permanent structure and activity relationship. The s-triazine and its derivatives have their own importance in heterocyclic compound due to their very good activities. The s-triazine has been associated with a wide range of therapeutic activities. Such as sleeping sickness and prortozoal diseases antibacterial antimicrobial, antitumor, muscles relaxant properties.



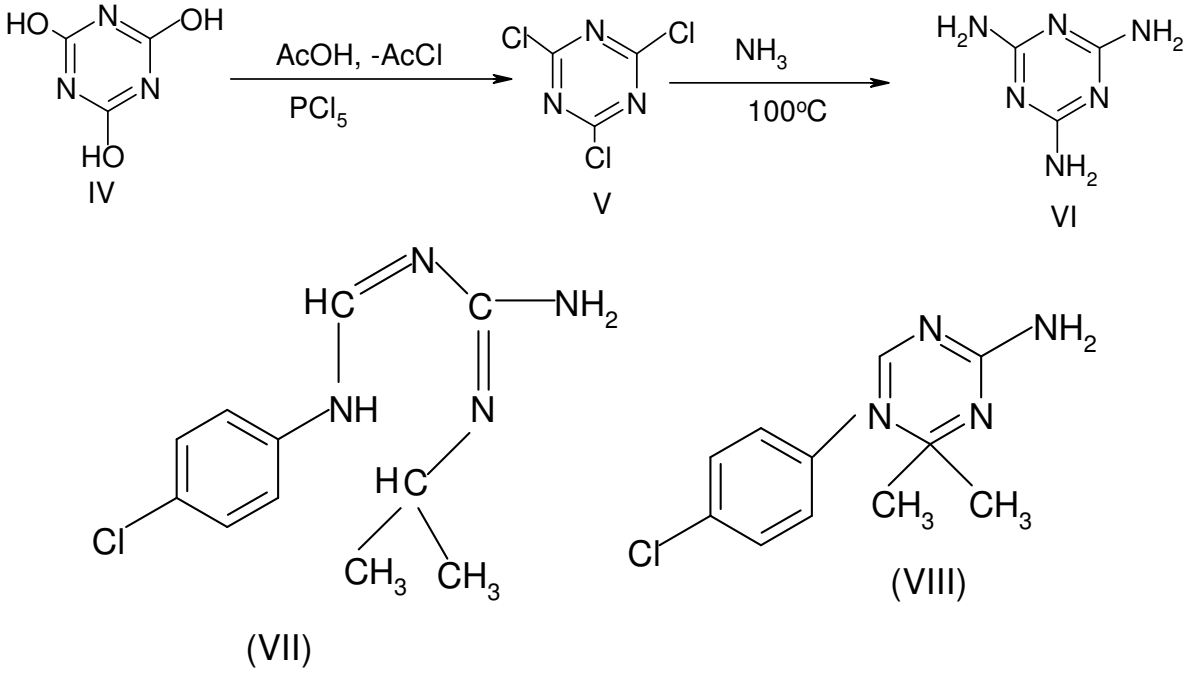
(I)
1,2,3-Triazine



(II)
1,2,4-Triazine

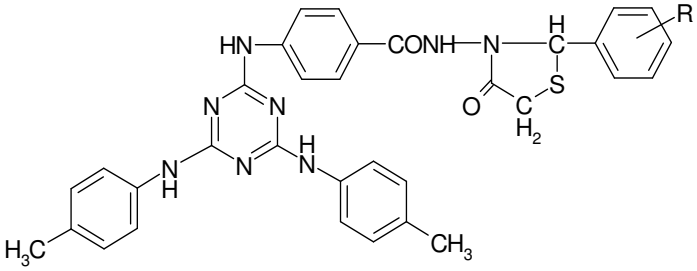


(III)
1,3,5-Triazine




Thiazole (IX) was first dercribed by Hantzsch and weber in 1887. Popp confirmed it struchure in 1889. Thiazole is structurally related to thiophene and pyridine but in most of its properties it resembles the later . Thiazole is one class of organic heterocyclic compounds in which a five membered di-unsaturated ring contains one atom of nitrogen in a non adjacent position and one atom of sulfur.

**Synthesis of Compounds:** The compounds selected for synthesis in the present study may be represented by the general formula given as under




| Ar | Ar | Ar |
|---|---|---|
| $C_6H_5$ | 4-$OCH_3$. $C_6H_4$ | 3-Cl. $C_6H_4$ |
| 4 $NO_2$. $C_6H_4$ | 2-OH. 4-$NO_2$. $C_6H_3$ | 2,4$(Cl)_3$.$C_6H_2$ |
| 3,4$(Cl)_2$. $C_6H_3$ | 2-OH.$C_6H_4$ | 2-$OCH_3$. $C_6H_4$ |
| 3-$NO_2$. $C_6H_4$ | 2. $C_4H_3N_2$ | 2,4,$(NO_2)_2$. $C_6H_3$ |
| 4-$CH_3$.$C_6H_4$ | 2-$ClC_6H_4$ | 3-Cl, 6-OH.$C_6H_3$ |
| | | 2-Br, 4--$(NO_2)_2C_6H_2$ |
| | 3,4.$(NO_2)_2$. NH.CH.$C_6H_3$ | 3-Cl-4F-$C_6H_3$ |

## Material and Methods

**Step I: Preparation of 2-(4'-methyl phenyl amino)-s-triazine:** p-toluidine (0.02 mol) was added slowly to cyanuric chloride (0.02 mol) in dioxane (30mL) with constant stirring for 4 hrs at 0 to $8^0$C. Then sodium carbonate (0.006mol) dissolved in water (12mL) was added drop wise to neutralize, HCl evolved during the reaction. Finally the contents were poured into ice. The solid separated out was filtered, washed with water, dried and recrystallized from alcohol to give (I). The purity was checked by TLC.

**Step II: Preparation of bis-2,4- (4'-methyl phenyl amino)- s-triazine:** p-toluidine (0.02mol) was added slowly to compound I (0.02mol) in dioxane (30mL) with constant stirring for 8 hrs at room temperature. Then sodium carbonate (0.006mole) dissolved in water (12mL) was added drop wise to neutralize HCl evolved during the reaction. Finally the contents were poured into crushed ice. The solid separated out was filtered, washed with water, dried and recrystallized from alcohol to give (II) The purity was checked by TLC.

**Step III: Preparation of bis 2,4-(4'-methyl phenyl amino)–s-triazine-6-yl-aminoethyl benzoate:** Ethyl-p-aminobenzoate (0.02mol) and compound II (0.02mol) were dissolved in dioxane (40mL). The reaction mixture was refluxed for 8 hrs, cooled and poured into crushed ice. Then sodium carbonate (0.06 mol) dissolved in water (12mL) was added to neutralize HCl evolved during the reaction. The solid separation out was filtered, washed with water, dried and recrystallized from alcohol to give (III) The purity of the compound was checked by TLC.

**Step IV: Preparation of bis-2,4-(4'-methylphenylamino)-s-triazine-6-ylaminobenzoyl hydrazone:** A mixture of compound III (0.02mol) in dioxane and hydrazine hydrate (0.02mol), was refluxed on a water bath for 6hrs. The product was isolated and crystallized from dioxane.

**Step V: Preparation of bis-2,4-(4'-methylphenylamino)-s-triazine-6-ylaminobenzoyl substituted benzylhydrazone:** A mixture of compound IV (0.02mol) and substituted aldehyde (0.01mol) in dioxane (20mL) was refluxed for 6hrs. The product was isolated and crystallized from methanol gave (V). The purity was checked by TLC.

**Step VI: Preparation 2-substitutedphenyl-3-bis-2,4-(4'-methylphenylamino) -s-triazine-6-ylaminobenzoylamino-5-H-4- thiazolidinone:** Thioglycolic acid (0.02mol) was added to compound V (0.02mol) in dry benzene (20mL) and refluxed for 6 hrs. The product was isolated by washing the upper organic layer with water and sodium bicarbonate solution and crystallized from dioxane. The purity of the compound was checked by TLC.

**Reaction Sequence**

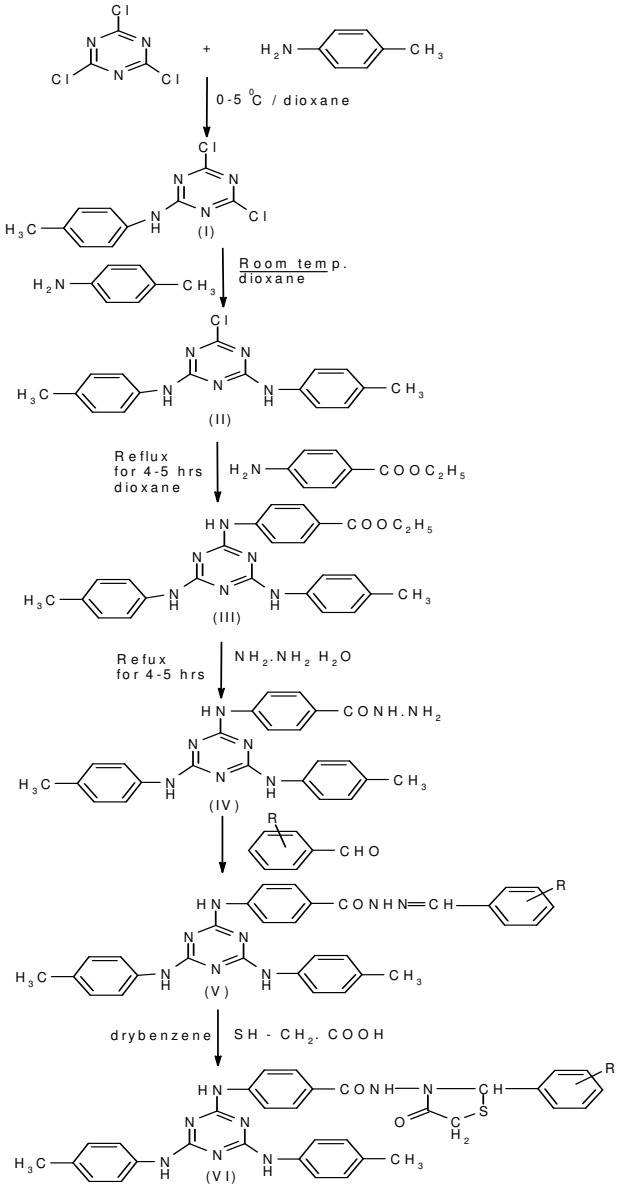


**Table-1**
**Physical characterization data of the synthesized thiazoline, derivatives**

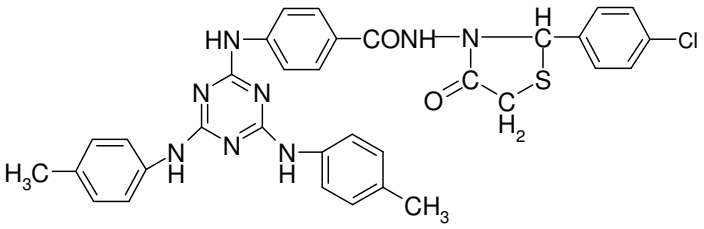
| **Compound** | **DKI a** | | | | | |
|---|---|---|---|---|---|---|
| Name | 2-(4-chlorophenyl)-3-bis-2,4-(4'-methylphenylamino)-s-triazine-6-ylaminobenzoylamino-5-H-4-thiazolidinone. | | | | | |
| M.F. | $C_{33}H_{29}N_8O_2SCl$ | |  | | | |
| M.wt. | 537.130 | | | | | |
| M.P. | 150 | | | | | |
| Yield. | 79 | | | | | |
| Elemental Analysis | C% | | N% | | H% | |
| | Calc | Found | Calc | Found | Calc | Found |
| | 63.22 | 63.29 | 16.58 | 18.53 | 5.57 | 5.58 |

**Table-2**
**Characterization of infra red data**

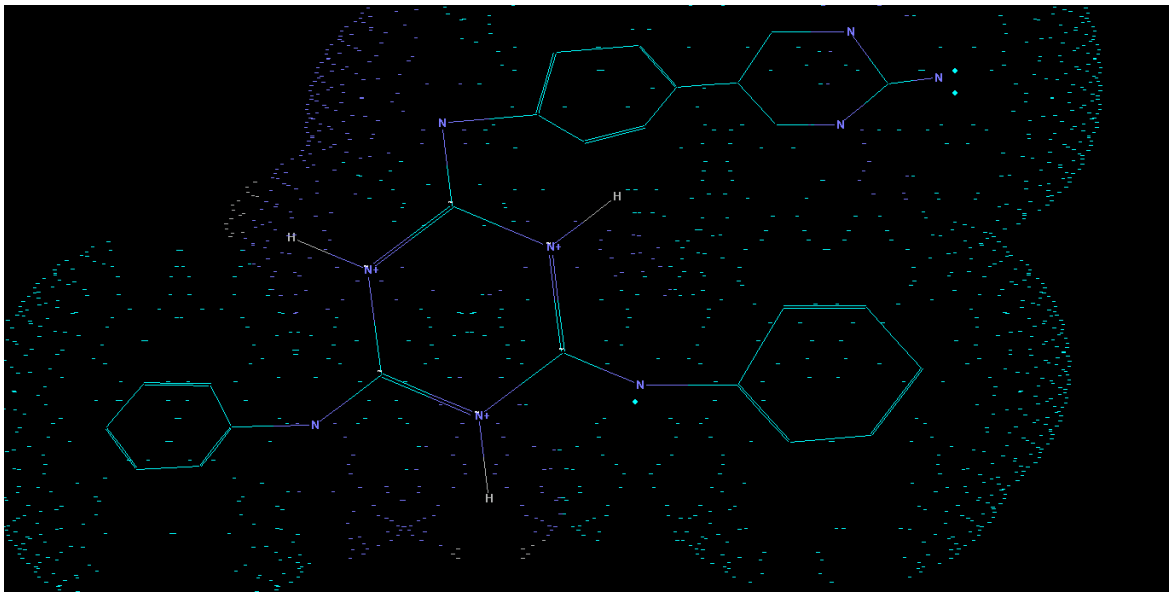
| **Type of vibration** | **Vibration mode** | **Frequency in cm$^{-1}$** |
|---|---|---|
| N-H | N-H str. | 3219.60 |
| Aromatic | Ar-H str. | 3188.40 |
| | C=C str. | 1570.12 |
| $-CH_3$ | C-H str. | 2960.83 |
| Ar-Cl | Ar-Cl-bending | 745.37 |
| >C=O | C=O str. | 1697.42 |
| $>CH_2$ | C-H str. | 1491.32 |
| -C-S | C-S bending | 709.62 |
| C-N | C-N bending | 710.15 |
| C-N | C=N str. | 1583.40 |
| Thiazolidinone ring breathing mode | C-H bending | 966.15 |
| Disubstituted Aromatic ring | Ar-H bending | 758.45 |

**Table-3**
**Characterization of NMR data**

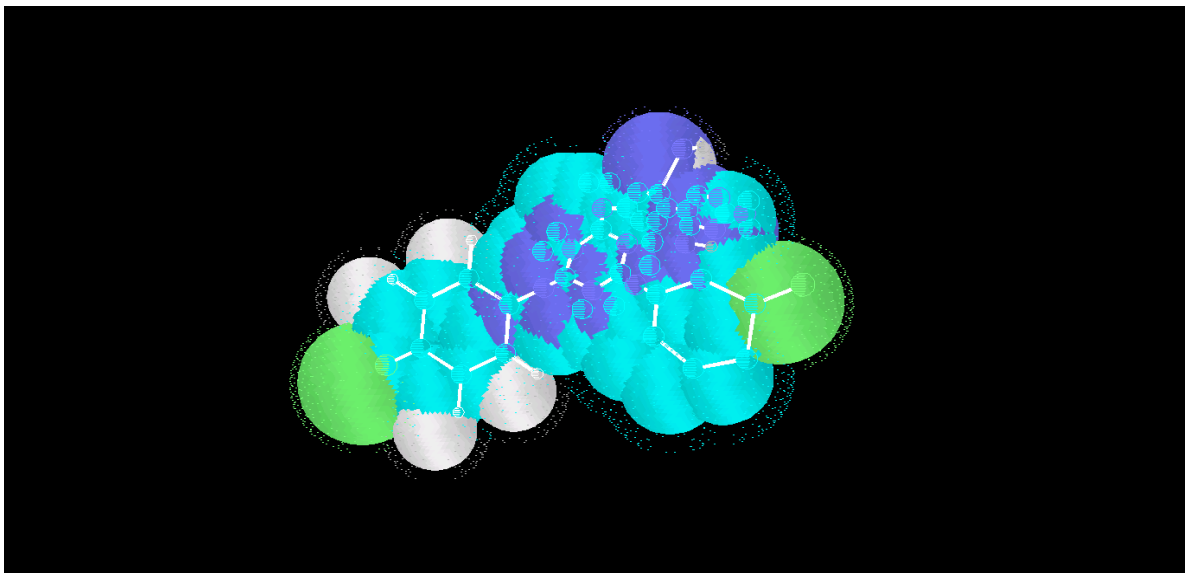
| **Signal No.** | **Signal position (δ ppm)** | **Integral value** | **No of Proton** | **Multiplicity** | **Inference** |
|---|---|---|---|---|---|
| 1 | 2.126 | 1.956 | 1H | singlet | $CH_2$ of thiazolidinone |
| 2 | 2.348 | 4.858 | 6H | singlet | $2CH_3$ |
| 3 | 3.544 | 2.872 | 2H | singlet | $CH_2$ of thiazolidinone |
| 4 | 6.145 | 3.942 | 4H | Sym.multiplet | Disubs. benzone ring |
| 5 | 6.445 | 6.854 | 8H | sym.multiplet | $2CH_3$ subs. benzone |
| 6 | 5.554 | 4.956 | 4H | sym.multiplet | Chloro subs. benzene |
| 7 | 5.237 | 3.979 | 3H | singlet | 3NH |
| 8 | 5.354 | 1.99 | 1H | singlet | CONH proton |

**Table-4**
**Computer simulated PC Model data for marked bonds and their subsequent angles**

| Compound code | Substituent | B.L. C-N | B.A. N-C | Dihed. Ang. C-N-C | Mol. Vol. | VDW | Dip. Mom | MMX Energy |
|---|---|---|---|---|---|---|---|---|
| DKI a | Br | 1.465 | 120.60 | 162.31 | 256 | 18.03 | 4.197 | 37.378 |
| DKI b | $C_l$ | 1.467 | 121.82 | 165.31 | 246 | 12.11 | 2.18 | 36.374 |
| DKI c | OH | 1.464 | 121.42 | 166.71 | 256 | 10.304 | 2.479 | 30.453 |
| DKI d | $NO_2$ | 1.466 | 120.43 | 178.41 | 256 | 15.44 | 2.312 | 34.376 |
| DKI e | OH,4-$OCH_3$ | 1.469 | 121.55 | 173.10 | 266 | 11.47 | 4.895 | 44.787 |
| DKI f | $NO_2$ | 1.460 | 120.55 | 165.91 | 256 | 29.96 | 3.736 | 32.462 |
| DKI g | -OH | 1.451 | 120.63 | 167.11 | 371 | 2.141 | 3.512 | 41.491 |
| DKI h | -$N(CH_3)_2$ | 1.465 | 121.66 | 167.71 | 363 | 10.74 | 2.189 | 39.266 |
| DKI i | 2-$C_l$ | 1.461 | 121.52 | 173.11 | 256 | 11.47 | 2.895 | 44.767 |
| DKI j | 3-$C_l$ | 1.462 | 120.64 | 165.91 | 266 | 29.96 | 2.736 | 43.482 |



**PC-Model: Structure of thiazoline, derivatives derivatives**



**Nano-Particals Structure in Synthesized Compounds**

**Table-5**
**Antibacterial Activity of the Synthesized thiazoline, Derivatives**

| *Comp. code* | *Bacillus subtilis* | | *Escherichia coli* | | *Klebsiella pneumoniae* | | *Staphylococcus aureus* | |
|---|---|---|---|---|---|---|---|---|
| | **2%** | **4%** | **2%** | **4%** | **2%** | **4%** | **2%** | **4%** |
| DKI a | +++ | +++ | ++ | +++ | + | ++ | ++ | +++ |
| DKI b | - | + | - | - | + | + | + | + |
| DKI c | ++ | +++ | +++ | ++++ | + | ++ | ++ | +++ |
| DKI d | ++ | +++ | +++ | ++++ | ++ | +++ | ++ | ++ |
| DKI e | - | + | + | - | - | + | + | ++ |
| DKI f | +++ | +++ | ++ | ++ | ++ | +++ | ++ | +++ |
| DKI g | - | + | - | - | + | + | + | + |
| DKI h | + | + | ++ | +++ | ++ | +++ | + | ++ |
| DKI i | +++ | ++++ | ++ | +++ | + | ++ | ++ | +++ |
| DKI j | + | ++ | ++ | ++ | + | + | ++ | + |
| Std: | +++ | ++++ | +++ | +++ | +++ | +++ | +++ | +++ |

**Table-6**
**Antifungal Activity of the Synthesized thiazoline, Derivatives**

| *Comp. code* | *Aspergillus niger* | | *Aspergillus flavus* | | *Trichoderma viride* | | *Cadida albicans* | |
|---|---|---|---|---|---|---|---|---|
| | **2%** | **4%** | **2%** | **4%** | **2%** | **4%** | **2%** | **4%** |
| DKI a | + | + | - | + | - | + | + | + |
| DKI b | +++ | +++ | ++ | +++ | + | ++ | ++ | +++ |
| DKI c | + | + | + | ++ | ++ | ++ | + | ++ |
| DKI d | ++ | +++ | +++ | +++ | ++ | +++ | ++ | ++ |
| DKI e | - | + | + | - | - | + | + | ++ |
| DKI f | +++ | +++ | ++ | +++ | ++ | +++ | ++ | +++ |
| DKI g | - | + | - | - | + | + | + | + |
| DKI h | + | ++ | ++ | ++ | + | + | ++ | + |
| DKI i | +++ | +++ | ++ | +++ | + | ++ | ++ | +++ |
| DKI j | + | ++ | ++ | ++ | + | + | ++ | + |
| Std: | +++ | ++++ | +++ | +++ | +++ | +++ | +++ | +++ |

For the present study filter paper disc diffusion method was used. Activity of synthesized compounds was determined in 2% and 4% solutions in DMSO against four bacteria and four fungi. The bacteria tested were *B. subtilis, E. coli, K. pneumonia* and *S.aureus*. The fungi tested were *A .niger, A. flavus, T. viride,* and *C.albicans.* The activity of the compounds was compared with standard drug streptomycin for Bacteria and nystatin for fungi. The zone of inhibition was measured in mm.

## Conclusion

The reaction of *p*-toluidine and cyanuric chloride in dioxane gave 2-(4'methyl phenyl amino) s-triazine (I). The reaction compound (I) with *p*- toluidine in dioxane gave bis -2,4,(4'-methyl phenyl amino)-s-triazine (II). The compound (II) was treated with ethyl p-amino benzoate in dioxane gave bis 2,4-(4'-methyl phenyl amino)–s-triazine-6'-yl-aminoethylbenzoate(III).The compound bis-2,4-(4'-methylphenylamino)-s-triazine-6-ylaminobenzoylhydrazone was obtained by reaction of compound (III) with hydrazine hydrate in dioxane. A mixture of compound and different aromatic aldehydes in dioxane were refluxed which yielded bis-2,4-(4'-methylphenylamino)-s-triazine-6-ylaminobenzoyl substituted benzylhydrazone (V). The Compound (V) was refluxed with thioglycolic acid which gave 2-substituted phenyl-3-bis-2,4-(4'-methylphenylamino)-s-triazine-6-ylaminobenzoylamino-5-H-4-thiazolidinone (VI).

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