# AN EFFECTIVE SYNTHESIS AND BIOLOGICAL SCREENING OF 2-(4-CHLOROPHENYL- 1,3,4-OXADIAZOL-2-*YL*-5-SULFANYL)-4-(QUINOLINE-8-YLOXY)-6-(ARYL AMINO )-*S*-TRIAZINE

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## Abstract:

A novel series of 2-(4-Chlorophenyl- 1,3,4-Oxadiazol-2-yl-5-Sulfanyl)-4-(Quinoline-8-yloxy)-6-(Arylamino)-S-Triazine have been synthesized by the condensation of 2-(4-Chlorophenyl-1,3,4-Oxadiazol-2yl-5-Sulfanyl)-4,6-dichloro-s-triazine and 8-hydroxyquinoline . The novel compounds structure has been established on the basis of their substituted aryl amine derivatives ((K-1 to K-10). All the compounds were characterized by Mass, FT-IR, 1H-NMR spectroscopy as well as elemental analysis. These new compounds were evaluated for their in vitro antibacterial activity and compare their biological screening against some standard drugs.

**Keywords:** 1,3,4-oxadiazol, s-triazine, Arylamino, quinoline-8-yloxy, antibacterial, biological screening.

## 1. Introduction

The massive expanding population of immune compromised patient results in a corresponding increase of diseases caused by bacteria, fungi and other yeast. Infection caused by these microorganisms pose a serious challenge to the medical community and highlight the importance and urgent need for new, more potent and selective non-traditional antimicrobial agent. The incidence of bacterial infections has increased dramatically in recent years1. The widespread use of antibacterial and antifungal drugs and their resistance against bacterial and fungal infections has led to serious health hazards. In continuation of our interest on chemistry of Nitrogen containing heterocycles play an important role, not only for life science industry but also in many other industrial fields related to special and fine chemistry. Among them 1,3,5-triazines represent a widely used lead structure with multitude of interesting application in numerous field.[1] Several derivatives of s-triazine show antimicrobial[2], antibacterial[3], and herbicidal activites.[4] They are also used for the treatment of HIV infection.[5,6] several investigators found s-triazine nucleus as potential therapeutic agents for diseases due to bacteria, malaria and cancer.[7] 1,3,5-Triazine are a class of compounds well known

for a long time and still continue the object of considerable interest, mainly due to their applications in different fields, including the production of herbicides and polymer photostabillizers.[8] Some s-triazine display important biological properties, for example hexamethyl melamine (HMM) and 2-amino-4-morpholino-s-triazine are used clinically due to their antitumor properties to react lung breast and ovarian cancer, respectively.[9] Hydroxymethyl pentamethyl melamine is also the hydroxylated metabolite which corresponds to the major active form of HMM.[10] More recently, significant aromatase inhibitory activities were observed for s-triazines of general structure. For the similar general structure antitumor activity in human cancer and murine leukemia cell lines were also observed. The s-triazine presents potential use as siderophore (microbial iron shelter) mediated ring[11] and the general structure presents potent corticotrophin-releasing factor$_1$ receptor antagonist activity.[12] The compound show potent activity against leukotriene $C_4$ ($LTC_4$) antagonist, which possess a protective effect on HCl, ethanol induced gastric lesions.[13] More recently it was discovered that the compound is a potent corticotrophin-releasing factor receptor antagonist.[14] Among several other s-triazine substituted cyclohexylamines tested[15], the substrate present a good invitro activity against the protozoan parasite Trypanosoma brucei, the causative organisms of Human Arican Trypanosomasis.[16] The diverse biological activities observed for different molecules containing the s-triazine unit have been further explore in order to discover new potential molecules through the synthesis of libraries by combinatorial approach.[17,18] Thus, investigation of s-triazine chemistry is an actual task both from theoretical and applied viewpoints.

## 2 . Experimental

All the melting points were recorded on Cintex melting point apparatus and are corrected. IR spectra in KBr were recorded on Schimadzu FTIR spectrophotometer in $cm^{-1}$. $^1$HNMR spectra were recorded in $CDCl_3$ or DMSO on a Bruker DRX-400 MHZ NMR instrument. Chemical shifts were reported in ppm using TMS as internal standard on δ scale. Mass spectra of compounds were recorded on mass spectrometer (Agilant 1100 series) . Completion of the reactions was monitored time to time by TLC using E-Merck 0.25 mm silica gel plates with using ethyl acetate : hexane (4 : 6) and toluene : acetone (8:2) as solvent system.

**Step – 1: Synthesis of methyl 4-chloro benzoate:** *p*-chloro Benzoic acid (0.1mol) in 200 ml methanol and 5.0 ml con.sulfuric acid was refluxed for 12 hrs. Excess solvent distilled off and collect the product. The pregress of reaction was monitored by TLC using toluene : acetone (8:2) as eluent.

**Step – 2: Synthesis of 4-chloro benzohydrazide:** A mixture of 4-chloro benzoate (0.1mol) and hydrazine hydrate (0.2mol) in methanol was heated for 14 hrs. and poured into ice. The product was filtered and washed with cold water. Crystallized from ethanol. The progress of reaction was monitored by TLC using toluene : acetone (8:2) as eluent.

**Step – 3: Synthesis of 5-(4-chlorophenyl)-1,3,4-oxadiazole-2-thiol:** The mixture of 4-chloro benzohydrazide (0.1 M), $CS_2$ (0.1 M) and KOH solution (0.05 M, 10ml) in methanol (82 ml) was refluxed for 8 to 10 hours. After the completion of reaction the resultant mixture was poured in to crushed ice. Product was filtered, washed with water and recrystallized from alcohol. The progress of reaction was monitored by TLC using toluene : acetone (7: 3) as eluent.

**Step – 4: Synthesis of 2-(4-chlorophenyl-1,3,4-oxadiazol-2-yl-5-sulfanyl)-4,6-dichloro-s-triazine:** To a stirred solution of cyanuric chloride (0.1 M, 18.4 gm) in THF 100 ml at 0-5$^0$C, The solution of 5-(4-chlorophenyl)-1,3,4-oxadiazole-2-thiol (0.1 M, 19.2 gm) in THF (100 ml) was added dropwise and PH was maintained neutral by the addition of 10 % $NaHCO_3$ solution . The stirring was continued at 0-5$^0$C for 2-3 hours. After the completion of reaction the stirring was stopped and the solution was treated with crushed ice. The solid product obtained was filtered and dried. The progress of reaction was monitored by TLC using ethyl acetate : hexane (6 : 4) as eluent. The crude product was purified by crystallization from absolute alcohol.

**Step – 5: Synthesis of 2-(4-chlorophenyl-1,3,4-oxadiazol-2-yl-5-sulfanyl)-4-(quinoline–8–yloxy)-6-chloro-s-triazine:** The solution of 8-Hydroxyquinoline (0.1 M) in THF was added drop-wise to well stirred suspenension of 2-(4-chlorophenyl-1,3,4-oxadiazol-2-yl-5-sulfanyl)-4,6-dichloro-s-triazine (0.1 M) in THF (100 ml) maintaining the temp 40$^0$C the PH was kept neutral by the addition of 10 % $NaHCO_3$ solution. The temp. Was gradually raised to 45$^0$C during 2 hours and futher maintained for 2 hr. After the completion of reaction the solution was poured in ice-cold water. The solid product was filtered and dried. The crude was purified by recrystalization from absolute alcohol.

**Step – 6: Synthesis of 2-(4-chlorophenyl-1,3,4-oxadiazol-2-yl-5-sulfanyl)-4-(quinoline–8–yloxy)-6-(arylamino)-s-triazine:** A mixture of 2-(4-chlorophenyl-1,3,4-oxadiazol-2-yl-5-sulfanyl)-4-(quinoline–8–yloxy)-6-chloro-s-triazine (0.005 M) and aryl amine (0.005 M) in dioxane (50.0 ml) was refluxed on heating mental with stirring at 100-110$^0$C for 5 hours. The PH was adjusted to neutral by addition of 10% $NaHCO_3$ solution. After the completion of reaction the content was added to ice-cold water. The product was filtered and dried the progress of reaction was monitored by TLC using ethyl acetate : hexane (4 : 6) eluent.

## 3. Results and Discussion

The base motif 2-(4-Chlorophenyl- 1,3,4-Oxadiazol-2-yl-5-Sulfanyl)-4-(Quinoline-8-yloxy)-6-(Arylamino)-S-Triazine and all derivatives of aryl amines (K-1 to K-10) were obtained in good amount of percentage yield by multi step synthesis.

**IR**: FTIR spectrum showed absorption bands of base motif and various substituted aryl amines (K-1 to K-10) at 1263cm$^{-1}$(<C=O - Streching in oxadiazole),1573cm$^{-1}$ (<C=N – Streching in oxadiazole), 813cm$^{-1}$(-C=N- Streching in S-triazine), 3392cm$^{-1}$(-NH- Stretching in amide),1238cm$^{-1}$(-C-O-C Stretching (asym.) in alkanyl ether), 989cm$^{-1}$ (-C-O-C Stretching (sym.) in alkanyl ether), 2848cm$^{-1}$ (-C-H- Stretching in methelene),1361cm$^{-1}$(-C-CH3- Stretching in aromatic ring), 1275cm$^{-1}$(-C-S-C Stretching, strong), 1130 cm$^{-1}$(<C-O - Streching in 8-hydroxyquinolino),1361 cm$^{-1}$ (<C-O - Streching in 8-hydroxyquinolino),732 cm$^{-1}$(-C-C l- Stretching in aromatic ring)1084cm$^{-1}$(-C-F- Stretching in aromatic ring), 522 cm$^{-1}$(-C-Br- Stretching in aromatic ring)

**1H-NMR:** The 1H-NMR spectrum of ((K-1 to K-10) showed characteristic signals at 6.63-7.94 ppm which were assigned to the aromatic rings protons. A signal at 1.68-2.10 ppm was assigned to the cyclohexyl aryl proton. A signal at 2.88 ppm was assigned to the methyl proton. The singlet 9.29 and 9.52 ppm were assigned to the arylamine protons, respectively.

**Mass:** Mass spectral data support the proposed structures. The mass spectrum showed various characteristic peaks. A base peak at 384*m/z* was assigned to the base motif molecular ion and different ion peak obtained at various substituted aryl amines (K-1 to K-10).

**4. Reaction Scheme**

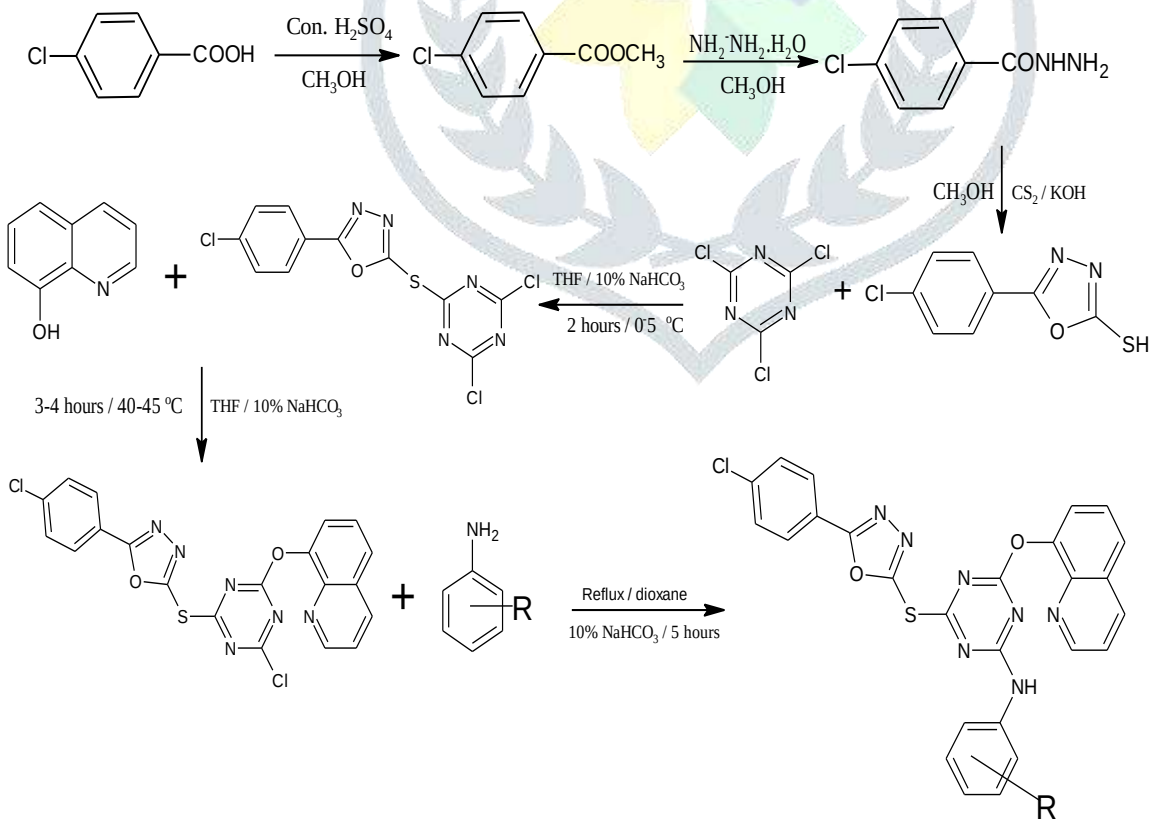



**Figure 1**

Where, R is substituted arylamines.

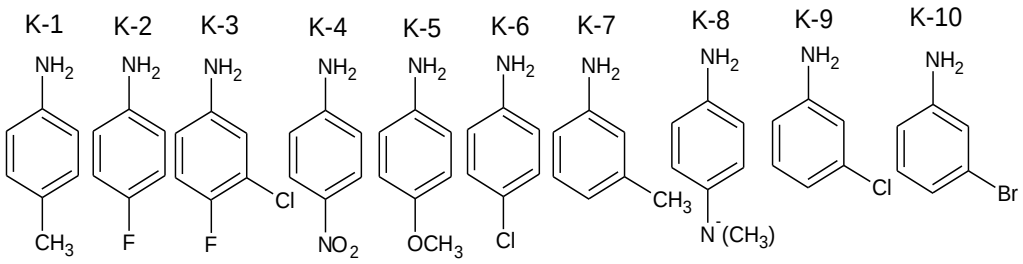



**Figure 2**

**Table-1: Physical properties of 2-(4-chlorophenyl-1,3,4-oxadiazol-2-yl-5-sulfanyl)-4-(quinoline–8–yloxy)-6-(arylamino)-s-triazine.**

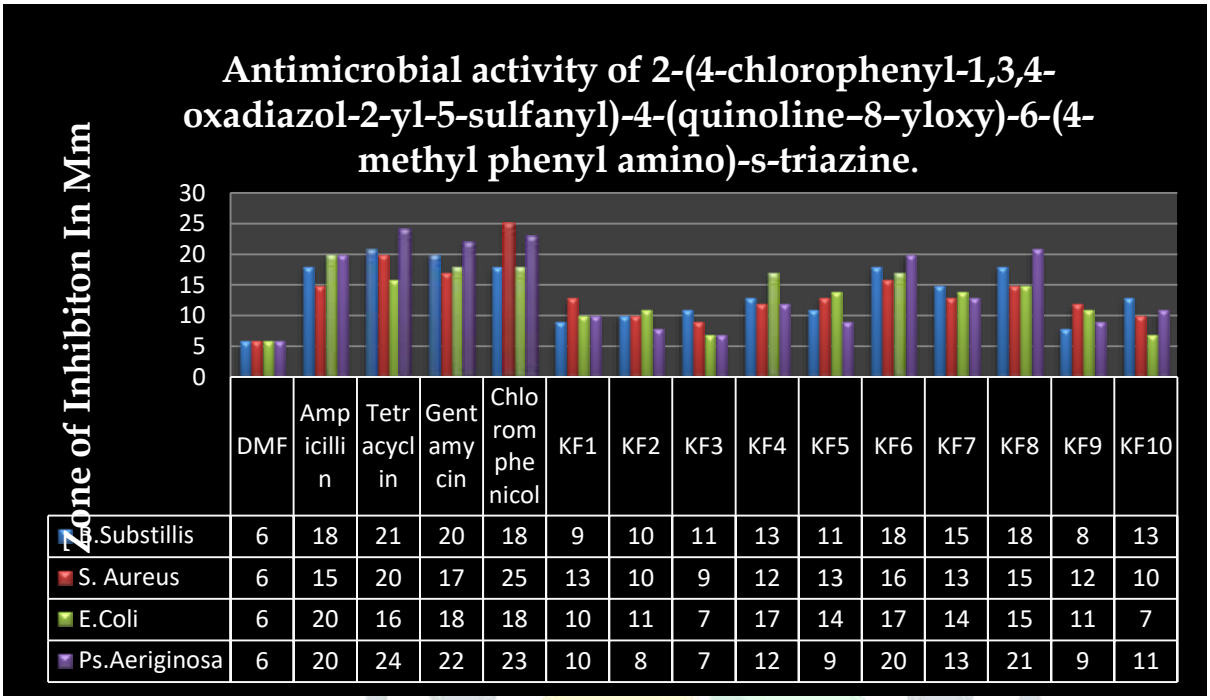
| Sr No. | Comp. | Molecular Formula | Mol. Weight | % of Yield | M.P (°C) | Elemental Analysis | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | %C | | %H | | %N | |
| | | | | | | Cal. | Found | Cal. | Found | Cal. | Found |
| 1 | K-F1 | $C_{27}H_{18}ClN_7O_2S$ | 539.9 | 78 | 148-151 | 60.05 | 60.08 | 3.36 | 3.39 | 18.16 | 18.19 |
| 2 | K-F2 | $C_{26}H_{15}ClFN_7O_2S$ | 543.4 | 79 | 175-178 | 57.41 | 57.43 | 2.78 | 2.79 | 18.02 | 18.04 |
| 3 | K-F3 | $C_{26}H_{14}Cl_2FN_7O_2S$ | 578.4 | 70 | 166-168 | 53.99 | 54.02 | 2.44 | 2.46 | 16.95 | 16.98 |
| 4 | K-F4 | $C_{26}H_{15}ClN_8O_4S$ | 570.4 | 72 | 230-232 | 54.69 | 54.71 | 2.65 | 2.68 | 19.63 | 19.67 |
| 5 | K-F5 | $C_{27}H_{18}ClN_7O_3S$ | 555.9 | 69 | 187-189 | 58.33 | 58.36 | 3.26 | 3.29 | 17.63 | 17.67 |
| 6 | K-F6 | $C_{26}H_{15}Cl_2N_7O_2S$ | 560.4 | 66 | 162-165 | 55.72 | 55.76 | 2.70 | 2.73 | 17.50 | 17.53 |
| 7 | K-F7 | $C_{27}H_{18}ClN_7O_2S$ | 539.9 | 70 | 197-199 | 60.05 | 60.09 | 3.36 | 3.39 | 18.16 | 18.19 |
| 8 | K-F8 | $C_{28}H_{21}ClN_8O_2S$ | 569.0 | 69 | 230-234 | 59.10 | 59.14 | 3.72 | 3.74 | 19.64 | 19.67 |
| 9 | K-F9 | $C_{28}H_{15}Cl_2N_7O_2S$ | 560.4 | 67 | 182-184 | 55.72 | 55.74 | 2.70 | 2.74 | 17.50 | 17.53 |
| 10 | K-F10 | $C_{26}H_{15}BrClN_7O_2S$ | 604.8 | 62 | 208-210 | 51.63 | 51.67 | 2.50 | 2.53 | 16.21 | 16.24 |

## 5. Biological Screening

This section deals with the in-vitro screening of newly prepared compounds of 2-(4-Chlorophenyl- 1,3,4-Oxadiazol-2-yl-5-Sulfanyl)-4-(Quinoline-8-yloxy)-6-(Arylamino)-S-Triazine and all derivatives of aryl amines (K-1 to K-10) for antimicrobial activity. The species *S.Aureus, E.coli, Ps.Aeriginosa* and *B.subtilis* have been taken for the antibacterial activities. Agar-cup method was carried out for the in-vitro screening for antimicrobial activity. All the compounds were screened against standard drugs like Ampicilin,

Tetracyclin, Gentamycine and Chloromphenicol. The results of the synthesized compounds are given for antimicrobial screening is mentioned in table as well as graphical chart in following Table-2.

**Graphical chart: Antimicrobial activity of 2-(4-chlorophenyl-1,3,4-oxadiazol-2-yl-5-sulfanyl)-4-(quinoline–8–yloxy)-6-(4-methyl phenyl amino)-s-triazine.**




| | DMF | Ampicillin | Tetracyclin | Gentamycin | Chloromphenicol | KF1 | KF2 | KF3 | KF4 | KF5 | KF6 | KF7 | KF8 | KF9 | KF10 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| B.Substillis | 6 | 18 | 21 | 20 | 18 | 9 | 10 | 11 | 13 | 11 | 18 | 15 | 18 | 8 | 13 |
| S. Aureus | 6 | 15 | 20 | 17 | 25 | 13 | 10 | 9 | 12 | 13 | 16 | 13 | 15 | 12 | 10 |
| E.Coli | 6 | 20 | 16 | 18 | 18 | 10 | 11 | 7 | 17 | 14 | 17 | 14 | 15 | 11 | 7 |
| Ps.Aeriginosa | 6 | 20 | 24 | 22 | 23 | 10 | 8 | 7 | 12 | 9 | 20 | 13 | 21 | 9 | 11 |

Figure-3

**5. Acknowledgement**

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