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# SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SOME NOVEL 1,3,5-TRIAZIN DERIVATIVES

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## ABSTRACT

We synthesized a novel series of substituted 4-(3-methylbenzo[*d*]isoxazol-6-yloxy)-6-(1H-benzo[*d*] imidazol-1-yl)-N-(4-(4-chlorophenyl)thiazol-2-yl)-1,3,5-triazin-2-aminesderivatives. The structures of the compounds were confirmed by spectral analysis. The compounds were examined for in-vitro antimicrobial activity against Gram-positive bacteria (*Staphylococcus aureus* and *Bacillus subtilis*), Gram-negative bacteria (*Escherichia coli* and *Salmonella typhi*), and antifungal activity against *Aspergillus niger*, *penicillin chrysogenum*, *Fusarium moneliforme* and *Aspergillus flavus.*

**KEYWORDS:** 2,4,6-trichloro1,3,5-triazine, benzisoxazole, 2-aminothiazole and benzimidazole.

## INTRODUCTION

Nitrogen containing heterocyclic play main role in industries and pharmaceutical activities. Among them 1,3,5-triazine represent a widely used lead structure with multitude of interesting application in numerous fields[1] Several derivatives of *s*-triazine show antibacterial[2] antimicrobial[3] and herbicidal activities.[4] They have found widespread applications in the textile, plastic, and rubber industries, and are used as pesticides, dyestuffs, optical bleaches, explosives, and surface active agents The replacement of a chlorine atom in cynuric chloride by basic group is greatly facilitated by the ring nitrogen atom of the symmetrically built *s*-triazine nucleus.

The Benzisoxazoles are biologically active compounds across a number of different therapeutic areas such as anti HIV[5], anticancer,[6] anti-inflammatory[7] analgesic and antimicrobial.[8]

In synthetic substituted thiazole derivatives, 2-aminothiazoles[9] have shown a variety of biological activities such as antibacterial, antifungal, antitubercular, anti-HIV, anti-inflammatory, anticancer, anticonvulsant, antidiabetic, antihypertensive, antiprotozoal, dopaminergic, plasminogen activator inhibitor-9, neuroprotective and antioxidant. This broad spectrum of activities makes 2-aminothiazole as an attractive moiety in medicinal chemistry. Benzimidazoles are an important group of heterocyclic compounds that are biologically active and of significant importance in medicinal chemistry. In light of the affinity they display towards a variety of enzymes and protein receptors, medicinal chemists would certainly classify them as privileged 'sub-structures' for drug dosing. The incorporation of the nucleus is an important synthetic strategy in studies of antimicrobial drug discovery. In the past few decades, benzimidazole and its derivatives have received much attention due to their chemotherapeutic values. Benzimidazole derivatives play important role in medical field with so many Pharmacological activities such as antimicrobial[10], anticonvulsant[11], antidiabetic[12] and anticancer[13] activity.

One major objective of organic and medicinal chemistry is to design and synthesize new molecules with high therapeutic indices which can overcome resistant microorganisms .Despite significant progress in antimicrobial therapy there is still much demand for novel antimicrobial drugs. Hence by considering the medicinal importance of benzisoxazole, 2-amino thiazole and benzimidazole and the potency of these clinically useful drugs in treatment of microbial infections and other activities encouraged the development of some more potent and significant compounds. We replace three chlorine atoms of 2,4,6-trichloro1,3,5-triazine by these moieties to synthesize new compounds which can be useful in multi therapy treatment.

## EXPERIMENTAL

All reagents were purchased from Sigma–Aldrich and Qualigens and were used without further purification.[1]H NMR spectra were recorded on a Bruker Spectrospin Avance DPX400 Ultrashield (400 and 300-MHz) spectrometer. IR spectra were recorded on FT-IR Bruker with KBr disc.All reactions were monitored by thin layer chromatography (TLC) on

silica gel with chloroform–acetone as mobile phase. The newly synthesized products were also separated and purified by column chromatography.

**Experimental Procedure**

**1) Synthesis of 6-(4,6-dichloro-1,3,5-triazin-2-yloxy)-3-methylbenzo[*d*]isoxazole :**

To a stirred solution of cynuric chloride (0.01M) in acetone at 0-5$^0$C, the solution of 3-methylbenzo[d]isoxazol-6-yl (0.01M) in acetone was added. The pH was adjusted neutral by adding 10% $NaHCO_3$ solution. The stirring was continued at the same temperature for 4hrs. After completion of the reaction stirring was stopped and the reaction mixture was poured onto crushed ice with constant stirring. The solid was filtered and washed with water. The product was recrystallized from acetone-ethanol. The physical constant data is given and synthetic scheme in Figure-1.

Yield: 90%

M.P.: 138$^0$C

**2)Synthesis of 4-(3-methylbenzo[*d*] isoxazol-6-yloxy-6-chlor (4-(4-chlorophenyl)thiazol-2-yl)-1,3,5-triazin-2-amine**

To a stirred solution of 6-(4,6-dichloro-1,3,5-triazin-2-yloxy)-3-methylbenzo[*d*]isoxazole (0.01M) in acetone at 35-45$^0$C, the solution of 4-(4-chlorophenyl)thiazol-2-amine (0.01M) in acetone was added and the pH was adjusted neutral by adding 10% $NaHCO_3$ solution. The stirring was continued at the same temperature for 4hrs. The reaction mixture was poured onto crushed ice with constant stirring. The solid was filtered and washed with water. The product was recrystallized from acetone-ethanol. The physical constant data is given and synthetic scheme in Figure-1.

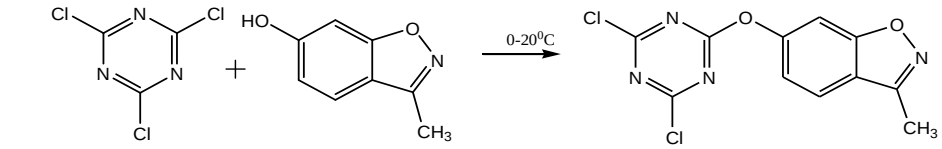
Yield: 80%

M.P.: 184$^0$C

**3)Synthesis of substituted4-(3-methylbenzo[d]isoxazol-6-yloxy)-6-(1H-benzo[*d*]imidazol-1-yl)-N-(4-(4-chlorophenyl)thiazol-2-yl)-1,3,5-triazin-2-amine**

To a mixture of 4-(3-methylbenzo[*d*] isoxazol-6-yloxy) -6-chloro-*N*-(4-(4-chlorophenyl) thiazol-2-yl)-1,3,5-triazin-2-amine (0.01M) and substituted benzimidazole (0.01M) in acetone (25ml) was heated under reflux for 4hrs. on water-bath at 80-90$^0$C. The pH was maintained neutral by adding 10% $NaHCO_3$ solution. The heating was continued at the same temperature for 4hrs. After completion of the reaction the reaction mixture was poured on

crushed ice and water. The solid obtained was filtered, dried and crystallized from acetone-ethanol. The physical constant data are given in Table-01 and synthetic scheme in Figure-01.

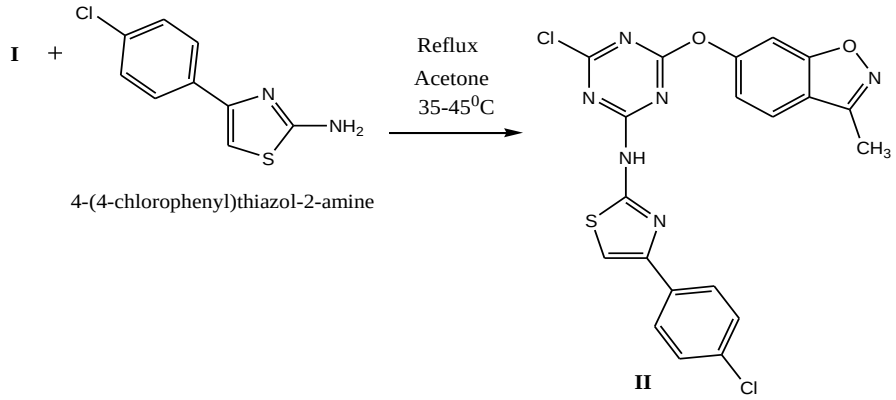



2,4,6-trichloro-1,3,5-triazine

3-methylbenzo[*d*]isoxazol-6-ol

6-(4,6-dichloro-1,3,5-triazin-2-yloxy)-3-methylbenzo[*d*]isoxazole

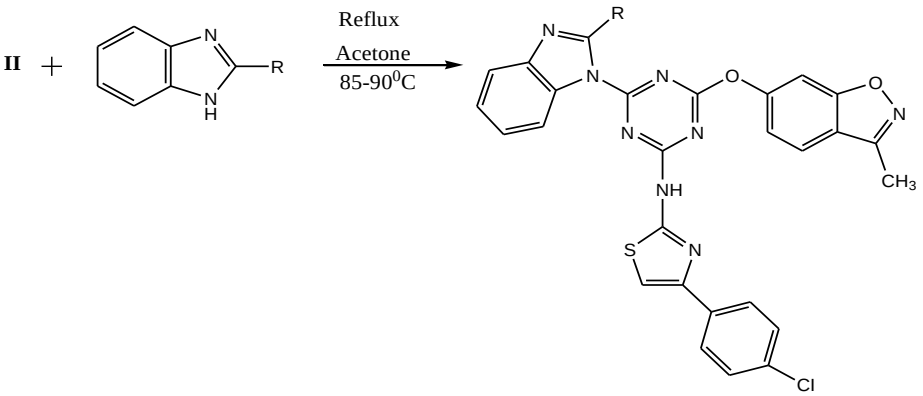
**I**




4-(4-chlorophenyl)thiazol-2-amine

**II**

4-(3-methylbenzo[*d*]isoxazol-6-yloxy)-6-chloro-*N*-(4-(4-chlorophenyl)thiazol-2-yl)-1,3,5-triazin-2-amine




4-(3-methylbenzo[*d*]isoxazol-6-yloxy)-6-(1*H*-benzo[*d*]imidazol-1-yl)-*N*-(4-(4-chlorophenyl)thiazol-2-yl)-1,3,5-triazin-2-amine

**Figure-01**

**Table-01: Analytical & physical data of substituted 4-(3-methylbenzo[d]isoxazol-6-yloxy)-6-(1H-benzo[d]imidazol-1-yl)-N-(4-(4-chlorophenyl)thiazol-2-yl)-1,3,5-triazin-2-amines**

| Sr. No. | R | M.P.$^0$C | Yield% |
|---|---|---|---|
| 3a. | H | 154 | 70 |
| 3b. | $CH_3$ | 158 | 80 |
| 3c. | $C_3H_7$ | 110 | 70 |
| 3d. | $C_6H_5$ | 150 | 65 |
| 3e. | p-C6H4Cl | 132 | 65 |
| 3f. | p-$C_6$H4F | 166 | 80 |
| 3g. | $CH_2C_6H_5$ | 148 | 65 |

**Antibacterial and antifungal activity of substituted 4-(3-methylbenzo[d]isoxazol-6-yloxy)-6-(1H-benzo[d]imidazol-1-yl)-N-(4-(4-chlorophenyl)thiazol-2-yl)-1,3,5-triazin-2-amines**

**Table 02: Antifungal activity**

| Sr. No. | Compound | *Aspergillus niger* | *Penicillium chrysogenum* | *Fusarium moneliforme* | *Aspergillus flavus* |
|---|---|---|---|---|---|
| 01 | 1 | RG | +ve | +ve | RG |
| 02 | 2 | -ve | -ve | -ve | -ve |
| 03 | 3a | -ve | -ve | -ve | -ve |
| 04 | 3b | -ve | -ve | -ve | -ve |
| 05 | 3c | -ve | -ve | -ve | -ve |
| 06 | 3d | -ve | -ve | -ve | -ve |
| 07 | 3e | -ve | -ve | -ve | -ve |
| 08 | 3f | -ve | -ve | -ve | -ve |
| 09 | 3g | -ve | -ve | -ve | -ve |
| 10 | DMSO | +ve | +ve | +ve | +ve |
| 11 | Griseofulvin | -ve | -ve | -ve | -ve |

**Legends-** **+ve- Growth (Antifungal activity absent)**

**-ve-No growth (Antifungal activity present)**

**RG- Reduced growth**

**Table 03: Antibacterial activity**

| Sr. No. | Compound | *Escherishia coli* | *Salmonella typhi* | *Staphylococcus aureus* | *Bacillus subtilis* |
|---|---|---|---|---|---|
| 01 | 1 | -ve | -ve | -ve | -ve |
| 02 | 2 | -ve | 13mm | 17mm | 16mm |
| 03 | 3a | -ve | 14mm | 17mm | 16mm |
| 04 | 3b | -ve | 12mm | 16mm | 17mm |
| -ve 05 | 3c | -ve | 14mm | 16mm | 17mm |
| 06 | 3d | -ve | 13mm | 16mm | 16mm |
| 07 | 3e | -ve | 14mm | 17mm | 17mm |
| 08 | 3f | -ve | 13mm | 17mm | 17mm |
| 09 | 3g | -ve | 14mm | 16mm | 17mm |
| 10 | DMSO | -ve | -ve | -ve | -ve |
| 11 | Griseofulvin | 14mm | 20mm | 36mm | 28mm |

**Legends- -ve- No Antibacterial activity**

**Zone of inhibition---mm**

**Spectral Data**

**1) 6-(4,6-dichloro-1,3,5-triazin-2-yloxy)-3-methylbenzo[*d*]isoxazole:**

IR (cm-1): 3211(Ar-H, asymm.), 3074 (Ar-H, symm.), 2829($CH_3$), 1588 (C=N), 1075 (C-O-C), 806( C-Cl)

$^1$HNMR: ∂ 2.06(s, 3H, $CH_3$), 7.1-7.7(3H, m, Ar-H),

**2)4-(3-methylbenzo[*d*]isoxazol-6-yloxy)-6-chloro-*N*-(4-(4-chlorophenyl)thiazol-2-yl)-1,3,5-triazin-2-amine:**

IR (cm-1): 3438(-N-H) ,3111(Ar-H, asymm.), 2968($CH_3$), 1562 (C=N), 1245 (C-O-C, asymm.), 1088(C-O-C, symm.), 826( C-Cl)

$^1$HNMR: ∂ 2.12(s, 3H, $CH_3$), 3.48( s, 1H, NH), 6.70-7.93 (8H, m, Ar-H)

***3a)4*-(3-methylbenzo[d]isoxazol-6-yloxy)-6-(2-(4-fluorophenyl)-1benzo[*d*]imidazol-1-yl)-N-(4-(4-chlorophenyl)thiazol-2-yl)-1,3,5-triazin-2-amine :**

IR (cm-1): 3439 (-N-H) ,3111(Ar-H), 2969 ($CH_3$), 1634 (C=N), 1088 (C-O-C, asymm.), 1038(C-O-C, symm.), 830 ( C-F), 826 ( C-Cl)

$^1$HNMR: ∂ 2.11(s, 3H, $CH_3$), 3.37 ( s, 1H, NH), 6.82-8.04 (15H, m, Ar-H)

**3b)4-(3-methylbenzo[d]isoxazol-6-yloxy)-6-(2-methyl-1H-benzo[*d*]imidazol-1-yl)-N-(4-(4-chlorophenyl)thiazol-2-yl)-1,3,5-triazin-2-amine :**

IR (cm-1): 3438 (-N-H) ,3112(Ar-H), 2969 ($CH_3$), 1633 (C=N), 1087 (C-O-C, asymm.), 1038(C-O-C, symm.), 826 ( C-Cl)

$^1$HNMR : ∂ 2.10 (s, 3H, $CH_3$), 2.60 (s, 3H, $CH_3$), 3.36 ( s, 1H, NH), 6.83-8.06 (11H, m, Ar-H)

**3c)4-(3-methylbenzo[d]isoxazol-6-yloxy)-6-(2-propyl-1H-benzo[*d*]imidazol-1-yl)-N-(4-(4-chlorophenyl)thiazol-2-yl)-1,3,5-triazin-2-amine :**

IR (cm-1): 3439(N-H) ,3112(Ar-H, asymm.), 2970 ($CH_3$), 1600 (C=N), 1090 (C-O-C, asymm.), 1040(C-O-C, symm.), 826 ( C-Cl)

$^1$HNMR: ∂ 2.12 (s, 3H, $CH_3$), 2.65 (s, 3H, $CH_3$), 3.40 ( s, 1H, NH), 3.50( pentate, 2H, $CH_2$), 6.81-8.09 (11H, m, Ar-H)

**3d)4-(3-methylbenzo[d]isoxazol-6-yloxy)-6-(2-benzyl-1H-benzo[*d*]imidazol-1-yl)-N-(4-(4-chlorophenyl)thiazol-2-yl)-1,3,5-triazin-2-amine:**

IR (cm-1): 3440 (N-H) ,3110(Ar-H, asymm.), 2968 ($CH_3$), 1620 (C=N), 1089 (C-O-C, asymm.), 1035 (C-O-C, symm.), 826 ( C-Cl)

$^1$HNMR: ∂ 2.13 (s, 3H, $CH_3$), 3.46 ( s, 1H, NH), 3.55( s, 2H, $CH_2$), 6.79-8.07 (16H, m, Ar-H)

## RESULT AND DISCUSSION

The compounds **1, 2, 3a-3g** were screened for their antibacterial activity against *E.Coli, Salmonella typhi, Staphylococcus aureus* and *Bacillus subtilis* by agar cup method using penicillin as standard and antifungal activity against *aspergillus niger, penicillium chrysogenum, Fusarium moneliforme, Aspergillus flavus* by poison plate method. Griseofulvin as reference standard. DMSO was used as control solvent. The investigation of antibacterial screening results indicate that compound **1, 2, 3a-3g** showed good activity against *Salmonella typhi, Staphylococcus aureus ,Bascillus subtilis* compared with standard drugs. Whereas all the compounds (**1, 2, 3a-3g**) showed no antibacterial activity against *E. Coli.*

The investigation of antifungal activity data revealed that compounds **2**, **3a-3g** showed promising activity against *Aspergillus Niger, Penicillum Chrysogenum, Fusarium moneliforme and Aspergillus Flavus.*

Compound **1** showed moderate activity against *Aspergillus Niger* and *Aspergillus Flavus* and no activity against activity against *Penicillium Chrysogenum, Fusarium moneliforme*.

All the newly synthesised substituted 4-(3-methylbenzo[d]isoxazol-6-yloxy)-6-(1H-benzo[d]imidazol-1-yl)-N-(4-(4-chlorophenyl)thiazol-2-yl)-1,3,5-triazin-2-amines have good antibacterial activity but excellent antifungal results against Gresiofulvin, the best marketed antifungal drug.

## CONCLUSION

In conclusion, the synthesized substituted 4-(3-methylbenzo[d]isoxazol-6-yloxy)-6-(1H-benzo[d]imidazol-1-yl)-N-(4-(4-chlorophenyl)thiazol-2-yl)-1,3,5-triazin-2-amines derivatives can be potentially useful as antimicrobial agents that can prompt future researchers to synthesize derivatives containing three bioactive moieties with the aim to obtain novel heterocyclic compounds with enhance activites, which will be useful in multidrug therapy.

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