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REVIEW ARTICLE **OPEN ACCESS**

Antibacterial Activity Reported in Recent Years for the Synthetic Derivatives of 1, 2, 4-Triazine

Mrinmoy Basak [1], Biplab Kumar Dey[1], Rosamund Jyrwa[1], Moksood Ahmed Laskar[1], SM Abdul Aziz Barbhuiya[2], Muslek Uddin Mazumder[2], Josef Yakin[1], Himangshu Deka[1], Nongmaithem Randhoni Chanu[1], Pal Gogoi[1], Mohidul Islam[1], Priyanka Goswami [1], Sajjidul Hoque Ansari[3], Md Rejwan Ahmed Choudhury*[1]

[1]Faculty of Pharmaceutical Science Assam down town University, Guwahati-26. Assam, India.
[2]Rahman Institute Pharmaceutical Science and Research, Assam, India
[3]NEF College of Pharmacy. Guwahati, Assam, India
Correspondence Email: rejwanahmed.ch@gmail.com

ABSTRACT

Compounds containing a variety of heterocyclic nucleus have been applied for long as antimicrobial agents by a number of researchers. Among all the various classes of nitrogen-containing heterocyclic compounds, especially triazine derivatives have always been vastly experimented as frameworks of many biological active compounds, natural or synthetic, with a variety of pharmacological effects. Especially 1,2,4-triazine derivatives have been widely used in such research, thus this article include a brief understanding of the various research work carried out recently for Antibacterial activity of 1,2,4-triazine derivatives.

Keywords: *1, 2, 4-triazine, Antibacterial, pharmacological effects*

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INTRODUCTION

In the past many years, the problem of multi-drug-resistant micro-organisms has reached quiet an alarming levels worldwide, and the synthesis of newer anti-infective compounds has emerged as an urgent need for the treatment of microbial infections. [1]. Heterocyclic organic chemistry is considered to be one of the most important and well-studied branch of medicinal chemistry. The most important feature of heterocyclic bioactive compounds is the presence of their various constituent heteroatoms, including nitrogen [2-5], sulfur [6-8], oxygen [9-11], and others [12].

These heteroatoms present affect directly the reactivity of the target activity (or toxicology) of the compounds, skeleton, interactions between the target drugs and different target inhibitors, and metabolism and pharmacokinetics. Heterocyclic compounds also have a great applicability in the pharmaceutical industry as various anticancer agents, antituberculosis agents, antimalarial, antimicrobials, analgesics, pesticides, hypnotics, and insecticides [13-16]. Among heterocycles, nitrogen-containing heterocyclic compounds have maintained the interest of researchers for many years of historical development in organic synthesis [17-18]. Among all triazine is one of the most important lead molecules which are widely used in the field of pharmaceuticals. Triazine is the species of six membered heterocyclic structures having the chemical formula $C_3H_3N_3$ [19].Triazine structure is same to the structure of benzene ring in which there are three nitrogen atoms which replace three carbon atoms present in it. The different position of nitrogen atoms in the ring distinguish the three isomer of triazine and the isomers are referred as 1, 2, 3-triazine, 1, 2, 4-triazine and 1, 3, 5-triazine [20].

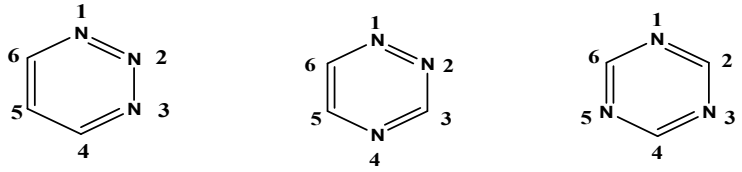


Fig.1. Various isomers of triazine.

Now a days, several studies have been carried out on the antibacterial activity of 1,2,4-triazines [21]. All 1,2,4-triazines derivatives that have a very wide range of practical applications consisting of 2, 4, 6- mono, di ortri-substituted, symmetrical and non-symmetrical compounds having various kinds of substituent. The most important reagent among all of them for obtaining these synthetic molecule transformations is cyanuric chloride due to the reactivity of the chlorine atoms towards nucleophiles [22].

Review on the synthetic work

In this part, important research articles has been incorporated which highlights the various synthetic procedures adopted for synthesizing triazine and quinoline derivatives

Taha et al (2020) in the research reacted 8-Hydrazinotetrazolo[5,1-*f*]-1,2,4-triazine with one or two carbon cyclizing reagents to yield various heterocyclic systems (Fig.2.). Their antimicrobial activity evaluation revealed that 2d, 3d, 8b, and 9a were the most active compounds although the activity was significantly less than that of the positive control. [23]

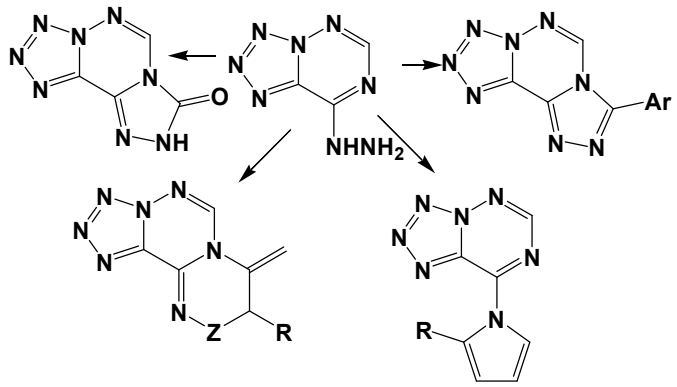


Fig. 2. Various heterocyclic systems

Zemanová et al (2017) synthesised Furo[2',3':4,5]pyrrolo[1,2-*d*][1,2,4]triazin-8(7*H*)-ones by reacting a carbohydrazide with triethyl orthoesters or by acetylation of the methyl 4*H*-furo[3,2-*b*]pyrrole-5-carboxylate followed by thionation of 4-acetylfuro[3,2-*b*]pyrrole-5-carboxylate and cyclisation of thione with hydrazinr. Triazine derivative 5a afforded the corresponding thione 7 by reaction with P2S5. This upon further reaction with alkyl- or acylhalogenides compounds 5 and 7 gave *N*(7)-substituted products 6 and 8, respectively. Finally, triazino-triazinone derivative 9 was synthesized by cyclisation of thione 8b with hydrazine. Compounds 5 - 9 (Fig.3.) were evaluated for their antibacterial activity. Later upom antibacterial evaluation only compounds 5a, 5c and 6b exhibit higher antibacterial activity on all bacterial strains with MIC values in the range 0.016 - 2.56 mM using standard 6-APA [24]

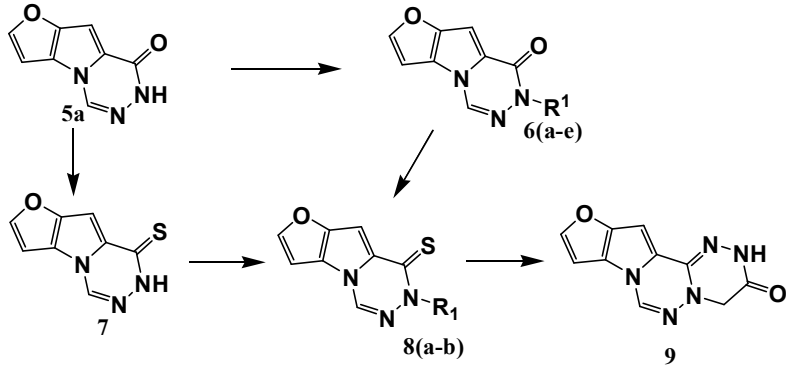


Fig.3. furo[2',3':4,5]pyrrolo[1,2-*d*][1,2,4]triazine derivatives

Alharbi et al (2019) synthesised new fluorine-substituted 3,5-disubstituted amino-1,2,4-triazines from aryl-amination of 2,2,2-trifluoro-*N*-[2-(5-hydroxy-3-thioxo-2,3-dihydro-1,2,4-triazin-6-yl)-4-nitrophenyl] acetamide followed by ammonolysis to produce *N*-(2-(5-amino-3-(arylamino)-1,2,4-triazin-6-yl)-4-nitrophenyl)-2,2,2-trifluoroacetamides (Fig.4.). Upon antibacterial evaluation some compounds showed interesting activity against the *Bacillus subtilis*, *Streptococcus faecalis*, *Micrococcus luteus*, and *Staphylococcus aureus* bacteria. [25]

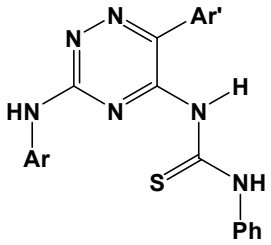


Fig.4. *N*-(2-(5-amino-3-(arylamino)-1,2,4-triazin-6-yl)-4-nitrophenyl)-2,2,2-trifluoroacetamides

Shokoohian et al (2020): new 1,2,4-triazine derivatives were synthesised by the Reaction of pyridine-2-(1H)-one derivatives (diamines) and 1,2-dicarbonyl compounds. Inhibitory properties of newly synthesized 1,2,4-triazine were assessed against 5 Grampositive and 5 Gram-negative pathogenic bacteria and was compared using antibiotic Gentamicin as standard and the result obtained showed significant antibacterial activity especially in compound 3d (Fig.5).[26]

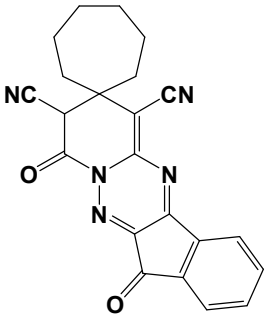
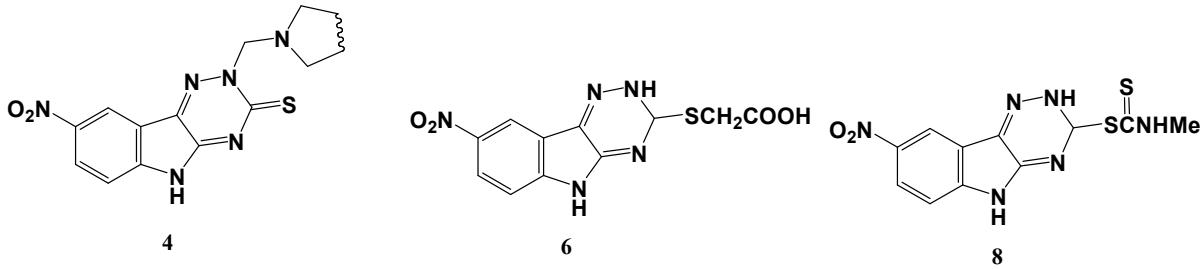


Fig.5. 1,2,4-triazine derivatives

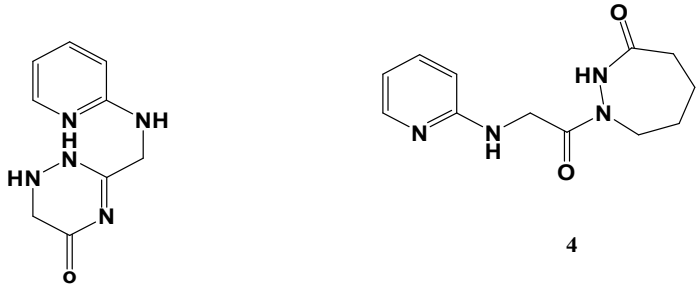
Bawazir et al (2020) synthesised a novel N2-alkyl-3-thioxo-8-nitro-1,2,4-triazino[5,6-b]indoles and 3-alkylated 3-thioxo-8-nitro-1,2,4-triazino[5,6-b]indoles by treatment of 8-nitro-1,2,4-triazino[5,6-b]indole-3 (2H,5H)thione using various alkylating agents. The synthesised compounds were subjected to antibacterial evaluation and promising antibacterial activity of 6, 8, and 4 (Fig.6) were obtained when Ampicillin was used as a reference. [27]



4 6 8

Fig.6. N2-alkyl-3-thioxo-8-nitro-1,2,4-triazino[5,6-b]indoles and 3-alkylated 3-thioxo-8-nitro-1,2,4-triazino[5,6b]indoles

Salih et al (2021) synthesised novel 3-[(pyridine-2-ylamino)methyl]-1,6-dihydro-1,2,4-triazine-5(2*H*)-one. The synthesized compounds were evaluated for their in vitro antibacterial activity against *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Bacillus cereus*, and *Enterococcus faecalis*. The inhibition zones were measured, expressed in mm and the minimum inhibitory concentration (MIC) is reported in μg/mL. The results show that compounds 3 and 4 (Fig.7) have a significant antimicrobial activity with the highest MIC value against all tested bacteria. [28]



3 4

Fig. 7. 3-[(pyridine-2-ylamino)methyl]-1,6-dihydro-1,2,4-triazine-5(2*H*)-one

Tang *et al* (2019) synthesied a series of novel chalcone derivatives containing the 1,2,4-triazine moiety. The synthgesised compounds were that subjected for antibacterial evaluation and it was found that compound 4a (Fig.8) demonstrated excellent antibacterial activities against *Ralstonia solanacearum* (R. solanacearum), The compounds were belived to act by act by causing folding and deformation of the bacterial cell membrane. [29]

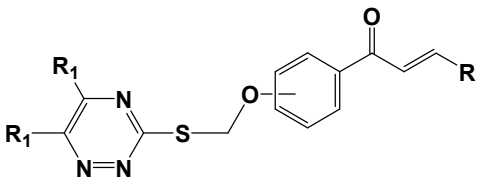


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Fig.8. Chalcone derivatives containing the 1,2,4-triazine moiety

Rahman *et al* (2018) synthesised new 3-thioxo-1,2,4-triazin-5-one derivatives by the utilization of facile condensation of (E)-4-(4'-bromo styryl)-2-oxo-3-buteneoic acid with thiosemicarbazide, dithioic formic acidhydrazide, and thiocarbahydrazide in different prescribed conditions. The compounds were evaluated for antibacterial activity against Gram-negative and Gram-positive bacteria as Escherichia Coli ,*Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and Staphylococcus Aureus and was found that 4, 6 and 8 (Fig 9) were significantly active against the mentioned strains of bacteria. [30]

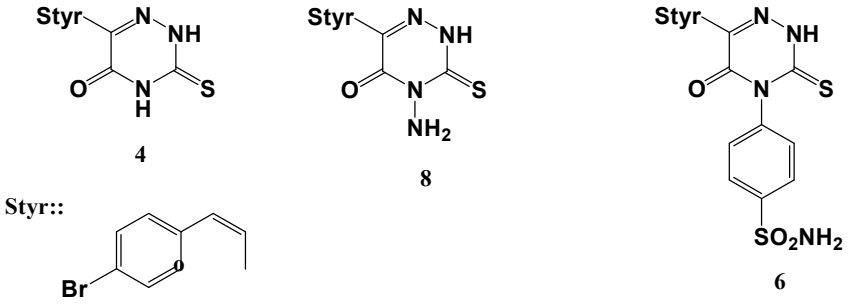

Fig.9. 3-thioxo-1,2,4-triazin-5-one derivatives

Arshad *et al* (2018) synthesised a series of 1, 2, 4-triazine derivatives possessing indole nucleus (Fig.10). In vitro antimicrobial activity of the synthesised compounds was performed against *S.* aureus, S. epidermidis, P. mirabilis and E. coli using disk diffusion method using ciprofloxacin as standard. Upon the evaluation the result revealed that some compounds of the synthesised series were found to exhibit significantly better antibacterial activity with less toxicity than Ciprofloxacin. [31]

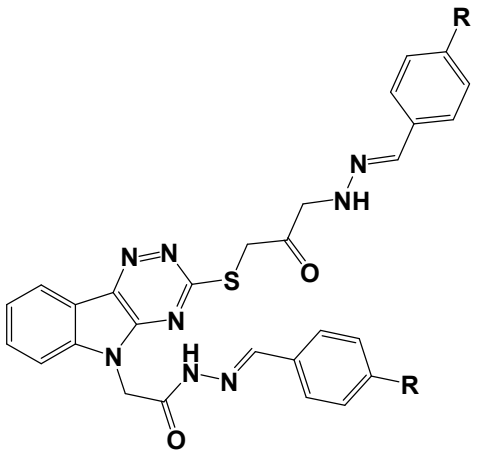

Fig. 10. 1, 2, 4-triazine derivatives possessing indole nucleus

Cai *et al* (2020) synthesised a series of novel 7-oxo-7H-thiazolo[3,2-b]-1,2,4-triazine-2-carboxylic acid derivatives (Fig. 11) by a multi-step procedure that included the generation of the compound S-alkylated derivatives from 6-substituted arylmethyl-3-mercapto-1,2,4-triazin-5-ones with ethyl 2-chloroacetoacetate, on ntramolecular cyclization. The synthesised series of copmpounds were that

evaluated for their antibacterial activity with Ciprofloxacin as standard against *S. aureus, B. subtilis, E. coli, P. aeruginosa*. The result obtained suggested that most of the compounds exhibited low to moderate activity against Gram-positive bacteria and Gram-negative bacteria. [32]

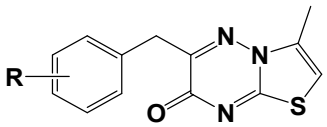

Fig. 11. 7-oxo-7H-thiazolo[3,2-b]-1,2,4-triazine-2-carboxylic acid derivatives

CONCLUSION

Now a day's antibacterial resistance have been an important concern for the global health as most of the bacterial strains have grown to be resistant against all the widely known antibiotics. Thus development of newer synthetic antibiotics has risen to be the need of the moment to tackle this unavoidable problem. As a known fact, triazine have proved to be one of the most effective moiety in development of newer antibiotics as a number of marketed drugs have found their core structure as various triazine derivatives. Thus this paper give collective information and insight to the newer or recent research work that have been carried out on the development of newer 1,2,4-triazine derivatives. This article have an illustrative information of 1,2,4-triazine as antibacterial agent which in turn help various researchers to carry out further and in depth research by utilizing the accumulated knowledge in this article

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