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A REVIEW ON SYNTHESIS AND BIOLOGICAL ACTIVITY OF HETEROCYCLIC COMPOUNDS BEARING 1, 3, 5-TRIAZINE LEAD MOIETY

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ABSTRACT

Triazine is the chemical species of six-membered heterocyclic ring compound with three nitrogens replacing carbon-hydrogen units in the benzene ring structure. The names of the three isomers indicate which of the carbon-hydrogen units on the benzene ring position of the molecule have been replaced by nitrogens, called 1,2,3-triazine, 1,2,4-triazine, and 1,3,5-triazine respectively. Symmetrical 1, 3, 5-triazine is the common. Triazines are prepared from cyanic acid amide by trimerization (1, 3, 5-triazine). Pyridine is the aromatic nitrogen heterocyclic compound having only one nitrogen, and diazines are with 2 nitrogen atoms, triazine having three nitrogen and tetrazines are with 4 nitrogen atoms on the benzene ring system. Triazines are weak base. Triazines have much weaker resonance energy than benzene, so nucleophilic substitution is preferred than electrophilic substitution. Heterocyclic bearing a symmetrical s-triazines or 1, 3, 5-triazines moieties, represent an interesting class of compounds possessing a wide spectrum of biological activities such as anti-cancer, antiviral, fungicidal, insecticidal, bactericidal, herbicidal and antimicrobial, antimalarial agents. They also find applications as dyes, lubricants and analytical reagents.

Key words: Triazine, Nucleophilic substitution, Cyanuric chloride, 1, 3, 5-triazine, s- Triazine

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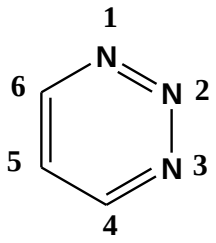
INTRODUCTION

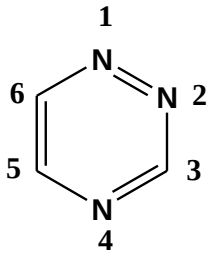
Triazine isomers

The triazine structure is a heterocyclic ring, analogous to the six-membered benzene ring but with three carbons replaced by nitrogens. The three isomers of triazine are distinguished from each other by the positions of their nitrogen atoms, and are referred to as 1,2,3-triazine,1,2,4-triazine, and 1,3,5-triazine.[1]

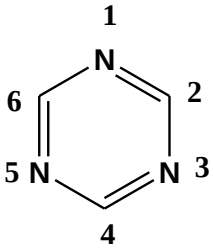
The three isomers Structure of triazine



1,2,3-triazine

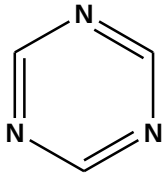


1,2,4-triazine



1,3,5-triazine or s-triazine

Selection of Lead Moiety and Nucleus Introduction



Triazine - **IUPAC name**: 1, 3, 5-triazine, s-triazine

1,3,5-triazine, also called s-triazine, is an organic chemical compound with the formula $(HCN)_3$. It is a six-membered heterocyclic aromatic ring. The atoms in triazine rings are analogous to those in benzene rings, which makes triazines aromatic compounds like benzene. One of several isomeric triazines s-triazine and its derivatives are useful in a variety of applications.[2]

The most common derivative of 1,3,5-triazine is 2,4,6-triamino-1,3,5-triazine, commonly known as melamine or cyanuramide shown in Table 1. Anticancer as a altretamine, triethylene melamine (TEM). Trichloro-1,3,5-triazine is the starting point for the manufacture of many herbicides such as simazin. Another important derivative is 2,4,6-trihydroxy-1,3,5-triazine better known as cyanuric acid.

Reported Biological Activity of Triazine Derivatives

The triazine compounds presumably act by inhibiting the action of an inducible membrane protein that normally functions to increase the efflux of the cytotoxic agent. The triazine

compounds (1,3,5-triazine derivatives) also exhibit anti-ulcer, anti-depressant and antiviral activity. [3]

Table-1: Physical and Chemical Properties of 1, 3, 5-Triazine

1.	Molecular formula	$C_3H_3N_3$
2.	Molar mass	81.03
3.	Appearance	White powder
4.	Molecular weight	81.08
5.	Melting point	351.59K
6.	Boiling Point	451.04 K
7.	Solubility	Acetone , DMF

Several six membered heterocyclic compounds contain triazine lead moiety have been reported to have a diverse type of biological property. It is also well established that various derivatives of triazine exhibit wide spectrum biological properties such as analgesic and anti-inflammatory activity, antifungal, antibacterial activity, histamine blockers, antitubercular and antioxidant activity.[4]

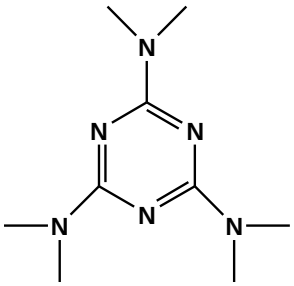
2,4,6-trisubstituted(dimethylamino)-1,3,5-triazine is an antitumor agent known as altretamine used in the treatment of ovarian cancer . Further report a number of derivatives of 2-aryl amino-4-(4-methoxy anilino)-6-(4-chlorophenyl/phenyl hydrazido)-1,3,5-triazine having anti-bacterial activity agents.4,6-bis-allylamino-1,3,5-triazin-2-yl derivatives which reverse acquired resistance to anti-cancer and anti-malarial agents.[5]

Triazine is also basic structure of some herbicides, examples are amitole, atrazine , cyanazine , simazine trietazine . Large volume of triazines is used in the manufacture of resin modifiers such as melamine and benzoguanamine. [34-35]

1,3,5-Triazine-2,4,6-triamine is reacted with formaldehyde to from a very durable thermoset resin. Benzoguanamine (2,4-Diamino-6-phenyl-1,3,5-triazine) is used to increase thermoset properties of alkyl, acrylic and formaldehyde resins. Triazines are also useful as chromophore groups in colorants and chlorine attached in triazine compounds undergo nucleophilic substitution reactions well with hydroxyl groups in cellulose fibers. Some triazine family compounds are used in pharmaceutical industry as coupling agent for the synthesis of peptide in solid phase as well as solution and as side chain of antibiotics. Triazine compounds are used in formulating bactericide and fungicide. They are used as preservatives in oil field applications. They are used as disinfectant, industrial deodorant and biocide in water treatment. They are used as bleaching agents. Derivatives of melamine, 1, 3, 5-triazine-2, 4, 6-triamine have been reported in the literature for various uses.

DRUGS CONTAINING 1, 3, 5-TRIAZINE HAVING ANTICANCER ACTIVITY

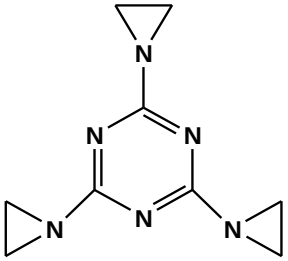
1. **Altretamine**



IUPAC name: N2, N2, N4, N4, N6, N6-hexamethyl-1,3,5-triazine-2,4,6-triamine

Altretamine is an Antineoplastic agent. It was approved by the FDA in 1990. It is used to treat refractory ovarian cancer. It is not considered a first-line treatment, but it can be useful as salvage therapy. It also has the advantage of being less toxic than other drugs used for treating refractory ovarian cancer.[39] The precise mechanism by which altretamine exerts its anti-cancer effect is unknown but it is classified by MeSH as an alkylating Antineoplastic agent. This unique structure is believed to damage tumor cells through the production of the weakly alkylating species formaldehyde, a product of CYP450 mediated N-demethylation. Administered orally.[40-42]

2. **Triethylenemelamine (TEM)**

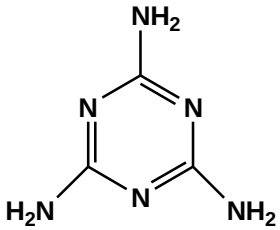


IUPAC name: 2, 4,6-Tris(aziridin-1-yl)-1,3,5-triazine

Triethylenemelamine is a drug used in chemotherapy.

COMPOUND CONTAINING 1,3,5-TRIAZINE NUCLEUS AVAILABLE IN MARKET

1. **Melamine**



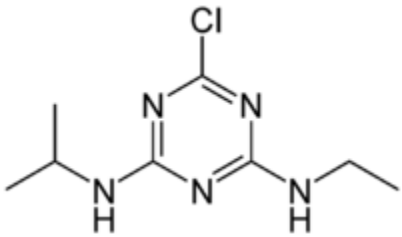
IUPAC name: 1,3,5-Triazine-2,4,6-triamine

Melamine is an organic base and a trimer of cyanamide, with a 1,3,5-triazine skeleton. Like cyanamide, it contains 66% nitrogen by mass and, if mixed with resins, has fire retardant properties due to its release of nitrogen gas when burned or charred, and has several other industrial uses. Melamine is also a metabolite of cyromazine, a pesticide. It has been reported that cyromazine can also be converted to melamine in plants.

Melamine is combined with formaldehyde to produce melamine resin, a very durable thermosetting plastic used in Formica, and melamine foam, a polymeric cleaning product. The end products include countertops, dry erase boards, fabrics, glues, housewares, dinnerware, cooking spoons, guitar saddles, guitar nuts, acoustic foam paneling, and flame retardants. Melamine is one of the major components in Pigment Yellow 150, a colorant in inks and plastics.

1,3,5-triazine is use as a reagent in organic synthesis, s-triazine also implement as the equivalent of hydrogen cyanide (HCN). Being a solid (vs a gas for HCN), triazine is sometimes easier to handle in the laboratory. One application is in the Gattermann reaction, used to attach the formyl group to aromatic substrates. It is a common reagent, and readily forms derivatives, which are used as pharmaceutical products.

2. **Atrazine**



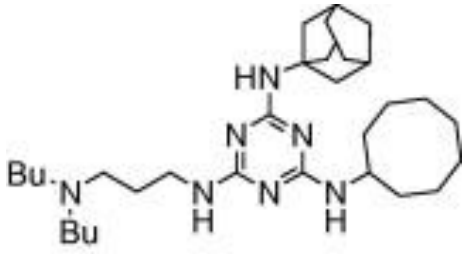
IUPAC name: 1-Chloro-3-ethylamino-5-isopropylamino-2,4,6-triazine

Atrazine is 2-chloro-4-(ethylamino)-6-(isopropylamino)-s-triazine, an organic compound consisting of an s-triazine ring is a widely used herbicide. Its use is controversial due to widespread contamination in drinking water and its associations with birth defects and menstrual problems when consumed by humans at concentrations below government standards. Although it has been banned in the European Union, it is still one of the most widely used herbicides in the world.[34-35]

Uses: Atrazine is used to stop pre- and post-emergence broadleaf and grassy weeds in major crops. The compound is both effective and inexpensive, and thus is well-suited to production systems with very narrow profit margins, as is often the case with maize. Atrazine is the most useful herbicide in conservation tillage systems, which are designed to prevent soil erosion.[36]

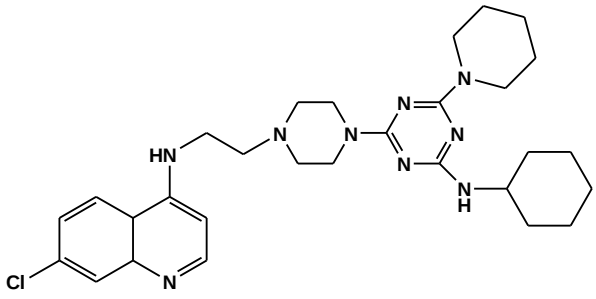
LITERATURE ON BIOLOGICAL ACITIVITY STUDIES OF DIFFERENT TRIAZINE DERIVATIVE

1. Synthesized and evaluated biological activity of novel 1,3,5-triazine derivatives as antimicrobial agents. Numerous studies have contributed to the development of natural and synthetic antimicrobial peptides as a prospective source of antibiotic agents. Based on the concept that cationic charge, bulk, and lipophilicity are major factors determining antibacterial activity in these peptides, designed and screened several combinatorial libraries based on 1,3,5-triazine as a template. A set of compounds were identified to show potent antimicrobial activity together with low hemolytic activity. [4]



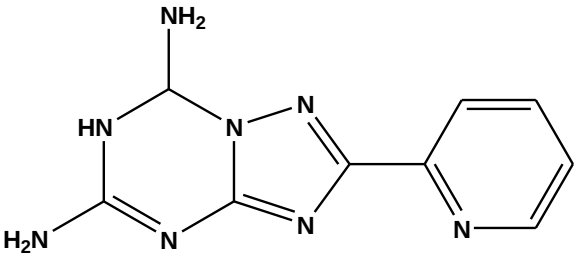
TZ-4 IC_{50} = 2.0 uM

2. Synthesized and performed bio-evaluation of hybrid 4-aminoquinoline triazines as a new class of antimalarial agents. The emergence and rapid spread of chloroquine resistant strains of *Plasmodium falciparum* has dramatically reduced the chemotherapeutic options. Towards this goal, a series of new class of hybrid 4-aminoquinoline triazines were synthesized and screened against CQ sensitive strain 3D7 of *P. falciparum* in an *in-vitro* model.[5]

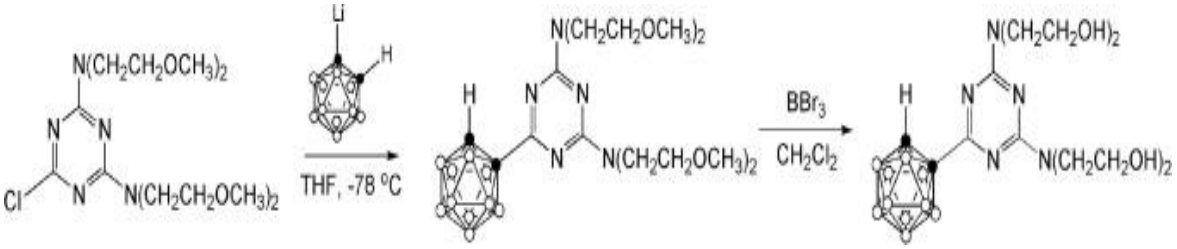


This is synthesize compound containing 1,3,5-triazine show antimalarial activity

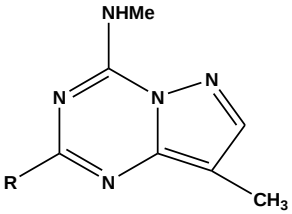
3. Antiproliferative activity of the synthesized l,2,4-triazolo[1,5-a][1,3,5]triazines were evaluated against breast, colon and lung cancer cell lines. The highest antiproliferative activity in the series was found for 2-(pyridine-3-yl)-7-(4-trifluoromethylphenyl)-6,7-dihydro[1,2,4]triazolo[1,5-a][1,3,5]triazin-5-amine.[6]



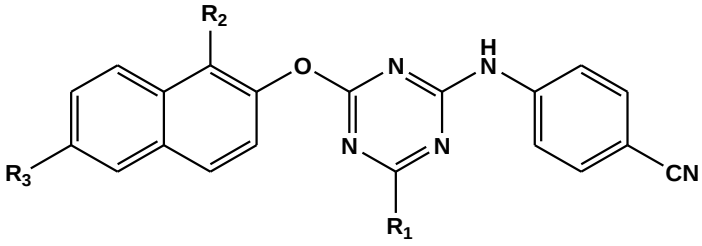
4. Synthesized and characterized polar functional group substituted mono and bis-(*o*-carboranyl)-1,3,5-triazine derivatives. Preliminary *in-vitro* studies revealed that compounds despite their low cytotoxicity, accumulated at high levels in B-16 melanoma cells.[13]



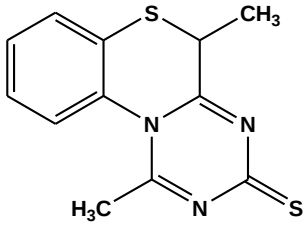
5. Evaluated pyrazolo [1,5-*a*] -1,3,5-triazine ring system as an adenine bioisostere. Preliminary biological testing has shown that compounds strongly inhibit LPS-induced TNFa release from human mononuclear cells from healthy subjects.[15]



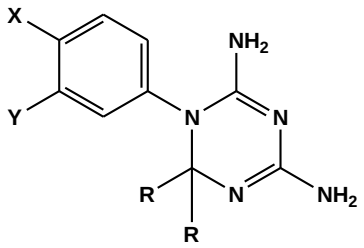
6. Synthesized diaryltriazine with potent anti-HIV activity. [16]



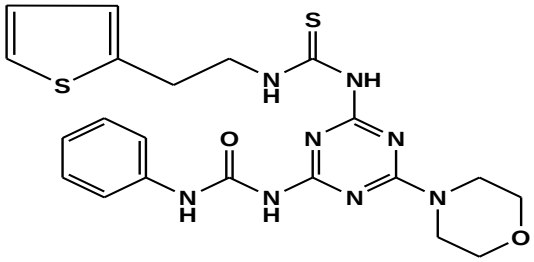
7. Synthesized and studied biological activity of some new 1,4-benzothiazines. Antibacterial activity was performed on gram-positive and gram-negative bacteria(*Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa.*[17]



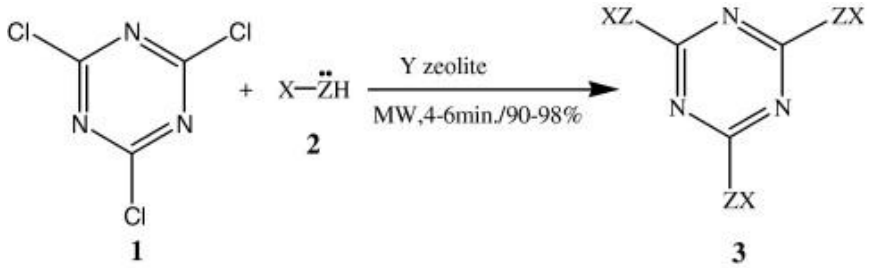
8. Reported 3D-QSAR analysis of cycloguanil derivatives highly active against dihydrofolate reductase resistant strain (T9/94) of *plasmodium falciparum*.[18]



9. Synthesized novel aliphatic thiourea derivative containing s- triazine moiety and reported on its antimicrobial activity. Antibacterial activity were performed on gram-positive and gram-negative bacteria (*Staphylococcus aureus, Pseudomonas aeruginosa)* and reported as mild active agents. .[19]



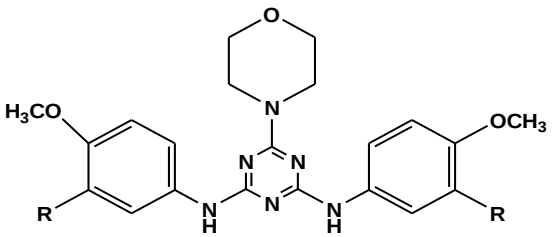
10. Synthesized and reported cytotoxic activity of trisubstituted-1,3,5-triazines. 1,3,5-Triazine derivatives were screened for photo toxicity as well as the cytotoxic activities against leukemia and adenocarcinoma derived cell lines in comparison to the normal human keratinocytes. .[21]



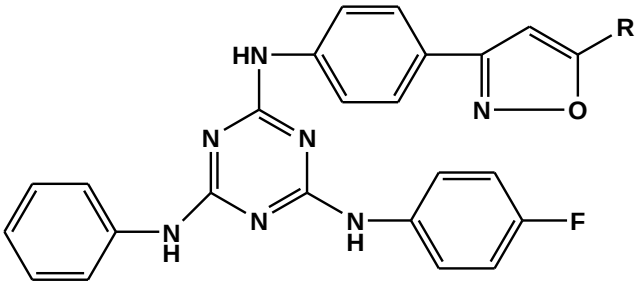
X = Ar/CH_3Ar/$(C_2H_5)_2$/$(CH_3)_2$/CH_3CO/CH_3/OCH_3Ar/NO_2Ar/ClAr/H, Z= O, NH

11. Synthesized and evaluated antitumor activity of a novel series of triaminotriazine derivatives and evaluated for their inhibition activities to colorectal cancer (CRC) cell

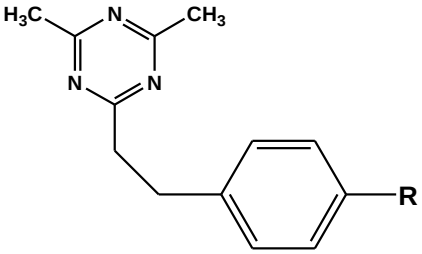
lines (HCT-116 and HT-29). Most of the synthesized compounds demonstrated moderate anti-proliferatory effects on both HCT-116 and HT-29 cell lines at the concentration of 10 μM. .[23]



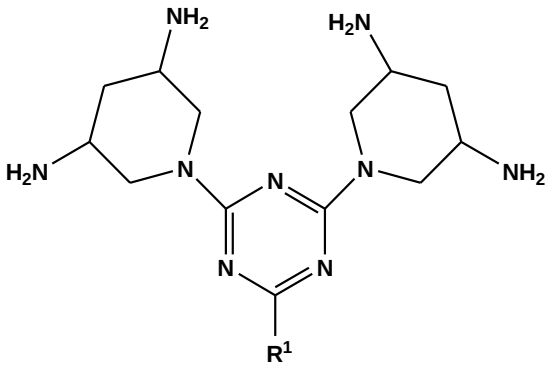
12. Synthesized and studied pyrazolines, isoxazolines and aminopyrimidines as biological potent agents. .[24]



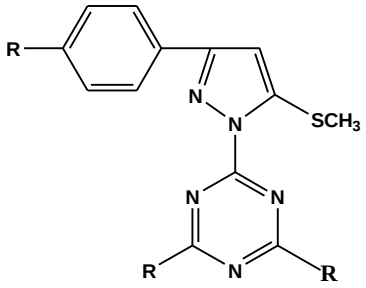
13. Synthesized and reported antibacterial activity various substituted s-triazines with gram-positive and gram-negative bacteria.[1]



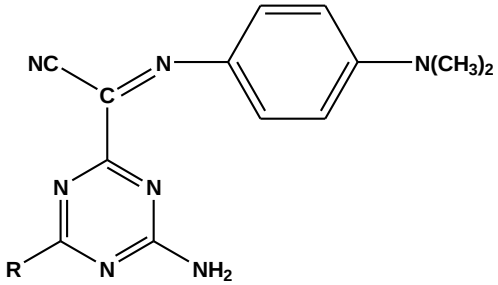
14. Reported the structure–activity relationships of novel antibacterial translation inhibitors: 3,5-Diamino-piperidinyl triazines.[26]



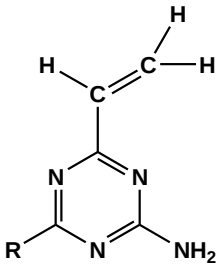
15. Synthesized 2,4,6-tri substituted triazine heterocycles and reported as *in-vitro* antileishmanial activity profile in promastigote model. Nine compounds have shown 94% inhibition against promastigotes at a concentration of 10 µg/mL.[45]



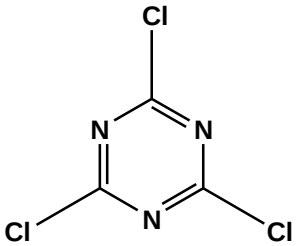
16. Synthesized and reported anticancer activity of novel 2,4-diamino-1,3,5-triazine derivatives. [28]



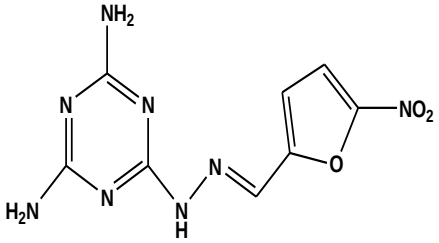
17. Synthesized and reported anticancer activity of novel alkenyl -1,3,5-triazine derivatives, it showed growth inhibitory activity in low micromolar concentrations against renal cancer A498 cell line and colon cancer cell line COLO 205.[29]



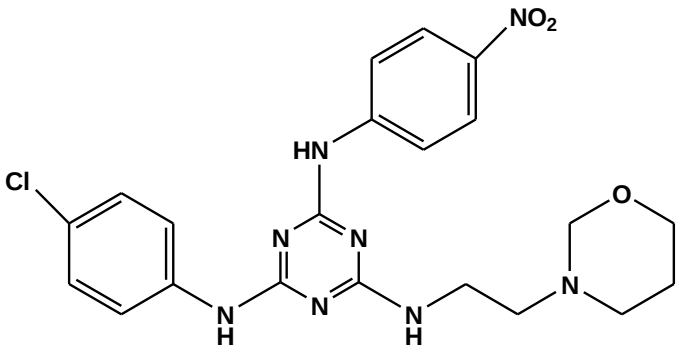
18. Synthesized 2,4,6-trichloro-1,3,5-triazine and its derivatives in organic synthesis.[30]



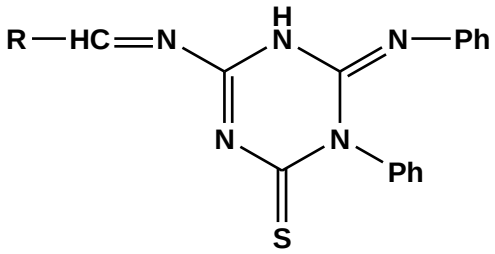
19. Synthesized a series of melamine-based nitro-heterocyclic with activity against *Trypanosomatid Parasites*.[33]



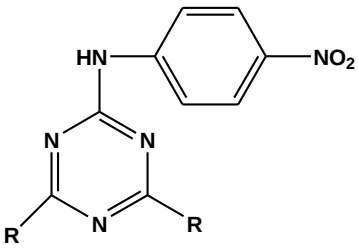
20. Evaluated triaminotriazine DNA helicase inhibitors with antibacterial activity and screened a chemical library in a DNA helicase assay involved the *Pseudomonas aeruginosa* helicase provided a triaminotriazine inhibitor with good antibacterial activity but associated cytotoxicity toward mammalian cells.[31]



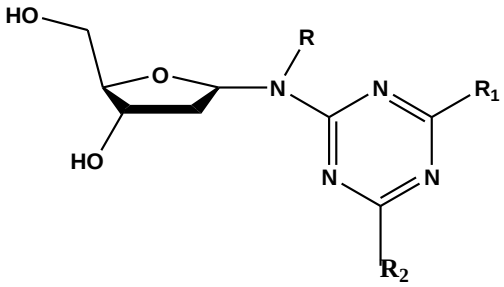
21. Synthesized and reported antibacterial activity of 1,3,5-thiadiazines and their isomerism into 1,3,5-triazines.[32]



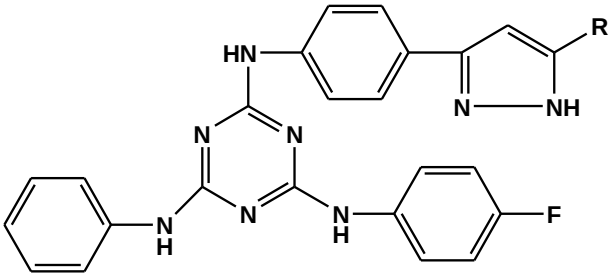
22. Synthesized 2,4,6-trisubstituted triazines and reported on its antimalarial activity against *P. falciparum*. Out of the 19 compounds synthesized eight compounds showed MIC in the range of 1–2 µg/mL.and its showed *in-vitro* antimalarial activity several times more active than cycloguanil[27].



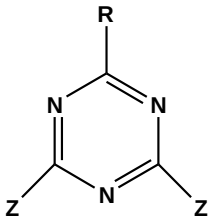
23. Synthesized and evaluated the stability of exocyclic triazine nucleosides.[47]



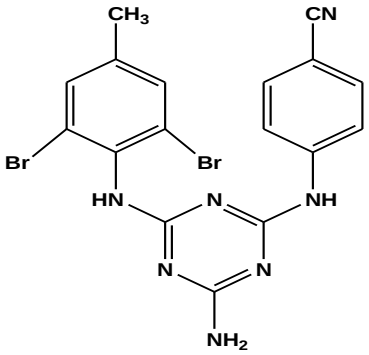
24. Synthesized chalcones pyrazolines, isoxazolines and aminopyrimidines as biological potent agents. Antibacterial activity performed on gram-positive and gram-negative bacteria .[20]



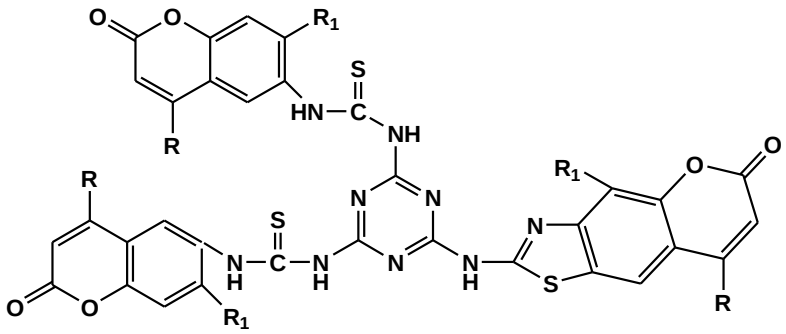
25. Evaluated the *in-vitro c*ytotoxic activities of 2-Alkyl-4,6-diheteroalkyl-1,3,5-triazines. Cytotoxic activities were carried out against leukemia and adenocarcinoma derived cell lines.[34]



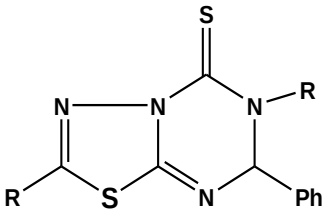
26. Synthesized series of Diaryltriazines and Diarylpyrimidines which were found to have highly potent Nonnucleoside Reverse Transcriptase Inhibitory action with possible applications as microbicides. An *in-vitro* model of monocyte-derived dendritic cells (MO-DC) and $CD4^+$ T cells, representing the primary targets of sexual human immunodeficiency virus (HIV) transmission, was used to evaluate the antiviral and immune suppressive activity of new classes of non-nucleoside reverse transcriptase inhibitors.[16]



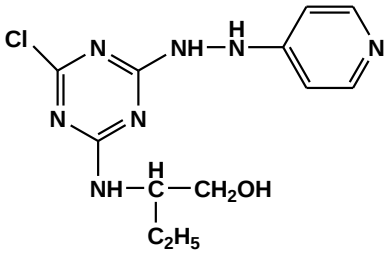
27. Synthesized and biologically active thiazolo-benzopyranyl-s-triazine derivative.[47]



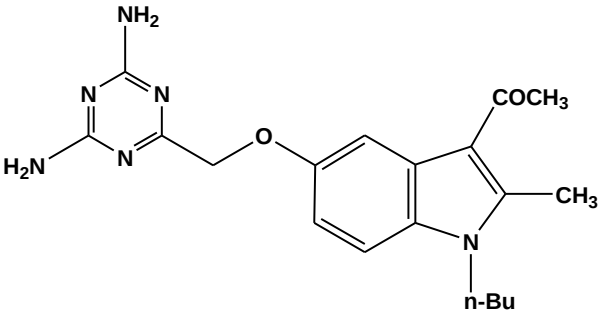
28. Synthesized thiadiazolo-s-triazines and evaluated their antiviral activity based on QSAR studies.[48]



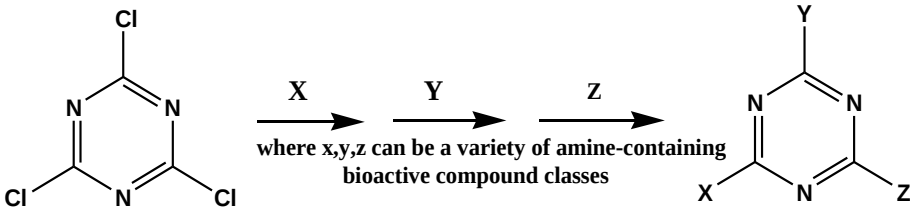
29. Synthesized new derivatives of isoniazid, pyrazinamide and 2-aminobutanol and reported on their anti-tubercular activity.[50]



30. Synthesized and reported antibacterial activity of new 1-n-butyl-3-acetyl-5-(2,4-diamino-1,3,5-triazin-6-yl)methoxy-2-methylinodole derivatives. Antibacterial activity performed on gram-positive and gram-negative bacteria.[51]



31. Evaluated the incorporation of carbohydrates and peptides into large triazine-based screening libraries using automated parallel synthesis. These compounds are useful anti-tubulin agents for treating cancer and proliferative diseases.[52]

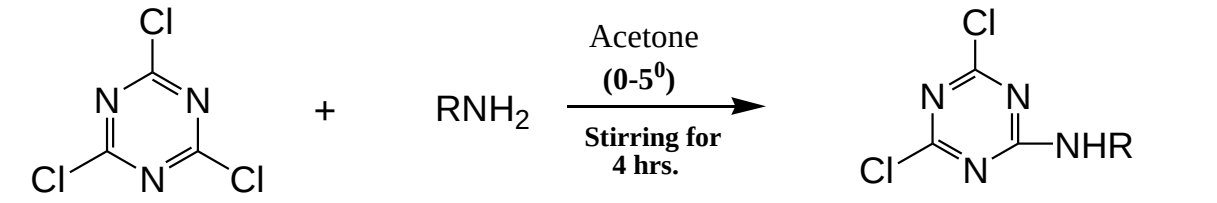


This is also synthesize by using nucleophilic substitution reaction and exhibit anticancer activity.

CHEMICAL REACTIVITY AND SUBSTITUTION REACTION

General scheme for synthesis of triazine derivative

I st STEP :

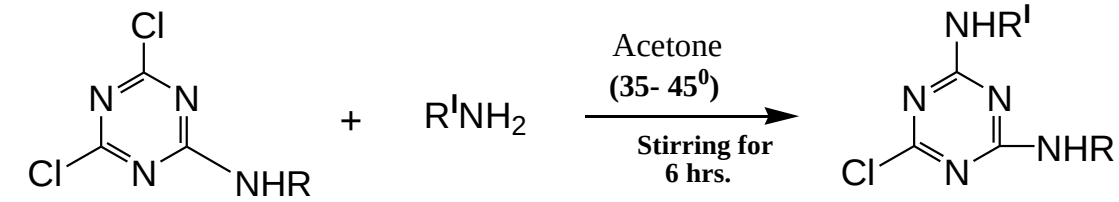


2,4,6-trichloro-1,3,5-triazine (Cyanuric Chloride) 0.1 Mol

Primary amines (Nucleophilic agent) 0.1 Mol

2-Substituted Amino- 4,6-dichloro- 1,3.5-triazine

II nd STEP :

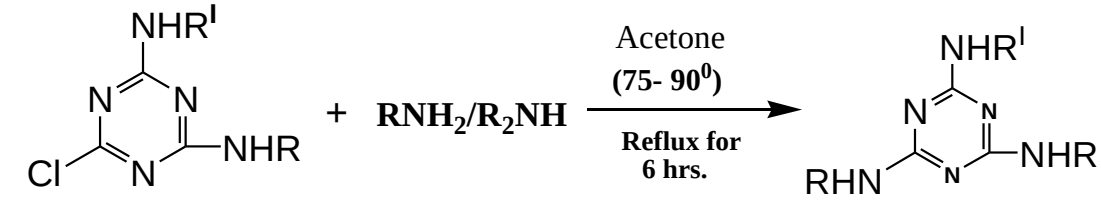


2-Substituted Amino-4,6-dichloro-1,3.5-triazine (0.1 Mol)

Primary amines (Neucleophilic agent) (0.1 Mol)

2,4-Disubstituted amino- 6-chloro-1,3.5-triazine

III rd STEP :



2,4-Disubstituted amino- 6-chloro-1,3.5-triazine

Various Primary or Secondary amines

2,4,6-Trisubstituted amino- 1,3.5-triazine

Synthesis of some novel 2,4,6- trisubstituted amino - 1,3,5 -triazine derivative.

CONCLUSION

1,3,5-triazine is one of the oldest heterocyclic compound available. Because of its low cost and easily availability, it emphasizes the sight of researcher for novel synthesis. Some dyes, lubricants and reagents derived from 1,3,5-triazine are already available in market. The present review paper showed that s-triazine derivatives represent an interesting class of compounds

possessing a wide spectrum of biological activities. As 1,3,5-triazine show nucleophilic substitution reaction a series of compound has been synthesized by using chemical reaction of 2,4,6-trisubstituted-1,3,5-triazines with various nucleophilic reagents like primary and secondary amine. These newly synthesized compound exhibit wide spectrum biological activity such as analgesic and anti-inflammatory, antifungal, antibacterial, histamine blockers, antitubercular and antioxidant. By using same approach series of compounds can be synthesized, characterize and evaluate for desire pharmacological activity with high potency and low toxicity.

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