Novel s-Triazine Based Heterocycles As Biologically Privileged Scaffolds

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Abstract

This review presents the studies of diverse bioactivities and unique applications of substituted s-triazine derivatives. s-triazine nucleus is emerged to be an active constituent in many standard drugs, and is known to increase the (biological) activity of the molecules. Novel substituted s-traizine based derivatives constitute an important class of compounds having antimicrobial, anticancer, antitumor, antiviral, antitubercular, antimalarial, insecticidal and herbicidal activities. It is hoped that this review will serve as a stimulant for new thoughts in the quest for drug discovery process.

Key Words: s-triazine, antimicrobial activity, anti-viral activity, anti-cancer activity

Introduction

A large numbers of drugs and biologically relevant molecules contain heterocyclic systems. The presence of hetero atoms or groupings imparts preferential specificities in their biological responses. Amongst the heterocyclic systems, s-triazine is a biologically important scaffold known to be associated with wide range of biological activities. Some of the prominent biological responses assigned to this moiety are antibacterial[1], antifungal[2], antiviral[3], antitubercular[4], anticancer[5], antiprotozoal[6], antimalarial[7], insecticidal and herbicidal[8] activities. This diversity in the biological response profiles of s-triazine has attracted the attention of many researchers to explore this moiety to its multiple potential against several activities. The triazine scaffold has provided the basis for the design of biologically relevant molecules with broad biomedical values as therapeutics. These are valuable bases for estrogen receptor modulators and also used as bridging agents to synthesize herbicides. Further substituted s-traizines have been used as NLO materials, which have a wide range of applications in optoelectronics and telecommunications. Several reports appeared that s-triazine is a potential nucleus for therapeutic agent against diseases caused by bacteria, malaria and cancer. Therefore, recent updates in s-triazine moiety are compiled in stepwise manner. In this context, the present article highlights the various explorations carried out on s-triazine heterocyclic systems.

Chemistry

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 (Figure 1).The six membered heterocycle consisting of three nitrogen atoms and three carbon atoms alternately located in the ring is known as symmetrical triazine (s-triazine) ring system; this heterocycle is ordinarily abbreviated as s-triazine.

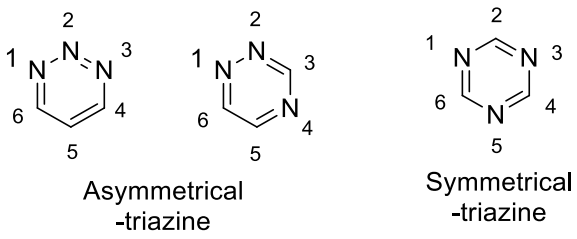


Figure 1: Triazine isomers

Out of the three isomers, 1,3,5-triazine or *s*-triazine and its derivatives are widely used in the pharmaceutical, textile, plastic, and rubber industries, and are used as pesticides, dyestuffs, optical bleaches, explosives, and surface active agents. 1,3,5 – Triazine or s-triazine is one of the oldest class of organic compound and was unknowingly first synthesized by Nef in 1895 by treating hydrogen cyanide with ethanol in an ether solution saturated with hydrogen chloride. The resulting salt was then treated with base and distilled to give 1,3,5-triazine in low yields, 10%. Nef incorrectly identified the product as a dimeric species. However, in 1954, Grundmann and Kreutzberger proved the compound to be a trimer of hydrogen cyanide, s-triazine [9, 10].

All of the s-triazine derivatives that have wide practical applications are 2,4,6-mono, di- or tri-substituted, symmetrical and non-symmetrical compounds bearing different substitutions. The most important reagent for obtaining these compounds is cyanauric chloride (2,4,6-trichloro-1,3,5-s-triazine). It is also important to stress that cyanuric chloride is commercially available and a very inexpensive reagent, which makes its applications even more attractive. *s*- Triazine is an extremely volatile crystalline solid which melts, at 86°C and boils at 114°C at one atmosphere. It is easily soluble in ether and in ethanol at 0-5°C. The relatively high melting point and extreme volatility are in accord with a highly symmetrical molecular structure.

As discovered by Banks[11], substitution reactions can be catalyzed by acid and in fact, the more electrophilic triazonium ion is more reactive[12] will be cyanuric chloride itself. An acid catalysis can also take place in aqueous medium, provided that nucleophilic reactant does not prevent protonation of the s-triazine ring. For this reason, the reaction of cyanuric chloride with alcohols and aromatic amines in particular can be catalyzed by acids.

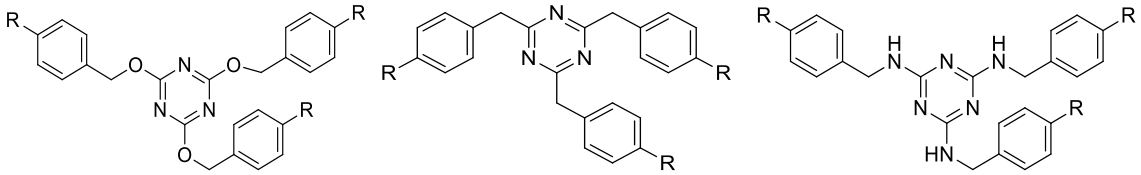
The ease of displacement of chlorine atoms in 2,4,6-trichloro-1,3,5-triazine by various nucleophiles, in the presence of a hydrochloride acceptor usually sodium carbonate, bicarbonate, hydroxide or tertiary amines, makes this reagent useful for the preparation of mono-, di- and tri-substituted 1,3,5-triazines. The substitution of chlorine can be controlled by temperature to run in a stepwise manner that is mono-substitution of chlorine at low temperature; 0-5 ºC, di-substitution at approximately room temperature; 40-45 ºC and tri-substitution at elevated temperatures; above 60-70 ºC[13, 14]. This property allows substitution of three different nucleophiles onto the same triazine core which provides a vast array of possible s-triazine derivatives and applications.

Biological evaluation of s-triazine derivatives

- **Antimicrobial activity**

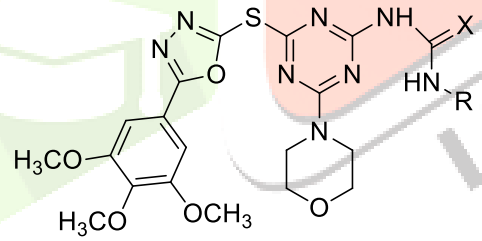
As multidrug-resistant bacterial strains proliferate; the necessity for effective therapy has stimulated research into the design and synthesis of novel antimicrobial molecules. Several reports have been presented here for the antimicrobial efficacy of s-triazine derivatives.

s-Triazine derivatives of the following type have been synthesized and their MIC values were determined against several Gram-positive and Gram-negative microorganisms[15]. The study suggested the key role of ethereal linkage to s-triazine ring towards various bioactivities.

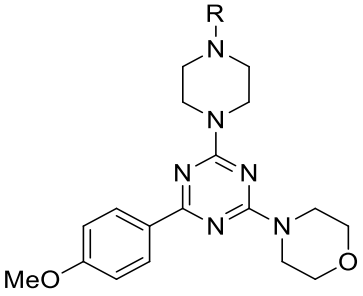


Where R=H, Cl, F etc.

In an effort to discover new candidates with improved antimicrobial activities Patel *et al.*[16] have synthesized various series of 2-[(3,4,5-trimethoxy phenyl-1,3,4-oxadiazoyl0-5-thio]-4-(morpholoino)-6-(phenyl ureido/thioureido)-s-triazine derivatives. Antimicrobial properties of these compounds were investigated against two Gram-positive and two-Gram negative bacteria and two fungal strains. Some of the compounds showed high *in vitro* antimicrobial activity. The results revealed that the presence of electron withdrawing group on the aromatic ring increase the activities compared to having an electron donating groups.

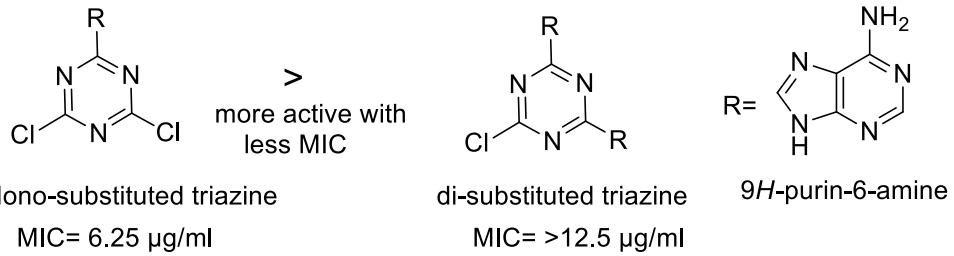


Lakum *et al.*[17] synthesized 1,3,5-triazine based analogues involving the substitution of various piperazines to the s-triazine ring and evaluated for their *in vitro* biological efficacy against Gram-positive and two-Gram negative bacteria and fungi. The prepared analogues exhibited a good antimicrobial activity profile.



Where R=H, Me, Et, COOMe etc.

Novel hybrids of *s*-triazines were prepared by Shanmugam and colleagues[18] which were screened for their antifungal activity. Mono substituted triazine compounds showed better activity than di and tri-substituted triazine hybrids.



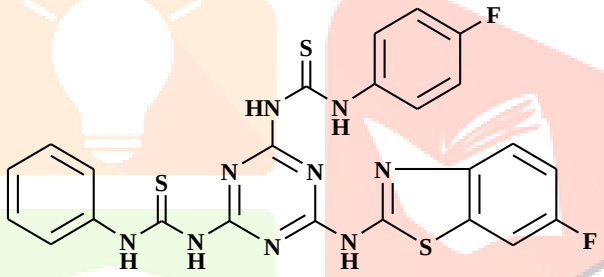
Mono-substituted triazine
MIC= 6.25 µg/ml

di-substituted triazine
MIC= >12.5 µg/ml

9*H*-purin-6-amine

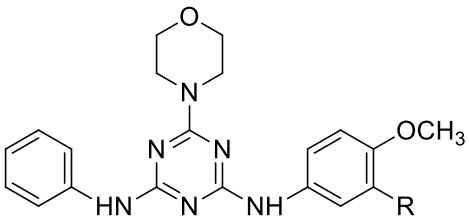
A series of 2,4,6-trisubstituted 1,3,5-triazines were synthesized and evaluated for their antimicrobial activity against two representative Gram-positive and Gram-negative bacteria and two fungi. Biological data revealed that most of the compounds found to have promising antimicrobial activities. Out of the synthesized compounds some of the compounds have shown MIC in the range of 6.25-12.5 µg/ml[19].

Sareen *et al.*[20] synthesized some fluorinated s-triazine derivative and evaluated their antimicrobial activity.

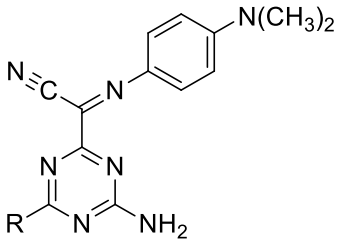
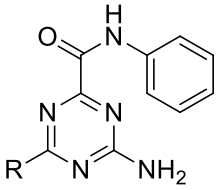


- **Anticancer activity**

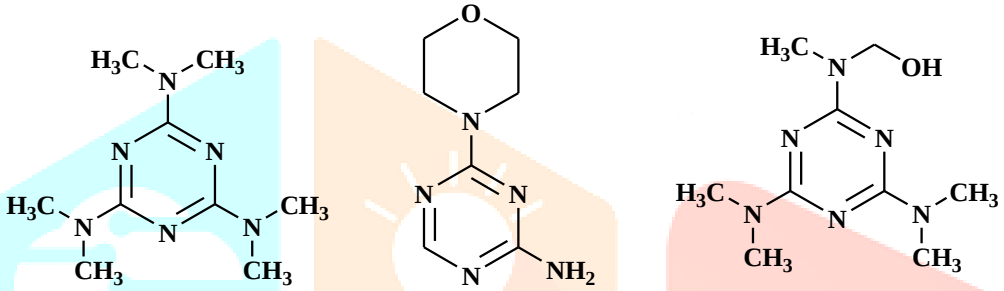
Zheng *et al.*[21] have synthesized some 1,3,5-triazine derivatives bearing amines and morpholine as potential anticancer agents.



A series of 2-(4,6-diamino-1,3,5-triazine-2-yl)-2-{[4-(dimethyl amino)-phenyl]imino}acetonitriles have been synthesized by Saczewski *et al.*[22] and screened for in vitro anticancer activity against the various human cancer cell line. These types of 1,3,5-triazine based scaffolds were found effective for further development with good cancerous cell growth inhibitory efficacies.

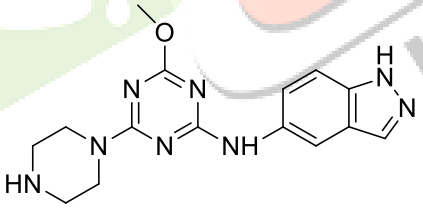



Some s-triazines display important biological properties, for example hexamethyl melamine (HMM) and 2-amino-4-morpholino-s-triazine are used clinically due to their antitumor properties to treat lung, breast and ovarian cancer, respectively[23]. Hydroxymethyl pentamethyl melamine is also the hydroxylated metabolite which corresponds to the major active form of HMM[24]. 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.

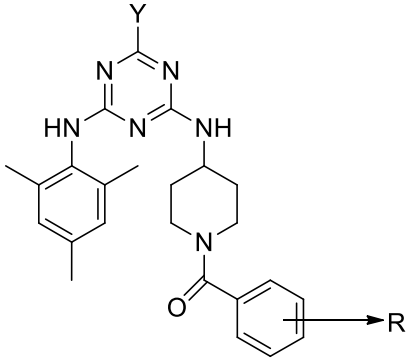


- **Anti-viral activity**

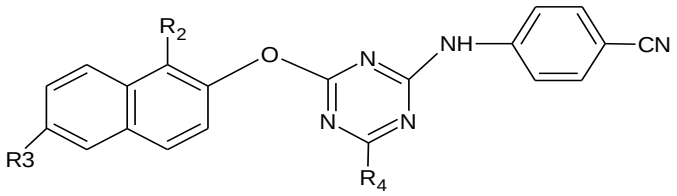
Kwang-Seok *et al.*[25] identified a novel inhibitor of Rho kinase (2-(1*H*-indazole-5-yl)amino-4-methoxy-6-piperazino triazine) and characterized its effect in biochemical, cellular, tissue and animal based assays.



A novel series of piperidine-substituted triazine derivatives have been synthesized by Xuwang Chen & co-workers[26] and evaluated for anti-HIV activities in MT-4 cells.

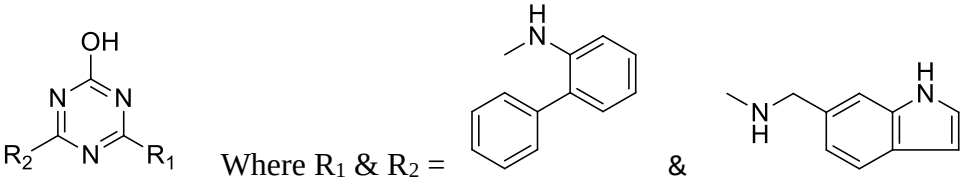


A series of novel 6-naphthyloxy substituted DATA (diaryl triazines) analogues bearing different substituents on the 6th position of triazine ring were synthesized and evaluated for their *in vitro* anti-HIV activity[27] in MT-4 cells.



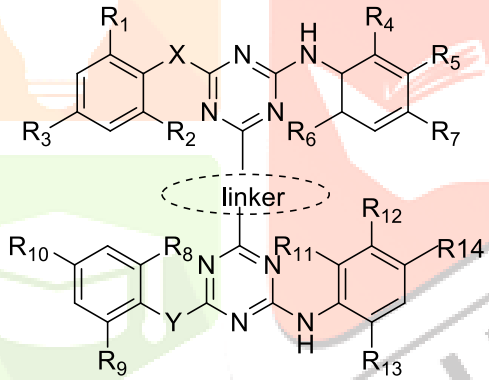
Where R_2, R_3=H, Br R_4=NH_2, NHMe

A series of 4, 6-diamino-[1, 3, 5]–triazin-2-ol have been designed and synthesized as novel HIV-1 Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs). Representative compound of this series showed excellent activity against wild type and drug-resistant RT enzymes and viral strains[28].



Where R_1 & R_2 = &

Venkatraj *et al.*[29] reports the synthesis and structure-activity relationship (SAR) study of a series of triazine dimmers as novel antiviral agents. These compounds were obtained through a bivalent ligand approach in which two triazine moieties are covalently connected by suitable linkers. Several compounds showed submicromolar activity against wild type HIV-1 and moderate activity against single mutant strains.



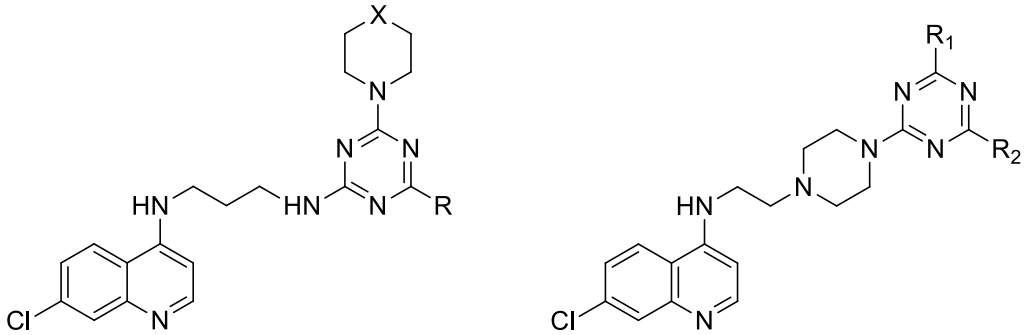
Where R_1, R_2, R_3, R^8, R^9, R^{10} = -Me, Br, OMe, CN etc.

R_4, R_5, R_6, R_7, R_{11}, R_{12}, R_{13}, R_{14}= Me, Br, OMe, CN etc.

Linker = $NH(CH_2)_2NH$, $NH(CH_2)_3NH$ etc.

- **Antimalarial activity**

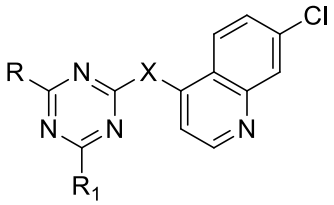
P. M. S. Chauhan *et al.*[30, 31] designed, synthesized a series of new class of hybrid 4-aminoquinoline triazines and screened for their antimalarial activities against *P. falciparum* in an *in vitro* model and CQ resistant strain of *P. yoelii* in an *in vivo* assay.



R_1/R_2= H, 2-Aminoethylmorpholine, n-Butylamine etc.

Rawat *et al.*[32] synthesized series of 4- substituted amino quinolinyl-triazine conjugates with different substituent and evaluated their *in vitro* antimalarial activity against

Chloroquine sensitive resistant strains of *plasmodium falciparum*. Among the synthesized compounds some of the synthesized compound appeared with promising anti-malarial activity at less cytotoxicity up to high concentration (48 µm).

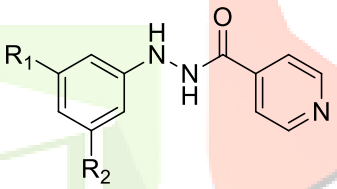


Where R=morpholine; R_1=3,5-dimethyl aniline; X=1,3-propanediamine

Furthermore, Gahtori and his co-workers[33] introduced docking studies of hybrid phenylthiazolyl-1,3,5-triazine derivatives to evaluate dynamic tool in the identification of specific motif in ongoing drug discovery for antifolates in antimalarial chemotherapy.

- **Antituberculosis activity**

A series of Isonicotino hydrazide, tetrahydroquinoline and various amino propyl-morpholine as well as amine linked s-triazines have been synthesized and studied their antituberculosis activity[34] against *mycobacterium tuberculosis* $H_{37}Rv$. Among the synthesized compounds some of the compound exhibited good to moderate activity with an MIC in the range 1.56 – 3.12 µg/ml and most of them were found to be nontoxic against VERO cells and MBMDMQs (mouse bone marrow derived macrophages).



Where R_1=1,2,3,4-tetrahydroquinoline, piperidine, aniline etc.

R_2=various amines

Sunduru and his research mates[35] designed and synthesized and SAR evaluation of 2,4,6-tri-substituted-*s*-triazines as novel antituberculosis agents. Out of 81 compounds assessed for *in vitro* growth inhibition of *M. tuberculosis* $H_{37}Rv$ strain, fifteen compounds displayed promising activity with an MIC range of 1.56-3.12 µg/ml.

- **Herbicidal, fungicidal, and insecticidal activity**

Zhao and colleagues synthesized and characterized a series of novel triazines containing arylmethylamino moieties as herbicidal, fungicidal, and insecticidal. In herbicidal screening[36] showed equipotent herbicidal inhibition as atrazine. Moreover, in fungicidal and insecticidal screening, respectively[37] exhibited 100% efficacy against *P. triticina*.

Brown and co-workers filed a patent to introduce 1,3,5-triazinyl phenyl hydrazones as effective insecticidal agents[38]. Tri-substituted *s*-triazine compounds clubbed to hydrazone were subjected to evaluate for insecticidal efficacy against *Spodoptera exigua* and *Helicoverpa zea* [39].

Regarding "traditional" industrial applications 1,3,5-triazines have been used as intermediates to build up agrochemical[40] & pharmaceutical[41].

- ***s*-Triazine in drug design**

Atrazine

Atrazine, containing one unsubstituted chlorine atom, is the most useful herbicide to control soil erosion. It drew much more attention due to selective disruption of photosynthesis to kill weeds, resulting in increased crop production. It is quite economical and effective herbicide which is widely used to prevent pre- and post-emergence broadleaf and grassy weeds in crops but due to its hazard side effects it has been barred in European countries.

Triethylenemelamine

This drug is used in chemotherapy. It was used for the treatment of retinoblastoma; however, due to aberrations it was no longer used.

Altretamine

Altretamine, also known as is *s*-triazine based antineoplastic drug. In the treatment of refractory ovarian cancer, orally administered altretamine was first approved by the FDA in 1990. Less toxicity of altretamine in dealing with cancer treatment proves its superiority than other drugs. It can be used in salvage therapy still it is not supposed to be a first-line treatment.

Conclusion

The present review has highlighted the potential of the s-triazine and its derivatives as a biologically privileged scaffold. Due to wide biological properties, novel s-triazine derivatives should be an intensive research which can alleviate the present disparate diseases. Through the examples cited in this review I have tried to emphasize the prospects of this heterocyclic system in lead identification, development in the drug discovery program.

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