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S-TRIAZINE DERIVATIVES: AS TODAY'S NEED AND TOMORROW'S LEAD

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ABSTRACT

Heterocyclic compounds have great value for researchers, as they have the potential to diversify their use with derivatization. Nitrogen-containing heterocycles are the first choice for researchers due to their improved pharmacological and physical properties. Specifically, derivatives of azines and azoles are more promising for synthesis and derivatization with versatile applications. The use of triazine scaffolds is expected to be greatly beneficial to future medicine development. S-triazines and their derivatives are very auspicious due to their easy synthesis and limitless applicability. In this review, the S-triazine derivatives that hold a notorious position, with their use in recent times, are discussed.

Keywords: triazine, heterocyclic, anti-cancerous, anti-fungal, anti-diabetic.

INTRODUCTION

Organic chemistry has been empowered with novel experimental and computational methods and has diverse applications in today's world [1]. Researchers are actively working on various organic compounds, based on heterocyclic scaffolds, which are bioactive and versatile [2]. An intriguing class of nitrogen-containing heterocyclic molecules is triazine [3]. Common nitrogen-containing heterocycles with various pharmacological actions are azines and azoles [4]. Triazine is a significant heterocyclic scaffold that offers a wide range of biological properties. The three isomeric forms of triazine, viz. 1,2,3-triazine; 1,2,4-triazine, and 1,3,5-triazine, differ according to the position of nitrogen. Of these, 1,3,5-triazine or s-triazine is considered more imperative than other triazine isomers [5]. Numerous synthetic s-triazine derivatives have been synthesized and tested for a variety of biological activities in various models, with desired results including anti-microbial, anti-bacterial, anti-fungal, anti-cancer, anti-viral, anti-inflammatory, anti-ulcer, anti-convulsant, anti-malarial, insecticidal, and herbicidal properties [5,6].

Derivatives of 1,2,3-triazine, formally known as v-triazine, synthesized from a variety of synthetic and natural compounds, exhibit strong cytotoxic and antibacterial properties. They show improved pharmaceutical properties when fused with heterocyclic moieties such as pyridine, pyrazolone, indole, thieno, indolo-benzo, triazole, and 1,2,4-triazine [7]. 1,2,3-triazine is the least stable isomer among the three triazine isomers, as the arrangement of nitrogen atoms in its structure decreases its resonance energy and makes it unstable. The v-Triazine ring is prone to nucleophilic substitution reaction due to its electron-deficient nature. Numerous synthetic derivatives with diverse properties are synthesized with various functional groups [8]. The 1,2,4-triazine (a-Triazine) ring is an asymmetric, significant, and versatile triazine scaffold for researchers. Similar to 1,2,3-triazine, it also undergoes nucleophilic substitution and facilitates the development of a range of biologically active synthetic derivatives. As it is more stable than 1,2,3-triazine, it seems to be a more promising triazine scaffold [9]. On the other hand, 1,3,5-triazine (s-triazine) is a symmetrical triazine isomer, with unique structure and reactivity, which makes it more suitable scaffold for the development of compounds with diverse biological and physical properties. It is more soluble in organic solvents like methanol[10].

Among all the isomers of triazine, 1,2,3-triazine is the least studied and moderately applicable, while 1,3,5-triazine is widely applied in experimental chemistry [15]. A number of synthetic derivatives formed with s-triazine are in commercial use [16]. Here we discussed numerous triazine derivatives that are useful in a certain way, and hold a renowned place in the world.

Table 1: Comparative Outlook of Triazine Isomers.

Property	1,2,3-Triazine (v-Triazine)	1,2,4 Triazine (a-Triazine)	1,3,5-Triazine (s- Triazine)
Molecular Formula	$C_3H_3N_3$	$C_3H_3N_3$	$C_3H_3N_3$
Molecular Weight	81.08 g/mol	81.08 g/mol	81.08 g/mol
Stability	Least Stable	Moderately Stable	Most Stable
Solubility	Low Solubility in Water	Low To Moderate Solubility in Water	Slightly Soluble in Water
Aromaticity	Least Aromatic	Moderately Aromatic	Aromatic And Stable
Reactivity	Most Reactive Towards Nucleophile [11]	Moderate Reactivity Towards Nucleophile [11]	Low Reactivity Towards Nucleophile [11]
Applications (Commercial)	Research And Pharmaceuticals [12]	Pharmaceuticals, Agrochemicals [13]	Herbicides, Drugs, Polymers [14]
Therapeutic Derivatives	Anticancer, Antimicrobial [12]	α-Glucosidase Inhibitors, Anti-Inflammatory [13]	Anticancer, Antimicrobial, Antibacterial Drugs [14]
Synthetic Uses	Heterocyclic Intermediate [12]	Scaffold For Complex Synthesis [13]	Widely Used in Industry [14]

All these derivatives are actively used in various fields and serve today's needs for society.

Applications of s-Triazine isomers in today's world

Various triazine derivatives demonstrate notable applications in medicinal chemistry, agriculture, material science, and pharmaceuticals [17]. Here is a list of some therapeutic agents actively used to treat many medical emergencies.

Table-2: s-triazine derivatives approved as specific drugs

Name of drug/ compound	Class	Uses
Altrtamine[18]	Hexamethyl melamine	Ovarian cancer treatment
Azacitidine [19]	4-amino-1-β-D-ribofuranosyl-s-triazine-2 (1H)-one	Anti-cancer drug mainly for Myelodysplastic syndromes
Tretamine [20]	triethylmelamine	Anti-cancer drug for retinoblastoma
Melasoprol [21]	Melaminophenylarsine and dimerceptopropanol	For the treatment of trypanosomiasis
Almitrine [22]	s-triazine triamino compound with 4-(bis(p-fluorophenyl) methyl)-1-piperazinyl	Respiratory stimulant for patients with chronic obstructive pulmonary disease
Bimiralisib (PQR309) [23]	5-(4,6-dimorpholino-1,3,5-triazine-2-yl)-4-trifluoromethyl) pyridine-2-amine	PI3K/mTOR inhibitor, Anti-breast cancer drug
Gedatolisib [24]	2,4-dimorpholinyl-1,3,5,-triazine derivative	Anti-cancer drugs for neoplasm, ovarian cancer, breast cancer, endometrial cancer, and advanced cancer
Decitabine [25]	5-aza-2'-deoxycytidine	Myelodysplastic syndromes and AML
Enasidenib [26]	s-triazine central core with derivatized arms	AML with IDH2 mutation
Vorasidenib [27]	s-triazine central core with derivatized arms	Grade 2 glioma with IDH1/IDH2 mutations

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Table 3: Other s-triazine derivatives showcasing better therapeutic values

Other s-triazine derivatives	Class	Uses
sulfonamide-1,3,5-Trizine-Thiazole derivative [28,29]	Hybrid Compounds	Antidiabetic (DPP-4 inhibitors)
s-Triazine Dipeptides with anti-proliferative and Apoptotic Activity [30]	s-Triazine dipeptide series	Antiproliferative, for Breast & colon cancer
Mono- and Bis(dimethylpyrazolyl)-s-Triazine Derivatives [31]	Pyrazolyl-triazine derivatives	Anticancer (EGFR/PI3K/AKT/mTOR INHIBITION)
Sulfapyridine/Sulphaguanidine-Triazine Hybrids [32]	Triazine-sulfonamide derivatives	Anticancer, antiproliferative against MCF-7, A549 cell lines
Imeglimin-Inspired 1,3,5-Triazine Derivatives bearing oxazine [33]	s-triazine-oxazine derivatives	Antidiabetic (DPP-4 inhibition
Aziridine- Functionalized 1,3,5-triazine derivatives {34}	s-triazine- aziridine derivatives	Anticancer agents
Imamine-1,3,5-triazine derivatives with better activity than Imatinib [35]	s-triazine-imamine derivatives	Anticancer, antiproliferative properties against MDA-MB-231 cells

The use of s-triazine derivatives is not limited to therapeutic agents. These derivatives are also used in other fields. One of the most important and commercial uses of s-triazine derivatives is in herbicides [36].

Table-4: List of granted and active patents of s-Triazine derivatives used as drugs

Type of Triazine derivatives	Assignee	Therapeutic Uses	Patent Number And Year
Triazine compound and pharmaceutically acceptable salt thereof	Shenzhen Forward Pharmaceuticals Co Ltd	EGFR-mediated diseases, including NSCLC	EP3705478B1 (2023)
Triazine Derivatives exhibiting coronavirus 3CL protease inhibitor	Hokkaido University NUC, Shionogi and Co Ltd	Antiviral (corona)	US11814368B2 (2023)
2,4,6-trisubstituted s-Triazine compounds, preparation and use	Nanjing Shiqi Pharmaceutical Co Ltd	anticancer,tissue fibrosis and atherosclerosis	US11390591B2 (2022)
PI3K Inhibiting 1,3,5-Triazine Derivatives	Council Of Scientific & Industrial Research	Anticancer (Pi3k Inhibition)	US9951040B2 (2018)
Pyrazino-Triazine Derivative for cancer	JW Pharmaceuticals Corp.	Anticancer (EGFR-Resistant NSCLC)	US9353119B2 (2016)
Triazine Derivative for Diabetes (Film Coated Tablet)	Poxel SA	Antidiabetic	US11813362B2 (2023)
Triazine Derivatives with Antibacterial and Anti-inflammatory Activity	Peptoide Co Ltd	Antibacterial And Antiinflammatory	US12012387B2 (2024)

Atrazine, simazine, propazine, cyanazine, desethylatrazine, desisopropylatrazine, terbuthylazine, cyprazine, atraton, terbutryn, prometon, prometryn, preben, ametryn, desmetryn, and dimethametryn are examples of herbicides consisting of s-triazine moiety [37]. Indiaziflam and

triaziflam are s-triazine compounds approved by the US-FDA as potential insecticides [5]. Countless research is being conducted on the s-triazine scaffold, many of which are patented for their outstanding results. Here, we enlist a few patents that have been granted and are still active nowadays.

Conclusion

In recent years, the s-triazine scaffold has showcased its outstanding and limitless activities in various fields. S-triazines fused with various aromatic rings show potent activity against multiple targets. Derivatized s-triazines with heterocyclic systems (like aziridine, pyrazolyl, oxazine, etc.) showing inhibition of multiple targets. The s-triazine core can improve selectivity, binding affinity, and metabolic stability. They can be decorous for the development of non-traditional antibiotics, especially against drug-resistant bacteria. Oncology, antimicrobial, neurology (CNS), immunotherapy, and drug delivery are major fields where triazine derivatives are in preclinical trials. Other Prospects of the triazine rings may include their use as prodrug linkers, design and development of safer chemicals for agricultural use, and the development of supramolecular architecture for imaging and diagnostic purposes.

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