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Anticancer Potential of Triazine Scaffold: A Brief Review

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Abstract

Triazine is an important class of heterocyclic compounds. Triazine is a six-membered heterocyclic compound with three carbons replaced by nitrogen in the benzene ring. Triazine and its compounds exhibit a wide variety of pharmacological activity such as antifungal, anti-HIV, anticancer, antioxidant, anti-inflammatory, analgesic, antihypertensive, antiviral, antimalarial, antiprotozoal, and antibacterial. The triazine ring has been modified at different positions to generate new molecules. The structure of the new derivatives was characterized by common analytical method. Some examples of triazine compounds commonly used in rational medicine are: Ceftriaxone as an antimicrobial agent and 6-Azacytosine as an antiviral agent. The present review article enumerates on the biological potential of triazine and how it is beneficial to discover more new compounds that could be better in terms of efficacy and lesser toxicity.

Keywords: Anticancer, Antimicrobial, Heterocyclic compounds, Rational medicine, Triazine derivatives

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Introduction

Health problems are growing day by day and have become the most severe clinical problem. Medicinal chemists are constantly doing a lot of researches and trials to find new medicines that could be used safely to treat such severe clinical problems. Medicinal chemistry occupies a strategic position at the interface of biology and chemistry and has tremendous scope.[1] There are several heterocyclic compounds which are currently in clinical use for infectious disease treatment.[2]

1, 2, 4-Triazine Ring

A heterocyclic six-membered ring which possesses three-carbon, three-nitrogen, and three-double bonds is known as triazine. Triazines are heterocyclic compounds that contain three atoms of carbon replaced by three atoms of nitrogen.[3] Triazine was first synthesized in 1889 by Bischler through the arylamidines of phosgene. Its molecular formula is $C_3H_3N_3$ and has a molecular mass of 81.08 g/mol which is soluble in acetone and DMF. Triazine (Figure 1) is a crystalline solid, white in color, a basic compound with a pungent odor.[4]

Nitrogen atoms are present in triazine ring at different positions, hence, there are three different isomers of triazines such as 1,2,3-triazine; 1,2,4-triazine; and 1,3,5-triazine, as shown in Figure 2.[5]

Certain heterocyclic aromatic nitrogen compounds include pyridines, diazines, triazoles, and tetrazines. Triazines compounds are weaker base and have much lower resonance energy than benzene, so nuclear replacement is preferable to electrophilic substitution.[5] Triazine shows difficult electrophilic substitution reaction and more frequent nucleophilic aromatic reaction. Triazine nucleus possesses less π-electron and is illustrated by two canonical compounds I and II (Figure 3). Calculated value indicated that compound I relates more than to ground state of particle.[6]

Triazine ring undergoes different types of chemical reaction such as nucleophilic substitution, photolysis, oxidation, hydrolysis, and biodegradation.[7] In the context, triazine scaffold has drawn many researchers attention because of its therapeutic activity and ease of work on it. Out of this, 1,2,4-triazine exhibits various biological activities such as antimicrobial,[8] anticancer,[9] anti-inflammatory,[10] antioxidant,[11] anticonvulsant,[12] antidiabetic,[13] and antitubercular[14] as reported in the literature.

There are different examples of commercially available drugs (Figures 4 and 5) which contain 1,2,4-triazine ring such as ceftriaxone (antimicrobial), apazone (anti-inflammatory and analgesic), azaribine (antifungal and antiviral), dihydromethyl furalazine (antibacterial), tirapazamine (anticancer), lamotrigine (anticonvulsant), 6-azacytosine (antiviral and antitumor), metribuzin (herbicide), and pymetrozine (insecticide). 1,2,4-triazine moiety containing most privileged derivatives are commercially available in the market (Figure 4).

Anticancer Activity of 1,2,4-Triazine

Malignancy is one of the world's utmost severe clinical complications and the instant leading origin of death, identified by a cell cycle deregulation that primarily results in a continuous loss of cell elongation and abnormal cell growth. The present situation demonstrates a need to identify and develop small anticancer agents with enhanced tumor selectivity, efficacy, and protection. Many organic researchers have reported excellent anticancer activity of 1,2,4-triazine derivatives.[15]

Xiang *et al.* prepared a range of pyrrolo[2,1-*f*][1,2,4]triazine compounds and analyzed for its enzyme production with p110α, β, δ, and γ isoforms of PI3K using a lipid kinase testing, as well as for its antitumor activity toward human cancer cells lines, BT-474, SK-BR-3, T47D, and SKOV-3 using SRB assay. The compound **1**

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displayed the best enzyme viability from this sequence and also inhibited tumor growth by 2.4 ± 0.5% (Table 1).[16]

Hassen *et al.* developed a range of substituted 1,2,4-triazine analogues and calculated for its antitumor potential. Compounds **2** and **3** showed moderate activities against renal cancer (UO-31) cell line with good growth inhibition (31.54–39.52%).[17]

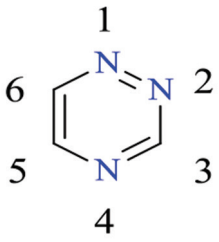

Figure 1: Structure of 1,2,4-triazine

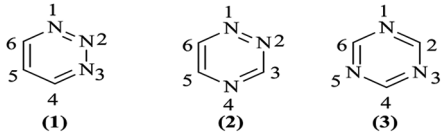

Figure 2: Tautomeric forms of triazine

Figure 3: Resonating structures of triazine

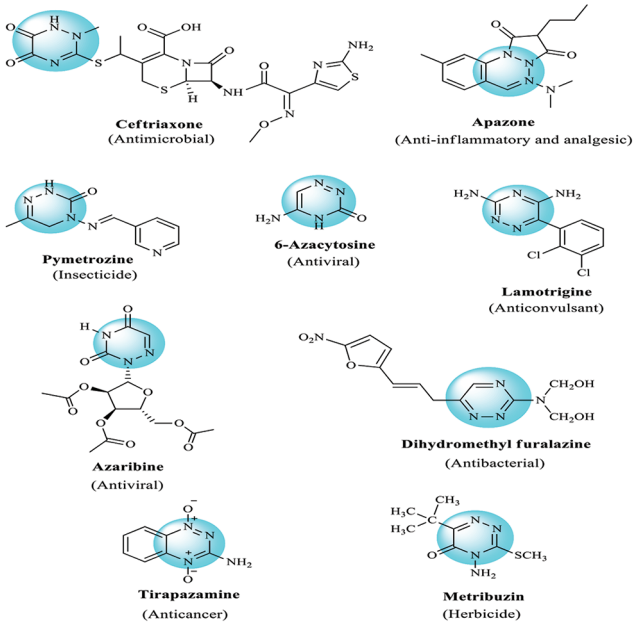

Figure 4: Marketed preparations containing 1,2,4-triazine as core moiety

Tiwari *et al.* developed 1,2,4-triazine products and investigated for their cytotoxicity on two cell lines, namely, breast cancer (MCF-7) and leukemia (K-562) using SRB assay. Reference drug used was adriamycin. Compounds **4d** (GI_{50} ≤ 10 μg/ml), **4c** (GI_{50} ≤ 10 μg/ml, and **4b** (GI_{50} ≤ 10 μg/ml) also showed excellent cytotoxic activity in comparison to rest of compounds, whereas **4a** (GI_{50} = 10.4 μg/ml) showed moderate anticancer activity against the positive control (GI_{50} ≤ 10 μg/ml). Compound **4d** demonstrated better anticancer potential due to the presence of electron withdrawing group (NO_2) at p-position. The results are shown in Table 2.[18]

Abou-Elregal *et al.* prepared a new class of 3-hydrazino-5,6-diphenyl-1,2,4-triazine derivatives and investigated its antitumor potential toward different cell lines such as HePG2 and MCF-7 by MTT method using doxorubicin as reference standard. Compounds **5, 6,** and **7** showed better results, whereas other compound showed no activity. The conclusion of antitumor potential of evaluated derivatives is depicted in Table 3.[19]

El-Kayyoubi developed 3-(4-chlorophenyl)-8-propylpyrimido[5,4-e][1,2,4]triazine-5,7(6H,8H)-dione and investigated it for antitumor activity by MTT assay against A-549 (lung cell line) using 5-fluorouracil and toxoflavin as reference standard. Compound **8** showed excellent activity against A-549 cell line. The observations of anticancer activity of prepared compounds are shown in Table 4.[20]

Zein *et al.* synthesized 1,2,4-triazine-6-one substances (**9a-9b**) and investigated it for anticancer potential against different cancer cell lines such as HCT-116 and HepG-2 using vinblastine as reference standard. Compound 6-(4-chlorophenyl)-1-phenyl-9-thioxo-6,7,8,9-tetrahydro-[1,2,4] triazine[1,2-a][1,2,4]triazine-4(3H)-one **(9b)** showed excellent potential toward HepG-2 and HCT-116 cell lines, while other substance (1,6-diphenyl-9-thioxo-6,7,8,9-tetrahydro[1,2,4] triazine-[1,2-a][1,2,4]triazino-4(3H)-one (**9a)** showed lowest potential through HepG-2 and HCT-116 cell lines. The results of anticancer activity are mentioned in Table 5.[21]

A novel group of substituted triazine sulfonamide products was performed by Matysiak *et al.* and examined for antitumor potential toward MCF-7 cell lines. Compound **10** showed highest cytotoxicity activity (IC_{50} values 2.602).[22]

A-Hasanen *et al.* developed fused 1,2,4-triazine compounds **(11 and 12)** which were tested for their anticancer activity. The inhibition activity versus MCF-7 (breast cancer cell line) was assessed using different sample concentration (0.00 to 5.00 to 12.50 to 12.50 to 25.00 to 50.00 μg/ml) and the surviving fraction was determined using ELISA reader color intensity. The data value of IC_{50} showed that compounds **11** and **12** (IC_{50} = 6.80 and 10 μg/ml) showed good anticancer activity (MCF-7 cell lines) as compared to doxorubicin.[23]

A range of innovative 2-(arylmethylthio)-4-chloro-5-substituted-N-(5-aryl-1,2,4-triazin-3-yl-benzenesulfonamide compounds was evaluated by Zolnowska *et al.* and was assessed for antitumor effects using diverse human cells. Compounds **13** and **14** were found to have maximum potential. Each compound

Table 1: Results of compound 1 (enzyme and cellular inhibition)

Comp.	*p110α IC_{50} (nm)*	*p110δ IC_{50} (nm)*	*p110 β IC_{50} (nm)*	*p110γ IC_{50} (nm)*	*BT474 (μm)*	*SKBR3 (μm)*	*T47D (μm)*	*SKOV-3 (μm)*
2	122	119	1293	663	2.4±1.1	2.4±0.5	0.8±0.1	2.3±0.8

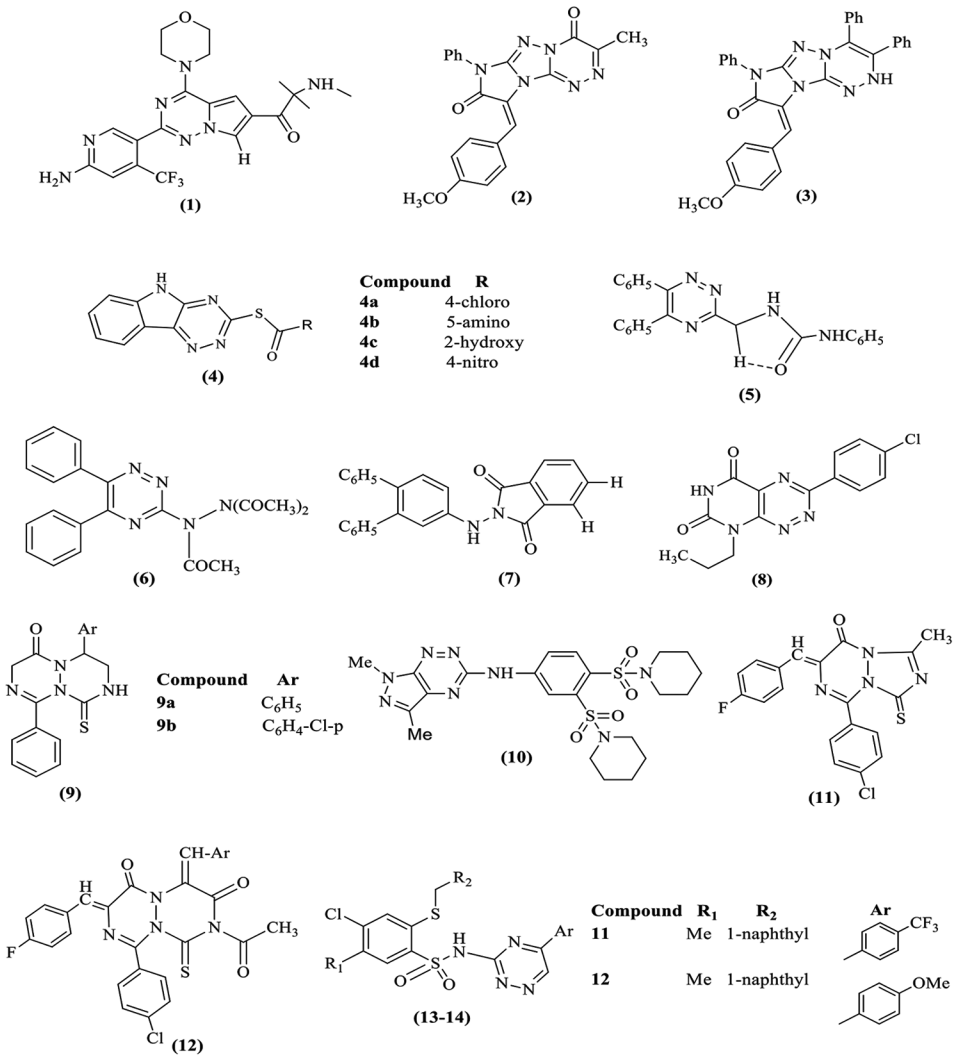

Figure 5: Structure of most active triazine containing anti-cancer compounds

Table 2: GI_{50} values (µg/ml) of standard and test compounds

Compound	*GI_{50} values (µg/ml)*	
	MCF-7	*K-562*
4a	17.2	10.4
4b	<10	>80
4c	<10	63.2
4d	<10	72.3
Adriamycin	<10	<10

Table 3: Anticancer screening results of compounds 5, 6, and 7

Compounds	*Cancer cell lines (IC_{50} = µM)*	
	HePG2	*MCF-7*
Doxorubicin	4.50±0.2	4.17±0.2
5	39.49±2.6	45.08±2.8
6	27.93±2.1	26.99±2.0
7	48.16±2.9	58.36±3.4

Table 4: IC_{50} value of compound 8

Compound	*IC_{50} (µM)*
8	3.6±0.2
Toxoflavin	0.7±0.1
5-fluorouracil	10.5±0.1

Table 5: IC_{50} values (µM) of compound 9

Cell line	*IC_{50} value*		
	9a	*9b*	*Vinblastine*
HCT-116	22.0	5.92	2.38
HepG-2	26.7	9.06	4.60

Table 6: Cytotoxicity profile of compounds 13-14

Compound	*IC_{50} (µM)*		
	HCT-116	*HeLa*	*MCF-7*
13	36±1	34±2	70±3
14	38±2	42±1	69±1
Cisplatin	3.8±0.2	2.2±0.2	3±0.1

was tested to calculate percentage viability of cell line against the different concentration and results are presented in Table 6.[24]

Conclusion

In this present review article, we have summarized the different pharmacological activities of triazine containing compounds. From this study, we have found that triazine containing compounds have

a wide range of biological activities such as antimicrobial, anticancer, antioxidant, anti-inflammatory, anticonvulsant, and antidiabetic. This review article established the fact that triazine scaffold can be utilised as useful template for further modification or derivatization to design more potent biological active compounds.

Authors' Declaration

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Authors' Contributions

Saloni Kakkar, Meenakshi, Ashu, and Priyanka did the literature review and framed the manuscript.

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