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Triazine: A Scaffold with Never Ending Pharmacological Potential

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Abstract: ***Background: The triazine moiety occupies a unique position in medicinal chemistry due to its extensive biological and pharmacological potential. Over the decades, the moiety has been investigated for developing molecules that may be used to treat a plethora of pathological conditions, including inflammation, cancer, and infections. Several lead molecules have been developed from the triazine moiety. The fusion of triazine with other heterocyclic rings, such as imidazoles and pyrroles, has produced several bicyclic compounds with biological activity. The broad spectrum of activities displayed by triazines and the development of several commercial drugs containing triazines have led to growing interest among chemists worldwide in this moiety over the years. In this review, commercially available triazine molecules are presented, and an attempt has been made to compile the works reported by various researchers over the past decade, primarily related to the structural variations among triazine derivatives exhibiting antimicrobial, anticancer, and other biological activities. The objective of this review was to summarise recent reports on triazines and their analogues concerning their biological potential. Conclusion: The content of the review would help update researchers working towards the synthesis and design of new molecules for the treatment of several diseases, particularly those produced from the triazine scaffold.***

Keywords: Triazine, Pharmacological Potential, Bioactivities.

I. INTRODUCTION

Triazines are six-membered heterocyclic ring systems that are analogous to benzene but have three carbon and three nitrogen atoms. They are found in various Regio-isomeric forms wherein the position of the nitrogen atom varies. These forms are 1,2,3-triazines, 1,2,4-triazines and 1,3,5-triazines [1] (Figure 1).

[Fig.1: Isomeric Forms of Triazine]

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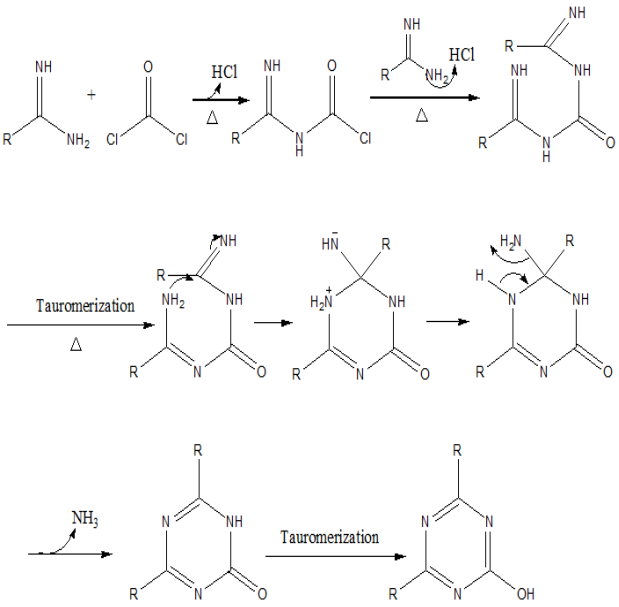
Owing to the broad spectrum of activities exhibited by this moiety, it holds a special position in medicinal chemistry. Among the three isoforms of triazine, 1,3,5-triazine, due to its symmetrical structure, has attracted considerable research interest as it facilitates the synthesis of diverse types of analogues.

Several methods have been reported for the synthesis of 1,3,5-triazines. The most commonly applied route involves the condensation of arylamidines with phosgene [1] (Pinner Triazine Synthesis, Figure 2), while the most frequently employed synthetic route for the derivatisation of triazines includes replacing the chlorine atoms of cyanuric chloride under different reaction conditions [1].

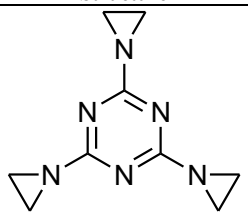
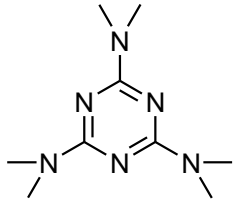
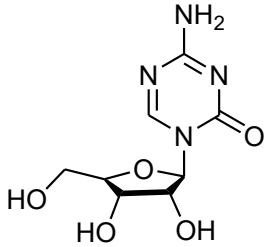
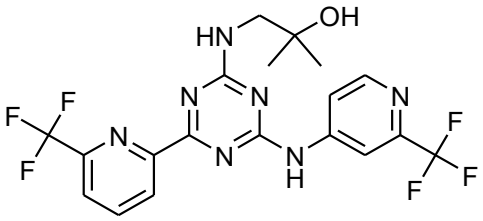
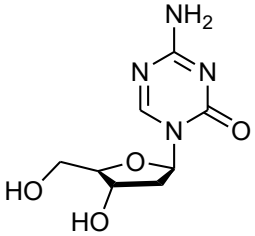
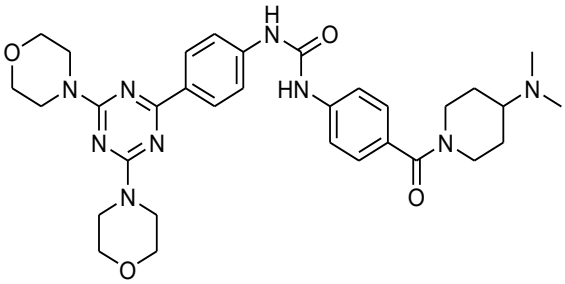
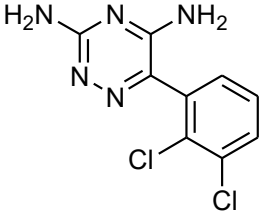


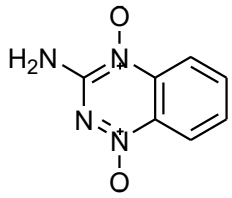
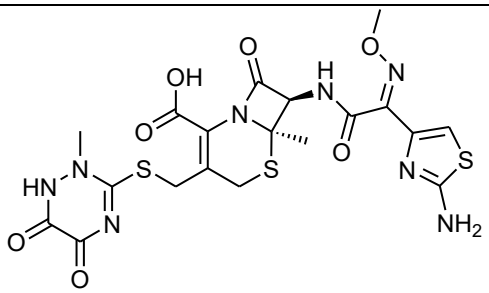
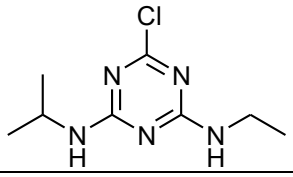
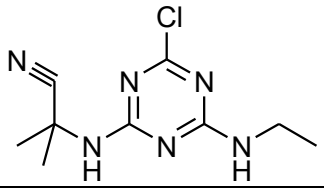
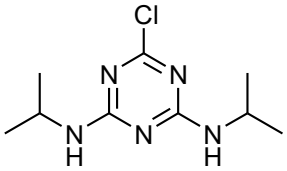
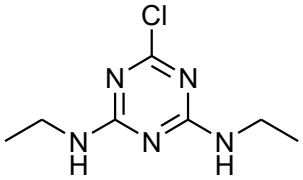
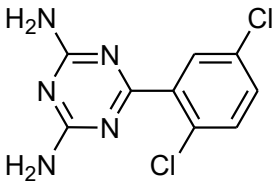
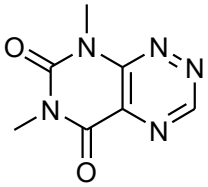
[Fig.2: Suggested Mechanism of Pinner Triazine Synthesis]

The triazine moiety has been known for demonstrating a wide array of pharmacological actions. This includes anticancer, antiulcer, antimicrobial, herbicide, and nematicidal properties, among others. The 1,3,5- and 1,2,4-triazine isomeric forms have been found in several commercially available medicinal agents used for the treatment of ailments (Table 1).

In addition to the presence of triazine moiety in the above drugs, chemists are perseveringly involved in the design and development of newer triazine-based compounds. Some of the noteworthy work is being documented in the present review.

Table 1. Triazine Bearing Commercially Available Drugs

S.No	Drug Name	Structure	Triazine Isoform	Therapeutic Use
1	Tretamine		1,3,5-Triazine	Anticancer [2]
2	Altretamine		1,3,5-Triazine	Anticancer [3]
3	Azacitidine		1,3,5-Triazine	Anticancer [4]
4	Enasidenib		1,3,5-Triazine	Anticancer [5]
5	Decitabine		1,3,5-Triazine	Anticancer [6]
6	Gedatolisib		1,3,5-Triazine	Anticancer [7]
7	Lamotrigine		1,2,4-Triazine	Antiepileptic [8]

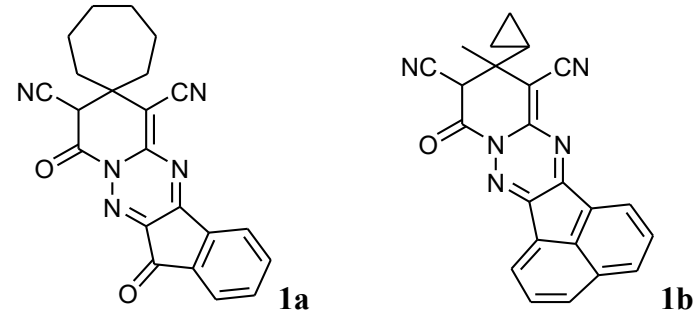
8	Tirapazamine		1,2,4-Triazine	Anticancer [9]
9	Ceftriaxone		1,2,4-Triazine	Antibiotic [10]
10	Atrazine		1,3,5-Triazine	Herbicide [11]
11	Cyanazine		1,3,5-Triazine	Herbicide [12]
12	Propazine		1,3,5-Triazine	Herbicide [13]
13	Simazine		1,3,5-Triazine	Herbicide [14]
14	Irsogladine		1,3,5-Triazine	Antiulcer [15]
15	Fervenulin		1,2,4-Triazine	Nematicidal [16]

II. THERAPEUTIC POTENTIAL

A. Antimicrobial Action

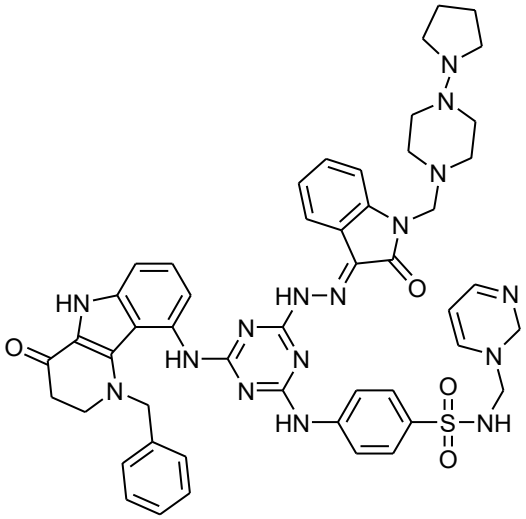
Shokoohian *et al* performed the reaction of pyridine-one and 1,2-dicarbonyl compounds to synthesize some 1,2,4-triazine derivatives [17]. Among the various synthesised triazine compounds, compound **1a** was found to exhibit the maximum antibacterial effect, and compound **1b** was found to be effective against Candida as an antifungal. In a study initiated by Jain *et al., s-triazine derivatives based on acarbazole, sulphonamido, and isatinimino were synthesised, and compound* ***2*** *exhibited the highest*

*potency against B. subtilis. In contrast, compounds **3** and **4** were found to be effective against E. coli* [18]. In the same study, compounds **5** and **6** were found to be potent against A. niger and A. flavus, respectively. Lakum *et al. synthesised two series of s-triazines by linking them with either piperazine or aniline to obtain five highly potent antibacterial compounds, **7a**, **7b**, **7c**, and 8a,* **8b** [19]. Al-Zaydi *et al. used both conventional and microwave-assisted synthesis methods to synthesise 1,3,5-triazine-4-aminobenzoic acid derivatives. They found that compounds 9a and 9b were more effective than ampicillin against MRSA and E. coli* [20]. Gunasekaran and group synthesised amphiphilic polymer of triazine to explore the antibacterial effects against MDRPA, and they found that compounds **10** and **11** not only displayed good antibacterial efficacy but also were able to provide synergistic effects when combined with chloramphenicol against MDRPA [21]. Swami and Bothara synthesised **12a** and **12b** derivatives, only to find that the compounds were moderately effective against both Gram-negative and Gram-positive bacteria [22]. The antifungal and antibacterial activity of some quinoline-based triazine derivatives was investigated by Rathavi and Thakor [23]. Among the ten synthesised derivatives, they found only compounds **13** and **14** to be effective, and that too only against E. coli. 1,3,5-triazine-based thiazole compounds were tested against Gram-positive and Gram-negative bacteria and fungi by Desai et al. Compounds **15a** and **15b** exhibited antimicrobial activity even superior to that of commercially available antibiotics [24]. Bhat and group performed the antibacterial, antifungal and anticancer efficacy testing of a series of 4-aminoquinolone-based 1,3,5-triazine derivatives. They found that while compounds **16a** and **16b** were the most promising as antimicrobial agents, compound **16c** was the most potent anticancer agent among all the analogues in the series [25]. Singh and coworkers synthesised two series of novel s-triazines with trisubstitution to evaluate the antibacterial effects of the molecules. Compounds **17a**, **17b, and 17c** were found to be equipotent to the standard drugs, whereas the other compounds in both series were either inactive or had very low potency. Dongre and Rathod synthesized a new series of s-triazines with 2-pyrazoline and found that compound **18** from the series was comparable to penicillin in antimicrobial action [26]. Raval and group obtained compound **19** from a series of triazine derivatives, with efficacy similar to griseofulvin in inhibiting the growth of *Candida albicans* and *Aspergillus niger*. Kavitha et al. incorporated a quinoline moiety into s-triazine to synthesise a new series of triazine compounds. A few compounds of the series were found to possess good efficacy against the tested bacteria [27]. Khan and coworkers synthesised chalconyl-substituted s-triazines, and compounds **20a** and **20b** were found to be as potent as the standard drug penicillin in antibacterial action [28]. Desai et al. prepared a series of fifteen novel triazine compounds and tested them against various microbes for antimicrobial action. Compounds **21**, **22** and **23** of all the synthesized compounds exhibited excellent antimicrobial action against the tested microbes [29]. The structures of the triazine derivatives with antimicrobial action are presented in Figure 3.



1a

1b



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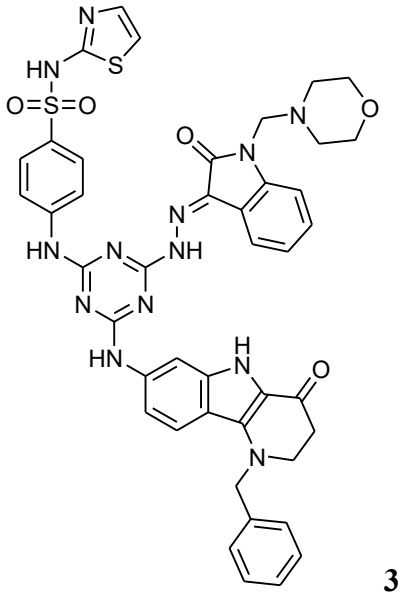

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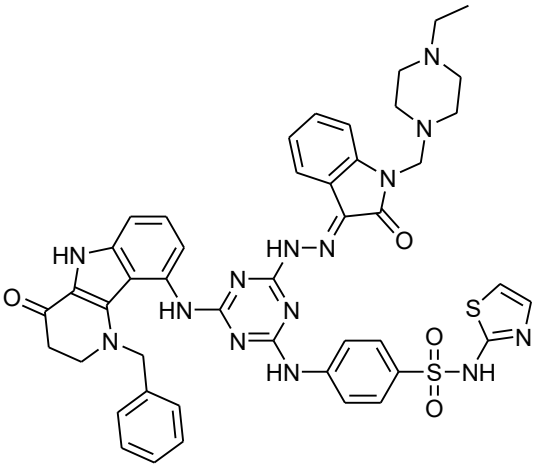

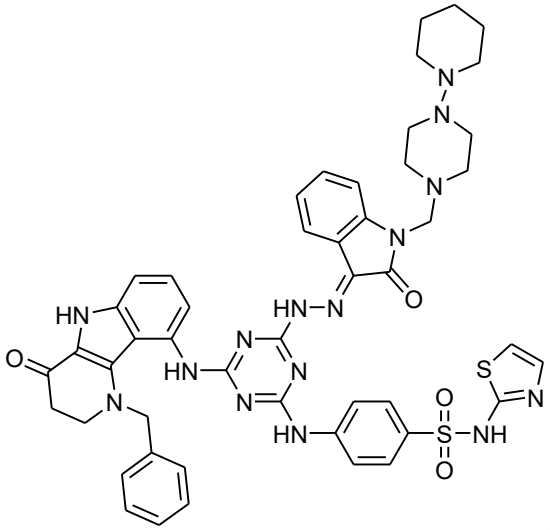

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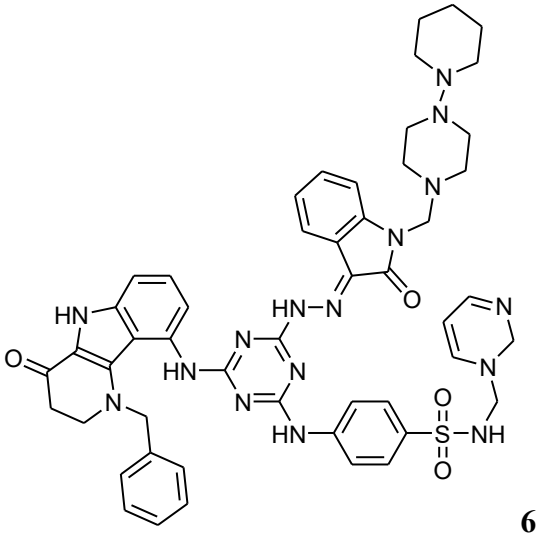

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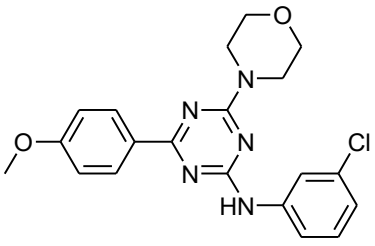

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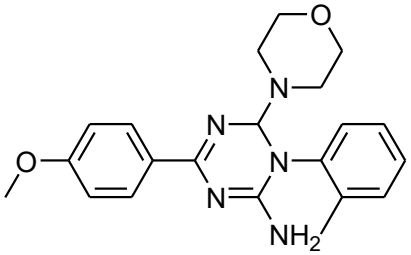
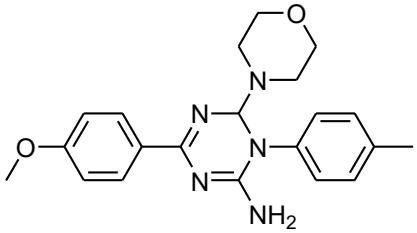


7b



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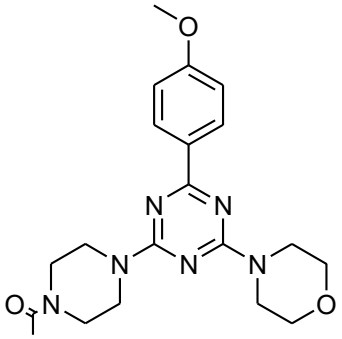

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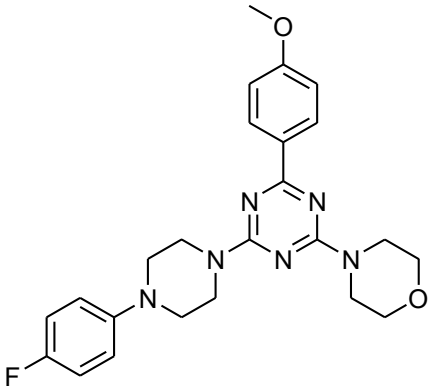

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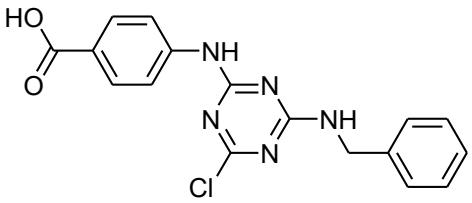

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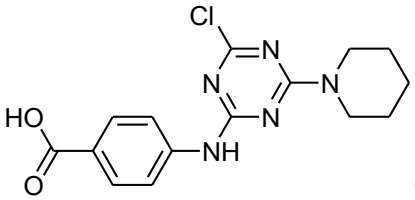

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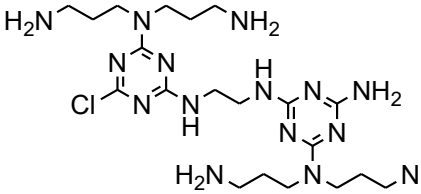

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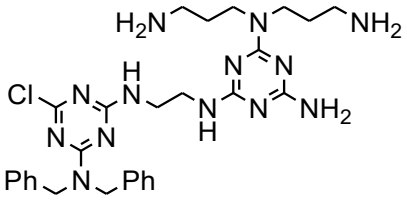

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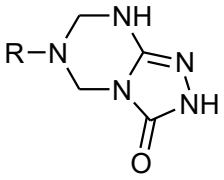

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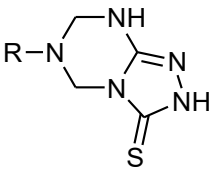

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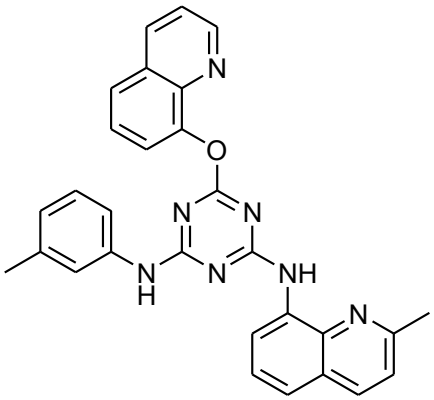

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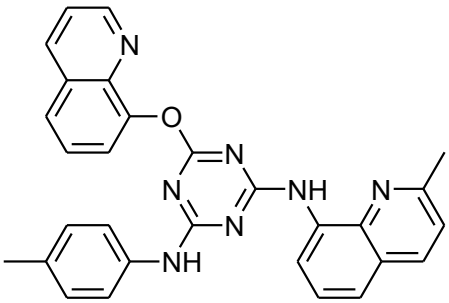

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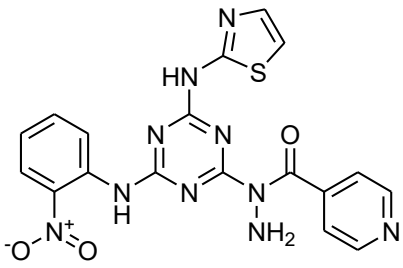
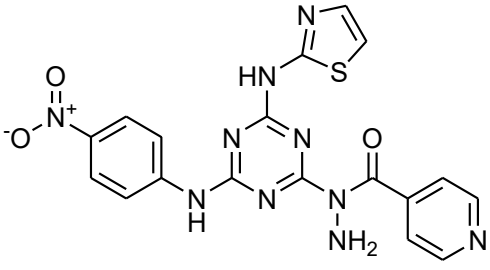


15a



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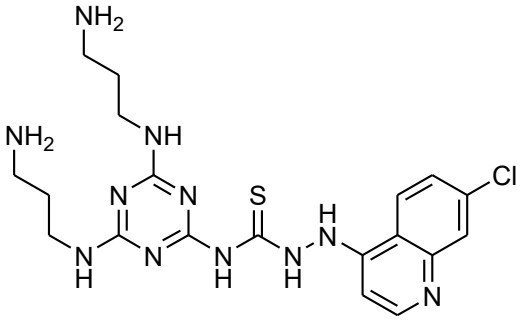

16a

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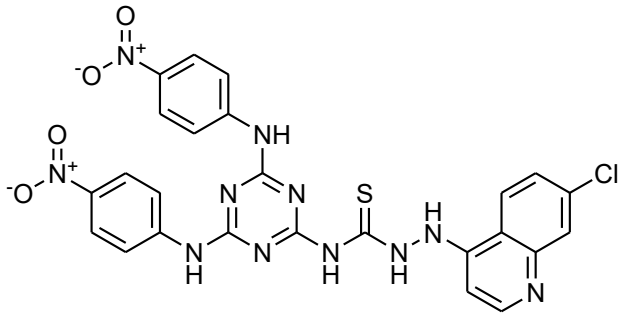

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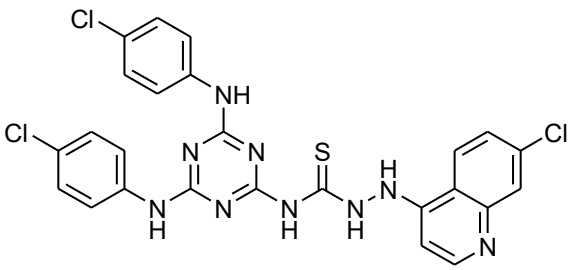

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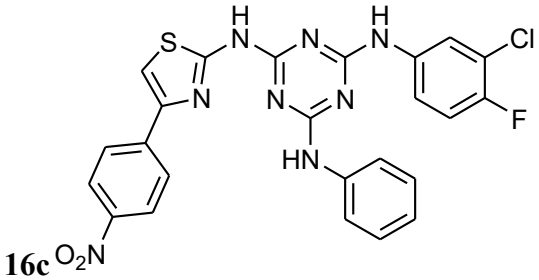

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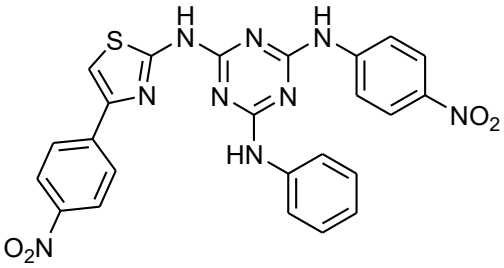

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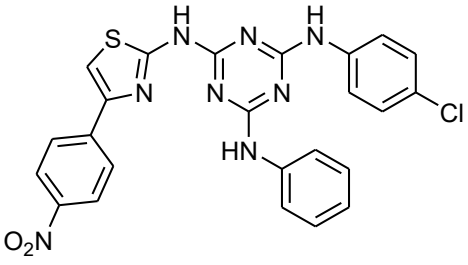

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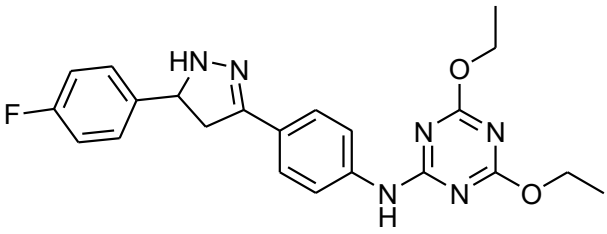

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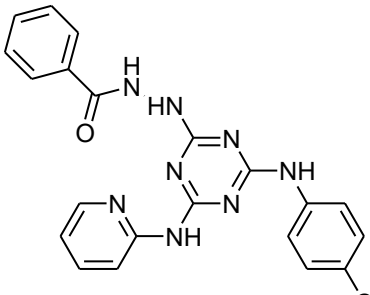

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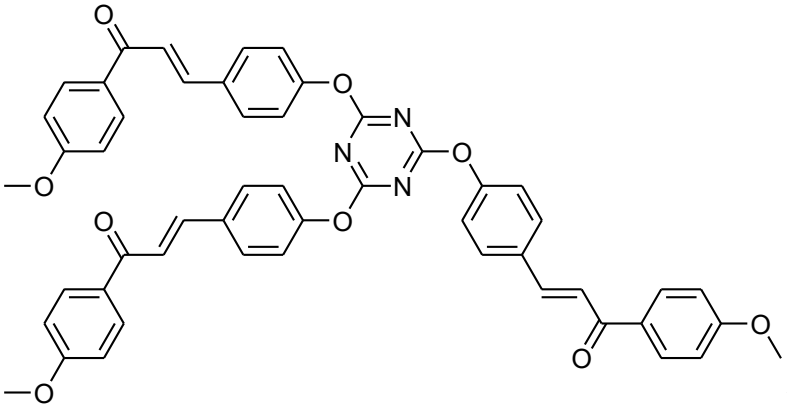

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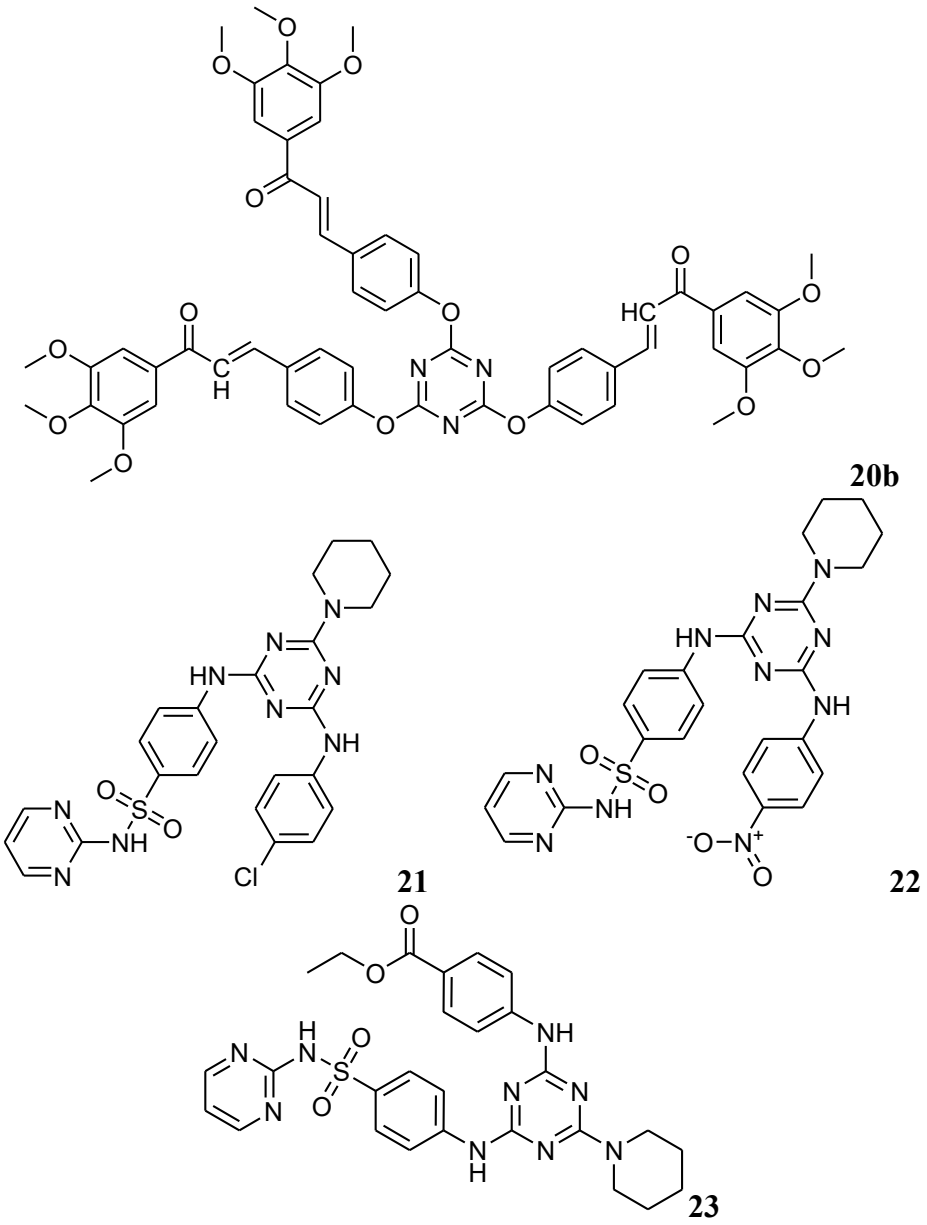
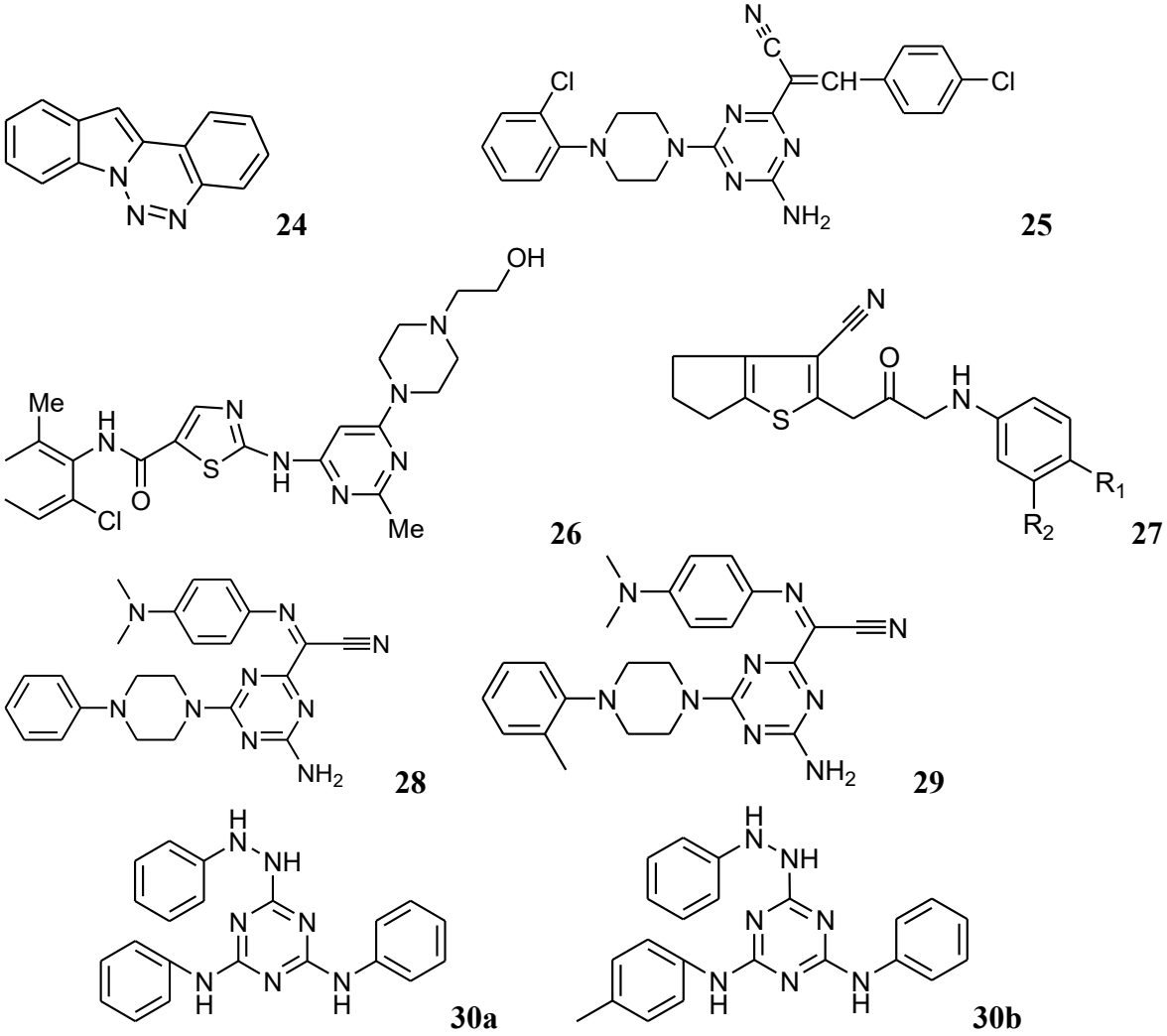


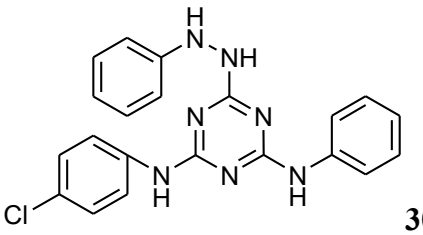
[Fig.3: Structures of Triazine Derivatives with Antimicrobial Action]

B. Anticancer Action

Cirrincione and coworkers in the late 20th century synthesised the indolo[1,2-c]benzo [1,2,3] triazine ring system **24** and tested the compounds for antitumor actions. The compounds were found to be able to initiate the inhibition of T and B cell lines as well as some solid tumors. Pomarnacka et al were able to obtain good anticancer properties in a novel derivative of triazines containing phenylpiperazino scaffold **25.** This compound had an IC50 value of 0.45 µM in the oesophagal cancer cell line KYSE-510. Said and Elshihawy were able to synthesise lead compounds **26** and **27** based on thieno and thiophene scaffolds possessing triazines for breast cancer inhibition, with the mechanism of tyrosine kinase inhibition [30]. The docking study of these compounds revealed that they formed hydrogen bonds with tyrosine kinase comparable to dastinib. It concluded that replacing the nitrogen of dastinib with a cyano function could result in better EGFR-TK inhibitors. Sączewski *et al. synthesised novel 1,3,5-triazine derivatives containing acrylonitriles and iminoacetonitriles and found that compounds **28** and **29** elicited antineoplastic effects in various human cancer cell lines, including 5637, DAN-G, MCF-7,* and LCLC-103H. Kothayer and coworkers synthesised a series of 1,3,5-triazine-2-carbohydrazides, and the anticancer potential was determined using a ubiquitin assay [31]. Compounds **30a**, **30b**, **30c**, and **30d** have demonstrated anticancer potential superior to that of the previously reported Rad6B Inhibitor. Cytotoxic effects of 1,3,5-triazines against lung cancer cell line A549 were reported by Balaha and group [32]. A molecular docking study of **31a, 31b, 31c,** and **31d** was also performed to investigate the interaction with hDHFR and elucidate the structure-activity relationship. Qiang and group synthesized novel 1,3,5-triazine derivatives bearing arylmethylene hydrazine motif and obtained compound **32** to be highly potent against HT-29, H460 and MDA-MB-231 cancer cell lines [33]. Sączewski and Bułakowska synthesised a series of novel 4-(E)-ethenyl-6-alkylamino-1,3,5-triazin-2-ylamine derivatives via the Wittig reaction and screened the compounds against 56 tumour cell lines.

Compounds **33** and **34** were found to be effective at low molar concentrations against the renal cancer A498 cell line and the colon cancer cell line COLO 205. Moreno and coworkers synthesised a series of 1,3,5-triazine-containing 2-pyrazoline derivatives and screened them against **58** tumour cell lines to obtain compound **35**, which had a GI50 value of 0.569 µM [34]. Yan and coworkers studied the effect of some triazine compounds on EGFR-TK. They evaluated the compound **36** on three breast cancer lines using an MTT assay to conclude that the compound is a potential lead candidate for an anticancer drug [35]. Srivastava *et al* designed a novel series of monastrol-1,3,5-triazine compounds and evaluated them for anticancer action against HeLa, MCF-7, HL-60, HepG2, and MCF-12A cell lines. Compound **37** was found to be the most effective of all the compounds and exhibited inhibition of EGFR downstream signalling in Western blot analysis [36]. Wróbel *et al. synthesised some 1,3,5-triazines and studied their* cellular effects in DLD-1 and HT-29 cell lines. Compound **38** exhibited dose-dependent cytotoxicity and, furthermore, induced apoptosis [37]. Marwa and coworkers designed and synthesised 1,3,5-triazines, finding compound **39** to be highly potent against the CAKI-1 cell line [38]. Certain 1,3,5-triazine derivatives have been known to target phosphoinositide 3-kinases and the mammalian target of rapamycin (mTOR), acting as antitumor agents. Triazines have also been reported to possess selective EGFR inhibitor actions by inhibiting receptor tyrosine kinases [39]. Recently, Barakar and coworkers prepared a small library of Schiff's bases that contained triazines and hydroxybenzylidene compounds. Two compounds, **40** and **41**, were found to have IC50 values equivalent to those of cisplatin against breast cancer cell lines [40]. Fiorot et al. studied hybrid molecules containing 1,3,5-triazine, 1,4-naphthoquinone, morpholine, and quinoline moieties against human metastatic melanoma cell lines (SKMEL-103). The compound exhibited a potent anticancer activity against the cell line [41]. The structure of the triazines with anticancer action, as presented in the above triazines, is shown in Figure 4.





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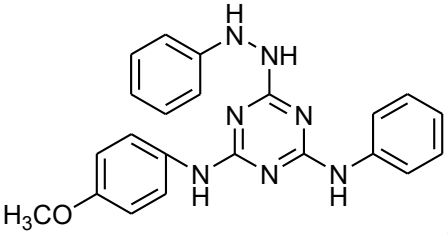

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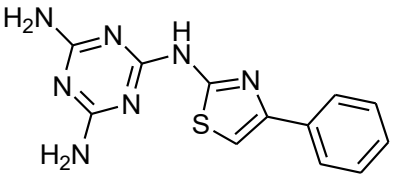

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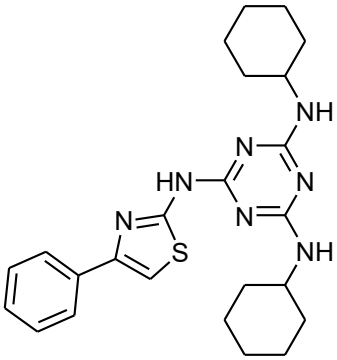

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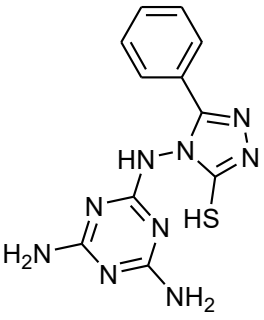

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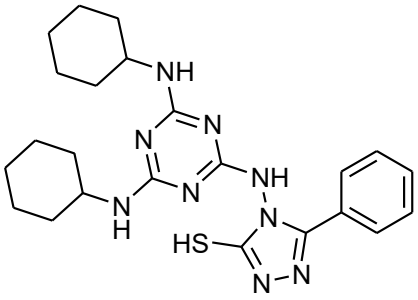

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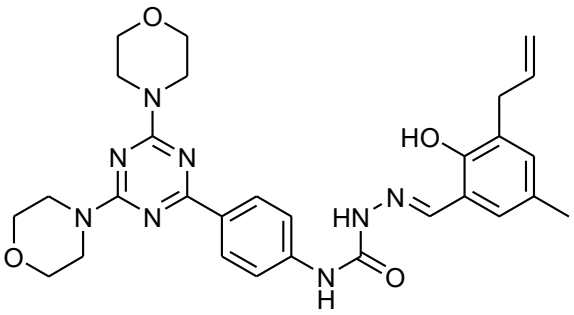

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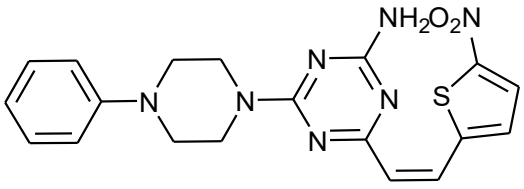

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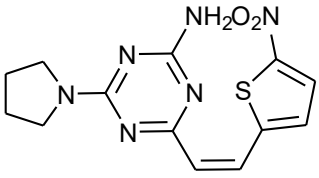

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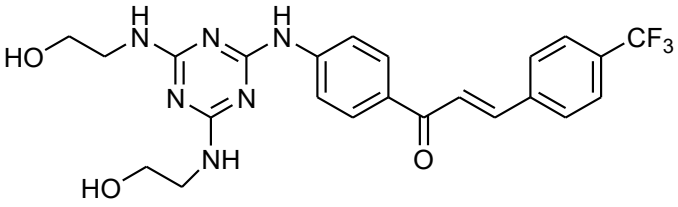

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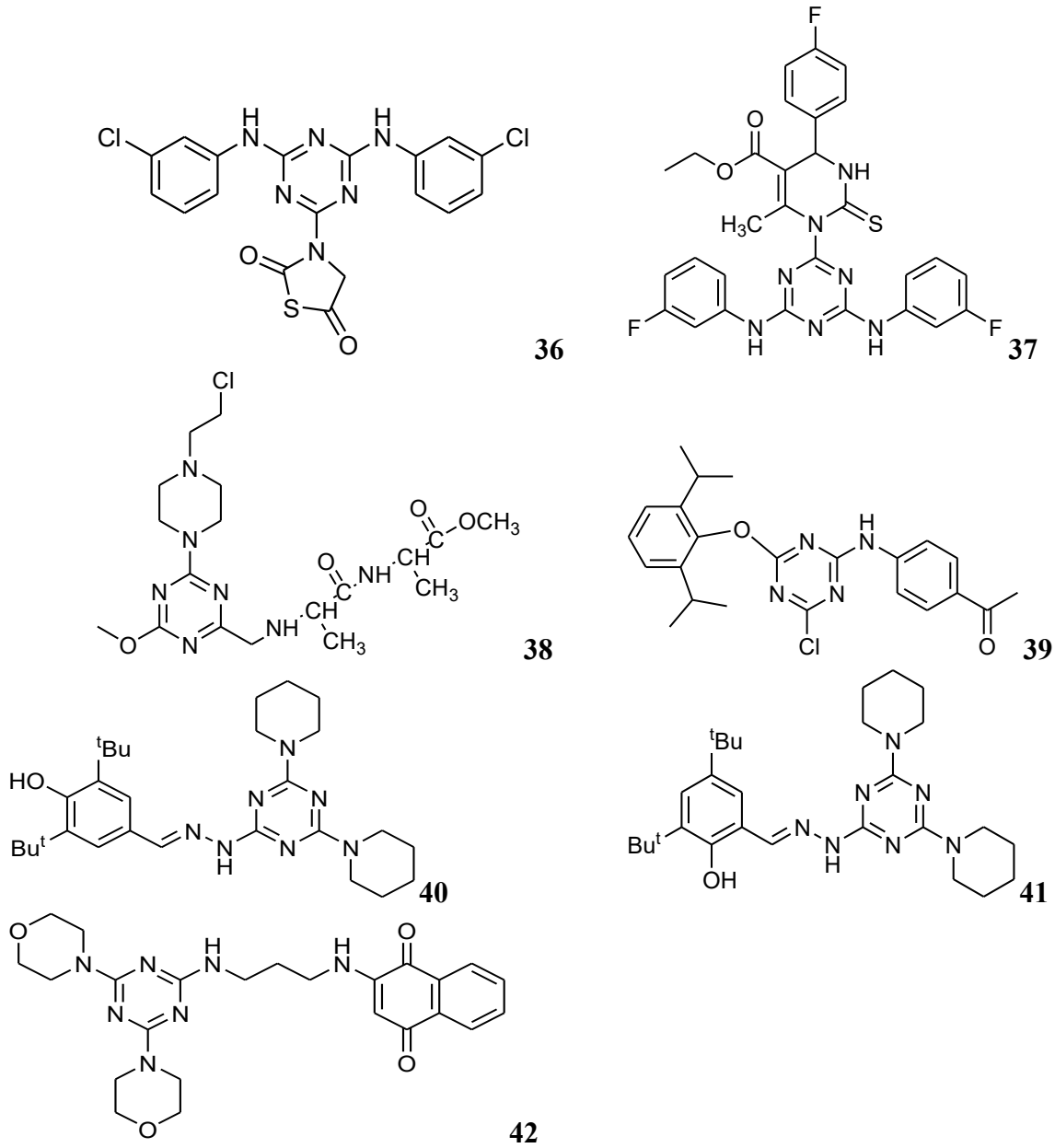
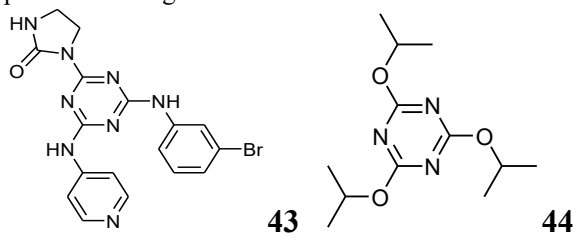


[Fig.4: Structures of Triazine Derivatives with Anticancer Action]

C. Antiviral Action

The synthesis and structure-activity relationship of imidazolin-based 1,3,5-triazine, **43**, was performed by Gao and Li, and the derivatives were evaluated against Enterovirus 71 and Coxsackievirus A16 [42]. The compounds exhibited considerable inhibition against both the tested virus in plaque reduction inhibitory assay with no cytotoxicity. Mibu and coworkers designed 2,4,6-trisubstituted symmetrical 1,3,5-triazine (TAZ) derivatives. Compound **44** exhibited highest antiviral potency against herpes simplex virus type 1 (HSV-1) [43]. This compounds are presented in Figure 5.

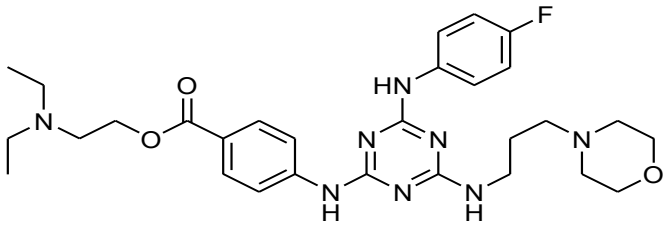


[Fig.5: Triazine Derivatives with Antiviral Action]

D. Other Pharmacological Actions

Qiang and coworkers tested 1,3,5-triazine procaine derivatives for nuclear factor-κB (NF-κB) inhibitory activity in lipopolysaccharide (LPS)-stimulated RAW264.7 cells [44]. Compound **45** exhibited significant cardioprotective effect through inhibition of NF-κB. Szacon *et al* synthesized a series of 20 N-substituted triazine compounds. The compound **46** exhibited effects on locomotion and body temperature, they also showed antinociceptive and serotoninergic actions [45]. Klenke and his group synthesised a series of 1,3,5-triazine-substituted polyamine analogues and evaluated their action against Plasmodium falciparum. Compounds of type **47** were found to be active against chlroquine resistant line K1 of *Plasmodiumfalciparum*. Modifications of triazine with quinoline yielded compound **48**, which exhibits antimalarial activity. Substitution of piperidine and morpholine on 4 or 6 position of triazine nucleus **49** also improved its

antimalarial potency. In a study, compound **50**, which contains anilinoacridine, was found to be a promising antimalarial. Anti-HIV compound **51** has been prepared based on triazines that are even better than zidovudine and nevirapine. Introducing amino groups into piperidine-substituted triazines **52** presented improved anti-HIV potential [46]. Jorgensen and coworkers have reported anti-HIV action of compound **53**. Morpholine containing triazine **54** has been prepared with anti- HIV action [47]. Some bistriazines have been reported by Zacharie and group and compound **55** has been found to possess good activity [48]. In a s-triazine library developed [49], some effective PDE4 inhibitors have been reported. Chauhan and coworkers substituted the 4- and 6-positions of triazine with pyrimidine and piperazine to obtain **56** with antileishmanial activity. Athar and his group achieved the conjugation of triazine and tetrazole to obtain compound **57**, which exhibits antiamoebic potential. Isoniazid conjugated triazine compound was prepared [49] to obtain compound **58** able to attenuate the growth of *Mycobacterium tuberculosis* at concentration of 3.125µg/mL.Triazine-based compounds have also been shown to have high efficacy in cell migration assays. Compound **59**, developed by Xia and his group, displayed activity against cholesterol transferases in the treatment of atherosclerosis. While searching for non-xanthine H2A2B AR antagonists, Pastorin synthesised a novel triazolotriazine, compound **60**. A novel triazine with an affinity of **61** for the cannabinoid CB2 receptor has been reported by Barth and his group. The structures of these compounds is presented in Figure 6.



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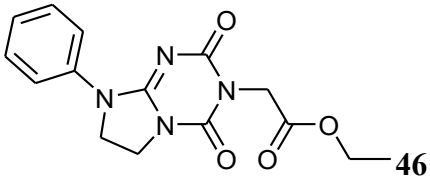

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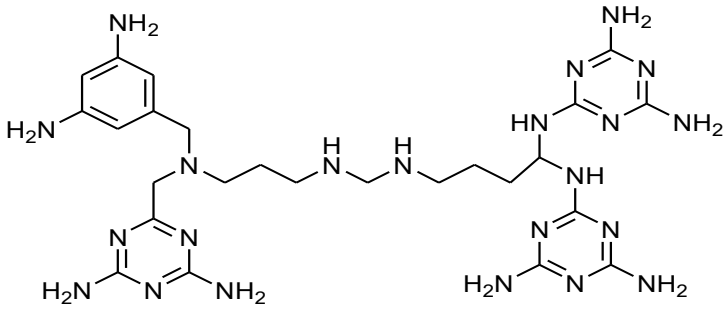

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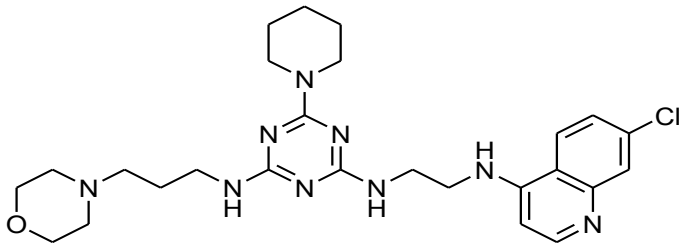

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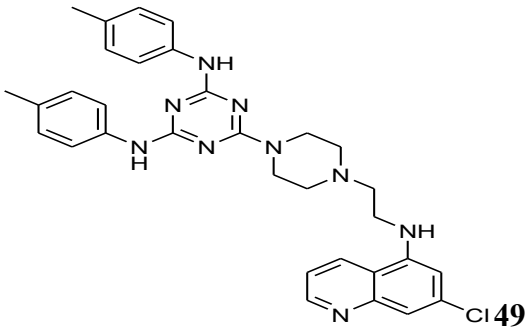

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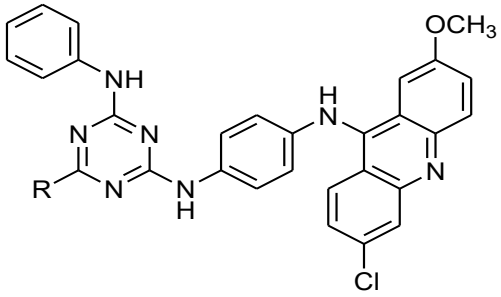

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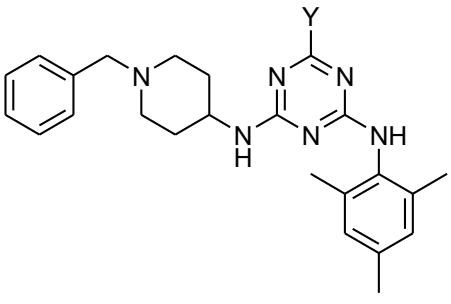

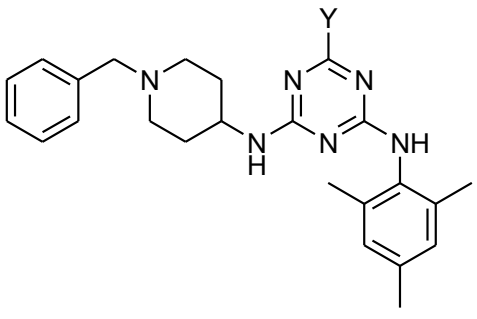

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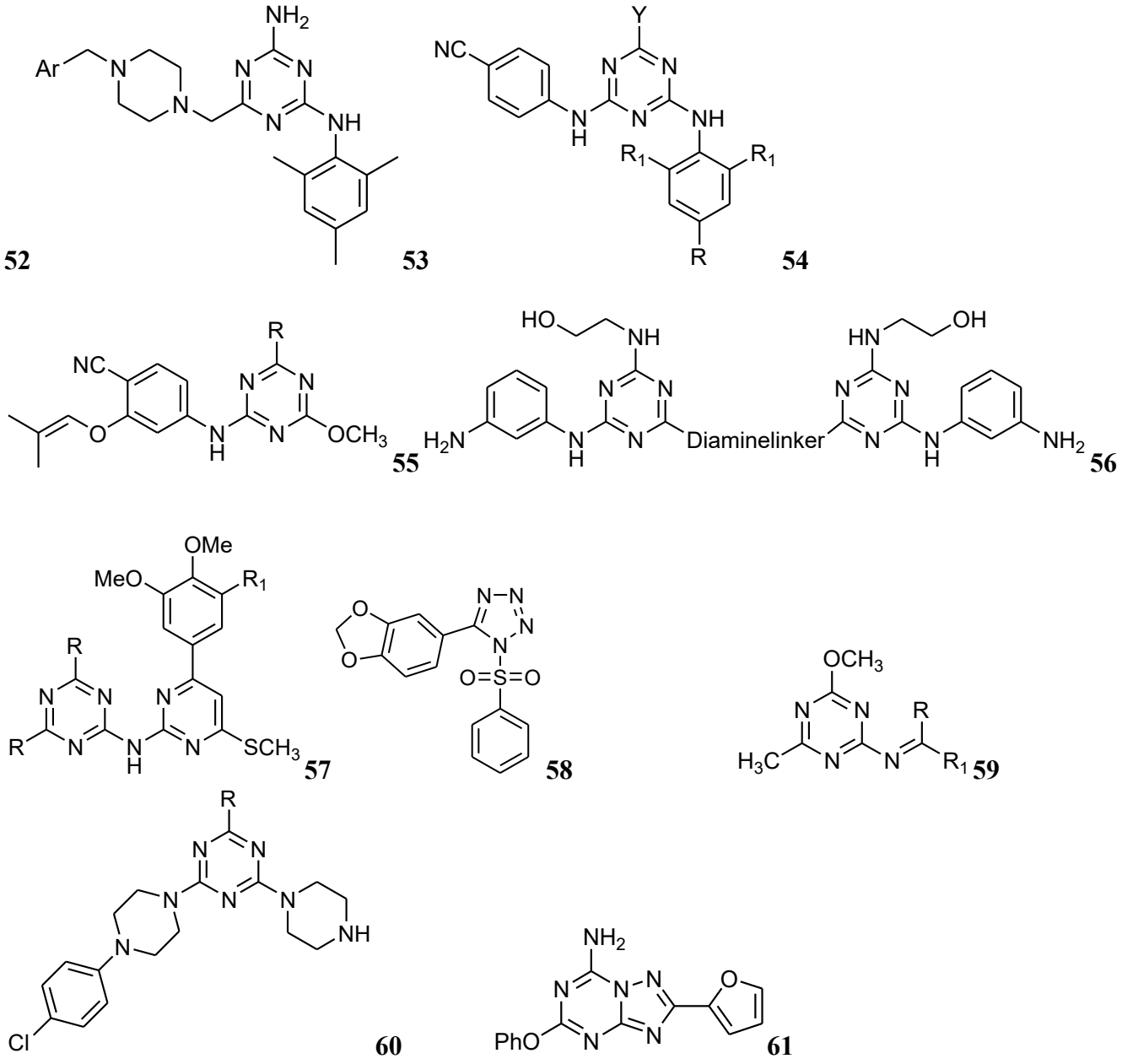

[Fig.6: Structure of Triazine with Vivid Pharmacological Actions]

III. CONCLUSION

The content reported herein highlights the importance of the triazine motif in exhibiting diverse pharmacological actions, particularly antimicrobial and anticancer properties. Compounds consisting of a 1,3,5-triazine scaffold have presented some interesting and prominent actions against various cancer cell lines, in particular. The success of obtaining new bioactives and generating lead molecules for developing novel drugs is highly anticipated from 1,3,5-triazine derivatives.

DECLARATION STATEMENT

After aggregating input from all authors, I must verify the accuracy of the following information as the article's author.

- **Conflicts of Interest/ Competing Interests:** Based on my understanding, this article has no conflicts of interest.
- **Funding Support:** This article has not been funded by any organizations or agencies. This independence ensures that the research is conducted with objectivity and without any external influence.
- **Ethical Approval and Consent to Participate:** The content of this article does not necessitate ethical approval or consent to participate with supporting documentation.
- **Data Access Statement and Material Availability:** The adequate resources of this article are publicly accessible.
- **Author's Contributions:** The authorship of this article is contributed equally to all participating individuals.

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