Review

The Applications of s-Triazine Based Compounds as Potential Antifungal Agents: A Mini-Review

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Review

The Applications of s-Triazine Based Compounds as Potential Antifungal Agents: A Mini-Review

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Abstract: Invasive fungal infections (IFIs) pose a serious threat to human health and are associated with high morbidity and mortality. In addition, the emergence of drug-resistant fungi has created an unmet medical need for the development of new classes of antifungal agents. The s-triazines are six-membered, nitrogen-containing heterocyclic scaffolds with a broad range of biological properties and have received considerable attention in medical chemistry. This review highlights recent literature reports of s-triazines derivatives as potential antifungal agents with a focus on their structure-activity relationships (SAR) which paves the way for the design and synthesis of more active s-triazine antifungal candidates.

Keywords: heterocyclic compound; s-triazine; antifungal; minimum inhibitory concentration

1. Introduction

It is estimated that invasive fungal infections (IFIs) cause approximately 1.5-2 million deaths every year, especially among immunocompromised patients and those undergoing invasive surgery [1,2]. Furthermore, the incidence of IFIs continues to be exacerbated by acquired immunodeficiency syndrome (AIDS), influenza, more recently by the COVID-19 outbreaks and the emergence of multidrug-resistant fungi [3,4]. In 2022, the World Health Organization developed a fungal priority pathogens list (WHO FPPL) to help galvanize global action, which classified four fungal pathogens (*Cryptococcus neoformans*, *Candida auris*, *Aspergillus fumigatus* and *Candida albicans*) as "critical" group and a further fifteen fungal pathogens (including *Candida glabrata*, *Candida parapsilosis*, *Candida krusei*, *Fusarium* spp. and the *Mucorales*) as medium or high priority group [5]. Currently, there are four main classes of antifungal drugs used in the clinic; these are the azoles (ketoconazole, fluconazole and itraconazole), echinocandins (caspofungin and micafungin), polyene antibiotics (amphotericin B and nystatin) and antimetabolites (5-fluorocytosine). However, limitations to the existing antifungal drugs include relatively narrow-spectrums of activity, multiple and diverse drug-drug interactions, limitations to access worldwide, and frequent acquired and innate drug resistance [6,7]. Overall, there is an urgent need to develop new antifungal agents with novel chemical scaffolds.

The triazine ring is one of the most important heterocyclic, pharmacologically active moieties in drug molecules. Triazine exists in three isomeric forms depending on the position of the nitrogen atom, namely 1,2,3-triazine, 1,2,4-triazine and 1,3,5-triazine known as s-triazine. Out of these three isomers, the rigid symmetrical structure of s-triazine has received much attention in medicinal chemistry and possess diverse biological profiles such as anti-bacterial [8], anti-viral [9], anti-cancer [10], anti-tubercular [11], anti-convulsant [12], etc. (Figure 1A). Moreover, many approved drugs

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(tretamine, altretamine, almitrine, enasidenib, bimiralisib and melarsoprol) bear a s-triazine moiety (Figure 1B), indicating the favorable safety and pharmacokinetic properties of s-triazine.

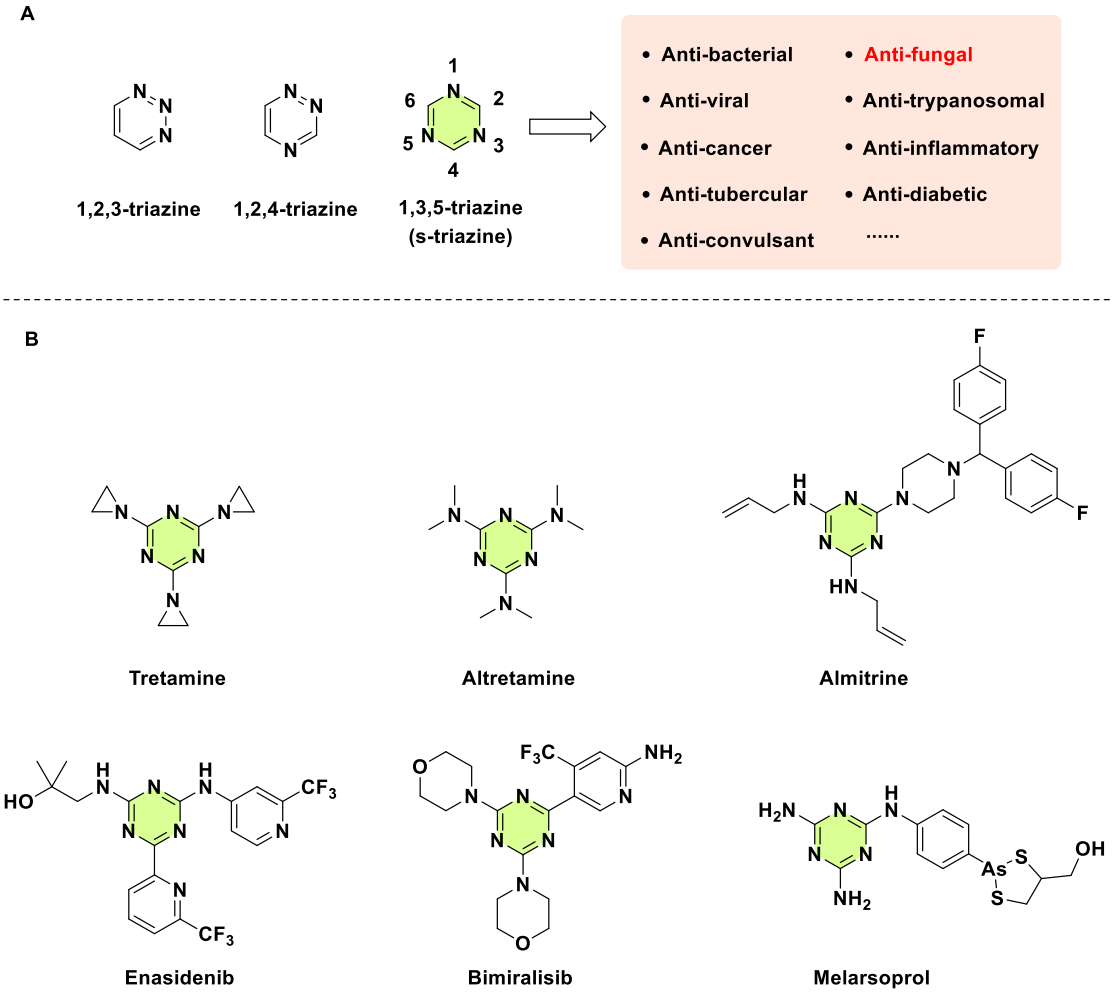
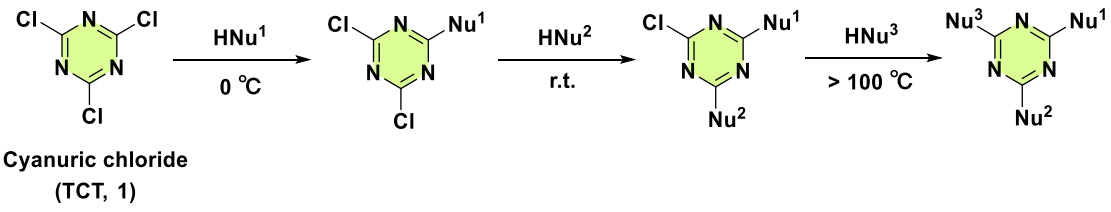


Figure 1. (A) Three isomers of triazine and the wide range pharmacological activities of s-triazine. (B) Some commercial drugs containing the s-triazine ring.

In addition, s-triazine is an ideal framework to construct novel drug candidates due to the ease in synthesizing the s-triazine core from simple starting materials or from the availability of cyanuric chloride (TCT, 1), alongside the ability to explore the chemical space within the core. Scheme 1 presents a temperature-dependent selective replacement of chlorine atoms in 1 with sequential nucleophilic substitutions (typically N-, O-, S-, or P-nucleophiles) that allow the extensive preparation of mono-, di- and tri-substituted s-triazine derivatives. Apart from their application in medicinal chemistry, s-triazine derivatives are also useful as herbicides, insecticides, corrosion inhibitor, energetics and new materials [13–16].



Scheme 1. General synthesis routine of substituted s-triazine from cyanuric chloride.

Although many reviews have summarized the synthesis, structure-activity relationships (SAR) and biological application of triazine derivatives, the antifungal profiles of s-triazine compounds

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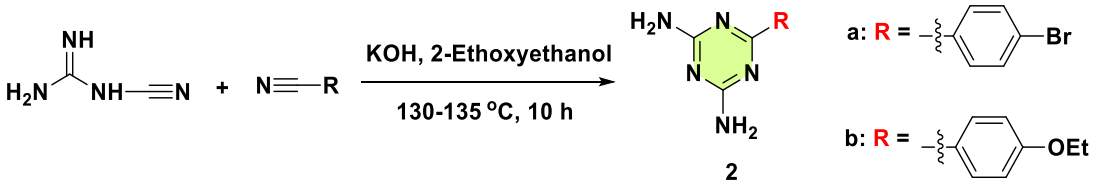
have rarely been introduced [17–21]. Given the grave need to develop novel lines of treatments against IFIs, we focus this review on highlighting examples of s-triazine derivatives as potential antifungal agents and their SAR from publications between 2014-2024. In this context, this review will provide an insight for the development of novel s-triazine derivatives in future antifungal research.

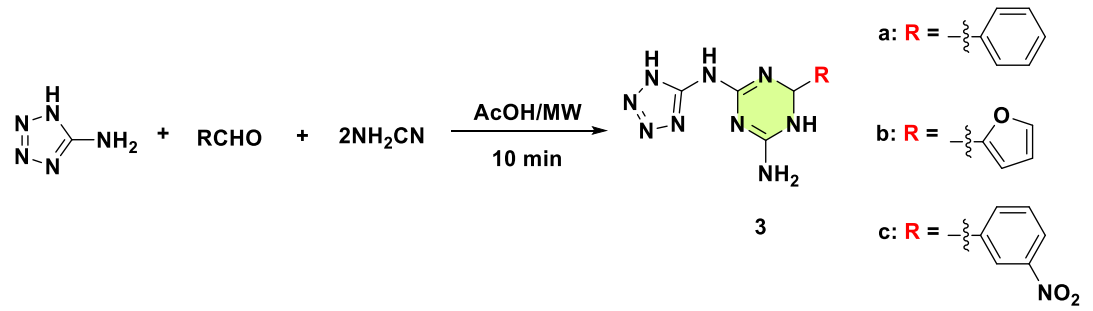
2. Antifungal Activities of S-Triazine Based Derivatives

Patil et al. reported synthesizing a series of s-triazine derivatives through a one-step reaction by mixing 2-cyanoguanidine with various substituted benzonitriles to yield fifteen 1,3,5-triazine-2,4-diamines derivatives (Scheme 2) [22]. The antifungal activity of each compound was examined against two fungal strains: *C. albicans* and *C. neoformans*. Compound **2a**, bearing 4-Br substituted phenyl, displayed moderate fungal growth inhibition (~25% at 32 μg/mL) against both fungi. Compound **2b**, bearing a 4-ethyl substituted phenyl, showed the highest growth inhibition (~30% at 32 μg/mL) against *C. neoformans*. The SAR suggested that either electron-withdrawing or electron-donating group substitution on the aryl did not play any role in the antifungal profiles.



Scheme 2. Synthesis of s-triazine derivative **2a**-**b**.

Mekheimer et al. synthesized and reported various N^2-(tetrazol-5-yl)-6-substituted-5,6-dihydro-1,3,5-triazine-2,4-diamines through the microwave reaction of 5-amino-1,2,3,4-tetrazole, cyanamide, and aromatic or heteroaromatic aldehydes (Scheme 3) [23]. These s-triazine/tetrazole analogs were subsequently screened for *in vitro* antimicrobial activity. Notably, compounds **3a-c** demonstrated excellent antifungal efficacy against *C. albicans* with minimum inhibitory concentration (MIC) values of 1.475×10^{-8}, 1.288×10^{-3} and 2.1851×10^{-4} μg/mL, respectively, which was significantly more efficacious than the reference fluconazole (MIC: 0.857 μg/mL). The substitution of the phenyl group with other aryl groups or a substitution on the benzene ring resulted in a loss of antifungal activity. Furthermore, compounds **3a-c** exhibited good inhibition of *Candida* 14α-demethylase enzyme, with IC_{50} values of 7.451 ± 0.404, 25.066 ± 1.358, and 3.369 ± 0.183 μg/mL, respectively, as determined by a rapid fluorescence-based screening method. Molecular docking studies indicated that compounds **3a-c** demonstrated good binding affinity to the human CYP51 protein (PDB code: 3LD6) and possessed acceptable ADME properties.



Scheme 3. Synthesis of s-triazine derivative **3a**-**c**.

Hybridization of different bioactive moieties into a single molecule have the potential to improve the efficacy, reduce toxicity, enhance the pharmacokinetic properties and overcome drug resistance [24]. Dinari et al. reported a series of s-triazine-quinazolinone hybrids (Figure 2) [25]. The synthesized compounds were screened for their *in vitro* antimicrobial activities. The trisubstituted s-

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triazine hydrazine intermediates **4a-f** displayed moderate to weak inhibitory activity against *C. albicans* with MICs ranging from 128 to 512 µg/mL. When a benzoxazinone moiety was added into the intermediates to afford target hybrids **5a-f**, their anti-*C. albicans* activity improved 1-2 fold. In general, the antifungal activity of s-triazine-quinazolinone hybrids was poor, and substantially inferior to their antibacterial activity.

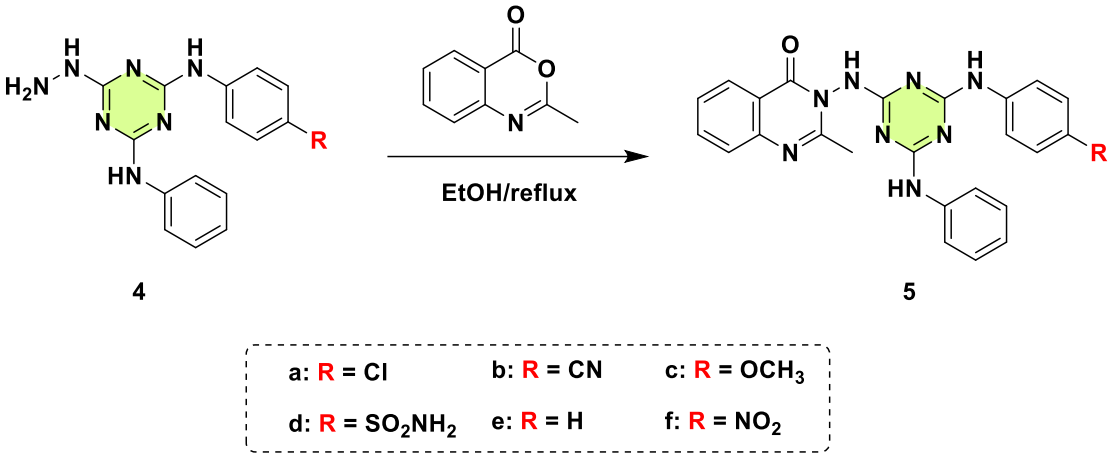

Figure 2. Chemical structures of s-triazine **4a-f** and **5a-f**.

Zala et al. synthesized twelve molecular hybrids of s-triazine with coumarin and s-triazine with benzothiazole (Figure 3) [26]. These compounds were evaluated for their *in vitro* antifungal activities against *Trichoderma rubrum* and *C. albicans*. The hybrid **6a** (MIC: 100 µg/mL) was most effective against the *T. rubrum* strain comparable to reference griseofulvin, whilst the remaining compounds had moderate activity with MICs ranging from 500-1000 µg/mL. Compounds **6b-d** gave MIC values of 250 µg/mL against the *C. albicans* strain, exhibiting a potency 2-fold greater than griseofulvin.

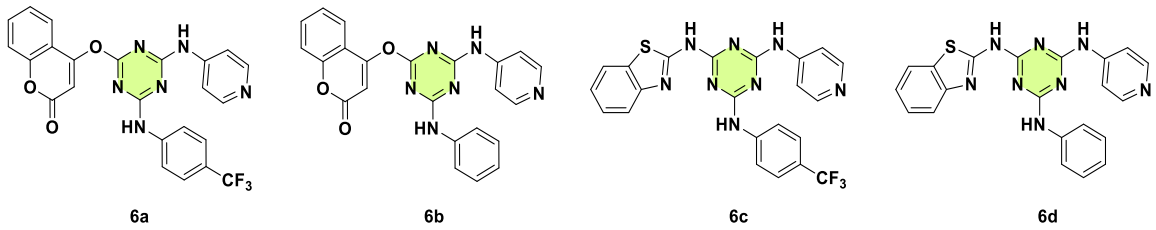

Figure 3. Chemical structures of s-triazine derivatives **6a-d**.

Sweta et al. synthesized clubbed coumarin and *N*-substituted piperazine s-triazine hybrids and tested their *in vitro* antifungal activity against *C. albicans* and *Saccharomyces cerevisiae* using the Kirby-Bauer disc diffusion method (Figure 4) [27]. The biological screening results indicated that compounds **7a** (inhibition zone: 20 mm), **7b** (inhibition zone: 19 mm) and **7d** (inhibition zone: 24 mm) displayed considerable anti-*C. albicans* activities, which were comparable to fluconazole and nystatin. Compound **7c** bearing dibenzo [b, f]-thiazapine piperazine showed a high inhibition effect against *S. cerevisiae*.

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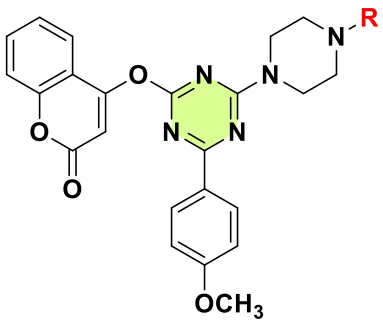


7

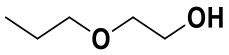
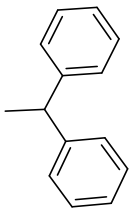
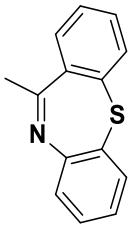
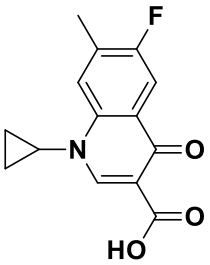
Compd. No	R	Zone of inhibition (mm)	
		C. albicans	*S. cerevisiae*
7a		20	/
7b		19	/
7c		/	20
7d		23	/
Fluconazole	-	≥22	≥19
Nystatin	-	≥15	≥17

Figure 4. Chemical structures and antifungal activities of s-triazine derivatives **7a**-**d**.

By fusion of triazine with other pharmacophoric fragments, Bhat et al. prepared a series of 4-aminoquinoline-s-triazine derivatives (Figure 5) [28]. Compounds **8a**-**e** were the most potent in this series against *C. albicans* with MIC 8 μg/mL. For *Aspergillus niger* and *A. fumigatus* strains, all the tested compounds showed moderate activity with MICs ranging from 8 to 32 μg/mL.

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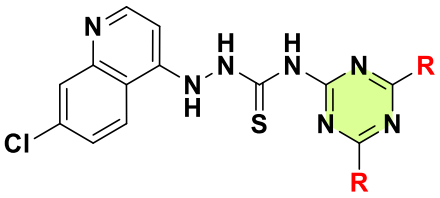


8

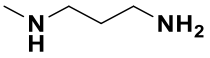
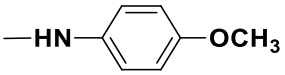
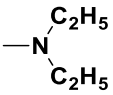
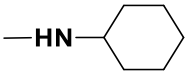
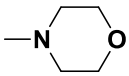
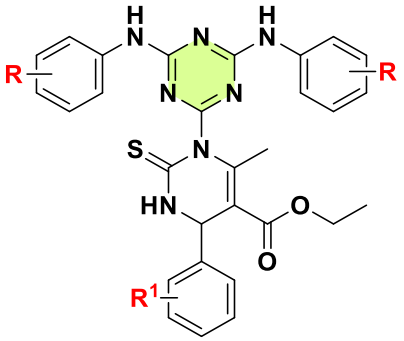
Compd. No	R	MIC (μg/mL)		
		C. albicans	*A. niger*	*A. fumigatus*
8a		8	8	8
8b		8	8	16
8c		8	32	16
8d		8	16	8
8e		8	8	16
Fluconazole	-	4	8	8

Figure 5. Chemical structures and antifungal activities of s-triazine derivatives **8a-e**.

Masih et al. synthesized a series of s-triazine-dihydropyrimidine hybrids (Figure 6) [29]. All synthesized compounds were evaluated for their *in vitro* antifungal activities against *C. albicans*, *C. glabrata*, *C. neoformans* and *Aspergillus niger*. These compounds exhibited mild to moderate antifungal activity against the four tested strains. Notably, most compounds demonstrated better inhibition of *Candida* spp. than *C. neoformans* and *A. niger*. Compared with the unsubstituted analogs, introduction of substituents at R/R^1 position could enhance the antifungal activity. For instance, compound **9a** exhibited no antifungal effect, whereas compound **9b** displayed the best and broad-spectrum activity against the tested strains with MIC of 1.25-5 μg/mL. Compounds **9c-f** showed promising antifungal activity against *C. albicans* (MIC: 2.5-5 μg/mL). However, no clear SAR between the R and R^1 substituents were observed.



9

Compd. No	R	R^1	MIC (μg/mL)			
			C. albicans	*C. glabrata*	*C. neoformans*	*A. niger*
9a	H	H	/	/	/	/
9b	3-Cl	4-OH	1.25	1.25	1.25	5

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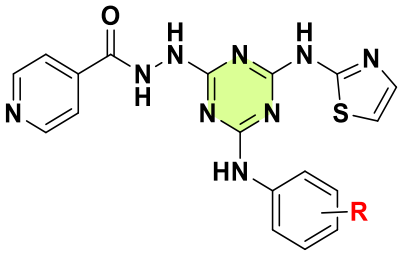
9c	3-Br	2-OH	5	10	5	/
9d	4-Cl	2-Cl	5	10	/	/
9e	4-CH_3	2-CH_3	5	/	/	/
9f	4-CH_3	4-OH	2.5	/	50	/
Amphotericin B	-	-	0.16	0.32	1.25	0.63

Figure 6. Chemical structures and antifungal activities of s-triazine derivatives **9a**-**f**.

Desai et al. reported multiple s-triazine based thiazole hybrids. The antifungal activities of synthesized compounds were investigated in *C. albicans*, *A. niger* and *A. clavatus* (Figure 7) [30]. The -NO_2 substituted aniline was determined as essential to increase pharmacological activity. For example, compounds **10a** and **10b** showed broad and excellent inhibition against three tested fungi. Besides, compounds **10c-d** possessed potent inhibition against *C. albicans* and *A. niger*, whose activities were lower or equal than that of griseofulvin.



10a-e

Compd. No	R	MIC (μg/mL) ± SD		
		C. albicans	*A. niger*	*A. clavatus*
10a	2-NO_2	25 ± 3.5	50 ± 3.55	25 ± 3.3
10b	4-NO_2	50 ± 2.25	25 ± 3.54	50 ± 3.47
10c	4-Cl	100 ± 1.23	50 ± 3	250 ± 3.46
10d	2,5-diCl	50 ± 2.27	100 ± 3	1000 ± 3.21
10e	4-F	100 ± 3.12	50 ± 3.43	100 ± 3.35
Griseofulvin	-	500 ± 2.64	100 ± 3	100 ± 3.46

Figure 7. Chemical structures and antifungal activities of s-triazine derivatives **10a**-**e**.

A series of s-triazine-benzenesulfonamide hybrids were evaluated for their antifungal activities against *C. albicans*, *A. niger* and *Aspergillus clavatus* also by Desai et al. (Figure 8) [31]. All hybrids displayed better inhibitory activity against *C. albicans* than *A. niger* and *A. clavatus*. Among them, compounds **11a-d** demonstrated mild antifungal activity (MIC: 250 μg/mL) against *C. albicans*, while the remaining compounds showed weak (MIC: 500-1000 μg/mL) or no activity against *C. albicans*. Additionally, **11b** was identified as the most effective agent (MIC: 250 μg/mL) against *A. niger* whereas it had no activity against *A. clavatus*. The SAR studies revealed that the antifungal activity of these s-triazine hybrids was significantly influenced by different R-substituents on the phenyl ring.

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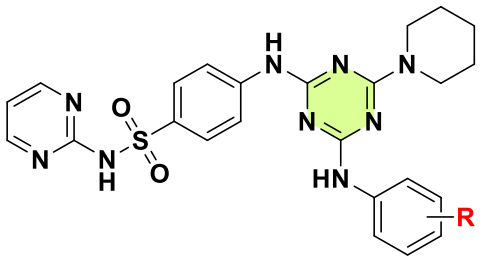
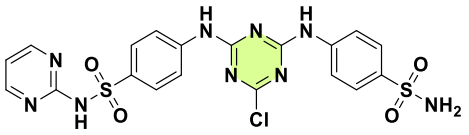


11

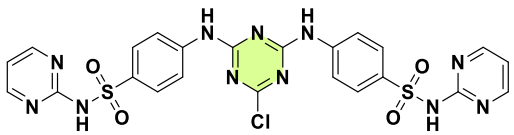
a: R = 3-Cl b: R = 2-CH_3 c: R = 4-CH_3 d: R = 3-Cl-2-CH_3

Figure 8. Chemical structures of s-triazine derivatives **11a-d**.

Similarly, s-triazine-bis-benzenesulfonamide hybrids 4-((4-chloro-6-((4-sulfamoylphenyl)amino)-1,3,5-triazin-2-yl)amino)-*N*-(pyrimidin-2-yl)benzenesulfonamide and 4,4'-((6-chloro-1,3,5-triazine-2,4-diyl)bis(azanediyl))bis(*N*-(pyrimidin-2-yl)benzenesulfonamide) were evaluated for *in vitro* antimicrobial activities against four bacterial strains and two fungal strains *A.niger* and *Schizophyllum commune* by Noureen and co-workers (Figure 9) [32]. Compound **12a** (inhibition zone: 20 ± 0.51 mm against *A.niger*) is more potent than **12b** and fluconazole. In studies against *S.commune*, **12a** (inhibition zone: 22 ± 0.65 mm) and **12b** (inhibition zone: 25 ± 0.72 mm) displayed higher potency than sulfanilamide, sulfadiazine, sulfamethazine and fluconazole. Moreover, the MIC values of the two compounds confirmed their antifungal activity. Cytotoxic studies indicated that compounds **12a** and **12b** had low hemolysis, suggesting a good safety profile.



12a



12b

Compd. No	MIC (μg/mL)	
	A.niger	*S.commune*
12a	250	250
12b	200	150
Sulfanilamide	500	1000
Sulfadiazine	1000	>1000
Sulfamethazine	1000	>1000
Fluconazole	500	1000

Figure 9. Chemical structures and antifungal activities of s-triazine derivatives **12a-b**.

Mohamed-Ezzat et al. evaluated the potential of s-triazine sulfonamides conjugate as anti-microbial, antitumor, and anti-SARS-CoV-2 agents (Figure 10) [33]. Compounds **13a-c** were the most active compounds against *C. albicans*, showing a zone of fungal inhibition with the values 12.3 ± 0.6, 13.3 ± 0.6 and 9.6 ± 0.6 mm, respectively. It is worth noting that replacement of pyrrolidine with piperidine or morpholine led to loss of anti-*C. albicans* potency. Additionally, **13a** also demonstrated remarkable anti-proliferative and antiviral potency.

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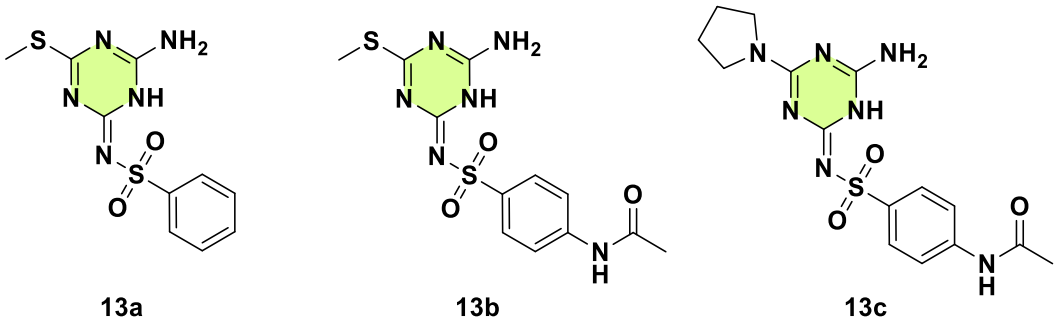


Figure 10. Chemical structures of s-triazine derivatives **13a-c**.

Kumawat et al. integrated multiple bioactive moieties such as adamantylamine, sulfamerazine, sulfadiazine, morpholine, thiazole and piperazine into the s-triazine core (Figure 11) [34]. *In vitro* antifungal activity of these s-triazine hybrids was evaluated against *Malassezia furfur*. 6 of 11 tested compounds revealed higher potency than ketoconazole. Notably, compound **14a** exhibited the highest activity against *M. furfur* (MIC: 8.13 ± 0.27 µg/mL), followed by **14b** (MIC: 9.34 ± 0.24 µg/mL) and **14c** (MIC: 12.21 ± 0.25 µg/mL). Furthermore, **14a** exhibited the highest antibacterial activity against *Pseudomonas chlororaphis*. *In-silico* pharmacokinetic and ADME-T analysis of compounds **14a** and **14b** revealed favorable druggability properties.

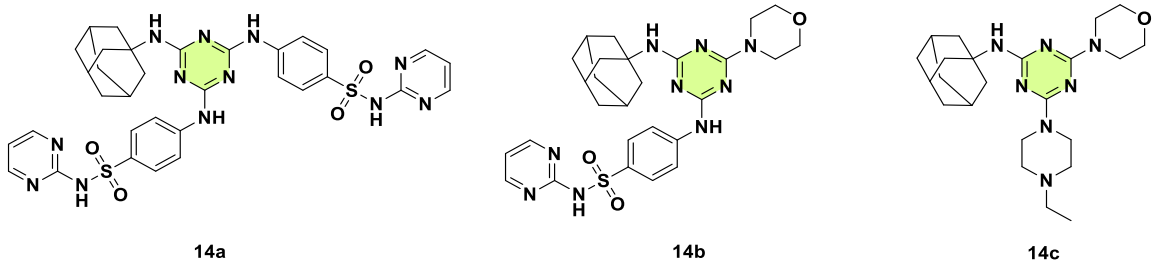
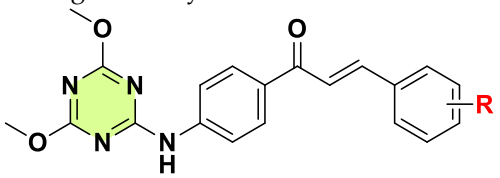


Figure 11. Chemical structures of s-triazine derivatives **14a-c**.

In another study, Shinde et al. synthesized a series of 4,6-dimethoxy-1,3,5-triazine and chalcone hybrids. Antifungal activity testing was performed using four fungal strains (*C. albicans*, *A. niger*, *Candida tropicalis* and *C. glabrata*) (Figure 12) [35]. Compound **15a** demonstrated the highest activity against *C. albicans* (inhibition zone: 85 mm) and *C. glabrata* (inhibition zone: 82 mm), while **15b** (inhibition zone: 85 mm) and **15c** (inhibition zone: 81 mm) showed excellent antifungal activity especially against *A. niger* and *C. tropicalis*, respectively. Generally, fluorine on the benzene ring of chalcones was found to be more effective in antifungal activity.



15a-c

Compd. No	R	Zone of inhibition (mm)			
		C. albicans	*A. niger*	*C. tropicalis*	*C. glabrata*
15a	3,4-diF	85	75	78	82
15b	4-F	67	85	74	68
15c	3-OCF_3	69	70	81	68
Miconazole	-	20	25	15	15

Figure 12. Chemical structures and antifungal activities of s-triazine derivatives **15a-c**.

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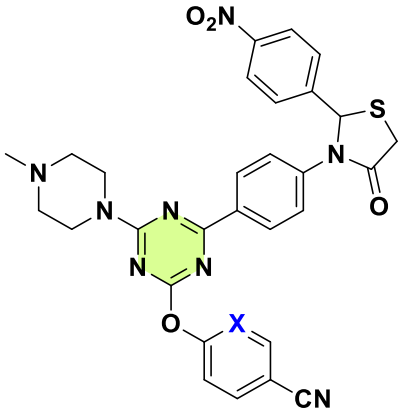
Patel et al. synthesized new thiazolidin-4-one fused s-triazine hybrids as potential antimicrobial and anticancer agents (Figure 13) [36]. The most active compounds **16a** and **16b** exhibited considerable activities (MIC: 3.12-25 µg/mL) against *A. niger* and *C. albican*, but they were less active than ketoconazole (MIC: 1.56 µg/mL). The SAR suggested that both benzonitrile and nicotinonitrile was beneficial to increase the corresponding pharmacological activities.

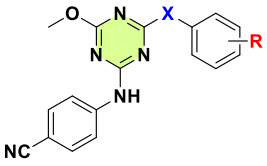


16

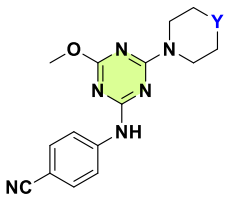
a: X = CH **b: X = N**

Figure 13. Chemical structures of s-triazine derivatives **16a**-**b**.

Mewada et al. have developed four classes of s-triazine based derivatives that incorporated the methoxy, 4-aminobenzonitrile moieties with phenol, thiophenol, aniline and piperazine/piperidine/morpholine to triazine nucleus (Figure 14) [37]. Compounds **17a** (MIC: 3.12 µg/mL against *C. albicans*), **17b** (MIC: 3.12 µg/mL against *A. clavatus*), **17c** (MIC: 3.12 µg/mL against *A. niger*), **17e** (MIC: 3.12 µg/mL against *A. clavatus*), **17f** (MIC: 3.12 µg/mL against *C. albicans*), **17g** (MIC: 3.12 µg/mL against *A. niger*) had the most growth inhibition of respective fungal strain. 3-Cl substituted phenol **17d** enhanced antifungal activity against *A. niger* and *A. clavatus* compared with the 3-Cl substituted thiophenol **17a**. The SAR indicated halogen substituted thiophenol compounds generated good inhibition of fungal strains among all the compounds.



17a-e



17f-g

Compd. No	X	R	Y	MIC (µg/mL)		
				C. albicans	*A. niger*	*A. clavatus*
17a	S	3-Cl	-	3.12	100	50
17b	S	4-Cl	-	12.5	50	3.12
17c	S	3-F	-	25	3.12	12.5
17d	O	3-Cl	-	12.5	50	6.25
17e	N	4-Br	-	200	100	3.12
17f	-	-	*N*-$COCH_3$	3.12	50	6.25
17g	-	-	-CH_2-	200	3.12	200
Ketoconazole	-	-	-	1.56	1.56	0.78

Figure 14. Chemical structures and antifungal activities of s-triazine derivatives **17a**-**g**.

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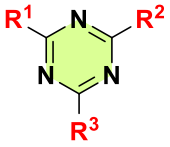
In a study by Singh et al., a series of 2,4,6-trisubstituted-s-triazine derivatives were synthesized and assessed for their antimicrobial activity (Figure 15) [38]. Compounds **18a-c** demonstrated antifungal potency comparable to fluconazole. For example, **18b** demonstrated the most significant antifungal activity against *C. albicans* (MIC = 3.125 µg/mL) and **18c** was most active against *C. tropicalis* (MIC = 6.25 µg/mL), which was equipotent to fluconazole. Replacement of *N*-aryl piperazine group (**18b**) with *N*-methyl (**18a**) made the compounds more active against *C. tropicalis*. Nevertheless, there was no clear SAR conclusion between the structures and antifungal activity.



18

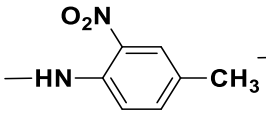
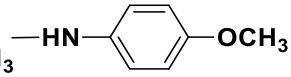
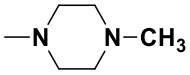
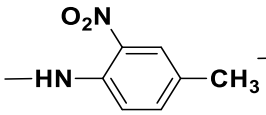
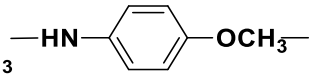
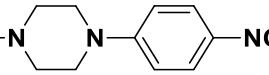
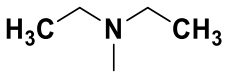
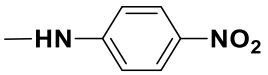
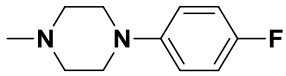
Compd. No	R^1	R^2	R^3	MIC (µg/mL) *C. albicans*	MIC (µg/mL) *C. tropicalis*
18a				6.25	12.5
18b				3.125	100
18c				50	6.25
Fluconazole	-	-	-	3.125	6.25

Figure 15. Chemical structures and antifungal activities of s-triazine derivatives **18a-c**.

A panel of s-triazine-based chalcone- and pyrimido[4,5-b][1,4]diazepines hybrids were developed by Moreno et al (Figure 16) [39]. The antifungal activity of these conjugates was evaluated against two yeasts *C. albicans*, *Cryptococcus neoformans*, three dermatophytes *Microsporum gypseum*, *Trichophyton rubrum*, *Trichophyton mentagrophytes*, and three filamentous fungi *A. fumigatus*, *A. niger*, and *A. flavus*. Among them, s-triazine-triazinyloxy-diazepine conjugate **19a** showed moderate antifungal activity against *T. rubrum* (MIC: 62.5 µg/mL), while s-triazine fused triazinylamino-diazepine **19b** was more active against *T. mentagrophytes* and *A. fumigatus* (MIC: 62.5 µg/mL, respectively). Hybrid **19c** showed marginal activity against *T. rubrum* and *A. niger*, **19d** showed similar activity *T. mentagrophytes* (MIC: 125 µg/mL, in all three cases). Hemolytic assay and *in silico* toxicity prediction demonstrated that most of the synthesized compounds are safe. Thus, these s-triazine-based chalcone/diazepine hybrids offer an excellent framework for further optimization.

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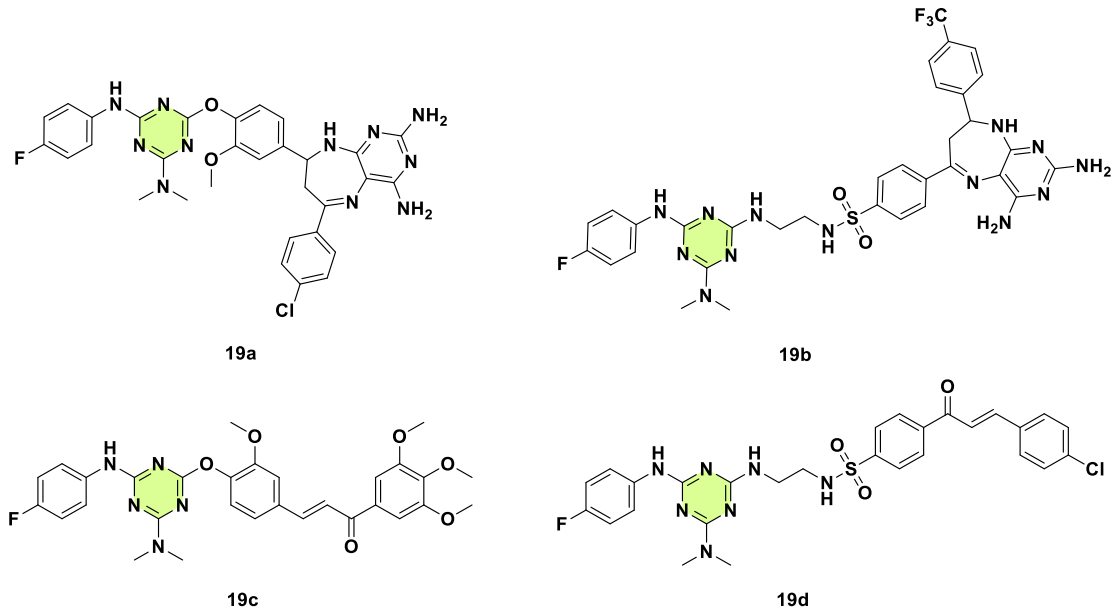

Figure 16. Chemical structures of s-triazine derivatives **19a-d**.

Recently, Maliszewski et al. conducted an *in vitro* study to investigate the antifungal potential of novel 2,4,6-trisubstituted s-triazine derivatives, which contained amino acids or short peptide chains, 2-chloroethylpiperazine, and a methoxy group (Figure 17) [40]. The study evaluated the activity against yeasts (*C. albicans*), and filamentous fungi (*A. fumigatus*, *A. flavus*, *Fusarium solani*, and *Penicillium citrinum*) using the microbroth dilution method. Antifungal agent ketoconazole and nystatin served as positive controls. All compounds were more effective against *C. albicans* than other filamentous fungi. In particular, the MIC values of compounds **20a-c**, which incorporated the –NH-PheOMe, –NH-Trp(Boc)-AlaOMe and –NH-Asp(OtBu)-AlaOMe functional groups, were found to be more efficacies against *C. albicans* at a lower dose (MIC: 7.81-62.50 μg/mL) than ketoconazole and nystatin (MIC: 250 μg/mL). The studied compounds also showed broad-spectrum antibacterial effects.

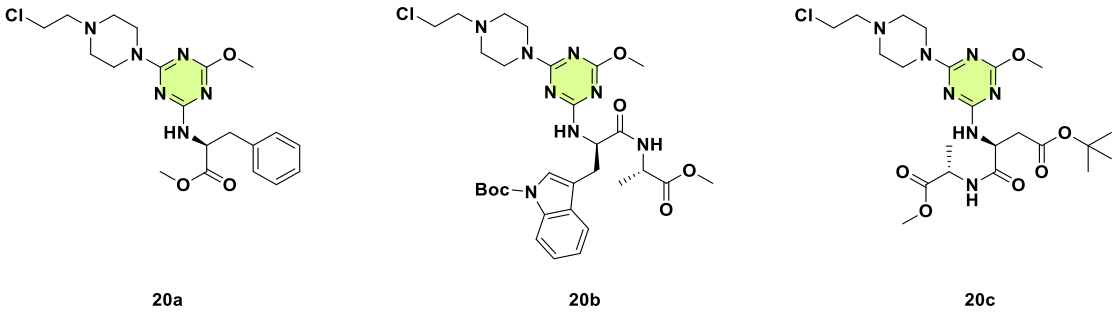

Figure 17. Chemical structures of s-triazine derivatives **20a-c**.

Conrad et al. screened several classes of prohibitin inhibitors for antifungal activity studies (Figure 18) [41]. They identified that three melanogenin analogs **21a-c** containing a s-triazine ring inhibited *C. albicans* growth at a concentration of 16.08 μg/mL, and compound **21c** completely blocked *C. albicans* growth. **21c** was further selected to determine the MIC by microbroth dilution method. Various pathogenic fungal strains were tested, including *C. albicans* SC5314, SN250, DAY185, and DAY286, *C. albicans* clinical isolates MC99 and MC102, fluconazole-resistant *C. albicans* clinical isolate 3147, *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, *Candida dubliniensis* and *S. cerevisiae*. **21c** had broad spectrum antifungal activity with MICs ranging from 4 to 16 μg/mL. Viability analysis of *C. albicans* by flow cytometry demonstrated that **21c** had fungicidal profiles with MIC of 8-16 μg/mL. Moreover, **21c** inhibited *C. albicans* hyphal formation at sublethal concentrations (≥ 1 μg/mL). Although **21c** targeted the inner mitochondrial integral membrane prohibitin proteins in human cancer cells, it did

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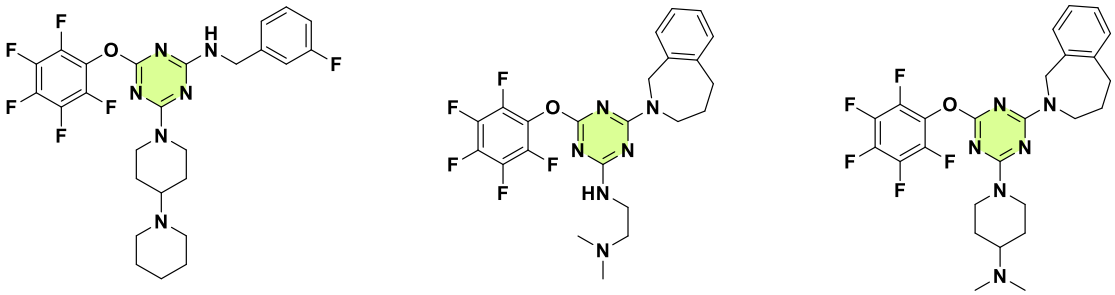
not impact *C. albicans* mitochondrial activity. The MIC of **21c** in prohibitin mutant strains (*phb1* or *phb2* Δ/Δ, *phb1* Δ/Δ-*phb2* Δ/Δ and *phb1* Δ/Δ-*phb2* Δ/Δ-*phb12* Δ/Δ) corresponded to the wild-type parental strain, indicating a new fungal-specific mode of action.



21a **21b** **21c**

Figure 18. Chemical structures of s-triazine derivatives **21a-c**.

Mena et al. screened 90 potential biological compounds from the JUNIA chemical library to assess their antifungal effects against *C. albicans* (Figure 19) [42]. One of s-triazine based compounds, namely (*Z*)-*N*-(2-(4,6-dimethoxy-1,3,5-triazin-2-yl)vinyl)-4-methoxyaniline (**22**), displayed rapid fungicidal activity against *C. albicans* and were also effective against fluconazole-resistant or caspofungin-resistant clinical isolated *C. albicans* strains. Confocal microscopy revealed that compound **22** could modulate the *C. albicans* cell wall by reducing the thickness of the mannan, thereby affecting *C. albicans* virulence. In the *Caenorhabditis elegans* infection model, **22** prolonged nematodes survival rate and increased the expression of immune related-genes, such as lys-1, lys-7, cnc-4, and pmk-1 that promote nematodes against *C. albicans* infection. Overall, this study indicates that **22** represented a promising lead compound for the treatment of *C. albicans* infections. Possible target identification and synthetic study are under investigation.

Dong et al. carried out a virtual screening of 287,000 compounds in the Specs 3D database for identifying secreted aspartic proteases 2 (SAP2, an important virulence factor) inhibitors of *C. albicans* (Figure 19) [43]. Seven compounds had an IC_{50} value lower than 100 μM. Among them, s-triazine based compound **23** showed certain SAP2 inhibitory activity (IC_{50} = 77.18 μM). Molecular docking revealed that the triazine core located in the active site of *C. albicans* SAP2 (PDB ID: 1EAG), three side chains form π–π interactions and hydrophobic with the active site amino acid residue. Interestingly, compound **23** was inactive in the antifungal assay (MIC > 64 μg/mL), which was consistent with the action mode of virulence inhibitors.

Alhameed et al. presented the synthesis and biological assessment of 4,6-disubstituted s-triazin-2-yl amino acid derivatives (Figure 19) [44]. Among them, s-triazine with piperidine, glycine, and aniline derivatives (**24a-c**) showed the best inhibitory capacity at 50 μg per disc of 15 ± 0.2, 13 ± 0.1, and 14 ± 0.2 mm, respectively. The MIC and minimum fungicidal concentration (MFC) values of **24a-c** against *C. albicans* ranged between 34.36-37.95 μM, and 68.72-75.90 μM, respectively. The SAR showed that piperidine is the key substitution for the antifungal activity. Additionally, non-substituted on the aniline appeared to be more active than chlorine and methoxy. Docking studies revealed that these synthesized compounds were well accommodated in the binding site of *C. albicans N*-myristoltransferase (NMT, PDB code: 1IYL), which could be used as potential NMT inhibitors to exert antifungal activity. Interestingly, all compounds were inactive against Gram-positive and Gram-negative bacteria.

Dongre et al. synthesized a series of 4,6-diethoxy-*N*-(4-(4,5-dihydro-5-phenylisoxazol-3yl)phenyl)-1,3,5-triazin-2-amine and screened for their *in vitro* antifungal activities against *A.niger*, *A.flavus*, *Penicillium chrysogenum* and *Fusurium moneliforme* by poison plate method (Figure 19) [45]. Most of the compounds inhibited fungal growth with compounds **25a-c** identified as the most active.

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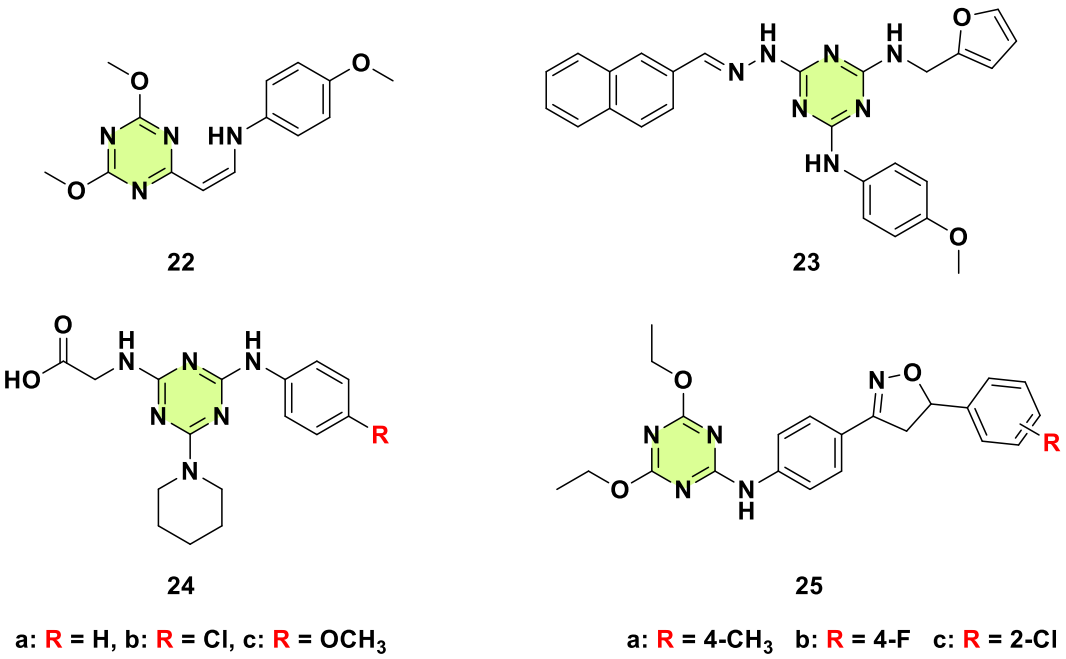

Figure 19. Chemical structures of s-triazine derivatives **22**-**25**.

Li et al. investigated and reported the antifungal properties of a 2,4,6-triamine-substituted s-triazine derivative **26** (ENOblock) by drug repurposing strategy (Figure 20) [46]. Compound **26** is the first reported non-substrate small-molecule inhibitor of human enolase [47]. As a homolog of human enolase, enolase 1 (Eno1) is also expressed in *C. albicans* and is essential for the growth and virulence of *C. albicans* [48]. Thus, the author first examined the antifungal activity of **26** against various fungal pathogens, including *C. albicans*, *C. neoformans*, *C. krusei*, *C. tropicalis*, *C. glabrata* and *C. parapsilosis*. As expected, the MICs of **26** against these tested strains ranged from 8.0 to 64.0 μg/mL. The combination of **26** and fluconazole significantly reduced the MICs and exhibited a significant synergistic effect. **26** alone or in combination with fluconazole showed remarkable inhibitory effects on hyphal and biofilm formation of *C. albicans* SC5314. Importantly, the combination of **26** and fluconazole showed *in vivo* activity against *C. albicans* SC5314 in a murine model of systemic candidiasis. The author determined **26** could directly interact with *Ca*Eno1 and inhibited the transglutaminase activity of this enzyme (IC_{50} = 12.6 μM). Taken together, **26** was identified as a novel antifungal lead for further modification.

Xie et al. then conducted a series of structural modifications of **26** (Figure 20) [49]. They designed and synthesized forty-two novel s-triazine derivatives by replacement of ENOblock PEG-containing side chains. Among them, the series compounds containing thiosemicarbazides moiety exhibited excellent synergistic activity with fluconazole against fluconazole-resistance *C. albicans* (combination MIC: 0.125-2.0 μg/mL, FICI: 0.127-0.25). Of particular note, compound **27** displayed activity against resistant *C. albicans* with MIC values 4.0 μg/mL and exhibited fungal-selective inhibitory effects on *C. neoformans* (MIC ≤ 0.125-0.5 μg/mL) and *C. glabrata* (MIC ≤ 0.125 μg/mL). It was concluded that the thiosemicarbazides moiety is an important pharmacophore for generating antifungal activity.

Furthermore, Xie and colleagues unified two amino-substituted moieties by 4-fluorophenylmethanamine, and replaced the PEG-amide containing side chains with hydrazone moiety (Figure 20) [50]. Therefore, several triazine hydrazone derivatives have been synthesized. Out of all derivatives, compound **28** not only showed excellent *in vitro* synergy in combination with fluconazole (combination MIC: 0.25-2.0 μg/mL, FICI range: 0.094-0.38) but also had direct antifungal potency against fluconazole-resistant *C. albicans* and *Candida auris* (MIC: 1.0-16.0 μg/mL). The SAR studies revealed that *ortho*-hydroxyl-substituted triazine hydrazones are the key pharmacophore. Moreover, **28** (10 mg/kg) effectively reduced the kidney burden in *C. albicans* SC5314, therefore highlighting this compound as a promising antifungal candidate.

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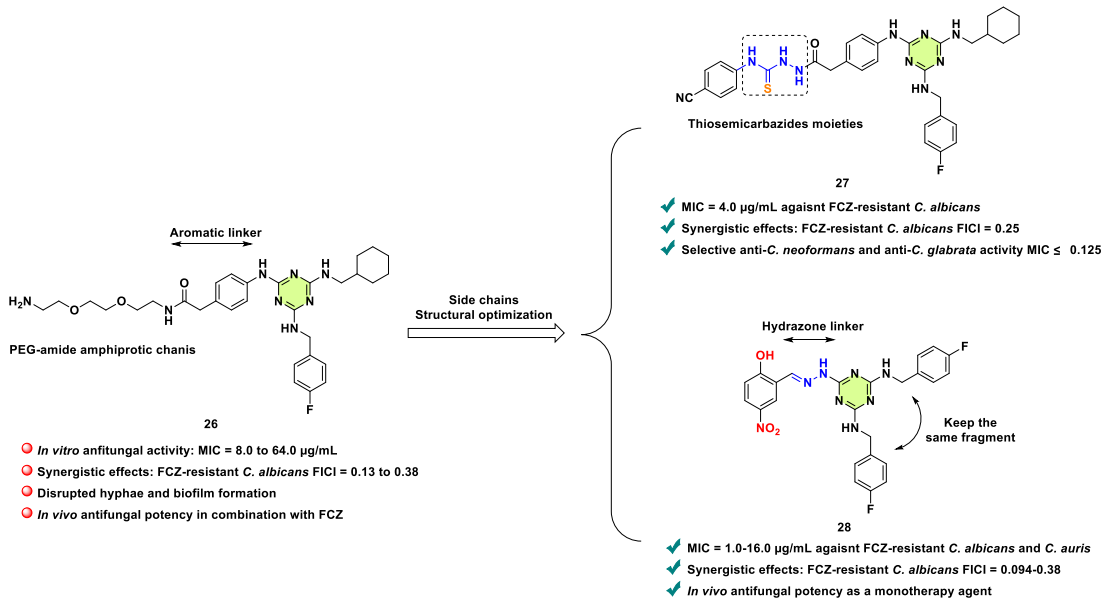

Figure 20. Design strategies and chemical structures of s-triazine derivatives **26**-**28**.

Haiba et al. designed and synthesized thirty-five new s-triazine derivatives based on the structure of gyrase inhibitor Astrazeneca arylaminotriazine III, and the derivatives were evaluated for their antibacterial and antifungal activities (Figure 21) [51]. Among them, 21 of 35 target compounds showed inhibitory against *C. albicans* with MICs ranging from 25 to 100 μg/mL. The most active compound **29** displayed a lower MIC of 25 μg/mL compared to the reference clotrimazole (MIC: 12.5 μg/mL). Interestingly, it had no antibacterial activity against *Staphylococcus aureus* and *Escherichia coli*.

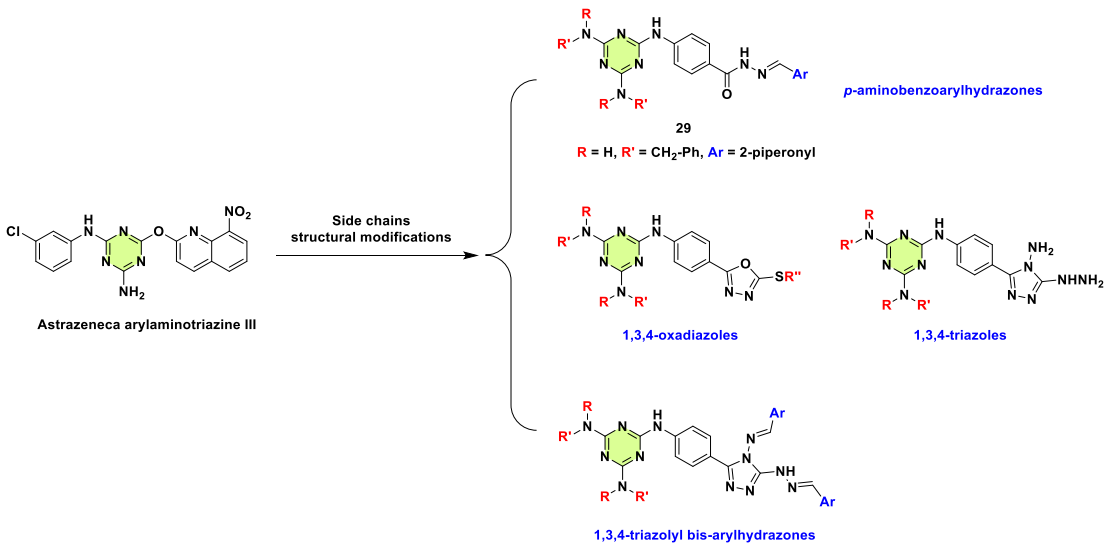

Figure 21. Design strategies and chemical structures of s-triazine derivative **29**.

Salaković et al. investigated eight symmetrical s-triazine derivatives characterized with the same *N*-alkane or *N*-cycloalkane substituent on the N^2 and N^4 position and evaluated them for their *in vitro* antifungal activity towards *A. flavus* (Figure 22) [52]. All analyzed compounds expressed significant antifungal activity, with compounds **30a-c** containing acyclic substituent and **30d** containing cyclic substituents possessed the highest inhibitory activities (inhibition zone: 20.3 ± 0.6 mm). The author also carried out a comparative molecular docking to analyze compounds' binding affinity on the enzymes of *A. flavus*.

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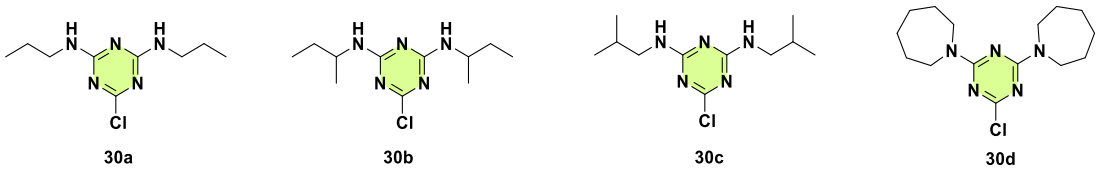

Figure 22. Chemical structures of s-triazine derivatives **30a-d**.

Sharma et al. reported the modification of amine-substituted s-triazine by incorporating different combinations of mono- or di-pyrazole, piperidine, benzylamine, aniline and diethylamine moiety (Figure 23) [53]. The activity of the derivatives against *C. albicans* was tested by the agar-well diffusion method. s-triazine bearing bis-pyrazole rings derivatives had no antifungal activity compared to mono-pyrazole. Among the mono-pyrazole compounds, the presence of the morpholine ring along with piperidine or diethylamine, like compounds **31a** (inhibition zone: 9 mm) and **31b** (inhibition zone: 8 mm), was good for anti-*C. albicans* activity.

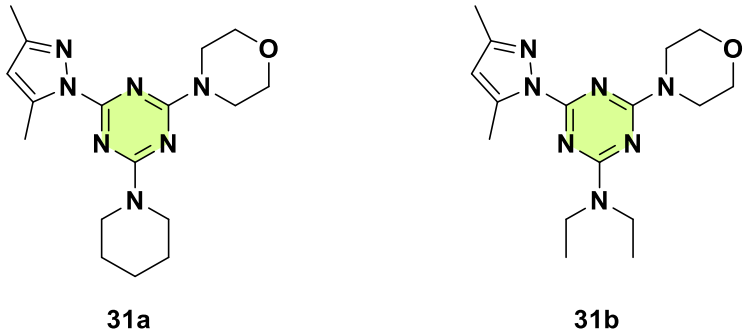

Figure 22. Chemical structures of s-triazine derivatives **31a-b**.

Triazine derivatives with additional N or S donor atoms exhibit strong chelating abilities and provide potential binding sites for complexation with various metal ions, thereby causing considerable biological activity [54]. Soliman et al. presented two novel zinc (II) pincer complexes $[Zn(BPT)(NO_3)_2]$ and $[Zn(BPT)(H_2O)Cl]ClO_4$ using bis-pyrazolyl-s-triazine (**32a**, BPT) ligand (Figure 24) [55]. The ligand and its metal complexes were screened for *in vitro* antimicrobial activity against a panel of pathogenic strains. It was found that Zn(II) complexes exhibited broad-spectrum antimicrobial activity against the Gram positive (*Bacillus subtilis*, *Bacillus cereus*) and Gram-negative bacteria (*E.coli*, *Pseudomonas aeruginosa*, *S. aureus*) as well as the fungus *C. albicans*. Particularly, one complex $[Zn(BPT)(NO_3)_2]$ had the minimum inhibitory effect against *C. albicans* (MIC: 2.8 µmol/mL), which was superior to amoxicillin (MIC: 3.0 µmol/mL). In comparison with the related work, Refaat et al reported two Zn(II) complexes, $[Zn(BPT)(NCS)_2]$ and $[Zn(BPT)(Br)_2]$, showed either weak or no antifungal activity against *C. albicans* and *A. fumigatus* [56].

Using the same ligand (**32a**), Soliman et al. continuously developed a novel Fe(III) pincer complex $[Fe(BPT)(CH_3OH)Cl_2]$ and a Co(II) complex $[Co(BPT)(NO_3)_2]$ with respective MIC values of 6.2 µmol/mL, 3.2 µmol/mL against *C. albicans* [57,58]. In contrast, the Ni(II) complexes were inactive against *C. albicans* and *A. niger* [59]. In another work reported by Soliman et al., similar Fe(III) complexes with mono- and bis-pyrazolyl s-triazine ligands (**32b-d**) showed good activity against *C. albicans* with MICs in the range of 18.8-37.5 µg/mL (Figure 24) [60]. Yousri et al. synthesized Co(II), Mn(II), and Ni(II) complexes with **32c** ligand [61]. The three studied complexes have certain inhibitory against *A. fumigatus* and *C. albicans*. It was noted that the antimicrobial activities of these metal complexes depend not only on the metal ion but also on the structure of s-triazine ligand.

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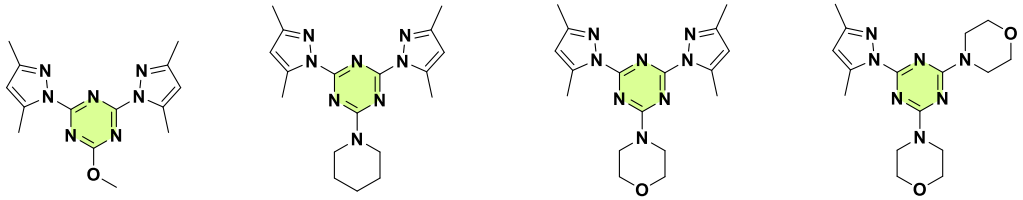

Figure 24. Chemical structures of s-triazine derivatives **32a-d**.

Soliman et al. also reported Mn(II) complexes with a new s-triazine bis-Schiff base chelating ligand (**33**, L) (Figure 25) [62]. Antimicrobial studies showed that the complex $[MnL(H_2O)_2](NO_3)_2$ are the best as antifungal and antibacterial agents. Al-Khodir et al. assessed the antimicrobial and anticancer activities of Ru(III) and Se(IV) complexes containing s-triazine chelating ligand [63]. The results showed that all Se(IV) complexes have a higher activity against *A. flavus* and moderate activity against *C. albicans* compared to Ru(III) complexes and amphotericin B. The 6-chloro-N^2-(4-chlorophenyl)-N^4-(pyrimidin-2-yl)-1,3,5-triazine-2,4-diamine) ligand (**34**, Figure 25) with Se(IV) complex introduced the most promising efficiency.

Martins et al. synthesized 2,4,6-tris(thiomorpholine)-1,3,5-triazine (**35a**, TMT), 2,4,6-tris(piperazine)-1,3,5-triazine (**35b**, PIPT) and their Sb(III) and Bi(III) complexes (Figure 25) [64]. The results from antimicrobial assays showed that Sb(III) complexes ($[SbCl_3(TMT)]$, $[Sb_3Cl_9(TMT)_2]$, $[Sb_2Cl_6(PIPT)].4H_2O$) had antifungal activity against *S. aureus*, *C. albicans*, *C. tropicalis* and *C. krusei* with MIC in the range of 512-1024 µg/mL. Additionally, two free ligands (TMT, PIPT) and $SbCl_3$ did not inhibit the growth of the evaluated microorganisms, suggesting that coordination of metal ions through s-triazine based ligands is a good strategy for the development of new antimicrobial agents.

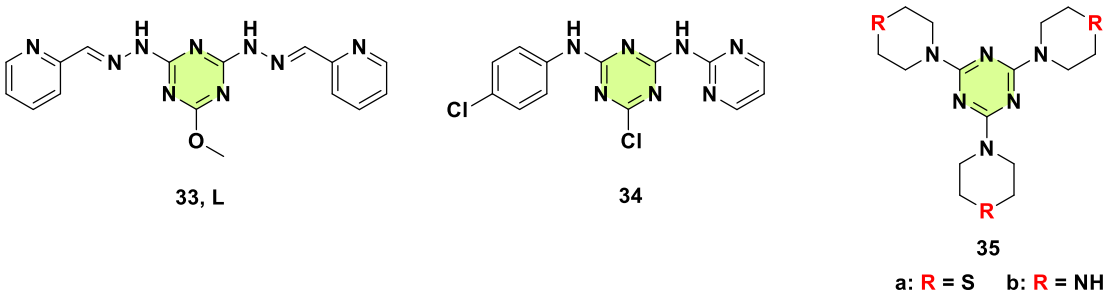

Figure 25. Chemical structures of s-triazine derivatives **33-35**.

Due to the branching capabilities of the s-triazine nucleus, many mono-, bi-, and tri-substituted compounds can be prepared by controlling the reaction conditions. In this regard, Bashiri et al. synthesized a collection of tris-*β*-lactams 1,3,5-triazine hybrids (**36**) and investigated their potential biological activities (Figure 26) [65]. Although some hybrid molecules showed antiproliferative, antibacterial and antioxidant properties, they were inactive against two tested fungi (*C. albicans* and *A. fumigates*).

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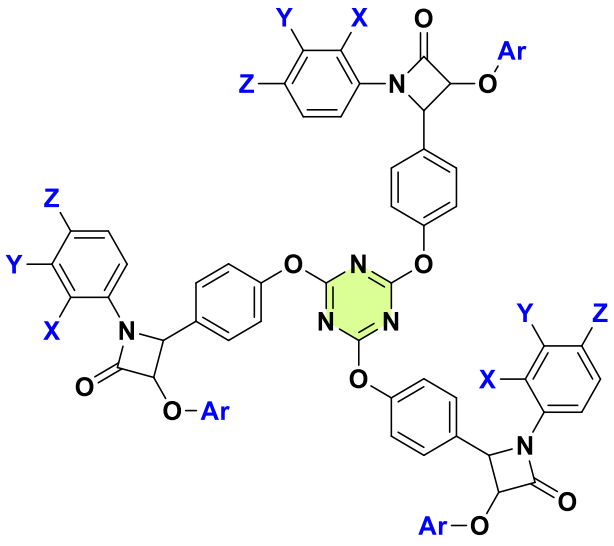

36

Ar = phenyl, naphthalenyl

X = H, OCH_3; Y = H or X + Y = $(CH)_4$

Z = CH_3, OCH_3, OEt_2, H, Cl, Br, NEt_2

Figure 26. Chemical structures of s-triazine derivatives **36**.

It is well known that Schiff bases (−NH−N=CH−) have numerous biological activities. Ramadan et al. synthesized and reported a novel class of dimeric s-triazine hydrazide derivatives (**37**) using 1,2-diaminoethane, 1,4-diaminocycloalkane, 1,4-diaminobenzene and 1,1′-biphenyl-4,4′-diamine as linkers (Figure 27) [66]. The synthesized compounds were investigated for their *in vitro* antimicrobial activity. Unfortunately, none of the dimeric s-triazine hydrazide showed anti-*C. albicans* activity. Also, Al-Rasheed et al. synthesized series of s-triazine based Schiff bases derivatives (**38-40**) (Figure 27) [67,68]. Some target compounds exhibited good antibacterial activity, however, none of them showed specific effect against tested fungi.

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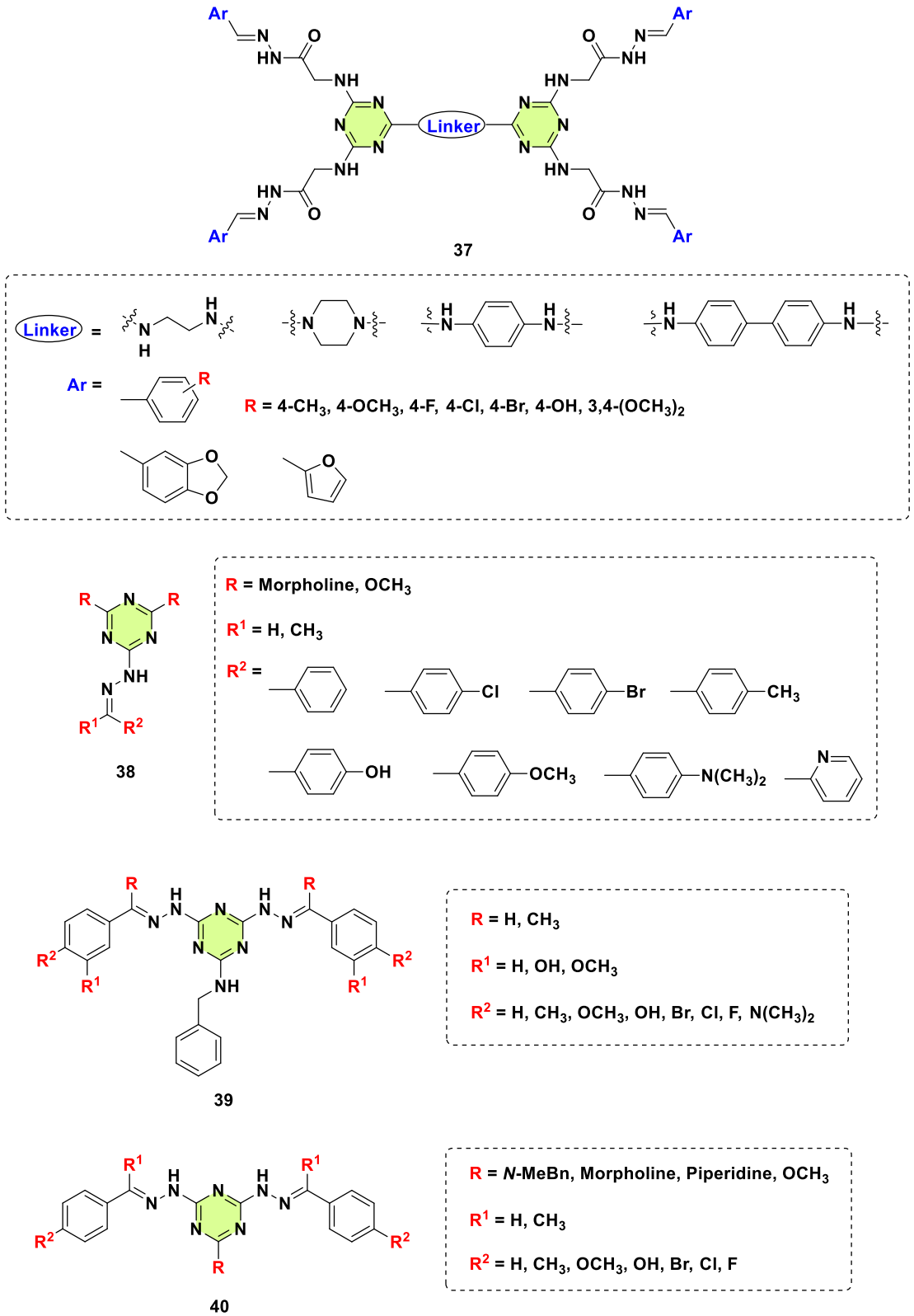

Figure 27. Chemical structures of s-triazine derivatives **37**-**40**.

Al-Zaydi et al. synthesized a series of s-triazine based aminobenzoic acid and their methyl ester analogs (**41a-e**) (Figure 28) [69]. *In vitro* MIC antifungal results showed all tested compounds have no inhibition activity against *C. albicans* (MIC > 200 μg/mL).

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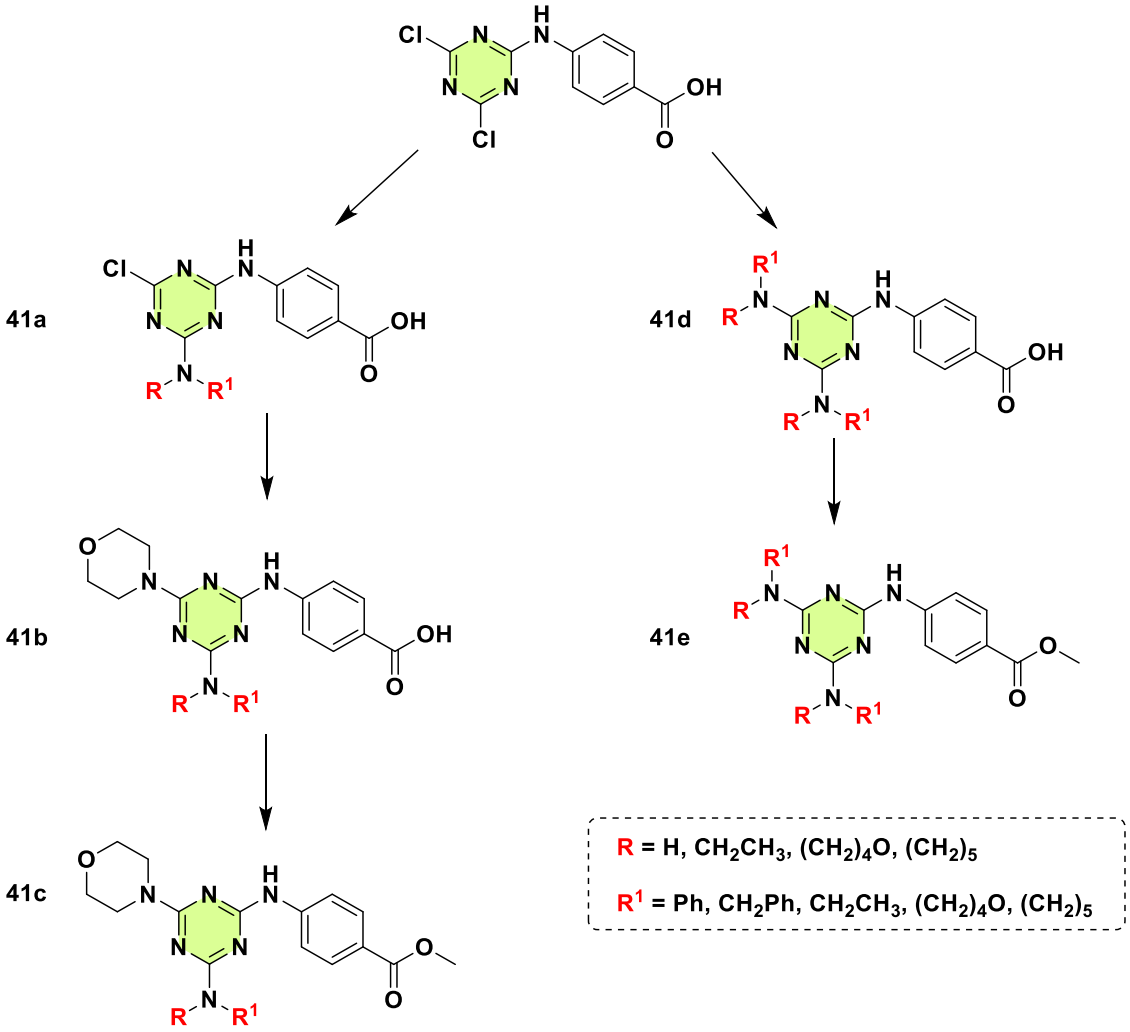

Figure 28. Chemical structures of s-triazine derivatives **41a-e**.

3. Conclusion and Future Prospects

There is an increasingly urgent need to develop new antifungal therapeutics, with over a billion people annually adversely affected by IFIs and 1.65 million individuals dying worldwide. Indeed, fungal infections have posed a heavy burden on the world health system. Current treatment of fungal disease is complicated by the efficacy, toxic side effects, bioavailability, and emergence of drug-resistant fungi.

s-Triazine displays a broad spectrum of pharmacological activities, playing a versatile scaffold for drug design and development. In recent years, various s-triazine compounds have been reported for their antifungal activities, and some of them exhibited promising *in vitro* and *in vivo* potency against both drug-sensitive and drug-resistant fungal pathogens. This review covers the recent advances of s-triazine compounds as potential antifungal agents and summarizes the structure-activity relationship. Moreover, the effect of different substituents installed on the s-triazine core has also been discussed. The efforts in synthesizing and SAR studies would bring new perspectives for further lead compound optimization.

Nevertheless, there remains ample room for the exploration of s-triazine compounds underlying antifungal activity. Due to the diverse reactivity of cyanuric chloride, various mono, di-substituted and tri-substituted s-triazine derivatives could be obtained providing convenience for conducting rational drug design. This lies in introducing active antifungal pharmacophores (imidazole, triazole, tetrazole, pyridine, pyrimidine, coumarin, chalcone, quinazolinone) of the s-triazine core via molecular hybridization. On the other hand, by carrying out structure-based drug design (SBDD), computer-aided drug design (CADD) and even proteolysis-targeting chimeras (PROTAC) technique,

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chemists can further construct multifunctional s-triazine derivatives, which possess like multi-targeting, membrane-targeting, protein-protein interactions inhibition, anti-virulence or anti-drug efflux characteristic. Promising compounds need further investigated, including susceptibility evaluation against other species, unraveling their mechanisms of action, and a deeper understanding of pharmacokinetic/pharmacodynamic (PK/PD) as well as *in vivo* studies. Through this integrative approach, novel s-triazine antifungal candidates with broad-spectrum, higher activities, and lower toxicity are worth expecting in future drug discovery.

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