Research article
International Journal of Heterocyclic Chemistry, Vol. 9, No. 2, pp. 49-79 (Spring 2019)

http://ijhc.iauahvaz.ac.ir

Diverse Chemical and Pharmacological Properties of Triazine Compounds

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Running title: A mini-review on triazines

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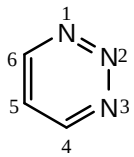
Abstract:

The 1,3,5-triazine is the common triazine moiety. Triazines are weak bases and have much weaker resonance energy than benzene, so nucleophilic substitution is preferred to electrophilic substitution. Heterocyclic bearing triazines moieties, represent an interesting class of compounds possessing a wide spectrum of biological activities such as antiviral, fungicidal, insecticidal, bactericidal, herbicidal and antimalarial, anti-HIV, anticancer, anti-inflammatory, analgesic, antihypertensive, cardiotonic, neuroleptic, nootropic, anti-histamine, tuberculostatic, anti-protozoal, estrogen receptor modulators, cyclin-dependent kinase inhibitors, and antiparasitic activities agents. They also find applications as dyes, lubricants and analytical reagents. Some dyes, lubricants, and reagents derived from triazine are already available on market. By using the same approach series of compounds can be synthesized, characterize and evaluate for desire pharmacological activity with high potency and low toxicity. The triazine derivatives possess diverse biological potential, easy synthetic routes for the synthesis, and attracted researchers for the development of new chemotherapeutic agents and it also revealed the importance of the nucleus.

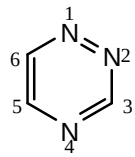
Keywords: 1,2,3-Triazines, 1,3,5-triazines, s-Triazines, 1,2,4-Triazines, synthesis, biological activities.

Introduction: Heterocyclic chemistry is essential to medicine. It composes various groups of organic compounds exhibiting a wide range of pharmacological activities [1]. Most pharmaceutical products that mimic natural products with pharmacological activities are heterocyclic. Triazine is a six-membered heterocyclic ring compound having three nitrogens in its structure by replacing carbon-hydrogen atoms in the benzene ring with the general formula $C_3H_3N_3$.

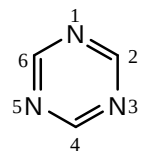
The three isomers of triazine are distinguished from each other by the positions of their nitrogen atoms and are referred to 1,2,3-triazine (**1a**), 1,2,4-triazine (**1b**), and 1,3,5-triazine (**1c**), [2,3].



1,2,3-Triazine (**1a**),



1,2,4-Triazine(**1b**)



1,3,5-Triazine or s-triazine (**1c**)

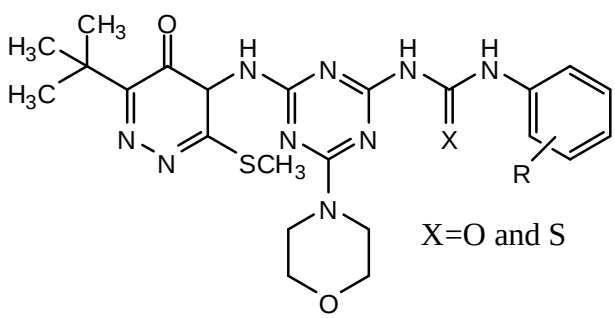
The three isomers indicated that the carbon-hydrogen atoms on the benzene ring have been replaced by nitrogens. These isomers are known as 1,2,3-triazine, 1,2,4-triazine, and 1,3,5-triazine respectively. The 1,2,4-triazine derivatives have been studied for their chemical reactivities, synthetic methodologies and their promising biological activities like 1,2,4-Triazine derivatives have been reported to possess a broad spectrum of biological activities including antimicrobial, antifungal, antiviral, anti-protozoal, anti-HIV, anticancer, anti-inflammatory, analgesic antihypertensive, cardiotonic, neuroleptic, nootropic, anti-histamine, cyclin-dependent kinase inhibitors, anti-tubercular, estrogen receptor modulators, antimalarial, antiparasitic and other anticipated activities [4-19]. The synthesis of 1,2,4-triazine derivatives is prepared by the different synthetic procedures.

The oxazolinone compounds are the most regular reagents used for the preparation of various 1,2,4-triazine derivatives. Some derivatives of s-triazine exhibited antimicrobial, antibacterial, and herbicidal [20,21], anti-HIV infection [22]. Some trisubstituted-1,3,5-triazine compounds are used as liposomes [23]. The s-triazine nuclei act as potential therapeutic agents against various diseases including bacterial infections, malaria, and cancer [24]. Trichlorotriazine derivatives have extensive use in the synthesis of activated dyes, whiteners, herbicides, and pharmaceutical agents. The 1,3,5-Triazine derivatives possess biological activities like antitubercular, antitumor,

anti-inflammatory, and anthelmintic. The 1,3,5-triazines is a widely used lead structure with a multitude of interesting applications in numerous fields [25,26] and a well-known class of compounds and considerable interest due to their applications in different fields like the production of herbicides and polymer photo stabilizers. Some s-triazines showed vital properties, for example, hexamethyl melamine (HMM) and 2-amino-4-morpholino-s-triazine are used clinically as antitumor properties to treat breast, lung, and ovarian cancer. Pentamethyl, hydroxymethyl, melamine is the hydroxylated metabolite which is the main active form of HMM. Recently, s-triazines of 4,4'-(6-(1H-imidazole-1-yl)-1,3,5-triazine-2,4-diyl)dimorpholine has significant aromatase inhibitory activities. The s-triazines are used as templates for molecular imprinting and the construction of three-helix bundle protein [21,27].

Biological Activities of Triazine compounds: The triazine compounds act by reducing the effect of an inducible membrane protein with the intention of general purposes to raise the efflux of the cytotoxic agents. The triazine compounds also exhibit anti-ulcer, anti-depressant, and antiviral activity [28]. Several six-membered heterocyclic compounds contain triazine lead moiety have been reported to have a diverse type of biological property. It is also well established that various derivatives of triazine exhibit wide spectrum biological properties such as analgesic and anti-inflammatory activity, antifungal, antibacterial activity, histamine blockers, antitubercular and antioxidant activity [29].

A series of cyanuric chlorides were tested for their *in vitro* antibacterial activity against the four strains of bacteria (G+ve, G–ve). Six compounds of the obtained series showed high antimicrobial activity. Compound **2d, 2i, 3f,** and **3j** were showed excellent activity against *Staphylococcus aureus.* Compound **3e, 3g,** and **3i** were showed good activity against *Bacillus subtillis*. Compound **3i** exhibited excellent activity against *E. coli* and compound **3c** showed excellent activity against *P. aeruginosa*. Compound **2d** and **2f** showed good activity against *C. albicans*. The presence of an electron-withdrawing group on the aromatic ring in series **3** and **4** increased the antimicrobial activity compared to compounds with electron-donating groups. It is necessary to optimize the by substituting a series of electron-withdrawing groups on the aromatic ring [21].



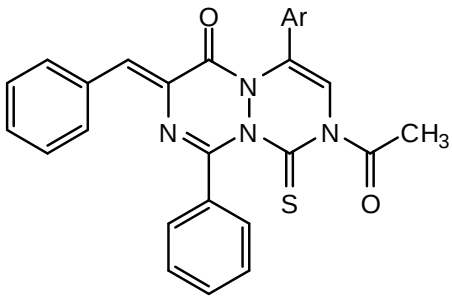
X=O and S

	X	R		X	R
2a	O	H	**3a**	S	H
2b	O	2-OCH_3	**3b**	S	2-OCH_3

Compounds **2a-i** and compounds **2a-j**

2c	O	2-CH_3	**3c**	S	4-OCH_3
2d	O	4-CH_3	**3d**	S	2-CH_3
2e	O	4-OCH_3	**3e**	S	4-CH_3
2f	O	2-Cl	**3f**	S	2-Cl
2g	O	4-Cl	**3g**	S	3-Cl
2h	O	4-F	**3h**	S	4-Cl
2i	O	4-Br	**3i**	S	4-NO_2
			3j	S	α-naphthyl

The characterization of some triazine analogs having the biodynamic heterocyclic rings with the anticipation to attain increased biological functions [21]. The biological activity of 1,2,4-triazino-[2,1-a]-1,2,4-triazine derivatives (**4**) [30]. The 1,2,4-triazine derivatives containing quinoline nucleus (**5**) exhibited antimicrobial activity [31]. Some quinazolinones derivatives fused with [1,2,4]-triazole, [1,2,4]-triazine and [1,2,4,5]-tetrazine rings (**6**) [32], 8-aryl-3,4-dioxo-2*H*,8*H*-6,7-dihydroimidazo[2,1-*c*] [1,2,4]triazines (**7**) [33], Some new nitrogen heterocyclic systems bearing 1,2,4-triazine moiety (**8**) [34] were exhibited antimicrobial activity.



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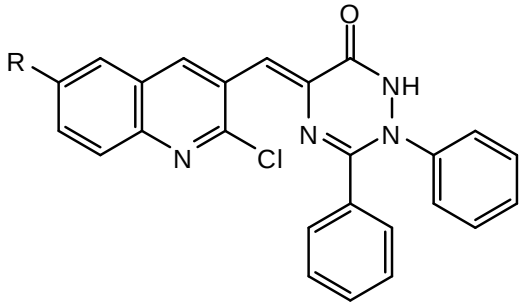

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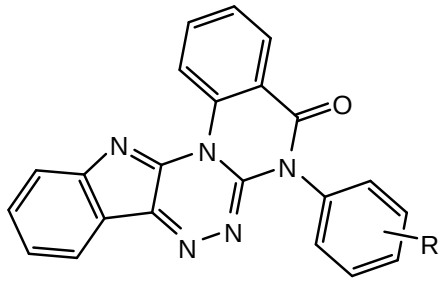

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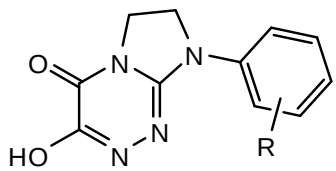

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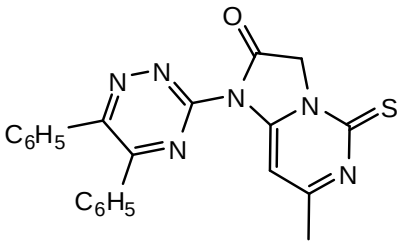

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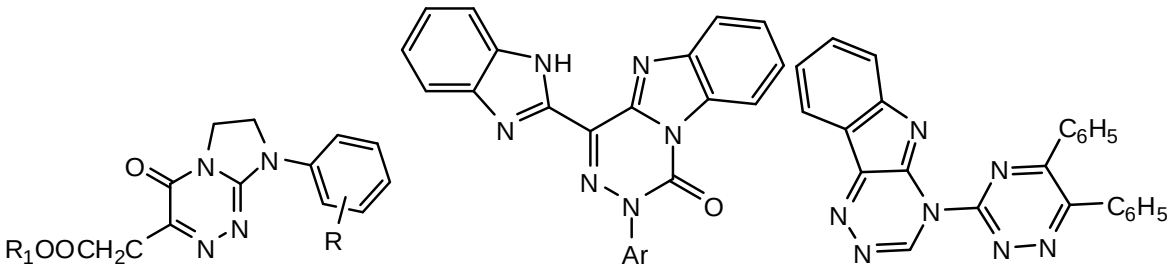
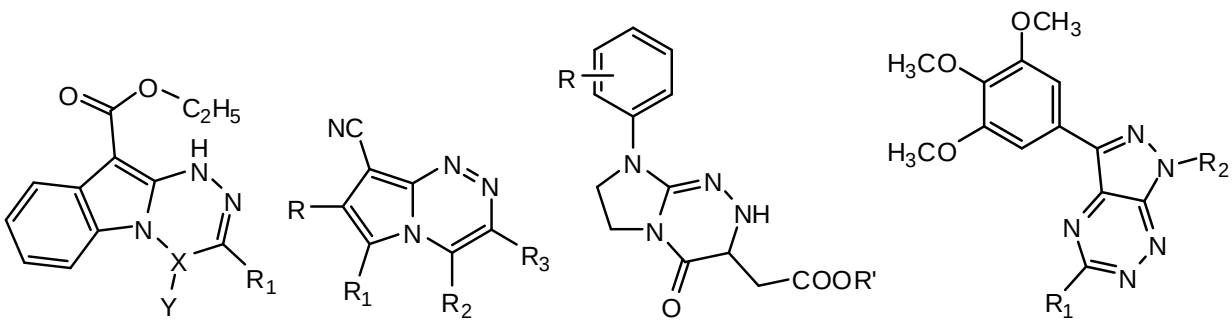
The crystal structure of derivatives of ethyl 1-(4-oxo-8-aryl-4,6,7,8-tetrahydroimidazo[2,1-c][1,2,4]triazin-3-yl)formate (**9**) showed anticancer activity [35]. A series of 2-aryl-4-(benzimidazol-2-yl)-1,2-dihydro[1,2,4]triazino-[4,5-a]benzimidazol-1-ones (**10**) with preferential

cytotoxicity against carcinoma cell lines [36]. The [1,2,4]triazino[4,3-*a*]indoles (**11** and **12**) were exhibited antiproliferative activity [37]. Some novel pyrrolo[2,1-*c*][1,2,4]triazines **(13)** from 2-diazopyrroles were showed antiproliferative activity [38]. The novel derivatives of methyl and ethyl 2-(4-oxo-8-aryl-2*H*-3,4,6,7-tetrahydroimidazo[2,1-c][1,2,4]triazin-3-yl)acetate compounds (**14**) from biologically active 1-aryl-2-hydrazinoimidazolines were exhibited antproiferative activity [39]. Some 3,7-diaryl-5-(3,4,5-trimethoxyphenyl)pyrazolo[4,3-e][1,2,4] triazines (**15**) were showed cytotoxic activity [40].

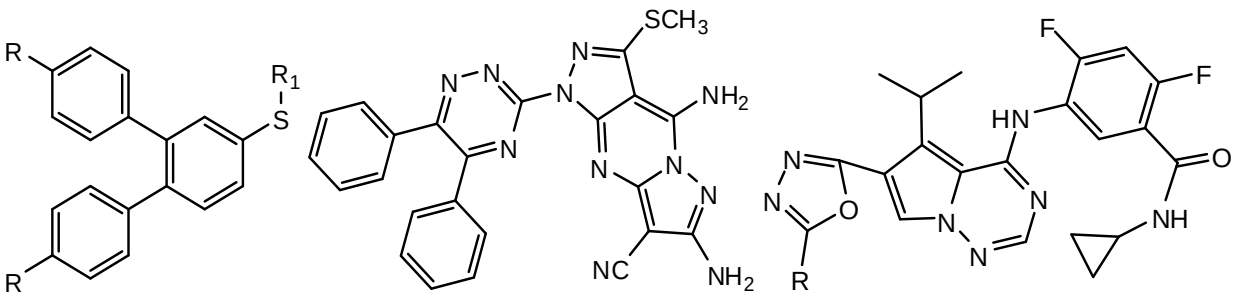


9 **10** **11**



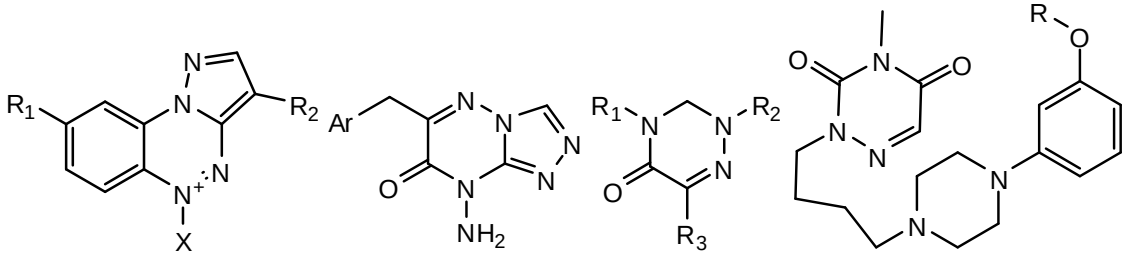
12 **13** **14** **15**

The novel 1,2,4-triazine derivatives (**16**) act as neuroprotective agents [41]. The synthesis of some novel pyrazolo[3,4-b]pyridine and pyrazolo[3,4-d]pyrimidine derivatives (**17**) bearing 5,6-diphenyl-1,2,4-triazine moiety showed potential antimicrobial activity [42]. The 4-[2,4-difluoro-5(cyclopropylcarbamoyl)phenylamino] pyrrolo[2,1-f][1,2,4]triazine (**18**) exhibited VEGFR-2 kinase inhibitor activity [43].



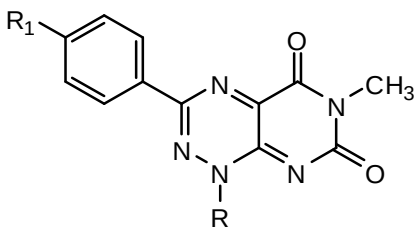
16 **17** **18**

The new pyrazolo[5,1-c][1,2,4] benzotriazines, pyrazolo[5,1-c]pyrido[4,3-e][1,2,4] triazines (**19**) and their open analogues found as cytotoxic agents in normoxic and hypoxic conditions [44]. The synthesis and structure elucidation of novel fused 1,2,4-triazine derivatives (**20**) as potent inhibitors targeting CYP1A1 activity [45]. The novel 1,2,4-triazine derivatives (**21**) with antiproliferative activity [46]. The [O-methyl-11C] 2-{4-[4-(3-methoxyphenyl)piperazin-1-yl]-butyl}-4-methyl-2H-[1,2,4]-triazine-3,5-dione (**22**) exhibited agonist 5-HT1A receptor PET ligand activity [47].



19 **20** **21** **22**

Nearly all colorectal cancers (CRCs) and subsets of other types of cancers have somatic mutations leading to β-catenin stabilization and increased β-catenin/TCF transcriptional activity. Inhibition of stabilized β-catenin in CRC cell lines seized their development and the potential of this mechanism for new cancer treatment. A panel of six candidate Wnt/β-catenin/Tcf-regulated genes and originated that two of them (Axin2, Lgr5) were reproducibly stimulated (9-10 fold) in rat intestinal epithelial cells (IEC-6) subsequently β-catenin stabilization by Wnt-3a ligand therapy. Two β-catenin/TCF antagonists (calphostin C, xanthothricin) and XAV939 (tankyrase antagonist) reduced Wnt-activated genes in a dose-dependent manner. The triazine compounds (**23** and **24**) were potently inhibited Wnt-mediated activation in the target genes. The mechanism of action for one of the series and demonstrated these novel small molecules inhibit β-catenin transcriptional activity by degrading β-catenin via a proteasome-dependent, but GSK3 β-, APC-, AXIN2- and bTrCP-independent, pathway. The compounds act at the level of β-catenin to inhibit Wnt/ β-catenin/TCF function and robust strategy for assessing the activity of b-catenin/TCF antagonists [48].



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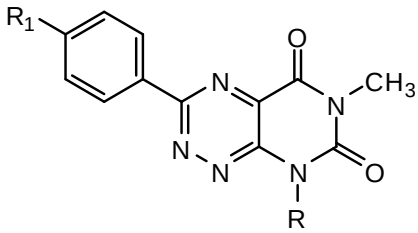

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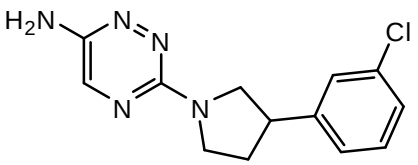
Inorganic pyrophosphatases are potential targets for the new antibacterial compounds. Pyrophosphatase-coupled high-throughput screening assays (HTSA) proposed to detect o-succinyl benzoic acid (OSB) coenzyme A synthetase inhibitors led to the unpredicted innovation of inorganic pyrophosphatase inhibitors. The 3-(3-aryl-pyrrolidin-1-yl)-5-aryl-1,2,4-triazines, a tetracyclic triazines 3-(3-(3-chlorphenyl)pyrolidin-1-yl)-1,2,4-triazin-6-amine (**25**) showed good antibiotic activity against various drug-resistant *S. aureus* strains, as well as activity versus *M. tuberculosis* and *B. anthracis*, at a non cytotoxic concentration to mammalian cells [49]. A series of 1,2,4-triazines possessing 1,2,3-triazole (**26**) and piperidine ring using 1-(1-substituted piperidin-4-yl)-1H-1,2,3-triazole-4-carbohydrazide (**27**). All the compounds were exhibited in vitro antifungal activity against different fungal strains such as *Candida albicans, Fusarium oxysporum Aspergillus flavus, A. niger,* and *Cryptococcus neoformans* [50].



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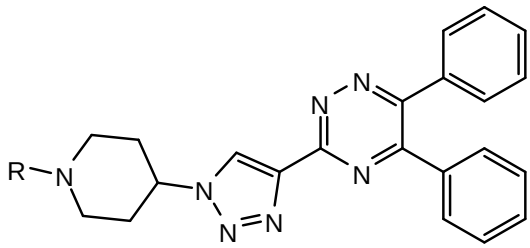

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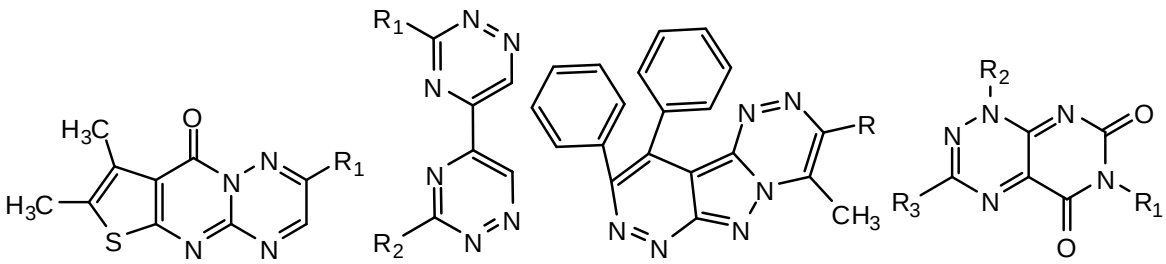
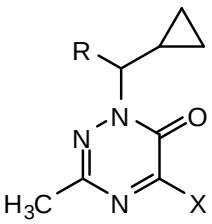
The thieno[20,30:4,5]pyrimido[1,2-b][1,2,4]triazines and thieno[2,3-d][1,2,4]triazolo[1,5-a] pyrimidine compounds were tested for their anti-inflammatory and analgesic activity. The thieno[2,3-d][1,2,4]triazolo[1,5-a]pyrimidine derivatives (**28**) were exhibited better biological activities than the thieno[2',3':4,5]pyrimido[1,2-b][1,2,4]triazines [51]. The 3-alkylthio-1,2,4-triazine dimers (**29**) are potently toxic to *Plasmodium falciparum* with lower toxicity to mammalian cells. They are equally effective against chloroquine-resistant *P. falciparum* [52]. The 3-Aminopyrazolo[3,4-d]pyridazine (**30**) was diazotized and coupled with active methylene reagents to afford the tricyclic pyridazino[3',4':3,4]pyrazolo[5,1-c]-1,2,4-triazines with substituents such as methyl, phenyl, ethoxycarbonyl, acetyl or benzoyl, depending on the

methylene reagent used. The in vitro antimicrobial activities for some of the compounds were evaluated against *E. coli, Pseudomonas aeruginosa, S. aureus,* and *C. albicans* were determined [53]. The pyrimido[5,4-e][1,2,4]triazine-5,7(1H,6H)-dione derivatives (**31**) were investigated as novel molecule amplifiers of heat shock factor-1 transcriptional activity. Lead optimization led to the discovery of a compound, which displayed potent HSF1 activity under mild heat stress (EC_{50} = 2.5 μM) and significant cytoprotection in both rotenone (EC_{50}= 0.23 μM) and oxygen-glucose deprivation cell toxicity models (80% protection at 2.5 μM) [54].



28 **29** **30** **31**

A series of 5-arylamino-1,2,4-triazin-6(1H)-ones (**32**) were evaluated as antagonists at the receptor of corticotropin-releasing factors. The formation of CYP-mediated oxidative reactive metabolites is related N3-phenylpyrazinone that was minimized by inclusion of the extra ring nitrogen presented in the triazinones [55]. The 5-Aryl-6-(4-methylsulfonyl)-3-(metylthio)-1,2,4-triazines were tested for their COX-1/COX-2 inhibitory, *in-vivo* anti-inflammatory, and analgesic activities. All these compounds were showed strong inhibition of COX-2 with IC_{50} values range of 0.1–0.2 μM and in most compounds have stronger anti-inflammatory and analgesic activities than indomethacin at doses level 3 and 6 mg/kg. The compound 5-(4-chlorophenyl)-6-(4-(methylsulfonyl) phenyl)-3-(methylthio)-1,2,4-triazine (**33**) was found selective COX-2 and most potent compound, its selectivity index of 395 as compared to celecoxib (405). The anti-inflammatory and analgesic effects were found higher than indomethacin [56]. The fluoroethyl compound, 2-(4-(4-(2-(2-fluoroethoxy)phenyl)piperazin-1-yl)butyl)-4-methyl-1,2,4-triazine-3,5-(2H,4H)dione (**34**) (FECUMI-101) act as a limited agonist 5-HT1AR ligand of the parent ligand CUMI-101. The [^{18}F]FECUMI-101 binding to 5-HT1AR ligand WAY100635. The [^{18}F]FECUMI-101 is a viable agonist ligand for quantification of high-affinity 5-HT1AR with PET antimicrobial peptides [57].



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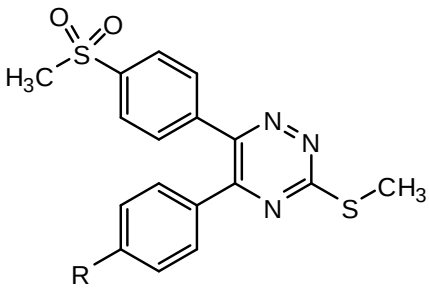

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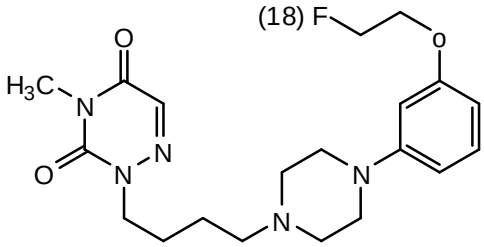

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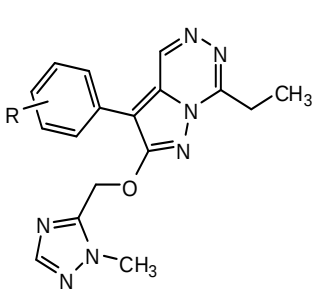
A 2,3,7-trisubstituted pyrazolo-[1,5-d][1,2,4]triazines (**35-38**) are high affinity ligands for the GABAA benzodiazepine binding site and some analogues show functional selectivity for agonism at α3-containing receptors [58]. The Imidazo[1,2-*b*][1,2,4]triazines (**39**) as a2/a3 subtype selective GABAA agonists for the treatment of anxiety [59]. The evaluation of pyrrolo[2,1f][1,2,4]triazine derivatives (**40**) as novel hedgehog signaling pathway inhibitors [60]. The proline isosteres in 2,4-disubstituted pyrrolo[1,2-f][1,2,4]triazine (**41**) act as inhibitors of IGF-1R kinase and IR kinase [61].



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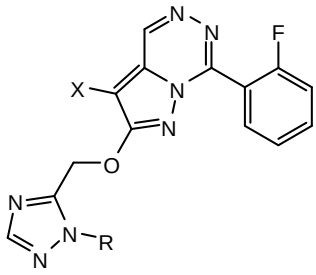

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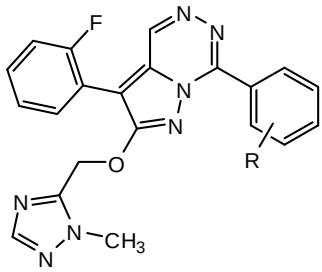

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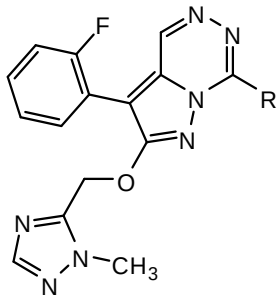

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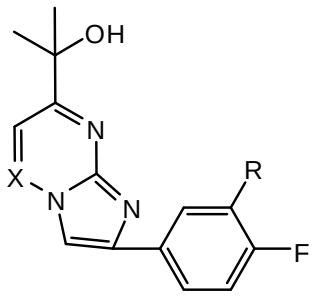
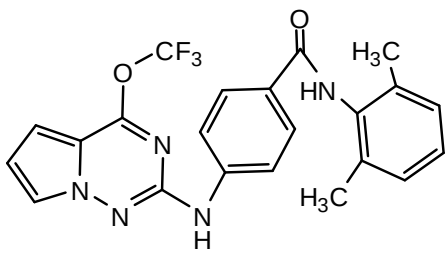


39 X=N or CH



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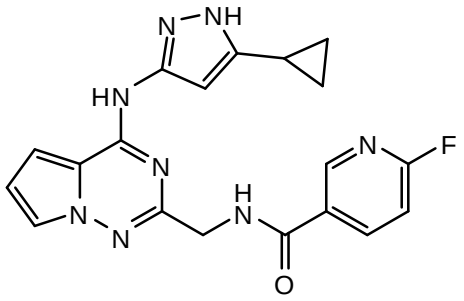

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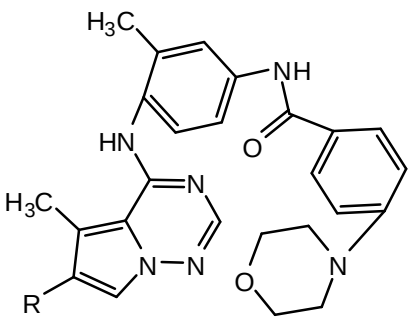
A series of compounds based on the pyrrolo[2,1-f][1,2,4]triazine (**42** and **43**) ring system have been identified as potent p38a MAP kinase inhibitors [62]. The structure-based bioisosterism design, biological evaluation of novel 1,2,4-triazin-6-ylthio-acetamides (**44**) as potent HIV-1 NNRTIs [63].



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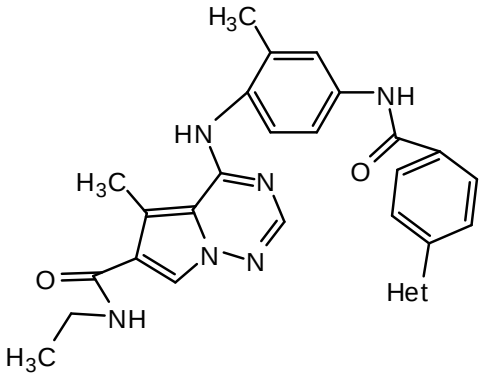

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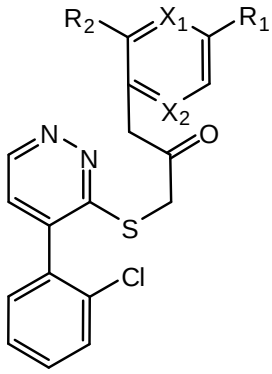
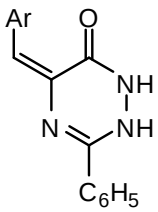
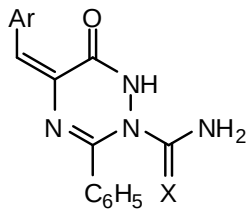


44

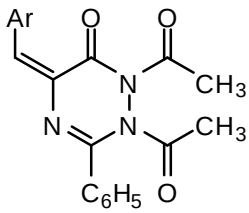
The 2,3,5-trisubstituted-1,2,4-triazin-6-ones (**45**,**46**). Acetylating compounds **45,46** with acetic anhydride yields the diacetyl derivative **47** and fused triazolo-1,2,4triazine derivative **48**, respectively. Treatment of compound **46a** with ethyl chloroacetate gives the corresponding fused 1,2,4-triazine derivative **49**. The 3-acetyl-5,5-disubstituted-1,2-dihydro-1,2,4-triazino-1,2,4-triazin-1,4,8-triones **50** was prepared via acetylating compound **46** with acetic anhydride. The cytotoxic activities of the compounds have been studied on the tumor cell line human colon carcinoma (HCT-116) cell using the MTT viability test. The antitumor activity of some1,2,4-triazine derivatives. The investigation of antitumor activity revealed that compounds **46b, 48a** and **50** are most potent against Human colon carcinoma (HCT-166) cell line, IC_{50} (1.96), IC_{50} (3.43), IC_{50} (2.69) respectively. While compound **47** has moderate activity, compounds **46a** and **49** have weak activity. Hence oxo and thioxo derivatives have good antitumor activity [64].



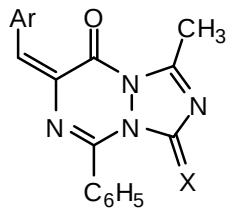
45 Ar=C_6H_4F



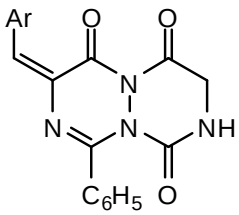
46a 46b a,x=O, b,x=S



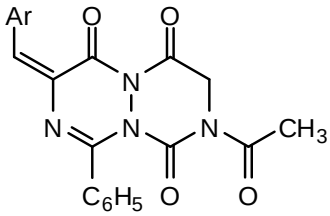
47



48a 48b



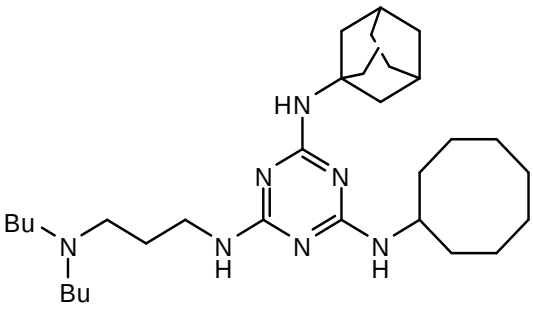
49



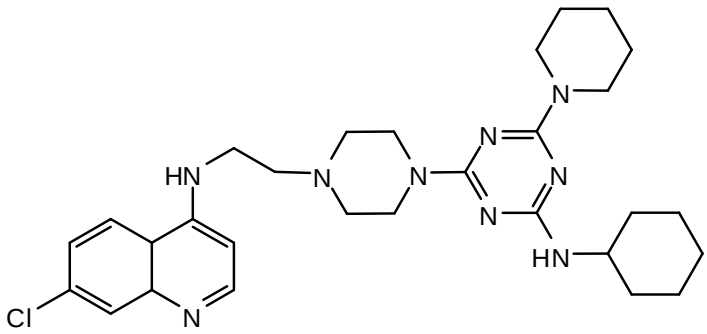
50

The development of antimicrobial peptides as a potential source of antibiotic drug, based on the cationic charge, lipophilicity, and bulk are main factors determining antibacterial activity in

these peptides (**51**), designed and screened different combinatorial libraries based on 1,3,5-triazine as an outline. A group of compounds was recognized to showed potent antimicrobial effects together with low hemolytic effect [29]. The bio-evaluation of hybrid 4-amino-quinoline triazines (**52**) as antimalarial agents, the appearance and rapid extend of chloroquine-resistant strains of *Plasmodium falciparum* has considerably reduced the chemotherapeutic alternatives. A series of hybrid 4-aminoquinoline triazines were tested *in-vitro* against the CQ sensitive strain of *P. falciparum* [65]. These triazines were showed antimalarial activity.

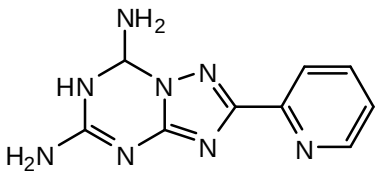


51 TZ-4 IC_{50}=2.0 uM



52

Antiproliferative activity of the l,2,4-triazolo[1,5-a][1,3,5]triazines were evaluated against breast, colon, and lung cancer cell lines. The highest antiproliferative activity in the series was found in compound 2-(pyridine-3-yl)-7-(4-trifluoromethylphenyl)-6,7-dihydro[1,2,4] triazolo [1,5-a][1,3,5] triazin-5-amine (**53**) [66]. The polar functional group substituted mono and bis-(*o*-carboranyl)-1,3,5-triazine compound (**54**), in preliminary *in-vitro* studies, revealed that compounds regardless of their low cytotoxicity, collected at high levels in B-16 melanoma cells [43]. The pyrazolo [1,5-*a*]-1,3,5-triazine is an adenine bioisostere (**55**). In biological testing has shown that compounds showed strongly inhibited LPS-induced TNFa release from human mononuclear cells from the healthy subject [67].



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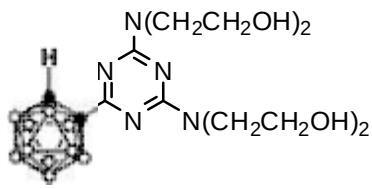

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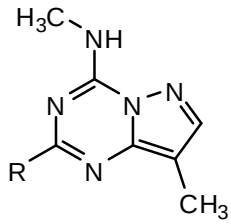
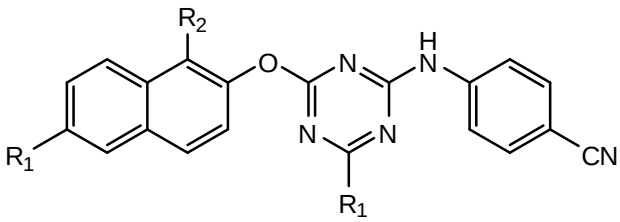


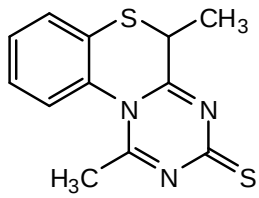
55

Some diaryltriazine derivatives (**56**) showed potent anti-HIV activity [83]. The antibacterial activity was performed on some new 1,4-benzothiazines (**57**) against gram-positive and gram-negative bacteria (*E. coli*, *S. aureus*, *P. aeruginosa* [68]. The 3D-QSAR analysis of cycloguanil

derivatives (**58**) showed highly active against dihydrofolate reductase resistant strain (T9/94) of *P. falciparum* [69].



56



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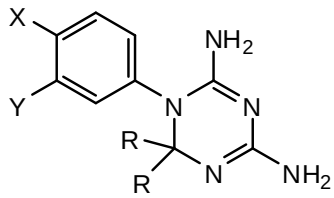
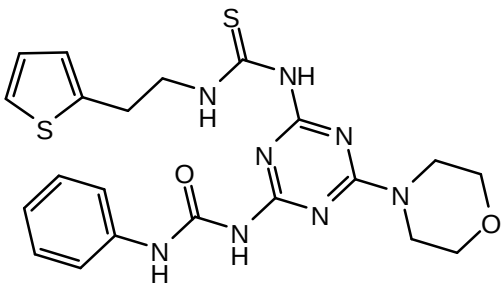


58

Aliphatic thiourea derivative (**59**) containing s-triazine moieties were reported as antimicrobial agents against gram-positive and gram-negative bacteria (*S. aureus*, *P. aeruginosa)* and showed mild active agents [70]. The cytotoxic activity of trisubstituted-1,3,5-triazines (**60,61**) was tested for phototoxicity and the cytotoxic effects against leukemia and adenocarcinoma-derived cell lines in contrast to the normal human keratinocytes [71].



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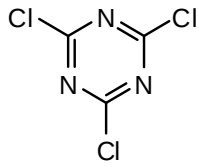
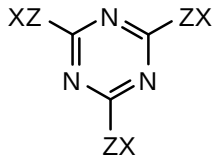
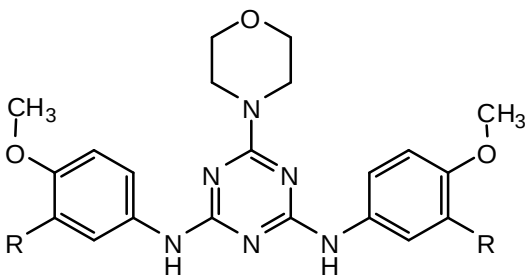


60



61 X=Ar/CH_3Ar/$(C_2H_5)_2$/ $(CH_3)_2$/CH_3CO/CH_3/ OCH_3Ar/NO_2Ar/ ClAr/H, Z=O,NH

The antitumor activity of a series of triaminotriazine derivatives (**62**) was tested for their inhibition actions to colorectal cancer (CRC) cell lines (HCT-116 and HT-29). Most compounds were exhibited moderate anti-proliferative activities on both HCT-116 and HT-29 cell lines at the 10μM level [72]. The antibacterial activity various substituted s-triazines (**63**) with gram-positive and gram-negative bacteria.



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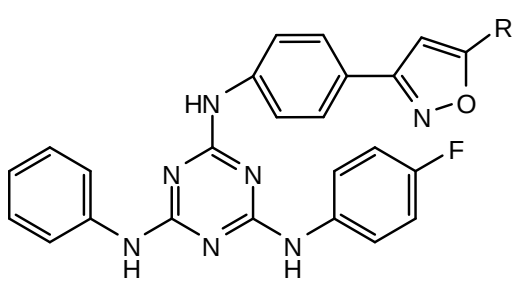
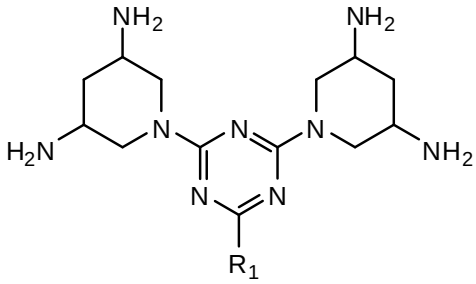
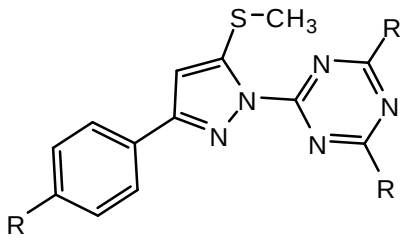


63

The 3,5-Diamino-piperidinyl triazines (**64**) act as antibacterial translation inhibitors [73]. The 2,4,6-trisubstituted triazine heterocycles (**65**) and reported as *in-vitro* antileishmanial activity in the promastigote model. Some compounds have shown 94% inhibition against promastigotes at a concentration of 10μg/mL [13].

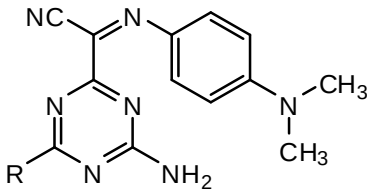


64



65

The 2,4-diamino-1,3,5-triazine derivatives (**66**) showed anticancer activity. The anticancer activity of alkenyl-1,3,5-triazine derivatives (**67**) was exhibited a growth inhibitory effect in low micromolar levels against renal cancer A498 cell line and colon cancer cell line COLO 205 [74,75]. The 2,4,6-trichloro-1,3,5-triazine (**68**) and its derivatives in organic synthesis [76]. A series of melamine-based nitro-heterocyclic showed activity against *Trypanosomatid Parasites* [77].



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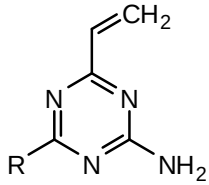

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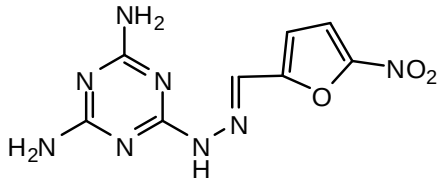
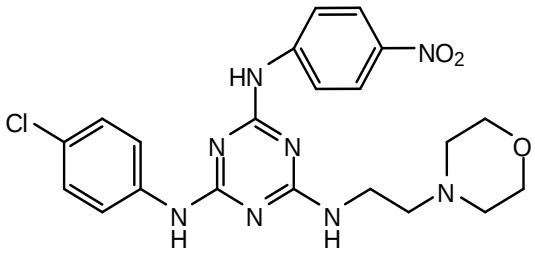


68

Evaluated triaminotriazine DNA helicase inhibitors with antibacterial activity and screened a library in a DNA helicase assay involved the *P. aeruginosa* helicase afforded a triaminotriazine (**69**) inhibitor with good antibacterial activity but associated cytotoxicity toward mammalian cells [78]. The antibacterial activity of 1,3,5-thiadiazines (**70**) and their isomerism into 1,3,5-triazines [79]. The 2,4,6-trisubstituted triazines (**71**) and reported on their antimalarial activity against *P. falciparum*. Some compounds showed MIC in the range of 1-2μg/mL and it showed *in-vitro* antimalarial activity several times more active than cycloguanil [80].



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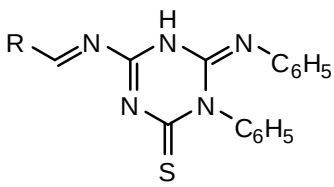

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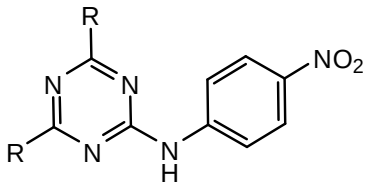
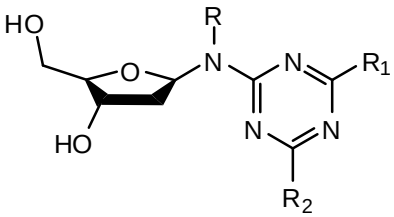


71

The exocyclic triazine nucleosides (**72**) [81], *in-vitro* cytotoxic effects of 2-Alkyl-4,6-diheteroalkyl-1,3,5-triazine compounds were carried out against leukemia and adenocarcinoma derived cell lines [82]. Diaryltriazines and Diarylpyrimidines (**73**) were found to have highly potent Non-nucleoside Reverse Transcriptase Inhibitory action with possible applications as microbicides. *In-vitro* activity of monocyte-derived dendritic cells (MO-DC) and CD4+T cells, the prime targets of sexual human immunodeficiency virus (HIV) transmission, was used to examine the antiviral and immune-suppressive activity of novel classes of non-nucleoside reverse transcriptase inhibitors [83].



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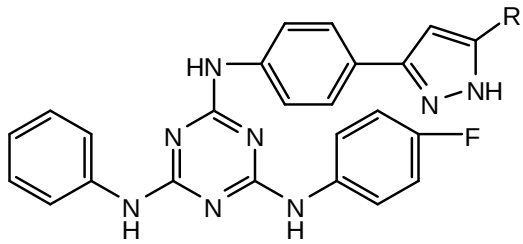
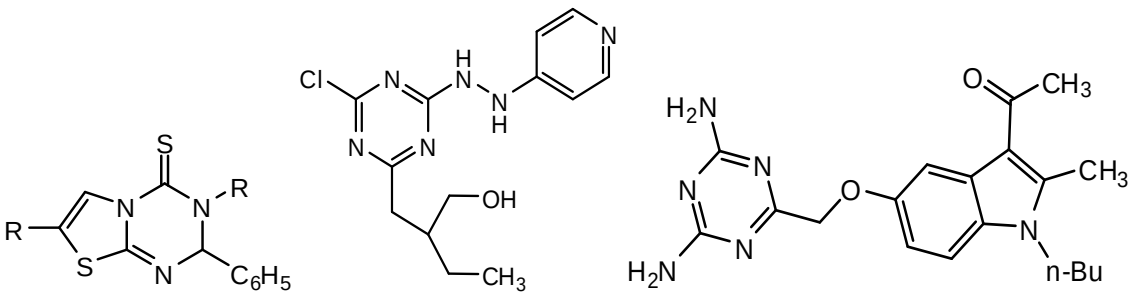


73

The thiadiazolo-s-triazines (**74**) were evaluated for their antiviral activity based on QSAR studies [84]. The derivatives of isoniazid, pyrazinamide, and 2-aminobutanol (**75**) were reported on their anti-tubercular activity [85]. The antibacterial activity of 1-n-butyl-3-acetyl-5-(2,4-diamino-1,3,5-triazin-6-yl)methoxy-2-methylinodole derivatives (**76**) were performed on gram-positive and gram-negative bacteria [86]. The inclusion of carbohydrates and peptides into huge triazine-based testing libraries using automated parallel synthesis. These compounds were useful anti-tubulin agents for cancer and proliferative disease treatments [87].



74 **75** **76**

DRUGS CONTAINING 1, 3, 5-TRIAZINE HAVING ANTICANCER ACTIVITY

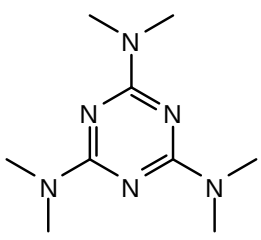
Some isomeric triazines s-triazine and its analogs were useful for a variety of purposes [88]. The most common analogs of 1,3,5-triazine are 2,4,6-triamino-1,3,5-triazine, generally known as cyanuramide or melamine. Anticancer as an altretamine, triethylene melamine (TEM). Trichloro-1,3,5-triazine is the starting point for the preparation of various herbicides like simazine. Another vital analog is 2,4,6-trihydroxy-1,3,5-triazine is known as cyanuric acid [89]. The 2,4,6-trisubstituted(dimethylamino)-1,3,5-triazine is an antitumor compound and known as altretamine used in ovarian cancer treatment. Various 2-aryl amino-4-(4-methoxy anilino)-6-(4-chlorophenyl/phenyl hydrazido)-1,3,5-triazine were showed anti-bacterial activity. The 4,6-bis-allylamino-1,3,5-triazin-2-yl compounds reverse acquired resistance to anti-malarial and anti-cancer compounds [90]. Triazine is also the basic structure of some herbicides, examples are amitole, atrazine, cyanazine, simazine trietazine. A large volume of triazines is used in the preparation of resin modifiers like melamine and benzoguanamine [91]. The 1,3,5-Triazine-2,4,6-triamine is reacted with formaldehyde from a stable thermoset resin. The benzoguanamine (2,4-Diamino-6-phenyl-1,3,5-triazine) is used to raise the thermoset properties of acrylic, alkyl, and formaldehyde resins. Triazine is also useful as chromophore groups in colorants and chlorine linked in triazines undergo nucleophilic substitution reactions well with hydroxyl groups in cellulose fibers. Some triazines are used in pharmaceutical industries as coupling agents for the preparation of peptides in the solid phase, solution, and as a side chain of antibiotics. Triazines are used in preparing bactericides and fungicides. They act as preservatives in oil field applications, industrial deodorant, disinfectant and biocide in water treatment, bleaching agents. Analogs of melamine, 1,3,5-triazine-2,4,6-triamine are reported for various uses.

Altretamine: Altretamine (N2,N2,N4,N4,N6,N6-hexamethyl-1,3,5-triazine-2,4,6-triamine) is an anticancer agent and used to treat ovarian cancer. It is not first-line therapy, but it can be helpful as salvage therapy. It is less toxic than other drugs used for the treatment of ovarian cancer [92]. The mechanism of altretamine as anti-cancer is not known but it is classified as an alkylating anticancer drug. This unique structure is believed to break tumor cells through the construction of the weakly alkylating species formaldehyde, a product of CYP450 that intervened in N-demethylation [93-95].

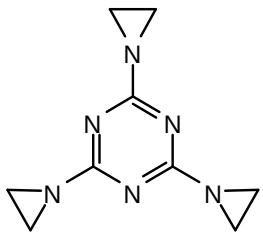
Triethylenemelamine (TEM): Triethylenemelamine (2,4,6-Tris(aziridin-1-yl)-1,3,5-triazine) is used in chemotherapy.

Melamine: Melamine **(**1,3,5-Triazine-2,4,6-triamine) is a trimer of cyanamide, with a 1,3,5-triazine nucleus. Like cyanamide, if mixed with resins, has fire retardant property due to its liberate of nitrogen gas when burned, and has some extra industrial uses. Melamine is also a metabolite of cyromazine, a pesticide [82,91]. Cyromazine can be converted to melamine in plants. Melamine is combined with formaldehyde to form melamine resin, a very stable thermosetting plastic used in formica, and melamine foam, a polymeric cleaning substance. The end products such as countertops, dry erase boards, fabrics, glues, housewares, dinnerware, cooking spoons, guitar saddles, guitar nuts, acoustic foam paneling, and flame retardants. Melamine is the main part of Pigment Yellow 150, a colorant in inks and plastics. The 1,3,5-triazine is used as a reagent in organic preparation, s-triazine is also executed as the equivalent of hydrogen cyanide (HCN).

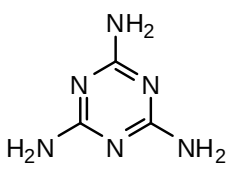
Atrazine: Atrazine is 2-chloro-4-(ethylamino)-6-(isopropylamino)-s-triazine, consist of an s-triazine ring is mainly used as an herbicide. Its use is contentious due to extensive contamination in drinking water and is linked with birth defects and menstrual problems when used by humans at levels below government standards. It was banned in the European Union, it is still one of the commonly used herbicides in the world [82,91]. Atrazine is used to stop the emergence of broadleaf and grassy weeds in most crops. This compound is effective and inexpensive and is well-suited to production systems with narrow profit margins. Atrazine is the most useful herbicide in protection tillage systems, which are considered to prevent soil erosion [96,97].



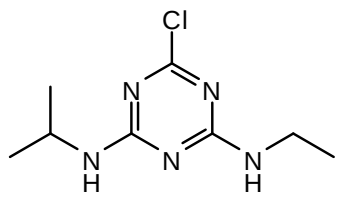
Altretamine



Triethylenemelamine

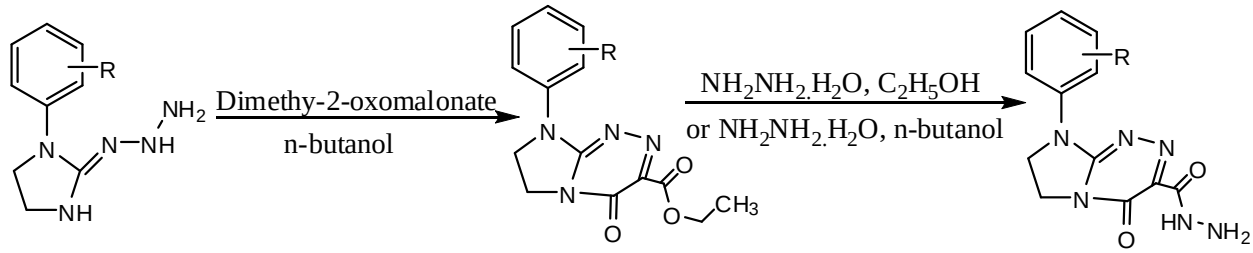


Melamine



Atrazine

CHEMICAL REACTIVITY AND SUBSTITUTION REACTION: The antitumoural properties of novel fused 1,2,4-triazine aryl derivatives (**I-XV**) and synthesis of compounds by different methods [97-101].

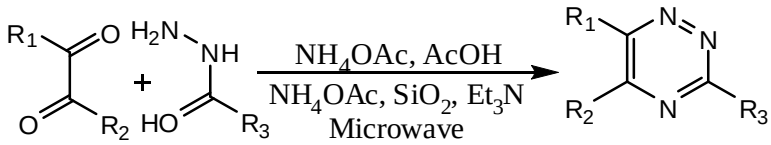


I-V **VI-X** **X1-XV**

I, VI, XI=R=H; **II, VII, XII** R=4-CH_3; **III, VIII, XIII** R= 4-CH_3O;

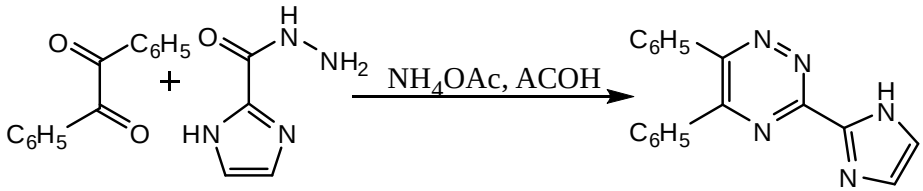
IV, IX, XIV R=3Cl; **V,X,XV** R=3,4-Cl

The new scope of 1,2,4-triazine synthesis by the application of microwave technology **(XVI).**

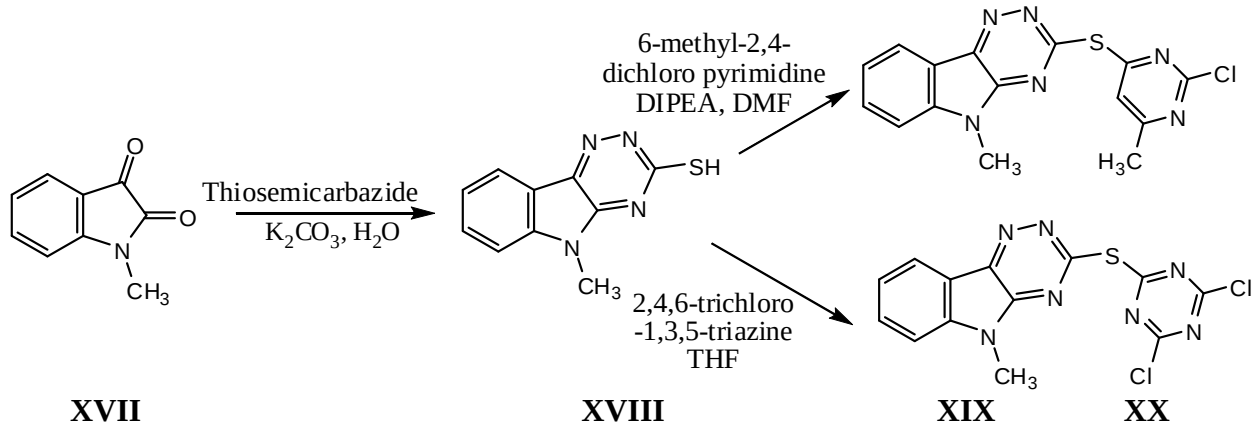


(**XVI**) R_1,R_2,R_3= CH_3, C_2H_5, C_6H_5, $COOC_2H_5$

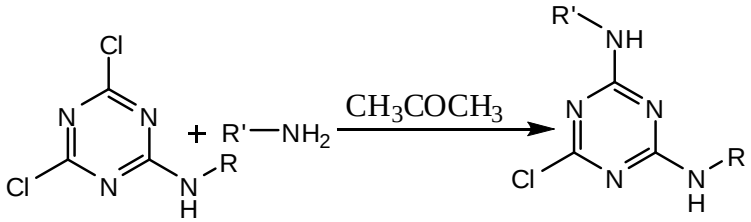
The synthesis and biological evaluation of new [1,2,4]triazino[5,6-b]indol-3-ylthio-1,3,5-triazines and [1,2,4]triazino[5,6-b]indol-3-ylthio-pyrimidines (**XVII**) against *Leishmania donovani* [65].



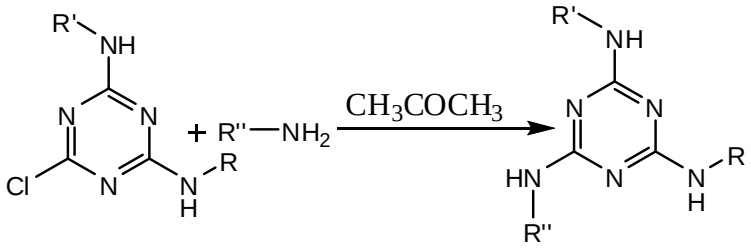
XVI



XVII **XVIII** **XIX** **XX**



XXI **XXII**



XXIII **XXIV**

Reaction of some 2,4,6-trisubstituted amino-1,3,5-triazine derivative [89].

Discussion: Triazines (1,3,5-triazine) are synthesized from cyanic acid amide by trimerization. Some compounds are synthesized using the substitution of triazine by some groups having structural as well as pharmacological importance. Some compounds are synthesized and exhibited different biological screening. These compounds reveal substantive biological activities. The hopeful results are in carrying of the fact that these agents are worth being optimized for some new drugs in the future. Triazines and their derivatives have exhibited a variety of biological activities like antimicrobial, antifungal, anti-HIV, anticancer, anti-inflammatory, analgesic, antihypertensive, cardiotonic, neuroleptic, nootropic, antimalarial, antihistaminic, antiviral, antitubercular, anti-protozoal, cyclin-dependent kinase inhibitors, estrogen receptor modulators, and antiparasitic activities [102-111]. The biological potential of triazine derivatives is cleared from the literature and clinically used drugs.

Conclusion: Triazines are the oldest heterocyclic compounds available. Because of its low cost and easy availability, it emphasizes the sight of researchers for novel synthesis. The triazine derivatives have a wide range of biological activities. As triazine show nucleophilic substitution reaction a series of the compound has been synthesized by using chemical reaction of 2,4,6-trisubstituted-1,3,5-triazines with various nucleophilic reagents like primary and secondary amine. These synthesized compounds exhibit wide spectrum biological activity such as analgesic and anti-inflammatory, antifungal, antibacterial, histamine blockers, antitubercular and antioxidant.

REFERENCES

[1]. Arshad, M., Khan, T.A., Khan, M.A.: 1,2,4-triazine derivatives: Synthesis and biological applications. Inter J Pharma Sci and Res, 5(4), 149-162 (2014).

[2]. Schroeder, H., Grundmann, C.: The Extension of the Pinner Synthesis of Monohydroxy-s-triazines to the Aliphatic Series. 2,4-Dimethyl-s-triazine. J Am Chem Soc., 78, 2447–2451 (1956).

[3]. Schroeder, H., Grundmann, C.: Triazines. XIV. The Extension of the Pinner Synthesis of Monohydroxy-s-triazines to the Aliphatic Series. 2,4-Dimethyl-s-triazine1-3. J. Am. Chem. Soc., 78, 2447–2451 (1956).

[4]. Holla, B.S., Gonsalves, R., Rao, S., Henoy, S., Gopalkrishna, H.N.: Synthesis of some new biologically active bis-(thadiazolotriazines) and bia-(thiadiazolotriazinyl)alkanes. Farmaco, 56, 899 (2001).

[5]. Jaiswal, S., Varma, P.C., O'Neill, L., Duffy, B., McHale, P.: An investigation of the biochemical properties of tetrazines as potential coating additives. Mater Sci Eng C Mater Biol Appl., 33(4), 1925-34 (2013).

[6]. Kidwai, M., Goel, Y., Kumor, R.: Microwave assisted synthesis and antifungal activity of 1,2,4-triazine, 1,2,4-triazole, tetrazole and pyrazoles derivatives. Indian J. chem., 37b, 174 (1998).

[7]. Abd, E.I., Samii, Z.K.: Synthesis and anti-inflammatory activity of some novel 1,3,4-oxadiazole derivatives. J. Chem. Technol, Biotechnol., 53, 143 (1992).

[8]. Abdel-Rahman, R.M., Morsy, J.M., Hanafy, F., Amene, H.A.: Synthesis of heterobicyclic nitrogen systems bearing the 1,2,4-triazine moiety as anti-HIV and anticancer drugs: Part I. Pharmazie, 54, 347, (1999).

[9]. Baliani, A., Bueno, G.J., Stewart, M.L., Yardley, V., Brun, R., Barrett, M.P., Gilbert, I.H.: Design and synthesis of a series of melamine-based nitroheterocycles with activity against Trypanosomatid parasites. J. Med. Chem., 48, 5570–5579 (2005).

[10]. Hay, M.P., Prujin, F.B., Gamage, S.A., Liyanage, H.D., Wilson, W.R.: Targeted 1,2,4-Benzotriazine 1,4-Dioxides: Potent Analogues of the Hypoxia-Selective Cytotoxin Tirapazamine. J. Med. Chem., 47, 475 (2004).

[11]. Henke, B.R., Consler, T.G., Go, N., Hale, R.L., Hohman, D.R., Jones, S.A., Lu, A.T., Moore, L.B., Moore, J.T., Orband-Miller, L.A., Robinett, R.G., Shearin, J., Spearing, P.K., Stewart, E.L., Turnbull, P.S., Weaver, S.L., Williams, S.P., Wisely, G.B., Lambert, M.H.: A new series of estrogen receptor modulators that display selectivity for estrogen receptor beta. J. Med. Chem., 45, 5492–5505 (2002).

[12]. Jensen, N.P., Ager, A.L., Bliss, R.A., Canfield, C.J., Kotecka, B.M., Rieckmann, K.H., Terpinski, J., Jacobus, D.P.: Phenoxypropoxybiguanides, prodrugs of DHFR-inhibiting diaminotriazine antimalarials. J. Med. Chem., 44, 3925–3931 (2001).

[13]. Agarwal, A., Srivastava, K., Puri, S.K., Prem, M.S.: Synthesis of 2,4,6-trisubstituted triazines as antimalarial agents. Bioorg Med Chem, 15, 531-535 (2005).

[14]. Ghaib, A., Menager, S., Verite, P., Lafont, O.: Synthesis of variously 9,9-dialkylated octahydropyrimido [3,4-a]-s-triazines with potential antifungal activity: IL Farmaco, 57, 109–116 (2002).

[15]. Lebreton, S., Newcombe, N., Bradle, M. Antibacterial single-bead screening. Tetrahedron, 59, 10213–10222 (2003).

[16]. Lubbers, T., Angehrn, P., Gmunder, H., Herzig, S., Kulhanek, J.: Design, synthesis, and structure-activity relationship studies of ATP analogues as DNA gyrase inhibitors. Bioorg. Med. Chem. Lett., 10, 821–826 (2000).

[17]. McKay, G.A., Reddy, R., Arhin, F., Belley, A., Lehoux, D., Moeck, G., Sarmiento, I., Parr, T.R., Gros, P., Pelletier, J., Far, A.R.: Triaminotriazine DNA helicase inhibitors with antibacterial activity. Bioorg. Med. Chem. Lett., 16, 891–896 (2005).

[18]. Malwad, V.V., Shirodkar, J.M.: Synthesis and Antibacterial Activity of New Tetrazole Derivatives. Ind. J. Chem., 42B, 621–626 (2003).

[19]. Srinivas, K., Srinivas, U., Harakishore, K., Jayathirha Rao, V., Bhanuprakash, K., Murthy, U.S.N.: Synthesis and antibacterial activity of various substituted s-triazines. Bioorg. Med. Chem. Lett., 15, 1121-1123 (2005).

[20]. Nishimura, N., Kato, A., Maeba, I. Synthesis of pyrrolo[2,1-f][1,2,4]triazine C-nucleosides. Isosteres of sangivamycin, tubercidin, and toyocamycin. Carbohydr Res., 331(1), 77-82 (2001).

[21]. Sarmah, K.N., Patel, T.V.: Synthesis, characterization, antimicrobial studies of certain s-triazine derived compounds and analogues. Arch Appl Sci Res, 3(6), 428-436 (2011).

[22]. Klenke, B., Stewart, M., Barrett, M.P., Brun, R., Gilbert, I.H. Synthesis and biological evaluation of s-triazine substituted polyamines as potential new anti-trypanosomal drugs. J Med Chem., 44(21), 3440-52 (2001).

[23]. Candiani, G., Frigerio, M., Viani, F., Verpelli, C., Sala, C., Chiamenti, L., Zaffaroni, N., Folini, M., Sani, M., Panzeri, W., Zanda, M.: Dimerizable redox-sensitive triazine-based cationic lipids for in vitro gene delivery. ChemMedChem., 2(3), 292-6 (2007).

[24]. Iino, Y., Karakida, T., Sugamata, N., Andoh, T., Takei, H., Takahashi, M., Yaguchi, S., Matsuno, T., Takehara, M., Sakato, M., Kawashima, S., Morishita, Y.: Antitumor effects of SEF19, a new nonsteroidal aromatase inhibitor, on 7,12-dimethylbenz[a]anthracene-induced mammary tumors in rats. Anticancer Res., 18(1A), 171-6 (1998).

[25]. Brzozowski, Z., Saczewski, F., Gdaniec, M. Synthesis, structural characterization and antitumor activity of novel 2,4-diamino-1,3,5-triazine derivatives. Eur J Med Chem., 35(12), 1053-64 (2000).

[26]. Smolin E. M. and Ropoport L. s-Triazines and Derivatives. Eds; Interscience publisher, New York, 1959.

[27]. Matsuno, T., Karo, M., Sasahara, H., Watanabe, T., Inaba, M., Takahashi, M., Yaguchi, S.I., Yoshioka, K., Sakato, M., Kawashima, S.: Synthesis and antitumor activity of benzimidazolyl-1,3,5-triazine and benzimidazolylpyrimidine derivatives. Chem Pharm Bull., 48(11), 1778-81 (2000).

[28]. Srinivas, K., Srinivas, U., Bhanuprakash, K., Harakishore, K.: Synthesis and antibacterial activity of various substituted s-triazines. Eur J Med Chem., 41, 1240-1246 (2006).

[29]. Raja, S.K., Ashok, K., Srivastava, K., Puri, S.K., Chauhan Prem, M.S.: Synthesis and bio-evaluation of hybrid 4-aminoquinoline triazines as a new class of antimalarial agents. Bioorg Med Chem., 18, 6530-6533 (2008).

[30]. Hassanen, J.A., Ashour, H.K.H., Zkaria, S.H.A.: Synthesis, Biological Activity and Mass Spectra Investigation of 1,2,4-Triazino-[2,1-a]-1,2,4-triazine Derivatives. Der Pharma Chemica., 4(5), 2091-2106 (2012).

[31]. Dawane, B.S., Kadam, S.N., Shaikh, B.M.: An efficient synthesis of 1, 2, 4-triazine derivatives and in vitro antimicrobial activity. Der Pharmacia Lett., 2(4), 126-131 (2010).

[32]. Pandey, S.K., Singh, A., Nizamuddin, A. Antimicrobial studies of some novel quinazolinones fused with [1,2,4]-triazole, [1,2,4]-triazine and [1,2,4,5]-tetrazine rings. Eur. J. Med. Chem., 44, 1188-1197 (2009).

[33]. Sztanke, K., Fidecka, S., dzierska, E.K.V., Karczmarzyk, Z., Pihlaja, K., Matosiuk, D.: Antinociceptive activity of new imidazolidine carbonyl derivatives: Part 4. Synthesis and pharmacological activity of 8-aryl-3,4-dioxo-2H,8H-6,7-dihydroimidazo[2,1-c] [1,2,4]triazines: Eur. J. Med. Chem., 40, 127–134 (2005).

[34]. Abdel-Monem, W.R. Synthesis and Antimicrobial Activity of Some New Nitrogen Heterocyclic Systems Bearing 1,2,4-Tiazine Moiety. Global J Sci Front Res Chem., 12(5), (2012).

[35]. Sztanke, K., Rzymowska, J., Niemczyk, M., Dybała, I., Kozioł, A.E.: Synthesis, crystal structure and anticancer activity of novel derivatives of ethyl 1-(4-oxo-8-aryl-4,6,7,8-tetrahydroimidazo [2,1-c][1,2,4]triazin-3-yl)formate. Eur. J. Med. Chem., 41, 539–547 (2006).

[36]. Styskala, J., Styskalova, L., Slouka, J., Hajduch, M.: Synthesis of 2-aryl-4-(benzimidazol-2-yl)-1,2-dihydro[1,2,4]triazino-[4,5-a]benzimidazol-1-one derivatives with preferential cytotoxicity against carcinoma cell lines. Eur. J. Med. Chem., 43, 449-455 (2008).

[37]. Barraja, P., Diana, P., Lauria, A., Montalbano, A., Almerico, A.M., Dattolo, G., Cirrincione, G.: Synthesis and Antiproliferative Activity of [1,2,4]Triazino[4,3-a]indoles. Anticancer Res., 24, 3775-3780 (2004).

[38]. Diana, P., Barraja, P., Lauria, A., Montalbano, A., Almerico, A.M., Dattolo, G., Cirrincione, G.: Pyrrolo[2,1-c][1,2,4,]triazines from 2-Diazopyrroles: Synthesis and Antiproliferative Activity. Eur. J. Med. Chem., 37, 267–272 (2002).

[39]. Sztanke, K., Rzymowska, J., Niemczyk, M., Dyba1a, I., Kozio, A.E.: Novel derivatives of methyl and ethyl 2-(4-oxo-8-aryl-2H-3,4,6,7-tetrahydroimidazo[2,1-c][1,2,4]triazin-3-yl)acetates from biologically active 1-aryl-2-hydrazinoimidazolines: Synthesis, crystal structure and anti-proliferative activity. Eur. J. Med. Chem., 41, 1373-1384 (2006).

[40]. Gucky, T., Frysova, I., Slouka, J., Hajduch, M., Dzubak, P.: Cyclocondensation reaction of heterocyclic carbonyl compounds, Part XIII: Synthesis and cytotoxic activity of some 3,7-diaryl-5-(3,4,5-trimethoxyphenyl)pyrazolo[4,3-e][1,2,4]triazines. Eur. J. Med. Chem., 44, 891-900 (2009).

[41]. Irannejad, H., Amini, M., Khodagholi, F., Ansari, N., Tusi, S.K., Sharifzadeh, M., Shafiee, A.: Synthesis and in vitro evaluation of novel 1, 2, 4-triazine derivatives as neuroprotective agents. Bioorg Med. Chem., 18, 4224–4230 (2010).

[42]. Ali, T.E.S.: Synthesis of some novel pyrazolo[3,4-b]pyridine and pyrazolo[3,4-d]pyrimidine derivatives bearing 5,6-diphenyl-1,2,4-triazine moiety as potential antimicrobial agents. Eur. J. Med. Chem., 44, 4385–4392 (2009).

[43]. Cai, Z., Wei, D., Borzilleri, R.M., Qian, L., Kamath, A., Mortillo, S., Wautlet, B., Henley, B.J., Jeyaseelan, R., Tokarski, S.J., Hunt, J.T., Bhide, R.S., Fargnoli, J., Lombardo, L.J. Synthesis, SAR, and Evaluation of 4-[2,4-Difluoro-5-(cyclopropylcarbamoyl)phenylamino]pyrrolo[2,1-f] [1,2,4] triazine-based VEGFR-2 kinase inhibitors. Bioorg: Med. Chem. Lett., 18, 1354–1358 (2008).

[44]. Ciciani, G., Coronnello, M.A., Guerrini, G., Selleri, S., Cantore, M., Failli, P., Mini, E., Costanzo, A.: Synthesis of new pyrazolo[5,1-c][1,2,4] benzotriazines, pyrazolo[5,1-c]pyrido[4,3-e][1,2,4] triazines and their open analogues as cytotoxic agents in normoxic and hypoxic conditions. Bioorg. Med. Chem., 16, 9409–9419 (2008).

[45]. EL-Massry, A.M., Asal, A.M., Khattab, S.N., Haiba, N.S., Awney, H.A., Helmy, M., Langer, V., Amer, A.: Synthesis and structure elucidation of novel fused 1,2,4-triazine derivatives as potent inhibitors targeting CYP1A1 activity. Bioorg. Med. Chem., 20, 2624–2637 (2012).

[46]. Krauth, F., Dahse, H.M., Ruttinger, H.H., Frohberg, P. Synthesis and characterization of novel 1,2,4-triazine derivatives with antiproliferative activity: Bioorg. Med. Chem., 18, 1816–1821 (2010).

[47]. Prabhakaran, J., Parsey, R.V., Majo, V.J., Hsiung, S-C., Milak, M.S., Tamir, H., Simpson, N.R., Heertum, R.L.V., Manna, J.J., Kumara, J.S.D.: Synthesis, in vitro and in vivo evaluation of [O-methyl-11C] 2-{4-[4-(3-methoxyphenyl)piperazin-1-yl]-butyl}-4-methyl-2H-[1,2,4]-triazine-3,5-dione: A novel agonist 5-HT1A receptor PET ligand. Bioorg. Med. Chem. Lett., 16, 2101–2104 (2006).

[48]. Zeller, J., Turbiak, A.J., Powelson, I.A., Lee, S., Sun, D., Showalter, H.D.H., Fearon, E.R.: Investigation of 3-aryl-pyrimido[5,4-e][1,2,4]triazine-5,7-diones as small molecule antagonists of β -catenin/TCF transcription. Bioorg. Med. Chem. Lett., 23, 5814–5820 (2013).

[49]. Lv, W., Banerjee, B., Molland, K.L., Seleem, M.N., Ghafoor, A., Hamed, M.I., Wan, B., Franzblau, S.G., Mesecar, A.D., Cushman, M.: Synthesis of 3-(3-aryl-pyrrolidin-1-yl)-5-aryl-1,2,4-triazines that have antibacterial activity and also inhibit inorganic pyrophosphatase. Bioorg. Med. Chem., 22, 406–418 (2014).

[50]. Sangshetti, J.N., Shinde, D.B.: One pot synthesis and SAR of some novel 3-substituted 5,6-diphenyl-1,2,4-triazines as antifungal agents. Bioorg. Med. Chem. Lett., 20, 742–745 (2010).

[51]. Ashour, H.M., Shaaban, O.G., Rizk, O.H., El-Ashmawy, I.M.: Synthesis and biological evaluation of thieno [2′,3′:4,5]pyrimido[1,2-b][1,2,4]triazines and thieno[2,3-d][1,2,4] triazolo [1,5-a] pyrimidines as anti-inflammatory and analgesic agents. Eur. J. Med. Chem., 62, 341-351 (2013).

[52]. Ban, K., Duffy, S., Khakham, Y., Avery, V.M., Hughes, A., Montagnat, O., Katneni, K., Ryan, E., Baell, J.B.: 3-Alkylthio-1,2,4-triazine dimers with potent antimalarial activity. Bioorg. Med. Chem. Lett., 20, 6024–6029 (2010).

[53]. Deeb, A., El-Mariah, F., Hosny, M. Pyridazine derivatives and related compounds. Part 13: Synthesis and antimicrobial activity of some pyridazino[3',4':3,4]pyrazolo[5,1-c]-1,2,4-triazines: Bioorg. Med. Chem. Lett., 14, 5013–5017 (2004).

[54]. Zhou, Y., Wei, L., Brady, T.P., Redddy. P.S.M.M., Nguyen, T., Chen, J., Au, Q., Yoon, S., Yip, G., Zhang, B., Barber, J.R., Chung Ng, S.: Pyrimido[5,4-e][1,2,4]triazine-5,7(1H,6H)-dione derivatives as novel small molecule chaperone amplifiers: Bioorg. Med. Chem. Lett., 19, 4303–4307 (2009).

[55]. Schmitz, W.D., Brenner, A.B., Bronson, J.J., Ditta, J.L., Griffin, C.R., Li, Y-W., Lodge, N.J., Molski, T.F., Olson, R.E., Zhuo, X., Macor, J.E.: 5-Arylamino-1,2,4-triazin-6(1H)-one CRF1 receptor antagonists. Bioorg. Med. Chem. Lett., 20, 3579–3583 (2010).

[56]. Irannejad, H., Kebriaieezadeh, A., Zarghi, A., Montazer-Sadegh, F., Shafiee, A., Assadieskandar, A., Amini, M. Synthesis, docking simulation, biological evaluations and 3D-QSAR study of 5-Aryl-6-(4-methylsulfonyl)-3-(metylthio)-1,2,4-triazine as selective cyclooxygenase-2 inhibitors. Bioorg. Med. Chem., 22, 865–873 (2014).

[57]. Majo, V.J., Milak, M.S., Prabhakaran, J., Mali, P., Savenkova, L., Simpson, N.R., Mann, J.J., Parsey, R.V., Kumar, J.S.D. Synthesis and in vivo evaluation of [^{18}F]2-(4-(4-(2-(2-fluoroethoxy) phenyl)piperazin-1-yl)butyl)-4-methyl-1,2,4-triazine-3,5(2H,4H)-dione ([^{18}F]FECUMI-101) as an imaging probe for 5-HT1A receptor agonist in nonhuman primates. Bioorg. Med. Chem., 21, 5598–5604 (2013).

[58]. Carling, R.W., Russell, M.G.N., Moore, K.W., Mitchinson, A., Guiblin, A., Smith, A., Wafford, K.A., Marshall, G., Atack, J.R., Street, L.J.: 2,3,7-Trisubstituted pyrazolo[1,5-d][1,2,4]triazines: Functionally selective GABAA α 3-subtype agonists. Bioorg. Med. Chem. Lett., 16, 3550–3554 (2006).

[59]. Xin M, Zhang, L., Tang, F., Tu, C., Wen, J., Zhao, X., Liu, Z., Cheng, L., Shen, H.: Design, synthesis, and evaluation of pyrrolo[2,1-f][1,2,4]triazine derivatives as novel hedgehog signaling pathway inhibitors. Bioorg. Med. Chem., 22, 1429–1440 (2014).

[60]. Jennings, A.S.R., Lewis, R.T., Russell, M.G.N., Hallett, D.J., Street, L.J., Castro, J.L., Atack, J.R., Cook, S.M., Lincoln, R., Stanley, J., Smith, A.J., Reynolds, D.S., Sohal, B., Pike, A., Marshall, G.R., Wafford, K.A., Tye, S.J.: Imidazo[1,2-b][1,2,4]triazines as a2/a3 subtype selective GABAA agonists for the treatment of anxiety. Bioorg. Med. Chem. Lett., 16, 1477-1480 (2006).

[61]. Sampognaro, A.J., Wittman, M.D., Carboni, J.M, Chang, C., Greer, A.F., Hurlburt, W.W., Sack, J.S., Vyas, D.M.: Proline isosteres in a series of 2,4-disubstituted pyrrolo[1,2-f][1,2,4]triazine inhibitors of IGF-1R kinase and IR kinase. Bioorg. Med. Chem. Lett., 20, 5027–5030 (2010).

[62]. Wrobleski, S.T., Lin, S., Hynes, J., Wu H, Jr., Pitt, S., Ren Shen, D., Zhang, R., Gillooly, K.M., Shuster, D.J., McIntyre, K.W., Doweyko, A.M., Kish, K.F., Tredup, J.A., Duke, G.J., Sack, S.J., McKinnon, M., Dodd, J., Barrish, J.C., Schievenb, G.L., Leftheris, K.: Synthesis and SAR of new pyrrolo[2,1-f][1,2,4]triazines as potent p38a MAP kinase inhibitors. Bioorg. Med. Chem. Lett., 18, 2739–2744 (2008).

[63]. Zhan, P., Li, X., Li, Z., Chen, X., Tian, Y., Chen, W., Liu, X., Pannecouque, C., De Clercq, E.: Structure-based bioisosterism design, synthesis and biological evaluation of novel 1,2,4-triazin-6-ylthioacetamides as potent HIV-1 NNRTIs. Bioorg. Med. Chem. Lett., 22, 7155–7162 (2012).

[64]. El-Hady, H.A., El-Sakka, S.S.: Syntheses and antitumor activity of some 1,2,4-triazine derivatives. Inter J Innovative Res in Sci, Engin and Tech, 3(4), 10854-10860 (2014).

[65]. Gupta, L., Sunduru, N., Verma, A., Srivastava, S., Gupta, S., Goyal, N., Chauhan, P.M.S.: Synthesis and biological evaluation of new [1,2,4]triazino[5,6-b]indol-3-ylthio-1,3,5-triazines and [1,2,4]triazino[5,6-b]indol-3-ylthio-pyrimidines against Leishmania donovani. Eur. J. Med. Chem, 45, 2359-2365 (2010).

[66]. Zhou, C., Jaeki, M., Zhigang, L., Young, A.: Synthesis and biological evaluation of novel 1,3,5-triazine derivatives as antimicrobial agents. Bioorg Med Chem., 8, 1308-1311 (2008).

[67]. Muller, P.R., Dominique, S., Christian, M., Guillaume, P.: Cyclic nucleotide phosphodiesterase type 4 inhibitors: Evaluation of pyrazolo[1,5-a]-1,3,5-triazine ring system as an adenine bioisostere. Eur J Med Chem., 43, 816-829 (2008).

[68]. Deshmukh, M.B., Deshmukh, S.A., Jagtap, S.S., Mulik, A.R. Synthesis and study of biological activity of some new 1, 4-benzothiazines. Indian J Chem., 46B, 852-859 (2007).

[69]. Singh, V., Tiwari, M.: 3D-QSAR analysis of cycloguanil derivatives highly active against A16V+S108T mutant of dihydrofolate reductase resistant strain (T9/94) of Plasmodium falciparum. Indian J Chem., 46B, 1042-1046 (2007).

[70]. Desai, A.D., Mahajan, H.D., Chikhalia, H.K.: Synthesis of novel aliphatic thiourea derivative containing s-triazine moiety as potential antimicrobial agents. Indian J Chem., 46B, 1169-1173 (2007).

[71]. Arya, K., Dandia, A.: Synthesis and cytotoxic activity of trisubstituted-1,3,5-triazines. Bioorg. Med. Chem., 17, 3298-3304 (2007).

[72]. Mingfang, Z., Chenghui, X., Jianwei, M., Yan, S.: Synthesis and antitumor evaluation of a novel series of triaminotriazine derivatives. Bioorg Med Chem., 15, 1815-1827 (2007).

[73]. Zhou, Y., Sun; Z., Froelich, J.M.: Structure–activity relationships of novel antibacterial translation inhibitors: 3,5-Diamino-piperidinyl triazines. Bioorg Med Chem., 16M, 5451-5456 (2006).

[74]. Sączewski, F., Bułakowska, A., Bednarski, P.: Synthesis and anticancer activity of novel 2,4-diamino-1,3,5-triazine derivatives. Eur J Med Chem., 41, 219-25 (2006).

[75]. Sączewski, F., Bułakowska, A.: Synthesis, structure and anticancer activity of novel alkenyl-1,3,5-triazine derivatives. Eur J Med Chem., 41, 611-615 (2006).

[76]. Blotny G. Recent applications of 2, 4,6-trichloro-1,3,5-triazine and its derivatives in organic synthesis. Tetrahedron, 62, 9507-9522 (2006).

[77]. Gorka, J.B., Mhairi, L.S., Vanessa, Y., Reto, B., Michael, P.B.: Design and Synthesis of a Series of Melamine-based Nitroheterocycles with Activity against Trypanosomatid Parasites. J. Med. Chem., 48(17), 5570–5579 (2005).

[78]. McKay, G.A., Reddy, R., Arhin, F., Belley, A., Lehoux, D., Moeck, G., Sarmiento, I., Parr, T.R., Gros, P., Pelletier, J., Far, A.R.: Triaminotriazine DNA helicase inhibitors with antibacterial activity. Bioorg Med Chem., 16, 1286-1290 (2006).

[79]. Pradip, P., Berad, B.N.: Synthesis and antibacterial activity of 1,3,5-thiadiazines and their isomerism into 1,3,5-triazines. Indian J Chem., 44B, 638-639 (2005).

[80]. Sunduru, N., Agarwal, A., Sanjay, B.K.: Synthesis of 2,4,6-trisubstituted pyrimidine and triazine heterocycles as antileishmanial agents. Bioorg Med Chem., 14, 7706-7715 (2006).

[81]. Mulwad, V.V., Jyoti, M.: Synthesis of biologically active thiazolo-benzopyranyl-s-triazine derivative. Indian J Chem., 42B, 621-626 (2003).

[82]. Menicagli, R., Simona, S., Giovanni, S., Francesca.: In Vitro Cytotoxic Activities of 2-Alkyl-4,6-diheteroalkyl-1,3,5-triazines. J. Med. Chem., 47(19), 46–47 (2004).

[83]. Xiong, Y-Z., Chen, F-E., Balzarini, J., Clercq, E.D.: Structural modulation of diaryltriazine with potent anti-HIV activity. Eur J Med Chem., 43, 1230-1236 (2008).

[84]. Pandey, V.K., Tusi, Z., Tandon, M.: Synthesis of thiadiazolo-s-triazines for their antiviral activity based on QSAR studies. Indian J. Chem., 42B, 2583-2588 (2003).

[85]. Shabadi, C.V., Shelar, B.A., Shelar, A.R.: New derivatives of isoniazide,pyrazinamide and 2-aminobutanol and their anti-tuberculosis activity. Indian J Chem., 38B, 508-510 (1999).

[86]. Gadaginamath, G.S., Kavali, R.S., Pujar, S.R.: Synthesis and antibacterial activity of some new1-n-butyl-3-acetyl-5-(2,4-diamino-1,3,5-triazin-6-yl)methoxy-2-methylinodole derivatives. Indian J Chem., 38B, 1226-1228 (1999).

[87]. Gustafson, G.R., Baldino, C.M., O'Donnell, M-M.E., Sheldon, A., Tarsa, R.J., Verni, C.J., Coffen, D.L.: Incorporation of carbohydrates and peptides into large triazine-based screening libraries using automated parallel synthesis. Tetrahedron Let., 54, 4051-4065 (1998).

[88]. Dreyer, C., Blume, A., Bauer, M., Bauer, J.: Fourth International Electronic Conference on Synthetic Organic Chem, 1-30 (2000).

[89]. Basedia, D.K., Dubey, B.K., Shrivastava, B.: A Review on Synthesis and Biological activity of Heterocyclic Compounds bearing 1,3,5-Triazine Lead Moiety. Am J PharmTech Res, 1(4), 174-193 (2011).

[90]. Gupta, L., Pal, P., Khan, S.: Synthesis and cytotoxicity of (tetrahydro-b-carboline)-1,3,5-triazine hybrids as anticancer agents. Eur J Med Chem., 45, 2265-2276 (2010).

[91]. Wackett, L.P., Sadowsky, M.J., Martinez, B., Shapir, N.: Biodegradation of atrazine and related s-triazine compounds: from enzymes to field studies. Appl. Microbiol. Biotechnol., 58(1), 39-45 (2002).

[92]. Cai, B., Han, Y., Liu, B., Ren, Y., Jiang, S.: Isolation and characterization of an atrazine-degrading bacterium from industrial wastewater in China. Lett Appl Microbiol., 40, 435-340 (1998).

[93]. Keldsen, N., Havsteen, H., Vergote, I., Bertelsen, K., Jakobsen, A.: Altretamine (hexamethyl melamine) in the treatment of platinum-resistant ovarian cancer: a phase II study. Gynecol Oncol., 88(2), 118–22 (2003).

[94]. Chan, J.K., Loizzi, V., Manetta, A., Berman, M.L.: Oral altretamine used as salvage therapy in recurrent ovarian cancer. Gynecol Oncol., 92(1), 368–71 (2004).

[95]. Malik, I.A.: Altretamine is an effective palliative therapy of patients with recurrent epithelial ovarian cancer. J Clin Oncol., 31(2), 69–73 (2001).

[96]. Crawford, J.J., Sims, G.K., Mulvaney, R.L., Radosevich, M.: Biodegradation of atrazine under denitrifying conditions. Appl Microbiol Biotechnol., 49, 618-623 (1998).

[97]. Damia, G., Incalci, D.M.: Clinical pharmacokinetics of altretamine. Clin Pharmacokinetics, 1998, 28(6), 439–48. Bichat, F., Sims, G.K., Mulvaney, R.L.: Microbial utilization of heterocyclic nitrogen from atrazine. Soil Sci Soc Am J., 63, 100-110 (1998).

[98]. Sztanke, K., Pasternak, K., Rzymowska, J., Sztanke, M., Szerszen, M.K.: Synthesis, structure elucidation and identification of antitumoural properties of novel fused 1,2,4-triazine aryl derivatives. Eur. J. Med. Chem., 43, 1085-1094 (2008).

[99]. Partridge, M.W., Stevens, M.F.G.J.: Pyrazolo-as-triazines: Part I. Chem. Soc., 1127 (1996).

[100]. Erickson, J.G. Chapter II.: The 1,2,4-Triazines. Chem Heterocycl. Comp., 10, 44 (1956).

[101]. Hysell, M., Siegel, J.S., Tor, Y.: Synthesis and stability of exocyclic triazine nucleosides. Org Biomol Chem., 3, 2946-2952 (2005).

[102]. Aksenov, A., Aksenova, V.: Use of the ring opening reactions of 1,3,5-triazines in organic synthesis. Chem Heterocyclic Comp, 45, 130-150 (2009).

[103]. Anton, V.D., Anna, V.D., Wai, K.C.: Synthesis and biological activity of fluorinated 7-aryl-2-pyridyl-6,7-dihydro[1,2,4]triazolo[1,5-a][1,3,5]triazin. J Fluorine Chem., 129, 429-434 (2008).

[104]. Anton, V.D., Anna, V.D.: Synthesis of regioisomeric5(7)-amino-6,7(4,5)-dihydro [1,2,4] triazolo[1,5-a][1,3,5]triazines. Tetrahedron, 63, 12888-12895 (2007).

[105]. Anton, V.D., Giorgia, P., Anna, V.D., Keung, A.C. A convenient method for the synthesis of 7-amino-substituted 1,2,4-triazolo[1,5-a][1,3,5]triazin-5-amines. Tetrahedron Lett, 49, 7180-7183 (2008).

[106]. Ashok, K., Srivastava, K., Raja, S.K., Puri, S.K., Prem, C.M.S.: Synthesis and bioevaluation of hybrid 4-aminoquinoline triazines as a new class of antimalarial agents. Bioorg. Med. Chem., 18, 6530-6533(2008).

[107]. Caroline, C., Sophie, G., Nohad, G., Michel, V., Christiane, G.: Terminal alkyne-functionalized triazine by Sonogashira coupling: synthesis of a potential cell signaling inhibitor via click chemistry. Tetrahedron Lett., 49, 4542-4545 (2008).

[108]. Lee C-H., Jin, G.F., Yoon, J.H., Jung, Y.J., Lee, J-D., Cho SD.: Synthesis and characterization of polar functional group substituted mono- and bis-(o-carboranyl)-1,3,5-triazine derivatives. Tetrahedron Lett., 49, 159-164 (2008) .

[109]. Mane, D.V., Chavan, V.P., Mane, A.S., Bhawsar, S.B., Shingare, S.B.: Synthesis and biological activity of 2,4-bis(substituted aniline)-6-(pyrazoyl)-s-triazines. Indian J heterocyclic chem., 19, 271-274 (2000).

[110]. Poul, P.L., Caro, B., Guen, R-L.F.: Selective reactivity of diamino Fischer-type carbene complexes towards 2,6-disubstituted and 2,4,6-trisubstituted pyrylium salts and 2,4,6-trichloro-1,3,5-triazine. J Organometallic Chem., 69, 3599-3605(2007).

[111]. Solankee, A., Kapadia, K., Solankee, P., Solankee, S.: Synthesis and studies of some novel s-triazine based aminopyrimidines, isoxazoles and 1,5-benzo- thiazepines. Indian J Chem., 46B, 1707-1712 (2007).