WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.045
Volume 3, Issue 8, 1100-1167. Review Article ISSN 2277 – 7105

# REVIEW OF PREPARATION, MOLECULAR SPECTROSCOPY AND BIOLOGICAL ACTIVITIES OF 1, 3, 5-TRIAZINES

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Article Received on
13 August 2014,

Revised on 09 Septe 2014,
Accepted on 03 Oct 2014

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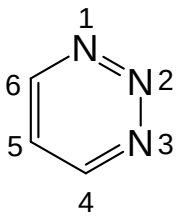
## ABSTRACT

The existing research in the field of drug discovery and development focused on the synthesis, characterization and biological evaluation of some new substituted 1,3,5-triazines as potential pharmacological agents against various multifactorial diseases. The present review focuses on the methods preparation, molecular spectroscopy and biological activities of various substituted 1, 3, 5-triazines. This review summarizes substituted 1,3,5-triazines which were biologically active with special attention on the most potent compounds.

**KEYWORDS:** Substituted 1, 3, 5-triazines, drug discovery and development.

## INTRODUCTION

Triazines are a class of organic nitrogen-containing six-membered heterocyclic compounds known for a long period of time. They can structurally be existing as three isomers varied with their position of nitrogen atoms on the benzene ring, and are referred to as 1, 2, 3-triazine (1), 1,2,4-triazine (2) and 1,3,5-triazine (3). In particular, considerable attention has been devoted to the development of 1, 3, 5-triazine derivatives in comparison with 1, 2, 3-triazine and 1, 2, 4-triazine derivatives, due to their variety of applications in different fields [1, 2].



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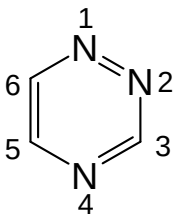

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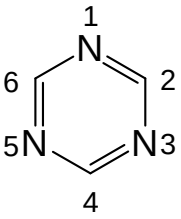
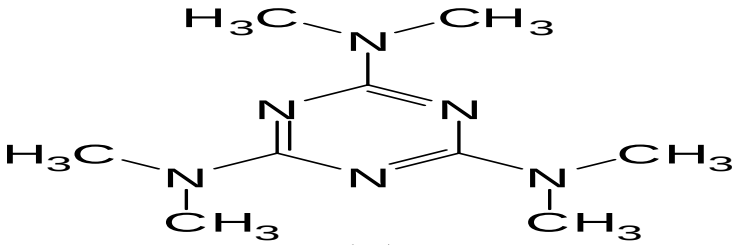


**(3)**

1, 3, 5-Triazines can also be called as symmetric or *s*-triazines. The chemistry of this group of compounds has been studied intensively since past two centuries due to their wide spread applications in the pharmaceutical, textile, plastic and rubber industries and are used as pesticides, dyestuffs, optical bleaches, explosives and surface active agents. In recent times, several studies have been carried out on the antitumor activity of 1, 3, 5-triazines. Some of these analogues, hexamethylmelamine (4), almitrine (5) and irsogladine (6) are clinically used as anticancer agents. Baker triazines (4, 6-Diamino-2, 2-dimethyl-1, 2-dihydro-1,3,5-triazine based analogs) are becoming increasingly important as pharmaceuticals. Baker triazine antifol (7) had been undergoing clinical trials as a drug candidate in cancer chemotherapy [3-8].



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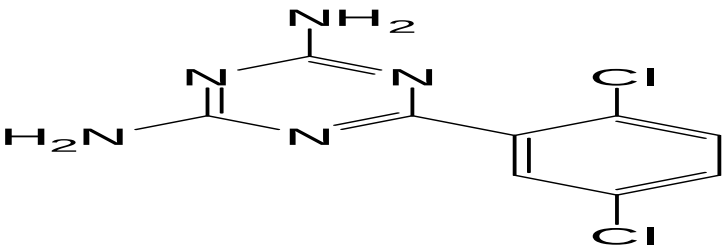

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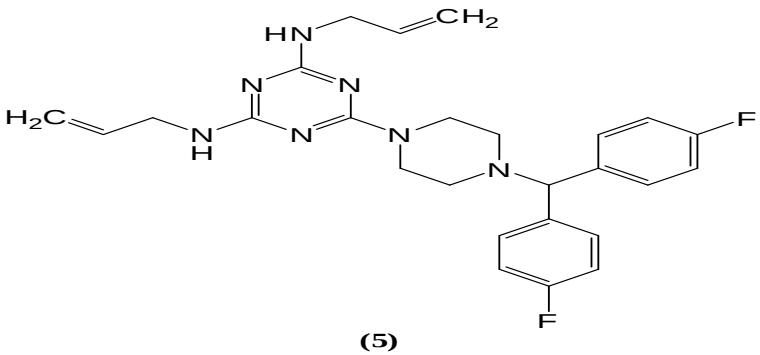

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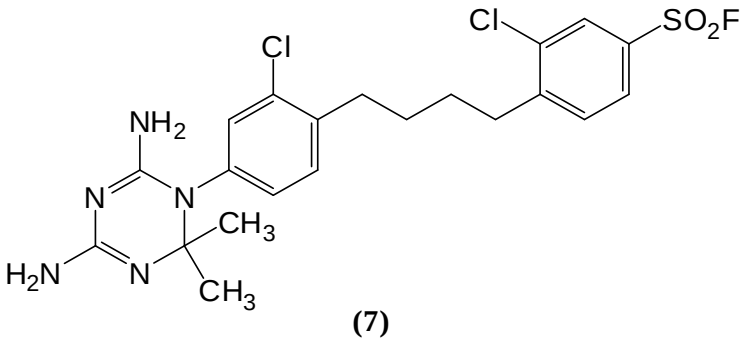
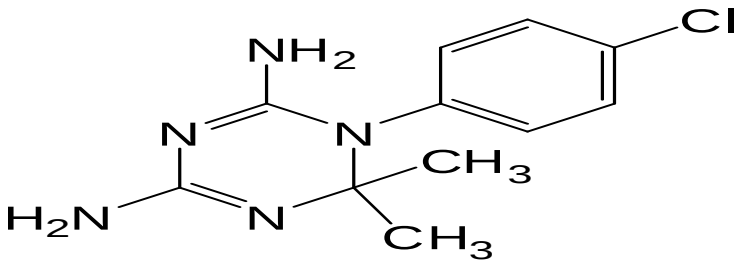


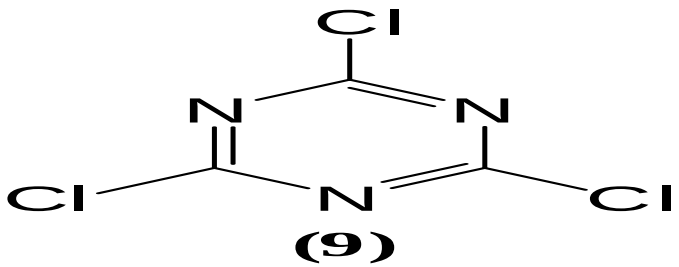

**(7)**

Although 1,3,5-triazines are well known in the context of anticancer drugs, this ring is also found in the drug used in the chemotherapy of malaria, as seen in case of cycloguanil (8) [9]. Recently, 2, 4, 6-trisubstituted-1, 3, 5-triazine scaffolds were discovered as a potent inhibitors of *M. tuberculosis* H37Rv [10].




**(8)**

All 1, 3, 5-triazine derivatives that have wide practical applications are 2,4 , 6-mono, di- or tri-substituted, symmetrical and nonsymmetrical compounds bearing different substituents. The most important reagent for obtaining these synthetic molecule transformations is cyanuric chloride (9), due to the reactivity of the chlorine atoms towards nucleophiles [11].

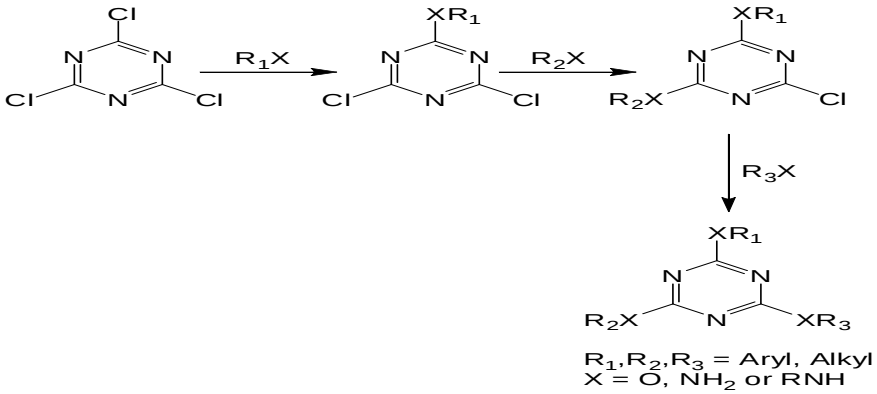



**(9)**

**Preparation of 1, 3, 5-Triazines**

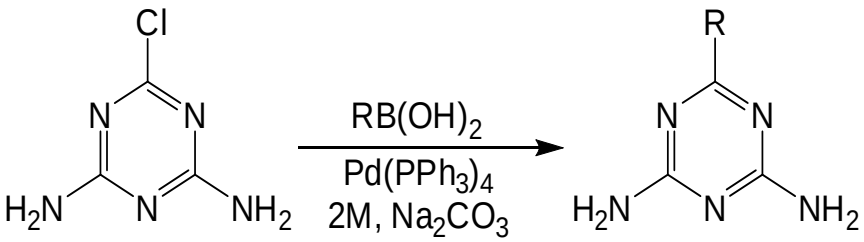
The synthesis of 1, 3, 5-triazines can be achieved with various different synthetic strategies using different starting materials. The possible synthetic routes of different types of 1,3,5-triazines such as fully unsaturated 1,3,5-triazines, dihydro-1,3,5-triazines and fused 1,3,5-triazines are reviewed as follows:

1. The nucleophilic displacement of chlorine from cyanuric chloride is the first method considered for the preparation of fully unsaturated 1, 3, 5-triazine derivatives. The three chloro substituents may be replaced sequentially depending upon the temperature of the reaction, and it is this property that makes cyanuric chloride so valuable in the synthesis of differently substituted 1,3,5-triazines (Scheme 1) [12].



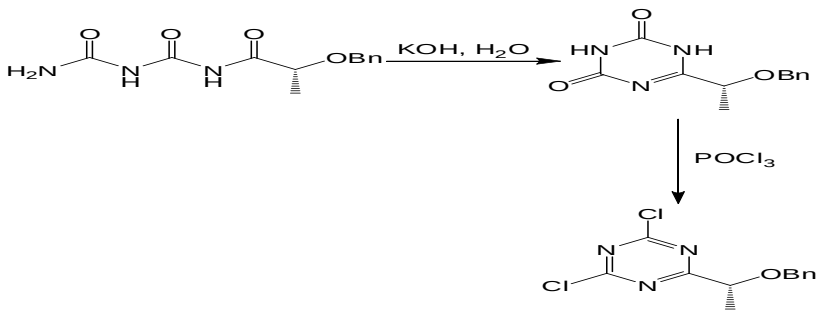

**Scheme 1**

1. The high yielding synthesis of 1, 3, 5-triazines was carried out *via* palladium-catalyzed Suzuki cross-coupling reactions of commercial available 6-chloro-2, 4-diaminotriazine and aryl boronic acids (Scheme 2) [13].



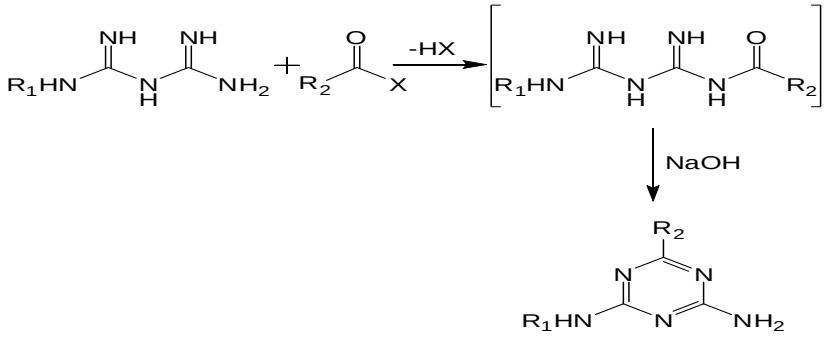

**Scheme 2**

1. (*R*)-2-Benzyloxy-N-ureidocarbonyl-propionamide was cyclized under basic condition to form 1,3,5-triazine-dione, which was then heated with phosphorous oxychloride to obtain the dichloro-1,3,5-triazine (Scheme 3) [14].



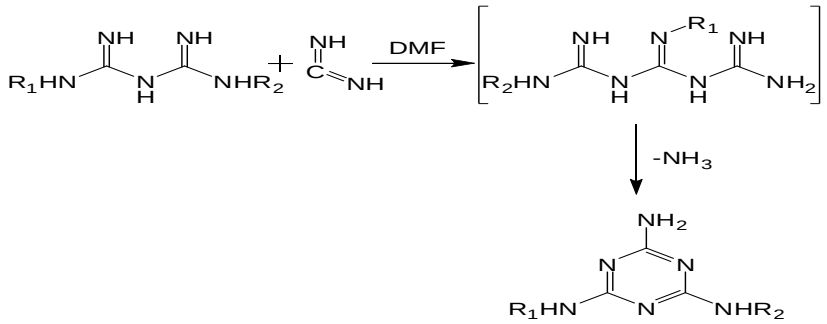

**Scheme 3**

1. Biguanide react with a variety of carboxylic acid derivatives in basic or neutral conditions to produce a wide range of 6-aryl or alkyl substituted-2, 4-diamino-1,3,5-triazines (Scheme 4) [15].



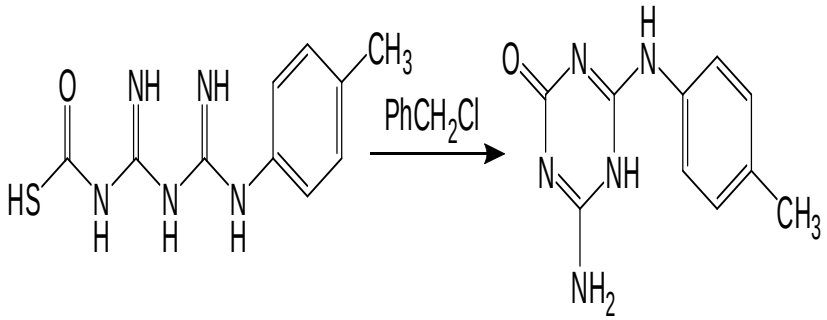
**Scheme 4**

1. Biguanides react with carbodiimides to form melamine derivatives in 60-70% yields (Scheme 5) [16].



**Scheme 5**

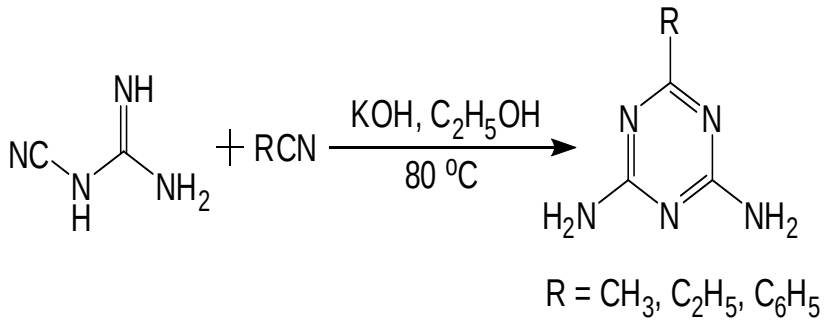
2. Using thiocarbamic substituted biguanide derivative as a starting material, targeted 4-amino-6-*p*-tolylamino-5H-1, 3, 5-triazin-2-one was synthesized by the treatment of benzylchloride and with the elimination of benzyl mercaptan (Scheme 6) [17].



**Scheme 6**

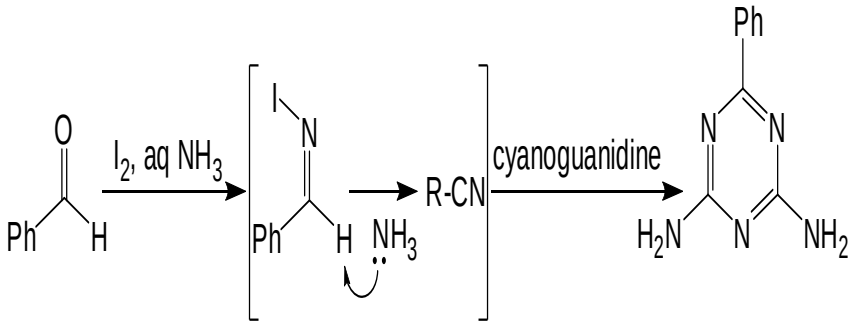
3. Nitrile is the most commonly used two-atom fragment to condense with cyanogunidine in the synthesis of 6-substituted-2, 4-diamino-1, 3, 5-triazines. The condensation is

catalyzed by potassium hydroxide and subjected to temperature between 82°C and 150°C for 1.5-44 h which is dependent on the nitriles used (Scheme 7) [18].



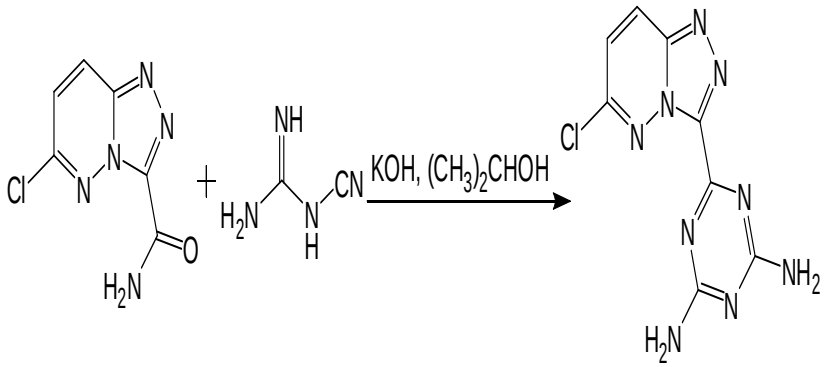

**Scheme 7**

4. As shown in Scheme 8, benzonitrile, which was produced *in situ* from the reaction of benzaldehyde with $I_2$/aq $NH_3$, was treated with cyanoguanidine (1.1 equiv) and KOH (2.2 equiv) at refluxing temperature for 24 h to obtain 2,6-diamino-4-phenyl-1,3,5-triazine with 78% yield [19].



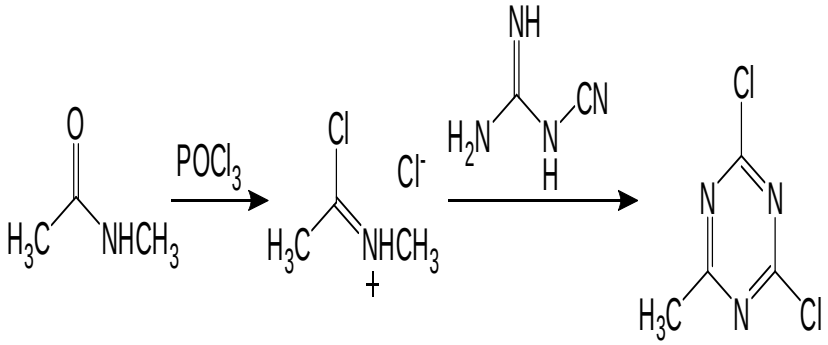

**Scheme 8**

5. Starting from 1,2,4-triazolo[4,3-b]pyridazine-3-carboxamide, a heterocyclic substituted-2,4-diamino-1,3,5-triazine was synthesized in the presence of potassium hydroxide in isopropyl alcohol (Scheme 9) [20].



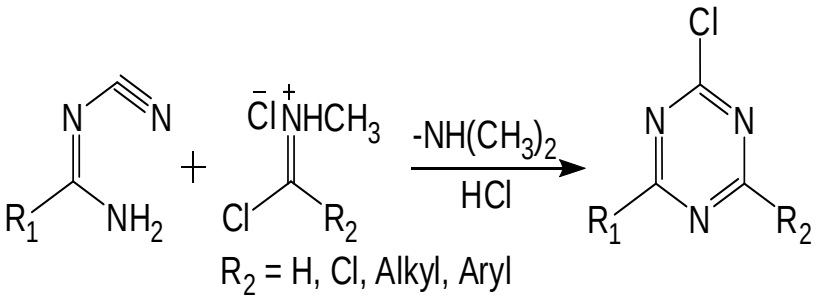

**Scheme 9**

6. Dichloro-1, 3, 5-triazines can be synthesized from the cyclocondensation reaction between cyanoguanidine and chloromethyleneiminium salts (Scheme 10) [21].



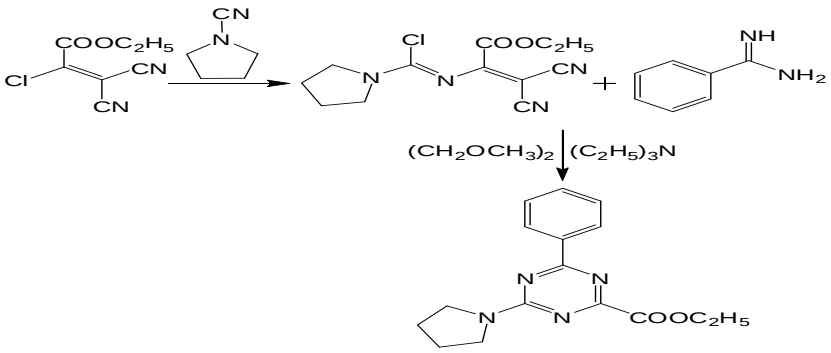
**Scheme 10**

7. As illustrated in Scheme 11, the synthesis of aryl- and alkyl-substituted 1,3,5-triazines may readily be achieved by the condensation of *N*-cyanoamidines with chloromethyleneiminium salts [22].



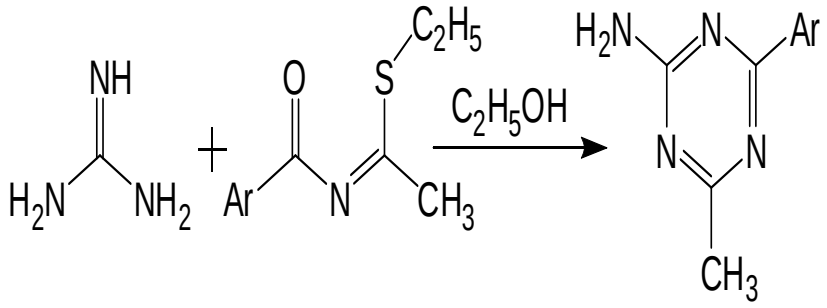
**Scheme 11**

8. Addition reaction of ethyl 2-chloro-3, 3-dicyanoacrylate with pyrrolidino nitrile gives 49-63% intermediate. In the presence of triethylamine, this intermediate reacts with the bisnucleophilic amidine $H_2NPhC{=}NH$ to give 1, 3, 5-triazines in 64-82% yield (Scheme 12) [23].



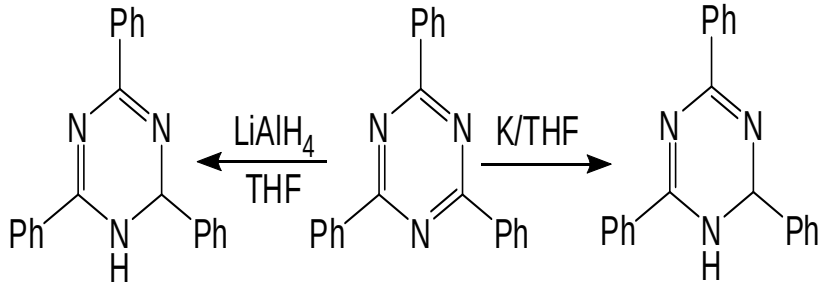
**Scheme 12**

9. The reaction of the N-aroylthioimidates with guanidine in ethanol gives 1, 3, 5-triazines in 60-93% yield. It provides one of the few methods to synthesize monoamino-1, 3, 5-triazines with different alkyl or aryl substitutions (Scheme 13) [24].



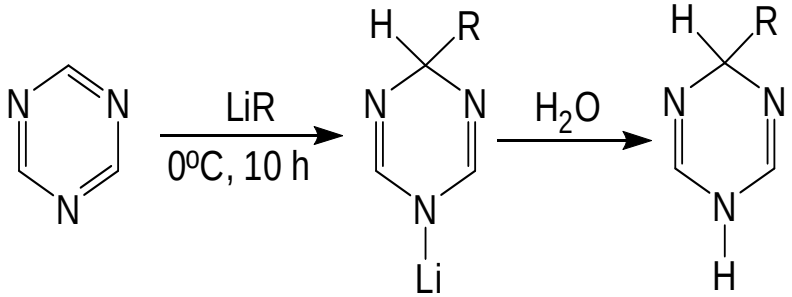

**Scheme 13**

10. The known reactions involve preparation of 2, 4, 6-triphenyl-1,2-dihydro-1,3,5 triazine from the reductions on 2,4,6-triphenyl-1,3,5-triazines using lithium aluminum hydride or by treatment with potassium in THF followed by hydrolysis (Scheme 14) [25].



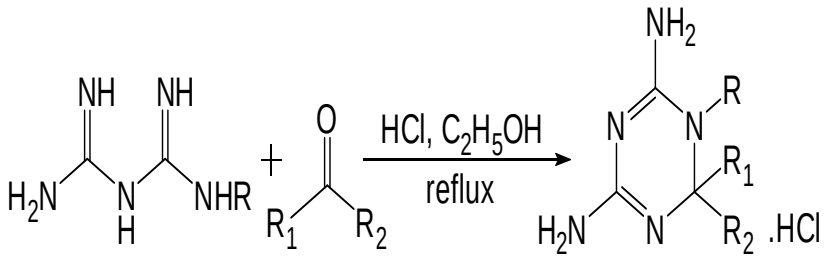

**Scheme 14**

11. Boesveld *et al.* have reported a series of addition products of mono substituted 1,4-dihydro-1,3,5-triazines, synthesized from the treatment of 1,3,5-triazine with an alkyllithium LiR [R=Me, n-Bu, t-Bu, Ph, $CH_2TMS$, $CH(TMS)_2$ or $Si(TMS)_3(THF)_3$] upon hydrolysis (Scheme 15) [26].



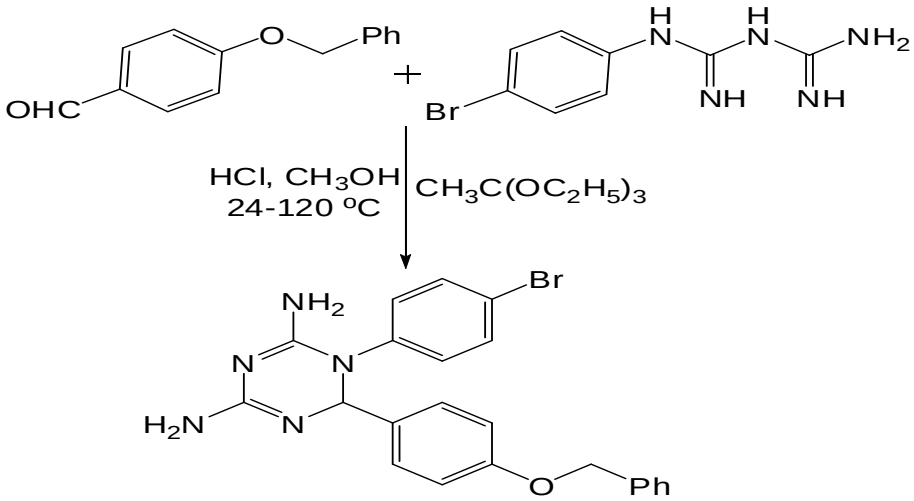

**Scheme 15.**

12. Various biguanides have been reported to react with aldehyde or ketone to give the corresponding 1, 2-dihydro-1, 3, 5-triazines (Scheme 16) [27].



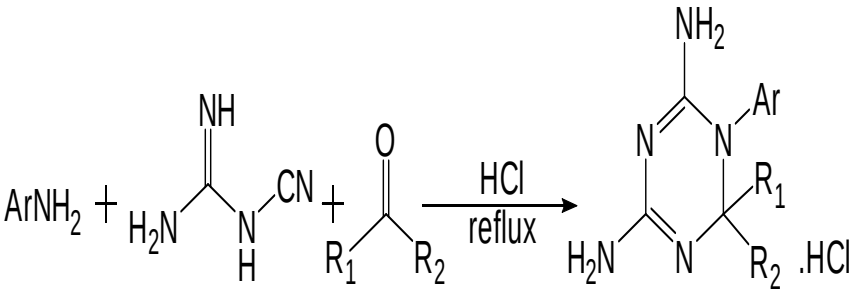

**Scheme 16**

13. An efficient synthesis of 1-aryl-4,6-diamino-1,2-dihydro-1,3,5-triazines using triethyl-orthoacetate as a water scavenger has also been reported in good yield from an acid-catalyzed reaction between corresponding arylbiguanide hydrochlorides and carbonyl compounds (Scheme 17) [28].



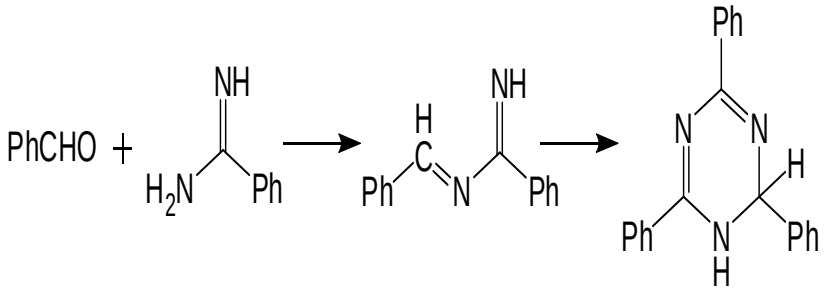

**Scheme 17**

14. Dicyanamide can be used as a starting material to prepare 1,2-dihydro-1,3,5-triazines. It can react with molecular equivalent of the aryl amine or its acid salt plus one equivalent of acid and a ketone or an aldehyde with the loss of one molecule of water to give the 1,2-dihydro-1,3,5-triazine nucleus (Scheme 18) [29].



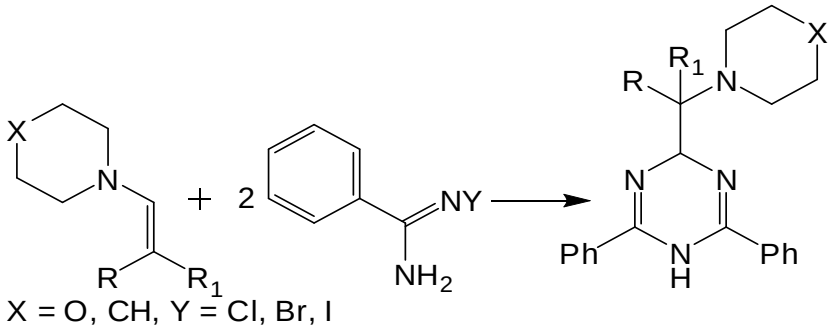

**Scheme 18**

15. Condensation of benzaldehyde with benzamidine gives 2, 4, 6-triphenyl-1,2- dihydro-1,3,5-triazine (Scheme 19) [30].



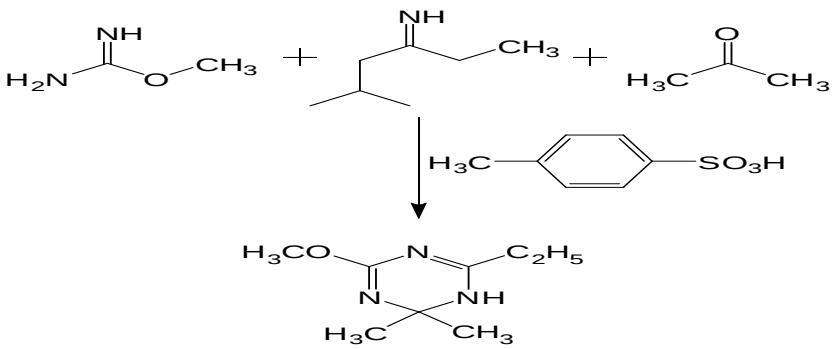

**Scheme 19**

16. The reaction of N-haloamidines with enamines derived from aldehydes forms 1,4-dihydro-1,3,5-triazines (Scheme 20) [31].



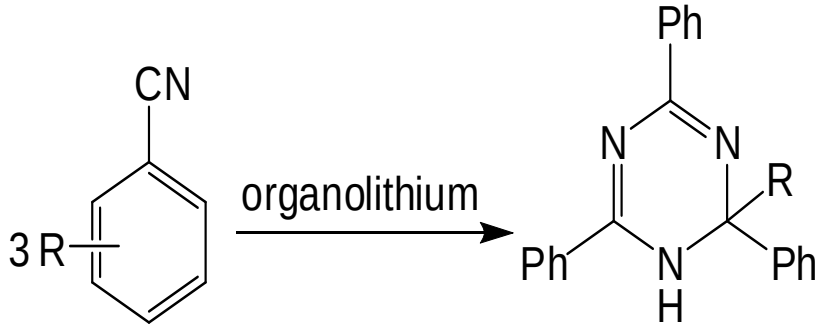

**Scheme 20**

17. A three-component condensation of isopropylpropionimidate with *O*-methylisourea tosylate in the presence of acetone gives 39.4% of 1, 2-dihydro-1,3,5-triazine (Scheme 21) [32].



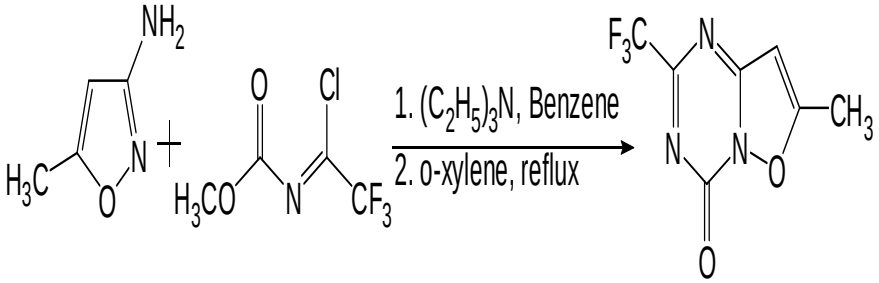

**Scheme 21**

18. Cook *et al*. obtained 2, 2, 4, 6-tetraphenyl-1, 2-dihydro-1, 3, 5-triazines as the sole product and succeeded in preparing a series of 1, 2-dihydro-1, 3, 5-triazines (Scheme 22) [33].



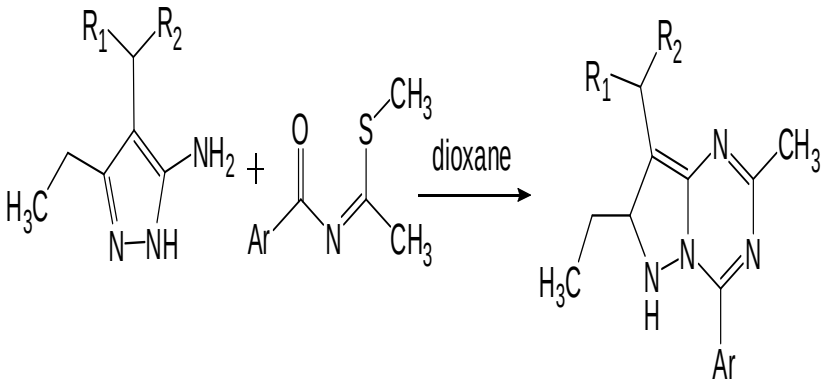

**Scheme 22**

19. 2-Trihalomethyl-4H-isoxazolo [2, 3-a]-1, 3, 5-triazin-4-ones have been synthesized by cyclization of 3-amino-5-methylisoxazole with N-(1-chloro-2, 2, 2-trihaloethylidene)-*O*-methyl-urethanes (Scheme 23) [34].



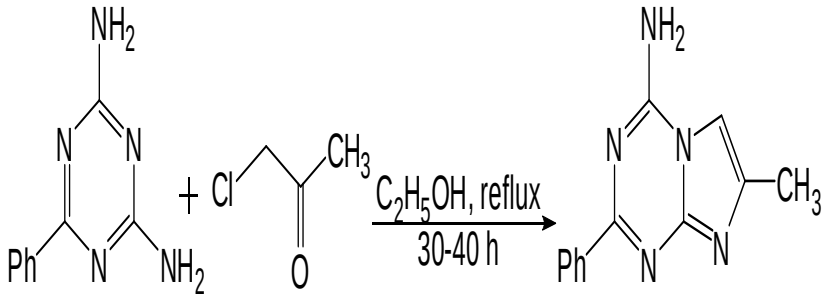

**Scheme 23**

20. The pyrazolo-[1, 5-a]-1, 3, 5-triazines have been prepared in a convergent fashion by the coupling of 3-aminopyrazole with aroyl thioimidates (Scheme 24) [35].



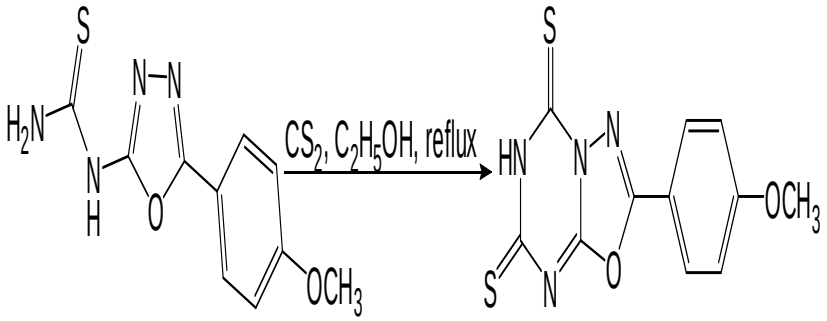

**Scheme 24**

21. The synthesis of 7-substituted-2-phenylimidazo[1, 2-a]-1, 3, 5-triazine-4-yl-amines also employs similar strategy by cyclization of 2,4-diamino-1,3,5-triazine in refluxing ethanol with 2-chloroacetone (Scheme 25) [36].



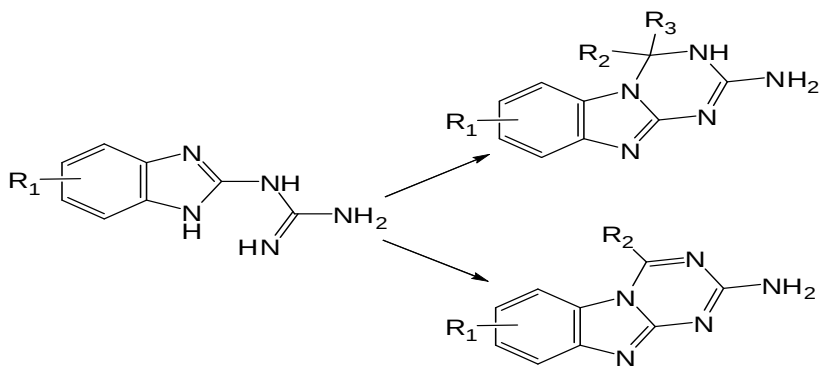

**Scheme 25**

22. $N^1$-(5-Aryl-1,3,4-oxadiazolo-2-yl)-ureas on cyclocondensation with $CS_2$/KOH afforded 2-aryl-1,3,4-oxadiazole[3,2-a]-1,3,5-triazine-5,7-(6H) dithione nucleo bases (Scheme 26) [37].



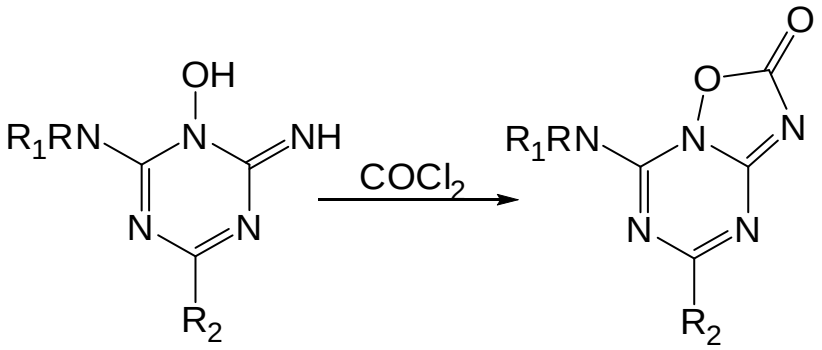

**Scheme 26**

23. 2-Amino-1, 3, 5-triazino[1, 2-a]benzimidazoles were obtained by a ring annelation from 2-guanidinobenzimidazoles (Scheme 27) [38].



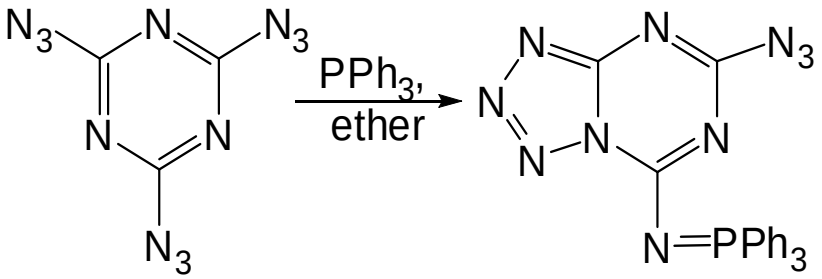

**Scheme 27**

24. Oxadiazolo-1, 3, 5-triazinederivatives which showed antihypertensive and vasodilating activity, have been prepared by cyclocondensation of 2,4-diamino-6-(diallylamino)-1,3,5-triazin-3-oxide with $COCl_2$ (Scheme 28) [39].



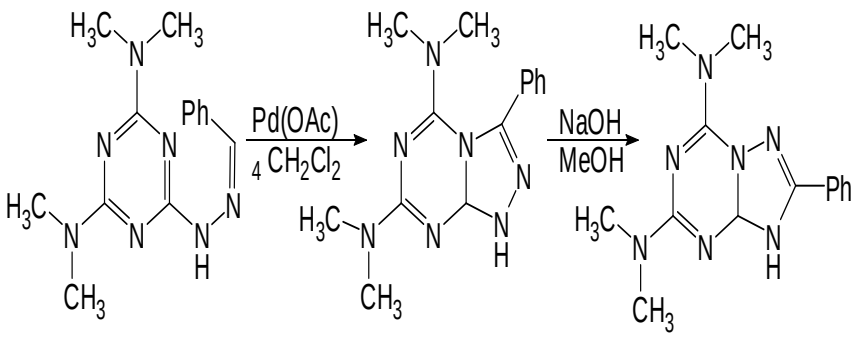

**Scheme 28**

25. 2-Triphenylphosphanimino-4-azidotetrazolo[5,1-a]-1,3,5-triazine has been obtained by reaction of 2,4,6-triazido-1,3,5-triazine with one equivalent of triphenylphosphine (Scheme 29) [40].



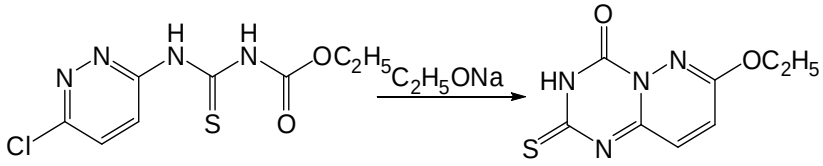

**Scheme 29**

26. 4-Diamino-6-hydrazone-1,3,5-triazines can be cyclized to 1,2,4-triazolo[4,3-a]-1,3,5-triazines with $Pb(OAc)_4$ in $CH_2Cl_2$. The product 1,2,4-triazolo[4,3-a]-1,3,5-triazines can be rearranged to 1,2,4-triazolo[1,5-a]-1,3,5-triazines in MeOH-NaOH (Scheme 30) [41].




**Scheme 30**

27. N-Carbethoxy-N′-(6′-chloropyridazinyl-3′) thiourea which is upon heating in the presence of sodium ethoxide afforded the compound 7-ethoxy-2-thioxopyridazino[2,3-a]-1,3,5-triazin-4(3H)-one (Scheme 31) [42].

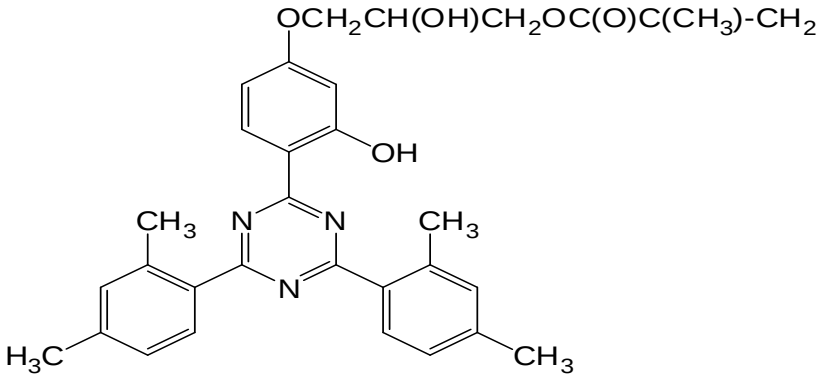



**Scheme 31**

**Molecular Spectroscopy of 1, 3, 5-Triazines**

**Ultraviolet Absorption Spectroscopy**

The ultraviolet (UV) absorption spectrum of 1, 3, 5-triazine derivative **(10)** displayed the double-band structure in the long-wavelength UV region observed for many intramolecularly hydrogen-bridged UV absorbers. The longer wavelength band at about 350 nm can be attributed to a $\pi\pi^*$ charge-transfer state, this is favored by the planar orientation enforced by the intramolecular hydrogen bond. The shorter wavelength band at about 300 nm arises from a local transition within the 1, 3, 5-triazine ring [43].

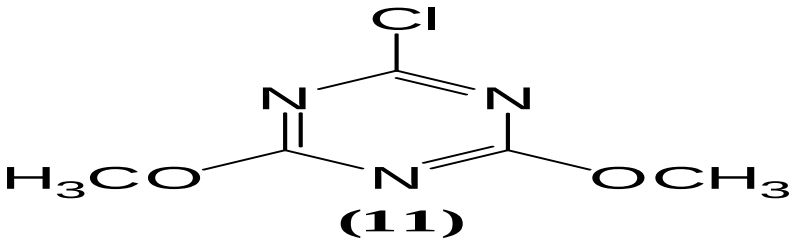



**(10)**

**Infrared Spectroscopy**

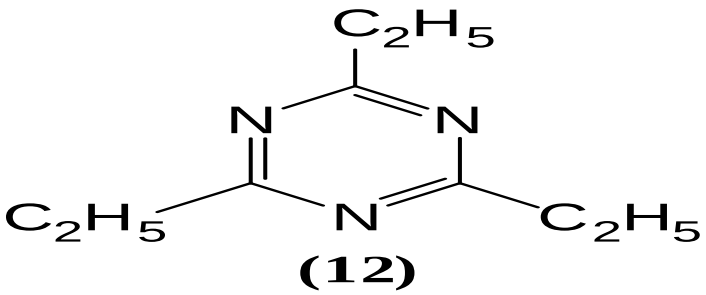
The infrared (IR) spectrum of 1, 3, 5-triazine **(3)** has two strong absorption bands at 1562 and 1408 $cm^{-1}$. These bands have been established as originating from the in-plane ring vibrations of the triazine ring. Triazine also exhibits a strong band at 735 $cm^{-1}$ and a medium strong band at 675 $cm^{-1}$. These bands are assigned to the carbon-hydrogen wagging and out-of-plane ring vibration, respectively. The solution spectra show well defined absorption bands. The spectrum of cyanuric chloride (9) differs from the parent 1, 3, 5-triazine with respect to all absorption bands. The strong bands appear at 1503 $cm^{-1}$, 1265 $cm^{-1}$, 854 $cm^{-1}$ and 800 $cm^{-1}$.

The 1503 $cm^{-1}$ band is due to the in-plane ring vibration of this triazine ring system, with a small band appearing at 1449 $cm^{-1}$. The 854 $cm^{-1}$ band is probably due to the carbon-chlorine stretching vibration. This stretching vibration has been shifted to shorter wave lengths, and is probably due to the *Meta* position of the chlorine atoms. The 800 $cm^{-1}$ band is assigned as the out-of-plane ring vibration, analogous to the 675 $cm^{-1}$ band in the parent triazine. Replacing one chloro group with a methyl group, on cyanuric chloride, shifts the 1503 $cm^{-1}$ band to 1538 $cm^{-1}$ and splits the band at 1265 $cm^{-1}$. With a phenyl group in place of a chloro group a band appears at 1538 $cm^{-1}$ with the 1503 $cm^{-1}$ band remaining constant and the intensity of the 1449 $cm^{-1}$ band increasing. The 854 $cm^{-1}$ band remains constant in the dichloro substituted triazines. In the other solution spectra (1666 $cm^{-1}$ to 909 $cm^{-1}$) the in-plane ring modes of the triazine ring system can be seen at 1562 $cm^{-1}$, 1508 $cm^{-1}$ and 1449$cm^{-1}$**.** However, the spectrum of 2-chloro-4, 6-dimethoxy-*s*-triazine **(11)** shows only a small shoulder band at 1503 $cm^{-1}$ and the 1449 $cm^{-1}$ band has been shifted to 1470 $cm^{-1}$.

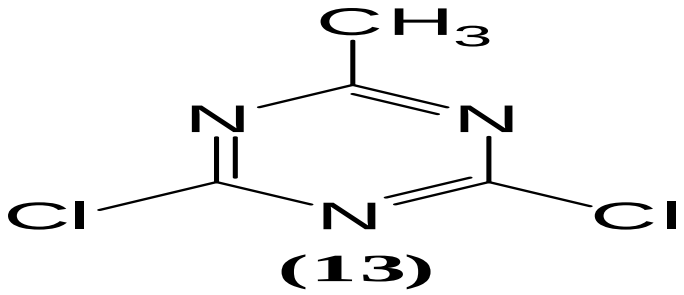



**(11)**

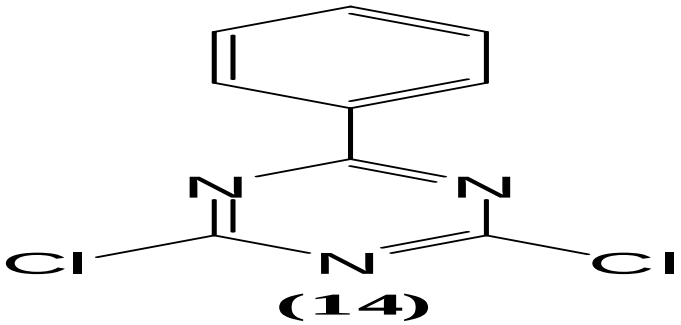
Most of the solution spectra of the triazine compounds contain a phenyl group and it is difficult to differentiate between the absorptions due to the triazine ring and phenyl ring. Both ring systems are capable of exhibiting bands in the 1666 $cm^{-1}$-1428 $cm^{-1}$ region. There is no doubt that the phenyl ring has absorption bands overlapping the triazine ring absorptions in this region. The slight shoulder band at 1600 $cm^{-1}$ can be seen clearly in most of the spectra of the triazine derivatives containing a phenyl group. This band does not seem to be present in the nonbenzene derivatives, so it can be attributed to the in-plane ring vibration of the monosubstituted benzene. The assignment of any other band in this region due primarily to the phenyl group is complicated by the overlapping of the ring absorptions. However, the absorption bands at 1562 $cm^{-1}$, 1492 $cm^{-1}$ and 1449 $cm^{-1}$, which are present in the solution spectra containing phenyl groups, are also present in the spectra of cyanuric chloride and 2,4,6-triethyl-*s*-triazine (12). Therefore, it can be assumed that the phenyl groups, if present, only intensify these absorptions and are not primarily responsible for them. The other region of interest is that above 833 $cm^{-1}$.



(12)



(13)



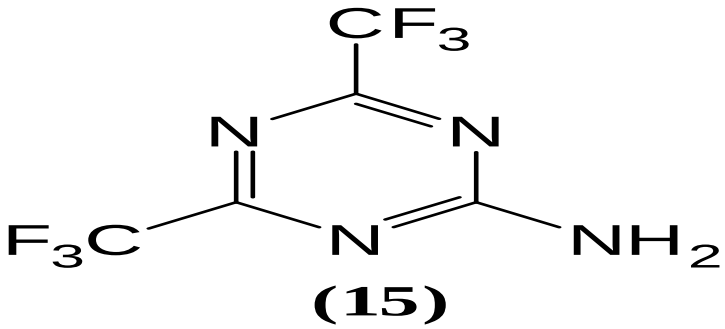
(14)

The 2-methyl-4,6-dichloro-*s*-triazine (13) spectrum has a small band appearing at 819 $cm^{-1}$, while the 800 $cm^{-1}$ band has been shifted to 793 $cm^{-1}$. In the spectrum of 2-phenyl-4,6-dichloro-s-triazine (14) the intensity of the 819 $cm^{-1}$ band increases and the 800 $cm^{-1}$ band seems to shift to 769 $cm^{-1}$ coinciding with the phenyl out-of-plane CH deformation vibrations. With monophenyl substitution the 819 $cm^{-1}$ does not seem to vary to any great extent. However, with two phenyl rings or a carboxy group present, this band is displaced to longer wave lengths. The second band of the phenyl CH deformation vibration remains steady between 704-694 $cm^{-1}$ [44-47].

**Nuclear Magnetic Resonance Spectroscopy**

In the $^{1}H$ NMR spectrum of 1, 3, 5-triazine derivative (15), the two equivalent protons of $NH_2$ group present at the 2-position on 1, 3, 5-triazine ring appear as a broad singlet at δ 8.04 ppm. Breitmaier *et al*. reported the $^{13}C$ NMR spectrum of unsubstituted triazine **(3)**. The

chemical shift and C, H-spin coupling constant of the ring carbons in unsubstituted triazine has been reported as δ 166.6 ppm, with $^{1}J_{CH}$ equal to 208 Hz [48, 49].



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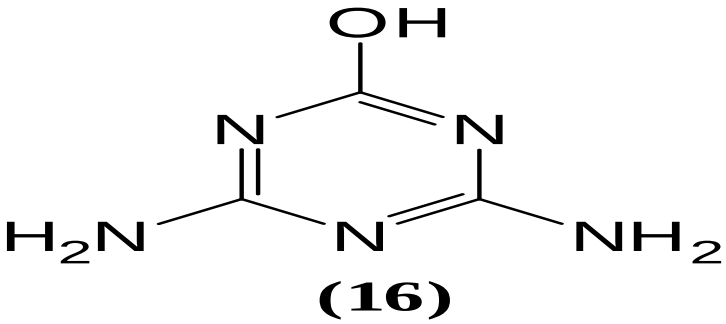
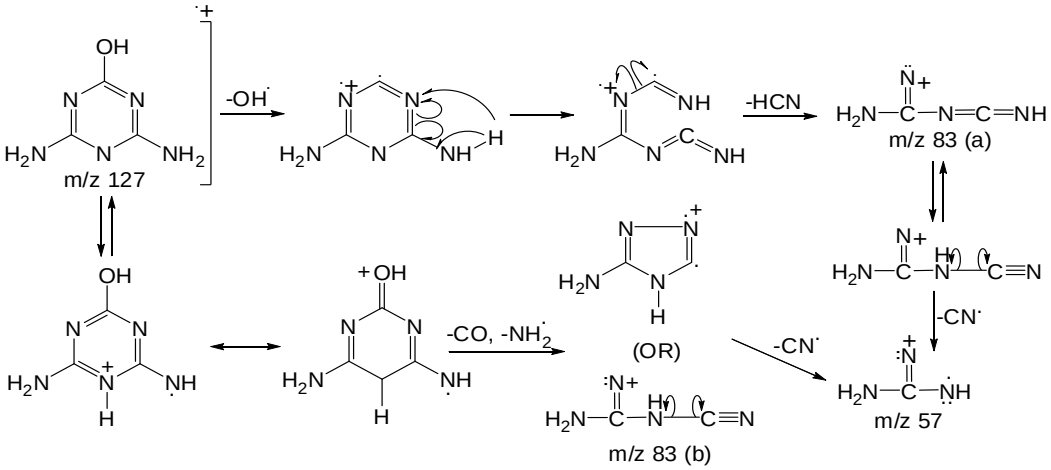


**(16)**

**Mass Spectroscopy**

The analysis of 2-hydroxy-diamino-atrazine (16) was performed in the electron-impact mode by direct inlet system-mass spectrometry (DIS-MS). Two proposed noteworthy fragmentation patterns due to the presence of the hydroxy group are shown in Scheme 32. The ion at *m/z* 127, which is the molecular ion in 2-hydroxy - diamino-atrazine. This ion is fragmented to the ion at *m/z* 57 either by subsequent loss of the OH radical, HCN, and the CN radical or by loss of CO, the $NH_2$ radical, and the CN radical [50].



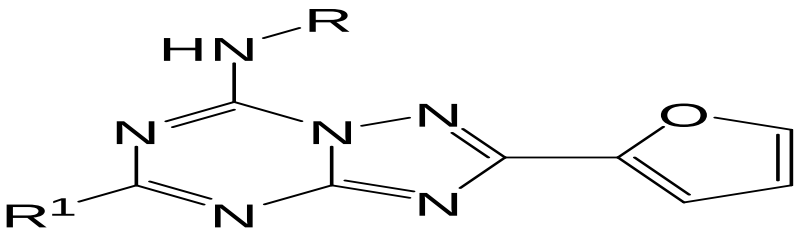

**Scheme 32**

**Biological Activity of 1, 3, 5-Triazines**

The enhanced interest in this class of compounds was aroused due to their potential therapeutic value. Some of the major biological activities were discussed below.

**Adenosine Receptor Antagonists**

Pastorin *et al.* have synthesized a series of 5,7-disubstituted-[1,2,4]triazolo[1,5-a][1,3,5]triazine derivatives (17) variously substituted at the C-5 and N-7 positions and evaluated their antagonistic activity at the adenosine receptor (AR) subtypes. In particular, compounds with a free amino group at the 7 position (18 and 19), showed good affinity at the rat (r) $A_{2A}$ AR (range 18.3-96.5 nM), while the introduction of a phenylcarbamoyl moiety at the N7 position (20, 21 and 22) slightly increased the affinity at the $hA_3$ AR (range 311-633 nM) [51].



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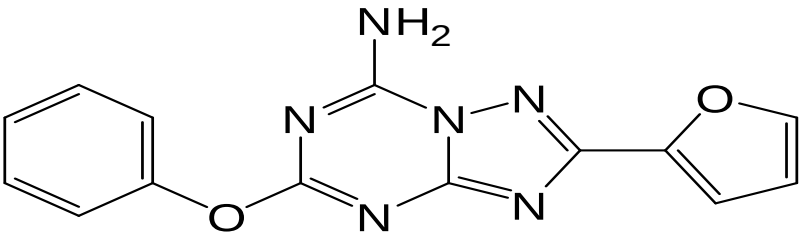
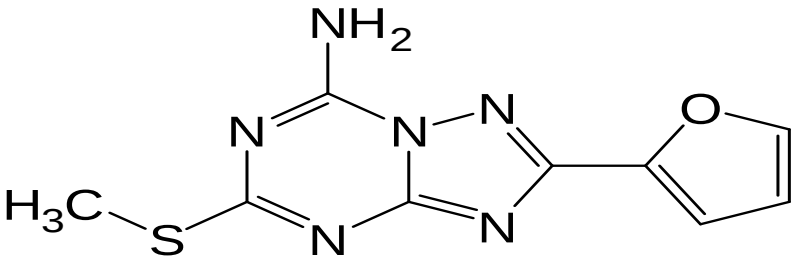
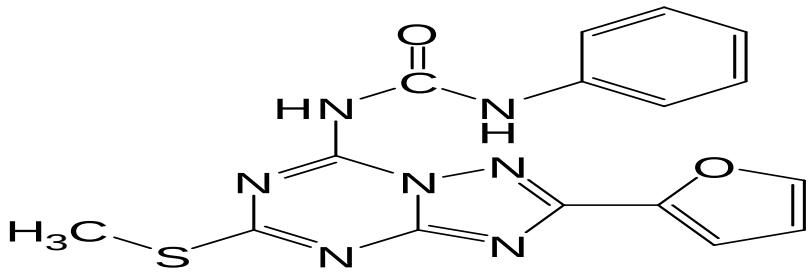


**(18)**



**(19)**



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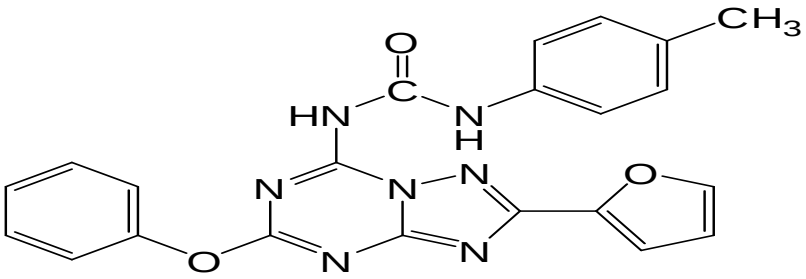
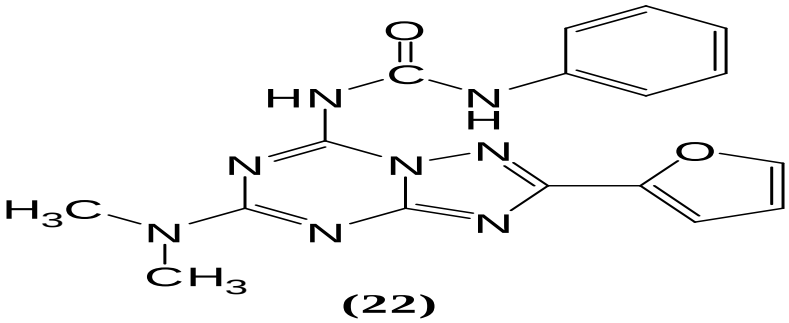
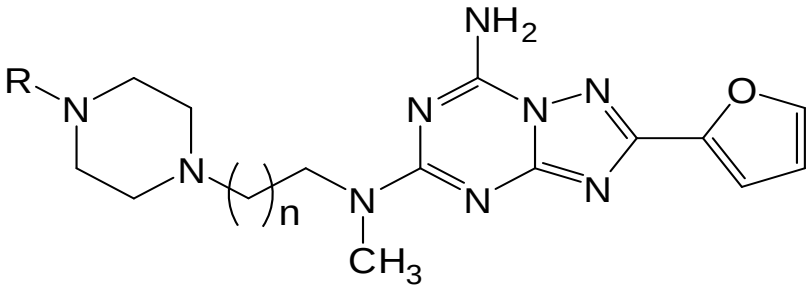


**(21)**



**(22)**

Vu *et al.* have synthesized a series of some new piperazine derivatives of 2-furanyl[1,2,4]triazolo[1,5-a][1,3,5]triazine derivatives (23) and screened for their potential as adenosine $A_{2a}$ receptor antagonists. Compound (24) has been found to be orally active in a mouse catalepsy model of Parkinson's disease [52].



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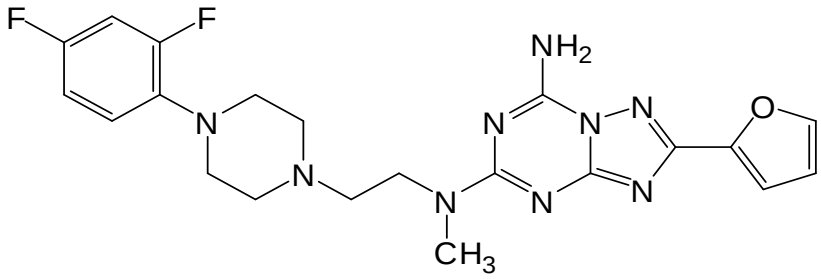
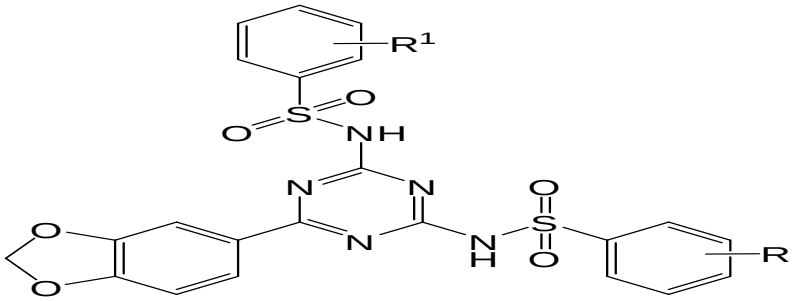


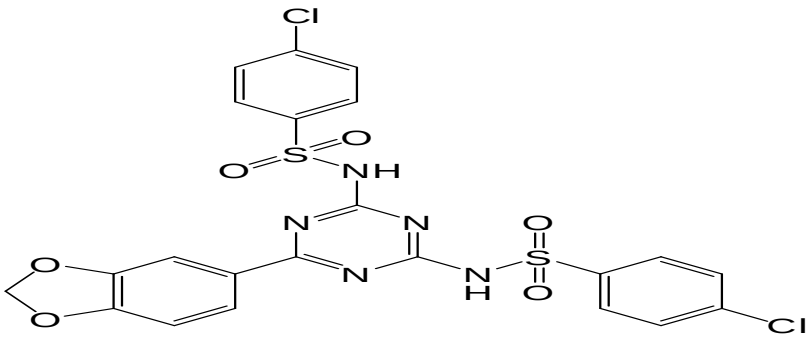
**(24)**

**Antiamoebic Activity**

Wani *et al.* have synthesized a series of compounds bearing triazine ring motif conjugated with a $SO_2NH$ function (25) and investigated for their antiamoebic potency. Compound (26) and (27) were obtained as excellent *Entamoeba histolytica* inhibitors with $IC_{50}$ values of 1.05 µM and 1.02 µM respectively [53].



**(25)**



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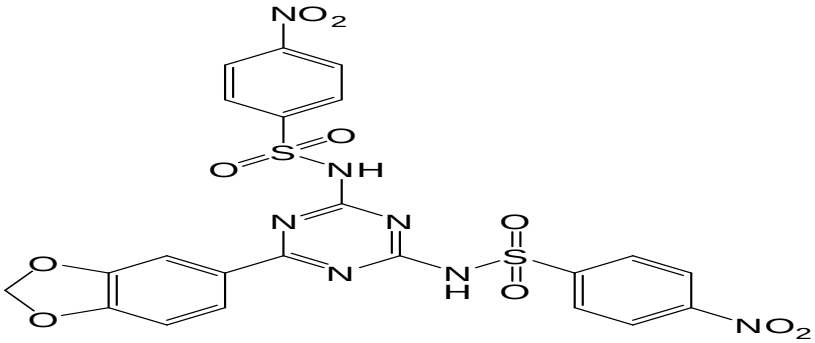
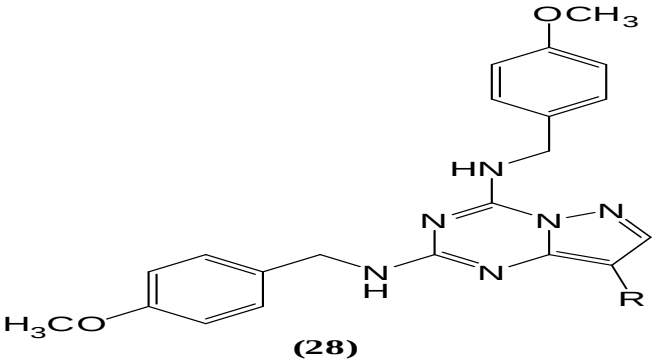


**(27)**

**Anticancer Activity**

Popowycz *et al.* have synthesized a series of pyrazolo[1,5-a]-1,3,5-triazine myoseverin derivatives (28) and evaluated their cytotoxicity, inhibition of tubulin polymerization and cell cycle effects. Compounds (29) and (30) are potent tubulin inhibitors and displayed specific antiproliferative activity in colorectal cancer cell lines at micromolar concentrations [54].



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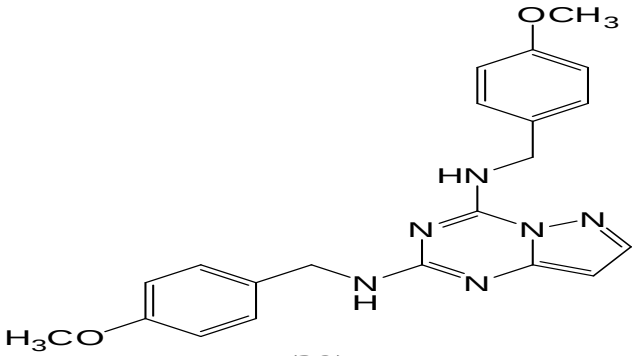

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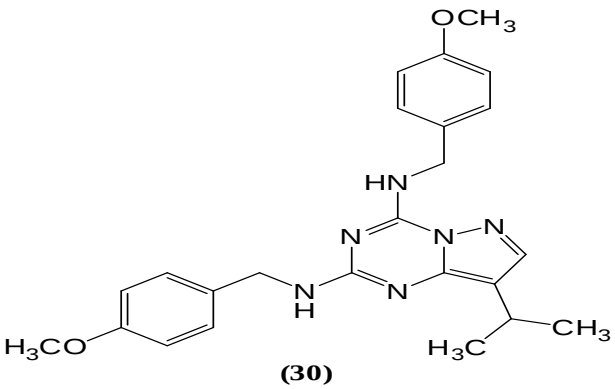
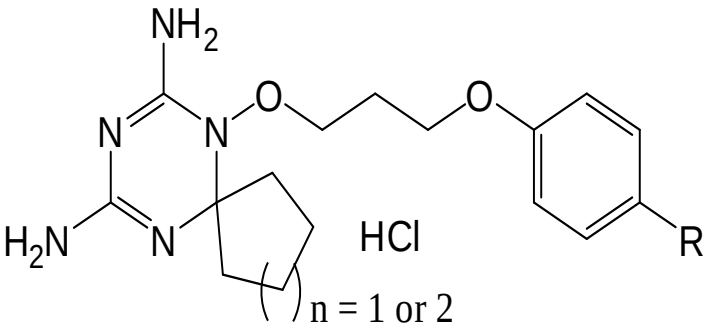


**(30)**

Ma *et al.* have synthesized a series of 1, 3, 5-triazaspiro[5.5]undeca-1,3-dienes (31) and tested for *in vitro* mammalian dihydrofolate reductase (DHFR) inhibitory activity and antiproliferative activity against A549 human lung-cancer cells. Compound (32) showed the highest antiproliferative activity against A549 cells with an $IC_{50}$ value of 27.1 nM [55].

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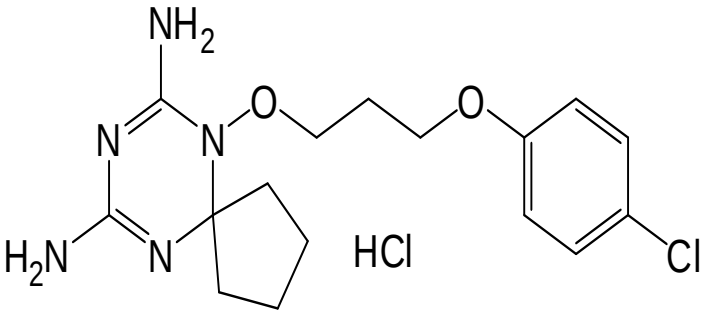
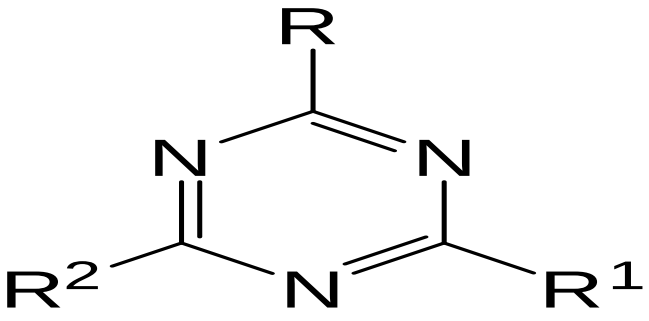



**(32)**

Zheng *et al.* have synthesized a series of triaminotriazine derivatives (33) and evaluated for their inhibition activity on colorectal cancer (CRC) cell lines (HCT-116 and HT-29). Most of the synthesized compounds demonstrated moderate antiproliferatory effects on both HCT-116 and HT-29 cell lines at the concentration of 10 µM. Compounds (34) and (35) exhibited prominent inhibition activities toward HCT-116, with $IC_{50}$s of 0.76 and 0.92 µM, respectively [56].

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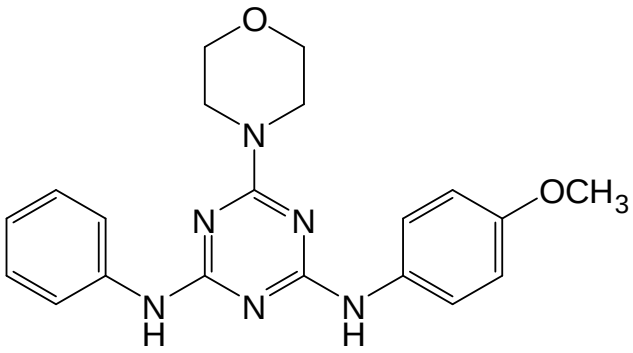

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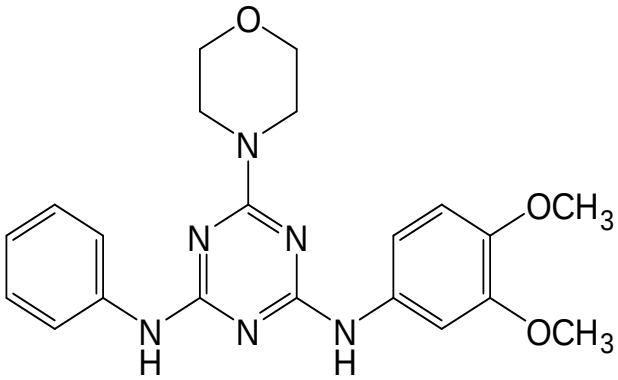
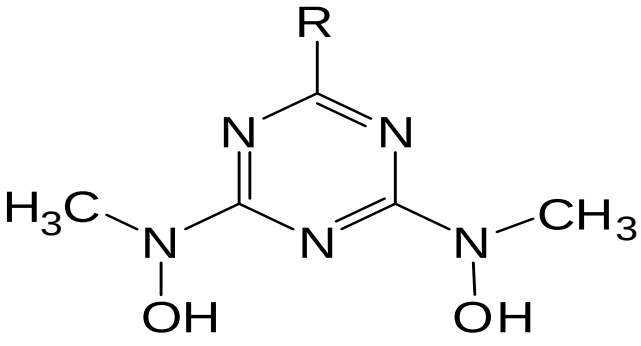


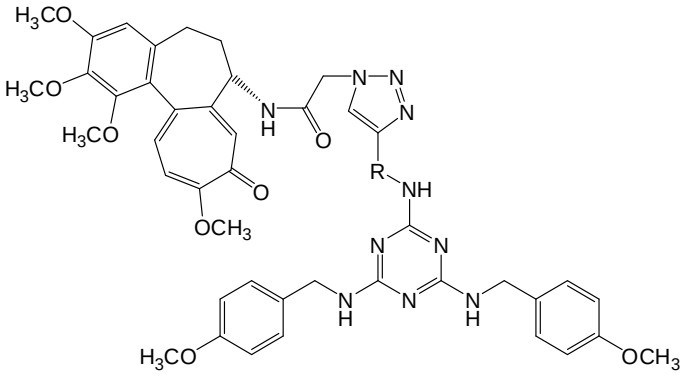
**(35)**

Sun *et al.* have synthesized and evaluated new specific tridentate iron(III) chelators of 2,6-bis[hydroxyamino]-1,3,5-triazine (BHT) (36) family for use in iron deprivation cancer therapy. Physical properties of BHT chelators are easily customizable allowing easy penetration through cellular membranes. Antiproliferative activity of new BHT chelators was studied on *MDA-MB-231* and *MiaPaCa* cells and compared to a clinically available new oral iron chelator, deferasirox (DFX). The antiproliferative activity of new chelators was found to correlate with iron(III) chelation ability and some of analogs showed substantially higher antiproliferative activity than DFX [57].

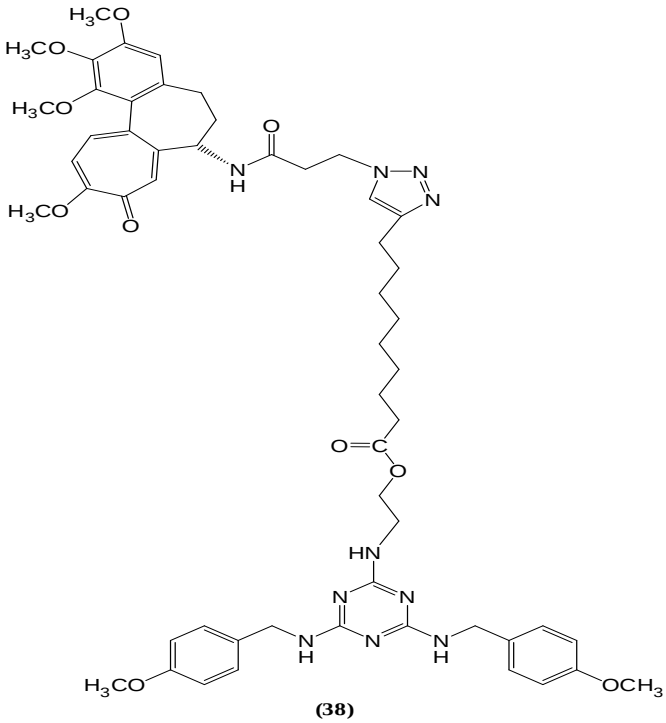


**(36)**

Malysheva *et al.* have synthesized a series of novel antimitotic hybrids by linking of azide-containing colchicine congeners with acetylene-substituted tubulizine type derivatives **(37)** using copper-mediated 1, 3-dipolar cycloaddition. All the obtained compounds exhibited good cytotoxicity against HBL100 epithelial cell lines ($IC_{50}$ = 0.599-2.93 µM). The highest activity among the heterodimers was achieved for ligand (38) ($IC_{50}$ = 0.687 ± 0.013 µM) [58].

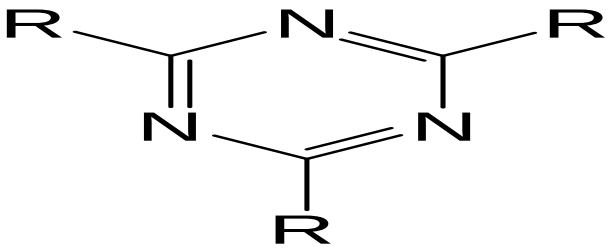


**(37)**



**(38)**

Arya *et al.* have developed a simple and environmentally friendly procedure for the synthesis of 1, 3, 5-triazine derivatives (39) under microwave irradiation in the presence of a HY zeolite. These compounds were screened for phototoxicity as well as the cytotoxic activities against leukemia and adenocarcinoma derived cell lines in comparison to the normal human keratinocytes. Compounds (40), (41), (42), (43) exhibited the highest activity [59].



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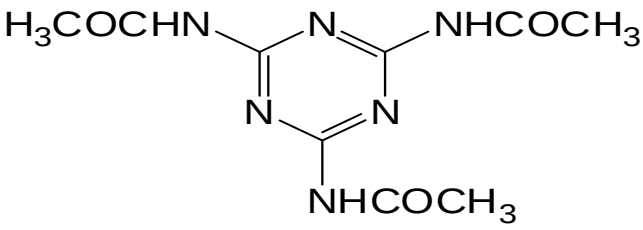

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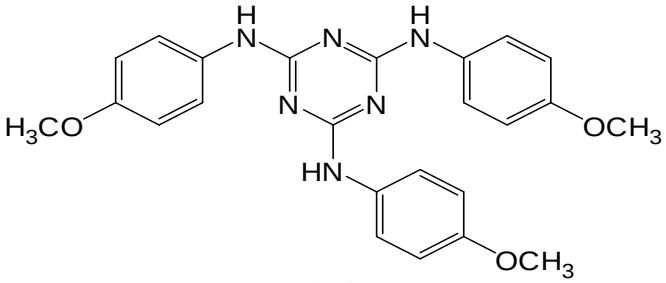

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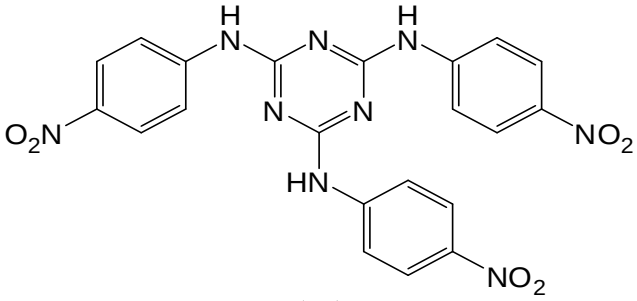
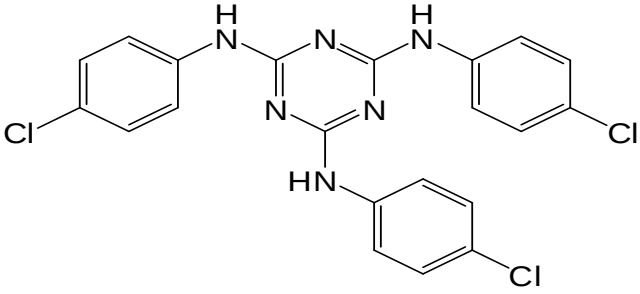
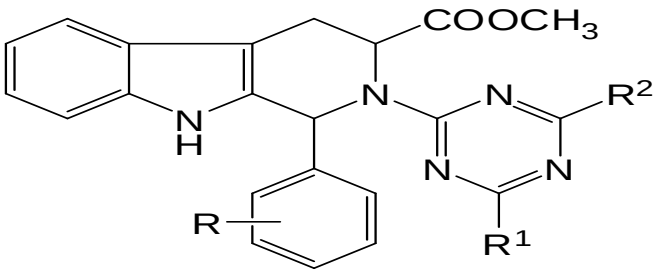


**(42)**

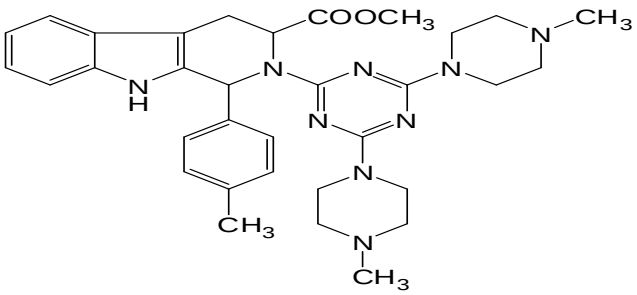


**(43)**

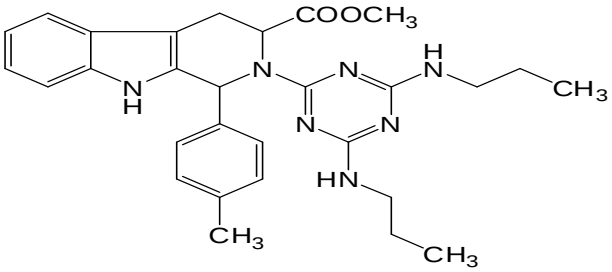
Kumar *et al.* reported the synthesis of a series of tetrahydro-β-carbolines-1, 3, 5-triazine hybrids (44) and evaluated for their cytotoxicity against a panel of human cancer cell lines and normal human fibroblasts (NIH3T3). This led to the discovery of racemic compounds (45), (46) and (47), which are selectively cytotoxic towards KB (oral cancer) cell line with $IC_{50}$ values of 105.8, 667 and 122.2 nM, respectively [60].



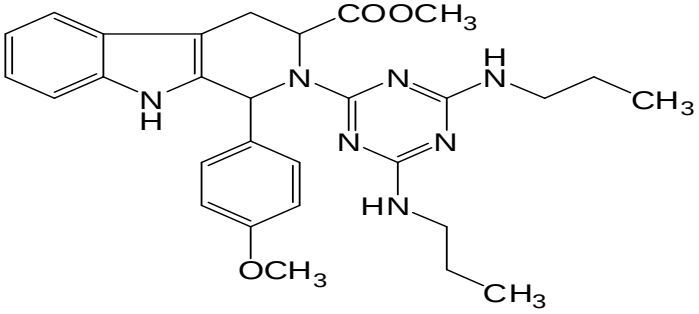
**(44)**



**(45)**

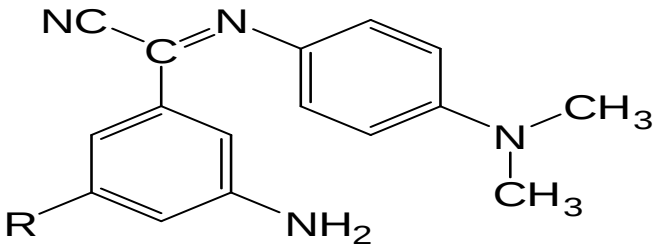


**(46)**

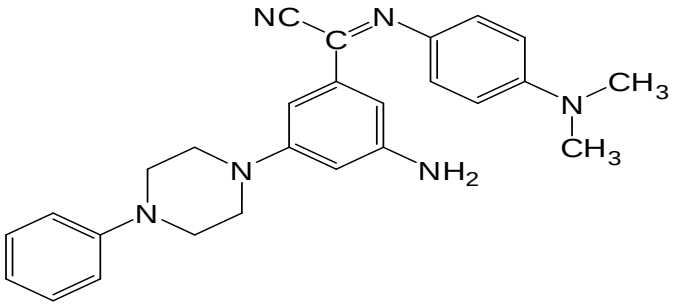


**(47)**

Sqczewski *et al.* have synthesized a series of 2-(4, 6-diamino-1,3,5-triazin-2-yl)-2-{[4-(dimethylamino)-phenyl]imino}acetonitriles (48) and evaluated for their *in vitro* antitumor activity. The compound (49) having remarkable activity against melanoma MALME-3 M cell line ($GI_{50}$ = 3.3 × $10^{-8}$ M, TGI = 1.1 × $10^{-6}$ M) [61].

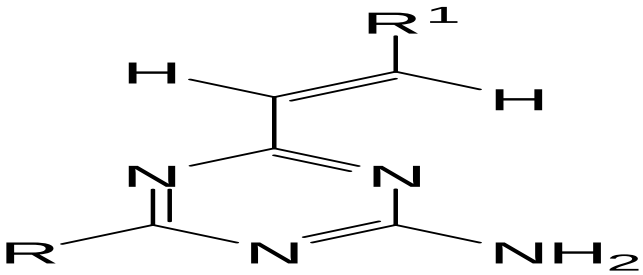



**(48)**

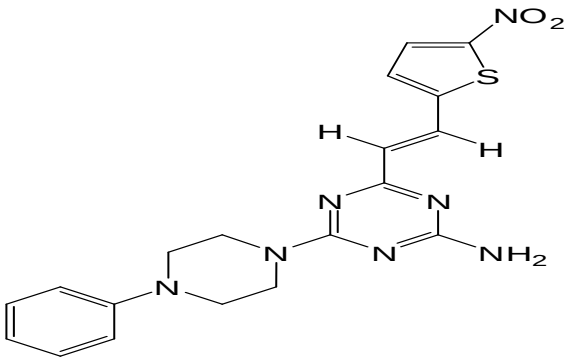



**(49)**

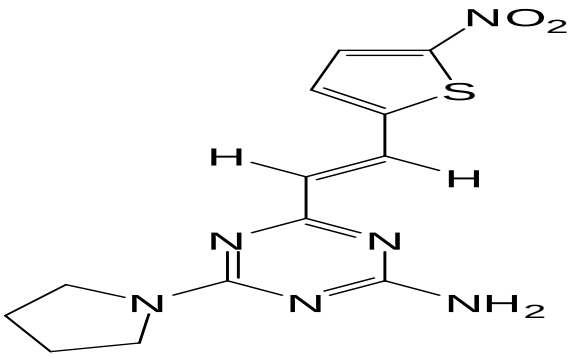
Sqczewski *et al.* have synthesized a series of 4-(*E*)-ethenyl-6-alkylamino-1, 3, 5-triazin-2-ylamine (50) derivatives. All the compounds prepared were screened for their activity against a panel of tumor cell lines and the compounds (51) and (52) showed 50% growth inhibitory activity in low micromolar concentrations against renal cancer A498 cell line and colon cancer cell line COLO 205, respectively [62].




**(50)**



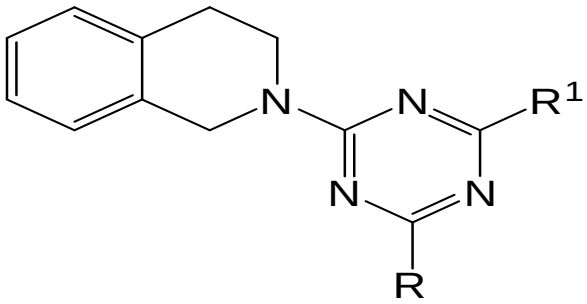
(51)



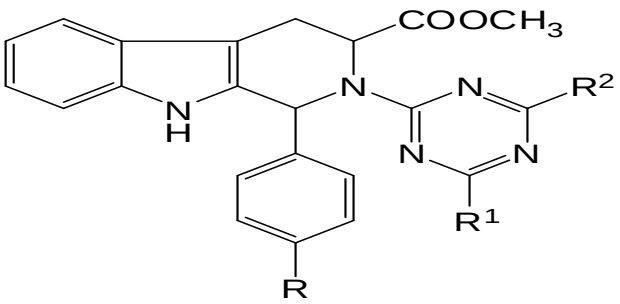
(52)

**Antileishmanial Activity**

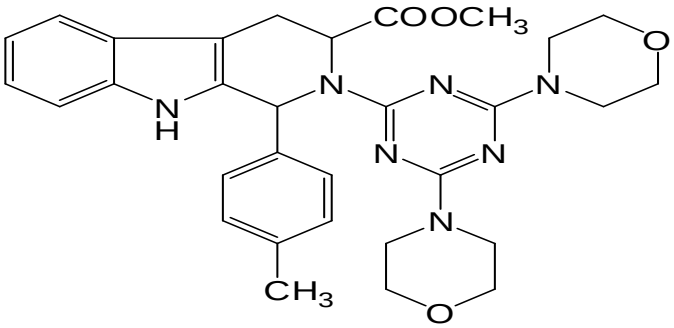
Kumar *et al.* have prepared a series of triazinotetrahydroisoquinolines and β-carboline derivatives (53 and 54) as novel antileishmanial agents. Among them, compounds (55), (56) and (57) have shown 78.0%, 78.6% and 68.0% *in vivo* inhibition against *Leishmania donovani* at a dose of 50 mg $kg^{-1}$ × 5 days, respectively [63].



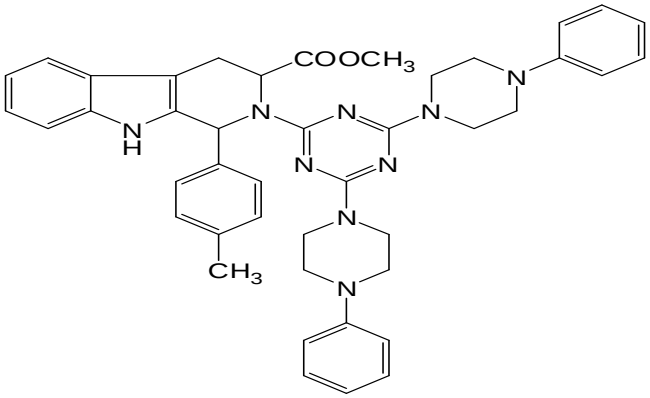
(53)



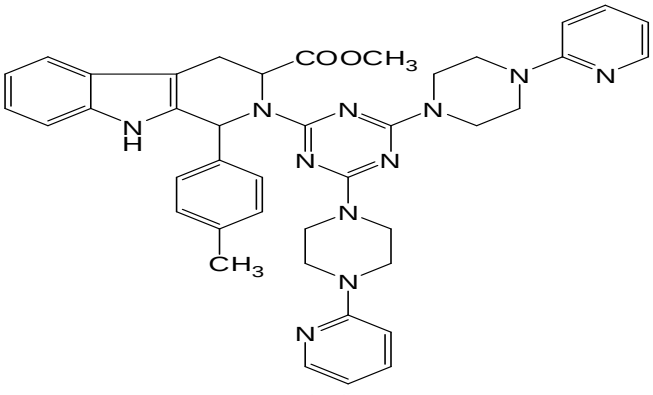
(54)



(55)

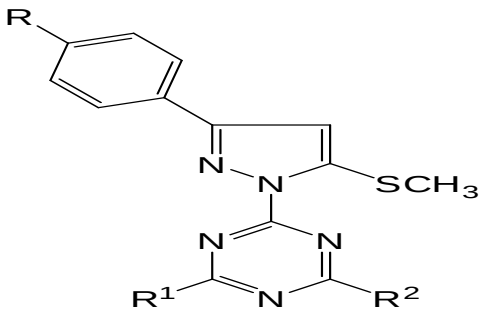


(56)



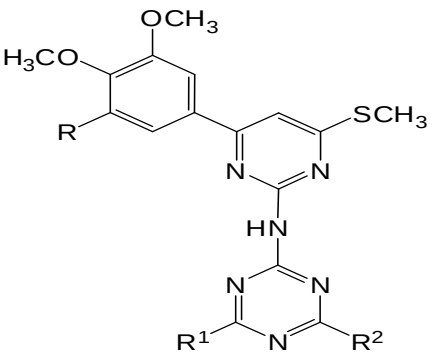
(57)

Sunduru *et al.* have synthesized a series of 2, 4, 6-trisubstituted triazines (58) and screened for its *in vitro* antileishmanial activity profile in promastigote model. Compounds have shown >94% inhibition against promastigotes at a concentration of 10 µg/mL [64].

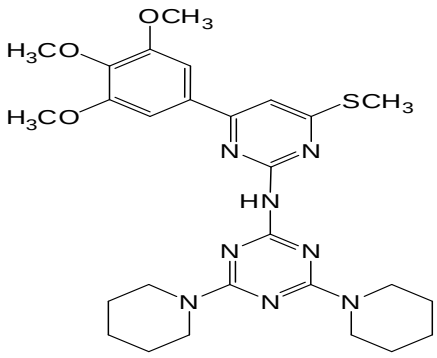



**(58)**

Sunduru *et al.* have synthesized a series of 2,4,6-trisubstituted-1,3,5-triazines **(59)** and screened for their *in vitro* and *in vivo* antileishmanial activity against *Leishmania donovani*. The compound **(60)** with good selectivity index (S.I.) was screened for its *in vivo* activity in golden hamsters (*Mesocricetus auratus*) infected with MHOM/IN/80/$Dd_8$ strain of *L. donovani*, which shown moderate *in vivo* inhibition of 48–56% at a dose of 50 mg/kg × 5, i.p. route for 5 days [65].

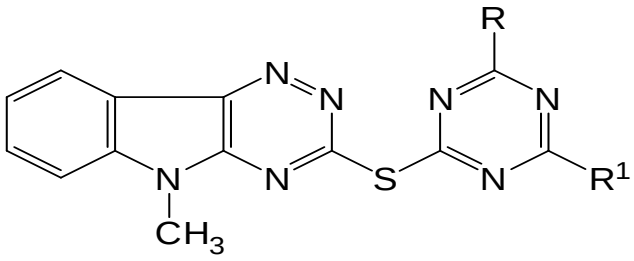



**(59)**

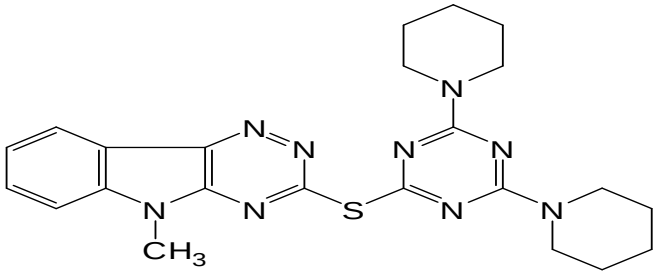



**(60)**

Gupta *et al.* have synthesized a series of [1,2,4]triazino[5,6-b]indol-3-ylthio-1,3,5-triazines (61) and screened for their *in vitro* antileishmanial activity against *Leishmania donovani*. Among all, compound (62), a triazino[5,6-b]indol-3-ylthio-1,3,5-triazine derivative was found to be the most active and least toxic with 20- & 10-fold more selectivity (S.I. = 56.61) as compared to that of standard drugs pentamidine and sodium stibogluconate (SSG), respectively [66].



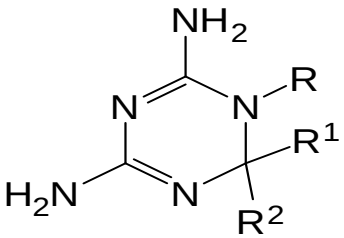
**(61)**



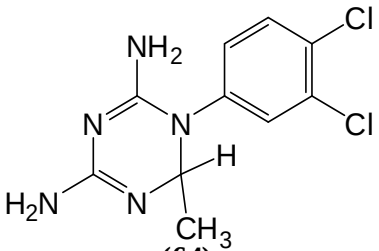
**(62)**

**Antimalarial Activity**

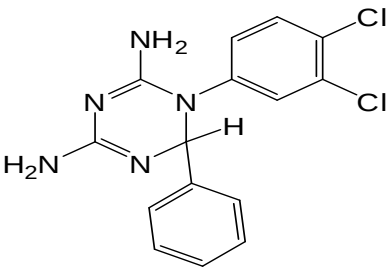
Vilaivan *et al.* have prepared a 96-membered solution-phase combinatorial mixture library of 4,6-diamino-1,2-dihydro-1,3,5-triazines (63). Screening of the library by iterative deconvolution method revealed two candidate leads (64 and 65) which are equally active against wild-type *Plasmodium falciparum* dihydrofolate reductase, but are about 100-fold more effective against the A16V + S108T mutant enzyme as compared to cycloguanil [67].



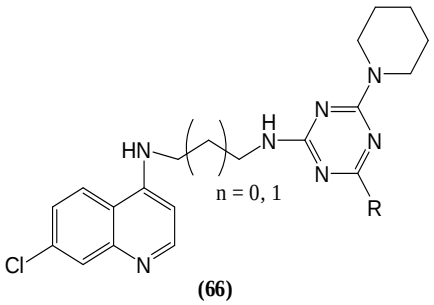
**(63)**



**(64)**

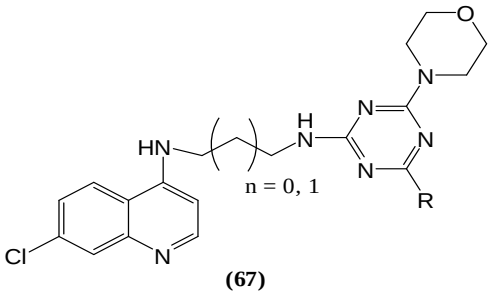


**(65)**

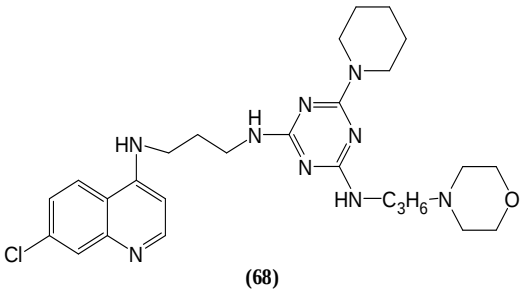


**(66)**

Sunduru *et al.* have synthesized a series of 4-aminoquinolines having triazine moiety (66 and 67) in the side chain and screened for their antimalarial activity. Compound (68) found to be the most active against CQ sensitive strain 3D7 of *Plasmodium falciparum* in an *in vitro* assay with an $IC_{50}$ of 5.23 ng/mL [68].

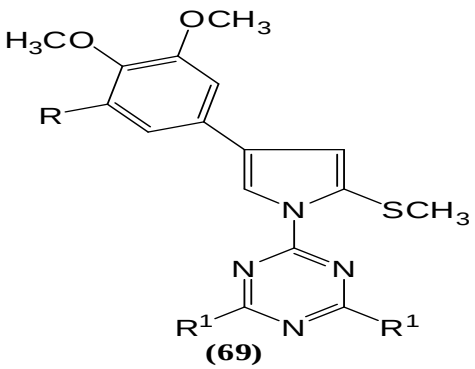



**(67)**

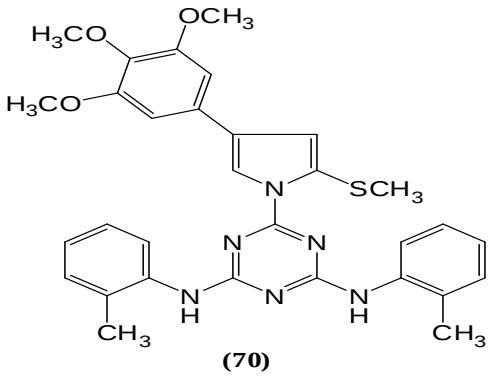



**(68)**

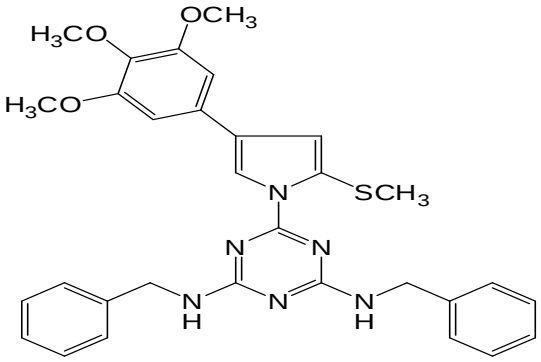
Katiyar *et al.* have synthesized a series of 2-[3, 5-substituted pyrazol-1-yl]-4,6-trisubstituted triazine derivatives (69) and screened against *Plasmodium falciparum* NF-54 strain. Of the screened compounds, six compounds (70, 71, 72, 73, 74, and 75) showed MIC in the range between 1 and 2 µg/mL. These compounds are 32 times more potent than the cycloguanil which was used as the standard drug [69].



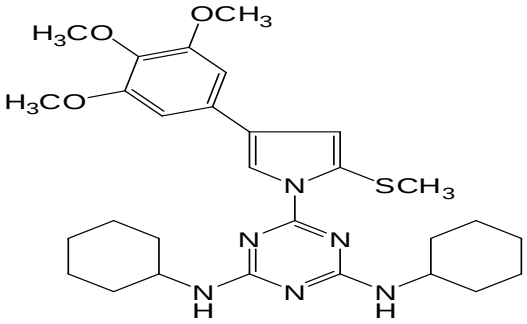

**(69)**



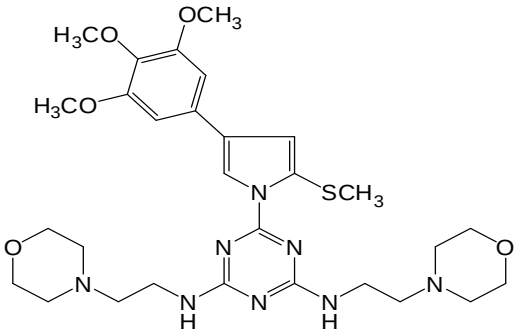

**(70)**



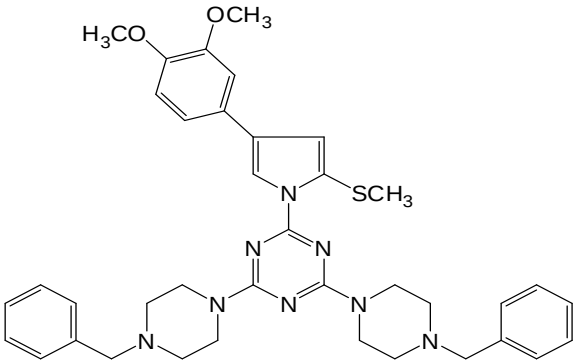
**(71)**



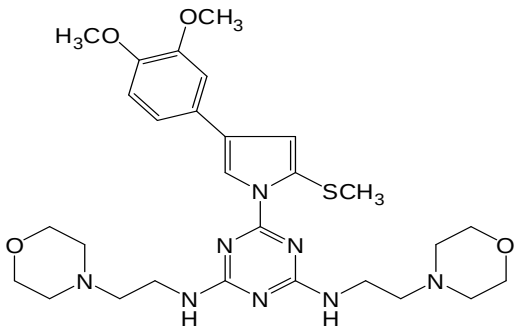
**(72)**



**(73)**

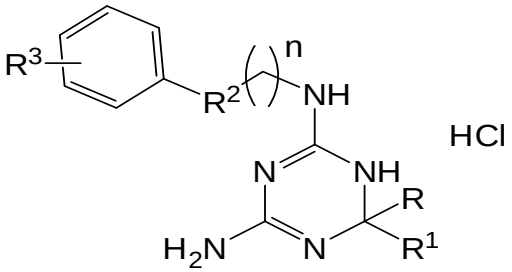


**(74)**



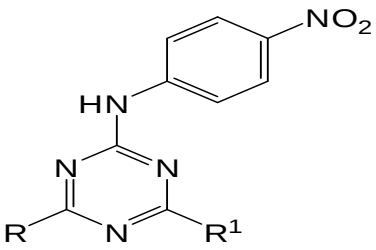
**(75)**

Gravestock *et al.* have discovered a small set of novel 2, $N^6$-disubstituted 1, 2-dihydro-1, 3, 5-triazine-4,6-diamines (76) and evaluated for their antimalarial activity [70].



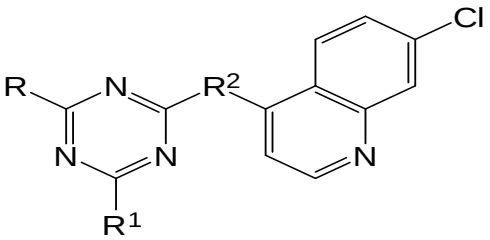
**(76)**

Agarwal *et al.* have prepared a series of some new 2, 4, 6-trisubstituted-1, 3, 5-triazines **(77)** and evaluated for their *in vitro* antimalarial activity against *Plasmodium falciparum*. Most of the compounds synthesized showed MIC in the range of 1–2 µg/mL [71].

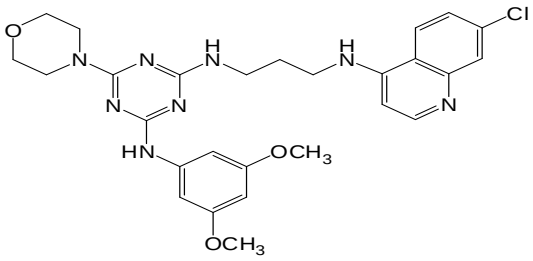


**(77)**

Manohar *et al.* have prepared a series 4-aminoquinoline–triazine conjugates (78) with different substitution pattern and evaluated for their *in vitro* antimalarial activity against chloroquine-sensitive and resistant strains of *Plasmodium falciparum*. Compound (79) exhibited promising antimalarial activity against both strains of *P. falciparum* [72].

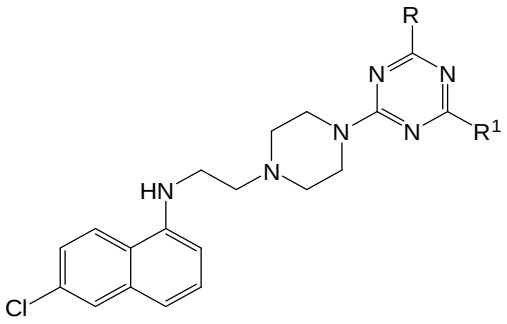


**(78)**

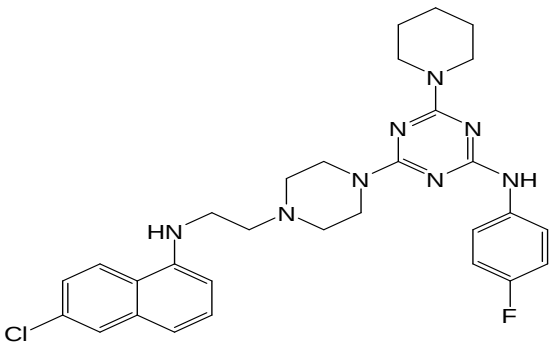


**(79)**

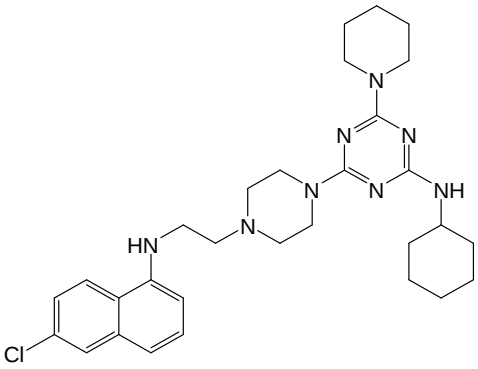
Kumar *et al.* have designed and synthesized a series of new class of hybrid 4-aminoquinoline triazines (80) and screened against CQ sensitive strain 3D7 of *Plasmodium falciparum* in an *in vitro* model. Compounds (81) and (82) exhibited more than 99% suppression on day 4 and on day 6 post treatment, compound (82) showed impressive 99.11% suppression against CQ resistant strain N-67 of *Plasmodium yoelii* in an *in vivo* assay [73].



**(80)**

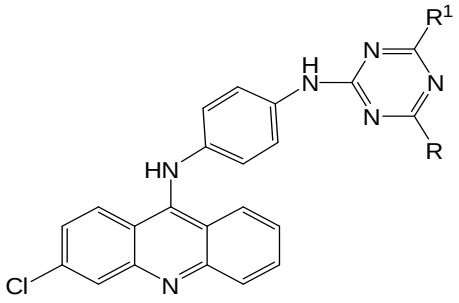


**(81)**

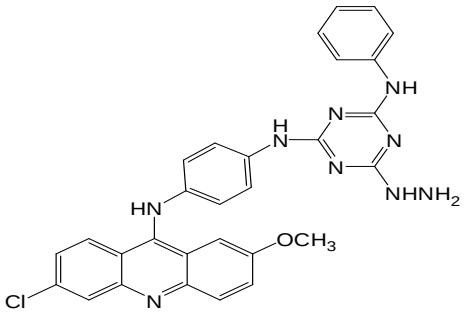


**(82)**

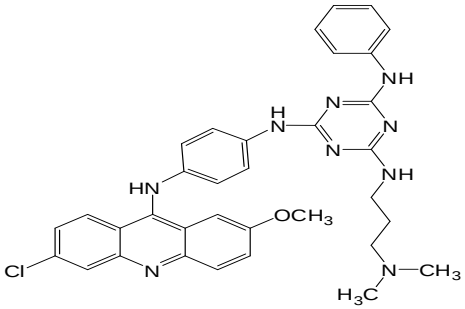
Kumar *et al.* have synthesized a new series of hybrid 9-anilinoacridine triazines (83) and were evaluated *in vitro* for their antimalarial activity against CQ-sensitive 3D7 strain of *Plasmodium falciparum* and their cytotoxicity was determined on VERO cell line. Of the evaluated compounds, compound (84) ($IC_{50}$ = 27 nM) displayed two times higher potency than CQ ($IC_{50}$ = 8.15 nM). Most of the compounds showed fairly high selectivity index. The compound (85) displayed >96.59% and 98.73% suppression, respectively, orally against N-67 strain of *Plasmodium yoelii* in swiss mice at dose 100 mg/kg for four days [21].



**(83)**

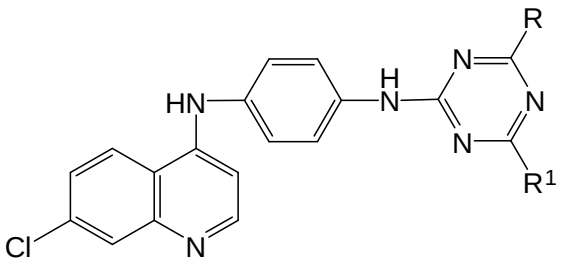


**(84)**

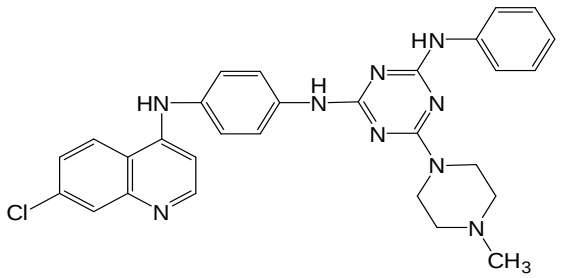


**(85)**

Kumar *et al.* reported a novel class of hybrid 4-anilinoquinoline triazines (86) and evaluated *in vitro* for their antimalarial activity against CQ-sensitive 3D7 strain of *Plasmodium falciparum* as well as for cytotoxicity toward VERO cell line. Compound (87) exhibited the antimalarial potency superior to CQ [75].



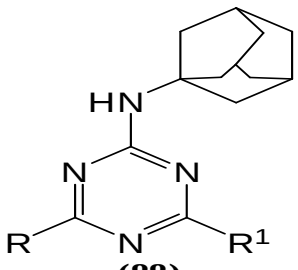
**(86)**



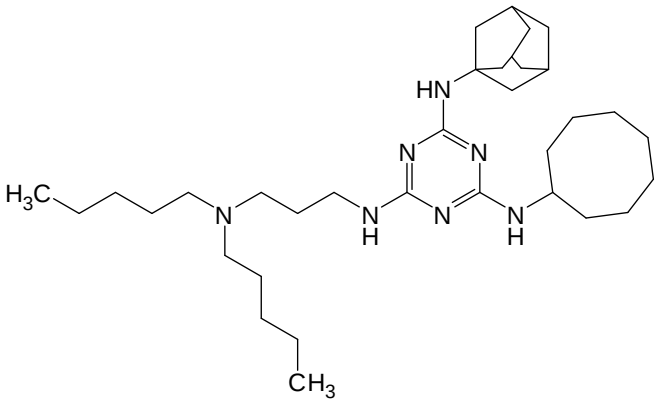
**(87)**

**Antimicrobial Activity**

Zhou *et al.* have designed and screened several combinatorial libraries based on 1,3,5-triazine as a template (88). Compound (89) was identified to show potent antimicrobial activity together with low hemolytic activity [76].

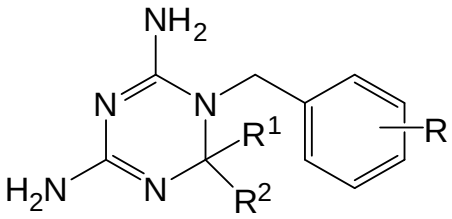


**(88)**

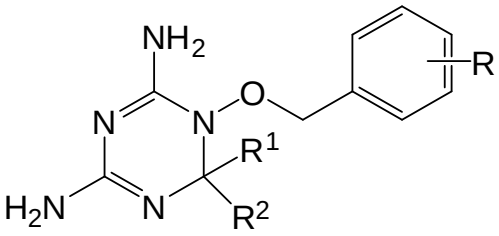


**(89)**

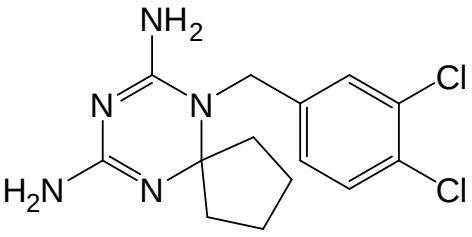
Maa *et al.* have prepared a series of $N^1$-benzyloxy-1,6-dihydro-1,3,5-triazine-2,4-diamine derivatives (90 and 91) and investigated for their antimicrobial activity against *S. aureus,* and *Mycobacterium smegmatis* which is taxonomically related to *M. tuberculosis*. Most of the compounds exhibited good activity against *M. smegmatis* as determined by comparison of diameters of the zone of inhibition of test compounds and standard antibiotics. Compound (92) showed potent antimycobacterial activity against *M. smegmatis* [77].



**(90)**

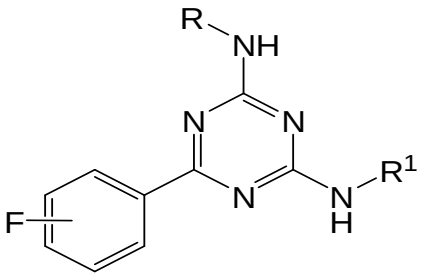


**(91)**

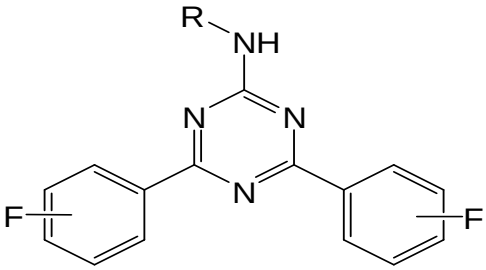


**(92)**

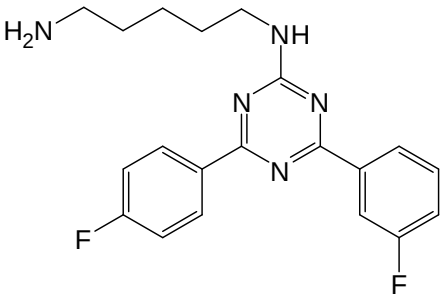
Saleh *et al.* have synthesized a series of 2-fluorophenyl-4, 6-disubstituted [1,3,5]triazines (93 and 94) and evaluated for their antimicrobial activity against three representative gram-positive bacteria and two fungi. The structure–activity relationship (SAR) demonstrates that the 3- or 4-fluorophenyl component attached directly to the triazine ring was essential for activity. Of these compounds, (95), (96) and (97) demonstrated significant activity against all selected organisms compared to control [78].



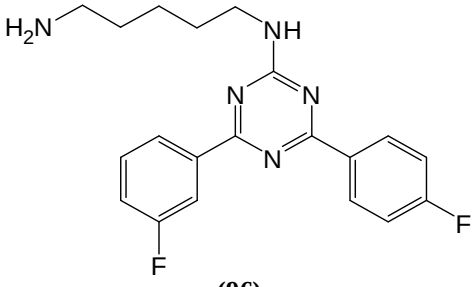
**(93)**



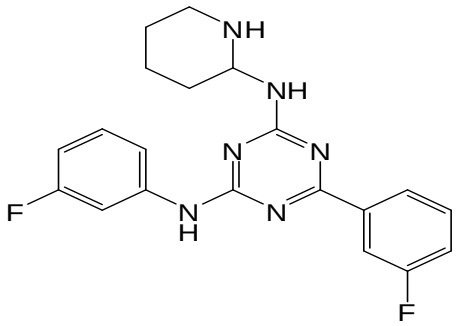
**(94)**



**(95)**

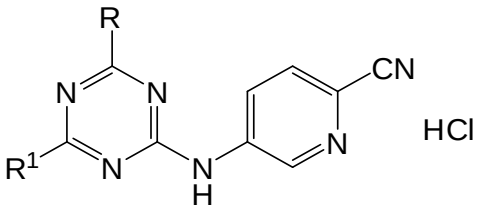


**(96)**

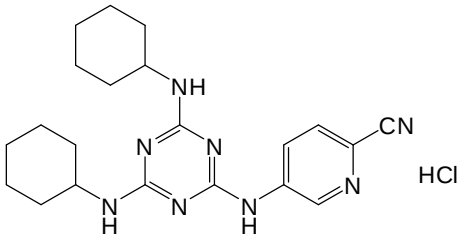


**(97)**

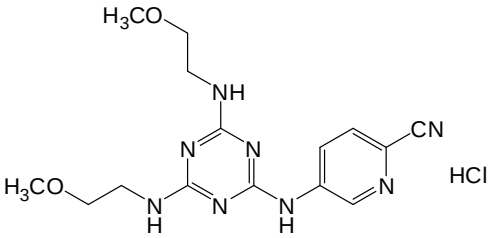
Gavade *et al.* have synthesized a series of 2, 4, 6-trisubstituted [1,3,5]triazines (98) and evaluated for their antimicrobial activity against two representative Gram-positive, Gram-negative bacteria and two fungi. Biological data revealed that among all the compounds screened, compounds (99), (100), (101), (102), (103), (104) and (105) found to have promising antimicrobial activity against all the selected pathogenic bacteria and fungi with MIC in the range of 6.25-12.5 µg/mL [79].



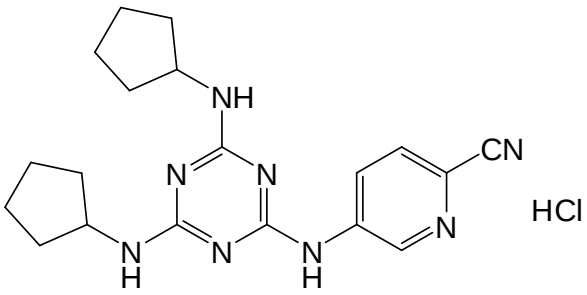
**(98)**



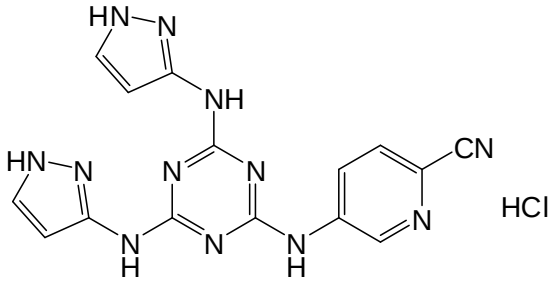
**(99)**



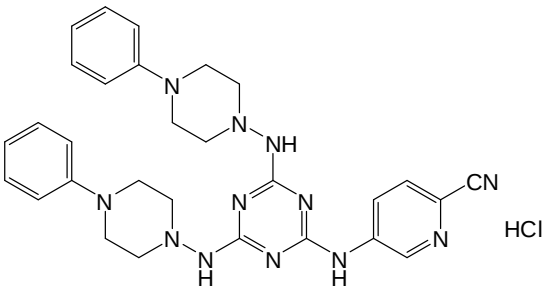
**(100)**



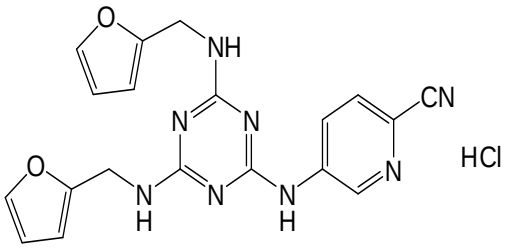

**(101)**



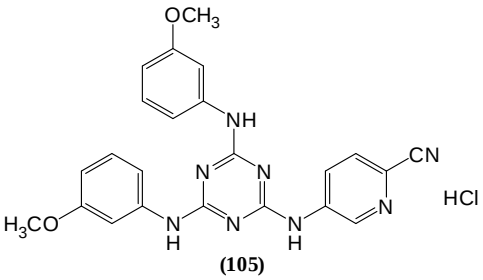

**(102)**




**(103)**

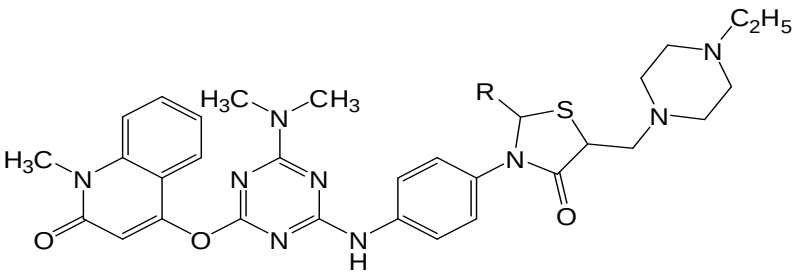



**(104)**



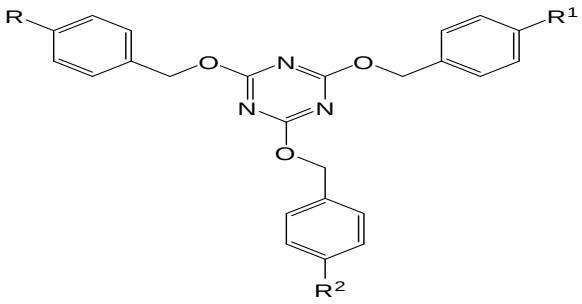

**(105)**

Patel *et al.* reported the thiazolidinone derivatives containing 1,3,5-triazine moiety (106) as potential antimicrobial agent [80].

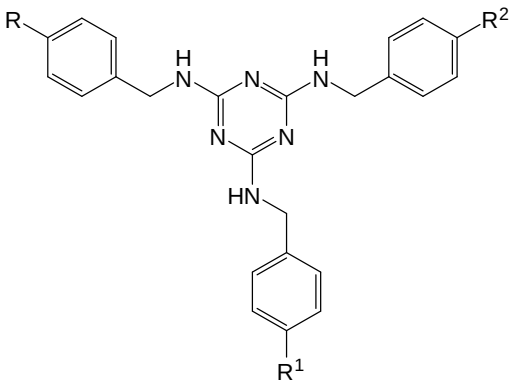


**(106)**

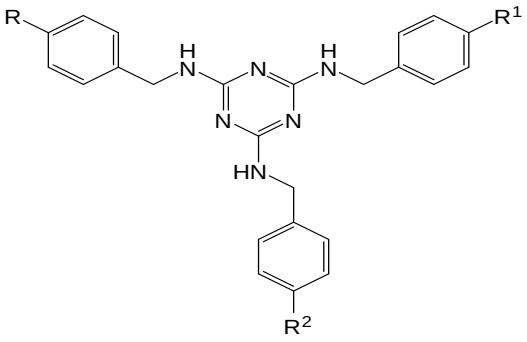
Srinivas *et al.* have synthesized various 2,4,6-trisubstituted s-triazines (107, 108 and 109) and screened for antibacterial activity against Gram-positive and Gram-negative organisms. These s-triazine derivatives displayed high *in vitro* antibacterial activities comparable to penicillin and streptomycin against tested microorganisms. Among them, compound (110) displayed significant large activity against both Gram-positive and Gram-negative microorganisms [81].



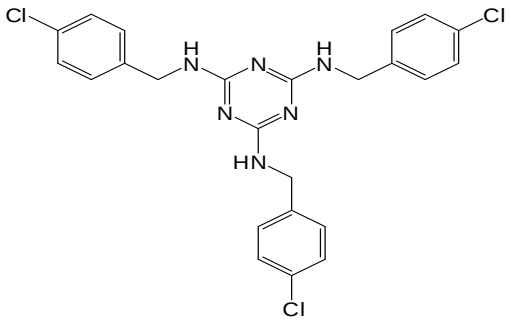
**(107)**



**(108)**

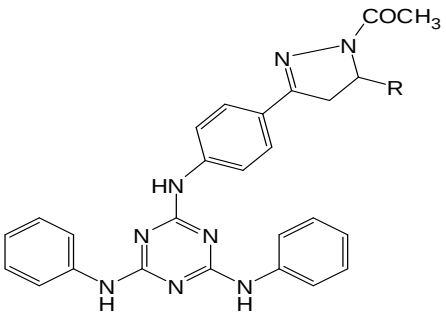


**(109)**

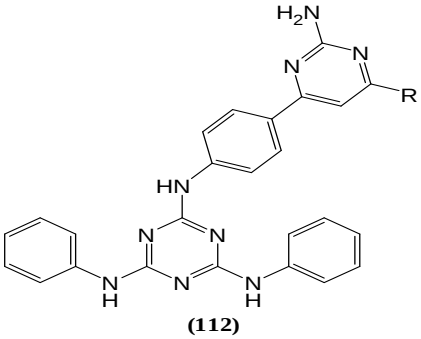


**(110)**

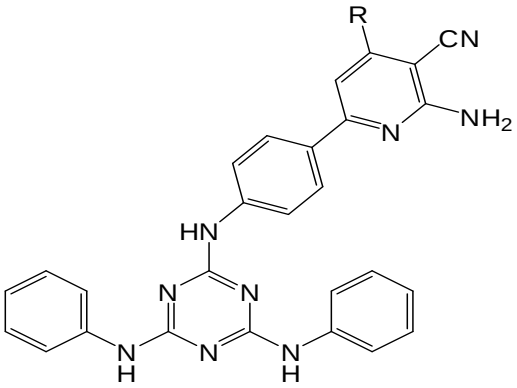
Solankee *et al.* synthesized a series of some new s-triazine based heterocyclic compounds (111, 112 and 113) and tested for their antibacterial activity. The Compound (114) exhibited the best antibacterial activity against all the bacteria tested with very low MIC and MBC, much lower than Ampicillin and almost 1.5 times lower in most cases than streptomycin [82].



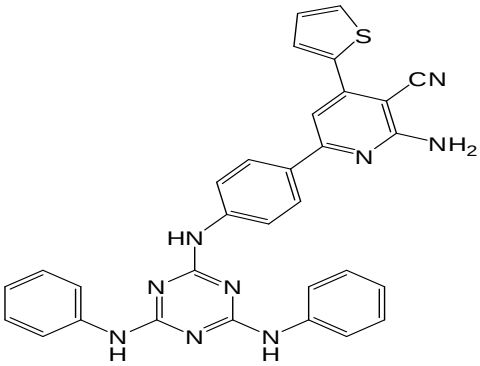
**(111)**



**(112)**

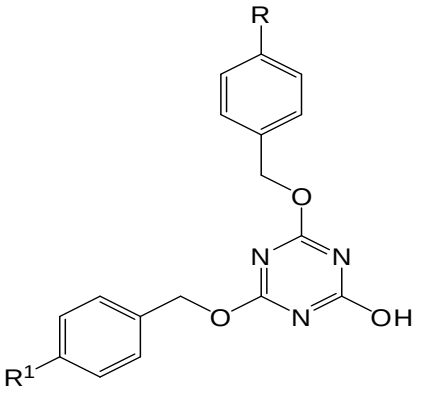


**(113)**

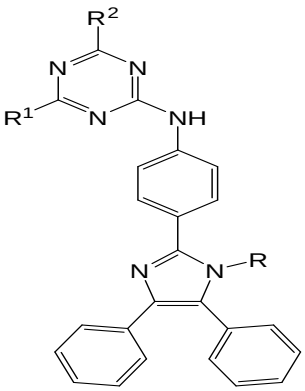


**(114)**

Srinivas *et al.* have synthesized a series of substituted-s-triazines (115 and 116) and evaluated for their *in vitro* antibacterial activity against six representative Gram positive and Gram negative bacterial strains. Many compounds have displayed comparable antibacterial activity against *Bacillus sphaericus* and significantly active against other tested organisms with reference to streptomycin [83].

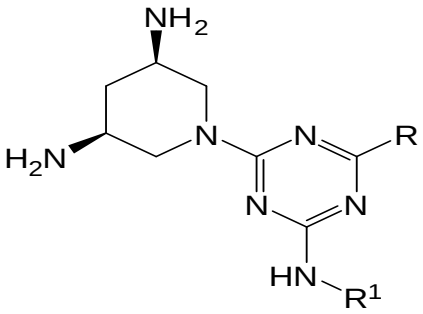


**(115)**



**(116)**

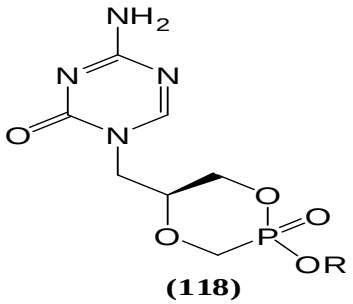
Zhou *et al.* have synthesized a series of 1, 3, 5-triazine derivatives **(117)** containing 3,5-diamino-piperidine moiety as major antibacterial translation inhibitors as aminoglycoside mimetics [84].



**(117)**

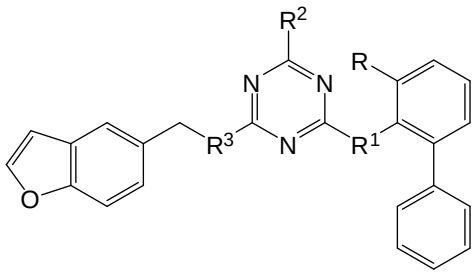
**ANTIVIRAL ACTIVITY**

Krecmerova *et al.* have prepared a new series of acyclic nucleoside phosphonates with 6-substituted 5-azacytosine base moiety (118) and evaluated activity against RNA viruses [85].



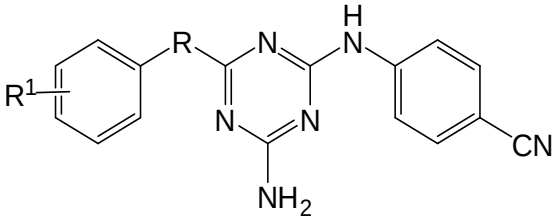
**(118)**

Liu *et al.* reported the discovery and SAR study of a series of 4,6-diamino-1,3,5-triazin-2-ol (119) compounds as novel HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTIs). Compounds showed excellent activity against wild-type and drug-resistant RT enzymes and viral strains. In addition, compounds from this series demonstrated favorable pharmacokinetic profile in rat [86].



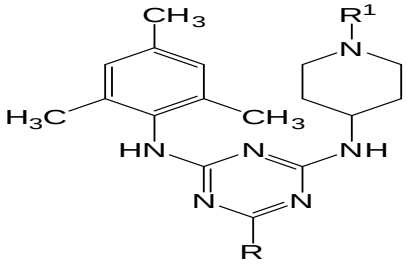
**(119)**

Ludovici *et al.* have discovered a series of diaryltriazines (DATAs) (120) and evaluated as a new class of potential non-nucleoside reverse transcriptase inhibitors (NNRTIs) [87].

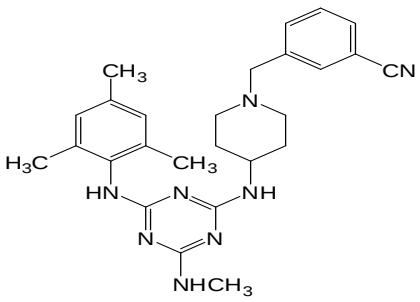


**(120)**

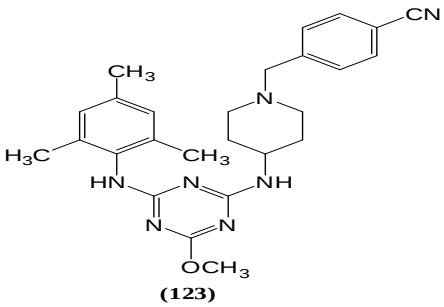
Chen *et al.* have prepared a novel series of piperidine-substituted triazine derivatives (121) and evaluated for anti-HIV activities in MT-4 cells. The compounds (122) and (123) displayed extremely promising activity against wild type HIV-1 with $EC_{50}$ values in low nanomolar concentration, better than that of nevirapine, delavirdine, zidovudine and dideoxycitidine, and higher potency towards the resistant mutant strain K103N/Y181C than that of nevirapine and delavirdine. Selected compounds were also assayed against reverse transcriptase with lower $IC_{50}$ values than that of nevirapine [88].



**(121)**



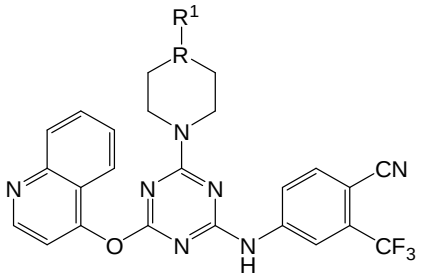
**(122)**



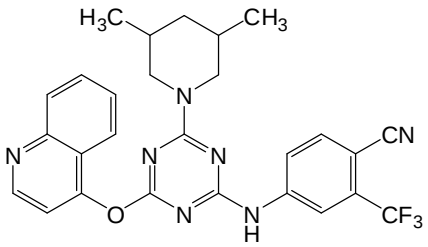
**(123)**

**ANTITUBERCULAR ACTIVITY**

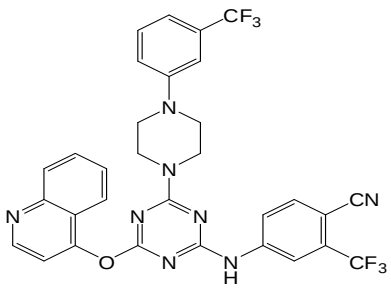
Patel *et al.* have reported the synthesis of a series of novel s-triazine analogs (124). Preliminary screening of target compounds against eight bacteria (*Staphylococcus aureus, Bacillus cereus, Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae, Salmonella typhi, Proteus vulgaris* and *Shigella flexneria*), four fungi (*Aspergillus niger, Aspergillus fumigatus, Aspergillus clavatus* and *Candida albicans*) and *Mycobacterium tuberculosis* H37Rv indicated that (125) and (126) were the most active compounds among twenty one studied. Thus, they were further subjected to *in vitro* biological evaluation against human prostate cancer cell line (DU-145) and the results indicated that they were distinctly active [89].



**(124)**



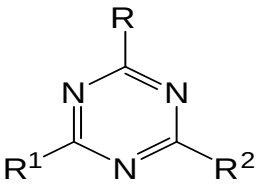
**(125)**



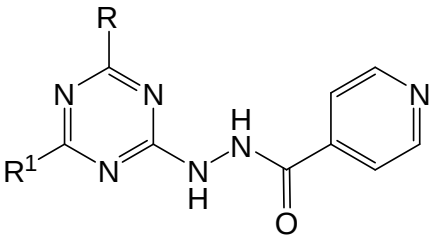
**(126)**

Sunduru *et al.* have synthesized a series of some novel 2,4,6-trisubstituted-1,3,5-triazines (127 and 128) and evaluated *in vitro* for the growth inhibition of *Mycobacterium tuberculosis* $H_{37}R_v$. Most of the compounds from this series exhibited good to moderate activity and most

of them were found to be nontoxic against VERO cells and MBMDMQs (mouse bone marrow derived macrophages) [90].



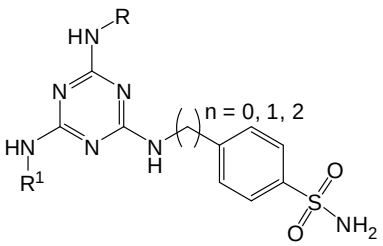
**(127)**



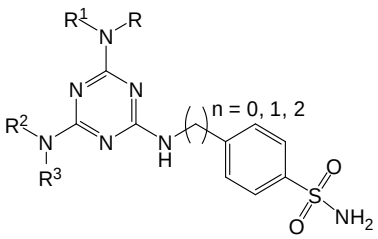
**(128)**

**Carbonic Anhydrase Inhibitors**

Garaj *et al.* have reported the synthesis of some aromatic benzenesulfonamides incorporating 1,3,5-triazine moieties in their molecules (129 and 130). This series was obtained by reaction of cyanuric chloride with sulfanilamide, homosulfanilamide or 4-aminoethylbenzenesulfonamide. The library of sulfonamides incorporating triazinyl moieties was tested for the inhibition of three physiologically relevant carbonic anhydrase (CA, EC 2.1.1) isozymes, the cytosolic *h*CA I and II, and the transmembrane, tumour-associated *h*CA IX. The new compounds inhibited *h*CA I with inhibition constants in the range of 31-8500 nM, *h*CA II with inhibition constants in the range of 14-765 nM and *h*CA IX with inhibition constants in the range of 1.0-640 nM. Structure–activity relationship was straightforward and rather simple in this class of CA inhibitors, with the compounds incorporating compact moieties at the triazine ring (such as amino, hydrazino, ethylamino, dimethylamino or amino acyl) being the most active ones, and the derivatives incorporating such bulky moieties (n-propyl, n-butyl, diethylaminoethyl, piperazinylethyl, pyridoxal amine or phenoxy) being less effective *h*CA I, II and IX inhibitors. Some of the new derivatives also showed selectivity for inhibition of *h*CA IX over *h*CA II (selectivity ratios of 23.33-32.00) [91].



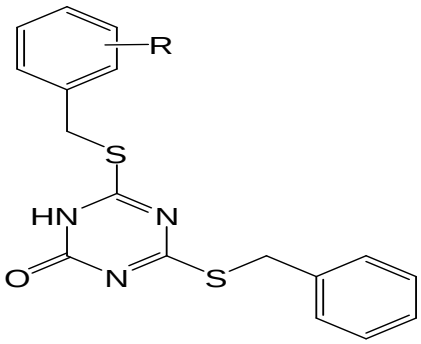
**(129)**



**(130)**

**Cathepsin B Inhibitors**

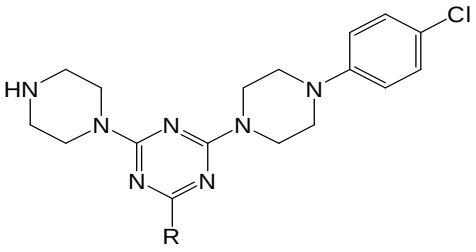
Sosic *et al.* have discovered a series of 6-substituted 4-benzylthio-1,3,5-triazin-2(1H)-ones **(131)** as inhibitors of cathepsin B [92].



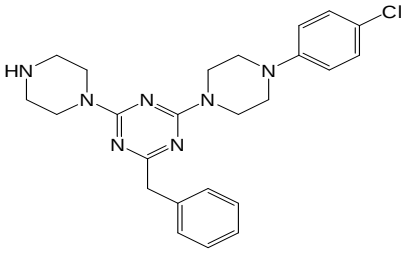
**(131)**

**Cholesteryl Ester Transfer Protein (Cetp) Inhibitors**

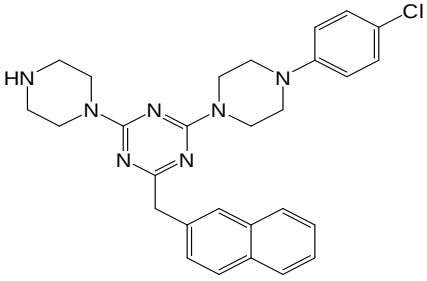
Xia *et al.* have reported the synthesis of substituted 1,3,5-triazines **(132)** and evaluated for their cholesteryl ester transfer protein (CETP) inhibitory activities. Among the most potent compounds were those with R= benzyl ($IC_{50}$ = 9 µM) **(133)** and R= [(2-naphthalenyl)methyl] ($IC_{50}$ = 5 µM) (134) [93].



**(132)**



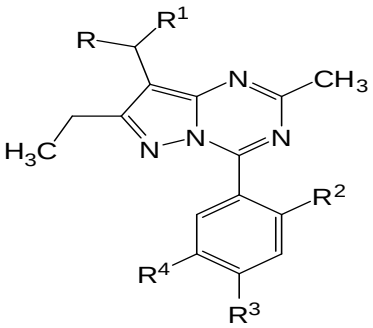
**(133)**



**(134)**

**Corticotropin-Releasing Factor Ligands**

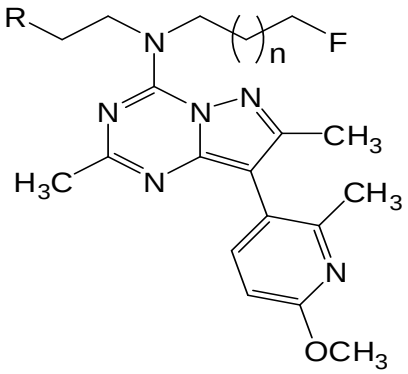
Gilligan *et al.* have prepared a series of pyrazolo-[1, 5-a]-1,3,5-triazines (135) and evaluated as corticotropin-releasing factor (CRF) ligands. Some are having high affinity for rat CRF receptors ($K_i \leq 10$ nM) [94].



**(135)**

**Crf$_1$r Pet Imaging Agents**

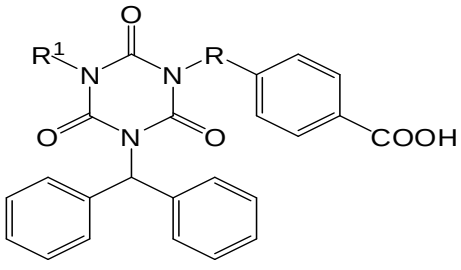
Zuev *et al.* have prepared a series of N-fluoroalkyl-8-(6-methoxy-2-methyl-pyridin-3-yl)-2,7-dimethyl-N-alkyl pyrazolo [1,5-a][1,3,5] triazin-4-amines (136) and evaluated as potential $CRF_1R$ PET imaging agents [95].



**(136)**

**Cytosolic Phospholipase A$_{2\alpha}$ Inhibitors**

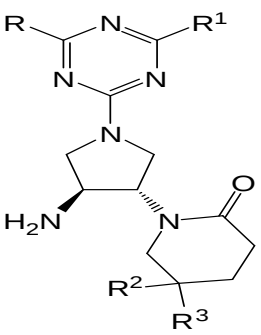
Gopalsamy *et al.* reported the synthesis of 1, 3, 5-triazin-2, 4, 6-triones (137) and evaluated as cytosolic phospholipase $A_{2\alpha}$ inhibitors [96].



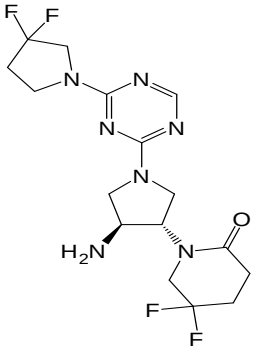
**(137)**

**Dipeptidyl Peptidase Iv (Dpp-4) Inhibitors**

Andrews *et al.* have synthesized a series of 1-((*3S, 4S*)-4-Amino-1-(4-substituted-1,3,5-triazin-2-yl) pyrrolidin-3-yl)-5,5-difluoropiperidin-2-ones (138) and tested for dipeptidyl peptidase IV (DPP-4) inhibitory activity. Advanced profiling in a rat PK/PD model and subsequent human projections identified (139) as having an acceptable human DPP-4 inhibition profile with a projected dose of 100 mg/q.d [97].



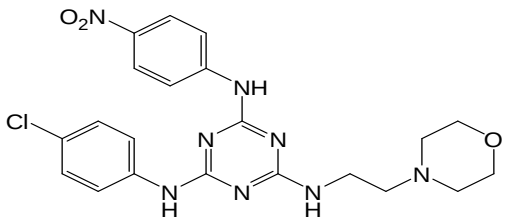
**(138)**



**(139)**

**Dnab Inhibitor**

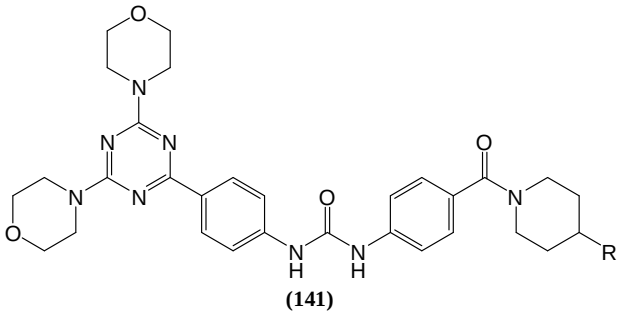
McKay *et al.* have discovered 1,3,5-triaminotriazine derivative (140) as potent inhibitor of the replicative helicase DnaB from *P. aeruginosa* [98].



**(140)**

**Dual Pi3k/Mtor-Inhibitors**

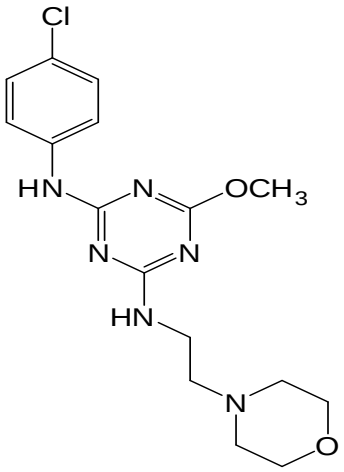
Dehnhardt *et al.* have recently described several highly potent triazine (141) scaffold-based, dual PI3K/mTOR-inhibitors that were efficacious in both *in vitro* and *in vivo* models [99].



**(141)**

**Egfr-T790m/L858r Inhibitor**

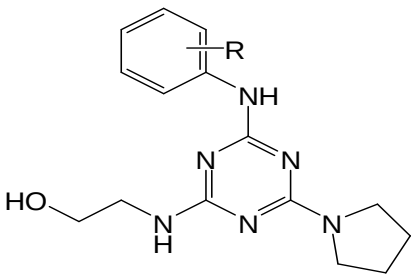
Bai *et al.* have discovered a 1, 3, 5-triazine derivative **(142)** as novel selective inhibitor for EGFR-T790M/L858R [100].



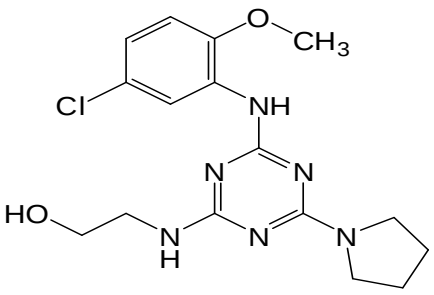
**(142)**

**Glucocerebrosidase Inhibitors**

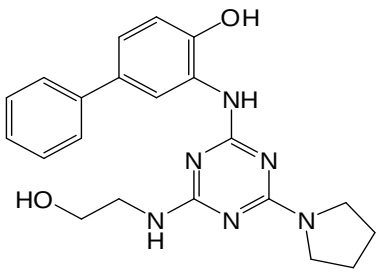
Huang *et al.* have prepared a series of 1, 3, 5-triazine-2, 4, 6-triamines (143) and analyzed as inhibitors of glucocerebrosidase. Compounds (144), (145) and (146) exhibited significant inhibitory activity [101].



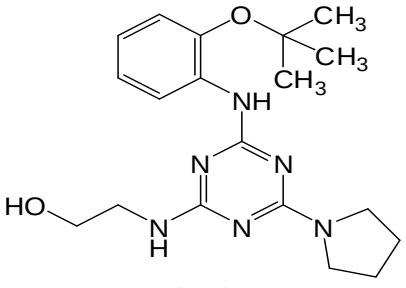
**(143)**



**(144)**



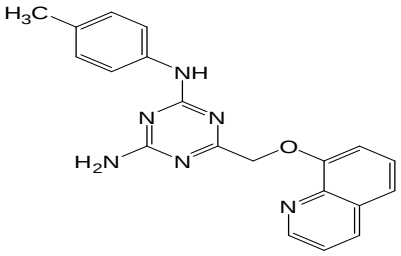
**(145)**



**(146)**

**A-Glucosidase Inhibitors**

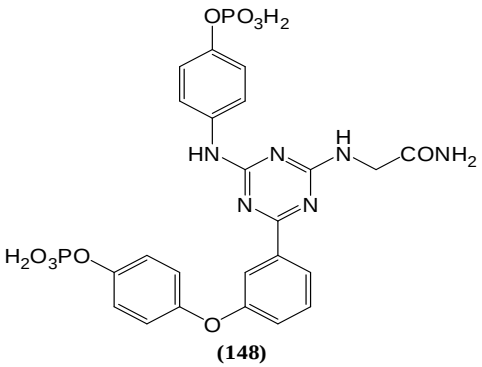
Park *et al.* have identified 1,3,5-triazine derivative (147) as novel inhibitor of α-glucosidase by applying a computer-aided drug-design protocol involving the structure-based virtual screening with docking simulations under consideration of the effects of ligand solvation in the scoring function. This inhibitor exhibited *in vivo* antidiabetic activity as well as a significant *in vitro* potency [102].



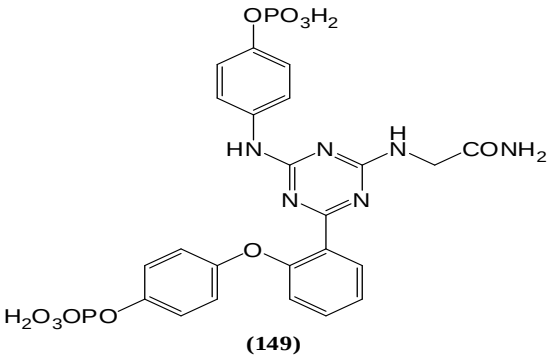
**(147)**

**Growth Factor Inhibitors**

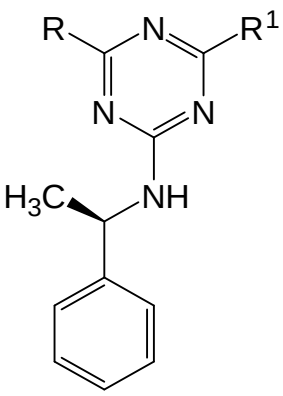
Courme *et al.* have reported the 1,3,5-trisubstituted triazine analogs (148-152) as non-peptidic, non-phosphate inhibitors of Grb2-SH2 (growth factor receptor-bound protein-2) [103].



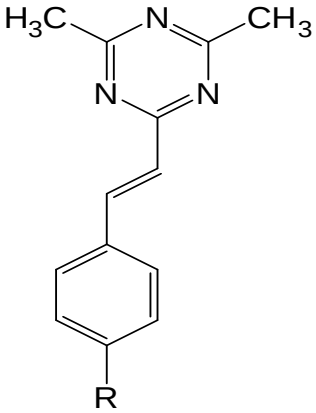
**(148)**



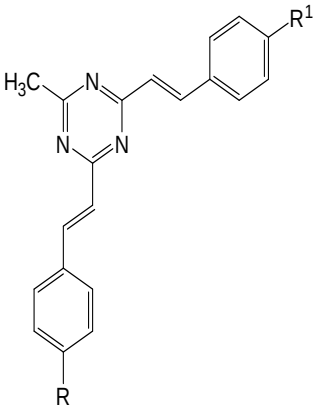
**(149)**



**(150)**



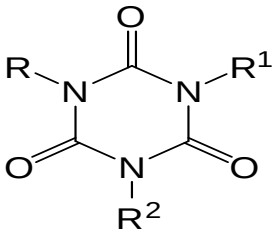
**(151)**



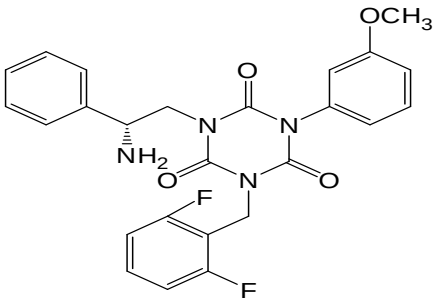
(152)

**Human Gonadotropin-Releasing Hormone (*H*gnrh) Receptor Antagonists**

Guo *et al.* have developed a series of asymmetric 1,3-dialkyl-1,3,5-triazine-2,4,6-triones (153) and evaluated as human gonadotropin-releasing hormone (*h*GnRH) receptor antagonists. Compound (154) is the potent among all the tested compounds with Ki value of 37nM [104].



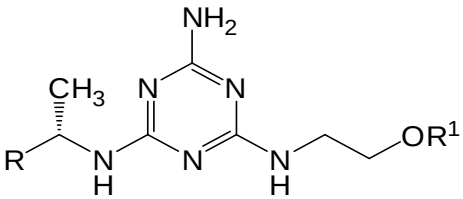
**(153)**



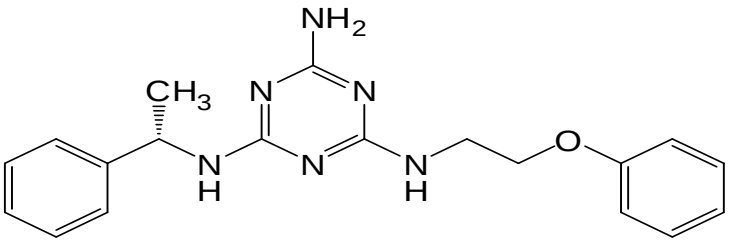
**(154)**

**5-Ht$_7$ Receptor Antagonist**

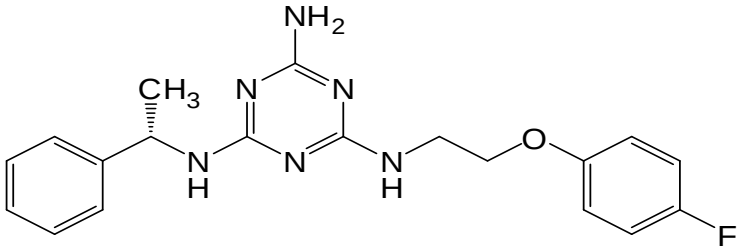
Mattson *et al.* have prepared a series of aminotriazines (155) and evaluated for their 5-HT$_7$ receptor antagonistic activity. Compounds (156) and (157) have high affinity for the 5-HT$_7$ receptor and do not bind to either the 5-HT$_{2C}$ or 5-HT$_6$ receptors [105].



**(155)**



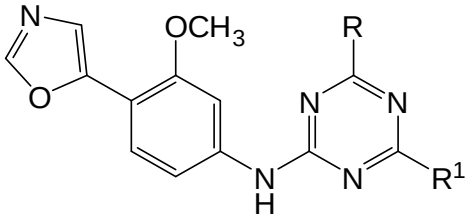
**(156)**



**(157)**

**Inosine Monophosphate Dehydrogenase (Impdh Ii) Inhibit- -Ors**

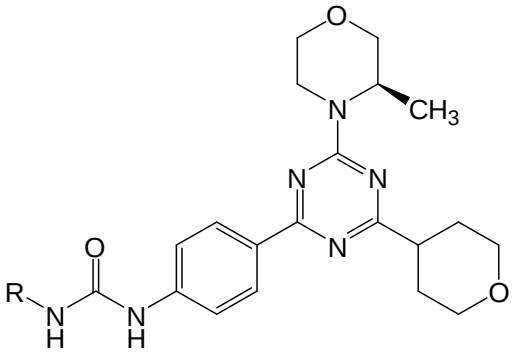
Pitts *et al.* have prepared a series of novel triazine-based small molecules (158) and screened for inosine monophosphate dehydrogenase (IMPDH II) inhibitory activity [106].



**(158)**

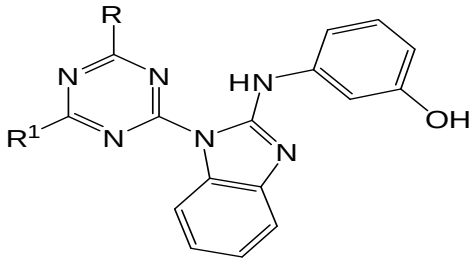
**Mtor Kinase Inhibitors**

Richard *et al.* have synthesized a series of triazines incorporating *(R)*-3-methylmorpholine moiety (159) and evaluated as potent inhibitors of the mammalian target of rapamycin (mTOR) with selectivity over PI3Kα. Analogs containing the *(R)*-3-methylmorpholine substituent and a pyridylureidophenyl group displayed greater than 500-fold selectivity for mTOR over the related lipid kinase PI3Kα. The addition of basic amines at the 4-position of the ureidophenyl ring was well-tolerated and offers the opportunity to develop mTOR inhibitors with improved physicochemical properties. Amide derivatives at this site resulted in reduced selectivity over PI3Kα but enhanced cellular activity [107].



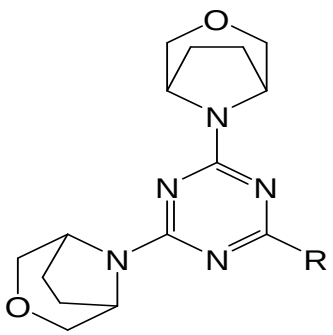
**(159)**

Peterson *et al.* have reported the discovery of triazine benzimidazole inhibitors (160) that inhibit mTOR kinase activity with up to 200-fold selectivity over the structurally homologous kinase PI3Kα. When tested in a panel of cancer cell lines displaying various mutations, a selective inhibitor from this series inhibited cellular proliferation with a mean $IC_{50}$ of 0.41 μM [108].

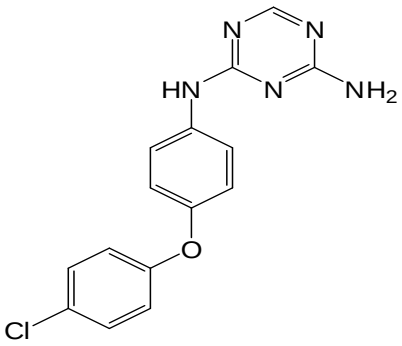


**(160)**

Verheijen *et al.* have reported the synthesis and biological evaluation of some new 2-arylureidophenyl-4-(3-oxa-8-azabicyclo[3.2.1]octan-8-yl)triazines (161) as highly potent and selective ATP competitive mTOR inhibitors [109].



**(161)**



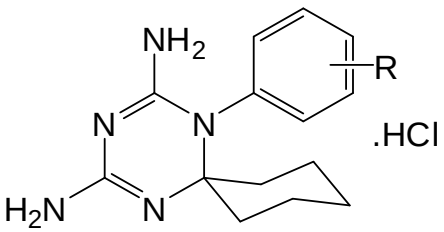
**(162)**

**$Na_v1.7$ Antagonist**

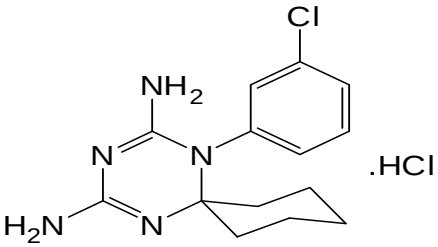
Bregman *et al.* have discovered a 1, 3, 5-triazine based hit compound (162) as novel and potent $Na_v1.7$ antagonist [110].

**Neuronal Voltage-Gated Sodium Channel Blockers**

Maa *et al.* have prepared a series of 2, 4-diamino-1, 3, 5-triazine derivatives (163) and investigated for their neuronal sodium channels binding activity. Compound (164) was found to have the best neuronal sodium binding activity among the series of triazines evaluated [111].



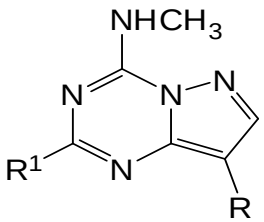

**(163)**



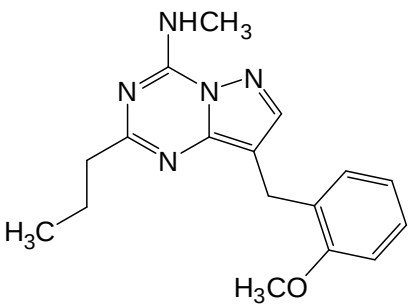

**(164)**

**Phosphodiesterase Type 4 Inhibitors**

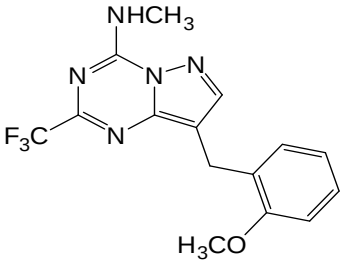
Raboisson *et al.* have prepared a series of 8-substituted pyrazolo[1,5-a]-1,3,5-triazines **(165)** and evaluated as a new structural class of potent phosphodiesterase type 4 inhibitors with high isoenzyme selectivity. Preliminary biological testing has shown that compounds **(166)** and (167) strongly inhibited LPS-induced TNFα release from human mononuclear cells from healthy subjects [112].




**(165)**



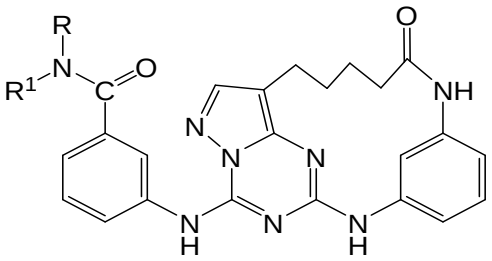

**(166)**



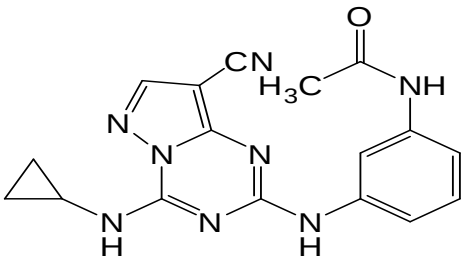
**(167)**

**Protein Kinase Ck2 Inhibitors**

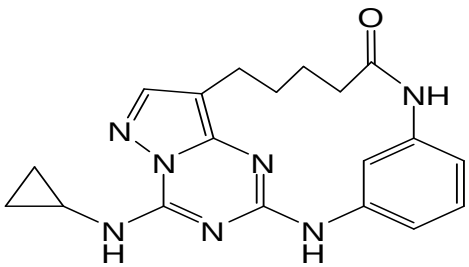
Nie *et al.* have designed and synthesized a series of macrocyclic derivatives based on the X-ray co-crystal structures of pyrazolo[1,5-a] [1,3,5]triazines (168-170) with corn CK2 (cCK2) protein. Bioassays demonstrated that these macrocyclic pyrazolo[1,5-a] [1,3,5]triazine compounds are potent CK2 inhibitors with $K_i$ around 1.0 nM and strongly inhibit cancer cell growth with $IC_{50}$ as low as 100 nM [113].



**(168)**

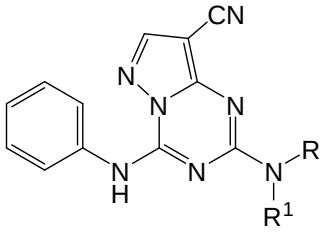


**(169)**

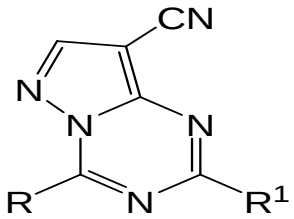


**(170)**

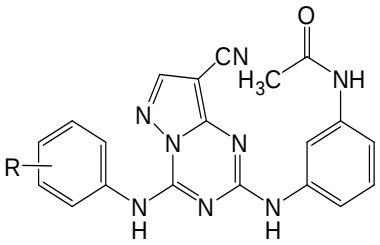
Nie *et al.* have described the design and synthesis of pyrazolo[1,5-a][1,3,5]triazines (171, 172 and 173) as novel protein kinase CK2 inhibitors. Using X-ray crystal structures of cCK2, protein structure-based design enabled us to identify the most potent CK2 inhibitors with $K_i$ < 1 nM. These compounds also showed strong inhibition against cancer cell growth [114].



**(171)**



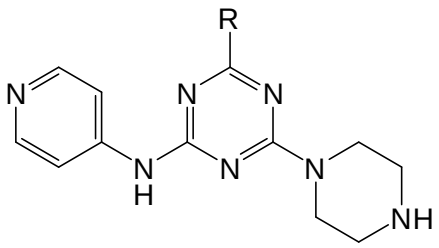
**(172)**



**(173)**

**Rock Inhibitors**

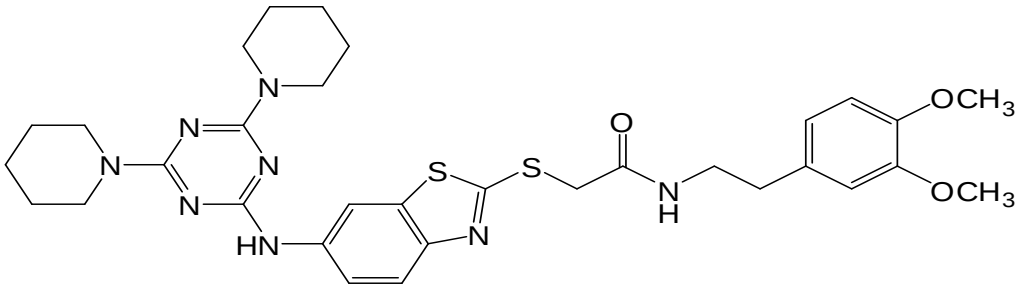
Ho *et al.* have reported the profile of a series of triazine and pyrimidine based ROCK inhibitors (174). An initial binding mode was established based on a homology model and the proposed interactions are consistence with the observed SAR. Compounds from the series are potent in a cell migration assay and possess a favorable kinase selective. *In vivo* activity was demonstrated in the spontaneous hypertensive rat model [115].



**(174)**

**B-Secretase Inhibitor (Bace-1)**

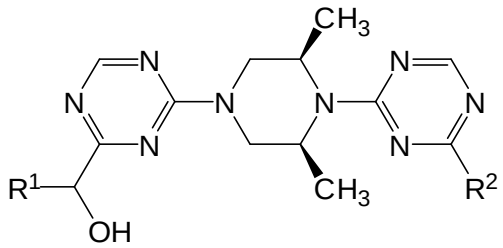
Xu *et al.* have identified the 1, 3, 5-triazine derivative (175) as potential non-peptide β-secretase inhibitor (BACE-1) with $IC_{50}$ of 2.8 µM [116].



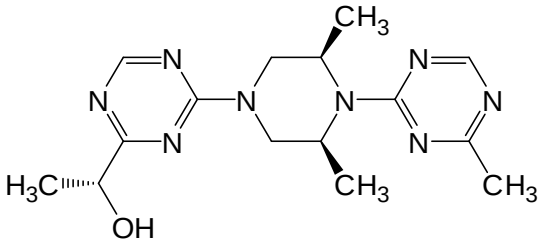
**(175)**

**Sorbitol Dehydrogenase Inhibitors (Sdis)**

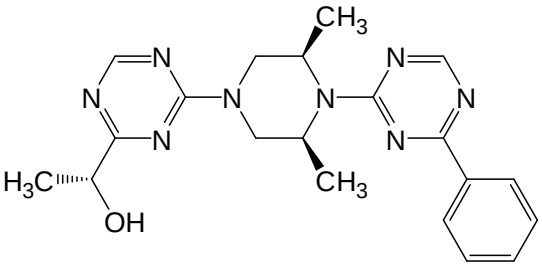
Mylari *et al.* have synthesized some new *(R)* 2-hydroxyethyl-triazine derivatives (176) as novel sorbitol dehydrogenase inhibitors (SDIs). Inhibitors, (177), (178) and (179) showed $IC_{50}$s in the range of 40-90 nM and all were orally active in reducing fructose production in the sciatic nerve of streptozotocin diabetic rats. The best inhibitor in this series was compound (177) which was quite potent and normalized sciatic nerve fructose by 114 and 96% at an oral dose of 10 mg/kg, in the acute and chronic tests, respectively [117].



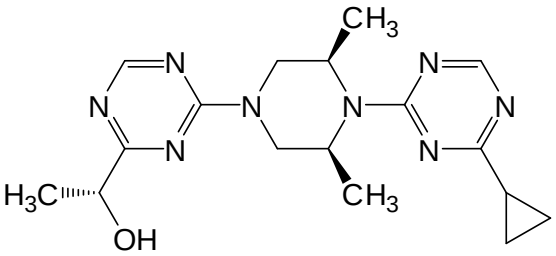
**(176)**



**(177)**



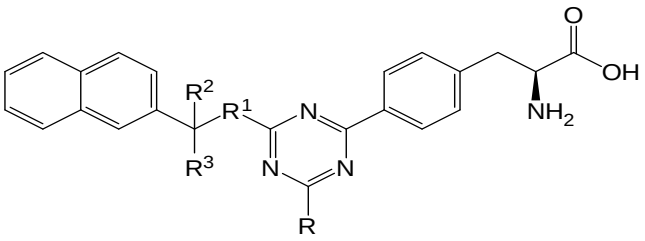
**(178)**



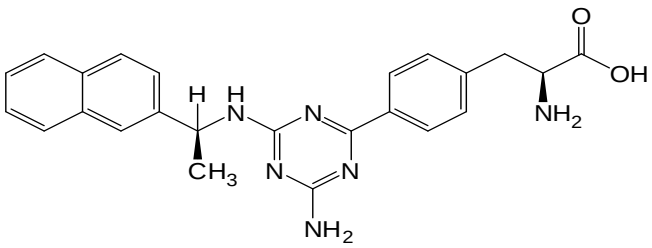
**(179)**

**Tryptophan Hydroxylase (Tph) Inhibitor**

Jin *et al.* have synthesized a series of substituted 3-(4-(1, 3, 5-triazin-2-yl)-phenyl)-2-aminopropanoic acids (180) as a novel class of tryptophan hydroxylase (TPH) inhibitors. TPH inhibitors, such as (181), can selectively inhibit peripheral 5-HT synthesis without effects on the central nervous system because of very poor systemic exposure and the inability to cross the blood brain barrier. This novel class of peripheral TPH inhibitors may provide potential treatments for a variety of gastrointestinal diseases caused by dysregulation of the serotonergic pathway in the periphery [118].



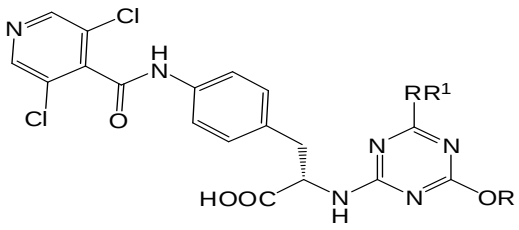
**(180)**



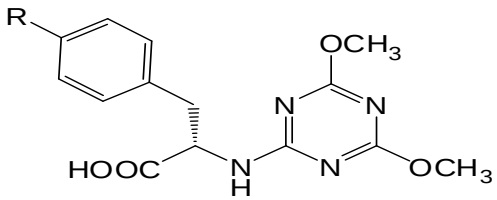
**(181)**

**Vla-4 Integrin Antagonists**

Porter *et al.* have synthesized a series of N-(triazin-1, 3, 5-yl) phenylalanine derivatives (182 and 183) and evaluated as potential VLA-4 integrin antagonists [119].



(182)



(183)

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