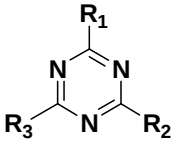
Chapter I

Introduction

1.1 General Introduction

1,3,5-Triazine forms an important class of heterocycles which have attracted much synthetic interest due to their wide range of biological activities such as antimicrobial[1,2,3], anticancer[4,5], antimalarial[6], antiviral[7], antibacterial[8,9,10], antiprotozoal[11], antifungal[12,13], antimycobacterial[14], ERM (erythromycin resistance methylase) methyltranseferase inhibitor[15], anti-typanosomal[16], antagonism[17], estrogen receptor modulation[18], cytotoxic activity[19], herbicidal[20], antiulcer[21], antiarthrite[22], local anaesthetic[23], anticonvulsant[24], analgesic[25], hypoglycemic[26], anti-inflamatory[27], and antihelmentic[28] activities. Recent studies, based on the s-triazine scaffold exhibiting significant anti-tumour and anti-HIV activity have led these to be considered as most promising molecules to be employed as lead structures in the discovery of newer medicinally potent chemotherapeutic agents.

s-Triazine contains alternate carbon and nitrogen bonds and is characterised by symmetrical hexameric ring **1.001 (Fig.- 1.1).** There are three isomers of triazines **1.002-1.004 (Fig.- 1.1)** which are either found as synthetic materials or in nature. These are as follows:-

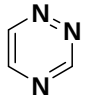


***s*-Triazine**

1.001

1,2,3-triazine

1.002



1,2,4-triazine or asymmetrical triazine or triazine

1.003

1,3,5-triazine or symmetrical triazine or cyanidine

1.004

Fig.- 1.1

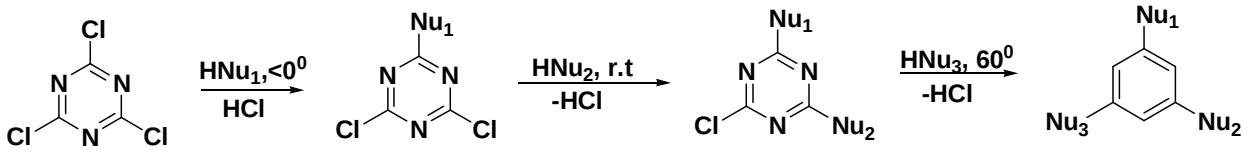
1,2,3-Triazine is found only in condensed systems such as 1,2-benzotriazine, while 1,2,4-triazines and 1,3,5-triazines are found in monocyclic systems[29].

The main aim of the present work has been to synthesize biologically active s-triazine derivatives which could benefit the society in combating the variety of body ailments. Due to highly symmetrical molecular structure of s-triazines they are extremely volatile, are weak bases, and have weaker resonance energy than benzene therefore nucleophilic substitution is preferred than electrophilic substitution. As the main objective of this work has been to synthesize biologically active materials from s-triazine, in reference to this, it is considered necessary to illustrate in the account to follow an overview of the imaginative breadth of the work which have been done in the engemeity and past by presenting a showcase of research of last years.

1.2 Synthesis of s-triazine derivatives:

1.2.1 Synthesis of s-triazine derivatives by Nucleophilic substitution reactions:

The ease of displacement of chlorine atoms in 2,4,6-trichloro-1,3,5-triazine **(TCT, 1.005)** by various nucleophiles, in the presence of a hydrochloride acceptor usually sodium carbonate, bicarbonate, hydroxide or tertiary amines, makes this reagent useful for the preparation of mono-, di- and tri-substituted 1,3,5-triazines. The substitution of chlorine can be controlled by temperature to run in a stepwise manner. Mono-substitution of chlorine occurs below or at 0°C di-substitution at 40-45°C and tri-substitution above 60°C. The substitution pattern also depends on the structure of the nucleophile, its basic strength and steric factors, the substituent already present in the s-triazine ring and the nature of solvent used. By controlling the temperature, time and optimization of variables, such as solvent and base, the substitution of chlorine in 2, 4, 6-trichloro-1, 3, 5-triazine with different substituents can be accomplished in one pot, if the correct order of addition of nucleophiles is followed[30]. **(Scheme-1.1)**



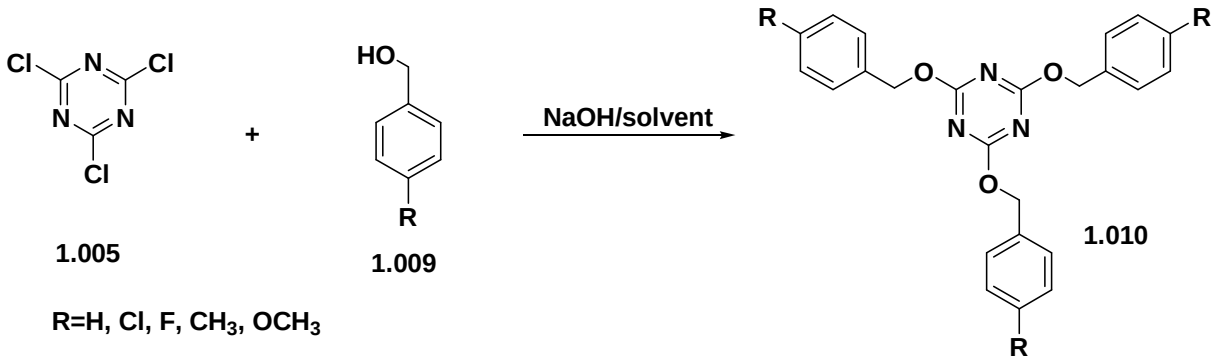
1.005 **1.006** **1.007** **1.008**

HNu_1, HNu_2, HNu_3 are nucleophiles

Scheme-1.1

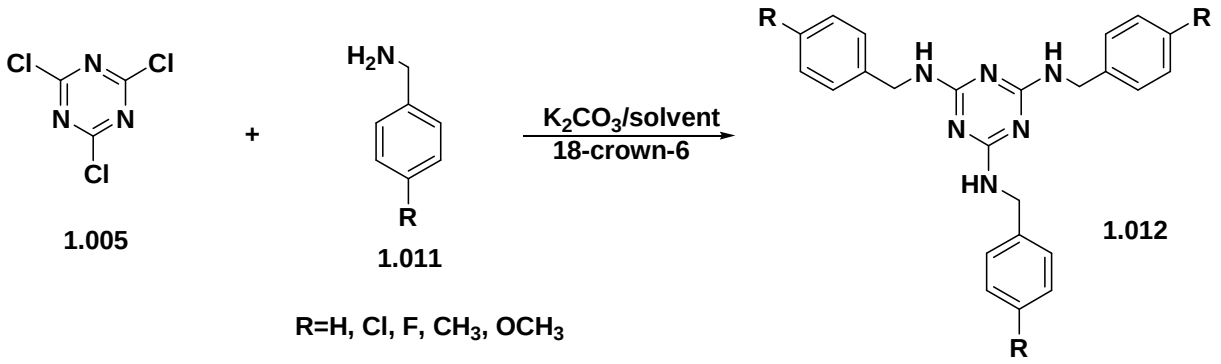
By nucleophilic substitution of s-triazine, Menicagli[31] synthesized in quantitative yeild, the symmetric and non symmetric mono, di, and tri-substituted alkoxy and amino 1,3,5-triazines in one pot in the presence of a catalytic amount of 18-crown-6.

By the reaction of benzyl alcohol derivatives **(1.009)** and cyanuric chloride **(1.005)** in presence of a base, Srinivas et al[32-33] synthesised various s-triazine derivatives **(1.010) (Scheme-1.2).**



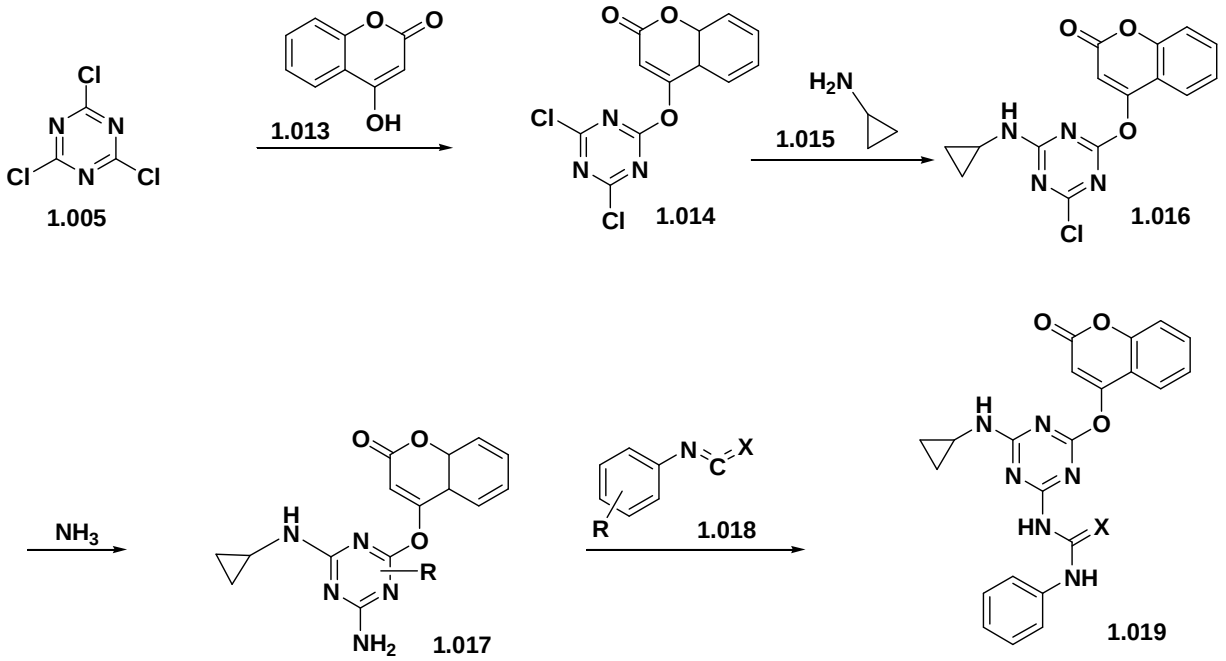
Scheme-1.2

By reacting cyanuric chloride **(1.005)** with corresponding benzylamine **(1.011)** in presence of anhydrous K_2CO_3 and 18-crown-6 as a catalyst in dry toluene, these authors synthesised **1.012. (Scheme-1.3)**



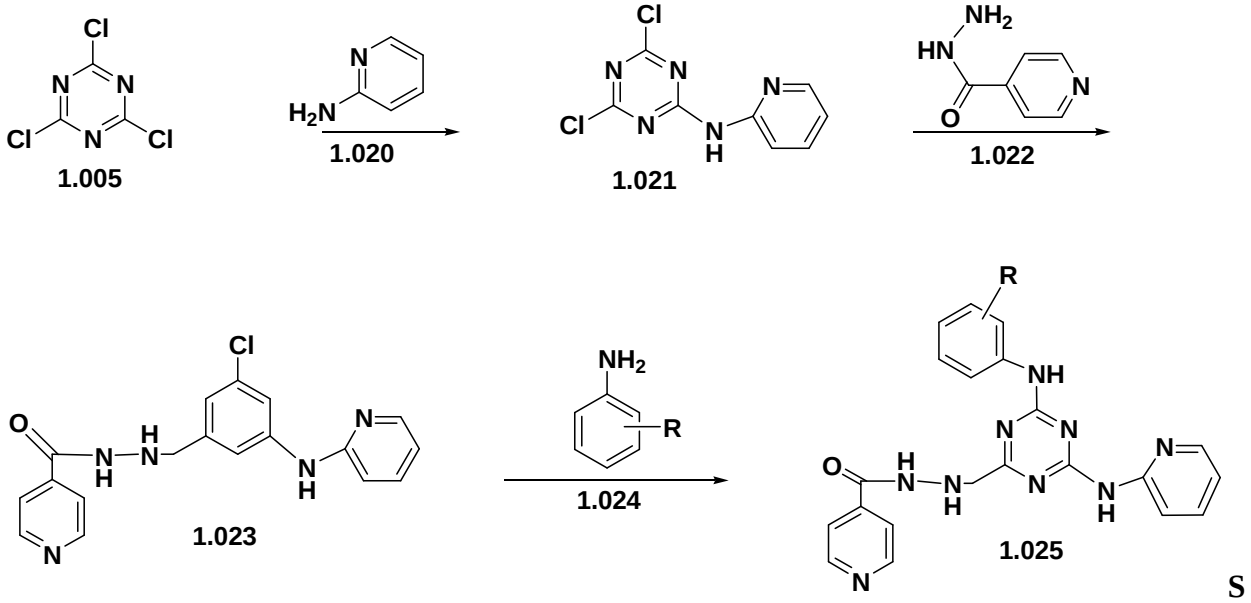
Scheme-1.3

Urea and thiourea derivatives **1.019** of s-triazine were synthesised by nucleophilic substitution of first chlorine atom of 2,4,6-trichloro-1,3,5-triazine **(1.005)** by 4-hydroxy coumarin, **(1.013)** followed by cyclopropylamine **(1.015)** and ammonia in appropriate conditions forms **1.017** which on further reaction with various substituted aryl isocyanate **(1.018)** and aryl isothiocyanate[34] yielded **1.019. (Scheme-1.4)**



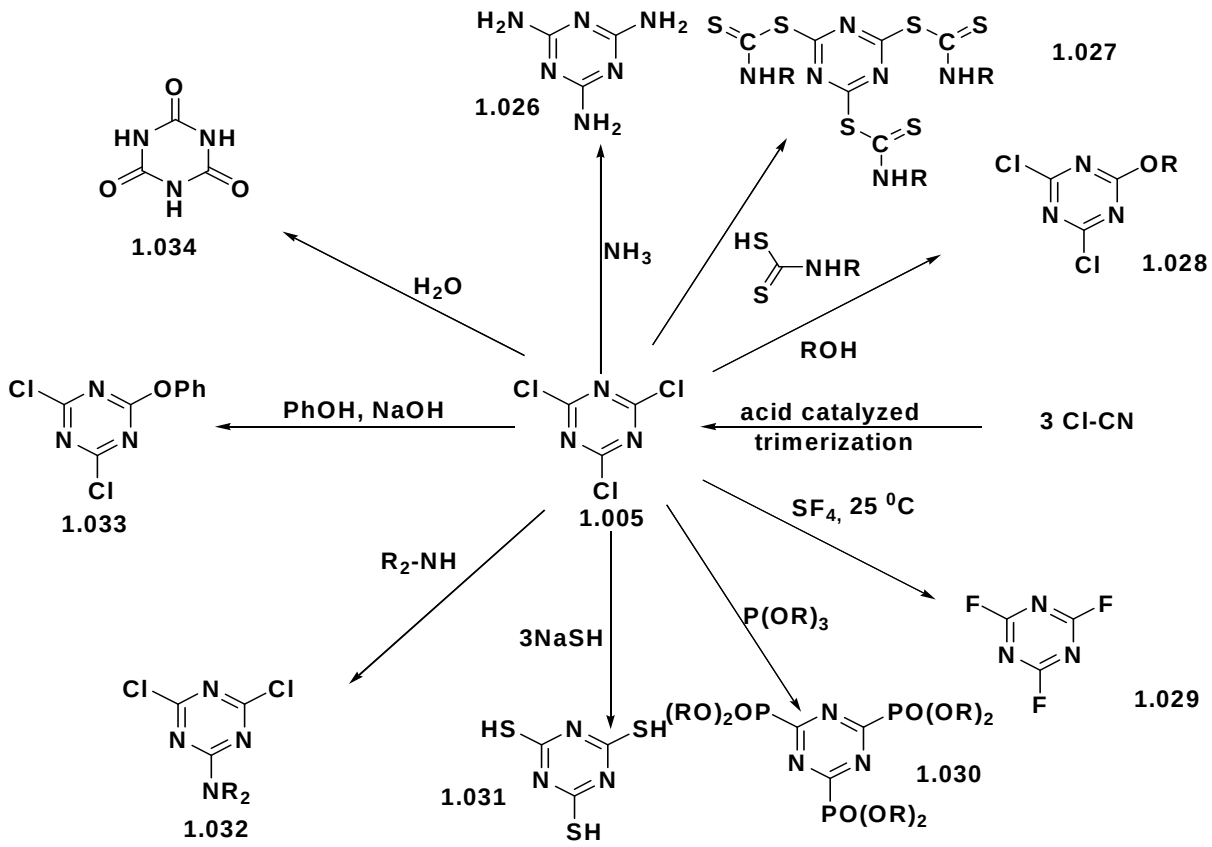
Scheme-1.4

Trisubstituted derivatives of s-triazine **1.025** were synthesised by the successive substitution of 2,4,6-trichloro-1,3,5-triazine **(1.005)** by aminopyrimidines **(1.020)**, isonicotinic acid hydrazide **(1.022)** and the last chlorine atom by various aromatic amines.[35] **(1.024) (Scheme-1.5).**



Scheme-1.5

Some other nucleophilic substitution reaction of 2,4,6-trichloro-1,3,5-triazine **(1.005)** have been

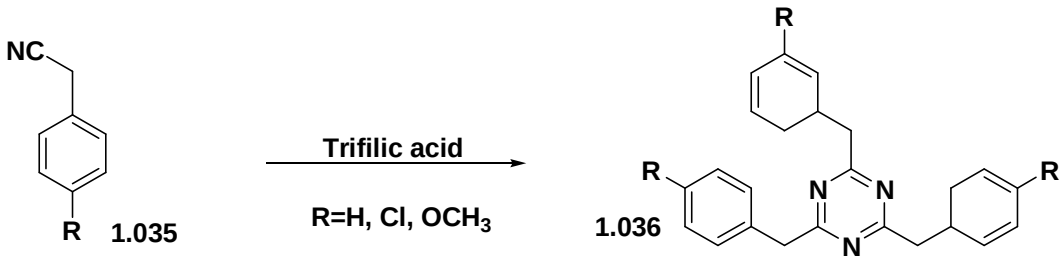


summarized below **(Scheme- 1.6).**

Scheme-1.6

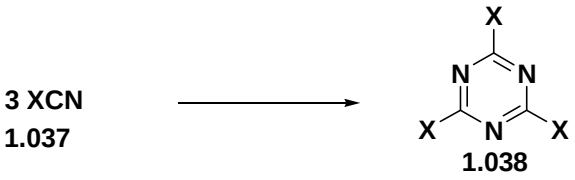
1.2.2 Synthesis of s-triazine derivatives by trimerization reactions:

By trimerization reaction of phenyl acetonitrile derivatives **(1.035)** in presence of trifilic acid [36], s-triazine derivatives were synthesized. **(Scheme-1.7)**



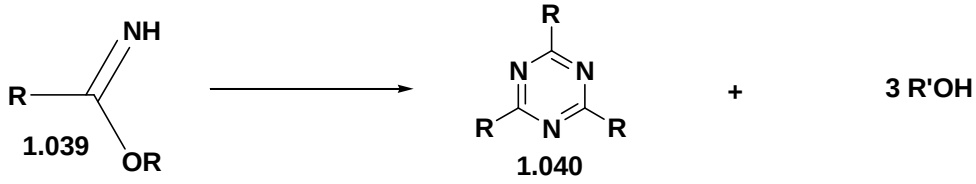
Scheme-1.7

The substituted triazines **(1.038)** were prepared by trimerizing compounds of the general formula XCN **(1.039)**, where X can be H, halogen, alkyl, aryl, amino, hydroxyl etc[37]. **(Scheme-1.8)**



Scheme-1.8

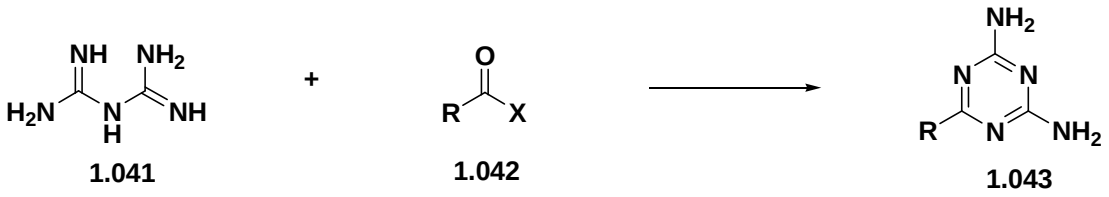
s-Triazine derivatives **1.040** were also synthesised by the trimerization of imidates **(1.039)** as reported by Fred.C.Schaefer et al[38]. **(Scheme-1.17)**



Scheme-1.9

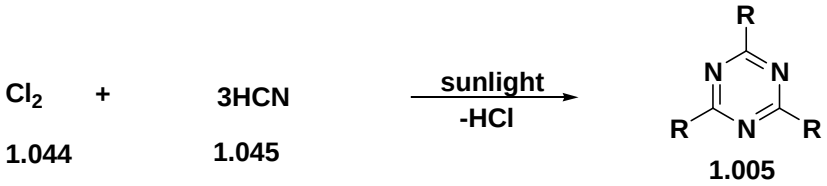
1.2.3 Synthesis of s-triazine derivatives by other methods

Cyclization of biguanidines (**1.041)** and allied compounds (**1.042**) yields trisubstituted s-triazine derivatives **1.043 (Scheme-1.10)[39].**



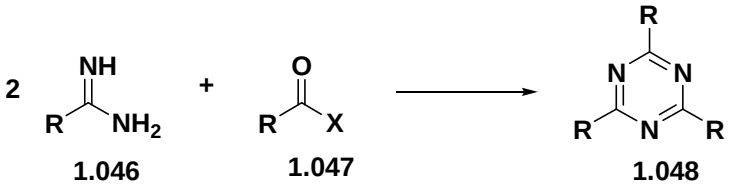
Scheme-1.10

Serrulas in 1828 prepared s-triazine by the action of chlorine **(1.044)** on anhydrous hydrocyanic acid (**1.045)** in presence of direct sunlight. **(Scheme-1.11)**[40]**.**



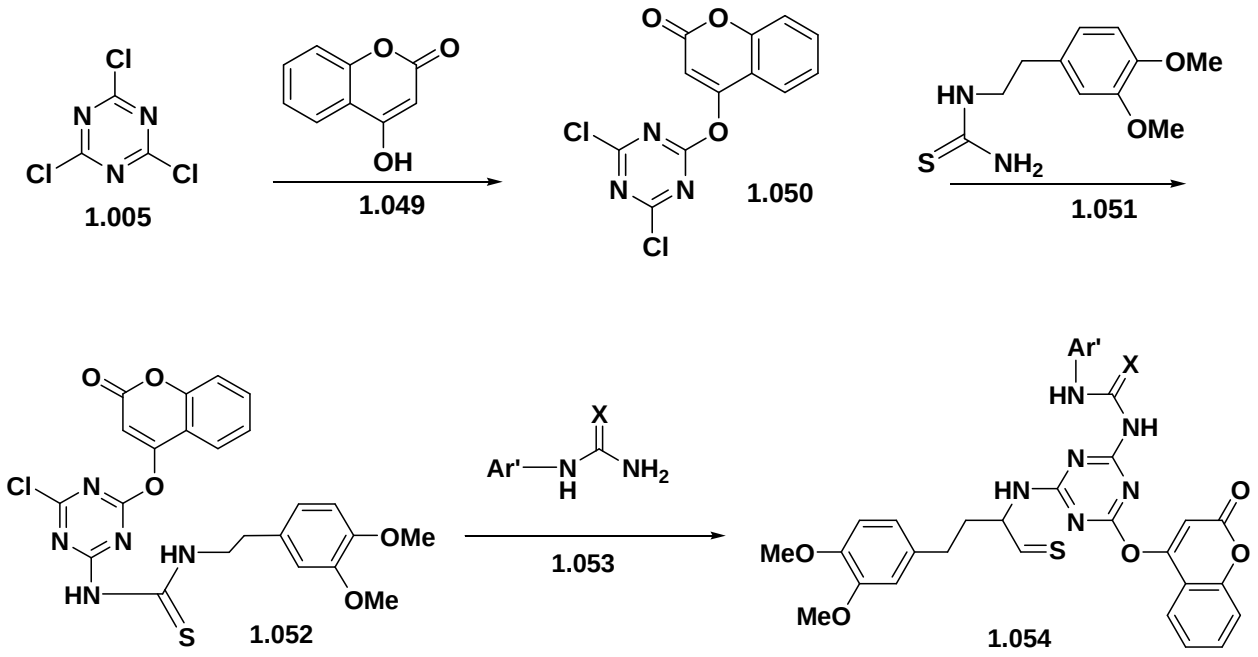
Scheme-1.11

On reacting amidines (**1.046)** or nitriles with acid anhydride and acid chloride (**1.047)**[41] substituted s-triazines **1.048** can be prepared **(Scheme-1.12)**.



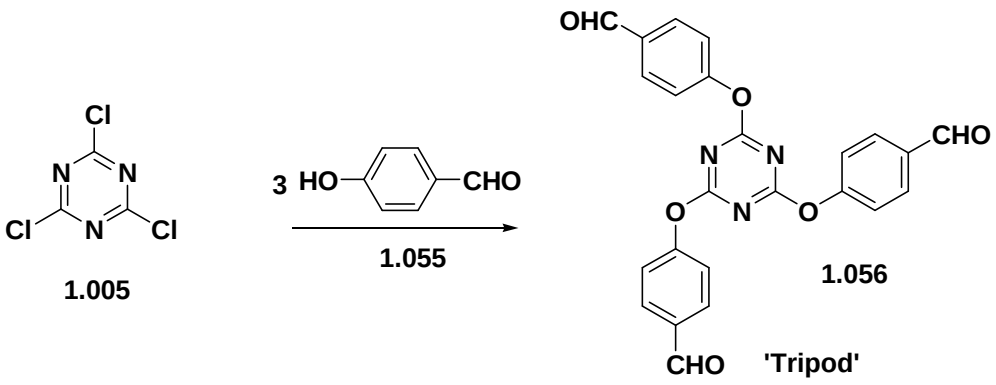
Scheme-1.12

Derivatives of 3,4-dimethoxyphenylethyl-1,3,5-triazinylthiourea **1.054** were prepared by the condensation of s-triazine with 4-hydroxycoumarin (**1.049)** and 3,4-dimethoxy phenylethylurea (**1.051)**, and various substituted phenyl urea/thiourea[42] (**1.053)** respectively **(Scheme-1.13)**.

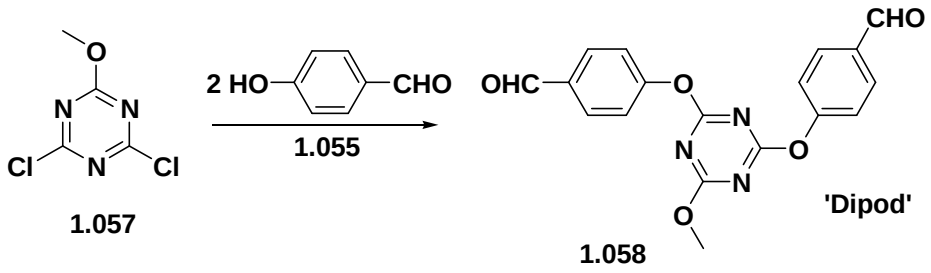


Scheme-1.13

Tahmaassebi and Sasaki[43], on reacting s-triazine with three equivalents of p-hydroxybenzaldehyde (**1.055)** obtained a triangular 'tripod' **1.056** in a single step **(Scheme-1.14).** If instead of s-triazine, 2,4-dichloro-6-methoxy-1,3,5-triazine (**1.057)** was used with two equivalents of p-hydroxybenzaldehyde (**1.055),** a linear dipod **1.058** could also be obtained. **(Scheme-1.15)** The tripod obtained are used for imprinting the silica surface.

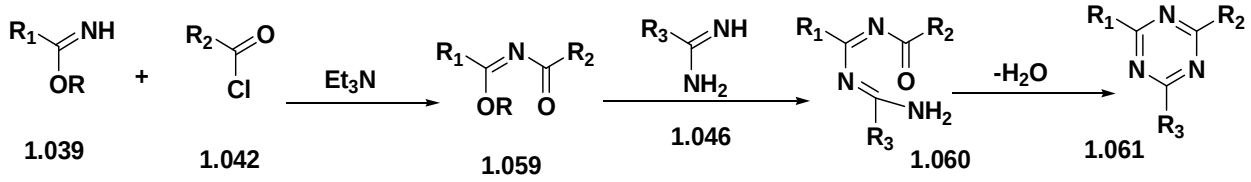


Scheme-1.14



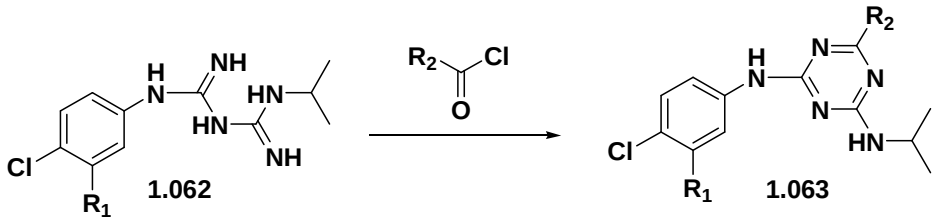
Scheme-1.15

The intermediate **1.059** obtained by the acylation of imidates **(1.039)** with acid chloride **(1.042)** in presence of triethylamine gave another intermediate **1.060** which on dehydration produced s-triazine **1.061** with different substituents[44].**(Scheme-1.16)**



Scheme-1.16

2,4-Diamino-6-substituted-s-triazine derivatives **1.063** can be synthesised in one pot, on treating proguanil or chloroproguanil **(1.062)** with acid chloride in pyridine at low temperature followed by refluxing, as reported by Ramdas Sathunuru et al[45]. **(Scheme-1.17)**



Scheme-1.17

Lowik D. et al and X.Yang et al. synthesised different macrocycles **1.065** and calix[n]arenes **1.064** respectively by linking triazine moieties with diamines. Due to the presence of multiple hydrogen bond donors and acceptors, these compounds exhibit promising binding properties.[46] **(Fig.-1.2)**

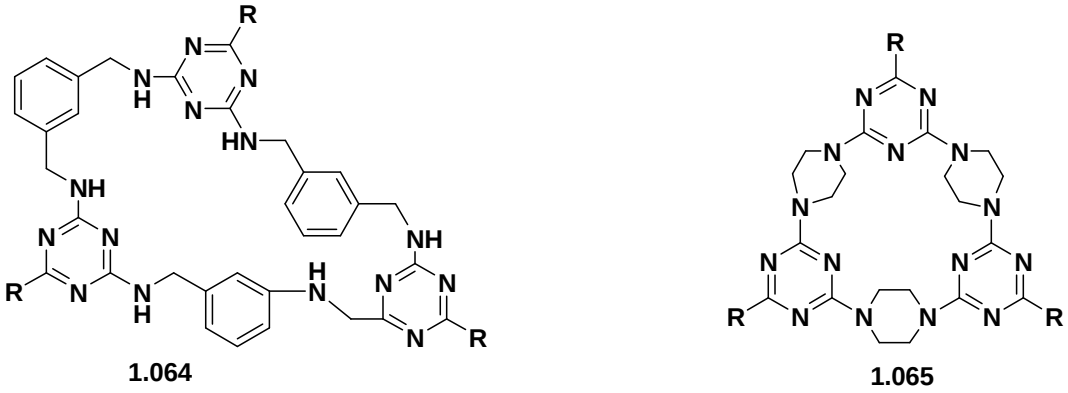


Fig. 1.2

Relevant Natural and useful compounds of s-triazines

Most important application of s-triazine is in the agricultural field as fungicides, insecticides and herbicides, for example, Anilazine **1.066** is used as fungicide, Menazon **1.067** and oxydihydrotriazines **1.068** are used as insecticides and Simazine **1.069**, Atrazine **1.070**, Hexacinone **1.071**, Chlorosulfuron **1.072**, Metsulfuron **1.073**, Dipropetryn, Prometon, Prometryn, Propazine, Simetryn, Thifensulfuron-methyl, Trietazine and Cyanazine are used as herbicides. **Fig.-1.3**

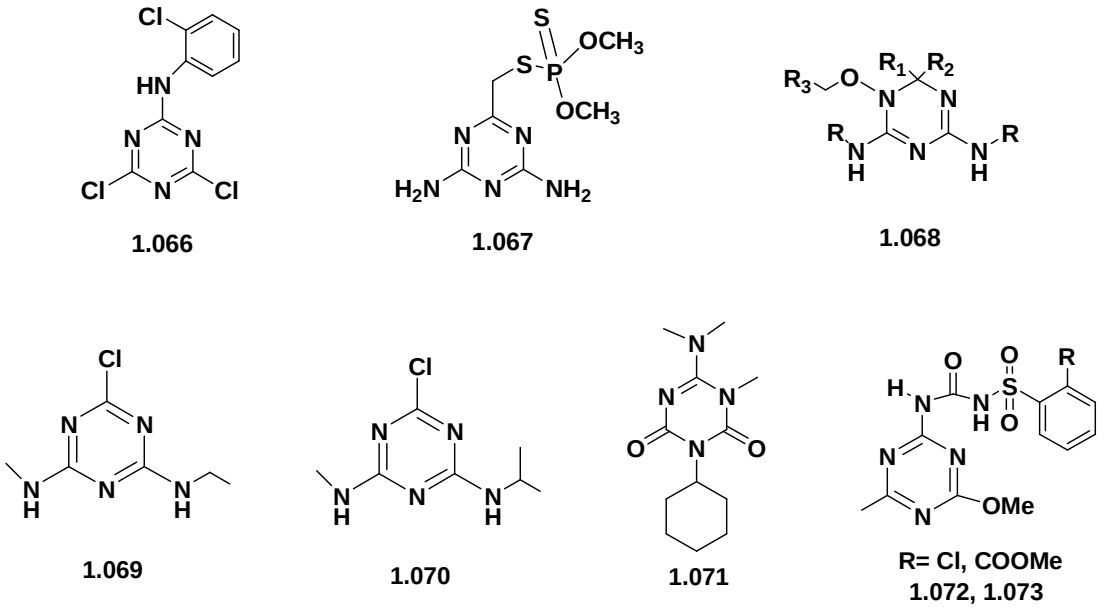


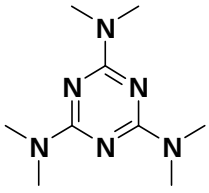
Fig.-1.3

1.3 Biological aspects of s-Triazine derivatives

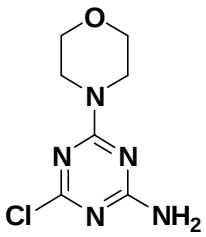
The most used triazine, melamine and its derivatives have revitalized the s-triazine chemistry as they are proved to be good precursors of a variety of oligomers, polymers, scavenging resins, superstructure assemblies components of host guest and ligand scaffolds for catalysis, in medicinal chemistry, in encapsulation of anticancer drugs and reduction of its toxicity. Triazines have great potential in medicinal chemistry both for their ability to be involved in intricate H-bond networks and for their π-interaction abilitiies. Some medicinally important triazines are described below:

1.3.1 Triazine as an Anticancer agents:

2-Amino-4-morpholino-s-triazine **1.074** and hexamethylmelamine (HMM) **1.075** are used clinically since 1991 due to their antitumor properties to treat breast, lung and ovarian cancer.[47] **(Fig1.4)**



1.075



1.074

Fig.1.4

Hydroxylated metabolite of HMM, hydroxymethylpentamethylmelamine (HMPMM) **1.076** corresponds to more active form of HMM. Recently, significant aromatase inhibitory activity and antitumor activity in human cancer and murine lukemia cell lines were observed[48] for 1,3,5-triazine for general structures **1.077** and **1.078** respectively **(Fig-1.5).**

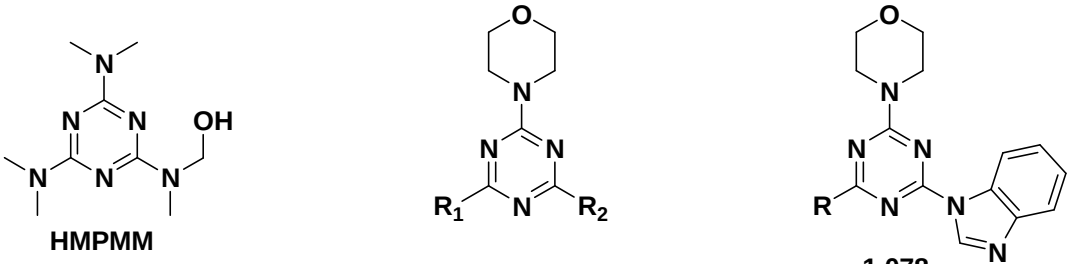


Fig. 1.5

According to M.A.Chirgos[49], triethylene melamine **1.079**, was found to be most active in increasing the survival time of mice with moloney virus leukemia and to supress splenomegaly in rouscher virus leukemia. **(Fig-1.6)**

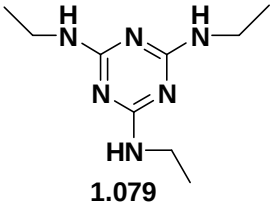


Fig. 1.6

Menicagli[50] reported that the replacement of an alkoxy residue of 2,4,6-trialkoxy-1,3,5-triazine, by an alkynyl moiety **1.080 and 1.081** was found to be moderately active against the HL 60 cell line, and enhanced the cytotoxicity of the molecule. **(Fig-1.7)**

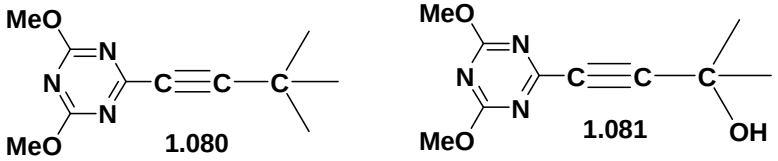


Fig. 1.7

Shin-ichi et al[51] have prepared four important s-triazine containing anticancer agents viz., ZSTK474, **(1.082)** ZSTK1178, ZSTK781 AND ZSTK116. All the compounds have shown different P13 inhibitory activities, amongst these ZSTK474 was found to be the most active apoptotic agent which induced apoptosis in cancer cells **[Fig - 1.8].**

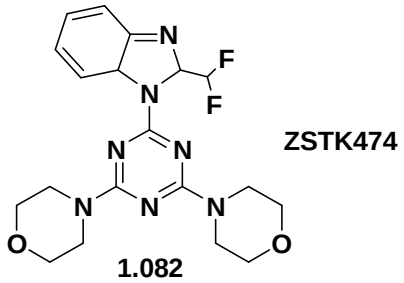


Fig.1.8

Ryo Shimizu et al[52], on the basis of their evaluation through QSAR developed a method for the synthesis of s-triazine anticytokinins. The s-triazine moiety in the compound acts as a antagonist and thus retards the process of cell division. Frederic C. Schaefer et al[53] prepared 'vinyl-amino-s-triazine' **1.083**, a promising agent of this series. **(Fig-1.9)**

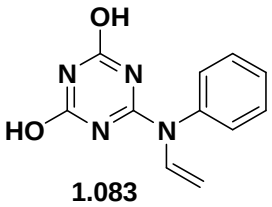
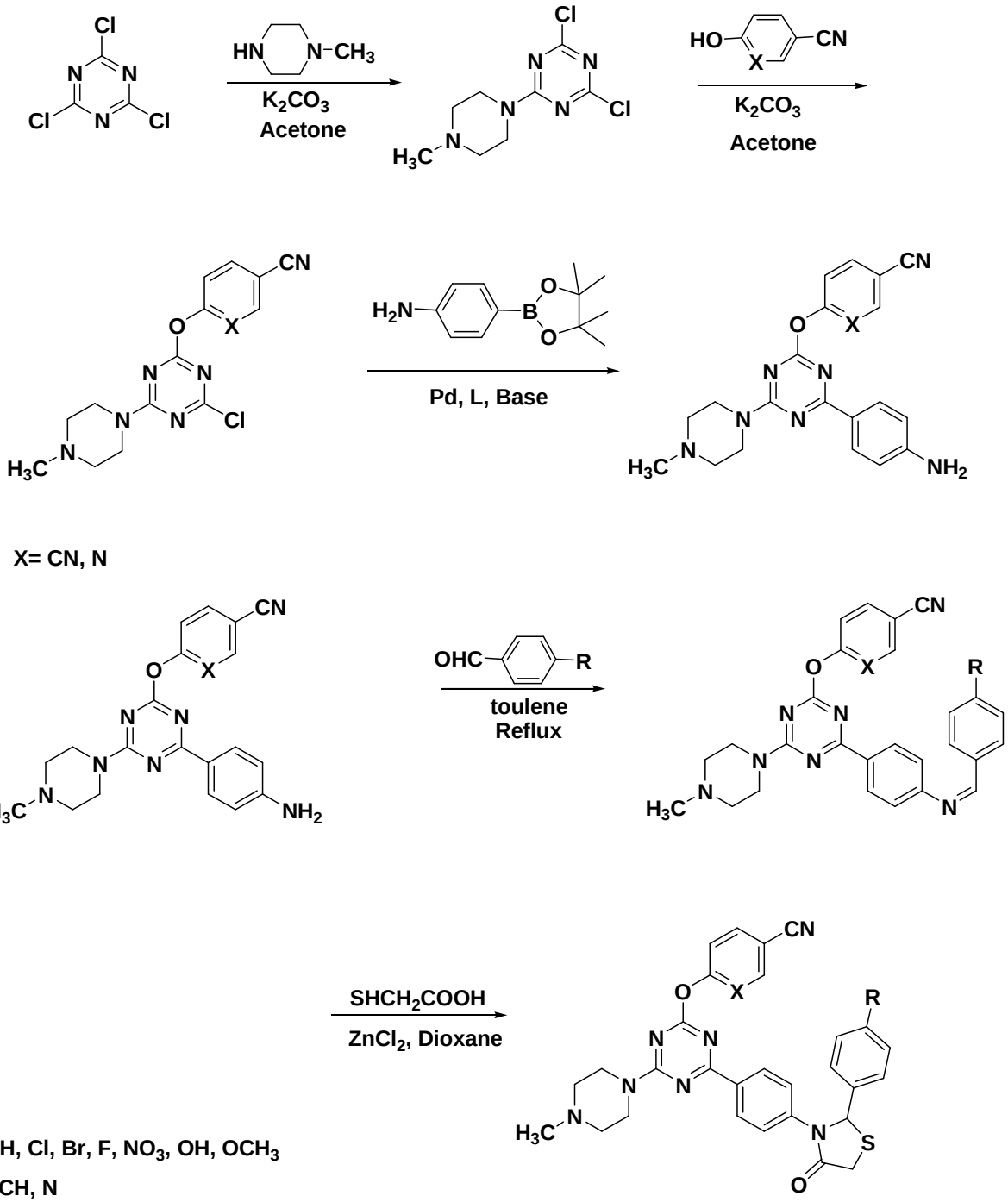


Fig.1.9

Premlata Kumari et al synthesised a new series of thiazolidin-4-one fused s-triazines **1.084** by applying an efficient palladium catalyzed C–C Suzuki coupling using catalyst system $Pd(OAc)_2$, Xphos and K_3PO_4 as a base in toluene solvent, **(Scheme-1.18)** and the synthesized analogs were screened for their in vitro antimicrobial as well as anticancer efficacy against prostate cancer PC3 cells. Both benzonitrile and nicotinonitrile were found essential to increase the different pharmacological properties. The bioassay results revealed that, the nicotinonitrile derivatives displayed outstanding inhibition against Gram-negative bacteria and prostate cancer PC3 cells, however most of the benzonitrile compounds displayed an exceptional in vitro antimicrobial activity against Gram-positive bacteria and fungal strains. Hence it was concluded that insertion of both benzonitrile and nicotinonitrile is essential to increase the different pharmacological activities of the resultant scaffolds[54]**.**

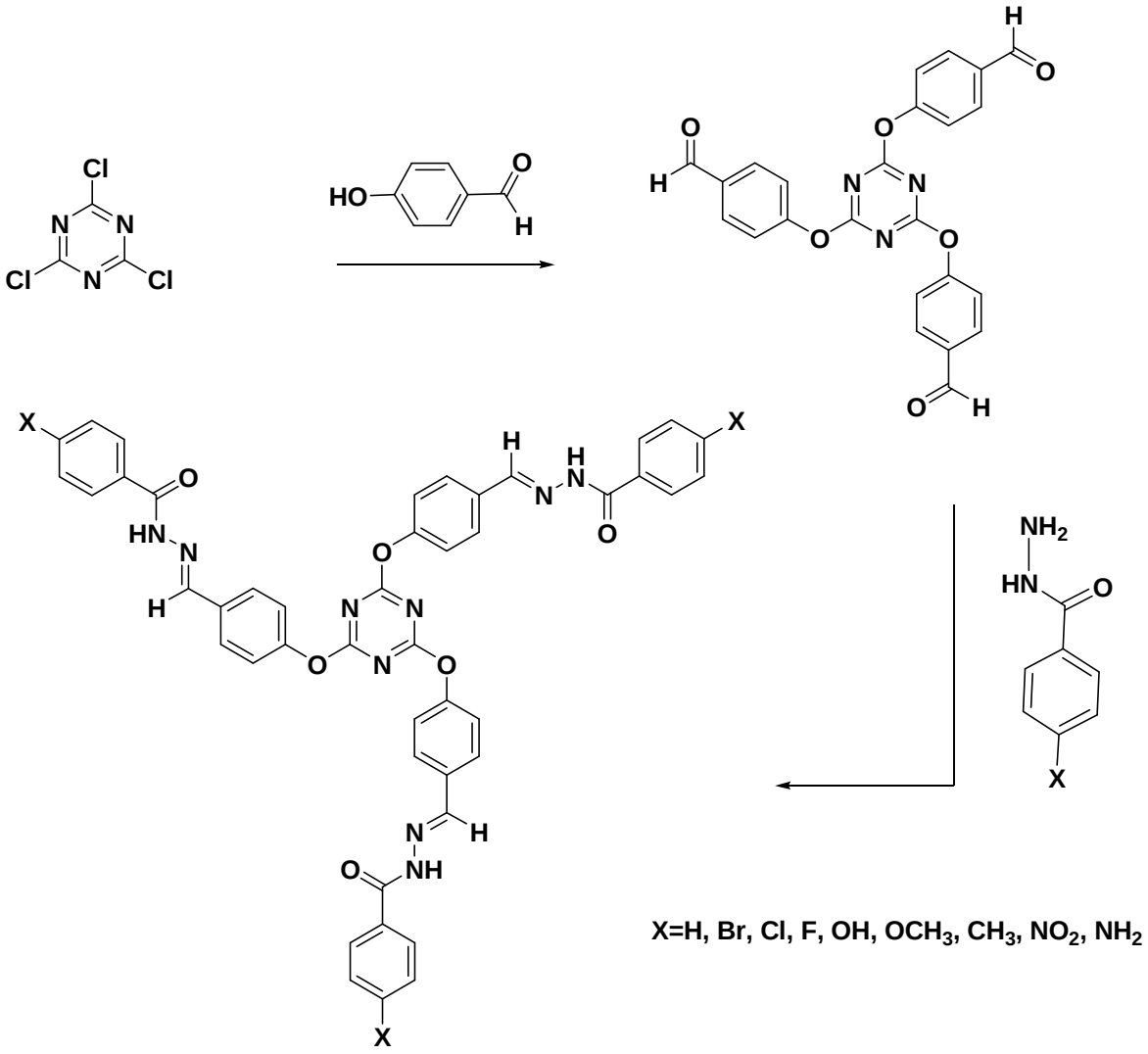


1.084

Scheme-1.18

S.S. Machakanur et al synthesised a series of novel trisubstituted triazine hydrazones by a three-fold condensation reaction of 2,4,6-tris(4-formylphenoxy)-1,3,5-triazine with p-substituted benzoic acid hydrazides **1.085 (Scheme-1.19).** These derivatives possessing hydrolysable

hydrazone linkages were then evaluated for their in vitro antiproliferative activity against the human cervix carcinoma cell line (HeLa) and human liver carcinoma cell line (HepG2). The compounds exhibited reasonably moderate in vitro cytotoxicity against HepG2 cell lines but lower activity against HeLa cell lines[55].

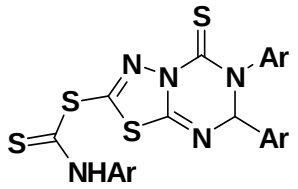


1.085

Scheme-1.19

1.3.2 Triazine as an Antifungal and Antibacterial agents:

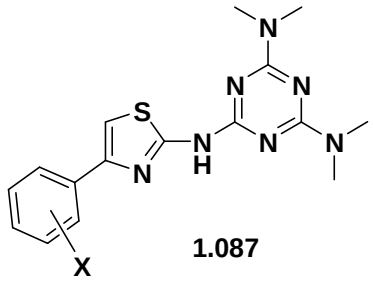
Lal Dhar S.Yadav et al[56] have synthesised a new antifungal series of compounds, with the general structure **1.086 (Fig.-1.10)** from dithiocarbamate. In vitro antifungal activity was confirmed against Aspergillus *niger* and Fusarium *oxysporum.*



1.086

Fig. 1.10

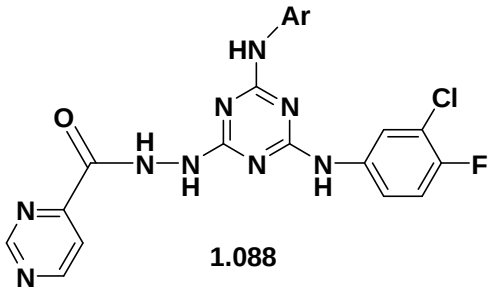
Phenyl-1,3-thiazole substituted amino-[1,3,5]-triazines **1.087**, as reported by Prashant Gahtori et al, were also potential antibacterial agents[57] **(Fig.1.11).**



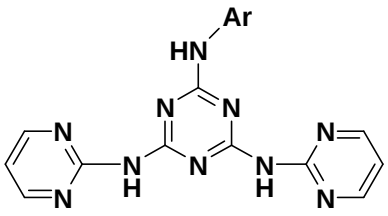
1.087

Fig.1.11

N'-{4-[3-chloro-4-fluorophenyl)amino]-6-[(-aryl)amino]-1,3,5-triazin-2-yl} isonicotinohydrazides **1.088** and N2(aryl)N4,N6-dipyrimidin-2-yl-1,3,5-triazine-2,4,6-triamines **1.089**, synthesised by B.B. Baldania and P.K. Patel et al[58] have reported that these compounds showed promising antibacterial and antifungal activities. **(Fig.1.12)**



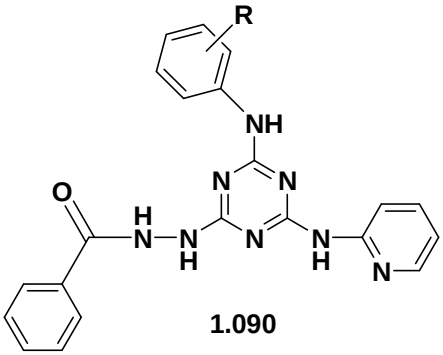
1.088



1.089

Fig.-1.12

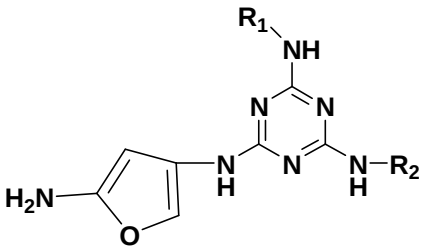
Jignesh P. Raval et al[59] have synthesised and evaluated N'(4-arylamino)-6-(pyridine-2-ylamino)-1,3,5-(triazine-2-yl)benzohydrazide **1.090** for antibacterial and antifungal activities. **(Fig.1.13)**



1.090

Fig.1.13

Scadao Nishigaki et al[60] synthesised and evaluated 2,4-disubstituted-6-[(5-nitro-2-furyl)vinyl]-s-triazine **1.091** for antibacterial and antifungal activities **(Fig.1.14)**.

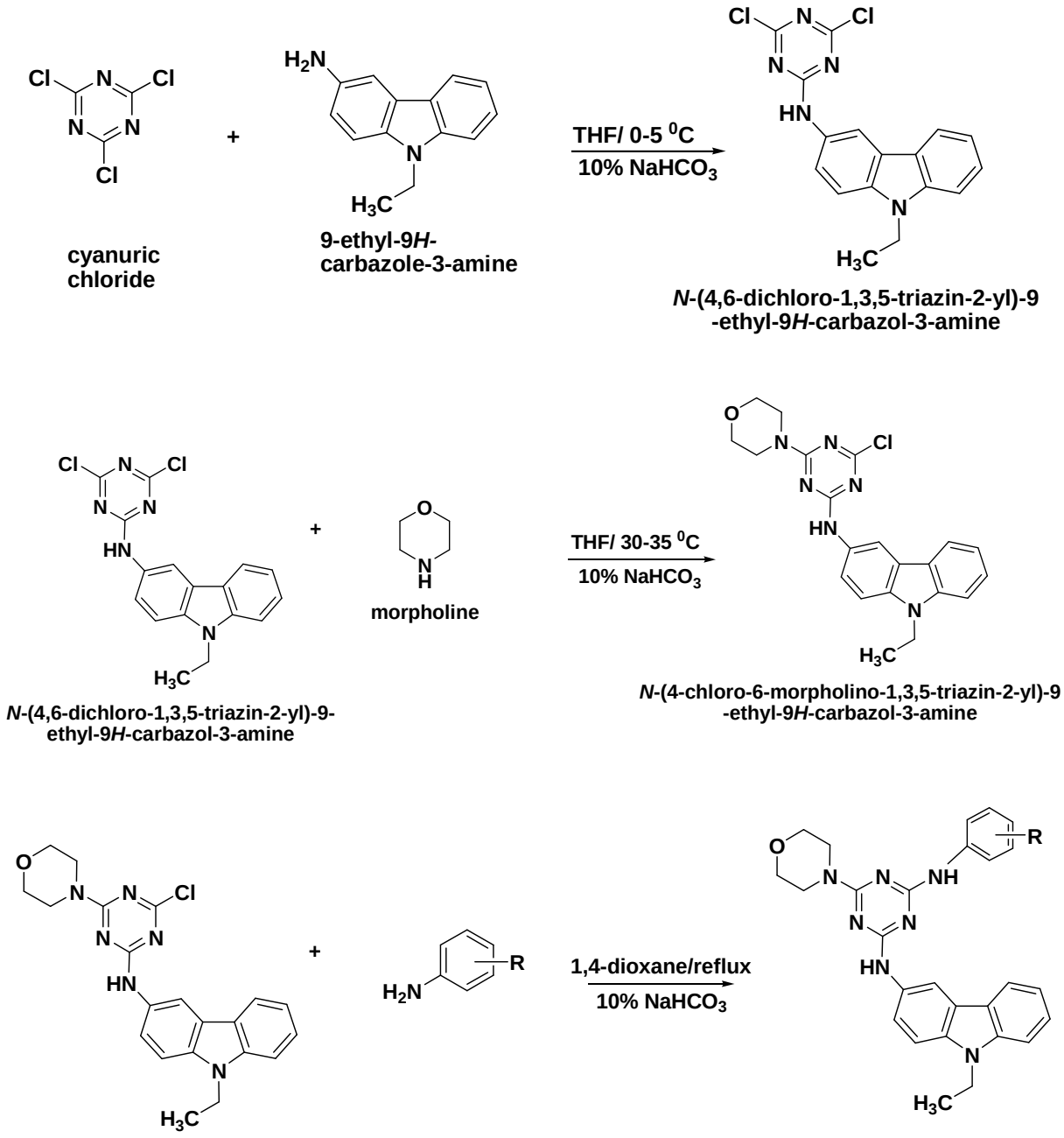


1.091

Fig.1.14

Anil Rathavi et al have synthesised triazine analogues which in addition to 9-ethyl-9H carbazol-3-amine contain morpholine, different amines as well as piperidine substituents on the C-6

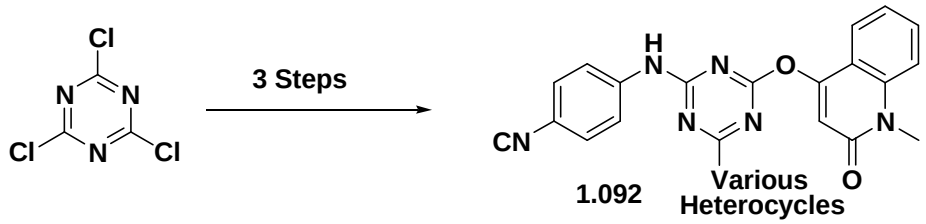
position of the ring. The title compounds were evaluated for their antimicrobial activiy and reported that most of the compounds showed promising antimicrobial activity[61] **(Scheme-1.20).**



Scheme-1.20

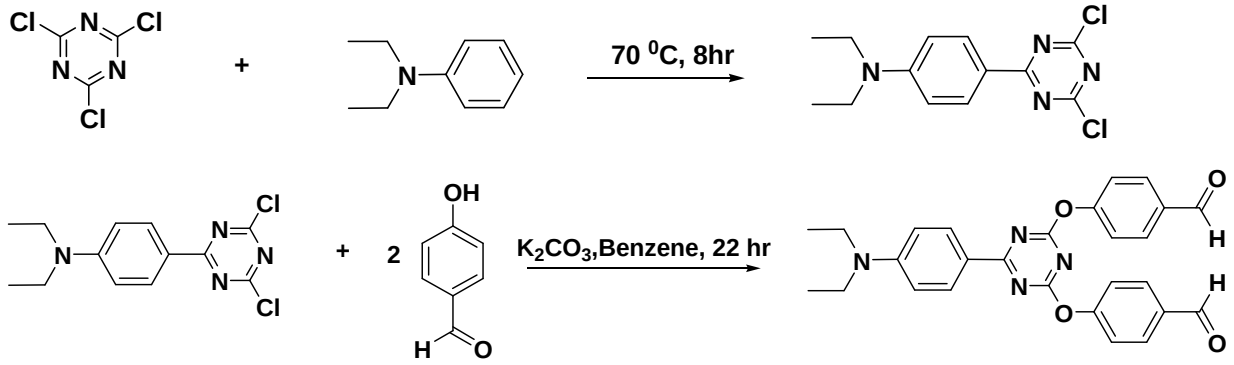
Kishor H. Chikhalia et al synthesised quinolone condensed s-triazine derivatives **1.092** endowed with different heterocycles and 4-aminobenzonitrile moiety and evaluated for their bioactivities

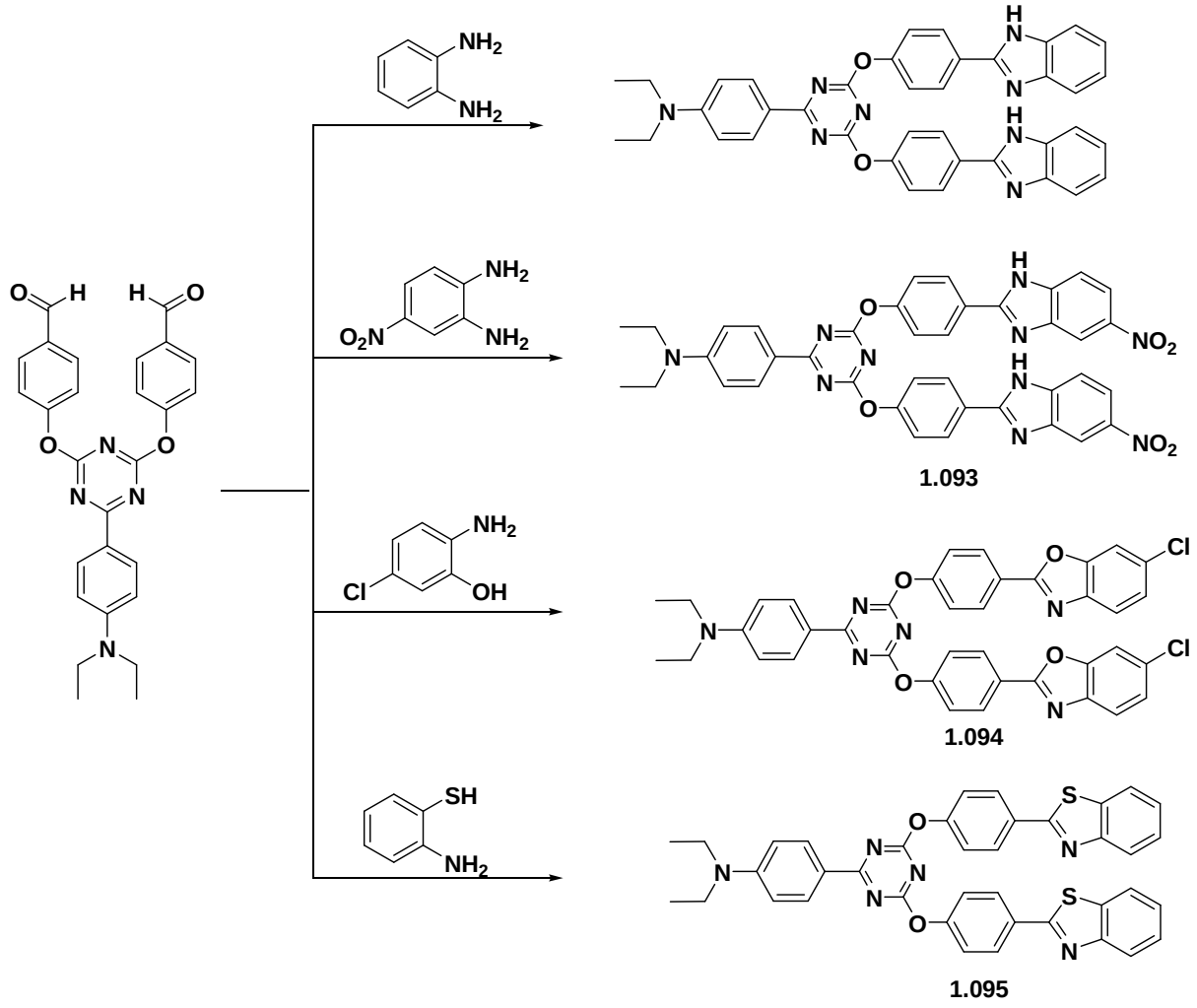
against bacteria and observed that the majority of the compounds possess a significant broad spectrum antitubercular (MIC: 12.5 mg/mL) and antimicrobial (MICs: 6.25–25 mg/mL) potential[62] **(Scheme-1.21).**



Scheme-1.21

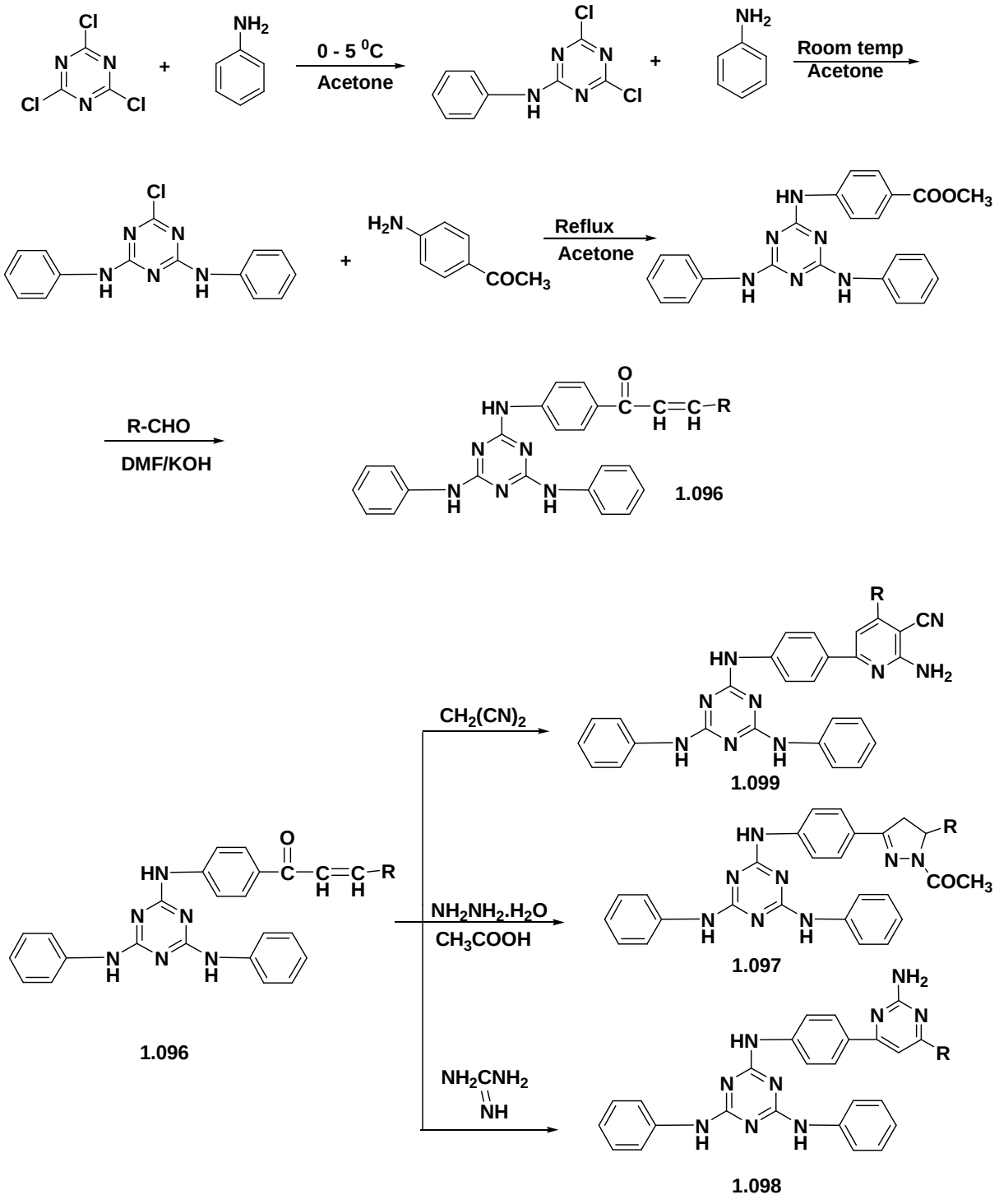
N. Sekar et al synthesised dipodal-benzimidazole **1.093**, benzoxazole **1.094** and benzothiazole **1.095** derivatives from cyanuric chloride and screened for anti-microbial activity, and concluded that the novel synthesised heterocycles showed excellent broad-spectrum antimicrobial activity and also that the compound containing oxazole nucleus is more active than imidazole and thiazole nucleus over tested bacterial and fungal strain[63] **(Scheme-1.22).**





Scheme-1.22

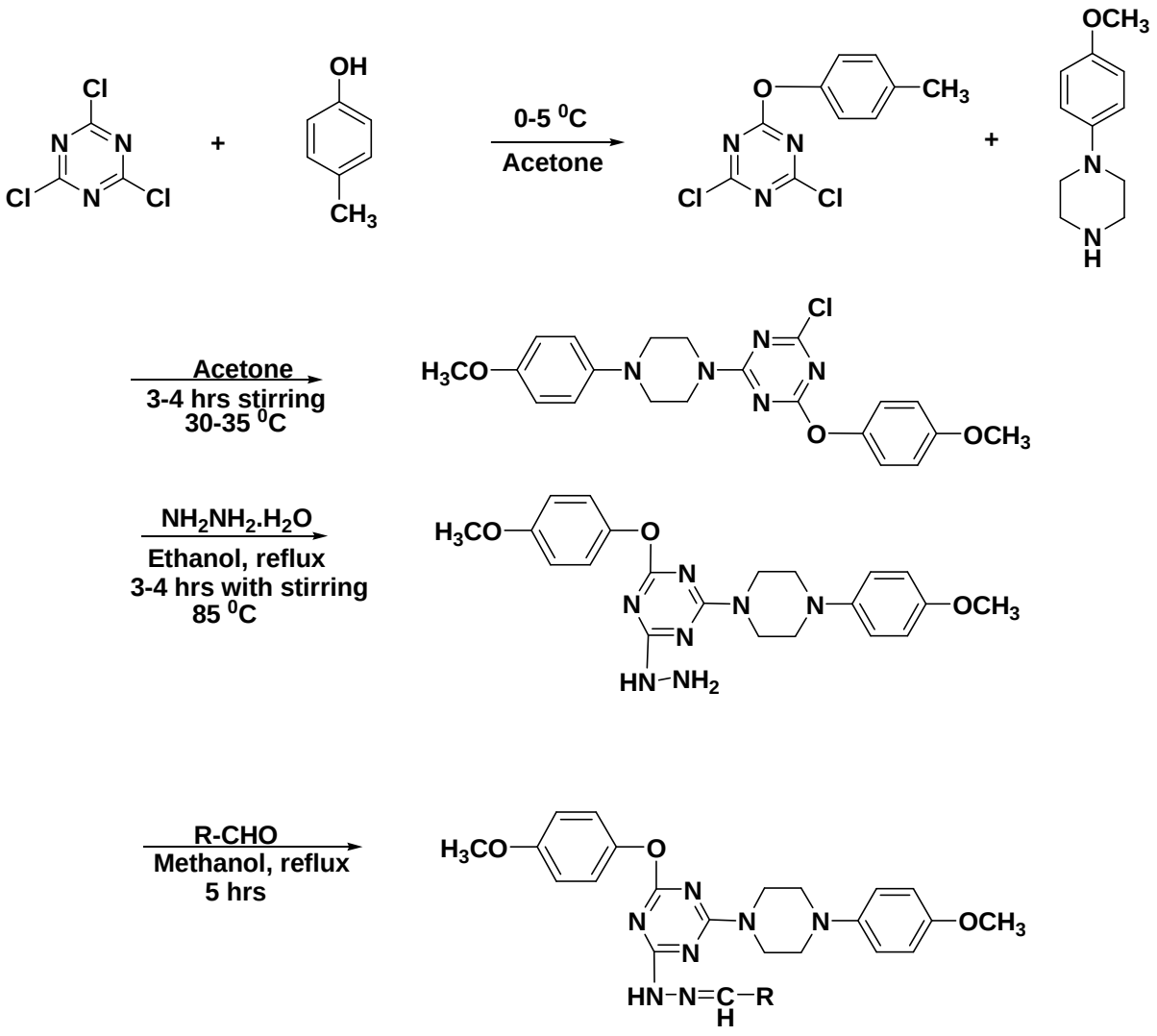
A.Solankee et al. synthesised corresponding acetylpyrazolines **1.097**, aminopyrimidines **1.098** and cyanopyridines **1.099** by the cylization of chalcones **(1.096)** with hydrazine hydrate in the presence of glacial acetic acid, guanidine nitrate in the presence of alkali and malononitrile in the presence of ammonium acetate respectively. The products were screened for antimicrobial activity and were found to exhibit antibacterial activity[64] **[Scheme-1.23].**



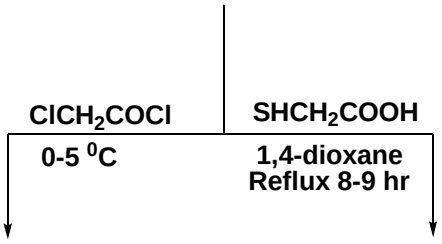
Scheme-1.23

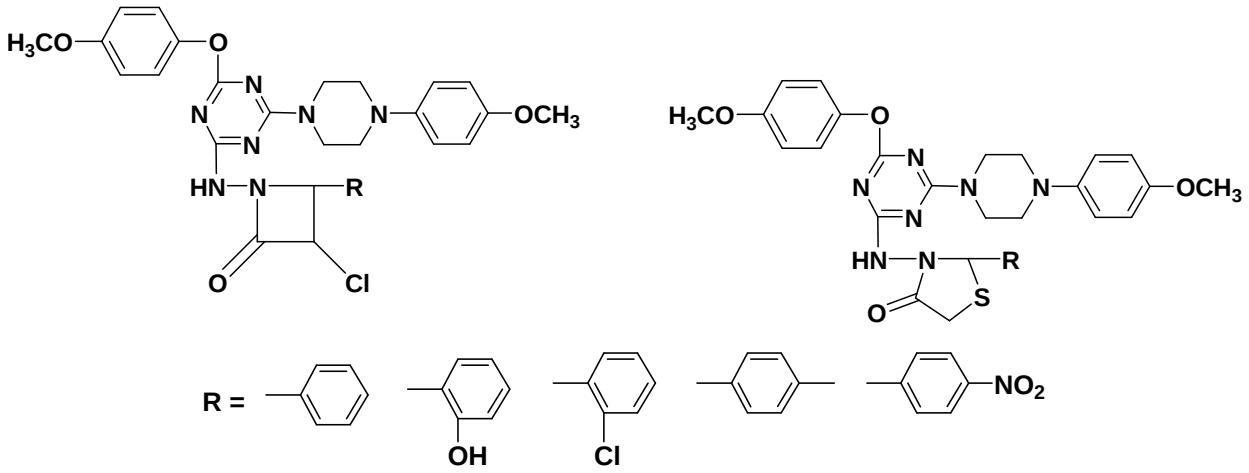
Himanshu D.Patel et al synthesised a novel series of compounds containing 2-(2-substituted benzylidene hydrazinyl)-4-(4-(4-methoxyphenyl) piperazin-1-yl)-6-(4-tolyl oxy)-1,3,5-triazine

1.100 (Scheme-1.24) The newly synthesized compounds were screened for antimicrobial activity and it was found that compounds bearing unsubstituted phenyl, 2- hydroxy, 2-chloro and 4-nitro substituents were active against tested organism. Further it was concluded that the antimicrobial activity is not affected by the electronic properties of the substituents[65].



1.100





Scheme-1.24

1.3.3 Triazine as an Anti-HIV agent:

A novel non-nucleoside reverse transcriptase inhibitors (NNRTIs), 2-(coumarin-4-yloxy)-4,6-(substituted)-s-triazine derivatives i.e., diaryltriazine (DATA) **1.101** as reported by Dharmesh H. Mahajan et al[66], modifications at position 4 and 6 of the coumarinyl-triazine, **1.102**, scaffold formed derivatives exhibiting moderate to good anti-HIV activity against selected HIV strains as compared to efavirenz and nevirapine[67] **(Fig. 1.15).**

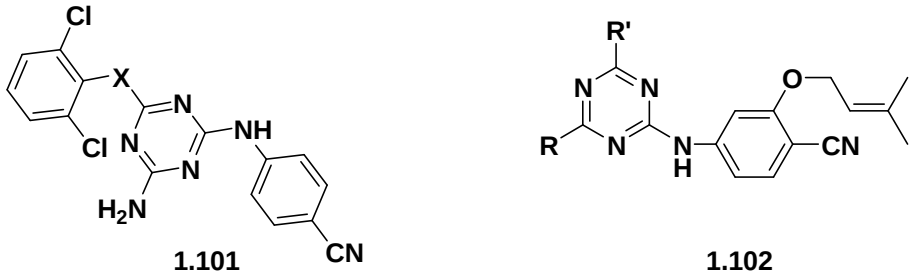
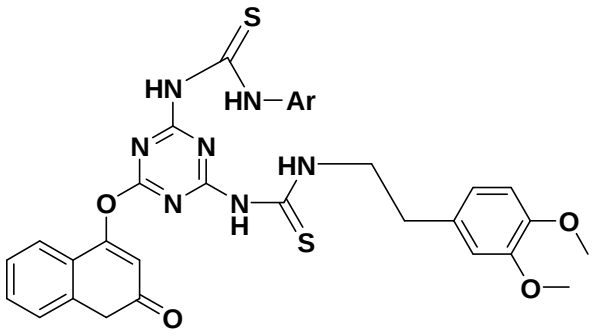


Fig.1.15

Rakesh B. Patel et al[68] have synthesized and evaluated phenyl ethyl triazinyl thiourea (PETT) **(1.103**) derivatives as potential anti-HIV agents.**(Fig. 1.16).**

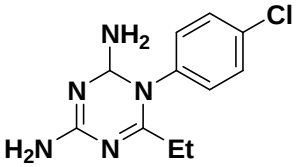


1.103

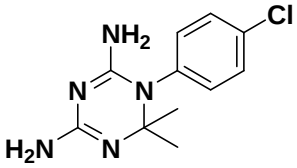
Fig. 1.16

1.3.4 Triazine as an Antimalarial agent:

Cynoguanil **(1.104)** and its allied compounds pyrimethamine **(1.105)** are potent inhibitors of Plasmodium falciparum dihydrofolate reductase (pf DHFR) and are considered to be one of the well defined target for malarial therapy[69] **(Fig. 1.17).**



1.105
Pyrimethamine



1.104
Cycloguanil

Fig.1.17

1.3.5 Triazines as an Anti-depressants:

4-Isopropylamino-2-amino-6-trifluoromethyl-s-triazine **1.106**, 4-cyclohexylamino-2-amino-6-trifluoromethyl-s-triazine **1.107**, (4-(4-methylpiperazine-1-yl)-2-amino-6-trifluoromethyl-s-triazine **1.108**, (4-(4-hydroxyethylpiperazine-1-yl)-2-amino-6-trifluoromethyl-s-triazine **1.109**, 2-benzalhydrazino-4-tertbutyl-6-piperazino-s-triazine **1.110**, showed anti-depressant activity against spontaneous motor activity, as reported by the Akihiro Tobe et al[70] **(Fig.-1.18).**

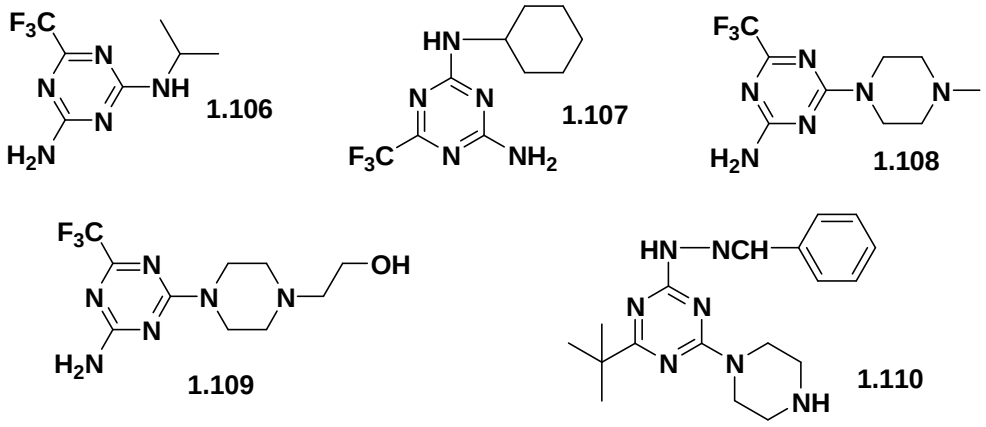


Fig.1.18

2-hydrazino-4-(4-methylpiperazine-1-yl)-6-trifluoromethyl-s-triazine **1.113** and 2-hydrazino-4-(4-acetylpiperazine-1-yl)-6-trifluoromethyl-s-triazine **1.112** potentiated hexabarbital time. 2-hydrazino-4-piperazino-6-trifluoromethyl-s-triazine **1.111** exhibited anti-morphine action.**(Fig.-1.19)**

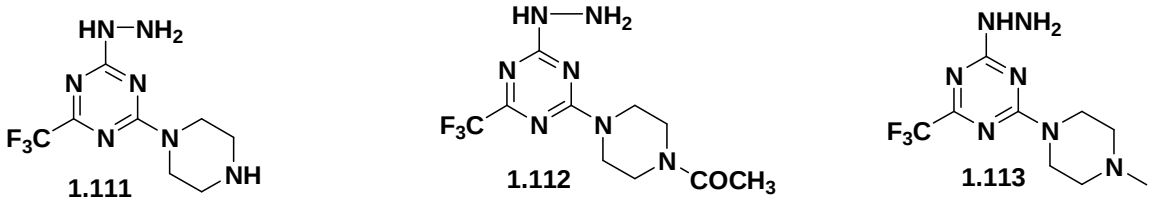


Fig.1.19

Moderate hypotension activities were shown by 2-amino-4-p-chloroanilino-6-trifluoromethyl-s-triazine **1.115** and 2-benzalhydrazino-4-morpholino-6-trifluoromethyl-s-triazine[71] **1.114 (Fig-1.20)**.

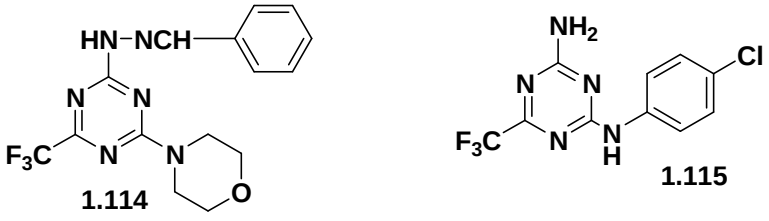


Fig. 1.20

1.3.6 Other medicinally important derivatives of s-Triazines:

From the work of Pearlmman and Banks[72] who have synthesised antihistamine compounds **1.117** containing amine and methoxy substituents in the s-triazine ring **(Fig.-1.21).** It is evident that s-triazine moiety has drawn considerable attention of chemists from early 50s.

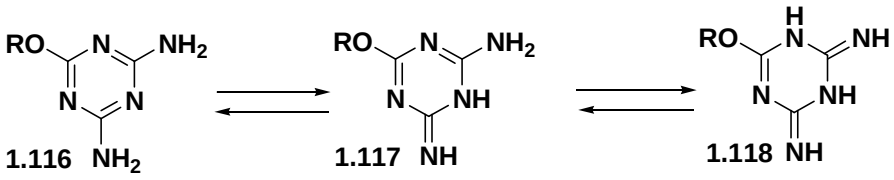


Fig.1.21

Andrenolytic activity[73] is shown by 2-isopropylamino-4-morpholino-6-trifluoromethyl-s-triazine **1.119** and 2-isopropylamino-4-methylamino-6-trifluoromethyl-s-triazine **1.120 (Fig.-1.22)**.

Fig.1.22

2-Amino-4-arylamino-6-mercapto-s-triazines **1.121** act as potential diuretic agents **(Fig.-1.23),** as reported by M.H.Shah et. al. **[74].**

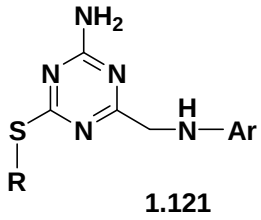
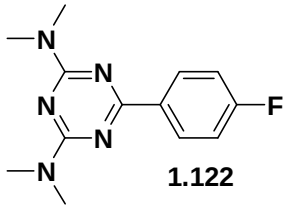


Fig.1.23

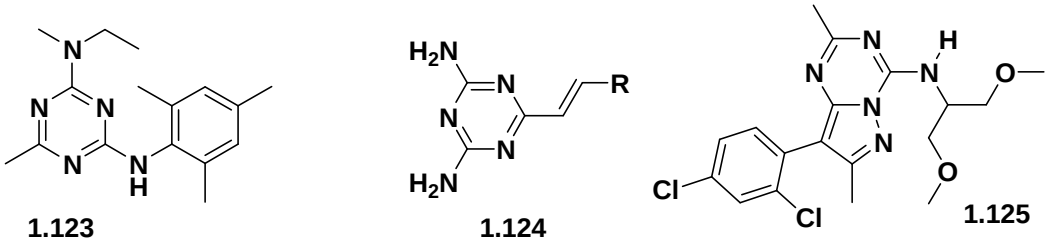
Rachael Vanderhoek et al[75] synthesized and evaluated bis-(dimethylamino)-s-triazynyl derivatives **1.122** as anti-inflammatory agents **(Fig-1.24).**



1.122

Fig.1.24

s-Triazine derivatives **1.123, 1.124, 1.125 (Fig.-1.25)** have been identified for its potential use as siderophore[76] (microbial iron shelter) mediated drug, a potent corticotrophin-releasing factor-1 receptor antagonist[77], and known to show potent activity against leukotriene C4 (LTC4) antagonist which has a protective effect on HCL[78].



1.123 1.124 1.125

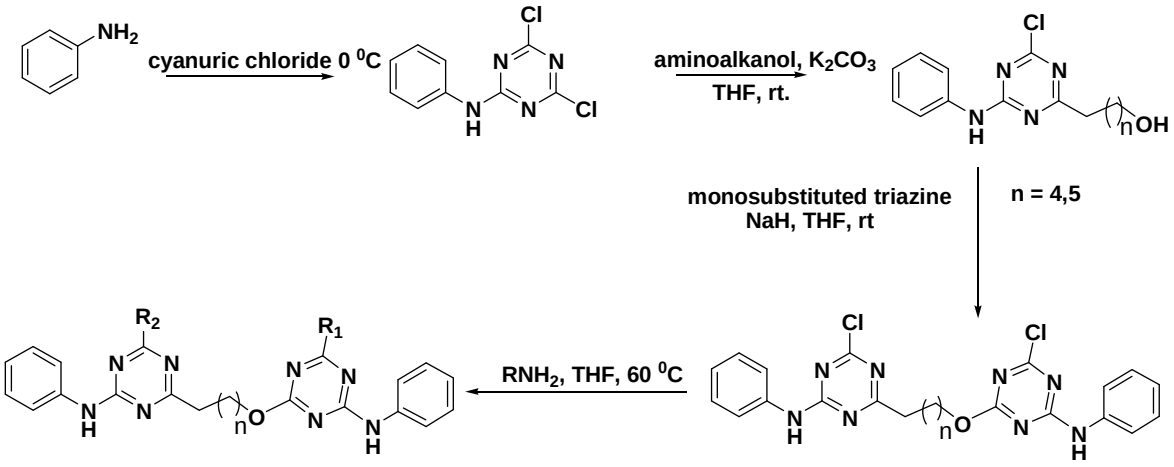
Fig.1.25

Low molecular weight triazine derivatives **1.126 (Fig.-1.26).** as protein, a mimetics for the treatment of auto-immune diseases[79].

1.126

Fig.-1.26

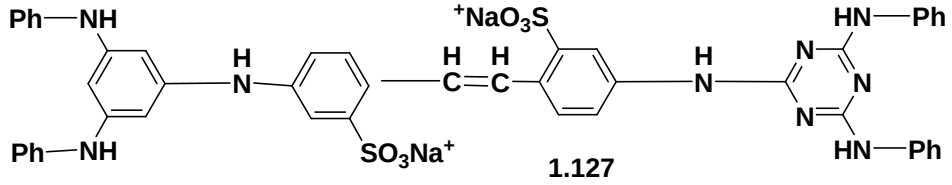
The authors[80] have synthesized novel compounds of triazine dimers as novel antileishmanial agents. Most of the synthesized derivatives exhibited better activity against intracellular anastigotes of L. donovani than the standard drug pentamidine and were not found to be cytotoxic **(Scheme-1.25).**



Scheme-1.25

1.4 Technical applications of s-Triazines:

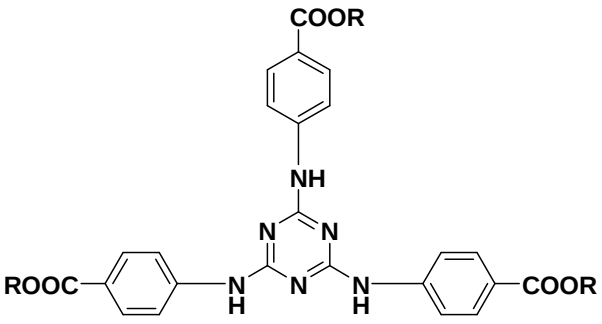
Triazines are used as optical brighteners[81] eg. sodium-6,6'-(ethene-1,2-diyl)bis(3-(4,6-bis(phenylamino)-1,3,5-triazinylamino)benzenesulfonate) **(1.127, Fig.-1.27).**



1.127

Fig.1.27

Triazines of the general structure were used as potential sunscreen agents[82] **(1.128, Fig.-1.28).**



1.128

Fig.-1.28

Cyanazine **1.129** Atrazine **1.130**, and Simazine **1.131 (Fig-1.30)** are some of the important s-triazine derived pesticides[83-85].

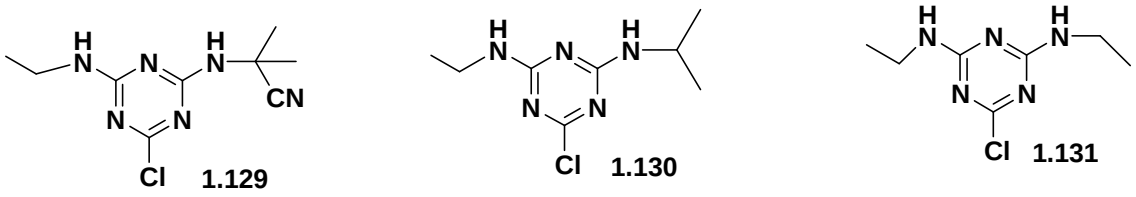
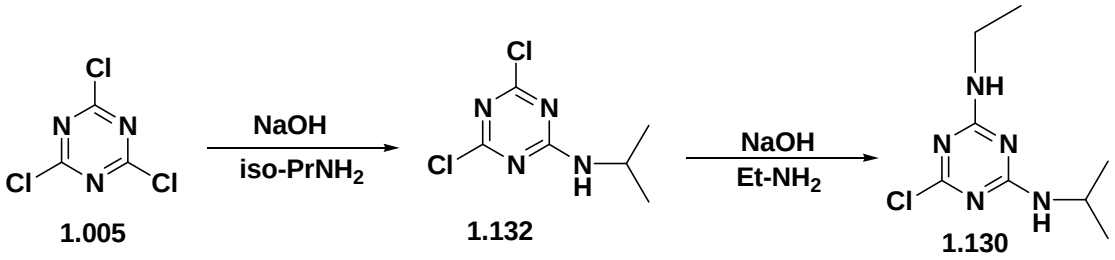


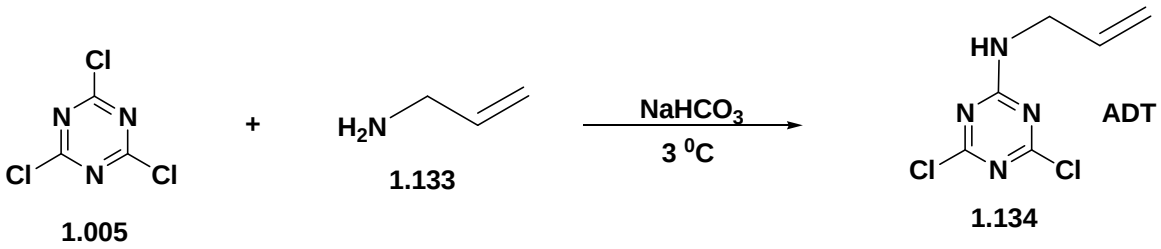
Fig.-1.29

Benita and Barton et. al. reported the synthetic route for Atrazine **(1.130)** from **1.132 (Scheme-1.26)**

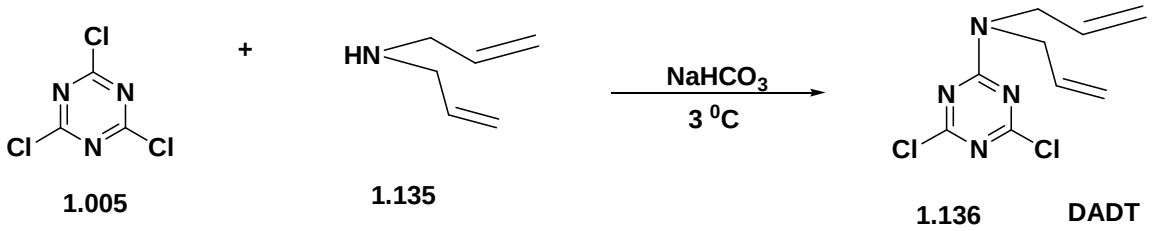


Scheme-1.26

The synthetic route for ADT **1.134** and DADT **1.135** monomers which are used as dentine binding agents[86]. It was developed by Lee and his co-workers **(Scheme-1.27, 1.28).**



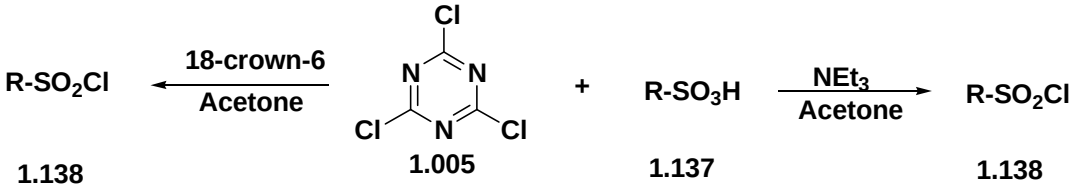
Scheme-1.27



Scheme-1.28

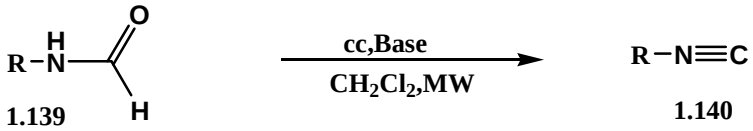
1.4.1 Triazine in Organic Synthesis:

Under neutral condition 2,4,6-triazine is used as a chlorinating agent for the preparation of sulfonyl chlorides **1.138** from sulfonic acids[87] **1.137**. Cyanuric chloride **1.005** with sulfonic acid and triethylamine or cyanuric chloride with sodium sulfonates in presence of catalytic amount of 18-crown-6 in acetone on heating under reflux forms alkyl and aryl sulfonyl chlorides **(Scheme-1.29).**



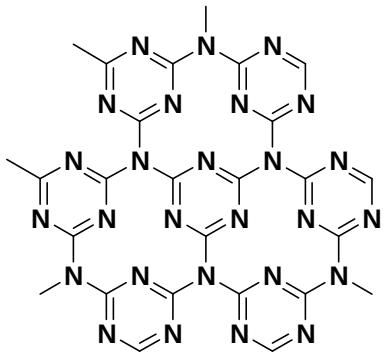
Scheme-1.29

Porcheddu et al[88] recently reported that cyanuric chloride in presence of a base converts formamides **(1.139)** to isonitriles **1.140** through the formation of an O-acylated intermediate.**(Scheme-1.30)**



Scheme-1.30

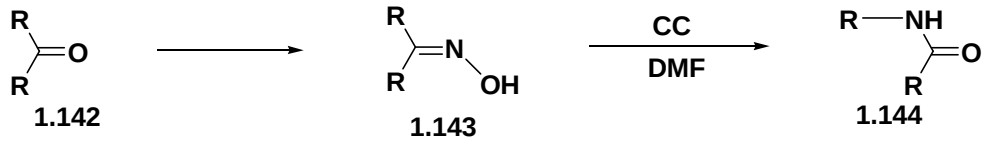
On heating cyanuric chloride with sodium azide in benzene at 220^0C, produces carbo nitride, which forms high quality nano tubes **1.141** by self assembly[89] **(Fig.-1.30).**



1.141

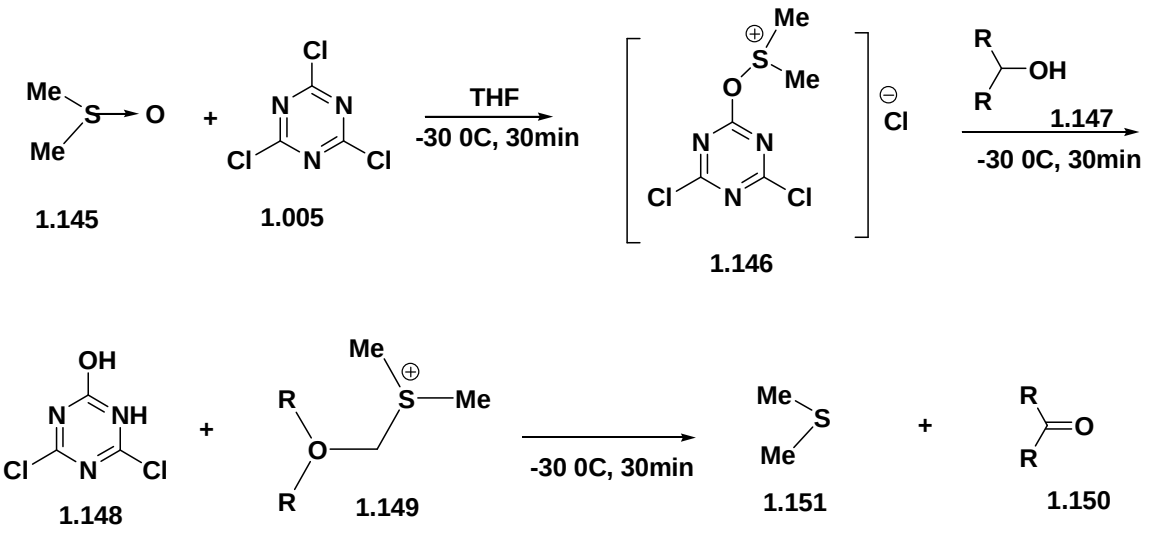
Fig.-1.30

s-Triazine provides a very mild and selective method for the conversion of ketoximes **(1.143)** to the corresponding amides[90-91] **1.144** during the Beckmann rearrangement.**(Scheme-1.31)**



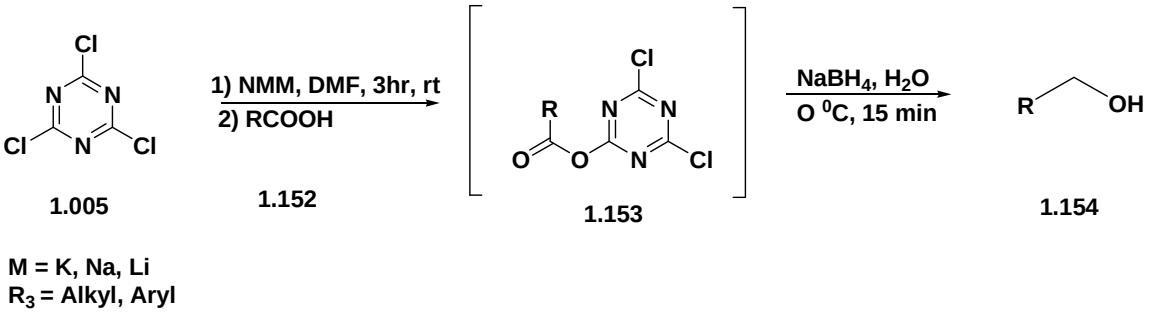
Scheme-1.31

In presence of s-triazine, alcohols **(1.147)** can be efficiently converted to the corresponding carbonyl compounds[92] **(1.150) (Scheme-1.32).**



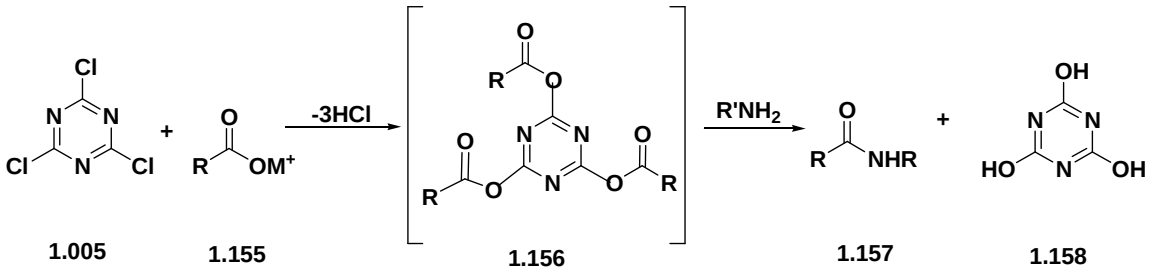
Scheme-1.32

As reported by the Falorni[93], carboxylic acid or N-protected amino acids, can be activated by cyanuric chloride and subsequently reduce to their corresponding alcohols with sodium borohydride in water. **(Scheme-1.33).** Following this procedure N-Z, N-Boc, N-Fmoc amino acids **(1.152)** can be easily reduced to their corresponding alcohols.**(1.154).**



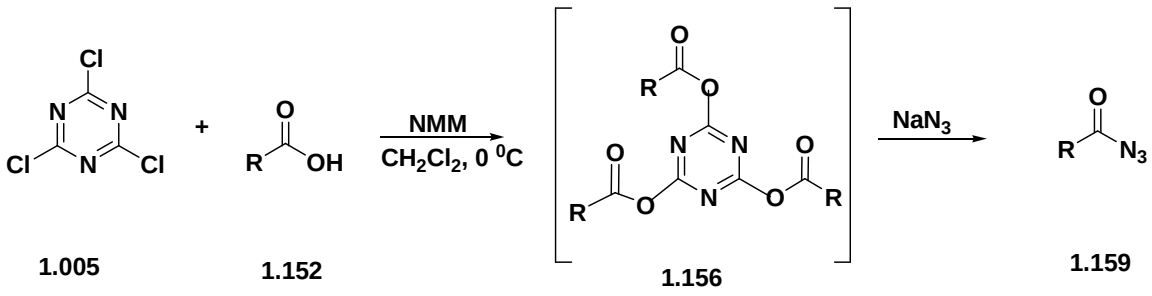
Scheme-1.33

During the preparation of amides **(1.157)**, Rayle and Fellmeth[94-95] successfully used cyanuric chloride and claimed that 2,4,6-triacyloxy-1,3,5-triazine **(1.156)** is an intermediate**.(Scheme-1.34)**



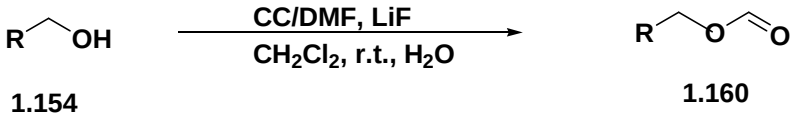
Scheme-1.34

Bandgar and Pandit[96] synthesised acyl azides **1.159** directly from carboxylic acid **(1.152)**, cyanuric chloride and NaN_2 after that following the similar procedure various aryl, heteroaryl, alkyl carboxylic acyl azides were obtained in high yields. **(Scheme-1.35).**



Scheme-1.35

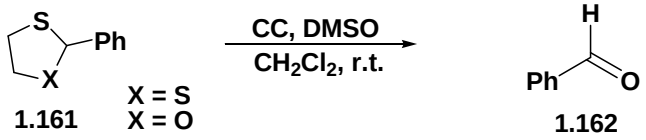
The DMF/cyanuric chloride complex can also be used for the selective protection of primary alcohol **(1.154)** by a formyl residue[97] **1.160 (Scheme-1.36)**



1.154 **1.160**

Scheme-1.36

An efficient deprotection of a variety of 1,3-dithioacetals and 1,3-oxathiolanes **(1.161),** in a short time under mild conditions, to their corresponding carbonyl compounds **1.162** using cyanuric chloride, the products isolated were pure and in high yeilds, as reported by Karimi[98] **(Scheme-1.37).**

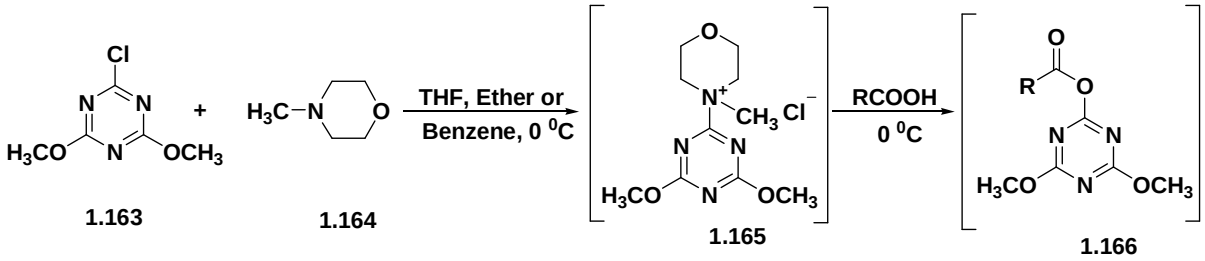


1.161 **1.162**

Scheme-1.37

1.5 Application of 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) in functional group transformations:

CDMT **(1.163)** has wide applications, it is commercially available and can easily be synthesised. It is used for the synthesis of substituted esters and amides. Kaminski et al[99] reported that CDMT reacts with NMM (N-methyl-morpholine) **(1.164)** to form 4-(4,6-dimethoxy-1,3,5-triazine-2-yl)-4-methylmorpholinium chloride (DMTMM) **(1.165),** it was isolated and fully characterised. DMTMM is a stable compound and can be stored at room temperature for several months without any decomposition. DMTMM on reacting with carboxylic acid forms an active ester **(1.166) (Scheme-1.38).**



1.163 **1.164** **1.165** **1.166**

Scheme-1.38

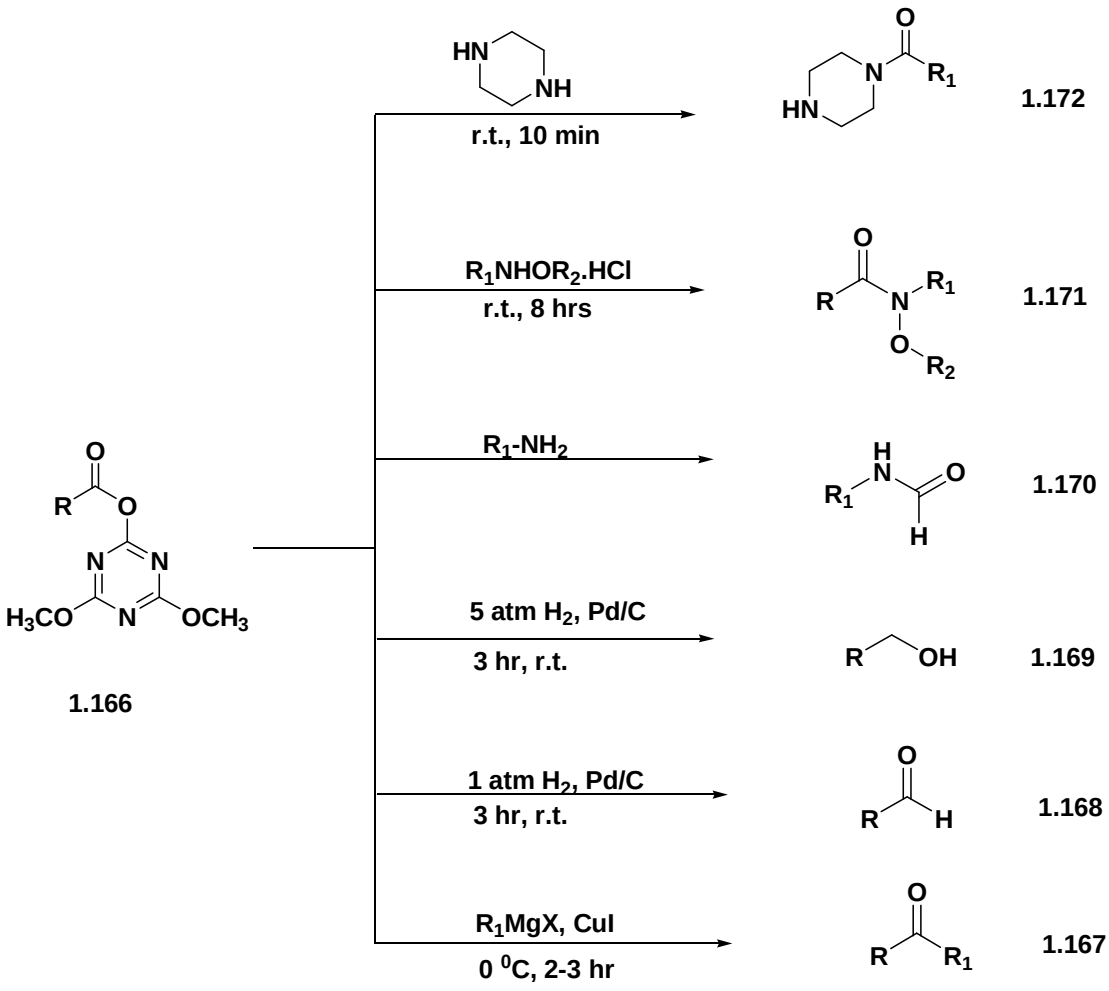
Weinreb amides **(1.171),** a useful precursor to ketones is prepared from the ester **(1.166)** by Giacomelli et al[100] **(Scheme-1.39).**

Corresponding aldehydes **(1.168)** were obtained, by the reduction of the active ester **(1.166)** by hydrogen and Pt/C[101] **(Scheme-1.39).**

In the presence of stoichiometric amount of CuI and Grignard reagent, activated esters of aromatic carboxylic acid and N-Boc or N-Z protected amino acids were converted to ketones[102] **(1.167) (Scheme-1.39).**

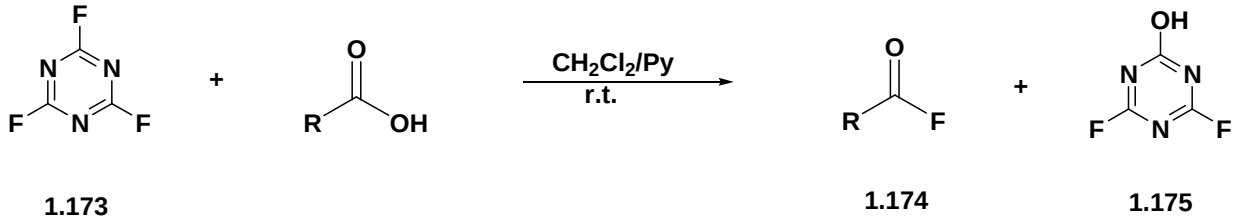
By the reaction of activated ester with piperazine at room temperature, monoacetylated piperazine **(1.172)** derivatives were prepared[103] **(Scheme-1.39).**

Amines and aminoacid esters were formylated by the use of active ester of formic acid[104] **(1.170) (Scheme-1.39).**



Scheme-1.39

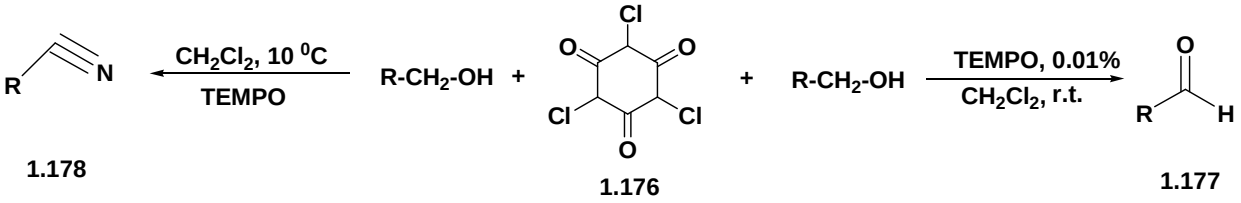
Cyanuric fluoride **1.173,** was prepared from cyanuric chloride[105]. Cyanuric fluoride easily converts carboxylic acids, N-Fmoc and N-Trt aminoacids, to corresponding fluorides. **(1.174) (Scheme-1.40)**



1.173 **1.174** **1.175**

Scheme-1.40

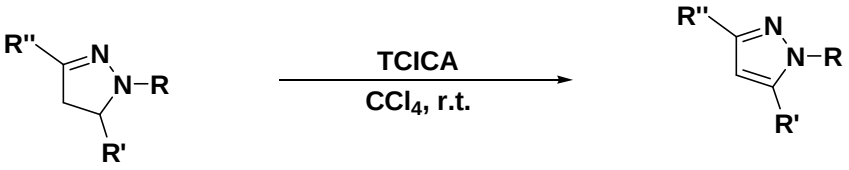
Giacomelli[106] reported that TCICA (1,3,5-trichloro-2,4,6-trioxo-s-triazine) **(1.176)** oxidises primary alcohols and N-protected-β-amino alcohols to aldehyde **1.177** and in presence of TEMPO it converts primary amines to their corresponding nitriles **1.178 (Scheme-1.41)**



1.178 **1.176** **1.177**

Scheme-1.41

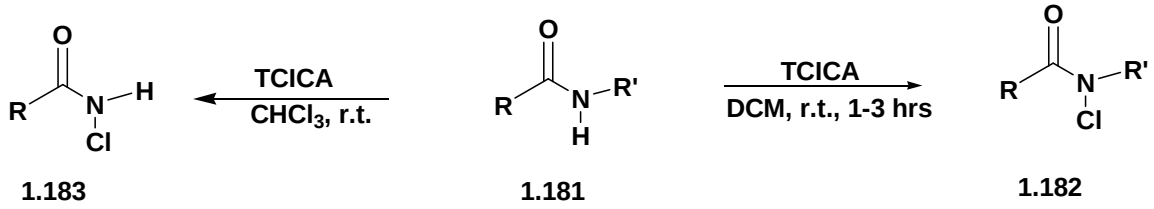
Zolfigol[107] et al. oxidised 1,3,5-trisubstituted pyrazolines **(1.179)** to their corresponding pyrazoles **1.180** in presence of TCICA **(Scheme-1.42).**



1.179 **1.180**

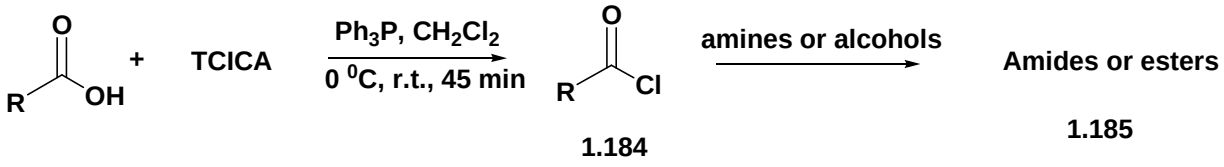
Scheme-1.42

N-chlorination of amides **(1.181),** lactams, and carbamates as intermediates[108] is also done in presence of TCICA in organic synthesis **(Scheme-1.143).**



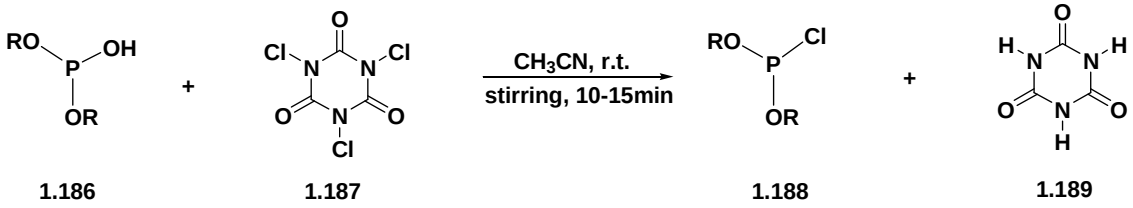
Scheme-1.43

Carboxylic acids on reaction with TCICA in presence of triphenylphosphine get converted into acid chlorides. This on reaction with amines or alcohols afforded corresponding amides or esters[109] **(Scheme-1.44).**



Scheme-1.44

On stirring TCICA **(1.187)** with dialkyl phosphites **(1.186)** in acetonitriles at room temperature for 15 min gives excellent yield of dialkyl chlorophosphates **1.188**[110] **(Scheme-1.45).**



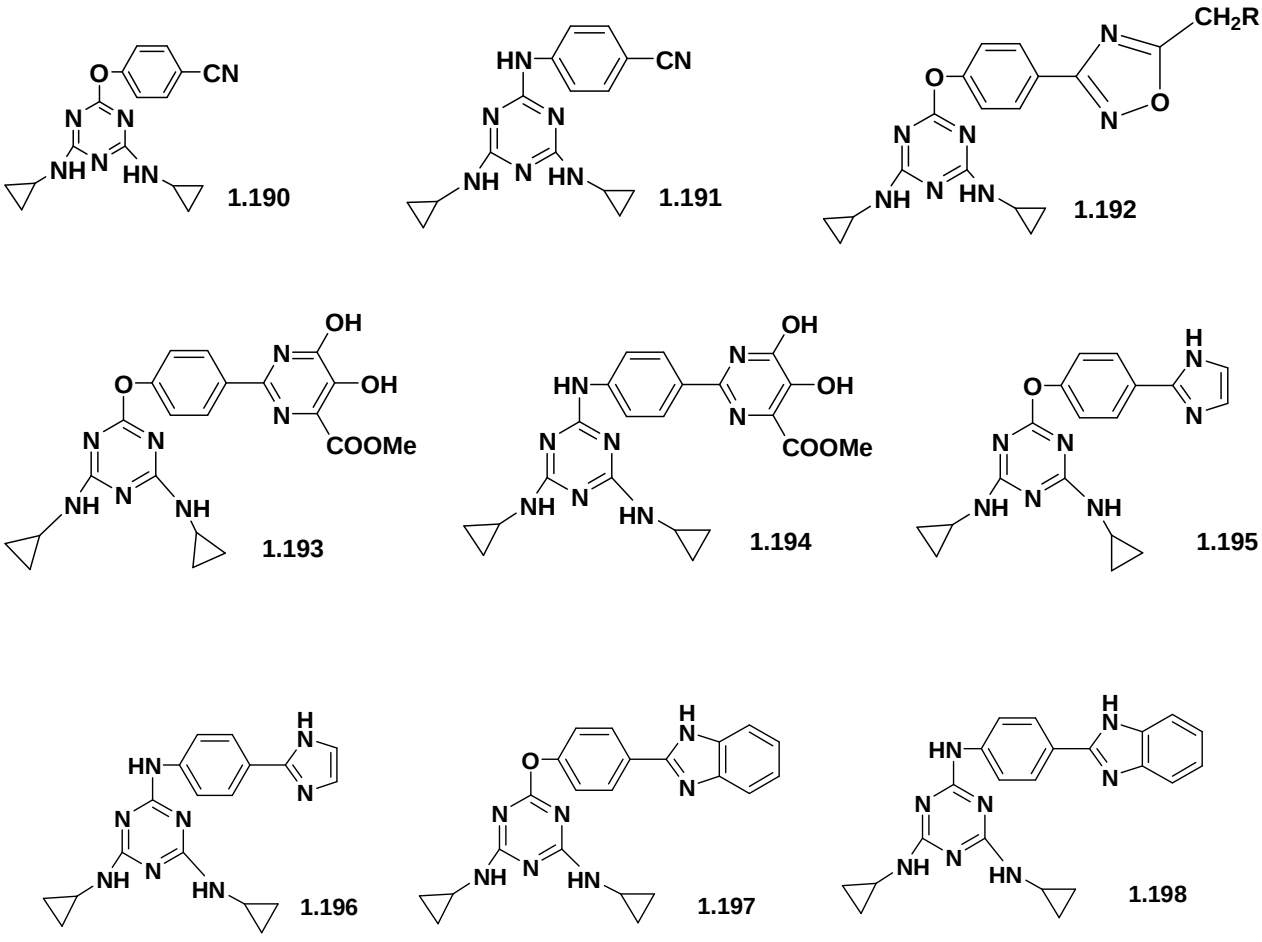
Scheme- 1.45

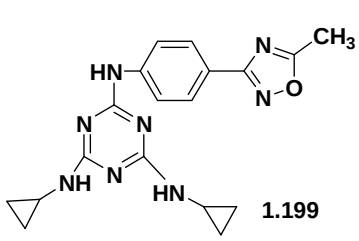
1.6 Brief outline of the present work:

Inspired by the impressive anti-HIV active profiles of s-triazine, our aim in the present work was to synthesize s-triazines which incorporated in its molecule the vital fragments of etravirine (which has the previous history of being highly active anti-HIV agent), on the premise that their presence in tandem in its molecular framework could produce a positive impact in enhancing the overall biological efficacy in the resulting molecules. It has been known from the literature[111-112] that sometimes the incorporation of the bioactive pharmacophores in the existing drug molecules exerts a profound influence on the biological activity of the parent drug molecule by providing

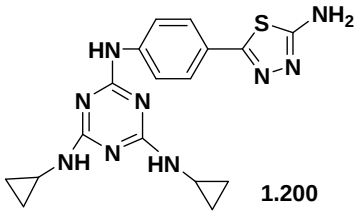
an additive effect on the overall potency of the molecule. An examination of literature pertaining to the bioactivity of s-triazines revealed that this molecule on the one hand is highly biologically active and on the other hand it provides a template to hold three bioactive pharmacophores together in the same molecule, by allowing the chlorine atoms of 2,4,6-trichloro-1,3,5-triazine to be replaced by oxygen and nitrogen bearing bioactive nucleophilic species. This concept of the drug design has formed the basis in the present study, to seek the structural modification of s-triazine nucleus to generate novel analogues (**1.190-1.210, Fig.1.31)** with the hope to obtain the molecules endowed with high biologically active profiles. It is with this idea in mind that the present study has been framed and proposed to be undertaken.

Structures of the compounds (1.190-1.210) are shown in fig 1.31 whose synthesis is proposed to be undertaken in the present work:

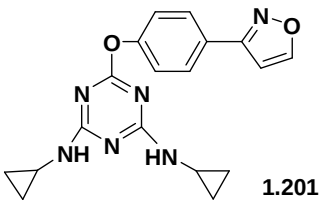




1.199



1.200



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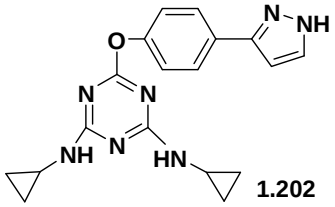

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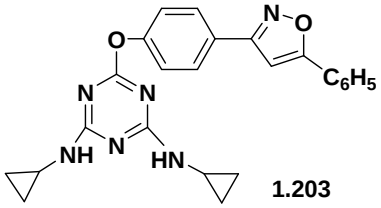

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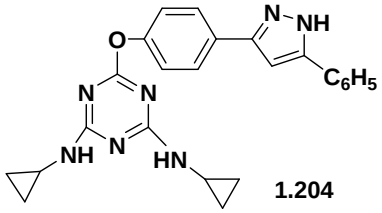

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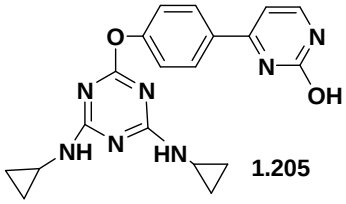

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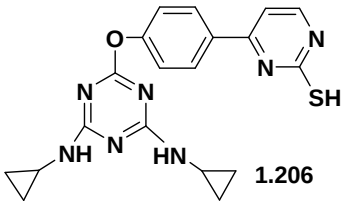

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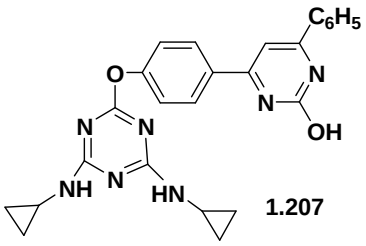

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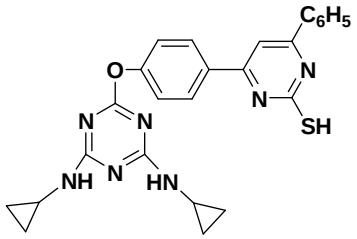
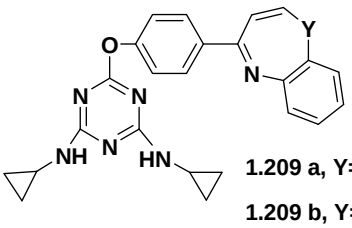


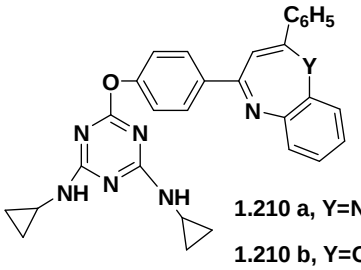
1.208



1.209 a, Y=NH

1.209 b, Y=O

1.209 c, Y=S



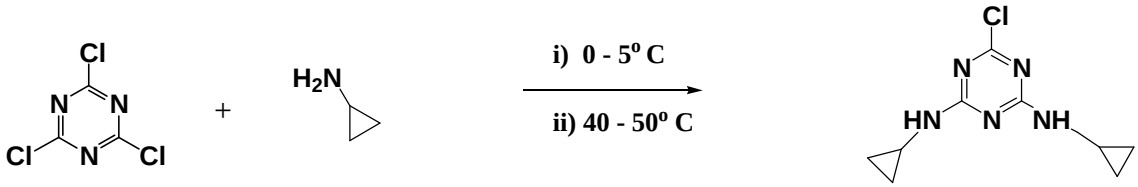
1.210 a, Y=NH

1.210 b, Y=O

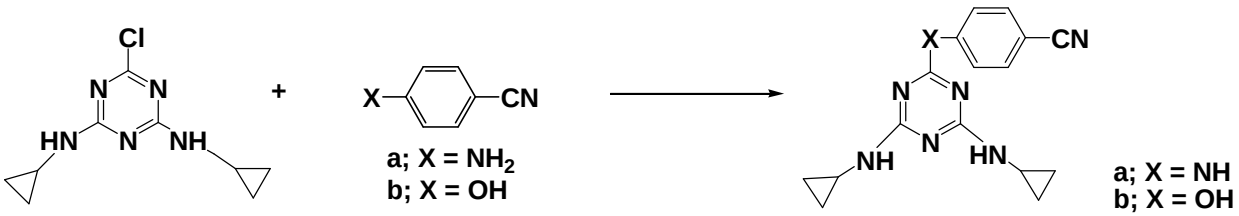
1.210 c, Y=S

Fig.-1.31

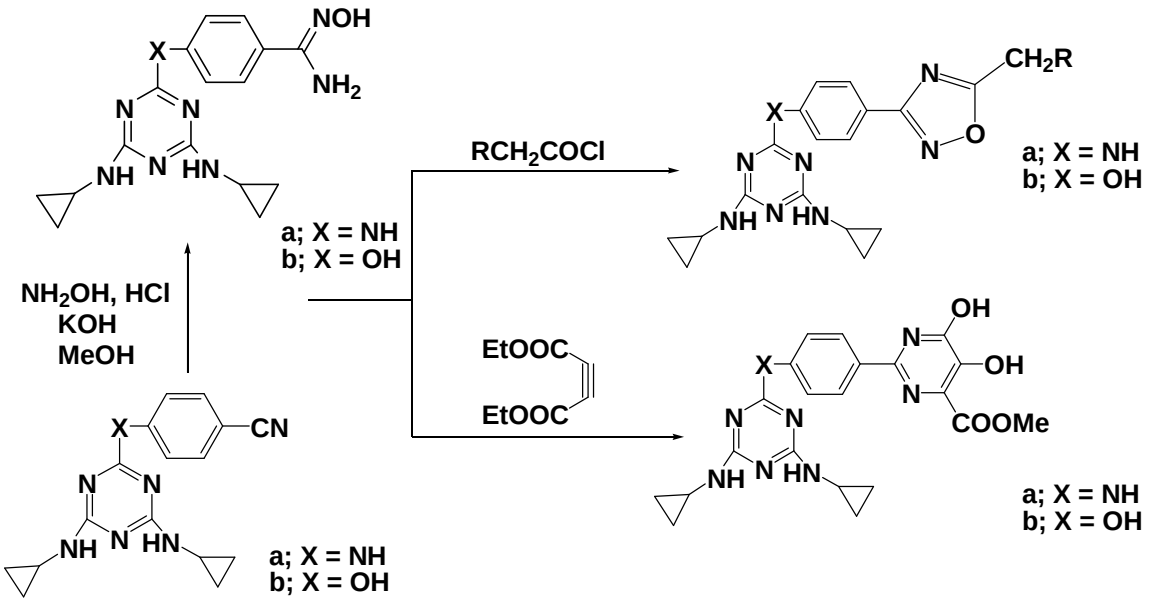
Structures of the final products whose synthesis has been described in the chapters II, III, IV, and V respectively, follows the scheme shown below:



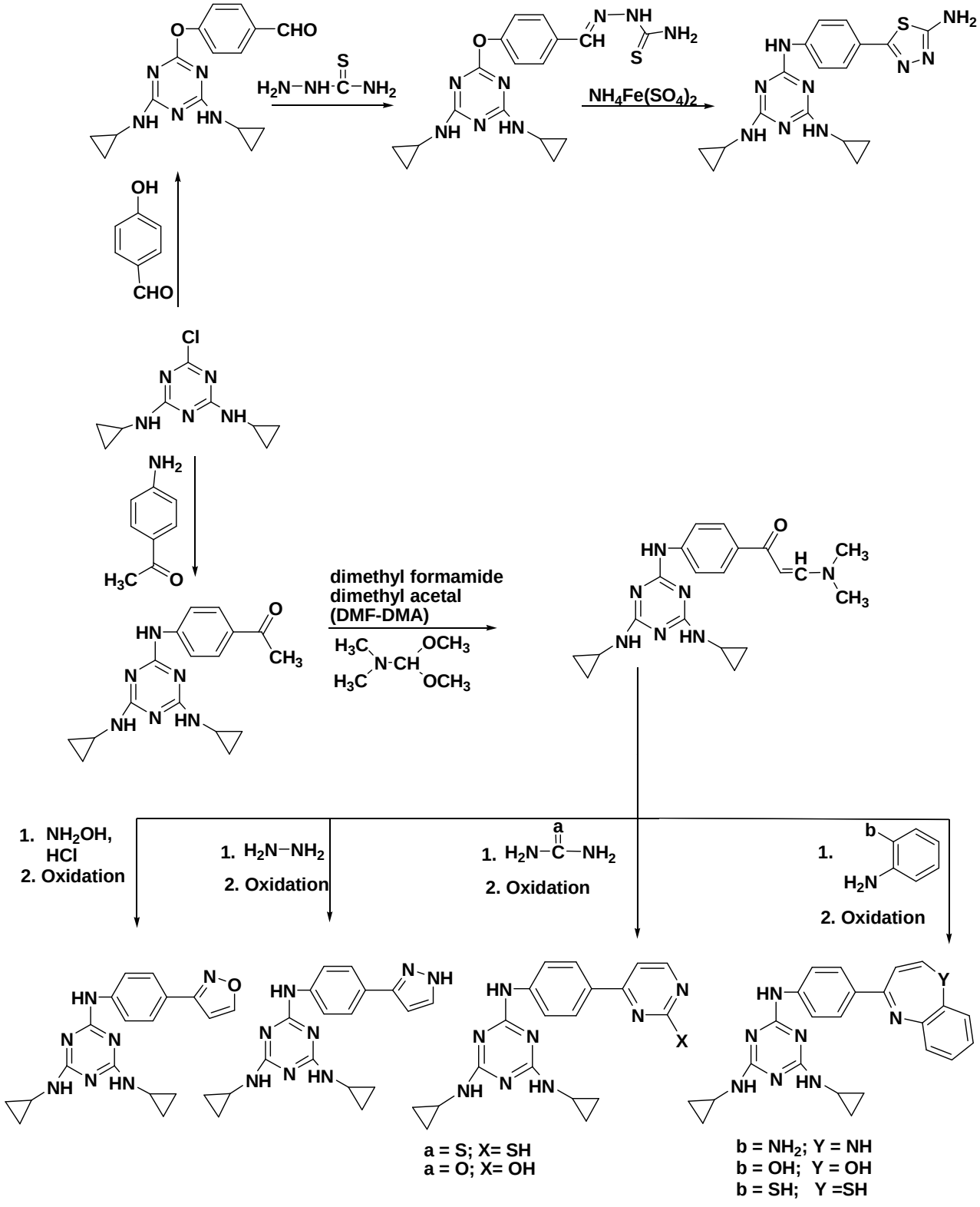
Scheme-1



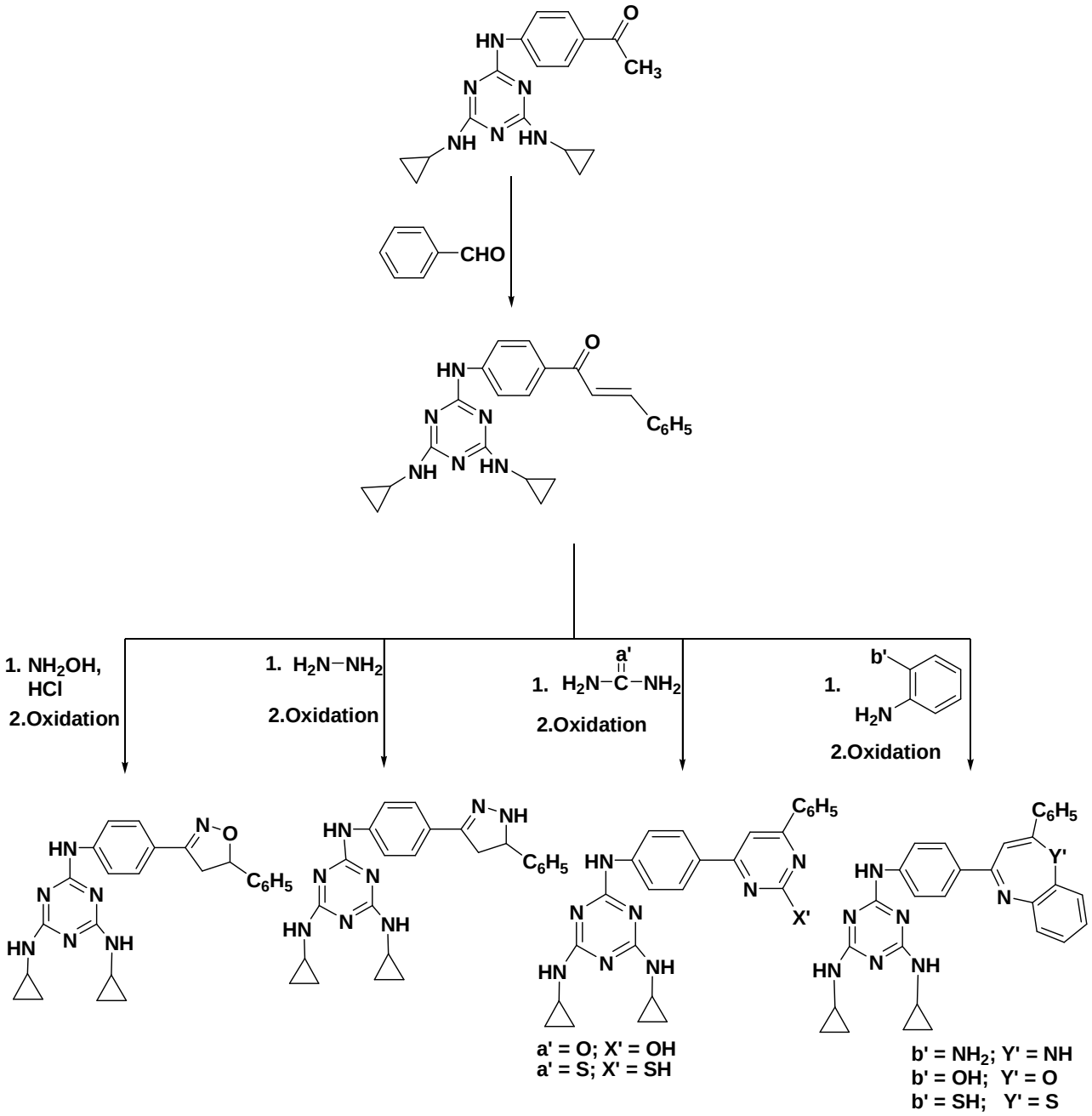
Scheme-2



Scheme-3


dimethyl formamide
dimethyl acetal
(DMF-DMA)
1. NH2OH, HCl
2. Oxidation
1. H2N–NH2
2. Oxidation
1. H2N–C(=a)–NH2
2. Oxidation
1.
2. Oxidation
a = S; X= SH
a = O; X= OH
b = NH2; Y = NH
b = OH; Y = OH
b = SH; Y =SH

Scheme-4


1. NH2OH, HCl
2.Oxidation
1. H2N−NH2
2.Oxidation
1. H2N−C(=a')−NH2
2.Oxidation
1.
2.Oxidation
a' = O; X' = OH
a' = S; X' = SH
b' = NH2; Y' = NH
b' = OH; Y' = O
b' = SH; Y' = S

Scheme-5

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