Chapter-II

Synthesis of Starting Materials

Abstract

This chapter describes the synthesis of imidate ester and amidine from 2-amino-4'-benzonitrile, thiosemicarbazone from 2-oxy-4'-benzaldehyde, dimethylaminomethylene ketone and chalcone from 2-oxy-4'acetylphenyl derivatives of cyanuric chloride, which have been used in the synthesis of a variety of fused heterocycles in **Chapter III, IV and V.** The structures of the compounds have been established on the basis of IR, ^{1}H-NMR and MS spectral data.

2.1 Introduction

The literature[1,2] is replete with examples showing that sometimes the coupling of biologically active molecules with bioactive pharmacophores such as isoxazole, pyrazole, oxadiazole, imidazole, pyrrole, pyridine, piperidine, piperazine, quinoline, pyrimidine heterocyclic scaffolds, produce interesting series of compounds with interesting biological properties. Based on this trend in the literature, it was expected that the incorporation of some of the above biologically active pharmacophores in s-triazine nucleus could produce compounds with impressive biological activities.

The quest to develop effective therapies for the treatment of HIV infection has demonstrated that clinical benefits can be achieved with drugs that target the protease[3,4,5] or reverse transcriptase[6,7,8] enzymes. The currently available agents however provide only transient benefit, due to the rapid emergence of drug resistant mutants of the virus[9]. Combination of drugs [HAART] have been tried in an attempt to avoid the problem of resistance with some promising results[10-14] and the combination therapy now represents the standard of care. However, there is a continuing need to identify improved agents within each class in order to provide the optimum clinical benefits.

Etraverine has recently emerged as one of the most active NNRTIs from the pyrimidine class of privileged heterocyclic scaffolds and has been the first to reach regulatory approval[15] from this class. It acts as an allosteric inhibitor and is at present used as an HIV-1 inhibitor[16]. In order to avoid the appearance of the drug resistance observed in Etraverine monotherapy resulting from the enzyme mutation, recently proper modifications in the substitution pattern of Etraverine have been sought which has resulted in the development of new broad spectrum of RT inhibitors[17].

Greatly encouraged by the impressive bioactive profiles of s-triazine, it is aimed in the present work to synthesize s-triazine molecules incorporating in them a wide variety of bioactive pharmocophores, especially the vital fragments of the highly active RT inhibitor the etravirine, on the premise that their presence in tandem in a single molecular framework of s-triazine could contribute significantly to the biological activity in the resulting molecules. In the synthetic strategies envisaged in the present work, the s-triazine molecule has been selected with this idea in mind, that this molecule on one hand is biologically highly active and on the other hand it can provide a template to hold three bioactive pharmacophores together in the same molecule. It was

thought that it could be interesting to access the favourable impact if any, if this substitution produced on the biological activity in the new materials through the additive or cumulative effects exercised by each of these moieties. If their role to produce a positive impact on activity was established, such structures were likely to form new targets in synthesis and for biological evaluations. It was with this idea; the present study was planned to be undertaken. It is believed that synthesis and biological evaluations of s-triazine incorporated with bioactive pharmacophores should prove to be a rational approach towards the study of their biological applications.

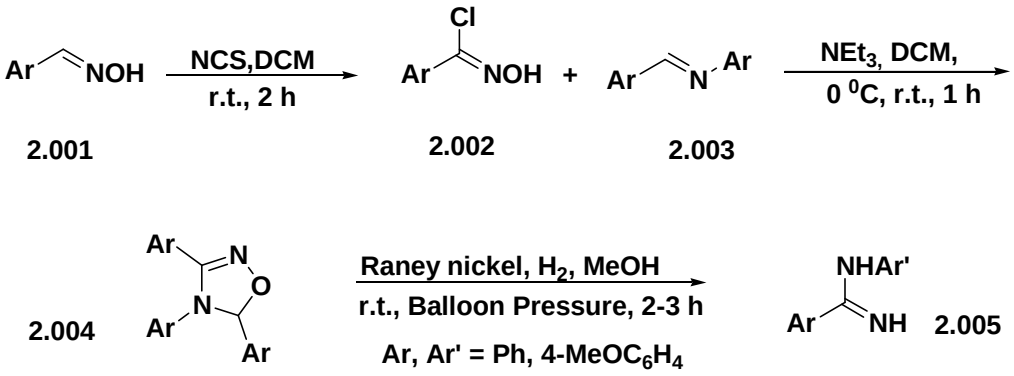
2.2 Chemistry of intermediates used in synthesis in the present work

2.2.1 Amidine derivatives

Several heterocyclic compounds can be synthesised from N-aryl amidines which show a wide spectrum of biological activities.

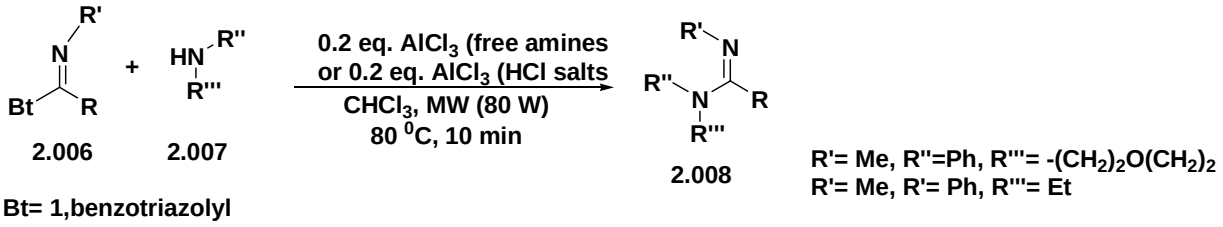
2.2.1.1 Synthesis of amidine derivatives:

a) Benzaldehyde oxime **(2.001)** with NCS forms corresponding benzohydroxymoyl chloride **(2.002),** it with imine **(2.003)** and triethylamine at 0 ^{0}C produces 4,5-dihydro-1,2,4-oxadiazole **(2.004)** in good yield. Oxadiazole with Raney nickel in methanol at room temperature undergoes hydrogenolysis and forms substituted amidine **(2.005)** in 74-91% yield **(Scheme-2.1)[18].**



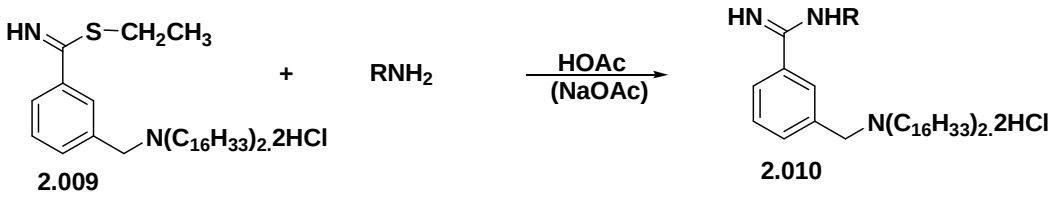
Scheme-2.1

b) Various polysubstituted amidines **(2.008)** can be synthesised in good yield by microwave reactions of primary and secondary amines **(2.007)** with imidoylbenzotriazoles **(2.006)** (**Scheme-2.2)**[19]**.**



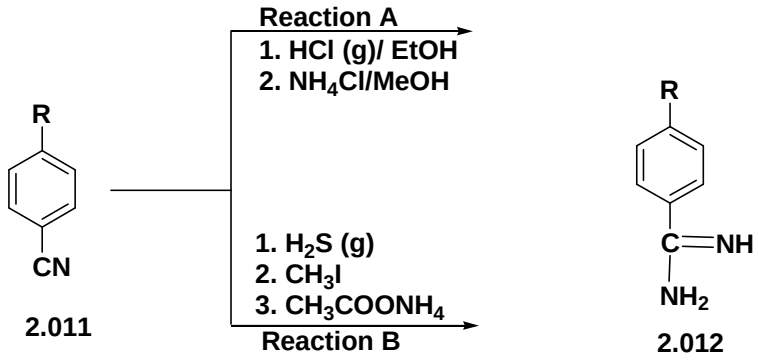
Scheme-2.2

c) Using a buffered protonic catalysis in non-aqueous medium, amidines **(2.010)** can be synthesised from thioimidate **(2.009) (Scheme-2.3)**[20]**.**



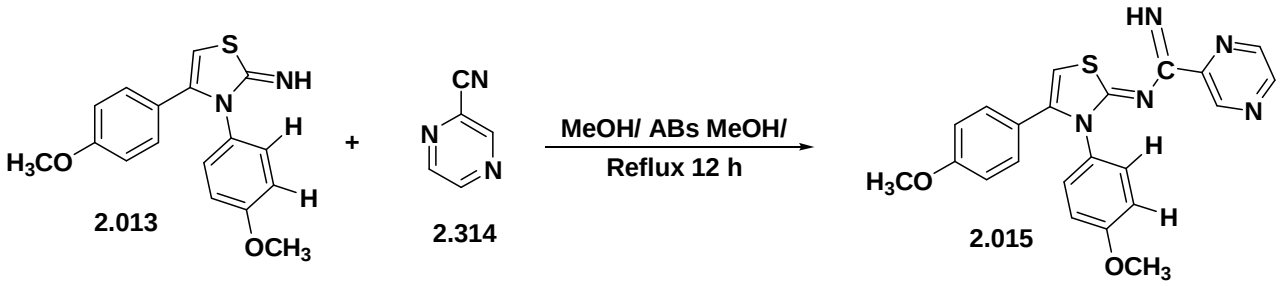
Scheme-2.3

d) Amidine derivatives **(2.012)** can be synthesised from nitriles **(2.011)** via either with Pinner reaction or through thioimidate route **(Scheme-2.4)**[21]**.**



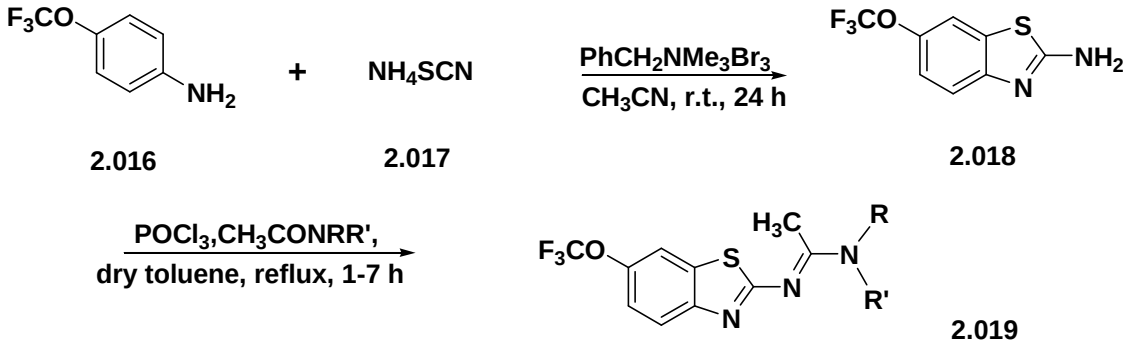
Scheme- 2.4

e) 2-Cyanopyrazine **(2.014)** is activated with sodium methoxide at room temperature and the refluxed in absolute methanol for 12 h with 1,4-(2-imino-4-(4-methoxyphenyl-thiazol-3-(2*H*)-yl)phenyl)ethanone **(2.013)** to give amidine derivative **(2.015) (Scheme-2.5)**[22]**.**



Scheme-2.5

f) On condensing 4-(trifluoromethoxy)aniline **(2.016),** with ammonium thiocyanate **(2.017)** and benzyltrimethylammonium tribromide in methyl cyanide gives 2-imino-6-(trifluoromethoxy)benzothiazole **(2.018)** which on reaction with acetamide and $POCl_3$ in dry toluene forms acetamide **(2.019) (Scheme-2.6)[23].**



Scheme-2.6

2.2.2 Imidate ester derivatives

Imidates, also called imidic acid ester, imido esters or imidoates, are esters of hypothetical iso-amides or imidic acids **(Fig-2.1).** Cyclic imidates are divided into three groups:

1) cyclic imidates with the oxygen function at exocyclic position
2) cyclic imidates with the imino-nitrogen at exocyclic position
3) cyclic imidates in which the imidate function lies with in the ring e.g. oxazolines and dihydro-oxazines **(Fig-2.2).**

Fig.-2.1

The amidine group is the nitrogen atom of the imidates. As compared to the amidines, imidates have smaller dipole moment, which shows that the conjugation in the imidates is less pronounced, however the conjugation favours the planar rearrangement of the imidate group**.**

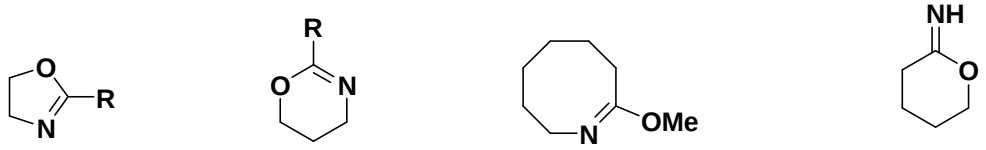
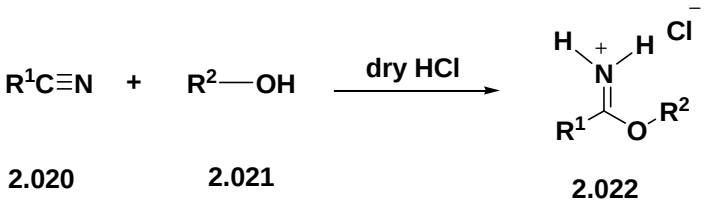


Fig.-2.2

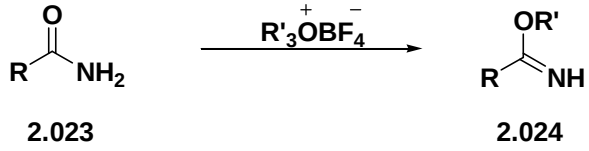
2.2.2.1 Synthesis of imidate ester derivatives:

a) Imidates **(2.022)** can be synthesised by Pinner reaction, in which under anhydrous conditions, a nitrile **(2.020)** is condensed with an alcohol **(2.021)** in presence of hydrogen bromide or hydrogen chloride at 0 ^{0}C **(Scheme-2.7)**[24]**.**



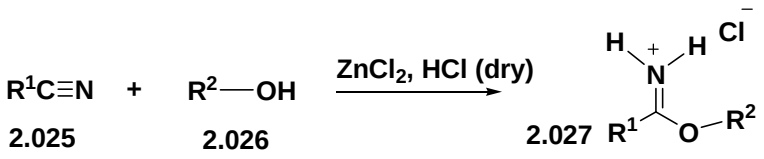
Scheme-2.7 Pinner Reaction

b) Amide **(2.023)** on treatment with 'Meerwein's reagent' easily produces imidate esters **(2.024) (Scheme-2.8)**[25]**.**



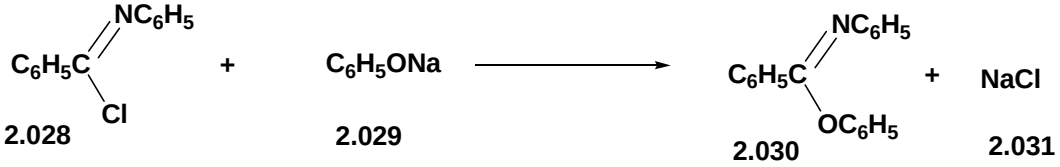
Scheme-2.8

c) Hoesch reaction: This reaction proceeds via imino chloride, in this method a nitrile **(2.025)** is condensed with a phenol **(2.026)** or a phenolic ether in presence of dry hydrogen chloride and zinc chloride **(Scheme-2.9)**[26]**.**



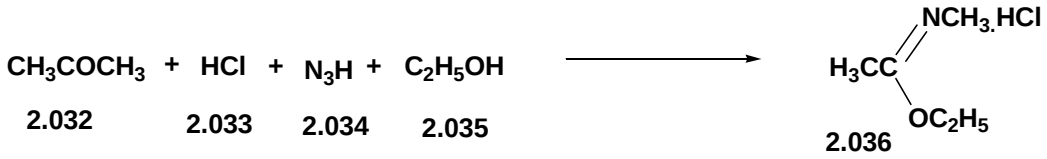
Scheme-2.9

d) Imino-chlorides **(2.028)** with alkoxide or phenoxide **(2.029)** forms imidates **(2.030) (Scheme-2.10)**[26]**.**



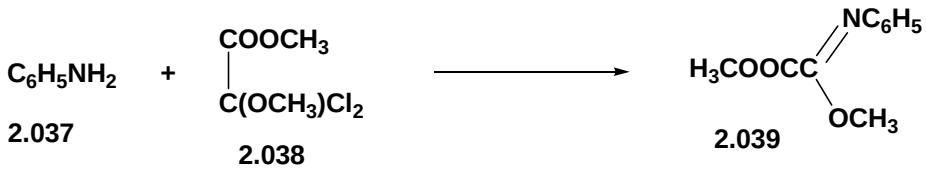
Scheme-2.10

e) Ketones **(2.032)** on reacting with hydrazoic acid **(2.034)**, hydrogen chloride **(2.033)** in presence of alcohol **(2.035)** produces imidates **(2.036) (Scheme-2.11)**[27]**.**



Scheme-2.11

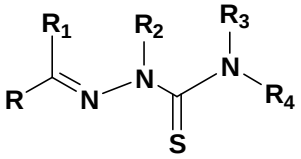
f) By the action of methyl methoxydichloroacetate **(2.038)** on aniline **(2.037)** in boiling xylene, methyl-*N*-phenylcarbmethoxyformimidate **(2.039)** has been prepared **(Scheme-2.12)**[28]**.**



Scheme-2.12

2.2.3 Thiosemicarbazone derivatives:

Semicarbazone is formed by the condensation of an aldehyde or a ketone with semicarbazide and thiosemicarbazone is an analogue of semicarbazone which has a sulfur aotm in place of an oxygen atom **(Fig-2.3).**



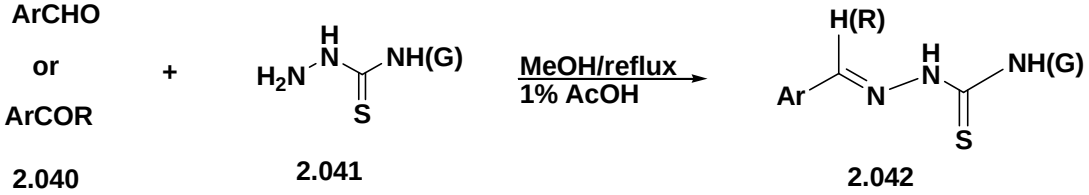
General formula for Thiosemicarbazones
R_1=R_2=R_3=R_4=H; or any organic substituent

Fig.-2.3

Thiosemicarbazones are thiourea derivatives which have widespread application in the chemotherapy[29]**.** Thiosemicarbazones exhibit antimicrobial, antitubercular, anti-viral, anticonvulsant, antihypertensive, anti-inflammatory, anesthetic, anti-cancer, cytotoxic and hyperglycemic[30] activities.

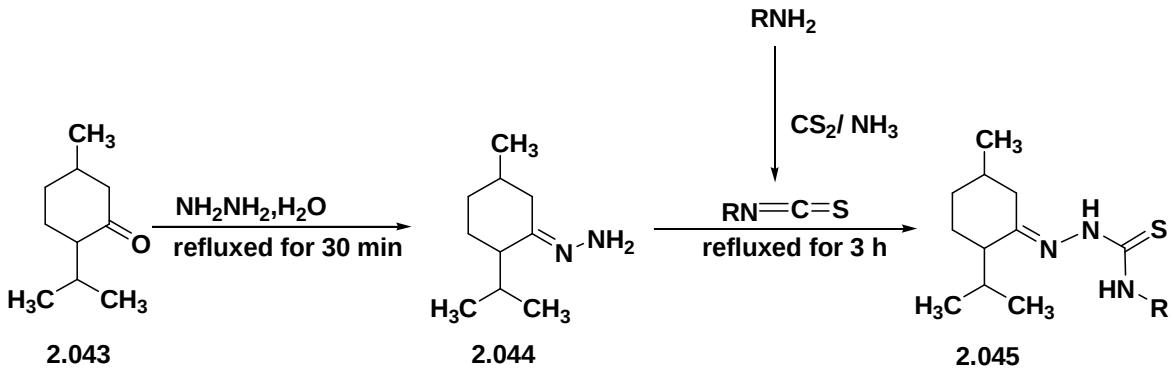
2.2.3.1 Synthesis of thiosemicarbazone derivatives:

a) Thiosemicarbazones **(2.042)** are prepared by refluxing either an aldehyde or a ketone **(2.040)** with thiosemicarbazide **(2.041)**. Aldehydes take less time and no acetic acid is required for the reaction whereas ketones require more time and 1% acetic acid is required **(Scheme-2.13)**[31]**.**



Scheme-2.13

b) Condensation of substituted of arylisothiocyanate with menthone hydrazone **(2.079)** forms thiosemicarbazones **(2.045) (Scheme-2.14)**[32]**.**

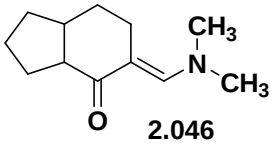


Scheme-2.14

2.2.4 Dimethylaminomethylene ketone derivatives:

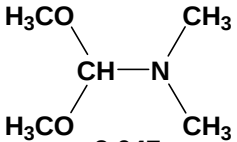
Pyrazoles and pyrimidines derivatives can be synthesised via dimethylaminomethylene ketone intermediate, these derivatives have great importance in medicinal chemistry.

N,N-dimethylformamide dimethyl acetal (DMF-DMA) **(2.047, Fig-2.5)** with appropriate methylene derivative forms dimethylaminomethylene ketone **(2.046, Fig-2.4).** *N,N*-Dimethylformamide dialkyl acetals (e.g. methyl, ethyl, benzyl, *t*-butyl), are very useful reagents in organic synthesis and are used for alkylation and formylation. As formylating agents they are used in the synthesis of amidines from amides and amines and enaminones from active methylene compounds whereas, as alkylating agent they have been used in the synthesis of thioethers from aromatic and heterocyclic thiols, esters from acids and ethers from phenols. They are found to be very useful intermediates in the synthesis of many biologically active compounds. The mechanism involves the generation of an oxo-stabilised carbenium ion[33,34].



2.046

Fig.-2.4



2.047

Fig.-2.5

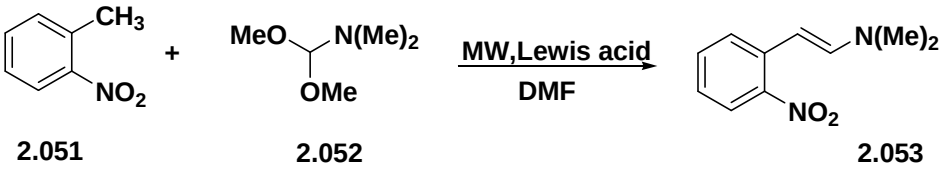
2.2.4.1 Synthesis of dimethylaminomethylene ketone derivatives:

a) By the condensation of methyl, aryl or heteroaryl ketones with DMF-DMA in refluxing xylene: By the equimolar addition of aryl methyl or heteroaryl ketones **2,048** or **2.050** with DMF-DMA in refluxing dry xylene for 3-4 hr formed **(2.049), (2.051)** respectively, by the loss of two molecules of methanol.**(Scheme-2.15 -1.16)**[35]**.**

Scheme-1.15

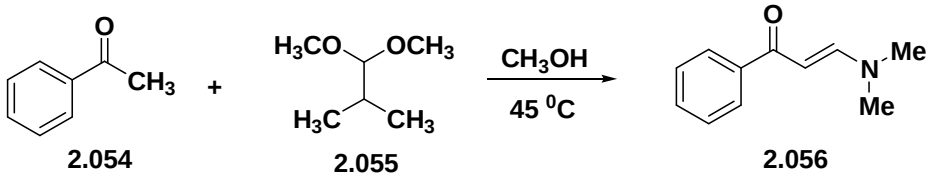
Scheme-2.16

b) 2-Nitrotoluene derivative **(2.051)** with copper(I) iodide in a mixture of DMF-DMA **(2.052)** and DMF at 180 ^{0}C in a sealed vial under microwave irradiation (20 min x 7) in an internal pressure of 8-10 bar, formed **(2.053)** in excellent yield (97%) **(Scheme-2.17)**[36]**.**



Scheme-2.17

c) On refluxing acetophenone **(2.054)** and DMF-DMA **(2.055)** at low temperature for 2-4 hr in dichloromethane, containing crushed, activated 5Å molecular sieves formed **2.056 (Scheme-2.18)**[37]**.**

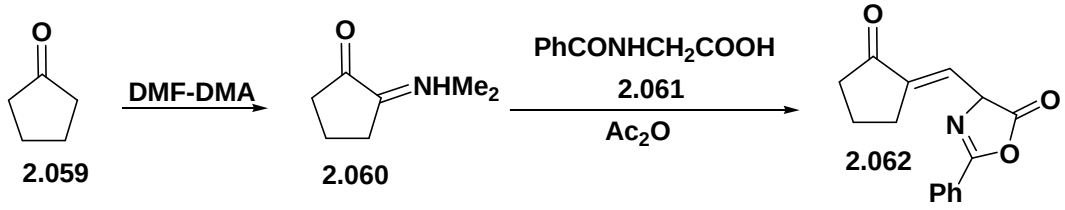


Scheme-2.18

d) By heating DMF-DMA with **2.057** formed **2.058** in better purity and higher yield **(Scheme-2.19)[38].**, which had previously been obtained by Vilsmeir reaction using ($DMF/POCl_3$)[39].

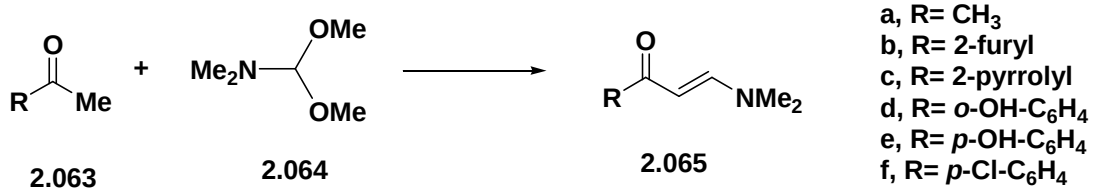
Scheme-2.19

e) Cycloalkanone **(2.059)** on heating with two equivalents of DMF-DMA for 16 hr formed α-aminoketone[40] **(2.060)** which on further reaction with **2.061** formed **2.062 (Scheme-2.20).**



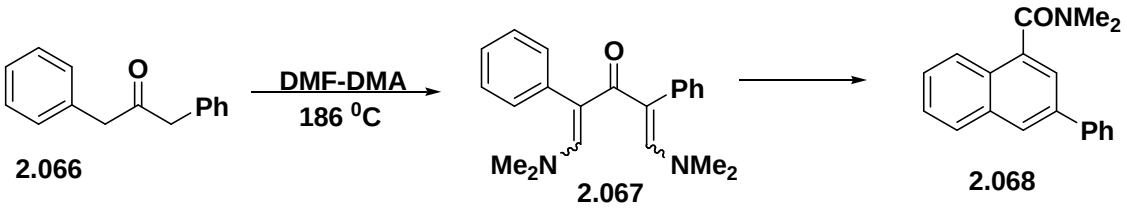
Scheme-2.20

f) Whereas on condensing the methylketones **2.063** with slight excess of DMF-DMA **(2.064)** in absence of solvent, on cooling formed products **2.065 (b-g)** in quantitative yield **(Scheme-2.21)[41].**



Scheme-2.21

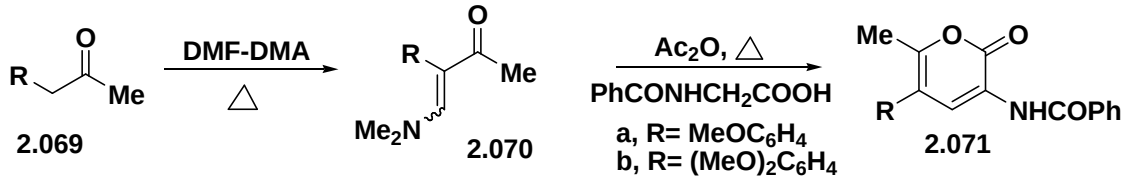
g) On heating **2.066** with DMF-DMA at 150-200 ^{0}C in a steel autoclave under nitrogen fromed **2.068 (Scheme-2.22)[42]**, (during the reaction the methylene ketone **2.067** were formed as an intermediate). This reaction also represents a novel transformation of 1,3-diaryl and 1,3-alkylacetones to naphthalene derivatives.



2.066 2.067 2.068

Scheme-2.22

h) Sterically hindered ketones, such as arylacetones **(2.069)** can be converted to 2H-pyran-2-ones **(2.071),** on heating **(2.069)** with DMF-DMA. The intermediate **(2.070)** formed undergoes cyclization in presence of acetic acid to give **(2.071) (Scheme-2.23)[43].**



2.069 2.070 2.071

Scheme-2.23

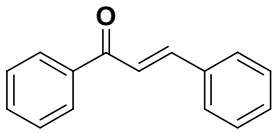
2.2.5 Chalcone derivatives:

Chalcones are α,β-unsaturated carbonyl systems **(2.072, Fig.-2.6).** Because of the conjugation:-

a) it has relatively low redox potential and have a greater tendency to undergo electron transfer reactions.

b) they have been reported to possess antibacterial[44], antitumour[45], anti-inflammatory[46], cytotoxic[47], antimalarial[48], antioxidant[49] activity.

c) the presence of β-enone system make the chalcones reactive towards the bidentate nucleophiles to give five, six and seven membered heterocyclic compounds.



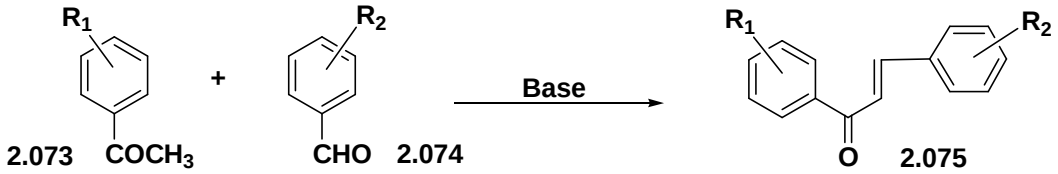
2.072

Chalcone

Fig.-2.6

2.2.5.1 Synthesis of chalcone derivatives:

a) Claisen Schmidt condensation: On reacting acetophenone **(2.073)** and benzaldehyde derivative **(2.074)** at 50 ^{0}C in presence of 10 – 60 % alkali or sodium ethoxide for 12 – 15 hr, α,β-unsaturated ketone called chalcone **(2.075)** is formed. It involves two steps, aldol condensation and dehydration **(Scheme-2.24)[50].**



Scheme-2.24

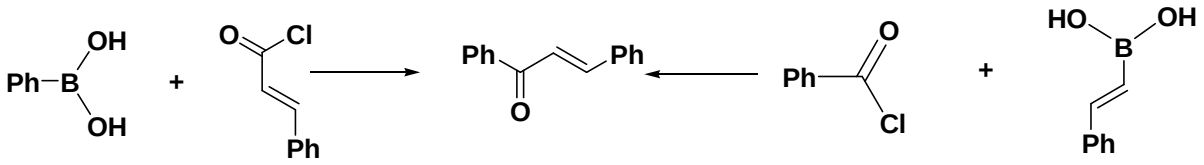
Use of solid base catalyst is more reliable as it is ecofriendly since it not only allows easy separation and recycling of the catalysts from the reaction mixture. The heterogenous catalysis gives better selectivity than homogenous catalysts.

Catalysts for Claisen-Schmidt condensation:

- Basic catalysts
  - Sodium hydroxide[51]
  - Potassium hydroxide[52]
  - Potassium carbonate[53]
  - Barium hydroxide[54]

- Acidic catalyst:
  - Dry HCl[55]
  - $AlCl_3$[56]
  - BF_3 or BF_3-Et_2O[57]
  - $Zn(Bpy)(OAc)_2$[58]
  - $Cp_2ZrH_2/NiCl_2$
  - Titanium(IV) chloride[59]
  - Silica-sulfuric acid[60]
  - $FeCl_3$[61]

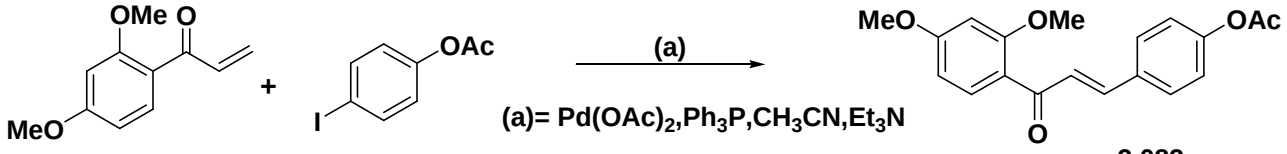
b) Suzuki reaction: Chalcones **(2.077)** can be synthesised by reacting cinnamyl chloride **(2.076)** with phenyl boronic acids **(2.075)** or by reacting benzoyl chloride **(2.078)** with phenyl vinyl boronic acids **(2.079) (Scheme-2.25)[62].**



2.075 **2.076** **2.077** **2.078** **2.079**

Scheme-2.25

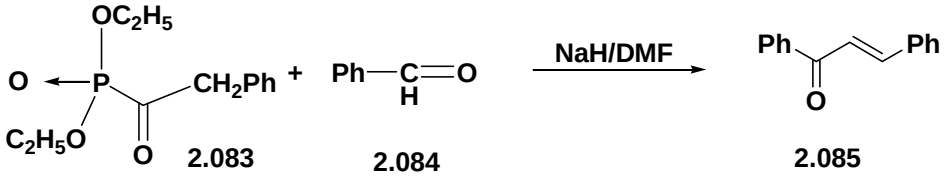
c) Heck reaction: Chalcones **(2.082)** can be synthesised by coupling of an aryl vinyl ketone **(2.080)** with an aryliodide **(2.081) (Scheme-1.26)[63].**



2.080 **2.081** **2.082**

Scheme-2.26

d) Wittig reaction: Chalcones **(2.085)** can be synthesised by the reaction of benzaldehyde **(2.084)** with phosphorane or phosphonate **(2.083)** carbanion derived from diethylphenacylphosphonate in presence of sodium hydride **(Scheme-2.27)[64].**



2.083 **2.084** **2.085**

Scheme-2.27

e) Chemical application of microwave and ultrasound irradiation has received much attention due to high selectivity and yield. Following heterogeneous catalysts have been used for the synthesis of chalcones under microwave irradiation :

- Potassium carbonate[65]
- Barium hydroxide[66]
- *p*-Toluene sufonic acid[67]
- KF-Al_2O_3[68]
- Zirconium tetrachloride[69]

- Piperidine[70]
- Aqueous alkali[71]

Following catalyst have been used in the synthesis of chalcones under ultrasound irradiation:

- Potassium carbonate[72]
- Basic Al_2O_3[73]
- Aminografted zeolite[74]
- $Ba(OH)_2$[75]
- pulverised KOH[76]
- KF-Al_2O_3[77]

2.3 Present work:

Owing to the impressive biological properties exhibited by, s-triazine and the heterocyclic scaffolds containing oxadiazole, imidazole, benzimidazole, thiadiazole, isoxazole, pyrazole, pyrimidine, benzodiazepine, benzothiazepine and benzoxazepine nucleus, it was thought of interest in the present work to prepare the molecules in which these bioactive pharmacophores could be brought together to become the part of a single molecular framework.

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 (shown in **Fig.-2.7**) with the hope to obtain the molecules endowed with high biologically active profiles. It is with this idea in mind that the present study was framed and was undertaken.

This chapter describes the procedure for the synthesis of active synthons such as amidines, imidate ester, thiosemicarbazones, dimethylaminomethylene ketones, and chalcones which are required in the subsequent chapter for the synthesis of five, six and seven membered heterocyclic rings from their reaction with bidentate nucleophiles such as, ethylenediammine, hydrazine hydrate and hydroxylamine hydrochloride (to give five membered rings), urea and thiourea (to give six membered rings), *o*-phenylenediamine, *o*-aminothiophenol and *o*-aminophenol (to give seven membered rings) from 2-phenoxyl and 2-phenylamino substituted derivatives of s-triazine

Inspired by the bioactive profile of the s-triazine nucleus containing three chlorine atoms in 2,4,6-trichloro-1,3,5-triazine (TCT) **(2.086)**, it was planned to first convert compound **2.086** into the corresponding 6-chloro-2,4-[dicyclopropylamino]-1,3,5-triazine derivative **2.088** from the reaction of its two chlorine atoms with cyclopropylamine **2.087** .The chlorine atoms of TCT are highly reactive species known to be activated for nucleophilic attack. The replacement of C_6-chlorine atoms of TCT with the indicated hydroxy and amine bearing pharmacophores resulted the corresponding 6-substituted derivatives **flow chart 2.1.**

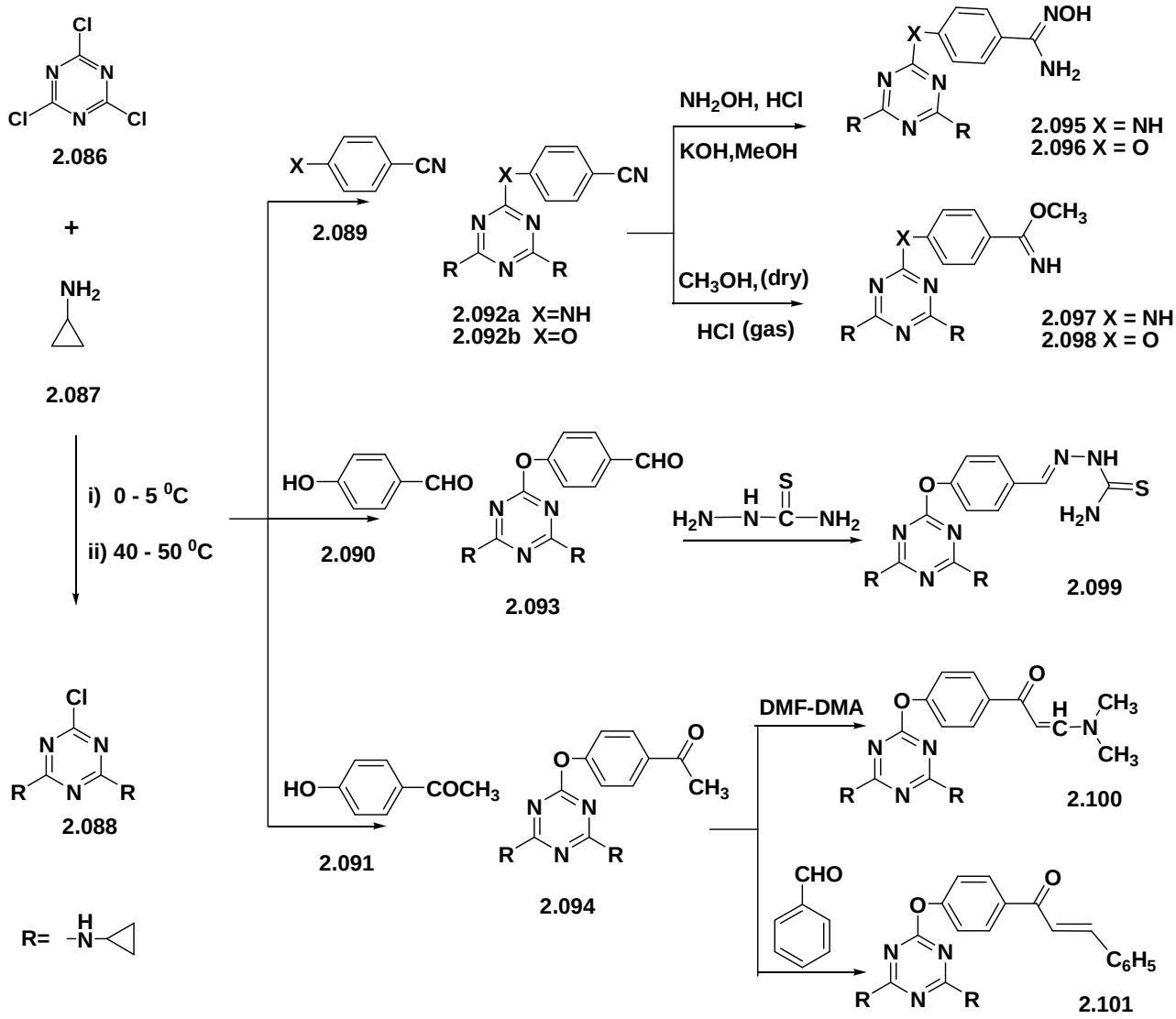
The **flow chart 2.1** shows how the active synthons were prepared from the above intermediates. The intermediate were obtained following the strategy shown in the flow chart**.** The aim of this chapter is to show how the key intermediate were prepared and were converted from the key intermediates to the active synthons.

The amidine derivatives **(2.095, 2.096)** and the imidate ester derivatives **(2.097, 2.098)** were formed on reaction of **2.092** with H_2N-OH.HCl + KOH in (MeOH)[78] and **2.092** with ROH (CH_3OH) + HCl[79] respectively.

The reaction of C_6-chlorine atom of TCT with *p*-hydroxybenzaldehyde yielded **2.093,** which on reaction with thiosemicarbazide provide a very convenient synthetic entry to the intermediate thiosemicarbazone[80] **2.099.**

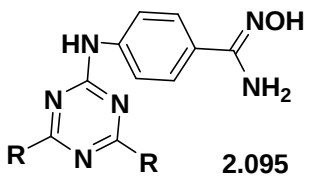
The reaction of C_6-chlorine atom of TCT with *p*-hydroxyacetophenone formed **2.094** which on reaction with DMF-DMA yielded corresponding dimethylaminomethylene ketone[81] **2.100,** whereas base catalysed condensation of **2.094** with benzaldehyde formed chalcone[82] **2.101 (flow chart 2.1).**

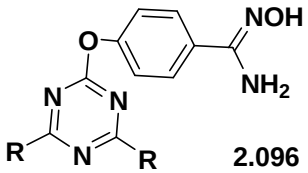
2.4 Scheme representing the synthesis of starting materials from cyanuric chloride:

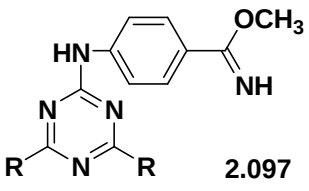


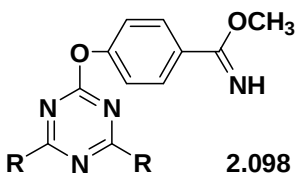
Flow Chart – 2.1

Structure of the compounds synthesized in this chapter:

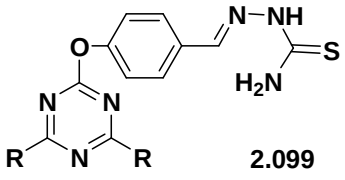




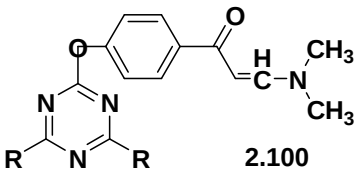




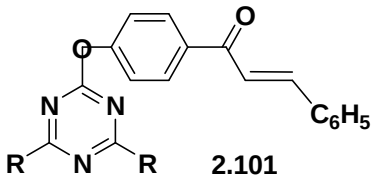
2.098



2.099



2.100



2.101

Fig.- 2.7

Table 2.01: Analytical and physical data of the compounds:

S. No.	Compd. No.	Molecular Formula	M.Wt.	M.P. (^{0}C)	Yield	Elemental Analysis (Calcd./exp.)			
						C	H	N	S
1	2.095	$C_{16}H_{20}N_8O$	340	170-172	86%	56.46/ 56.30	5.92/ 5.80	32.92/ 32.39	
2.	2.096	$C_{16}H_{19}N_7O_2$	341	181-183	85%	56.29/ 56.45	5.61/ 5.25	28.72/ 28.66	
3.	2.097	$C_{17}H_{21}N_7O$	339	72-74	69%	60.16/ 59.95	6.24/ 6.50	28.89/ 28.85	
4.	2.098	$C_{17}H_{20}N_6O_2$	340	81-83	65%	59.99/ 59.45	5.92/ 5.77	24.69/ 24.87	
5.	2.099	$C_{17}H_{20}N_8OS$	384	254-256	85%	53.11/ 53.06	5.24/ 5.12	29.15/ 29.10	8.34/ 8.79
6.	2.100	$C_{20}H_{24}N_6O_2$	380	174-176	66%	63.14/ 63.29	6.36/ 6.55	22.09/ 23.20	
7.	2.101	$C_{24}H_{23}N_5O_2$	413	180-182	70%	69.72/ 69.84	5.61/ 5.42	16.94/ 16.62	

Table 2.02: Spectral data of the compounds:

S. No.	Compound No.	IR (KBr) cm^{-1}	^1H NMR
1.	2.095	3570 [broad OH str.] 3337 [NH str] 3029 [C-H str. ArH] 1644 [C=N str.] 1584 [NH bending] 1447 [C=C str. ArH] 1165 [C-N str.] 824 [C-N str. *s*-triazine]	7.18 -7.45 [4H, dd, (phenylamino)] 6.36 [1H, s, NH (phenylamino)] 5.50 [1H, s, OH] 3.60 [2H, d, NH cyclopropylamino] 2.40 [2H, m, CH cyclopropane] 1.12 [2H, d, NH_2] 0.47 - 0.59 [8H, m, CH_2 cyclopropane] [M^+]: 340
2.	2.096	2600-3510 [broad OH str.] 3310 [NH str. (NH_2 group)] 2855 [C-H str. ArH] 1635 [NH bending] 1580 [C=N str.] 1170 [C-N str.] 1080 [C-O str.] 812 [C-N str. *s*-triazine]	7.23 -7.27 [4H, dd, (phenoxyl)] 5.54 [1H, s, OH] 4.59 [2H, d, NH cyclopropylamino] 2.40 [2H, m, CH cyclopropane] 1.17 [2H, d, NH_2] 0.40 - 0.56 [8H, m, CH_2 cyclopropane]
3.	2.097	3310-3340 [NH str.] 3012 [C-H str.] 1636 [C=N str.] 1592 [NH bending] 1548 [C=C str. ArH] 1170 [C-N str.] 1097 [C-O str.] 806 [C-N str. *s*-triazine]	7.97 [2H, s, NH] 6.99 -7.45 [4H, dd, (phenylamino)] 6.06 [1H, s, NH (phenylamino)] 4.70 [2H, d, NH cyclopropylamino] 3.59 [3H, t, CH_3] 2.40 [2H, m, CH cyclopropane] 0.43-0.63 [8H, m, CH_2 cyclopropane] [M^+]: 339
4.	2.098	3355 [NH str.] 1590 [NH bending] 1610.[C=N str.] 1170 [C-N str.] 1150 [C-O str.] 805 [C-N str. *s*-triazine]	8.27 [2H, s, NH] 7.51 -7.54 [4H, dd, (phenoxyl)] 4.44 [2H, d, NH cyclopropylamino] 3.59 [3H, t, CH_3] 2.40 [2H, m, CH cyclopropane] 0.32-0.53 [8H, m, CH_2 cyclopropane]
5.	2.099	3337 [NH str.] 3029 [C-H str. ArH] 1644 [C=N str.] 1584 [NH_2 bending] 1120 [C-O str.] 1020 [C=S str.] 682 [C-S str.] 824 [C-N str. *s*-triazine]	10.80 [1H, s, NH thiadiazole] 8.25 [1H, s, =CH thiadiazole] 6.69-7.43 [4H, dd, (phenoxyl)] 6.72 [2H, d, NH_2 thiadiazole] 3.51 [2H, d, NH cyclopropylamino] 2.40 [2H, m, CH (cyclopropane)] 0.46-0.58 [8H, m, CH_2 (cyclopropane)] [M^+]: 384, [M^++2]: 386
6.	2.100	3350 [NH str.] 2900 [C-H str.] 1698 [C=O str. α,β-unsaturated] 1570 [C=C unsaturated str.] 1150 [C-N str.] 807 [C-N str. *s*-triazine]	8.12 [1H, d, =CH-N] 7.09-7.70 [4H, dd, (phenoxyl)] 5.66 [1H, d, =CH-C=O] 3.47 [2H, d, NH (cyclopropylamino] 2.63 [6H, s, $2CH_3$] 2.40 [2H, m, CH (cyclopropane)] 0.42-0.56 [8H, m, CH_2 (cyclopropane)] [M^+]: 380
7.	2.101	3220-3340 [NH str.] 2924 [C-H str.Ar. H] 1696 [C=O str. α,β-unsaturated] 1558 [C=C unsaturated str.] 1332 [C-N str.] 825 [C-N str. *s*-triazine]	8.00 [1H, d, =CH-Ar] 7.45 [1H,d, =CH-C=O] 7.21-7.27 [5H, m, arene] 7.05-7.69 [4H, dd, (phenoxyl)] 3.50 [2H, d, NH (cyclopropylamino] 2.40 [2H, m, CH (cyclopropane)] 0.46-0.58 [8H, m, CH_2 (cyclopropane)] [M^+]: 413

2.5 Analysis of the spectral data for the elucidation of structure of the compounds 2.095 - 2.101:

Structures of the compounds were established on the basis of microanalysis, IR, ^{1}H NMR and MS spectral data. Physical data were found to be in agreement to the structures assigned to the molecules. The physical data are presented in the **table 2.1** and **2.2** and the spectral graphs of the compounds are shown in the **spectral charts 2.1** to **2.4**

Infrared spectra:

IR spectrum of the compound **2.095** exhibited a doublet at 3250 cm^{-1} which broadens to 3337 cm^{-1} for NH stretching. Appearance of a characteristic broad peak at 3570 cm^{-1} was assigned to the –OH of the amidine group and disappearance of peak at 2220 cm^{-1} (C-N str. of benzonitrile) provided a strong evidence for the formation of **2.095** from **2.092a.** Bands at 3029 cm^{-1} (C-H str. ArH), 1447 cm^{-1} (C=C str. ArH), 1644 cm^{-1} (C=N str.), 1165 cm^{-1} (C-N str.), and 824 cm^{-1} (C-N str. *s*-triazine) ascertain the structure assigned to the compound **2.095.** The compound **2.096** showed approximately the same absorption peaks with an additional peak at 1080 cm^{-1} (C-O str.).

The formation of the compound **2.097** and **2.098** from **2.092** was clearly indicated by the appearance of peaks at 3310-40 cm^{-1} and 3355 cm^{-1} (NH str. for imidate), and at 1097 cm^{-1} and 1150 cm^{-1} (C-O str.) respectively. Other peaks present in the spectrum of the compound **2.097** and **2.098** were found in the same region as in **2.094.**

The formation of the compound **2.099** was ascertained by the appearance of peaks at 3337 cm^{-1} (NH str.), 1584 cm^{-1} (NH_2 bending), 1020 cm^{-1} (C=S str.) 682 cm^{-1} (C-S str.) and 1644 cm^{-1} (C=N str.) in the spectrum. Peaks at 3029 cm^{-1} (C-H str. ArH), 1644 cm^{-1} (C=N str.), and 1120 cm^{-1} (C-O str.) corroborated strongly the formation of **2.099** from **2.093.**

The formation of compound **2.100** from **2.094** was indicated by the appearance of peaks at 1698 cm^{-1} (C=O str. for α,β-unsaturated carbonyl group) and 1570 cm^{-1} (C=C str.for α,β-unsaturated carbonyl group) in the spectrum.

Appearance of peaks at 1696 cm^{-1} (C=O str. for α,β-unsaturated carbonyl group) and 1558 cm^{-1}(C=C str.for α,β-unsaturated carbonyl group) in its spectrum clearly suggested the formation of **2.101** from **2.094.**

^{1}H NMR Spectra:

^{1}H NMR spectrum of **2.095** on a 400 MHz spectrometer in $CDCl_3$ displayed characteristic signals for the presence of protons in the molecule. An upfield singlet at δ 5.50 was due to the proton of OH group. Another upfield singlet at δ 6.36 for one proton was attributed to NH of phenylamino group, and an upfield singlet at δ 1.12 was due to NH_2 group and a double doublet at δ 7.18 - δ7.45 was due to the presence of aromatic protons of benzene ring and phenylamino group. The multiplet at δ 2.40 and at δ 0.47 – δ 0.59 were due to the protons of cyclopropyl ring. Apart from an upfield singlet for one proton of NH group at δ 6.36, same peaks were observed in ^{1}H NMR spectrum of **2.096.**

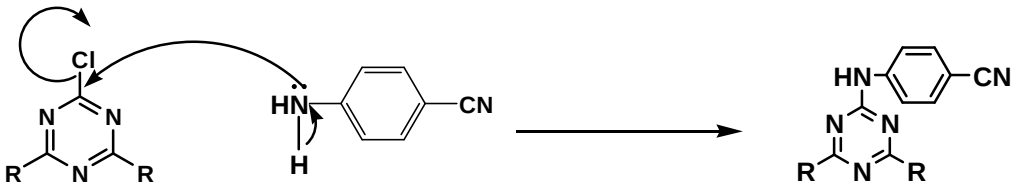
The structure of the compound **2.097** was ascertained by the presence of two singlets for NH groups one at δ 6.06 (phenylamino group) and the other at δ 7.97 for C=NH group, it also showed a triplet at δ 3.59 for 3 protons of OCH_3 group. Similar peaks were observed in the spectrum of **2.098** except for a singlet at δ 6.06 for NH of phenylamino group.
The structure of thiosemicarbazone **2.099** was confirmed by the presence of downfield singlet at δ 10.80 for NH group, an upfield singlet at δ 6.72 for NH_2 group, and a singlet at δ 8.25 for =CH.
The structure assigned to compound **2.100** was evident by the presence of two doublet at δ 8.12 for =HC-N and δ 5.66 for =HC-C=O) for two protons linked to carbon of α,β-unsaturated carbonyl group and a sharp singlet at δ 2.63 for six protons of two methyl groups attached to nitrogen atom.

Formation of chalcone **2.101** was confirmed by the appearance of two doublets at δ 7.45 for =HC-C=O and δ 8.00 for =HC-Ar for two protons of the carbon of α,β-unsaturated carbonyl group and a downfield multiplet of five protons of phenyl ring at δ 7.21- δ 7.27.

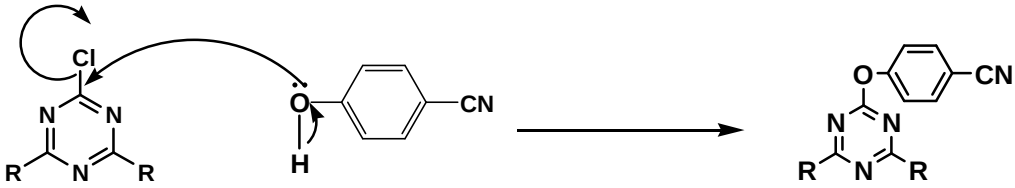
2.6 Mechanism of the reactions:

6- Chloro-4,6-dicyclopropylamino-1,3,5-triazine was the key intermediate from which amino and hydroxyl derivative were obtained. It is assumed that the products are formed by the nucleophilic displacement of the chlorine atom of 6- Chloro-4,6-dicyclopropylamino-1,3,5-triazine.

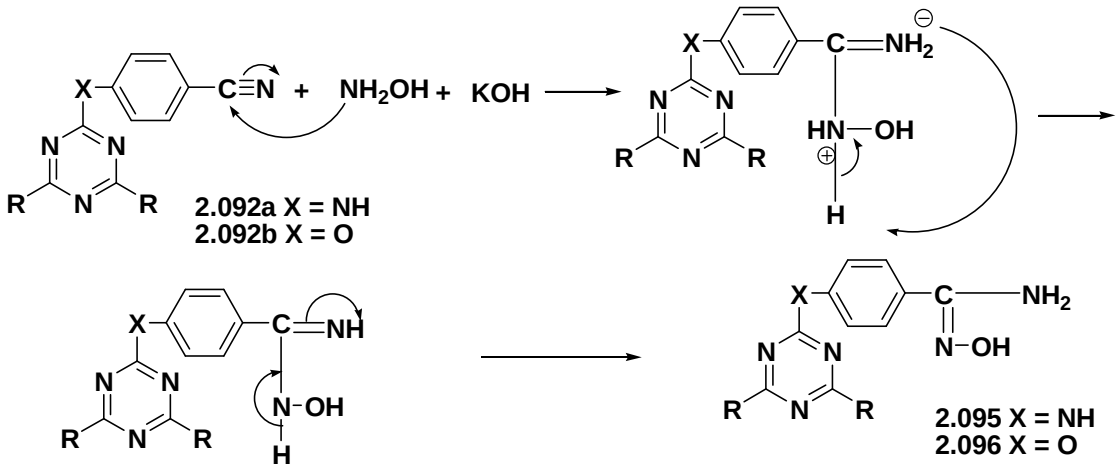
2.6.1 Mechanism of formation of phenylamino derivative 2.092a:



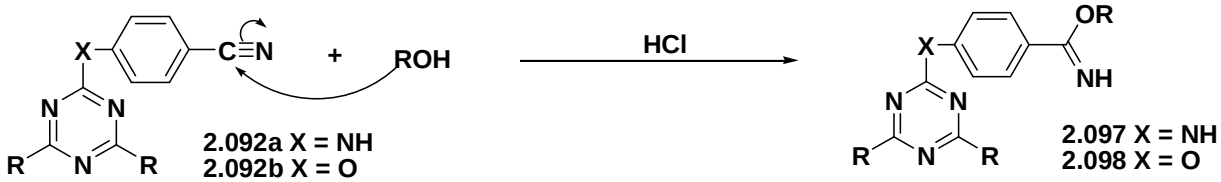
2.6.2 Mechanism of formation of phenoxyl derivative 2.092b:



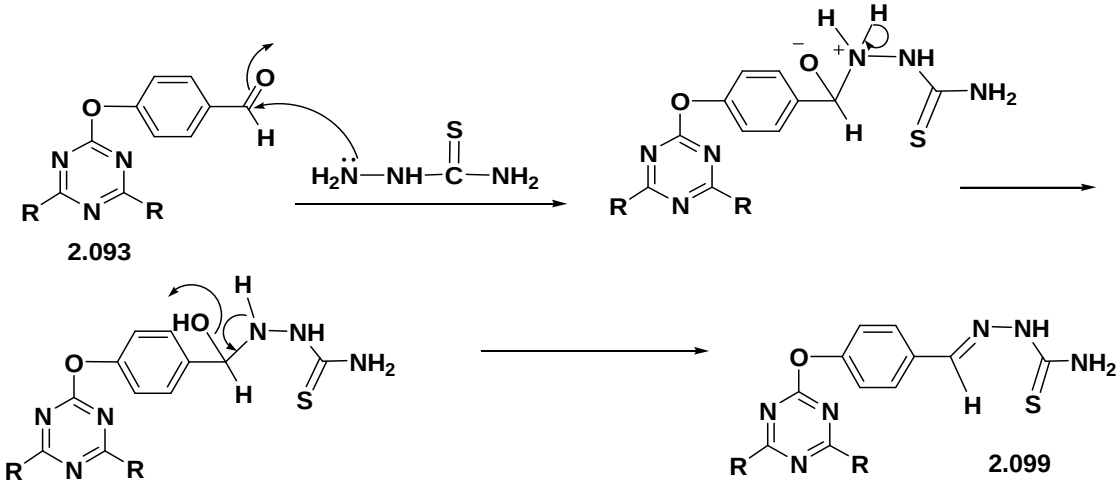
2.6.3 Mechanism of formation of amidine derivatives 2.095 and 2.096:



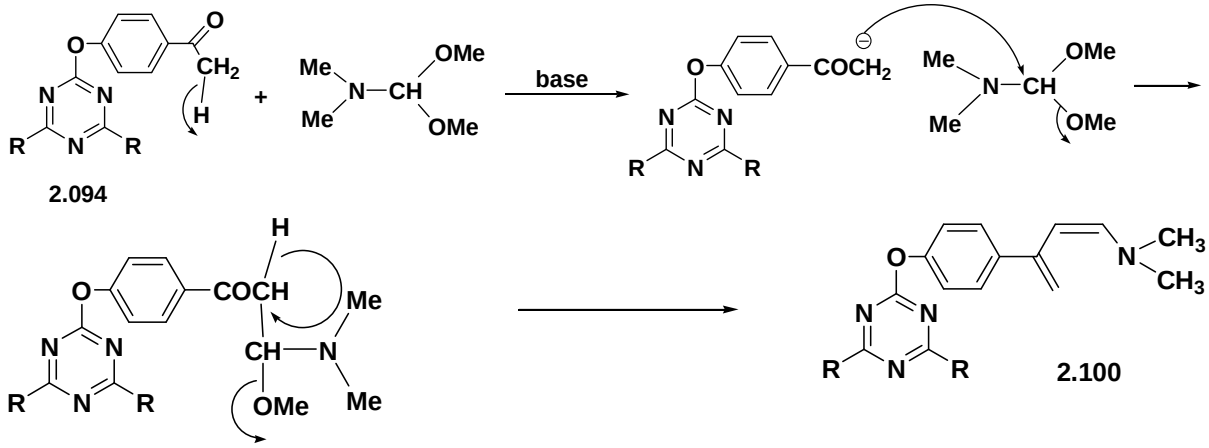
2.6.4 Mechanism of formation of imidate ester derivatives 2.097 and 2.098:



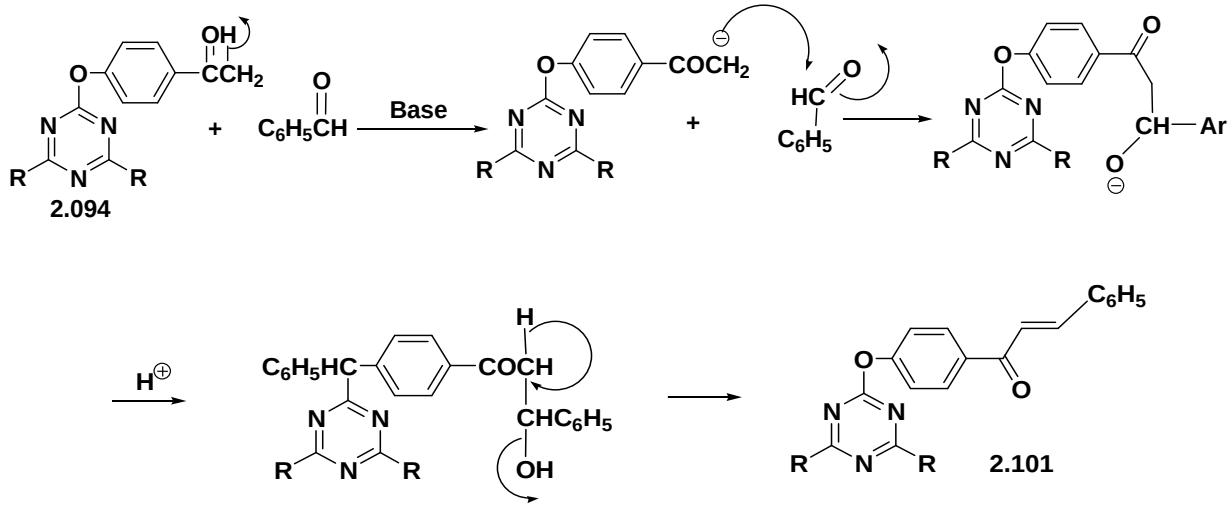
2.6.5 Mechanism of formation of thiosemicarbazide 2.099:



2.6.6 Mechanism of formation of dimethylaminomethylene derivative 2.100:



2.6.7 Mechanism of formation of chalcone derivative 2.101:



2.7 Experimental Analysis:

1. Melting points were determined in an open glass capillaries and are uncorrected.
2. Silica gel (G) plates were used to check the purity of the compounds. Iodine was used as visualising agent.
3. Bruker model alpha-T instrument was used to record IR Spectra
4. ^{1}HNMR and ^{13}C NMR spectra were recorded on Bruker BioSpin GmbH using TMS as an internal reference and $CDCl_3$ as solvent. Chemical shift is expressed in δ ppm.
5. ESI mass spectra were recorded on an Agilent 1100 LC-QTOF mass spectrometer.
6. All samples were dried under reduced pressure.
7. Spectral and physical data are given in the **table 2.01** and **2.02.**

SYNTHETIC PROCEDURES:

Procedures for the preparation of the compounds are described below in a stepwise manner:

Preparation of 6-chloro-4,6-dicyclopropylamino-1,3,5-triazine (2.088)

To a solution of cyanuric chloride (1.84 g, 0.01 mole) in 10 mL of dry THF and cyclopropylamine (0.54 g, 0.0095 mole) in dry THF (5 mL) anhydrous K_2CO_3 (1.38 g, 0.01 mole) was added and the reaction mixture was stirred at 5 ^{0}C for an hour. The progress of the reaction was checked by TLC (toluene: acetone 6:4). To the reaction mixture a solution of cyclopropylamine (0.54 g, 0.0095 mole) in dry THF (5 mL) and anhydrous K_2CO_3 (1.38 g, 0.01 mole) were further added below 35 ^{0}C and the reaction mixture was stirred overnight. The progress of the reaction was checked again by TLC (toluene: acetone 6:4). The mixture was poured on crushed ice and neutralized with dil HCl. The residue was filtered and washed with cold water and recrystallized from ethanol to give **2.088,** yield 80%; m.p. 203-205 ^{0}C.

Preparation of 4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-ylamino)benzonitrile (2.092a)

To a mixture of 6-chloro-4,6-dicyclopropylamino-1,3,5-triazine **(2.088)** (0.23 g., 0.001 mol) and p-aminobenzonitrile (0.14 g, 0.0012 mol) in DMF (15 mL) potassium ter. butoxide (0.22 g., 0.002 mol) was added and stirred for 24 h at room temperature. The progress of the reaction was checked by TLC (toluene: acetone 6:4). The mixture was poured into crushed ice and neutralized

with 5% aqueous HCl. The residue obtained was filtered, dried, and recrystallized from alcohol to give **2.029a,** yield 82%, m.p. 195-199 ^{0}C.

Preparation of 4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-yloxyl)benzonitrile (2.092b)

To a mixture of 6-chloro-N,N-dicyclopropyl-1,3,5-triazine-2,4-diamine **(2.088)** (0.23 g., 0.001 mol) and p-hydroxybenzonitrile (0.14 g, 0.0012 mol) in DMF (15 mL) potassium ter. butoxide (0.22 g., 0.002 mol) was added and stirred for 24 at room temperature. The progress of the reaction was checked by TLC (toluene: acetone 6:4). The mixture was poured into crushed ice and is neutralized with 5% aqueous HCl. The residue obtained was filtered, dried, and recrystallized from alcohol to give **2.092b,** yield 72%, m.p. 190-195 ^{0}C.

Preparation of 4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-yloxy)benzaldehyde (2.093)

To the solution of p-hydroxybenzaldehyde (0.38 g, 0.0035 mol) and **2.088** (0.68 g, 0.003mol) in DMF (10 mL) was added potassium-tert-butoxide (0.67 g, 0.006 mol), and then stirred at room temperature until the reaction is completed. The mixture was poured into crushed ice and neutralized with 5% aqueous HCl. The residue obtained was filtered, dried, and recrystallized from alcohol to give **2.093,** yield 70%, m.p. 180-185 ^{0}C.

Preparation of 1-(4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-yloxy)phenyl)ethanone (2.094):

A mixture of 6-chloro-4,6-dicyclopropylamino-1,3,5-triazine **2.088** (0.23 g., 0.001 mol) and p-hydroxyacetophenone (0.16 g, 0.0012 mol) in acetone (15 mL) was refluxed for 6 h, and sodium carbonate solution was periodically added to neutralized HCl evolved during the reaction. The progress of the reaction was checked by TLC (toluene: acetone 6:4). The mixture was poured onto crushed ice. The solid separated out was filtered, washed with water and recrystallized from ethanol to give **2.094**, yield 82%; m.p. 194-196 ^{0}C.

Preparation of (4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-ylamino)-N'-hydroxybenzamidine (2.095):

A mixture of hydroxylamine hydrochloride (1.0 g, 0.01 mol) in methanol (10 mL) and potassium hydroxide (1.0 g, 0.01 mol) in methanol (10 mL) was stirred at room temperature for 15 min and the precipitated KCl was removed by filtration. The filtrate was added to the nitrile **2.092a,** (3.07 g, 0.01 mol), and the solution was stirred overnight at 40 ^{0}C. It was cooled to room temperature

and concentrated. The residue obtained was triturated with water and dried. The product obtained was purified on silica column (eluent: petroleum ether/ EtOAc) to give **2.095**, yield 86%; m.p. 170-172 ^{0}C.

Preparation of (4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-yloxy)-N'-hydroxybenzamidine (2.096):

The mixture of hydroxylamine hydrochloride (1.0 g, 0.01 mol) in methanol (10 mL) and potassium hydroxide (1.0 g, 0.01 mol) in methanol (10 mL) was stirred at room temperature for 15 min and the precipitated KCl was removed by filtration. The filtrate was added to the nitrile **2.092b,** (3.08 g, 0.01 mol), and the solution was stirred overnight at 40 ^{0}C, the cooled to room temperature and concentrated. The residue obtained was triturated with water and dried. The product obtained was purified on silica column (eluent: petroleum ether/ EtOAc) to give **2.096**, yield 85%; m.p. 181-183 ^{0}C.

Preparation of (4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-ylamino)-N'-ethylimidate (2.097):

To a solution of **2.092a** (0.30 g., 0.001 mol) in absolute ethanol (10 mL), HCl gas was passed for 8 h , after the completion of the reaction diethyl ether was added to it. Progress of the reaction was checked by TLC. The precipitate of imidate hydrochloride **2.097,** was filtered and dried to give **2.097,** yield 69%; m.p. 72-74 ^{0}C.

Preparation of (4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-yloxy)-N'-ethylimidate (2.098):

To a solution of **2.092b** (0.30 g., 0.001 mol) in absolute ethanol (10 mL), HCl gas was passed for 8 h , after the completion of the reaction diethyl ether was added to it. Progress of the reaction was checked by TLC. The precipitate of imidate hydrochloride **2.098,** was filtered and dried to give **2.098,** yield 65%; m.p. 81-83 ^{0}C.

Preparation of 1-(4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-yloxy)benzylidene)thiosemicarbazide (2.099):

The solution of **2.093** (0.933 g, 0.003 mol) and thiosemicarbazide (0.78 g, 0.0033 mol) in ethanol (10 mL) was refluxed for 3 h. Progress of the reaction was checked by TLC ($CHCl_3$/CH_3OH/AcOH 3:1:0.05). After completion of the reaction, the solid obtained was filtered, washed with ethanol, and dried to give **2.099,** yield 85% : m.p. 254-256 ^{0}C.

Preparation of 1-(4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-yloxy)phenyl)-3-(dimethylamino)prop-2-en-1-one (2.100):

2.094 (2.47 g, 0.0076 mol) was dissolved in *N*,*N*-dimethylformamide dimethyl acetal (15.0 mL)and the solution was refluxed for 1 hour and concenterated. The residue was triturated with hexane, filtered and washed with hexane to give **2.100,** yield 66%; m.p. 174-176 ^{0}C.

Preparation of 1-(4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-yloxy)phenyl)-3-phenylprop-2-en-1-one (2.101):

2.094 (3.25 g, 0.01 mol), was dissolved in DMF (25 mL) and benzaldehyde (1.06 g, 0.01 mol) was added to it. Then a solution of 40% aqueous KOH (5 mL) was added to the reaction mixture with constant stirring at room temperature for 24 h, and then it was poured onto crushed ice and neutralized with dil HCl. The product separated out was filtered, washed with water, dried and recrystallized from alcohol to give **2.101,** yield 70%; m.p. 180-182 ^{0}C.

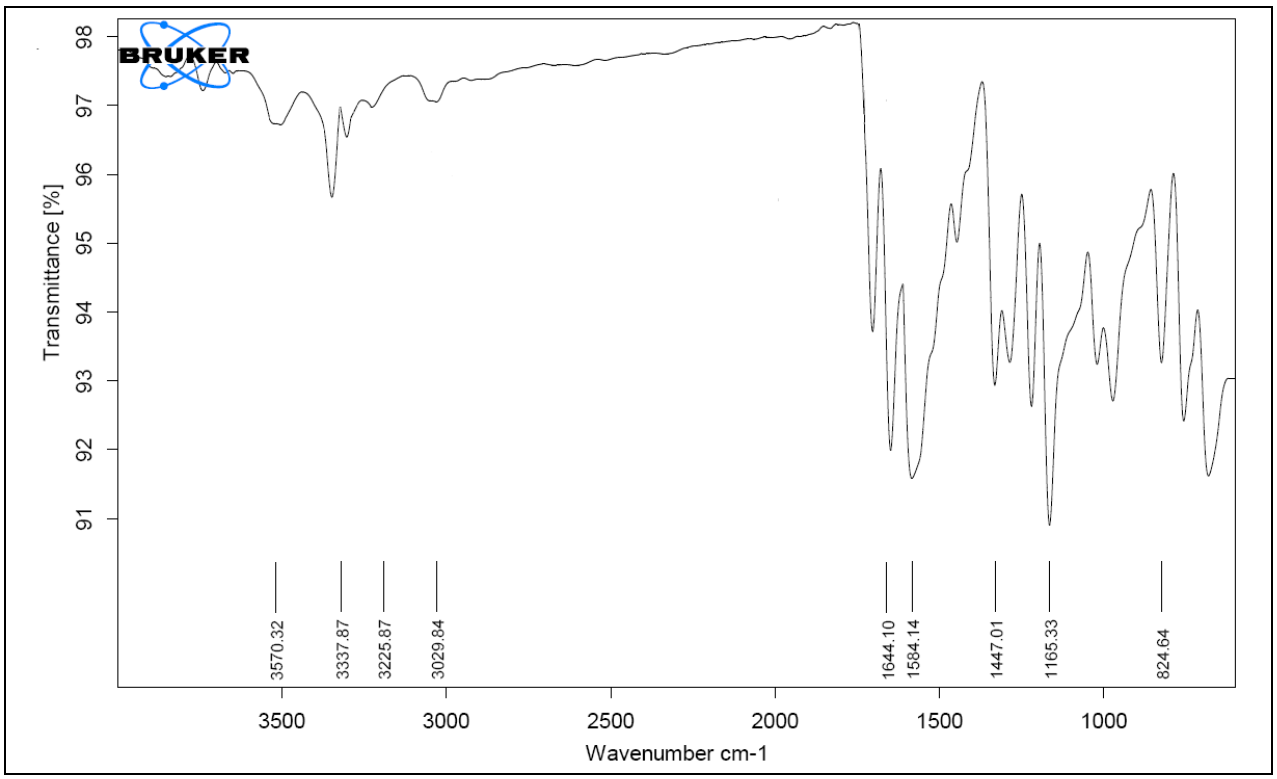


Chart-2.1 IR spectrum of (4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-ylamino)-N'-hydroxybenzamidine (2.095)

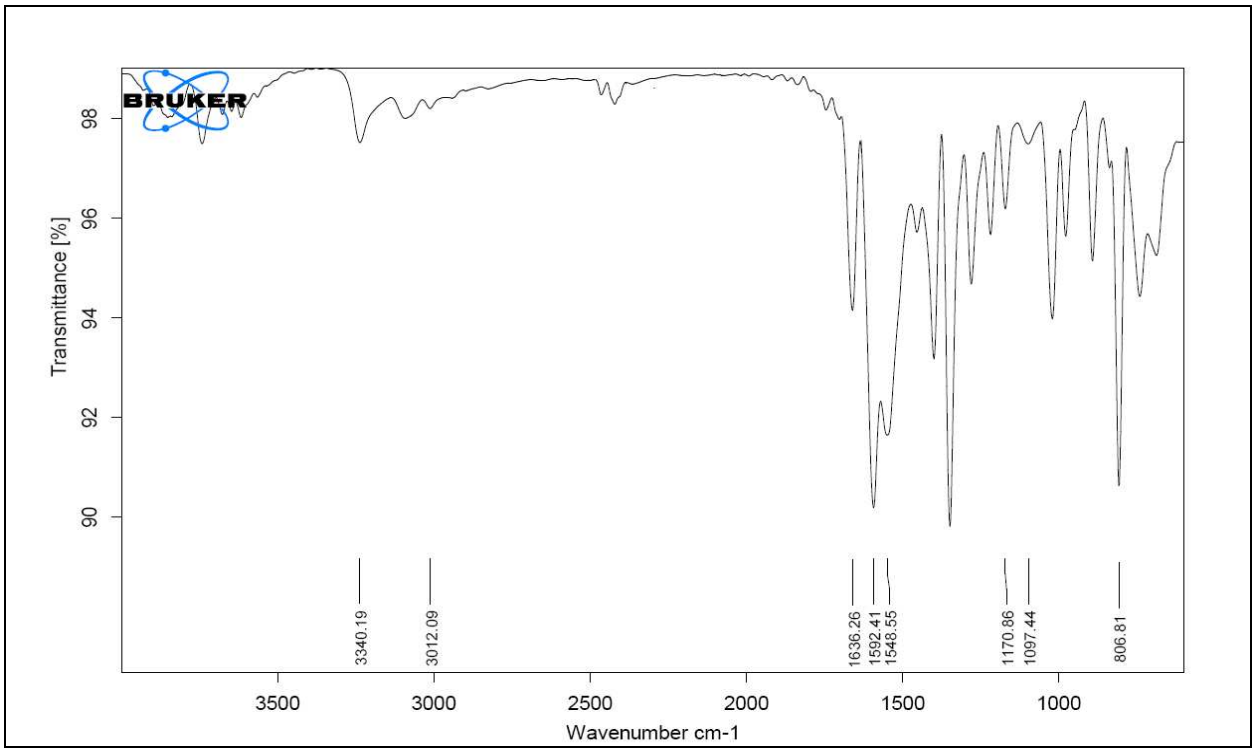


Chart-2.2 IR spectrum of (4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-ylamino)-N'-ethylimidate (2.097)

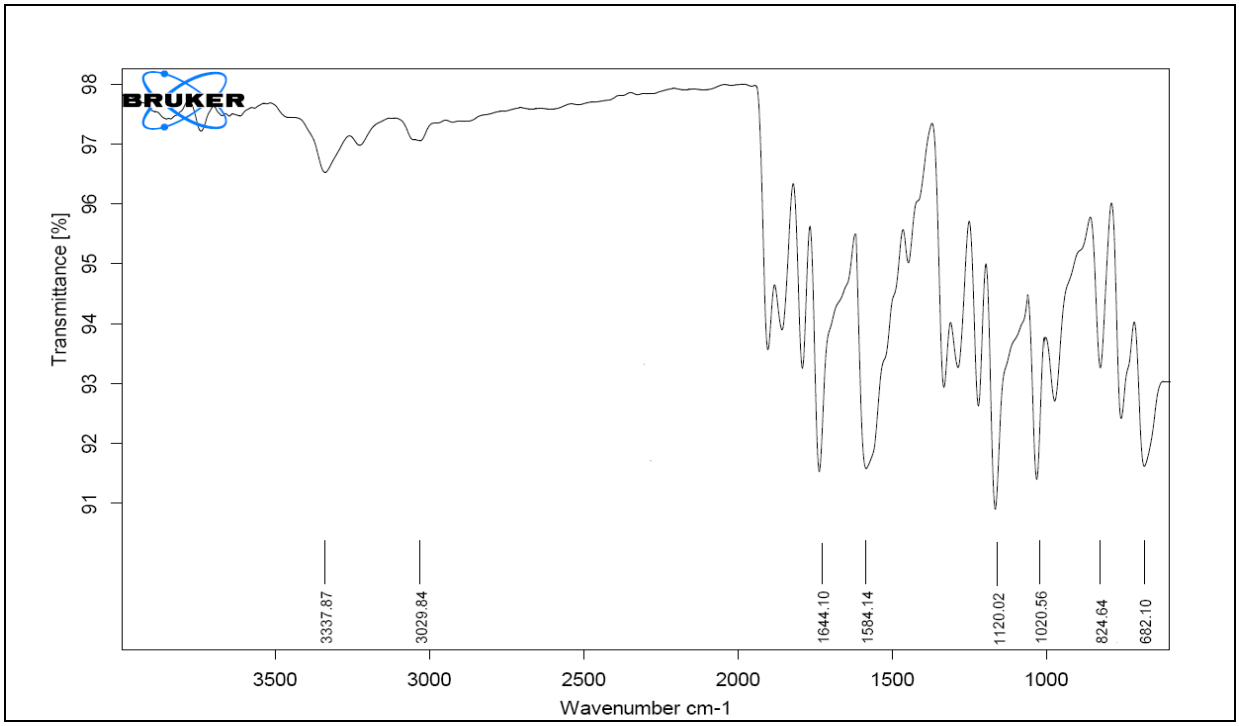


Chart-2.3 IR spectrum of 1-(4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-yloxy)benzylidene)thiosemicarbazide (2.099)

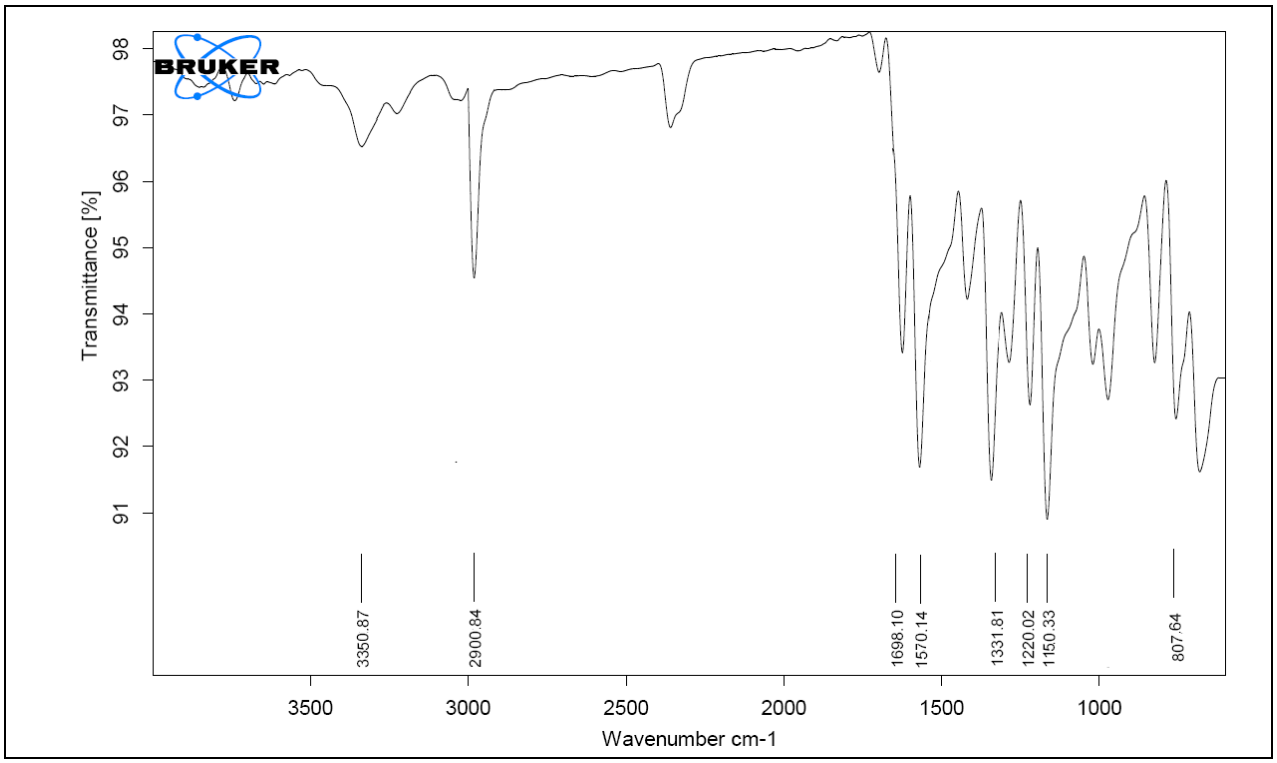


Chart-2.4 IR spectrum of 1-(4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-yloxy)phenyl)-3-(dimethylamino)prop-2-en-1-one (2.100)

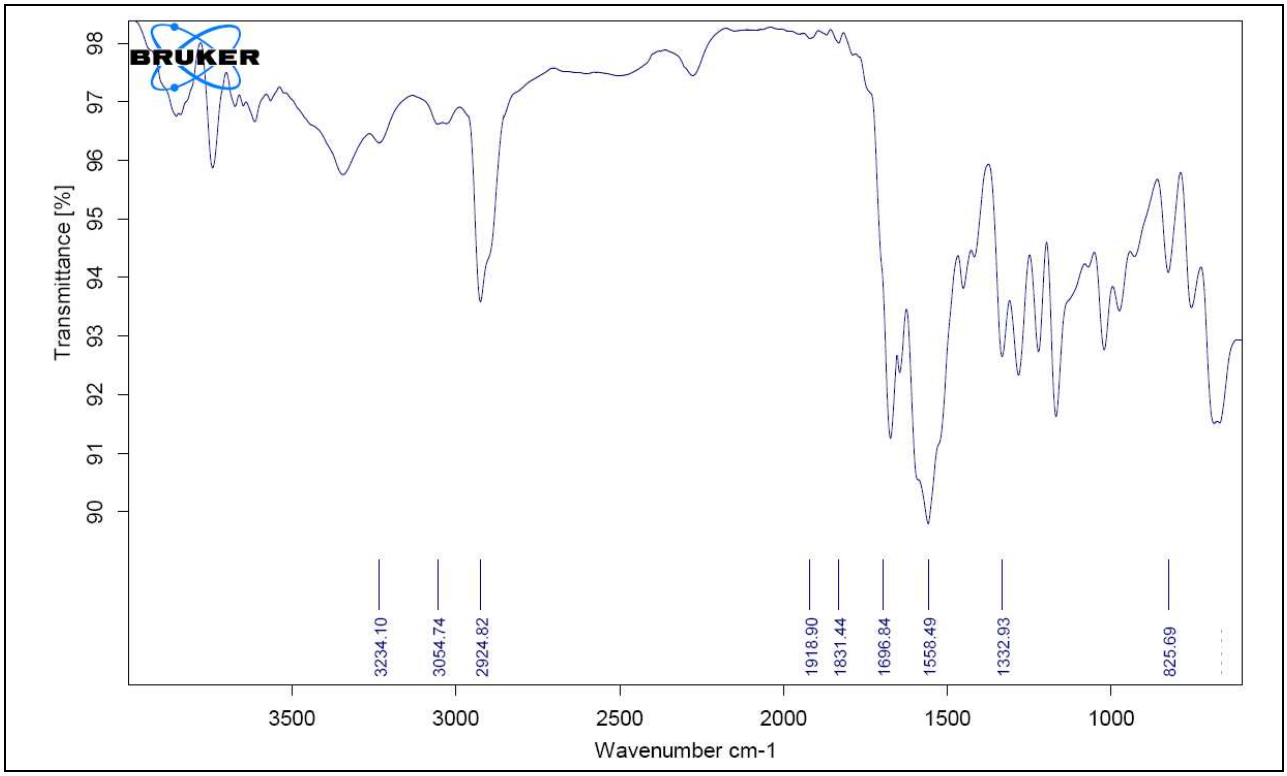


Chart-2.5 IR spectrum of 1-(4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-yloxy)phenyl)-3-phenylprop-2-en-1-one (2.101)

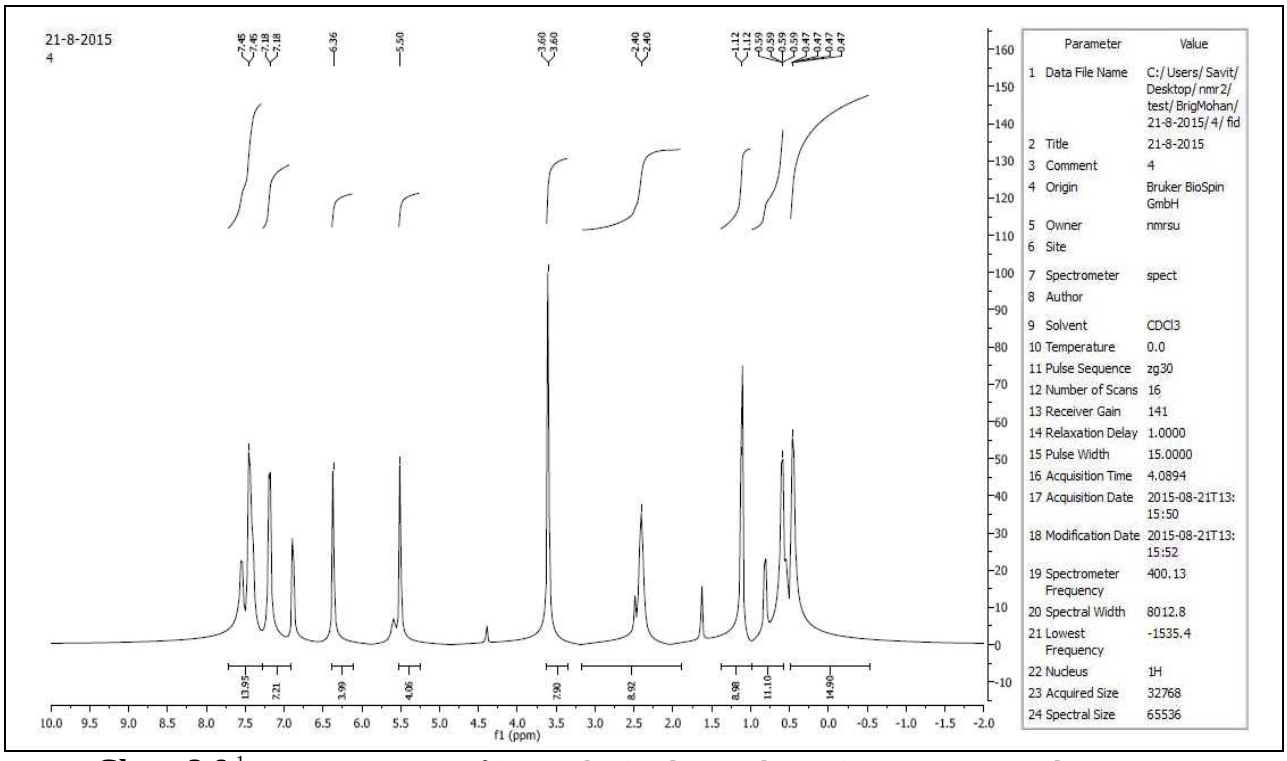


Chart-2.6 ^{1}H NMR spectrum of (4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-ylamino)-N'-hydroxybenzamidine (2.095)

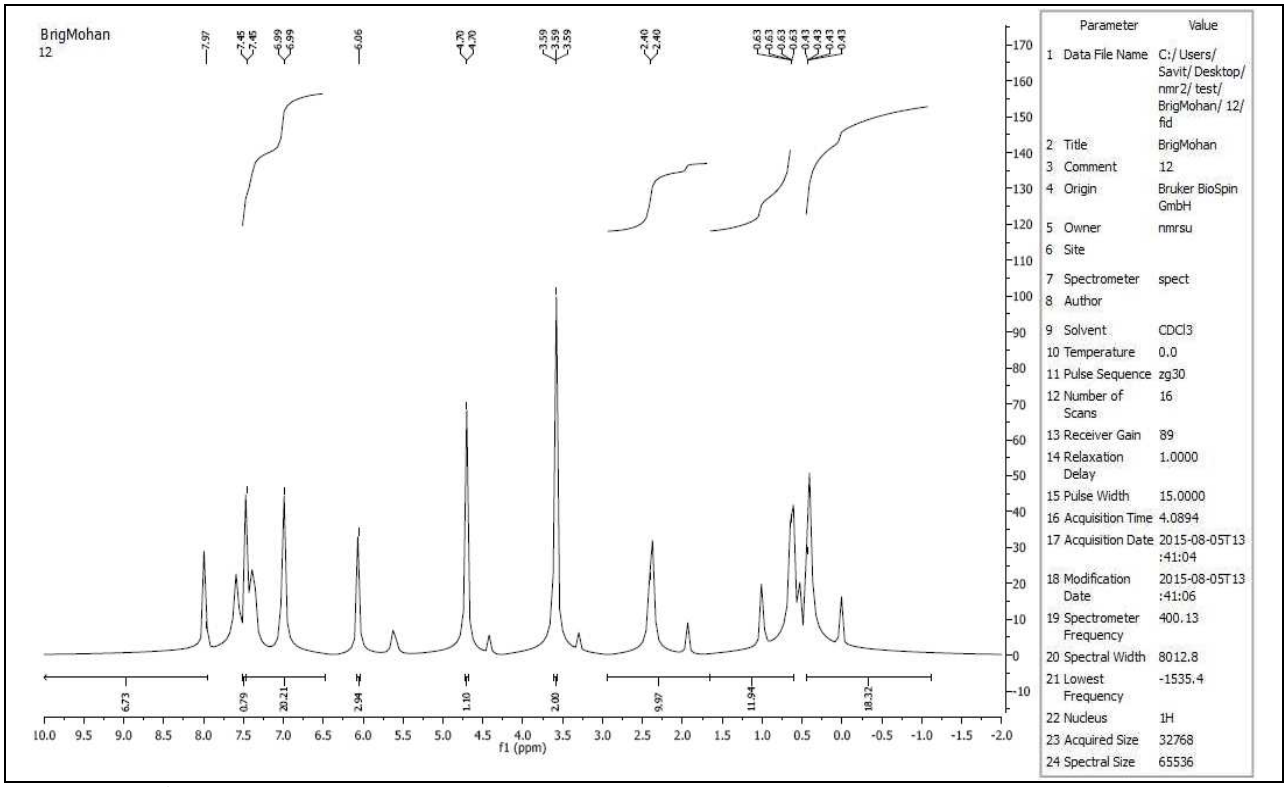


Chart-2.7 ^{1}H NMR spectrum of (4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-ylamino)-N'-ethylimidate (2.097)

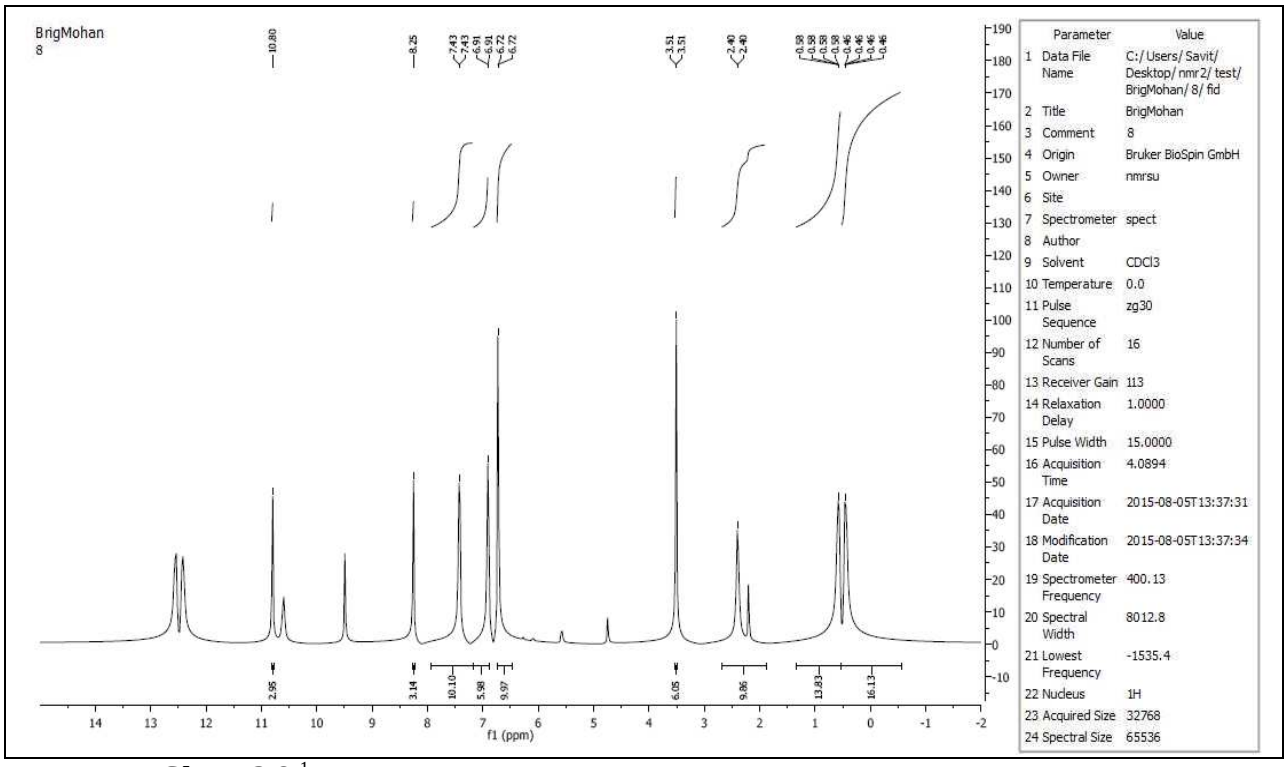


Chart-2.8 ^{1}H NMR spectrum of 1-(4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-yloxy)benzylidene)thiosemicarbazide (2.099)

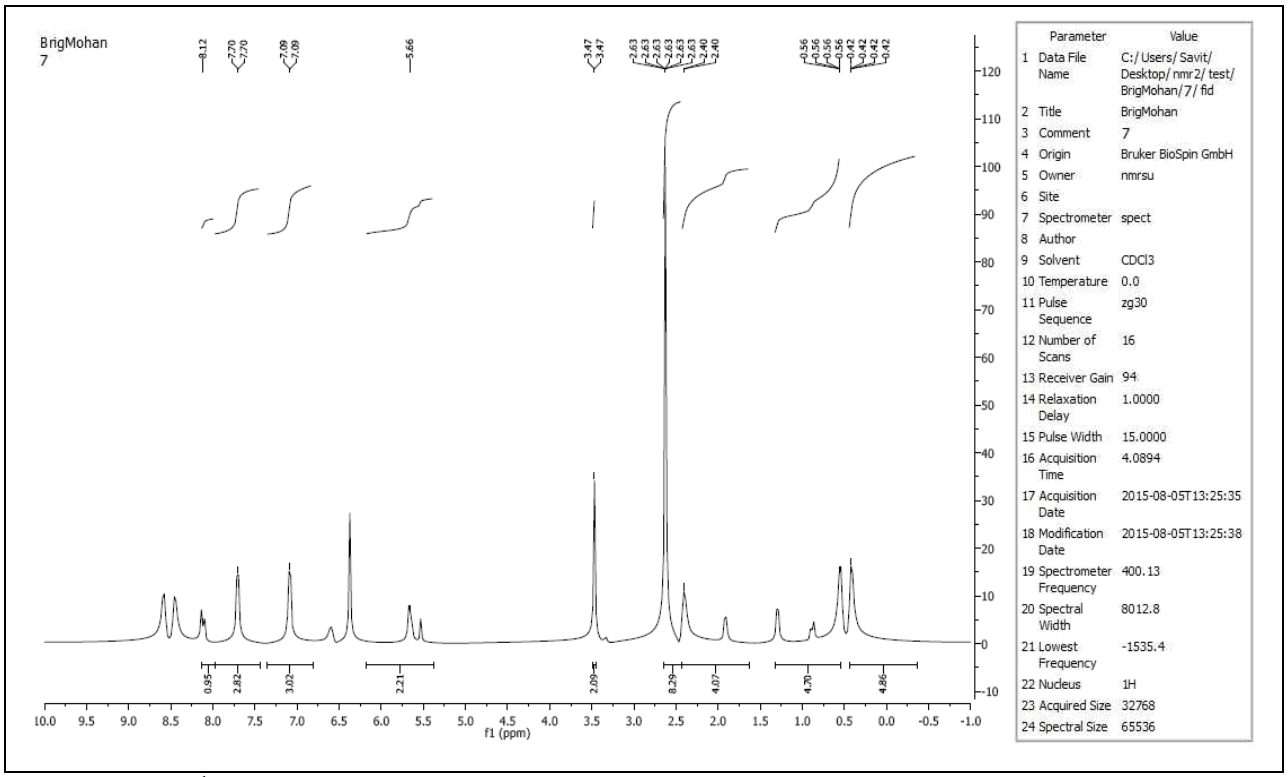


Chart-2.9 ^{1}H NMR spectrum of 1-(4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-yloxy)phenyl)-3-(dimethylamino)prop-2-en-1-one (2.100)

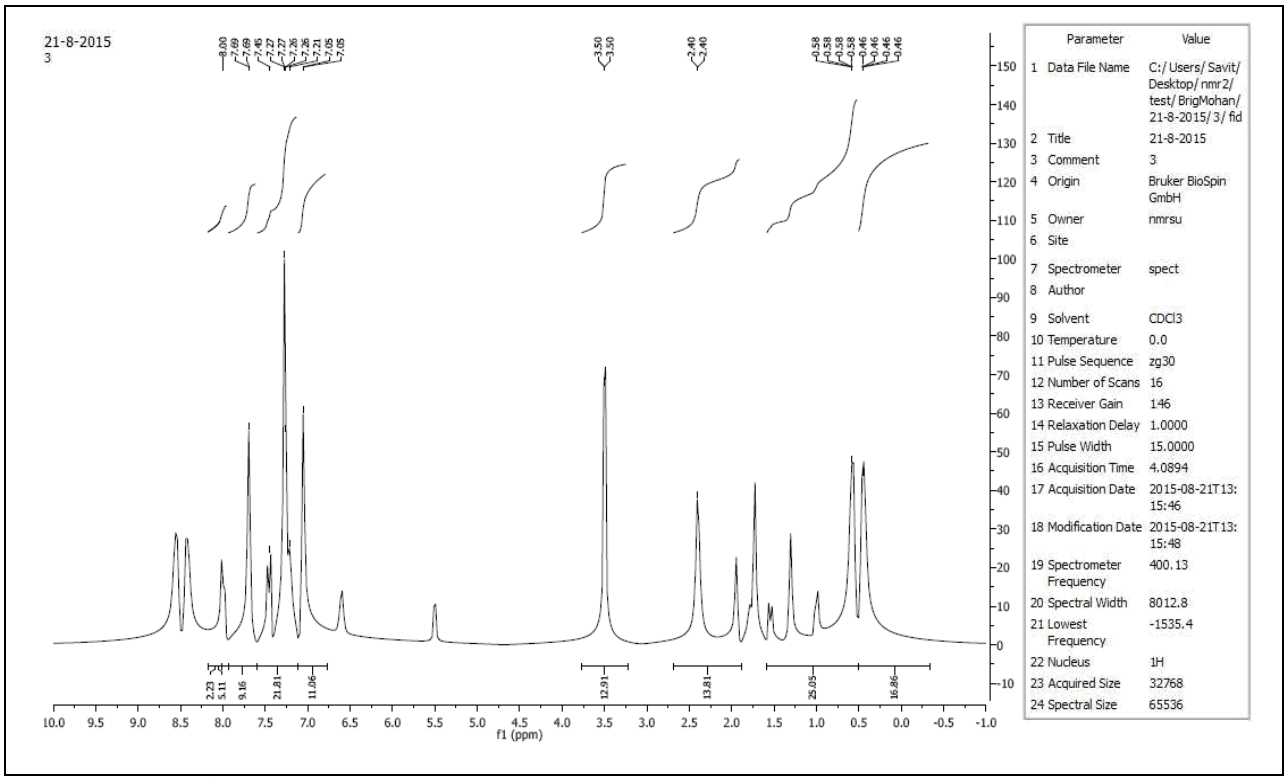


Chart-2.10 ^{1}H NMR spectrum of 1-(4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-yloxy)phenyl)-3-phenylprop-2-en-1-one (2.101)

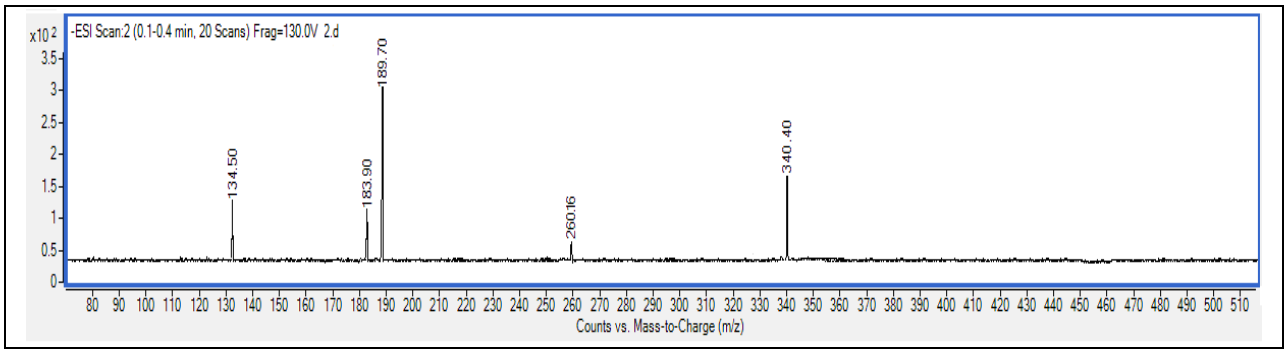


Chart-2.11 Mass spectrum of (4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-ylamino)-N'-hydroxybenzamidine (2.095)

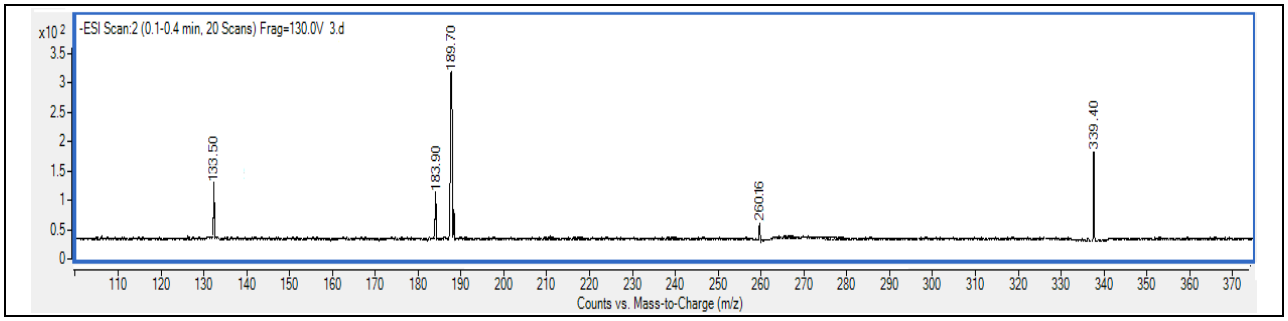


Chart-2.12 Mass spectrum of (4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-ylamino)-N'-ethylimidate (2.097)

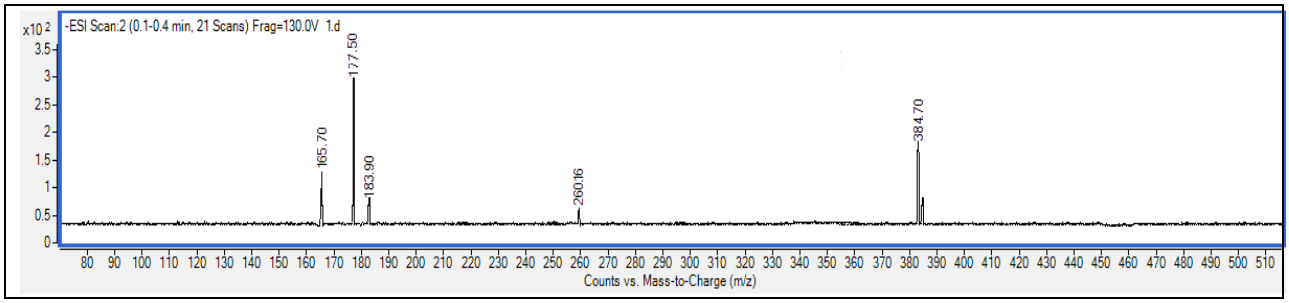


Chart-2.13 Mass spectrum of 1-(4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-yloxy)benzylidene)thiosemicarbazide (2.099)

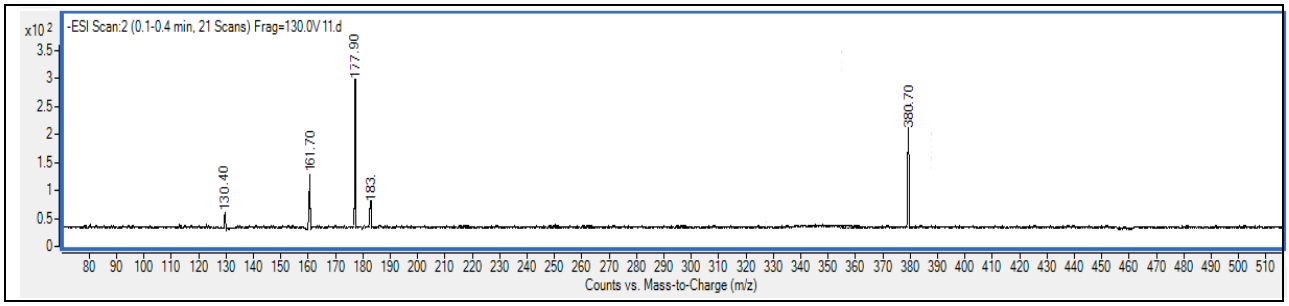


Chart-2.14 Mass spectrum of 1-(4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-yloxy)phenyl)-3-(dimethylamino)prop-2-en-1-one (2.100)

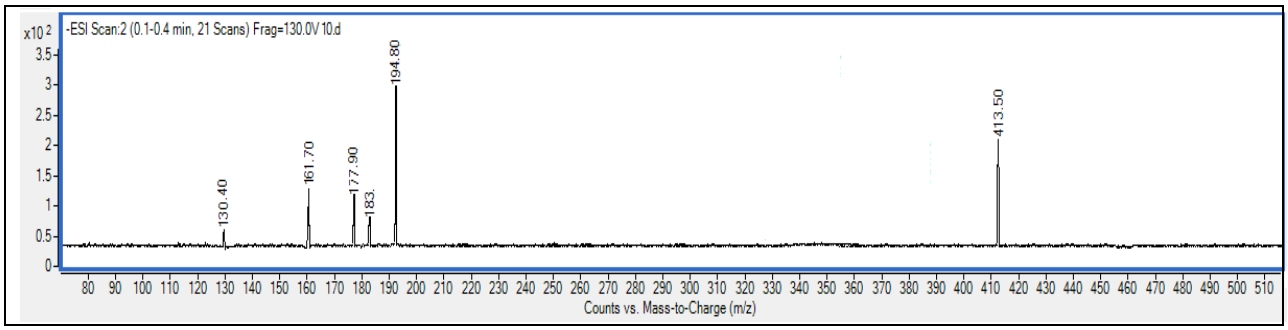


Chart-2.15 Mass spectrum of 1-(4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-yloxy)phenyl)-3-phenylprop-2-en-1-one (2.101)

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