Chapter-IV

Synthesis of pyrimido incorporated analogues of s-triazine linked through an aminophenyl and oxyphenyl bridge

Abstract

The synthesis of various pyrimidine ring incorporated analogues **4.051 - 4.056** from the respective dimethylamino methylene ketone and chalcone derivatives derived from s-triazine following the strategies depicted in the schemes- **4.12 - 4.17** has been described in this chapter. The structures of all the compounds have been established on the basis of spectral data.

4.1 Introduction

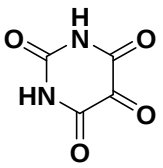
Pyrimidines have occupied a unique and important place in the fields of medicinal chemistry. It is well known that uracil, thymine and cytosine are essential constituents in nucleic acids; thiamine, which possess antiberiberi activity, was the first vitamin discovered in B series; barbiturates are widely used as sedatives; pyrimethamine (Daraprim, Malocide) is potent against erythrocytic parasites in antimalarial study; aminometradine (Mictine) is an orally effective diuretic; and the 5-halogen-substituted uracil derivatives have recently been reported as antitumour and antivira agents. Other pyrimidine derivatives have been found to possess fungicidal, antibacterial, antimitotic, antithyroid, and surface anaesthesia activities. Pyrimidine derivative, Etraverine has emerged as one of the most potent anti-HIV agent. Owing to such high activity profile pyrimidine is considered as 'privileged scaffold' in medicinal chemistry, as it is capable of providing ligands to functionally and structurally discrete biological receptors[1,2].

Its unique biological properties have drawn attention towards the utilities of pyrimidine incorporated heterocyclic structures in medicinal chemistry. Keeping this in view the present chapter describes the synthesis of some novel pyrimidine substituted analogues of s-triazine. It was mentioned in the chapter-1 that s-triazine has unique biological activity profile and can be moulded into a variety of compounds through nucleophilic substitution reactions. The proposed heterocycles **(Fig. 4.2)** have been synthesised with the assumption that the incorporation of pharmacologically active pyrimidine scaffolds into the molecular framework of s-triazine could produce interesting series of novel compounds with enhanced biological activity.

Considering the medicinal properties Etravirine, this was approved in 2008 by the U.S federal Drugs administration to be used in combination therapy for HIV infections. In view of this it was thought worthwhile to incorporate vital fragments of etravirine into a single molecular framework of s-triazine and pyrimidine ring.

4.2 Biological aspects of Pyrimidine

Pyrimidine exists in nature as a part of complex system forming an integral part of genetic materials viz DNA and RNA[3]. Alloxan **4.001** is known as diabetogenic in animals[4]. The three important constituent of nucleic acids Uracil **4.002**, Thymine **4.003**, Cytosine **4.004** contain pyrimidine ring[5] **(Fig-4.1)**.



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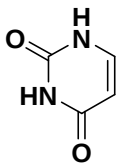

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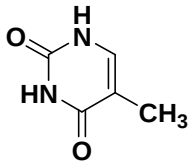

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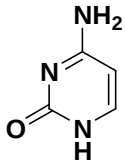

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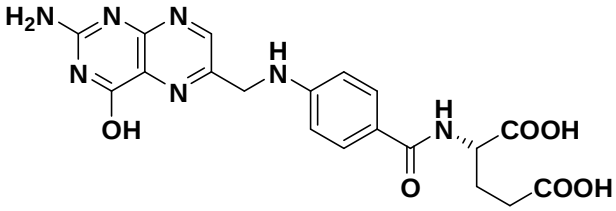

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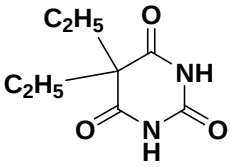

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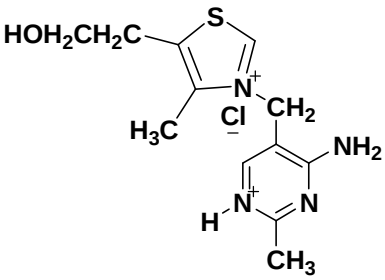

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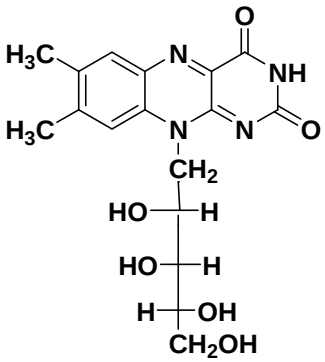
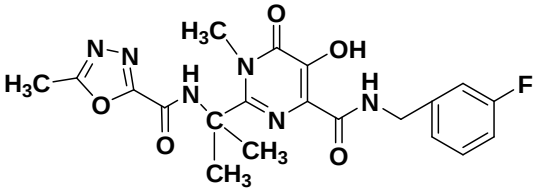
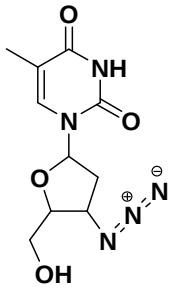


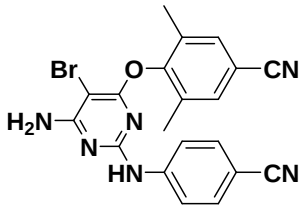
4.008



4.009



4.010



4.011

Fig.-4.1

Many vitamins also contain pyrimidine ring like thiamine[5] **4.007**, riboflavin[5] **4.008** and folic acid[5] **4.005**. Barbitone[6] **4.006**, the first barbiturate hypnotic sedative and anticonvolsant is a pyrimidine derivative[7,8] **(Fig-4.1)**.

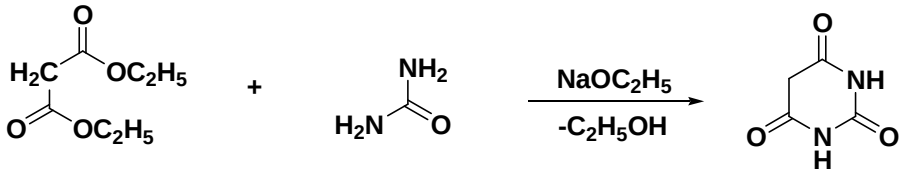
It is considered as a promising structural moiety for drug design as its derivatives form a vital component in a number of useful drugs and are associated with many therapeutic and biological activities[9,10]**,** Condensed pyrimidine derivatives have found wide clinical applications as cardiovascular[11], anti-inflamatory[12], anti-cancer[13,14,15], anti-tumour[16], anti-malarial and anti-tubercular[17,18], 5-HT2A receptor antagonists[19], CDC25B phosphatase inhibitors[20], anti-microbial[21]**,** antibacterial, anti-fungal[22], analgesic[23] and anti-HIV[24] agents. Pyrimidine derivatives are also used as human A2A adenosine receptor antagonists[25] and calcium-sensing receptor antagonists[26].Pyrimidine derivatives such as raltegravir **4.009**, azidothiamidine (AZT) **4.010**, and etravirine **4.011**, show impressive anti-HIV activity **(Fig-4.1)**.

4.3 Synthetic aspects of pyrimidine

Due to the interesting medicinal properties of pyrimidine nucleus extensive reseach work has been done on their synthesis and pharmacological properties which has led to the discovery of new synthetic routes and has resulted in the accumulation of vast amount of patented literature for its synthesis in the last few decades[27].

Generally pyrimidines are synthesised from those compounds in which the ring is formed from two fragments which provide C-C-C and N-C-N atoms respectively[28].

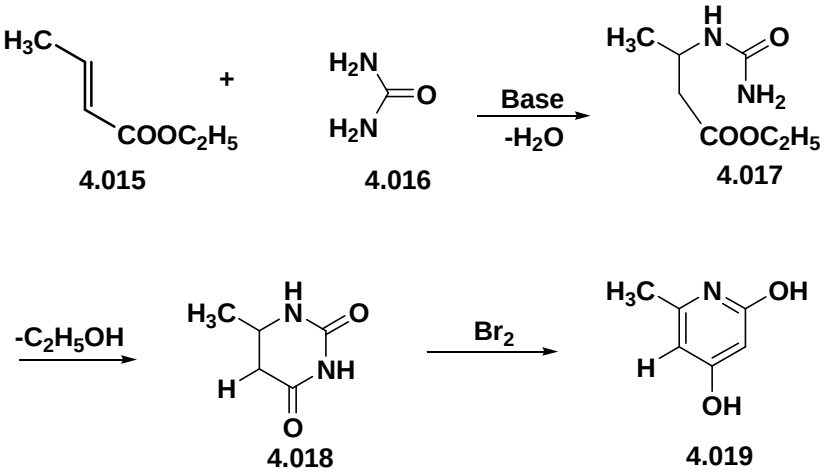
Barbituric acid **(4.014)** can be synthesized by the condensation of malonic ester **(4.012)** and urea **(4.013)** in presence of a base **(Scheme-4.01)**[29].



4.012 **4.013** **4.014**

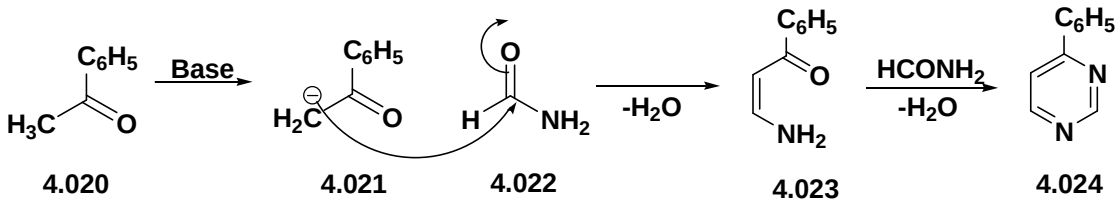
Scheme-4.01

i) A dihydropyrimidine **(4.018)** is formed by the condensation of urea **(4.016)** with ethyl crotonate (**4.015)** in presence of a base which on oxidation yields corresponding pyrimidine **(4.019) (Scheme-4.02)[28].**



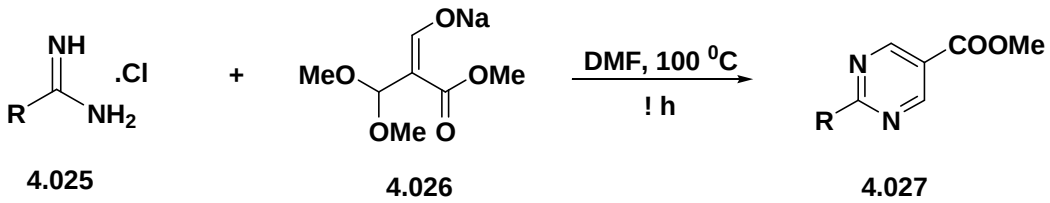
Scheme-4.02

ii) *β*-enaminoketones **(4.023)** is formed by the reaction of formamide **(4.022)** with active methyl group[50] of acetophenone **(4.020)** which in presence of excess of formamide cyclizes to 4-phenyl pyrimidine **(4.024) (Scheme-4.03)[29].**



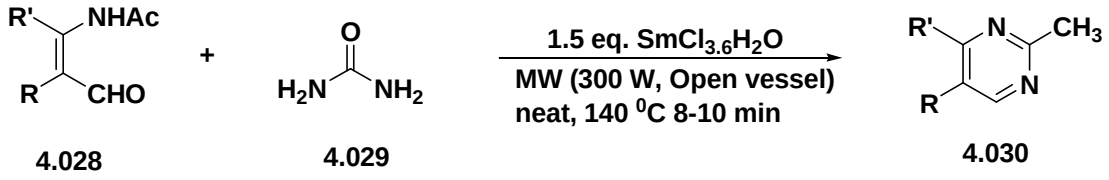
Scheme-4.03

iii) Sodium salt of 3,3-dimethoxy-2-methoxycarbonylprope-1-ol **(4.026)** reacts with a variety of amidinium **(4.025)** salt to produce corresponding 2-substituted pyrimidine -5-carboxylic ester **(4.027)[30] (Scheme-4.04).**



Scheme-4.04

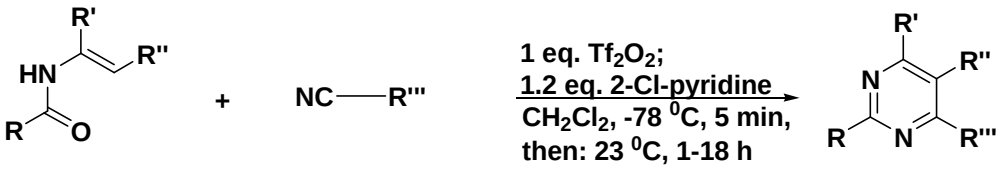
iv) An efficient and novel synthesis[31] of pyrimidine **(4.030)** involves samarium chloride catalyzed cyclization of *β*-formyl enamide **(4.028)** with urea **(4.029)** as a source of ammonia under microwave irradiation **(Scheme-4.05).**



4.028 **4.029** **4.030**

Scheme-4.05

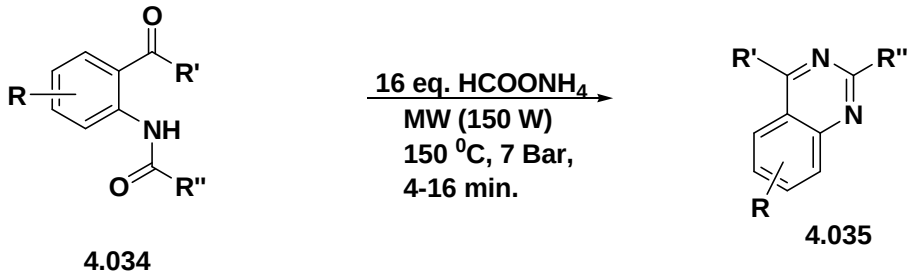
v) A single step synthesis of various corresponding pyrimidine **(4.033)** and quinazoline derivatives from *N*-vinyl and *N*-aryl amides involves amide activation with 2-chloropyridine and trifluoromethanesulfonic anhydride followed by the addition of nitrile **4.032** to the reaction intermediateto allow it to undergo by its cyclomerization[32] **(Scheme-4.06).**



4.031 **4.032** **4.033**

Scheme-4.06

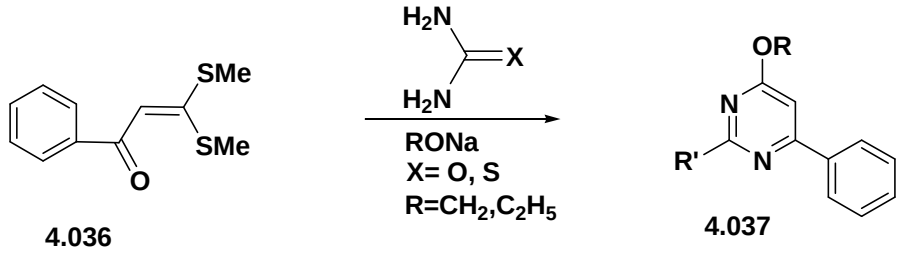
vi) Several *o*-aminoacylbenzene derivatives are acylated by the photochemically induced Fries rearrangement[33] of anilides, these acylamides **4.034** undergo rapid microwave assisted cyclization in presence of ammonium formate to 2,4-disubstituted qunazolines **4.035** (and benzquinazolines) **(Scheme-4.07).**



4.034 **4.035**

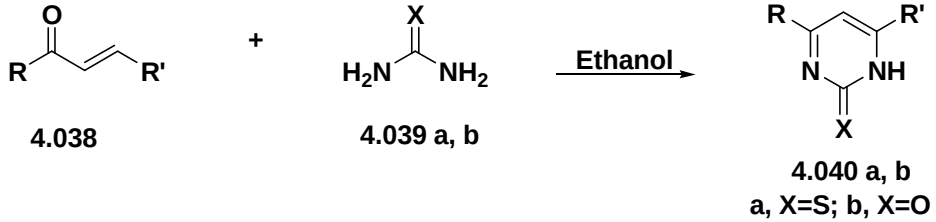
Scheme-4.07

vii) α-Oxoketene-*S*,*S*-acetals **4.036** reacts with different nucleophiles like urea and thiourea in the presence sodium alkoxide to yield **4.037** (hydroxyl and mercapto pyrimidine)[34] **(Scheme-4.08).**



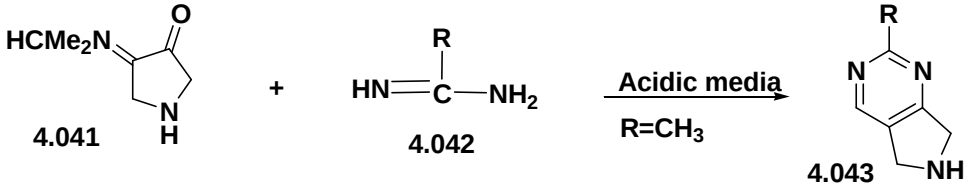
Scheme-4.08

viii) Chalcones **4.038** on reaction with thiourea in presence of alcoholic basic medium forms thio-pyrimidines **(4.040 a)** and with urea in presence of acidic solution produces oxo-pyrimidines[35] **(4.040 b) (Scheme-4.09).**



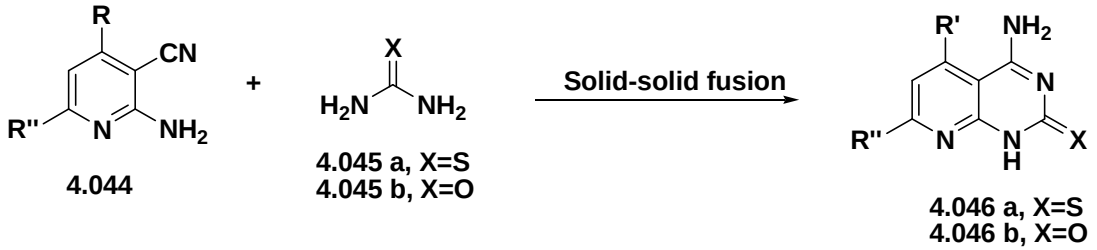
Scheme-4.09

ix) On refluxing[36] 4-dimethylaminomethylene-3-pyrrolidone **(4.041)** with acetamide hydrochloride and Et_3N in ethanol produces **4.043** whereas with guanidine carbonate and sodium acetate in ethanol yields amino pyrimidines **(Scheme-4.10)**.



Scheme-4.10

x) Pyrimidine derivatives **(4.046 a, b)** can be synthesized by the reaction of 2-amino-3-cyano-4,6-disubstituted pyridine[37] **(4.044)** with urea and thiourea **(4.045 a, b)** in an oil bath **(Scheme-4.11).**



Scheme-4.11

The strategy described in the **schemes 4.08, 4.09, 4.10, and 4.11** was employed in the present work to incorporate pyrimidine ring on to the s-triazine nucleus through phenylamino or phenoxyl spacer.

4.4 Present work

This chapter focuses on the synthesis of newer series of pyrimidines condensed s-triazine derivatives attached at its 6-position through a phenoxyl and phenylamino spacer due to its extensively explored chemotherapeutic activities and broad spectrum of biological properties such as antibacterial, fungicidal, insecticidal, antihypertensive, tranquilizing, analgesic, antidiabetic[4] etc.

Our endeavor in the present chapter was to synthesize the proposed materials **4.051-4.056 [Fig. 4.2]** containing pyrimidine nucleus using amidine, dimethylamino ketone, and chalcone as versatile novel precursors appended to s-triazine nucleus as these contained active functional groups which have been exploited in a variety of synthetic operations to the construction of novel fused heterocyclic systems.

In the present work the emphasis was to develop synthetic strategies, which in addition of being highly innovative, were simple in operation, required inexpensive materials and were applicable to a wide range of functionalized substrates for the synthesis of pyrimidine derivatives.

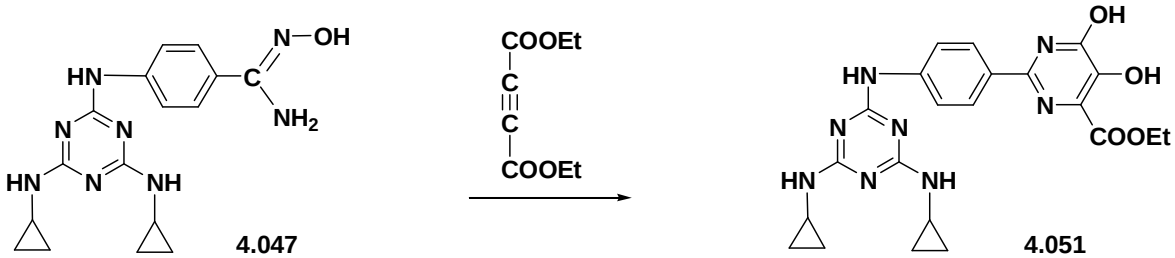
The amidine, dimethylamino ketone, and chalcone derivatives, realized from 2-(4'acetyl phenoxyl/phenylamino) appended s-triazine **(4.047-4.050)** were used in the synthesis of their pyrimidine substituted analogues **(4.051-4.056) (Scheme: 4.12-4.17).**

4.5 Results and discussion

In the present work it was thought of interest to construct a system, which contained pyrimidine and s-triazine nucleus in the same molecular framework due to their broad spectrum of biological activities. The compounds **4.051-4.056 (Fig.-4.2)** containing the above bioactive pharmacophores have been synthesized in the present work from **4.047-4.050** following the strategy shown in the **schemes- 4.12-4.17.** Amidine derivatives **(4.047 and 4.048)** on reaction with acetylenedicarboxylate yielded the pyrimidine analogues **(4.051 and 4.052)** respectively. Similarly dimethylaminomethylene **(4.049)** and chalcone **(4.050)** on reaction with urea and thiourea in presence of a base in ethanol gave the corresponding pyrimidine derivatives **(4.053, 4.054, 4.055 and 4.056) (Scheme-4.14, 4.15, 4.16 and 4.17).**

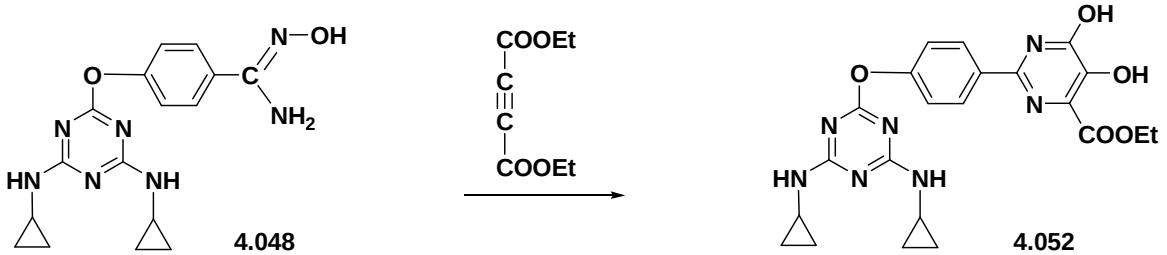
Pyrimidine and pyrimidine based drugs belong to the class of privileged scaffolds by virtue of their ability to form ligands to a number of functionally and structurally deiscrete biological receptors. Recently 6-aminopyrimidine derivative with 4-cyano aryloxy and 4-cyano phenyl amino fragments at its 2 and 4 positions respectively (Etravirine TMC: 125) has emerged as a most potent RT inhibitor and has been approved by FDA for its application as anti-HIV drug.
Inspired by the impressive anti-HIV active profiles of s-triazine, our aim in the present work was to synthesize s-triazine molecules which incorporated in its molecule the vital fragments of etravirine (which has the previous history of being highly active anti-HIV drug), on the premise that their presence in tandem in a single molecular framework could produce a positive impact in enhancing the overall biological efficacy in the resulting molecules. It has been known from the literature[38, 39] 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. 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 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 proposed to be undertaken.

On account of remarkable pharmacodynamic applications of pyrimidine and s-triazine this study was undertaken to bring these heterocyclic scaffolds into a single molecular framework, to access the impact of this substitution on the efficacy of the parent molecules.



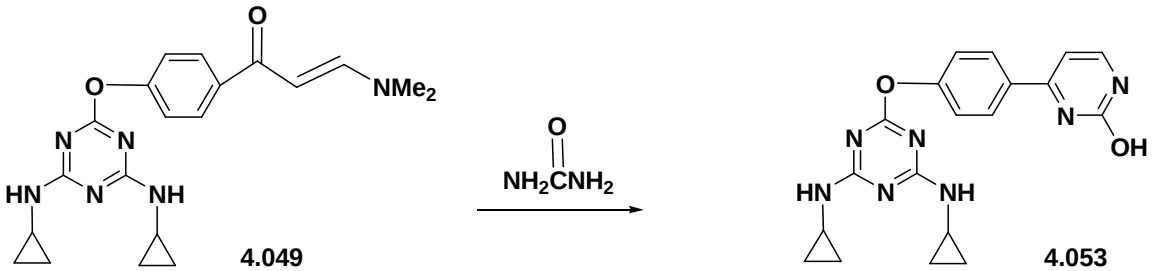
4.047 **4.051**

Scheme-4.12



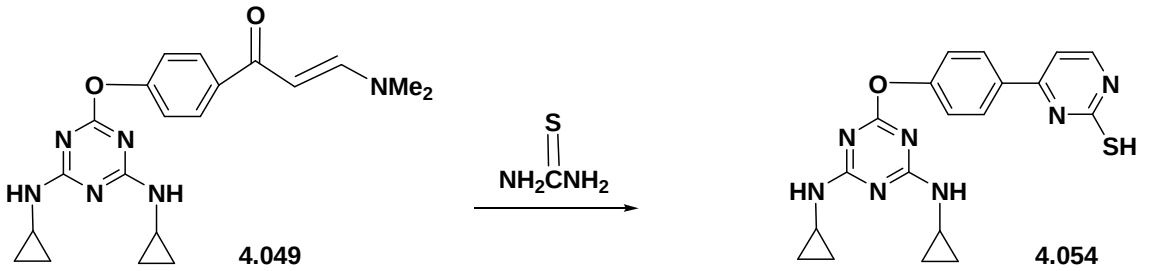
4.048 **4.052**

Scheme-4.13



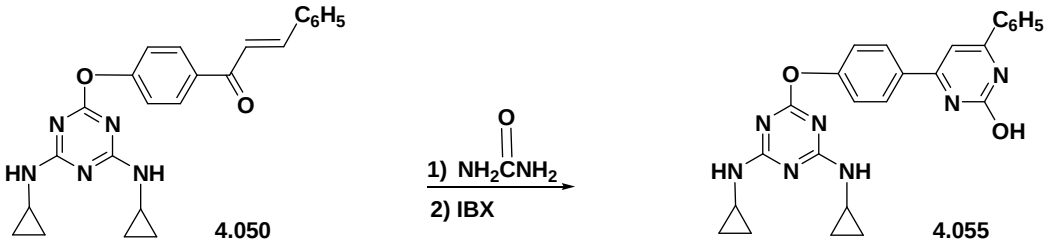
4.049 **4.053**

Scheme-4.14

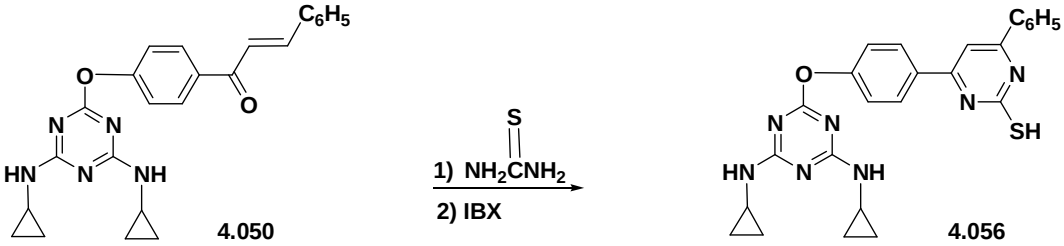


4.049 **4.054**

Scheme-4.15

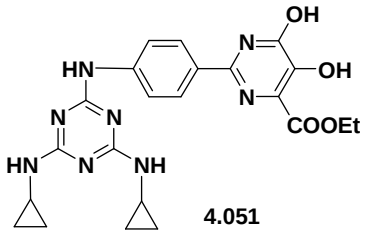


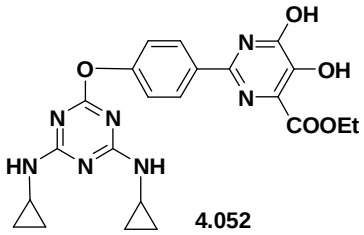
Scheme-4.16

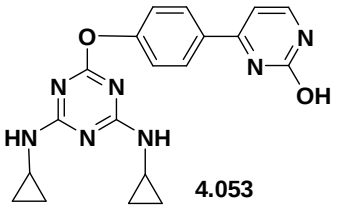


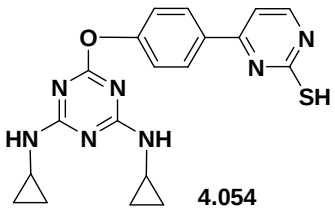
Scheme-4.17

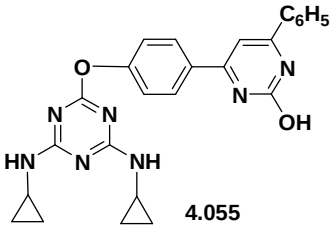
Structure of the compounds whose synthesis is described in the chapter:











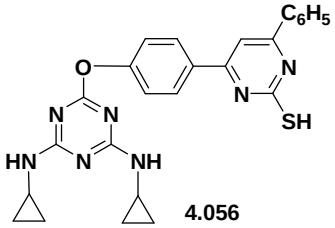


Fig.-4.2

Table 4.01: Physical and analytical data of the compounds 4.051-4.056:

S. No. I	Compd. No. II	Molecular Formula III	M.W. IV	M.P. (^{0}C) V	Yield (%) VI	Elemental analysis VII			
						(calcd/ found) C	(calcd/ found) H	(calcd/ found) N	(calcd/ found) S
1.	4.051	$C_{22}H_{24}N_8O_4$	464	130-132	66%	56.89/ 56.99	5.21/ 5.01	24.12/ 24.05	
2.	4.052	$C_{22}H_{23}N_7O_5$	465	120-122	69%	56.77/ 55.75	4.98/ 5.01	21.06/ 21.10	
3.	4.053	$C_{19}H_{19}N_7O_2$	377	190-192	75%	60.47/ 60.20	5.07/ 5.03	25.98/ 25.85	
4.	4.054	$C_{19}H_{19}N_7OS$	393	180-182	76%	58.00/ 58.20	4.87/ 4.91	24.92/ 24.95	8.15/ 8.20
5.	4.055	$C_{25}H_{23}N_7O_2$	453	184-186	80%	66.21/ 66.10	5.11/ 5.12	21.62/ 21.58	
6.	4.056	$C_{25}H_{23}N_7OS$	496	210-212	79%	63.95/ 63.85	4.94/ 4.90	20.88/ 20.80	6.83/ 6.40

Table 4.02: Spectral data of compounds 4.051-4.056:

S. No.	Compd No.	IR (KBr) cm^{-1}	^{1}H NMR
I	**II**	**III**	**IV**
1.	4.051	3615 [OH str.] 3335 [NH str.] 3059 [C-H str. ArH] 1741 [C=O str. ester] 1612 [C=N str.] 1555 [C=C str. ArH] 1220 [ester group] 1167 [C-N str.] 1020 [C-O str.] 810 [C-N str. s-triazine]	17.99 [1H, s, OH] 8.75 [1H, s, OH] 7.20-7.66[4H, m, (phenylamino)] 6.33 [1H, s, NH (phenylamino)] 4.32 [2H, q, CH_2 (ester)] 3.68 [2H, m, NH (cyclopropylamine)] 2.41 [2H, m, CH (cyclopropylamine)] 1.37 [3H, t, CH_3 (ester)] 0.46-0.57 [8H, m, CH_2 (cyclopropylamine)]
2.	4.052	3558 [OH str.] 3059 [C-H str. ArH] 1739 [C=O str. ester] 1644 [C=N str.]	18.03 [1H, s, OH] 13.45 [1H, s, OH] 7.08-7.58 [4H, m, (phenoxyl)] 4.33 [2H, q, CH_2 (ester)]

		1557 [C=C str. ArH] 1281 [ester group] 1221 [C-N str.] 1021 [C-O str.] 824 [C-N str. s-triazine]	3.51 [2H, m, NH (cyclopropylamine)] 2.40 [2H, m, CH (cyclopropylamine)] 1.36 [3H, t, CH_3 (ester)] 0.43-0.56 [8H, m, CH_2 (cyclopropylamine)]
3.	4.053	3235 [OH str.] 3010 [C-H str. ArH] 1743 [C=O str. keto form] 1682 [C=O str. enol form] 1590 [C=C str. ArH] 1529 [C=N str.] 1169 [C-N str.] 1037 [C-O str.] 805 [C-N str. s-triazine]	17.33 [1H, s, OH] 7.79 [1H, s, CH (pyrimidine ring)] 7.04-7.40 [4H, m, (phenoxyl)] 6.69 [1H, s, CH (pyrimidine ring)] 3.51 [2H, m, NH (cyclopropylamine)] 2.40 [2H, m, CH (cyclopropylamine)] 0.43-0.56 [8H, m, CH_2 (cyclopropylamine)]
4.	4.054	3057 [C-H str. ArH] 2559 [S-H str.] 1568 [C=C str. ArH] 1632 [C=N str.] 1168 [C-N str.] 1099 [C-O str.] 763 [C-S str.] 827 [C-N str. s-triazine]	8.37 [1H, s, CH (pyrimidine ring)] 7.42 [1H, s, CH (pyrimidine ring)] 7.07-7.57 [4H, m, (phenoxyl)] 3.53 [2H, m, NH (cyclopropylamine)] 3.47 [1H, s, SH] 2.40 [2H, m, CH (cyclopropylamine)] 0.45-0.58 [8H, m, CH_2 (cyclopropylamine)]
5.	4.055	3337 [OH str.] 3029 [C-H str. ArH] 1584 [C=C str. ArH] 1547 [C=N str.] 1165 [C-N str.] 1057 [C-O str.] 824 [C-N str. s-triazine]	17.42 [1H, s, OH] 7.41-7.73 [4H, m, arene] 7.15 [1H, s, CH (pyrimidine ring)] 7.08-7.60 [4H, m, (phenoxyl)] 3.53 [2H, m, NH (cyclopropylamine)] 2.40 [2H, m, CH (cyclopropylamine)] 0.46-0.59 [8H, m, CH_2 (cyclopropylamine)]
6.	4.056	2922 [C-H str. ArH] 2259 [S-H str.] 1580 [C=C str. ArH] 1568 [C=N str.] 1168 [C-N str.] 1099 [C-O str.] 686 [C-S str.] 827 [C-N str. s-triazine]	7.78 [1H, s, CH (pyrimidine ring)] 7.41-7.73 [4H, m, arene] 7.08-7.60 [4H, m, (phenoxyl)] 3.53 [2H, m, NH (cyclopropylamine)] 3.57 [1H, s, SH] 2.40 [2H, m, CH (cyclopropylamine)] 0.46-0.59 [8H, m, CH_2 (cyclopropylamine)]

Table 4.03: MS and ^{13}C NMR spectral data of compounds:

S. N0.	Compd. No.	MS	^{13}C NMR 76-78 [$CDCl_3$ solvent]
1.	4.051	---	9 [4CH_2, cyclopropylamine]; 15 [CH_3, ester]; 23 [2CH, cyclopropylamine]; 61 [CH_2, ester]; 117, 129 [4CH, phenylamino]; 134, 144 [2C, phenylamino]; 145, 154, 159 [4C, pyrimidine]; 161 [2C, s-triazine]; 163 [C-O]; 170 [C=O, ester].
2.	4.052	---	9 [4CH_2, cyclopropylamine]; 15 [CH_3, ester]; 23 [2CH, cyclopropylamine]; 61 [CH_2, ester]; 119, 130 [4CH, phenoxyl]; 137, 153 [2C, phenoxyl]; 145, 154, 159 [4C, pyrimidine]; 163 [2C, s-triazine]; 174 [C-O]; 170 [C=O, ester].
3.	4.053	[M^+]: 377	9 [4CH_2, cyclopropylamine]; 23 [2CH, cyclopropylamine]; 112, 159, [2CH, pyrimidine]; 120, 131 [4CH, phenoxyl]; 131, 148 [2C, phenoxyl]; 160 [C, pyrimidine]; 161 [C-OH, pyrimidine]; 163 [2C, s-triazine]; 174 [C-O].
4.	4.054	[M^+]: 393, [M^++2]: 395	9 [4CH_2, cyclopropylamine]; 23 [2CH, cyclopropylamine]; 112, 158, [2CH, pyrimidine]; 120, 130 [4CH, phenoxyl]; 131, 148 [2C, phenoxyl]; 158 [2C, pyrimidine]; 163 [2C, s-triazine]; 167 [C-SH, pyrimidine]; 174 [C-O].
5.	4.055	[M^+]: 453	9 [4CH_2, cyclopropylamine]; 23 [2CH, cyclopropylamine]; 111 [CH, pyrimidine]; 119, 130 [4CH, phenoxyl]; 128, 129, 130 [5H, arene]; 138 [C, arene]; 159 [C-OH, pyrimidine]; 161 [2C, pyrimidine]; 163 [2C, s-triazine]; 174 [C-O].
6.	4.056	[M^+]: 469, [M^++2]: 471	9 [4CH_2, cyclopropylamine]; 23 [2CH, cyclopropylamine]; 112 [CH, pyrimidine]; 119, 130 [4CH, phenoxyl]; 128, 129, 130 [CH, arene]; 138 [C, arene]; 159 [CH, pyrimidine]; 163 [2C, s-triazine]; 168 [C-SH, pyrimidine]; 174 [C-O].

4.6 Interpretation of spectral data for the elucidation of structure of compounds 4.051-4.056:

Structures of the compounds were established on the basis of microanalysis, IR, ^{1}H NMR ^{13}C NMR and MS spectral data. Physical data were found to be in agreement to the structures assigned to the molecules. The physical data is presented in the table **4.01, 4.02** and **4.03** and the spectral graphs of the compounds are shown in the spectral charts **4.1** to **4.21.**

Infrared spectra

The peaks which appeared at 3335 cm^{-1} (NH str. of phenylamino), 3615 cm^{-1} (–OH str.), 1741 cm^{-1} (C=O str. ester), 1220 cm^{-1} (ester group), 3059 cm^{-1} (CH str. ArH) and 1555 cm^{-1} (C=C str. ArH) in the IR spectrum of the compound **4.051** clearly suggested its formation from **4.047**. Similar interpretation when applied to **4.052** indicated the structure of **4.052.**

The peaks at which appeared at 1529 cm^{-1} (C=N str. pyrimidine ring), 3235 cm^{-1} (OH str.) and 1037 cm^{-1} (C-O str.) in the IR spectrum of the compound **4.053** clearly suggested the formation of pyrimidine ring in the compound. Appearance of additional peaks at 2559 cm^{-1} (SH str.), 763 cm^{-1} (C-S str.) provided further evidence for the formation of **4.054.**

The formation of the compound **4.055** from **4.050** was ascertained by the appearance of peaks at 3337 cm^{-1} (OH str.), 3029 cm^{-1} (C-H str. ArH), 1584 cm^{-1} (C=C str. ArH), 1165 cm^{-1} (C-N str.) and 1057 cm^{-1} (C-O str.) and on the basis of disappearance of peak at 1570 cm^{-1} (C=C str. α,β-unsaturated ketones). Similar interpretation ascertained the formation of compound **4.056** from **4.050.** The appearance of additional peaks at 2259 cm^{-1} (SH str.) and 686 cm^{-1} (C-S str.) substanciated further its proposed structure.

^{1}H NMR

^{1}H NMR was recorded at 400 MHz in $CDCl_3$; It displayed two downfield singlets at δ 17.99 and δ 8.75 for two protons of OH groups, and a singlet at δ 6.33 for one proton of NH group, a double doublet at δ 7.20 – δ 7.66 for four protons of phenylamino group. Appearance of a quartet at δ 4.32 and a triplet at δ 1.37 clearly indicated the presence of ethyl part of the ester group in the compound **4.051.** Similar ^{1}H NMR spectrum is obtained for the compound **4.052** except for downfield signals at δ 7.20-7.66 for NH of phenylamino group.

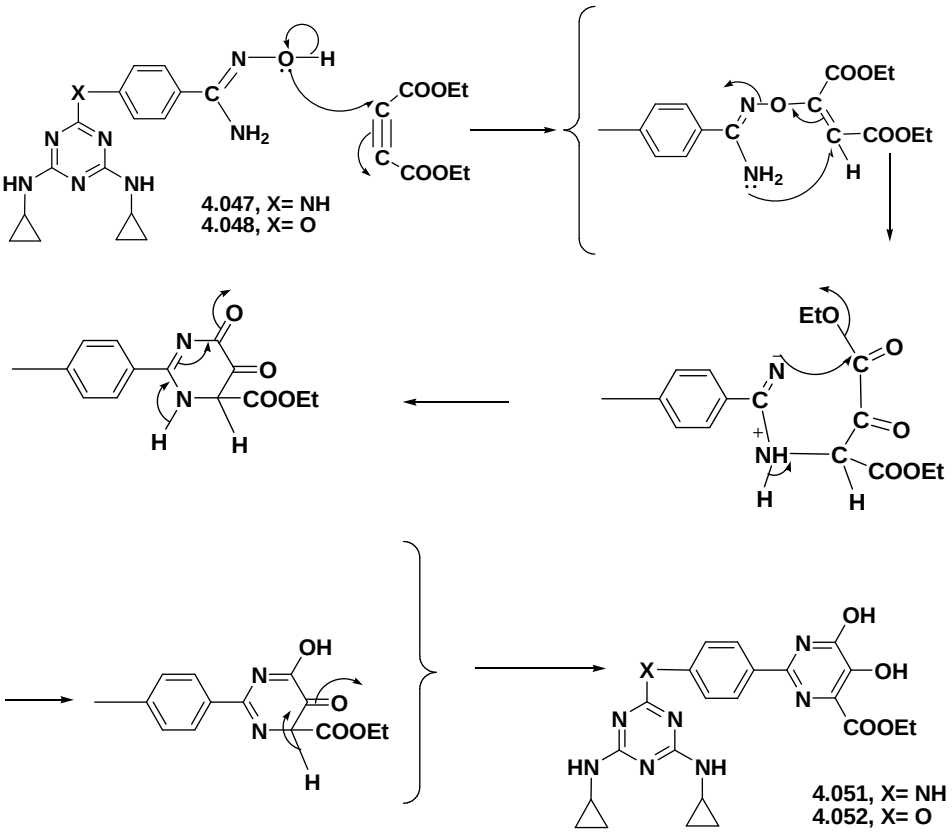
Appearance of a downfield singlet at δ 17.33 for a proton of OH group and two singlets at δ 7.79 and δ 6.69 for the protons of pyrimidine ring and the disappearance of two doublets at δ 8.12 and δ 5.66 for CH=N- and =CH-C=O groups respectively and disappearance of a sharp singlet at δ 2.63 for 2 CH_3 groups of CH-N-$(CH_3)_2$ supported the formation of **4.053** from **4.049.** Similar ^{1}H NMR when applied to **4.054** corroborated its formation from **4.049.**

Appearance of a downfield singlet at δ 17.42 for one proton of OH group and a singlet at δ 7.15 for pyrimidine ring and the disappearance of two doublets 7.45 and 8.00 of **4.050** for two protons

of α,β-unsaturated ketones supported the formation of **4.055** from **4.050.** Similarly the formation of the compound **4.056** from **4.050** was established on the basis of its ^{1}H NMR.

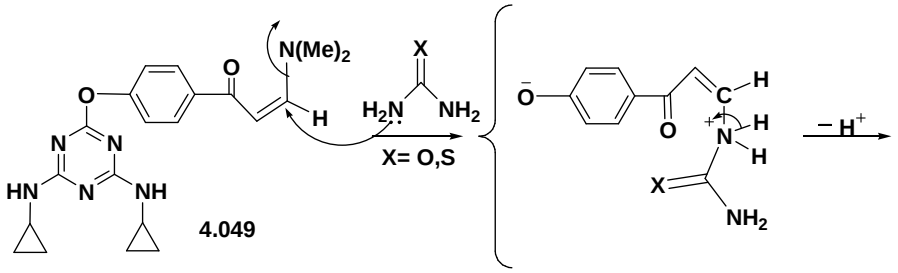
4.7 Mechanism of formation of compounds (4.051-4.056):

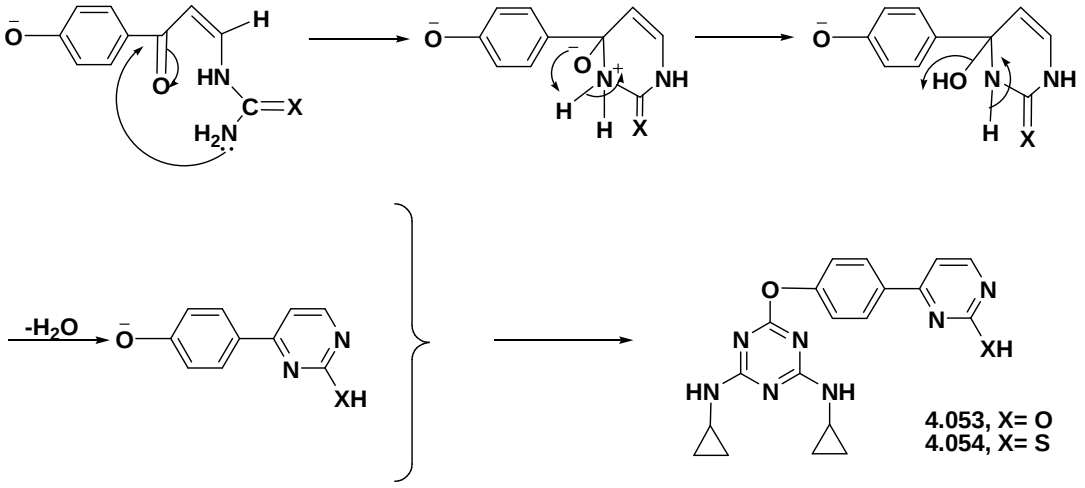
4.7.1 Mechanism of formation of compound 4.051 and 4.052 from 4.047 and 4.048:



Scheme-4.22

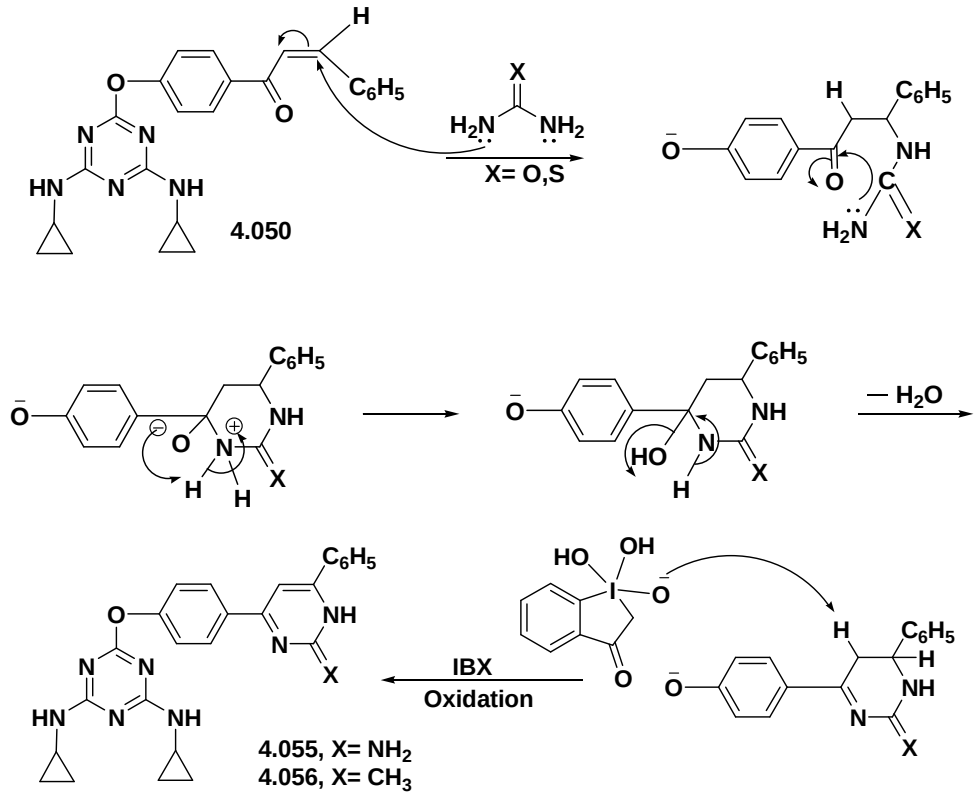
4.7.2 Mechanism of formation of compound 4.053 and 4.054 from 4.049:





Scheme-4.23

4.7.1 Mechanism of formation of compound 4.055 and 4.056 from 4.050:



Scheme-4.25

4.8 Experimental Section

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 visualizing 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 4.01- 4.03**.

Synthetic procedures:

Preparation of ethyl 2-(4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-ylamino)phenyl)-5,6-dihydroxypyrimidine-4-carboxylate (4.051):

4.047 (2.38 g, 0.007 mol) and diethyl acetylenedicarboxylate (1.0 ml, 0.008 mol) in chloroform (20 ml) was refluxed overnight. The solution was cooled to room temperature, volatiles were evaporated and the residue was refluxed in xylene (3 ml) for 3 h. On cooling, the solid mass which separated out, was filtered and washed with diethyl ether to give **4.051**, (66% yield); m.p. 130-132 ^{0}C.

Preparation of ethyl 2-(4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-yloxy)phenyl)-5,6-dihydroxypyrimidine-4-carboxylate (4.052):

4.048 (2.38 g, 0.007 mol) and diethyl acetylenedicarboxylate (1.0 ml, 0.008 mol) in chloroform (20 ml) was refluxed overnight. The solution was cooled to room temperature, volatiles were evaporated and the residue was refluxed in xylene (3 ml) for 3 h. On cooling, the solid mass which separated out, was filtered and washed with diethyl ether to give **4.052**, (69% yield); m.p. 120-122 ^{0}C.

Preparation of ethyl 4-(4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-yloxy)phenyl)pyrimidin-2-ol (4.053):

The reaction mixture, containing urea (0.12 g, 0.002 mol), sodium ethoxide (0.14 g, 0.002 mol) and dimethyaminomethylene ketone derivative **(4.049)** (0.53 g, 0.0014 mol) was refluxed in ethanol (30 ml) for 14 h. After removing the solvent by distillation the residue was refluxed in glacial acetic acid (5 ml just enough to dissolve the sodium salt of the pyrimidine) for 15 min.The reaction mixture was poured on crushed ice, the precipitate obtained was recrystallized from chloroform to yield **4.053**, (75% yield); m.p. 190-192 ^{0}C.

Preparation of ethyl 4-(4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-yloxy)phenyl)pyrimidine-2-thiol (4.054):

The reaction mixture, containing thiourea (0.152 g, 0.002 mol), sodium ethoxide (0.140 g, 0.002 mol) and dimethyaminomethylene ketone derivative **(4.049)** (0.53 g, 0.0014 mol) was refluxed in ethanol (30 ml) for 12 h. After removing the solvent by distillation the residue was refluxed in glacial acetic acid (5 ml just enough to dissolve the sodium salt of the pyrimidine) for 15 min.The reaction mixture was poured on crushed ice, the precipitate obtained was recrystallized from chloroform to yield **4.054**, (76% yield); m.p. 180-182 ^{0}C.

Preparation of ethyl 4-(4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-yloxy)phenyl)-6-phenylpyrimidin-2-ol (4.055):

Chalcone **4.050** (0.359 g, 0.87 mmol) with urea (0.11 g, 0.001 mol) and 0.1 g NaOH in 25 ml of 80% dilute ethanol was refluxed for 12 h, the solution was then concentrated and cooled, the precipitate obtained was dissolved in DMSO and stirred at 45 ^{0}C for 13 h with iodobenzoic acid (0.4 g, 1.53 mmol). After cooling the reaction mixture it was quenched in aqueous $Na_2S_2O_3$ (1.0 ml) and then basified with saturated aqueous $NaHCO_3$ (1.0 ml). The desired product was extracted with EtOAc (5.0 ml), the organic layer was washed with water (10.0 ml) and brine (10.0 ml), dried over ($MgSO_4$), and concentrated to yield **4.055,** (80% yield); m.p. 184-186 ^{0}C.

Preparation of ethyl 4-(4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-yloxy)phenyl)-6-phenylpyrimidine-2-thiol (4.056):

Chalcone **4.050** (0.359 g, 0.87 mmol) with thiourea (0.11 g, 0.0015 mol) and 0.1 g NaOH in 25 ml of 80% dilute ethanol was refluxed for 10 h, the solution was then concentrated and cooled, the precipitate obtained was dissolved in DMSO and stirred at 45 ^{0}C for 13 h with iodobenzoic acid (0.4 g, 1.53 mmol). After cooling the reaction mixture it was quenched in aqueous $Na_2S_2O_3$ (1.0 ml) and then basified with saturated aqueous $NaHCO_3$ (1.0 ml). The desired product was extracted with EtOAc (5.0 ml), the organic layer was washed with water (10.0 ml) and brine (10.0 ml), dried over ($MgSO_4$), and concentrated to yield **4.056,** (79% yield); m.p. 210-212 ^{0}C.

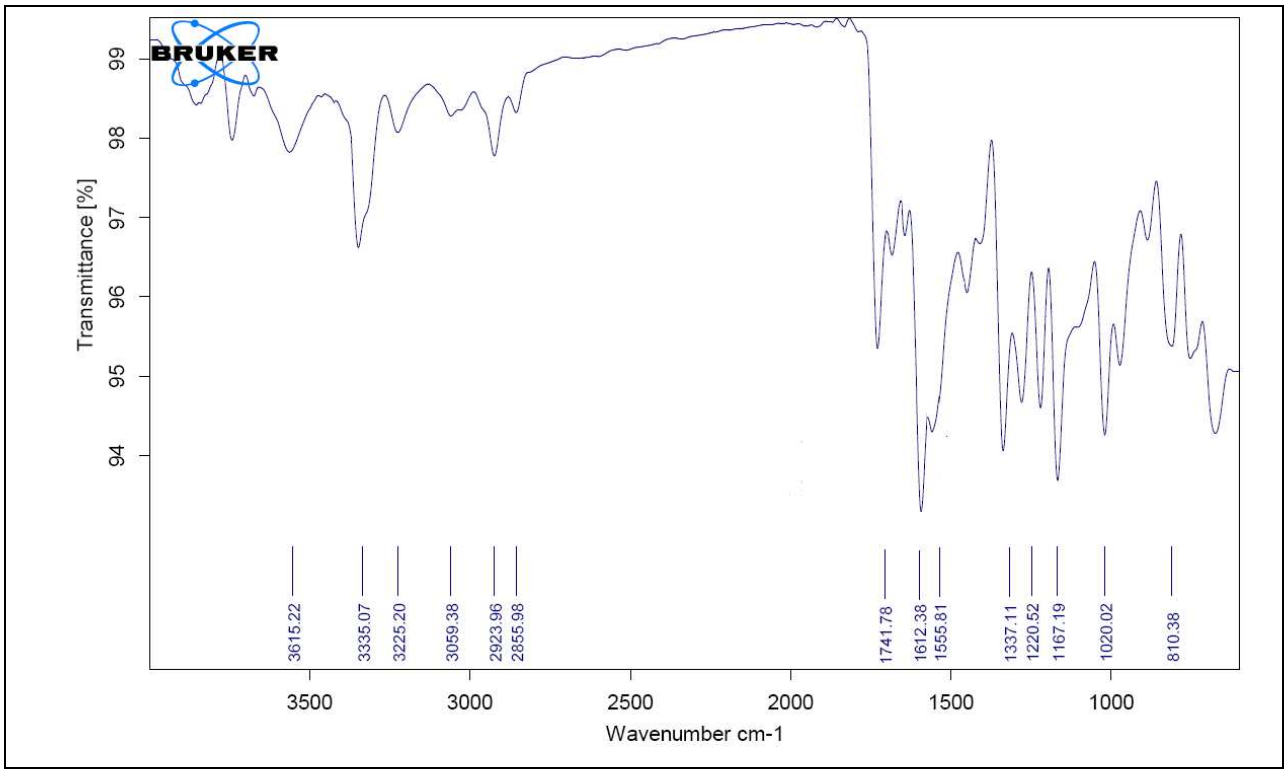


Chart-4.1 IR spectrum of 2-(4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-ylamino)phenyl)-5,6-dihydroxypyrimidine-4-carboxylate (4.051)

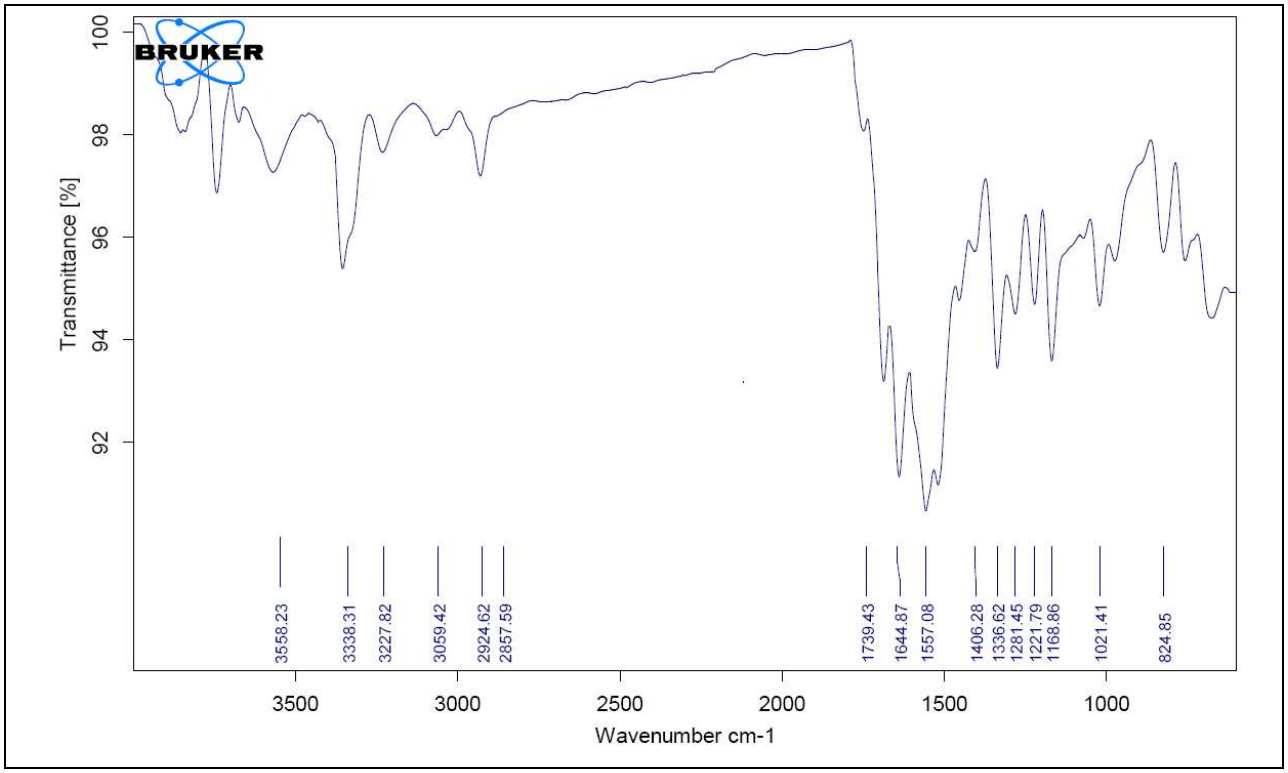


Chart-4.2 IR spectrum of ethyl 2-(4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-yloxy)phenyl)-5,6-dihydroxypyrimidine-4-carboxylate (4.052)

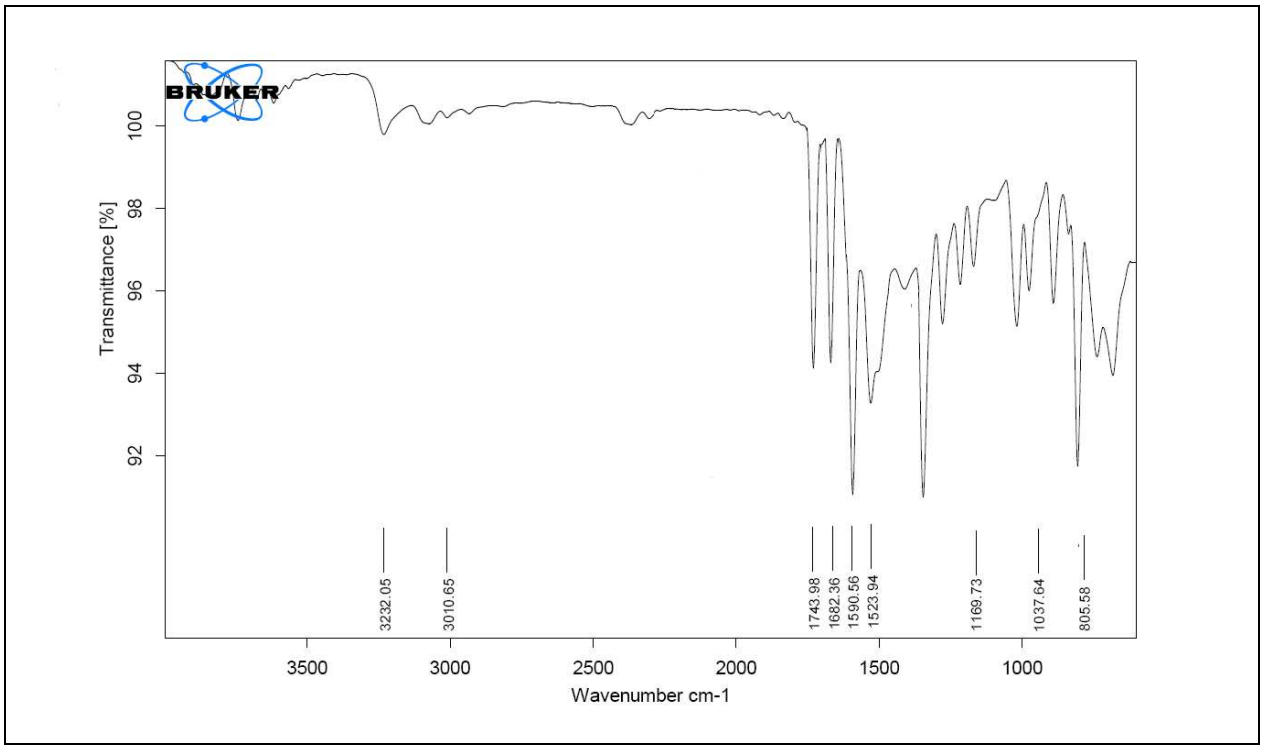


Chart-4.3 IR spectrum of 4-(4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-yloxy)phenyl)pyrimidine-2-ol (4.053)

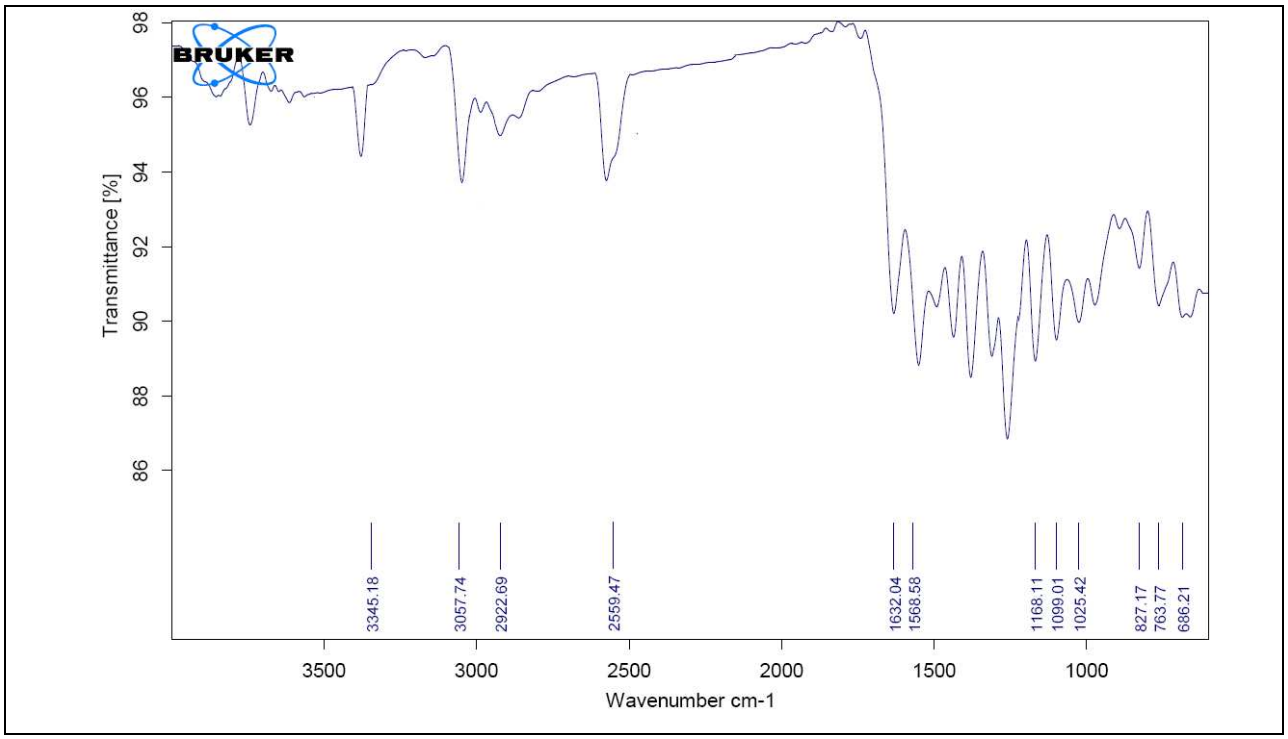


Chart-4.4 IR spectrum of 4-(4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-yloxy)phenyl)pyrimidine-2-thiol (4.054)

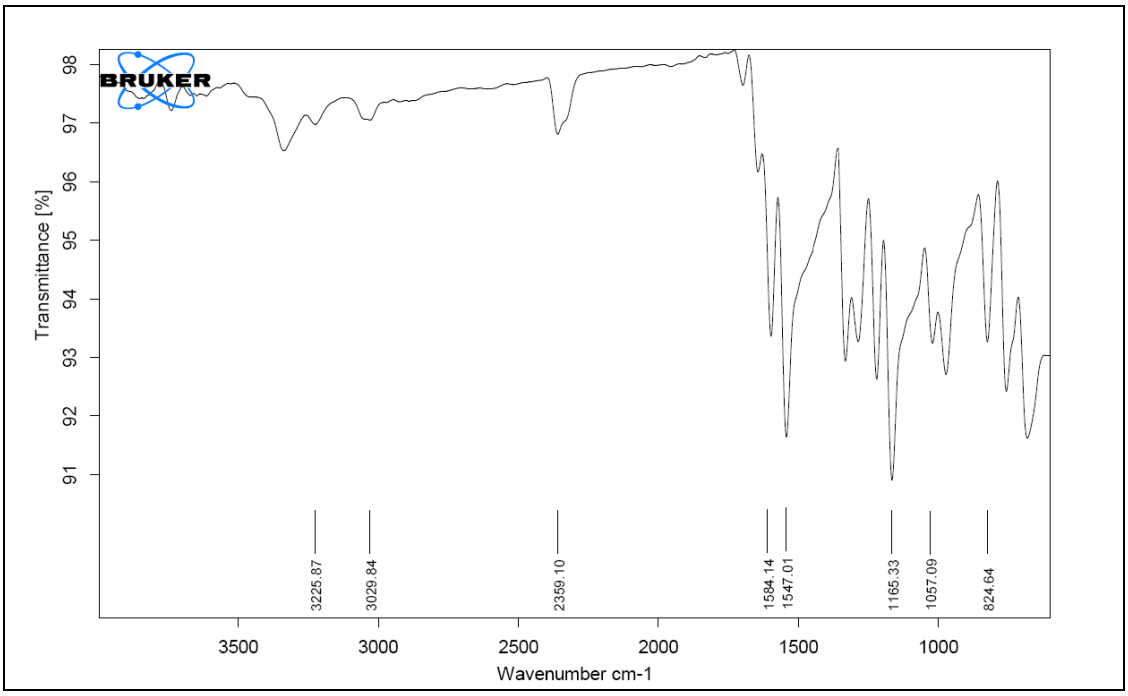


Chart-4.5 IR spectrum of 4-(4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-yloxy)phenyl)-6-phenylpyrimidin-2-ol (4.055)

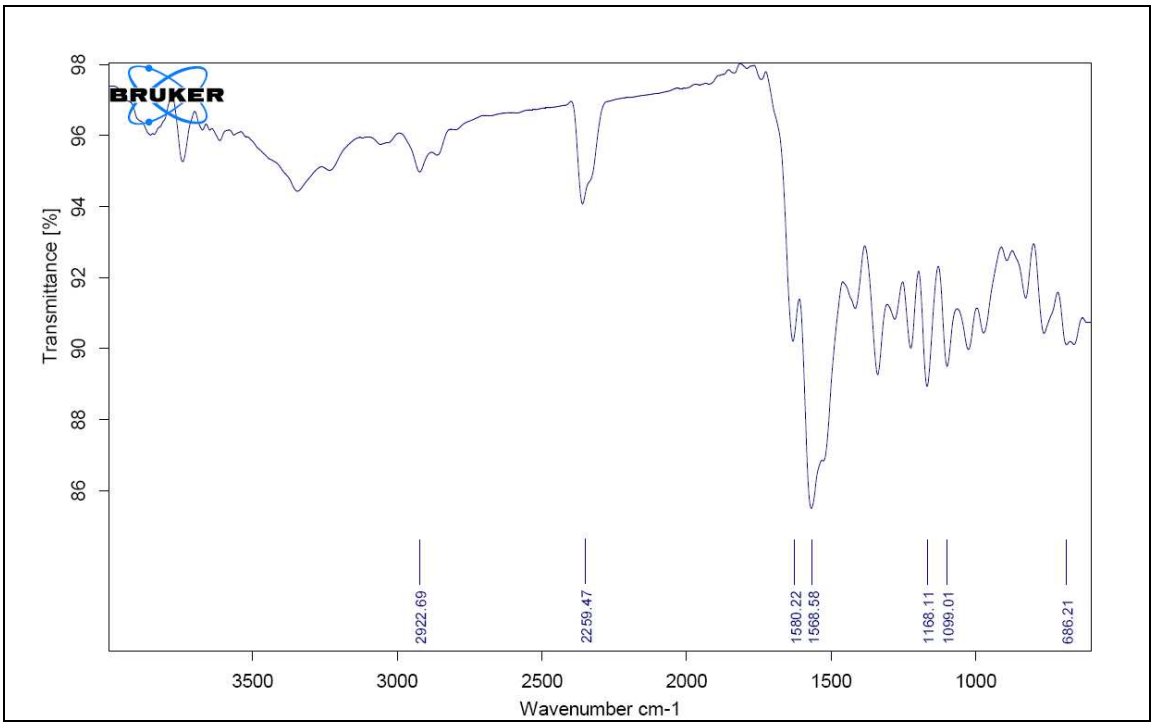


Chart-4.6 IR spectrum of 4-(4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-yloxy)phenyl)-6-phenylpyrimidin-2-thiol (4.056)

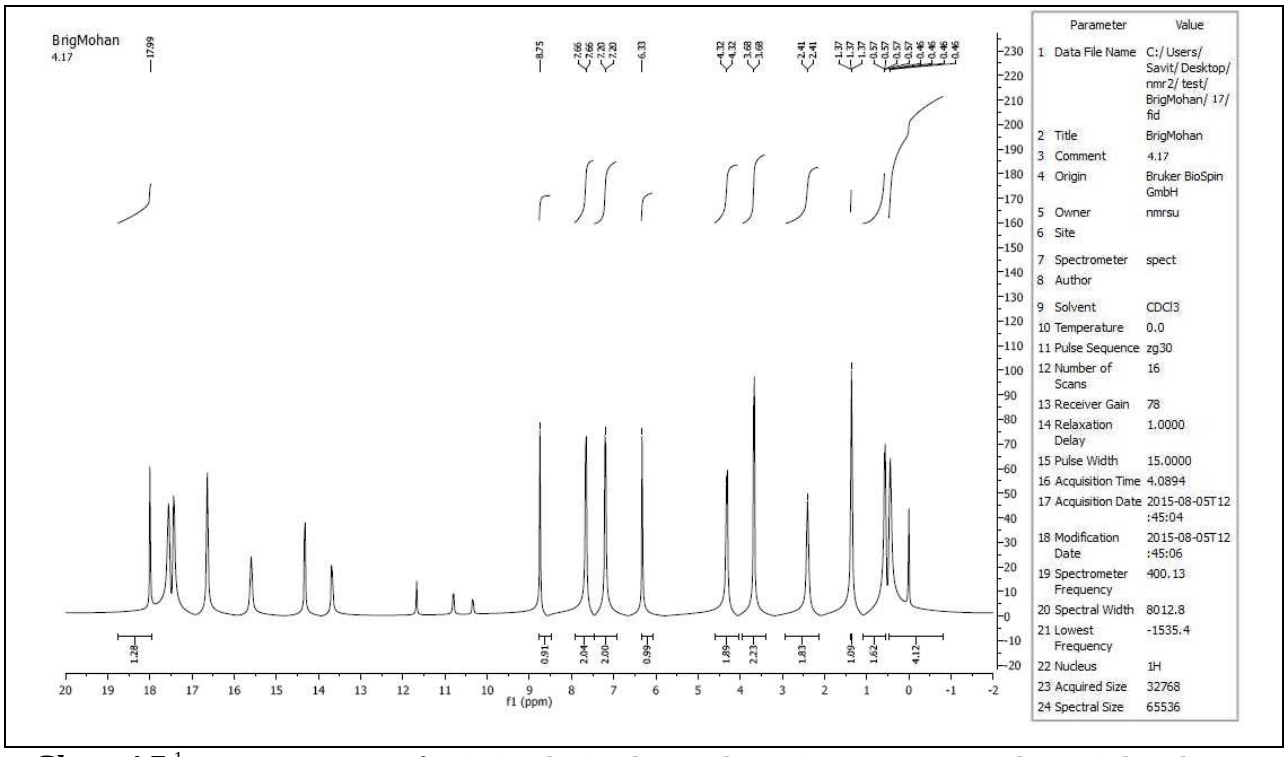


Chart-4.7 ^{1}H NMR spectrum of 2-(4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-ylamino)phenyl)-5,6-dihydroxypyrimidine-4-carboxylate (4.051)

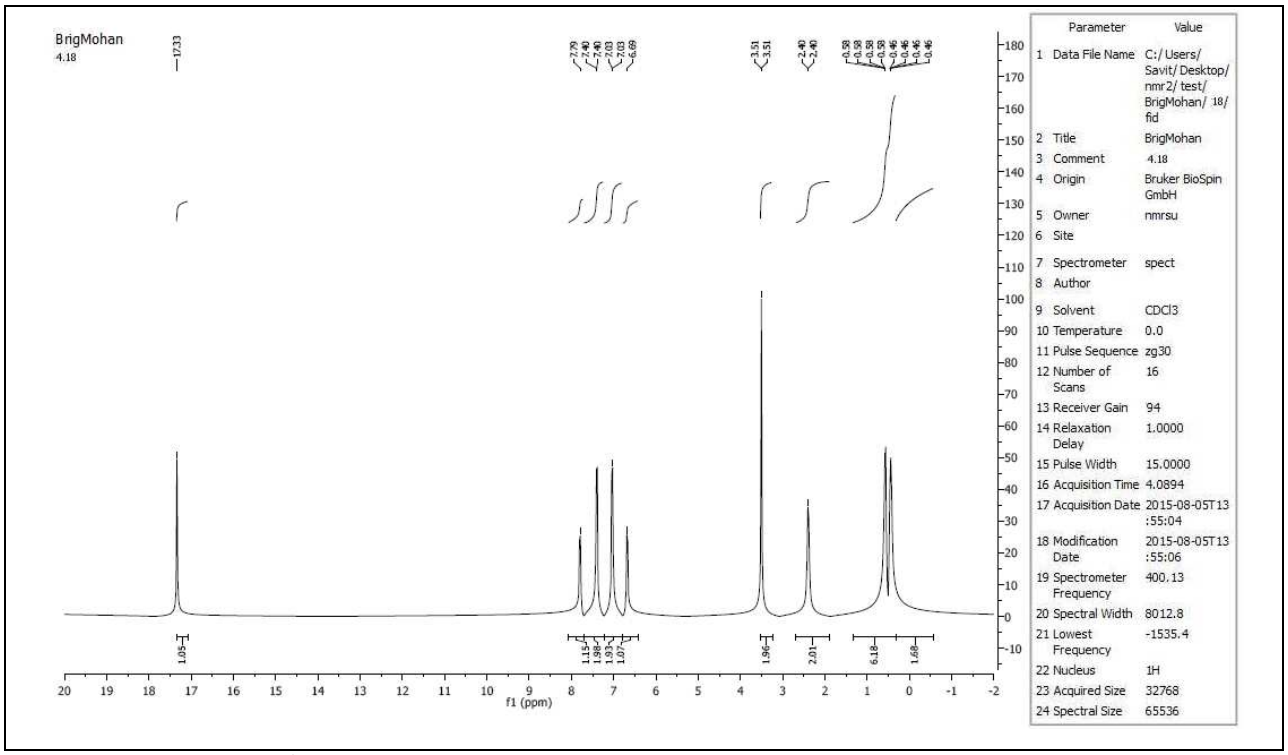


Chart-4.8 ^{1}H NMR spectrum of 4-(4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-yloxy)phenyl)pyrimidine-2-ol (4.053)

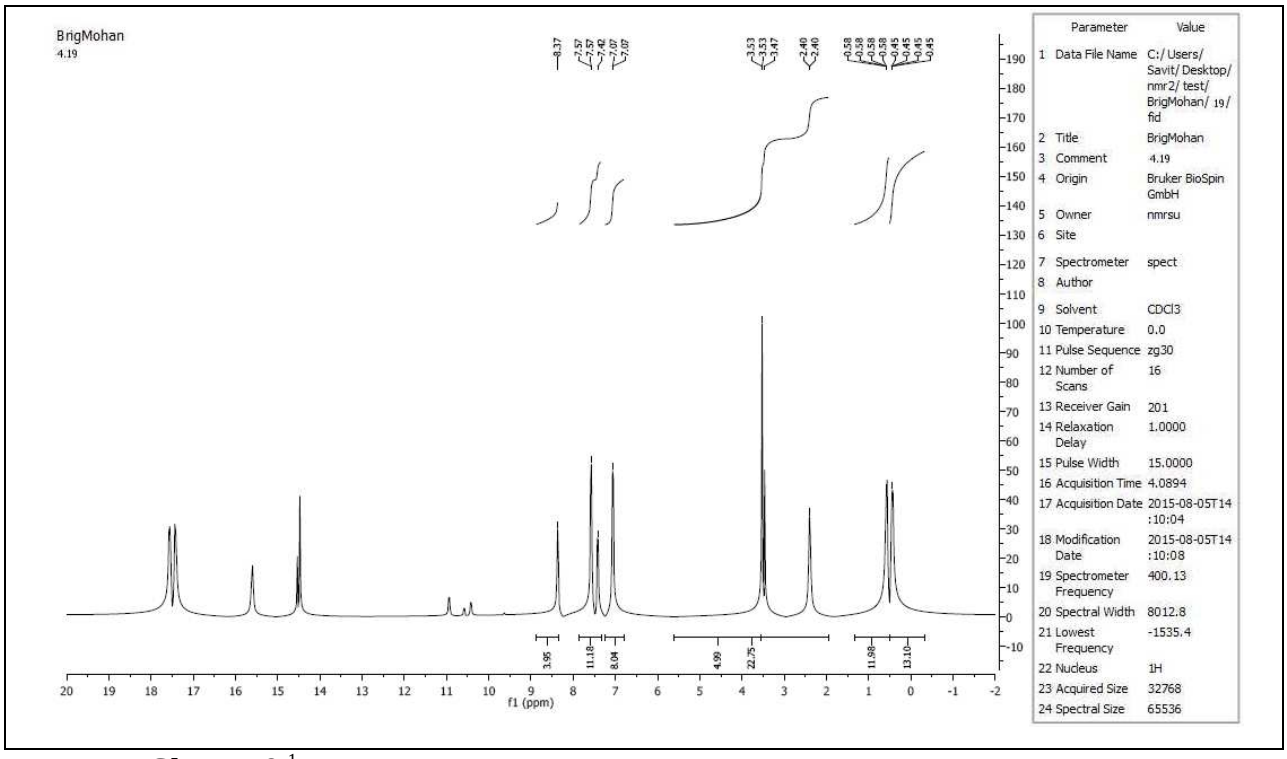


Chart-4.9 ^{1}H NMR spectrum of 4-(4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-yloxy)phenyl)pyrimidine-2-thiol (4.054)

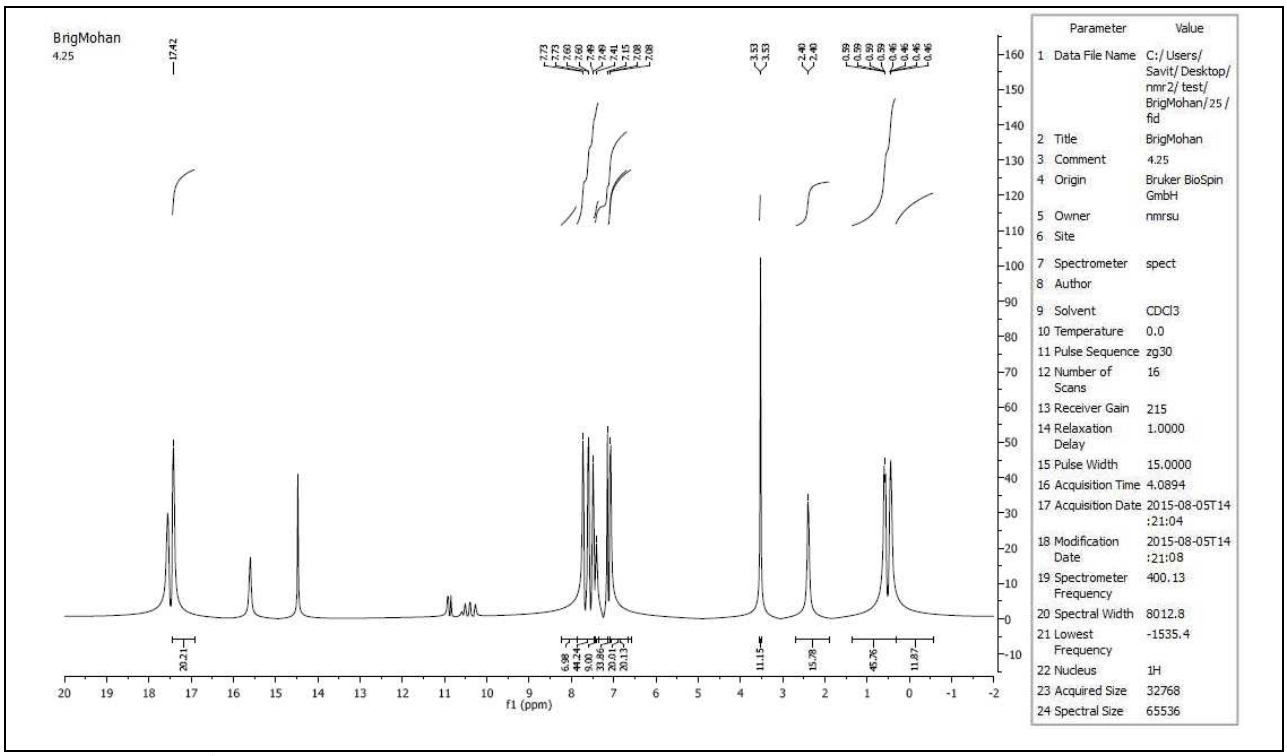


Chart-4.10 ^{1}H NMR spectrum of 4-(4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-yloxy)phenyl)-6-phenylpyrimidin-2-ol (4.055)

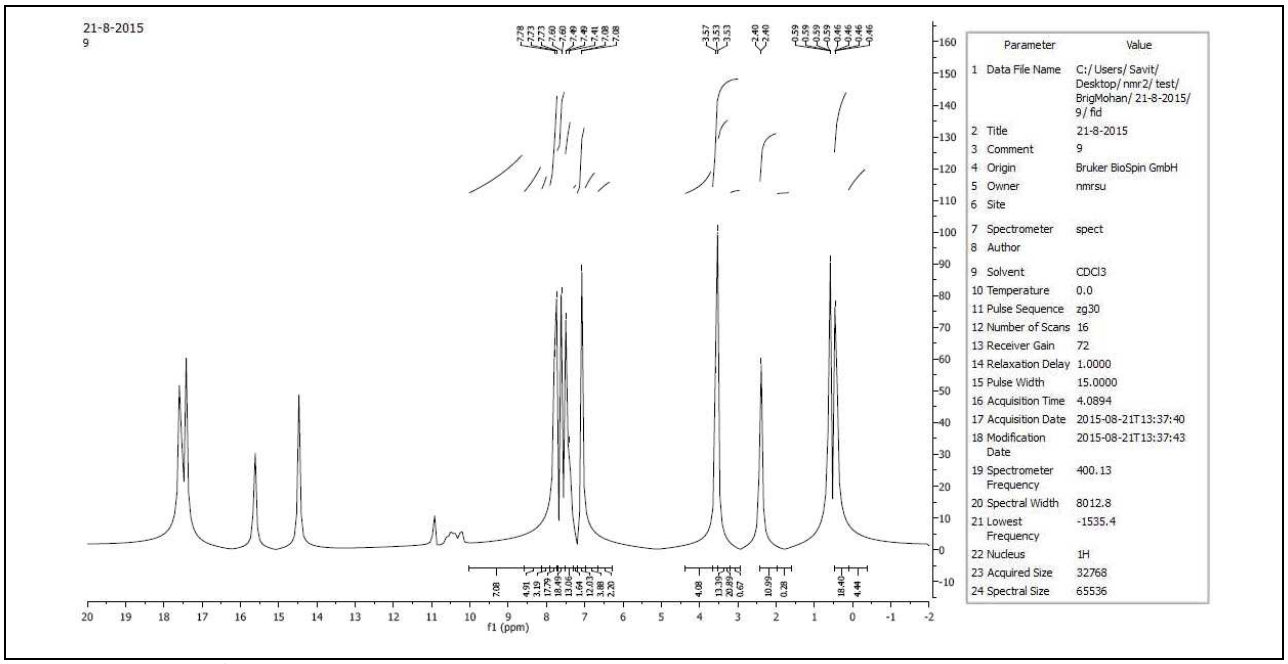


Chart-4.11 ^{1}H NMR spectrum of 4-(4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-yloxy)phenyl)-6-phenylpyrimidin-2-thiol (4.056)

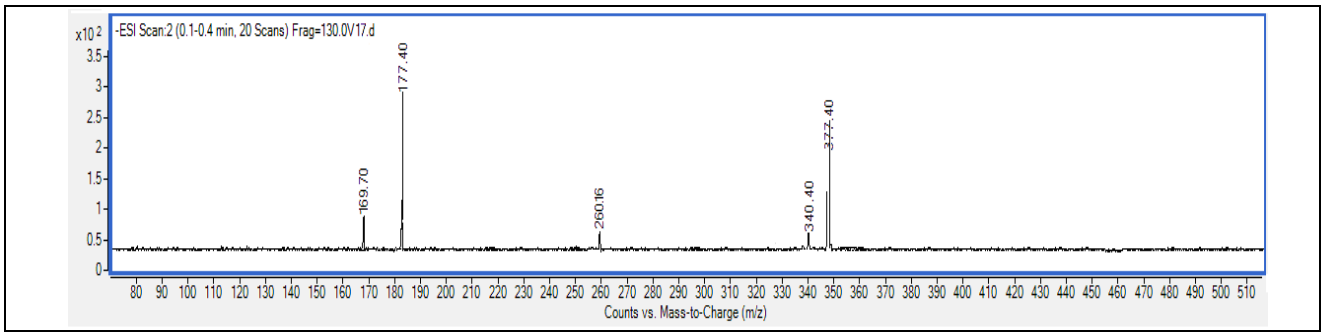


Chart-4.12 Mass spectrum of 4-(4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-yloxy)phenyl)pyrimidine -2-ol (4.053)

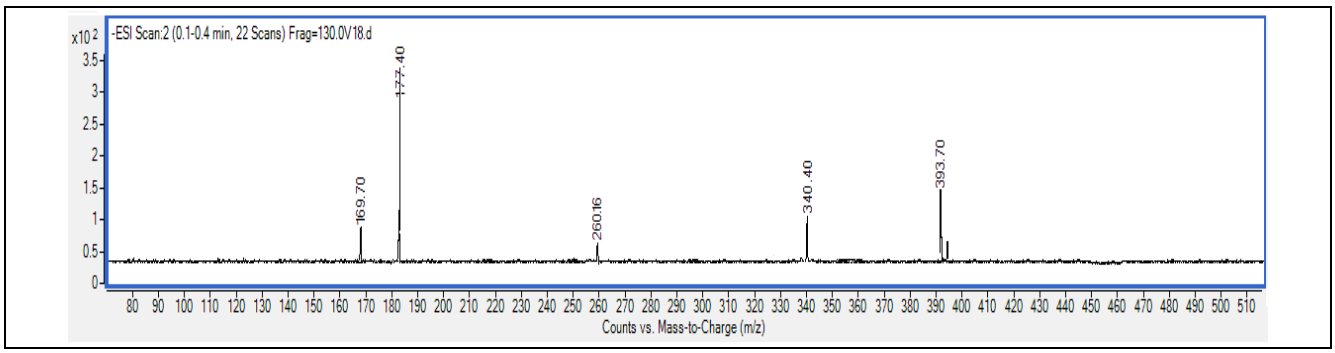


Chart-4.13 Mass spectrum of 4-(4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-yloxy)phenyl)pyrimidine -2 -thiol (4.054)

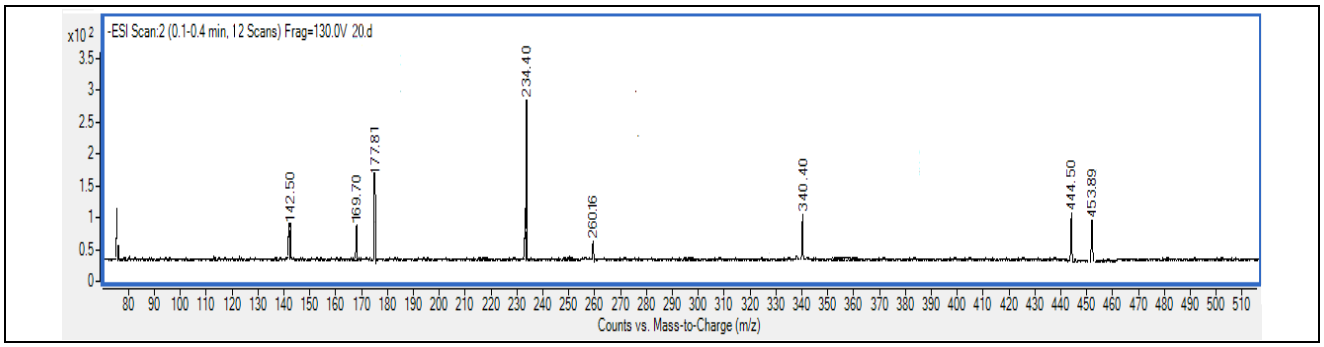


Chart-4.14 Mass spectrum of 4-(4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-yloxy)phenyl)-6-phenylpyrimidin-2-ol (4.055)

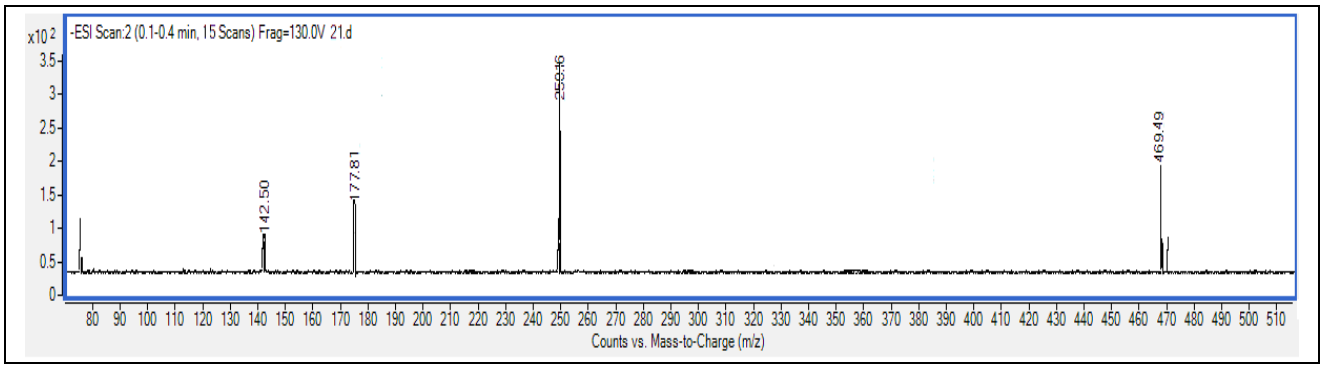


Chart-4.15 Mass spectrum of 4-(4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-yloxy)phenyl)-6-phenylpyrimidin-2-thiol (4.056)

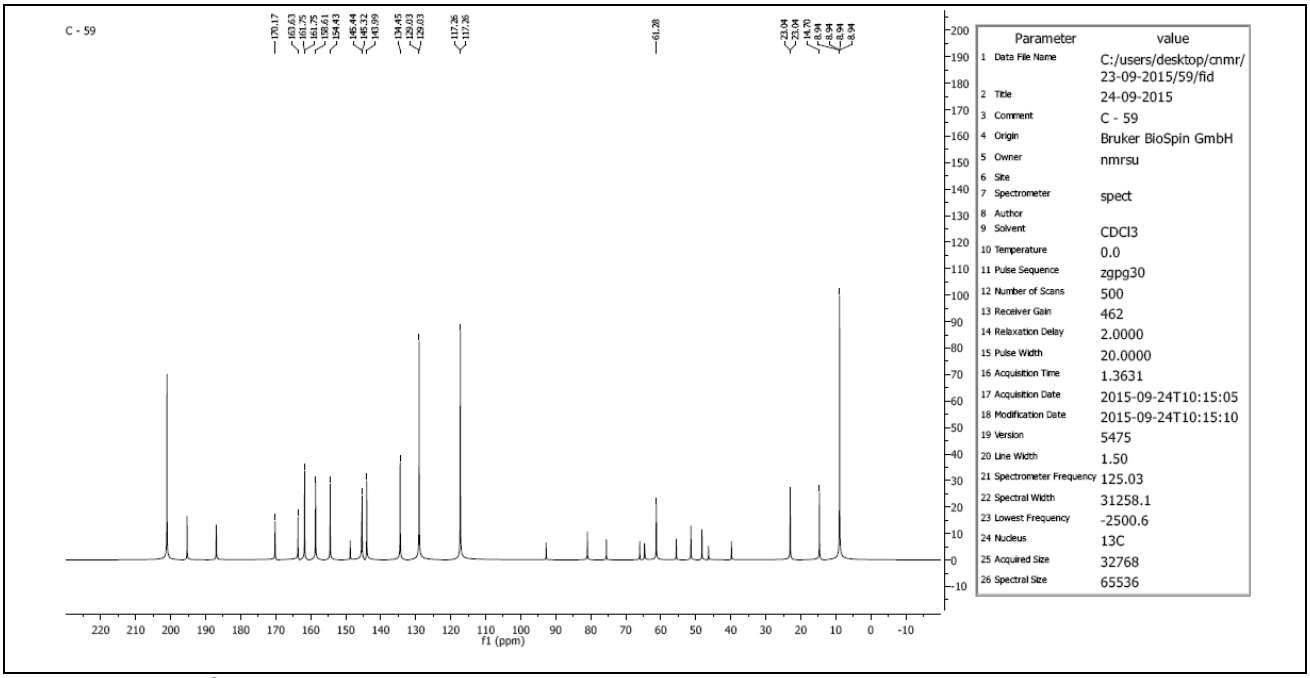


Chart-4.16 ^{13}C NMR spectrum of 2-(4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-ylamino)phenyl)-5,6-dihydroxypyrimidine-4-carboxylate (4.051)

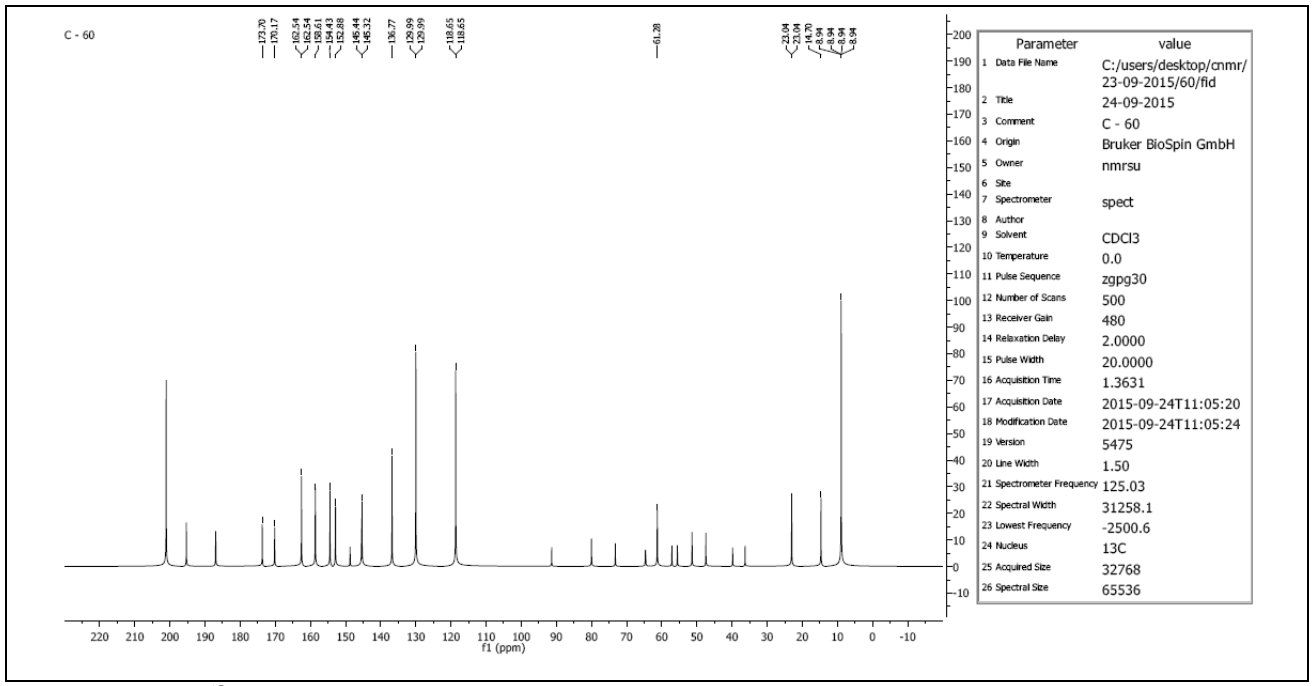


Chart-4.17 ^{13}C NMR spectrum of ethyl 2-(4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-yloxy)phenyl)-5,6-dihydroxypyrimidine-4-carboxylate (4.052)

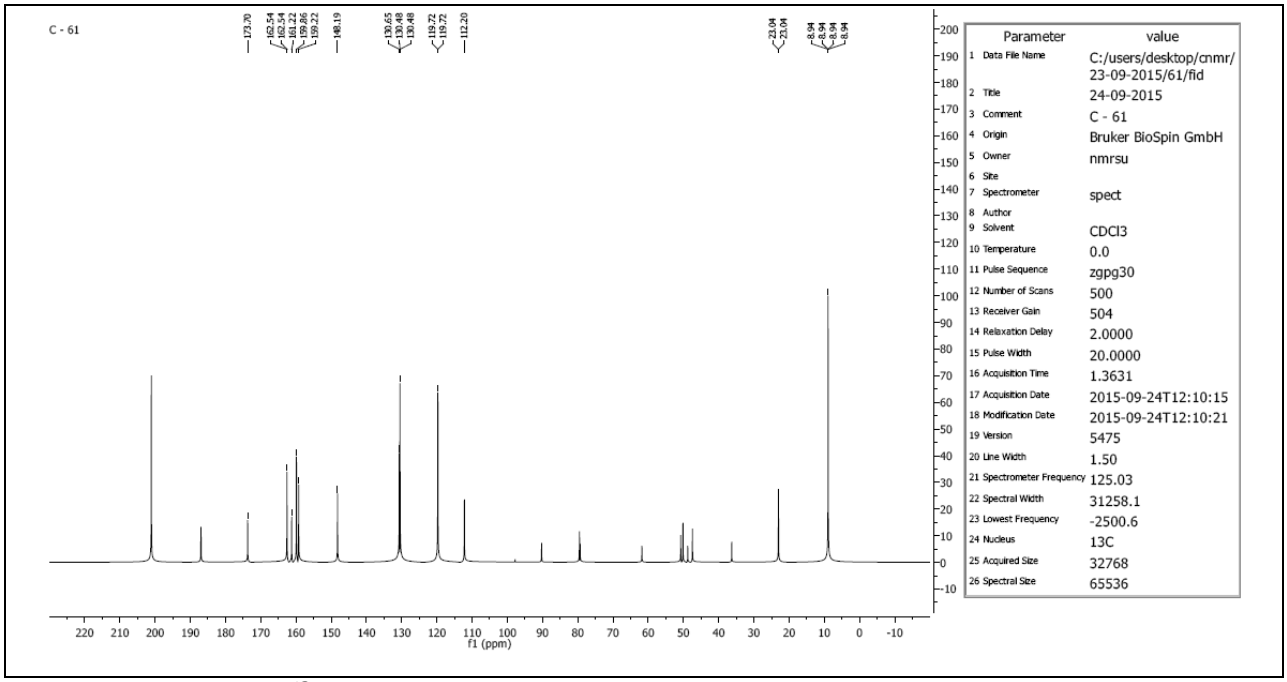


Chart-4.18 ^{13}C NMR spectrum of 4-(4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-yloxy)phenyl)pyrimidine-2-ol (4.053)

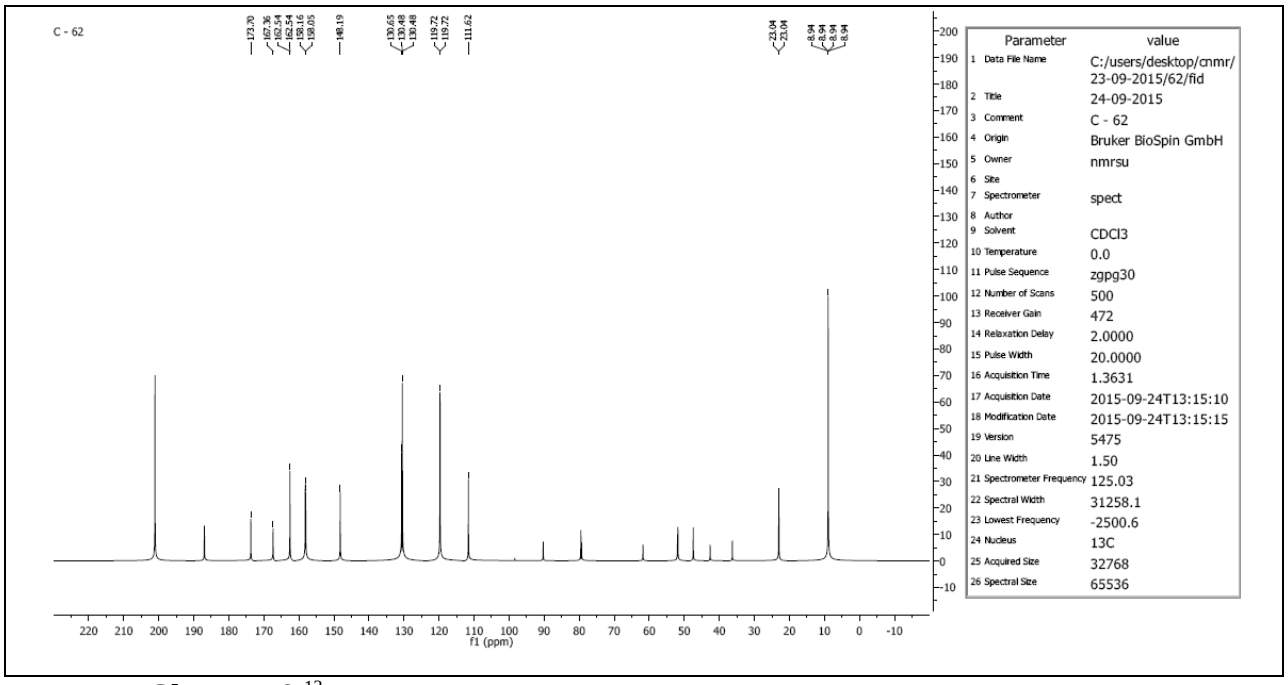


Chart-4.19 ^{13}C NMR spectrum of 4-(4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-yloxy)phenyl)pyrimidine-2-thiol (4.054)

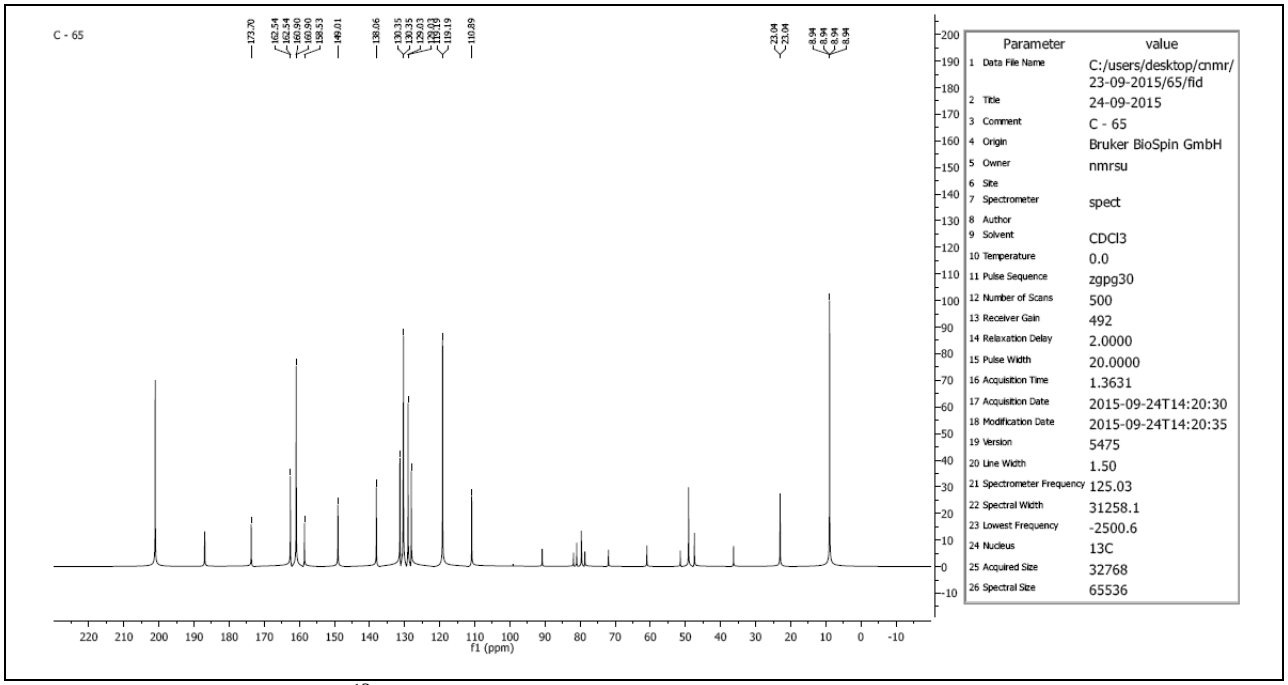


Chart-4.20 ^{13}C NMR spectrum of 4-(4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-yloxy)phenyl)-6-phenylpyrimidin-2-ol (4.055)

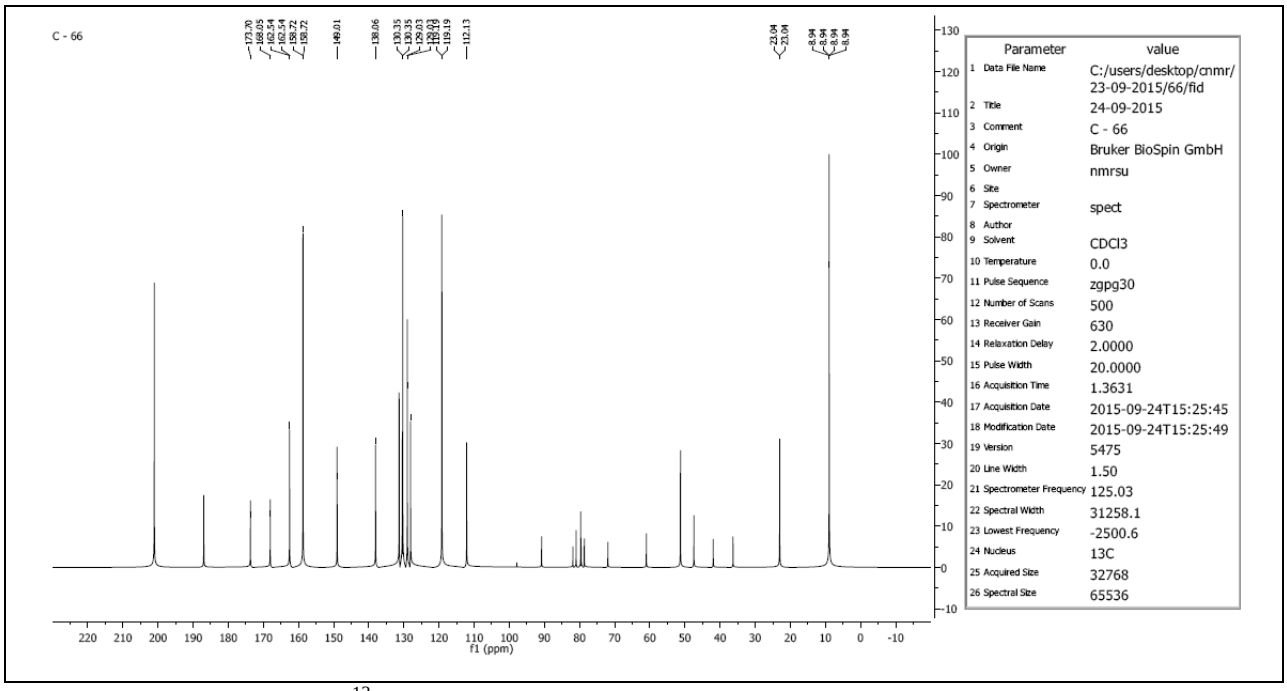


Chart-4.21 ^{13}C NMR spectrum of 4-(4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-yloxy)phenyl)-6-phenylpyrimidin-2-thiol (4.056)

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