Chapter-V

Synthesis of benzodiazepino, benzothiazepino, benzoxazepino incorporated analogues of 1,3,5-s-triazine linked on its 6-position through a phenoxyl bridge

Abstract

This chapter describes the synthesis of 6-(phenoxyl-4')-4''-1,5-benzodiazepino, 1,5-benzothiazepino, and 1,5-benzoxazepino incorporated analogues of 1,3,5-s-triazines **5.062 - 5.067** from the corresponding chalcone and dimethylaminomethylene ketone derivatives following the strategies depicted in the schemes **5.18 - 5.23** respectively. The structures of the compounds were unequivocally established on the basis of their spectral data.

5.1 Introduction

Benzodiazepines are highly versatile substrates[1] that have found wide application in the synthesis of a variety of heterocyclic systems. Due to its wide range of biological properties they have been considered as the most important privileged structures for the discovery of potent drug molecules. Moreover, benzodiazepine derivatives have been used as as a dipeptide mimics or non peptide scaffolds in search of peptidomimetics either as a ligand of diverse G-protein coupled receptors such as fibrinogen, cholecystokinin, integrin, vassopressin, bradykinin, oxytocin or k-opioid receptors or as enzyme inhibitors[2-3]. Azepines due to their diverse pharmocological properties form an important pharmacophore in exhibiting broad spectrum of biological properties[4-6] including the anti-HIV activity.

Incorporation of certain bioactive pharmacophores in the existing drug molecule sometimes exerts an immense influence on the biological properties of the parent molecule. Depending on these observations it was believed that incorporation of the bioactive azepine moiety[4] onto the s-triazine motif in the same molecular framework through a phenoxyl bridge could produce interesting series of compounds with enhanced biological properties.

This chapter describes the synthesis of various azepine incorporated analogues of s-triazine from the corresponding active synthons, the dimethylaminomethylene ketone and chalcone. The heterocyclic systems with seven atoms have shown vast commercial success and their benefits to society in the modern treatment of mental illness (and in a wide variety of other diseases) which has caused the chemistry of these systems to evolve into a major area of research in the field of medicines[7].

5.2 Biological aspects

5.2.1 Biological aspects of benzodiazepines:

Benzodiazepines and their polycyclic derivatives due to their broad spectrum of biological activities have found wide applications in pharmaceutical industry[8-10]. They are used as tranquilizers, as potent virucides and as a non-nucleoside inhibitor of HIV-1 reverse transcriptase[11-12] and thus constitute a class of psychopharmacopea. They exhibit antifungal, anti-inflammatory, analgesic[13], antidepressive, sedative[14], antibacterial[15], antifeedant[16], antiinflammatory, antihypnotic, anticonvulsant[17] properties.

Few derivatives of benzodiazepines are known to be used as muscle relaxant[18], anticonvulsant[19], antiobesity[20], calcium channel blockers[21] and vassopressin receptor antagonists[22-23]. Few of its derivatives are highly pharmacologically active compounds such as TIBO (**5.001)** and Nevirapine (**5.002) [Fig- 5.01]** which are active anti-HIV agents[24-25]. Clobazam[26] and clazapine[27] act as an effective anti-epileptic and antipsychotic agents.

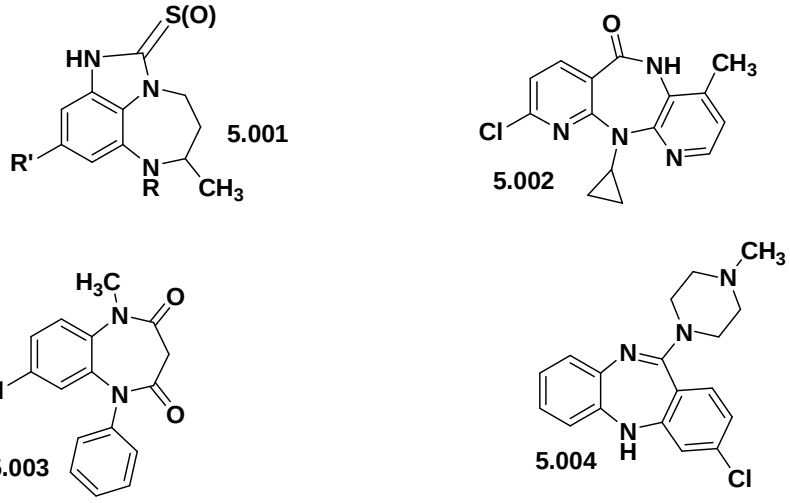


Fig-5.1

5.2.2 Biological aspects of benzothiazepines:

Benzothiazepines form another class of compounds which have been patented as chemotherapeutic agents[28]. Benzothiazepines show a wide range of biological activities such as antiasthemic, antihypertensive, analgesic, cardiovascular modulator[29], vasodialator[30], calcium antagonist, platelet aggregation inhibitor, antiulcer[31], antiamnesia, antidementia[32], antifungal[33], antiinsecticidal[34], antibacterial activities. Besides imparting antitubercular activity, incorporation of fluorine to the benzothiazepine nucleus not only enhances the antifungal activity of the compound[4] it also enhances the pharmacological properties by increasing the solubility in lipid materials and fat deposits in the body[4]**.** They have recently been reported to have anticancer[35], haemodynamic[36] antitumour[37], and spasmolytic[38] properties. Benzothiazepine derivatives such as 'Diltiazem' **(5.005)** have been used in the treatment of hypertension, angina pectoris, arrhythmias and other related cardiac disorders, it also increases the supply of blood and oxygen to the heart[39-40]**.** Clothiapine **(5.006)** acts as a 5-HT_2 receptor and also has antimuscarinic potential[41].

Thiazesim **(5.007)** used as psychotopic agents[42], and clentiazem **(5.008)** have been reported to have antiatherogenic effect[43]**.**

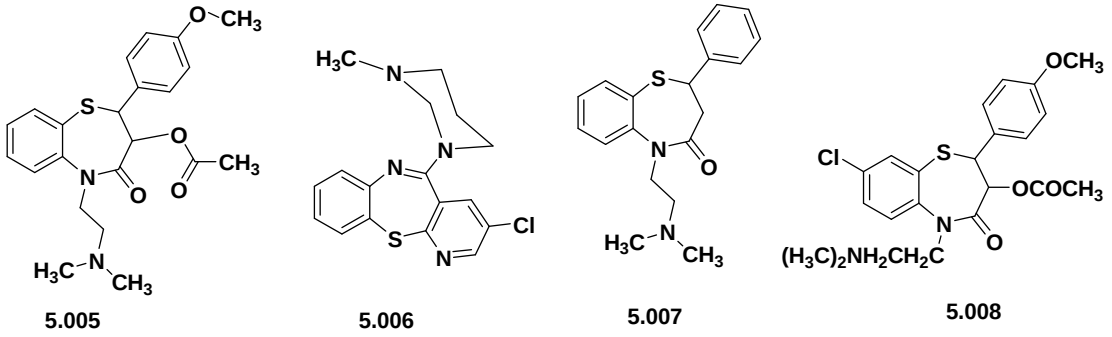


Fig.-5.2

5.2.3 Biological aspects of benzoxazepines:

Benzoxazepines have been mainly known for their biological and pharmaceutical properties. They show wide range of biological activities such as anticonvulsant[40,41] and CNS depressant activities. They have been used as an effective orexin receptor antagonist for the treatment of obesity and sleep disorders[43]**.** Loxapine **(5.009)** has neuroleptic biochemical profile with mainly antidopaminergic activiy at D_2-type receptors and are effective for the treatment of schizophrenia[44] and hence are used as antipsychotic agents. Amoxapine[45] **(5.010)** binds to D2 receptors and inhibits the norepinephrine neurotransmitter to block neuronal norepinephrine re-uptake and hence acts as an antidepressant.

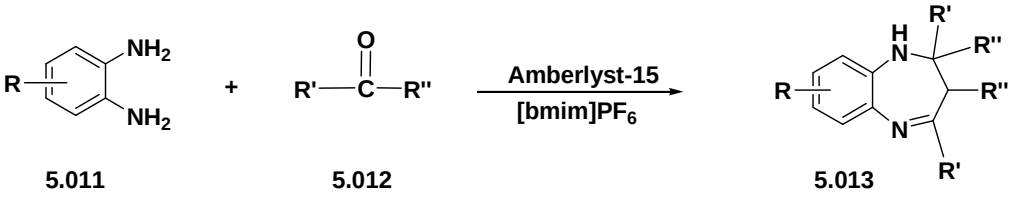
Fig.-5.3

5.3 Synthetic Aspects

On account of its broad spectrum of medicinal properties, the development of a variety of methods for the synthesis of these molecules has been devised. This has led to the accumulation of variety of synthetic strategies to this class of compounds. In reference to this, it is considered necessary to represent a brief outline of the available literature for the synthesis of these heterocyclic systems.

5.3.1 Synthesis of 1,5-benzodiazepines:

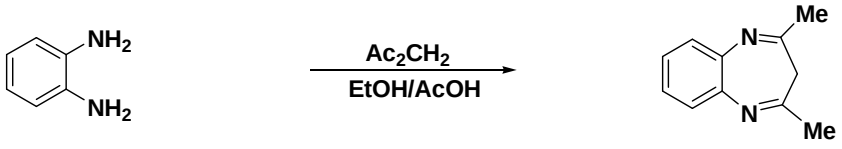
i) Various ketones **5.012** on raection with *o*-phenylenediamine derivative **(5.011)** in presence of Amberlyst-15[46] gives 1,5 benzodiazepine derivatives **(5.013) (Scheme-5.01).**



5.011 5.012 5.013

Scheme-5.01

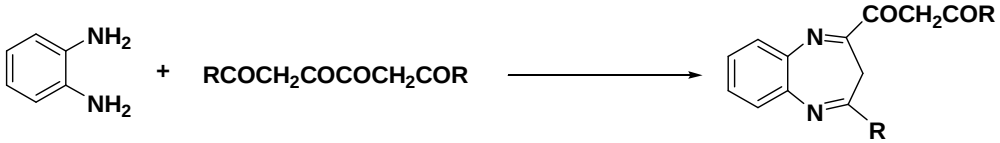
ii) Condensation of *o*-phenylenediamine **(5.014)** with acetylacetone in ethanol-acetic acid forms 1,5 benzodiazepine derivatives[47] **(5.015) (Scheme-5.02).**



5.014 5.015

Scheme-5.02

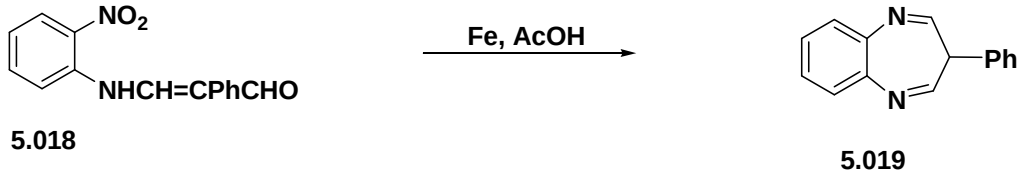
iii) 1,5 Benzodiazepine **(5.017)** can be synthesized by the reaction of tetraketones **5.016** with *o*-phenylenediamine **(5.014) (Scheme-5.03)[48].**



5.014 5.016 5.017

Scheme-5.03

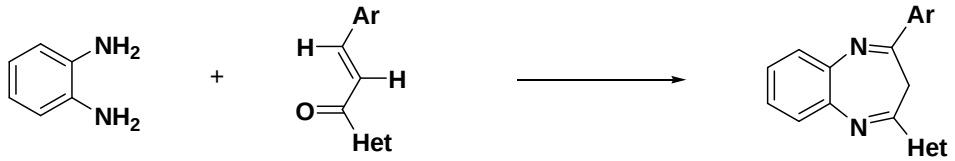
iv) The reduction of *o*-nitroamine derivative **5.018** with iron and acetic acid or tin and hydrochloric acid[49] produces 3-phenylbenzodiazepine **(5.019) (Scheme-5.04).**



5.018 **5.019**

Scheme-5.04

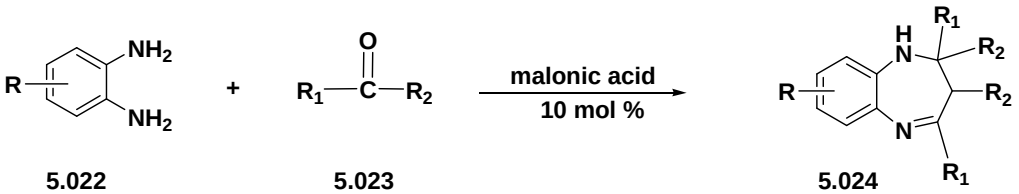
v) Chalcones **5.020** on reaction with **5.014** in presence of 1-2 drops of piperidine in alcoholic solution produces **5.021**[50] **(Scheme-5.06).**



5.014 **5.020** **5.021**

Scheme-5.05

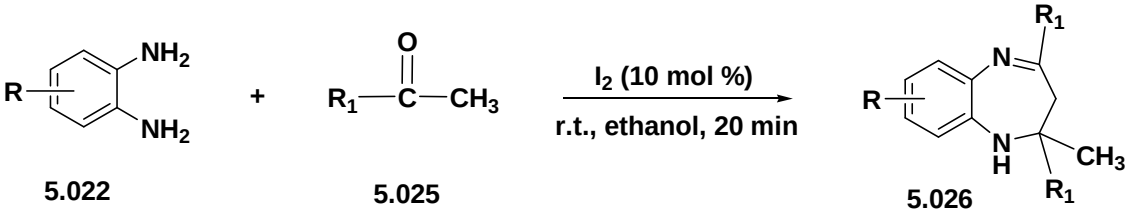
vi) 1,5-Benzodiazepine **(5.024)** can be synthesized by the reaction of *o*-phenylenediamine **(5.022)** and ketone **5.023** in presence of 10% cesium chloride[51] **(Scheme-5.06).**



5.022 **5.023** **5.024**

Scheme-5.06

vii) An improved method for the synthesis of various 1,5-benzodiazepine **(5.026)** from *o*-phenylenediamine **5.022** and acetone **5.025** at room temperature is achieved by the use of molecular iodine as a catalyst[52] **(Scheme-5.07).**

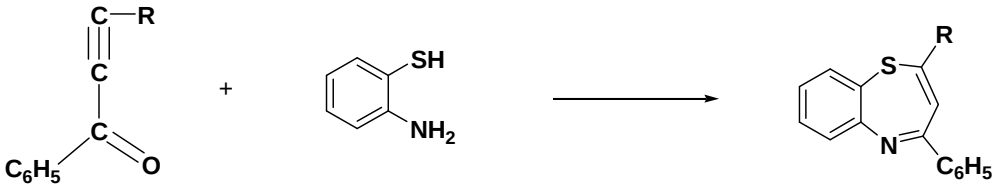


5.022 **5.025** **5.026**

Scheme-5.07

5.3.2 Synthesis of 1,5-benzothiazepines:

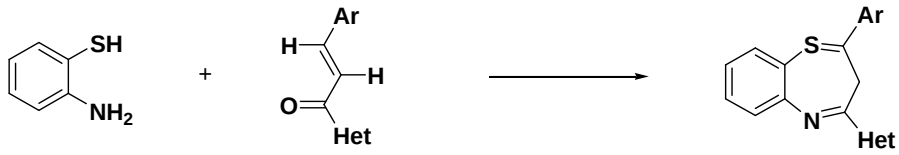
i) 2,4-Disubstituted-1,5-benzothiazepines **(5.029)** can be synthesized by the reaction of 2-aminothiophenol **5.028** with acetylenic ketones[53] **(5.027) (Scheme-5.08).**



5.027 **5.028** **5.029**

Scheme-5.08

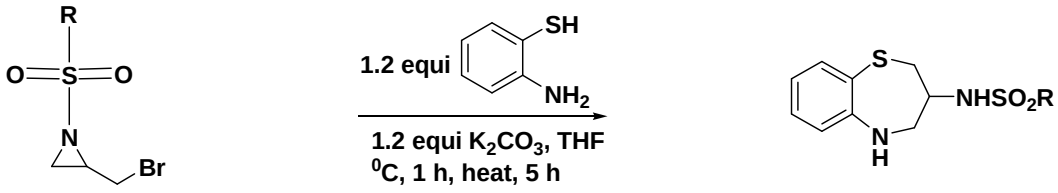
ii) Chalcones **5.008** on reaction with 2-aminothiophenol **5.028** in presence of 1-2 drops of piperidine in alcoholic solution produces **(5.030)**[54] **(Scheme-5.09).**



5.028 **5.020** **5.030**

Scheme-5.09

iii) On refluxing 2-(bromomethyl)aziridines **(5.031)** and 1.2 equivalents of 2-aminothiophenol in THF in presence of potassium carbonate for 5 h produces 3-sulphonamido-1,5-benzodiazepines[55] **(5.032) (Scheme-5.10).**

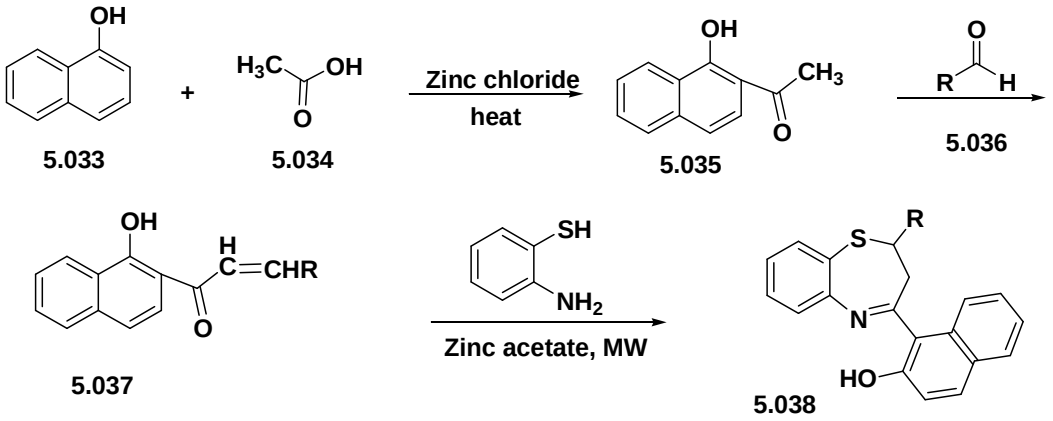


5.031 **R= Ph, 4-MeC$_6$H$_4$, Me** **5.032**

Scheme-5.10

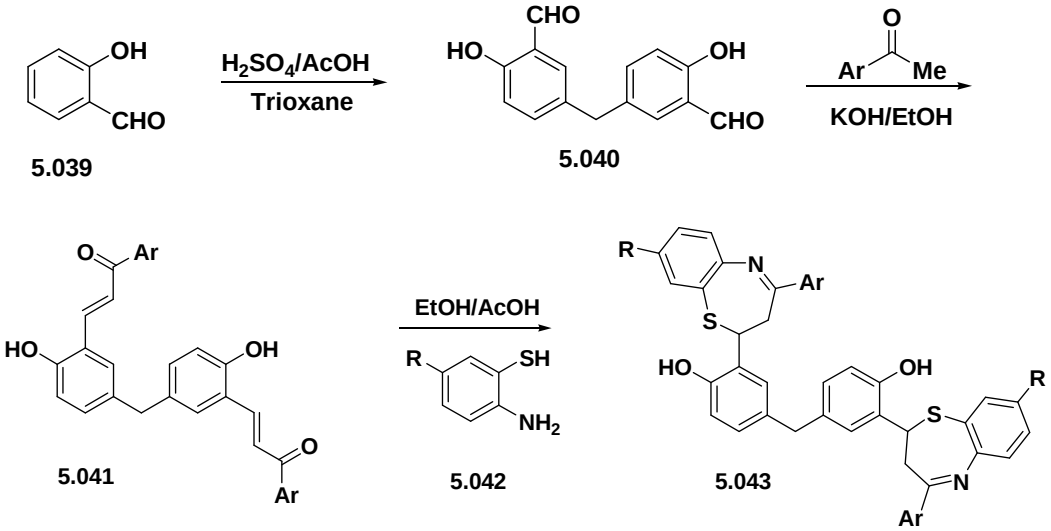
iv) α-Naphthol **(5.033)** with acetic acid **(5.034)** undergoes acetylation, which on subsequent reaction with aromatic aldehydes **(5.036)** forms substituted-prop-2-en-one **(5.037)**, cylcocondensation of it with 2-aminothiophenol in presence of zinc acetate under microwave

irradiation produces 2,3-dihydro-2-substituted-4-(naphthalene-2'-ol)-yl-1,5-benzodiazepines[56] **(5.038) (Scheme-5.11).**



Scheme-5.11

v) Salicylaldehyde **(5.039)** with trioxane in presence of a mixture of acetic acid and conc. sulphuric acid forms 5-(3-formyl-4-hydroxybenzyl)-2-hydroxybenzaldehyde **(5.040)** which on condensation with methyl ketones in presence of 60% aqueous KOH at room temperature forms methylene-bis-chalcones **(5.041)**. It on refluxing with 2-amino-5-methythiophenol **(5.042)** in presence of acetic acid produces methylene-bis-8-substituted-[1,5]-benzothiazepines **(5.043)** in an excellent yield[57] **(Scheme-5.13).**



Scheme-5.13

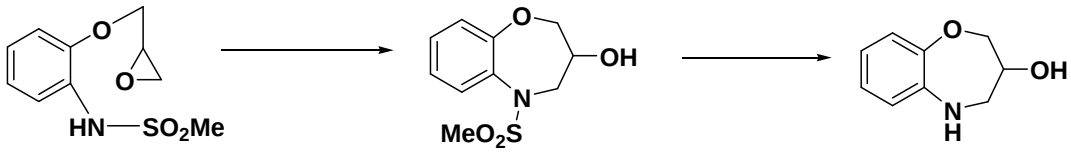
5.3.3 Synthesis of 1,5-benzoxazepines:

i) On reacting 2-aminophenol **(5.044)** and 1,3-dibromopropane **(5.045)** in anhydrous DMF in presence of sodium hydride[58] 2,3,4,5-tetrahydro-1,5-benzoxazepine **(5.046)** has been synthesized **(Scheme-5.14).**

5.044 5.045 5.046

Scheme-5.14

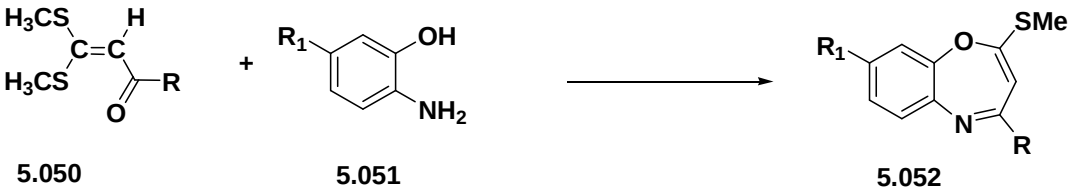
ii) *N*-Mesylated-2-aminophenol derivative **(5.047)** on cyclization produces 3-hydroxy-5-(methylsulphonyl)-2,3,4,5-tetrahydro-1,5-benzoxazepine **(5.048)** which on demesylation affords 3-hydroxy-2,3,4,5-tetrahydro-1,5-benzoxazepine[59] **(5.049) (Scheme-5.15).**



5.047 5.048 5.049

Scheme-5.15

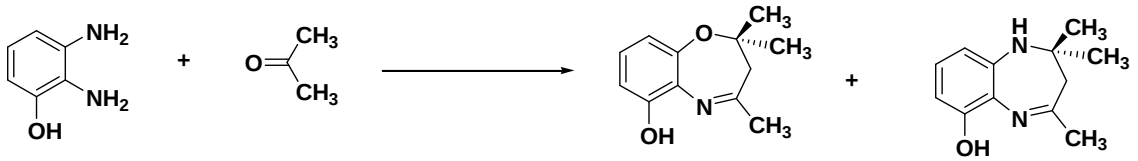
iii) Treatment of α-oxoketene-*S*,*S*-acetals **(5.050)** with 2-aminophenol **(5.051)** produces the corresponding 1,5-benzoxazepine[58] **(5.052) (Scheme-5.16).**



5.050 5.051 5.052

Scheme-5.16

iv) 2,3-Diaminophenol **(5.053)** and ketones **(5.054)** through microwave assisted acid catalysis synthesizes amino-1,5-benzoxazepines **(5.055)** and 1,5-benzodiazepines **(5.056)** in 3:4 ratio in one pot solvent free conditions[60] **(Scheme-5.17).**



5.053 5.054 5.055 5.056

Scheme-5.17

5.4 Present work

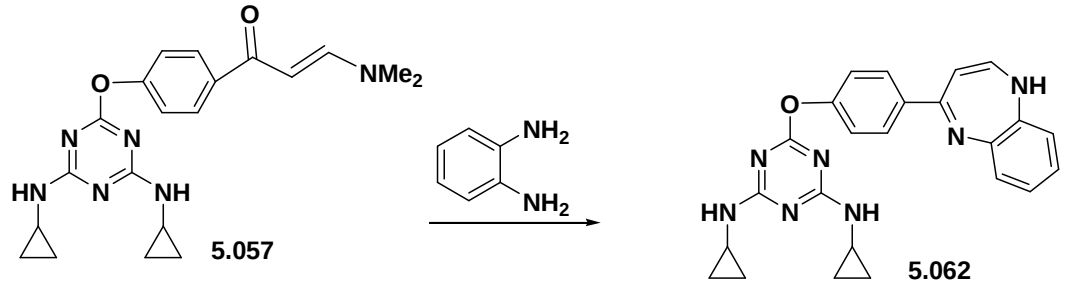
As already stated s-triazine derivatives having active pharmacophores on their 2,4 and 6 positions have been reported in the literature to exhibit impressive pharmocological properties[61-72]**.** Besides this, azepines are also found to be pharmacologically active[1-4]. In view of this, it was believed that incorporation of azepine nucleus to s-triazine framework could produce compounds with enhanced biological properties.

Dimethylamino methylene ketones and chalcones can construct a variety of fused heterocyclic systems. In view of the interesting properties exhibited by azepines[9,37,41] and s-Triazine, our aim in the present work was to synthesize s-triazine molecules incorporated in its molecule with the azepine nucleus, 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 which was achieved through its dimethylaminomethylene ketone and chalcone derivatives.

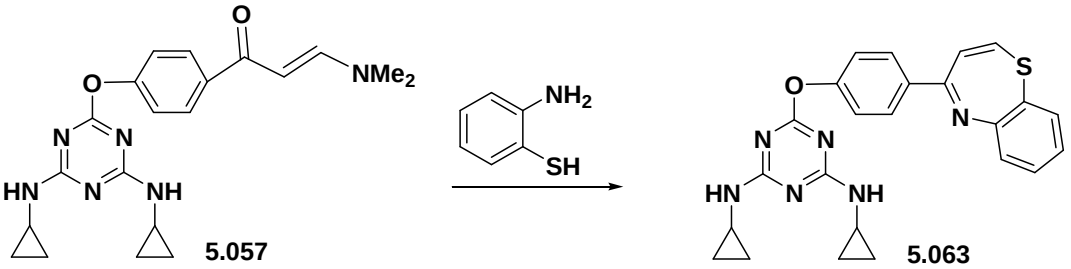
5.5 Results and Discussion:

In view of the impressive pharmacodynamic applications[72,31,22] of benzo-substituted 1,5-azepine and its derivatives, it was considered of interest in the present work to construct a system, which carried benzo-substituted 1,5 azepines, and s-triazine nucleus in the same molecular framework. The synthesis of such compounds **5.062-5.067 (Fig.-5.5)** carrying the bioactive pharmacophores was achieved in the present work from s-triazine nucleus, following the strategy shown in the schemes- **5.18** to **5.23**. This synthesis consisted of the treatment chalcones and dimethyl aminomethylene ketone with *o*-phenylenediammine, *o*-aminothiophenol, *o*-aminophenol in ethanol to form the corresponding 1,5-benzodiazepines **(5.062** and **5.065) (Scheme-5.18** and **5.21)**, 1,5-benzothiazepine **(5.063** and **5.066) (Scheme-5.19** and **5.22)**, and 1,5-benzoxazepine

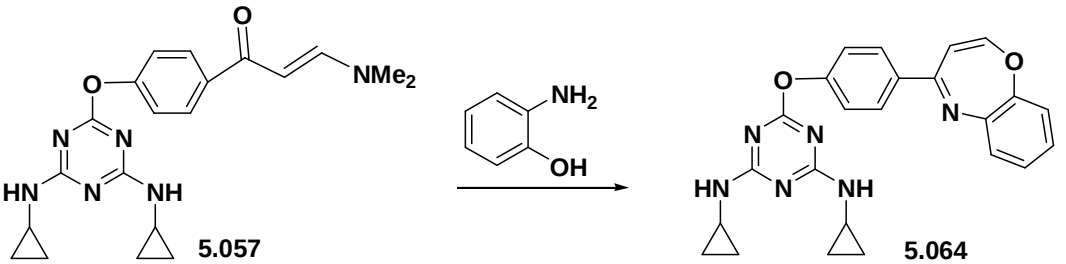
(5.064 and **5.067) (Scheme-5.20** and **5.23)** respectively. Structures of the compounds were unambiguously on the basis of their elemental and spectral analysis.



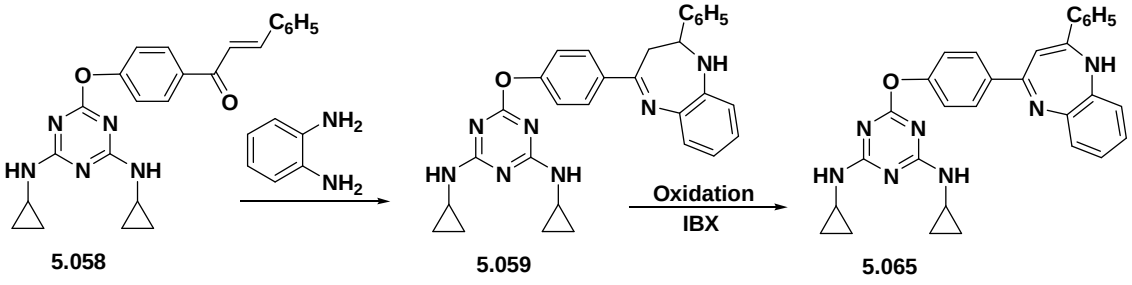
Scheme-5.18



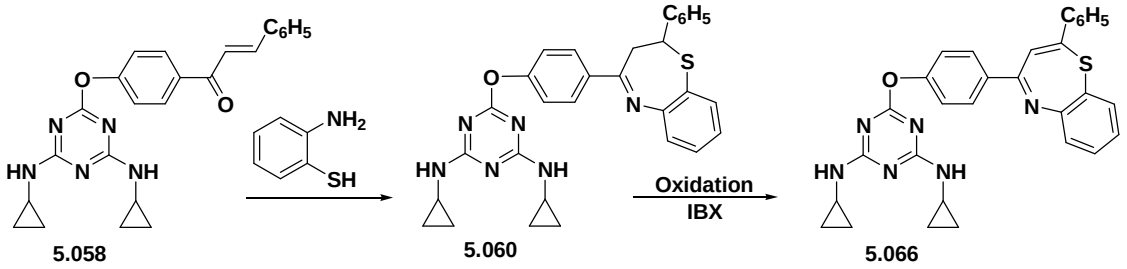
Scheme-5.19



Scheme-5.20

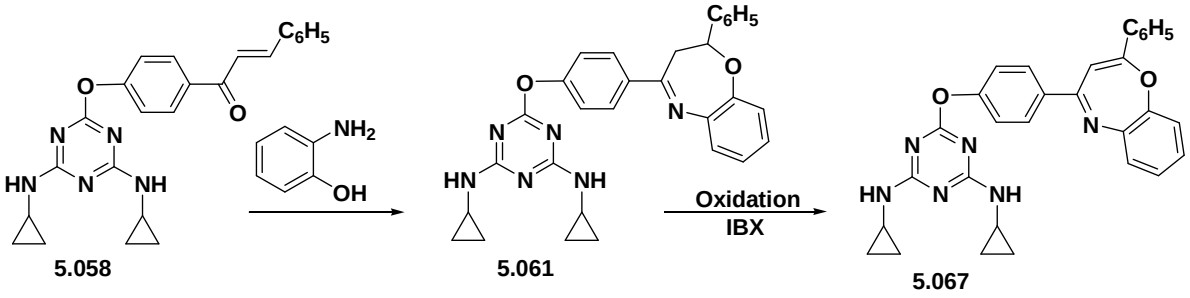


Scheme-5.21



5.058 5.060 5.066

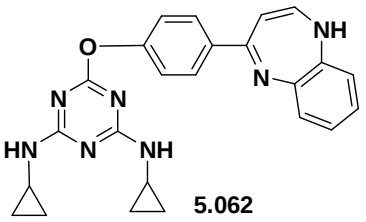
Scheme-5.22



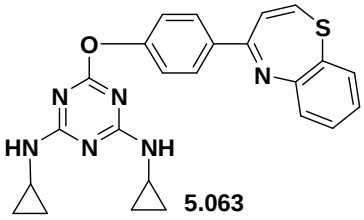
5.058 5.061 5.067

Scheme-5.23

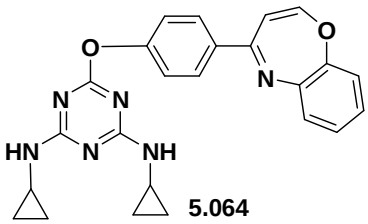
Structure of the compounds whose synthesis is described in this chapter:



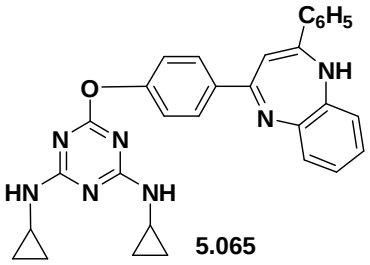
5.062



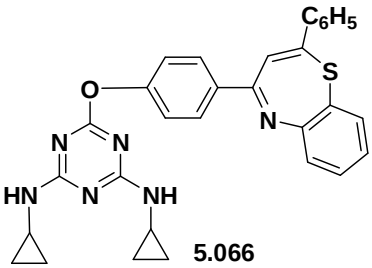
5.063



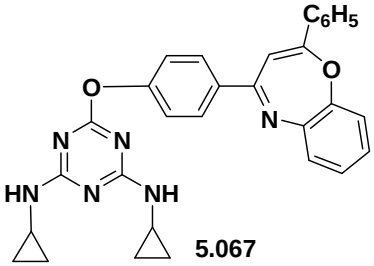
5.064



5.065



5.066



5.067

Fig.-5.9

Table 5.01: Physical and analytical data of the compounds 5.062-5.067:

S. No.	Comd. No.	Molecular Formula	M.W.	M.P. (^{0}C)	Yield (%)	Elemental analysis (calcd/exp)			
						C	H	N	S
1.	5.062	$C_{24}H_{23}N_7O$	425	176-178	67%	67.75/ 66.19	5.45/ 5.01	23.04/ 23.95	
2.	5.063	$C_{24}H_{22}N_6OS$	442	187-189	75%	65.14/ 64.90	5.01/ 5.21	18.99/ 17.70	7.25/ 6.99
3.	5.064	$C_{24}H_{22}N_6O_2$	426	182-184	71%	67.59/ 66.20	5.20/ 4.80	19.71/ 19.45	
4.	5.065	$C_{30}H_{17}N_7O$	501	170-172	70%	71.84/ 70.40	5.43/ 4.40	19.55/ 18.45	
5.	5.066	$C_{30}H_{26}N_6OS$	518	181-183	80%	69.48/ 68.10	5.05/ 4.80	16.20/ 15.98	6.18/ 5.90
6	5.067	$C_{30}H_{26}N_6O_2$	502	165-167	75%	71.70/ 70.45	5.21/ 4.45	16/.72 15.44	

Table 5.02: Spectral data of compounds:

S. No.	Compd. No.	IR(KBr)cm^{-1}	^{1}H NMR
1.	5.062	3380 [NH str.] 3000[C-H str. ArH] 1640 [NH bending] 1590 [C=C str. ArH] 1560 [C=N str.] 1170 [C-N str.] 1090 [C-O str.] 824 [s-triazine]	11.53 [1H, s, NH, benzodiazepine] 8.57 [1H, s, CH (benzodiazepine)] 7.50-6.92 [4H, dd, phenoxyl] 7.27 [1H, s, CH, phenyl] 7.10 [1H, s, CH, phenyl] 6.78 [1H, s, CH, phenyl] 6.62 [1H, s, CH, phenyl] 5.24 [1H, s, CH, benzodiazepine] 3.51 [2H, d, NH, cyclopropylamine] 2.40 [2H, m, CH, cyclopropylamino] 0.45- 0.69 [8H, m, CH_2, cyclopropanamino]
2.	5.063	2955 [C-H str. ArH] 1555 [C=C str. ArH] 1550 [C=N str.] 1165 [C-N str.] 1070 [C-O str.] 695 [C-S str.] 804 [s-triazine]	6.93-7.50 [4H, dd, CH, phenoxyl] 7.49 [1H, s, CH, phenyl] 7.46 [1H, s, CH, phenyl] 7.29 [1H, s, CH, phenyl] 7.26 [1H, s, CH, phenyl] 6.70 [1H, s, CH, benzothiazepine] 6.52 [1H, s, CH, benzothiazepine] 3.50 [2H, d, NH, cyclopropylamine] 2.40 [2H, m, CH, cyclopropylamino] 0.45-0.58 [8H, m, CH_2, cyclopropylamino]
3.	5.064	2950 [C-H str. ArH] 1550 [C=C str. ArH] 1590 [C=N str.] 1160 [C-N str.] 1180 [C-O str.] 807 [s-triazine]	6.93-7.50 [4H, dd, CH phenoxyl] 7.35 [1H, s, CH phenyl] 7.15 [1H, s, CH phenyl] 6.93 [1H, s, CH phenyl] 6.96 [1H, s, CH phenyl] 6.73 [1H, s, CH, benzoxazepine] 6.42 [1H, s, CH, benzoxazepine] 3.52 [2H, d, NH, cyclopropylamine] 2.40 [2H, m, CH, cyclopropylamino] 0.45- 0.59 [8H, m, CH_2, cyclopropylamino]

4.	5.065	3335 [NH str.] 2920[C-H str. ArH] 1644 [C=N str.] 1610 [NH bending] 1559 [C=C str. ArH] 1168 [C-N str.] 1021 [C-O str.] 810 [s-triazine]	9.35 [1H, s, NH, benzodiazepine] 6.92-7.51 [4H, m, phenoxyl] 7.23-7.39 [5H, m, benzene ring attached to benzodiazepine ring] 7.29 [1H, s, CH, phenyl] 7.11 [1H, s, CH, phenyl] 6.78 [1H, s, CH, phenyl] 6.65 [1H, s, CH, phenyl] 5.63 [1H, s, CH, benzodiazepine] 3.57 [2H, d, NH, cyclopropylamine] 2.40 [2H, m, CH, cyclopropylamino] 0.39-0.75 [8H, m, CH_2, cyclopropylamino]
5.	5.066	3116 [C-H str. ArH] 1510 [C=C str. ArH] 1618 [C=N str.] 1272 [C-N str.] 729 [C-S str.] 809 [s-triazine]	7.54 [1H, s, CH, phenyl] 7.51 [1H, s, CH, phenyl] 7.33 [1H, s, CH, phenyl] 7.31 [1H, s, CH, phenyl] 6.96-7.53 [4H, dd, CH, phenoxyl] 7.23-7.33 [5H, m, CH, benzene ring attached to benzothiazepine ring] 6.73 [1H, s, CH, benzothiazepine] 3.51 [2H, d, NH, cyclopropylamine] 2.41 [2H, m, CH, cyclopropylamino] 0.43-0.55 [8H, m, CH_2, cyclopropylamino]
6.	5.067	2923 [C-H str. ArH] 1540 [C=C str. ArH] 1644 [C=N str.] 1169 [C-N str.] 1075 [C-O str.] 805 [s-triazine]	6.96-7.52 [4H, dd, CH, phenoxyl] 7.38 [1H, s, CH, phenyl] 7.21 [1H, s, CH, phenyl] 7.02 [1H, s, CH, phenyl] 7.05 [1H, s, CH, phenyl]] 7.27-7.36 [5H, m, benzene ring attached to benzothiazepine ring] 6.57 [1H, s, CH, benzoxazepine] 3.53 [1H, d, NH, cyclopropylamine] 2.41 [1H, m, CH, cyclopropylamine] 0.44-0.56 [8H, m, CH_2, cyclopropylamine]

Table 5.03: MS and 13CMR spectral data of compounds:

S. N0.	Compd. No.	MS	^{13}C NMR 76-78 [$CDCl_3$ solvent]
1.	5.065	[M^+]: 501	9 [4CH_2, cyclopropylamine]; 23 [2CH, cyclopropylamine]; 92 [CH, benzodiazepine]; 119, 120, 123, 124 [CH, arene]; 121, 131 [4CH, phenoxyl]; 127, 128 [CH, benzene attached to benzodiazepine]; 134, 137, 143, 147 [C, benzodiazepine]; 136, 150 [2C, phenoxyl]; 137 [C, benzene]; 162 [2C, s-triazine]; 173 [C-O].
2.	5.066	[M^+]: 518 [M^+ +2]: 520	9 [4CH_2, cyclopropylamine]; 23 [2CH, cyclopropylamine]; 110 [CH, benzothiazepine]; 119, 130, 124, 129 [CH, arene]; 121, 131 [4CH, phenoxyl]; 127, 145, 146, 154 [C, benzothiazepine]; 128, 130 [CH, benzene attached to benzothiazepine]; 136, 150 [2C, phenoxyl]; 137 [C, benzene]; 162 [2C, s-triazine]; 174 [C-O].
3.	5.067	[M^+]: 502	9 [4CH_2, cyclopropylamine]; 23 [2CH, cyclopropylamine]; 93 [CH, benzoxazepine]; 117, 118, 124, 125 [CH, arene]; 121, 131 [4CH, phenoxyl]; 127, 128, 130 [CH, benzene attached to benzoxazepine]; 136, 150 [2C, phenoxyl]; 133 [C, benzene]; 138, 141, 148, 161, [C, benzoxazepine]; 162 [2C, s-triazine]; 174 [C-O].

5.6 Interpretation of spectral data for the elucidation of structure of compounds 5.062-5.067:

Structures of the compounds were established on the basis of their 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 **5.01**-**5.03** and the spectral graphs of the compounds are shown in the spectral charts **5.1** to **5.12.**

Infrared spectra

Appearance of a band at 3380 cm^{-1} [NH str.], and peaks at 1640 cm^{-1} [NH bending], 1560 cm^{-1} [C=N str.] of diazepine ring, with additional peaks at 3000 cm^{-1} [C-H str. ArH], 1590 cm^{-1} [C=C str. ArH] and 1090 cm^{-1} [C-O str.] and disappearance of a band at 1570 cm^{-1} [C=C str.of α,β-

unsaturated ketone] in **5.057** clearly indicated the incorporation of 1,5-benzodiazepine ring in the compound **5.062**. Similarly, the structures of the compounds **5.063** and **5.064** were ascertained on the basis of the appearance of the additional peaks at 695 cm^{-1} [C-S str. (thiazepine ring)] and at 1180 cm^{-1} [C-O str. (oxazepine ring)] in the IR spectrum of these compounds respectively.
Appearance of the peaks at 3335 [NH str. (diazepine)], 1610 [NH bending], 2920 [C-H str. ArH], 1559 [C=C str. ArH], 1644 [C=N str.] and 1168 [C-N str.] and disappearance of a band at 1558 cm^{-1} [C=C str.of α,β-unsaturated ketone] in **5.065** clearly indicated the incorporation of diazepine ring in the compound **5.065** from its precursor **5.058**. Similarly, the structures of the compounds **5.066** and **5.067** were ascertained on the basis of the appearance of additional peaks at 729 cm^{-1} [C-S str. (thiazepine ring)] and at 1075 cm^{-1} [C-O str. (oxazepine ring)] in the IR spectrum of these compounds respectively.

^{1}H NMR

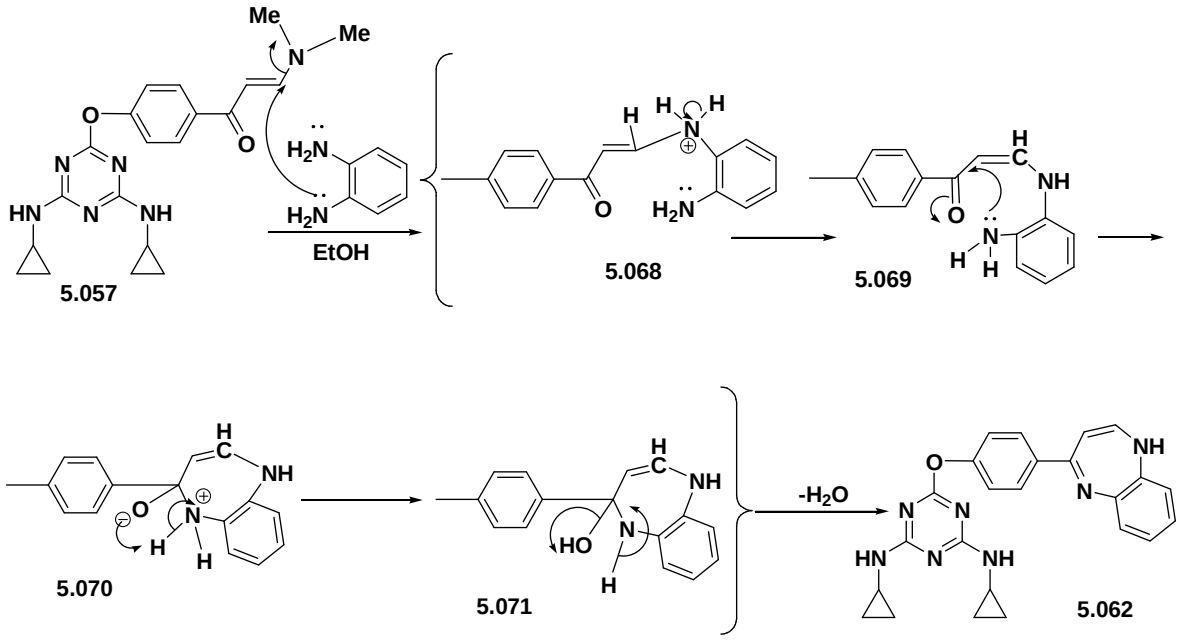
The formation of benzodiazepine ring in the compound **5.062** was established by the appearance of a downfield singlet at δ 11.53 for one proton of NH, singlets at δ 8.57 and δ 5.24 accounted for the presence of a diazepine ring in the compound, a complex multiplet at δ 6.62 – δ 7.50 was attribitued to the benzene ring and phenoxyl substituent and disappearance of doublets at δ 8.12 and δ 5.66 for CH=CH group and a sharp singlet at δ 2.63 for two methyl groups attached to CH-N-$(CH_3)_2$ confirmed the formation of **5.062** from its precursor **5.057.**
Similarly the structures of the compounds **5.063** and **5.064** were established on the basis of its ^{1}H NMR spectra. They showed the signals approximately in the same regions, with the absence of signal for one proton of 1,5-benzodiazepine ring.

The structure of the compound **5.065** was established by the appearance of singlet at δ 9.35 for one proton of NH of 1,5-diazepine ring, a singlet at δ 5.63 which accounted for one proton of diazepine ring, a multiplet at δ 6.65 - δ 7.29 was due to four protons of benzene ring attached to 1,5-benzodiazepine ring and a complex multiplet at δ 6.92 -δ 7.51 was attributed to the benzene ring and phenoxyl substituent.

Similarly the structures of the compounds **5.066** and **5.067** were established on the basis of its ^{1}H NMR spectra. They showed the signals approximately in the same regions, with the absence of signal for one proton of 1,5-benzodiazepine ring.

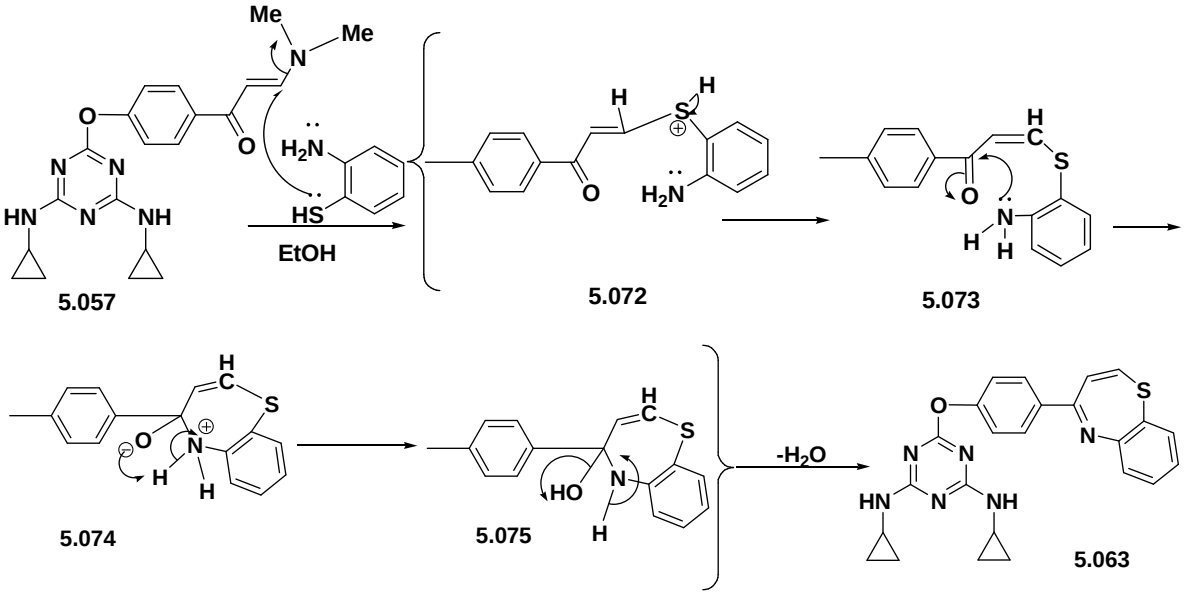
5.7 Mechanism of formation of compounds (5.062-5.067):

5.7.1 Mechanism of formation of compound 5.062 from 5.057:



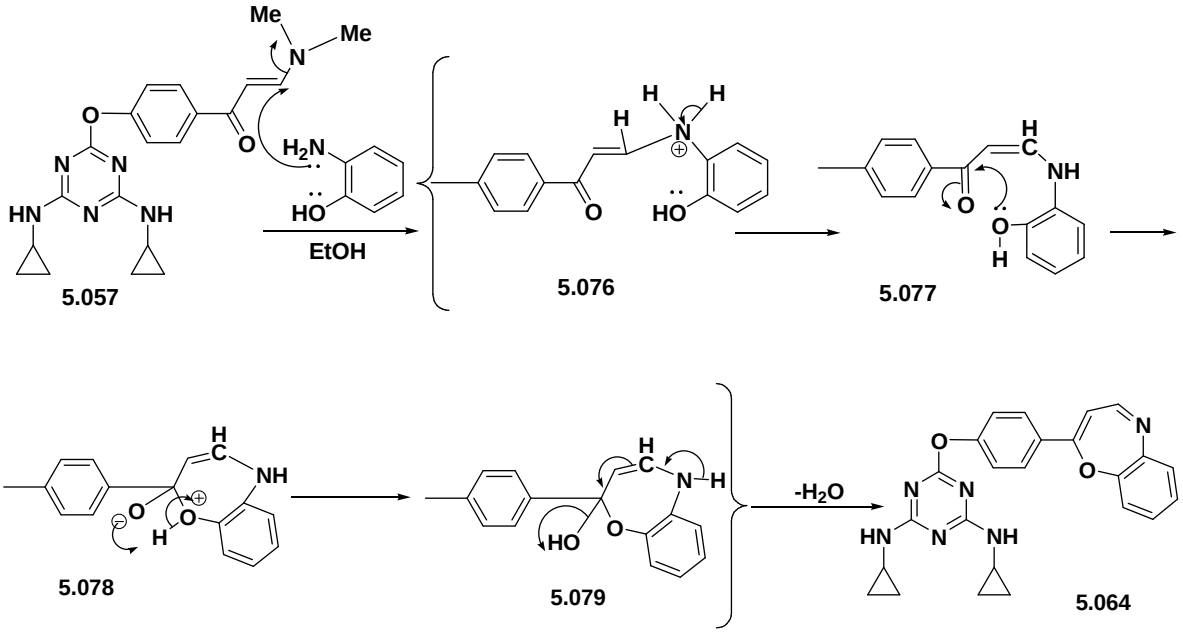
Scheme-5.24

5.7.2 Mechanism of formation of compound 5.063 from 5.057:



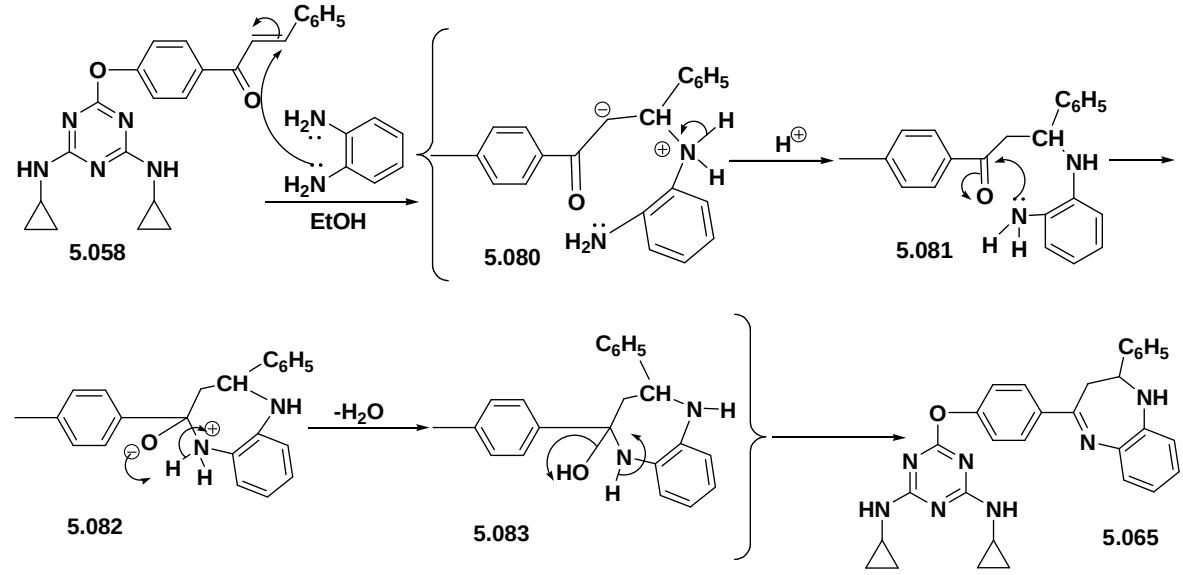
Scheme-5.25

5.7.3 Mechanism of formation of compound 5.064 from 5.057:



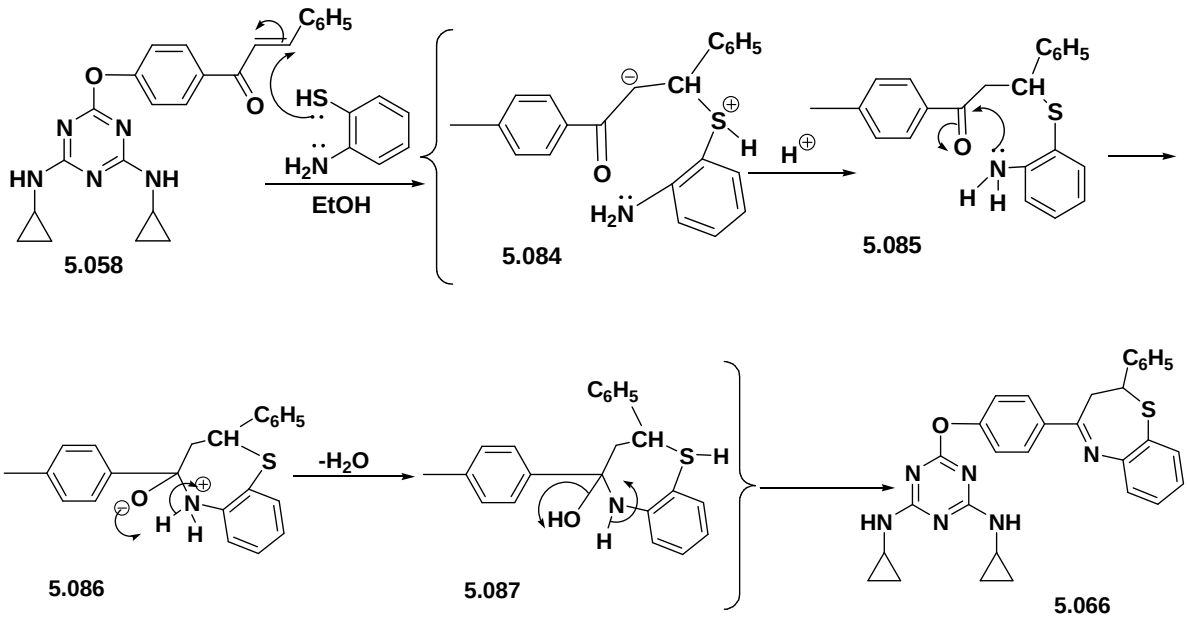
Scheme-5.26

5.7.4 Mechanism of formation of compound 5.065 from 5.058:



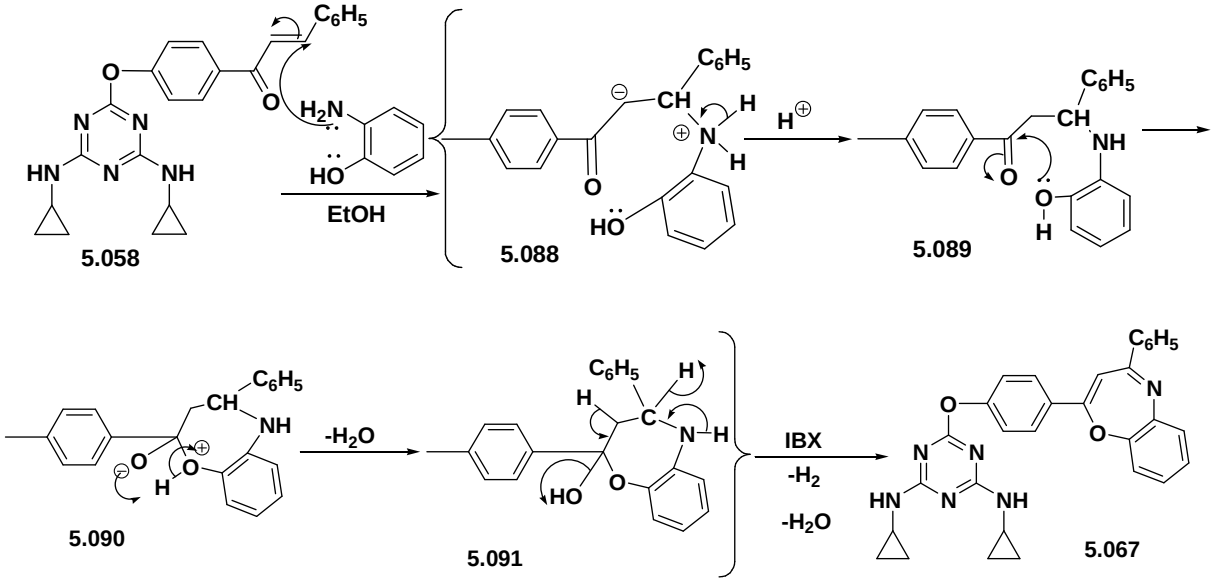
Scheme-5.27

5.7.5 Mechanism of formation of compound 5.066 from 5.058:



Scheme-5.28

5.7.6 Mechanism of formation of compound 5.067 from 5.058:



Scheme-5.29

5.8 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 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 5.01- 5.03.**

Synthetic procedures:

Preparation of 6-(4-((2Z,4E)-1*H*-benzo[b][1,4]diazepin-4-yl)phenoxy)-N^2,N^4-dicyclopropyl-1,3,5-triazine-2,4-diamine (5.062):

A mixture of *o*-phenylenediamine (1.08 g, 0.01 mol), dimethylaminomethylene ketone derivative **(5.057)** (0.532 g, 0.0014 mol) in ethanol (25 ml) was refluxed for 14 h. After distilling off the solvent under reduced pressure the residue was quenched in crushed ice and extracted with chloroform, washed with water and dried over anhydrous Na_2SO_4 to give **5.062,** (yield 66 %); m.p. 176-178 ^{0}C.

Preparation of 6-(4-((2Z,4E)-benzo[b][1,4]thiazepin-4-yl)phenoxy)-N^2,N^4-dicyclopropyl-1,3,5-triazine-2,4-diamine (5.063):

A mixture of *o*-aminothiophenol (1.25 g, 0.01 mol), dimethylaminomethylene ketone derivative **(5.057)** (0.68 g, 0.0014 mol) in ethanol (25 ml) was refluxed for 15 h. After distilling off the solvent under reduced pressure the residue was quenched in crushed ice and extracted with chloroform, washed with water and dried over anhydrous Na_2SO_4 to give **5.063,** (yield 66 %); m.p. 187-189 ^{0}C.

Preparation of 6-(4-((2Z,4E)-benzo[b][1,4]oxazepin-4-yl)phenoxy)-N^2,N^4-dicyclopropyl-1,3,5-triazine-2,4-diamine (5.064):

A mixture of *o*-aminophenol (1.09 g, 0.01 mol), dimethylaminomethylene ketone derivative **(5.057)** (0.380 g, 0.001 mol) in ethanol (20 ml) was refluxed for 15 h. After distilling off the solvent under reduced pressure the residue was quenched in crushed ice and extracted with

chloroform, washed with water and dried over anhydrous Na_2SO_4 to give **5.064,** (yield 66 %); m.p. 182-184 ^{0}C.

Preparation of 6-(4-((2Z,4E)-2-phenyl-1*H*-benzo[b][1,4]diazepin-4-yl)phenoxy)-*N*^{2},*N*^{4}-dicyclopropyl-1,3,5-triazine-2,4-diamine (5.059):

To the mixture of chalcone derivative **(5.058)** (1.23 g, 0.003 mol) and *o*-phenylenediamine (1.08 g, 0.01 mol) in ethanol (20 ml) was added 2-3 drops of piperidine and refluxed for 15 h and then 1.0 ml of AcOH was added to it, again refluxed for 2 h. Ater distilling off the solvent it was allowed to stand at room temperature. The solid separated out was filtered, washed with 20 ml of cold aqueous ethanol (50:50 by v/v) and dried to give **5.059,** (yield 66 %); m.p. 168-170 ^{0}C.

Preparation of 6-(4-((2Z,4E)-2-phenylbenzo[b][1,4]thiazepin-4-yl)phenoxy)-*N*^{2},*N*^{4}-dicyclopropyl-1,3,5-triazine-2,4-diamine:

To the mixture of chalcone derivative **(5.058)** (0.454 g, 0.0011 mol) and *o*-aminothiophenol (0.70 g, 3.1 mmol) in ethanol (20 ml) was added 2-3 drops of piperidine and refluxed for 15 h and then 1.0 ml of AcOH was added to it, again refluxed for 2 h. Ater distilling off the solvent it was allowed to stand at room temperature. The solid separated out was filtered, washed with 20 ml of cold aqueous ethanol (50:50 by v/v) and dried to give **5.060,** (yield 66 %); m.p. 180-182 ^{0}C.

Preparation of 6-(4-((2Z,4E)-2-phenylbenzo[b][1,4]oxazepin-4-yl)phenoxy)-*N*^{2},*N*^{4}-dicyclopropyl-1,3,5-triazine-2,4-diamine:

To the mixture of chalcone derivative **(5.058)** (0.454 g, 0.0011 mol) and *o*-aminophenol (0.70 g, 10.1 mol) in ethanol (20 ml) was added 2-3 drops of piperidine and refluxed for 15 h and then 1.0 ml of AcOH was added to it, again refluxed for 2 h. Ater distilling off the solvent it was allowed to stand at room temperature. The solid separated out was filtered, washed with 20 ml of cold aqueous ethanol (50:50 by v/v) and dried to give **5.061,** (yield 66 %); m.p. 164-166 ^{0}C.

General procedure for the oxidation of 5.059, 5.060 and 5.061

To a solution of azepine (1.5 mmol) in DMSO (1.0 ml) was added iodoxybenzoic acid (0.4 g, 1.53 mmol) and stirred at 45 ^{0}C for 13 h. After cooling the mixture to room temperature saturated solution of $Na_2S_2O_3$ (1.0 ml) was added to it and then basified with saturated solution of $NaHCO_3$ (1.0 ml). It was extracted with EtOAc (5.0 ml), the organic phase was washed with

water (10 ml) and brine (10 ml) and dried over $MgSO_4$, and concentrated to give the desired product.

5.065:- (yield-67%); m.p. 170-172 ^{0}C.

5.066:- (yield-75%); m.p. 181-183 ^{0}C.

5.067:- (yield-74%); m.p. 165-167 ^{0}C.

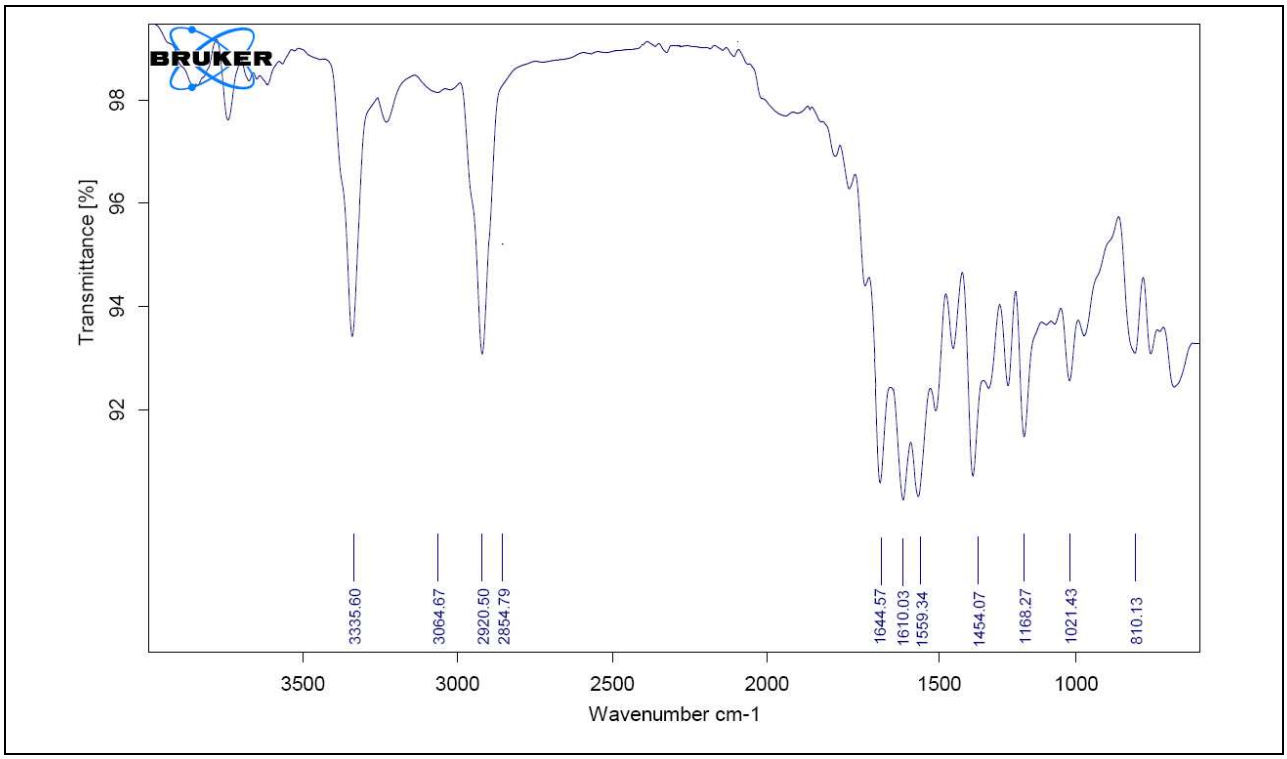


Chart-5.1 IR spectrum of 6-(4-((2*Z*,4*E*)-2-phenyl-1*H*-benzo[*b*][1,4]diazepin-4-yl)phenoxy)-N^2,N^4-dicyclopropyl-1,3,5-triazine-2,4-diamine (5.065)

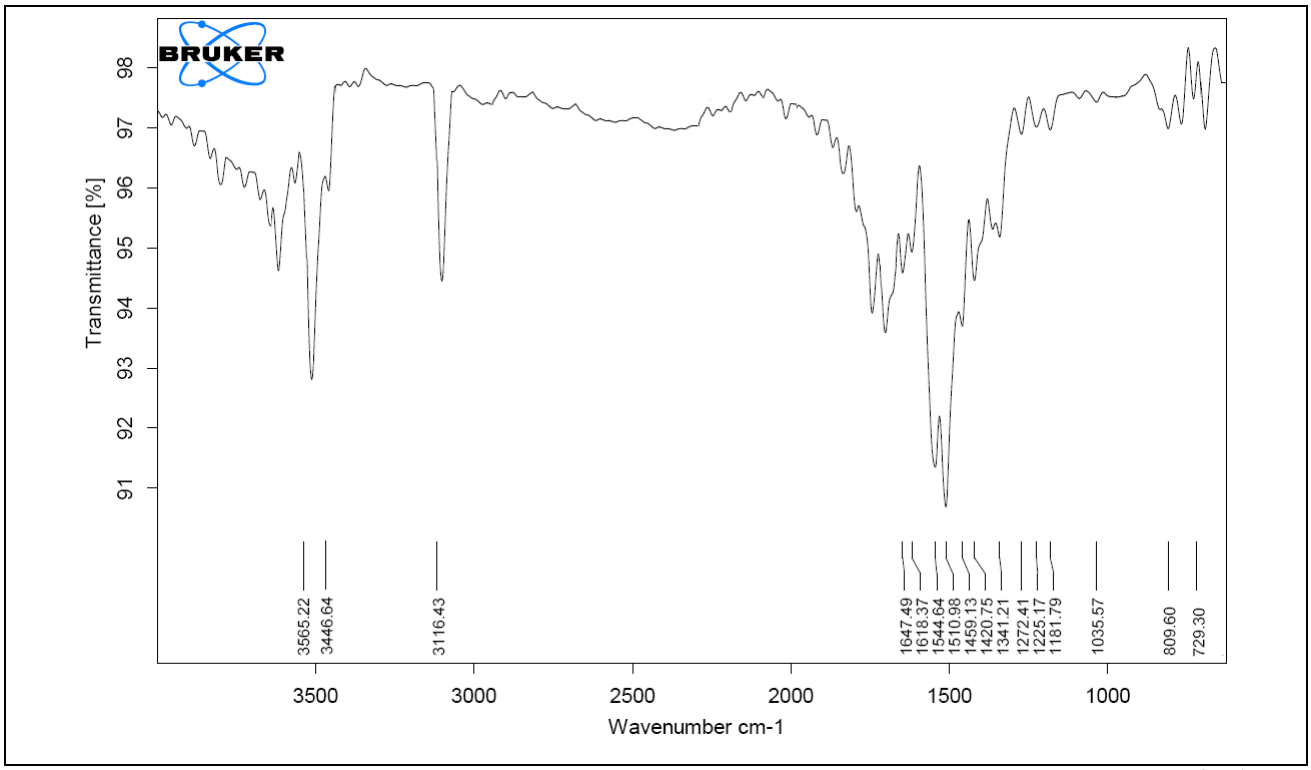


Chart-5.2 IR spectrum of 6-(4-((2*Z*,4*E*)-2-phenylbenzo[*b*][1,4]thiazepin-4-yl)phenoxy)-N^2,N^4-dicyclopropyl-1,3,5-triazine-2,4-diamine (5.066)

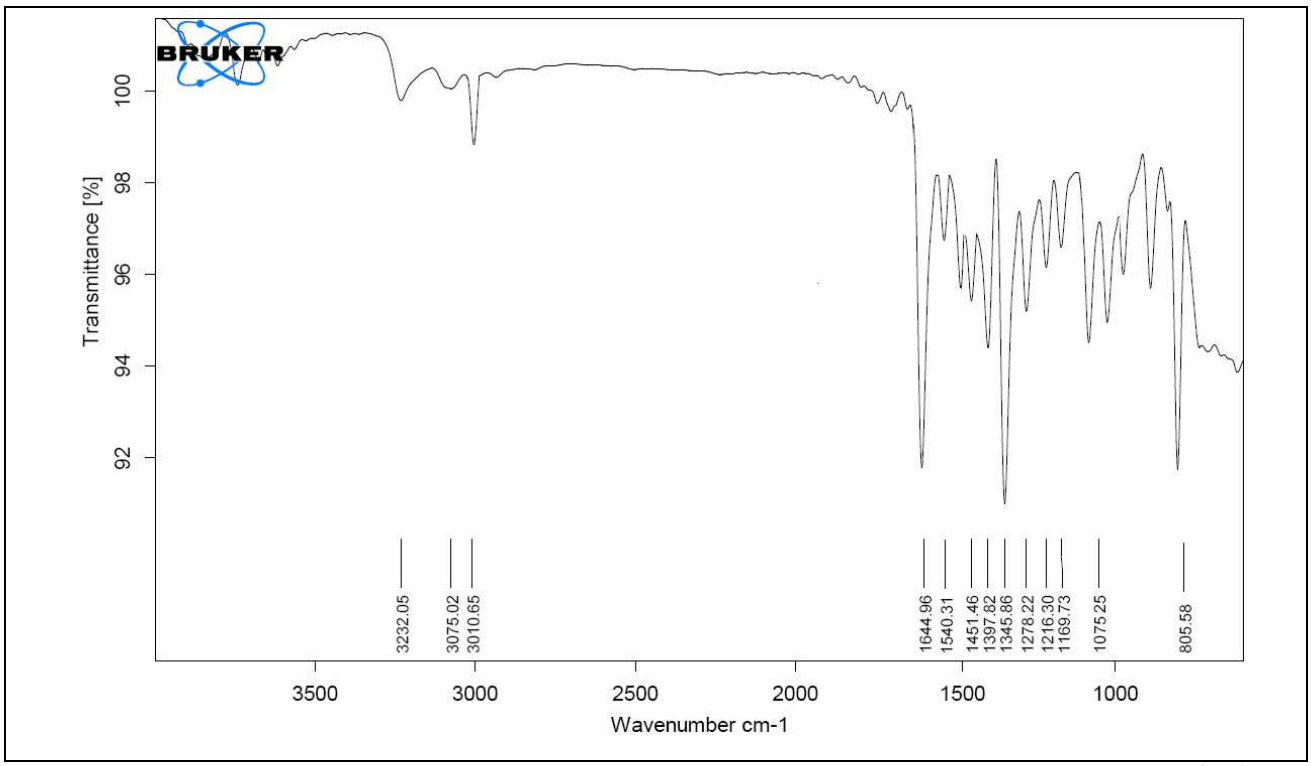


Chart-5.3 IR spectrum of 6-(4-((2*Z*,4*E*)-2-phenylbenzo[*b*][1,4]oxazepin-4-yl)phenoxy)-N^2,N^4-dicyclopropyl-1,3,5-triazine-2,4-diamine (5.067)

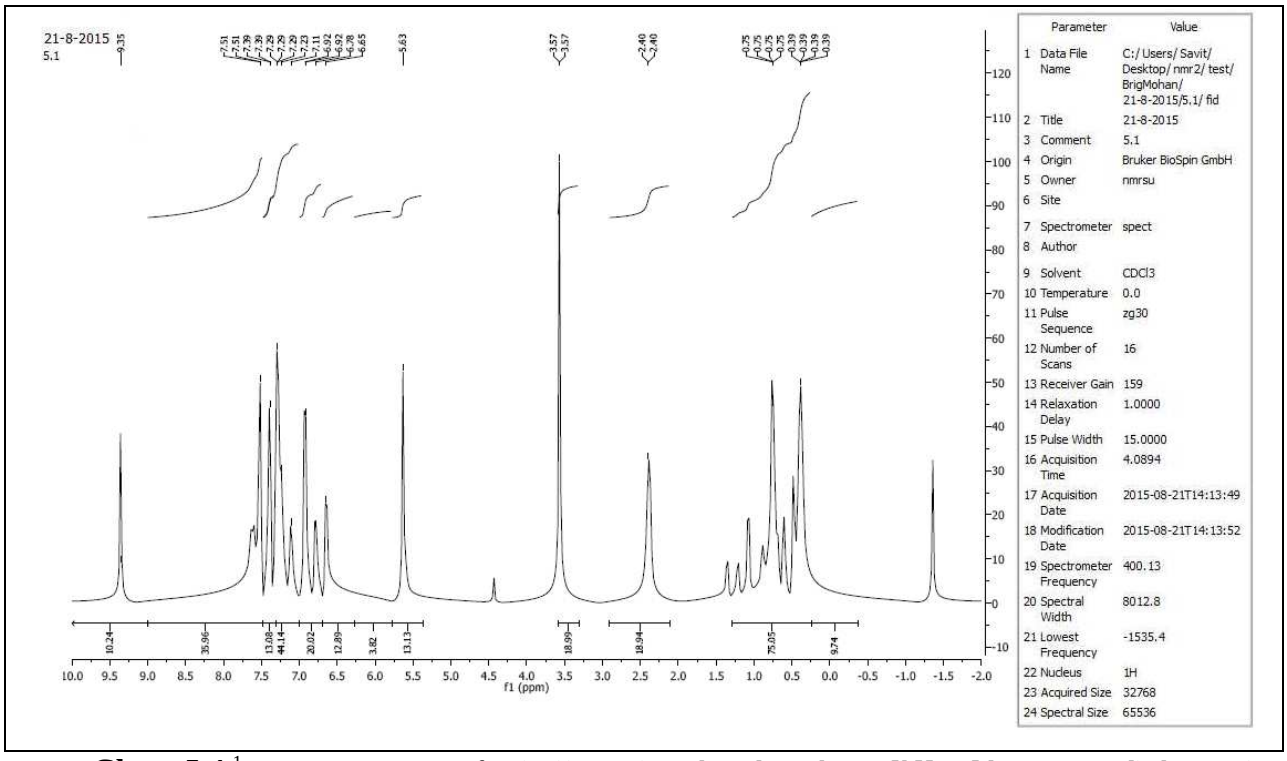


Chart-5.4 ^{1}H NMR spectrum of 6-(4-((2*Z*,4*E*)-2-phenyl-1*H*-benzo[*b*][1,4]diazepin-4-yl)phenoxy)-N^2,N^4-dicyclopropyl-1,3,5-triazine-2,4-diamine (5.065)

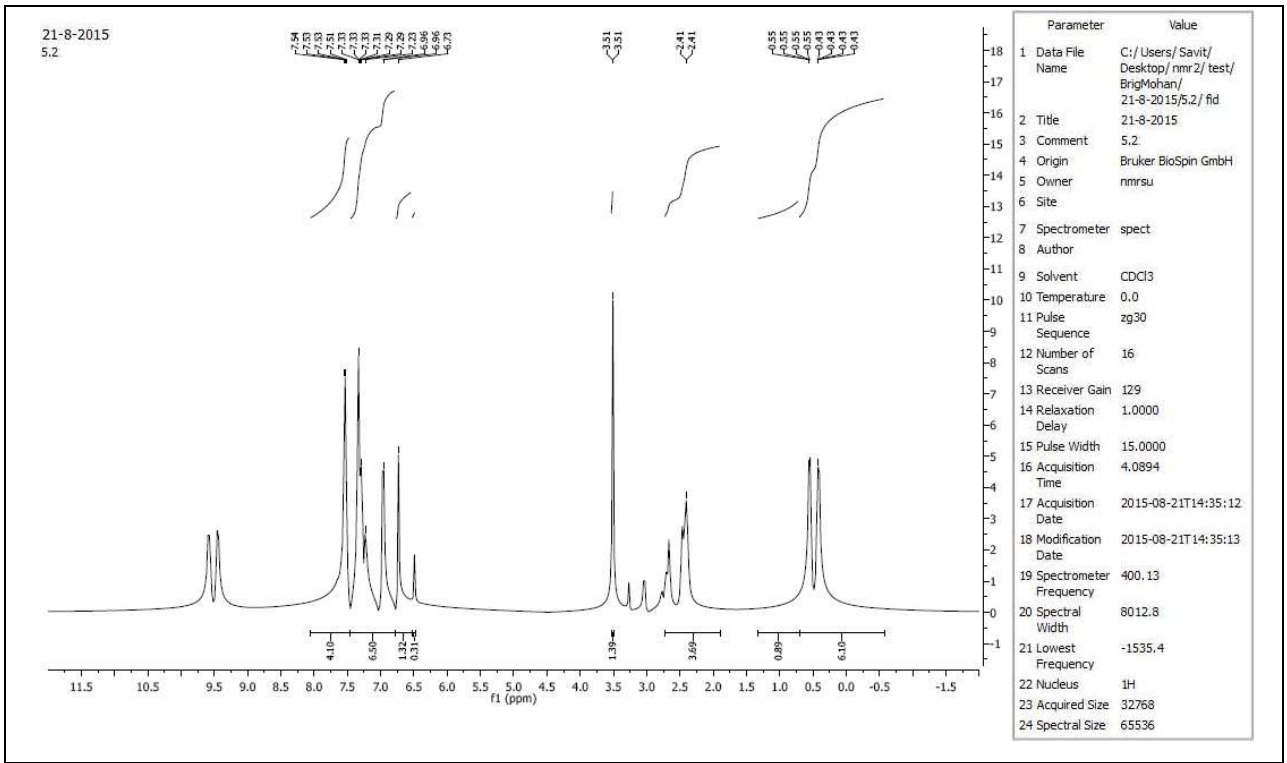


Chart-5.5 ^{1}H NMR spectrum of 6-(4-((2*Z*,4*E*)-2-phenylbenzo[*b*][1,4]thiazepin-4-yl)phenoxy)-N^2,N^4-dicyclopropyl-1,3,5-triazine-2,4-diamine (5.066)

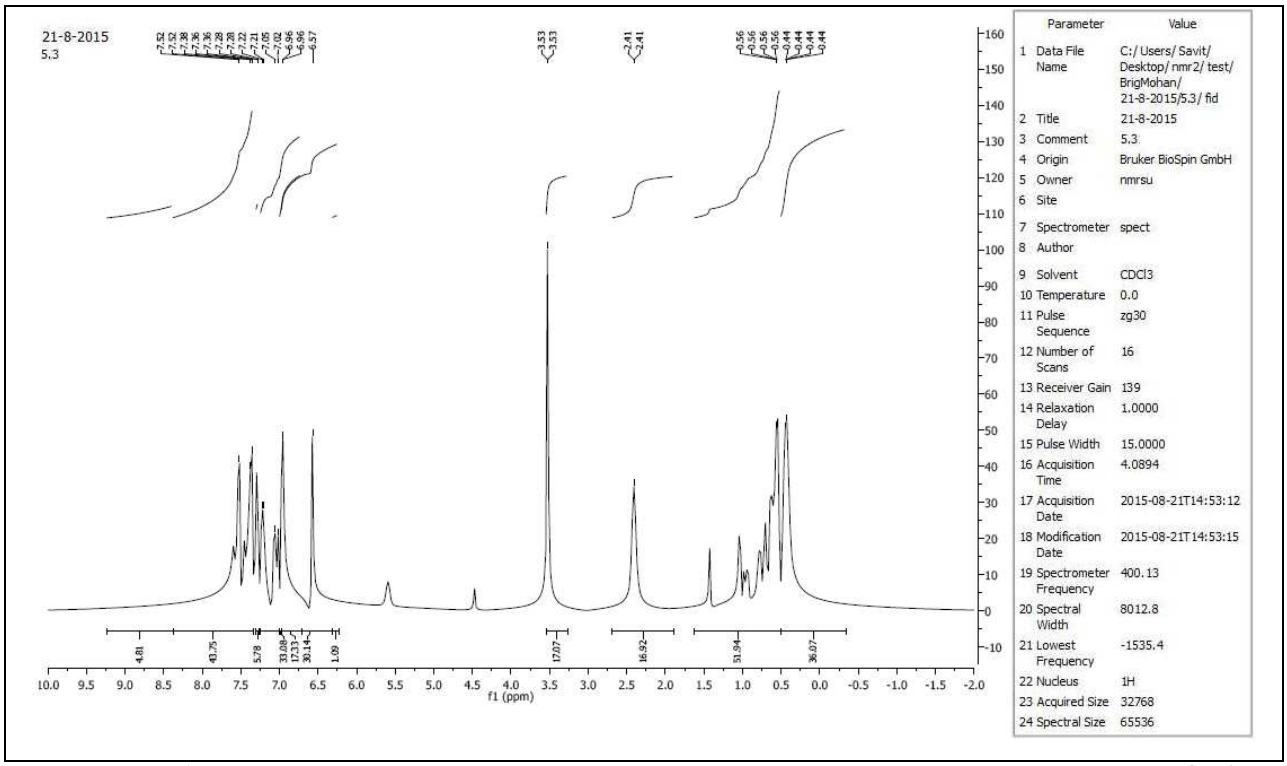


Chart-5.6 ^{1}H NMR spectrum of 6-(4-((2*Z*,4*E*)-2-phenylbenzo[*b*][1,4]oxazepin-4-yl)phenoxy)-N^2,N^4-dicyclopropyl-1,3,5-triazine-2,4-diamine (5.067)

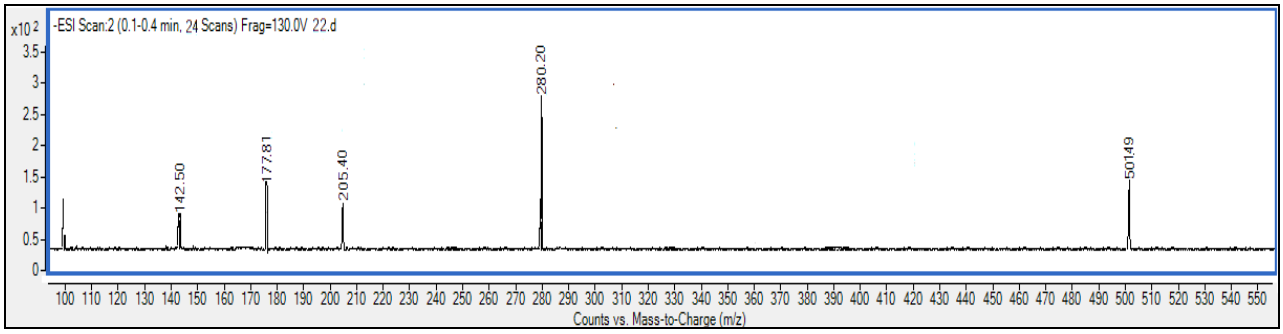


Chart-5.7 Mass spectrum of 6-(4-((2*Z*,4*E*)-2-phenyl-1*H*-benzo[*b*][1,4]diazepin-4-yl)phenoxy)-N^2,N^4-dicyclopropyl-1,3,5-triazine-2,4-diamine (5.065)

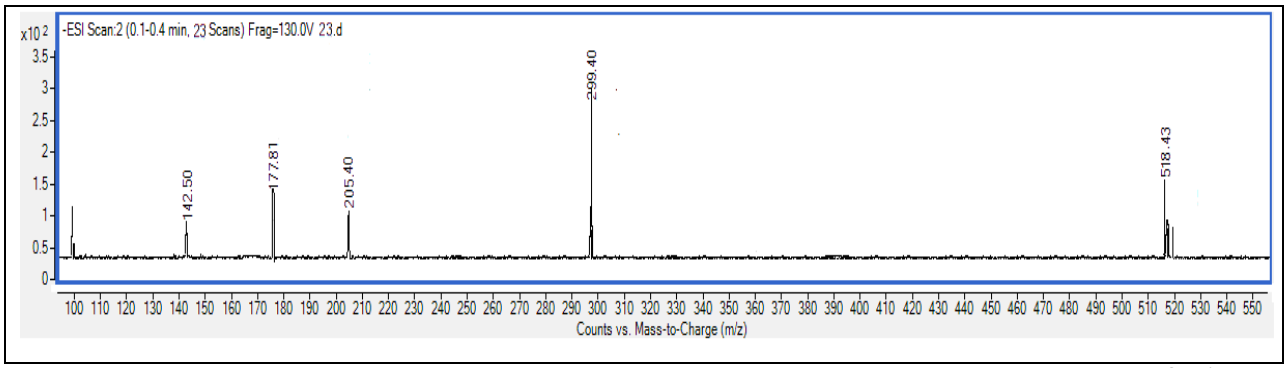


Chart-5.8 Mass spectrum of 6-(4-((2*Z*,4*E*)-2-phenylbenzo[*b*][1,4]thiazepin-4-yl)phenoxy)-N^2,N^4-dicyclopropyl-1,3,5-triazine-2,4-diamine (5.066)

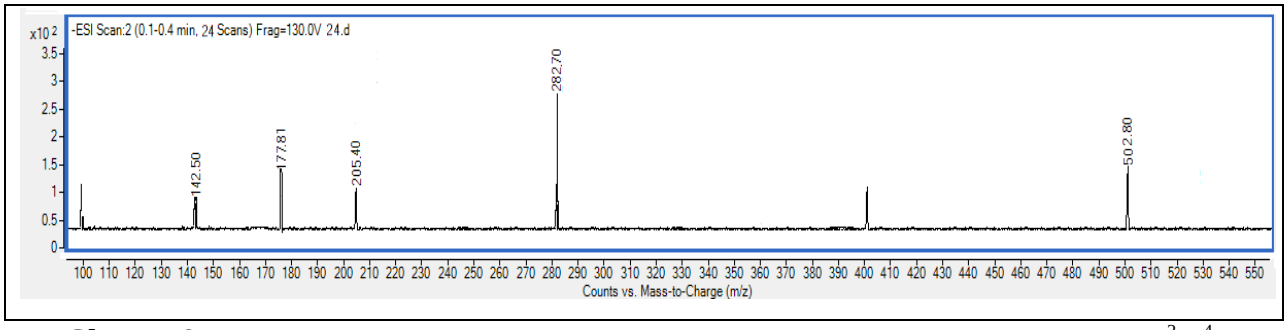


Chart-5.9 Mass spectrum of 6-(4-((2*Z*,4*E*)-2-phenylbenzo[*b*][1,4]oxazepin-4-yl)phenoxy)-N^2,N^4-dicyclopropyl-1,3,5-triazine-2,4-diamine (5.067)

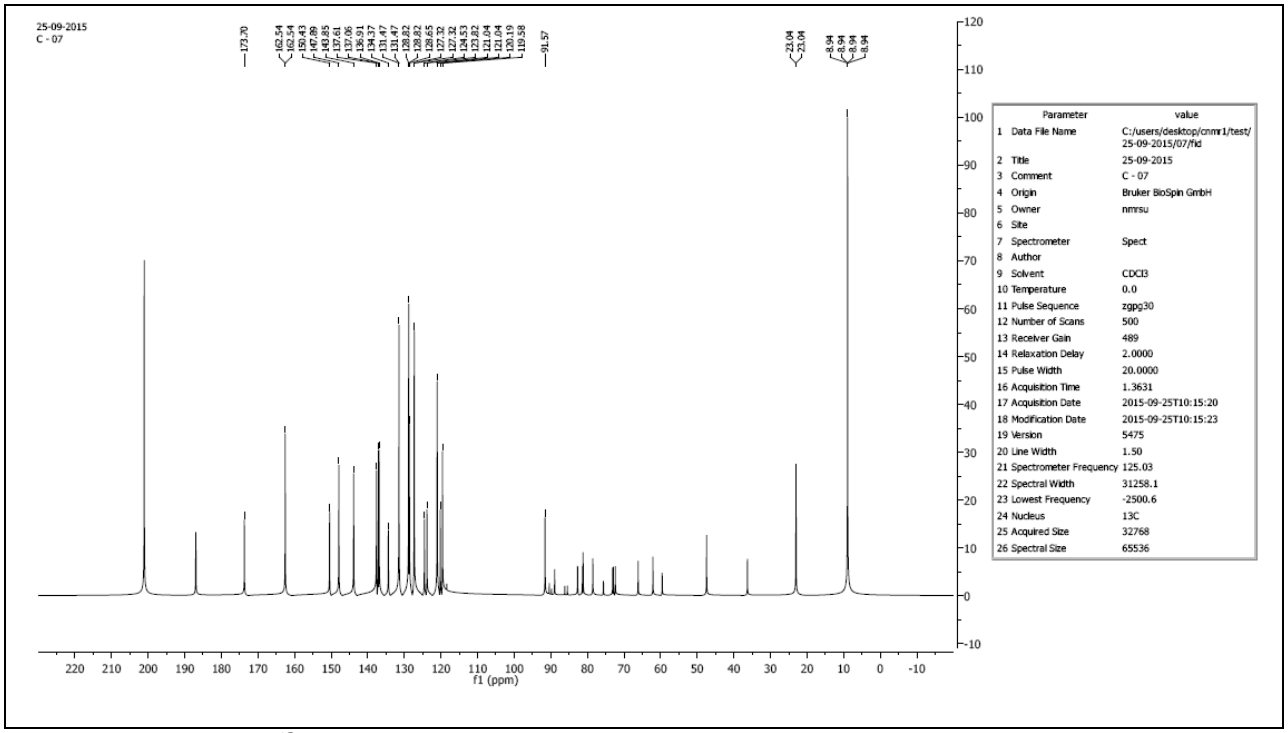


Chart-5.10 ^{13}C NMR spectrum of 6-(4-((2*Z*,4*E*)-2-phenyl-1*H*-benzo[*b*][1,4]diazepin-4-yl)phenoxy)-N^2,N^4-dicyclopropyl-1,3,5-triazine-2,4-diamine (5.065)

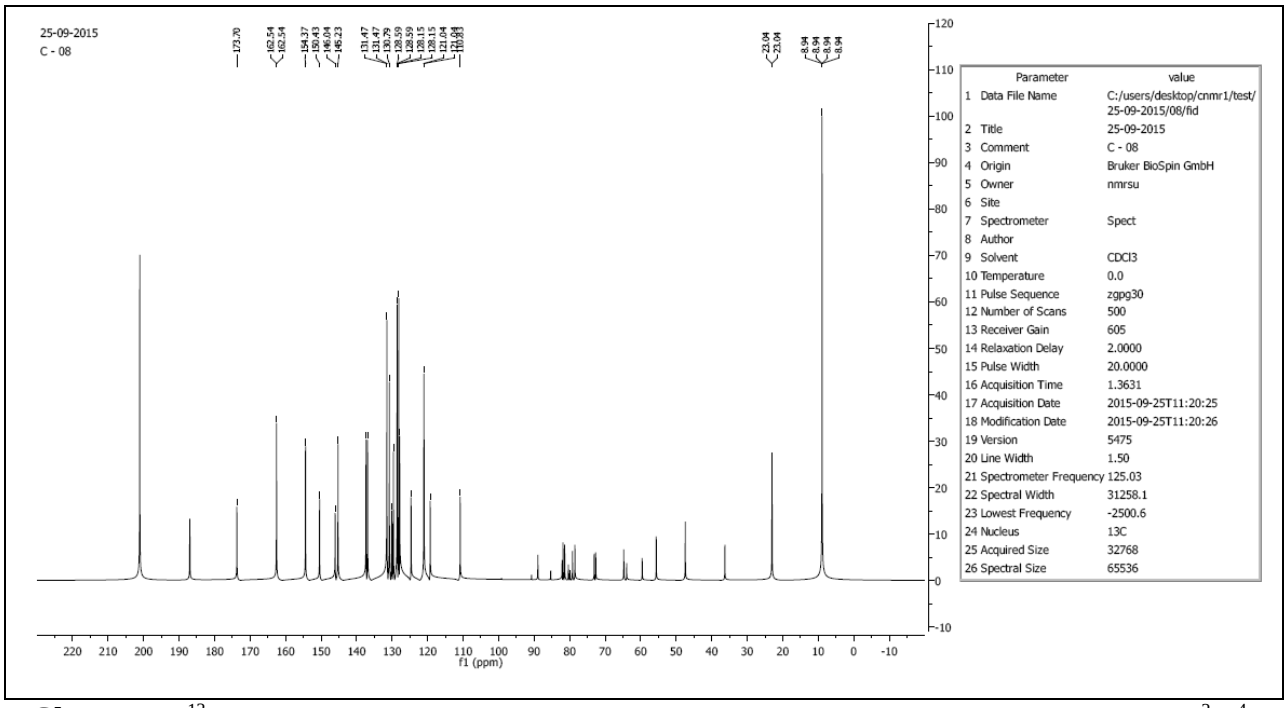


Chart-5.11 ^{13}C NMR spectrum of 6-(4-((2*Z*,4*E*)-2-phenylbenzo[*b*][1,4]thiazepin-4-yl)phenoxy)-N^2,N^4-dicyclopropyl-1,3,5-triazine-2,4-diamine (5.066)

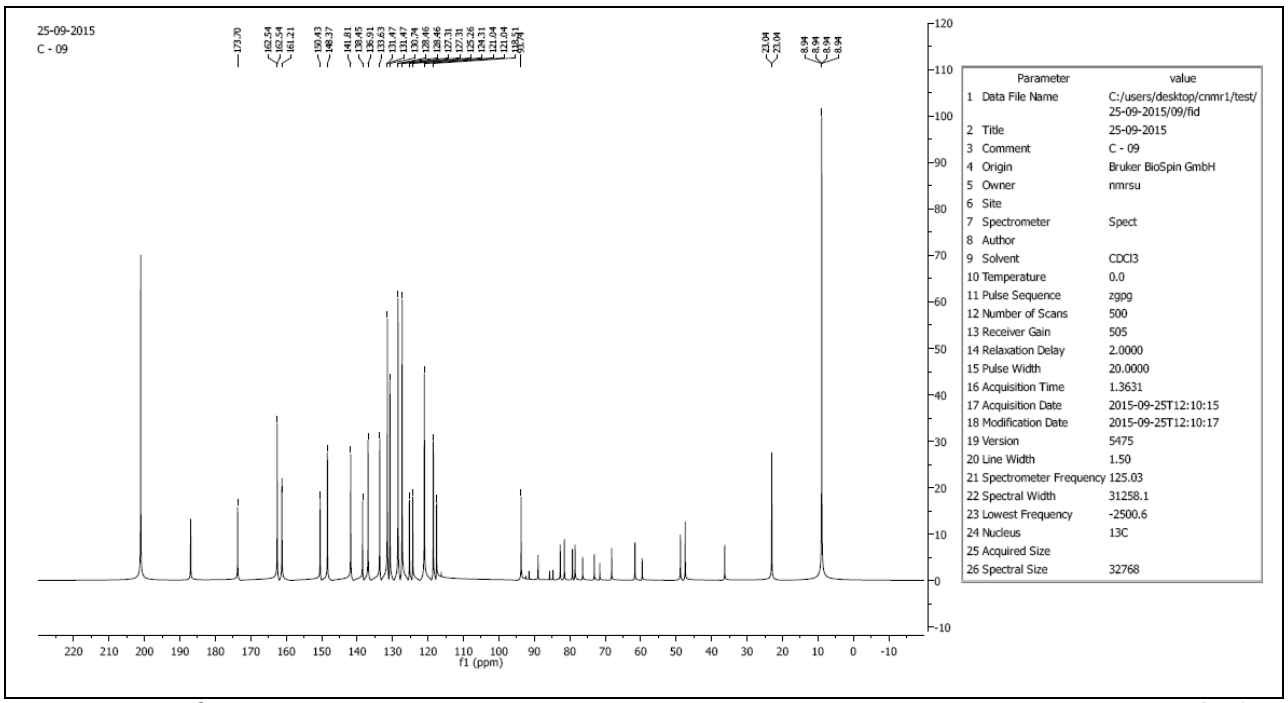


Chart-5.12 ^{13}C NMR spectrum of 6-(4-((2*Z*,4*E*)-2-phenylbenzo[*b*][1,4]oxazepin-4-yl)phenoxy)-N^2,N^4-dicyclopropyl-1,3,5-triazine-2,4-diamine (5.067)

References:

1. Padalkar Vikas S., Gupta Vinod D., Phatangare Kiran R., Patil Vikas S., Umape Prashant G., Sekar N., "Synthesis of novel dipodal-benzimidazole, benzoxazole and benzothiazole from cyanuric chloride: Structural, photophysical and antimicrobial studies", *Journal of Saudi Chemical Society*, **2014,** 18, 262–268.

2. Dourlat J., Liu W. Q., Gresh N., and Garbay C., "Novel 1,4-benzodiazepine derivatives with antiproliferative properties on tumour cell lines", *J. Pharm. Sci.*, **2007**, 11, 2221-39.

3. Hristine G. J., Krista R. W., Michael S. W., Nicholas B. S. D., Zhimin X. V. P., Rachel M. W. and Carrie H. L., "The 1,4-Benzodiazepine-2,5-dione small molecule template results in melanocortin receptor agonists with nanomolar potencies", *J. Med. Chem.*, **2008**, 51, 1423-31.

4. Pathak V. N., Joshi R. and Gupta N., "Synthesis, spectral studies and antimicrobial activity of 7-chloro-2-alkyl/aryl-4-alkyl/aryl-3arylidene-3*H*-1,5-benzodiazepine", *Ind. J. Chem.*, **2007**, 46B, 1191-97.

5. Pant U. C., Chandra H. and Goyal S., "Synthesis of 1,5-benzothiazepine: Part XXX-Synthesis and antimicrobial studies of 10-Substituted-6a,7-dihydro-6H-7-(4-flourophenyl[1]benzopyrano[3,4-c][1,5]benzothiazepines", *Ind. J. Chem.*, **2006**, 46B, 752-57.

6. Andronati K. S., Kostenko E. K., Karaseva T. L., "Synthesis and pharmacological properties of 3-amino-1,2-dihydro-3H-1,4-benzodiazepin-2-one derivatives", *Pharm. Chem. J.*, **2002**, 7, 356-59.

7. Ben-Cherif W., Gharbi R., Sebai H., Dridi D., Boughattas N. A. and Attia M., "Neuropharmacological screening of two 1,5-benzodiazepine compounds in mice", *C. R. Biol.*, **2010**, 333, 214-19.

8. Dabhi Harish R., Rana Arjunshin K. and Shah Arihant R.," Synthesis, characterization and biological evaluation of some novel isoxazole and benzodiazepine derivatives", *Journal of Chemical and Pharmaceutical Research*, **2014**, 6(11):771-775.

9. Wang Lan-Zhi, Li Xiao-Qing and An Ying-Shuang., "1,5-Benzodiazepine derivatives as potential antimicrobial agents design, synthesis, biological evaluation, and structure- activity relationships", *Org. Biomol. Chem.*, **2015**, 13, 5497.

10. Dong Z.-Q., Shi H., Chen S.-L., Chen H.-X., Jiang W. B., Liu F.-M. and Hong M.-L., "Synthesis of 1,5-benzodiazepine derivatives containing 1,2,3-triazole moiety via 1,3-dipolar cycloaddition reaction", *J. Heterocyclic Chem.*, **2014**, 51, 1844–1848.

11. Puodziunaite B. D., Janciene R. and Kosychova L., "On the synthetic way to novel peri-annelated imidazo[1,5]benzodiazepines as the potent non-nucleoside reverse transcriptase inhibitor", *ARKIVOC*, **2000**, (iv), 512-522.

12. Kosychova L., Plectaitiene L. and Staniulyte Z., " A convenient synthesis of novel substituted imidazo[1,2-a][1,5]benzodiazepine derivatives", *ARKIVOC*, **2006**, (xiii), 158-64.

13. Satyanarayan K. and Rao M. N., "Synthesis of 3-[4[2,3-dihydro-2-(substituted aryl)-1,5-benzothiazepin-4-yl]phenyl]sydnones as potential anti-inflammatory agents", *Ind. J. Pharm. Sci.*, **1993**, 55, 230-233.

14. Kusanur R. A., Ghate M. and Kulkarni M., "Synthesis of spiroindolo-1,5-benzodiazepines from3-acetyl coumarins for use as possible antianxiety agents", *J. Chem. Sci.*, **2004**, 116, 265-270.

15. Jadhav K. P., and Ingled D. B., "Synthesis of 2,4-diaryl-2,3-dihydro-1,5-thiazepines and their 1,1-dioxides as antibacterial agent", *Ind. J. Chem.*, **1983**, 22B, 180-190.

16. Reddy R .J., Ashok D. and Sharma P. N., "Synthesis of 4,6-bis(2'-substituted-2',3'-dihydro-1,5-benzothiazepines-4'-yl)resorcinols as potential antifeedants", *Ind. J. Chem.*, **1993**, 32B, 404-406.

17. Dessaro G., Chimirri A. and Dessarro A., "5H-[1,2,4]oxadiazolo[5,4-d][1,5]benzothiazepines as anticonvulsant agent in D-Ba/2 mice", *Eur. J. Med. Chem.*, **1995**, 30, 925-29.

18. Ekonomopoulou M. T., Tsoleridis C. A., Argyraki M., Polatoglou E., Stephanidou-Stephanatou J. and Iakovidou-Kritsi Z., "Cytogenetic activity of newly synthesized 1,5-benzodiazepines in normal human lymphocyte cultures", *Genet. Test. Mol. Biomarkers*, **2010**, 14 377-383.

19. Neels H. M., Sierens A. C. and Naelaerts K., "Therapeutic drug monitoring of old and newer anti-epileptic drugs", *Clin. Chem. Lab. Med*., **2004**, 42, 1228-55.

20. Oh S., Kim S.J., Hwang J.H., Lee H.Y., Ryu M. J., Park J., Kim S.J., Jo S.Y., Kim K.Y., Lee C., Kweon K. R., Shong M. and Park S.B., " Antidiabetic and antiobesity effects of ampkinone, a novel small molecule activator of AMP-activated protein kinase", *J. Med. Chem.*, **2010**, 53, 7405-13.

21. Xiang K., Earl D.E., Davis K.M., Giovannucci D. R., Greenfield L.J. and Tietz E. I., "Chronic benzodiazepine administration potentiates high voltage-activated calcium currents in hippocampal CA1 Neurons", *J. Pharmacol. Exp. Ther.*, **2008**, 327, 872-83.

22. Steffan R. J., Failli A.A., "Preparation of pyrrolobenzodiazepine carboxamide vasopressin agonists", *PCT Int. App.*, **2000**, 228, WO 0046.

23. Hoekstra W.J. and Dyatkin A.B., "Preparation of tricyclic benzodiazepines as vasopressin antagonists", *PCT Int. App.*, **2000**, 398, WO 0043.

24. Nawrocka W., Sztuba B. and Opolski A., "Synthesis and antiproliferative activity in vitro of novel 1,5-benzodiazepines", *Arch. Phar. Med. Chem.*, **2001**, 334, 3-10.

25. Braccio M. D., Grossi G., Roma G., Vargiu L., Mura M. and Marongiu E.M., "1,5-Benzodiazepines: Synthesis and biological evaluation of tricyclic and tetracyclic 1,5-benzodiazepine derivatives of nevirapine analogues", *Eur. J. Med. Chem.*, **2001**, 36, 935-49.

26. Miura Y., Amano S., Torii R. and Ihara N., "Clobazam shows a different antiepileptic action profile from clonazepam and zonisamide in Ihara epileptic rats", *Epilepsy Res.*, **2002**, 49, 189-202.

27. Glamkowski E. J. and Chiang Y., "Tetracyclic benzodiazepines: Synthesis of the novel benzo[c]pyrrolo[1,2,3-e,f][1,5]benzodiazepine ring system and derivatives with potential antipsychotic activity", *J. Heterocycl. Chem.*, **2009**, 24, 599-1604.

28. Grandolini G., Perioli L. and Ambrogi V., "Synthesis of some new 1,4-benzothiazepine and 1,5-benzothiazepine tricyclic derivatives with structural analogy with TIBO and their screening for anti-HIV activity", *Eur. J. Med. Chem.*, **1999**, 34, 701-09.

29. Kamble R. R. and Sudha B. S., "Synthesis and pharmacological evaluation of 1,5-benzothiazepine derivatives", *Phosphorus Sulfur Silicon Relat. Elem.*, **2008,** 183, 1691-1709.

30. Bariwal J. B., Upadhyay K. D., Manvar A. T., Trivedi J.C., Singh J. S., Jain K. S. and Shah A.K., "1,5-Benzothiazepine, a versatile pharmacophore: A review", *Eur. J. Med. Chem.*, **2008**, 43, 2279-90.

31. Rani P., and D. Kishore, "Synthesis of tetrazolo, triazolo and quinazolino annulated analogues of the priveleged nucleus of pyrrolo-[1,5]-benzodiazepines of medicinal interest", *IJSRR*, **2013**, 2(2), 85-93.

32. Dandia A., Singh R., and Khaturia S., "Efficient microwave enhanced solvent-free synthesis of potent antifungal agents: Fluorinated benzothiazepine fused β-lactam derivatives", *Chem Pharma Bull.*, **2007**, 128(5), 524-529.

33. Mane R. A. and Ingle D. B., "Synthesis and biological activity of some new 1,5-benzothiazepines containing thiazole moiety 2-aryl-4-(4'-methyl-2-substituted-aminothiazo-5-yl)-2,3-dihydro-1,5-benzothiazepine", *Ind. J. Chem.*, **1982**, 21B, 973-74.

34. Cherkupally S. R., Gurrala P. R., Adki N. and Avula S., "Synthesis and biological study of novel methylene-bis-benzofuranyl-1,5-benzothiazepines", *Org. Commun.*, **2008**, 4, 84-94.

35. Ahmed N. K., Can. Pat. Appl. 1991, Waters, J., Furnace-Door, *U.S. Appl.*, 441083, **1980**.

36. Dumont L., Derouin M., Chartland C., Archambeault P., Gaeceau D. and Calle G., "Peripheral vasodilator and cardiac properties of 1,5-benzothiazepine calcium", *Can. J. Physco. Pharm.*, **1991**, 69, 512-19.

37. Martínez Walter R., Militão Gardenia C. G., da Silva Teresinha G., Silva Ricardo O. and Menezes Paulo H., "Synthesis of novel [3,1]-benzothiazepine and [3,1]-benzoxazepine derivatives with antitumoral activity" *RSC*, **2014**, 4, 14715-14718.

38. Narta H., Muruta S. and Suzuki T., "Synthesis and pharmacological properties of azido derivatives of 1,5-benzothiazepine fused Ca antagonist", *Chem. Pharma. Bull.*, **1990**, 38, 407-10.

39. Dandia A., Singh R. and Khaturia S., "Efficient microwave enhanced solvent free synthesis of potent antifungal agents: Fluorinated benzothiazepine fused *β*-lactam derivatives", *J. Fluorine Chem.*, **2007**, 128, 524-29.

40. Ganjali M. R., Razavi T. and Dinarv R., "New diltiazam potentiometric membrane sensor stand on theriotical calculation as a useful device for diltiazam hydrochloride analysis in pharmaceutical formulation and urine", *Int. J. Electrochem. Sci*., **2008**, 3, 1543-58.

41. Ansari F. L., Umbreen S., Hussain L., Makhmoor T., Nawaz S. A., Lodhi M. A., Khan S. N., Shaheen F. and Choudhary M. I., "Synthesis and biological activities of chalcone and 1,5-benzothiazepine derivatives: Promising new free-radical scavengers, and esterase, urease, and alpha-glucosidase inhibitors", *Chem. Biodivers.*, **2005**, 2, 487-96.

42. Opera T. I., Davis A. M. and Teague S. J., "Is there a difference between leads and drugs? A historical prospective", J. Chem. Inf. Comput. Sci., **2001**, 41, 1308-15.

43. Hagiwara M., Adachi S. and Nagao T., "High affinity binding of DTZ323, a novel derivative of diltiazam, to rabbit skeletal muscle L-type Ca channels", *Pharm. and Exp. Ther.*, **1997**, 281, 173-79.

44. Biavalli M. W., Veira P. C. and De-silva M. F., "Biological activity of quinoline alkaloid from Raitionea echinata and X-ray structure of flinaorsiama', *J. Braz. Chem. Soc.*, **2002**, 13, 66-77.

45. Apiquian R., Fresan A., Ulloa R. E., Fuente-Sandoval C., Herrera-Estrella M., Vazquez A., Nicolini H. and Kapur S., "Amoxapine as an atypical antipsychotic: A comparative study vs risperidine", *Neuropsychopharmacology*, **2005**, 30, 2236-44.

46. Yadav J. S., Reddy B. V. S. and Anuradha K., "Diarylazepine derivatives as potent a typical neuroleptic drugs: Recent advances", *Green Chem.*, **2002**, 4, 592-4.

47. Theile J. and Steimmig G., "Mitteilungen uber siebengliedrige rings aus *β*-diketonene and *o*-diaminen, Berichte der deutschen chemischen", *Gesellschft.*, **1907**, 40, 955-57.

48. Finar I. L., "The Preparation and properties of some 2,3-benzo-1,4-diazepines", *J. Chem. Soc.*, **1958**, 4094-97.

49. Rupe H. and Huber A., "Oxymethylene-aldehyde. II. Kondensationen mit oxymethylen-phenylacetaldehyde", *Hel. Chimica Acta.*, **1927**, 10, 846-58.

50. Prakash O., Kumar A., Sadhana A., Prakash R., Singh S. P., Claramunt R. P., Sanz D., Alkortac I. and Elguero J., "Study of the reaction of chalcone analogs of dihydroacetic acid and *o*-aminothiophenol: Synthesis and structure of 1,5-benzothiazepines and 1,4-benzothiazines", *Tetrahedron*, **2005**, 61, 6642-51.

51. Langade M. M., "One pot method for green synthesis of 1,5-benzothiazepines", *Der. Pharma. Chemica.*, **2011**, 3, 273-76.

52. Praveen A., Patil V. A., Baseer M. A. and Ahmed S. K., "Mechanostic synthesis of 1,5-benzothiazepines using molecular iodine", *Int. J. Indus. Chem.*, **2011**, 2, 144-53.

53. Masquelin T., Obrecht D., "A novel Access to 2,4-substituted quinoline from acetylinic ketones", *Tetrahedron*, **1997**, 53, 641-46.

54. Ushirogochi A., Tominaga Y. and Matsuda Y., "Synthesis of 1,5-benzodiazepines", *Heterocycles*, **1980**, 14, 7-10.

55. Michinori K., Matthias D., Guido V. and Noerbert D. K., "Regio- and stereo controlled synthesis of novel 3-sulphonamido-2,3,4,5-tetrahydro-1,5-benzothiazepines from 2-

(bromomethyl)- or 2-(sulphonyloxymethyl)aziridines", *Org. Biomol. Chem.*, **2008**, 6, 1902-04.

56. Vyawahare D., Ghodke M. and Nikalje A. P., "Green synthesis and pharmacological screening of novel 1,5-benzothiazepines as CNS", *Int. J. Pharm. Pharm. Sci.*, **2010**, 2, 27-29.

57. Shyam R., Ghorela V. S., Singh V. K. and Kumar S., "Synthesis and antimicrobial activity of novel methylene-bis-8-substituted-[1,5]-benzothiazepines", *Rasayan J. Chem.*, **2010**, 3, 293-98.

58. Levai A., "Synthesis and chemical transformations of 1,4-, 4,1- and 1,5-benzoxazepines", *J. Heterocyclic Chem.*, **2001**, 38, 1011-23.

59. Coulson C. J. and Wooldridge K. R. H., "The synthesis and mass spactra of 3-hydroxy-2,3,4,5-tetrahydro-1,5-benzoxazepine and related compounds", *J. Chem. Soc.*, **1971**, 1164-67.

60. Neochoritis C. G., Tsoleridis C. A., Stephanidou-Stephanitou J., Kontogiorgis C. A. and Hadjipavlovlou-Litina D. J., "1,5-benzoxazepines vs 1,5-benzodiazepines: One pot microwave assisted synthesis and evaluation for antioxidant activity and lipid peroxidation inhibition", *J. Med. Chem.*, **2010**, 53, 8409-20.

61. Bhushan Singh R., Das N., Jana S., Das A.; "Synthesis and in vitro antibacterial screening of some new 2,4,6-trisubstituted-1,3,5-triazine derivatives", *Lett. Drug Des.Discov*., **2012**, 9, 316–321.

62. Patel R. V., Kumari P., Rajani D. P., Chikhalia K. H.; "Synthesis and studies of novel 2-(4-cyano-3-trifluoromethylphenylamino)-4-(quinoline-4-yloxy)-6-(piperazinyl/piperidinyl)-s-triazines as potential antimicrobial, antimycobacterial and anticancer agents", *Eur. J. Med. Chem.*, **2011**, 46, 4354–4365.

63. Sunduru N., Gupta L., Chaturvedi V., Dwivedi R., Sinha S., Chauhan P. M., "Discovery of new 1,3,5-triazine scaffolds with potent activity against Mycobacterium tuberculosis H37Rv.", *Eur. J. Med. Chem.*, **2010**, 45, 3335–3345.

64. Patel, A. B., Patel, R. V., Kumari, P., Rajani, D. P., Chikhalia, K. H.; "Synthesis of potential antitubercular and antimicrobial s-triazine-based scaffolds via Suzuki cross-coupling reaction" *Med. Chem. Res*, **2012**, 22, 367–381.

65. Patel R. V., Kumari P., Rajani D. P., Chikhalia K. H., "Synthesis and studies of novel 2-(4-cyano-3-trifluoromethylphenylamino)-4-(quinoline-4-yloxy)-6-(piperazinyl/piperidinyl)-s-

triazines as potential antimicrobial, antimycobacterial and anticancer agents", *Eur. J. Med. Chem.*, **2011**, 46, 4354–4365.

66. Gahtori H. P., "Design, facile synthesis, antibacterial activity and structure–activity relationship of novel di- and tri-substituted 1,3,5-triazines", *Lett. Drug Des. Discov.*, **2012**, 9, 329–335.

67. Patel P. K., Patel R. V., Mahajan D. H., Parikh P. A., Mehta G. N., Pannecouque C., De Clercq E. and Chikhalia K. H.; "Different Heterocycles Functionalized *s*-Triazine Analogues: Design, Synthesis and *In Vitro* Antimicrobial, Antituberculosis, and Anti-HIV Assessment", *J. Heterocyclic Chem.*, **2014**, 51,1641–1658.

68. Rodrigues C. A., Frade R. F., Albuquerque I. S., Perry M. J., Gut J., Machado M., Rosenthal P. J., Prudêncio M., Afonso C. A., Moreira R., "Targeting the erythrocytic and liver stages of malaria parasites with s-triazine-based hybrids", *Epub*, **2015**, 5, 883-90.

69. Gahtori P., Ghosh S. K., Singh, B., Singh, U. P., Bhat H. R., Uppal A., "Synthesis, SAR and antibacterial activity of hybrid chloro, dichloro-phenylthiazolyl-s-triazines", *Saudi Pharm. J.* **2012**, 20, 35–43.

70. Singh U. P., Bhat H. R., Gahtori P., "Antifungal activity, SAR and physicochemical correlation of some thiazole-1,3,5-triazine derivatives", *J. Mycol. Med.*, **2012**, 22, 134–141.

71. Patel R. V., Kumari, P., Rajani D. P., Chikhalia, K. H., "Synthesis, characterization and pharmacological activities of 2-[4-cyano-(3-trifluoromethyl)phenylamino)]-4-(4-quinoline/coumarin-4-yloxy)-6-(fluoropiperazinyl)-s-triazines" *J. Fluorine Chem.*, **2011b**, 132, 617–627.

72. Lloyd D., Nab H. Mc, "*Advances in Heterocyclic Chem.*, **1998**, 71.