Synthesis and Characterization of 1,3,5-Triazine and Naphthalimide Conjugates as Anticancer Agents

Thesis Submitted

In the partial fulfilment of requirement of degree

Masters of Science

In

Chemistry

By

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THAPAR INSTITUTE
OF ENGINEERING & TECHNOLOGY
(Deemed to be University)

UNDER THE SUPERVISION OF

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Patiala-147004

Punjab, India

July 2019

CERTIFICATE

This is to certify that the thesis entitled **"Synthesis and characterization of 1,3,5-triazine and naphthalimide conjugates as anticancer agents"** submitted by **Mr. Saurabh Gupta** in the partial fulfillment of the requirement for the degree of **Masters of Science in Chemistry** from **Thapar Institute of Engineering and Technology, Patiala** is a bonafide piece of work carried out under the guidance and supervision **Dr. Kamaldeep Paul** Associate Professor, School of Chemistry and Biochemistry, Thapar Institute of Engineering and Technology, Patiala and no part of project has been submitted for award of any other degree in this or any other university.

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This is to certify above statement made by student concerned is correct and true to the best of my knowledge.

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Candidate's Declaration

I hereby declare that the matter embodied in this project entitled "**Synthesis and characterization of 1,3,5-triazine and naphthalimide conjugate as anticancer agents**" is an authentic research work done by me in the partial fulfilment of the requirement for the Award of degree of **Masters of Science in Chemistry,** submitted in the **School of Chemistry and Biochemistry, Thapar Institute of Engineering and Technology, Patiala** under the supervision of **Dr. Kamaldeep Paul** Associate Professor, School of Chemistry and Biochemistry, Thapar Institute of Engineering and Technology, Patiala. All the ideas and references has been duly acknowledged

In keeping with the general practise in reporting scientific observations, due acknowledgement has been made whenever the work described is based on the findings of other investigators. Any oversight due to error of judgement is regretted

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SAURABH GUPTA

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Saurabh Gupta

SAURABH GUPTA

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ABSTRACT

Cancer, one of the most threatening diseases in the world that implicates unchecked cell growth and cell division of abnormal cells. When a cell is individually damaged and cannot repair itself, it frequently endures a so called programme that is cell death or apoptosis. The molecules bearing heteroatoms, for instance nitrogen, oxygen and sulfur helps to strengthen the framework through hydrogen bonding with DNA. The anticancer activity is usually related to the force of interaction between DNA and molecule The heterocyclic acquaintance tri-substituted-1,3,5-triazine withstand an intense pharmacophore because of its existence in bulk of bioactive molecules. Derivatives of 1,3,5-triazine bears excellent bioactivity *viz.* antimicrobial, antitumour, antiprotozal, leishmanicidal, antimalarial and antiviral. In this work, we have synthesized 1,3,5-triazine and naphthalimide base conjugates followed by substitution with primary and secondary amines in good to moderate yields. The synthesized compounds were characterized by ^{1}H NMR spectroscopic technique. These compounds will further be used to evaluate their anticancer activity.

1. INTRODUCTION

In developed as well as developing countries, cancer is creating health milestone obstruction embroil a great spatiotemporal variation in cell physiology.[1] Cancer, one of the most threatening disease in the world, abides an immensely combative disease that implicates unchecked cell growth and cell division of abnormal cells. When a cell is individually damaged and cannot repair itself, it frequently endures a so called programme that is cell death or apoptosis. Most the cancer form a lump called tumor or growth.[2] Tumor is generally referred to as abnormal of cell accordingly, it can be non-cancerous (benign) or cancerous (malignant). Benign tumor expands narrowly and don't spread in the body, hence, it is not considered as cancerous but can be dangerous if they occur against vital organs like brain. Metastasis, the main aspect of cancer, occurs when a malignant tumor spread in body and invade the other tissues. The greater part of diseases is seen by advancement of cells without delimitation due to non-obstruction of vital compounds and proteins administering cell division and expansion.[3] the out curb growth of cells is attributed to as cancer and invade other tissues. Aggregation of defects or mutation in DNA of cell becomes cancerous. The hazard of cancer is attributed due to genetic effects and infection.[4] Damage of DNA, lead to cancer may be due to environmental factors and poor life style such as smoking, heavy alcohol and many more (**Figure 1**).

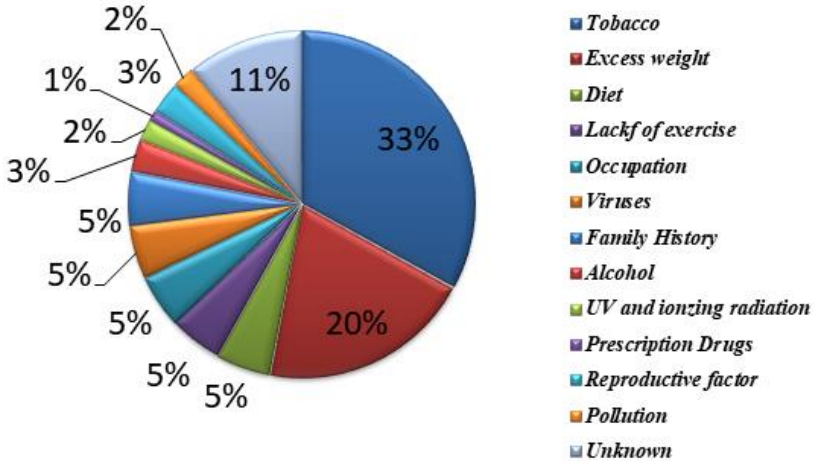


Figure 1. Estimate % of cancer cases caused by various factors

The bulk of comprehensive deaths are due to non-communicable diseases. In 21st century it has been establish that in every country of world, cancer is expected to noxious as preeminent root of death. In 2015, World Health Organisation (WHO) predicted that before age of 70 years, cancer is first or second prominent source of death in 91 of 172 countries.[5] The

percentage of cases of incidence and mortality due to different type of reaction has been shown in **Figure 2**.

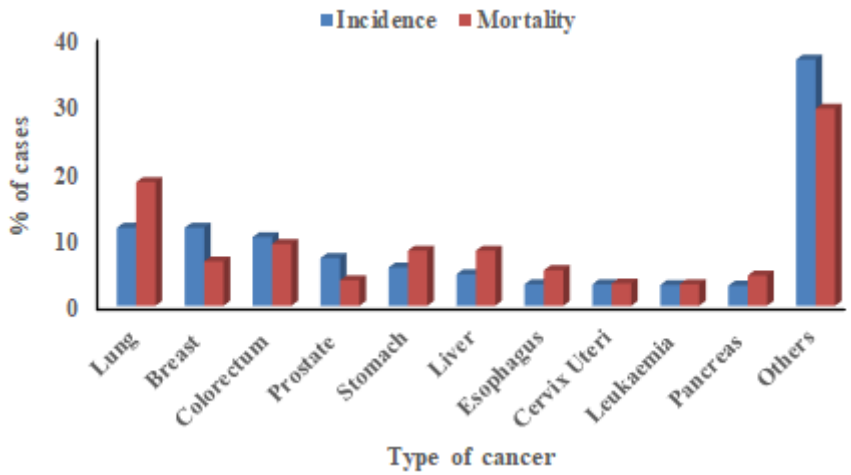


Figure 2. The distribution of types of cancer cases and death rate for most common cancer worldwide in 2018.[5]

The molecules bearing heteroatoms, for instance, nitrogen, oxygen and sulfur helps to strengthen the framework through hydrogen bonding with DNA. The anticancer activity is usually related to the force of interaction between DNA and molecule. In recent years, 1,3,5-triazine derivatives have deliberately turned into more momentous. They are perceived as abnormally favourable intermediates for establishment of inventive biological materials. The triazine ring is an important moiety conjugated in many pharmacologically essential compounds. Our present work is to synthesis and characterization of triazine hybridised with naphthalimide conjugates.

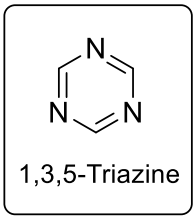
2. REVIEW OF LITERATURE

In pursuit of unique promoter with healing capability is one of the main interests in medicinal chemistry. A figure related to heterocyclic moieties like indole, benzimidazole, pyrazole, triazine, perimidine and naphthalimide etc. acquire an adequate aspect in pharmaceuticals and medicinal chemistry. These moieties exhibit their utilization in oncology as an impressive feedback to the targets. Adopting the particular fraction as their support, plenty of drugs are formed for medication of cancer. So, exploration is being going on to build competent conjugated moieties and to analysis the anticancer activities of these moieties.

1,3,5-Triazine and its biological applications

Triazine is a class of heterocyclic compounds with three nitrogen atoms and having a six membered ring. The possible isomers of triazine that alter in the arrangement of nitrogen atoms in the ring are 1,2,3-triazine, 1,2,4-triazine and 1,3,5-triazine are intermittently

spotlight for research in medicinal chemistry as these displayed diverse range of biological activities.[6]



1,3,5-Triazine or s-triazine or symmetric triazine is similar to benzene ring containing three nitrogen atoms. The heterocyclic acquaintance tri-substituted-1,3,5-triazine withstand an intense pharmacophore because of its existence in bulk of bioactive molecules. Derivatives of 1,3,5-triazine bears excellent bioactivity *viz.* antimicrobial, antitumour, antiprotozal, leishmanicidal, antimalarial and antiviral. Triazine derivatives likewise showed potent DHFR inhibitory activity for significant antitumor properties. Furthermore, a considerable accord of consideration have also been compensated to 1,3,5-triazine substituted compounds having antitumor activity and kinase inhibitors (**Figure 3**).[7]A large portion of the medication that are approved by the FDA have 1,3,5-triazine as their fundamental moiety.

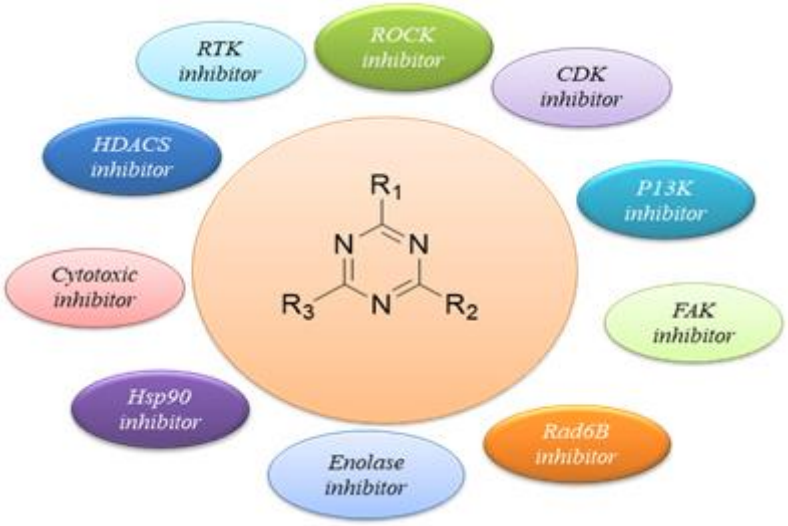
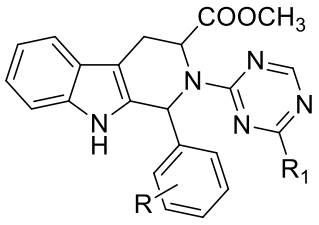


Figure 3. Inhibitory activities of 1,3,5-triazine

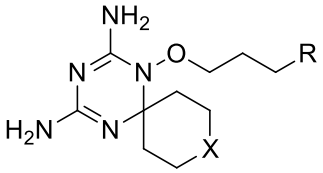
Kumar *et al.* examined the cytotoxicity across eight human cancer cell lines of newly synthesized series of 1,3,5-triazine and β-carbolines hybrid compounds. It was detected that compounds **1j**, **1k** and **1l** exhibited cytotoxicity against KB cell line with IC_{50} 105.8 μM, 664.7 μM and 122.2 μM, respectively. Compound **1l** exhibit 2.5 times more selectivity against MCF7 cells with an IC_{50} of 740 μM.[8]



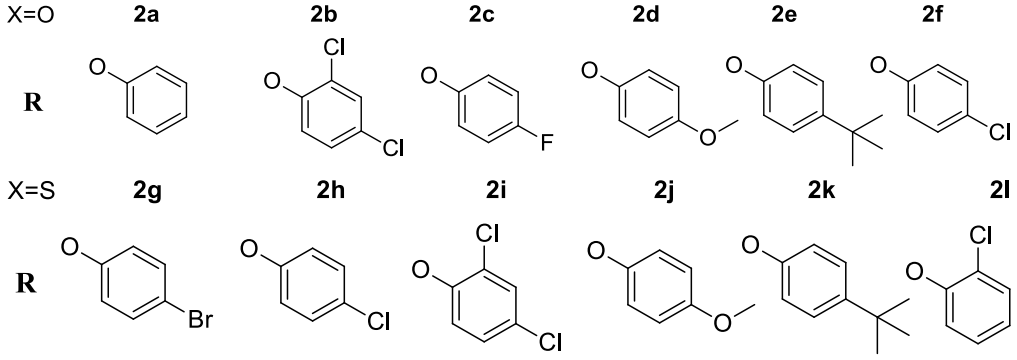
1a-l

	R	R1	Isomer
1a	4-methoxy	N-methyl piperazine	DL, cis
1b	4-methoxy	N-methyl piperazine	DL, trans
1c	3,4,5-trimethoxy	N-methyl piperazine	DL, trans
1d	3,4,5-trimethoxy	N-methyl piperazine	DL, cis
1e	4-methoxy	N-ethyl piperazine	L, trans
1f	4-methoxy	N-propyl piperazine	L, trans
1g	-H	N-methyl piperazine	D, cis
1h	4-methoxy	N-methyl piperazine	D, cis
1i	4-chloro	N-methyl piperazine	DL, trans
1j	4-methyl	N-methyl piperazine	DL, trans
1k	4-methoxy	Propylamine	DL, cis
1l	4-methoxy	Propylamine	DL, trans

Zhou *et al.* discovered the synthesis of dihydro-1,3,5-triazine subordinates with a heteroatom spiro-ring was on the foundation of molecular docking study and the biological performance of the compounds were evaluated. Excellent inhibitions were shown by compounds **2b**, **2e**, **2g** and **2i** with value of IC_{50} 7.46 μM, 3.72 μM, 6.46 μM, 4.08 μM, respectively. The studies identified 24 derivatives with broad spectrum of antiproliferative activity against a number of tumor cell lines i.e., HCT116, HL-60, A549, MDA-MB-231 and Hep-G2 with IC_{50} values in range of 0.001 to 0.79 mM.[9]

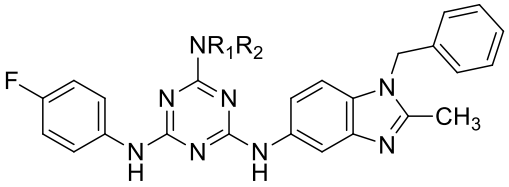


2a-l

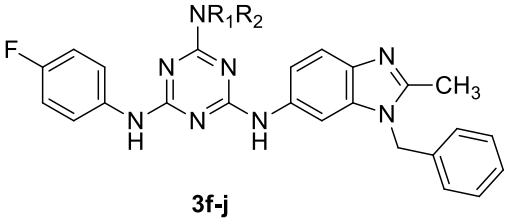


Singla *et al.* incorporated a series of molecular hybridized compounds of triazine-benzimidazoles foolowed by substitution 4-fluoroaniline. These synthesized compounds were expedited replaced with different type's amines. These triazine-benzimidazole molecules were appraised towards 60 human cancer cell lines and it was investigated that compounds **3a**, **3d** and **3j,** were the most active against MG-MID cell line having GI_{50} 1.77 μM, 1.94

μM and 2.87 μM, respectively. Futher evaluation with dihydrofolate reductase of these compounds were studied and observed that compound **3j** was exceedingly potent against the dihydrofolate reductase inhibition with IC_{50} 2.0 μM.[7]



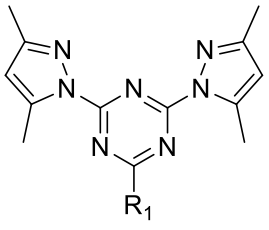
3a-e



3f-j

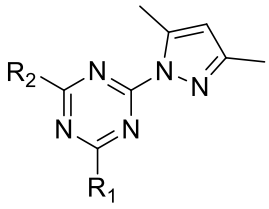
	NR_1R_2
3a	Piperidin-1-yl
3b	4-Aminofluorophenyl
3c	4-Methylpiperazin-1-yl
3d	Pyrrolidin-1yl
3e	Ethylenediamine
3f	2-Aminobenzonitrile
3g	Pyrrolidin-1-yl
3h	Ethylenediamine
3i	Ethanolamine
3j	2-Aminoethylmoprholine

Farooq *et al.* prepared a series of derivatives of mono-pyrazolyl triazine and di- pyrazolyl triazine. The four cell lines mainly, HepG2 (hepatocellular carcinoma), LoVo (colorectal carcinoma) K562 (leukemia), and MCF 7 (breast carcinoma) were chosen to study the anticancer activity of the compounds. The studies revealed that cytotoxicity was induced in all four categories of tumor cell lines by the triazine compounds. The compounds having piperidine moiety in structures **4a** and **5g** were most effective against cancer cells having IC_{50} values between 5 to 9 μM. The synthesized molecules were examined in embryos of zebrafish for checking *in-vivo* activity and advancement of toxicity of compounds in animals.[10]



4a-4e

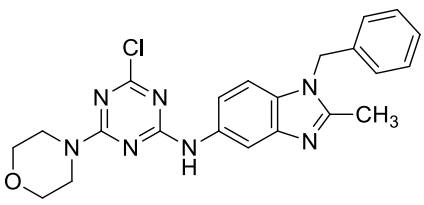
	R_1
4a	Piperidine
4b	Morpholine
4c	Benzyl amine
4d	N-methylbenzylamine
4e	Methoxy



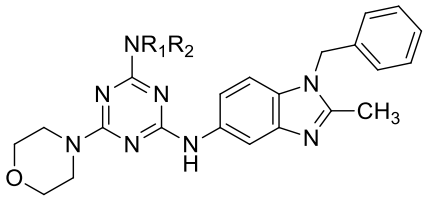
5a-5g

	R_1	R_2
5a	Piperidine	Benzylamine
5b	Morpholine	Benzylamine
5c	Morpholine	Aniline
5d	Morpholine	Piperidine
5e	Morpholine	Diethylamine
5f	Morpholine	Morpholine
5g	Piperidine	Piperidine

Singla *et al.* prepared series of hybrid compounds of triazine and benzimidazole moieties with distinct substitution of amine at triazine ring. The inhibitory activities concentrations of synthesized compounds were checked against 60 cancer cell lines. Broad spectrum of antitumor activity was displayed by compounds **7**, **6b** and **6c** having GI_{50} values of 9.79 μM, 2.58 μM and 3.81 μM, respectively. Substantial interactions of compounds were depicted by DNA binding studies. DHFR inhibition of mammalian was also exhibited by these compounds and it was depicted that compound **6f** proved to be excellent representative of DHFR inhibitor with IC_{50} 1.05 μM. [11]



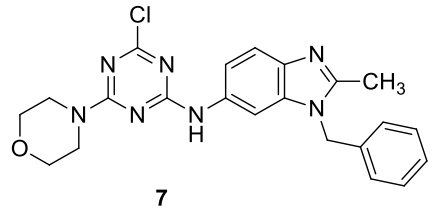
6



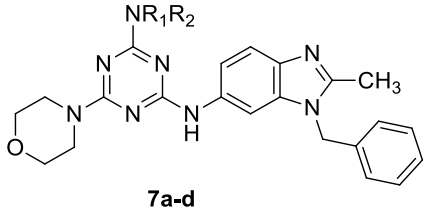
6a-f

NR_1R_2

6a morpholine
6b 4-fluoroaniline
6c piperidine
6d *N*-methylpiperazine
6e pyrrolidine
6f 1,2-ethylenediamine



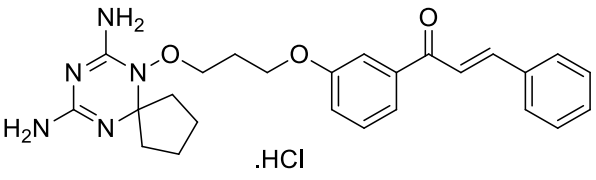
7



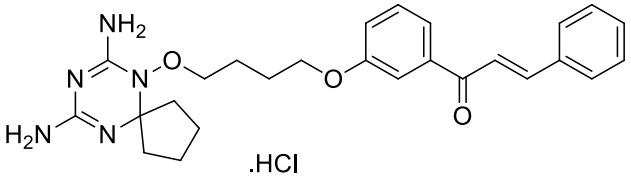
7a-d

7a morpholine
7b piperidine
7c pyrrolidine
7d *N*-methylpiperazine

Ng *et al*. prepared a novel series of 15 derivatives *via* diether linkage of 4,6-diamino-1,2-dihydro-1,3,5-triazine with chalcones. Synthesized compounds were tested towards DHFR and TrxR. The antiproliferative activity was exhibited by these compounds towards the MCF-7 and HCT116 cells. Compounds **8a** and **8b** were further evaluated to restrain biological DHFR and TrxR activities in HCT116 cells. It has been observed that compounds **8a** and **8b,** could utilize their anticancer activity by multitarget action at biological level that was implemented by this study.[12]



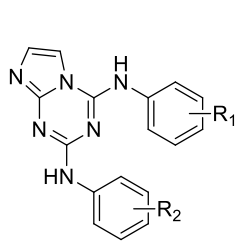
8a



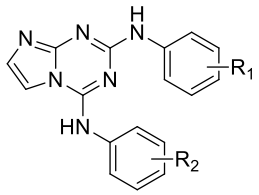
8b

Dao *et al.* synthesized a series of triazinic inhibitors of Focal Adhesion Kinase (FAK) and evaluated for antiangiogenic activity towards HUVEC cells and antitumour activity against

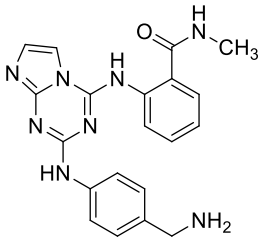
various cancer cell lines. Importantly, these new compounds displayed IC_{50} values of 10^{-7} - 10^{-8} M, and IC_{50} value of 50 nM was displayed by the best inhibitor towards FAK enzymatic activity. High levels of FAK were displayed by various inhibitors that significantly inhibited the proliferation of tumour cell lines.[13]



9a-e



10a-e

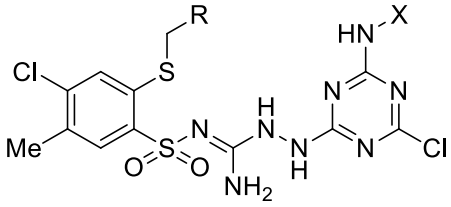


11

	R_1	R_2
9a	2-CO_2CH_3	3,4,5-trimethoxy
9b	2-$CONHCH_3$	3,4,5-trimethoxy
9c	3-CO_2CH_3	3,4,5-trimethoxy
9d	2-$CONHCH_3$	2-OCH_3 -4-morpholino
9e	2-$CONHCH_3$	4-$CH_2NHAlloc$

	R_1	R_2
10a	2-CO_2CH_3	3,4,5-trimethoxy
10b	2-$CONHCH_3$	3,4,5-trimethoxy
10c	3-CO_2CH_3	3,4,5-trimethoxy
10d	2-$CONHCH_3$	2-OCH_3- 4-morpholino
10e	2-$CONHCH_3$	4-$CH_2NHAlloc$

Zolnowska *et al.* prepared and examined the anti-malignant activity of novel series of triazine and guanidine derivatives. These compounds were active towards Hela, MCF-7, and HCT-116 tumour cell lines. Studies displayed that against Hela cancer cell lines, compound **12d** selectively exhibited outstanding cytotoxic effect with value of IC_{50} 17 μM and it also exhibited excellent inhibitory action against hCA IX (KI = 41 nM).[14]

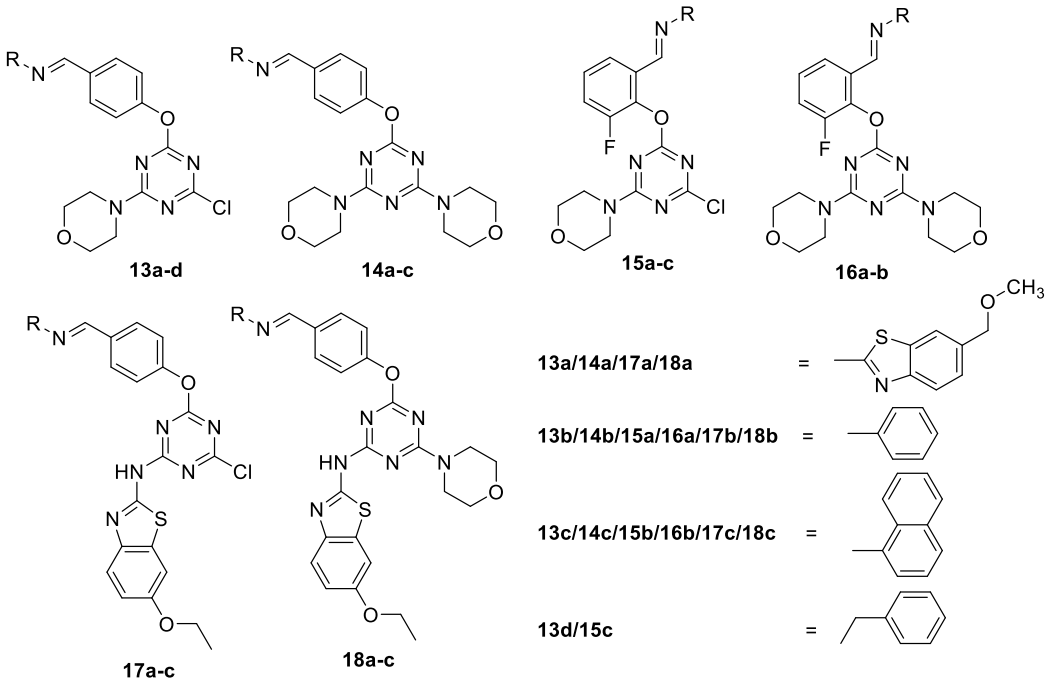


12a-l

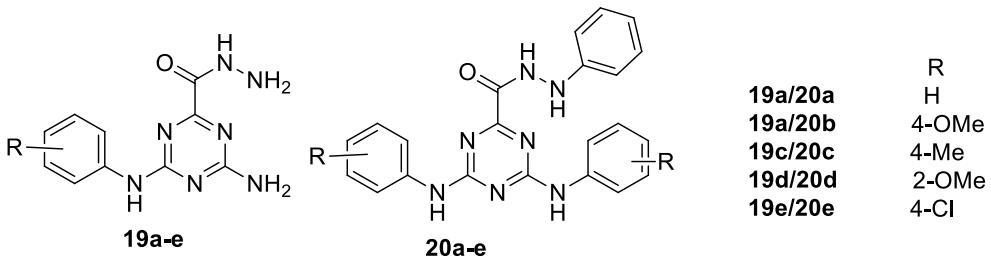
	R	X
12a	C_6H_5	4-$(H_2NSO_2)C_6H_4$
12b	3-$CF_3C_6H_4$	4-$(H_2NSO_2)C_6H_4$
12c	4- $CF_3C_6H_4$	4-$(H_2NSO_2)C_6H_4$
12d	1-naphthyl	4-$(H_2NSO_2)C_6H_4$
12e	C_6H_5	4-$(H_2NSO_2)C_6H_4CH_2$
12f	3-$CF_3C_6H_4$	4-$(H_2NSO_2)C_6H_4CH_2$
12g	4- $CF_3C_6H_4$	4-$(H_2NSO_2)C_6H_4CH_2$
12h	1-naphthyl	4-$(H_2NSO_2)C_6H_4CH_2$
12i	C_6H_5	3-$(H_2NSO_2)C_6H_4$
12j	3-$CF_3C_6H_4$	3-$(H_2NSO_2)C_6H_4$
12k	4- $CF_3C_6H_4$	3-$(H_2NSO_2)C_6H_4$
12l	1-naphthyl	3-$(H_2NSO_2)C_6H_4$

Shanmugam *et al*. discovered and synthesize a new arrangement of anticancer agents by utilizing s-triazine through amine and Schiff base analogue. To check the antiproliferative properties and *in vitro* cytotoxicity, all derivatives were screened against HT-1080 and HeLa cell lines. The compounds **13c, 13d** and **14c** were evaluated for their mitochondrial layer potential (MMP), receptive oxygen species (ROS) properties and apoptosis (AO/EtBr) action

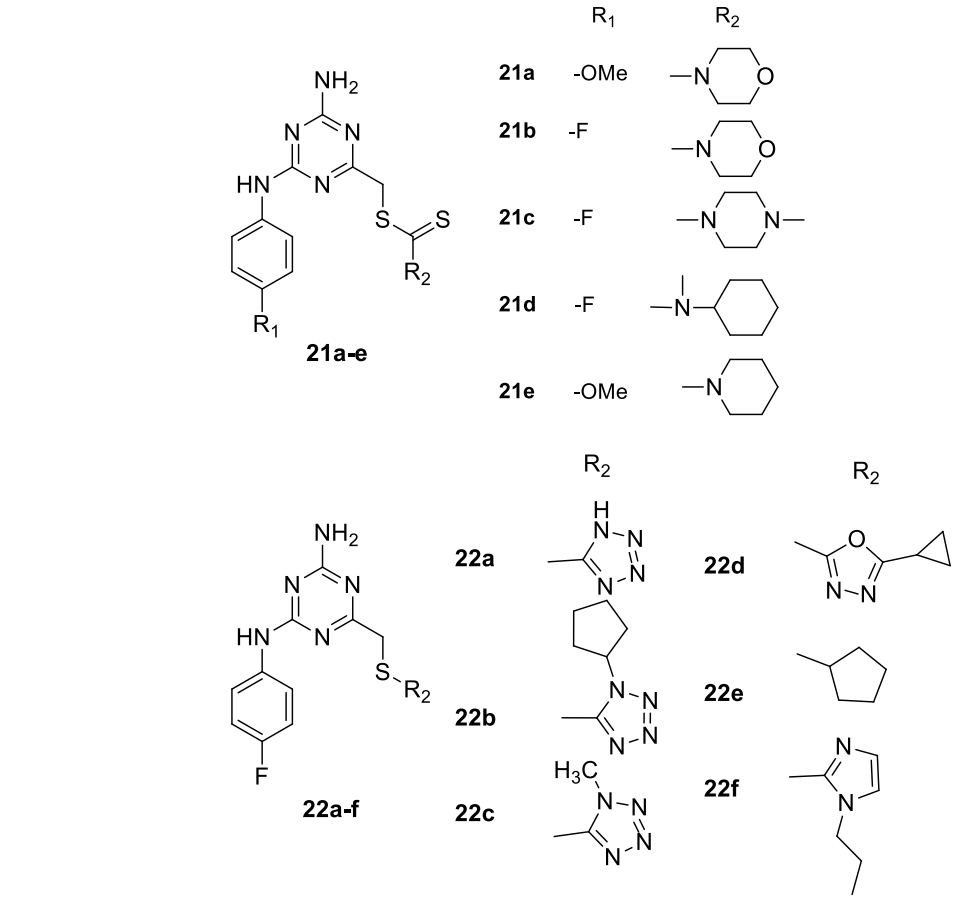
towards HT-1080 malignant growth cell line. Excellent anticancer activities were found for these compounds.[15]



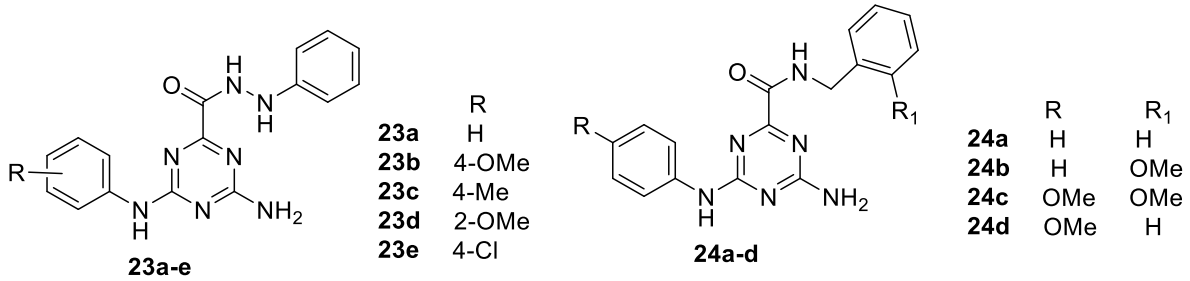
Kothayer *et al.* worked on triazine based moieties to form derivatives **19a–e** and **20a–e**. These compounds were observed to restrain Rad6B ubiquitin conjugation. Their *in-vitro* antitumor activity was examined towards various cancer cell lines *viz.*, H1299, HT29, OV90, A2780, and MDA-MB231 cancer cells. These derivatives displayed better IC_{50} values against different malignant cell lines and the derivatives from **20a-c** showed less IC_{50} values (3.3–22 μM) in comparison to TZ9.[16]



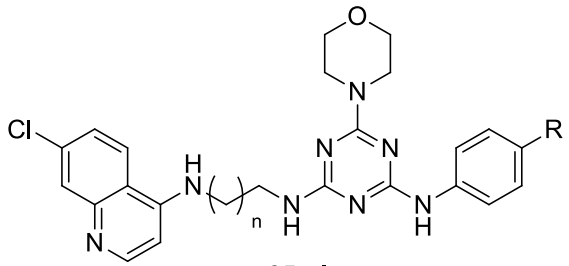
Pogorelcˇnik *et al.* worked on human DNA topoisomerase IIa (htIIa) that is an approved focus on the advancement of antitumor agents. From the studies it was found that novel 4-amino-6-(phenylamino)-1,3,5-triazines derivatives **21a, 21b** and **22a** worked as monocyclic htIIa inhibitors focusing on the ATP restricting site. Compound **21d** showed cytotoxic effect in HepG2 cell lines and selectivity towards HUVEC cell lines.[17]



Kothayer *et al.* formed a series of 1,3,5-triazine-2-carbohydrazides and -carboxamide derivatives based on molecular hybridization. These triazine analogues were examined for antitumor activity towards MDA-MB-231 and MCF-7 malignant cell lines. The compounds **23a-e**, exhibited significantly low value of IC_{50} towards MDA-MB-231 cell line. The derivatives **23a-e** were most active against MDA-MB-231 cells, and derivative **24c** was most effective towards MCF-7 cells.[18]



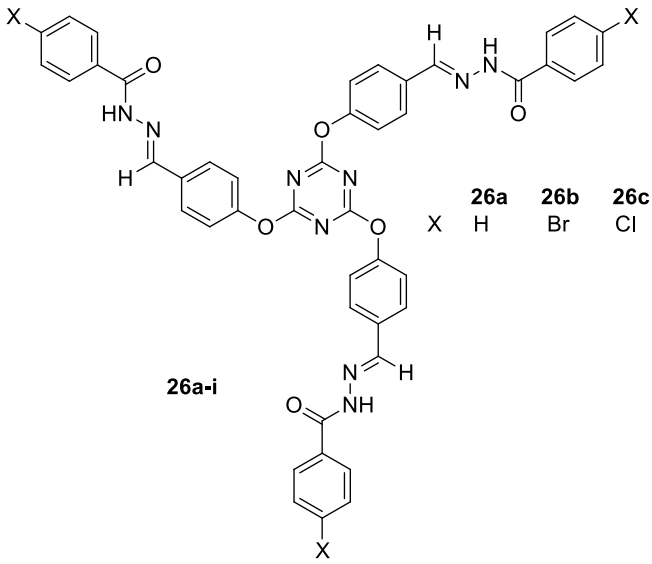
Manohar *et al.* made a new series of 4-amino quinoline-triazine based hybrid and examined their anticancer activity towards tumor cell lines (NCI 60). The synthesized derivatives displayed apoptosis effect and also showed activity on a spectrum of cell lines. The study of both compounds **25h** and **25k** revealed that they displayed excellent inhibition towards NCI 60 cell lines.[19]



	n	R		n	R
25a	1	H	**25g**	2	OMe
25b	2	H	**25h**	1	OMe
25c	3	H	**25i**	3	OMe
25d	1	Et	**25j**	2	F
25e	2	Et	**25k**	1	F
25f	3	Et	**25l**	3	F

25a-l

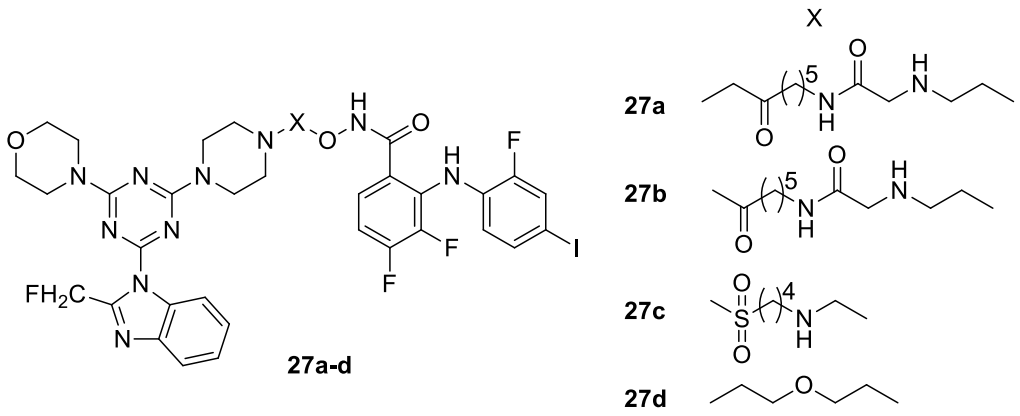
Machakanur *et al.* incorporated trisubstituted triazine hydrazones series and examined for anticancer activity. The formed molecules were examined towards HepG2 and HeLa cell lines to obtain the anticancer activity and it was depicted that these compounds displayed reduced activity towards Hela cells and constrained cytotoxicity towards HepG2 cell lines.[20]



	26a	**26b**	**26c**	**26d**	**26e**	**26f**	**26g**	**26h**	**26i**
X	H	Br	Cl	F	OH	OCH_3	CH_3	NO_2	NH_2

26a-i

Dort *et al.* prepared a series of compounds which were inhibitors of PI3K ($54 < IC_{50}$ (μM) < 341) and MEK1 ($0.015 < IC_{50}$ (μM) < 56.7) in enzymatic inhibition assays. MEK1 and PI3K inhibitions were evaluated with **27b** and **27d** against A549 and D54 cancer cell lines. *In vivo* efficiency of 14 derivatives was depicted through oral administration in A549 lung and D54 glioma cancer bearing mice. It was examined that molecule **27d** displayed 67% and 95% inhibition against Akt phosphorylation and ERK1/2 tumors, respectively. Their P13K and MEK1 activities were confirmed by western blot analysis.[21]



3. RESEARCH GAP AND OBJECTIVES

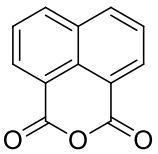
The deep study of literature suggested that triazine and naphthalimide scaffolds individually exhibit convincing anticancer properties. The compounds containing pharmacophore active moieties naphthlimide and 1,3,5-triazine in one structure have not been reported till now in the literature. To accomplish this gap, our main objective is to design new molecules by the consolidation of two biological active moieties *viz.*, 1,3,5-triazine and naphthalimide as drug candidates and characterize the synthesized molecules using NMR spectroscopic technique.

4. EXPERIMENTAL

4.1 Material and Methods

All the solvents and chemicals used were taken from Sigma-Aldrich, Loba, Spectrochemicals and were used as purchased. Melting points (^oC) were calculated with the help of melting point digital apparatus (equiptronics). To record ^1H NMR spectra of compounds in $CDCl_3$ as solvent Bruker 400 MHz NMR was used using tetramethylsilane as an internal standard the chemical shift was indicated as ppm and *J* values were calculated in Hz. Thin layer chromatographic technique was used to monitor the reactions and silica gel mesh 60-120 was used for column chromatography. Chloroform and ethyl acetate were the accepted solvents for TLC and column chromatography.

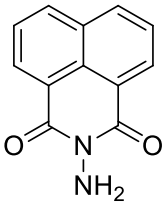
4.2. Synthesis of benzo[*de*]isochromene-1,3-dione (2):



Acenaphthene (**1**) (2.0 g, 12.98 mmol) was mixed in 50 ml acetic acid in 100 ml RBF and potassium dichromate (10 g, 65 mmol) was mixed in portion to the reaction on ice bath and was permitted to mix at room temperature (RT) for 15 min. The reaction was stirred with constant heating for 3h. Time to time TLC was checked to screen the reaction. 250 ml H_2O was added in the reaction mixture on completion of reaction. Formed

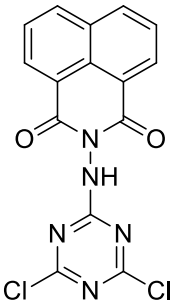
precipitates were filtered. Yield: 95%; colour: yellow; m.pt.: 148-151 ^{o}C

4.3. Synthesis of 2-amino-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (3):



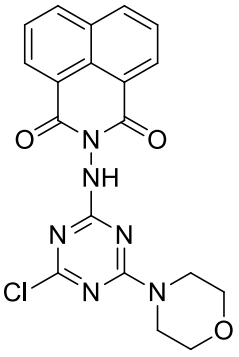
Benzo[*de*]isochromene-1,3-dione (**2)** (1 g, 5.05 mmol) was dissolved in 20 ml ethanol and then add hydrazine hydrate (160 mg, 5.05 mmol) to the reaction mixture and was permitted to stir at room temperature for 1 h. On completion the reaction mixture was filtered and washed with ethanol to get solid residue. Yield: 92%; colour: yellow; m.pt.: 165-168 ^{o}C

4.4. Synthesis of 2-((4,6-dichloro-1,3,5-triazin-2-yl)amino)-5*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (5):



2-Amino-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (**3**) (1 g, 4.71 mmol) was dissolved in 20 ml isopropyl alcohol and then added cyanuric chloride (**4**) (1.04 g, 5.45 mmol) to the reaction mixture and was stirred at RT for about 6 h. After completion of reaction, 250 ml of water was added to it and the product formed was filtered and purified with the help of column chromatography using ethyl acetate and chloroform as eluents. Yield: 80%; colour: creamish; m.pt.: 172-175 ^{o}C

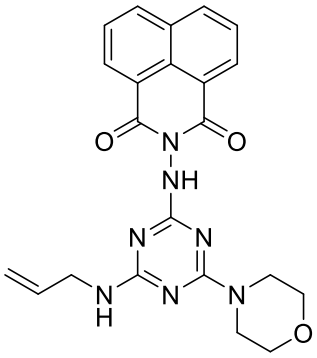
4.5. Synthesis of 2-((4-chloro-6-morpholino-1,3,5-triazine-2-yl)amino)-5*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (7):



2-((4,6-dichloro-1,3,5-triazine-2-yl)amino)-5*H* benzo[*de*]isoquinoline1,3(2*H*)-dione (**5**) (500 mg, 13.80 mmol) was added to 10 ml isopropyl alcohol. Morpholine (**6**) (120 mg, 13.80 mol) was mixed in the reaction mixture and it was stirred at RT. for 3 h. The reaction was monitored by TLC. 250 ml of water was poured to the reaction mixture after completion of reaction the product formed was filtered and purified by using column chromatography with chloroform and ethyl acetate as eluents.. Yield: 75%; colour: white; m.pt.: 208-211 ^{o}C

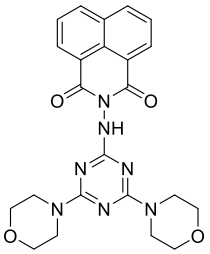
4.6. Synthesis of 2-((4-amino(substituted)-6-morpholino-1,3,5-triazin-2-yl)amino)-1*H*benzo[*de*]isoquinoline-1,3(2*H*)-dione (8a-b): compound **7** (100 mg, 24.39 mmol) was dissolved in 10 ml isopropyl alcohol. Different amines (36.58 mmol) were added in the reaction and it was permitted to reflux for 10-15 h. Screening of reaction was done by using TLC. After the reaction was completed, 100 ml of water was added to it and the precipitates formed were filtered and purified with the help of column chromatography using ethyl acetate and chloroform as eluents.

4.6.1. Spectral data of 2-((4-(allylamino)-6-morpholino-1,3,5-triazin-2-yl)amino)-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (8a):



Yield: 71%; colour: white; m.pt.: 240-246 ºC; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.64 (d, *J* = 7.24 Hz, 2H, ArH), 8.27 (d, *J* = 8.16 Hz, 2H, ArH), 7.79 (t, *J* = 7.68 Hz, 2H, ArH), 5.89-5.76 (m, 1H, CH-allyl), 5.14 (dd, 2H, CH_2-allyl), 3.91 (br (s), 2H, CH_2-allyl), 3.63 (br (s), 8H, 4 × CH_2 morph)

4.6.2. Spectral data of 2-((4,6-dimorpholino-1,3,5-triazin-2-yl)amino)-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (8b):

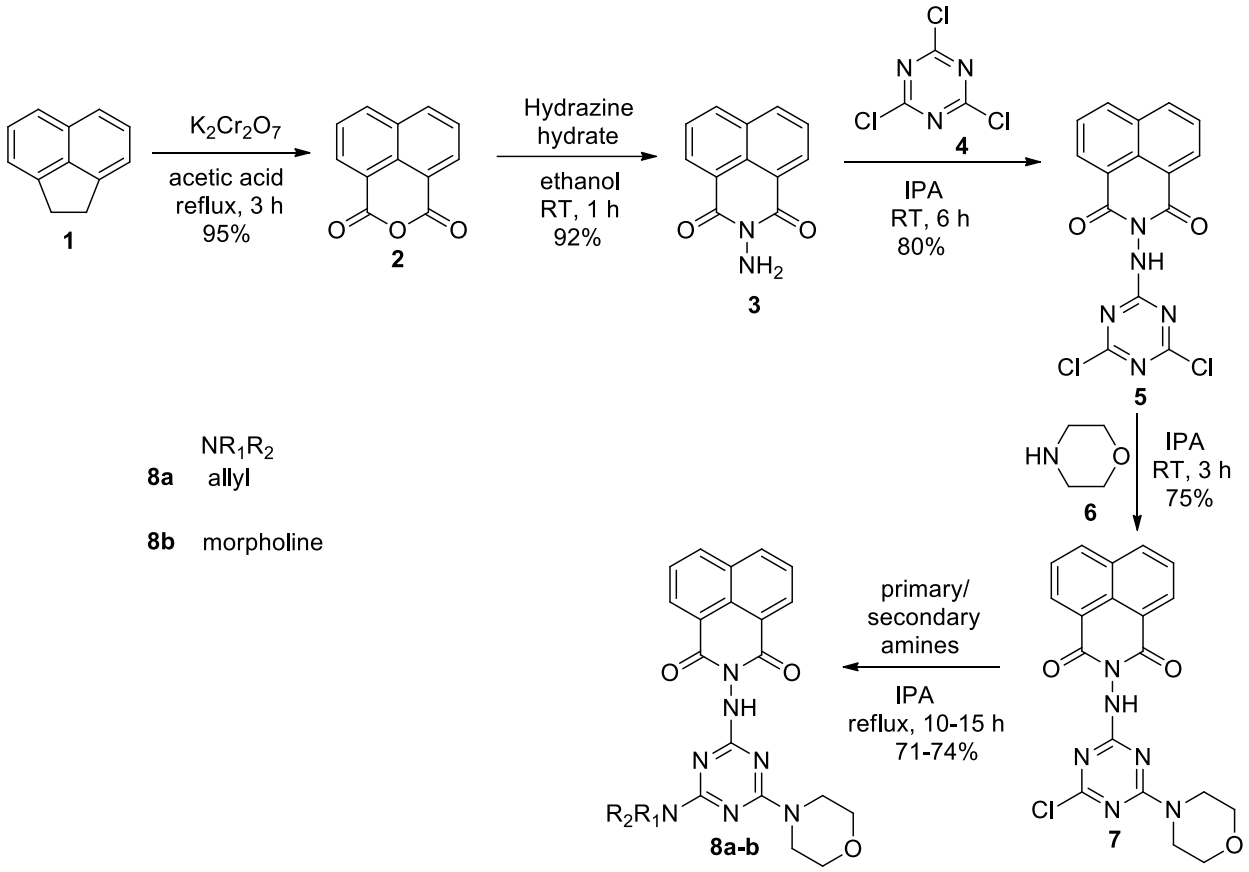


Yield: 74%; colour: white; m.pt.: 233-247 ºC; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.67 (d, *J* = 5.80 Hz, 2H, ArH), 8.29 (d, *J* = 6.48 Hz, 2H, ArH), 7.82 (t, *J* = 6.08 Hz, 2H, ArH), 3.64 (br (s), 16H, 8 × CH_2 morph)

5. RESULTS AND DISCUSSION

1,3,5-Triazine derivatives (**8a-b**) were synthesized by commercially available acenaphthene as starting material mentioned in **Scheme 1**. Acenaphthene (**1**) was reacted with potassium dichromate in acetic acid for 3 h at refluxing temperature to obtain a yellow coloured benzo[*de*]isochromene-1,3-dione (**2**) in 95% yield (m.pt.: 148-151 ºC). Compound **2** was further reacted with hydrazine hydrate in presence of ethanol at room temperature for 1 h and after work up with ethanol, obtained yellow colour compound 2-amino-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (**3**) in 92% yield. Compound **3** on further reaction with

cyanuric chloride (**4**) in isopropyl alcohol gave a cream coloured compound 2-((4,6-dichloro-1,3,5-triazine-2-yl)amino)-5*H*-benzo[*de*]isoquinolin-1,3-(2*H*)-dione (**5)** in 80% yield. Intermediate 2-((4-Chloro-6-morpholino-1,3,5-triazine-2-yl)amino)-5*H* benzo[*de*]isoquinoline1,3(2*H*)-dione (**7**) was obtained in 75% yield by reaction of morpholine (**6**) with derivative **5** in isopropyl alcohol for 3 h at room temperature. To obtain the targeting compounds allyl amine, morpholine were treated with intermediate **7** in presence of isopropyl alcohol for 10-12 h at refluxing condition to obtain derivatives **8a** and **8b** in 71% and 74% yields, respectively. All the targeted compounds were well characterized by ^{1}H NMR spectroscopic method.



Scheme 1. Synthesis 2-((4-amino(substituted)-6-morpholino-1,3,5-triazin-2-yl)amino)-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (8a-b)

^{1}H NMR spectrum of derivative (**8a**) showed broad splitting pattern from δ 8.64-3.63 ppm that corresponds to six aromatic protons and characteristic peaks of allyl group (one proton showed multiplet at δ 5.89 ppm corresponding to CH of allyl , two protons showed doublet of

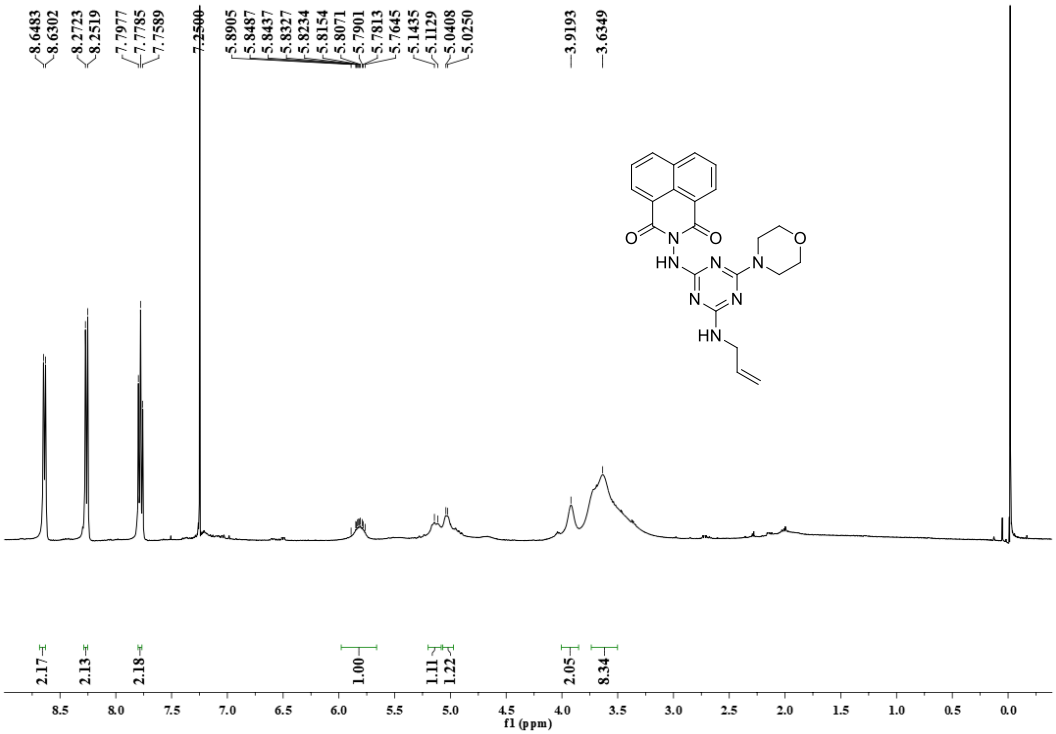


Figure 4. ^{1}H NMR spectrum of derivative **8a**

doublet at δ 5.14 ppm corresponding to two protons of CH_2 groups of allyl, two protons showed broad singlet at δ 3.91 ppm corresponding to two protons of N-CH_2 group of allyl). Formation of compound **8a** was confirmed by broad singlet appeared at δ 3.64 ppm corresponding to eight protons of CH_2 of morpholine ring in aliphatic region.

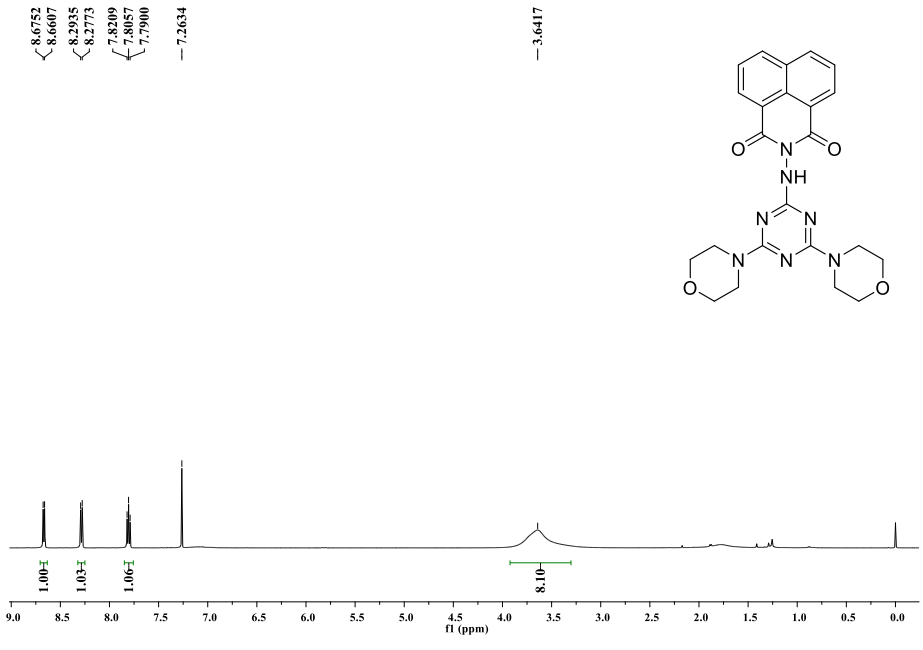


Figure 5. ^{1}H NMR spectrum of derivative **8b**

^{1}H NMR spectrum of deriavtive **8b** exhibited broad splitting pattern from δ 8.67-3.64 ppm corresponding to six aromatic protons and formation of compound **8b** was confirmed by a characteristic peak of morpholine ring of a broad singlet at δ 3.64 ppm corresponding to sixteen protons of eight CH_2 groups of two morpholine rings in aliphatic region.

6. CONCLUSION:

- Intermediates such as **5** and **7** were synthesized in gram scale with good yields.
- Two derivatives of naphthalimide and 1,3,5-triazine hybrids molecules **8a** and **8b** were synthesized in good yields and formation compound was characterized by ^{1}H NMR spectroscopy.
- Synthesized molecules will be used further for investigation of their biological activities as antitumor agents.

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