Chapter 3

1,3,5-Triazine Based Compounds: Synthesis and Anti-Cancer Activities

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Abstract

The emergence of heterocyclic compounds containing one or more nitrogen atoms has gained much attention owing to their various biological activities. Among different nitrogen containing heterocyclic compounds, compounds with 1,3,5-triazine motif have recently gained a special attention for their potent anti-proliferative activities. In this focus book chapter, we highlight the recent advance in the development of 1,3,5-triazine based anti-cancer compounds reported since the year 2010.

Keywords

1,3,5-Triazine, Anti-Cancer Agents, Heterocycles,
Biologically Active Molecules, Chemotherapy, Drugs

3.1 Introduction

Cancer is one of the leading causes of death worldwide, accounting for 8.2 million deaths in 2012 [1]. The most common forms of cancer are lung cancer (1.59 million deaths), liver cancer (745,000 deaths), colorectal cancer (694,000 deaths), stomach cancer (723,000 deaths), breast cancer (521,000 deaths), and esophageal cancer (400,000 deaths) [1]. Cancer is also a leading cause of death in children ages 5-14 [2]. It is estimated that 1 in 285 children is diagnosed with cancer before the age of 20 in United States [3].

Among different techniques used to cure cancer, chemotherapy (use of drugs to kill cancer cells) is most popular and well-studied [4]. Although a plenty of compounds have been discovered as effective anti-cancer agents so far, the search of safer, cheaper, and more efficient anti-cancer drugs is still one of the hottest topics of research worldwide.

In the recent past, compounds containing one or more heterocyclic rings have shown promising anti-cancer and other biological activities [5-12]. Especially, compounds possessing triazine ring in their structures have shown promising anti-cancer activities.

Triazines are a class of nitrogen-containing heterocycles with molecular formula $C_3H_3N_3$. Triazines exist in three isomeric forms i.e. 1,2,3-triazine, 1,2,4-triazine, and 1,3,5-triazine (Figure 1).

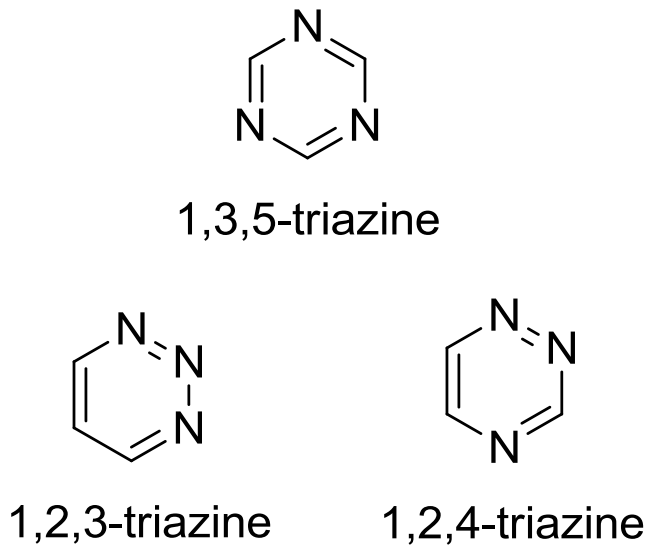
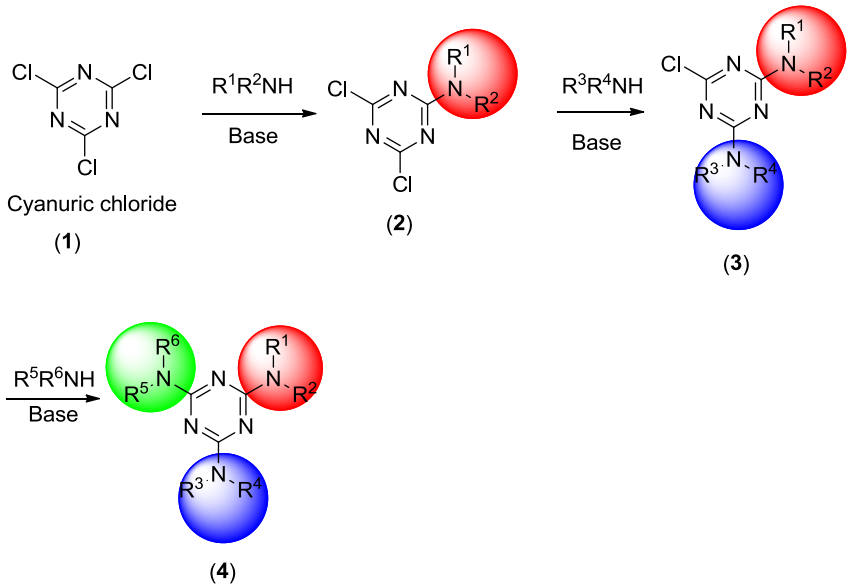


Figure 1. *Structures of three isomeric forms of triazine.*

Among three isomers, 1,3,5-triazine is most common and studied one. The common method of synthesis of 1,3,5-triazine derivatives is starting from cyanuric chloride, a chlorinated derivative of 1,3,5-triazine [13]. The ease of displacement of chlorine atoms of cyanuric chloride by a variety of nucleophiles in the presence of different bases has made this reagent very useful for selective preparation of mono-, di-, and tri-substituted-1,3,5-triazines. The substitution pattern also depends upon the structure of nucleophiles, strength of base used, steric factors, substituents in the triazine ring, and solvents. Scheme 1 depicts the general scheme of synthesis of 1,3,5-triazine derivatives using amines as nucleophilic species.



Scheme 1. *Synthesis of different 1,3,5-triazine derivatives.*

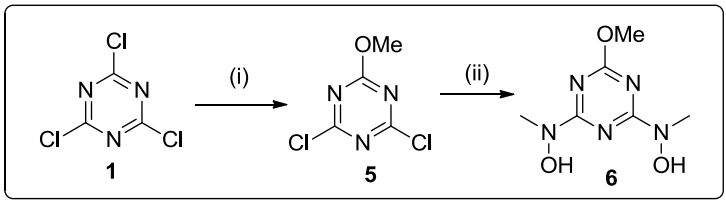
Because of significant amount of work done in this area, it is important to focus on those recent reports in which 1,3,5-triazine based compounds have been discovered as anti-cancer agents. In this focus book chapter, we highlight the recent advance in the development of 1,3,5-triazine based anti-cancer compounds reported since the year 2010.

3.2 Synthesis and Anti-Cancer Actvities of 1,3,5-Triazine Derivatives

Sun and co-workers synthesized compound 6 by monosubstitution of a chlorine atom of 1 with a methoxy group, followed by treatment with an excess of *N*-methylhydroxylamine (Scheme 2). Compound 6 displayed potent ant-cancer activities against MiaPaCa and MDA-MB-231 cell lines (IC_{50} values of 0.6 and 5 μM against MiaPaCa and MDA-MB-231 cell lines, respectively) [14]. The activity of compound 6 was much better than standard drug DFX (Scheme 2).

Kumar and co-workers and co-workers synthesized some 1,3,5-triazine based tetrahydro-β-carbolines (9-11) by using the synthetic strategy depicted in Scheme 3 [15].

(A)



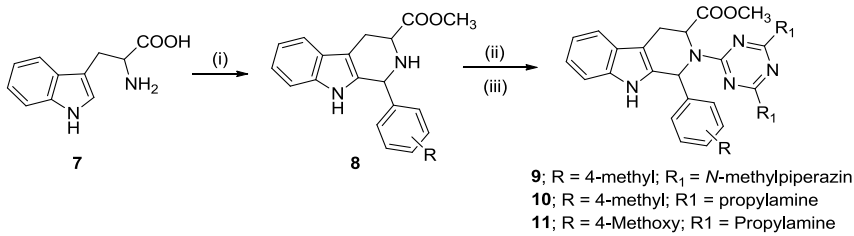
(B)

Cytotoxicity, IC_{50} (μM) of **6**		
MiaPaCa	MDA-MB-231	Foreskin fibroblasts
0.6 ± 0.2	5.0 ± 2.0	100 ±10

Cytotoxicity, IC_{50} (μM) of Deferasirox		
MiaPaCa	MDA-MB-231	Foreskin fibroblasts
4 ± 1	10 ± 2.5	100 ±10

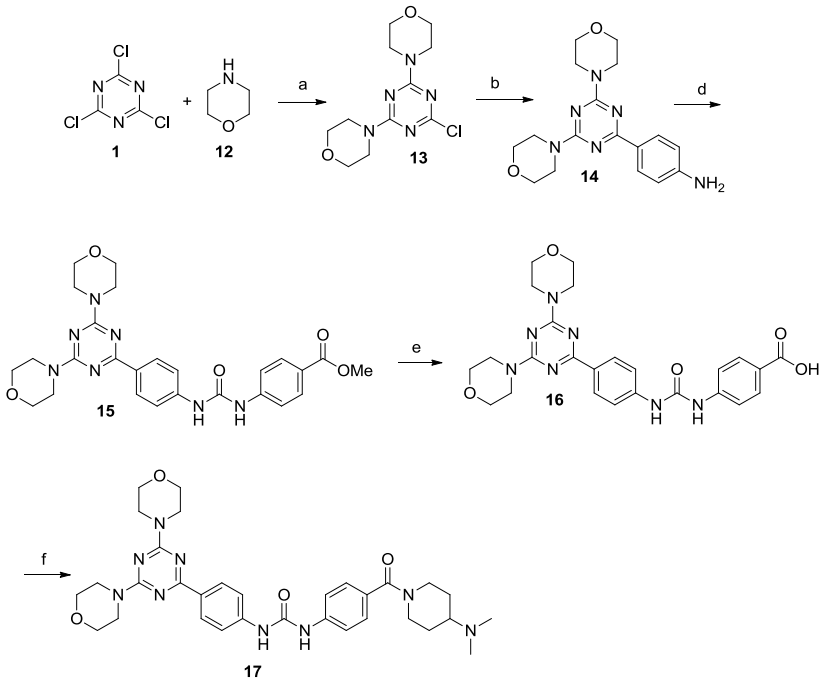
Scheme 2. *(A) Reagent and conditions: (i) MeOH, 2,6-lutidine; (ii) MeNHOH, excess; (B) Anti-cancer activities of compound 6 and Deferasirox.*

First, the tetrahydro-β-carbolines (8) were synthesized *via* Pictet-Spengler cyclization of methyl ester of tryptophan with different substituted benzaldehydes, followed by nucleophilic substitution of one chloro group of cyanuric chloride and then displacement of the remaining two chloro groups with different amines as shown in scheme 3. All compounds were then assayed for their anti-proliferation effects against eight human cancer cell lines and normal human fibroblasts (NIH3T3) [15]. Among all compounds screened, 9, 10, and 11 displayed promising cytotoxic effects against KB (oral cancer) cell lines with IC_{50} values of 105.8, 664.7, and 122.2 nM, respectively.



Scheme 3. *Reagents and Conditions: (i) Thionyl chloride, MeOH, various benzaldehydes, (ii) Cyanuric chloride, K_2CO_3, THF, 0 ℃ - r.t. (iii) Amines, K_2CO_3, THF, Reflux.*

Venkatesan and co-workers synthesized compound 17 by using the synthetic route shown in scheme 4 [16]. First, the chlorines atoms of cyanuric chloride 1 were replaced with 2 equivalents of morpholine 12 to yield 13, followed by displacement of third chlorine by a 4-aminophenyl group employing Suzuki coupling to give compound 14. The compound 14 was then reacted with methyl 4-isocyanatobenzoate in DCM to give compound 15 in a quantitative yield, followed by ester group hydrolysis to yield compound 16. The acid derivative 16 was then reacted with *N*(Me)2-piperidnine in the presence of HOBt/EDCI and triethylamine to furnish compound 17 in 52% yield. The compound 17 showed excellent *in vitro* inhibiting potential against PI3KR, PI3Kγ, and mTOR along with good microsomal stability (Table 1). The compound 17 was also evaluated against a panel of 236 other human protein kinases at 10 μM concentration, and was found to be highly selective for PI3K and mTOR.

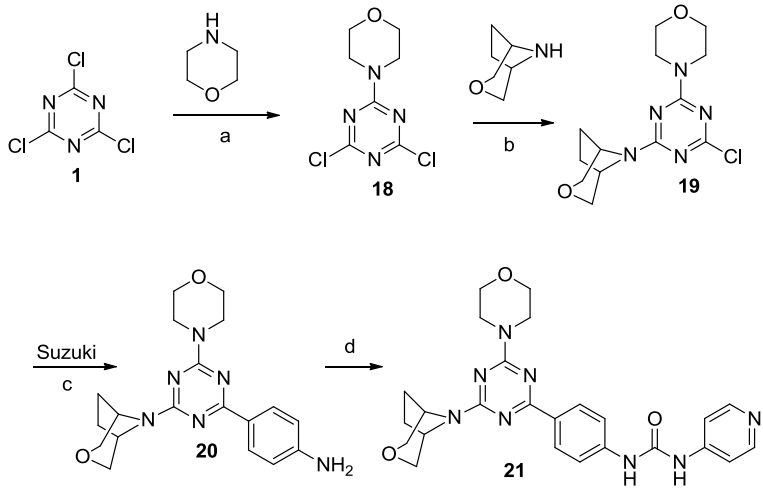


Scheme 4. *Reagents and conditions. (a) Et_3N (5q.), acetone, crushed ice, -20 ℃-0 ℃; (b) 4-Aminophenylboronic acid, pinacol ester (1.2 eq), $Pd(Ph_3P)_4$ (5 mol%), DME, 2M Na_2CO_3, reflux, 8h; (d) Methyl-4-isocyanatobenoate (1.1 eq), CH_2Cl_2, RT; (e) 5N NaOH (3 eq), MeOH, THF, 70 ℃, 12h; (f) Amines (2 eq), HOBt (1.5 eq), Et_3N (2 eq), THF, rt, 12h.*

Table 1. *In vitro activity of compound 17.*

IC_{50} (nM)				
PI3K-α	**PI3K-γ**	**PI3K-γ**	**MDA-361**	**PC3-MM2**
0.4	5.4	1.6	4.0	13.1

Later on, the same group discovered compound 21 bearing a 3-oxa-8-azabicyclo[3.2.1]octane moiety to be potent and orally efficacious dual PI3K/mTOR inhibitor displaying an excellent *in vitro* cell activity (table 2) and a good *in vivo* efficacy in the MDA-361 xenograft model [17]. The synthesis of compound 21 is displayed in scheme 5.

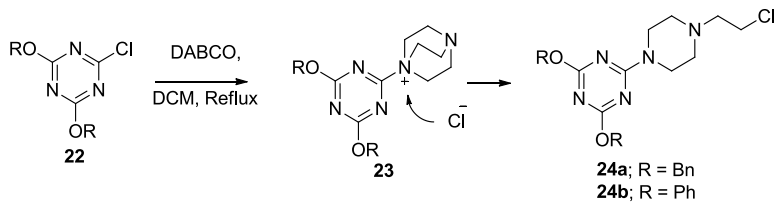


Scheme 5. *Reagents and conditions: (a) morpholine (1.1 equiv), Et_3N (2 equiv), acetone, crushed ice 20 ℃ to 0 ℃; (b) 1.1 equiv of 5, Et_3N (2 equiv), CH_2Cl_2, room temperature; (c) 4-aminophenylboronic acid, pinacol ester (1.2 equiv), $Pd(Ph_3P)_4$ (5 mol %), DME, 2 M Na_2CO_3, 120 ℃/30 min, microwave irradiation; (d) triphosgene (0.6 equiv), Et_3N (3 equiv), CH_2Cl_2, room temperature, 15 min, then 4-aminopyridine (5 equiv), 2-6 h.*

Table 2. *In vitro enzyme inhibition and cell proliferation inhibition IC50 (nM) values and calculated c log P values of 21.*

PI3K-α	PI3K-γ	mTOR	MDA361	PC3	c log P
8	74	0.42	22	29	2.12

Kolesinska and co-workers synthesized compounds 24a and 24b by replacement of chlorine of corresponding starting triazines by DABCO as shown in scheme 6.



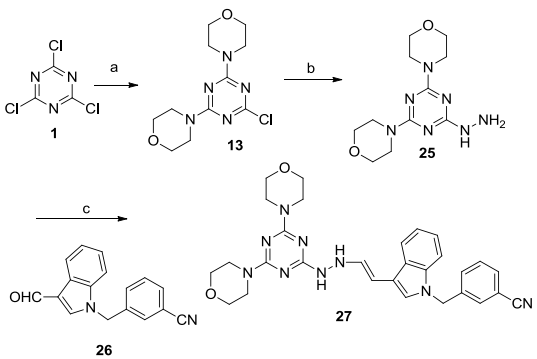
Scheme 6. *Reagent and conditions. DABCO (10 mmol), DCM (10 mL), Reflux.*

Both compounds showed good tendency to inhibit different cancer cell lines such as breast cancer T47D, prostate cancer LNCaP, colorectal cancer SW707, lung cancer A549, and lymphoblastic leukemia Jurkat [18]. The IC_{50} values of both compounds against these cancer cell lines are given in table 3.

Table 3. *IC50 values of compound 24a and 24b against different cancer cell lines.*

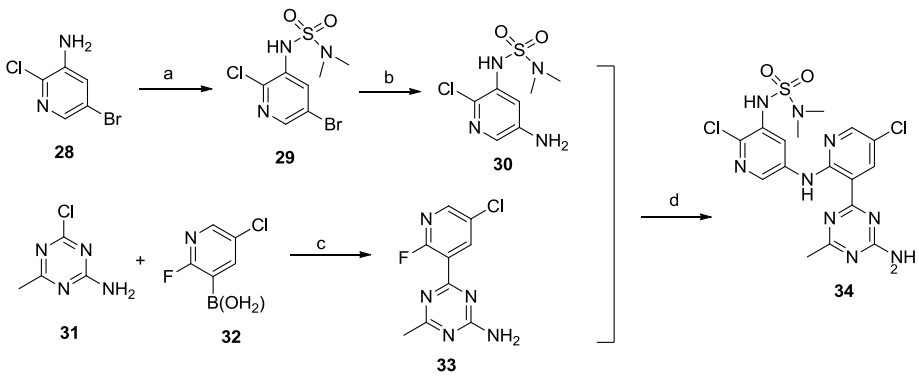
Compd	**Cell line/IC_{50} [µg/mL] mean ± SD**				
	breast cancer T47D	**prostate cancer LNCaP**	**colorectal cancer SW707**	**lung cancer A549**	**lymphoblastic leukemia Jurkat**
24a	1.40 ± 0.33	0.99 ± 0.52	3.45 ± 0.28	2.06 ± 0.66	0.62 ± 0.15
24b	2.60 ± 0.99	1.47 ± 0.95	2.93 ± 0.81	2.67 ± 1.33	2.93 ± 0.36

Zhu and co-workers synthesized compound 27 by using the synthetic strategy shown in scheme 7. First, the replacement of two chlorine atoms of cyanuric chloride with morpholine, followed by substitution with hydrazine gave compound 25 as a pale yellow solid [19]. Condensation of compound 25 with aldehyde 26 in EtOH/acetic acid afforded the target compounds 27 in a quantitative yield. Compound 27 was then evaluated for its anti-proliferative effects against five cancer cell lines (H460, HT-29, MDA-MB-231, U87MG, and H1975). It showed strong anti-proliferative activity against H460, HT-29, and MDA-MB-231 cell lines with IC_{50} values of 0.05, 6.31, and 6.50 µM, respectively.



Scheme 7. *Reagents and conditions. (a) Morpholine (2eq), TEA (3 eq), Acetone/Water, -10 ℃, 1h, rt; (b) 80% $NH_2NH_2.H_2O$, 80 ℃; (c) CH_3COOH (cat.), EtOH, rt.*

Wurtz and co-workers synthesized compound 34 by using the synthetic strategy shown in Scheme 8 [20]. Compound 30 was prepared from commercially available 3-amino-5-bromopyridine 28 by its treatment with dimethylsulfamoyl chloride to afford compound 29 which was then converted into compound 30 by palladium-catalyzed cross-coupling followed by hydrolysis with 1 N HCl. On the other hand, compound 33 was synthesized by Suzuki coupling of 31 with boronic acid 32. Base-promoted SNAr displacement of the 2-fluoropyridine 33 with compound 30 afforded desired compound 34 in quantitative yield.



Scheme 8. *Reagents and conditions: (a) $N(Me)_2SO_2Cl$, pyridine, DMAP; (b) (i) $Pd_2(dba)_3$ (5 mol %), Xantphos (10 mol %), benzophenone imine (1.1 equiv), NaO-t-Bu (4 equiv), DMF, microwave, 140 ℃, 20 min; (ii) THF, 1 N HCl, RT, 30 min; (c) $(4\text{-}NMe_2C_6H_4Pt\text{-}Bu_2)_2PdCl_2$ (Amphos, 5 mol %), KOAc (3 equiv), 100 ℃, 1,4-dioxane, 16 h; (d) LiHMDS or NaHMDS (4 equiv.), DMF or THF, 0 ℃ to rt.*

Compound 34 was found to be promising PI3K [21] inhibitor displaying moderate selectivity over the mammalian target of rapamycin (mTOR) in the enzyme assay. In a U87 MG cellular assay measuring phosphorylation of Akt, compound 34 displayed potent IC_{50} value of 24 nM along with good oral bioavailability in rats (F = 63%) (Tables 4 and 5).

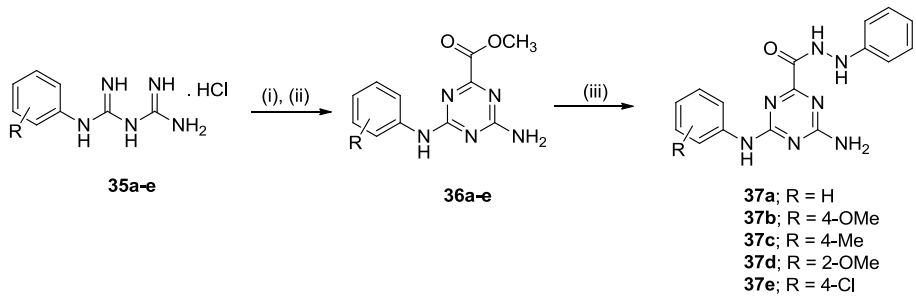
Table 4. *Enzyme and cellular assay of compound 34 against PI3K.*

Compd	PI3K Ki (nM)	pAkt (U87 MG) IC_{50} (nM)	cLogP
34	12	24	2.1

Table 5. *Pharmacokinetic properties of compound 34.*

Compd	*In vivo* rat PK				
	i.v.			po	
	CL (L/h/ kg)	Vdss (L/ kg)	MRT (h)	%F	AUC (ng h/mL)
34	0.39	0.97	2.5	63	3360

Kothayer and co-workers synthesized 4-amino-6-(arylamino)-*N*-phenyl-1,3,5-triazine-2-carbohydrazides (37a-e) in two steps from commercially available arylbiguanide hydrochloride salts (35a-e) (Scheme 9) [22]. First, neutralization of the arylbiguanide hydrochloride salt with sodium methoxide/methanol was performed, followed by treatment with dimethyloxalate to afford methyl 4-amino-6-(arylamino)-1,3,5-triazine-2-carboxylates (36a-e) in a good range of yields. Reaction of intermediates (36a-e) with phenylhydrazine afforded corresponding triazine carbohydrazides (37a-e) in 91-96% yield (Scheme 9).



Scheme 9. *Synthesis of 4-amino-6-(arylamino)-N-phenyl-1,3,5-triazine - 2-carbohydrazides (3a-e). Reagents and conditions: (i) $NaOCH_3$, CH_3OH, rt, 3 h; (ii) dimethyloxalate, CH_3OH, reflux, 4 h; (iii) phenylhydrazine, AcOH, EtOH, reflux, 12 h.*

Compounds 37a-e were tested for their *in vitro* anti-cancer activity against MDA-MB-231 and MCF-7 cell lines (Table 6). All compounds showed potent

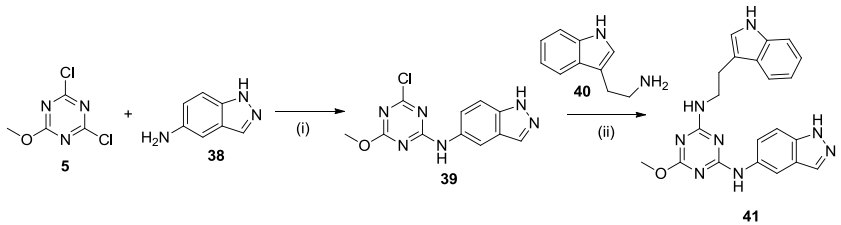
activity against MDA-MB-231 cell lines, whereas moderate activity was observed against MCF-7 cell lines (Table 6).

Table 6. *Growth inhibitory activity of compounds 37a-e against different cell lines.*

Compound	MDA-MB-231	MCF-7	MCF10A
37a	3.67 (0.46)	31.3 (3.1)	>100
37b	4.79 (0.40)	38.0 (2.5)	>100
37c	4.65 (0.13)	16.6 (0.2)	>100
37d	2.71 (0.21)	53.2 (4.8)	>100
37e	2.48 (0.72)	25.5 (5.2)	>100

Results are expressed as triplicate mean values (standard deviation in parentheses).

Ryu and co-workers synthesized compound 41 from 2,4-dichloro -6-methoxy-1,3,5-triazine (5) by using the synthetic strategy shown in scheme 10 [23]. Treatment of triazine 5 with 5-aminoindazole (38) using Et_3N as a base gave triazinyl indazolamine 39. Further reaction of compound 39 with tryptamine (40) in methanol afforded 41 in 72% yield.



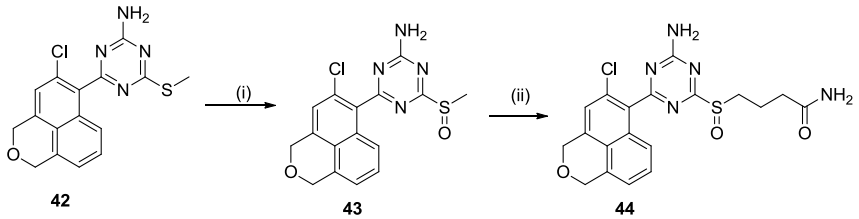
Scheme 10. *Reagent and Conditions: (i) Et_3N (1.35 eq.), MeOH, rt, overnight, 99%; (ii) Et_3N (1.35 eq.), MeOH, reflux, 4h, 72%.*

Compound 41 showed a good tendency to inhibit PAK4 activity along with moderate activity against LNCap and PC-3 cells lines (table 7). The activity against LNCap cell lines was about 3 times over PC-3 cells lines.

Table 7. *Anti-cancer activity of compound 41.*

Compd	IC_{50} (µM)			
	LNCap cells		PC-3 cells	
	Viability	AR luciferase	Viability	AR luciferase
41	14.47 ±1.26	2.50 ±0.28	47.47 ±0.92	1.96 ±0.50

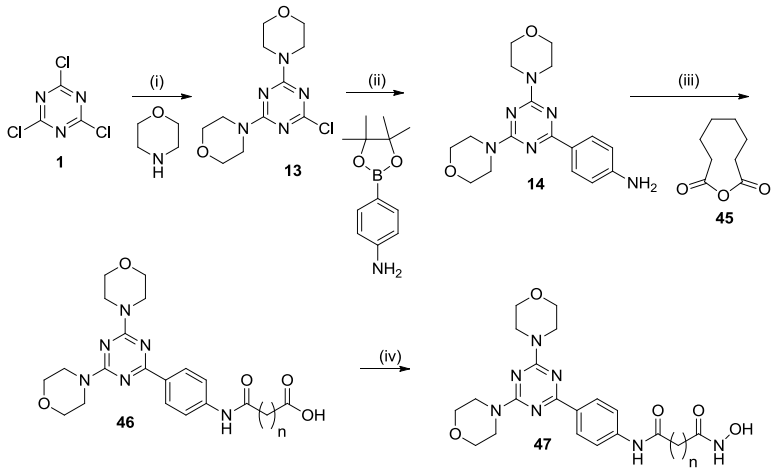
Suda and co-workers synthesized compound 44 in two steps synthesis as shown in scheme 11 [24].



Scheme 11. *Reagents and conditions: (i) mCPBA, CH_2Cl_2, rt, 3 h, 78%; (ii) 2-aminoethan-1-ol, HOBT, EDC.HCl, DIPEA, DMF, rt.*

Compound 44 showed a high binding affinity for *N*-terminal Hsp90a (K_d = 0.52 nM) along with strong *in vitro* cell growth inhibition of HCT116 (IC_{50} = 0.098 µM) and NCI-N87 (IC_{50} = 0.066 µM) cell lines. Compound 44 also displayed high oral bioavailability in mice (F = 44.0%) along with satisfactory anti-tumor efficacy in a human NCI-N87 gastric cancer xenograft model (tumor growth inhibition = 136%).

Zhao and co-workers synthesized compound 47 by using the synthetic strategy outlined in Scheme 12 [25]. The replacement of two chlorine atoms of cyanuric chloride with 2 equivalents of morpholine gave compound 13, followed by replacement of third chloride atom by 4-aminophenyl groups using Suzuki coupling to afford compound 14. Compound 14 was then reacted with suberic anhydride to give acid 8 which on condensation with hydroxylamine in the presence of isobutyl chloroformate gave desired hydroxamic acid 47.



Scheme 12. *Reagents and conditions: (i) Et_3N, CH_3COCH_3; (ii) $Pd(Ph_3)_4$, K_2CO_3, DMF; (iii) THF, 0 ℃; (iv) $NH_2OH.HCl$, ClCOOBu-i, THF.*

Compound 47 was then evaluated for its potential of inhibiting human histone deacetylases and anti-proliferative effect against HCT-116, MCF-7, and HeLa cancer cell lines. The results are illustrated in table 8. DNA flow cytometric analysis showed that compound 47 could induce apoptosis and cell cycle arrest at G2/M phase in HCT-116 cells.

Table 8. *In vitro enzyme inhibition and cell proliferation inhibition IC_{50} (nM) values and calculated c log P values of 47.*

Compd	HDACs (% of inhibition at 1 μM)	HDACs IC_{50} (M)a	HCT-116 IC_{50} (M)	MCF-7 IC_{50} (M)	HeLa IC_{50} (M)
47	77.6	0.31 x 10-6	0.7 x 10-6	7.9 x 10-6	12.6 x 10-6
SAHA	90.2	0.06 x 10-6	1.4 x 10-6	1.5 x 10-6	1.6 x 10-6

Pogorelcnik and co-workers discovered that triazine based compound 48 could show moderate *in vitro* inhibitory activity against human DNA topoisomerase Iiα with an IC_{50} value of 229 μM (Figure 2) [26]. Compound 48 also displayed moderate anti-proliferative activity against hepatocellular

carcinoma (HepG2) and human umbilical vein endothelial (HUVEC) cell lines with IC_{50} values of 20.53 and 122 µM, respectively.

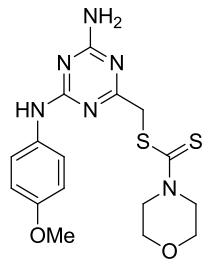


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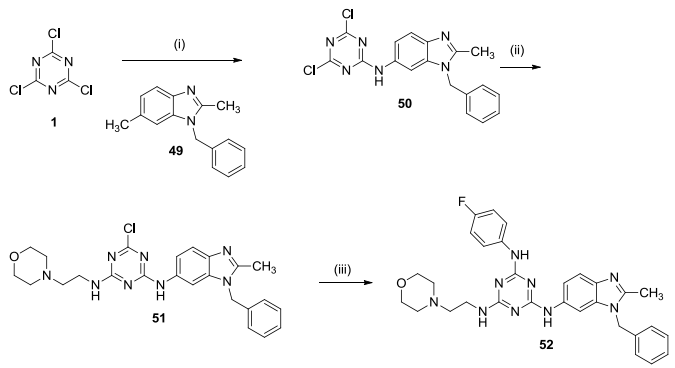
Figure 2. *Structure of compound 48.*

Singla and co-workers synthesis of compound 52 by using the synthetic strategy depicted in scheme 13 [27]. First, one chlorine atom of 2,4,6-trichloro-1,3,5-triazine (1) was replaced by 3-benzyl-2-methyl -3H-benzimidazol-5-ylamine (49) to afford compound 50. Second chlorine atom displacement of compound 50 by 2-aminoethylmorpholine afforded compound 51 which was then converted into compound 52 by replacement of third chlorine atom by *p*-fluoro aniline (Scheme 13).



Scheme 13. *Synthesis of monosubstituted, disubstituted and trisubstituted triazines. Reagents and conditions: (i) 10% $NaHCO_3$, THF, 0-5 ℃; (ii) 2-Aminoethylmorpholine, 10% $NaHCO_3$, THF, room temperature; (iii) p-fluoro aniline, K_2CO_3, 1,4-dioxane, 110 ℃.*

Compound 52 displayed potent anti-tumor activity with a GI_{50} value of 2.87 μM. Compounds 52 was also displayed inhibition of dihydrofolate reductase with an IC_{50} value of 2.0 nM (Table 9).

Table 9. *Median growth inhibitory (GI_{50}, μM), total growth inhibitory (TGI, μM) and median lethal concentrations (LC_{50}, μM) of compound 52 against different cancer cell lines.*

Compd	Cancer Cell lines	GI50	TGI	LC50
52	I	1.96	6.82	55.0
	II	3.21	18.5	38.5
	III	2.60	8.51	24.0
	IV	2.72	12.0	15.3
	V	1.91	4.08	24.2
	VI	4.01	27.4	62.3
	VII	3.03	19.3	14.6
	VIII	4.41	43.9	62.5
	IX	2.04	8.99	20.6
	MIG-MIDa	2.87	16.6	35.2

I, leukemia; II, non-small cell lung cancer; III, colon cancer; IV, CNS cancer; V, melanoma; VI, ovarian cancer; VII, renal cancer; VIII, prostate cancer; IX, breast cancer.

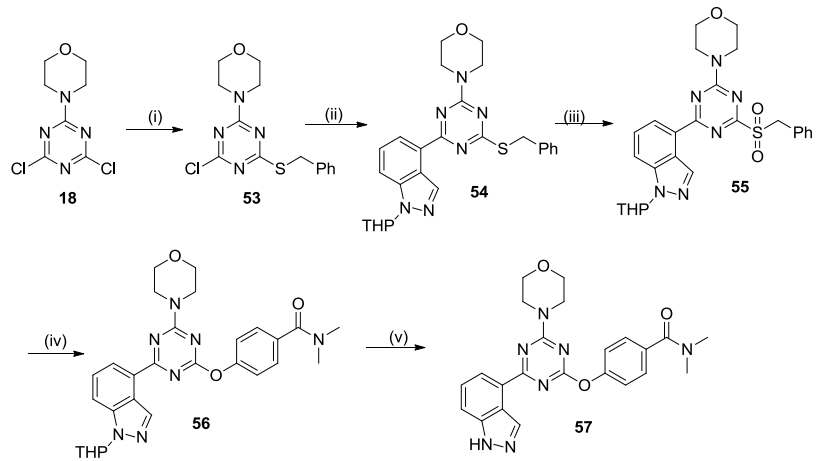
[a] Full panel mean-graph midpoint (μM).

Dugar and co-workers synthesized compound **57** from compound **18** by using the synthetic route shown in scheme 14 [28]. Replacement of one chlorine atom of **18** with benzyl mercaptan, followed by Suzuki coupling of resulting compound **53** with aryl borate afforded compound **54**. Compound **54** was then oxidized into compound **55** using ozone as an oxidizing agent. Replacement of sulfonyl group by 4-hydroxy-*N*, *N*-dimethylbenzamide, followed by deprotection of THP group afforded the desired compound **57**.

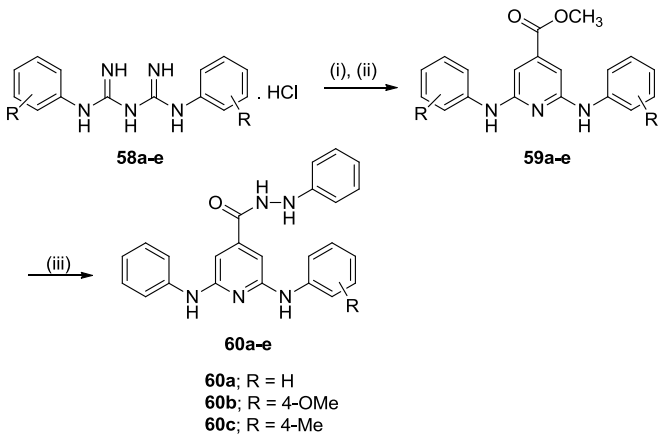
Compound **57** displayed potent inhibition of PI3Kα with an IC_{50} value of 60 nM. Compound **57** also potently inhibited the ovarian cancer (A2780) cell

lines with an EC_{50} value of 500 nM. Compound 57 showed good oral bioavailability with an AUC of 5.2 μM at a dose of 3 mpk in mice.

Kothayer and co-workers synthesized *N*'-phenyl-4,6-bis (arylamino) -1,3,5-triazine-2-carbohydrazides (60a-c) from bisarylbiguanide hydrochloride salts [29] (58a-e) by using the synthetic route depicted in scheme 15 [30]. First, the neutralization of the bis-arylbiguanide hydrochloride salt was performed with sodium methoxide/methanol, followed by reaction with dimethyloxalate in refluxing methanol yielding methyl 4,6-bis(arylamino)-1,3,5-triazine-2 -carboxylates (59a-c) in good yield following recrystallization from methanol. Further treatments of compounds (59a-e) with phenylhydrazine in refluxing ethanol catalyzed by glacial acetic acid afforded the desired new triazines (60a-c) in good moderate to good yields following recrystallization from ethanol-water (3:1) (Scheme 15).



Scheme 14. *Reagents and conditions: (i) Benzyl mercaptan, DIPEA, morpholine, THF, 0 ℃, 5 h; (ii) aryl borate, $Pd(PPh_3)_4$, Na_2CO_3, DME/water (4:1), 90 ℃, 18 h; (iii) oxone, THF/water (1:1), 0°C−RT, 25 h; (1v) RX, DMF, K_2CO_3, RT, 24 h; (v) methanesulfonic acid, methanol/ water (2:1), 55 ℃, 1 h.*



Scheme 15. *Reagents and conditions: (i) $NaOCH_3$, CH_3OH, room temp 3 h; (ii) dimethyloxalate, CH_3OH, $NaOCH_3$ reflux, 12 h; (iii) phenylhydrazine, EtOH, AcOH, reflux 18 h.*

Compounds 60a-c showed moderate to potent activities against different cancer cell lines as shown in table 10. All three compounds showed most potent activities against MDA-MB231 cell lines (Table 10).

Table 10. *Activity of compounds 60a-c against different cancer cell lines.*

Cell lines	**IC_{50} (µM)**		
	60a	**60b**	**60c**
OV 90	8	12	5
A2780	7.1	6.3	3.6
MCF-7	6	7.2	4.2
MDA-MB231	2.5	4.2	3.5
A549	14.6	10.8	11.6
H1299	11	5	22
HT-29	9.5	5.8	5.2

3.3 Conclusion

Collectively, 1,3,5-triazine motif has emerged as a valuable scaffold for potent anti-cancer activities displaying IC_{50} values in nano to micromolar

concentration range against a wide variety of cancer cell lines. Some of these compounds have also shown promising oral bioavailability (%F) which further highlights the extra advantage of three nitrogen atoms present in the triazine ring. Moreover, the synthesis of most of these compounds is straightforward and economical usually from commercially available cyanuric chloride. It is believed that the information in this book chapter will be very much help for medicinal chemists in designing and synthesizing more potent anti-cancer drugs based upon 1,3,5-triazine scaffold in future.

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Abbreviations

1. AUC = Area Under the curve
2. DABCO = 1,4-Diazabicyclo[2.2.2]octane
3. DCM = Dichloromethane
4. DFX = Deferasirox
5. DME = 1,2-Dimethoxyethane
6. EDCI = 1-Ethyl-3-(3-dimethylaminopropyl)

   Carbodiimide
7. Et_3N = Triethylamine
8. %F = % Fraction

9. GI = Gross inhibition
10. HOBT = Hydroxybenzotriazole
11. HUVEC = Human umbilical vein endothelial cell
12. i.v. = Intravenous
13. K_d = Dissociation constant
14. LiHMDS = Lithium bis(trimethylsilyl)amide
15. m-TOR = Mammalian target of rapamycin
16. MCF-7 Cells = Human breast adenocarcinoma cell line
17. MIA PaCa = Miapaca pancreatic cancer
18. NaHMDS = Sodium bis(trimethylsilyl)amide
19. PC = Prostate Cancer
20. PI3K = Phosphoinositide 3-kinase
21. LiHMDS = Lithium bis(trimethylsilyl)amide
22. TGI = Total growth inhibition

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