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Developments On 1,2,4-Triazine Scaffold Substitutions For Possible Anticancer Agents

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Abstract

Recent literature studies reveal that heterocyclic scaffolds containing a 1,2,4-triazine ring have gained due significance owing to their pharmacological relevance. This article gives an insight on the different methods used for synthesis of 1,2,4-triazine, its derivatives such as N-oxides, N,N'- dioxides, benzo and hetero-fused systems. The main focus will be on the anti-cancer activities of the 1,2,4-triazine moiety.

Key words: 12,4-triazine, synthesis, structure-activity relationship (SAR), anti-cancer agents

Introduction

Triazines are class of molecules containing three nitrogen atoms in a six membered carbon- nitrogen ring. There are three possible isomers of triazine viz. 1,2,3- triazine, 1,2,4-triazine and 1,2,5-triazine which differ on the basis of the nitrogen atom position. Out of these, 1,2,4-triazine has been studied for its various medicinal properties like anti tumor agent, anti HIV agent, CRF receptor antagonist, anti microbial, anti inflammatory (**Figure 1**) [1-2]. The article is divided into three classes of anticancer 1,2,4-triazine substituents, namely, benzofused triazines, heterofused triazines and uncondensed triazines.

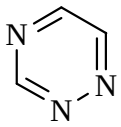


Figure 1. Structure of 1,2,4-Triazine

There are many FDA approved drugs available with 1,2,4-triazine scaffold like Azaribine (antiviral), Lamotrigine (anti-epileptic) and Tirapazamine (anticancer drug), etc. This article briefly outlines the various synthesis methods, the pharmacological activity in particular, as anti-cancer agents, SAR studies and mode of the action of these 1,2,4-triazine derivatives.

1,2,4-BENZOTRIAZINES

1,2,4-benzotriazine-1,4-dioxides (BTO), corresponding to Tirapazamine (TPZ, **Figure 2**) is the most commonly studied benzotriazine being bioreductive hypoxia activated prodrugs.

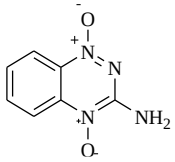
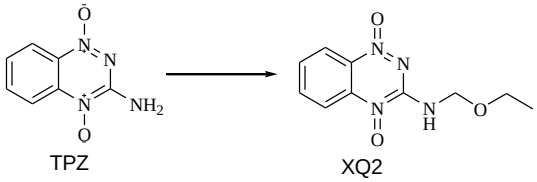


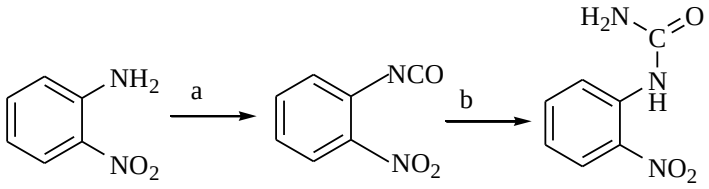
Figure 2. Structure of Tirapazamine (TPZ)

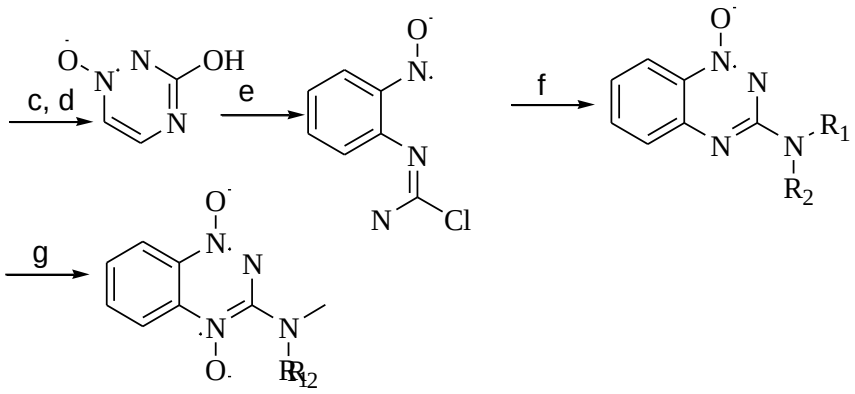
For example, XQ2, an analogue of TPZ is shown to induce G2/M arrest and apoptosis in human lung adenocarcinoma and it further prevented the human cancer cell proliferation in both normoxia and hypoxia (Scheme 1) [3].



Scheme 1. The structure of XQ2

Jiang *et al.* [4] reported synthesis of 3-amino-1,2,4-benzotriazine-1,4-dioxide analogues as shown in **Scheme 2**. The synthesized 15 analogues were screened for their cytotoxic activities in hypoxia and surprisingly, they exhibited higher cytotoxic activities compared to TPZ.



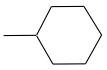
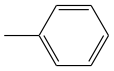
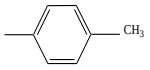
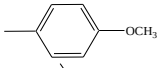
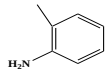
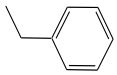
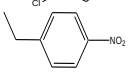


The synthetic route of compounds 1a-o. Reagents and conditions: (a) $(COCl_2)_3$, toluene, reflux, 3 h; (b) NH_3 (c) NaOH (d) AcOH; (e) $POCl_3$, reflux, 3 h (f) R1-NH-R2, ethanol, reflux, 12 h; (g) $AcOH/H_2O2$, 50° C, 24 h.

Scheme 2. Synthesis of 3-amino-1,2,4-benzotriazine-1,4-dioxide analogues

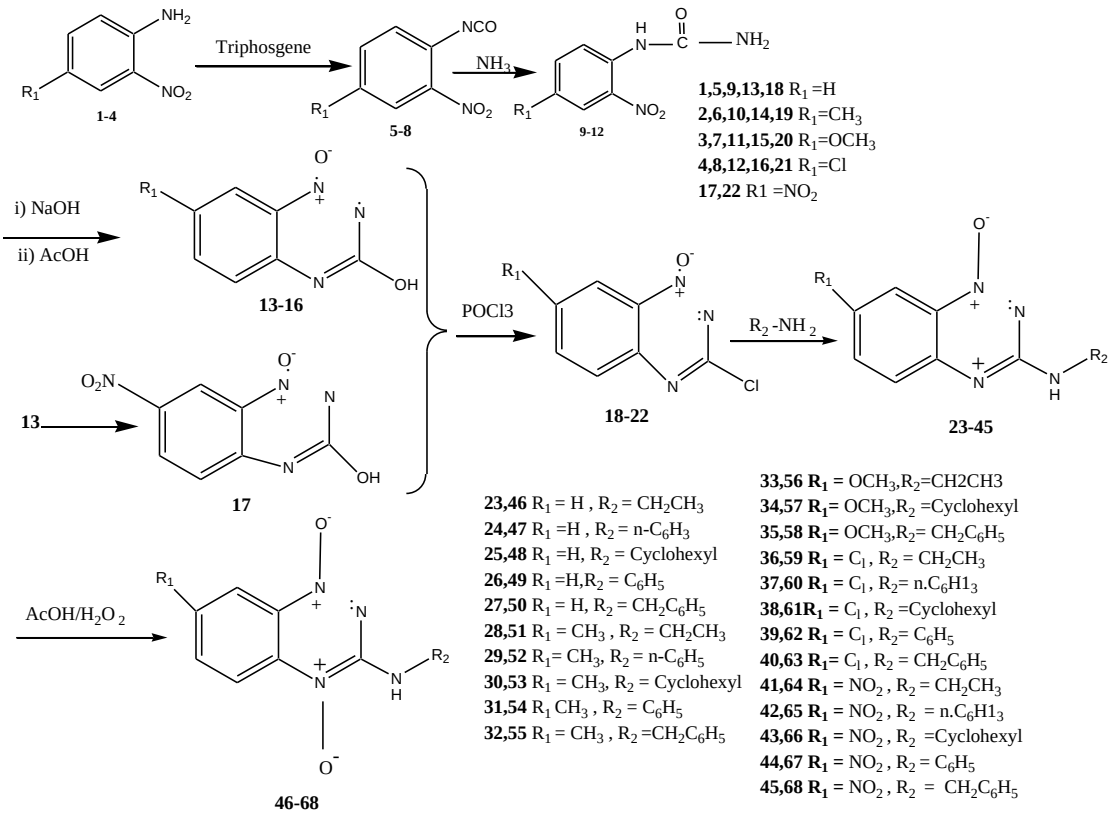
Three tested compounds showed higher hypoxic selectivity against Molt-4 and HL-60 cell lines (**Table 1**).

Table 1: Cytotoxicity of the target compounds against five human cancer cell lines in vitro

Compound	R^1	R^2	Cytotoxicity (IC_{50} µM) [a]				
			Molt-4	HL-60	K 562	HeP – G2	PC-3
Tpz	H	H	4.6±0.3	7.0±2.6	5.2±0.8	19.1±2.2	22.3±4.7
1a	$-CH_2CH_3$	H	3.3±0.8	9.0±4.2	4.5±2.3	13.5±0.7	13.3±2.6
1b	$-(CH_2)_7CH_3$ – n	H	4.9±1.5	7.2±2.8	4.7±0.5	17.4±8.8	18.2±1.7
1c	$-CH_2CH=CH_2$	H	3.0±1.0	25.8±6.0	11.2±3.4	>56	>5.6
1d	CH_2CH_2OH	H	2.6±1.7	10.7±1.3	3.7±0.6	23.2±3.1	22.4±5.3
1e		H	1.9±1.0	3.6±1.2	6.6±1.0	13.3±0.7	15.9±4.8
1f		H	1.3±0.7	2.5±1.1	2.6±1.1	9.5±2.1	10.5±3.6
1g		H	1.4±1.1	2.9±0.9	2.4±0.7	15.0±6.4	17.0±3.2
1h		H	1.1±0.2	1.5±0.8	2.5±0.9	10.6±0.5	10.3±2.0
1i		H	0.6±0.4	0.9±0.2	2.9±0.2	10.1±0.5	12.0±10.6
1j		H	2.3±1.8	8.3±2.8	10.6±1.1	17.4±7.4	16.1±2.4
1k		H	2.2±0.6	2.5±0.4	1.9±0.1	8.2±1.3	10.7±0.9
1l		H	2.3±0.7	5.8±1.6	2.2±1.0	9.7±1.5	10.6±0.9
1m		H	0.8±0.3	1.4±0.8	3.1±0.8	7.7±0.8	7.4±2.5
1n	$-CH_2CH_3$	H	>17.6	>49	>55	>107	>107
1o		$-CH_2CH_3$	>16.1	>60	>47	>95	>95

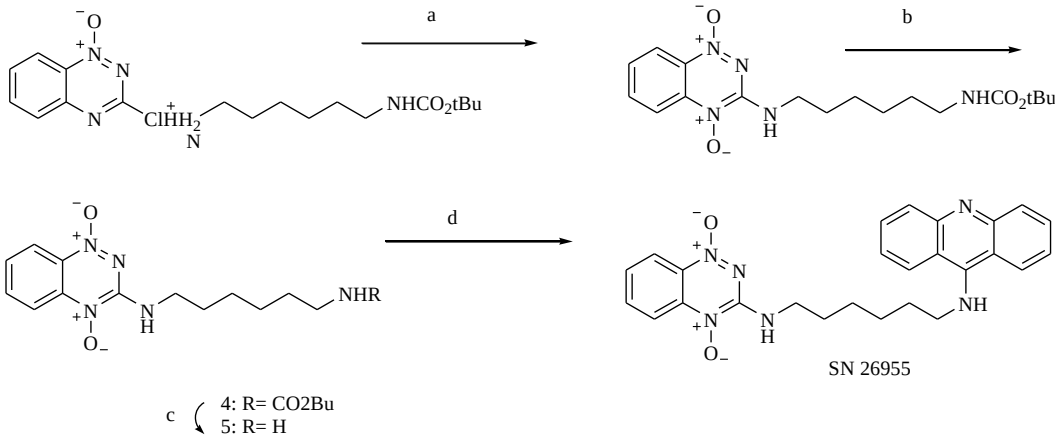
[a] Each experiment was independently performed three times and expressed as means ± SD .

Again, Jing and others synthesized a series of novel 3-amino-1,2,4-benzotriazine-1,4-dioxide derivatives and screened for their *in vitro* cytotoxicity (**Scheme 3**).



Scheme 3. Design and synthesis of the TPZ derivatives

Yvette *et. al.* synthesized an TPZ analogue, SN26955 with attachment of an acridine scaffold for effective DNA targeting as shown in **Scheme 4** [6].



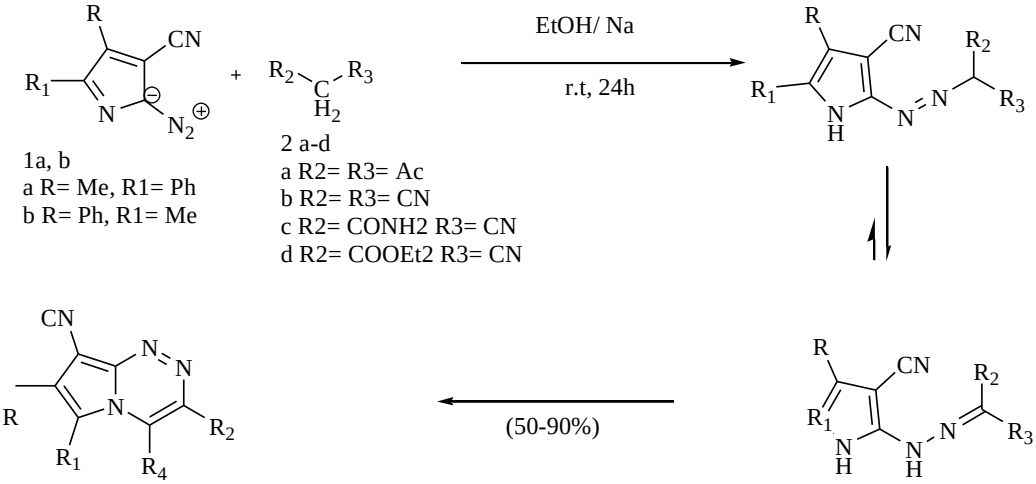
Structure of SN26955 showing the TPZ moiety on the left attached via a linker onto a DNA-intercalating acridine ring. Reagents and conditions: (a) DCM, Et3N, 20° C; (b) m-CPBA, DCM (d) HCl, MeOH

Scheme 4. TPZ analogue for effective DNA targeting

Heterofused derivatives

Dian and co. synthesized 1,2,4-triazine fused with five membered ring, pyrrolo [2,1-c][1,2,4] triazines as shown in **Scheme 5**. The synthesized pyrrolotriazines were evaluated for cytotoxic activity [7].

The Scheme 5 for synthesis was:



1a, b
a R= Me, R1= Ph
b R= Ph, R1= Me

2 a-d
a R2= R3= Ac
b R2= R3= CN
c R2= CONH2 R3= CN
d R2= COOEt2 R3= CN

4 a- g

a R= Me, R1= Ph, R2= Ac, R4= Me
b R= Me, R1= Ph, R2= CN, R4= NH2
c R= Me, R1= Ph, R2= CONH2, R4= NH2
d R= Ph, R1= Me, R2= CONH2, R4= NH2
e R= Ph, R1= Me, R2= COOEt, R4= NH2
f R= Me, R1= Ph, R2= COOEt, R4= NH2
g R= Ph, R1= Me, R2= CN, R4= NH3

a R= Me, R1= Ph, R2= R3= Ac
b R= Me, R1= Ph, R2= R3= CN
c R= Me, R1= Ph, R2= CONH2, R3= CN
d R= Ph, R1= Me, R2= CONH2, R= CN
e R= Ph, R1= Me, R2= COOEt, R3= CN
f R= Me, R1= Ph, R2= COOEt, R3= CN
g R= Ph, R1= Me, R2= R3= CN

The results obtained are shown in **Table 2**, taking into consideration the growth inhibitory power (GI50).

Table 2

Inhibition of in vitro tumour cell growth by pyrrolotriazines 4a – e

Cell Line	Cytotoxicity (GI_{50} in μM)[a,b,c]				
	4a	4b	4c	4d	4e
Leukaemia					
CCRF – CEM	87.6	>100	17.0	>100	39.8
HL-60(TB)	ND	>100	7.65	>100	ND
K-562	84.5	>100	26.1	>100	31.8
MOLT-4	68.0	>100	23.4	>100	30.6
RPMI – 8226	ND	>100	20.4	>100	22.7
SR	>100	>100	24.8	>100	36.1
Non-Small cell bone cancer					
A549/ATCC	>100	>100	17.5	>100	39.9
EKVX	88.7	27.9	3.34	>100	38.0
HOP-62	47.8	32.3	26.1	>100	85.6
HIO – 92	>100	18.2	14.5	ND	ND
NCI – H226	ND	16.9	11.0	>100	ND
NCI – H23	37.9	24.4	6.97	>100	38.3
NCI – H322M	>100	>100	20.8	>100	58.4
NCI – H460	>100	>100	14.3	>100	39.8
NCI –H522	35.2	48.9	18.1	>100	27.8
Colon Cancer					

COLO 205	>100	>100	16.4	>100	32.9
HCC – 2998	57.3	ND	ND	>100	32.5
HCT – 116	84.9	78.3	13.5	>100	42.1
HCT - 15	>100	88.4	14.8	>100	37.5
HT 29	>100	>100	10.5	>100	33.7
KM12	>100	>100	18.6	>100	30.7
SW - 620	>100	>100	21.9	>100	40.6
CNS Cancer					
SF – 268	42.7	28.2	23.1	>100	37.7
SF – 295	>100	37.9	15.2	>100	34.1
SF – 539	ND	ND	20.9	>100	30.9
SNB – 19	ND	ND	ND	>100	21.3
SNB – 75	18.8	10.5	17.9	ND	ND
U251	>100	42.2	23.4	>100	38.0
Melanoma					
LOX IMVI	>100	>100	19.7	>100	34.6
MALME-3M	>100	26.9	24.4	>100	20.8
M14	>100	>100	15.3	>100	34.9
SK-MEL-2	>100	51.3	15.7	>100	42.3
SK-MEL-28	>100	>100	15.4	>100	21.6
SK-MEL-5	>100	30.4	15.1	>100	39.9
UACC-257	>100	71.6	17.0	>100	25.4
UACC-62	>100	56.7	5.51	>100	23.9
Ovarian Cancer					
IGROV1	>100	52.5	24.7	>100	22.2
OVCAR 3	>100	>100	24.9	>100	29.4
OVCAR – 4	16.4	2.77	13.1	>100	10.9
OVCAR – 5	>100	>100	24.7	>100	>100
OVCAR – 8	>100	24.8	21.5	>100	28.4
SK-OV-3	>100	33.6	21.5	70.4	23.9
Renal Cancer					
786-O	>100	84.8	20.9	>100	56.2
A498	>100	>100	13.4	>100	26.8
ACHN	>100	63.6	16.4	>100	29.9
CAK1-1	>100	37.1	16.1	>100	52.6
RXF 393	ND	ND	ND	>100	98.4
SN12C	>100	>100	22.4	>100	37.9
TK – 10	80.1	30.5	12.3	>100	37.0
UO – 31	>100	28.8	13.3	>100	33.4

The pyrrolotriazines such as **4c** and **4e** showed an interesting broad spectrum antiproliferative activity (**Table 3**).

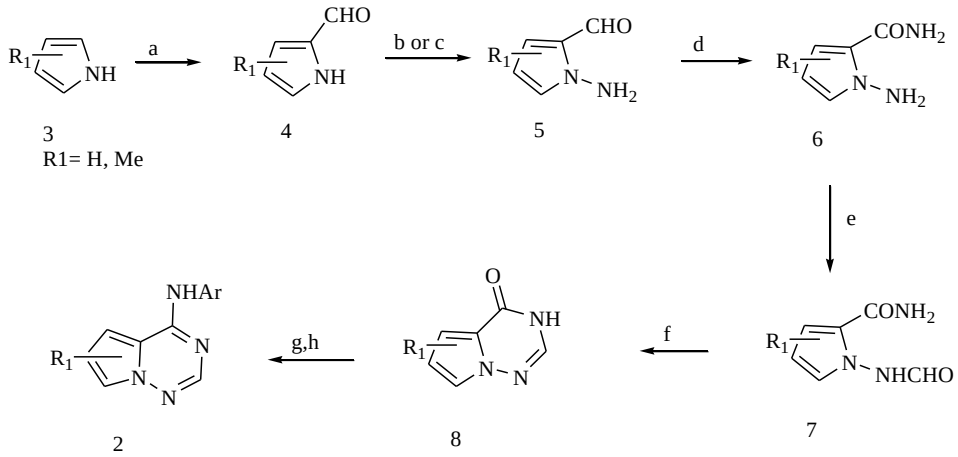
Table 3

Cell Line	**Cytotoxiety (Gl_{50} in µM)[a,b,c]**				
	4a	**4b**	**4c**	**4d**	**4e**
Prorate Cancer					
PC-3	ND	ND	ND	>100	82.5
DU – 145	>100	>100	23.3	>100	83.9
Breast Cancer					
MCF7	>100	ND	ND	>100	39.4
NCI/ADR-RES	>100	>100	16.5	>100	38.8
MDA-MB-	54.7	17.1	12.2	>100	51.7
HS 578T	39.8	62.1	22.8	>100	24.6
MDA-MB-435	>100	>100	16.4	>100	32.0

MDA-N	>100	>100	18.5	>100	27.0
BT-549	69.3	28.5	14.8	>100	40.4
T-47D	19.7	19.6	18.4	>100	53.7

[a] Data obtained from NCT's in vitro disease-oriented tumour cells screen
[b] Gl_{50} is the molar concentration causing 50% growth inhibition of tumour cells. Compounds with Gl_{50} > 100 µM are considered inactive.
[c] ND = Not Determined

Hunt et al. identified the pyrrolo[2,1-f][1,2,4]triazine nucleus as a novel kinase inhibitor templat ewhich effectively mimics the well-known quinazoline kinase inhibitor scaffold [8]. The scheme followed for the production of anti-cancer chemicals was:

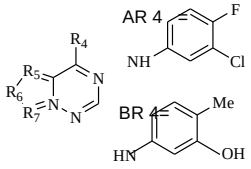


Reagents: (a) DMF, POCl3, 1,2- dichloroethane; (b) hydroxylamine- O-sulfonic acid, KOH, water; (c) O-mesityllenesulfonylhydroxylamine, NaH, CH2Cl2; (d) KOH; (e) HCO2H, NaOAc; (f) NaOMe, MeOH; (g) POBr3; (h) 3-chloro- 4- fluoro-phenylamine

Scheme 6. Synthesis of pyrrolo[2,1-f][1,2,4]triazine nucleus

Like the quinazoline-based kinase inhibitors, the pyrrolotriazine-based inhibitors bind in the ATP pocket (Table 4).

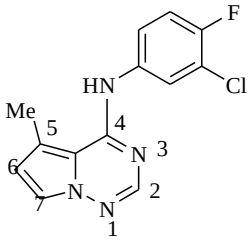
Table 4. Enzymatic and Cellular Activity of Pyrrolotriazine Kinase Inhibitors



					biochemical IC_{50}(µM)		cellular IC_{50} (nM)	
Compd	**R4**	**R5**	**R6**	**R7**	**VEGFR-2**	**EGFR**	**HUVEC: EGF/EGF**	**DiFi**
9	A	H	H	H	>10	0.118	>2500/345	1840
10	A	Me	H	H	>10	0.100	>2500/602	3060
11	A	H	Me	H	>2	0.151	>2500/509	1600
12	A	H	H	Me	>2	3.25	>2500/>2500	>10000
13	B	H	H	H	1.44±0.95	0.51	360/ND[a]	>10000
14	B	Me	H	H	0.066	0.346	98±88/270	>10000
15	B	H	Me	H	0.405	0.654	213±89/644	>10000
16	B	H	H	Me	>10	29.4	477±92/101	>10000
14	B	Me	Me	H	0.023	0.200	310/ND	>10000

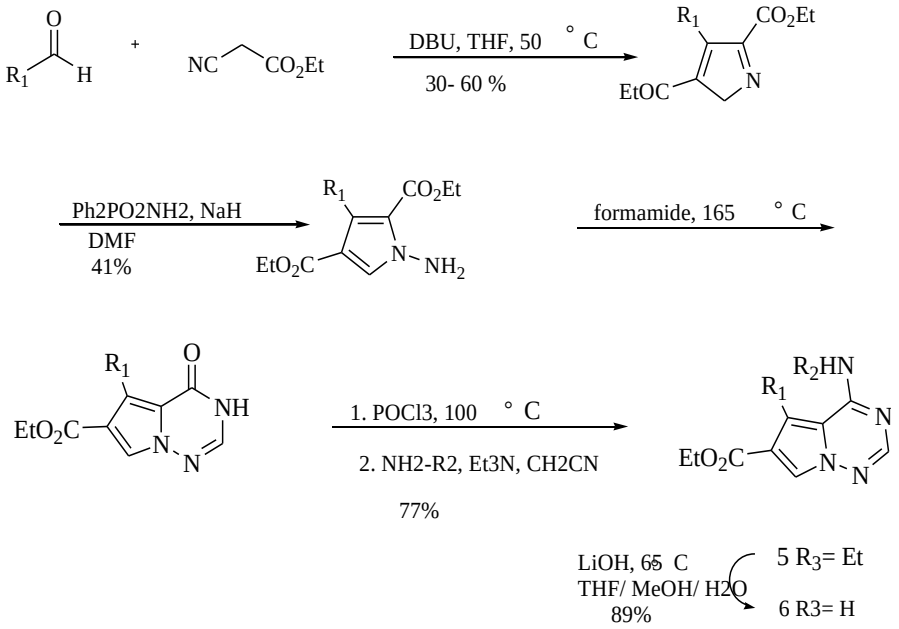
[a] ND = not determined

Fink *et al.* reported further SAR studies on pyrrolo [2,1-*f*][1,2,4] triazine derivatives to extend their use as both EGFR and HER2 inhibitors [9].

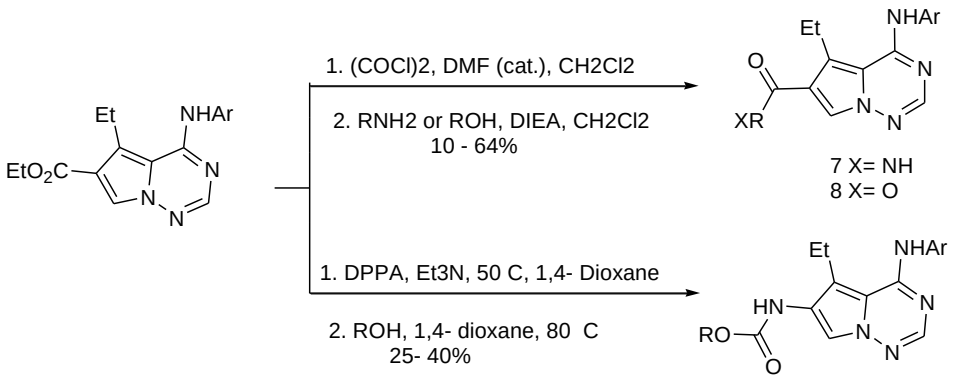


EGFRIC50 : 0.100?M
VEGFR-2 IC 50 :10?M
Figure 3: Novel kinase inhibitor template .

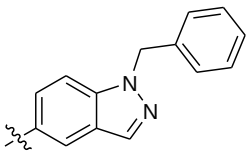
EGFR and HER2 are receptor tyrosine kinases belonging to the family of ErbB kinases [10]. The various schemes followed for development of anti cancer drugs were:



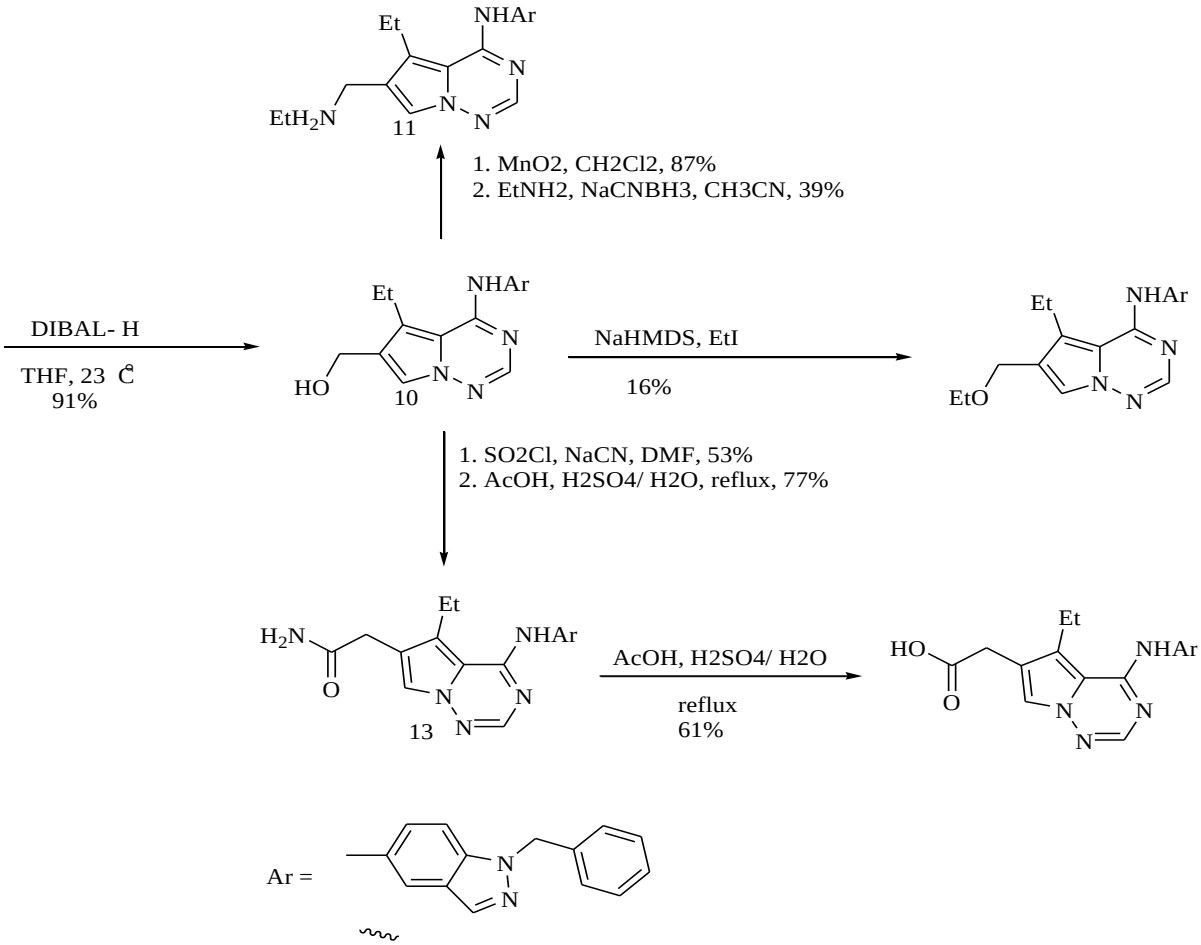
Scheme 7



Ar =



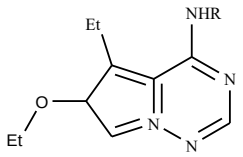
Scheme 8

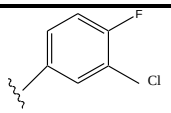
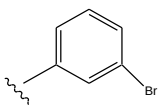


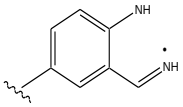
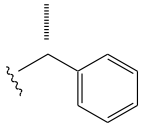
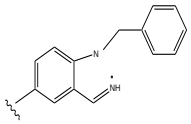
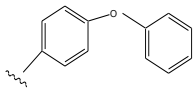
Scheme 9

It was observed that when the C-4 is relatively small aniline ring or 5 or 6 bicyclic fused ring **(5a-b)** then the activity of the enzyme is inhibited the most. The structure- activity relationships at various positions are as follows:

Table 5. Structure-activity relationship for C4 position



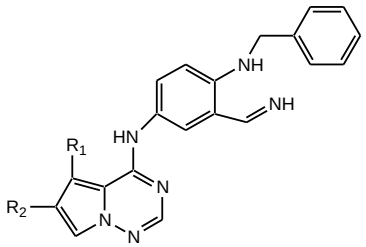
Compound	R	HER 2[a,b] IC 50 (μM)	EGFR [b] IC 50 (μM)
5a		2.8	0.09
5b		3.0	0.06

5c		3.3	0.05
5d		7.2	0.20
5e		0.18	0.12
5f		0.82	0.61

[a]IC $_{50}$ values are reported as the mean of atleast three determinations. Variability around the mean valve was <15%.

At C-5 position, the activity of HER2 and EFGR was completely destroyed with increase in shape and size of the substituent.

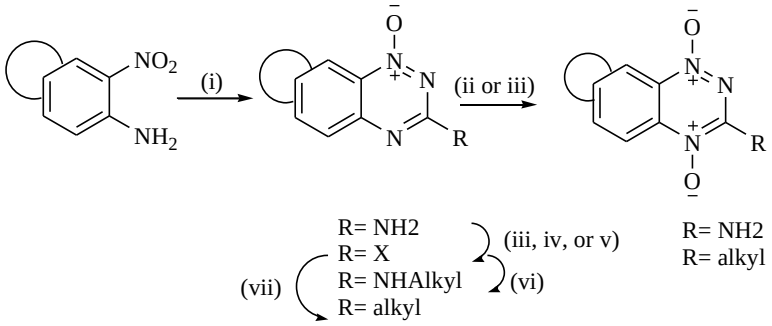
Table 6. Structure-Activity relationship for the C-5 and C-6 positions



Compound	R^1	R^2	HER 2 IC 50 [a] (µM)	EGFR IC 50[a] (µM)
5e	Et	CO_2Et	0.20	0.20
5g	H	CO_2Et	0.39	0.12
5h	Me	CO_2Et	0.20	0.20
5i	iPr	CO_2Et	0.21	0.20
5j	nPr	CO_2Et	1.2	0.95
5k	Bn	CO_2Et	>25	>25
6	Et	CO_2H	0.04	0.02
7a	Et	$C(O)NH_2$	0.11	0.12
7b	Et	C(O)NHMe	0.13	0.07
7c	Et	$C(O)NMe_2$	0.50	0.20
9a	Et	NHC(O)OBn	0.17	0.21
10	Et	CH_2 OH	0.73	0.49
11	Et	CH_2 NHEt	9.7	7.4
12	Et	CH_2 OEt	1.4	0.95
13	Et	$CH_2C(O)NH_2$	2.4	1.1
14	Et	CH_2CO_2H	0.68	1.6

[a]IC $_{50}$ values are reported as the mean of at least three determinations. Variability around the mean value was <15%.

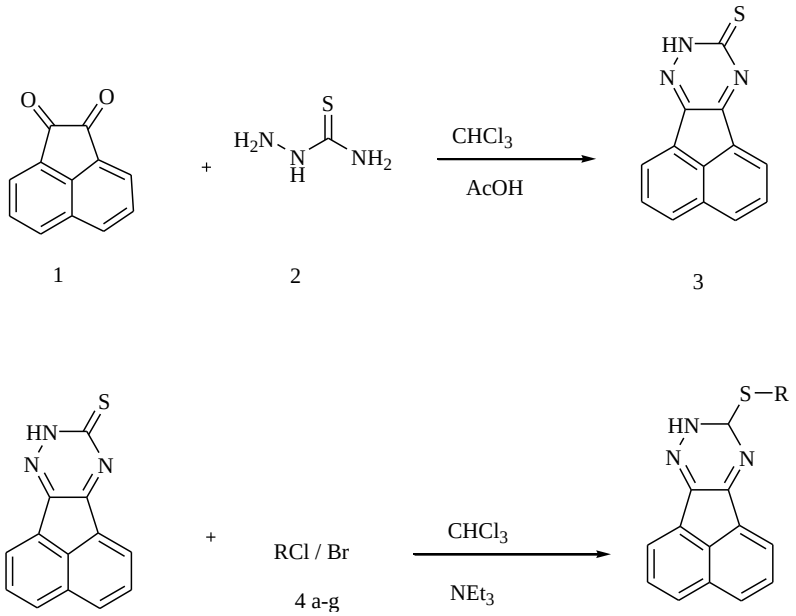
Hay *et. al.* [11] designed a series of novel tricyclic triazine di-*N*-oxides (TTO) related to tirapazamine.



Reagents: (i) NH_2CN, HCl, heat, then 30% NaOH, heat (ii) CH_3CO_3H, CH_3CO_2H; (iii) $NaNO_2$, CF_3CO_2H; (iv) DMF, $POCl_3$, heat; (v) t- $BuNO_2$, CH_2I_2, CuI, THF, heat (vi) $R_2CH_2CH_2NH_2$, DME, heat; (vii) Stille or Heck coupling; (viii) CF_3CO_2H, DCM

Scheme 10. Synthesis of novel tricyclic triazine di-*N*-oxides (TTO)

Mohammadi et al. synthesized 9-(alkythio)-acenapthol [1,2-e]-1,2,4-triazine analogues and studied cytotoxic activity. 9-(alkylthio) acenaphtho[1,2-e]-1,2,4-triazines were synthesized via the reaction of acenaphtho-9,10-quinone with thiosemicarbazide, and then with the benzyl chloride derivatives [12].

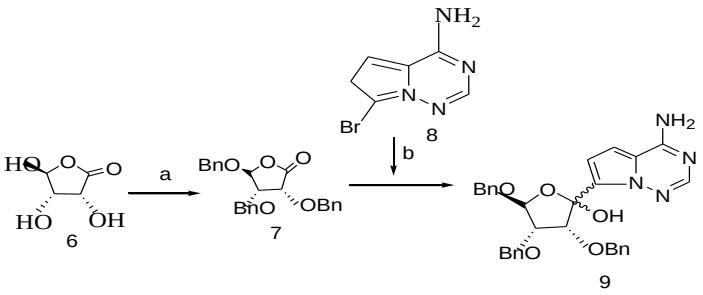


Scheme 11. Synthesis of 9-(alkythio)-acenapthol [1,2-e]-1,2,4-triazine analogues

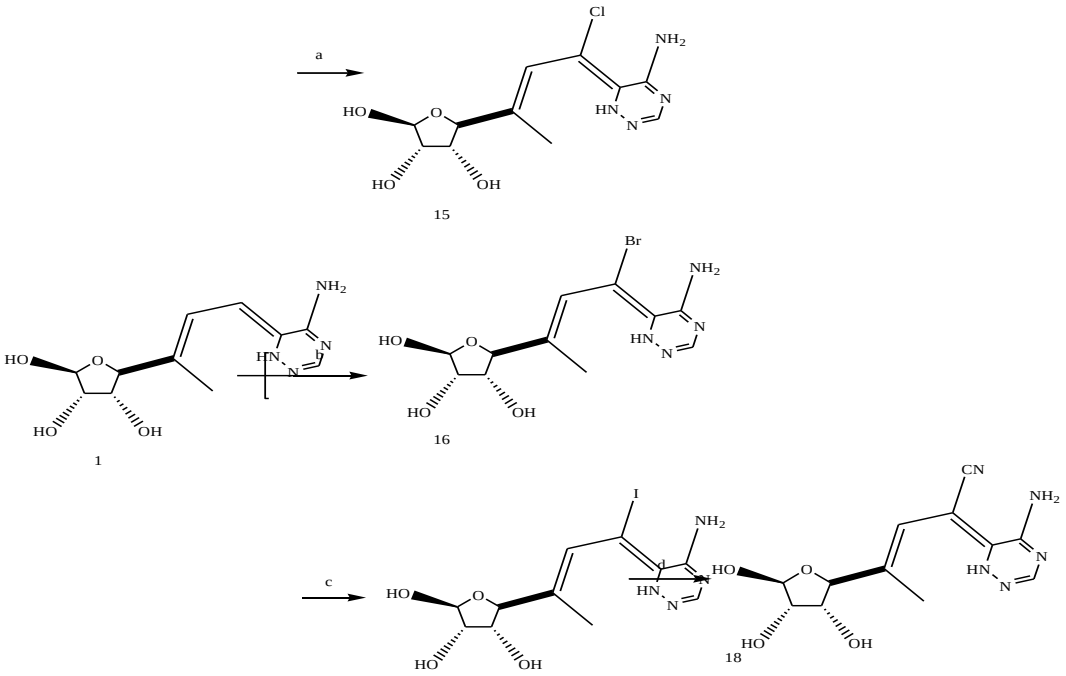
Cytotoxicity assay The in vitro cytotoxic activities for prepared acenaphtho derivatives are shown in **Table 7**.

Table 7. Cell growth inhibitory activity of synthetic acenphtho derivatives assessed by the MTT reduction assay.			
Comp.no	**IC_{50} [a] (µM)**		
	HL-60 cells	**MCF-7 cells**	**MOLT-4 cells**
5a	48.4±8.7	NA[b]	30.1±5.6
5b	36.0±5.4	NA	28.0±4.6
5c	51.2±7.6	NA	30.3±8.2
5d	NA	NA	NA
5e	30.1±3.6	NA	33.6±2.9
5f	ND[c]	61.9±20.6	65.5±20.4
5g	ND	NA	NA
Cisplatin	3.0±0.1	23.7±6.8	3.0±0.2
Doxorubicin	0.014±0.002	0.221±0.095	0.017±0.002
[a]Values represent mean ±S.E.M [b]NA: not active. [c]ND:not determined.			

Li et al. synthesized two novel series of pyrrolo[2,1-f][1,2,4]triazine *C*-nucleosides and evaluated for their cytotoxic activity [13].



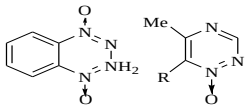
Scheme 12. Synthesis of C-nucleoside.9.Reagents and conditions: a) CCl3C(NH)OBn, CF3 SO3H, dioxane,0o C,3h,80%: b) nBuLi, THF,-78o ,3h,10-30% .



Scheme 13 Structural variation at position 7. Reagents and conditions . a) NCS, DMF,O ^{0} C to rt, 2 days, 20% . b) NBS,DMF, O^{0}C to rt 1 hr,25%: c) NIS,DMF, O^{0}C to rt 4 days, 43 % : d) (i) Zn(O), $Zn(CN)_2$ $Pd(P(tBu_3))_2$ DMA,150^{0} C,1hr, (ii)PS-TPP,21 hr, 13% over 2 steps.

UNCONDENSED 1, 2, 4-TRIAZINES

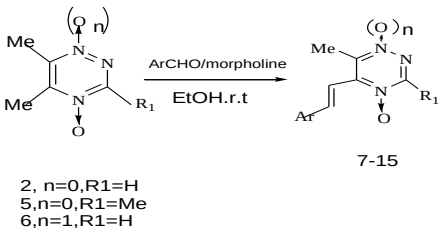
Cerecetto let al. synthesized novel 5-(2-arylethenyl)-1,2,4-triazine *N*-oxide and *N,N*'-dioxide derivatives in order to obtain compounds as selective hypoxic cell cytotoxins [14].



Tirapazamine 1

No	R
2	---Me
3	--CH=CHPh
4	-CH=CH-(2-thienyl)-NO_2

Figure 1: Structures of Tirapazamine and 1,2,4 -Triazine N4 -Oxide early developed.



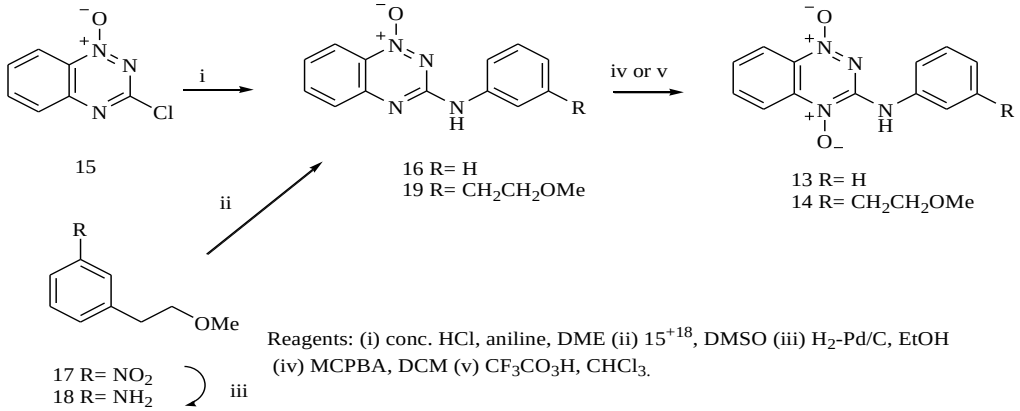
2, n=0,R1=H
5,n=0,R1=Me
6,n=1,R1=H

7-15

No	R1 (n=0)	Ar
7	H	Cl
8		MeO
9		Me2 N
10		1,3-benzodioxol-5-yl
11		5-ON_2-2-furyl
12	Me	MeO
13		Me2 N
	R1 (n=1)	
14	H	MeO
15		Me 2 N

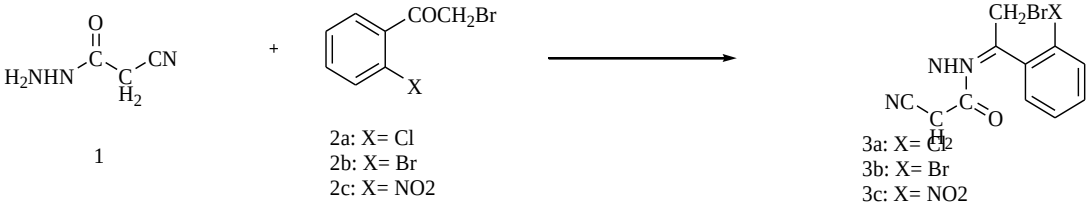
Scheme 14. Ppreparation of 5(2-arylethenyl)-1-2-triazine N-oxide and N,N1 -dioxide derivatives.

Pruijn etal. studied the influence of lipophilicity on the extravasculartransport properties of the hypoxic cytotoxintirapazamine (TPZ, **1**) [15].

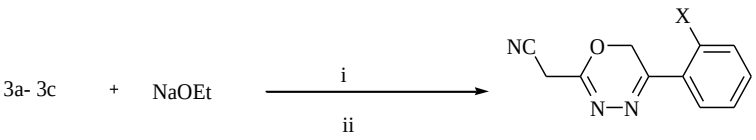


Scheme 15

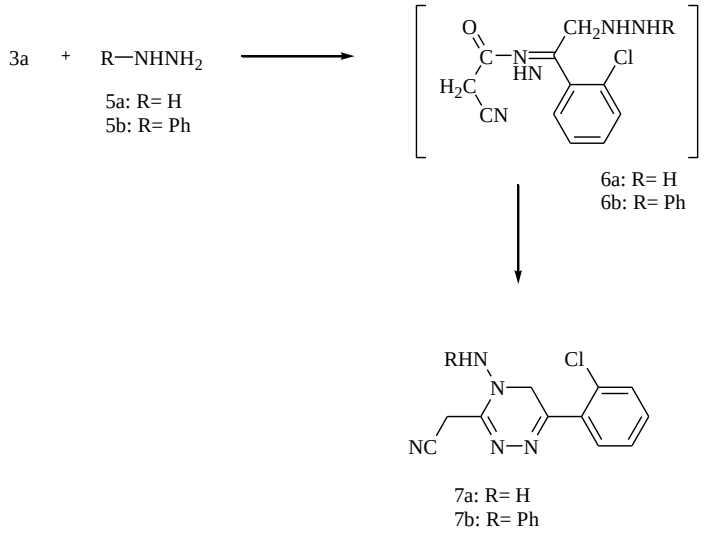
Mohareb et al. synthesized compounds containg 1,3,4 oxadiazine, 1,2,4-triazine and pyrazole derivatives by employing hydrazide-hydrazones [16]. The scheme of synthesis was as follows:



Scheme 16: Reagents and conditions: 1, 4- dioxane (0.01 mole equiv.), heat 2b, stirring at r.t. 2h, yield 80% (3a), 72% (3b), 88% (3c)



Scheme 17: Reagents and conditions: (i) NaOEt, EtOH (0.01equiv.), heat in a boiling water bath 4hrs (ii) HCl in ice/water, pH, 70% (4a), 78% (4b), 63% (4c)



Scheme 18: Reagent and conditions: 1,4- dioxane (0.01) equiv., heat 3 h, ice/ water with HCl, 60% (7b)

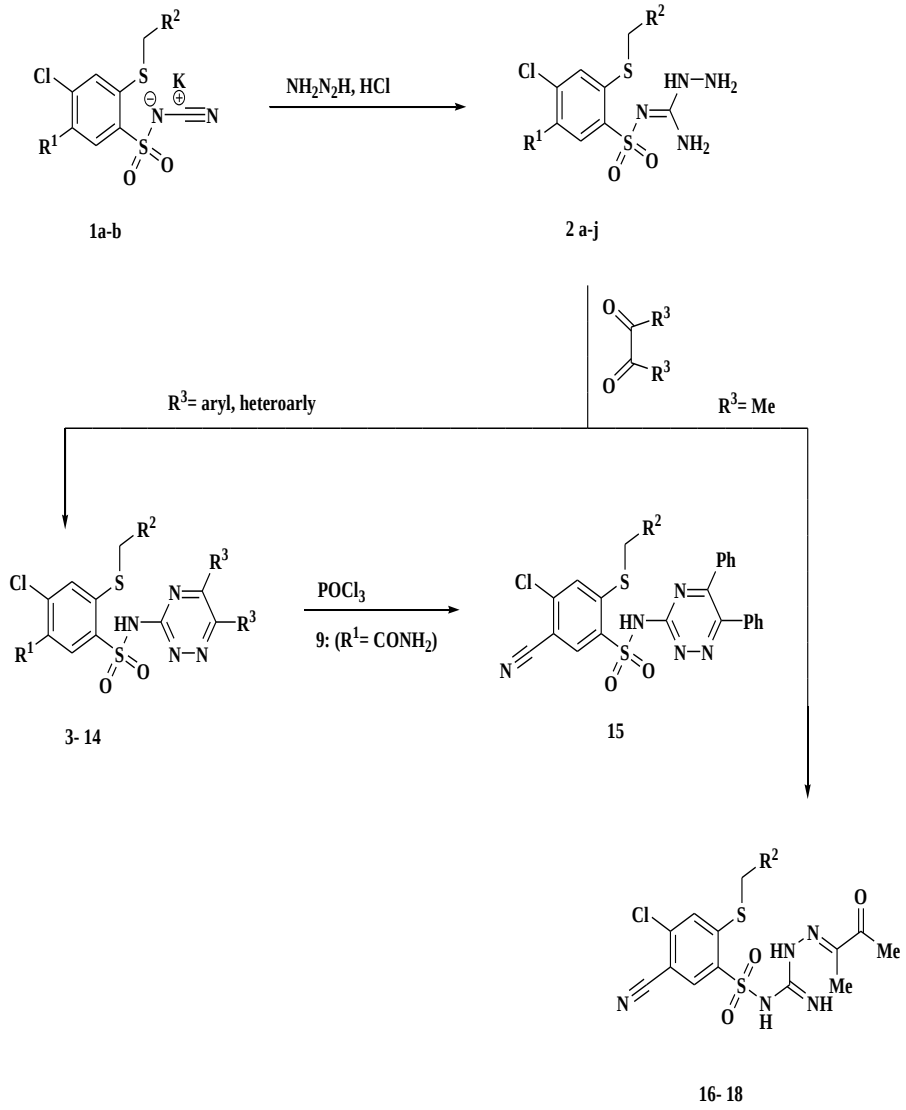
Some of the synthesized products showed high inhibitory effect towards the three cell lines.

Table 8. Effect of compounds 3-15c on human tumor cells

Compound	GI_{50} (μM)		
	MCF-7	**NCI-H 460**	**SF-268**
3a	66.6±12.2	12±6.2	24.8±3.2
3b	20±0.4	24.3±0.8	32±0.8
3c	30±0.6	17.3±1.4	22.3±1.5
4a	40.6±12.6	32.6±8.6	60.4±14.8
4b	72.7±17.5	40.2±12.8	50.0±9.01
4c	11.8±0.6	14.5±0.8	16.7±1.6
7a	35.4±10.2	24.1±0.8	18.9±6.8
7b	38.0±1.8	44.0±0.8	20.5±1.1
9a	22.0±0.2	30.6±1.4	38.4±0.6
9b	50.1±0.7	23.2±4.8	18.4±1.8
11a	11.9±0.5	14.1±0.6	20.3±0.5
11b	70.9±0.9	43.6±1.8	56.8±0.8
13a	66.6±16.9	38.9±10.8	50.8±8.6
13b	40.6±12.2	32.6±8.6	60.4±14.8
13c	22.0±0.2	30.6±1.4	38.4±0.6
15a	20±0.4	24.3±0.8	32±0.8
15b	70.9±0.9	43.6±1.8	56.8±0.8
15c	2.5±0.5	10.4±0.6	8.0±0.4
Doxorubicin	0.0428±0.008	0.0940±0.008	0.0940±0.007

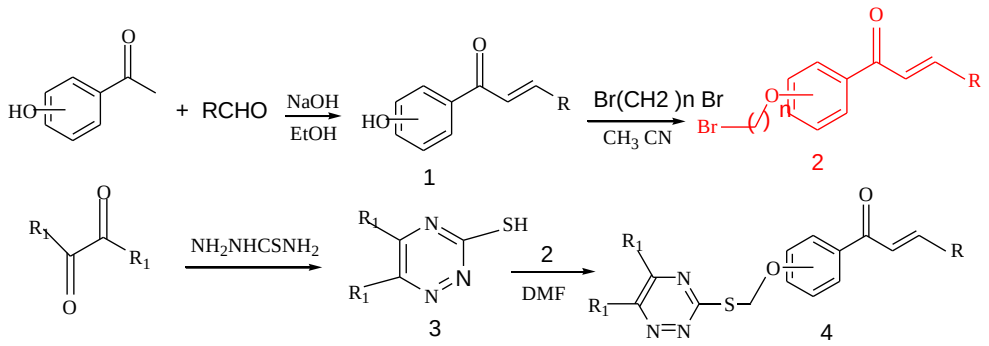
Table 8. Effect of compounds 3-15c on human tumour cells

Jaroslaw etal. described the syntheses of a number of 4-chloro-2-mercaptobenzenesulfonamide possessing bulky aromatic/heterocyclic moieties substituting the sulfonamide functionality [17].



Scheme 19. Syntheses of a number of 4-chloro-2-mercaptobenzenesulfonamide

Tang et al. [18] have synthesized novel chalcone derivatives containing a 1,2,4-triazine moiety and evaluated for TMV (tobacco mosaic virus) antiviral activity.

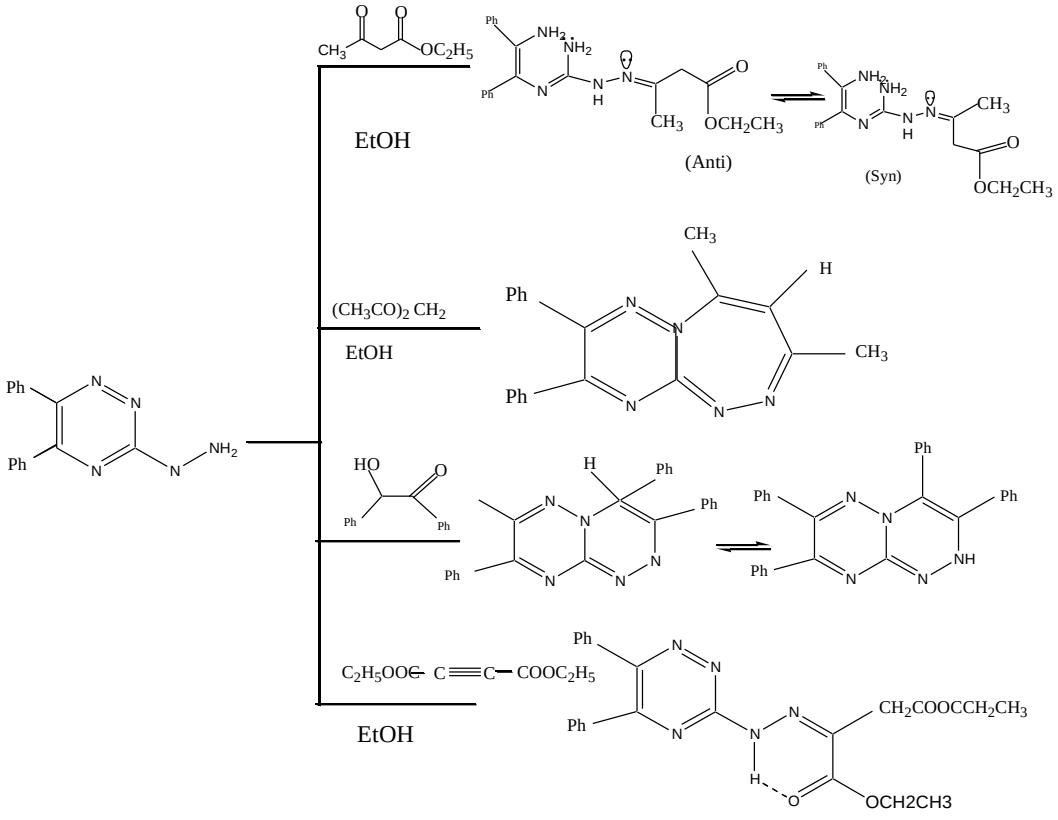


4a: O=4, n=4, R=4-NO2 -Ph, R1 =-Ph:
4c: O=4, n=2, R=2-OMe-Ph, R1 =-Ph:
4e: O=4, n=2, R=-Ph, R1= -Ph:
4g:O=4: n=2: R= 2,4-di-OMe-Ph,R1 =-Me
4i: O=4,n=2 : R=3,4 -di -OMe-Ph, R1 =-Ph:
4k:O=4: n=2:R=3-NO2 -Ph, R1 =-Ph:
4m:O=2,n=2:R=2-F-Ph,R1 =Ph:
4o:O=2,n=2:R=4-Methiazole,R1 =Ph;
4q:O=4,n=2,R=4-Br-Ph,R1 =Me
4s:O=4,n=2,R=4-F-Ph,R1 =Ph:
4u:O=4,n=2, R=4-Cl-Ph,R1 =Ph;
4w:O=4,n=2,R=4-Methiazole,R1 =Ph:

4b: O=2, n=2, R=2,-OMe-Ph, R1=-Ph
4d: O=4, n=2, R=2,4-di-OMe-Ph, R1=-Ph
4f: O=4 n=2, R=2-furan, R1=-Ph
4h: O=4, n=2, R=2-Cl-Ph,R1=-Ph
4j: O=4, n=2, R=4-OMe-Ph,R1=-Ph
4l: O=2, n=2, R=4-F-Ph,R1=-Ph
4n: O=2, n=2, R=N,N-di-Me-Ph,R1=-Ph
4p: O=2, n=2, R=3-Me-Ph,R1=-Ph
4r: O=4, n=2, R=4-Bu-Ph,R1=-Ph
4t: O=2, n=2, R=2-thiophene,R1=-Ph
4v: O=4, n=3, R=4-Cl-Ph,R1=-Ph

Scheme 19. Syntheses of novel chalcone derivatives containing a 1,2,4-triazine moiety

Mohsen et al. exploited various reactions of 3-hyrazino-5,6-diphenyl-1,2,4-triazine with various carbonyl compounds such as ethyl acetoacetate, acetylacetone, benzoin, isatin, phthalic anhydride, phenyl isocyanate and acetic anhydride [19].



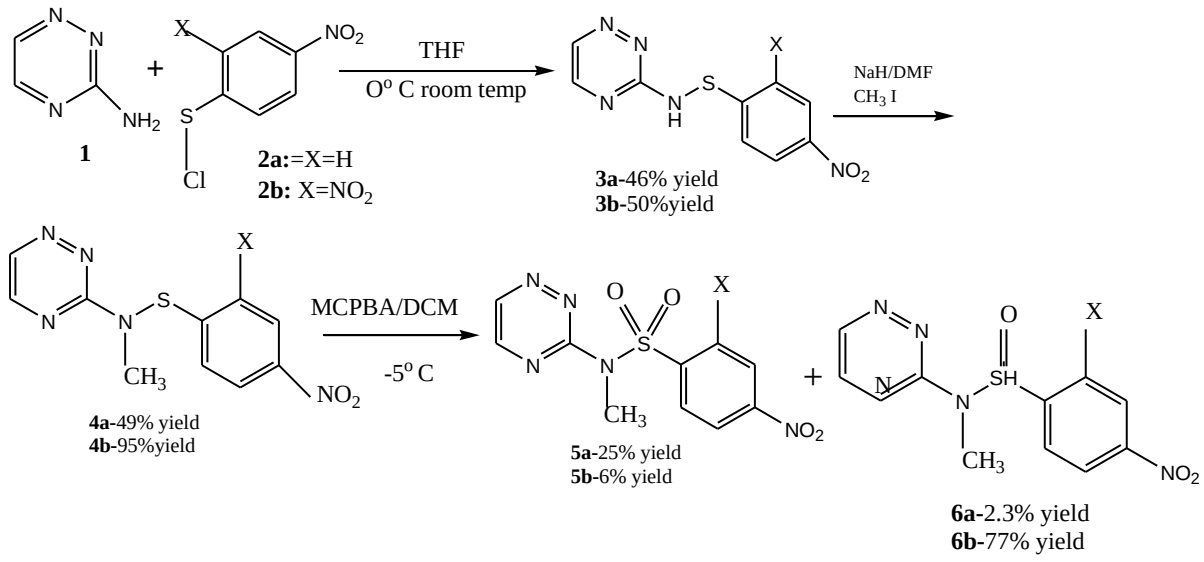
Scheme 20. Reactions of 3-hyrazino-5,6-diphenyl-1,2,4-triazine with various carbonyl compounds

The effective dose calculated as IC50, which correspond to the compound concentration resulted in 50% mortality in the total cells count and presented in (Table 9).

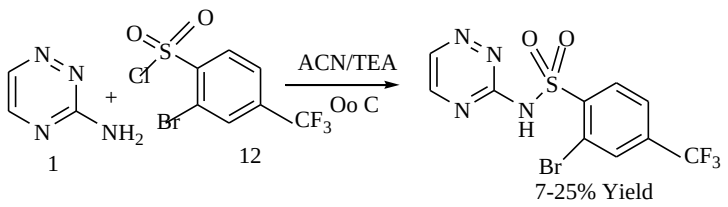
Table 9. Cytotoxic activity of some compounds against human tumor cells.

No.	Compounds DOX	In vitro cytotoxicity IC_{50} (μM) ·	
		HePG 2 4.50±0.2	MCF-7 4.17±0.2
1	2	31.75±2.5	35.38±2.4
2	4	7.21±0.8	9.72±0.9
3	14	72.13±3.9	68.23±3.8
4	16	39.49±2.6	45.08±2.8
5	12	61.84±3.5	67.14±3.7
6	13	27.93±2.1	26.99±2.0
7	11	19.18±1.7	21.10±1.8
8	10	82.34±4.6	72.15±4.1
9	3	55.35±3.2	49.27±3.0
10	9	76.58±4.1	91.48±5.2
11	15	48.16±2.9	58.36±3.4
12	6	9.11±1.0	12.84±1.1
·IC_{50} (μM) : 1-10 (very strong) .(11-20)strong.21-50 (moderate).51-100 (weak) and above 100(noncytotoxic).			

Branowska et al. [20] have very recently synthesized 1,2,4-triazine sulfonamides and evaluated *in vitro* anticancer activity. to verify whether they exhibited anticancer activity against the human breast cancer cell lines MCF-7 and MDA-MB-231.



Scheme 21.Synthesis of sulphonamides 5 and 6 starting from sulpenyl chloride 2a,b.



1 12

Scheme 22. Synthesis of sulphonamide 7

Conclusion

There are a number of anti cancer agents with 1,2,4-triazine scaffold making it a very important scaffold for cancer related studies and cure. As shown in this mini-review, several kinds of anticancer agents were described along with synthetic strategy. Therefore, this scaffold shows a promising result as anti tumour agents and can be used as anti-cancer drugs in the future.

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