Journal of Indian Research (ISSN: 2321-4155)
Vol.8, No.1, January-March 2020, 37-52

SYNTHETIC ROUTES, CHARACTERIZATION AND BIOLOGICAL SIGNIFICANCE OF 1, 2, 4-TRIAZINE DERIVATIVES:COMPREHENSIVE REVIEW

Aarfah Majid*
A. M. Lawal**
M.Ashid****
B.K.Sarma*****
Ajit Joshi******

ABSTRACT

When the three carbon-hydrogen units are replaced by three nitrogen atoms in a six-membered heterocyclic ring system homologous to benzene ring system,this system of compounds are called as triazines.$C_3H_3N_3$ is the general formula of triazines. Triazines are known to have three isomeric forms, depending on position of which of the carbon atoms of benzene ring is being replaced by the nitrogen unit.1,2,4-Triazine heterocyclic compounds as well as its derivatives are known to possess a wide variety of applications such as anti-viral, anti-HIV, anti-hypertensive, analgesic, anti-cancer, cyclin-dependent kinase inhibitors, anti-inflammatory, anti-malarial, cardiotonic and estrogen receptor modulators. They also possess properties like lubricants, analytical reagents as well as dyes. This paper reviews the literature on biological potential of 1,2,4-triazine derivatives.

Keywords: Dyes, Heterocyclic, Inhibitors,Isomeric,Reagents,Triazines.

INTRODUCTION

Heterocyclic Chemistry is one of the most important and significant part of the chemistry. The scientific discipline at the intersection of chemistry and pharmacy including designing, synthesizing and development of pharmaceutical drugs. Heterocyclic compounds (five, six and seven members) have special applications in the field of synthetic organic chemistry and

* **Aarfah Majid,** Department of Chemistry, Mewar University, Gangrar, Chittorgarh. **Corresponding Author Email:** aarfahwani786@gmail.com.

****M.Ashid,** Department of Chemistry, Mewar University, Gangrar, Chittorgarh

*****B.K.Sarma ,**Department of Chemistry, Mewar University, Gangrar, Chittorgarh

******A. M. Lawal,** Department of Chemistry, Mewar University, Gangrar, Chittorgarh

*******Ajit Joshi,** Department of Chemistry, UkaTarsadia University, Bardoli

biological activity. More than eighty percent of the medicines possess heterocyclic nucleus in their structure. Majority of natural products particularly alkaloids, which are being used as medicines with the development of civilization for mankind and other living things, have heterocyclic moieties as their constituents. Derivatives1-10of pyrazole, Imidazole, pyrimidine, thiadiazole, pyridine, thiazole, quinolineetc, are very important synthons for drug designing and also in the field of synthetic medicines.

These heterocyclic systems possess various pharmacological activities viz., analgesic, anti-tumor, anti-viral, anti-cancer, anti-bacterial, anti-parasitic, anti-malarial, anti-radiation, anti-neoplastic, and anti-hypertensive etc. The triazine structure is a heterocyclic ring homologous to six membered benzene ring in which three carbon atoms are replaced by three nitrogen atoms. The difference in the position of three nitrogen atoms distinguish the isomers of triazine which are referred to as,1,2,3-triazine heterocyclic,1,2,4-triazine heterocyclic and 1,3,5-triazine heterocyclic molecules [1]

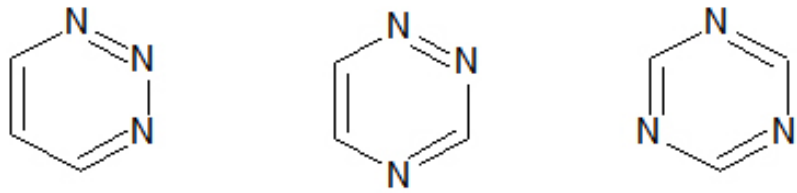
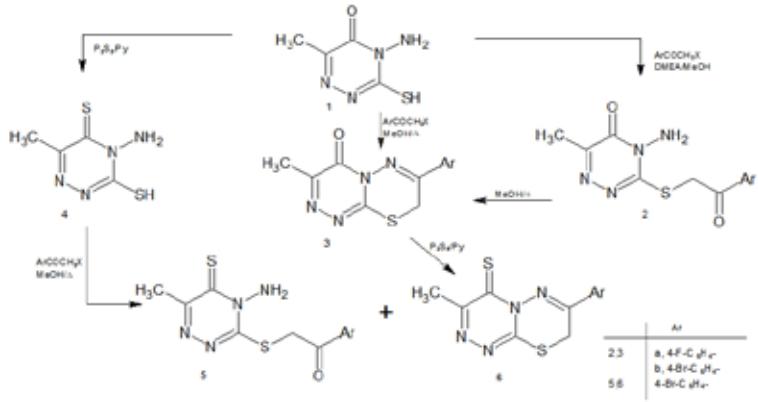


Figure 1: Three Heterocyclic N -atoms

From the past few years, the interest in synthesizing heterocyclic compounds containing, 1,2,4-triazine ring is increasing day by day because of their significance in biological problems.1,2,4-triazine molecule is a heterocyclic molecule analogous to benzene in which three carbon atoms are replaced by three nitrogen atoms. In recent years, there has been increasing interest in the synthesis of heterocyclic compounds containing a 1,2,4-triazine ring because of their biological significance. Several 1,2,4-triazine derivatives have been demonstrated to be of herbicidal, anti-hypertensive, anti-viral activity as well as activity against *Staphylococcus aureus, Bacillus cereus* and P388 Lymphocytic leukemia.1,2,4-triazines are regarded as 6-aza being analogues to pyrimidine bases, needless to say that pyrimidine, in general, have a great biological importance. Further 1,2,4-triazine derivatives have been reported to possess biological activities including against tuberculosis, analgesic, anti-hypertensive, anti-HIV, anti-viral, cyclin-dependent kinase inhibitors, anti-parasitic,neuroleptic, anti-inflammatory,anti-hy pertensive,analgesic,cardiotonic,anti-malarial [2-22].

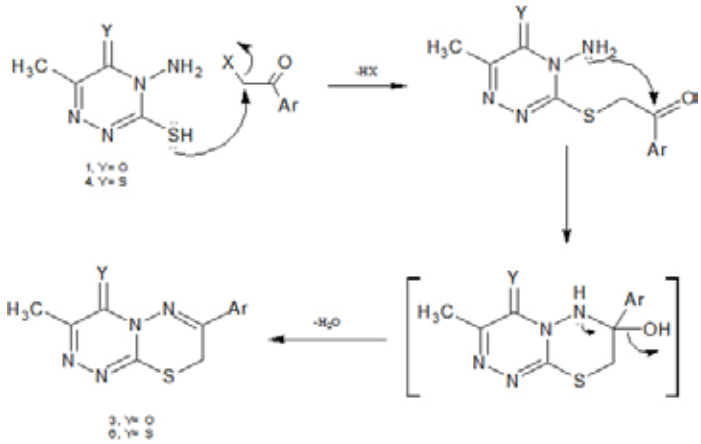
TRIAZINE DERIVATIVES AND THEIR BIOLOGICAL APPLICATION;

The reaction between thiocarbohydrazide with pyruvic acid results in the formation of 4-Amino-3-mercapto-6-methyl-1,2,4-triazin-5(4H)-one (2) according to Dornow*et. al*.[38]. The condensation reaction between 2-phenyl-4-(4-floro benzylidene)-1,3-oxazol-5-one and hydrazine hydrate, semicarbazide and thiosemicarbazide then followed by cyclization with the removal of water molecule results in the formation of 2,3,5-trisubstituted-1,2,4-triazine-6-one[23].



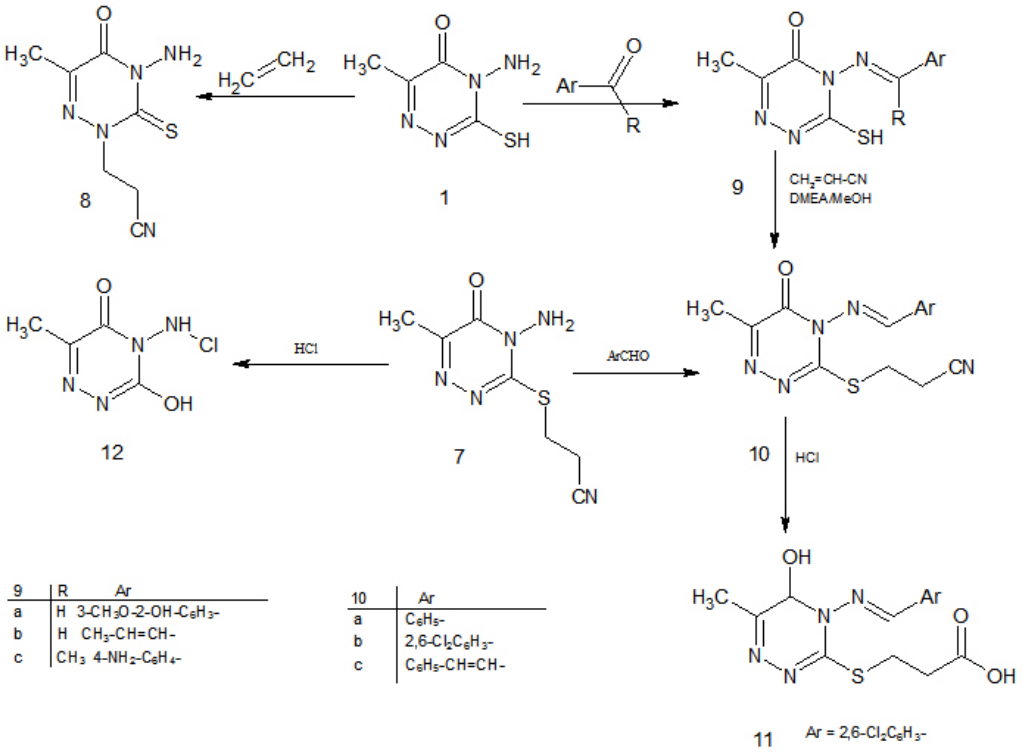
SCHEME 1

Treatment of (1)with 4-fluolophenacyl chloride and/or 4-bromophenacyl bromide in methanol at room temperature in the presence of N,N-dimethylethylamine (DMEA)afforded high yields of the corresponding phenacylthio derivatives 2a,b which were cyclized to 8H-7-aryl-3-methyl-as-triazino [3,4-1b], 3[4] thiadiazin-4-ones (3a,b) by heating in methanol for one hour. Compounds 3a, bwere also obtained via the reaction of 1 with phenacyl halides in boiling methanol. Thiation of compound (1)with phosphorus pentasulfide in boiling anhydrous pyridine afforded 4-amino-3-mercapto-6-methyl-1,2,4-triazine-5(4H)-thione (3),in 63 % yield. Treatment of compound 4 with 4-bromophenacyl bromide in boiling methanol yielded a separable mixture of 4-amino-3-(4-bromophenacyl)thio-6-methyl-2,4-triazine-5(4H)-thione(4) and 8H-7-(4-bromophenyl)-3-methyl-as-triazino[3,4-bI], 3[4] thiadiazine- 4-thione (6) in 65 % total yield, which on further heating for 2 hrs.,gave (6)as a sole product in 60 % yield. Compounds (5)and (6)were separated from the mixture by treatment with boiling dilute acetic acid that dissolved (5). Compound (6)was obtained by another pathway when 3b was treated with phosphorus pentasufide in boiling anhydrous pyridine (Scheme 1).



SCHEME 2

Isolation of the phenacylthio derivatives 2a, b and (5), at different reaction conditions, suggests a mechanism for formation of the triazino [3,4-b] [1,3,4] thiadiazines3a,b and compound (6). In such mechanism, a nucleophilic attack of the phenacyl halides occurs by the mercapto group to give the S-alkylated products 2a,b and compound (5); and then an internal nucleophilic attack by the NH_2 group on the CO takes place with a loss of a H_2O molecule to afford the final products (3) and (6) (Scheme 2).



SCHEME 3

Compound (7) was condensed with benzaldehyde, 2,6-dichlorobenzaldehyde and cinnamaldehyde in methanol to afford the corresponding arylideneamino derivatives 10a-c in 72-84% yields. Condensation of compound(1)with vanillin, crotonaldehyde and 4-aminoacetophenone gave the corresponding anils9a-c in 60-82 % yields. In case of the condensation reaction with crotonaldehyde or cinnamaldehyde, an inseparable mixture of *Z'E* isomers was obtained in 1:4 ratio (according to ^{13}C NMR). 4-(2,6-Dichlorobenzylidene) amino-3-(2-cyanoethyl)thio-6-methyl- 1,2,4-triazin-5(4H)-one (10b) was also obtained in 73% yield when 9 (Ar= 2,6-$C_{12}C_6H$,-)'6 was treated with acrylonitrile in boiling methanol in the presence of DMEA. Acid hydrolysis of 10b afforded the corresponding acid 11 in 51 % yield, while compound 7, under the same reaction conditions, gave 4-amino-3-hydroxy-1,2,4-triazin-5(4H)-one as a hydrochloride salt (12) in 38 % yield (Scheme 3).

The structures of the newly synthesized compounds were confirmed by analytical data, IR, 'H NMR, ^{13}C NMR and mass spectra.

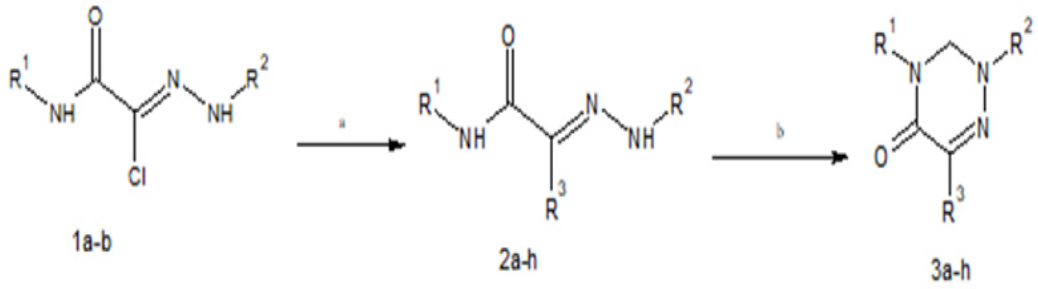
In this literature review this has been found that standard disc method was adopted for testing the anti-microbial activity of the compounds 2a, 3a,4,5,7,9a, 10b and 11. Filter paper discs were moistened with the tested compound solution in dimethylsulphoxide of specific concentration 1 mg/disc and carefully placed on agar culture plates that have been previously inoculated separately with the microorganisms; *Aspergillus niger, Aspergillus flaws, Aspergillus fumigatus, Penicillium notatum, Candida albicans* and *Staphyllococus saureus.* After incubation, the diameter of the growth inhibition around the disc was measured. Compounds 2a, 4, 5 and 11 were found to be active against *A. fumigatus, C. albicans and S. aureus;* compounds 2a, 4 and 11 showed activity against *P.notatum*; compounds (4)and (5) showed activity against *A. niger* while, no compound(s) was found to possess marked activity against A. *flavus* (Table 1).

Table 1: Diameters of the Inhibition Zones (mm) Exhibited by the Tested Compounds

No.	*A. niger*	*A. flavus*	*A. fumigatus*	*P. notatum*	*C. albicans*	*S. aureus*
2a	-	-	11	6	17	5
3a	-	-	-	-	-	-
4	12	-	17	13	15	26
5	19	-	12	-	21	7
7	-	-	-	-	-	-
9a	-	-	-	-	-	-
10b	-	-	-	-	-	-
11	-	-	9	5	12	4

A number of small molecules possessing 1,2,4-triazine scaffold have been shown to exhibit a great variety of pharmacological effects, from last few years. On the application of these compounds, such as 5-lipoxygenase (5-LO) inhibitors, herbicides, bactericides, fungicides, antimicrobials, and gonadotropin-releasing hormone receptor (GnRH-R) antagonists ,several reports have been published. Even for fused 1,2,4-triazine compounds, not only anti-tumor and anti-metastatic activities against a wide range of cancer cells but also kinase inhibiting activities could be observed.

In 2007, cancer accounted for 7.9 million death cases (around 13% of all deaths). Deaths from cancer worldwide are projected to continue rising, with an estimated 12 million deaths in 2030. Heterocyclic compounds containing an amidrazone scaffold, novel 1,2,4-triazines as efficient anti-cancer drugs with low cytotoxicity and good bioavailability properties were synthesized. The straightforward synthesis of eight 1,2,4-triazin-5-ones 3a–h is represented in Scheme 4.



1a:	R^2=C_6H_5	**2a, 3a:**	R^2=C_6H_5; R^3=$(CH_3)_2N$	**2e, 3e:**	R^2=C_6H_5; R^3= piperidine
1b:	R^2=4-Cl-C_6H_4	**2b, 3b:**	R^2=4-Cl-C_6H_4; R^3=$(CH_3)_2N$	**2f, 3f:**	R^2=4-Cl-C_6H_4; R^3=piperidine
		2c, 3c:	R^2=C_6H_5; R^3=pyrrolidine	**2g, 3g:**	R^2= C_6H_5; R^3=morpholine
1-3:	R^1=2-Cl-C_6H_4	**2d, 3d:**	R^2=4-Cl-C_6H_4; R^3=pyrrolidine	**2h, 3h:**	R^2=4-Cl-C_6H_4; R^3=morpholine

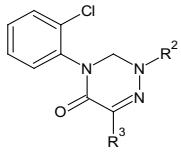
Scheme 1. Reagents and conditions: (a) dimethylamine for **2a-b,** pyrrolidine for **2c-d**, piperidine for **2e-f**, morpholine for **2g-h,** dioxane, room temperature, 12 h and (b) H_2CO, TsOH, EtOH, 1-2h, reflux.

SCHEME 4

Hydrazonoyl chlorides 1a–b as starting compounds for triazinone synthesis was prepared according to known literature procedures. Conversion of 1a–b with the respective amines in dioxane led to amidrazone intermediates 2a–h. One to two hours of refluxing 2a–h with formaldehyde in the presence of p-toluen-sulfonic acid yielded nearly pure 1,2,4-triazin-5-ones. 3a–h of refluxing 2a–h with formaldehyde in the presence of p-toluen sulfonic acid yielded nearly pure 1,2,4-triazin-5-ones 3a–h (Scheme 1).

Among the eight1,2,4-triazin-5-ones synthesized, 3a–d showed the highest anti-proliferative effect on the human leukemia cell line K-562 with a moderate growth inhibition efficacy on the human umbilical vein endothelial cell line (HUVEC). Though the most potent compound 3c is obviously less active against K-562 than Imatinib, the preferred drug for treating chronic myeloid leukemia (CML), a comparable low growth inhibiting effect on HUVEC was found. Cytotoxicity of 3c against HeLa cells is ranging at similar values. In contrast to doxorubicin, an established but highly cytotoxic drug for the treatment of acute myeloid leukemia (AML), lymphoma, sarcoma, and carcinoma, 3c showed a five times lower anti-proliferative activity against K-562, but a 22 times lower cytotoxicity on HeLa cells (Table 2).

Table 2: Substitution Patterns, Lipsinki's 'Rule-of-Five' descriptors, experimental log P values (Log P_{exp})

	R^2	R^3	Mw^2	nON^2	$nOHNH^2$	Log P_{cak} [a]	logP_{exp}
3a	C_6H_5	$N(CH_3)_2$	328.80	5	0	3.5	3.6
3b	4-Cl-C_6H_4	$N(CH_3)_2$	363.25	5	0	4.2	4.2
3c	C_6H_5	Pyrrolidine	354.84	5	0	3.9	4.0
3d	4-Cl-C_6H_4	Pyrrolidine	389.29	5	0	4.6	4.6
3e	C_6H_5	Piperidine	368.87	5	0	4.4	4.6
3f	4-Cl-C_6H_4	Piperidine	403.31	5	0	5.1	5.0
3g	C_6H_5	Morpholine	370.84	6	0	3.3	3.5
3h	4-Cl-C_6H_4	Morpholine	405.28	6	0	4.0	4.0
Imatinib	-	-	493.62	8	2	3.9	1.22[22]
Doxorubicin	-	-	543.52	12	7	0.57	0.71[23]

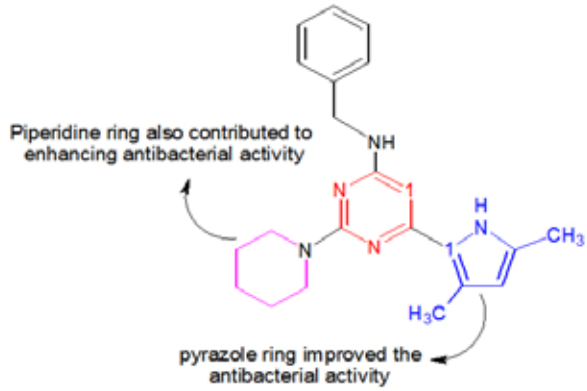
n.d.: not determined.[a]Lipsinki descriptors: Mw, molecular weight; nON, number of hydrogen acceptors; nOHNH, number of hydrogen donors; log P_{calo} log P values calculated by molinspiration property calculator for the neutral species; log $P_{exp,}$ experimentally determined log P values by RP-HPLC.

These results suggest that there is little correlation between cytotoxicity and anti-proliferative activity for the 1,2,4-triazin-5-ones. If one compares the effect of R3 on the anti-proliferative activity against K-562 cells, an optimum exists for the pyrrolidine moiety. 4-Chloro substitution on the phenyl ring R2 not only raises the log P values, but lowers the effect on K- 562. Interestingly the existence of the chlorine atom in 3b and 3d seems to raise the growth inhibiting effect on HUVEC cells. An introduction of a morpholine group leads to a distinct decrease of any activity. Considering the estimated new cases (44,790 men and woman) and deaths (21,870 men and woman) from leukemia in the United States in 2009 [27] and the proceeding emergence of resistances against chemotherapeutic agents (multi-drug resistance), there is a demand for novel, more effective anti-cancer agents. Taking 1,2,4-triazin-5-one as lead structure for the development of less toxic and selective anti-leukemia drugs, further chemical modifications in the substitution patterns of the aromatic groups are envisioned for optimization of pharmacological activity. An introduction of hydrogen donor groups may be considered as well.

Melting points were determined on a Boetius hot-stage apparatus. Elemental analyses were performed by Leco Microlab, Inc., and determined values are within 0.4% of theory. NMR spectra were recorded on a Gemini 2000 operating at 399.96 MHz for 1HNMR and at 100.6 MHz for ^{13}C NMR spectra in DMSO-d6 which was also used as internal standard. Chemical shifts are given in 'd' units and refer to the center of the signal. EI-mass spectra were obtained

with an AMD402 mass spectrometer (AMD Intectra) at 70 eV. Reactions were monitored by TLC (Silica gel 60 F254, Merck) using chloroform/ether (7:3, v/v) and heptane/ ethylacetate (3:1, v/v) and compounds were detected with ultraviolet light (254 nm). Compounds 1a, 2a, 2b, 2e, 2g,17 1b,16 and 3e18 were obtained by published procedures[24].

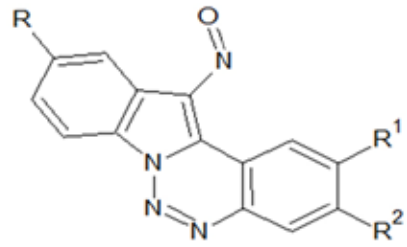
The development of new antibiotic resistant drugs has not been fulfilled yet and this question is accepted on priority universally. Recently, Albericio *et al.,* [25] have designed and synthesized a new class of pyrazole-containing 1,3,5-triazine derivatives and evaluated therein *in vitro* anti-microbial activity against a panel of bacterial and fungal strains using modified Kirby-Bauer disk diffusion method [26]. Compound 13 exhibited promising anti-bacterial activity against Gram-negative (*P. aeruginosa*, Zone of Inhibition (ZoI): 19 mm) and Gram positive (*M. luteus*, ZoI: 22 mm) bacterial strains. The SAR revealed that the presence of piperidine with benzylamine on the triazine ring proves to be a key factor for enhancing the anti-bacterial activity against *P. aeruginosa* and *M. luteus* bacterial strains. The combination of 1,3,5-triazine with pyrazole and piperidine rings was a promising scaffold for the development of new active anti-biotics in the near future. A set of novel 2,4,6 tri-substituted 1,3,5-triazines were synthesized and tested for *in vitro* antimicrobial activity by Mane and co-workers [27].



13

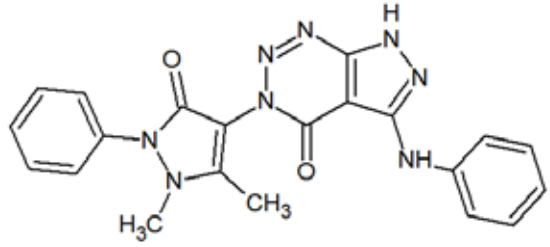
Girolamo Cirrincione *et al*. [28] synthesized some indolo [1,2-c]benzo[1,2,3]triazine analogs. Synthesized compounds were evaluated for *in vitro* anti-tumor activity against a panel of leukemia-, lymphoma-, carcinoma and neuroblastoma derived cell lines. Some of the synthesized compounds inhibited the proliferation of T and B cell lines at sub-micromolar concentrations and their activity against solid tumor cell lines was in the micromolar range. Indolobenzotriazine analog 14 showed most potent anti-tumor activity with IC_{50} in range of 0.08-0.7 µM. This compound was fully inhibitory to all the resistant cell lines thus suggesting that it neither is subject to the pump mediating the efflux of many antitumor drugs nor interferes with the DNA synthesis. The compounds (14) (IC_{50} range = 0.3-2.7 µM) and 15 (IC_{50} range = 1.9-9.5µM) displayed lower anti-proliferative activity against cell lines derived from solid tumors than that of Doxorubicin. All the synthesized compounds were also screened for antimicrobial activity.

All indolobenzotriazines were proved to be fairly potent and selective inhibitors of streptococcus and staphylococcus. Compounds (16) and (17) showed most potent antifungal activity. Compounds (18), (19), and (20) displayed most potent anti-bacterial activity. SAR studies revealed that maximum *in vitro* anti-tumor activity correlates with the presence of either a chlorine atom at position 10 (14) or a methyl group at position 2 (15). Furthermore, the absence of substituents at positions 10, and 2 (16), or the substitution of a chlorine atom for a methoxy (19) or nitro (20) group at position 10 or the substitution of a methyl group for a chlorine atom (18) at position 2 significantly decreased the activity.Moving the chlorine atom from position 2 to 3 (17) partially restores the anti-tumor activity *in vitro*. Maximum potency of anti-fungal activity correlates with the absence of substituents (16) or the presence of a chlorine atom at position 3 (17). Compound(17) was found to be the only compound capable of potently inhibiting the proliferation of both animal and fungal cells, whereas the derivatives endowed with the highest *in vitro* anti-tumor activity (14-15) were totally ineffective on the fungal growth. The potent and selective anti-bacterial activity is correlated with the presence of a chlorine atom at position 2 (18) or with a methoxy (19) or nitro (20) group at position 10.



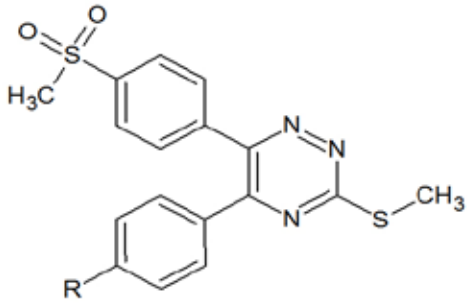
14 R=Cl, R_1=R_2=H, (IC_{50} Range= 0.08-0.7μM);
15 R=R_2=H, R1=CH_3, (IC_{50} Range = 1.9-9.5 μM);
16 R=R_1=R_2=H;
17 R=R_1=H, R_2=Cl;
18 R=R_2=H, R_1=Cl;
19 R=OCH_3, R_1=R_2=H;
20 R=NO_2, R_1=R_2=H

Samir Bondock *et al.* [29] synthesized a series of pyrazolo[3,4-d]triazine and screened them for *in vitro* anti-microbial activity against *Bacillus thuringiensis*, *Klebsiella pneumonia*, *Botrytis fabae* and *Fusarium oxysporum* by the agar diffusion method. Compound (21) exhibited significant anti-fungal activity. It was concluded that incorporation of anti-pyrine to the coumarin nucleus at position 3, via a carboxamide linker produces a high antimicrobial activity.



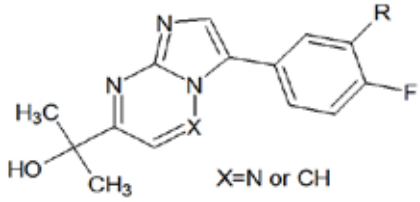
21

H. Irannejad *et al*. [30] reported that a series of 5-Aryl-6-(4-methylsulfonyl)-3-(metylthio)-1,2,4-triazine derivatives were synthesized and their COX-1/COX-2 inhibitory activity as well as *in vivo* anti-inflammatory and analgesic effects were evaluated. All of compounds showed strong inhibition of COX-2 with IC_{50} values in the range of 0.1– 0.2 μM and in most cases had stronger anti-inflammatory and analgesic effects than indomethacin at doses 3 and 6 mg/kg. Among them, 5-(4-chlorophenyl)-6-(4-(methyl sulfonyl) phenyl)-3-(methyl thio)-1,2,4-triazine was the most potent and selective COX-2 compound; its selectivity index of 395 was comparable to celecoxib (SI = 405). Evaluation of anti-inflammatory and analgesic effects showed its higher potency than indomethacin and hence, could be considered as a promising lead candidate for further drug development. Furthermore, the affinity data of these compounds were rationalized through enzyme docking simulation and 3D-QSAR study by k-Nearest Neighbour Molecular Field Analysis (22).



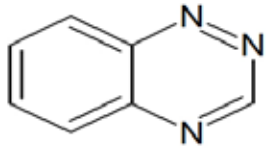
22

S. R. Jennings *et al.* [31] reported the Imidazo[1,2-b][1,2,4] triazines as a2/a3 subtype selective GABAA agonists for the treatment of anxiety

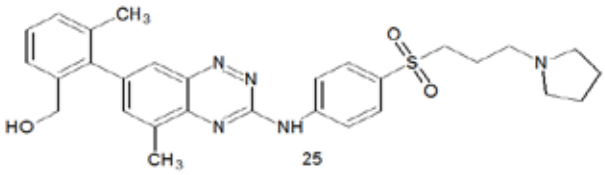


23

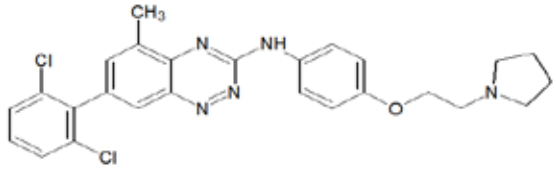
The prominent heterocyclic substrate which is present in numerous pharmacologically active molecules is 1,2,4-benzotriazine nucleus fused to a benzene ring.Many 1,2,4-benzotriazine possessing a wide spectrum of pharmacological activities (24).



The preclinical study of 3-amino-1,2,4-benzotrizine analogous to 25 and 26 have shown anti-tumor activity against sarcoma[32] due to their activities as inhibitors of Src kinases, and they may be effective as anti-neoplastic agents against pancreatic and breast, and stomach cancer cell lines.

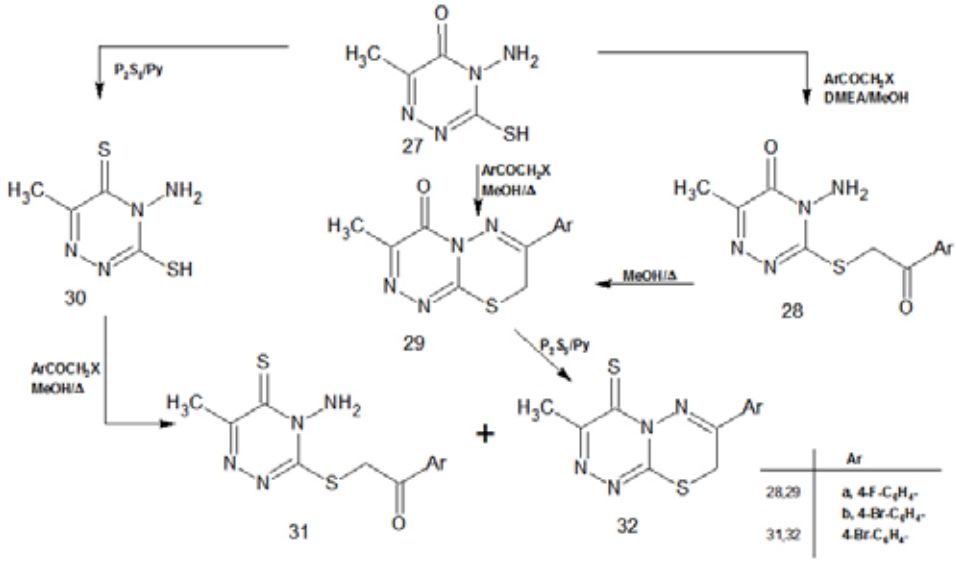


25



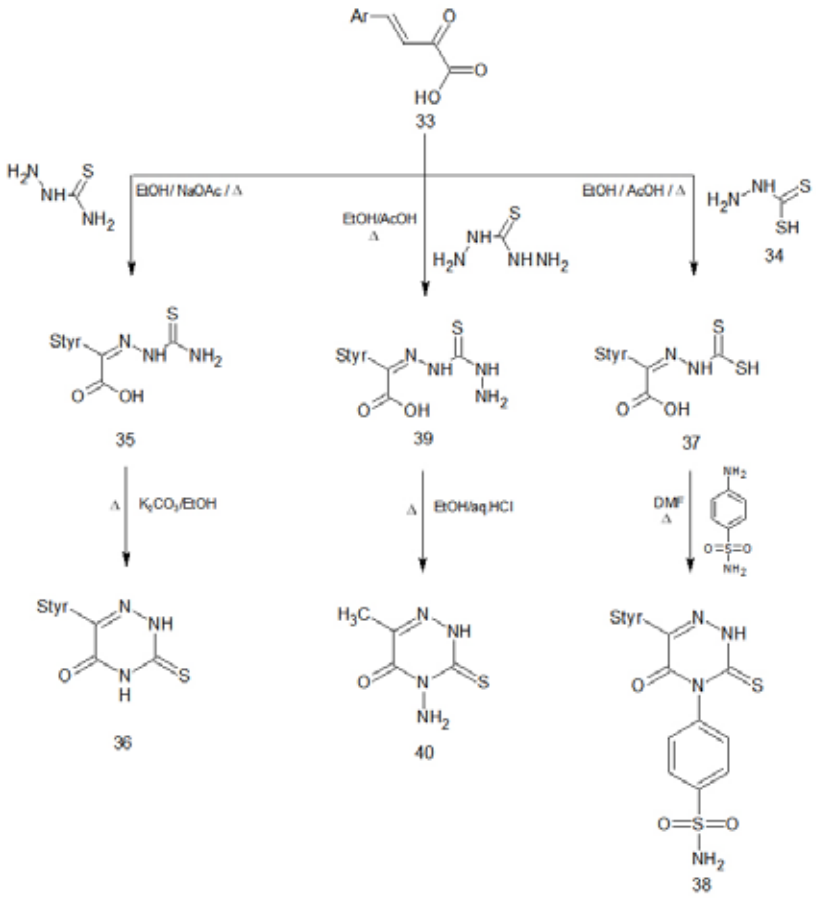
26

The anti-tumor activity, the SAR and whatever described the possible mode of action of 1,2,4-triazine derivatives, their N-Oxides, N,N-dioxides as well as the benzo- and hetero-fused systems are also being reported[33]. 3-Sulfanilamido5-dimethylethyl-1,2,4-triazine is manufactured and used as sulfa drug[34]. The 5-thioxo derivatives and 4-Amino-3-mercapto-6-methyl-1,2,4-triazin-5(4H)-one were allowed to react with phenacyl halides by giving different conditions of reaction to synthesize the derivatives of S-phenacyl derivatives [35] (Scheme 5).



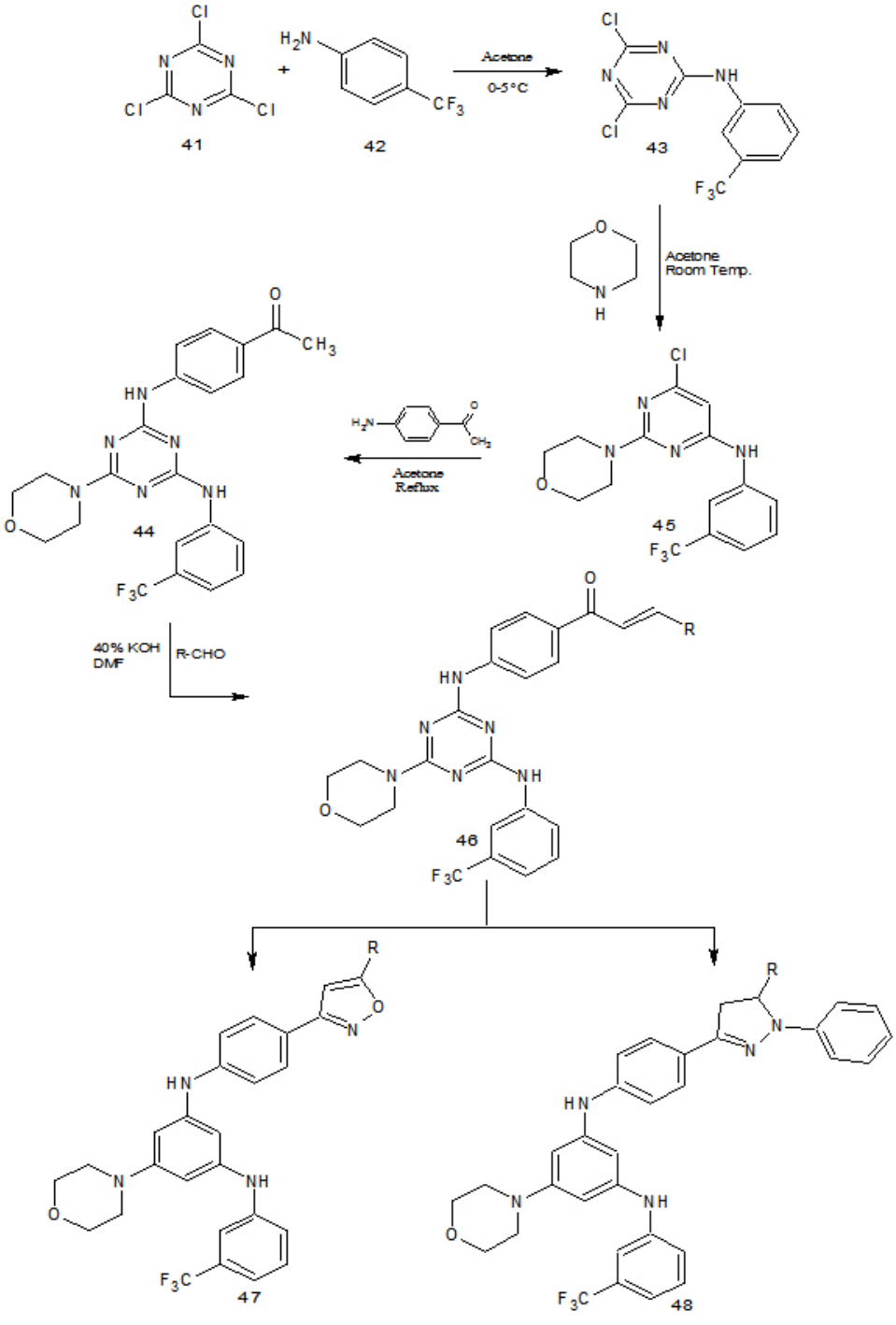
SCHEME 5

Reda *et al.* [36] have synthesized an affordable derivative of 1,2,4-triazin by the condensation reaction of 3-thioxo-1,2,4-triazine-5-one. A simple condensation afforded some new 3-thioxo-1,2,4-triazin-5-one derivatives (36, 38 and 40). Utilizing a facile condensation of (E)-4-(4'-bromo styryl)-2-oxo-3-buteneoic acid with thiosemicarbazide, dithioic formic acid hydrazide, and thiocarbahydrazide in different conditions. Structures of these compounds were confirmed by elemental and spectral analysis. The preliminary biocidal activity of these products were evaluated against some microbial and compared to Mycostatine and piperacillin as anti-biotics were most of the derivatives exhibiting good activity.



SCHEME 6

S-Triazine based chalcones results in the formation of derivatives of heterocyclic compounds like phenyl pyrazolines as well as isoxaxoles (Scheme 7), and then the structure of newly synthesized compounds were analyzed by elemental analysis and spectroscopic techniques like IR,^{1}H NMR,^{13}C NMR. The screening for antimicrobial activity have been done for the newly synthesized compounds against selected gram positive and gram negative like *S. aureus, S. pygenus, E. coli, P. aeruginosa* respectively and have also shown activity against fungal strains [37].


Cl
N
Cl
N
Cl
41
H_2N
+
CF_3
42
Acetone
0-5°C
NH
43
F_3C
O
N
H
Acetone
Room Temp.
45
44
CH_3
HN
NH
F_3C
Acetone
Reflux
40% KOH
DMF
R-CHO
R
46
47
48

SCHEME 7

CONCLUSION

It has been seen and identified from the literature survey and from the drugs used clinically that the biological potential of 1,2,4-triazine derivatives are very significant. The literature survey also revealed that 1,2,4-triazine derivatives have biological properties in diverse aspects. It has also been experienced that there are several easy synthetic routes to synthesize new chemo-therapeutic agents from 1,2,4-triazine derivatives.Importance of 1,2,4-triazine nucleus has attracted many researchers towards the heterocyclic chemistry.

REFERENCES

1. Schroeder, H & Grundmann, C.(1956). Triazines-XIV. *J. Am. Chem. Soc*. **78**, 2447-2451.
2. Kidwai, M.; Goel, Y.& Kumar,R. (1999).'Microwave assisted synthesis and antifungal activity of 1,2,4-triazine,124-triazole,tetrazole and pyrazoles derivative'. *Indian Journal of Chemical* **37b**,174.
3. Holla, B. S.; Gonsalves, R.; Rao, S.; Henoy, S.& Gopalkrishna, H.N.(2001). 'Synthesis of some new biologically active bis-(thadizolotriazines) and bia-(thiadiazolotriazinyl) alkanes'. *Farmaco* **56**,899.
4. Abdel-Rahman, R.M.; Morsy, J.M.; Hanafy, F.& Amene, H.A.(1999). 'Synthesis of heterobicyclic nitrogen systems bearing the 1,2,4-triazine moiety as anti-HIV and anticancer drugs:Part 1'. *Pharmazie* **54**,347.
5. Partridge, M.W. & Stevens, M.F.G.J(1966). 'Pyrazolo-as-triazines:part-1'.*Chem. Soc*.**1127**.
6. Abd, E.I.& Samii, ZK(19920. 'Synthesis and anti-inflammatory activity of some novel 1,3,4-oxadiazole derivatives'. *Journal of Chemistry Technol. Biotechnol.***143**.
7. Heilman, W.P.; Heilman, R.D; Scozzie, J.A.; Wayner, R.J.; Gullo, J.M.; & Riyan, Z.S.(1979). 'Synthesis and antihypertensive activity of novel 3hydrazino-5-phenyl-1,2,4-triazine'. *J.Med.Chem.***22**,671.
8. Hay, M.P., Prujin, F.B., Gamage, S.A.; Liyanage, H.D. & Wilson, W.R.(2004). 'Targeted 1,2,4-Benzotriazine 1,4-Dioxides,potent Analogues of the hypoxia-Selective CytotoxinTirapazamine'. *J.Med.Chem.***47**,475.
9. Baliani A., Bueno G.J., Stewart M.L., Yardley V., Brun R., Barrett M.P., Gilbert I.H., 'Design and synthesis of a series of melamine-based nitro-heterocycles with activity against trypanosomatid parasites'. *J.Med. Chem.* **48**,5570-5579.
10. Kosary, I.;.Kosztreiner, E ; Rabloczky, G. & Kurhy, M.(1989). *Eur.J.Med. Chemical.***24**,97-105.
11. Henke, B.R.; Consler, T.G.; Go, N.; Hale, R.L.; Hohman, D.R.; Jones, S.A.; Lu, A.T.; Moore, L.B.;Moore, J.T.; Orband, L.A.; Robinett, R.G.; Shearin, J.; Spearing, P.K.; Stewart, E.L.; Turnbull, P.S.;Weaver, S.L .; Williams, S.P.; Wisely, G.B.& Lambert, M.H.(2002). 'A new series of estrogen receptor modulator that display selectivity for estrogen receptor beta'. *Journal of Medicinal Chemistry***45**,5492-5505.

12. Baliani, A.; Bueno, G.J.; Stewart, M.L.; Yardley, V.; Brun, R.; Barrett, M.P. & Gilbert, I.H.(2005). 'Design and synthesis of a series of melamine-based nitrohetrocycles with activity against trypanosomatid parasites'. *Journal of Med. Chem.***48**,5570-5579.

13. Lubbers, T.; Angehrn, P.; Gmunder, H.; Herzig, S. & Kulhanek, J.(2000). 'Design,synthesis and structure-activity relationship studies of ATP analogues as DNA gyrase inhibitors'. *Bioorg. Med. Chem. Lett.***10**,821-826.

14. Srinivas, K.; Srinivas, U.; Harakishore, K.; Jayathirha Rao, V. & Bhanuprakash, K. (2005).'Synthesis and antibacterial activity of various substituted S-triazine'.*Bioorg.Med. Chem.lett*. **15**,1121-1123.

15. Malwad, V.V. & Shirodkar. J.M.(2003). 'Synthesis and Antibacterial Activity of new Tetrazole Derivatives'.*Ind.J.Chem.***42b**,621-626.

16. Ghaib, A.; Menager, S.; Verite, P. & Lafont, O.(2002). 'Synthesis of variously 9,9-dialkylated octahydropyrimido{3,4-a}-s-triazines with potential antifungal activity' *IL Farmaco.* **57**,109-116.

17. Jensen,N.P.; Ager, A.L.; Bliss, R.A.; Canfield, C.J.; Kotecka, B.M.; Rieckmann, K.H.; Terpinski, J. & Jacobus, D.P.(2001). 'Phenoxypropoxy biguanides, prodrugs of DHFR-inhibiting diamino triazine antimalarials'. *J.Med.Chem.***44**,3925-3931.

18. Lebreton, S.; Newcombe, N. & Bradle, M.(2003). 'Antibacterial single-bead screening'. *Tetrahedron*.**59**, 10213–10222 (2003).

19. A. Ghaib, S. Menager, P. Verite, O. Lafont; 'Synthesis of variously 9,9-dialkylated octahydropyrimido [3,4-a]-s-triazines with potential antifungal activity': *IL Farmaco***57**, 109–116 (2002).

20. Kuo, G-H; DeAngelis, A; Emanuel, S; Wang, A; Zhang, Y; Connolly, P J; Chen, X; Gruninger, R H ; Rugg, C; Pesquera, A F ; Middleton, S A; Jolliffe, L & Murray, W V (2005). 'Synthesis and Identification of [1,3,5]Triazine-pyridine Biheteroaryl as a Novel Series of Potent Cyclin-Dependent Kinase Inhibitors'. *J. Med. Chem.***48**, 4535–4546.

21. McKay, G A; Reddy, R; Arhin, F; Belley, A; Lehoux, D; Moeck, G; Sarmient I O; Parr T R; Gros, P; Pelletier, J & Far, A R(2005). 'Triaminotriazine DNA helicase inhibitors with antibacterial activity'.*Bioorg. Med. Chem. Lett.***16**, 891–896.

22. Agarwal, A.; Srivastava, K; Puri, S K; & Chauhan, P M S(2005). 'Syntheses of. 2,4,6-trisubstituted triazines as antimalarial agents'.*Bioorg. Med. Chem. Lett.***15**, 531–533.

23. A. Heba; Hady, El & Sahar S. El Sakka(2014). 'Syntheses and antitumor activity of some 1,2,4 – triazine derivatives'*IJIRSET*,**3**, 10854-10860.

24. Krautha, F. ; Dahse, H.M.; Rüttinger, H.H & Frohberga, p.(2010). 'Synthesis and characterization of novel 1,2,4-triazine derivatives with antiproliferative activity'. *Bioorganic& Medicinal Chemistry***18,** 1816–1821.

25. Sharma, A. ; Ghabbour, H. ; Khan, S.T. ; de la Torre, B.G. ; Albericio, F. & El-Faham, A. (2017). 'Novel pyrazolyl-s-triazine derivatives, molecular structure and antimicrobial

activity'.*J. Mol. Struct.***1145,** 244-253.

26. Bauer, A.W.; Kirby, W.M.; Sherris, J.C. & Turck, M.(1966). 'Antibiotic Susceptibility Testing by a Standardized Single Disk Method'. *Am. J.Clin.Pathol.***45,** 493-496.
27. Gavade, S.N. ; Markad, V.L. ; Kodam, K.M. ; Shingare, M.S.& Mane, D.V.(2012).'Synthesis and biological evaluation of novel 2,4,6-triazine derivatives as antimicrobial agents'. *Bioorg. Med. Chem. Lett.***22,** 5075-5077.
28. Cirrincione, G.; Almerico, A.M.; Barraja, P.; Diana, P.; Lauria, A.; Passannanti, A.; Musiu, C.; Pani, A. et al.(1999). *J. Med. Chem.,***42**(14), 2561-2568.
29. Bondock, S.; Rabie, R.; Etman, H.A.; Fadda, A.A.(2008). *Eur. J. Med. Chem.*, **43**(10), 2122-2129.
30. Schmitz, W. D. ; Brenner, A. B. ; Bronson, J. J. ; Ditta, J. L. ; Griffin, C. R. *et al*.(2010). *Bioorg. Med. Chem. Lett.***20**, 3579–3583 (2010).
31. Carling, R. W. ; Russell, M. G. N; Moore, K. W. ; Mitchinson, A. ; Guiblin, A. ; Smith, A.; Wafford, K. A. ; Marshall, G. ; Atack, J. R. & Street, L. J. (2006). *Bioorg. Med. Chem. Lett.***16**, 3550–3554.
32. Noronha,G.; Barrett, K.; Boccia, A.; Brodhag, T.; Cao, J.; Chow, C. P.; Dneprovskaia, E.; Doukas, J.; Fine, R.; Gong, X.; Gritzen, C. *et al*.(2007). *Bioorganic Med. Chem. Lett.***17**, 602.
33. Stella, C.; Barbara, P.; Virginia, S.; Anna, C. ; Alessandra, M ; Paola B.; Patrizia, D.; Girolamo, C.(2017).'1,3,5-Triazines: A promising scaffold for anticancer drugs development'. *Eur J Med Chem.***142**,523-549.
34. (a) Kono S., Zoga S. and Komaki T.; *Japanese Patent*, 6720, 313(1968).
    (b) Kono S., Zoga S. and Komaki T.;*Chem. Abstr.,* 69, 36183a (1968).
35. El-Brollosy, Nasser R.(2000).'Synthesis and reactions of some new 1,2,4-triazine derivatives of biological interest'. *Phmphorus. Sulfur und Silicon.***163**,77-89.
36. Reda M., Abdel-Rahman & Bawazir ,Wafa A.(2018).Various Routes to Synthesise 3-Thioxo-1,2,4-Triazine-5-One Derivatives as Antimicrobial Agents'. *International Journal of Organic Chemistry*,**8**: 191-200.
37. Solankee, A. & Tailor, R. (2015).'Synthesis, characterisation and biological screening of s - triazine based chalcones and its derivatization into phenyl pyrazolines, isoxazoles'. *International Letter of Chemistry,Physics and Astronomy*,**47**:109-119.
38. Dornow, A., Menzel, H., & Marx, P.(1964). "Synthesis of nitrogen containing heterocycles, XXVII. About 1.2.4-triazines, I presentation of some news-triazolo [3.2-c]-as-triazines'. *Chemical Reporters*, **97** (8): 2173-2178.