Chemistry Research Journal, 2023, 8(3):85-99
Available online www.chemrj.org

Review Article

ISSN: 2455-8990
CODEN(USA): CRJHA5

Triazine Analogues: A Comprehensive Study on Synthesis and Biological Properties

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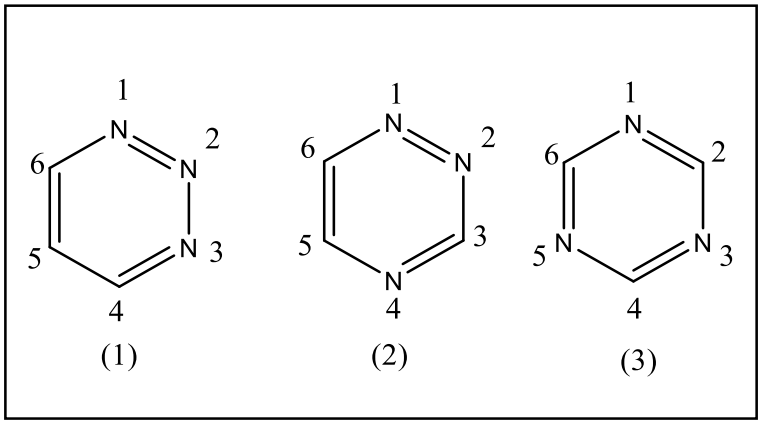
Abstract This paper is a review of literature concerning with the synthesis and biological importance of Triazines. Triazines are heterocyclic compounds with a variety of biological activities that have been increasingly studied in recent years due to their versatile structure (three isoforms) and the different derivatives that can be synthesized from them to ensure functional motifs. Triazines have a high significance in the field of pharmaceutical chemistry with wide-spectrum of pharmacological activities so useful for design and formation of novel drugs. Some triazine analogues are recently screened in clinical trials which may lead to potent type drugs with no side effects as presently available pharmacological agents.

Keywords Triazines, antidepressant, anticancer, anticonvulsant

Introduction

1,3,5-Triazine, also referred as s-triazine (symmetric triazine), is one of the three possible isomers of a six membered ring containing three nitrogen atoms in an alternate sequence with carbon atoms [1]. There are three isomeric forms depending on the positions of the nitrogen atoms, namely, 1,2,3-triazine (1), 1,2,4-triazine (2), and 1,3,5-triazine (3) (Fig. 1) [2].

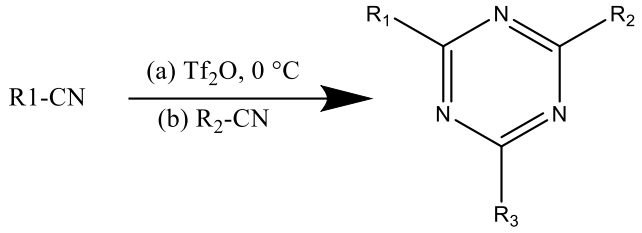


Among them, 1,2,3-triazine is the least explored so far [3], but clinically, its derivatives are the most acceptable due to their potent efficacy and minimal side effects [4], 1,2,3-triazine derivatives like tubercidin, toyocamycin, sangivamycin, 2-azaadenosine and 2-aza-2-desamino-5,8-dideazafolic acid are the important active moieties in pharmaceutical field. Compounds with a 1,2,4-triazine nucleus have been the most widely evaluated for their

therapeutic potential and pharmacological activity [5], 6-azacytosine, 6-azauracil, azaribine, tirapazamine, dihydromethyl furalazine, vardenafil, apazone, lamotrigine, ceftriaxone, pymetrozine, fervenulin (planomycin), reumycin and toxoflavin (panthothricin) are 1,2,4-triazine moieties used in clinical practices. Meanwhile, the 1,3,5-triazine moiety offers access to a multitude of useful molecules due to its specific structure and electronic properties that allow the sequential introduction of various substituents in the preparation process of mono-, di- and tri-substituted 1,3,5-triazines [6]. S-triazine is an oldest known organic compound, broadly used as a lead structure in ammeline, aceto-guanide, acetoguanamine, cyanuric acid and melamine. Some s-triazine containing drugs are hexamethylmelamine (altretamine), 2-amino-4-morpholino-s-triazine, hydroxymethyl-pentamethyl melamine, triethylenemelamine (tretamine), dioxadet, irsogladine, cycloguanil, almitrine, S9788 and DW1865 [7].

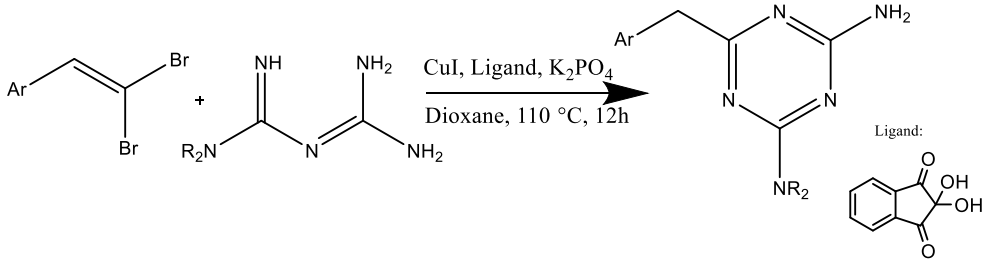
1. General methods for synthesis of Triazines.

Scheme 1- A solution of 2.82 g (10 mmol) of triflic anhydride in 15 ml of toluene was added dropwise to a solution containing 10 mmol of nitrile 1 in 15 ml of toluene at 0ºC. The resulting solution was stirred 3h at 0ºC and then a solution of 20 mmol of nitrile in 15 ml toluene was added and the reaction mixture heated at reflux for 24 h[8].



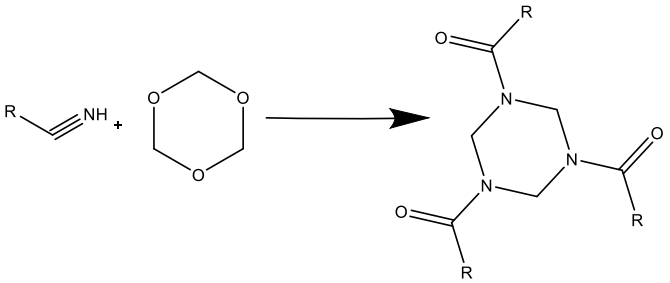
Scheme 1: One-Pot Synthesis of 1,3,5-Triazine Derivatives.

Scheme 2- The reaction was performed with 1 mmol of 1,1-dihaloalkenes and 0.5 mmol of dimethylbiguanide hydrochloride using Cu^{1+} catalyst (10 mol %), ligand 2.2′-bipyridine/ Iinhydin/ Glycine (20 mol %), K_3PO_4 (20 mol %), and dioxane (5 ml) at 110°C for 12h in a sealed reaction tube, to obtain the resultant triazine[9].



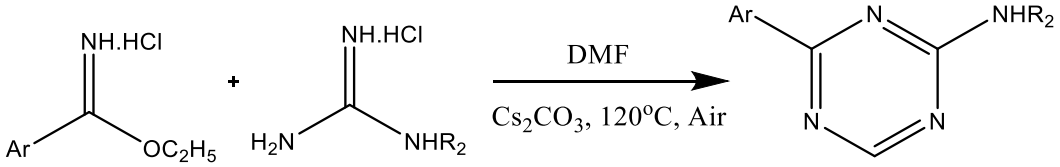
Scheme 2: Copper-catalyzed synthesis of substituted triazines

Scheme 3- To a solution of 11.0g (0.16 mol) of freshly distilled butyronitrile in 70ml of dry 1,2-dichloroethane, 2g of phenylsulfonic acid functionalized mesoporous silica was added. Another solution of 11.0g (0.16 mol) of butyronitrile and 7.2g (0.08mol) of trioxane in 50ml of 1,2-dichloroethane was added dropwise to the solution with stirring under reflux[10].



Scheme 3: Environmentally benign synthesis of 1,3,5-triacylperhydro-1,3,5-triazines.

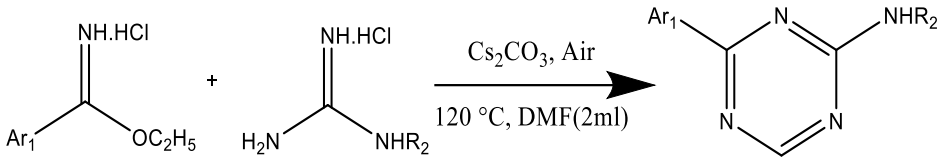
Scheme 4- In a glass vile aryl aldehyde was taken in THF solvent and I_2 gas was passed through the solution and then liquid ammonia was added to the mixture. To this mixture 1-ethynylguanidine was added and a little water was also added and the reaction mixture was heated at 80ºC for 15-20 mins in microwave[11].



Scheme 4: Microwave-Assisted synthesis of Triazines.

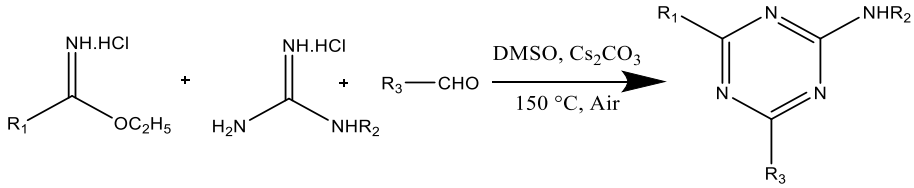
Scheme 4- Base-Mediated Synthesis

Substituted benzimidate hydrochloride (0.3 mmol), guanidine hydrochloride (0.33 mmol), Cs_2CO_3 (1.5 mmol, 489 mg), and DMF (2ml) were added to a 25ml Schlenk tube charged with a magnetic stirrer. The reaction mixture was stirred at 120°C for 24h without exclusion of air. Resulting, in the formation of 4-Aryl-1,3,5-triazin-2- amines[12].



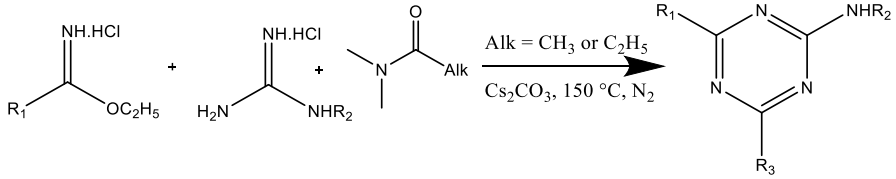
Scheme 5a: Synthesis of 4-Aryl-1,3,5-triazin-2- amines

Substituted benzimidate hydrochloride 1 (0.3 mmol), guanidine hydrochloride 2 (0.9 mmol), aldehyde 5 (0.6 mmol), Cs_2CO_3 (2.1 mmol, 684 mg), and anhydrous DMSO (3ml) were added to a 25ml Schlenk tube charged with a magnetic stirrer. The reaction mixture was stirred at 150°C for 24h without exclusion of air[12].



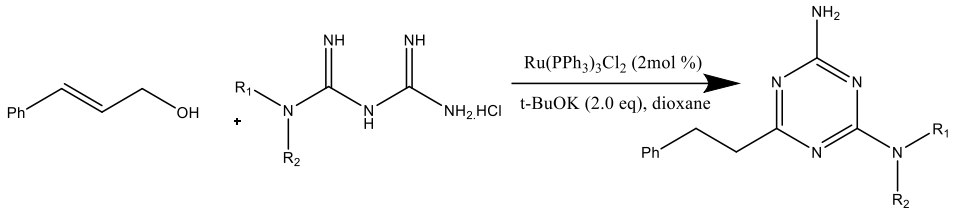
Scheme 5b: Synthesis of Disubstituted 1,3,5-Triazin-2-amines

Substituted benzimidate hydrochloride (0.3 mmol), guanidine hydrochloride (0.33 mmol), Cs_2CO_3 (1.5 mmol), and anhydrous DMA/DMP (2ml), were added to a 25ml Schlenk tube charged with a magnetic stirrer. The reaction mixture was stirred at 150 °C for 24h under nitrogen atmosphere (1 atm)[12].



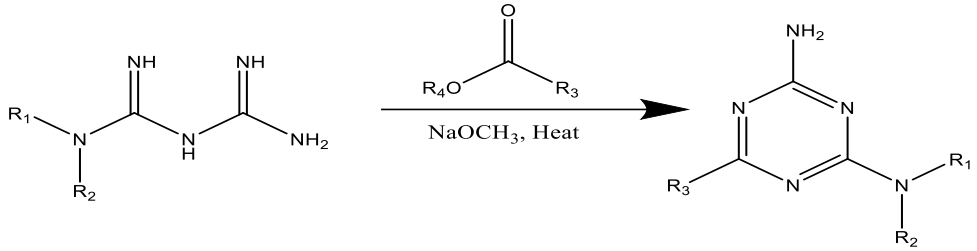
Scheme 5c: Synthesis of 4-Alkyl-6-aryl-1,3,5- triazin-2-amines

Scheme 6- An efficient ruthenium-catalyzed synthesis of alkyl-1,3,5- triazies from arylallyl alcohols and biguanides has been developed. To a mixture of biguanidehydrochloride(0.5mmol), allyl alcohol(0.5mmol) and t-BuOK(1.0mmol) in dry dioxane(5ml) was added $Ru(PPh_3)_3Cl_2$ (2mol%). The reaction mixture was stirred at 120ºC under N_2 atmosphere[13].



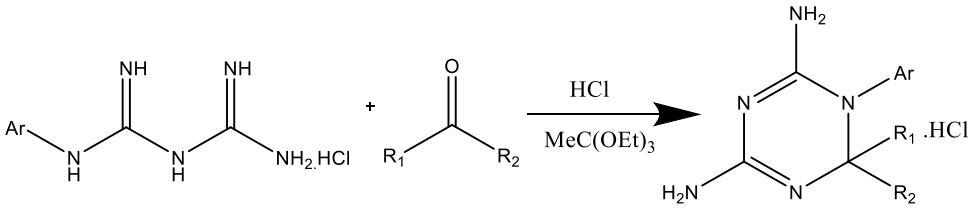
Scheme 6: Ruthenium-catalyzed synthesis of triazines.

Scheme 7- In a round bottom flask Biguanidehydrochloride (3mmol), NaOMe (1mmol) and an ester(1mmol) [like, isopropyl palmitate, methyl benzoate, methyl salicylate, methyl cinnamate and diethyl oxalate] were mixed in anhydrous methanol (4ml) and were heated under reflux for 2h, to obtain the resultant 1,3,5-triazine derivatives[14].



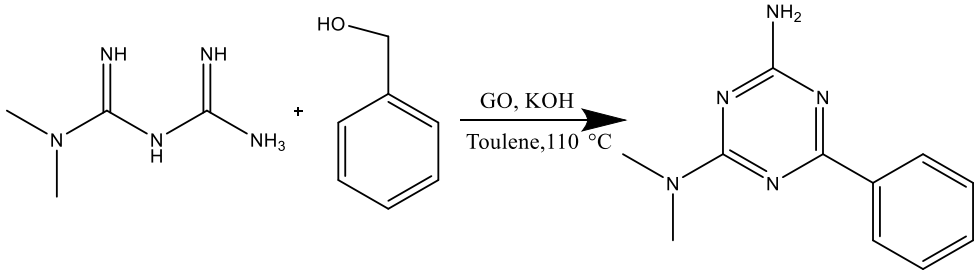
Scheme 7: Synthesis of biguanide-derived 1,3,5-triazine derivatives

Scheme 8- To a suspension of the arylbiguanide.HCl (1mmol) in absolute methanol (5ml) containing the ketone (5 eq) and triethyl orthoacetate (0.75ml) was added conc. HCl (0.025ml). The reaction mixture was stirred at room temperature until a negative biguanide test was obtained (24–120 h). After evaporation of the solvent, the residue was triturated with acetone–ether [15].



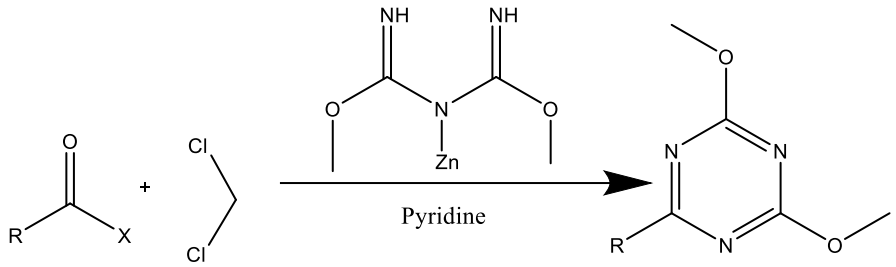
Scheme 8: Synthesis of 1-aryl-4,6-diamino-1,2-dihydro-1,3,5-triazines.

Scheme 9 - The reaction conditions were benzyl alcohol (1.0 mmol) and N,N-dimethylbiguanide (1.0 mmol) were added to a vile containing base [KOH] (1.5 mmol) with graphene oxide (30 mg) in toluene (2 ml) under O_2 atmosphere. The above reaction mixture was heated at 110ºC for 24 h to get the derired product[16].



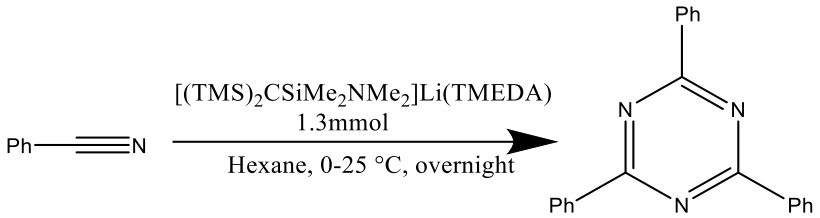
Scheme 9: Graphene oxide catalysed synthesis of triazine

Scheme 10- Under N_2, a solution of acid chloride or anhydride (4.0 mmol) in anhydrous CH_2Cl_2 (10ml) was added dropwise (30 min) to a stirred mixture of zinc dimethyl imidodicarbonimidate (651 mg, 2.0 mmol) and powdered 4 Å molecular sieves (4 g) in distilled pyridine (15ml). After the addition was complete, the mixture was stirred at rt for the period of 1h[17].



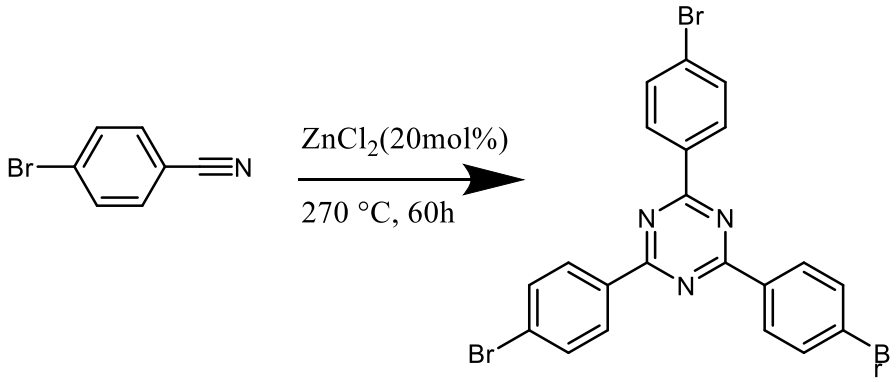
Scheme 10: Condensation of Acid Chlorides with Zinc Salt.

Scheme 11- The reaction of bis(silyl-substituted) methyllithium and a hydrogen-free nitrile is shown in reaction. The reaction of benzonitrile (10 mmol) in the presence bis(silyl-substituted) methyllithium (1.3 mmol) in hexane for overnight results in formation of the desired triazine in 91% yield[18].



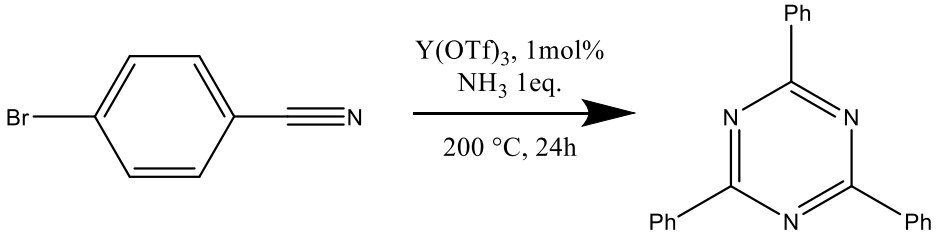
Scheme 11: Bis(silyl-substituted)-methyllithium-mediated triazine synthesis.

Scheme 12- Bromobenzonitrile and ZnCl2 in a molar ratio 5:1 were heated at 270 °C for 60h to give the corresponding 2,4,6-tris(4-bromophenyl)-1,3,5- triazine and the yield of the desired product was 69%[19].



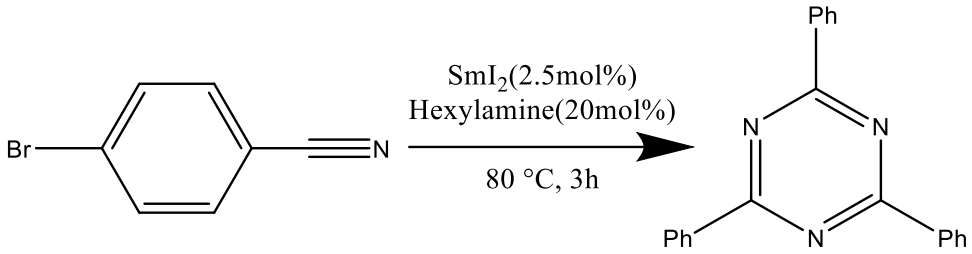
Scheme 12: $ZnCl_2$-catalyzed triazine synthesis.

Scheme 13- Yttrium(III) triflate or lanthanum triflate catalyzed ammonia-assisted nitrile trimerization. In the presence of 1 mol% $Y(OTf)_3$, the reaction of a 1:1 molar mixture of benzonitrile and ammonia at 200°C for 24h gave the corresponding triazine[20].



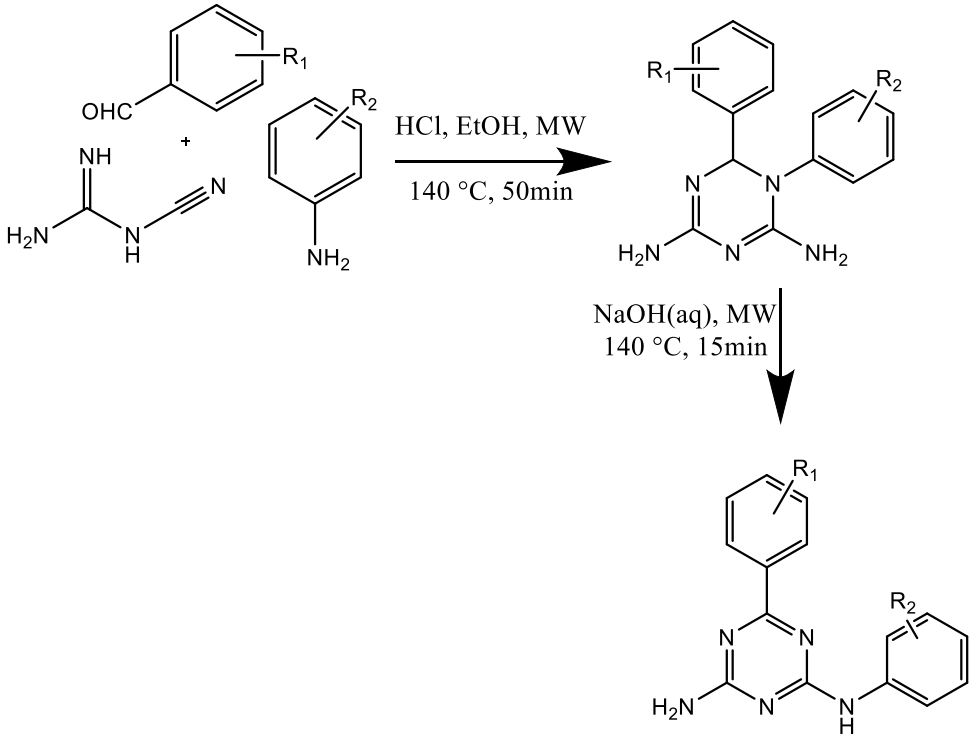
Scheme 13: Yttrium (III) trifluoromethanesulfonate-catalyzed triazine synthesis.

Scheme 14- SmI_2-catalyzed nitrile cyclotrimerization in the presence of amine co-catalysts. In a typical procedure, a mixture of SmI_2 (2.5 mol%), hexylamine (20 mol%), and benzonitrile was stirred at 80°C for 3h. The desired triazine 178 was obtained in 96% yield. Various arylnitriles react to give the corresponding s-triazines[21].



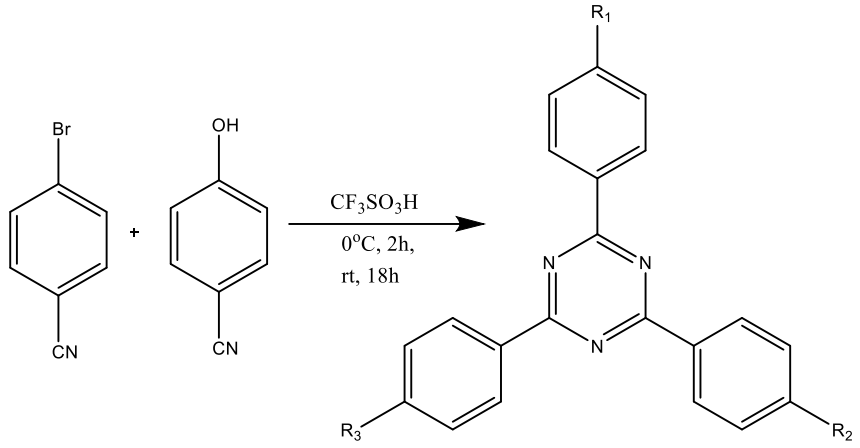
Scheme 14: Synthesis of triazines.

Scheme 15- To a solution of cano-guanidine (0.21 g, 2.5 mmol), a substituted benzaldehyde (2.5 mmol), and an aniline (2.5 mol) in EtOH (2ml) in a 10 ml seamless pressure vial, conc. HCI (0.21ml, 2.5 mmol) was added. The reaction mixture was heated at 140°C for 50 min by irradiation in the microwave reactor operating at maximal microwave power up to 150 W. Then, an aq. solution of NaOH (5N, 1ml) was added to the reaction mixture and heating was continued for another 15 min at 140 °C. After cooling, the precipitated product was filtered, washed with water and recrystallized from suitable solvents[22].



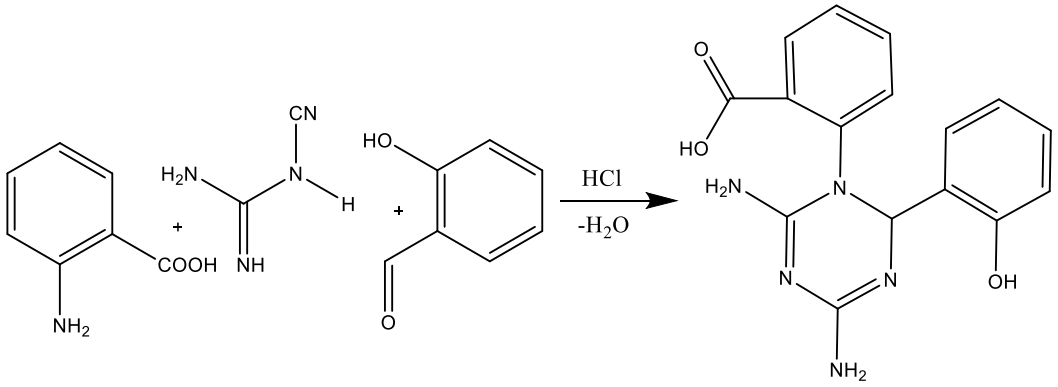
Scheme 15: Synthesis of Triazines.

Scheme 16- To ice-cooled (0ºC) trifluoromethanesulfonic acid (0.300 ml, 0.510 g, 3.30 mmol), an anhydrous $CHCl_3$ solution (20 ml) containing 4-bromobenzonitrile (0.100 g, 0.55 mmol) and 4-hydroxybenzonitrile (0.164 g, 1.37 mmol) was added dropwise over 30 minutes. After additional stirring (18h) at room temperature, water (50 ml) was added and the resulting precipitate was filtrated off [23].



Scheme 16: Synthesis of triazines.

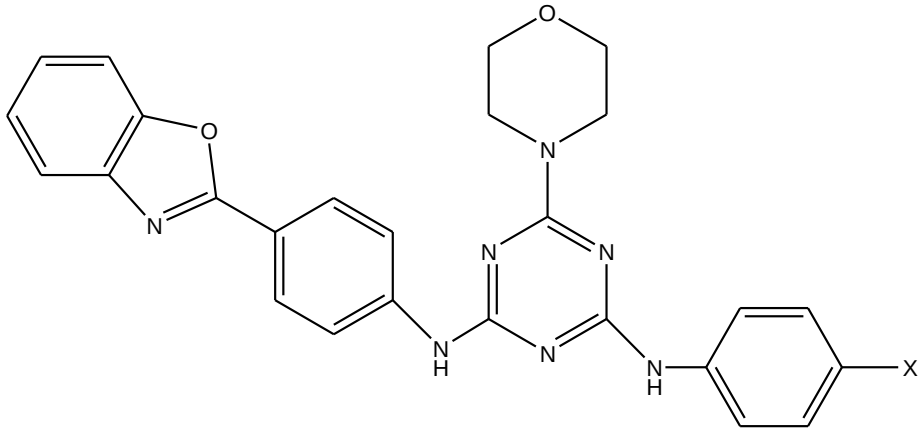
Scheme 17 - o-Amino benzoic acid / p- Amino benzoic acid (0.01M) was dissolved in 20ml of 1:1 HCl. To this equimolar concentration (0.01M) of dicyanodiamide and salicylaldehyde were added. The contents were subjected to microwave irradiation in Pyrex beaker at an interval of (30 seconds) at 300W for about 3 minutes [24].



Scheme 17: Synthesis of triazine using HCl

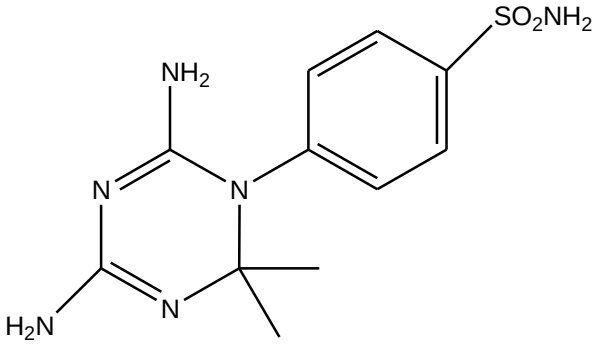
2. Biological activity of Triazines.

Anticancer activity: s-triazine derivatives were evaluated for their in vitro inhibitory activity against the growth of PA-1 (Ovarian cancer), A549 (Lung cancer), MCF-7 (Breast cancer), and HT-29 (Colon cancer). Tri-substituted s-triazine derivatives (13e–g) with morpholino group on s-triazine scaffold exhibited potent anticancer activities compared to di-substituted s-triazine derivatives [25].

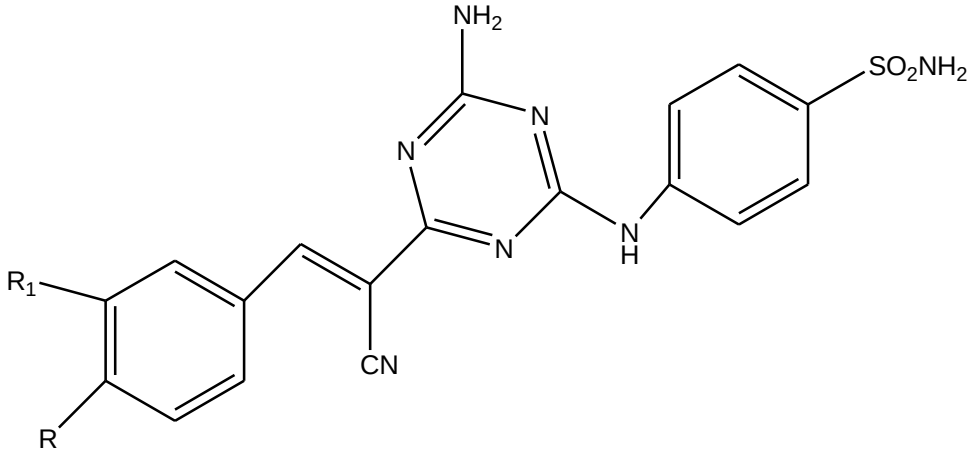


Compound	X (F Group)
13e	**H**
13f	**OCH_3**
13g	**F**

Human CA IX efficiently inhibited in series (A) by compound **5a** (KI = 134.8 nM). Meanwhile, in series (B) the most active inhibitor was **12i** (KI = 38.8 nM). US-NCI protocol was followed to evaluate the anticancer activity of target compounds against panel of sixty cancer cell lines. Compound 12d, exposed the best activity towards breast cancer (MDA-MB-468) with GI% = 62% [26].

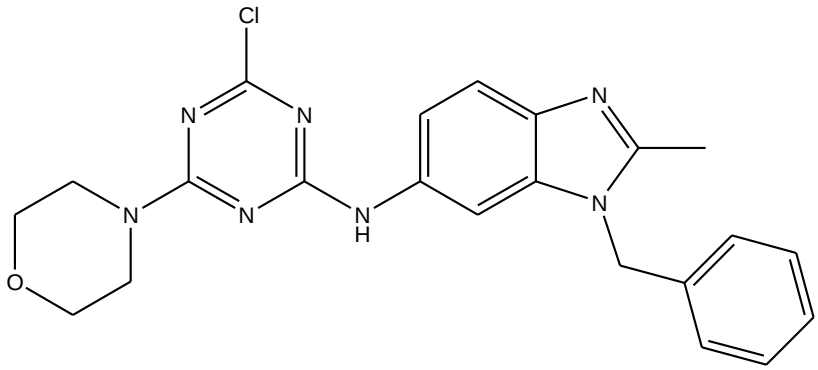


5a

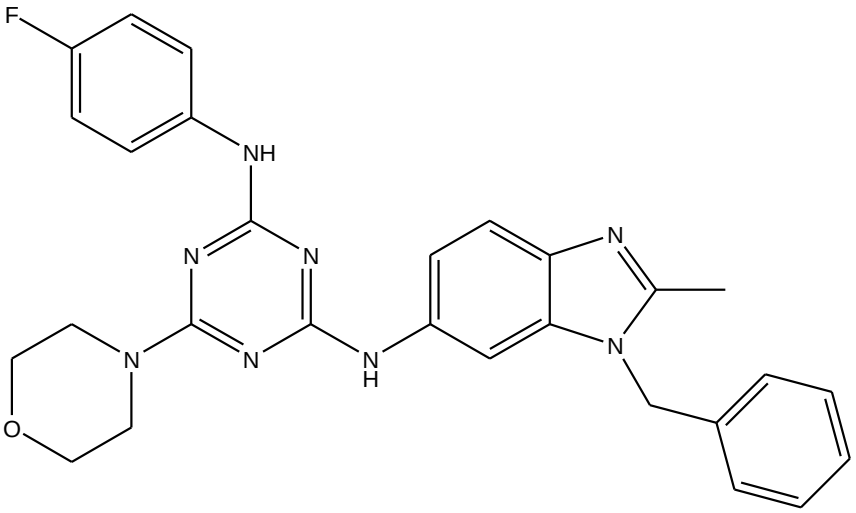


Compound	R	R_1
12d	$N(CH_3)_2$	H
12i	H	F

A new series of triazine–benzimidazole hybrids were evaluated for their inhibitory activities over 60 human tumor cell lines at one dose and five dose concentrations. **Compounds 6b, 8 and 9** showed broad spectrum of antitumor activities with GI50 values of 9.79, 2.58 and 3.81 μM, respectively. DNA binding studies also indicated strong interaction properties of these compounds. These synthesized compounds also showed inhibition of mammalian dihydrofolate reductase (DHFR). **Compound 6b** was depicted as the most active member of DHFR inhibitor with IC_{50} value of 1.05 μM. Molecular modelling studies were used to identify the stabilized interactions of Compound 6b within the active site of enzyme for DHFR [27].



6b



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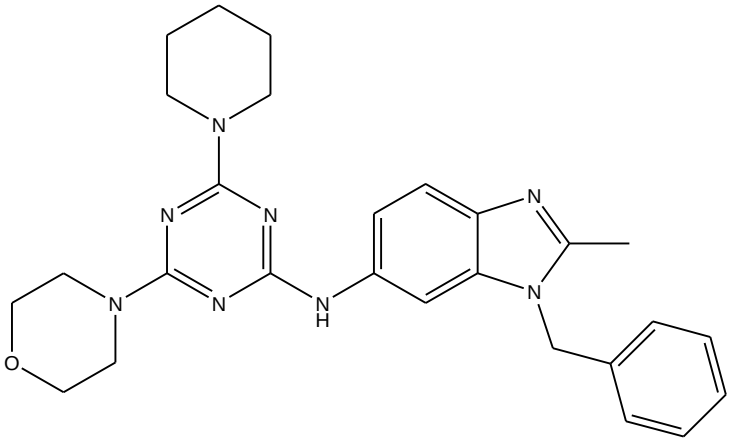
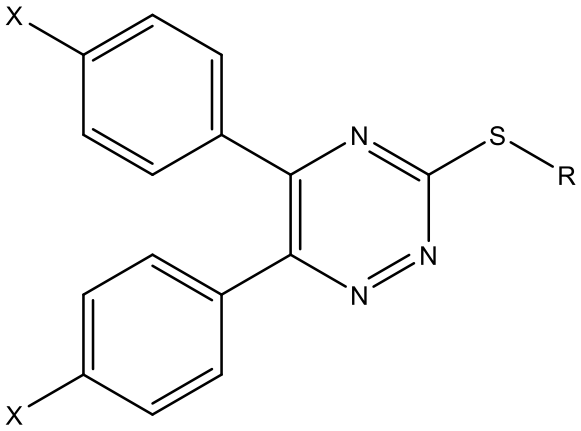
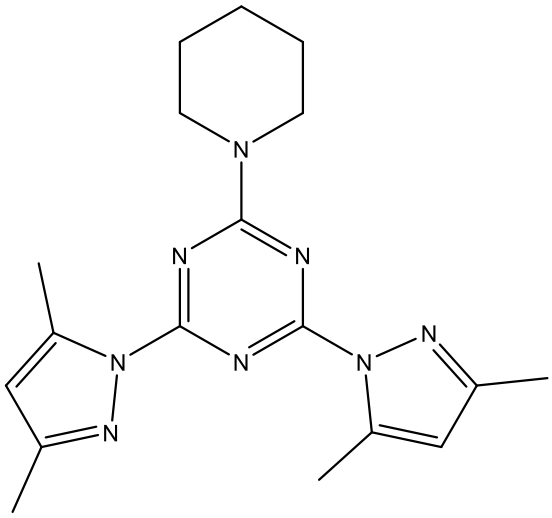


9

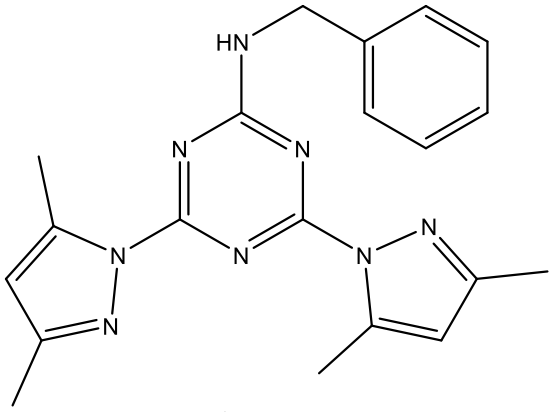
Anticonvulsant activity: 1,2,4-triazine derivatives were evaluated as dual anticonvulsive and 15-lipoxygenase inhibitors. Molecular docking study revealed their possible antiseizure mechanism of action through $GABA_A$ receptor [28].



Antimicrobial activity: Triazine compounds were evaluated for their in vitro antibacterial and antifungal activities against microbial strains such as Gramnegative bacteria (E. coli ATCC 25922, P. aeruginosa ATCC 75853), Gram-positive bacteria (M. luteus ATCC 10240, Methicillin-resistant Staphylococcus aureus (MRSA) ATCC 43300), and fungi (C. albicans ATCC 10145) by the agar-well diffusion method. The results of antimicrobial testing against strains were obtained as zone of inhibition (mm) [29].

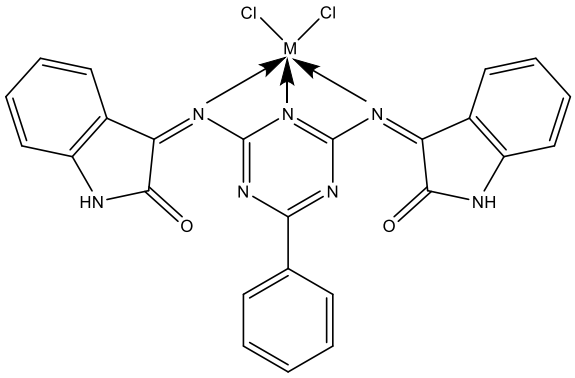


4b

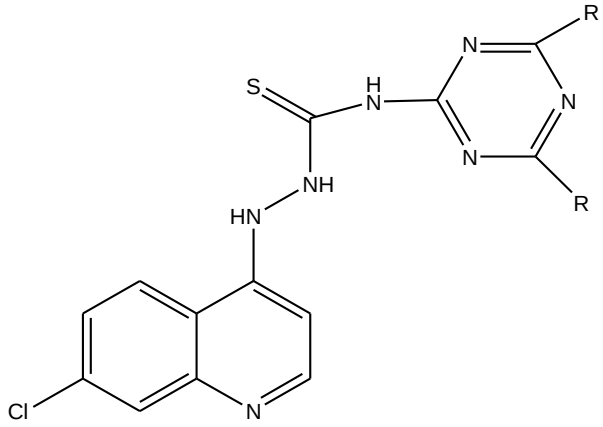


4c

Anti-inflammatory activity: Anti-inflammatory activity data of the Schiff base and its metal complexes were evaluated by carrageenan-induced rat paw edema method. it is found that the Schiff base and metal(II) complexes possess higher anti-inflammatory activity compared to the standard [30].

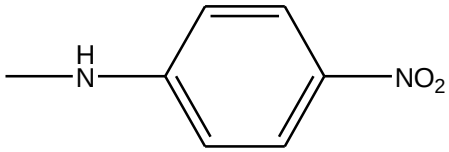


Antibacterial activity: The newly synthesized triazine derivatives were screened for their in vitro antibacterial and antifungal activity against Bacillus subtilis, Bacillus cereus, Staphylococcus aureus, Proteus vulgaris, Escherichia coli, Pseudomonas aeruginosa and Candida albicans, Aspergillus niger, Aspergillus fumigatus using cefixime and fluconazole as standard. Antibacterial screening results suggest that compound **7c** showed potent activity against S. aureus, P. aeruginosa, and P. vulgaris. In antifungal screening, compound **7b** showed significant activity against A. niger, A. fumigatus and moderate activity against C. albicans [31].

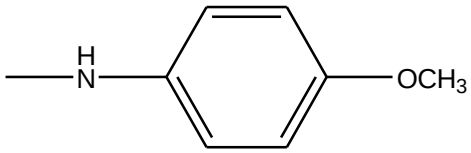


Compound **R (F Group)**

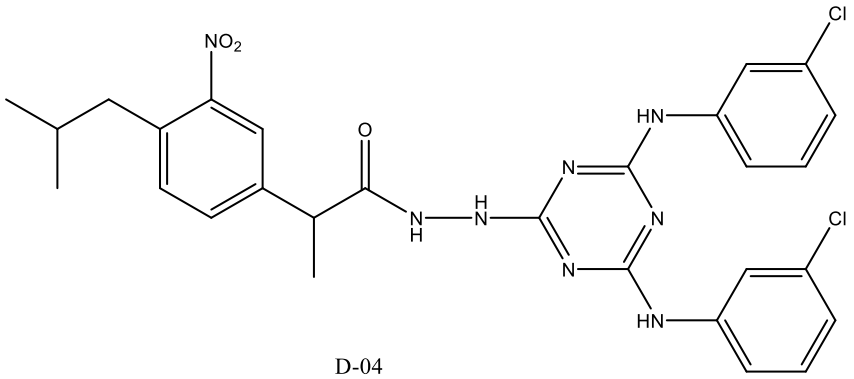
7c



7d

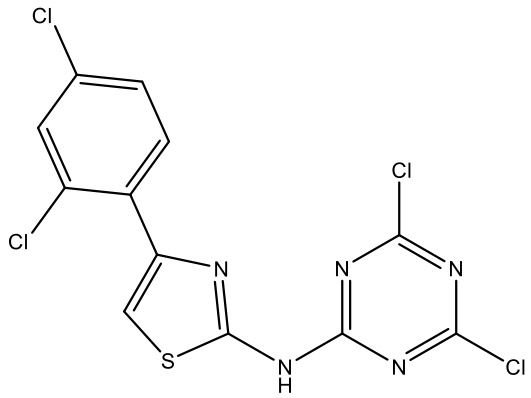


Analgesic activity: The synthesized nitrated Ibuprofen derivatives possesses either moderate analgesic activity or little but higher analgesic activity. **D-04** the activity increases to 15% compare to Ibuprofen. On consideration of structure-activity it has been observed that the introduction of nitro group in benzene ring enhance the analgesic activity and without introduction of nitro group show less analgesic activity [32].



D-04

Antidepressant activity: mono-, di-, or tri-substituted phenylthiazolyl-1,3,5-triazine derivatives identified by antidepressant-like activity in mice using tail suspension assay. These insights illustrate effectiveness of hybrid analogue **10** as a novel antidepressant agent and provide a molecular level insight that these identified entities may be a CRF1 antagonist. Fortunately, the present work offers a guidance of future antidepressant lead building and prospective screens [33].



10

Conclusion

Triazines are well known heterocyclic in terms of their biological applications. These scaffold have different therapeutic implementations like anticonvulsant, antibacterial, antimicrobial etc. These biological efficient and potent molecules have vast applications in many fields including medicine and agrochemicals. Off course these are the molecules which are facilitating human life in many ways and in the same way they have many paths of synthesis also. This review is an attempt to explore and compile the various reported synthetic pathways for Triazines. This exploration and compilation of different synthetic pathways of Triazines will efficiently assist researchers to fetch out details of different methods for synthesis of Triazines and also will aid for the establishment of new protocol which can be applied to bulk scale production of Triazines scaffold in commercial and environmental friendly way.

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