Review Article

Triazine Derivatives and its Pharmacological Potential - A Review

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ABSTRACT

Triazine are the important scaffold in the drug discovery process. Various synthetic derivatives of triazines are prepared and evaluated for its various biological activities in the different model. Some analogs of the triazine derivatives are more potent than the corresponding standard drugs. Hence the triazines ae considered to be the lead molecule for the future drugs. The present review article discusses about the pharmacological activities of triazines such as anti-microbial, anti-cancer, anti-inflammatory etc.

Keywords: Triazines, drug discovery, lead molecule, anti-cancer, anti-microbial.

INTRODUCTION

Triazines are six membered ring compounds containing three nitrogen atoms. Depending on the position of the nitrogen atoms, three different triazine systems namely 1,3,5 triazine(s-Triazine), 1,2,4 triazine and 1,2,3 triazines are possible.[1] Symmetrical and asymmetrical isomers of triazines are generally distinguished by the different arrangement of three nitrogen atoms in the benzene ring.[2]

1,2,3 Triazine

1,2,4 Triazine

1,3,5 Triazine

Triazines are prepared from 2-azidocyclopropene through thermal rearrangement (1,2,3-triazine), from 1,2-dicarbonyl compound with amidrazone by condensation reaction (1,2,4-triazine) and from cyanuric acid amide by trimerization (1,3,5-triazine). Among them 1,3,5-triazines represent a widely used lead structure with multitude of interesting applications in numerous fields. This simple molecule is well-known in organic chemistry and has been used in a variety of applications as its 2,4,6-mono-, di- or trisubstituted derivatives bearing different substituents.[3]

Table 1: Physical and Chemical Properties of Triazine

Molecular formula	$C_3H_3N_3$
Molecular weight	81.08
Melting point	85-86°C
Boiling point	144°C
Description	White crystalline solid,volatile and hygroscopic
Solubility	Easily soluble in most organic solvents[5]

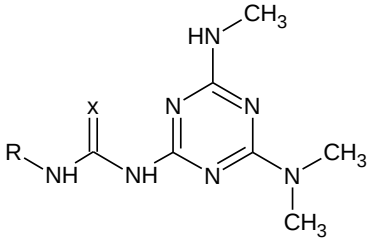
1,3,5 triazines were found to be a potential core to develop less toxic bioactive compounds.[4] The present review aimed to discuss about various pharmaceutical potentials of the nucleus. It has interesting pharmacological properties, including anti-cancer, herbicidal, insecticidal, anti-HIV, anti- malarial, Anti -bacterial, Anti -mycobacterial and anti-microbial activities etc.

PHARMACOLOGICAL ACTIVITIES

Anti-microbial activity

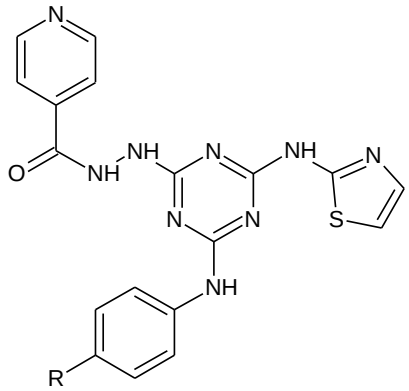
The researcher has reported that 1,3,5 -triazine core molecule exhibiting excellent antimicrobial activity including anti-bacterial and anti-fungal activity.

The triazines derivatives were synthesized starting from cyanuric chloride (2,4,6 trichloro 1,3,5 triazine) and different nucleophile. All the synthesized compounds were screened for their minimum inhibitory concentration against two gram -positive (*Staphylococus aureus* and *Bacillus subtilis*) and two gram negative (*E.coli* and *Pseudumonoas aeruginosa*) by broth dilution method. The results showed the synthesized compounds produced good deal of activity against gram positive bacteria, while they were moderately active against *E. coli* and much less active *against P. aeruginosa* of gram-negative bacterial strains.[6]



X=S,O

The 1,3,5 triazine based Thiazole derivatives were synthesized. All the newly synthesized compounds were evaluated against gram positive bacteria and gram-negative bacteria and fungi. Results revealed that majority of synthesized compounds showed varying degrees of inhibition against the species. The obtained anti-microbial activity of tested compounds could be correlated to structural variations and modifications of the respective compounds. The presence of nitro (NO2) group at position 2 and 4 in the structure produced highest inhibition at MIC 12.5&25 µg/mL .[7]

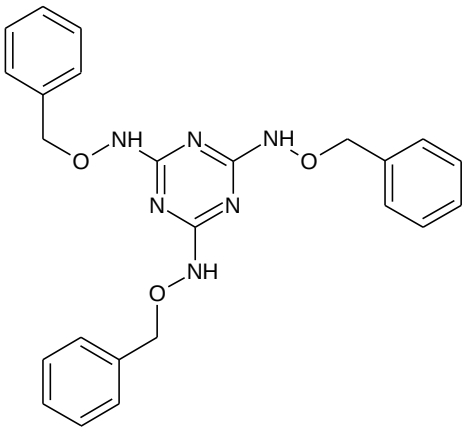


The Thiazole 1,3,5- triazine derivatives were synthesized and they were screened for Anti-fungal activity (i,e) minimum inhibitory concentration and minimum fungicidal concentration against *Candida albicans, C.glabrata, C.neoformans* & *Aspergillus niger* using broth dilution method. The results depicted that target compounds exhibit numerous degree of inhibition pattern on tested fungal strains. The compound with rigid di-phenyl fragment along with substituted phenyl thiazole fragment, exerts significant to potent activity against all strains.[8]

The series of novel 6-aryl-2,4 disubstituted schiffs base 1,3,5 triazine derivatives are synthesized and evaluated for invitro anti-bacterial activity against E.coli and staphylococcus aureus strain and invitro anti-fungal activity against candida albicans and Aspergillus niger strains by using serial dilution method. The results revealed that the compound with chlorine electron with drawing group produced good anti-bacterial and anti-fungal activity when compared to other compounds against the strains. The presence of electron withdrawing group is responsible for enhanced activity against the strains.[9]

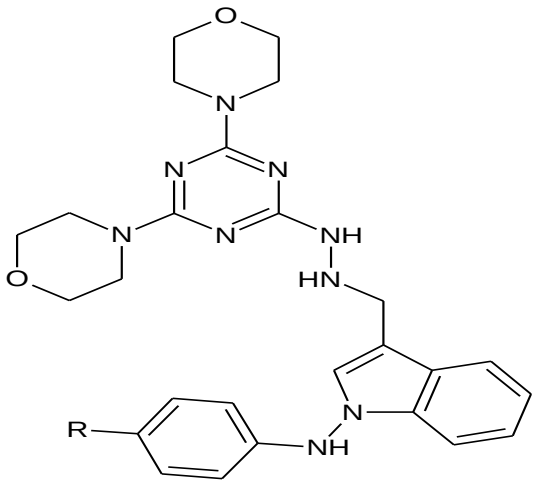
Anti- tubercular activity

The one pot synthesis of 2,4,6 tri substituted 1,3,5 triazine were carried out by the reactions of cyanuric chloride with aromatic /aliphatic amines ,amide and water under microwave using catalyst. The compound showed highest anti-tuberculotic activity (72% inhibition) against *Mycobactrium tuberculosis*.[10]



Anti – cancer activity

The 6-hydrazinyl -2,4 bismorpholino pyrimidine and 1,3,5 triazine derivatives were synthesized. These synthesized compounds were evaluated for their Anti-proliferative activity against H 460 (human lung cancer), HT-29 (human colon cancer) & MDA-MB-231(human breast cancer) cancer cell lines together by MTT assays. The 1,3,5 triazine derivatives were potent than the pyrimidine derivatives against H 460 cancer cell lines but less effective against other cell lines[11].



The tri arm shaped 1,3,5 triazine hydrazones were synthesized and evaluated for anti -cancer activity. The anti- proliferative activity of synthesized compounds were carried out against human liver carcinoma cell lines (Hep G2) and human cervix carcinoma cell lines (He La). The compounds which possess a nitro group showed 58.91 % inhibition against Hep G 2 cells whereas compounds with chloro substituents produces 28.36% inhibition against HeLa cells.[12]

The series of 21 compounds of 2-(4-cyano -3-trifluoro methylphenyl - amino)-4-(quinoline 4-yloxy)-6-(piperazinyl) or piperidinyl triazine were synthesized .The invitro anti- cancer activity was studied against human prostate cancer cell lines DU-145.Among them compound 33 was found to be active against with GI 50 of 14.1µg/ml concentration.[13]

Interestingly, the di and tri substituted s-triazines were synthesized which were assessed for anti -cancer evaluation against four cancer cell lines such as PA-1 (ovarian cancer), A549 (lung cancer), MCF-7 (breast cancer) and HT-29(colon cancer). The tri substituted s-triazines were more potent than the disubstituted compounds.[14]

The 2,4 diamino 1,3,5 triazine derivatives were synthesized and subjected to evaluate their invitro anti-tumour activity against a tumour cell lines. Among the synthesized compounds the one with 5- nitro thienyl moiety showed excellent activity (log GI50<-8.00 to -5.00) to all cell lines and found potent against some cell lines of leukemia, CNS cancer (SF -539) and breast cancer T-47D.[15]

The metformin (N,N Dimethyl biguanide) analogs and metformin salts that inhibit the proliferation and invasion of HS578T Triple negative breast cancer cells are compared with metformin alone. The designed metformin derivatives showed potent invitro and in vivo anti tumour effect .[16]

The microwave assisted one pot synthesis of trisubstituted 1,3,5 triazine derivatives. The phototoxicity of the titled compounds was investigated first on a cell line of human tumour HL-60 (human promyelotic leukemia). This given compound produced activity and substitution for a methyl group leads to inactive derivatives.[17]

Anti-inflammatory activity

The triaminotriazine aniline methoxyamide derivatives bearing 4-methyl -1,4-diazepan 1-yl substituents. The synthesized derivatives showed excellent in vitro and in vivo oral activity in animal model of acute and chronic inflammatory diseases with IC 50 of 44 and 85nM against p38α and TNFα respectively.[18]

The 2-alkyl/aryl -4,6 dimethoxy -s-triazine analogs were synthesized and anti-inflammatory activity was studied. The compounds bearing phenyl,(s)-2-Me) Bu and thiophene substituents were found to be active against rest of the compounds.[19]

Invitro anti-inflammatory evaluation of bis (dimethylamino)-s-triazinyl derivatives showed 16,46 and 100% Inhibition of inflammation at dose levels of 7.5, 30 and 75mg/kg respectively.[20]

Human adenosine receptor antagonist

The 1,2,4 triazolo(1,5)-1,3,5 triazine derivatives are synthesized and evaluated against human adenosine receptor. Among the fused triazine derivatives, the compound with long chain ether containing amine substituents exhibited potent antagonistic activity.[21]

Protein Kinase CK_2 Inhibitor

A Series of compounds with a variety of substitution on the C4 -Aromatic compounds were synthesized and the result showed all the compounds were potent inhibitors of human CK2 with K_i<1nM.[22]

Anti-amoebic activity

In vitro anti-amoebic potency of the tetrazole and triazine linked with sulphonamide groups were evaluated. Activity results concluded that the presence of s-triazine core rather than tetrazole increased anti amoebic activity of the compounds.[23]

PI3K inhibitor

The regioselective synthesis of 5- and 6-methoxybenzimidazole-1,3,5-triazine were done and Studies showed that 6-substituted benzimidazol-1,3,5-triazine derivatives were ten-times more potent as PI3K inhibitors than 5-substituted derivatives that diminished activity in all isomers.[24]

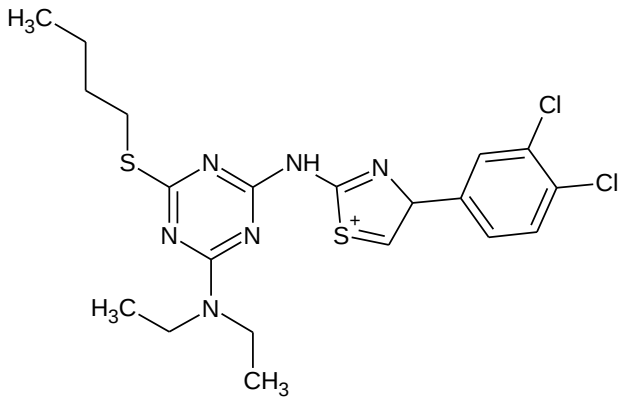
A panel of 4- and 6-substituted analogs were synthesized and evaluated. Out of all synthesized compounds, 4-methoxy6-amino substituent showed 1000-fold more activity (IC50 = 0.22 nM) than corresponding 4-methoxy-6-aza analogue (IC50 = 1290 nM) against p110a, p110b and p110d enzymes. [25]

Furthermore, 4-substituted solubilized derivatives of 2-(difluoromethyl)-1-[4,6-di(4morpholinyl)-1,3,5-triazin-2-yl]-1H-benzimidazole (ZSTK474) were synthesized. Amongst them, 4-aminoalkoxy substituted compound (43) was found to be a more potent PI3K inhibitor and also showed good aqueous solubility (25 mg/ml) for the hydrochloride salt.[26]

Anti-malarial activity

A library of 22 derivatives of 9-anilinoacridine triazine as hybrid antimalarial agents was synthesised. The in vitro activity was determined against chloroquine (CQ) sensitive 3D7 strain of Plasmodium falciparum and their cytotoxicity was determined on VERO cell line. In this evaluation (IC_{50} = 4.21 nM) and (IC50 = 4.27 nM) were two-times more potent with reference to chloroquine (IC50 = 8.15 nM).[27]

The hybrid phenyl thiazolyl -1,3,5 triazine were synthesized and evaluated for anti-malarial chemotherapy. The given compound showed excellent anti-malarial activity with % dead (ring and schizonots)=12.0 at 50µg/ml dose.[28]



Anti-methamphetamine Action

In vivo testing of 2-amino-4-(4-(hydroxy ethyl)-piperazin-1-yl)-6-tri-fluro-methyl S-triazine showed anti-methamphetamine activity in mice and rats by suppressing of unconditioned avoidance response, taming effect, decrease in exploratory behavior and cataleptogenic activity. It showed 0.6 – 0.7 times more activity than standard chlorpromazine drug .[29]

Alzeimer's disease treatment

The symmetrical triazine analogs were synthesized to inhibit the multiple pathologies human AchE, BuchF and amyloid -β- aggregation in the treatment of Alzheimer's disease. The height inhibition of ameloid β-fibils with 89.9% was shown by the synthesized compounds.[30 ,31]

Anti – angiogenic properties

The diaryl amino 1,3,5 triazine derivatives as FAK (Focal Adhesion Kinase) inhibitors were synthesized. The anti – angiogenic activity were done on HUVEC cells. The synthesized compounds revealed that mode of interaction with the FAK kinase domain is highly similar as compared with the complex of TAE -226.[32]

Anti – trypanosomal drugs

The triazine substituted polyamine were synthesis and it is evaluated for anti – trypanosomal activity against the protozoan parasite trypanosomal brucei strain. The result revealed that the tetra triazine substituted polyamine exhibits an excellent activity against T.brucei rhodesiense at IC_{50}=0.27um and T.brucei IC_{50} -0.10um.[33]

Anti – Viral Agents

The synthesis of benimidazolyl and triazolyl 1,3,5 – triazone derivatives were carried out and their invitro pharmacological profile showed that were active against HSV – 1 in VERO cells. The results displayed the best inhibition activity at 3.5ug/ml (SI =358) than aeyclovir.[34]

Treatment of Auto – Immune disease

The series of 2,4,6, trisubstituted S- triazine derivatives were synthesized and evaluated. The compounds showed excellent in vivo activity in a standard rodent model for auto – immune. The compounds also played a significant role in other rodent models .[35]

CRFI – receptor Antagonists

8 - substituted pyridyl pyrazolol [1,5-a] – 1,3,5 trizine derivatives were synthesized as corticotropin – releasing factor receptor – 1 antagonist (or) anxiolytic (or) Anti – depressant drugs. One of the compounds showed most potend CRF, antagonist with IC_{50}=6.1+/-0.6nm. It also showed anxiolytic efficacy in 'elevated plus maze' and 'defensive withdrawals' test in rats .[36]

CONCLUSION

This review article presented a various pharmacological properties of the tiazine derivatives. The tiazines derivatives showed anti-cancer activity against various cell lines. The various synthetic triazine derivatives are more potent against various bacterial, fungal and other mycobacterial stains. The review revealed that triazine are the important phamacophore in the drug discovery.

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