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Review On Synthesis And Biological Evaluation Of Novel Piperidine-Substituted Triazine Derivatives

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Abstract

We have gone through aliterature study and investigated that piperazine and triazine core compound incorporating in single molecular frame and it could be lead to the novel potent and biological importance drugs like anti-inflammatory, anti-tuberculosis etc. many compounds contains piperazine, triazine core. These cores have been accomplished inhibitory activity against inflammation. Earlier, natural products containing heterocyclic moiety have provided the most valuablesource of novel scaffolds to propose fresh therapeutic agents, and various naturally occurring phenolic compounds have been found as potent pharmacological agents. 1,3,5-triazine is reported as an central core in numerous biological target molecule.

Keywords: 1,3,5-triazine, piperzine, anti-inflammatory, antimicrobial activity, biological study.

Introduction

The bacterial infections are severe day by day because of growing infectious diseases and high peakof number multidrug-resistant microbial pathogens. There are lot of antibiotics and chemotherapeutics compounds are existing, the appearance of aged and novel antibiotic-resistant bacterial strains. In the previous decades leads to a substantial necessitate for innovative classes of anti-bacterial agents.[1] The anti-inflammatory drugs are therapeutically significant in rheumatic arthritis and in action of different inflammatory circumstances, except their therapeutic utility has been partial due to their frequently gastrointestinal side effects. Consequently, there is a critical requirement for novel targets that are necessary for the plan and growth of novel anti-inflammatory agents as an alternative.[2]the cytokines are intercellular messengers applicable for mass defense mechanisms in inflammatory, immune and hematogenic responses. While numerous of them are transient, produced by a variety of cells acting as

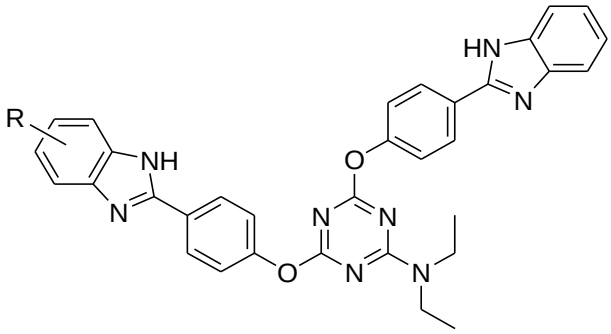
consistent response mediators. The Interference of this biological resistance mechanism and constant extreme cytokine production contributes to pathogenesis of inflammatory diseases. The tumor necrosis factor alpha (TNF- α) and interleukin-6 (IL-6) are the two essentialand multifunctional pro-inflammatory cytokines, isolated in the pathogenesis of inflammatory, cancer diseases, neurodegenerative, autoimmune and cardiovascular during a sequence of cytokine pathways.[3] The most important type pro-inflammatory cytokine TNF-α is a huge number of biological activities associated to pathology of autoimmune diseases such as rheumatoid arthritis (RA),[4] Crohn's disease,[5] systemic lupus erythematosus,[6] and multiple sclerosis,[7] septic shock,[8] and AIDS.[9] Alternatively, cytokine interleukin-6 (from the sequence of cytokine signaling path) give the beginning and expansion of the inflammatory development and is consider as an essential intermediary in a series of inflammatory diseases but has not received the preferred interest in drug discovery.[10] TNF- α and IL-6 are the most biological and pharmaceutically essential molecular focal point for the action of the above mentioned diseases. The existing biopharmaceuticals (TNF soluble receptor (Enbrel TM) and TNF antibody (Remicade TM) are luxurious, complicated to administer orally and have major side effects on lengthened medical use. Consequently, there is a critical therapeutic require to find out little molecule agents to deal with more production of TNF-α. The 1,3,5-triazine derivatives containing various amino groups on the position 2, 4 or 6, such as furazil, tretamine, and dioxadet, have shown as anticancer activity.[11] The 2,4-diamino-6-(2,5-dichlorophenyl)-1,3,5-triazine is an anti-gastric ulcer agent was shown to possess antiangiogenic properties in connection with an anticancer effect.[12] The various nitrogen containing heterocyclic classes (e.g., indoles, pyrimidines, pyridines, oxyindoles, pyrroles and pyrimidones, fused heterocycles) have been reported for their pro-inflammatory cytokine inhibitory activity.[13] While the natural medicinal significance of heterocyclic derivatives of aryl ureas have been reported in the literature i.e. *N*-2,4-pyrimidine-*N*,*N*-phenyl/alkyl ureas shows inhibitor of tumor necrosis factor alpha (TNF- α),[14] substituted urea derivatives SA13353 were presented as an effective inhibitor of TNF-α production.[15]

Various analogues like pyrido-quinazolone has many biological significance such as anticancer agents, antifungal and antibacterial. On the basis of recent literature and our logical research to improve the anti-inflammatory and antimicrobial activity of the compound based on triazine core and related scaffold are studied.

Literature Survaey.

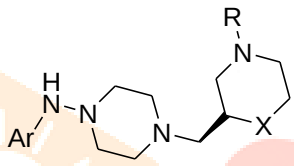
Padalkar*et al.*[16] has been reported the synthesis of novel benzimidazole, benzoxazole and benzothiazole derivatives and gone through for antimicrobial activity. The structure of 4,4-(6-(4-diethylaminophenyl)-1,3,5-triazine-2,4-diyl)bis(oxy)dibenzaldehyde (DIPOD) was recognized from *p*-hydroxybenzaldehyde and 4-(4,6-dichloro-1,3,5-triazin-2-yl)-*N*,*N*-diethylaniline. The reaction of DIPOD with o-phenylenediamine or o-amino phenol or o-amino thiophenol in ethanol furnishedbenzimidazole, benzoxazole and benzothiazole.Novel heterocyclic showed better wide-ranging antimicrobial activity

against bacterial strain (*E. coli*, *S. aureus*) and fungal strain (*C. albicans*, *A. niger*). The obtainedresult was compared with standard Streptomycin and Fluconazole drug.



1

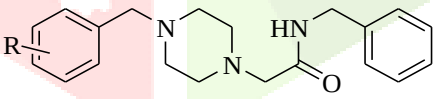
John G. Cumming & co-workers *et al.*[17] has reported the synthesis of new *N*-aryl piperazine-1-carboxamide series **2** of human CCR2 chemokine receptor antagonists.



2

Where,
X = -H, -Me, -Et, $-CH_2Ph$, $-CH_2C$-Pr, $-(CH_2)_3Ph$, etc

Hoh-Gyu Hahn *et al.*[18]reported the synthesis of unique 1,4-substituted piperazine derivatives **3, 4** and studied their antidepressant activity against DA, NE, and serotonin neurotransmitter inhibition was approved using the neurotransmitter transporter assay.



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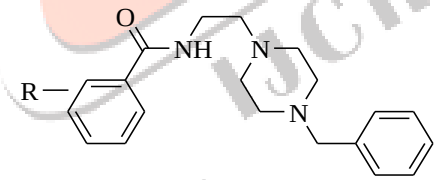
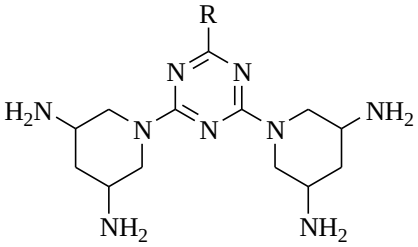


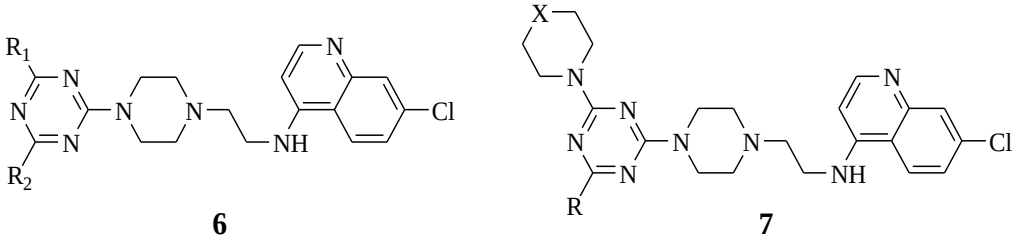
4

Zhou *et al.*[19] reported the synthesis and nicely designated with nine nitrogen atoms wchich is excellent in conjugation with proteins, it is biological activity in antibacterial activity of 3, 5-diamino piperidinyltriazines**5**.



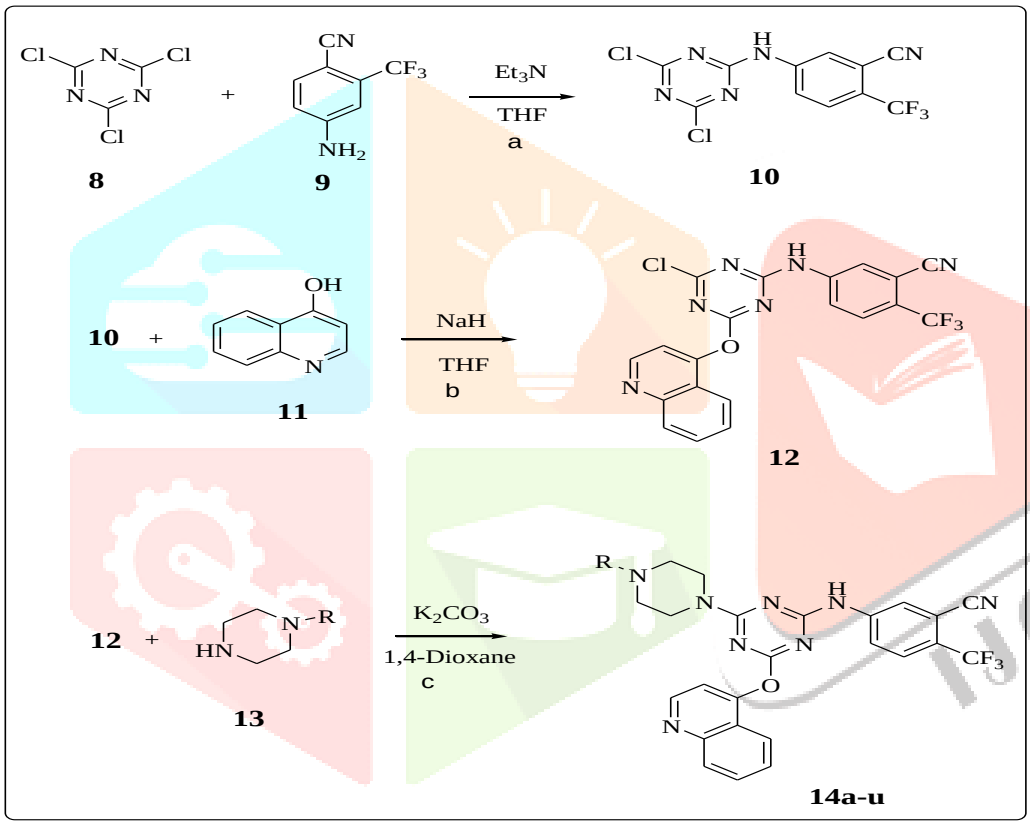
5

Interestingly, there is sequence of 4-aminoquinoline triazines**6**, **7** derivatives have been synthesized by Chauhan P.M.S. and co-worker *et al.*[20-21] screened for *in vitro* antimalarial activities against CQ sensitive strain 3D7 of *Plasmodium falciparum* and CQ resistant strain N-67 of P. *yoelii*in an *in vivo* assay.



6 **7**

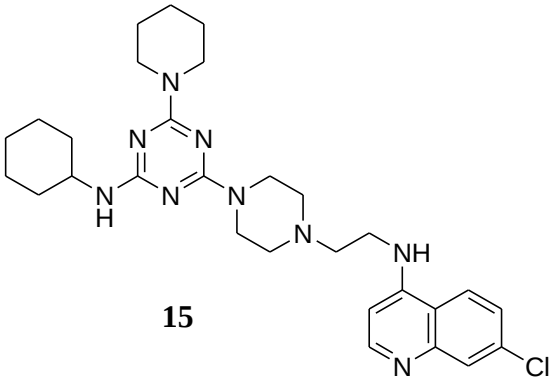
Patel *et al*.[22] reported a series of imporatances-triazine derivatives and tested for their biological evaluations of *s*-triazine as potential antimicrobial, antimicobacterial agents.



Scheme 1 : Reagent and conditions: a) 0-5 °C , THF, 7 hr.; b) 45 °C , THF, 14 hr.; c) 1,4-Dioxane, K_2CO_3 , Reflux, 12-20 hr.

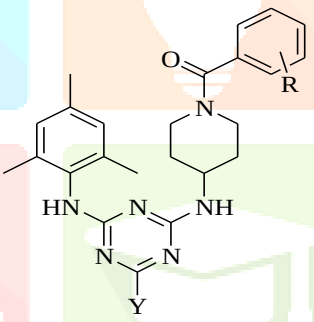
Simanek*et al.*[23] reported a complex dendrimers with varied peripheries structure, less complex molecules tailored for specific applications including DNA and RNA delivery and drug designdendrimers for potential therapeutic applications including infectious disease and cancer. These syntheses have been executed at scales that range from high milligrams to over a kilogram. The nucleus of early dendrimers was a simple diamine, including piperazine, yielding the so-called bow-tie structures, middle period targets boast either a trispiperazinyltriazine center or a 'super-core' with six piperazine groups. The *p*-amino benzylamine was replaced by piperazine and then by aminomethylpiperidine with more exotic diamines sprinkled in throughout.

Gupta *et al.*[24] reported the synthesis and bioevalution of 4-aminoquinoline triazine as a antimalarial agent. A series of new hybrid 4-aminoquinoline triazine were synthesized and screened against CQ strain 3D7 of *P. Falciparum* in vitro.



15

Xuwang Chen & co-authers[25,26]identified a novel series of triazine substituted piperidine**16, 17** derivatives and screened for anti-HIV activities in MT-4 cells. Many hybrids have exhibited potent activity against wild type HIV-1 with EC-50 values in little nanomolar concentration than that of standeredsDelavirdine, Dideoxycitidine, Zidovudine and Nevirapine.



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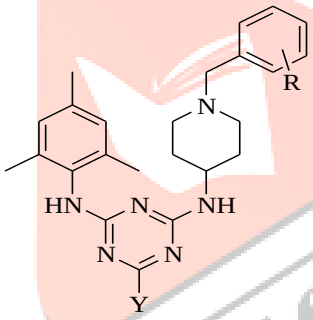
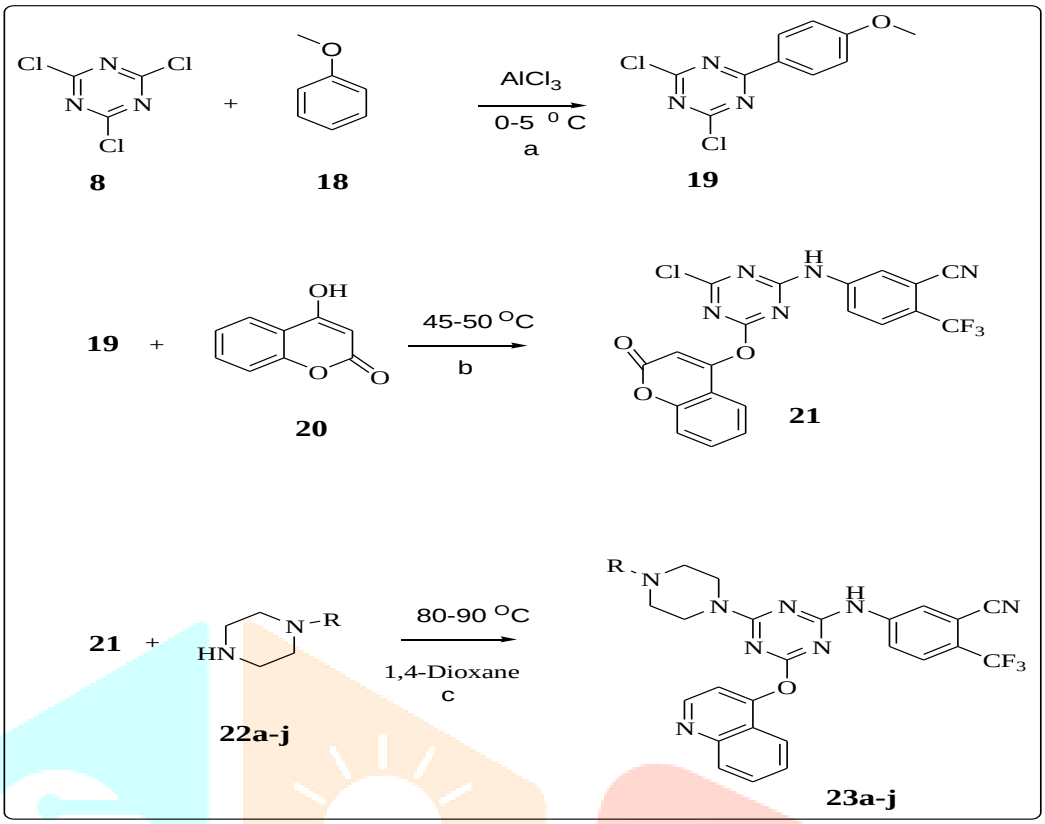


17

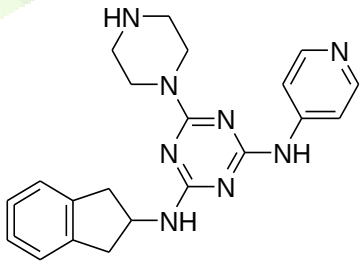
Where **R** = -OMe, -NO_2,-CN, -COOH, -F. **Y** = OMe, -NH_2, -NHMe.

More recently, Desai *et al.*[27] have synthesized a variety of *N*-substituted piperazine annulated s-triazine derivatives and performed bioevaluation of a sequence of 2,4,6-trichloro-1,3,5-s-triazine analogues which on substitution with anisole, 4-hydroxy coumarin and different *N*-substituted piperazine derivatives on the C-6 position of s-triazine nucleus. The resultant compounds were screened for their in vitro antimicrobial activity against gram negative bacteria (*E. coli, K. pneumoniae*), gram-positive bacteria (*S. aureus, B. subtilis*) and fungal species (*C. albicans and S. cerevisiae*) using the disc diffusion method. Most of the synthesized compounds were appeared with promising antimicrobial activity.



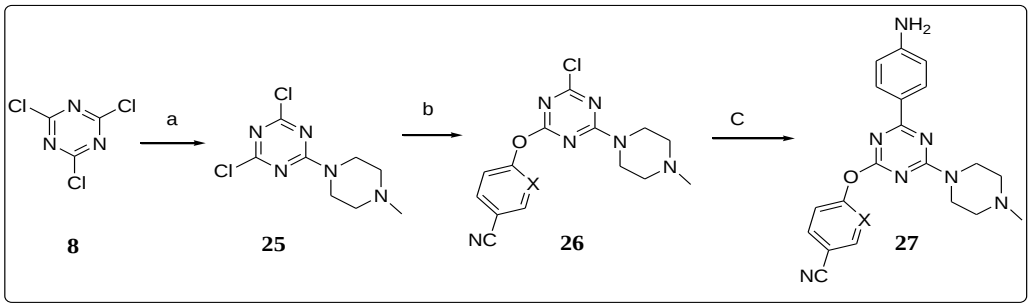
Scheme 02 : Reagent and conditions: a) 0-5 °C , THF, 7 hr.; b) 45 °C , THF, 14 hr.; c) 1,4-Dioxane, K_2CO_3 , Reflux, 12 hr.

Shen *et al.*[28] are reported a various triazine derivatives **24** as ROCK1 (Rho-associated protein kinases) inhibitors by with a computational protocol that combines molecular docking, binding free energy calculations, molecular dynamics (MD), simulations and binding energy decomposition analysis. The some of them showed promising potency.



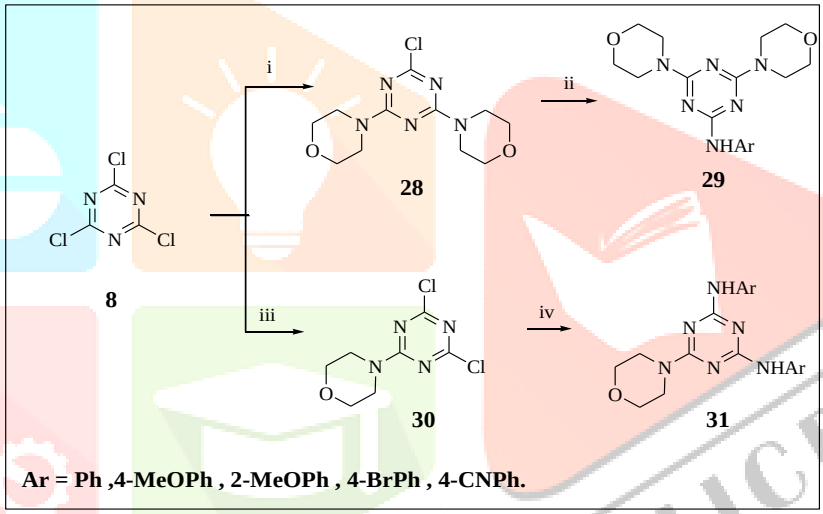
24

Patel *et al.*[29]earlier showed facile synthesis of benzonitrile/nicotonitrile based s-triazines as new potential antimycobacterial agents. A general strategy to synthesize 4/ 6-(4-(4-methylpiperazin-1-yl)-6-(4-(4-oxo-2-phenylthiazolidin-3-yl) phenyl)-1, 3, 5-triazin-2-yloxy) benzonitriles / nicotinonitriles was developed by applying an efficient palladium-catalyzed Suzuki coupling and synthesized compounds were characterized by spectral analysis.



Scheme 3: Reagents and Conditions: a) *N*-methylpiperazine, K_2CO_3, acetone, 0-5 °C ; b) 4-hydroxy benzonitrile / 6-hydroxy nicotinonitrile, K_2CO_3, acetone, 30 °C; (c) 4-amino phenyl boronic acid pinacol ester, $Pd(OAC)_2$, Xphos, K_3PO_4, toluene, 100 °C.

Konstantin *et al.*[74]**(Comp-28-31)** have accomplishedmicrowave assisted solvent free synthesis of malamine with flexible aromatic *N*-substituents.



Scheme 04: Reagent and conditions: i) morpholine (2 equi.), DCM, rt.; ii) $ArNH_2$(2 equi.), silica gel(2 g/mmol),MWI 800W, 3min.; iii) morpholine(1 equi.), Na_2CO_3(1 equi.), DCM, 0^0C.; iv)$ArNH_2$(4 equi.), silica gel(2 g/mml)), MWI 800 W, 3 min.

Conclusion

Various 2,4,6-trisubstituted-*s*-triazine piperazine derivatives are crucial and play important role in biological activity evaluation. They synthsize all synthesis efficientlywith better yield to make more potentialto *s*-triazines-piperazine useful and attractive antimicrobial agents. All the compounds were invariably substituted with piperazine, *N*-piperazine or aryl substituted piperazine as one of the substituents of *s*-triazine scaffold are potent drugs.

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Conflict of Interest

The authors declared that they do not have any conflict of interest regarding this research article.

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