Indian Journal of Drugs, 2018, 6(1), 9-48 **ISSN: 2348-1684**

Review Article

1,3,5-TRIAZINE: A VERSATILE SCAFFOLD

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Received: 06.09.2017
Accepted: 22.03.2018

Access this article online

Website:
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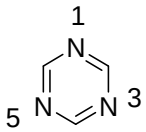
ABSTRACT

1,3,5-Triazine molecule is the most versatile moiety having diverse types of biological activities such as analgesic, antibacterial, antifungal, antimalarial and antiviral activities. This review contains chemical, biological and pharmacological aspects of 1,3,5-triazine analogs, reported to till date.

KEY WORDS: (1,3,5-Triazine, IC50 value, Anticancer activity, antibacterial activity, antiviral activity.

INTRODUCTION

Drug discovery and development is a multidisplinary, creative, innovative and highly regulated process. Searching a lead has been a great challenge in pharmaceutical research. Lead candidates are those with promising charactarisatics for development into new drugs. Optimization of 'lead' refers to process used to manipulate analog to improve its chemical stability, potency and biological or therapeutic effectiveness (Kundu et al. 2012). Nitrogen containing heterocyclic ring systems has an important role, not only for life science industry but also in many other industrial fields related to special and fine chemistry (Smolin, 1959) 1,3,5-Triazine ($C_3H_3N_3$, **1**) is an organic analog whose chemical structure has a six-membered heterocyclic aromatic ring consisting of three carbon atoms and three nitrogen atoms. Atoms in triazine rings are analogous to those in benzene rings, which makes triazines, aromatic analogs like benzene.



1

1,3,5-Triazine (or s-triazine) and its analogs are a class of of nitrogen-containing heterocyclic analogs well known for a long time, and still continue object of considerable interest, mainly due to their applications in different fields, including production of herbicides, polymer photostabilisers,

agrochemical and medicinal properties. The nature and structure of substituents in sym-triazine ring is the main determine properties of these analogs (Pogosyan, et al. 1987).

CHEMISTRY

Presence of s-triazine analogs was very interesting, since various 1,3,5-triazines can be formed from ammonia, hydrogen cyanide and water, components believed to be plentiful in primordial soup. Therefore, triazines may have been rich on early Earth (Minard et al. 1998). The main practical method for preparation of substituted 1,3,5-triazine analogs is based on functionalization of cheap, commercially available compound cyanuric chloride by successive, controlled nucleophilic substitution of each chloride, taking advantage of decrease of reactivity with number of substituents (Thurston et al. 1951). s-Triazine analogs containing electron-donating groups like amino group in the positions 2, 4 or 6, a stronger bond is generated which causes more restriction to free rotation (Díaz-Ortiz, 2003, Brewer et al. 1999). Substitution of a chlorine atom in cyanuric chloride by basic group is really facilitated by ring nitrogen atom of symmetrically built s-triazine nucleus. 2,4,6-Trisubstituted-s-triazine analogs prepared by replacement of one chlorine atom at 0-5^{0}C, second one at 35-45^{o}C and third one at 80-100^{o}C (Kaiser et al. 1951, Patel et al. 2003).

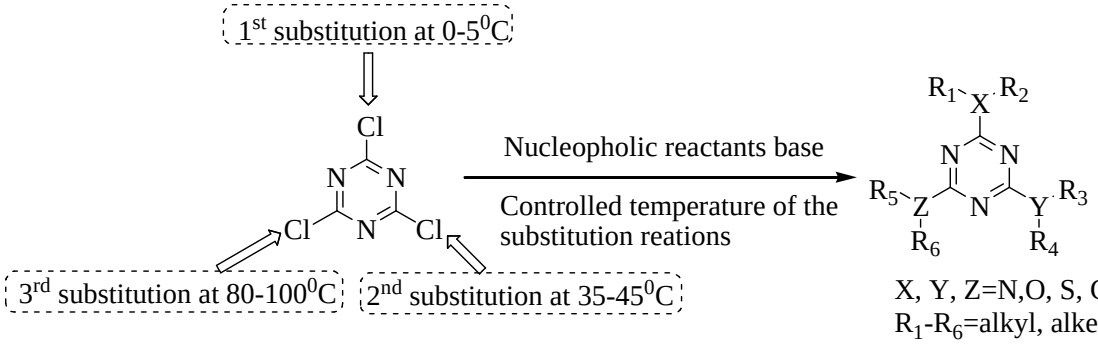


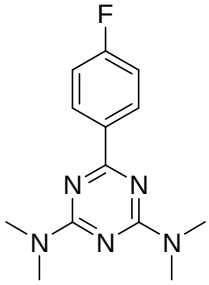
Fig.-1: Synthesis of polyfunctional 1,3,5-triazine analogs taking advantage of differential reactivity of cyanuric chloride.

PHARMACOLOGICAL ACTIVITIES

Till date various 1,3,5-triazine analogs have been synthesized and reported to have diverse activities.

Analgesic activity

Vanderhoek et al. (1973) synthesized bis (dimethy1amino)-s-triazine analogs as anti-inflammatory agents. The most potent analog **2** revealed 100% inhibition of inflammation at dose 75 mg/kg, showing at least 2.5 times more potency than Indomethacin in granuloma pouch technique.



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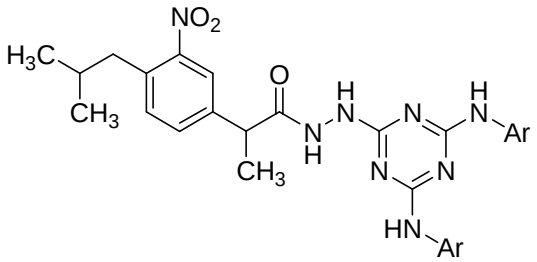
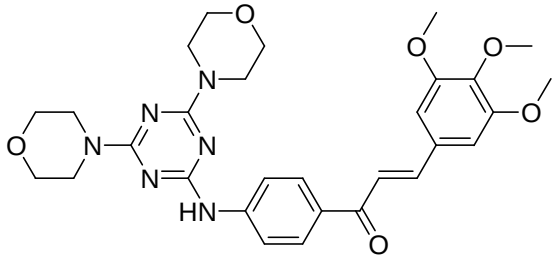
Kansara et al. (2009) prepared a new series of Ibuprofen substituted 1,3,5-triazine analogs. Analogs **3-6** showed analgesic activity same as Ibuprofen by flick tail model. Analog **7** showed increase 15% activity as compare to Ibuprofen. Analogs containing nitro group exhibited moderate to higher analgesic activity as compare to the parent analog.



3 Ar=2-Methoxy phenyl, **4** Ar=4-Methoxy phenyl, **5** Ar=4-Chloro phenyl **6** Ar=Phenyl, **7** Ar=3-Chloro phenyl Elshemy et al. (2017) prepared poly-substituted s-triazines and also evaluated their anti-inflammatory activity. Most active analogs as anti-COX-2 such as **8** (IC_{50}=1.34 µM), **9** (IC_{50}=0.55 µM) and **10** (IC_{50}=0.74µM) were relatively more potent or equal to Celecoxib (0.78 µM). Anti-inflammatory activity of analogs was evaluated by using paw thickness inhibition assay. Analogs **8** and **11** were the most active with a paw thickness change (50%).



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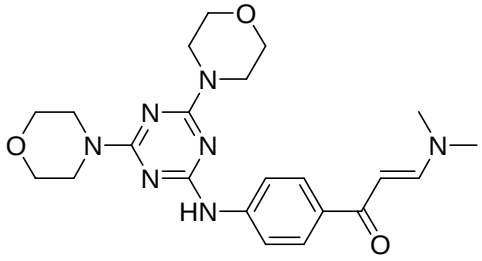

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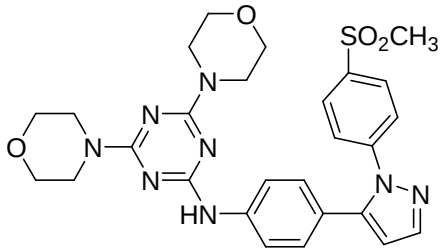

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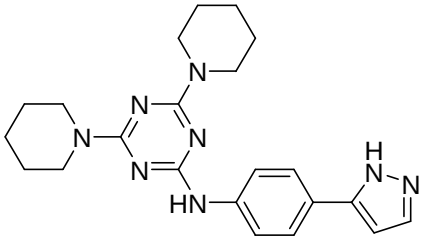
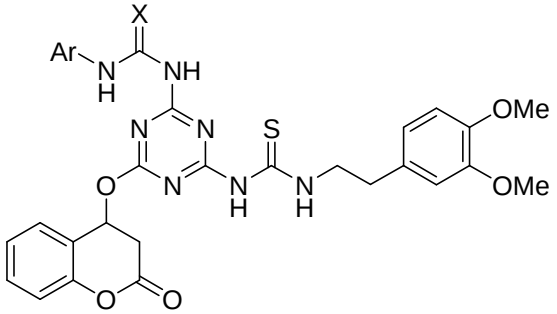


11

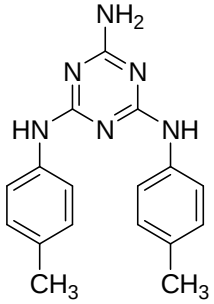
Anti-HIV activity

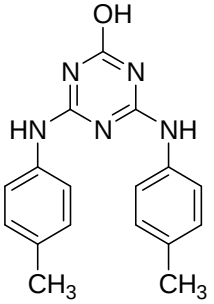
Patel et al. (2007) synthesized 1,3,5-triazine analogs and also evaluated their antibacterial and anti-HIV potencies. Analog **12** displayed significant zone of inhibition against *E. coli* and *B. subtilis* while analog **13** against *S. typhi* and **14** against *S. aureus* displayed excellent antibacterial activity. Analogs **15-19** exhibited maximum zone of inhibition against *B. subtilis*, *S. aureus*, *E. coli* and *S. typhi*. Antimicrobial screening results revealed that analog with substituents like methoxy, methyl and halo in aromatic group enhance antibacterial activity.



12 Ar=4-OCH_3-C_6H_4, X=O, **13** Ar=3-CH_3-C_6H_4, X=O, **14** Ar=2-CH_3-C_6H_4, X=O, **15** Ar=C_6H_5, X=S, **16** Ar=2-CH_3-C_6H_4, X=S, **17** Ar=3-CH_3-C_6H_4, X=S, **18** Ar=4-CH_3-C_6H_4, X=S, **19** Ar=3-Cl-C_6H_4, X=S

Viira et al. (2016) synthesized s-triazine analogs as HIV-1 non-nucleoside reverse transcriptase inhibitors. Analogs **20** and **21** showed efficient HIV-1 RT inhibition, with an IC_{50} of 5.6 ±1.1 µM and 0.16 ± 0.05 µM in a cell-based assay using infectious HIV-1, respectively. s-Triazines have ability to bind with HIV-RT in the NNRTI site and inhibit HIV infection.

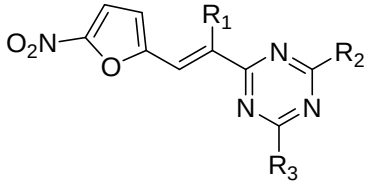




20 (IC_{50}=5.6 ±1.1) **21**(IC_{50}=0.16 ± 0.05 µM)

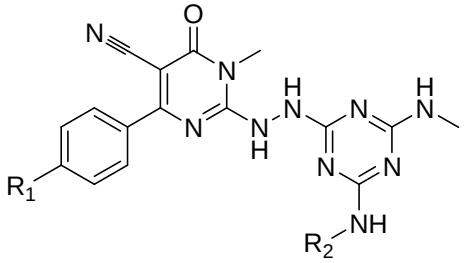
Anti-microbial activity

Nishigaki et al. (1969) synthesized 2,4-disubstituted 6-[(5-nitro-2-furyl)vinyl]-s-triazines and 2,4-diamino-6-(5-nitro-2-furyl)-s-triazines and screened for their antimicrobial activity. Compunds **22-29** revealed significant antibacterial activity. Analogs **22**, **26** and **27** showed excellent activity against *P. vulgaris*. SAR of synthesized analogs showed that insertion of a vinyl group between two hetero rings enhances *in vitro* activity.



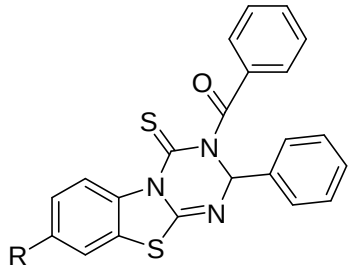
22 R_1=H, R_2=$NHCH_3$, R_3=NH_2, **23** R_1=H, R_2=$N(CH_3)_2$, R_3=NH_2, **24** R_1=CH_3, R_2=$N(CH_3)_2$, R_3=NH_2, **25** R_1=CH_3, R_2=$N(CH_3)_2$, R_3=$NHCOCH_3$, **26** R_1=H, R_2=NH_2, R_3=NH_2, **27** R_1=CH_3, R_2=NH_2, R_3=NH_2, **28** R_1=CH_3, R_2= $NHCOCH_3$, R_3= $NHCOCH_3$, **29** R_1=C_2H_5, R_2=NH_2, R_3=NH_2

Modha et al. (2001) synthesized s-triazines and evaluated for their *in vitro* antimicrobial potency and also antitubercular activity towards *Mycobacterium tuberculosis H*37. Analog **30** showed potent activity against *B. megaterium* and *S. typhosa.* Analogs **31**-**37** showed maximum activity against *B. megaterium* and *S. typhosa*. Analogs **31**-**33**, **36**, **38** and **39** showed significant antibacterial activity against *E. coli*. Analogs **31**, **35**, **36** and **40** showed higher antitubercular activity (up to 92% inhibition). Analog **41** exhibited potent activity with a MIC value of 6.25 µg.



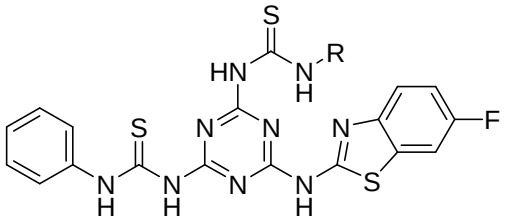
30 R_1=H, R_2=C_2H_5, **31** R_1=H, R_2=3-Cl-4-F-C_6H_3, **32** R_1=H, R_2=2,4-Cl_2-C_6H_3, **33** R_1=H, R_2=3,5-Cl_2-C_6H_3, **34** R_1=Cl, R_2=3-Cl-C_6H_4, **35** R_1=Cl, R_2=4-Cl-C_6H_4, **36** R_1=Cl, R_2=3-Cl-4-F-C_6H_3, **37** R_1=Cl, R_2=2,4-Cl_2-C_6H_3, **38** R_1=H, R_2=4-$COCH_3$-C_6H_4, **39** R_1=Cl, R_2=4-$COCH_3$-C_6H_4, **40** R_1=H, R_2=3-Cl-C_6H_4, **41** R_1=H, R_2=2,4-$(CH_3)_2$-C_6H_3,

Kriplani et al. (2006) prepared some benzothiazolotriazine analogs and also evaluated their antibacterial activity against *E.coli, Pseudomonas aeruginosa and Staphylococcus aureus* by using paper disc method. Analogs **42** and **43** showed potential antibacterial activity.



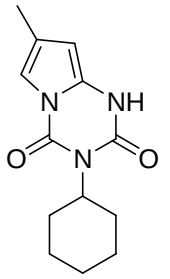
42 R=Br, **43** R=NO_2

Sareen et al. (2006) synthesized 1,3,5-triazine analogs as potential antimicrobial agents by using agar diffusion method. Antifungal screening results revealed that analogs **44**-**47** show maximum inhibition.



44 R=2-FC_6H_4, **45** R=4-FC_6H_4, **46** R=2-$CF_3C_6H_4$, **47** R=4-$OCH_3C_6H_4$

Mares et al. (2006) screened s-triazine analogs for antifungal activity towards *Magnaporthe grisea*. Analog **48** and **49** showed good antifungal activity.



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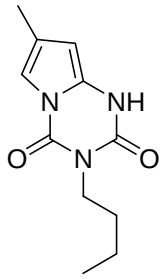
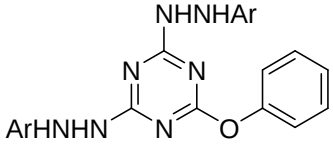


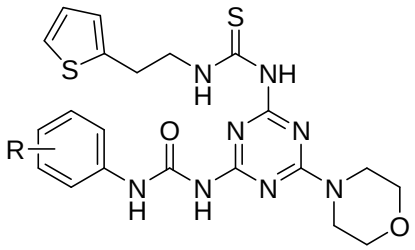
49

Chaudhari et al. (2006) prepared bisaryl hydrazino-s-triazine analogs and also screened for their antimicrobial activity. Analogs **50**-**52** displayed significant antibacterial activity. Analogs **53**-**55** exhibited higher antifungal activity.



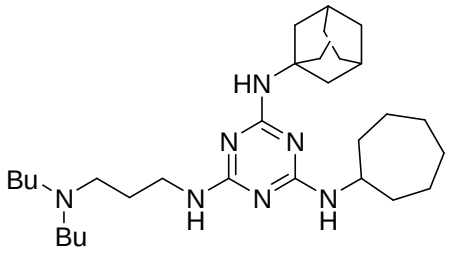
50 Ar=4-Chloro-phenyl, **51** Ar=4-Bromo-phenyl, **52** Ar=4-Nitro-phenyl, **53** Ar=Phenyl, **54** Ar=4-Methyl-phenyl, **55** Ar=4-Methoxy-phenyl

Desai et al. (2007) prepared s-triazine analogs as antimicrobial agents. Analogs **56** and **57** for *E. coli*, **58** and **59** for *S. aureus*, **60** for *S. typhi*, **57** and **61** for *B.subtillus* exhibited maximum zones of inhibition. Screening results revealed that methyl and halo groups at ortho, meta and para positions to ureido linkage against all micro-organisms result in increase in antimicrobial activity as compared to the parent analog.



56 R=H, **57** R=4-Cl, **58** R=3-Cl, **59** R=2-CH_3, **60** R=3-CH_3, **61** R=3-NO_2

Zhou et al. (2008) prepared 1,3,5-triazine analogs and screened their antimicrobial activity. Analogs **62-64** showed good antibacterial activity with IC_{50} value in low micromolar range. Dye leakage assay results showed that these analogs kill microbe probably via disrupting membrane integrity of cell.



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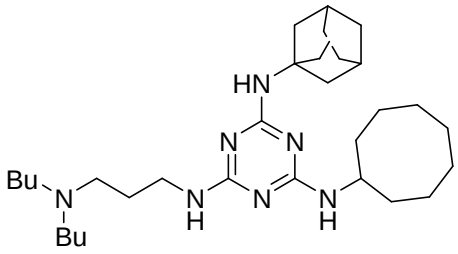

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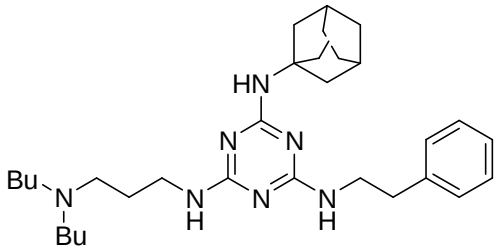
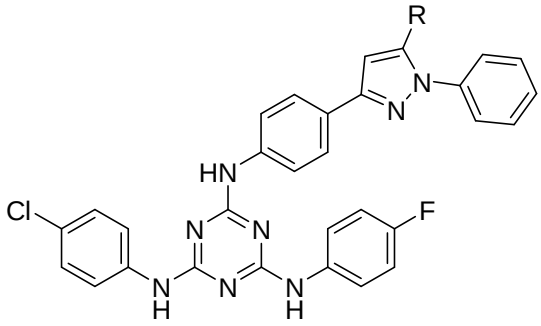


64

Solankee et al. (2008) prepared a series of 1,3,5-triazine analogs and screened their *in vitro* antibacterial activity by agar diffusion method of A. L. Barry. Analogs **65**-**67** are found to be active against *S. aureus*. Analogs **65**, **68** and **70** showed activity against *B. subtilis*. Analog **70** showed significant activity against *E. coli*. Analogs **65**, **69** and **71** were found to be active against *S. paratyphi-B*.



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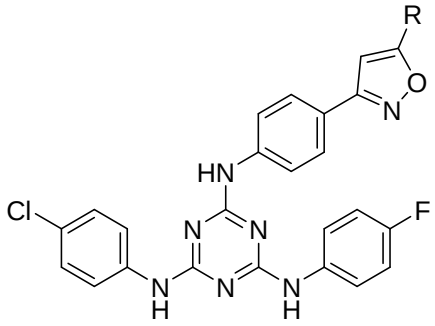
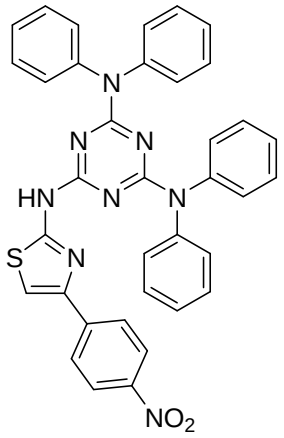


70-71

65 R=2-Cl-C_6H_4, **66** R=4-Cl-C_6H_4, **67** R=2-OCH_3-C_6H_4, **68** R=C_6H_5, **69** R=3-Cl-C_6H_4, **70** R=2-OCH_3-C_6H_4, **71** R=2-Cl-C_6H_4

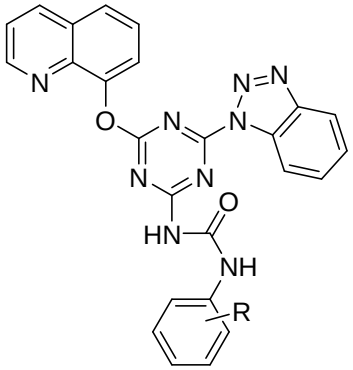
Gahtori et al. (2008) prepared s-triazines as antibacterial agents against Gram positive (*B. subtilis, B. cereus, Staphylococcus aureus*) and Gram-negative micro-organism (*S. typhi, E. coli, K. aerogenes*) by using broth dilution method, with reference to Streptomycin. Among all the synthesized analogs,

analog **72** showed potent antibacterial activity. Screening datas showed that phenyl-1,3-thiazole substituted amino-s-triazine analogs exhibit good antibacterial activity.



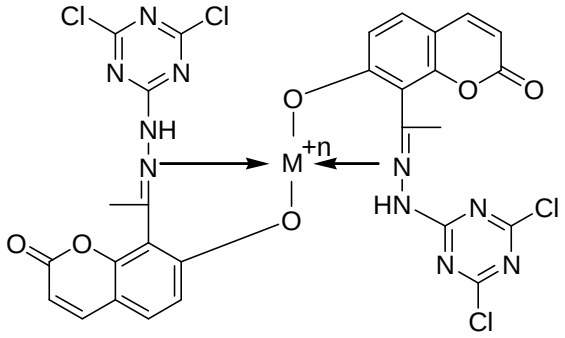
72

Vora et al. (2009) prepared a new series of s-triazine derived with quinolines and evaluated their antibacterial activity using broth dilution method. Analogs **73**-**76** were found to be equal active against some bacteria as compared to Gentamycin, Ampicillin and Chloramphenicol. Analogs **74** and **75** showed significant antifungal activity against *A. Niger*.



73 R=2-NO_2, **74** R=3-CH_3, **75** R=3-Cl, **76** R=4-Cl

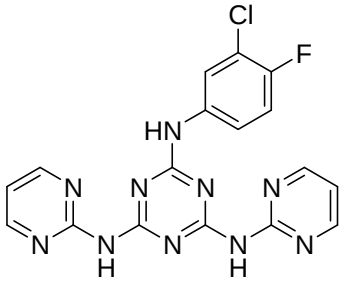
Jani et al. (2009) synthesized s-triazines and also evaluated their antimicrobial activity. Antimicrobial activity datas revealed that metal complexes show significant antibacterial and antifungal activities. The Cu(II), Fe(II) and Fe(III) complexes **77** showed significant activity where other complexes showed moderate activity.

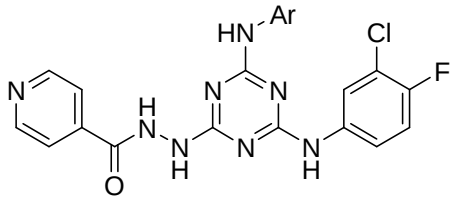


77

Baldaniya et al. (2009) prepared s-triazine analogs and evaluated their antibacterial and antifungi activities. Analog **78** was found to be significantly active against *E.coli.* Analog **79** was most active against *S. aureus*. Analog **80** showed moderate antifungal activity. Results revealed that introduction of

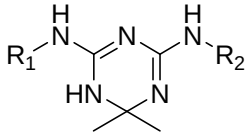
-OH, -OCH_3, -NO_2, -Cl and -Br groups to heterocyclic frame work enhanced antibacterial and antifungal activities.





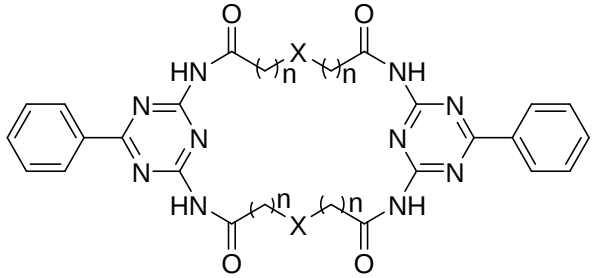
78 **79** Ar=2-OCH_3-C_6H_4, **80** Ar=4-NO_2-C_6H_4

Maeda et al. (2009) prepared some new 4,6-di(substituted)amino-1,2-dihydro-1,3,5-triazine analogs as topical antiseptic agents. Analog **81** and **82** revealed potent antibacterial activity against Vancomycin-resistant enterococcus. Synthesized new 4,6-di(substituted)amino-1,2-dihydro-1,3,5-triazine analogs had remarkable and acute bactericidal properties and thus may be promising new antiseptic agents.



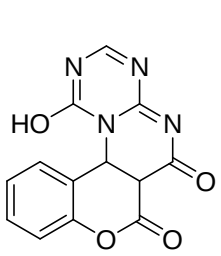
81 R_1=4-Methyl benzyl, R_2=Octyl, **82** R_1=Octyl, R_2=Hexyl

Aghatabay et al. (2009) prepared ligands containg s-triazine moity and also evaluated their antimicrobial activity by disk diffusion test. Analogs **83** and **84** showed slightly stronger activity against *Bacillus cereus* (**83** MIC=3.125 and **84** MIC=6.25 µgmL^{-1}) and *Micrococcus luteus* (**83** MIC=3.125 and **84** MIC=6.25 µgmL^{-1}) compared with Gentamycin. These two analogs showed same activity as compared to Gentamycin against *Klebsiella bacteria* (6.25 µg mL^{-1}). All the tested analogs showed superior activity (MIC=1.56 µgmL^{-1}) against *Hanseniaspora guilliermondii* culture compared with Nystatin. Analogs **83** and **84** displayed stronger activity against yeast cultures *Kluyveromyces fragilis* (MIC=1.56 µgmL^{-1}) and *Debaryomyces hansenii* (MIC=1.56 µgmL^{-1}) in comparison with Nystatin, showing MIC values 6.25 and 12.50 µgmL^{-1} on same micro-organisms, respectively. Inhibition activity of analogs seems to be governed in certain degree by percentage amount of sulphur presence in analogs because dithio **83** and **84** macrocycles showed more activity against most micro-organisms, compared to monothio macrocycles.



83 n=1, X=S-S, **84** n=2, X=S-S

Mohamed et al. (2009) prepared some s-triazine analogs and evaluated their antimicrobial activity by cup plate method. Analogs **85-87** displayed significant antimicrobial activity against all micro-organisms at conc. 0.05 mL, 0.1 mL dose levels and were comparable to Amoxicillin.



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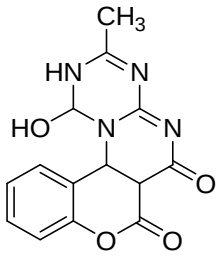

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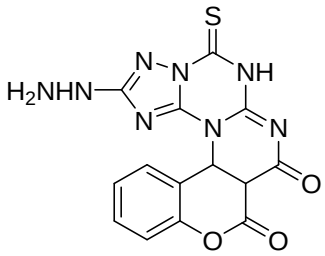
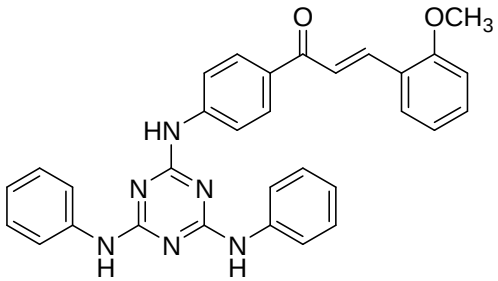


87

Solankee et al. (2010) synthesized some new chalcone based s-triazine analogs and screened for their antibacterial activity by using disc-diffusion method. Among all tested analogs, analogs **88** and **89** were the most active analogs. 4-Nitrophenyl substituted analog **90** was also most active analog only against Gram positive bacteria. Screening results revealed that 2-thienyl analogs exhibit best activity and followed by 2-furanyl analogs.



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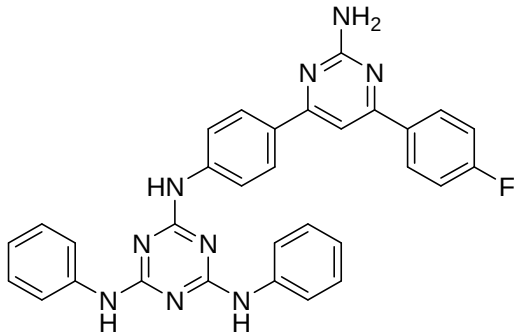

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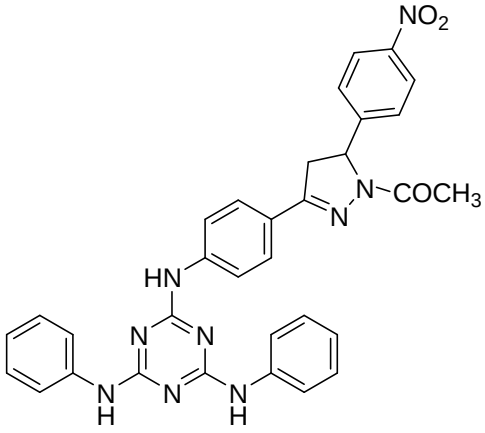
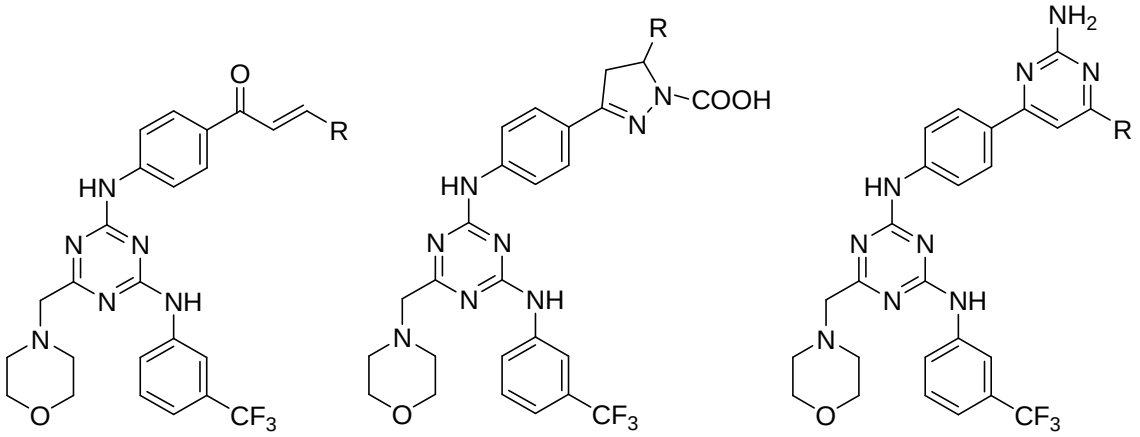


90

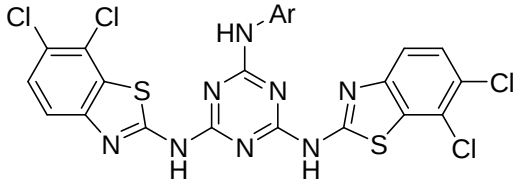
Solankee et al. (2016) synthesized chalcone, amino pyrimidine, acetyl pyrazoline containing s-triazine and screenrd their antimicrobial by broth dilution modal and antitubelar activity against *Mycobacterium tuberculosis* H37Rv using Lowenstein-Jensen MIC modal. Analogs **91**, **92** and **94** showed significant antibacterial activity against *P. aeruginosa* (MIC=50 µg/mL). Analogs **95** and **97** were most active antifungal agent with relatively low cytotoxicity. Anlog **96** showed good antibacterial activity against *S. aureus* (MIC = 50 µg/mL). Analogs **93** and **98** showed significant antitubercular activity. Analogs containing electron withdrawing atom/group such as methoxy, chloro and nitro at meta or para position were identified as the most potent antibacterial agents.



91-93 **94-96** **97-98**

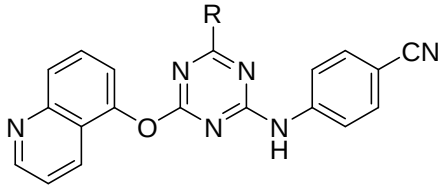
91 R=3-OCH_3-C_6H_4, **92** R=2-OC_4H_3, **93** R=4-$N(CH_3)C_6H_4$, **94** R=3-OCH_3-C_6H_4, **95** R=2-Cl-C_6H_4, **96** R=2-OC_4H_3, **97** R=2-Cl-C_6H_4, **98** R=4-$N(CH_3)C_6H_4$

Baldaniya et al. (2010) synthesized some N^2-(Aryl)-N^4,N^6-bis (6, 7-dichloro-1, 3-benzothiazol-2-yl)-1, 3, 5-triazine-2, 4, 6-triamines **99-112** and screened for their antibacterial and also antfungal activities. Screening results revealed that introduction of -OH, $-OCH_3$, $-NO_2$, -Cl and -Br groups to heterocyclic frame work enhance both antibacterial and antifungal activities.



99 Ar=C_6H_5, **100** Ar=4-NO_2-C_6H_4, **101** Ar=3,4,$(Cl)_2C_6H_3$, **102** Ar=3-NO_2-C_6H_4, **103** Ar=4-CH_3-C_6H_4, **104** Ar=4-OCH_3-C_6H_4, **105** Ar=2-OH, 4-NO_2-C_6H_3, **106** Ar=2-OH-C_6H_4, **107** Ar=2-Cl-C_6H_4, **108** Ar=3-Cl-C_6H_4, **109** Ar=2,4,5,$(Cl)_3$-C_6H_2, **110** Ar=2-OCH_3-C_6H_4, **111** Ar=2,4-$(NO_2)_2$-C_6H_3, **112** Ar=3,4-$(Cl)_2$-2-NO_2-C_6H_2

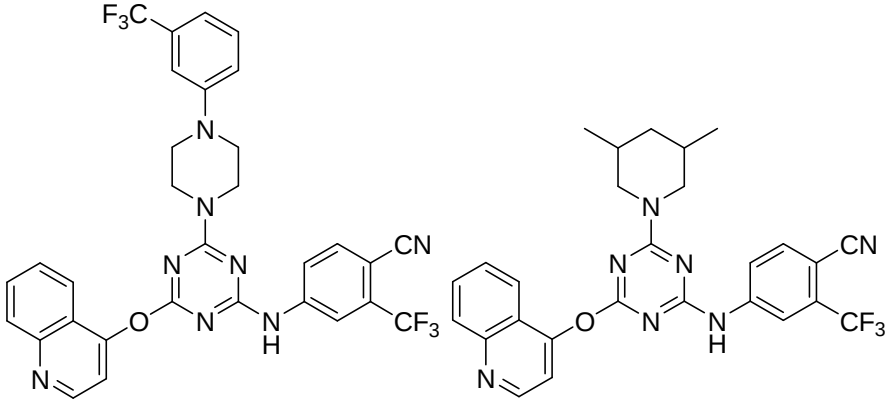
Patel et al. (2010) prepared 1,3,5-triazines and also evaluated for their *in vitro* antimicrobial activity by using broth dilution method. Analogs **113-118** revealed significant activity against *P. aeruginosa*. Analogs **114**, **116**, **117** and **119** showed the potent activity against *S. Aureus*. Analogs **113** and **120** revealed potent activity against *B. subtilis*. Analog **120** revealed significant activity against *C. albicans* and *A. Niger*. Results revealed that activity may be due to presence of piperazine systems with halogen, methoxy group(s) and piperidine entities.



113 R=4-Benzyl-piperidine, **114** R=1-(2-Fluoro-phenyl)-piperazine, **115** R=1-(4-Fluoro-phenyl)-piperazine, **116** R=1-(3-Trifluoromethyl-phenyl)-piperazine, **117** R=1-[(4-Chloro-phenyl)-phenyl-methyl]-piperazine, **118** R=1-(2,3,4-Trimethoxy-benzyl)-piperazine, **119** R=3,5-Dimethyl-piperidine, **120** R= 1-(4-Methoxy-phenyl)-piperazine

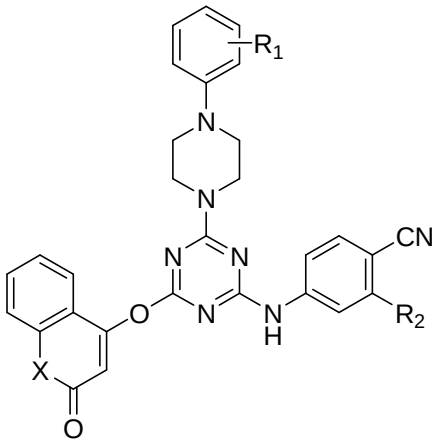
Patel et al. (2011) prepared 2-(4-cyano-3-trifluoromethylphenyl amino)-4-(quinoline-4-yloxy)-6-(piperazinyl/piperidinyl)-s-triazines as potential antimicrobial, antimycobacterial and anticancer agents. Analog **121** showed excellent activity against *S. aureus, B. cereus, E. coli, Pseudomonas aeruginosa, S. typhi* and *S. flexneria*. Analog **121** displayed inhibitory activity against all fungi at MIC range of 12.5-25 µg/mL and inhibition zone range of 25-28 mm. Analog **122** displayed excellent

activity at MIC=6.25 µg/mL against *S. aureus*, *P. vulgaris* and against *E. coli*, *S. typhi* and *S. flexneria* at MIC=12.5 µg/mL. Analog **122** displayed complete inhibition (99%) against *M. tuberculosis* H37Rv at MIC of 3.12 µg/mL using Lowensteine-Jensen MIC method. Analog **122** was most potent analog with GI_{50} value of 14.1 µg/mL, followed by **121** with GI_{50} value of 24.6 µg/mL. Analogs **121** and **122** displayed complete inhibition of DU-145 cell growth at concentration level of 35.3 µg/mL and 47.1 µg/mL, respectively and found potent than that of standard drug.



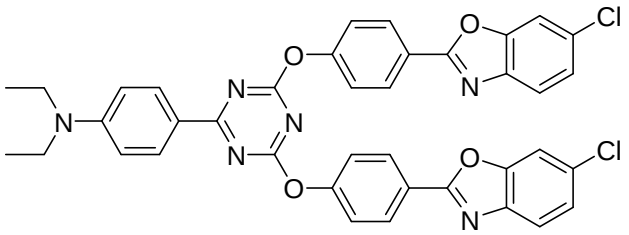
121 **122**

Patel et al. (2011a) prepared a series of s-triazines and also evaluated antibacteria and antifungi activities using paper disc diffusion technique and agar streak dilution method, respectively. Analogs **123** and **124** showed the highest inhibitory ability against *Staphylococcus aureus* (MIC = 6.25 µg/mL) and *Shigella flexneria* (MIC = 12.5 µg/mL, 26 mm zone of inhibition). Compund **124** showed good potency (26 mm zone of inhibition) at 12.5 mg/mL against *Bacillus cereus* with similar MIC of analog **123** (25 mm zone inhibition). Analog **125** revealed strong inhibitory effect against *Shigella flexneria* (MIC=12.5 µg/mL, 25 mm zone of inhibition). Analog **123** was the most potent inhibitor against *A. clavatus* (MIC=25 µg/ mL) and *A. niger* (MIC=12.5 µg/mL). Analog **123** and **124** possessed the highest antifungal activity against *C. albicans* at 25 µg/mL (24 mm zone of inhibition). Analogs **123** and **124** displayed complete inhibition (99%) against *M. tuberculosis* H37Rv at MIC of 3.12 µg/mL and exhibited better efficacy than Pyrazinamide.



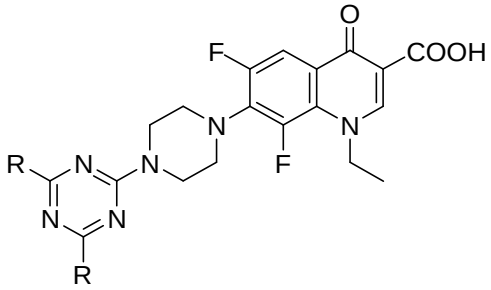
123 R_1=3-CF_3, R_2=CF_3, X=N-CH_3, **124** R_1=4-CF_3, R_2=H, X=N-CH_3, **125** R_1=3-CF_3, R_2=H, X=N-CH_3

Padalkar et al. (2011b) synthesized some new benzimidazole, benzoxazole and benzothiazole substituded s-triazine analogs and evaluated their antimicrobial activity. Analog **126** displayed potent antibacterial towards *E. coli*, *S. aureus* and antifungal activity towards *C. albicans*, *A. niger* strains. Screening results revealed that analogs containing oxazole display better antibacterial and antifungal activity than benzimidazole and benzothiazole analogs.



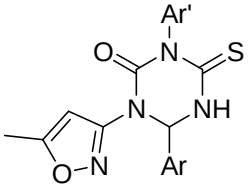
126

Sunduru et al. (2011) synthesized fluoroquinolone-1,3,5-triazine analogs and also evaluated their antimicrobial activity. Analog **127** was 2 fold more active against *K. pneumoniae* and Methicillin-resistant and Vancomycin-resistant *S. aureus* than Norfloxacin. Analogs **128** and **129** were 2-4 fold more active against methicillin-resistant and methicillin-resistant and vancomycin-resistant *S. aureus* than that of Norfloxacin. SAR study of synthesized analogs reveals that analogs having ethyl group as N-1 substituent are more potent than that of molecules having 4-(trifluoromethyl)benzyl group as N-1 substituent.



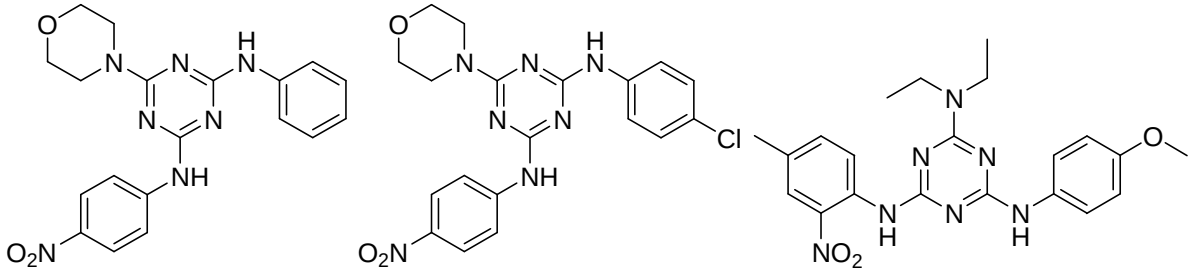
127 R= n-propylamine, **128** R= N-methylpiperazine, **129** R= n-butylamine

Rajanarendar et al. (2011) synthesized 1-(5-methyl-3-isoxazolyl)-3,6-diaryl-4-thixo-1,3,5-triazinan-2-ones and screened their antimicrobial activity. Analog **130** showed better activity against all the test micro-organisms as compared to standard drugs. Analog **131** and **132** showed good antimicrobial activity against all microbes. SAR of synthesized analogs revealed that chloro and methoxy substituted analogs display enhanced activity than other substituted analogs.



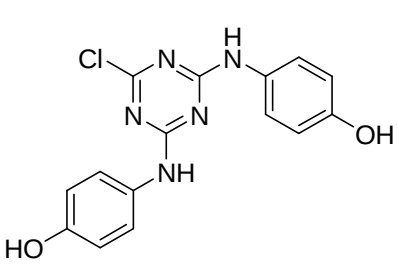
130 Ar= 4-Cl-C_6H_4, Ar'=4-Cl-C_6H_4, **131** Ar= 4-OCH_3-C_6H_4, Ar'=4-Cl-C_6H_4, **132** Ar= C_6H_5, Ar'=4-Cl-C_6H_4

Singh et al. (2012) prepared some new 2,4,6-trisubstituted-1,3,5-triazine derivatives and also evaluated their antimicrobial activity by broth microdilution method. Analogs **133** and **134** exhibited good *in vitro* activities against *B. subtilis, B. cereus, S. epidermis* and *S. aureus*. Analogs **135** displayed broad spectrum activity comparable to Streptomycin and may be due to substitution of electron releasing group at para position of phenyl rings.



133 **134** **135**

Ghosh et al. (2012) synthesized di- and tri-substituted 1,3,5-triazines and also evaluated antimicrobial activity. Analogs **136**-**141** showed significant activities against *B. subtilis S. aureus* and *S. faecalis, P. mirabilis, E. coli* and *P. aeruginosa*. Screening results revealed that tri-substituted triazines demonstrate more activity than their di-substituted counterpart.



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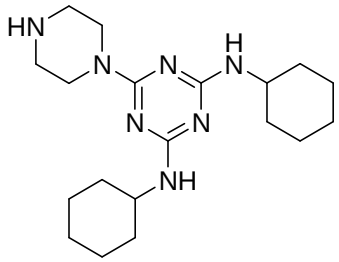

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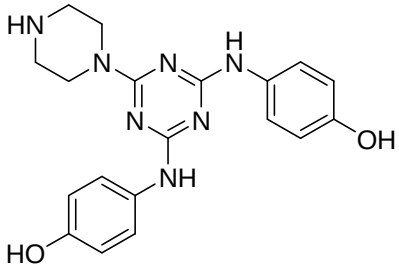

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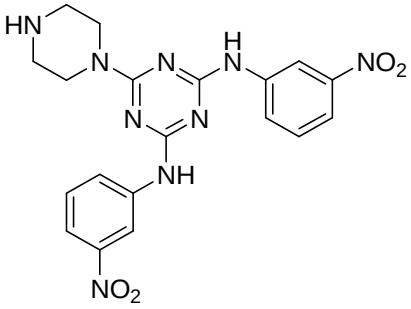

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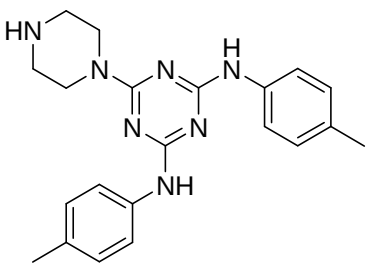

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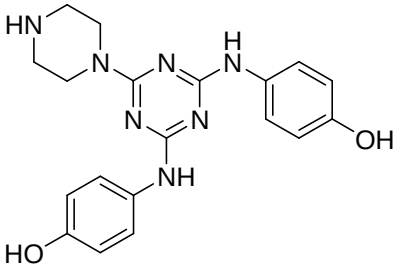
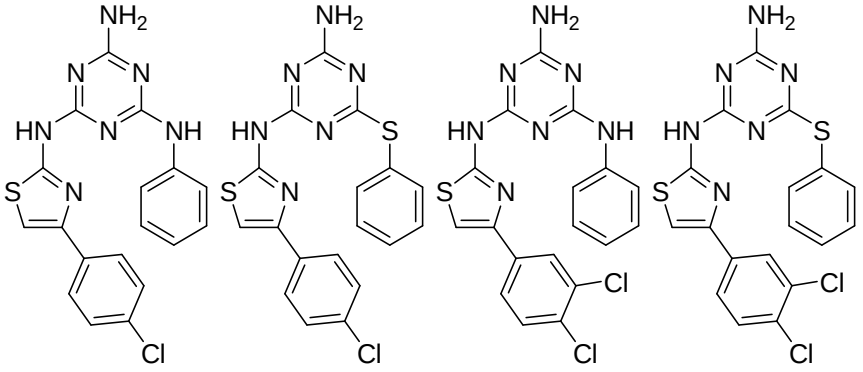


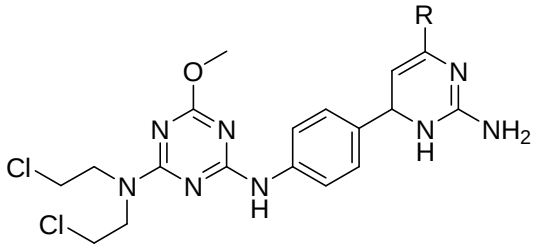
141

Gahtori et al. (2012) prepared phenylthiazolyl-s-triazines and also screened their antibacterial activity. Analogs **142** and **143** showed more activity as compare to Penicillin against *S. typhimurium* and *E. coli*. Analogs **142** and **143** showed equipotent activity as compare to Penicillin and more activity as compare to Streptomycin against *S. aureus*. Analogs **144** and **145** showed equipotent activity as compare to Penicillin against *E. coli*.



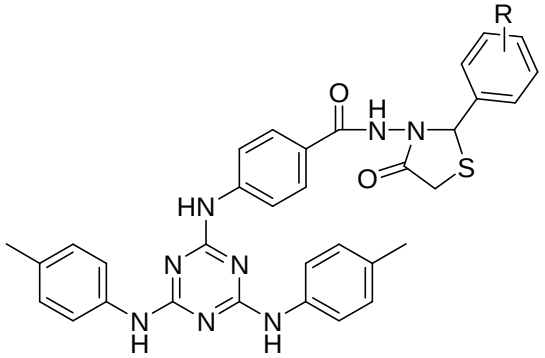
142 **143** **144** **145**

Kathiriya et al. (2012) synthesized 1,3,5-triazine analogs and screened their antimicrobial activity by using cup plate method. Analogs **146**-**149** showed comparable antibacterial and antifungal activities as compare to Ampicillin, Chloramphenicol, Norfloxacin and Griseofulvin at 50 µg/mL concentrations.



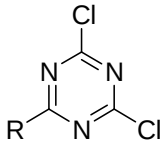
146 R=3-OH C_6H_4, **147** R=4-OH C_6H_4, **148** R=4-NO_2 C_6H_4, **149** R=4-N, $N(CH_3)_2C_6H_4$

Ahirwar et al. (2012) prepared s-triazines and evaluated their antimicrobial activity. Screened analogs **150-161** showed moderate to significant antimicrobial activity.

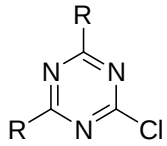


150 R=2-Cl, **151** R=3-Cl, **152** R=4-Cl, **153** R=2-NO_2, **154** R=3-NO_2, **155** R=4-NO_2, **156** R=2-Br, **157** R=3-Br, **158** R=4-Br, **159** R=2-OH, **160** R=3-OH, **161** R=4-OH

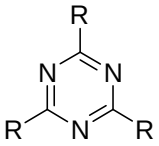
Shanmugam et al. (2013) prepared s-triazine analogs and also evaluated for *in vitro* antimicrobial activity using Streptomycin and Amphotericin B as standards. Analog **162** showed better activity against *C. Albicans* and *C. Albicans*-6 with MIC = 12.5 µg/mL). Analogs **162-168** and **171-174** showed significant antifungal potency as compare to Amphotericin B against *A. niger*, *C. albicans* and *F. oxysporum*. Among them, analog **167** showed maximum activity (MIC = 6.25–25 µg/mL) against all the fungal strains screened, except *A. Flaves* (MIC =100 µg/mL). Analogs **163** and **169-171** showed good activity against *S. typhi*. Analog **174** showed one fold increased activity against *S. aureus*, *B. subtilis* and *P. aeruginosa* than Streptomycin. Screening results showed that purine moieties show better antifungal activity than pyrimidines moieties.



162-166



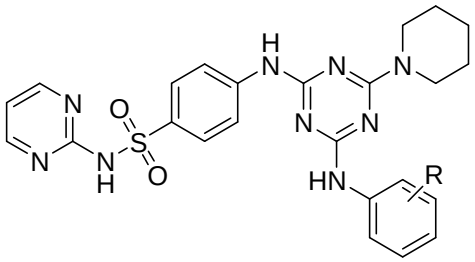
167-169



170-174

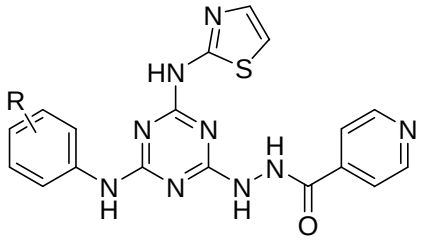
162 R=Adenine, **163** R=Guanine, **164** R=Cytosine, **165** R=Thymine, **166** R=Uracil, **167** R=Adenine, **168** R=Guanine, **169** R=Uracil, **170** R=Adenine, **171** R=Guanine, **172** R=Cytosine, **173** R=Thymine, **174** R=Uracil

Desai et al. (2016a) synthesized s-triazines and screened antimicrobial activity. Analogs **175-177** showed activity against *E. coli* at MIC 25 µg/mL. Analog **176** showed significant activity against *P. aeruginosa* at MIC 25 µg/mL. Analog **177** showed significant activity against *P. aeruginosa* at MIC 25 µg/mL. Data revealed that replacement of hydrogen on phenyl ring from para position with electron withdrawing groups like halogen, nitro and ester remarkably enhanced antimicrobial activity. Present study can lead medicinal chemists to design and synthesize similar analogs with enhanced biological potency in future.



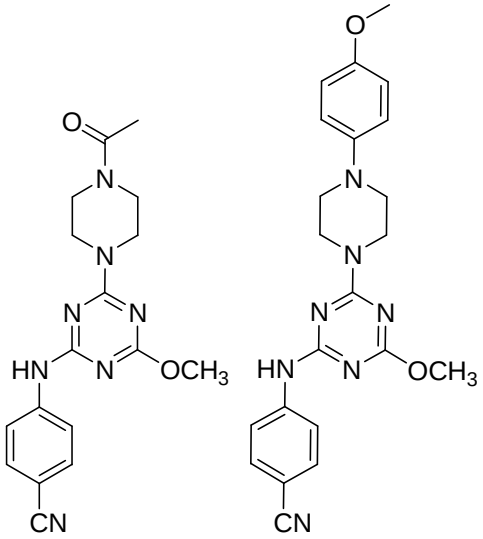
175 R= 4-Cl, **176** R= NO_2, **177** R= $COOC_2H_5$

Desai et al. (2016b) synthesized s-triazines and their screened antimicrobial activity by using serial broth dilution modal. Analogs **178** and **179** showed more antibacterial and antifungal activities than Ciprofloxacin and Griseofulvin. Analogs **178** and **179** showed highest inhibition against bacterial strains *E. coli* and *P. aeruginosa*, respectively at MIC 12.5 µg/mL. Analogs having electron withdrawing groups such as fluoro and nitro showed potentantimicrobial activity against tested microorganisms.



178 R= $2NO_2$, **179** R= $4NO_2$

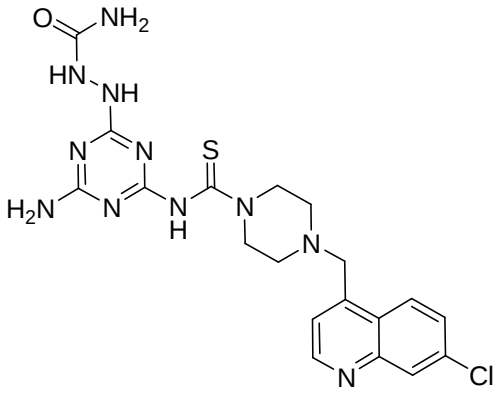
Mewada et al. (2016) prepared 1,3,5-triazine analogs and also evaluated their antimicrobial and antitubercular activities against *M. tuberculosis* H37Rv. Analogs **180** showed good antibacterial and antifungal acticities with IC_{50} value 3.12 µg/mL. Analog **181** showed good antituberculosis activity. Screening data shoed that thiophenol derivatives were found to be more active than other heterocyclic derivatives (–Thiophenol >-piperazine > -Aniline >-phenol). 6-Methoxy-1,3,5-triazin-2-yl)amino)benzonitrile derivative with enhanced bioactivities lead to provide enough scope to develop new scaffolds for further drug discovery process.



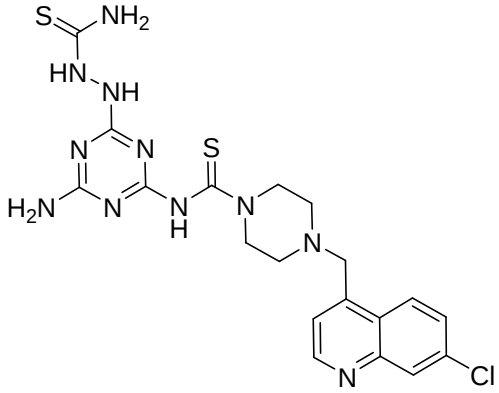
180 **181**

Pathak et al. (2016) prepared s-triazine derivatives and their screened antimicrobial activity. Analog **182** showed maximum activity against *B. subtilis, P. Mirabilis, E. Coli* and *P. vulgaris* with MIC=3.125 µg/mL. Analog **183** showed maximum activity against *S. aureus*, *B. cereus*, *P. aerugenosa, E. coli* and *P. vulgaris* with MIC=3.125 µg/mL. Screened data showed that analogs with semicarbazide and

thiosemicarbazide substitutation on 1,3,5-triazine nucleus were more potent antibacterial agent than other synthesize analogs.

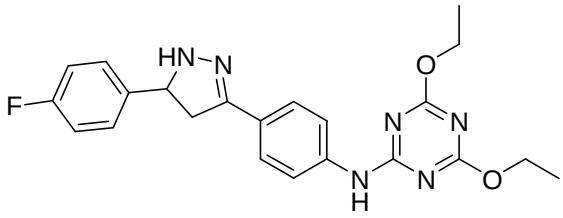


182



183

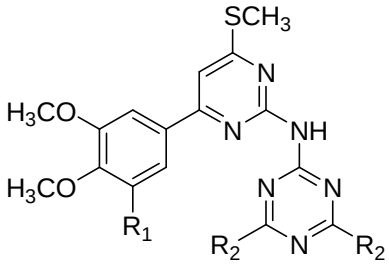
Dongre et al. (2016) prepared s-triazine derivatives and their screened antimicrobial activity by disc diffusion method. Analog **184** showed significant activity against *E. coli*, *S. typhi* and *St. aureus.* Analogs having chloro, fluoro and methoxy groups potent antimicrobial activity against tested microorganisms. Fused 2-pyrazoline s-triazine moieties showed enhanced drug activity.

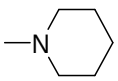
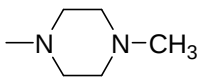


184

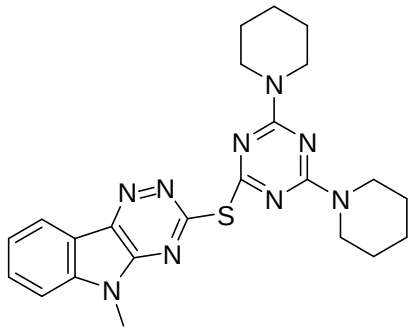
Antileishmanial activity

Sunduru et al. (2009) prepared s-triazine analogs and evealuatd for their antileishmanial activity against *L. donovani*. Analog **185** with good selectivity index (S.I) had shown significant *in vivo* inhibition of 56.58 % at a dose of 50 mg/Kgx5, I.P route for 5 days in golden hamsters (*Mesocricetus auretus*) infected with MHOM/IN/80/Dd_8 strain of *L. donovani*. Analog **186** showed lowest IC_{50} of 0.89 µg/mL with comparable 50% cytotoxic concentration (CC_{50}) value of 36.24 µg/mL and had the maximum selectivity index of value 40.71, which were several folds better than Pentamidine and Sodium Stilbogluconate.



185 R_1=OCH_3, R_2=  , **186** R_1=H, R_2=  (IC_{50}=0.89 µg/mL)

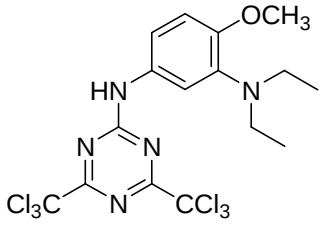
Gupta et al. (2010) prepared heterocyclic fused 1,3,5-triazine analogs and evaluated their *in vitro* antileishmanial potency towards *Leishmania donovani*. Among all the synthesized analogs, analog **187** was found to be the most active analog with an IC_{50} of 4.01 µM and a MIC of 20.54 µM. This analog was also found to be least toxic with a CC_{50} of 227.04 µM and thus made it to 20- & 10-fold more selective than Pentamidine and Sodium stibogluconate, respectively, with a selectivity index of 56.57.



187 (IC_{50}=4.01 µM and MIC=20.54 µM)

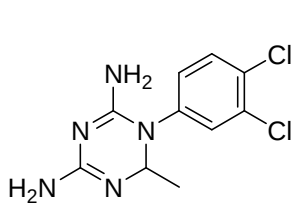
Antimalarial activity

Werbel et al. (1987) synthesized s-triazine analogs as antimalarial agents. Analog **188** showed good antimalarial potency.

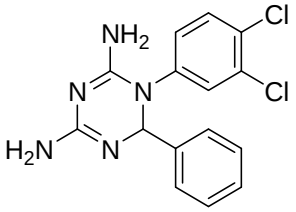


188

Vilaivan et al. (2003) prepared 4,6-diamino-1,2-dihydro-1,3,5-triazines and evaluated against A16V+S108T mutant dihydrofolate reductase of *Plasmodium falciparum*. Among the all tested analogs, analogs **189** and **190** were most potent inhibitors. These analogs showed approx similar activty as compare to Cycloguanil towards wild-type DHFR.

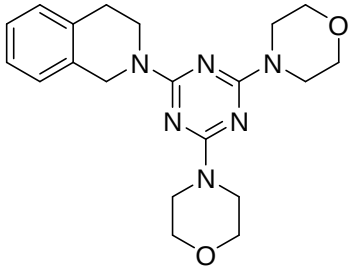


189

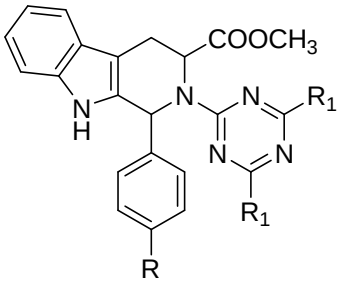


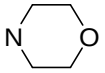
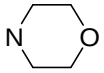
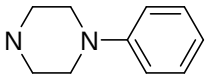
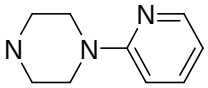
190

Kumar et al. (2006) synthesized substituted triazino tetrahydroisoquinoline analogs and β-carbolines as novel antileishmanial agents. Analogs **191** and **192** showed 55.6% and 53.3% *in vivo* inhibition, respectively, towards *L. donovani* at dose of 50 mg kg^{-1} for 5 days. Among synthesized analogs, analogs **193-195** showed 78.0%, 78.6% and 68.0% *in vivo* inhibition against *L. donovani* at a dose of 50mg kg^{-1} × 5 days, respectively. SAR study of β-carboline analogs revealed that p-tolyl group at C-1 is crucial in cis isomers for antileishmanial activity.

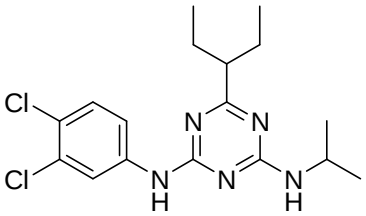


191



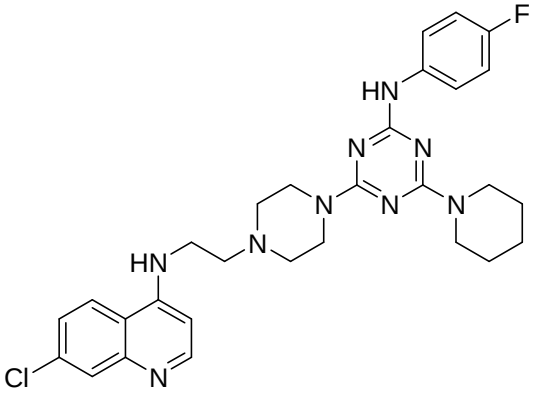
192 Isomer =(±) cis, R=Cl, R_1=  , **193** Isomer =(±) cis, R=CH_3, R_1=  , **194** Isomer =(±) cis, R=CH_3, R_1=  and **195** Isomer =(±) trans, R=CH_3, R_1= 

Guan et al. (2007) prepared s-triazine as potential malaria prophylactic and radical cure agents. Analog **196** also showed moderate causal prophylactic activity in *P. yoelii* sporozoite-challenged mouse test.

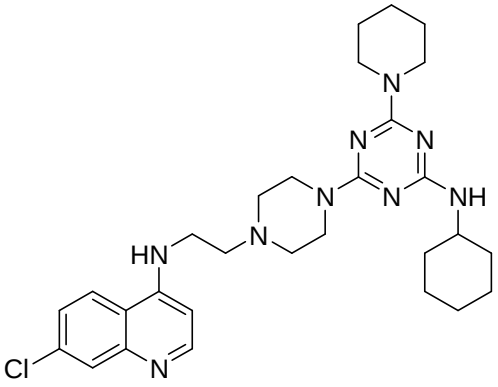


196

Kumar et al. (2008) synthesized 4-aminoquinoline triazine analogs and screened their antimalarial activity against chloroquine (CQ) sensitive 3D7 strain of *P. falciparum*. Analogs **197** and **198** showed good antimalarial activity *in vivo* against *P. yoelii* by ip route at a dose of 50 mg/kg/day and showed more than 99% suppression on day 4 and on day 6 post treatment. 4-Aminoquinoline triazine analogs may lead to development of the more potent molecules. Basic nature of side chain of 4-aminoquinoline was crucial for accumulation of drug within acidic food vacuole of parasite along pH gradient.

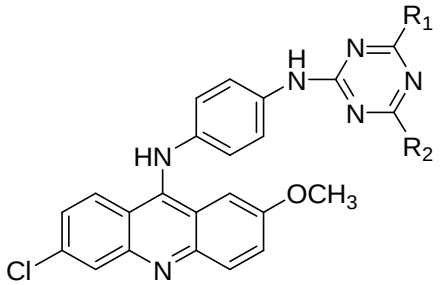


197



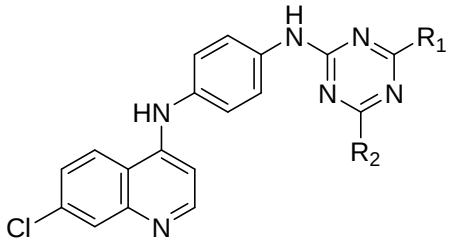
198

Kumar et al. (2009) prepared 9-anilinoacridine triazines as antimalarial agents. Analogs **199-203** exhibited good *in vitro* antimalarial activity with high selectivity index. Analogs **201** (IC_{50}=4.21 nM) and **203** (IC_{50}=4.27 nM) revealed two times higher potency than chloroquine (IC_{50}=8.15 nM). Analogs **199** and **204** showed 96.59% and 98.73% suppression, respectively, towards N-67 strain of *Plasmodium yoelii* in swiss mice at oral dose 100 mg/kg for four days.



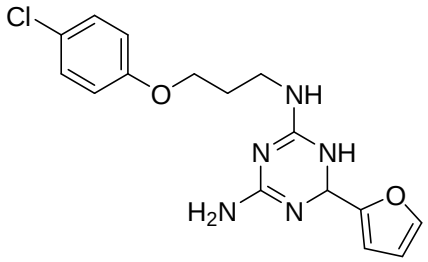
199 R_1=Aniline, R_2=4-(2-Aminoethyl)morpholine, **200** R_1=Aniline, R_2=N,N-Dimethylethylenediamine**, 201** R_1=Aniline, R_2=N,N-Dimethylpropylenediamine (IC_{50} = 4.21 nM)**, 202** R_1=Aniline, R_2=2-Amino-1-ethanol, **203** R_1=Aniline, R_2=Hydrazine (IC_{50} = 4.27 nM), **204** R_1=p-fluoro-aniline, R_2=4-(2-Aminoethyl)morpholine

Kumar et al. (2011) prepared s-triazine derivatives as antimalarial agents. Analogs **205-209** exhibited superior antimalarial potency as compared to Chloroquine against chloroquine-sensitive 3D7 strain of *Plasmodium falciparum*. Analogs **210** and **211** were found to be orally active at a dose of 100 mg/kg ×4 days against chloroquine-resistant strain of *P. yoelii*. Efficacy of orally active analogs **210** and **211** was significant, considering hybrid nature of analogs able to overcome CQ-resistance.

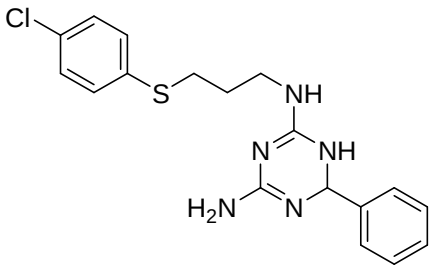


205 R_1=anilino, R_2=*N*-methyl piperazino, **206** R_1=anilino, R_2=*N*-ethyl piperazino, **207** R_1=anilino, R_2=4(3-aminopropyl)morpholino, **208** R_1=p-toluidino, R_2=4(3-aminopropyl)morpholino, **209** R_1=p-toluidino, R_2=methylamino, **210** R_1=piperidino, R_2=*N*-ethyl piperazino, **211** R_1= piperidino, R_2=4(3-aminopropyl)morpholino

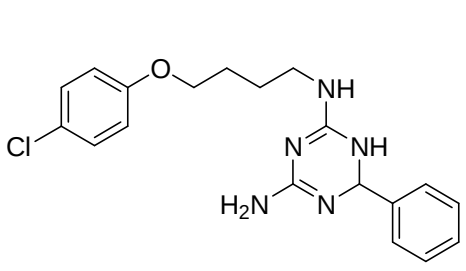
Gravestock et al. (2011) prepared 1,3,5-triazines as antimalarial agents. Analogs **212-215** were more potent than Cycloguanil. Analog **212** (IC_{50}=0.99 µM) was approximately 5-fold more active than Cycloguanil.



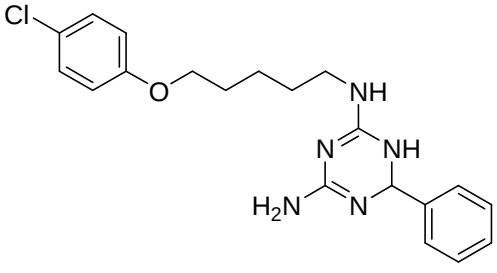
212 (IC_{50}=0.99 µM)



213

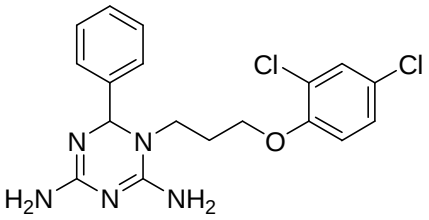


214



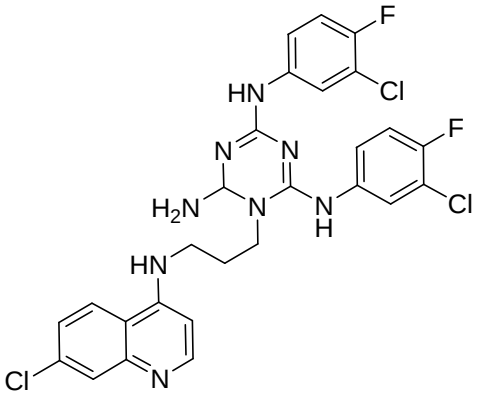
215

Lourens et al. (2016) prepared s-triazine derivatives and also screened their antiplasmodial activity. Analog **216** was the most potrnt analog with IC_{50}=2.66nM. In biochemical enzyme assay, analog inhibit parasitic DHFR.



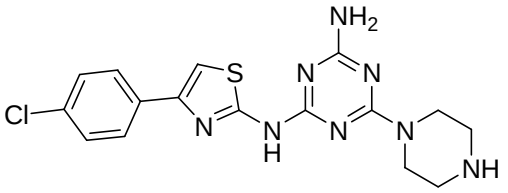
216

Bhat et al. (2016) prepared s-triazine derivatives and also screened their antimalarial activity. Among screened analogs, analog **217** was found to be most active against Chloroquine sensitive strain and good *in vitro* antimalarial activity incomparison to Chloroquine.

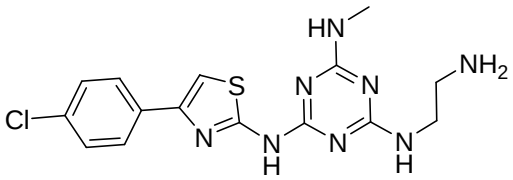


217

Kalita et al. (2016) prepared s-triazine derivatives and also screened their antimalarial activity. Analogs **218** and **219** exhibited good antimalarial activity against *Plasmodium falciparum* with IC_{50} value 26.97 and 32.5µg/mL, respectively.



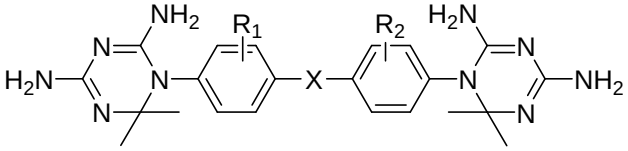
218 (IC_{50}=26.97µg/mL)



219 (IC_{50}=32.5µg/mL)

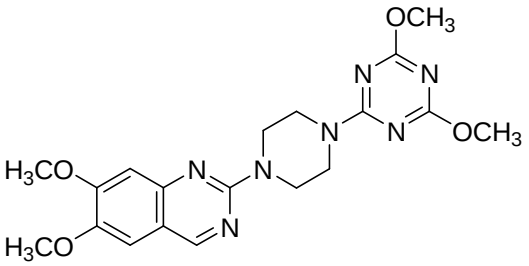
Antitrypanosomal activity

Turner et al. (1985) prepared s-triazines and evaluated their antitrypanosomal potency. Analog **220** and **221** showed good antitrypanosomal activity.



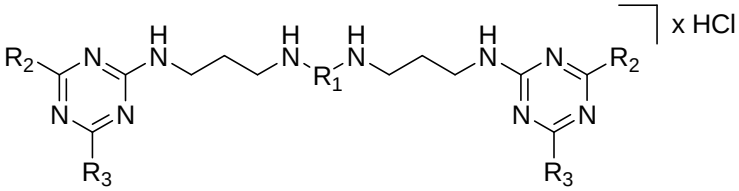
220 X=OCH_2O, R_1=H, R_2=H, **221** X=N=N, R_1=H, R_2=H

Campbell et al. (1987) prepared s-triazines and also screened for α_1-adrenoceptor affinity and antihypertensive activities. Analog **222** showed potent activity. Like Prazosin, analog **222** proved to be a potent, competitive antagonist of α_1-mediated vasoconstrictor action of Norepinephrine.

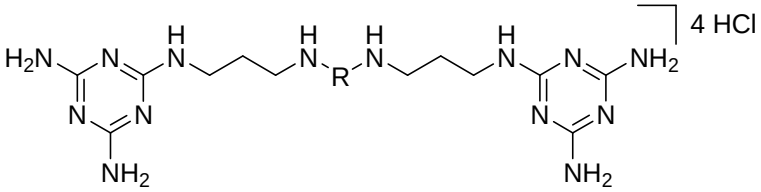


222

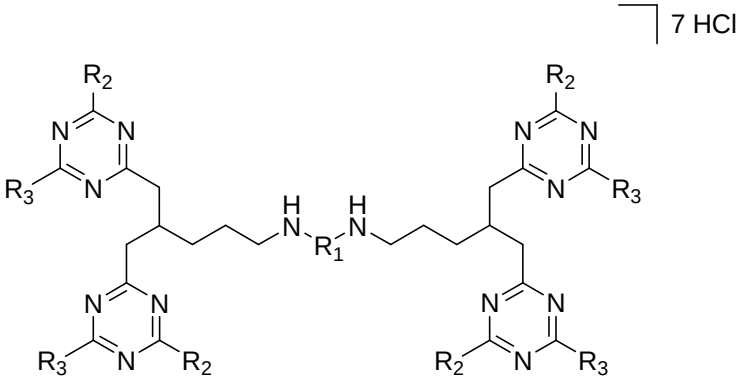
Klenke et al. (2001) synthesized s-triazine substituted polyamine analogs attached to a variety of melamine analogs as potential antitrypanosomal agents. Analogs **223-225** showed 10-fold increase in antitrypanosomal activity. Analog **226** showed 80-fold increase in activity as compared with **231**. Methylated analogs **227-230** showed 2-20-fold higher antitrypanosomal activity as compared to analog **232**. Tetratriazine substituted polyamine **233** showed an excellent toxicity profile with high activity against *Trypanosoma brucei rhodesiense* (IC_{50}=0.27 µM) and *Trypanosoma brucei brucei* (IC_{50}=0.10 µM) and a low cytotoxicity against rat L-6 cells (MIC=177 μM).



223 R_1=$(CH_2)_9$, R_2=NH_2, R_3=NHMe, X=4, **224** R_1=$(CH_2)_9$, R_2=NH_2, R_3=NMe_2, X=5, **225** R_1=$(CH_2)_9$, R_2=NHMe, R_3=NHMe, X=4, **226** R_1=$(CH_2)_9$, R_2=NMe_2, R_3=NMe_2, X=5, **227** R_1=$(CH_2)_{12}$, R_2=NH_2, R_3=NHMe, X=5, **228** R_1=$(CH_2)_{12}$, R_2=NH_2, R_3=NMe_2, X=5, **229** R_1=$(CH_2)_{12}$, R_2=NHMe, R_3=NHMe, X=5, **230** R_1=$(CH_2)_{12}$, R_2=NMe_2, R_3=NMe_2, X=5

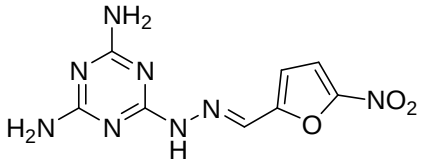


231 R=-$(CH_2)_9$-, **232** R=-$(CH_2)_{12}$-



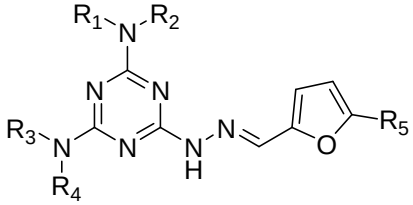
233 R=$(CH_2)_9$, R_1=NHMe, R_2=NHMe (IC_{50}=0.27 µM against *T. brucei rhodesiense* and IC_{50}=0.10 µM against *T. brucei brucei*)

Stewart et al. (2004) synthesized s-triazine derivatives as trypanocidal agents. Analog **234** showed potent acticity against *T. brucei* and against *T. brucei rhodesiense*.



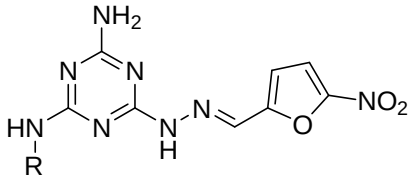
234 (IC_{50}=0.23 µM against *T. brucei* and IC_{50}=0.025 µM against *T. brucei rhodesiense*)

Baliani et al. (2005) synthesized a series of melamine-based nitroheterocycles as potential antitrypanosomal agents. Analogs **235** and **236** were able to cure mice infected with *T. brucei brucei* at a dose of 20 mg/kg for 4 days.



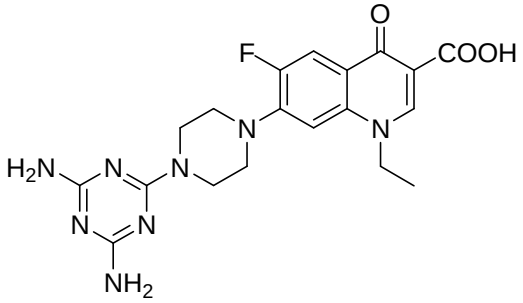
235 R_1=R_2=R_3=R_4=H, R_5=NO_2, **236** R_1=R_2=R_3=H, R_4=CH_3, R_5=NO_2

Baliani et al. (2009) synthesized some new melamine analogs as trypanocidal agents. Analogs **237** and **238** showed potent antitrypanosomal activity. Results revealed that replacement of nitro group by another group, fails to yield analogs with substantial trypanocidal activity, indicating that nitro group is necessary for activity.



237 R= *i*Pr and **238** R=Bu

Chollet et al. (2009) synthesized fluoroquinolones, difluoromethylornithine and artesunate substituted melamina analogs as antitrypanosomal activity. Analog **239** was eight times more active than Norfloxacin (IC_{50}=5.2 µM). Analogs **240** and **241** were 4-5 times more active than Artesunate.



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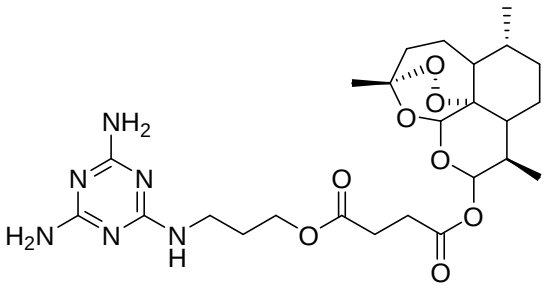

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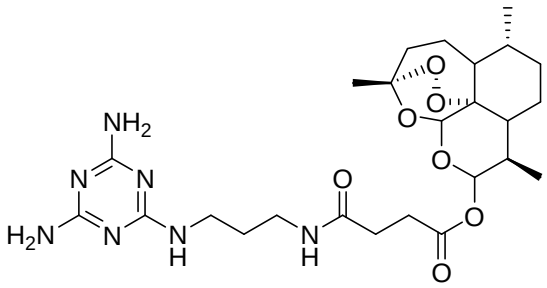
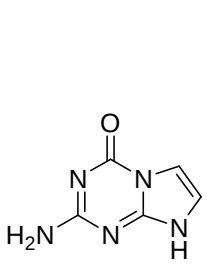


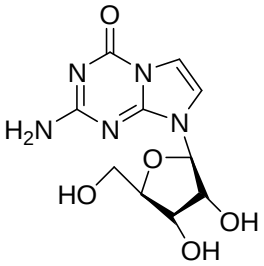
241

Antiviral activity

Kim et al. (1978) synthesized s-triazine analogs and evaluated their antiviral activity. Analogs **242** and **243** showed approximately equal and moderate antiviral activity against rhino viruses as compare to Ribavirin, respectively.

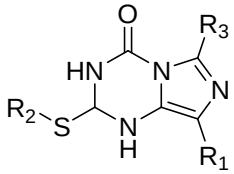


242



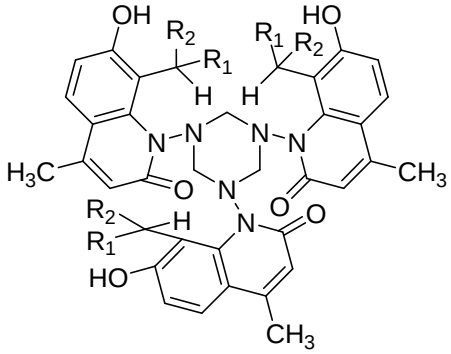
243

Golankiewicz et al. (1995) prepared benzyl-substituted imidazo[1,5-*a*]-1,3,5-triazine analogs and evaluated their antiviral activity against ortho- and paramyxo viruses. Analogs **244** and **245** showed inhibition against *influenza A* virus at a concentration of 4.1 and 5.3 µM, respectively. Analog **246** and **247** revealed inhibition against respiratory syncyntial virus at a concentration of 21.9 and 15.7 µM, respectively.



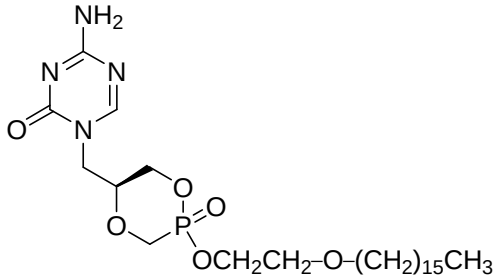
244 R_1=$CH_2C_6H_4$-4-CH_3, R_2=$CH_2C_6H_4$-4-CH_3, R_3=H, **245** R_1=$(CH_2)_5OCH_2C_6H_5$, R_2=$CH_2C_6H_4$-4-CH_3, R_3=H, **246** R_1=CH_3, R_2=$CH_2C_6H_5$, R_3=CH_3, **247** R_1=CH_3, R_2=$CH_2C_6H_4$-4-CH_3, R_3=CH_3

Pandey et al. (2004) prepared a series of s-triazine analogs and evaluated for their antiviral activity against *Japanese encephalitis virus* and *Herpes simplex virus*-1 on vero cells. Analog **248** showed 60% activity towards *Japanese encephalitis virus* and 70% towards *Herpes simplex virus*-1. Analog **248** and **249** also showed antihypertensive activity. Results revealed that even a slight variation in molecular configuration may cause a deep effect on antihypertensive activity.



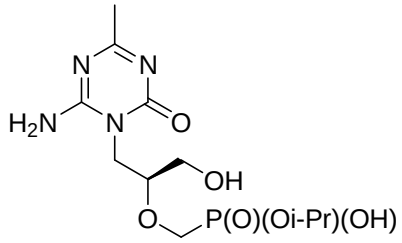
248 R_1=H, R_2=Phthal-amido, **249** R_1=*o*-OH-C_6H_4, R_2=Salicyl-amido

Krecmerova et al. (2007) prepared ester prodrugs of cyclic 1-(*S*)-[3-hydroxy-2-(phosphonomethoxy)propyl]-5-azacytosine as antiviral agents. Analog **250** showed potent activity.



250

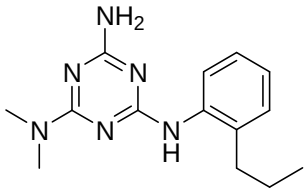
Krecmerova et al. (2010) prepared some s-triazine analogs as antiviral agents. Analog **251** showed anti-RNA-viral activity against *Sindbis virus* at 20 µg/mL.



251

Anticancer activity

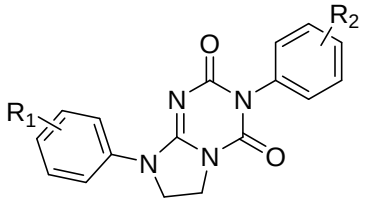
Koh et al. (2013) synthesized Metformin derivative and screened antiproliferative and antiinvasive activities of triple-negative breast cancer cells. Analog **252** displayed stronger antiproliferative and antinvasive activities than Metformin against Hs578T triple-negative breast carcinoma cells. Analog **253** showed about five fold stronger *in vivo* antitumor efficacy than Metformin, while this analog exerted approximately 100 fold more potent *in vitro* inhibitory action on proliferation and invasion of breast cancer cells.



252 (IC_{50}=0.28 mM against Hs578T and MDA-MB-231 cells)

Antinociceptive activity

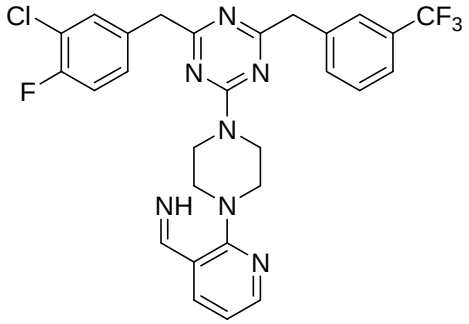
Matosiuk et al. (2002) prepared s-triazines. Analogs **253** and **254** showed good depressive action on the central nervous system and antinociceptive activity in behavioural tests.

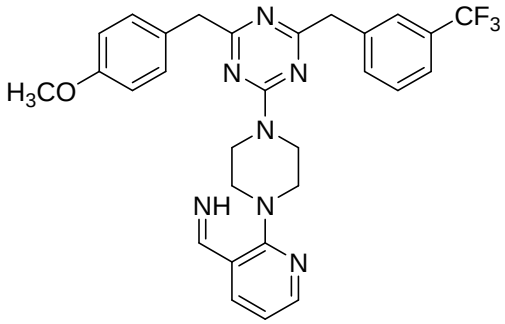


253 R_1=H, R_2=4-Cl, **254** R_1=H, R_2=3-Cl

Anti-alzheimer activity

Maqbool et al. (2016) synthesized cyanopyridine-triazine hybrids as anti-alzheimer agents. Analogs **255** and **256** revealed significant inhibitory potency on acetylcholinesterase with IC_{50} values 0.059 and 0.080 µM, respectively. Analogs **255** and **256** exhibited highest anti-$Ab_{1–42}$ aggregation potency with IC_{50} values of 10.1 and 10.9 µM, respectively. Cyanopyridine-triazine hybrids can be considered very promising lead analogs for treatment of Alzheimer's disease.

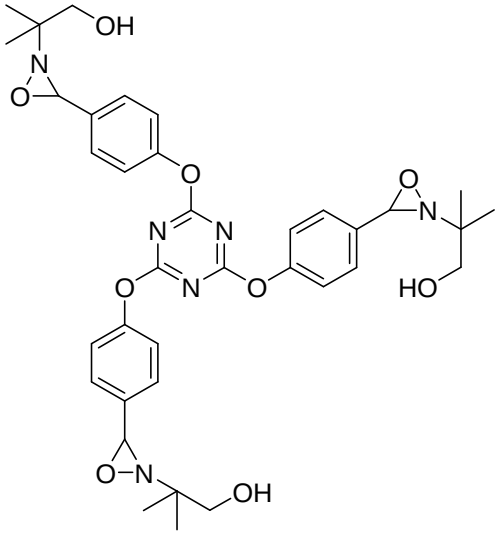




255 **256**

Adenosine receptor antagonistic activity

Peng et al. (2002) prepared triazine analogs. Trisoxaziridine **257** caused 50% reduction of number of *P. carinii* tropozoites as compare to Trimethoprim-Sulfamethoxazole (TMP-SMX). Hexaoxaziridine showed comparable activity to TMP-SMX at 1 µg/mL. Activity of Trisnitronyl nitroxide **258** against *P. carinii* at a concentration of of 1 µg/mL was comparable to that of TMP-SMX.



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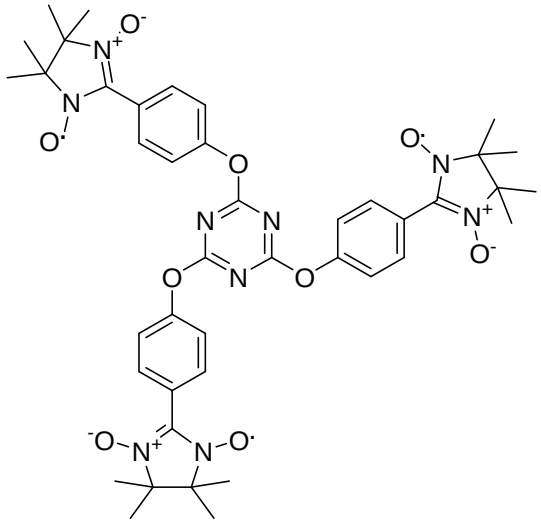
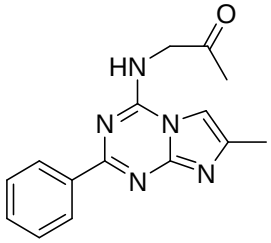


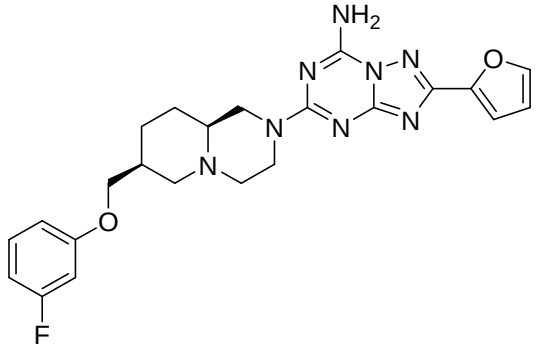
258

Novellino et al. (2002) synthesized 1,3,5-triazines as novel A_1 adenosine receptor antagonists. Analog **259** exhibited the best combination of affinity at A_1AR (K_i =12 nM) and selectivity over A_{2A}AR and A_3AR subtypes (K_is > 10000 nM).



259

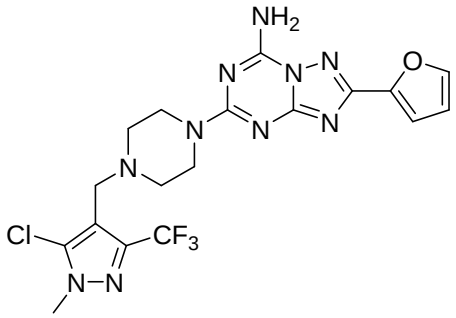
Peng et al. (2004) prepared a series of bicyclic piperazine analogs of triazolotriazine as potent and selective adenosine A_{2A} receptor antagonists. The most potent and selective A_{2a} antagonist **260** had a K_i value of 0.2 nM and was 16500-fold selective with respect to A_1 receptor.



260

Vu et al. (2004) synthesized s-triazine analogs as adenosine A_{2a} receptor antagonists. Analog **261** was more active than analog **262**. Selectivity level of A_{2b} receptor was quite significant because lead analog

263 (ZM-241385, highly potent and selective adenosine A_{2a} receptor antagonist) displayed little selectivity toward this receptor (A_{2b} *K*i =30 nM).



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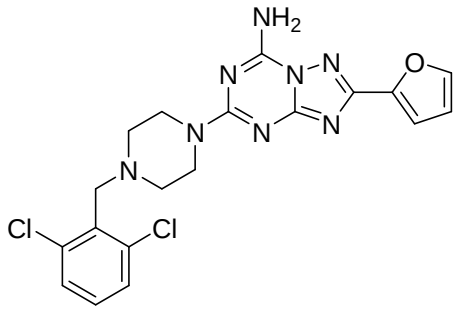

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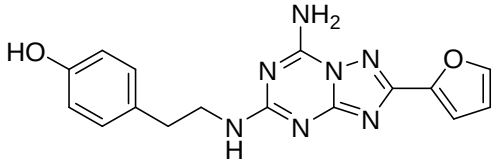
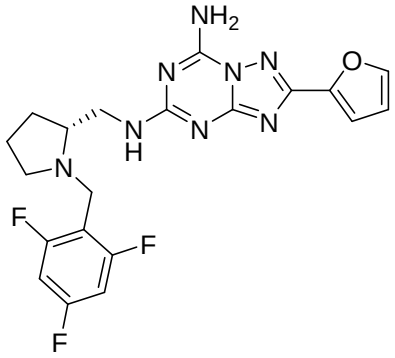


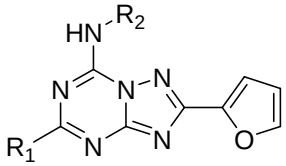
263

Vu et al. (2005) prapared 1,3,5-triazine analogs as adenosine A_{2a} receptor antagonists. Potency and selectivity level of analog **264** were comparable to analog **263**, one of the most potent and selective adenosine A_{2a} antagonist.



264

Pastorin et al. (2010) prepared s-triazines as adenosine receptor antagonists. Addition of arylacetyl or arylcarbamoyl groups at N-7 position on pyrazolo-triazolopyrimidine nucleus were increased affinity at hA_{2B} and hA_3 ARs, respectively. Analogs **265** and **266** displayed significant affinity at rat A_{2A} AR (range 18.3-96.5 nM). Analog **267** showed promising activity in adenylyl cyclase assays at A_{2B} AR, with an EC_{50} ranging from 3.4 to 8.8 µM.



265 R_1=OC_6H_5, R_2=H, **266** R_1=SCH_3, R=H, **267** R_1=OC_6H_5, R_2=$CONHC_6H_5$

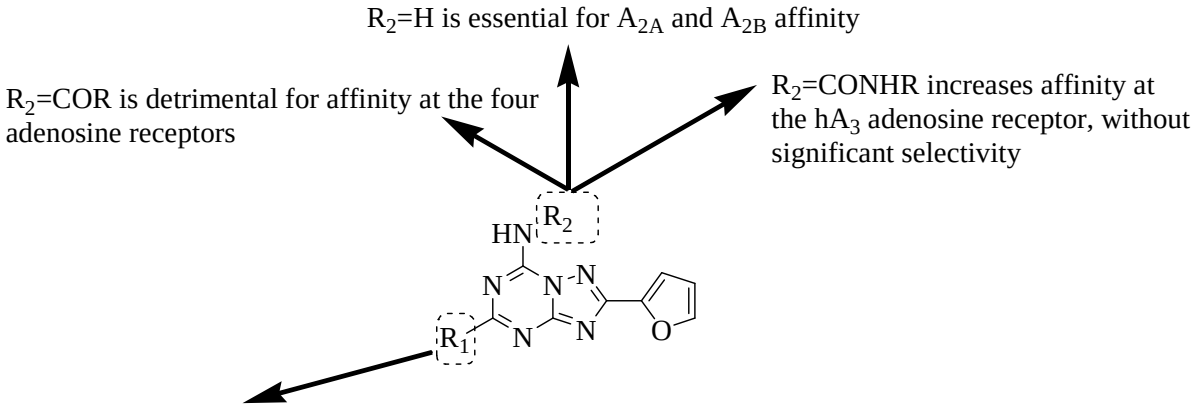
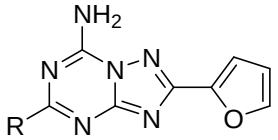
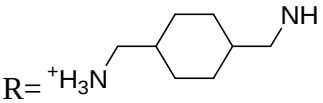
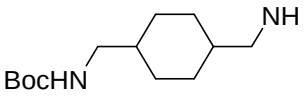


Fig.-2: Summary of the most relevant SAR features of the novel triazolotriazine analogs

Federico et al. (2011) prepared a new series of 1,2,4-triazolo[1,5-a]-1,3,5-triazine as human A_{2A} adenosine receptor antagonists with improved water solubility. Analogs **268** and **269** were more potent at hA_{2A} AR than corresponding analog **270**. Analog **268** displayed an affinity at hA_{2A} AR of 11.5 nM and good selectivity versus A_1, was the most potent analog of this series. Analog **268** (K_i=11.5 nM) and analog **269** (K_i=16.9 nM) were readily water-soluble upto 10 mM.



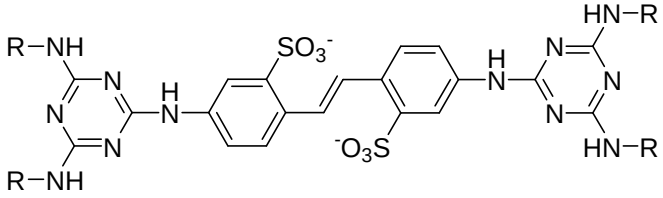
268 R=NH-$(CH_2CH_2O)_2$-$(CH_2)_2NH_3^+$, **269** R=  ,



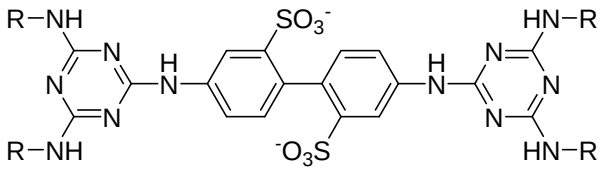
270 R= BocHN

Antiamoebic activity

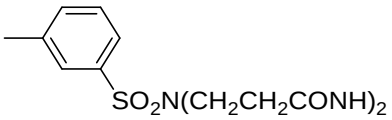
Ding et al. (1998) prepared s-triazine analogs based on stilbene **271** and more active biphenyl analog **272** and screened their antiviral activity against respiratory syncytial virus. Analog **272** displayed good antiviral potency towards respiratory syncytial virus in cotton rats. Results revealed that these inhibitors act by binding to F-protein and thus block viral fusion and infectivity.



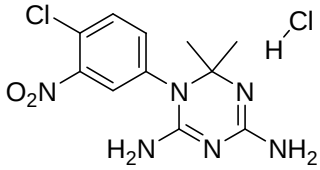
271



272 (IC_{50}=0.05 μM)

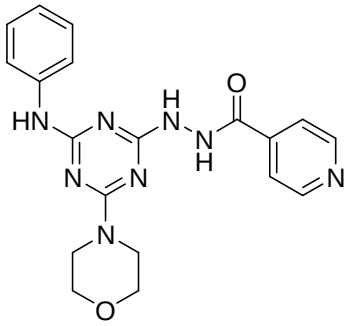


Lee et al. (1999) synthesized dihydrophenyl triazine analogs as dihydrofolate reductase inhibitors. Analog **273** was the most active inhibitor with an IC_{50} value of 0.006 µM and a K_i value of 2×10^{-4} µM.



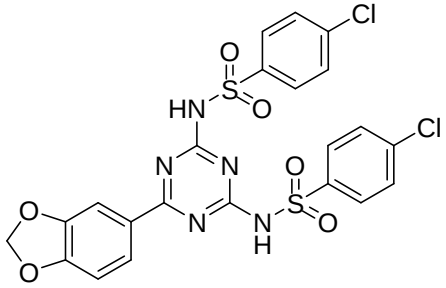
273 (IC_{50}=0.006 µM)

Sunduru et al. (2010) synthesized s-triazines and screened their *in vitro* antitubercular activity against *Mycobacterium tuberculosis* H37Rv. Screening result showed that analog **274** was the most active analog. Screening results revealed that incorporation of antitubercular drug isonicotinohydrazide increased potency of 1,3,5- triazines.

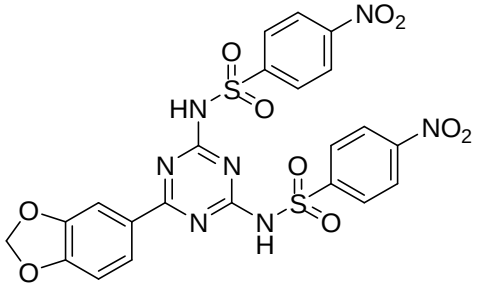


274

Wani et al. (2012) prepared 1,3,5-triazine analogs and also evaluated their antiamoebic potency. Analogs **275** and **276** showed stronger antiamoebic activity than Metronidazole. Replacement of tetrazole by triazine ring showed increase in antiamoebic activity. Some electron withdrawing groups at position-4 of phenyl ring of sulfonamide fragment of triazine ring incorporated control antiamoebic therapy.



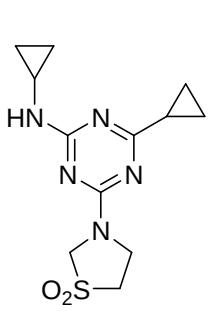
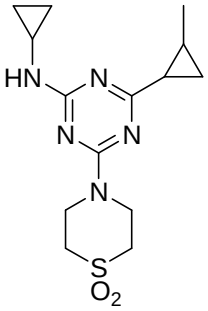
275 (IC_{50} = 1.05 µM)



276 (IC_{50}=1.02µM)

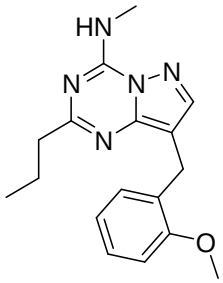
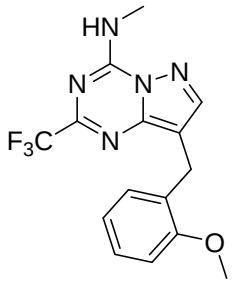
4-Phosphodiesterase inhibitory activity

Leroux et al. (1999) prepared 1,3,5-triazines and screened for their tracheal smooth muscle relaxant and type 4 phosphodiesterase inhibitory properties. Analogs **277** and **278** are more selective inhibitors of PDE-4.

277 **278**

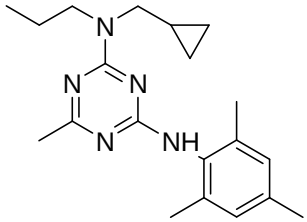
Raboisson et al. (2008) synthesized pyrazolo[1,5-a]-1,3,5-triazine analogs as cyclic nucleotide phosphodiesterase type 4 inhibitors. Among these analogs, analogs **279** and **280** emerged as the most potent PDE-4 inhibitors, which was 100 fold more potent than Rolipram (1.2 µM) and 2.5 fold when compared to Ariflo (30 µM). Analogs **279** and **280** strongly inhibit cytokine production in LPS-induced human blood mononuclear cell preparations.

279 (IC_{50}=11 nM) **280** (IC_{50}=13 nM)

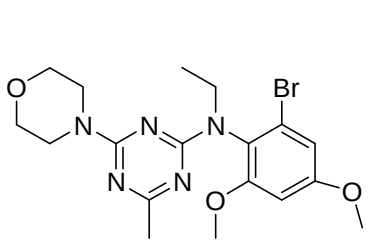
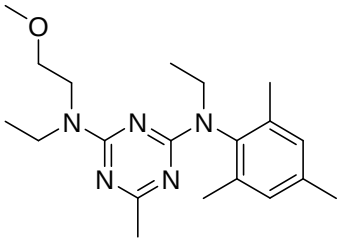
Non-Peptide Corticotropin-Releasing Hormone antagonistic acitivity

Whitten et al. (1996) synthesized some s-triazine analogs as corticotropin-releasing factor1 receptor antagonists. Analog **281** showed potent activity.



281

Arvanitis et al. (1999) synthesized s-triazine analogs as Non-peptide corticotropin-releasing hormone antagonists. Analog **282** and **283** showed good Non-Peptide Corticotropin-Releasing Hormone inhibition activity. SAR of synthesized analogs showed that bromine, methyl and trifluoromethyl groups at 2-position of phenyl ring are compatible with good binding affinity. Isopropyl, dimethylamino, cyano, methoxy, trifluoromethoxy and acetyl substituents at 4-position of phenyl ring contribute to good binding affinity. Hydrogen or a methoxy group at 6-position of phenyl ring appears to be optimal.

282 **283**

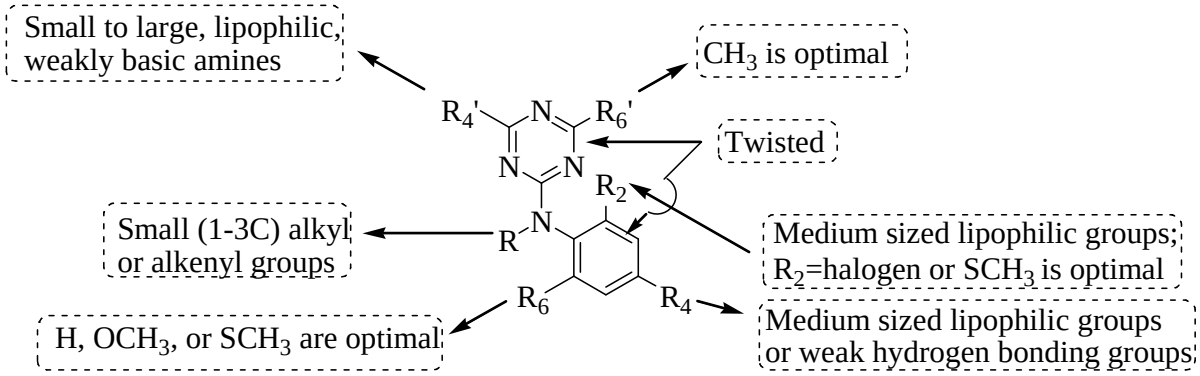
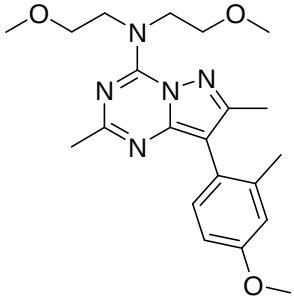


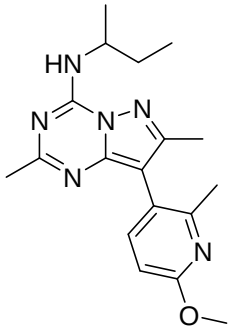
Fig.-3: Summary of SAR of 2-anilinopyrimidines and -triazines as Non-Peptide Corticotropin-Releasing Hormone antagonists

Gilligan et al. (2009a) prepared s-triazine analogs as selective and centrally active Corticotropin-Releasing Factor Receptor-1 (CRF-1) antagonists. Analog **284** showed potent, selective CRF1 antagonist (activity $hCRF_1$ IC_{50} = 4.7 ± 2.0 nM) with less affinity for CRF-binding protein and biogenic amine receptors. Analog **284** was orally active in defensive withdrawal (situational anxiety) and elevated plus maze model in rat. Analog **284** (BMS 561388) was advanced to clinical studies in humans on basis of its favorable preclinical profile.



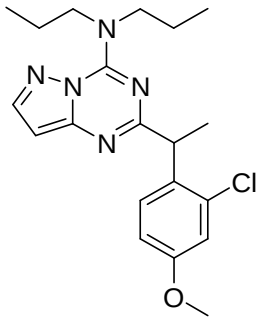
284 (IC_{50}=4.7 ± 2.0 nM)

Gilligan et al. (2009b) prepared 8-(pyrid-3-yl)pyrazolo[1,5-*a*]-1,3,5-triazine analogs as potent, orally bioavailable CRF-1 antagonists. Analog **285** (BMS-562086) showed potent, selective CRF-1 antagonist activity ($hCRF_1$ IC_{50}=6.1± 0.6 nM) with less affinity for CRF-binding protein and biogenic amine receptors. This analog was orally active in defensive withdrawal and elevated plus maze models in rats with little action on locomotor or rotorod activity.



285

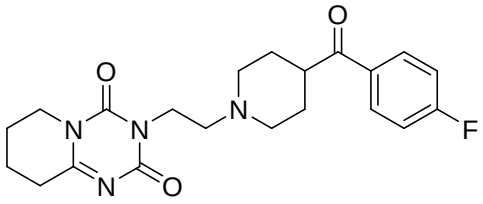
Saito et al. (2011) synthesized pyrazolo[1,5-a][1,3,5]triazines as corticotropin-releasing factor 1 receptor antagonists. Pyrazolotriazine analog **286** showed quite potent activities in receptor affinity and antagonist activity (EC_{50} = 26 nM).



286 (IC_{50}=20 nM)

5-HT$_2$ antagonistic acitivty

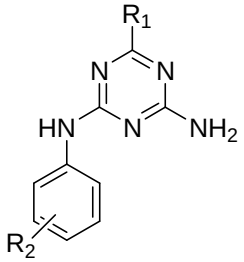
Watanabe et al. (1992) synthesized bicyclic 1,3,5-triazine-2,4(*3H*)-dione analogs and screened their 5-HT_2 antagonistic potency. Analog **287** showed good *in-vitro* 5-HT_2 antagonist potency and *in vivo* potency comparable to Ketanserin. These results showed that 6,7,8,9-tetrahydro-2*H*-pyrido-[1,2-*a*]-1,3,5-triazine-2,4(3*H*)-dione ring systems is useful component of 5-HTz antagonists. The central 5-HT_2 antagonist activity of analog **287** acceptables for development of analog for treatment of myocardial ischemia associated with unstable angina.



287

Antidiuretic acitivity

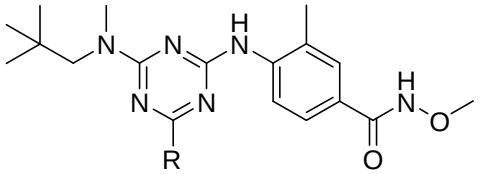
Shah et al. (1968) synthesized 2-amino-4-arylamino-6-mercapto-s-triazines and related analogs as antidiuretic agents. Analog **288** showed very good diuretic activity, which was better than Hydrochlorothiazide. Analogs **288-296** revealed an activity better than or comparable to Hydrochlorothiazide. Analog **290** was the most active. Analog **297** showed powerful saluretic action.



288 R_1=H, R_2=3-F, R_2=H, **289** R_1=H, R_2=3-Cl, **290** R_1=H, R_2=4-Cl, **291** R_1=SH, R_2=4-Cl, **292** R_1=SH, R_2=2-CH_3, **293** R_1=$SCH_2CH{=}CH_2$, R_2=2-CH_3, **294** R_1=SH, R_2=3-CH_3, **295** R_1=OH, R_2=3-CH_3, **296** R_1=H, R_2=4-CH_3, **297** R_1=$SCH_2CH{=}CH_2$

p38 MAP Kinase inhibitor activity

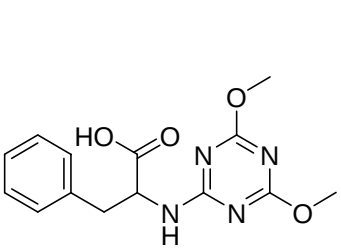
Leftheris et al. (2004) synthesized triaminotriazine aniline amides as inhibitors of p38 MAP Kinase. Analog **298** displayed *in vitro* and *in vivo* oral activity in animal models of acute and chronic inflammatory disease. Analog **298** represents an attractive starting point for design and synthesis of potent and selective p38 inhibitors with superior pharmacokinetic profiles.



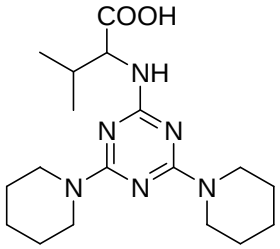
298 R=4-methyl-1,4-diazepan-1-yl

MAO inhibitor activity

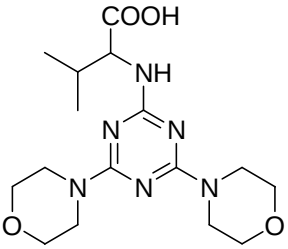
Khattab et al. (2015) synthesized s-triazine amino acid derivatives as MAO inhibitor. Analogs **299**-**301** showed MAO-A inhibition activity comparable to Clorgyline.



299



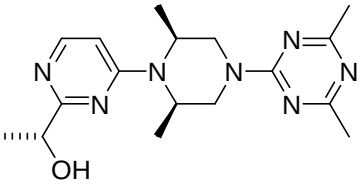
300



301

Sorbitol dehydrogenase inhibitor acitivity

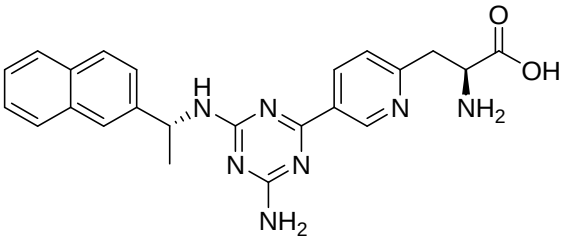
Mylari et al. (2002) synthesized 1-(*R*)-{4-[4-(4,6-dimethyl[1,3,5]triazin-2-yl)- 2*R*,6*S*-dimethylpiperazin-1-yl]pyrimidin-2-yl}ethanol as sorbitol dehydrogenase inhibitor. Analog **302** showed good oral activity (50 µg/kg) in normalizing elevated fructose levels in sciatic nerve of chronically diabetic rats and sustained duration of action (>24 h).



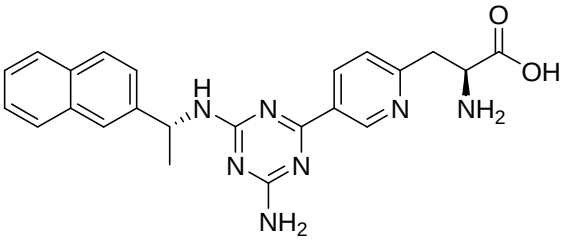
302

Tryptophan hydroxylase inhibitor acitivity

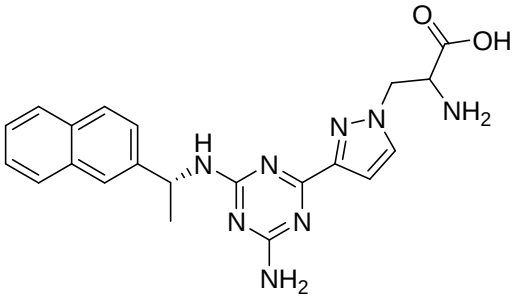
Shi et al. (2008) prepared some s-triazine analogs as tryptophan hydroxylase inhibitors. Analogs **304**-**306** significantly reduced *in vitro* activity against tryptophan hydroxylase-1. Screening datas revealed that 4'-phenylalanine moiety is essential to potency.



303



304



305

SUMMARY

Article contains complete detail of pharmacological properties of s-triazine moiety based analogs and focuses their role in new leads identification and drug discovery and to find possible future directions

in the development of potent and specific analogs of s-triazine-based analogs for many biological targets. 1,3,5-Triazine is a versatile moiety in many pharmacologically active analogs and is present in numerous clinically used drugs such as Altretamine, Hydroxymethylpentamethylmelamine, Triethylenemelamine, Dioxadet, Irsogladine, Cycloguanil, Almitrine etc. Newly synthesized s-triazine analogs showed broad spectrum pharmacological activities such as antibacterial, antifungal, analgesic, anti-HIV, antileishmanial, antitrypanosomal, antimalarial and antiviral activities.

FUTURE DIRIECTIONS

Synthesis of new molecular designed 1,3,5-triazine analogs may give up successful results in medicinal chemistry. Moreover, the rationale design of recently published 1,3,5-triazine analogs may facilitate the active research to derive significant drug candidates with a targeted site of action. Now, many researchers are interested in new synthesis of s-triazine derivetives because low cost and easily availability of s-triazine derivatives. The diverse pharmacological activities observed for different analogs containing s-triazine moiety have been further explored in order to discover other new potential molecules through the synthesis of libraries by combinatorial approaches. This article encourages many researchers to use this moiety for the design of new analogs with increased medicinal properties.

ACKNOWLEDGEMENT

Authors are special thankful to the principal, Devsthali Vidypeeth College of Pharmacy, Lalpur, Rudrapur (U.S. Nagar)-283148, Uttarakhand, India for providing necessary research facilities.

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