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An extensive review on 1,2,3 and 1,2,4-triazines scaffold-valuable lead molecules with potent and diverse pharmacological activities

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ABSTRACT

Triazine is the chemical species of six-membered heterocyclic ring compound with three nitrogens replacing carbon-hydrogen units in the benzene ring structure. The names of the three isomers indicate which of the carbon-hydrogen units on the benzene ring position of the molecule have been replaced by nitrogens, called 1,2,3-triazine, 1,2,4-triazine, and 1,3,5-triazine respectively. Symmetrical 1, 3, 5-triazine is the common. Triazines are prepared from cyanic acid amide by trimerization (1, 3, 5-triazine). Pyridine is the aromatic nitrogen heterocyclic compound having only one nitrogen, and diazines are with 2 nitrogen atoms, triazine having three nitrogen and tetrazines are with 4 nitrogen atoms on the benzene ring system. Triazines are weak base. Triazines have much weaker resonance energy than benzene, so nucleophilic substitution is preferred than electrophilic substitution. Heterocyclic bearing a symmetrical s-triazines or 1, 3, 5-triazines moieties, represent an interesting class of compounds possessing a wide spectrum of biological activities such as anti-cancer, antiviral, fungicidal, insecticidal, bactericidal, herbicidal and antimicrobial, antimalarial agents. They also find applications as dyes, lubricants and analytical reagents.

Key words: Triazines, Heterocyclics, pharmacological activity

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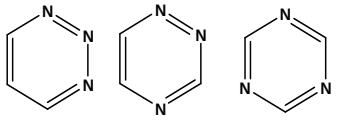
INTRODUCTION

Heterocyclic chemistry is fundamental to biology and medicine. It is not implausible to say that we are living in the age of heterocyclic chemistry. It constitutes a large group of organic molecules exhibiting a wide range of biological activities which is basis of life and society. The majority of pharmaceutical products that mimic natural products with biological activity are heterocyclic in nature.The triazine structure is a heterocyclic ring, analogous to the six-membered benzene ring but with three carbons replaced by nitrogens. The three isomers of triazine are distinguished from each other by the positions of their nitrogen atoms, and are referred to 1,2,3-triazine,1,2,4-triazine and 1,3,5-triazine[1].



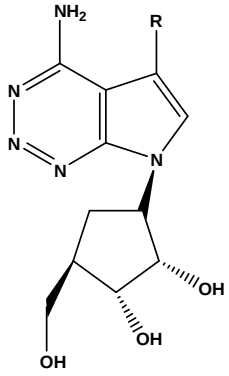
1 2 3

Out of the above three possible triazine nucleus, 1,2,3-triazine is the least explored one, till date. But, clinically 1,2,3-triazine derivatives are more acceptable because of potent efficacy and minimal side effect. 1,2,3-triazine represents a widely used lead structure with multitude of interesting applications in the numerous pharmacological fields, Thus various pharmacological activities have been reported and explored out till date[2-4]**.**

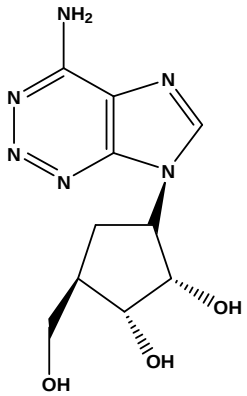
1,2,4-Triazine derivatives have been reported to possess a broad spectrum of biological activities including antifungal, anti-HIV, anticancer, antiinflammatory, analgesic anti hyperte- nsive, cardiotonic, neuroleptic, nootropic, antihistaminergic, tuberculostatic, antiviral, anti-protozoal, estrogen receptor modulators, antimalarial, cyclin-dependent kinase inhibitors, antimicrobial, antiparasitic, activities.[5-8]

1,3,5-Triazines can also be called as symmetric or *s*-triazines. The chemistry of this group of compounds has been studied intensively since past two centuries due to their wide spread applications in the pharmaceutical, textile, plastic and rubber industries and are used as pesticides, dyestuffs, optical bleaches, explosives and surface active agents. In recent times, several studies have been carried out on the antitumor activity of 1,3,5-triazines. [9-10].

Drugs containing 1,2,3-triazine ring have got its origin from natural and synthetic sources as exemplified by Tubercidin (**4**), Toyocamycin (**5**) and Sangivamycin (**6**),which have significant pharmacological activities. Tubercidin inhibits the growth of several strains of bacteria. Tubercidin and its 5-substituted derivatives inhibit both DNA and RNA viruses at the concentrations that inhibit DNA, RNA and protein synthesis in mice and human cell lines. Toyocamycin is a known antineoplastic antibiotic with specific antitumor activity. Sangivamycin is active against L1210 leukemia, P338 leukemia and lewis lung carcinoma and under clinical trials against colon cancer, gall bladder cancer and acute myelogenous leukemia in humans. 2-Aza-adenosine (**7**) exhibits five times greater cytotoxicity than 8-azapurine, against human epidermoid carcinoma cells *in vitro* [11].



4 R= H,
5 R = CN,
6 R = $CONH_2$



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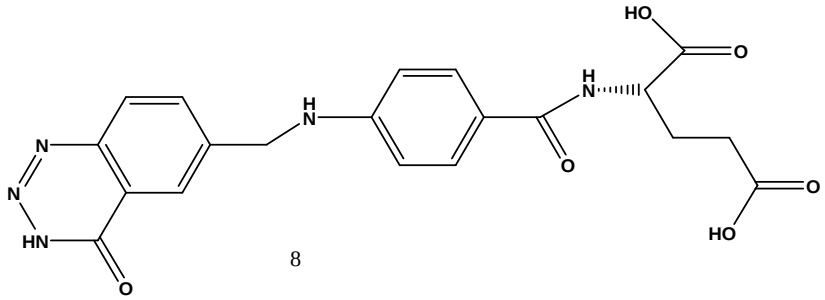
2-Aza-2-desamino-5,8-dideazafolic acid (**8**) is an inhibitor of recombinant mouse thymidylate synthase. Inhibition by compound (**8**) is found to be competitive with 5,10 methylene tetrahydro folate as variable substrate. It is also a substrate for murine folylpolyglutamate synthetase with kinetic characteristics comparable to those of aminopterin. It is also found to inhibit the growth of L1210 cells (IC50 = 0.52 µM) [12]. 1,2,3-Triazines fused with heterocyclic moiety show high reactivity, chemical and biological effects [13].



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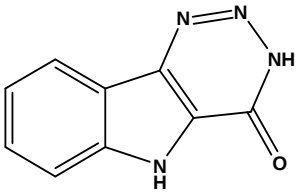
1. Synthetic Analogs of 1,2,3-Triazines, Showing Various Pharmacological Activities

Laura Garuti *et al*. [13] synthesized and evaluated antiproliferative activity of 3-substituted l*H*-indole[3,2-*d*]-1,2,3-triazin-4(3*H*)-ones. They compared antiproliferative activity of the synthesized compounds with daunorubicin against chronic myeloid leukaemia and non-hodgkin lymphoma

human cells *in vitro*. Compound (**9**) showed the most effective antiproliferative activity against human chronic myeloid leukaemia.The lower activity of compound (**9**), with regard to daunorubicin, and the greater selectivity of action, against chronic mieloid leukaemia, might be used in polychemotherapy protocols.



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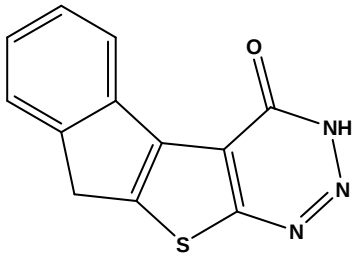
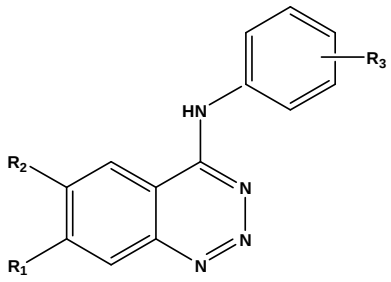
Ali M. M. *et al*. [14] synthesized some new indeno[2,1_*b*] thiophenes, and indeno[1,2:4,5] thieno [2,3-*d*][1,2,3]triazines. The prepared compounds showed antitumor activity, partly by increasing free radicals production and partly by depletion of intracellular catalase, glutathione peroxidase, glutathione reductase, reduced glutathione. Among the synthesized compounds, compound (**10**) was most potent with IC_{50} of 6µg/mL. This compound lead to an increased level of NO with decrease in the level of total protein, RNA and DNA.



10

Jin-Ling Lv *et al*. [15] synthesized a series of substituted 1,2,3-benzotriazines based on the structures of vatalanib succinate (PTK787) and vandetanib (ZD6474). The antiproliferative effects of synthesized compounds were tested on microvascular endothelial cells (MVECs) using the MTT assay.Compounds **11** (bearing 3'-chloro, 4'-fluoro aniline group) **12** (bearing 3', 4'-dichloro aniline group) and **13 (**bearing 4-chloro group were the potent compounds in inhibiting prolife- ration of MVECs with GI50 values of 7.98 µM and 11.02 µM,respectively except compound **13** .



11 R_1=Cl$(CH_2)_3$O,R=CH_3O, R_3=3-Cl,4-F, (GI_{50}=7.98 µM),

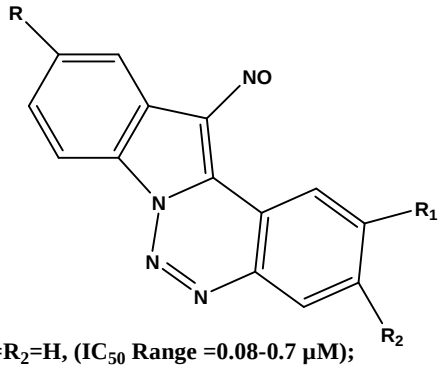
12 R_1=Cl$(CH_2)_3$O,R=CH_3O, R_3=3-4di-Cl (GI_{50}=11.02 µM

13 R_1=Cl$(CH_2)_3$O,R=CH_3O, R_3=4-Cl (GI_{50}= >80 µM

Girolamo Cirrincione *et al*. [16] synthesized some indolo [1,2-*c*]benzo[1,2,3]triazine analogs. Synthesized compounds were evaluated for their *in vitro* antitumor activity against a panel of leukemia-, lymphoma-, carcinoma and neuroblastoma derived cell lines. Some of the synthesized compounds inhibited the proliferation of T and B cell lines at submicromolar concentrations and their activity against solid tumor cell lines was in the micromolar range. Indolobenzotriazine

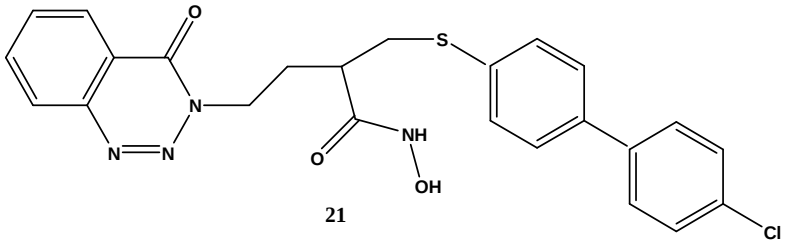
analog **14** showed most potent antitumor activity with IC50 in range of 0.08-0.7 µM. This compound was fully inhibitory to all the resistant cell lines thus suggesting that it neither is subject to the pump mediating the efflux of many antitumor drugs nor interferes with the DNA synthesis. The compounds **14** (IC50 range = 0.3-2.7 µM) and **15** (IC50 range = 1.9-9.5µM) displayed lower antiproliferative activity against cell lines derived from solid tumors than that of Doxorubicin. All

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



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

Thierry Le Diguarher *et al.* [17] prepared 5-substituted 2-bisarylthiocyclopentane carboxylic acids as specific matrix metalloproteinase (MMP) inhibitors. They reported that compound (**21**) is found to be a very potent and specific inhibitor of MMP-2, -3, -9, and -13. However, this compound has only modest bioavailability (<30%), a fact attributed to the presence of the hydroxamate function. Conformational analysis of compound (**21**) modeled in the three-dimensional structure of MMP-2 suggested that the P1 and P1' groups adopt a trans/trans orientation relative to the zinc binding group. Compound (1*R*,2*S*,5*R*)- (**22**) was most active compound against MMP-2, 3, 9 and13 than the other diastereoisomer. The profile is comparable to those for the hydroxamates CGS 27023A and trocade but with better selectivity versus MMP-1. The calculated distances of the sulfur atom and the carbonyl of the triazine moiety are compatible with hydrogen bonding interaction with the amide proton of Ala192/Leu191 and Ala194, respectively. Replacement of the 4-chlorophenyl ring of **22** with the heteroaryl groups 4-pyridyl (**23**), 2-thiazolyl (**24**), 2-benzothiazolyl (**25**), and 4-triazolyl (**26**) increased IC50 values across the board by 1 or 2 orders of magnitude.Replacement of the 4'-chloro of **22** by 4-methylthio (**27**) and 4-cyano (**28**) group showed substantial improvement in potency. In these cases, IC50 values for MMP-2, 3, 9, and13 are shifted into the nanomolar range. Compounds (**22**), (**29**) and (**30**)**,** administered intraperitoneally (i.p.) led to the significant dose-dependent reduction in the number of metastases (>60% at 200 mg) and marked reduction of their size (100% inhibition of the occurrence of metastases with diameter over 1 mm). On the basis of their *in vivo* activities in a mouse metastasis model and their good oral bioavailabilities, compounds (1*R*,2*S*,5*R*)- (**22**) and (**29**) were identified as suitable candidates for the further development.



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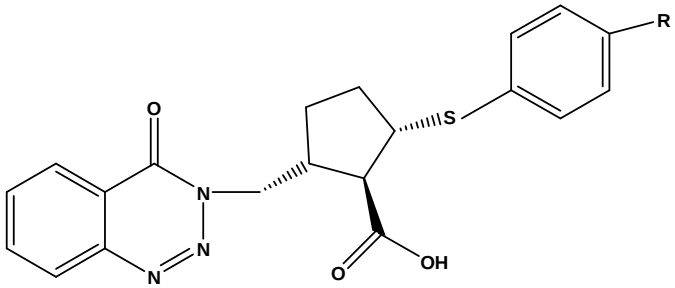
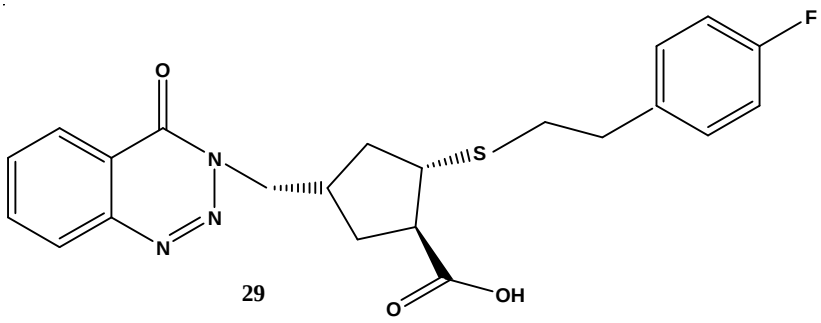


22 R = 4- Chloro phenyl
23 R = 4-Pyridyl
24 R = 2-Thiazolyl
25 R = 2-Benzthiazolyl
26 R = 4-Triazolyl
27 R = 4-Methylthio
28 R = 4-Cyano



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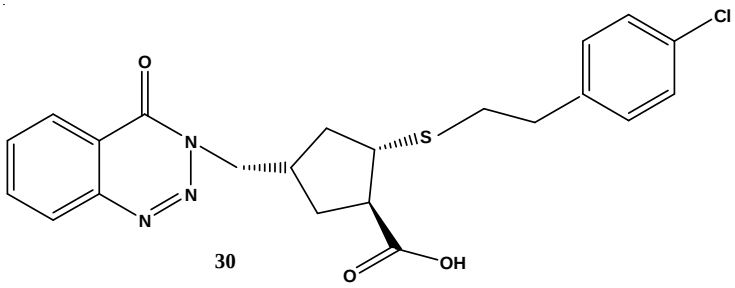
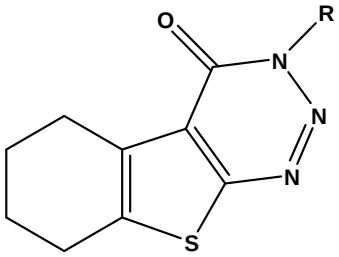


30

Janardhanan Saravanan *et al*. [4] synthesized some 3-substituted amino-4,5-tetramethylene thieno [2,3-*d*][1,2,3]-triazin-4(3*H*)-ones. Synthesized compounds were evaluated for their antimicrobial activity by agar diffusion method using Ampicillin and Miconazole nitrate as standard drugs.

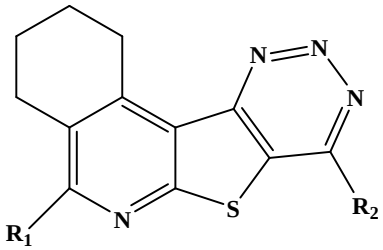
The compounds (**31**-**34**) showed considerably greater antimicrobial activity than the compounds (**35**-**41**).Screening data showed that the compound (**31**) with 4-fluorophenyl substitution exhibited excellent inhibition against tested Gram positive bacteria (MIC=6.75 µg/mL) and Gram negative bacteria (MIC=12.5 µg/mL). Compound (**34**) with 4-chlorophenyl substituent at R on triazin-4-one nucleus, was potent against all types of bacterial (MIC range =12.5-25 µg/mL) and fungal employed (MIC range = 12.5-37.5µg/mL). The MIC study of synthesized compounds confirmed that the potency of the title compounds is based on the substituents attached to the phenyl group. The tested compounds having methyl, ethyl, phenyl, 2-methyl phenyl,3-methyl phenyl, 4-methyl phenyl, 2-

chlorophenyl,3-chlorophenyl and 3-chloro-4-flurophenyl substituent's at the 3-position were less active against all the tested organisms. Antimicrobial results of the synthesized compounds concluded that lipophillic groups like chloro, fluoro substitutions on the phenyl ring play an important role in enhancing the antimicrobial properties of this class of compounds.



31 R = 4-Fluorophenyl, 32 R = 2-Chlorophenyl
33 R = 3-Chlorophenyl,34 R = 4-Chlorophenyl
35 R = H, 36 R = Methyl, 37 R = ethyl,
38 R = Phenyl, 39 R = 2-Methyl phenyl,
40 R = 3-Methyl phenyl, 41 R = 4-Methyl phenyl

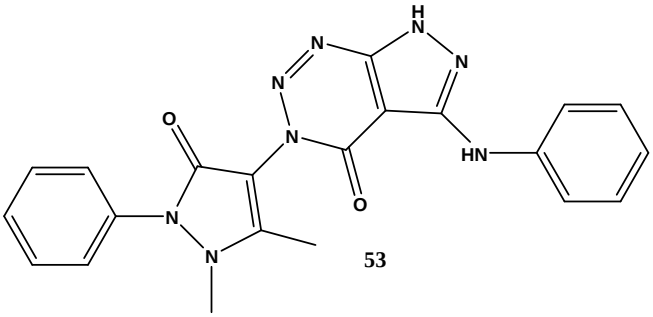
James C. A. Hunt *et al*. [18] synthesized a new series of pyridothieno-1,2,3-triazines and screened them for antifungal activity against *Erysiphe graminis*. Compounds **42** with R1= Morpholino, R2= OC3H7 and **43** with R1= Pyrrolidino, R2= OCH3 groups displayed significant antifungal activity with 94% and 92% inhibition, respectively. Compound **44** exhibited potent antifungal activity (with 100% inhibition).Compounds **45** with R1= Morpholino, R2= OC2H5, **46** with R1=Morpholino, R2= SCH3, **47** with R1= Morpholino, R2= SC2H5 and **48** with R1= Morpholino, R2=MeOCH2CH2O groups also showed potent antifungal activity (with 100% inhibition). Compounds **49** with R1= N(C2H5)2, R2= OCH3, **50** with R1= PhCH2(Me)N, R2= OCH3, **51** with R1= MeOCH2CH2(Me)N, R2= OCH3 and **52** with R1= MeOCH2CH2(Me)N, R2= MeOCH2CH2O groups also showed potent antifungal activity. Compounds **44-52** (with 100% inhibition) showed more antifungal activity as compared standard drug Fenpropimorph with 97% inhibition.They concluded that incorporation of oxygen atoms into the side chains of the pyridothieno-1,2,3-triazines has increased the solubility of the compounds by 10-fold whilst retaining biological activity.



42 R_1 = Morpholino, R_2 = OC_3H_7,
43 R_1 = Pyrrilidino, R_2 = OCH_3,
44 R_1 = Morpholino, R_2 = OCH_3,
45 R_1 = Morpholino, R_2 = OC_2H_5,
46 R_1 = Morpholino, R_2 = SCH_3,
47 R_1 = Morpholino, R_2 = SC_2H_5,
48 R_1 = Morpholino, R_2 = $OCH_2CH_2OCH_3$,
49 R_1 = $N(C_2H_5)_2$, R_2 = OCH_3,
50 R_1 = $PhCH_2(Me)N$, R_2 = OCH_3,
51 R_1 = $MeOCH_2CH_2(Me)N$, R_2 = OCH_3,
52 R_1 = $N(CH_3)CH_2CH_2OCH_3$, R_2 = $OCH_2CH_2OCH_3$

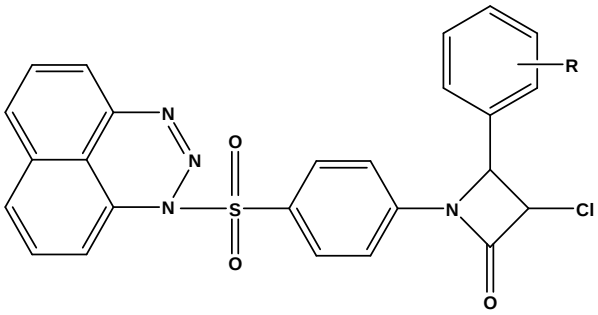
Samir Bondock *et al*. [19] synthesized a series of pyrazolo[3,4-*d*]triazine and screened them for *in vitro* antimicrobial activity against *Bacillus thuringiensis*, *Klebsiella pneumonia*, *Botrytis fabae* and *Fusarium oxysporum* by the agar diffusion method. Compound **53** exhibited significant antifungal activity. It was concluded that

incorporation of antipyrine to the coumarin nucleus at position 3, via a carboxamide linker produces a high antimicrobial activity.



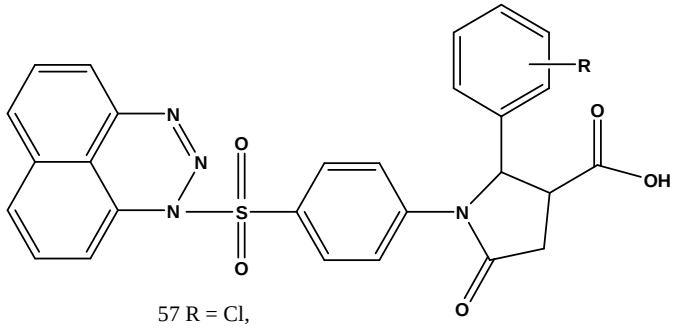
53

Tarun M. Patel *et al*. [20] synthesized some 1-(4-(1*H* naphtho[1,8-de][1,2,3]triazin-1 ylsulfonyl) phenyl)-3-chloro-4-arylazetidin-2-one derivatives. Antibacterial activity of all the compounds was studied against Gram-positive bacteria (*Staphylococcus aureus* and *Bacillus subtilis*) and Gram negative bacteria (*E.coli* and *klebsiella promioe*) at 50µg/Ml by agar cup plate method.Compounds **54**, **55** and **56** bearing chloro, methoxy and hydroxy groups at 4-position showed significant antibacterial activity. Compounds containing hydrogen, methyl and bromo substitutions at 4-position and hydroxy at 2-position were found to be less or moderate active than standard drug (Tetracycline). Compound **54** also exhibited maximum antifungal activity as compared to other tested compounds at 1000 ppm.



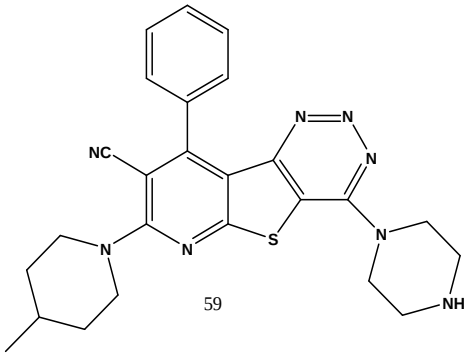
54 R = 4-Cl,
55 R = 4-OCH_3,
56 R = 4-OH

Tarun kumar M. Patel *et al*. [21] synthesized some 1-(4-(1*H*-naphtho[1,8-de][1,2,3]triazin-1-ylsulfonyl)phenyl)-5-oxo-2-arylpyrrolidine-3-carboxylic acid derivatives. The antibacterial activity of all the synthesized compounds was studied against Gram-positive bacteria (*Staphylococcus aureus* and *Bacillus subtilis*) and Gram-negative bacteria (*E.coli* and *klebsiella promioe*) at 50 µg/mL by agar cup plate method. Compounds **57** and **58** bearing 4-chloro and 4- methoxy groups respectively, showed significant antibacterial activity. Compounds containing hydrogen, methyl and bromo substitutions at 4-position were found to be less or moderate active than standard drug (Tetracycline). Compound **57** also exhibited maximum antifungal activity as compared other tested compounds at 1000ppm.



57 R = Cl,
58 R = OCH_3

Jose M. Quintela *et al*. [22] synthesized a series of pyridothienotriazines and evaluated them for antiprotozoal activity against *Philasterides dicentrarchi*. Pyridothienotriazines incorporating a piperazine group is directly related to the antiprotozoal activity of the compounds against *P. dicentrarchi*. Pyridothienotriazine (**59**) showed the activity (0.8 mg/L in physiological phosphate-buffered saline and 1.5 mg/L in sea water) which is comparable with standard drugs niclosamide and oxyclozanide (0.8 mg/L). Pyridothienotriazines (**60**-**65**) showed significant antiparasitic activity. Comparison of the compounds (**60**) and (**61**) indicated that substitution of the ethoxy group at the 7th position by a phenyl and the cyano group at the 8th position by a hydrogen atom produces 4-fold increase of the lethal dose values. All the compounds of this series, particularly **59**, possess significant antiprotozoal activity.



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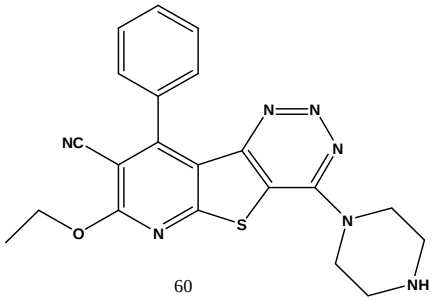

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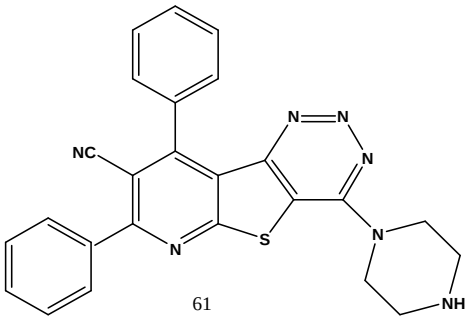

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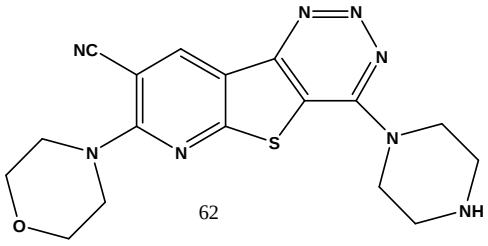

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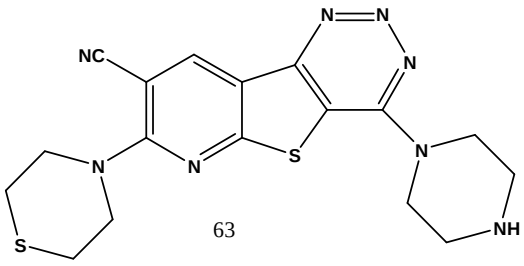

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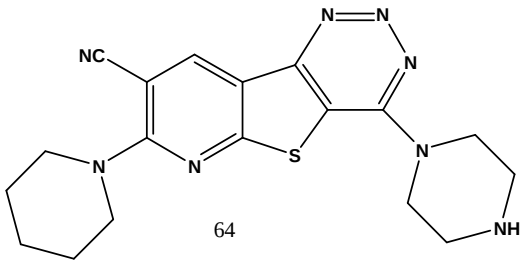

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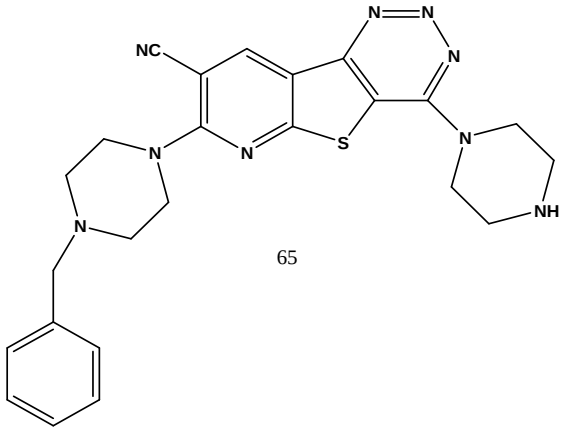
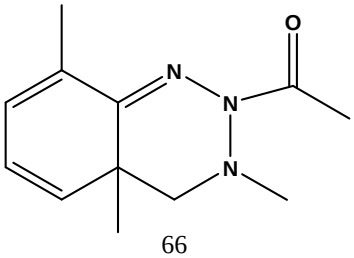


65

F. Kiuchi *et al*. and J. Feldmesser *et al.* [23-24] observed structure–activity tendencies of N-acyl cyclic amines and Nsubstituted amides. They concluded that the hydrophobic/ hydrophilic balance of the compounds controls the nematocidal activity. Keiji Nishiwaki *et al*. [42] synthesized some tetrahydrobenzotriazines as a new class of nematocide. Compound (**66**), having acetyl group, showed the strongest activity (100% of the revised death rate). Decanoyl derivative (**67**), having long acyl chain, also showed high nematocidal activity (97%). Nematocidal activity of the compound (**68)** was 5 times stronger than that of the compound (**69**).Compounds **66**, **68** and methyl isothiocyanate (standard drug), killed all the nematodes within 24 hours. They revealed that this may be due to the hydrophobic nature or bulkiness of the methyl group. Nematocidal activity of the tested compounds gradually decreased as the length of the acyl chains increased. In the phenylurea and phenylthiourea substituted tetrahydrobenzotriazines, introduction of a methyl group on the nitrogen atom increased the nematocidal activity.



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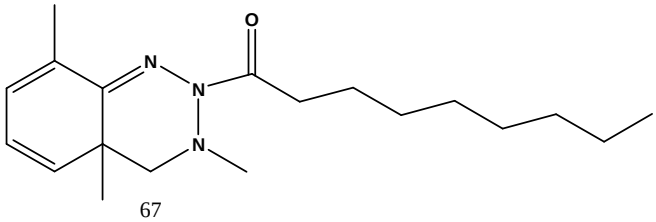
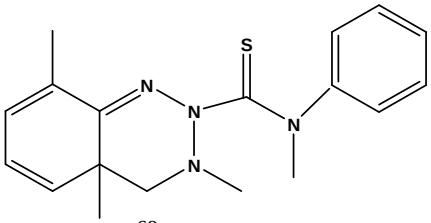


67



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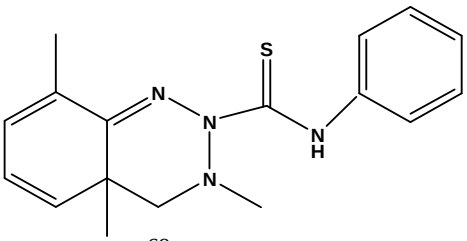
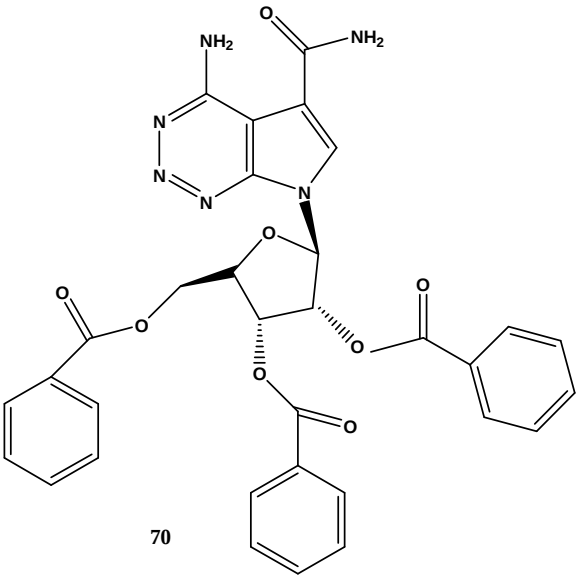


69

Michael T. Migawa *et al*. [25] synthesized some new 4,5-disubstituted 7-(β -D ribofuranosyl) pyrrolo [2,3-*d*][1,2,3] triazines as analogs of triciribine. Synthesized compounds (**70**-**78**) were evaluated for their antiviral activity. Most of the pyrrolotriazine analogs (**70**-**72**, **76**-**78**) were inactive or weakly active against human cytomegalovirus (HCMV) and herpes simplex virus type 1 (HSV-1). The 2-aza analog of sangivamycin (**74**) was active against HCMV and HSV-1.

Activity of the compound (**74**) was most likely due to its high cytotoxicity. Compound (**78**) shown modest activity against HCMV and was cytotoxic at the concentrations of only two to three times of antiviral concentrations. They concluded that in comparison to triciribine, the newly synthesized analogs were less active against HIV-1 and more

cytotoxic. Steven Krawczyk *et al*. [26] synthesized some 4-substituted imidazo[4,5-*d*][1,2,3]triazine(2-azapurine) nucleoside derivatives. Synthesized compounds were tested for their activity against human cytomegalovirus (HCMV) and for cytotoxicity in the cells used to propagate the virus [human foreskin fibroblasts, (HFF's)]. They reported that the unsubstituted compound (**79**) was slightly active against HCMV in plaque and it was not cytotoxic to stationary HFF's at the highest tested concentration. Thiomethyl substituted analog (**80**) was the most active compound and comparable to ganciclovir albeit with greater cytotoxicity.



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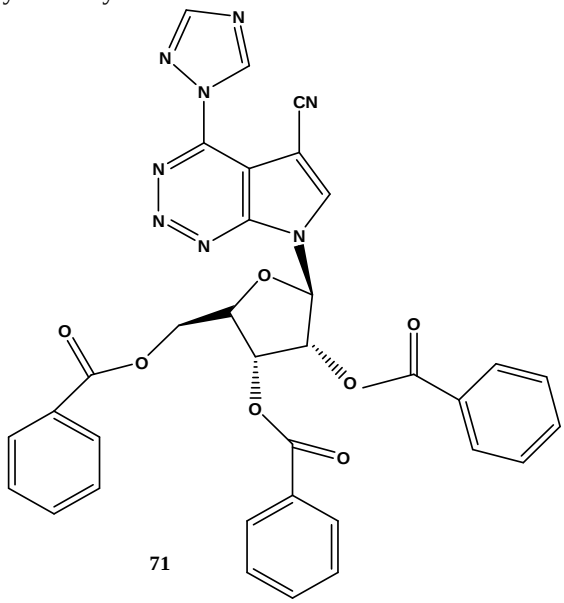

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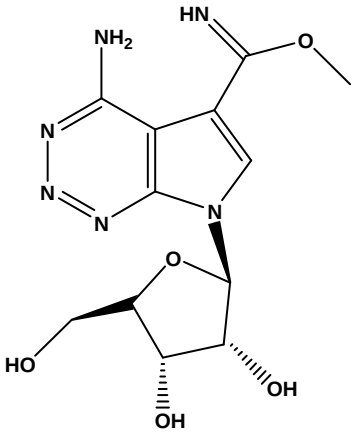

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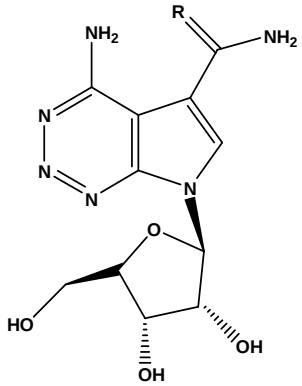
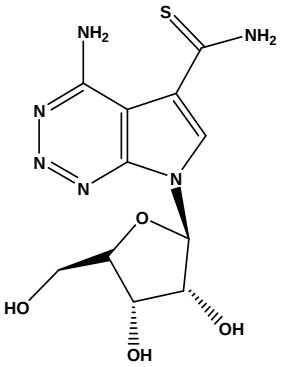
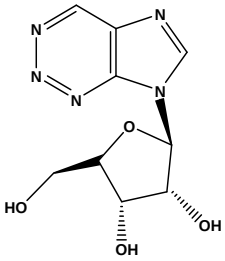


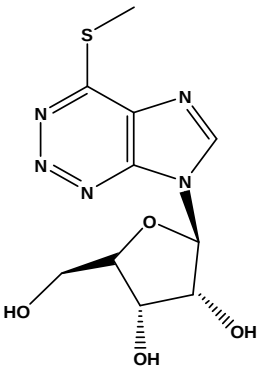
73 R = NNH_2,
74 R = O,
75 R = NOH,
76 R = NCN



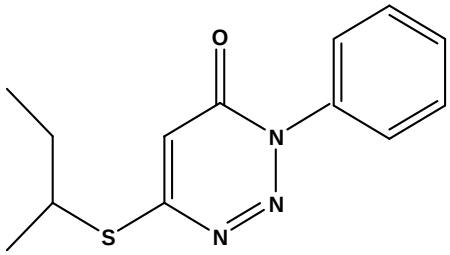
77



78

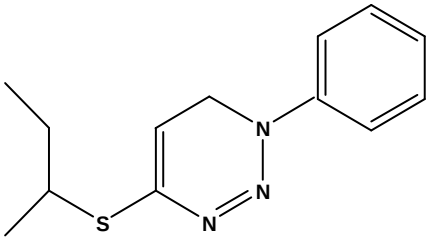


79



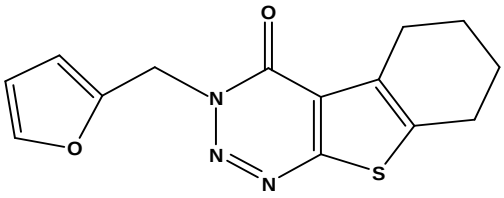
80

GL Viswanatha *et al*. [2] synthesized some bicyclothieno 1,2,3-triazine analogs and screened them for analgesic, anti-inflammatory and antiarthritic activities. All the tested analogs showed significant analgesic, anti-inflammatory and antiarthritic activities. Compound **81** (50 mg/kg, i.p.) was found to be more potent than pentazocin (4 mg/kg i.p) in hot plate test. In the motor coordination test, using rotarod apparatus, compound **81** (100 mg/kg, i.p.) exhibited significant sedative effect that was evidenced by reduction in the endurance time. They revealed that the mechanism of analgesic effect of tested compounds could be due to blockade of the effect or the release of endogenous substances that excite the pain nerve endings similar to that of standard drug pentazocin and other NSAIDs.

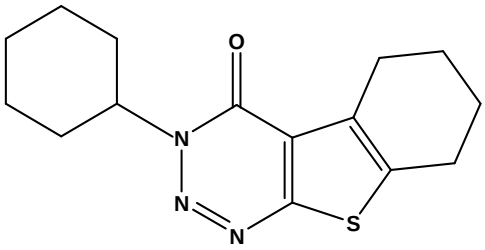


81

Srinath R. *et al*. [27] synthesized some new thieno 1,2,3-triazin-4-ones. All the synthesized compounds were screened for antidepressant activity by using tail suspension, reserpine induced hypothermia and forced swim models. Compounds (**82**) and (**83**) showed significant activity against all models at 50 mg/kg. Compound (**82**) also exhibited significant activity against all models 25 mg/kg. At both dose levels (25 mg/kg and 50 mg/kg), Anti-depressant activity of both the compounds (**82**) and (**83**) was comparable to standard drug Imipramine (20 mg/kg).

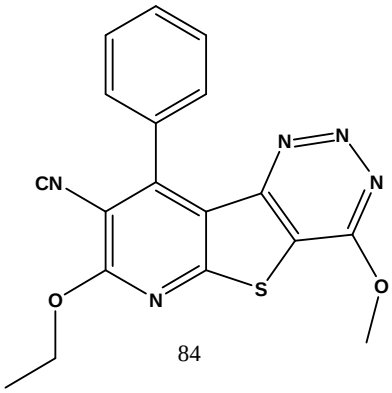


82



83

Jose Maria Quintela *et al*. [28] synthesized some pyridotheino and pyridoditheinotriazines and evaluated them for antihistaminic and cytotoxic activities. Compounds (**84**) and (**85**) were found to be strong inhibitors under all the conditions tested, while compound (**86**) was found to be a good inhibitor under all the conditions except the condition when it was preincubated with ovoalbumin. Compounds (**87**), (**88**) and (**89**) were found to be good inhibitors in the immunological experiments but were practically inactive under chemical stimulus. Compounds (**90**) (IC50 = 0.25µg/mL) and (**91**) (IC50 = 0.05µg/mL) showed *in vitro* cytotoxic activity against several human and mouse tumoral cell lines. The nitrogen-substituted compounds (**92**) and (**93**) also showed significant inhibitory action. The oxygen-substituted analog (**94**) surprisingly acted as an inducer of the liberation of histamine in some assays. The screening data showed that the replacement from ethoxy to aminobenzyl did not produce any change in the activity. They revealed that a common mechanism of action of the compounds was perhaps related to the alkylating properties of the masked imminium ion. Pyridotheino- (**90**) and pyridodithieno-(**91**) compounds showed remarkable activity against several human and mouse tumoral cell lines.



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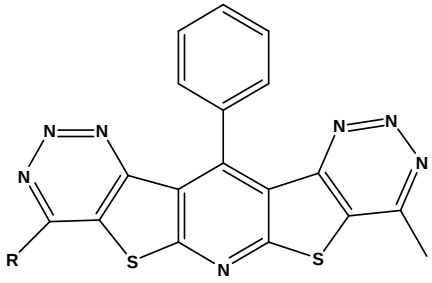
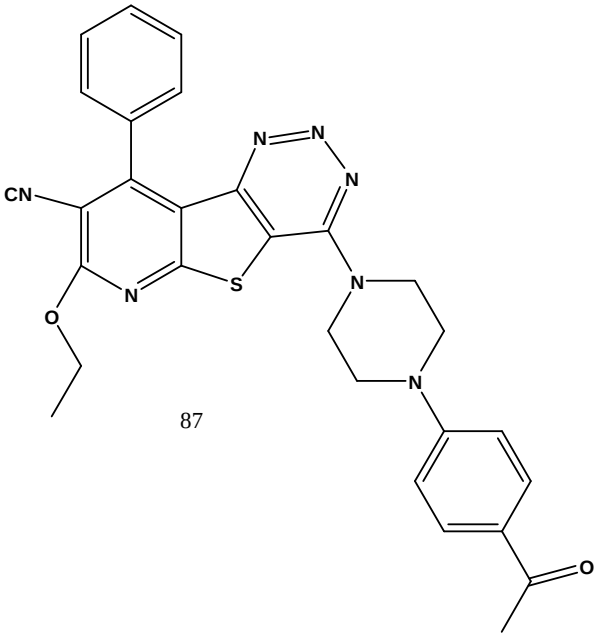
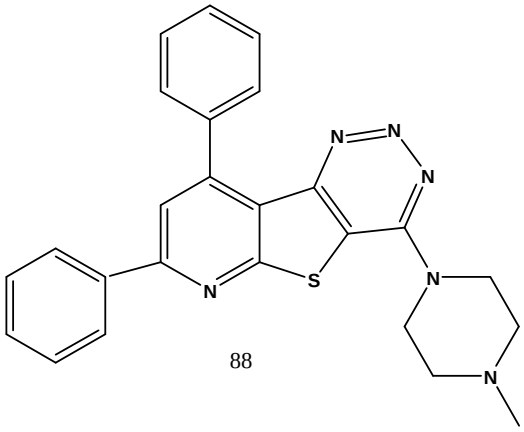


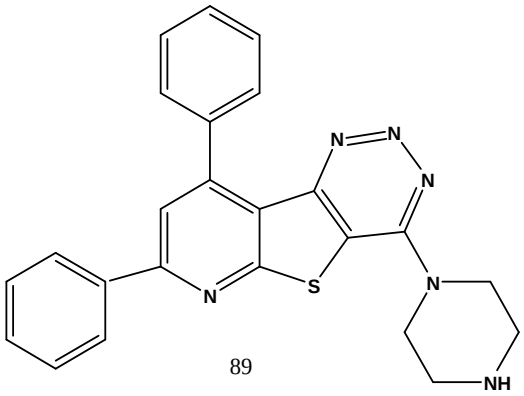
85 R = OC_2H_5,
86 R = $NHNH_2$



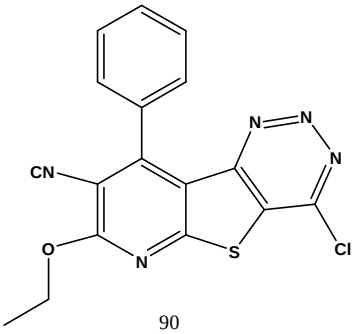
87



88



89



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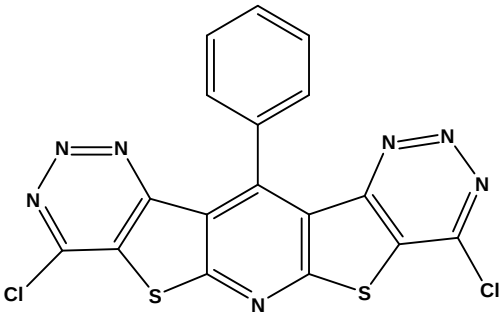

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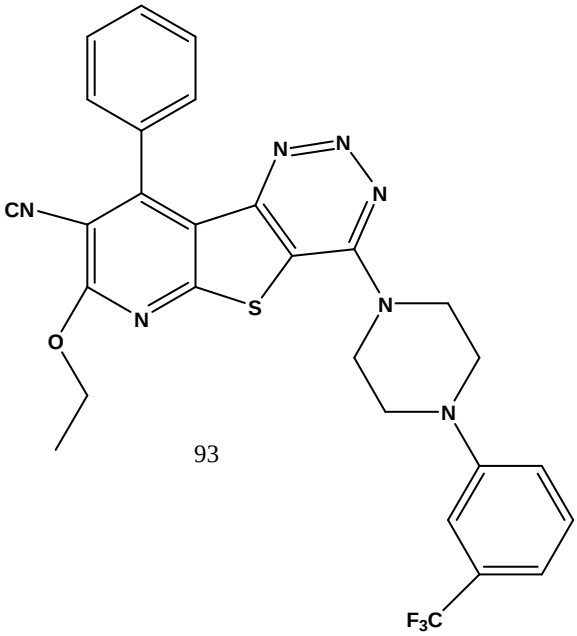

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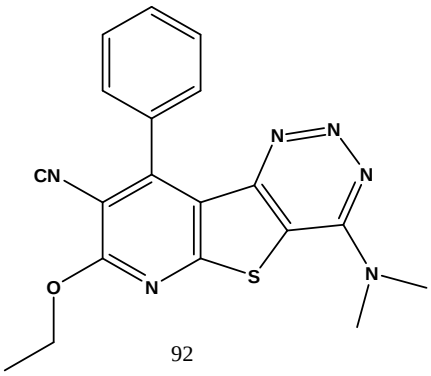

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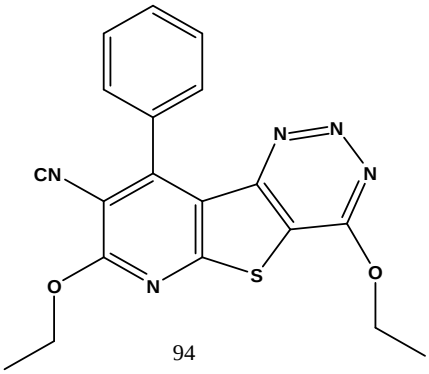
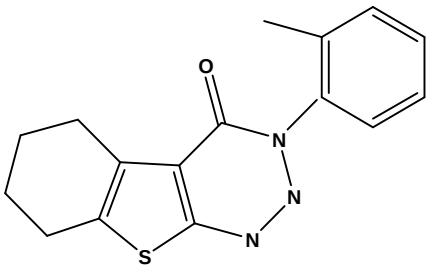
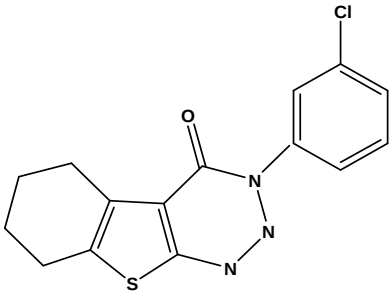


94

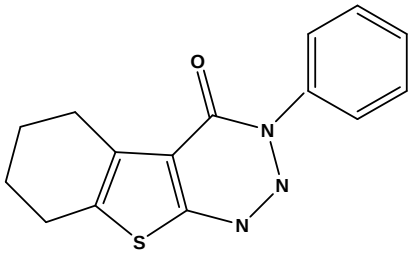
Gollapalle L. Viswanatha *et al*. [29] synthesized some 3*H*-benzo[4,5]thieno[2,3-*d*][1,2,3]triazin-4-ones and evaluated their antihistaminic activity. All the compounds showed very good *in vitro* antihistaminic activity. Sedative action of the synthesized compounds was found to be less in comparison to standard drug chlorpheniramine maleate.Compounds (**95**) and (**96**) were found to possess competitive antagonism as compared to the standard drug.Compound (**97**) was found to possess non-competitive antagonism at H1-receptor site and showed very low sedative potential as compared to the standard drug.



95

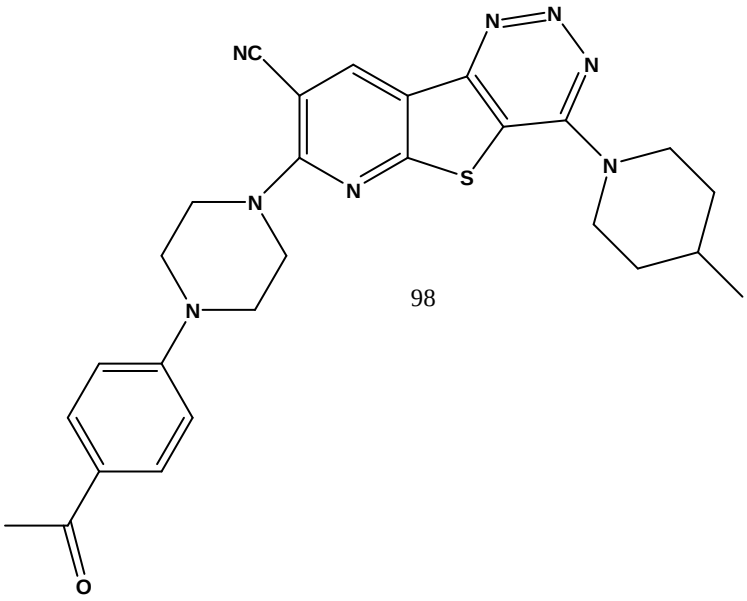


96

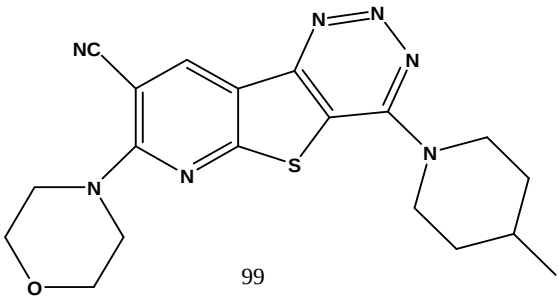


97

Jose Ma Quintela *et al*. [30] synthesized some 8-cyanopyrido[3',2':4,5]thieno[3,2-*d*]triazine derivatives as inhibitors of nitric oxide and eicosanoid biosynthesis. Most of the synthesized compounds exhibited considerable activity. SAR study of the synthesized compounds reveals that the 8- cyanopyridothieno-1,2,3-triazines with a chloro substituent (R2 = Cl) at position C-4 of the triazine nucleus and a nitrogen heterocycle at C-7 (R1) are found to be good inhibitors of PGE2 production, and reductions of about 50% of the control value are obtained in most cases. Compound with an *N*-(*p*-acetylphenyl)piperazine group at C-7 (R1), is found to be much more effective (95% inhibition), practically suppressing the generation of PGE2. Presence of an amino group or a linear amine at C-7 and a bromo instead of a chloro substituent atom at C-4 is associated with a total loss of activity on PGE2 production. Compounds carrying a morpholine substituent at C-7 and different heterocycles at C-4 (R2), a moderate decrease (30-40%) in accumulation of both metabolites at 10 µM. At 10 µM concentration, compound bearings morpholine at C-7 and 4-methylpiperidine at C-4 is an active compound inhibiting around 90% production of NO and PGE2. While compounds containing heterocycles other than morpholine at C-7 position show 50% inhibitory action on both metabolites generation. The presence of acyclic amines in C-7 position does not improve the effectiveness of these compounds. 8 Cyano pyrido thieno-1,2,3-triazines (**98**) and (**99**) were the potent inhibitor with IC50 values of 11.2 and 3.4 µM on nitrites and 0.9 and 0.6 µM on prostaglandin E2 production on murine macrophages, respectively. They concluded that the effect of compounds (**98**) and (**99**) could be due to their action on the degree of induction/ expression of NOS and COX proteins caused by LPS in macrophages. These compounds might be of benefit for the prevention and treatment of autoimmune diseases, septic shock, and different inflammatory pathologies.

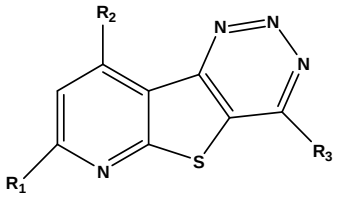


98



99

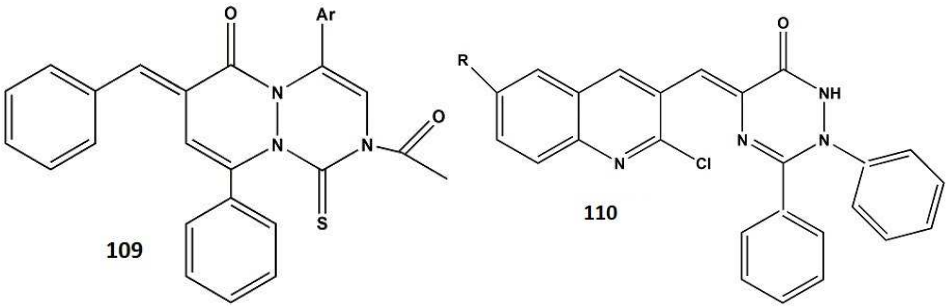
Raymond D. Youssefyeh *et al*. [31] synthesized a new series of pyrido[3',2':4,5]thieno[3,2-*d*]-N-triazines and evaluated them for antiallergic activity. Most of the synthesized compounds showed significant antiallergic activity with a mechanism of action similar to that of disodium cromoglycate (DSCG) for the prophylaxis of asthma. DSCG is a well established drug that inhibits release of the mediators of anaphylaxis and thus provides a prophylactic treatment of asthma. Compounds (**100**-**103**) were found to be more potent inhibitors of AIR (antigen-induced release of histamine) than disodium cromoglycate (I50 value = 3 µM) when added simultaneously with antigen. The potent compound **101** (I50 value = 0.05 µM) was 60 times more potent than DSCG as an inhibitor of AIR in the rat peritoneal mast cells (RMC) assay. Compounds of this series were also tested orally for inhibition of passive cutaneous anaphylaxis (PCA) in the rat, either at a single dose (**102**, **104** and **105**, 25 mg/kg PO) or at multiple dose levels (**100**, **101**, **103**, **106**, and **107**). Compound **108** was an orally potent inhibitor of the IgE-mediated passive cutaneous anphylaxis in the rat (ED50 = 1.5 mg/kg PO); however, it was virtually inactive *in vitro*, suggesting *in vivo* metabolism to an active form. Compounds with reasonably low oral ED50 values were **100** (5.2 mg/kg) and **106** (3.6 mg/kg). Substitution of the hydrogen in the 4-position by hydroxy (**100**), amino **(102**), ethoxyethyl (**105**), methylamino (**108**), or a sulfhydryl groups (**103**) resulted in compounds that inhibited AIR from RMC. However, replacement of the 4-hydrogen by an ethoxy, chloro, methyl carbazate, or methylthio groups did not result in compounds capable of inhibiting AIR. Replacement of the 7-methyl (**100**) with a phenyl group (**101**) resulted in a compound that was also an active inhibitor of PCA (ED50 = 3 mg/kg). Compound (**101**) was potent as an inhibitor of AIR from RMC and also oral PCA.



100 $R_1 = CH_3$, $R_2 = H$, $R_3 = OH$,
101 $R_1 = C_6H_5$, $R_2 = H$, $R_3 = OH$,
102 $R_1 = CH_3$, $R_2 = H$, $R_3 = NH_2$,
103 $R_1 = CH_3$, $R_2 = H$, $R_3 = SH$,
104 $R_1 = CH_3$, $R_2 = H$, $R_3 = NHNHCOOCH_3$,
105 $R_1 = CH_3$, $R_2 = H$, $R_3 = O(CH_2)OC_2H_5$,
105 $R_1 = CH_3$, $R_2 = H$, $R_3 = OH$,
106 $R_1 = CH_3$, $R_2 = H$, $R_3 = OC_2H_5$,
107 $R_1 = CH_3$, $R_2 = H$, $R_3 = NHCH_3$,
108 $R_1 = CH_3$, $R_2 = H$, $R_3 = H$

2. Synthetic Analogs of 1,2,4-Triazines, Showing Various Pharmacological Activities

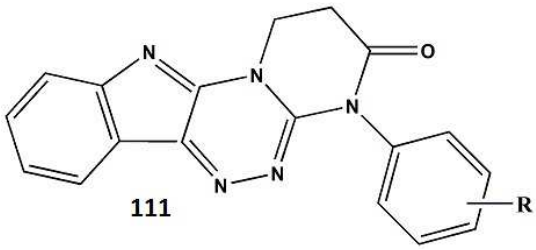
J A Hassanen et al.[32] reported the synthesis, biological activity and mass spectral investigation of 1,2,4- triazino-[2,1-a]-1,2,4-triazine derivatives **109**. B S Dawane et al.[33] have synthesized 1,2,4-triazine derivatives containing quinoline nucleus **110** and evaluated *in vitro* antimicrobial activity.



109

110

S K Pandey et al.[34] reported the antimicrobial studies of some novel quinazolinones derivatives fused with [1,2,4]-triazole, [1,2,4]-triazine and [1,2,4,5]-tetrazine rings **111.** K Sztanke et al.[35] have synthesized 8-aryl-3,4-dioxo-2*H*,8*H*-6,7-dihydroimidazo[2,1-*c*] [1,2,4]triazines **112** and tested them for pharmacological activity.



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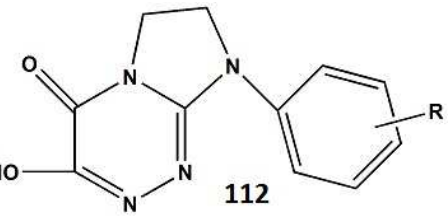
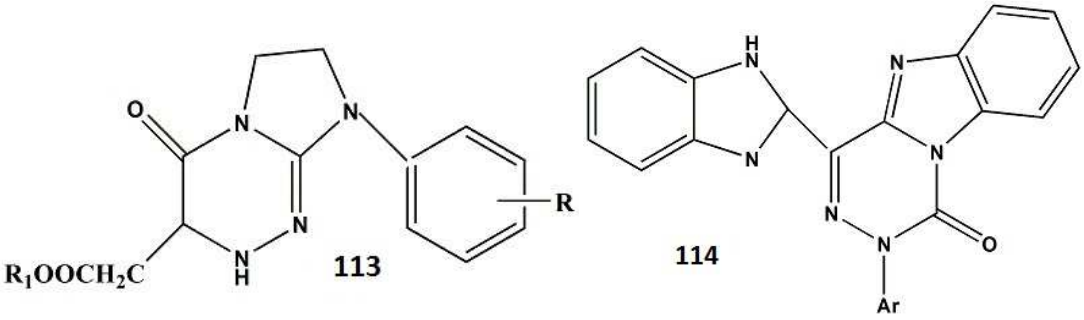
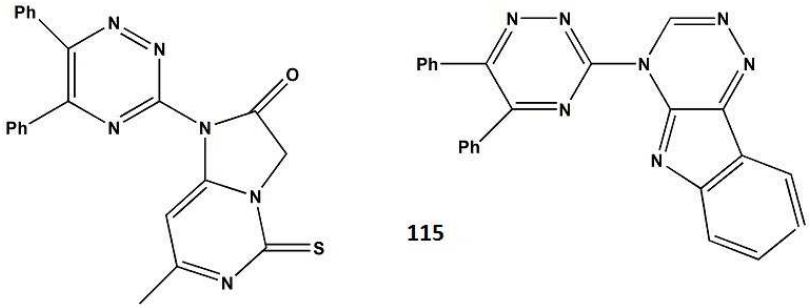


112

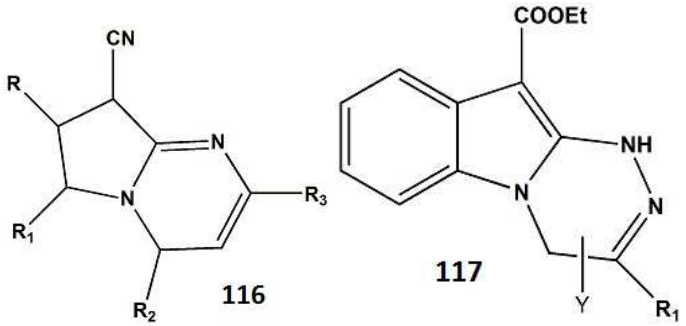
K Sztanke et al.[36] reported the synthesis, crystal structure and anticancer activity of novel derivatives of ethyl 1-(4-oxo-8-aryl-4,6,7,8-tetrahydroimidazo[2,1-c][1,2,4]triazin-3-yl)formate **113**. J Styskala et al [37]have synthesized a new series of 2-aryl-4-(benzimidazol-2-yl)-1,2-dihydro[1,2,4]triazino-[4,5-a]benzimidazol-1-one derivatives **114** with preferential cytotoxicity against carcinoma cell lines.



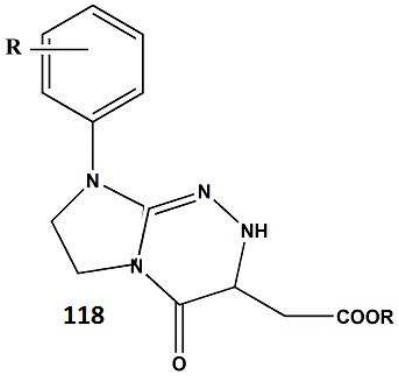
W R Abdel-Monem et al.[38] have synthesized and screened antimicrobial activity of some new nitrogen heterocyclic systems bearing 1,2,4-triazine moiety **115**.



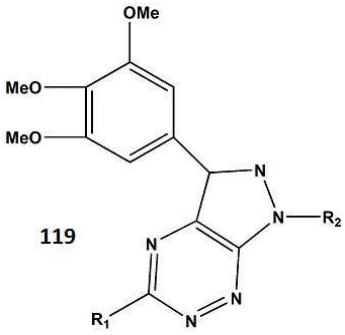
P Barraja et al.[39] reported the synthesis and antiproliferative activity of [1,2,4]triazino[4,3-*a*]indoles **116**. P Diana et al.[40] have synthesized some novel pyrrolo[2,1-*c*][1,2,4]triazines **117** from 2-diazopyrroles and evaluated their antiproliferative active



K Sztanke et al [41] reported the synthesis, crystal structure and antproiferative activity of novel derivatives of methyl and ethyl 2-(4-oxo-8-aryl-2*H*-3,4,6,7-tetrahydroimidazo[2,1-c][1,2,4]triazin-3-yl)acetates **118** from biologically active 1-aryl-2-hydrazinoimidazolines.T T Gucky et al [42] havesynthesized and tested cytotoxic activity of some 3,7-diaryl-5-(3,4,5 trimethoxyphenyl) pyrazolo [4,3-e][1,2,4]triazines **119.**

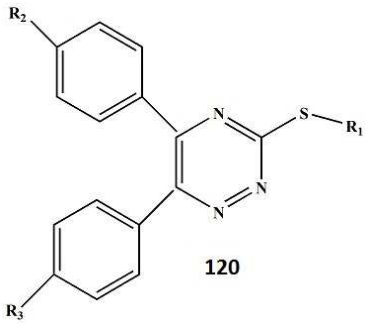


118



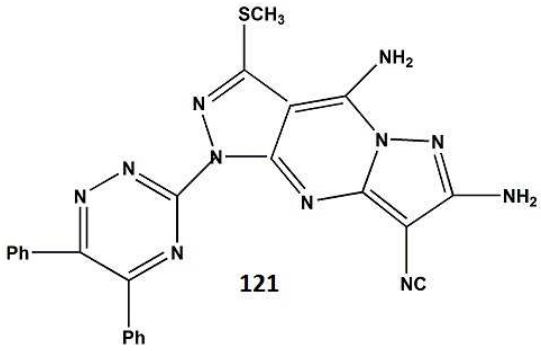
119

H Irannejad et al.[43] reported the synthesis and *in vitro* evaluation of novel 1,2,4-triazine derivatives as neuroprotective agents **120**.



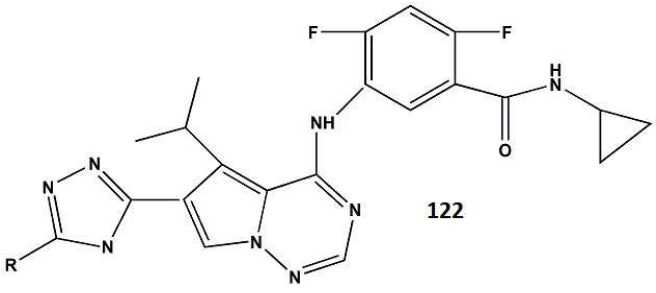
120

T El S Ali et al[44] reported the synthesis of some novel pyrazolo[3,4-b]pyridine and pyrazolo[3,4-d]pyrimidine derivatives bearing 5,6-diphenyl-1,2,4-triazine moiety as potential antimicrobial agents **121**.



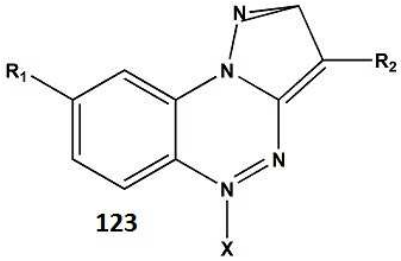
121

ZCai etal[45]have reported the synthesis,SAR and evaluation of 4-[2,4-difluoro-5(cyclopropyl carbamoyl) phenylamino]pyrrolo[2,1-f][1,2,4]triazine-based VEGFR-2 kinase inhibitors **122**.



122

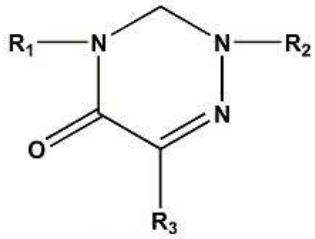
G Ciciani et al[46]have reported the synthesis of new pyrazolo[5,1-c][1,2,4] benzotriazines, pyrazolo[5,1-c]pyrido[4,3-e][1,2,4] triazines and their open analogues as cytotoxic agents in normoxic and hypoxic conditions. A M EL Massry et al[47] reported the synthesis and structure elucidation of novel fused 1,2,4-triazine derivatives as potent inhibitors targeting CYP1A1 activity **123** and **124.**



123

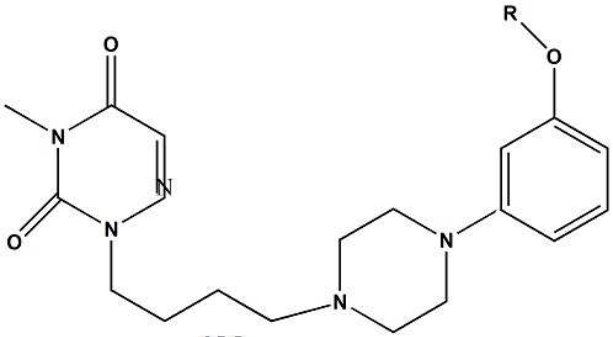
124

F Krauth et al[48] reported the synthesis and characterization of novel 1,2,4-triazine derivatives with antiproliferative activity **125**.



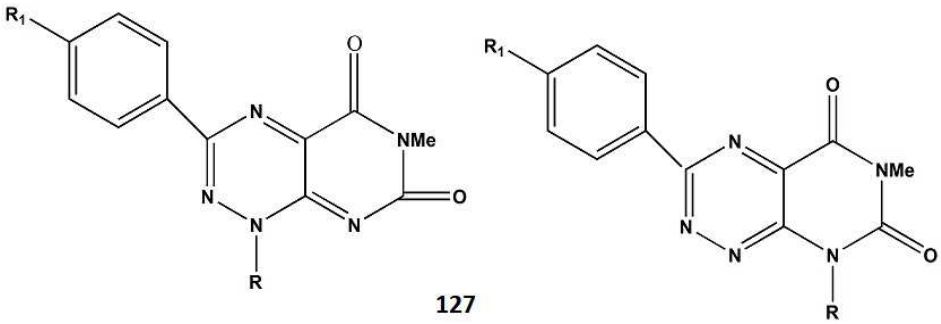
125

J. Prabhakaran et al[49] reported the synthesis, in vitro and in vivo evaluation of [O-methyl-11C] 2-{4-[4-(3-methoxyphenyl)piperazin-1-yl]-butyl}-4-methyl-2H-[1,2,4]-triazine-3,5-dione: A novel agonist 5-HT1A receptor PET ligand **126**.



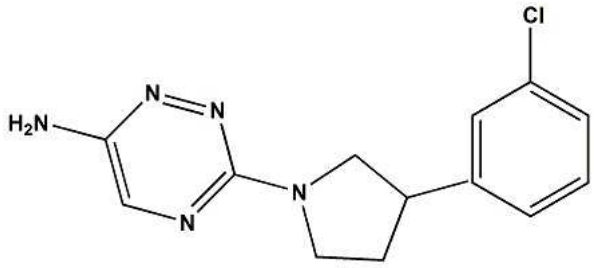
126

J. Zeller et al[50] studied a panel of six candidate Wnt/ β-catenin/Tcf-regulated genes and found that two of them (Axin2, Lgr5) were reproducibly activated (9–10 fold) in rat intestinal epithelial cells (IEC-6) following β-catenin stabilization by Wnt-3a ligand treatment. Two previously reported β -catenin/TCF antagonists (calphostin C, xanthothricin) and XAV939 (tankyrase antagonist) inhibited Wnt-activated genes in a dose-dependent fashion **127**.



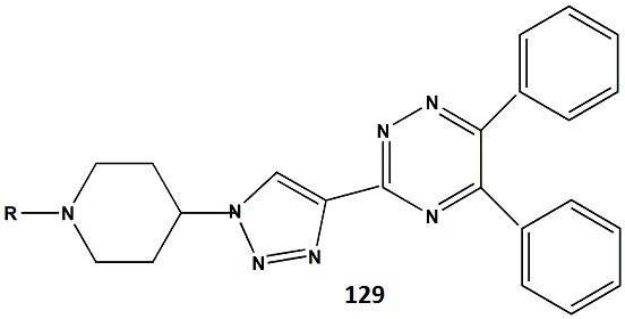
127

W. Lv et al[51] reported a pyrophosphatase-coupled high-throughput screening assay intended to detect o-succinyl benzoic acid coenzyme A (OSB CoA) synthetase inhibitors led to the unexpected discovery of a new series of novel inorganic pyrophosphatase inhibitors**128**.



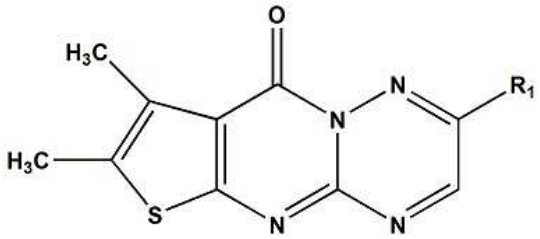
128

J. N. Sangshetti et al[52] reported an improved protocol for the synthesis of a novel series of 1,2,4-triazines possessing 1,2,3-triazole and piperidine ring using 1-(1-substituted piperidin-4-yl)-1H-1,2,3-triazole-4-carbohydrazide, benzil, ammonium acetate and $ZrOCl_2.8H_2O$ as a catalyst in ethanol–water has been presented.All the synthesized compounds were screened for in vitro antifungal activity. **129**.



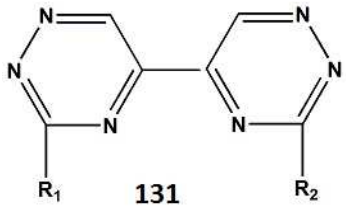
129

H. M. Ashour et al[53] have synthesized a new series of thieno[20,30:4,5]pyrimido[1,2-b][1,2,4]triazines and thieno[2,3-d][1,2,4]triazolo[1,5-a] pyrimidines. The newly synthesized compounds were evaluated for their anti-inflammatory and analgesic activity using diclofenac Na as a reference standard **130**.



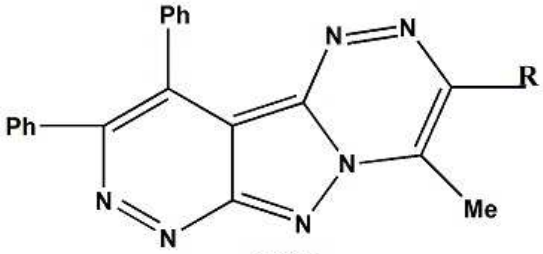
130

K. Ban et al[54]reported the discovery of 3-alkylthio-1,2,4-triazine dimers that are potently toxic to Plasmodium falciparum, with single digit nanomolar activity, and up to several thousand-fold lower toxicity to mammalian cells. They are equipotent against chloroquine-resistant strains of P. falciparum **131**.



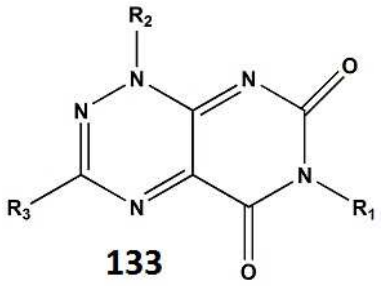
131

Deeb et al[55]reported. The synthesis of 3-Aminopyrazolo[3,4-d]pyridazine which was diazotized and coupled with active methylene reagents to afford the tricyclic pyridazino [3 ,4 :3,4] pyrazolo[5,1-c]-1,2,4-triazines with substituents such as methyl, phenyl, ethoxycarbonyl, acetyl or benzoyl, depending on the methylene reagent used. The in vitro antimicrobial activities for some of the synthesized compounds were evaluated against Escherichia coli, Pseudomonas aeruginosa, and Staphylococcus aureus and Candida albicans were determined **132.**



132

Y. Zhou et al[56] reported that pyrimido[5,4-e][1,2,4]triazine-5,7(1H,6H)-dione derivatives were investigated as novel small molecule amplifiers of heat shock factor-1 transcriptional activity. Lead optimization led to the discovery of compound, which displayed potent HSF1 activity under mild heat stress (EC_{50} = 2.5 μM) and significant cytoprotection in both rotenone (EC_{50}= 0.23 μM) and oxygen-glucose deprivation cell toxicity models (80% protection at 2.5 μM) **133**.

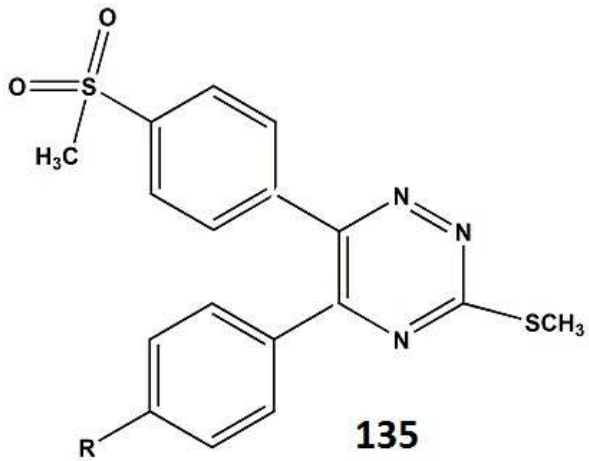


133

W. D. Schmitz et al[57] reported a series of 5-arylamino-1,2,4-triazin-6(1H)-ones was synthesized and evaluated as antagonists at corticotropin releasing factor receptor.Formation of CYP-mediated oxidative reactive metabolites previously observed in a related N3-phenylpyrazinone structure was minimized by incorporation of the additional ring nitrogen found in the triazinones **134**.

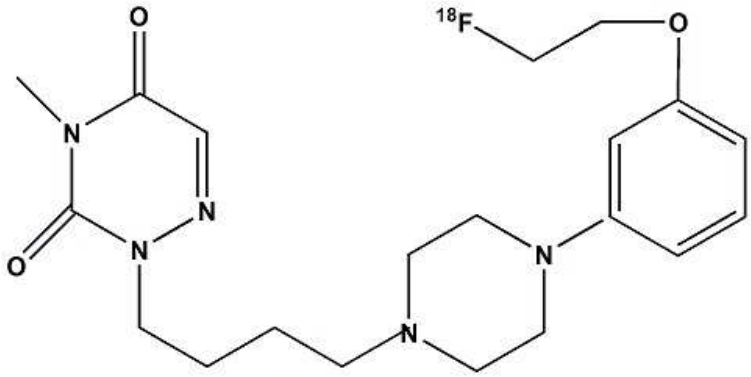
134

H. Irannejad et al [58] reprted that a series of 5-Aryl-6-(4-methylsulfonyl)-3-(metylthio)-1,2,4-triazine derivatives were synthesized and their COX-1/COX-2 inhibitory activity as well as in vivo anti-inflammatory and analgesic effects were evaluated. All of compounds showed strong inhibition of COX-2 with IC_{50} values in the range of 0.1–0.2 μM and in most cases had stronger anti-inflammatory and analgesic effects than indomethacin at doses 3 and 6 mg/kg. Among them, 5-(4-chlorophenyl)-6-(4-(methylsulfonyl) phenyl)-3-(methylthio)-1,2,4-triazine was the most potent and selective COX-2 compound; its selectivity index of 395 was comparable to celecoxib (SI = 405). Evaluation of anti-inflammatory and analgesic effects showed its higher potency than indomethacin and hence could be considered as a promising lead candidate for further drug development. Furthermore, the affinity data of these compounds were rationalized through enzyme docking simulation and 3D-QSAR study by k-Nearest Neighbour Molecular Field Analysis **135**.



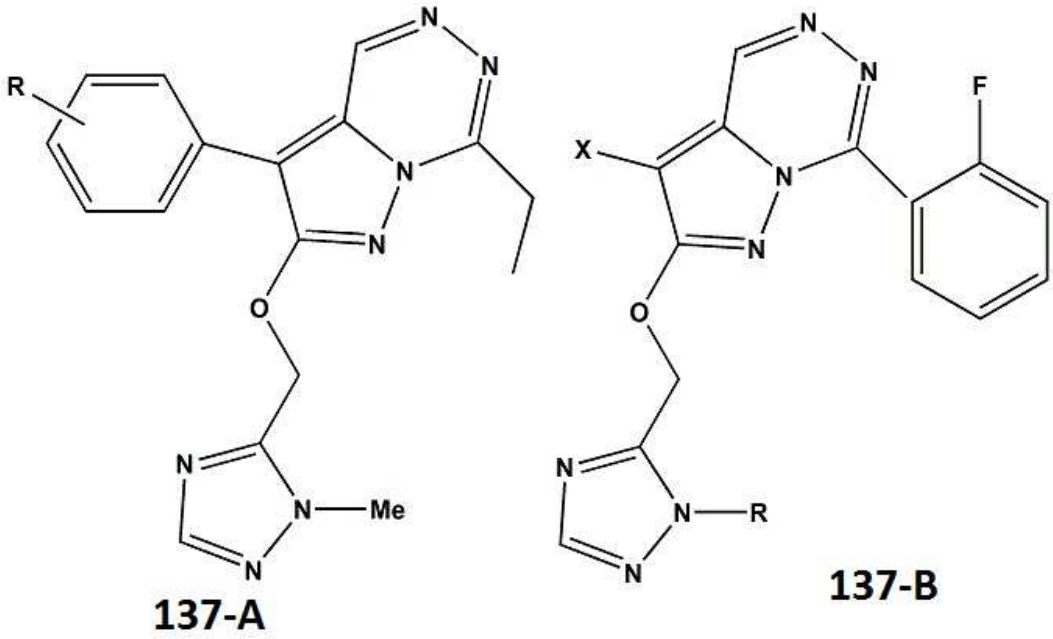
135

V. J. Majo et al [59] identified the fluoroethyl derivative, 2-(4-(4-(2-(2 fluoroethoxy) phenyl) piperazin -1-yl) butyl)-4-methyl-1,2,4-triazine-3,5(2H,4H)dione (FECUMI-101) (Ki = 0.1 nM; Emax = 77%; EC_{50} = 0.65 nM) as a partial agonist 5-HT1AR ligand of the parent ligand CUMI-101. FECUMI-101 is radiolabeled with F-18 by O-fluoroethylation of the corresponding desmethyl analogue with [^{18}F]fluoroethyltosylate in DMSO in the presence of 1.6 equiv of K_2CO_3 in 45 ± 5% yield (EOS). PET shows [^{18}F]FECUMI-101 binds specifically to 5-HT1AR enriched brain regions of baboon. The specificity of [^{18}F]FECUMI-101 binding to 5-HT1AR was confirmed by challenge studies with the known 5-HT1AR ligand WAY100635. These findings indicate that [^{18}F]FECUMI-101 can be a viable agonist ligand for the in vivo quantification of high affinity 5-HT1AR with PET **136.**

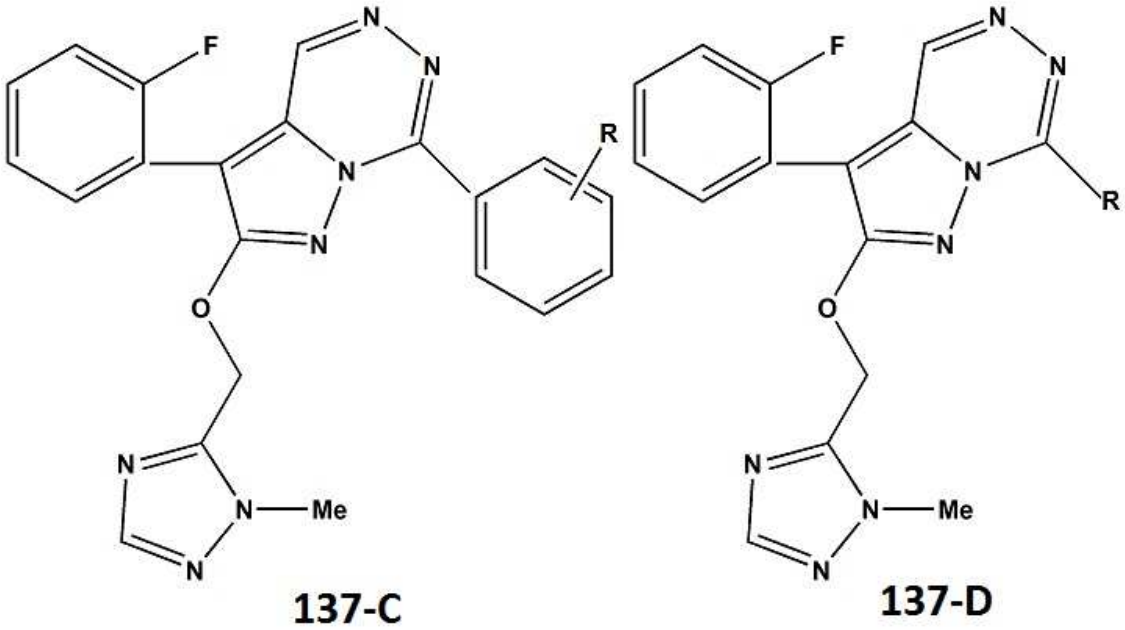


136

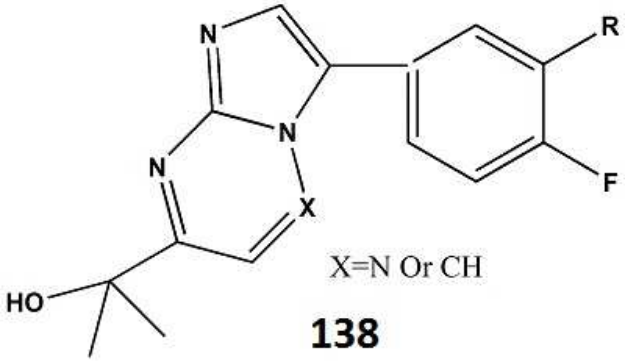
R. W. Carling et al [60] devised a novel synthetic routes have been for the preparation of previously inaccessible 2,3,7-trisubstituted pyrazolo-[1,5-d][1,2,4]triazines. These compounds are high affinity ligands for the GABAA benzodiazepine binding site and some analogues show functional selectivity for agonism at α3-containing receptors over a1-containing receptors with the lead compounds **137(**A-D).



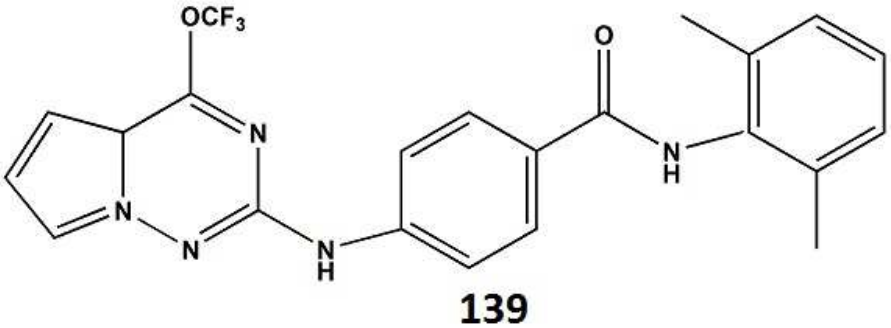
137-A **137-B**



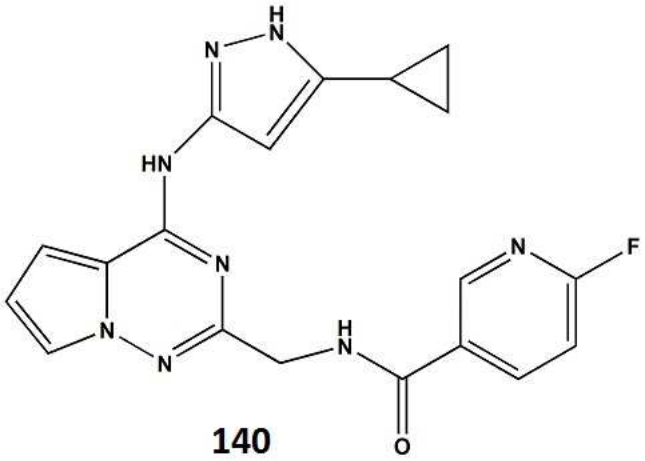
S. R. Jennings et al [61] reported the Imidazo[1,2-*b*][1,2,4]triazines as a2/a3 subtype selective GABAA agonists for the treatment of anxiety **138**.



M. Xin et al [62] reported the design, synthesis, and evaluation of pyrrolo[2,1 f][1,2,4]triazine derivatives as novel hedgehog signaling pathway inhibitors **139**.

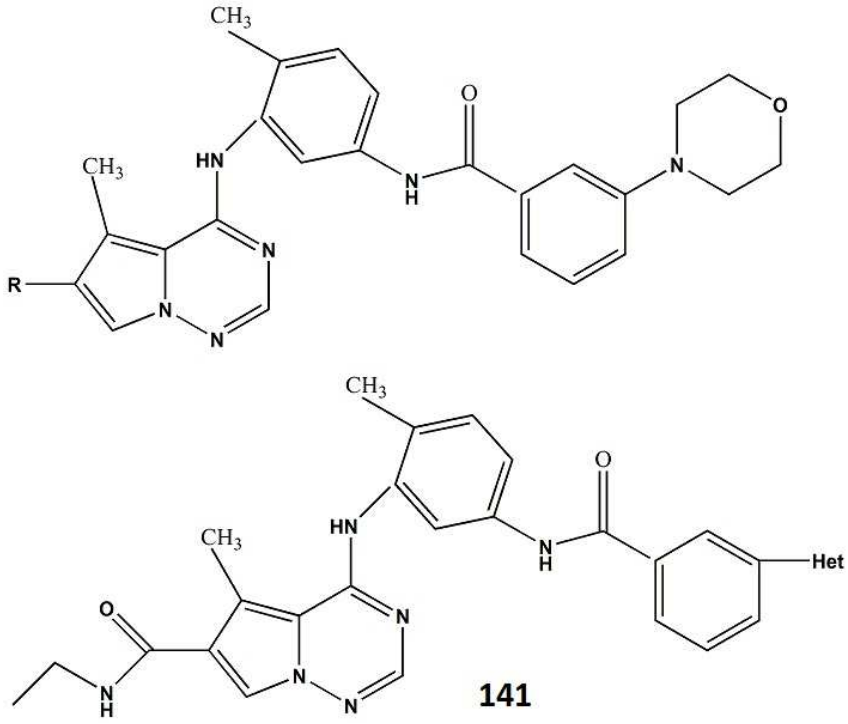


J. Sampognaro et al [63] reported the proline isosteres in a series of 2,4-disubstituted pyrrolo[1,2-f][1,2,4]triazine inhibitors of IGF-1R kinase and IR kinase **140.**



140

S. T. Wrobleski et al [65] reported a novel series of compounds based on the pyrrolo[2,1-f][1,2,4]triazine ring system have been identified as potent p38a MAP kinase inhibitors. The synthesis, structure–activity relationships (SAR), and in vivo activity of selected analogs from this class of inhibitors are reported. Additional studies based on X-ray co-crystallography have revealed that one of the potent inhibitors from this series binds to the DFG-out conformation of the p38a enzyme **141.**



141

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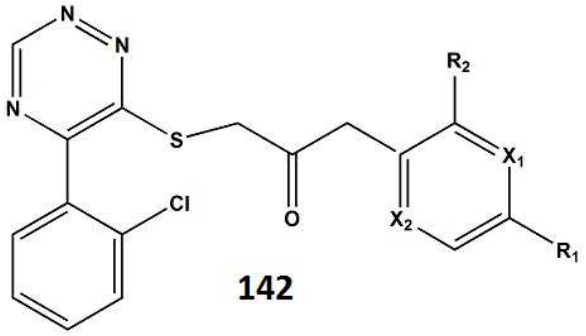
P. Zhan et al [66] reported the structure-based bioisosterism design, synthesis and biological evaluation of novel 1,2,4-triazin-6-ylthioacetamides as potent HIV-1 NNRTIs **142.**



142

CONCLUSION

The biological potential of 1,2,3 and 1,2,4-triazine derivatives is cleared from the literature and clinically used drugs. The literature revealed that 1,2,3 and 1,2,4-triazine derivatives possess diverse biological potential, easy synthetic routes for the synthesis and attracted researchers for development of new chemotherapeutic agents and it also revealed the importance of the nucleus.

Summary and future directions

Extensive research is required on 1,2,3 and 1,2,4-triazine moiety to find novel analogs suitable for clinical applications in the cancer treatment.

Acknowledgement

The author is thankful to KC Reddy Institute of Pharmaceutical Sciences, Jangamguntapalem, Medikonduru,Guntur District for availing the facilities of Laboratory, text- and e-journal access in their library sections.

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