III.1 Introduction of Triazine

Triazines are six-membered ring compounds containing three nitrogen atoms. Depending on the position of the nitrogen atom, three different triazine systems namely, 1,3,5-triazine (s-triazine, 1), 1,2,4-triazine (2) and 1,2,3-triazine (3) are possible (Figure 1). Among them 1,2,3-triazine is the novel class of heterocycles. In addition to the name of 1,2,3-triazine, Vtriazine or beta triazine can also be found in older literature. Out of the above three possible triazine nucleus, 1,3,5-triazine is the least explored one, till date. But, clinically 1,3,5-triazine derivatives are more acceptable because of potent efficacy and minimal side effect. So by looking at its clinical output and safety margin, the 1,3,5-triazine nucleus is becoming the prime choice of the researchers for further study. Currently 1,3,5-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.

![Figure 1](image)

The best known 1,3,5-triazine derivative is melamine with three amino substituents used in the manufacture of resins. Another triazine extensively used in resins is benzoguanamine. Triazine compounds are often used as the basis for various herbicides such as cyanuric chloride (2,4,6-trichloro-1,3,5-triazine). Chlorine-substituted triazines are also used as reactive dyes. These compounds react through a chlorine group with hydroxyl groups present in cellulose fibres in nucleophilic substitution, the other triazine positions contain chromophores. Mixtures of Triazines and water are also used to remove H₂S from natural gas. A series of 1,2,4-triazine derivatives known as BTPs have been considered in the liquid-liquid extraction community as possible extractants for use in the advanced nuclear reprocessing of used fuel. BTPs are molecules containing a pyridine ring bonded to two 1,2,4-triazin-3-yl groups. Triazine-based molecules have been used as bridging ligands to bind three dinuclear arene ruthenium (or osmium) compounds to form metallaprisms. S-Triazine derivatives represent an important class of compounds due to their potential to be biologically active. They are known to be anti-protozoals, anticancer agents, estrogen...
receptor modulators, antimalarials, cyclindependent kinase modulators, and antimicrobials. Cyanuric chloride, an inexpensive, easily available reagent, of low toxicity and less corrosive than other similar reactants, has been widely used in organic reactions. 1,3,5-triazines (or s-triazines) are a class of compounds well known for a long time and still continue the object of considerable interest mainly due to their application in different fields, including the production of herbicides and polymer photostabilizers. Some 1,3,5-triazines display important biological properties; for example hexamethylmelamine (HMM) & 2-amino-4-morpholino-s-triazine are used clinically due to their antitumor properties to treat lung, breast and ovarian cancer, respectively. The diverse biological activities observed for different molecule containing the 1,3,5-triazine unit have been further explored in order to discover other new potential molecules through the synthesis of libraries by combinatorial approaches. Certain 1,3,5-triazine derivatives are also used as chiral stationary phases, for example, the chiral solvating agent for the determination of enantiomeric excess by NMR spectroscopy and determination of absolute configuration by circular dichroism.

III.2 Drugs containing 1, 2, 3-triazine ring.

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 (Figure 2). 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.7

\[
\begin{align*}
\text{4} & \quad R = \text{H}, \\
\text{5} & \quad R = \text{CN}, \\
\text{6} & \quad R = \text{CONH}_2 \\
\text{7} & \\
\end{align*}
\]

Figure 2
III.3 Drugs Containing 1, 3, 5-Triazine Having Anticancer Activity

Altretamine is an Antineoplastic agent. It was approved by the FDA in 1990. It is used to treat refractory ovarian cancer. It is not considered a first-line treatment, but it can be useful as salvage therapy. It also has the advantage of being less toxic than other drugs used for treating refractory ovarian cancer (Figure 3). The precise mechanism by which altretamine exerts its anti-cancer effect is unknown but it is classified by MeSH as an alkylating Antineoplastic agent. This unique structure is believed to damage tumor cells through the production of the weakly alkylating species formaldehyde, a product of CYP450 mediated N-demethylation. Administered orally. 

![Altretamine](image)

Triethylenemelamine is a drug used in chemotherapy (Figure 4).

![Triethylenemelamine](image)

Melamine is an organic base and a trimer of cyanamide, with a 1, 3, 5-triazine skeleton. Like cyanamide, it contains 66% nitrogen by mass and, if mixed with resins, has fire retardant properties due to its release of nitrogen gas when burned or charred, and has several other industrial uses. Melamine is also a metabolite of cyromazine, a pesticide. It has been reported that cyromazine can also be converted to melamine in plants (Figure 5).

Melamine is combined with formaldehyde to produce melamine resin, a very durable thermosetting plastic used in Formica, and melamine foam, a polymeric cleaning product.
The end products include countertops, dry erase boards, fabrics, glues, housewares, dinnerware, cooking spoons, guitar saddles, guitar nuts, acoustic foam paneling, and flame retardants. Melamine is one of the major components in Pigment Yellow 150, a colorant in inks and plastics. 1,3,5-Triazine is use as a reagent in organic synthesis, s-triazine also implement as the equivalent of hydrogen cyanide (HCN). Being a solid (vs a gas for HCN), triazine is sometimes easier to handle in the laboratory. One application is in the Gattermann reaction, used to attach the formyl group to aromatic substrates. It is a common reagent, and readily forms derivatives, which are used as pharmaceutical products.

Atrazine is 2-chloro-4-(ethylamino)-6-(isopropylamino)-s-triazine, an organic compound consisting of an s-triazine ring is a widely used herbicide. Its use is controversial due to widespread contamination in drinking water and its associations with birth defects and menstrual problems when consumed by humans at concentrations below government standards. Although it has been banned in the European Union, it is still one of the most widely used herbicides in the world.\textsuperscript{11-12} Atrazine is used to stop pre- and post-emergence broadleaf and grassy weeds in major crops. The compound is both effective and inexpensive, and thus is well-suited to production systems with very narrow profit margins, as is often the case with maize. Atrazine is the most useful herbicide in conservation tillage systems, which are designed to prevent soil erosion.\textsuperscript{13}
III.4 Methods for the Preparation Of S-Triazine

1, 3, 5-Triazine derivatives have been known for a long period of time. They have found widespread applications in the pharmaceutical, textile, plastic and rubber industries and are used as pesticides, dyestuffs, optical bleaches, explosives and surface active agents. A number of preparative methods are known.

1. By trimerizing compounds of the general formula XCN (Figure 7). This is a very general reaction, in which X may be H, Halogen, alkyl, aryl, amino, hydroxyl etc.

\[
\begin{array}{c}
3 \text{X-CN} \\
\rightarrow \\
\text{X} \atop \text{N} \atop \text{N} \atop \text{X} \atop \text{N} \atop \text{N} \atop \text{X} \atop \text{N} \atop \text{N} \atop \text{X} \atop \text{N} \atop \text{N} \atop \text{X} \\
\end{array}
\]

**Figure 7**

2. By cyclisation of biguanidines and related compounds (Figure 8).

\[
\begin{array}{c}
\text{NH} \atop \text{NH} \\
\text{H}_2\text{N} \atop \text{NH} \atop \text{NH}_2 \\
\rightarrow \\
\text{X} \atop \text{N} \atop \text{N} \atop \text{X} \atop \text{N} \atop \text{N} \atop \text{X} \\
\end{array}
\]

**Figure 8**

3. By reaction of amidines or nitriles with acid anhydride and acid chlorides (Figure 9).

\[
\begin{array}{c}
\text{NH} \\
\text{R}_2\text{NH}_2 \\
\rightarrow \\
\text{X} \atop \text{N} \atop \text{N} \atop \text{X} \atop \text{N} \atop \text{N} \atop \text{X} \\
\end{array}
\]

**Figure 9**

4. Various methods for the synthesis of s-triazine derivatives have been reviewed by scientists.\textsuperscript{14-16}

5. Cyanuric chloride or 2,4,6-trichloro-s-triazine was prepared in 1828 by Serullas,\textsuperscript{17} who obtained it through the action of chloride on anhydrous hydrocyanic acid in direct sunlight.
s-Triazine derivatives that have wide practical applications are 2,4,6-mono, di- or trisubstituted, symmetrical and nonsymmetrical compounds bearing different substituents. Cyanuric chloride is a weak base because of the low basicity of s-triazine nucleus, as well as the presence of nitrogen atoms in the alpha positions to the chlorine atoms. The replacement of a chlorine atom in cyanuric chloride by basic group is greatly facilitated by the ring nitrogen atom of the symmetrically built s-triazine nucleus. Cyanuric chloride is commercially available and a very inexpensive reagent, which makes its applications even more attractive.

At 0 °C cyanuric chloride is therefore already susceptible to alcoholyis and aminolysis as well as hydrolysis.

As discovered by Banks, these substitution reactions can be catalyzed by acid and in fact, the more electrophilic triazonium ion is more reactive will be cyanuric chloride itself. An acid catalysis can also take place in aqueous medium, provided that nucleophilic reactant does not prevent protonation of the triazine ring. For this reason, the reaction of cyanuric chloride with alcohols and aromatic amines in particular can be catalyzed by acids.

Zollinger investigated the reaction of cyanuric chloride with aniline in benzene and showed that it is catalyzed by acid and base or both.

To prevent a possible acid catalysis in the substitution of a chlorine atom in cyanuric chloride by -OH, - OCH₃ or - OC₂H₅ to give hydroxy and alkoxy dis chloro - s - triazine, the reaction is best carried out in the presence of an acid binding medium preferably sodium bicarbonate.

The reaction of cyanuric chloride with ammonia or with amine; depending upon the temperature of the reaction may replace one, two or all of the chlorine atoms.

2,4,6 - Trichloro-s-triazine is mono aminated at temperature 0-5°C depending on the nucleophilicity of the amine and on the solvent with ammonia and alkyl amine. One chlorine atom is replaced at 0-5°C, second at 35-45°C and third at 80-100°C.
III.5 Literature on Biological Activity Studies of Different Triazine Derivative

Yongquin Wei et al.\textsuperscript{25} have worked on a polymeric cobalt compound [Co(DCNT)(H$_2$O)]$_n$ with novel topology: Synthesis, structure, luminescence, and magnetic property. The hydrothermal reaction of Co(NO$_3$)$_2$. 6H$_2$O and a new designed ligand H$_2$DCNT yields a three-dimensional polymer [Co(DCNT) (H$_2$O)], H$_2$DCNT=2,4-bis(4-carboxyphenylamino)-6-diethylamino-1,3,5-triazine (Figure 11). In the structure [Co(DCNT) (H$_2$O)]$_n$ each DCNT$_2^-$ has three coordination sites, one nitrogen atom in the triazine ring coordinating to Co(II) and two carboxylates adopting bridging mode, which make the infinite Co(II) chains array uniformly and evenly toward crystallographic c-axis. Luminescent and magnetic properties of [Co(DCNT) (H$_2$O)]$_n$ were also studied.

![Figure 11](image)

Jignesh P. Raval et al.\textsuperscript{26} have reported synthesis and In vivo antimicrobial activity of N’-[4(arylamino)-6-(pyridin-2-ylamino)1,3,5-triazin-2-yl]benzohydrazide. Variety of N’-(4-(arylamino)-6-(pyrazin-2-ylamino)-1,3,5-triazin-2-yl)isonicotinohydrazide, were synthesized by using 2-aminopyridine, isonicotinic acid hydrazide and cyanuric chloride (Figure 12). The structures of these compounds were confirmed by IR, NMR ($^1$H & $^{13}$C) spectral analysis. The newly synthesized compounds were also evaluated for antimicrobial activity against variety of bacterial strains and some of these compounds have shown significant antibacterial and antifungal activities.
Sonika Jain and coworkers\cite{27} have reported synthesis and antimicrobial evaluation of some novel trisubstituted s-triazine derivatives based on isatinimino, sulphonamido and Azacarbazole (Figure 13).

Hybrid 4-aminoquinoline triazines have been synthesized and evaluated as a new class of antimalarial agents. The emergence and rapid spread of chloroquine resistant strains of \textit{Plasmodium falciparum} has dramatically reduced the chemotherapeutic options. Towards this goal, a series of new class of hybrid 4-aminoquinoline triazines (Figure 14) were synthesized and screened against CQ sensitive strain 3D7 of \textit{P. falciparum} in an \textit{in-vitro} model.\cite{28}
Basedia and co-workers have synthesized fused heterocyclic compounds 1,3,4-oxadiazolo[3,2-a]-s-triazine derivatives based on microwave mediate multi-component reaction (MCRs). They have found that multi-component reactions (MCRs) are economically and environmentally very advantageous because multi-step syntheses produce considerable amounts of waste mainly due to complex isolation procedures often involving expensive, toxic and hazardous solvents after each step. Simpler procedures, equipment, lower costs, time and energy and environmentally friendly. All the synthesized compounds were characterized using physical and spectral analysis. Antimicrobial activity of synthesized compounds was carried out by cup-plate method. All the synthesized compounds show a moderate biological activity. Among them, 11 compounds have shown better significant antibacterial and antifungal activity respectively (Figure 15).

Some novel heterocyclic rings 1,3,4-oxadiazole fused with 1,3,5-triazine have been synthesized and screened for biological activity. Hence, the authors have synthesized fused heterocyclic compounds as a substituted aryl- 1,3,4-oxadiazolo-[3,2-a]-1,3,5-triazine derivatives. The structures of all the compounds were confirmed by physical and spectral analysis. The newly synthesized compounds were evaluated for antimicrobial activity against a variety of bacterial strains and fungal strains. Some of these compounds have shown significant antibacterial and antifungal activity (Figure 16).
A series of novel compounds $N$-(4-(arylamino)-6-(thiazol-2-ylamino)-1,3,5-triazin-2-yl)isonicotinohydrazides were synthesized by a series of multistep reactions. Newly synthesized compounds have been characterized by IR, $^1$H NMR, $^{13}$C NMR and mass spectral data. Antimicrobial screening of title compounds was examined against Gram-positive bacteria ($Staphylococcus aureus$, $Streptococcus pyogenes$), Gram-negative bacteria ($Escherichia coli$, $Pseudomonas aeruginosa$) and three fungi ($Candida albicans$, $Aspergillus niger$, $Aspergillus clavatus$) by using serial broth dilution method. Synthesized compounds showed potent inhibitory action against test organisms. Screened compounds (Figure 17) were associated with considerably higher antibacterial and antifungal activities than commercially used antibiotics.$^{31}$

El-Faham et al. have developed novel series of s-triazine-Schiff base derivatives employing ultrasonic irradiation and characterized by NMR ($^1$H and $^{13}$C), FT-IR, and elemental analysis. The use of ultrasonic irradiation has allowed the preparation of the target products with better
yields in shorter reaction time and excellent purities compared to the conventional heating. X-ray single crystal diffraction experiments verified the molecular structure of four from the new prepared s-triaizne-Schiff base derivatives (Figure 18). The molecular structures of the studied compounds were computerized using DFT/B3LYP method. The effects of substituent at the triazine and phenyl ring on the electronic and spectroscopic properties of the studied compounds were also investigated. The natural atomic charges showed that pipridino-s-triazine derivatives are richer in electrons than those having morpholino derivatives. The anti-proliferative effects for the prepared compounds were tested against three different cancer cell lines.\textsuperscript{32}

Suda et al. have designed and synthesized a new series of 2-amino-6-(1\textit{H},3\textit{H}-benzo[\textit{de}]isochromen-6-yl)-1,3,5-triazines replacing the methyl group of the sulfur atom with hydrogen bond acceptors able to interact with the side chain of Lys58, residue involved in a hydrogen bond with the natural Hsp90 inhibitor geldanamycin.\textsuperscript{33} Among the new compounds, derivative CH5138303 (Figure 19), stimulated the best antiproliferative activity, both \textit{in vitro} and \textit{in vivo}, and the highest enzyme affinity (Kd = 0.48 nM. Additionally, CH5138303 displayed an improved PK profile with a total systemic exposure (AUC) of 24 μg h/ml (i.v.) and 54 μg h/ml (p.o.) compared with CH5015765 which showed an AUC of 8.55 μg h/ml (i.v.) and 7.65 μg h/ml (p.o.).
Arshad and coworkers have reported a comparative theoretical and experimental study of four triazine-based hydrazone derivatives. The hydrazones are synthesized by a three step process from commercially available benzil and thiosemicarbazide. The structures of all compounds were determined by using the UV-Vis., FT-IR, NMR (¹H and ¹³C) spectroscopic techniques and finally confirmed unequivocally by single crystal X-ray diffraction analysis. Experimental geometric parameters and spectroscopic properties of the triazine based hydrazones were compared with those obtained from density functional theory (DFT) studies. The model developed they have comprises of geometry optimization at B3LYP/6-31G (d, p) level of DFT. Optimized geometric parameters of all four compounds showed excellent correlations with the results obtained from X-ray diffraction studies. The vibrational spectra show nice correlations with the experimental IR spectra. Moreover, the simulated absorption spectra also agree well with experimental results (within 10–20 nm). The molecular electrostatic potential (MEP) mapped over the entire stabilized geometries of the compounds indicated their chemical reactivates (Figure 20). Furthermore, frontier molecular orbital (electronic properties) and first hyperpolarizability (nonlinear optical response) were also computed at the B3LYP/6-31G (d, p) level of theory.³⁴

\[ \text{Figure 20} \]

Synthesis of 2,4,6-trisubstituted-1,3,5-triazine derivatives have been proposed by Popiolek and coworkers. The newly synthesized compounds were obtained by sequential nucleophilic substitution of chlorine atoms in cyanuric chloride (Figure 21). Structure of all synthesized compounds were confirmed by spectral and elemental analysis.³⁵
III.6 Literature on Biological Activity Studies of Different Triazine Derivative Fused With Coumarin

Coumarins are cinnamic acid derived phenolic compounds which are found in fungi, bacteria and plants, particularly in edible plants of different botanical families. The name coumarin is derived from ‘coumarou’, which is the vernacular name of Tonka bean (*Dipteryx odorata willd.*, Fabaceae), from which coumarin was isolated in 1820. Coumarin comes under the benzopyrone family of compounds, all of which consist of a benzene ring joined to a pyrone ring. Most useful coumarins having biological potential are two types (Figure 22):

![Figure 22](image)

4-hydroxy coumarin 4-methyl-7-hydroxy coumarin

Some important compounds isolated from coumarin are Warfarin, Acenocoumarol, Armillarisin A, Novobiocin, Clorobiocin, Hymecromone etc. coumarin and its derivatives could be synthesized in laboratory by Pechmann reaction, perkin reaction, Reformatsky reaction and Knovenegal reaction. Coumarins have been under extensive studies for their
versatile biodynamic activities, for example coumarins with phenolic hydroxyl group have the ability to scavenge reactive oxygen species and thus prevent the formation of 5-HETE and 5-HHT in arachadonic acid pathway of suppression of inflammation. Recently, in vivo studies have revealed the role of coumarins in hepatotoxicity and also in depletion of cytochrome P450. Similarly 1-azacoumarins which is part of quinoline alkaloids are known for their diverse biological activity and recently, a 6-functionalized 1-aza coumarins are undergoing human clinical trials as an orally active antitumor drug in view of its farnesyl protein-inhibiting activity in the nanomolar range. Furthermore, several synthetic coumarins with a variety of pharmacophoric groups at C-3, C-4 and C-7 positions have been intensively screened for anti-microbial, anti-HIV, anti-cancer, lipidlowering, anti-oxidant, and anti-coagulation activities. Specifically, coumarin-3-sulfonamides and carboxamides were reported to exhibit selective cytotoxicity against mammalian cancer cell lines.\(^{38}\)

Mulwad et al have treated 3-formyl-4-hydroxycoumarin treated with semicarbozide to give 4-hydroxy-2-oxo-2H[1]-benzopyran-3-aldehyde semicarbzones, which on oxidative cyclization with bromine in gl. Acetic acid in the presence of anh. sodium acetate gives 3-(5-amino-1,3,4-oxadiazol--yl)-4-hydroxy-2H[1]-benzopyran-ones followed by reaction with aromatic aldehyde gives compound which on reaction with phenyl isocyanate gives the desired compound (Figure 23).\(^{39}\)

![s-Triazine derivatives based quinoline demonstrate a wide range of biological activity has been discussed by Kavitha et al. In their investigation 4, 7 -dichloroquinoline as taken as starting material and was treated with ethylene diamine afforded 4-substituted-7-chloroquinoline, Which further reacted with 1, 5-disubstituted cyanuric chloride yielded 1,3,5-triazine chloroquinoline derivatives. All the synthesized compounds were characterized using IR, \(^1\)H, \(^13\)C NMR, mass spectral studies and elemental analysis. The final compounds](#)
were screened for their antibacterial activity using *E. coli*, *S. aureus* and *S. typhi* and antifungal activity (Figure 24).

Moreover, Kavitha and coworkers have demonstrated s-Triazine derivatives based quinoline and their biological activity. They have treated 4,7-dichloroquinoline with ethylene diamine, which afforded 4-substituted 7-chloroquinoline. It was further reacted with 1,5-disubstituted cyanuric chloride yielding 1,3,5-triazine chloroquinoline derivatives. All the synthesized compounds were characterized using IR, $^1$H, $^{13}$C NMR, mass spectral studies and elemental analysis. The final compounds were screened for their antibacterial activity using *E. coli*, *S. aureus* and *S. typhi* and antifungal activity (Figure 25).

Metal complexes of 7-hydroxy coumarin hydrazone of s-triazine derivatives derived from 7-hydroxy-8-aceto-N-(4’,6’-dichloro-1’,3’,5’-striazone) (Figure 26) coumarin hydrazone and transition metals have been synthesized and screened for their antibacterial, antifungal and antiseptic activity by Jani and coworkers. The geometry of the complexes has been proposed. The ligand system co-ordinates with the metal ion in a bidentate manner through the nitrogen atom of hydrazone group.
Among all heterocycles, the triazine scaffold occupies a prominent position, possessing a broad range of biological activities has been discussed by Singla and coworkers. Triazine was found in many potent biologically active molecules with promising biological potential like anti-inflammatory, anti-mycobacterial, anti-viral, anti-cancer etc. which makes it an attractive scaffold for the design and development of new drugs. The wide spectrum of biological activity of this moiety has attracted attention in the field of medicinal chemistry. Due to these biological activities, their structure reactivity relationship has generated interest among medicinal chemists and this has culminated in the discovery of several lead molecules. The outstanding development of triazine derivatives in diverse diseases within very short span of time proves its magnitude for medicinal chemistry research. Therefore, these compounds have been synthesized as target structure by many researchers, and were further evaluated for their biological activities. They have compiled and discussed the biological potential of s-triazine derivatives, which could provide a low-height flying bird's eye view of the triazine derived compounds to a medicinal chemist, for a comprehensive and target oriented information for the development of clinically viable drugs (Figure 27).
A new series of s-triazine derivatives, aryl amino s-triazine and aryl ureido s-triazine has been synthesized by the condensation of aryl amine and aryl ureido with 2- [4'-methyl - 6' - chloro -2H- chromen -2' -one-7'-oxy]-4-(3'-acetyl aminophenyl)-6-chloro s-triazine (Figure 28) in acetone as a solvent and Potassium carbonate using as a neutralizing agent. The structures of all these compounds were confirmed on the basis of their analytical and spectral data. The title compounds were screened for their antibacterial activity.

![Figure 28](image)

A series of 2-[4-cyano-(3-trifluoromethyl)phenyl amino]]-4-(4-quinoline/coumarin-4-yloxy)-6-(fluoropiperazinyl)- s-triazines has been synthesized by a simple and efficient synthetic protocol (Figure 29). The antimicrobial activity of the compounds was studied against several bacteria (Staphylococcus aureus MTCC 96, Bacillus cereus MTCC 619, Escherichia coli MTCC 739, Pseudomonas aeruginosa MTCC 741, Klebsiella pneumoniae MTCC 109, Salmonella typhi MTCC 733, Proteus vulgaris MTCC 1771, Shigella flexneria MTCC 1457) and fungi (Aspergillus niger MTCC 282, Aspergillus fumigatus MTCC 343, Aspergillus clavatus MTCC 1323, Candida albicans MTCC 183) using paper disc diffusion technique and agar streak dilution method. Newly synthesized compounds were also tested for their in vitro antimycobacterial activity against Mycobacterium tuberculosis H37Rv using BACTEC MGIT and Lowenstein–Jensen MIC method.

![Figure 29](image)

Synthesis and antibacterial activity of new Oxadiazolo[1,3,5]triazine, 1,2,4-Triazolo and Thiadiazolo[1,3,4]oxadiazole derivatives (Figure 30).
III.7 Biological Activity Studies of Different Triazine Derivative Fused With Phenyl Urea

In 2007, Desai and coworkers synthesized some novel aliphatic thiourea derivative containing s-triazine moiety and reported on its antimicrobial activity. Antibacterial activity were performed on gram-positive and gram-negative bacteria (*Staphylococcus aureus*, *Pseudomonas aeruginosa*) and reported as mild active agents (Figure 31).46

To develop new anticancer agents two new series of 2,4-bismorpholino-1,3,5-triazine derivatives were prepared, and hydrazinyl derivatives47,48 and the 1,3,5-triazin-2-ylhydrazinecarboxamide49 displayed antiproliferative activity against the cancer cell lines H460, HT-29 and MDA-MB-231 with IC_{50} values in the nanomolar range. Compounds shown in figure 32 resulted particularly active against the H460 cell line with IC_{50} values of 0.07 and 0.05 μM, respectively. Preliminary SAR studies suggested that the presence of 1-benzyl-1H-indol-3-yl-methylene moiety is crucial for the antiproliferative activity of this class of compounds; and that, a smaller group on the benzene resulted advantageous for the
activity. For the series of bis(morpholino-1,3,5-triazine) bearing arylmethylene hydrazine moiety, the arylmethylene group and the $N$-phenylmethanamide linker were found essential for the anticancer activity. The most promising compound of the series, derivative, showed IC₅₀ values of 0.75, 0.34 and 0.60 μM against H460, HT-29 and MDA-MB-231 cell lines. It was also demonstrated that the antiproliferative activity of potent compounds was not related to a mechanism of inhibition of mTOR kinase (Figure 32).

![Figure 32](image)

Naik and coworkers have synthesized some novel triazine derivatives containing 7-hydroxy-4-methyl coumarin and phenylurea substitutions.⁴⁴

![Figure 33](image)

Several $N'$-{4-[(3-chloro-4-fluorophenyl) amino]-6-[(aryl) amino]-1,3,5-triazin-2-yl} isonicotinohydrazides and $N2$-(Aryl)-$N4$, $N6$-dipyrimidin-2-yl-1,3,5-triazine-2,4,6-triamines were prepared (Figure 34). All newly synthesized compounds have been tested for their antibacterial activity against gram (+)ve and gram (-)ve bacteria and also on different strains of fungi. Introduction of -OH, -OCH₃, -NO₂, -Cl and –Br groups to the heterocyclic frame work enhanced antibacterial and antifungal activities.⁵⁰
Some novel 1-{4-Chloro-6-[3-(6-methoxy-benzothiazol-2-ylazo)-2,6-dimethyl-quinolin-4-yloxy]-[1,3,5] triazin-2-yl}-(substituted phenyl)-urea (Figure 35) were synthesized and studied for their microbial activity. These compounds were prepared by the condensation of substituted phenylurea with [4-(4,6-Dichloro-[1,3,5]triazin-2-yloxy)-2,6-dimethyl-quinolin-3-yl]-{(6-methoxy-benzothiazol-2-yl)-diazene which was prepared by the reaction between 3-[(6-methoxy-benzothiazol-2-yl)-diazinyl]-2,6-dimethyl-4-hydroxyquinoline and cyanuric chloride. 3-[(6-methoxy-benzothiazol-2-yl)-diazinyl]-2,6-dimethyl-4-hydroxyquinoline prepared by coupling of 2,6-dimethyl-4-hydroxyquinoline and diazotized 2-amino-6-methoxy benzothiazole. All the compounds were characterized by elemental analysis and spectral studies.51

Novel 4, 6-dimethoxypyrimidin-2-amine and urea derivatives fused with trichloro s-triazine has been synthesized by Parikh and coworkers. All the synthesized compounds were characterized by conventional and instrumental methods. Their structures were determined and important biological properties has been studied (Figure 36).52
A series of urea and thiourea derivatives of s-triazine have been developed based on high yielding nucleophilic substitution of 2,4,6-trichloro-1,3,5-triazine by 4-hydroxy coumarin, cyclopropylamine and ammonia at suitable conditions (Figure 37). These were further treated with various substituted aryl isocyanate and aryl isothiocyanate. All the synthesized compounds were evaluated for their antibacterial activities against various Gram-positive and Gram-negative strains of bacteria. A few compounds showed good to superior in vitro antibacterial activity against *S. aureus*, *B. subtilis*, *E. coli* and *P. aeruginosa* respectively. The new synthesized compounds were characterized using IR, $^1$H-NMR and elemental analysis.53

Novel 2-(coumarin-4-yloxy)-4,6-(substituted)-s-triazine derivatives i.e., diaryltriazine (DATA) has been reported as novel non-nucleoside reverse transcriptase inhibitors (NNRTIs), were synthesized and their activities against human immunodeficiency virus HIV-1 (III-B), HIV-2 (ROD), and the double RT mutant HIV-1 (K103N and Y181C) were assessed. Modifications at positions 4 and 6 of the coumarinyl-triazine scaffold generated interesting derivatives displaying good to moderate anti-HIV activity against selected HIV
strains as compared to Nevirapine and Efavirenz. The synthesized compounds were characterized by FTIR, $^1$H-NMR, and mass spectral data together with elemental analysis (Figure 38).\textsuperscript{54}

![Figure 38](image)

Patel et al. have discovered novel candidates with improved antimicrobial activities. They have performed \textit{in vitro} biological evaluation of various series of 2-(N-methylamino)-4-(N,N-dimethylamino)-6-(arylthiourea)-3-triazine and (N-methylamino)-4-(N,N-dimethylamino)-6-(arylurea)-3-triazine. All the synthesized compounds were screened \textit{in vitro} for their antibacterial activity against two different gram-positive bacteria (\textit{S. aureus}, \textit{B. subtilis}) and two different gram-negative bacteria (\textit{P. aeruginosa}, \textit{E. coli}) using the broth dilution method (Figure 39).\textsuperscript{55}

![Figure 39](image)

A series of segmented poly (urethane-urea)s containing 1,3,5 triazine in the hard block and hexamethylene spacers in the soft block was prepared. The hard to soft segment ratio was varied systematically, to afford a series of polymers in which the chromophore concentration varied from 4.2\% to 18.1\%. Although triazine emission is located in the UV region, the films with higher content of the chromophore emitted a visible blue light (425 nm) when excited at
the very red-edge of the absorption band. The photo physical properties of the materials were strongly dependent on the relative amount of triazine moieties along the main chain. Isolated moieties emit in copolymers with small amount of triazine groups, indicating that even though in solid state, these moieties tend to be apart. Two photophysical consequences were observed when the amount of triazine increases: there is some energy transfer process involving isolated moieties with consequent decrease of the lifetime and an additional red-edge emission attributed to aggregated lumophores. The mono-exponential decay observed for the isolated form is substituted by a bi-exponential decay of the aggregated species. The materials were not strong emitters, but since the N-containing triazine moieties are good electron transport groups, the polymers have potential application as electron transport enhancers in various applications (Figure 40).\textsuperscript{56}

![Figure 40](image-url)
III.8 Biologically Active Compounds Containing Triazine and other Substitutes Using Cyanuric Chloride

1, 3, 5-triazine derivatives have received considerable attention owing to their broad biological activities, which have made it an indispensable anchor for development of new therapeutic agents. Owing to fast development of new drugs possessing 1, 3, 5-triazine nucleus, many research reports are generated in a short span of time. Although only a few compounds have at present progressed into human clinical trials, the prospect of finding safe agents useful in therapy, particularly in the cancer setting, is still positive. To our knowledge, few systematic reviews on triazines have been conducted to date. They have highlighted various inhibitors with 1, 3, 5-triazine core (Figure 41) which targeting different kinases with an aim to help medicinal chemists for developing structure-activity relationship on 1, 3, 5-triazine derived compounds for antitumor activity.57

A Series of 2,4,6-trisubstituted 1,3,5 triazines (Figure 42) have been synthesized and evaluated for their in-vitro antifungal activity against Candida albicans by Sarmah and coworkers. Out of 10 compounds, all of them showed antifungal activity in the range of 1000 μg/ml to 10 μg/ml. All the compounds were found active against the said fungus. The promising results were in support of the fact that the compounds have worth to be optimized.
for some novel drugs in future. The newly synthesized compounds were characterized using IR, $^1$H-NMR.\(^{58}\)

![Figure 42](image)

Figure 42

Bhat et al have developed a novel series of hybrid 4-aminoquinolines-1,3,5-triazine by means of aromatic nucleophilic displacement of chlorine atoms of 2,4,6-trichloro-1,3,5-triazine. Afforded title analogs were subsequently characterized by elemental analysis, FT-IR, $^1$H NMR, $^{13}$C NMR and mass spectroscopy and subjected to screening against chloroquine sensitive RKL\(_2\) strain of Plasmodium falciparum in 96 well-microtitre plates. However, synthesized derivatives exhibited mild to moderate antimalarial activity and acute toxicity studies of the most active compounds were shown to have no significant change in body insight and toxic sign (Figure 43).\(^{59}\)

![Figure 43](image)

Figure 43

Synthesis and anticancer activity of novel 2-amino-4-(4-phenylpiperazine)-1,3,5-triaine derivatives were described by Pomarnacka and coworkers. Four compounds were evaluated for in vitro assays of growth inhibition against several human tumor cell lines. In vitro cytotoxicity activity was found for 2-{2-amino-4-[4-(2-chlorophenyl)piperazino]-1,3,5-
triazin-6-yl]-3-(4-nitrophenyl) acrylonitrile (IC\textsubscript{50} = 0.45 \text{um}), whilst other tested compounds were inactive.\textsuperscript{60} (Figure 44)

Recently, Ng et al have discussed that the dihydrofolate reductase (DHFR) and thioredoxin reductase (TrxR) enzymes are involved in the process of tumor cell growth and survival. The 4,6-diamino-1,2-dihydro-1,3,5-triazine scaffold was well-established as a useful scaffold for DHFR inhibition, while chalcones have been reported to be inhibitors of TrxR. In their study, 15 novel compounds designed by the structural combination of the 4,6-diamino-1,2-dihydro-1,3,5-triazine and chalcone scaffolds via a di-ether linker have been successfully synthesized and characterized. All of the compounds demonstrated dual inhibition against DHFR and TrxR when they were assessed by \textit{in vitro} enzyme assays. The compounds also exhibited antiproliferative activity against the MCF-7 and HCT116 cells. The more potent analogs (Figure 45) were found to inhibit cellular DHFR and TrxR activities in HCT116 cells. Therefore, the study provided compelling evidence that compounds shown in figure 6 could exert their anticancer property \textit{via} multi-target inhibition at the cellular level.\textsuperscript{61}

In 2017, Lee et al have discussed regarding dry eye disorders, which is a significant health problem for which limited therapeutic options are available. CFTR is a major pro-secretory chloride channel at the ocular surface. They have previously identified, by high-throughput screening, aminophenyl-1,3,5-triazine CFTRact-K089 that activated CFTR with EC\textsubscript{50} ~250 nM, which when delivered topically increased tear fluid secretion in mice and showed efficacy in an experimental dry eye model. Functional analysis of aminophenyl-1,3,5-triazine
analogs elucidated structure-activity relationships for CFTR activation and identified substantially more potent analogs. The most potent compound, fully activated CFTR chloride conductance with EC$_{50}$ $\sim$30 nM, without causing cAMP or calcium elevation. Compound shown in figure 7 was rapidly metabolized by hepatic microsomes, which supports its topical use. Single topical administration of 25 pmol 12 increased tear volume in wildtype mice with sustained action for 8 hours, and was without effect in CFTR-deficient mice. Topically delivered compound may be efficacious in human dry eye diseases (Figure 46).  

![Figure 46]

Derosa et al have prepared 1,2,4-, and 1,3,5-triazine derivatives, by Armistead and Bebbington, respectively, were effective as phosphoryl transferase inhibitors and used in the treatment of cardiovascular diseases. (Figure 47)  

![Figure 47]

A variety of N'-(4-(arylamino)-6-(pyrazin-2-ylamino)-1,3,5-triazin-2-yl)isonicotinohydrazides (Figure 48) were synthesized by using 2-aminopyridine, isonicotic acid hydrazide and cyanuric chloride by Raval and coworkers. The structures of these compounds were confirmed by IR, NMR ($^1$H & $^{13}$C) spectral analysis. The newly synthesized compounds were also evaluated for their antimicrobial activity against variety of bacterial strains and some of these compounds have shown significant antibacterial and antifungal activities.
Rusinov et al have developed a series of substituted 2-amo-3-ethoxycarbonylpyrazines containing indole, resorcinol, thiophenol, ethyl cyanoacetate, indandione, and antipyrine moieties via reactions of nucleophilic substitution of hydrogen in the initial 2-aminopyrazine-1-oxides. Some of the synthesized compounds inhibit the reproduction of measles viruses and exhibit a weak antiviral activity with respect to Marburg virus. However, most of the new substituted pyrazines (Figure 49) were not cytotoxic and exhibit no activity against orthopoxviruses and measles viruses.\(^{65}\)

In 2017, Three series of novel 8-morpholinoimidazo[1,2-a] pyrazine derivatives bearing phenylpyridine/phenylpyrimidine-carboxamides have been synthesized by Xu and coworkers. They have evaluated all the synthesized compounds for their IC\(_{50}\) values against three cancer cell lines (A549, PC-3 and MCF-7). Most of the target compounds exhibited moderate cytotoxicity against the three cancer cell lines. Two selected compounds were further tested for their activity against PI3K kinase, and the results indicated that compound showed inhibitory activity against PI3K kinase with an IC\(_{50}\) value of 1.25 \(\mu\)M. Structure-activity relationships (SARs) and pharmacological results indicated that the replacement of the thiopyranopyrimidine with an imidazopyrazine was beneficial for the activity and the position of aryl group has a significant influence to the activity of these compounds. The compounds, in which an aryl group substituted at the C-4 position of the pyridine ring were more active than substituted at the C-5 position. Moreover, the cytotoxicity of compounds bearing phenylpyrimidine-carboxamides was better than that of the compounds bearing phenylpyridine-carboxamides.
Furthermore, the substituents on the benzene ring also had a significant impact on the cytotoxicity and the pharmacological results showed that electron donating groups were beneficial to the cytotoxicity (Figure 50).  

![Figure 50](image)

David et al have synthesized some novel 2-amino-3,5-dicyano-6-(substituted)pyrazine derivatives and evaluated for antimicrobial activity (Figure 51).  

![Figure 51](image)

Kumar et al have synthesized a novel class of hybrid 4-anilinoquinoline triazines (Figure 52) and evaluated in vitro for their antimalarial activity against CQ-sensitive 3D7 strain of *P. falciparum* as well as for their cytotoxicity toward VERO cell line. Five compounds exhibited the antimalarial potency superior to CQ. Two compounds were found to be orally active at a dose of 100 mg/kg 4 days against CQ-resistant strain of *P. yoelii*. Inhibition of b-hematin formation assay and molecular docking study has been conducted in order to gain insight into the mechanism of action of proposed targets for the 4-anilinoquinoline and triazine moiety of the hybrid compounds.  

![Figure 52](image)
III.9 Synthesis of Triazine Derivatives Functionalized by Pyrazine and Other Heterocycles

Solankee et al have reacted developed novel chalcones upon refluxing of ketone and different substituted aromatic and heterocyclic aldehydes in suitable solvent. Further chalcones on cyclisation with malononitrile in presence of ammonium acetate and hydrazine hydrate in presence of acetic acid gave cyanopyridines and acetyl pyrazoline (Figure 53), respectively. All the synthesized compounds have been characterized by their physical data and spectral data.69

1,2,4-Triazine 4-oxides were found to enter into the reactions of nucleophilic substitution of hydrogen with S-nucleophiles (arenethiols) in the presence of acylating agents and trifluoroacetic acid. The reactions proceeded with loss of the N-oxide function to form 5-
arylthio-1,2,4-triazines. 2-amino-3-ethoxycarbonylpyrazine 1-oxides and 2-amino-4-oxopterin 8-oxides react with arenethiol analogously (Figure 54).  

![Figure 54](image)

Binggeli et al have demonstrated that pyrazine and triazine derivatives of 1,2,4,5-tetrahydro Benzo or Thieno azepine and their pharmaceutically acceptable salts (Figure 55) and tested for their affinity towards metabotropic glutamate receptors and are therefore useful in the treatment or prevention of acute or chronic neurological disorders.  

![Figure 55](image)

Karmer et al have invented new compositions comprising compounds, which are molecular combinations of aphthalocyanine and a mono-azo dyestuff linked via specific linking groups (Figure 56). Further aspects was to improved shading process for textile materials and also use of these shading compositions for shading textiles.  

![Figure 56](image)
Blotny et al. have discussed about 1,3,5-Triazine derivatives which were known for a long period of time. They have found widespread applications in the pharmaceutical, textile, plastic, and rubber industries, and are used as pesticides, dyestuffs, optical bleaches, explosives, and surface active agents. The chemistry of this group of compounds has been studied intensively.

Reaction of 3-amino-1,2,4-triazine (3-atz) or 2-aminopyrazine (2-apz) with Cu(hfac)$_2$x H$_2$O led to the formation of the monometallic and trimetallic complexes Cu(hfac)$_2$(3-atz)$_2$, Cu$_3$(hfac)$_6$(3-atz)$_2$, Cu(hfac)$_2$(2-apz)$_2$ and Cu$_3$(hfac)$_6$(2-apz)$_2$. The azine molecules behave as both monodentate and bridging bidentate ligands. The Cu(II) ions exhibit a range of coordination geometries. The complex was distorted octahedral with the Jahn–Teller axis lying along one of the O–Cu–O axes. The central Cu(II) ion is also distorted octahedral with the Jahn–Teller axis lying along the N–Cu–N axis, while the terminal Cu(II) ions are five-coordinate. Structure analysis reveals that addition of the amino substituent makes the ligands more coordinating, leading to shorter CuAN bonds. The results in a stronger magnetic super exchange pathway and the complex exhibits antiferromagnetic behavior at low temperatures.

Fauber et al. have identified a 2-amino-5-aryl-pyrazine (Figure 57) as an inhibitor of human lactate dehydrogenase A (LDHA) via a biochemical screening campaign. Biochemical and biophysical experiments demonstrated that the compound specifically interacted with human LDHA. Structural variation of the screening hit resulted in improvements in LDHA
biochemical inhibition and pharmacokinetic properties. A crystal structure of an improved
compound bound to human LDHA was also obtained and it explained many of the observed
structure–activity relationships.\(^7\)

![Figure 57](image)

In 2008, Adib et al have described an efficient, one-pot, multi-component synthesis of 3-
amino-2-arylimidazo[1,2-a]pyridines, 3-amino-2-arylimidazo[1,2-a]pyrazines, and 3-amino-
2-arylimidazo[1,2-a]pyrimidines (Figure 58). They have heated a mixture of a 2-
aminopyridine, 2-aminopyrazine or 2-aminopyrimidine, a benzaldehyde, and imidazoline-
2,4,5-trione under solvent-free conditions afforded imine derivatives of the title compounds
in excellent yields. Single-crystal X-ray analysis conclusively confirms the structure of these
bridgehead bicyclic 5–6 heterocycles.\(^6\)

![Figure 58](image)

A range of novel heterocyclic -amino acids (Figure 59) has been reported by Adlington and
coworkers. They have synthesized diamines and amidrazones with â-amino acid vicinal
tricarbonyl reactive substrates.\(^7\)

![Figure 59](image)

Mikami et al have discovered a clinical Candidate \(N\-((1S)-1-(3-Fluoro-4-
(trifluoromethoxy)phenyl)-2-methoxyethyl)-7-methoxy-2-oxo-2,3-dihydropyrido

[2,3-b]pyrazine-4(1H)-carboxamide (TAK-915) (Figure 60): A Highly Potent, Selective, and Brain-Penetrating Phosphodiesterase 2A Inhibitor for the Treatment of Cognitive Disorders.\textsuperscript{78}

\begin{center}
\includegraphics[width=0.5\textwidth]{figure60.png}
\end{center}

Figure 60

In recent time, Chu et al have developed an efficient protocol for the synthesis of trisubstituted pyrrolo[1,2-a]pyrazines (Figure 61) through three components cyclization and one-pot cascade reaction. Various trisubstituted pyrrolo[1,2-a]pyrazines were obtained by this metal-free process in moderate to good yields.\textsuperscript{79}

\begin{center}
\includegraphics[width=0.5\textwidth]{figure61.png}
\end{center}

Figure 61

Transition metal-catalyzed reactions are generally used for carbon–carbon bond formation on pyrazines and include, but are not limited to, classical palladium-catalyzed reactions like Sonogashira, Heck, Suzuki, and Stille reactions. Also a few examples of carbon–heteroatom bond formation in pyrazines were known. This perspective reviews recent progress in the field of transition metal-catalyzed cross-coupling reactions on pyrazine systems. It deals with the most important C–C- and C–X-bond formation methodologies\textsuperscript{80} (Figure 62).
Adlington et al have described the reaction of diamines and amidrazones with \( \alpha \)-amino acid vicinal tricarbonyls (Figure 63) and shown to be a versatile route towards novel heterocyclic \( \alpha \)-amino acids. This route was also applicable to parallel synthesis and has allowed the formation of a range of heterocyclic amino acid systems.\(^8\) 

Chauhan et al have discussed that new compound for leishmaniasis is therefore a pressing concern for the anti-infective research program. They have synthesized 19 compounds of triazine dimers as novel antileishmanial agents. Most of the synthesized derivatives exhibited better activity against intracellular amastigotes (IC\(_{50}\) ranging from 0.77 to 10.32 \( \mu \text{M} \)) than the control, pentamidine (IC\(_{50}\) = 13.68 \( \mu \text{M} \)), and are not toxic to Vero cells. Two compounds showed significant \textit{in vivo} inhibition of 74.41\% and 62.64\%, respectively, in L. donovani/hamster model. Moreover, expansion of Th1-type and suppression of Th2-type immune responses proved that compound (Figure 64) stimulates mouse macrophages to
prevent the progression of leishmania parasite. The molecular docking studies involving
PTR1 protein PDB further validated the concepts involved in the design of these compounds.
Among the investigated analogues, compound shown in figure has been emerged as the
potential one to enlarge the scope of the study.\textsuperscript{82}

![Figure 64](image)

\textbf{Figure 64}

One year ago, Hasmi et al have developed a convenient synthetic protocol for the formation
of [1,3,4]thiadiazolo- and [1,2,4]oxadiazolo- substituted 2,4-dicyclopropylamino-6-phenoxy-
s-triazines (\textbf{Figure 65}) by utilizing the versatility of thiosemicarbazone and amidine
intermediates respectively.\textsuperscript{83}

\begin{center}
\textbf{Figure 65}
\end{center}

Several specific synthetic protocols were developed by Afonso and coworkers, for the
preparation from cyanuric chloride of a range of symmetric and non-symmetric di- and tri-
substituted 1,3,5-triazines containing alkyl, aromatic, hindered, chiral and achiral hydroxyalkyl, ester and imidazole groups via sequential nucleophilic substitution of the C-Cl bond by C-O, C-N and C-S bonds. (Figure 66).

Patel et al have synthesized a series of 2-[4-cyano-(3-trifluoromethyl)phenyl amino]-4-(4-quinoline/coumarin-4-yloxy)-6-(fluoropiperazinyl) s-triazines by a simple and efficient synthetic protocol. The antimicrobial activity of the compounds was studied against several bacteria (Staphylococcus aureus MTCC 96, Bacillus cereus MTCC 619, Escherichia coli MTCC 739, Pseudomonas aeruginosa MTCC 741, Klebsiella pneumoniae MTCC 109, Salmonella typhi MTCC 733, Proteus vulgaris MTCC 1771, Shigella flexneria MTCC 1457) and fungi (Aspergillus niger MTCC 282, Aspergillus fumigatus MTCC 343, Aspergillus clavatus MTCC 1323, Candida albicans MTCC 183) using paper disc diffusion technique and agar streak dilution method. Newly synthesized compounds were also tested for their in vitro antimycobacterial activity against Mycobacterium tuberculosis H37Rv using BACTEC MGIT and Lowenstein–Jensen MIC method (Figure 67).
Figure 67
III.10 Introduction to Thiazole Derivatives

The thiazoles and benzothiazoles (Figure 68) are found in a wide variety of bioactive molecules and natural products. The terrestrial and marine organisms / microorganisms have been a prominent source of these heterocycles. These naturally occurring secondary metabolites or polyketides are often bioactive and a large bulk of literature is being published related to their isolation, chemistry and biology.

Thiazole and its derivatives have been of great scientific exploitation and interest as these are accompanied with almost all the biological and pharmacological activities, like antibacterial, antiprotozoal, antimalarial, anticancer, treat allergies, genemodulating activities, anti schizophrenia, antihypertension, anti-inflammation, anti-HIV infections and many more.

The complex natural product antibiotics containing nitrogen heterocycle thiazole are secondary metabolites produced by actinomycetes, Gram-positive mycelial sporulating bacteria, largely of the genus Streptomyces. Many among this thiopeptide antibiotic family possess similar biological profile, with almost no activity against Gram-negative bacteria, whereas very active against Gram positive bacteria by inhibiting protein synthesis and are in many cases effective against methicillin-resistant Staphylococcus aureus (including multidrug-resistant S. aureus strains (MRSA)). Their mode of action is based on inhibition of bacterial protein translation by blocking the ribosomal GTPase-associated center or by inhibiting the translation factor EF-Tu.
III.11 Biologically Active Compounds Containing Benzothiazole Derivatives

Recently, the first structure-activity relationships for a benzothiazole scaffold acting as an antagonist at GPR35 was presented by Abdalhameed and coworkers. The novel analogues were designed based on a lead compound that was previously determined to have selective activity as a GPR35 antagonist. The synthetic route was modular in nature to independently explore the role of the middle and both ends of the scaffold. The activities of the analogues illustrate the importance of all three segments of the compound (Figure 69).94

Lindsley et al. have demonstrated that glutamate is the major excitatory transmitter in the mammalian central nervous system (CNS), exerting its effects through both ionotropic and metabotropic glutamate receptors. The metabotropic glutamate receptors (mGlus) belong to family C of the G-protein-coupled receptors (GPCRs). The eight mGlus identified to date are classified into three groups based on their structure, preferred signal transduction mechanisms, and pharmacology (group I: mGlu1 and mGlu5; group II: mGlu2 and mGlu3; group III: mGlu4, mGlu6, mGlu7, and mGlu8). Noncompetitive antagonists, also known as negative allosteric modulators (NAMs), of mGlu5 offer potential therapeutic applications in diseases such as pain, anxiety, gastresophageal reflux disease (GERD), Parkinson’s disease (PD), fragile X syndrome, and addiction. The development of structure-activity relationships (SAR) in a (3-cyano-5-fluorophenyl)biaryl series using our functional cell-based assay was described. Further characterization of a selected compound, 3-fluoro-5-(2-methylbenzo[d]thiazol-5-yl)benzonitrile (Figure 70), in additional cell based assays as well as in vitro assays designed to measure its metabolic stability and protein binding indicated its potential utility as an in vivo tool. Subsequent evaluation of the same compound in a pharmacokinetic study using intraperitoneal dosing in mice showed good exposure in both plasma and brain samples. The compound was efficacious in a mouse marble burying model of anxiety, an assay known to be sensitive to mGlu5 antagonists. A new operant model of
addiction termed operant sensation seeking (OSS) was chosen as a second behavioral assay. The compound also proved efficacious in the OSS model and constitutes the first reported example of efficacy with a small molecule mGlu5 NAM in this novel assay.\(^95\)

Recently Cindric et al. have designed and synthesized novel 2-imidazolinyl substituted benzo[b]thieno-2-carboxamides bearing either benzimidazole or benzothiazole subunit and biological activity. The antiproliferative activities were assessed \textit{in vitro} on a panel of human cancer cell lines. Tested compounds showed moderate activity while cytotoxicity on normal fibroblasts was lower in comparison with 5-fluorouracile. The variations of 2-imidazolinyl substituent at heteroaromatic subunits in different positions led to different cytotoxic properties. The strongest selective activity against HeLa cells was observed for the benzothiazole derivative (Figure 71) with 2-imidazolinyl group at the benzo[b]thiophene subunit with a corresponding IC\(_{50} = 1.16\) mM. Additionally, several biological experiments were performed to explain the mode of biological action. Fluorescence microscopy evidenced nuclear subcellular localization of compounds 3a, 4a and 4c. Additionally, detailed DNA binding studies confirmed a strong DNA groove binding for derivatives 4a and 4c while DNase I footprinting experiments evidenced sequence-selective binding of compound 4c in the A-T rich side. Furthermore, topoisomerase suppressive effect was for compounds 4a-4c.\(^96\)
In 2017, Shaik and coworkers have developed a series of 2-anilinopyridinyl-benzothiazole Schiff bases. They have rationally designed molecules by performing molecular modeling experiments on some selected molecules. The binding energies of the docked molecules were better than the E7010, and the Schiff base with trimethoxy group on benzothiazole moiety (Figure 72) was the best. This was followed by the synthesis of a series of the designed molecules by a convenient synthetic route and evaluation of their anticancer potential. Most of the compounds have shown significant growth inhibition against the tested cell lines and the compound exhibited good antiproliferative activity with a GI50 value of 3.8 mM specifically against the cell line DU145. In agreement with the docking results, compound shown in figure exerted cytotoxicity by the disruption of the microtubule dynamics by inhibiting tubulin polymerization via effective binding into colchicine domain, comparable to E7010. Detailed binding modes of compound with colchicine binding site of tubulin were studied by molecular docking. Furthermore, compound induced apoptosis as evidenced by biological studies like mitochondrial membrane potential, caspase-3, and Annexin V-FITC assays.

Garware et al98 have described the synthesis of benzothiazoles and evaluated for their anthelmintic activity. 2-amino benzothiazole was first converted to 6 substituted derivatives of 2-amino benzothiazole by nitration and bromination reaction to yield 6-nitro-2-amino benzothiazole and 6-bromo-2-amino benzothiazole (Figure 73) respectively. All the derivatives including 2-amino benzothiazole were further treated with chloroacetyl chloride to form chloroaacetamido derivatives of benzothiazole. Further the product was treated with various heterocyclic and aromatic amines. The synthesized compounds were confirmed by IR, 1H NMR and Mass spectral data. Synthesized substituted benzothiazole derivatives were investigated for their anthelmintic activity against Indian adult earthworms (pheretima posthuma) at various concentrations (25 mg/ml and 50 mg/ml). It was observed that the new synthesized compounds possessing electron withdrawing group like nitro and bromo groups
at 6\textsuperscript{th} position of benzothiazole nucleus and chloro, fluoro substituted at 3\textsuperscript{rd} position of aromatic amine exhibited higher anthelmintic activity when compared to that of other synthesized compounds. The present research focus on the different methods of synthesis of substituted benzothiazoles with potential anthelmintic activity that are now in developing phase.

![Figure 73](image)

Through a structure-based molecular hybridization approach, a series of novel benzothiazole derivatives bearing indole-based moiety were designed, synthesized and screened for in vitro antitumor activity against four cancer cell lines (HT29, H460, A549 and MDA-MB-231). Most of them showed moderate to excellent activity against all the tested cell lines. Among them, compounds Figure 74 with substituted benzyl-1H-indole moiety showed better selectivity against HT29 cancer cell line than other compounds. One compound exhibited excellent antitumor activity with IC\textsubscript{50} values of 0.024, 0.29, 0.84 and 0.88 mM against HT29, H460, A549 and MDA-MB-231, respectively. Further mechanism studies indicated that the marked pharmacological activity of compound might be ascribed to activation of procaspase-3 (apoptosis-inducing) and cell cycle arrest, which had emerged as a lead for further structural modifications. Furthermore, 3D-QSAR model (training set: q2 \(\frac{1}{4} 0.850\), r2 \(\frac{1}{4} 0.987\), test set: r2 \(\frac{1}{4} 0.811\)) was built to provide a comprehensive guide for further structural modification and optimization.\textsuperscript{99}

![Figure 74](image)

In 2015, Bhoi et al have found that the benzothiazole and Schiff base moieties are crucial functionalities due to their wide variety of biological activities and have a wide range of
therapeutic properties. Keeping in view the importance of these organic moieties, a new series of 2-Aminobenzothiazole containing novel Schiff bases derivatives were synthesized by sequential reaction. The structures of the synthesized compounds were confirmed by their analytical and spectral data. The synthesized compounds were evaluated for their in vitro antibacterial activity against gram positive and gram negative bacteria (Figure 75). Synthesized compounds showed significant activity against microorganisms, which can be correlated with the privileged heterocyclic structural scaffolds.100

Several complexes of Cu (II) are formed by refluxing purified copper palmitate with 3-substituted 1-phenyl amino methanamide (R₁ = H, R = CH₃) in the ratio 1:1.7 using ethanol as a solvent for four hrs. Resultant solution was filtered hot and complexes were recrystallized using petroleum ether solvent. Granular solid complexes of different colors like light blue, green gray and blackish were obtained in sufficient yield (Figure 76).101
Prabhu et al have evaluated synthesized compounds for antibacterial and antifungal activities against *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Micrococcus luteus*, *Bacillus cereus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Aspergillus niger* and *Candida albicans*. Microbiological results indicated that the synthesized compounds possessed a broad spectrum of activity against the tested microorganisms at MIC values between 36.4-12.4 μgmL⁻¹. Among the synthesized three compounds with para positioned –Cl, –Br, –NO₂ substituents, exhibited most potent *in vitro* antimicrobial activity (Figure 77). The activity contributions for substituent effects of these compounds were determined from the correlation equation for predictions of the lead optimization.¹⁰²
A series of some novel 2-amino benzothiazole derivatives (Figure 78) were synthesized and evaluated for anti-inflammatory activity. The synthesized compounds were synthesized from the substituted aromatic amines through the intermediate substituted 1-phenylthiourea oxidation by bromine water in acidic medium. The purity of the synthesized compounds were judged by their C, H and N analysis and the structure was analyzed on the basis of IR, \(^1\)HNMR and Mass spectral data. The anti-inflammatory activities of new compounds were determined by \(\lambda\)-Carrageenan-induced mice paw edema method using diclofenac sodium as a standard. Among the compounds tested three compounds Bt2 (5-chloro-1,3-benzothiazole-2-amine), Bt (6-methoxy-1,3-benzothiazole-2-amine) and Bt7 (6-methoxy-1,3-benzothiazole-2-amine) were the most active compounds in these series when compared with diclofenac sodium. In the SAR study, the phenyl ring substituted with chloro at 5 position, methoxy substitution at 4 and 6-position in benzothiazole ring system showed better anti-inflammatory activity.\(^{103}\)

\[
\text{R = H, Cl, NO}_2, \text{Br, OCH}_3 \\
\]

Figure 78

Alagille et al have designed and synthesized a small series of 2-aryl-imidazo[2,1-b]benzothiazole (Figure 79), representing a combination of motifs from the two most potent amyloid imaging agents, PIB and IMPY. The binding affinity of the new compounds ranged from 6 to 133 nM. Among the best compounds, one (Ki = 6 nM) was labeled with \(^{11}\)CH\(_3\) for PET imaging whereas (Ki = 10.9 nM) can be labeled with \(^{123}\)I for SPECT imaging.\(^{104}\)

\[
\text{X = OME, Me, F, Br, } \\
\text{Y = NO}_2, \text{I, Br, NMe}_2 \\
\]

Figure 79

A series of 2-amino-substituted benzothiazoles (Figure 80) were synthesized by treating with KSCN in presence of bromine/glacial acetic acid with different substituted anilines, structures
of the all synthesized compounds were established using spectral analysis and examined their antihelmintic activity.\textsuperscript{105}

\begin{tikzpicture}
\node[anchor=north west,inner sep=0] at (0,0) {\includegraphics[width=\textwidth]{figure80.png}};
\end{tikzpicture}

\textbf{Figure 80}

Bondock et al have found a new class of antimicrobial agents, a series of thiazole, thiophene, pyrazole and other related products containing benzothiazole moiety prepared via the reaction of \(N\)-(benzothiazol-2-yl)-2-cyanoacetamide with appropriate chemical reagents. These compounds were screened for their antibacterial activity against Gram-positive bacteria (\textit{Staphylococcus aureus} and \textit{Streptococcus pyogenes}), Gram-negative bacteria (\textit{Pseudomonas phaseolicola} and \textit{Pseudomonas fluorescens}) and antifungal activity against \textit{Fusarium oxysporum} and \textit{Aspergillus fumigatus}. Among the synthesized compounds, thiophene (\textbf{Figure 81}) showed equal activity with chloroamphenicol against \textit{S. aureus} (MIC 3.125 mg/mL), while its activity was 50\% lower than of chloroamphenicol against \textit{S. pyogenes}. Thiazole and pyrazolo[1,5-a]pyrimidines were found to exhibit the most potent \textit{in vitro} antifungal activity with MICs (6.25 mg/mL) against \textit{A. fumigatus} and \textit{F. oxysporum}. Structures of the newly synthesized compounds were established by elemental analysis and spectral data.\textsuperscript{106}

\begin{tikzpicture}
\node[anchor=north west,inner sep=0] at (0,0) {\includegraphics[width=0.5\textwidth]{figure81.png}};
\end{tikzpicture}

\textbf{Figure 81}
III.12 Synthesis and Activity of Triazine Derivatives Fused With Benzothiazole or other Heterocycles

Kumar et al have developed two new series of s-triazine derivatives appended with benzimidazoles and benzothiazole derivatives and structure–activity relationships on anticancer activity of these compounds were probed. *In vitro* inhibitory activity against the growth of six cancer cell lines, viz., MCF-7, MDAMB-231, PC-3, DU-145, HT-29 and HGC-27 was evaluated for synthesized analogues. Among the two series of compounds, derivatives containing benzimidazole scaffold were found to be relatively potent over benzothiazole analogues (Figure 82). In accordance with our previous observation, within benzimidazole derivatives, tri-substituted s-triazine derivatives were found to be more potent over di-substituted derivatives irrespective of cell lines. Structure–activity relationships provided useful insights into these classes of compounds and paved the way to design novel analogues with more potency.107

![Figure 82](image)

Padalkar and coworkers have synthesized some new benzimidazole, benzoxazole and benzothiazole derivatives and screened for antimicrobial activity (Figure 83). The structure of 4,40-((6-(4-(diethylamino)phenyl)-1,3,5-triazine-2,4-diyl)bis(oxy))dibenzaldehyde (DIPOD) was established from p-hydroxy benzaldehyde and 4-(4,6-dichloro-1,3,5-triazin-2-
yl)-N, N-diethylaniline 3. The reaction of DIPOD 5 with different o-phenylenediamine or o-amino phenol or o-amino thiophenol in ethanol gave benzimidazole, benoxazole and benzothiazole. Novel heterocycles showed excellent broad-spectrum antimicrobial activity against bacterial strain (Escherichia coli, Staphylococcus aureus) and fungal strain (Candida albicans, Aspergillus niger) cultures. Activity data was compared with standard Streptomycin and Fluconazole drug. Photophysical and thermal properties of synthesized compounds were also studied.108

Some 1-\{(4-Chloro-6-[3-(6-methoxy - benzothiazol-2-ylazo)-2,6-dimethyl-quinolin-4-yloxy]-[1,3,5] triazin-2-yl\}-(substituted phenyl)-urea were synthesized and studied for their microbial activity by Mistry and coworkers. These compounds were prepared by the condensation of substituted phenylurea with [4-(4,6-Dichloro-[1,3,5]triazin-2-yloxy)-2,6-dimethyl-quinolin-3-yl]-\{(6- methoxy-benzothiazol-2-yl)-diazene (Figure 84) which was prepared by the reaction between 3-\{(6- methoxy-benzothiazol-2-yl)-diazinyl\}-2,6-dimethyl-4-hydroxyquinoline and cyanuric chloride. 3-\{(6-methoxy-benzothiazol-2-yl)-diazinyl\}-2,6-dimethyl-4-hydroxyquinoline prepared by coupling of 2,6-dimethyl-4-hydroxyquinoline and diazotised 2-amino-6-methoxy benzothiazole. All the compounds were characterized by elemental analysis and spectral studies.109
Novel series of N2-(aryl) N4,N6-bis (1,3 benzothiazol-2-yl)-1,3,5 triazine -2,4,6 triamines have been synthesized from the 2,4,6, trichloro-triamine and 2-amino benzothiazoles. They were characterized by the IR, NMR Spectra. The product has been tested for their antimicrobial activities against gram+ve and gram−ve bacteria.\textsuperscript{110}

Sareen et al have demonstrated that cyanuric chloride has been reacted selectively with nucleophilic reagents, 6-fluoro-2aminobenzothiazole, phenyl thioureas and different substituted thioureas to give 2-(6-fluorobenzothiazole-2'-ylamino)-4-(phenylthioureido)-6-(substituted thioureido)-1,3,5-triazine (Figure 85). These compounds were evaluated for their antimicrobial activity. The structure of all these compounds have been confirmed by spectral analysis.\textsuperscript{111}
Triazine derivatives have other applications such as, preparation of cyanuric chloride ESIPT benzothiazole derivatives and their use in organic light-functional materials has been demonstrated (Figure 86). The use of cyanuric chloride three chlorine atoms on different reactivity, controlling different reaction conditions to give different substituents triazine ESIPT substituted benzothiazole derivatives. Three compounds of the present invention obtained its structural formula as follows: three compounds were obtained by the present invention emit a strong blue, green and orange fluorescence, can be configured in different proportions to obtain different color light.\textsuperscript{112}

![Figure 86](image)

The syntheses of 2-amino-s-triazino[1,2-\(a\)]benzimidazoles from 2-guanidinobenzimidazoles were successfully carried out by a ring annulation reaction (Figure 87). The regiochemistry of the ring closure of 5-methyl-2- guanidinobenzimidazole with diethyl azodicarboxylate, aldehydes, acetone, diethyl ethoxymethylene malonate and orthoesters, leading to the formation of s-triazine ring was studied. High regioselectivity was not observed in any of these reactions. However, the synthesis of s-triazino[1,2-\(a\)]benzimidazole system was found to be more regioselective than its 3,4-dihydro analogue. NOESY experiment indicated that the compound, 2-amino-4,4-dimethyl-3,4-dihydro-s-triazino[1,2-\(a\)]benzimidazole existed predominantly as the 3,4- dihydro tautomer in dimethyl sulfoxide. It was found to inhibit bovine dihydrofolate reductase with IC\textsubscript{50} 10.9 \(\mu\)M.\textsuperscript{113}

![Figure 87](image)
The synthesis of novel fused pyrimidines and imidazole derivatives from 2-amino-s-triazino[1,2- a]benzimidazoles (Figure 88) were successfully carried out by a ring annelation reaction in a very good yield by El-Feky and coworkers. Among all compounds, one compound was screened for analgesic activity against acetic acid irritation and has shown protection equal to the reference drug (diclofenac sodium). The acute toxicity study revealed that compound was safe up to 300 mg/kg and there is no sign and symptoms of toxicity and mortality for 72 hours.¹¹⁴

![Figure 88](image)

A series of 6-bromo-2-ethyl-3-(substitutedbenzo[d]thiazol-2-yl)quinazolin-4(3H)-ones was synthesized using appropriate synthetic route and evaluated experimentally by the Maximal Electro Shock (MES) and the PTZ-induced seizure methods. Among the tested compounds, 3-(benzo[d]thiazol-2- yl)-6-bromo-2-ethylquinazolin-4(3H)-one (Figure 89) has shown significant activity against tonic seizure by the MES model and 6-bromo-2-ethyl-3-(6-methoxybenzo[d]thiazol-2-yl)quinazolin-4(3H)-one against clonic seizure by PTZ-induced seizure model. Not one of the selected compounds demonstrated any sign of neurotoxicity and hepatotoxicity.¹¹⁵

![Figure 89](image)

Sareen and coworkers have identified trisubstituted ureas as a promising new chemical series of allosteric modulators of the calcium sensing receptor (CaSR), further they have explored the SAR around the urea substitution, leading to the discovery of benzothiazole urea compound (Figure 90). This compound was a potent calcimimetic with an EC₅₀ = 20 nM (luciferase assay). Evaluated in an in vivo model of chronic renal failure (short term and long
term in 5/6 nephrectomized rats), benzothiazole urea significantly decreased PTH levels after oral administration while keeping calcemia within the normal range.\textsuperscript{111}

\textbf{Figure 90}

In 2013, Welker and coworkers have selected pyridine benzothiazole biaryl (R = 4-F) with optimized pharmacokinetics that inhibited S473Akt phosphorylation in U87-MG cells with IC\textsubscript{50}=6.3nM for \textit{in vivo} tests (\textbf{Figure 91}). Inhibition of the PI3K/Akt pathway induced in liver by iv injection of HGF was observed starting at 0.1 mg/kg with maximal inhibition at 1mg/kg. A time course study showed that at 3mg/kg maximal inhibition lasted for and significant inhibition lasted for 24 hours. Experiments in U87-MG (PTEN null) glioblastoma, A549 (KRAS mutant) lung adenocarcinoma and HCT11618,57 (KRAS and PI3KR mutant) colon adenocarcinoma tumor xenografts showed dose-dependent tumorostatic effect with ED 0.26 mg/kg. However subsequent in vivo experiments demonstrated accumulation in liver of a deacylated metabolite that inhibits PI3K\textalpha{} at nM concentrations, which precluded further development of this compound.\textsuperscript{116}

\textbf{Figure 91}
Jin et al have described the investigation of a series of 5,7-disubstituted imidazo[5,1-f][1,2,4]triazine (Figure 92) inhibitors of insulin-like growth factor-1 receptor (IGF-1R) and insulin receptor (IR). Structure-activity relationship exploration and optimization leading to the identification, characterization, and pharmacological activity of compound, a potent, selective, well-tolerated, and orally bioavailable dual inhibitor of IGF-1R and IR with in vivo efficacy in tumor xenograft models, was discussed.\textsuperscript{117}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure92.png}
\caption{Figure 92}
\end{figure}

Hu and coworkers have discovered the novel imidazo[4,5-b]pyridines as potent and selective inhibitors of PDE10A. The investigation began with their recently disclosed ketobenzimidazole, which exhibited single digit nanomolar PDE10A activity but poor oral bioavailability. To improve oral bioavailability, they turned to novel scaffold imidazo[4,5-b]pyridine (Figure 93), which not only retained nanomolar PDE10A activity but was also devoid of the morpholine metabolic liability. Structure–activity relationship studies were conducted systematically to examine how various regions of the molecule impacted potency. X-ray cocystal structures of two compounds in human PDE10A helped to elucidate the key bonding interactions. Five of the most potent and structurally diverse imidazo[4,5-b]pyridines with PDE10A IC\textsubscript{50} values ranging from 0.8 to 6.7 nM were advanced into receptor occupancy studies. Four of them achieved 55–74\% RO at 10 mg/kg po.\textsuperscript{118}
A novel 2,7-disubstituted-pyrrolo[2,1-f][1,2,4]triazine scaffold has been designed as a new kinase inhibitor platform mimicking the bioactive conformation of the well-known diaminopyrimidine motif by Ott and coworkers. They have described synthesis, and validation of this new pyrrolo[2,1-f][1,2,4]triazine (Figure 94) scaffold for inhibitors of anaplastic lymphoma kinase (ALK). Importantly, incorporation of appropriate potency and selectivity determinants has led to the discovery of several advanced leads that were orally efficacious in animal models of anaplastic large cell lymphoma (ALCL). A lead inhibitor (30) displaying superior efficacy was identified and in depth in vitro/in vivo characterization was presented.119

Phosphoinositide 3-kinase (PI3K) is an important target in oncology due to the deregulation of the PI3K/ Akt signaling pathway in a wide variety of tumors. A series of 4-amino-6-methyl-1,3,5-triazine sulfonamides (Figure 95) were synthesized and evaluated as inhibitors of PI3K by Wurz and coworkers. The synthesis, in vitro biological activities, pharmacokinetic and in vivo pharmacodynamic profiling of these compounds was described.
The most promising compound was found to be a pan class I PI3K inhibitor with a moderate (>10-fold) selectivity over the mammalian target of rapamycin (mTOR) in the enzyme assay. In a U87 MG cellular assay measuring phosphorylation of Akt, one compound displayed low double digit nanomolar IC$_{50}$ and exhibited good oral bioavailability in rats (Foral = 63%). One compound also showed a dose dependent reduction in the phosphorylation of Akt in a U87 tumor pharmacodynamics model with a plasma EC$_{50}$ = 193 nM (91 ng/mL).\textsuperscript{120}

![Figure 95](image)

A series of bicyclic piperazine derivatives of triazolotriazine and triazolopyrimidines was synthesized by Peng and coworkers. Some of these analogues have shown high affinity and excellent selectivity for adenosine A2a receptor versus the adenosine A1 receptor. Structure-activity-relationship (SAR) studies based on octahydropyrrolo[1,2-$a$]pyrazine and octahydropyrido[1,2-$a$]pyrazine (Figure 96) with various capping groups were reported. Among these analogues, the most potent and selective A2a antagonist has a $K_i$ value of 0.2 nM and is 16 500-fold selective with respect to the A1 receptor. Among a number of compounds tested, two compounds exhibited significantly improved metabolic stability. Three compounds showed good oral efficacy in rodent catalepsy models of Parkinson’s disease.\textsuperscript{121}

![Figure 96](image)
3.1 Current Research Work

Our group is involved in the development of various synthetic methodologies for the synthesis of triazines containing various heterocycle and other substituents biological interest. Substitution of Chloro functionality in the cyanuric chloride offers various triazines. Reports reveal that coumarins (4-hydroxy coumarine, 4-methyl-7-hydroxy coumarin), phenyl urea and aryl amines substituted triazines which might have potential biological activities were less studied. Very promising results may obtain with these modifications to 1,3,5-triazine skeleton. As discussed in introduction, the tremendous biological potential of 1,3,5-triazines substituted either with coumarin or phenyl urea motivated us to combine the both functionality in triazine. For this modification, 4-hydroxy coumarin, 4-methyl-7-hydroxy coumarin, phenyl urea was required as a precursor which was synthesized by reported the procedure in literature.\textsuperscript{122-124}

To synthesize the desired compounds we have utilized cyanuric chloride as main synthon as the removal of chlorine functionality using various nucleophiles under basic conditions was well studied. The reaction of cyanuric chloride with coumarins and followed by phenyl urea and aromatic amines in specific reaction condition afforded the novel highly substituted 1, 3, 5- triazines. The newly synthesized compounds were characterized by IR, Mass, \textsuperscript{1}H NMR, \textsuperscript{13}C NMR spectroscopy and elemental analysis. All the synthesized compounds were screened for \textit{in vitro} antimicrobial activity against Gram-positive \textit{Bacillus subtilis} and \textit{Staphylococcus aureus} and Gram-negative bacteria \textit{Escherichia coli, Pseudomonas aeruginosa} and fungi \textit{Aspergillus niger}. 
3.2 Results and Discussion

Scheme-III.1: Synthesis of coumarin functionalized triazines 2a & 2b.

Scheme-III.2: Reaction of phenylurea with compound 2a and 2b
Scheme-III.3 : Synthesis of coumarins, phenylurea and arylamino substituted 1,3,5-triazines.

The condensation of the 4-hydroxy coumarin and 7-hydroxy-4-methyl coumarin with cyanuric chloride in acetone and 10 % NaHCO₃ at 0-5 °C with stirring afforded 4-((4,6-dichloro-1,3,5-triazin-2-yl)oxy)-2H-chromen-2-one 2a and 4-((4,6-dichloro-1,3,5-triazin-2-yl)oxy)-2H-chromen-2-one 2b in good yield, respectively (Scheme III.1). Further to synthesize the intermediates 1-(4-chloro-6-((2-oxo-2H-chromen-4-yl)oxy)-1,3,5-triazin-2-yl)-3-phenylurea 3a and 1-(4-chloro-6-((4-methyl-2-oxo-2H-chromen-7-yl)oxy)-1,3,5-triazin-2-yl)-3-phenylurea 3b the reaction of phenyl urea with 2a and 2b was carried out under stirred reaction conditions at room temperature using acetone as solvent (Scheme III.2). The desired compounds were synthesized by the reaction aromatic amines 4a-j with compound 3a and 3b.
using tetrahydrofuran under reflux condition. In all reaction steps, the work up of products was very easy and simple to give analytically pure compounds (Table III.1).

### Table III.1 : Physical properties of compounds AYC-35-54.

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>R</th>
<th>Yields (%)</th>
<th>Melting range</th>
</tr>
</thead>
<tbody>
<tr>
<td>AYC-35</td>
<td>H</td>
<td>93</td>
<td>210-212</td>
</tr>
<tr>
<td>AYC-36</td>
<td>4-OCH₃</td>
<td>86</td>
<td>220-222</td>
</tr>
<tr>
<td>AYC-37</td>
<td>4-CH₃</td>
<td>91</td>
<td>215-217</td>
</tr>
<tr>
<td>AYC-38</td>
<td>4-NO₂</td>
<td>89</td>
<td>218-220</td>
</tr>
<tr>
<td>AYC-39</td>
<td>4-Cl</td>
<td>90</td>
<td>150-152</td>
</tr>
<tr>
<td>AYC-40</td>
<td>4-Br</td>
<td>92</td>
<td>215-217</td>
</tr>
<tr>
<td>AYC-41</td>
<td>3-NO₂</td>
<td>86</td>
<td>225-227</td>
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<td>AYC-42</td>
<td>3-Cl</td>
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<td>165-167</td>
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<td>3-F</td>
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<td>201-203</td>
</tr>
<tr>
<td>AYC-45</td>
<td>H</td>
<td>88</td>
<td>198-200</td>
</tr>
<tr>
<td>AYC-46</td>
<td>4-OCH₃</td>
<td>86</td>
<td>204-206</td>
</tr>
<tr>
<td>AYC-47</td>
<td>4-CH₃</td>
<td>86</td>
<td>268-270</td>
</tr>
<tr>
<td>AYC-48</td>
<td>4-NO₂</td>
<td>89</td>
<td>260-262</td>
</tr>
<tr>
<td>AYC-49</td>
<td>4-Cl</td>
<td>91</td>
<td>245-248</td>
</tr>
<tr>
<td>AYC-50</td>
<td>4-Br</td>
<td>78</td>
<td>271-273</td>
</tr>
<tr>
<td>AYC-51</td>
<td>3-NO₂</td>
<td>88</td>
<td>273-275</td>
</tr>
<tr>
<td>AYC-52</td>
<td>3-Cl</td>
<td>90</td>
<td>268-270</td>
</tr>
<tr>
<td>AYC-53</td>
<td>4-F</td>
<td>92</td>
<td>280-282</td>
</tr>
<tr>
<td>AYC-54</td>
<td>3-F</td>
<td>86</td>
<td>242-244</td>
</tr>
</tbody>
</table>

The melting of compounds 2a and 2b are resembles with reported data.¹²⁵,¹²⁶ The ¹H NMR signals of compound 3a showed 2-NH of phenylurea at 11.19 and 10.59, ArH obtained between 6.57 to 7.73 and C=CH proton of coumarin ring at 5.61 δ ppm. Mass spectrum shows 409 (m/z). IR values were obtained at 3440, 3250, 2848, 1716, 858 cm⁻¹. Compound 3b showed ¹H NMR signals at 11.18 and 10.58 for 2-NH, while ArH were appeared between
7.32 to 7.87, -C=CH proton of coumarin ring at 6.41, -CH₃ protons at 2.44 δ ppm. Mass spectrum of compounds 3b was (m/z) at 423. IR signal appeared at 3450, 3217, 2840, 2741, 1712, 1532, 762 cm⁻¹. The spectral data suggested the formation of desire compounds.

The ¹H NMR signal of 1-(4-((4-methoxyphenyl)amino)-6-((2-oxo-2H-chromen-4-yl)oxy)-1,3,5-triazin-2-yl)-3-phenylurea AYC-36 (R=4-OCH₃) showed at 2-NH at 11.58 and 10.56, aromatic amines -NH at 9.87, aromatic protons were appeared between 6.64 to 7.85, -C=CH proton of coumarin ring at 5.59, -OCH₃ proton at 3.81 δ ppm. Mass spectrum showed (m/z). IR signals gave at 3280, 3161, 2953, 2838, 1742, 1719, 1510, 866, 758 cm⁻¹. These data are associated with desired compound.
3.3 Antimicrobial Activity

Table III.2: Antimicrobial activity of selected compounds (Zone of inhibition in mm)

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>R</th>
<th>Gram-positive</th>
<th>Gram-negative</th>
<th>Fungi</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>B.subtilis</td>
<td>S.aureus</td>
<td>E.coli</td>
</tr>
<tr>
<td>AYC-35</td>
<td>H</td>
<td>3.50</td>
<td>3.00</td>
<td>8.00</td>
</tr>
<tr>
<td>AYC-36</td>
<td>4-OCH₃</td>
<td>3.50</td>
<td>3.00</td>
<td>4.00</td>
</tr>
<tr>
<td>AYC-37</td>
<td>4-CH₃</td>
<td><strong>3.50</strong></td>
<td><strong>4.25</strong></td>
<td>4.00</td>
</tr>
<tr>
<td>AYC-38</td>
<td>4-NO₂</td>
<td>3.50</td>
<td>3.25</td>
<td>4.00</td>
</tr>
<tr>
<td>AYC-39</td>
<td>4-Cl</td>
<td>3.50</td>
<td>3.00</td>
<td>-</td>
</tr>
<tr>
<td>AYC-40</td>
<td>4-Br</td>
<td><strong>3.75</strong></td>
<td><strong>3.75</strong></td>
<td>-</td>
</tr>
<tr>
<td>AYC-45</td>
<td>H</td>
<td>3.00</td>
<td>-</td>
<td><strong>4.25</strong></td>
</tr>
<tr>
<td>AYC-47</td>
<td>4-CH₃</td>
<td>3.25</td>
<td>-</td>
<td>3.50</td>
</tr>
<tr>
<td>AYC-50</td>
<td>4-Br</td>
<td>3.25</td>
<td>-</td>
<td>3.50</td>
</tr>
<tr>
<td>AYC-51</td>
<td>3-NO₂</td>
<td>3.50</td>
<td>-</td>
<td><strong>4.00</strong></td>
</tr>
<tr>
<td>AYC-52</td>
<td>3-Cl</td>
<td>3.50</td>
<td>3.00</td>
<td>3.50</td>
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<tr>
<td>AYC-53</td>
<td>4-F</td>
<td>3.00</td>
<td>-</td>
<td><strong>4.25</strong></td>
</tr>
</tbody>
</table>

*Concentration 1000 microgram per ml, - = No inhibition
Among the tested compounds AYC-37 and AYC-38 exhibited potent inhibition against Gram-positive \( B.\text{subtilis} \) and \( S.\text{aureus} \) and Gram-negative \( E.\text{coli} \) and \( P.\text{aeruginosa} \) bacteria. While compound AYC-36 and AYC-37 were active against Fungi \( A.Niger \). However, AYC-36 was moderate against bacteria strain. Compounds AYC-45, AYC-51 and AYC-53 were showed good inhibition against Gram-negative \( E.Coli \) bacteria. AYC-35 has showed excellent inhibition against Gram-negative \( E.Coli \) bacteria. We found that compound AYC-37 emerged as potent active against all microbial. Remaining compounds have shown moderate inhibition against microbial strains (Table III.2).
3.4 Conclusion

We have proposed an easy and simple synthesis for substituted 1,3,5-triazines functionalized with coumarin, phenylurea and aryl amines. The reaction cyanuric chlorides with two different coumarins afforded the intermediates under basic condition. Followed by reaction with phenylurea and different amines under developed reaction conditions yielded the desired trisubstituted 1,3,5-triazines. The workup of reaction was easy in all three steps no unusual treatment was required. All the synthesized compounds were characterized by using spectral and elemental analysis. Among the synthesized compounds selected compounds were screened against Gram-positive and Gram-negative bacteria and fungi and examined zone of inhibition. Out of them, compound AYC-37 has shown significant inhibition against all microorganisms up to the 4.00 to 8.00 mm. Compounds AYC-37 and AYC-40 were good against Gram-positive bacteria. Compounds AYC-37, AYC-40, AYC-42, and AYC-51 were active against Gram-negative bacteria. Compounds AYC-36 and AYC-37 were active against fungi.
3.5 Experimental Section

$^1$HNMR (400 MHz) and $^{13}$CNMR (100 MHz) spectra were recorded in DMSO, and TMS was used as an internal reference on a Bruker AVANCE II spectrometer. Mass spectra were determined using direct inlet probe on a GCMS-Agilent mass spectrometer. IR spectra were recorded on KBr discs, using FTIR-Bruker spectrophotometer. Melting points were measured in open capillaries and are uncorrected. Laboratory grade chemicals were purchased from Loba, Molychem, Himedia, Spectrochem and are used without purifications. 4-hydroxy coumarins and 7-hydroxy-4-methyl coumarins were prepared by reported procedures$^{57,58}$ and are used after crystallization.

 Procedure for the synthesis of phenylurea:

The solution of aniline (5 gm) in gl. Acetic acid was added solution of sodium cyanate (4 gm) slowly dropwise at room temperature with stirring. Maintained the temperature during the course of addition of sodium cyanate solution. After completion of the addition, kept the reaction mixture at room temperate for 2 hr and filtered the separated product. Washed with coldwater and dried to yield crude product and used without purification.

 General procedure for the synthesis of 2a and 2b.

A solution of 4-hydroxy coumarin and 7-hydroxy-4-methyl coumarin (10 mmol) in 10 ml of 10% NaHCO$_3$ was added drop wise to the mixture of cyanuric chloride (1.84 gm, 10 mmol) and acetone (10 ml) at 0-5 0C with stirring during the time period of 2 -3 hr. The reaction was being monitored by TLC using Toluene: Acetone (1:4). After completion of the reaction, reaction mixture was poured into crushed ice with stirring. The separated white solid product was filtered, washed with cold water and dried to yield the desired product 92 %. The product was used for next step without purifications.

 General procedure for the synthesis of 3a and 3b.

A solution of phenylurea (3.5 gm, 25 mmol) and 10% NaHCO$_3$ was added to the mixture of compound 2a or 2b (25 mmol) in acetone (20 ml) drop wise with stirring at room temperature. After completion of the reaction, the reaction was further stirred for 2 hr at rt. The reaction was being monitored by TLC using Toluene: Acetone (1:4) and then poured into crushed ice with stirring. The separated product was filtered, washed with cold water and dried to yield the desired product in good yield 82 %.
General procedure for the synthesis of AYC-35-54.

A mixture of compounds 3a or 3b with aryl amines 4a-j and THF was refluxed on oil bath for 7-8 hrs. The reaction was being monitored by TLC Toluene: Acetone (1:4). After completion of the reaction, the reaction was poured in to crushed ice with stirring. The separated product was filtered, wahsed with cold water and dried. The crude product was treated with hexane and pet ether to furnished the desired compounds in good yield 75 to 88%.

Spectral data of 1-(4-chloro-6-((2-oxo-2H-chromen-4-yl)oxy)-1,3,5-triazin-2-yl)-3-phenylurea 3a:

White solid; melting range : 212-214; Rf: 0.21; IR (KBr): 3424, 3376, 2976, 2785, 1724, 1454, 1101, 851 cm\(^{-1}\); \(^1\)H NMR: \(\delta 5.71\) (s, 1H, Ar), 6.57 - 7.73 (m, 8H, Ar-H), 10.59 (s, 1H, NH), 11.19 (s, 1H, NH); MS \(m/z\): 409 (M\(^+\)); Anal. Calcd. for C\(_{19}\)H\(_{12}\)ClN\(_5\)O\(_4\): C, 55.69; H, 2.95; N, 17.09 %. Found: C, 55.68; H, 2.91; N, 17.08%.

Spectral data of 1-(4-chloro-6-((4-methyl-2-oxo-2H-chromen-7-yl)oxy)-1,3,5-triazin-2-yl)-3-phenylurea 3b:

White solid; melting range: 238-240; Rf: 0.21; IR (KBr): 3434, 3356, 2874, 2745, 1714, 1434, 1101, 851 cm\(^{-1}\); \(^1\)H NMR: \(\delta 2.44\) (s, 3H, CH\(_3\)), 6.42 (t, 1H, ArH), 7.32 - 7.87 (m, 7H, Ar-H), 10.58 (s, 1H, NH), 11.18 (s, 1H, NH); MS \(m/z\): 423 (M\(^+\)); Anal. Calcd. for C\(_{20}\)H\(_{14}\)ClN\(_5\)O\(_4\): C, 56.68; H, 3.33; N, 16.52 %. Found: C, 56.65; H, 3.31; N, 16.49%.

Spectral data of the synthesized compounds AYC-35-54.

1-(4-((2-oxo-2H-chromen-4-yl)oxy)-6-(phenylamino)-1,3,5-triazin-2-yl)-3-phenylurea AYC-35: Cream solid; Rf: 0.18; IR (KBr): 3276, 3242, 3122, 2961, 1715, 1525, 1110, 802, 755 cm\(^{-1}\); \(^1\)H NMR: \(\delta 5.66\) (s, 1H, Ar), 6.64 - 7.85 (m, 15H, Ar-H), 9.86 (s, 1H, NH), 10.56 (s, 1H, NH), 11.19 (s, 1H, NH); \(^{13}\)C NMR: 99, 116, 117, 119, 122, 125, 126, 128, 130, 138, 141, 151, 153, 155, 158, 161, 178; MS \(m/z\): 466 (M\(^+\)); Anal. Calcd. for C\(_{25}\)H\(_{18}\)N\(_6\)O\(_4\): C, 64.37; H, 3.89; N, 18.02 %. Found: C, 64.38; H, 3.91; N, 18.03%.

1-(4-((4-methoxyphenyl)amino)-6-((2-oxo-2H-chromen-4-yl)oxy)-1,3,5-triazin-2-yl)-3-phenylurea AYC-36: White solid; Rf: 0.17; IR (KBr): 3280, 3161, 2953, 2838, 1742, 1719, 1510, 866, 758 cm\(^{-1}\); \(^1\)H NMR: \(\delta 3.86\) (s, 3H, OCH\(_3\)), 5.59 (s, 1H, ArH), 6.64-7.85 (m, 13H,
Ar-H), 9.67 (s, 1H, NH), 10.56 (s, 1H, NH), 11.02 (s, 1H, NH); MS m/z: 496 (M+); Anal. Calcd. for C_{26}H_{20}N_{6}O_{5}: C, 62.90; H, 4.06; N, 16.93%; Found: C, 62.89; H, 4.02; N, 16.95%.

1-(4-((2-oxo-2H-chromen-4-yl)oxy)-6-(p-tolylamino)-1,3,5-triazin-2-yl)-3-phenylurea AYC-37: Cream solid; Rf: 0.16; IR (KBr): 3380, 3261, 2953, 2838, 1742, 1520, 868, 758 cm\(^{-1}\); MS m/z: 480 (M+); Anal. Calcd. for C_{26}H_{20}N_{6}O_{4}: C, 64.99; H, 4.20; N, 17.49%; Found: C, 64.96; H, 4.19; N, 17.48%.

1-(4-((4-nitrophenyl)amino)-6-((2-oxo-2H-chromen-4-yl)oxy)-1,3,5-triazin-2-yl)-3-phenylurea AYC-38: Yellow solid; Rf: 0.16; IR (KBr): 3289, 3261, 2893, 2818, 1719, 1515, 865, 752 cm\(^{-1}\); MS m/z: 511 (M+); Anal. Calcd. for C_{25}H_{17}N_{7}O_{6}: C, 58.71; H, 3.35; N, 19.17%; Found: C, 58.67; H, 3.38; N, 19.13%.

1-(4-((4-chlorophenyl)amino)-6-((2-oxo-2H-chromen-4-yl)oxy)-1,3,5-triazin-2-yl)-3-phenylurea AYC-39: Cream solid; Rf: 0.18; IR (KBr): 3380, 3151, 2853, 2738, 1721, 1515, 870, 749 cm\(^{-1}\); MS m/z: 501 (M+); Anal. Calcd. for C_{25}H_{17}ClN_{6}O_{4}: C, 59.95; H, 3.42; N, 16.78%; Found: C, 59.93; H, 3.41; N, 16.75%.

1-(4-((4-bromophenyl)amino)-6-((2-oxo-2H-chromen-4-yl)oxy)-1,3,5-triazin-2-yl)-3-phenylurea AYC-40: Yellow solid; Rf: 0.17; IR (KBr): 3339, 3212, 2817, 1698, 1494, 1093, 875, 756 cm\(^{-1}\); MS m/z: 545(M+); Anal. Calcd. for C_{25}H_{17}BrN_{6}O_{4}: C,55.06; H, 3.14; N, 15.41%. Found: C, 55.04; H, 3.11; N, 15.40 %.

1-(4-((3-nitrophenyl)amino)-6-((2-oxo-2H-chromen-4-yl)oxy)-1,3,5-triazin-2-yl)-3-phenylurea AYC-41: Cream solid; Rf: 0.18; IR (KBr): 3367, 3208, 2841, 1720, 1584, 1162, 875, 751 cm\(^{-1}\); MS m/z: 511 (M+); Anal. Calcd. for C_{25}H_{17}N_{7}O_{6}: C, 58.71; H, 3.35; N, 19.17%. Found: C, 58.70; H, 3.33; N, 19.15%.

1-(4-((3-chlorophenyl)amino)-6-((2-oxo-2H-chromen-4-yl)oxy)-1,3,5-triazin-2-yl)-3-phenylurea AYC-42: Yellow solid; Rf: 0.17; IR (KBr): 3387, 3247, 2864, 1728,1519, 1157, 866, 756 cm\(^{-1}\); MS m/z: 500 (M+); Anal. Calcd. for C_{25}H_{17}ClN_{6}O_{4}: C, 59.95; H, 3.42; N, 16.78%. Found: C, 59.94; H, 3.40; N, 16.77 %.

1-(4-((4-fluorophenyl)amino)-6-((2-oxo-2H-chromen-4-yl)oxy)-1,3,5-triazin-2-yl)-3-phenylurea AYC-43: Yellow solid; Rf: 0.16; IR (KBr): 3305, 3221, 2825, 1721, 1511, 1084, 875, 754 cm\(^{-1}\); MS m/z: 484 (M+); Anal. Calcd. for C_{25}H_{17}F_{1}N_{6}O_{4}: C, 61.98; H, 3.54; N, 17.35%. Found: C, 61.97; H, 3.54; N, 17.35%. 

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1-(4-((3-fluorophenyl)amino)-6-((2-oxo-2H-chromen-4-yl)oxy)-1,3,5-triazin-2-yl)-3-phenylurea AYC-44: Yellow solid; Rf: 0.17; IR (KBr): 3280, 3161, 2953, 2838, 1742, 1719, 1510, 866, 758 cm⁻¹; MS m/z: 484 (M⁺); Anal. Calcd. for C₂₅H₁₇FN₆O₄: C, 61.98; H, 3.54; N, 17.35%. Found: C, 61.96; H, 3.52; N, 17.33%.

1-(4-((4-methyl-2-oxo-2H-chromen-7-yl)oxy)-6-(phenylamino)-1,3,5-triazin-2-yl)-3-phenylurea AYC-45: White solid; Rf: 0.16; IR (KBr): 3280, 3195, 2961, 2602, 1733, 1571, 1154, 801, 679 cm⁻¹; ¹H NMR: δ 2.46 (s, 3H, CH₃), 6.35 (s, 1H, Ar), 6.41 (d, 1H, Ar-H, J=13.2), 6.70 - 7.81 (m, 11H, Ar-H), 9.86 (s, 1H, NH), 10.50 (s, 1H, NH), 11.15 (s, 1H, NH); MS m/z: 480 (M⁺); Anal. Calcd. for C₂₆H₂₀N₆O₄: C, 64.99; H, 4.20; N, 17.49%. Found: C, 65.01; H, 4.23; N, 17.45%

1-(4-((4-methoxyphenyl)amino)-6-((4-methyl-2-oxo-2H-chromen-7-yl)oxy)-1,3,5-triazin-2-yl)-3-phenylurea AYC-46: Gray solid; Rf: 0.16; IR (KBr): 3310, 3142, 2928, 2589, 1724, 1531, 1176, 825, 756 cm⁻¹; ¹H NMR: δ 2.46 (s, 3H, CH₃), 3.86 (s, 3H, OCH₃), 6.35-6.42 (t, 3H, Ar-H), 6.69 - 7.85 (m, 9H, Ar-H), 9.79 (s, 1H, NH), 10.23 (s, 1H, NH), 11.03 (s, 1H, NH); MS m/z: 510 (M⁺); Anal. Calcd. for C₂₇H₂₂N₆O₅: C, 63.52; H, 4.34; N, 16.46%. Found: C, 63.50; H, 4.31; N, 16.43%

1-(4-((4-methyl-2-oxo-2H-chromen-7-yl)oxy)-6-(p-tolylamino)-1,3,5-triazin-2-yl)-3-phenylurea AYC-47: Yellow solid; Rf: 0.15; IR (KBr): 3210, 3158, 2922, 1712, 1491, 1154, 856, 752 cm⁻¹; MS m/z: 494 (M⁺); Anal. Calcd. for C₂₇H₂₂N₆O₄: C, 65.58; H, 4.48; N, 16.99%. Found: C, 65.56; H, 4.46; N, 16.98%

1-(4-((4-methyl-2-oxo-2H-chromen-7-yl)oxy)-6-((4-nitrophenyl)amino)-1,3,5-triazin-2-yl)-3-phenylurea AYC-48: Yellow solid; Rf: 0.14; IR (KBr): 3374, 3294, 2757, 1708, 1511, 1261 872, 759 cm⁻¹; ¹H NMR: δ 2.46 (s, 3H, CH₃), 6.35 (s, 1H, Ar-H), 6.42 (d, 1H, Ar-H), 6.58 – 8.04 (m, 11H, Ar-H), 9.98 (s, 1H, NH), 10.85 (s, 1H, NH), 10.99 (s, 1H, NH); MS m/z: 525 (M⁺); Anal. Calcd. for C₂₆H₁₉N₇O₆: C, 59.43; H, 3.64; N, 18.66%. Found: C, 59.45; H, 3.61; N, 18.63%

1-(4-((4-chlorophenyl)amino)-6-((4-methyl-2-oxo-2H-chromen-7-yl)oxy)-1,3,5-triazin-2-yl)-3-phenylurea AYC-49: Cream solid; Rf: 0.15; IR (KBr): 3280, 3195, 2961, 2602, 1733, 1571, 1154, 801, 679 cm⁻¹; MS m/z: 515 (M⁺); ¹H NMR: δ 2.24 (s, 3H, CH₃), 6.69 (s, 1H, Ar-H), 6.73 – 7.86 (m, 11H, Ar-H), 9.98 (s, 1H, NH), 10.54 (s, 1H, NH), 11.11 (s, 1H, NH);
$^{13}$C NMR: 22, 110, 115, 117, 119, 123, 126, 127, 128, 136, 138, 141, 150, 159, 160, 162, 166, 166, 178; Anal. Calcd. for C$_{26}$H$_{19}$ClN$_6$O$_4$: C, 60.65; H, 3.72; N, 16.32%. Found: C, 60.61; H, 3.73; N, 16.30%.

1-(4-((4-bromophenyl)amino)-6-((4-methyl-2-oxo-2H-chromen-7-yl)oxy)-1,3,5-triazin-2-yl)-3-phenylurea AYC-50: Cream solid; Rf: 0.15; IR (KBr): 3380, 3265, 2961, 2702, 1713, 1471, 1124, 841, 779 cm$^{-1}$; MS m/z: 558 (M$^+$); Anal. Calcd. for C$_{26}$H$_{19}$BrN$_6$O$_4$: C, 55.83; H, 3.42; N, 15.02%. Found: C, 55.80; H, 3.40; N, 15.03%.

1-(4-((4-methyl-2-oxo-2H-chromen-7-yl)oxy)-6-((3-nitrophenyl)amino)-1,3,5-triazin-2-yl)-3-phenylurea AYC-51: Yellow solid; Rf: 0.14; IR (KBr): 3281, 3201, 2962, 2079, 1731, 1573, 1263, 975, 861, 735 cm$^{-1}$; MS m/z: 525 (M$^+$); Anal. Calcd. for C$_{26}$H$_{19}$N$_7$O$_6$: C, 59.43; H, 3.64; N, 18.66%. Found: C, 59.43; H, 3.61; N, 18.64%.

1-(4-((3-chlorophenyl)amino)-6-((4-methyl-2-oxo-2H-chromen-7-yl)oxy)-1,3,5-triazin-2-yl)-3-phenylurea AYC-52: Cream solid; Rf: 0.15; IR (KBr): 3261, 3221, 2962, 2179, 1758, 1543, 1253, 875, 867, 755 cm$^{-1}$; MS m/z: 515 (M$^+$); Anal. Calcd. for C$_{26}$H$_{19}$ClN$_6$O$_4$: C, 60.65; H, 3.72; N, 16.32%. Found: C, 60.62; H, 3.73; N, 16.30%.

1-(4-((4-fluorophenyl)amino)-6-((4-methyl-2-oxo-2H-chromen-7-yl)oxy)-1,3,5-triazin-2-yl)-3-phenylurea AYC-53: Cream solid; Rf: 0.16; IR (KBr): 3314, 3217, 2924, 1698, 1528, 1207, 1108, 861, 745 cm$^{-1}$; MS m/z: 498 (M$^+$); Anal. Calcd. for C$_{26}$H$_{19}$FN$_6$O$_4$: C, 62.65; H, 3.84; N, 16.86%. Found: C, 62.63; H, 3.83; N, 16.84%.

1-(4-((3-fluorophenyl)amino)-6-((4-methyl-2-oxo-2H-chromen-7-yl)oxy)-1,3,5-triazin-2-yl)-3-phenylurea AYC-54: Cream solid; Rf: 0.16; IR (KBr): 3324, 3217, 2916, 1718, 1498, 1225, 1047, 875, 724 cm$^{-1}$; MS m/z: 498 (M$^+$); Anal. Calcd. for C$_{26}$H$_{19}$FN$_6$O$_4$: C, 62.65; H, 3.84; N, 16.86%. Found: C, 62.62; H, 3.83; N, 16.83%. 

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$^1$H NMR spectrum of compound 3a

$^1$H NMR spectrum of compound AYC-35
$^1$H NMR spectrum of compound AYC-36

Expanded $^1$H NMR spectrum of compound AYC-36
1H NMR spectrum of compound 3b

Expanded 1H NMR spectrum of compound 3b
$^1$H NMR spectrum of compound AYC-45

Expanded $^1$H NMR spectrum of compound AYC-45
$^1$H NMR spectrum of compound AYC-46

Expanded $^1$H NMR spectrum of compound AYC-46
$^1$H NMR spectrum of compound AYC-48

Expanded $^1$H NMR spectrum of compound AYC-48
$^1$H NMR spectrum of compound AYC-49

$^{13}$C NMR spectrum of compound AYC-49
PART III  Section 1

Mass spectrum of compound AYC-35

Mass spectrum of compound AYC-36
Mass spectrum of compound AYC-37

Mass spectrum of compound AYC-45
Mass spectrum of compound AYC-46

Mass spectrum of compound AYC-48
IR spectrum of compound AYC-35

![IR Spectrum of AYC-35](image)

IR spectrum of compound AYC-36

![IR Spectrum of AYC-36](image)
IR spectrum of compound AYC-49

IR spectrum of compound AYC-51
3.6 References


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