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Title: Role of Molecular Hybridisation In Synergism of Pharmacological Activities of Heterocycles: A Review

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Abstract

Different approaches of administration of drugs have been used from time to time. Three most commonly used approaches are taking two or more drugs simultaneously, combination therapy with use of more than two drugs in a single tablet and development of hybrid molecules. Nowadays, concept of hybridisation with multiligand approach has gained popularity. The present review portrays the biological potential of hybrids especially as antitubercular and anticancer agents. A comparison of hybrid potency with their individual counterpart is discussed here for evaluating the effect of molecular hybridisation.

Key words: molecular hybrids, antitubercular, anticancer, heterocycles.

Introduction

The rising curiosity on new-fangled drug discovery is frequently advanced as drugs do not raise endurance effectively adjacent to increasing cancer cases worldwide. Molecular hybridization is a new technique in design of drug and its development based on the hydridisation of pharmacophoric entities of different bioactive substances so as to produce a new hybrid compound with improvement in both affinity and efficacy. The molecular hybridization could be considered an approach of normal plan of latest ligands and prototypes depend upon the detection of pharmacophore moieties from molecular structure of three or more identified bioactive derivative that, during the ample union of these entities, direct to the propose a new hybrid architecture that sustain previous individuality of the mother templates. [1]

A huge number of heterocycles have been found to possess diverse types ofbiological activities like anti-viral, anti-tumor, anti-convulsant, analgesic, anti-oxidant, anti-depressant, herbicidal, insecticidal, fungicidal, anti-bacterial, anti-microbial, cyclooxygenase inhibitory,

ISSN: 0971-1260
Vol-22-Issue-16-August-2019

anti-microbial and so on [2]. As heterocyclic compounds, many derivatives containing the s-triazine moiety are being reported that have capability to work as drugs and also have properties that are possessed by reactive dyes [3]. Triazole derivatives have considerable and repeated insecticidal activity, or they are used in agrochemical structures that are attribute of lots of organic energetic compounds at the same time as cytochrome enzyme also slow down the peptide inhibitor. The imidazole and a triazole are antifungal agents attached to a non-symmetric carbon atom with their useful pharmacophore behavior, few examples include Fluconazole, Ketoconazole, and Ptraconazole 1, 2, 4-triazole. Voriconazole is used as analgesic,antiasthmatic, anticholinergic, antibacterial activities [4]. The pyrimidines and their derivatives have also been considered since past century as they also hold a various pharmacological activity and a spacious assortment of organic activities alongside unrelated DNA and RNA, diuretic, anticancer, virus as well as anti-HIV, polio herps viruses, cardiovascular and so forth.[5]Click chemistry was discovered by Sharpless in laboratory by copper (I)catalyzedazide alkyne cycloaddition (CuAAC) that give end product in the invention of large number of compounds like 1,2,3-triazoles in extremely good yields. [6]

The nitrogen containing heterocycles are important as far as their medicinal values areconcerned. [7] Triazine is an example of such heterocycles. On the basis of structure there are three isomers of triazine and are called as 1,2,4-triazine, 1,2,3-triazine and 1,3,5-triazine. Recent discovery has revealed that 2,4,6-trisubstituted-1,3,5-triazine scaffolds inhibits*Mycobacterium tuberculosis* (Mtb) H37RV. Apart from this, derivatives of s-triazine also possess a wide range of pharmacological activities.[8]The pyrimidines and their various derivatives have also been studied since past century as they also possess welldiversified pharmacological property.

Mycobacterium tuberculosis (TB) is a major health issueand it is todays' leading infectious disease. According to findings ofglobal project by WHO, antitubercular drug resistance still persists worldwide. Although there are reports of new compounds having antitubercular activity in recent years, but no new drug has hit the market since aboutfifty-five years[9]. In the current medication, it requires almost nine months for complete cure. Due toincreasein MDR strains and incidences of death due to TB have elevated the interest of discovery and development of new drugs having novel mode of action [10]. Moreover, present drugs are less potent and have prolonged associated effects. Hence, it is essential to produce new antitubercular drugs.[11]

Cancer is a group of diseases where the cells grow abnormally and multiply through uncontrolled cell division. Cancer cells are more metabolically active than normal cells. It

ISSN: 0971-1260
Vol-22-Issue-16-August-2019

gradually invades and destroys nearby normal cells by forming a lump called a tumor. Not all tumors or lumps are benign tumors are not cancer. It is localized and of small size that tends to grow quite slowly. It does not spread to other parts of the body and is rarely life threatening. Both external and internal factors such as dietary fat intake, solvent and pesticide exposure, exposure to ionizing radiation (causing acute leukemias, thyroid cancer, breast cancer, lung cancer and others), smoking cigarette, some virus (HIV, HPV and Hepatitis B virus) and unhealthy lifestyle (being overweight, inadequate physical exercise, in excess of alcohol, insufficient vegetables and fruit, extra sugar and red meat) can cause cancer. Once the DNA is affected, there are no standard control projects that inhibit cell over enlargement or the attack on additional tissues in tumor cells. Cancer is one of the most widespread and leading deadliest disease, and suffers one third of the world's population by this disease. Thus, molecule containing Triazole moiety show anti- Cancer activities and might be able to protect the drug resistance to certain extent.Cefatrizine is an anti-bacterial agent and Tazobactumis well known anti-cancer agent[12]

In order to evaluate the importance of molecular hybridisation in designing new lead molecule, following review was undertaken. In the present work, review of biologically important molecule is done. A study of some hybrids formed by fusion of these pharmacophoric groups was done. This would be helpful for identifying and designing new lead compounds.

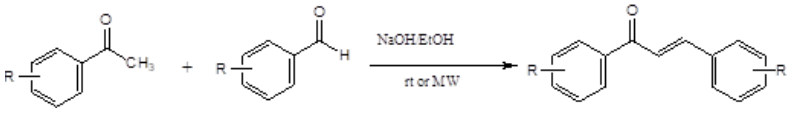
I) Biological activity of chalcones

In order to synthesize heterocyclic compounds chalcones act as intermediate and also constitute an important group of natural products similar to that in case of flavanoids in which the two aromatic rings are connected to each other by a three carbon α, β unsaturated carbonyl moiety. Chalcones are likewise starting material in the synthesis of numerous organically vital heterocycles, for example, benzothiazepine, 1, 4-diketones, pyrazolines, and flavones. In this manner the synthesis of chalcones has created immense attention in field of medicinal chemistry. The customary techniques for synthesis of 1,3-diaryl-2-propenones includes the utilization of solid bases. There are additionally a few reports on acid catalyzed aldol condensation, e.g. BF_3, $AlCl_3$, $NiCl_2$ and $RuCl_3$. Chalcones and its derivatives have pulled attention because of various pharmacological applications. They have shown a wide range of pharmacological activities [13].

Generally, chalcones are prepared by simple Claisen-Schmidt condensation reactions of substituted or simple arylaldehydes with substituted or simple acetophenones. This

ISSN: 0971-1260
Vol-22-Issue-16-August-2019

reaction is generally base catalyzed, however there are many reactions of chalcones synthesis which are acid catalyzed, solid and resin supported and performed in microwave. But these reactions have the drawbacks like low yield, time consuming, require expensive reagents and catalysts [14].



Scheme I: Synthesis of chalcone

Chalcones also undergoes ring closure reactions with hydrazine, guanidine, malononitrile and so on (fig-1) and give a number of derivatives such as pyrazoline, pyrimidine, iso-oxazole, cyanopyridine etc. The carbonyl functionality in chalcones plays a key role as an attractive site for 1,3 dinucleophiles to form such types of heterocyclic ring systems. This kind of reactions are generally carried out in the presence of NaOH or ethanolic KOH solutions but in literatures the use of other reagents like piperidine is also reported.

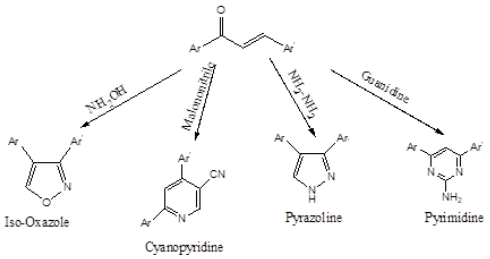


Figure 1: Derivative of chalcones

Inhibition of numerous biologically important enzymes such as aldose reductase, xanthine oxidase, epoxide hydrolase, quinone reductase, protein tyrosine kinase, monoamine oxidase, lipoxygenase and so on, have been reported by a number of chalcones derivatives.

The chalcone synthesis by condensation of 4-hydroxy-3-methylacetophenone with different aldehyde in methanolic KOH were also reported and were further reacted with hydrazine for their cyclization in order to give pyrazoline derivatives (fig-2). Many of these derivatives were characterized and were also reported to possess antimicrobial activities against *Mycobacterium tuberculosis* $H37_{RV.}$ [15]

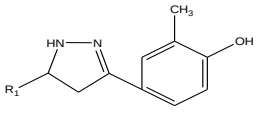


Fig-2

ISSN: 0971-1260
Vol-22-Issue-16-August-2019

II) BIOACTIVITY OF HETEROCYCLIC COMPOUNDS BEARING 1,3,5-TRIAZINE MOIETY

Triazine is a heterocyclic compound with six member and is similar to benzene ring by replacing three C-H units by nitrogen. There are three isomers of triazine, 1,2,3-triazine(fig-3), 1,2,4-triazine(fig-4) and 1,3,5-triazine(fig-5) the 1,3,5-triazine is symmetrical and is very common and is prepared by a trimerization process of cyanic acid amide.

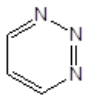
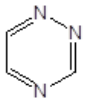




Fig 3 Fig 4 Fig 5

Triazine act as a weak base and due to its less resonance energy than that of benzene it shows nucleophilic substitution than that of electrophilic substitutions. In case of symmetrical s-triazine (i.e 1,3,5-triazine) moieties, along with diverse biological activities such as antiviral, anticancer, fungicidal, insecticidal, bacterial, herbicidal, they are also having applications as dyes, lubricant, and analytical reagent.[16]

2, 4, 6-trisubstituted (dimethyl amino)-1,3,5-triazine(fig-6) which is also known as altretamine act as an antitumor agent and used in the treatment of ovarian cancer. This unique structure produces the weakly alkylating species formaldehyde and damage tumour cells. Another common drug is Triethylenemelamine (TEM) (fig-7). It plays a vital role in chemotherapy.

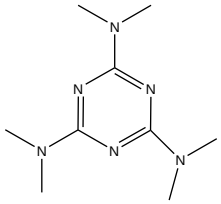
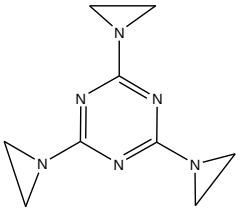



Fig-6 Fig-7

There are many compounds that contain 1, 3, 5-triazine nucleus are available out of which Melamine and Altrazine are the most common. Malamine (fig-8) is a trimer of cyanamime and is an organic base. having 66% nitrogen similar to that of cyanamide and shows the fire-retardant property on mixing with resins due to the release of nitrogen gas when burnt, Whilealtrazine (fig-9) is widely used as herbicide.

ISSN: 0971-1260
Vol-22-Issue-16-August-2019

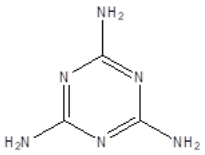


Fig 8

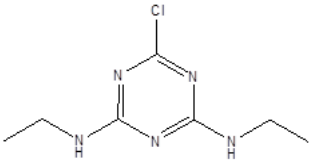


Fig 9

For the synthesis of nitrogen containing heterocyclic compounds and the utility for various biological receptors has been attracting interest therefore triazine heterocyclic motif containing nitrogen is playing major role at different target and provide varied pharmacological properties as it inhibits the action of protein that normally function to enhance the activity of cytotoxic agent.

The importance of triazine nucleus was further supported by discovery of a new series of pyrimidine triazine derivative as effective inhibitor of mycobacterium tuberculosis H37RV. The substituted pyrimidine-triazine compounds were found to potray more anti-tubercular activity than that of the non-substituted one. This confirms that the hybrid may bet active due to the presence of triazine moiety. [17]

An inhibitory property of 1,3,5-triazine-azomethane conjugates against *Mycobacterium tuberculosis* was observed and there is also reports on the pyrimidine and indole thio-pyrimidine substituted derivatives(fig-10).[1]

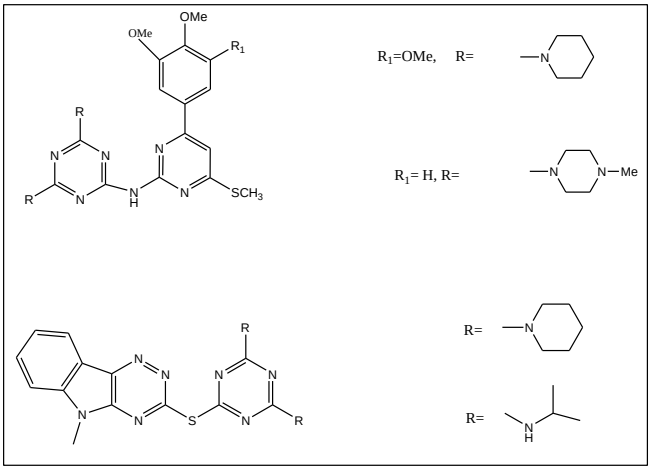


Fig-10

The synthesis of s-triazine derivatives (fig-11) was done and screened them for their antimicrobial activity. The compounds were found to be non-toxic and promising antimicrobial agents. Among the synthesized compounds seven were showing inhibitory concentration (MIC) in the range 6.25-12.5µg/ml. [18]

ISSN: 0971-1260
Vol-22-Issue-16-August-2019

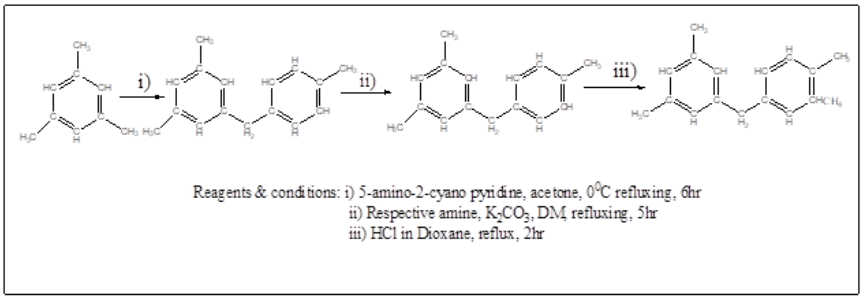


Fig -11

III) BIOACTIVITY OF TRIAZINE BASED CHALCONES AND THEIR DERIVATIVES

Triazine derivatives bearing the pharmacophoric moiety have been reported in order to analyze the antiviral activities both in vivo and in vitro against *EnecphalomycocarditicsVirus* (EMCV) and *Japaneses Encephalitis Virus* (JEV). The derivatives of pyrazoline (fig-12) have been reported to possess wide range of therapeutic activities as antibacterial, anti-fungal, anticancer. As substituted pyridines consist of biological activities, specially cyanopyridines (fig-13) which possess antitubercular, antibacterial, and anticancer, antifungal activities. Therefore, synthesis of hybrid of s-triazine and chalcones was carried out [19].

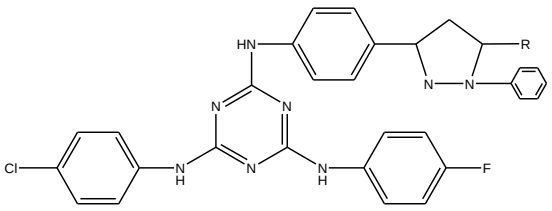


Fig-12

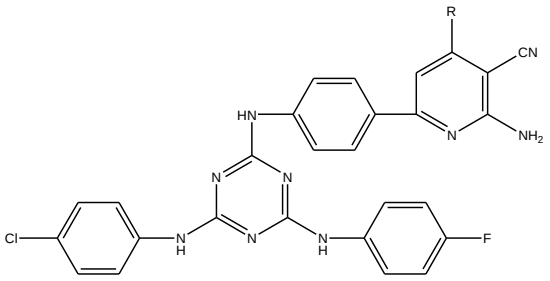


Fig-13

1,3,5-triazine(s-triazine) derivatives are used as biophores, due to similarity in terms of structure with naturally abundant heteroaromatic molecules (like nucleotides and nucleotides bases). A fusion library of chalcone-triazine have been reported in order to get a combination of a fluorophore (chalcone)and a biophore(triazine) with increased biological activities. In cyanuric chloride by substituting the three chlorides by different groups like amine, alcohols, sulfur, methoxy, and so on, the diverse biological property of the triazine moiety can easily be manipulated. Evaluate of their properties showed that these have strong fluorescence.

ISSN: 0971-1260
Vol-22-Issue-16-August-2019

Two of the Chalcone-Triazine compounds (fig-14) were selected and were tested on cancer liver cells (Chang and HepG2). Incubation of these compounds were performed for one hour and the images were evaluated with the use of fluorescein isothiocyanatefilters. The two CT compounds were found to be cell permeable and act as a powerful tool for imaging studies. The fluorescent property of the two CT groups plays a vital role in order to investigate the cellular mechanism and identification of target molecule. [20]

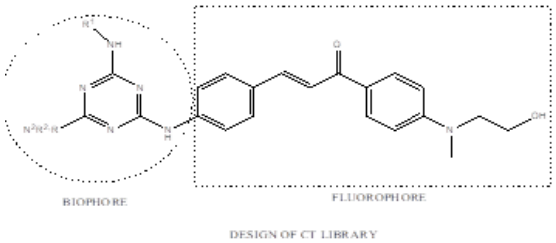


Fig 14

Dichalcones (fig-15) series bearing the s-triazine moiety have been reported by Khan.F.G*et al*(2015). For this synthesis the reaction of sodium salt of 4-hydroxy benzaldehyde with 2,4-dichloro-6-methoy-1,3,5-triazine was done using phase transfer catalyst. In this reaction 2,4-bis(4-formylphenoxy)-6-methoxy-1,3,5-triazine was used as intermediate. The derivatives of these dichalcones bearing the s-triazine moiety were synthesized and their antimicrobial activities were determined by disc diffusion method. According to the data they were found to possess antimicrobial activity against *Proteus vulgaris, Staphylococcus aureus, Xanthomonas citri*and *Erwinia cartovora*.[16]

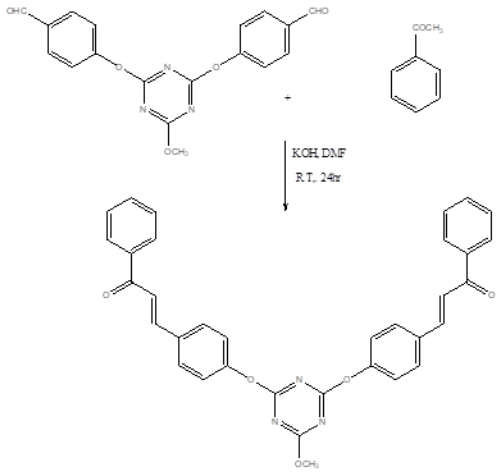


Fig 15

A series of ten new trichalcones (fig-16) derivatives containing the s-triazine moiety were reported. The intermediate used in this synthesis was 2,4,6-tris(p-formylphenoxy)-1,3,5-

ISSN: 0971-1260
Vol-22-Issue-16-August-2019

triazine. The trichalcone derivatives were synthesized and their antimicrobial activity were determined by disc diffusion method. Their antibacterial activities against *Xanthomonas citri, Proteus vulgaris, Staphylococcus aureus,* and *Erwinia cartovora*were reported, along with this these compounds were also evaluated for their antifungal activity against *Alternaria* and *Curvularialunata.*[17]

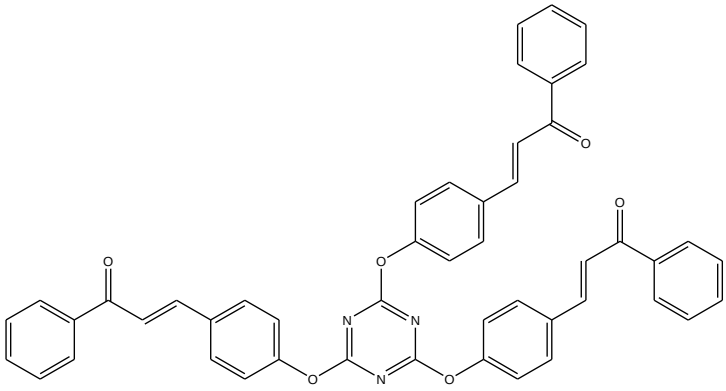


Fig-16

The derivatives of heterocyclic compounds like phenyl pyrazolines and isoxazoles was prepared by cyclization of S-triazine based chalcones(fig-17). Among these pyrazoline derivatives containing the phenyl moiety at 5th position possess the property of good film, blue photoluminescence and electroluminescence. Along with this pyrazoline derivatives also plays a vital role in agrochemical as herbicides and in pharmaceutical industries as active pharmaceuticals. Pyrazoline derivatives are found to possess several biological activities. Along with this many chemotherapeutic agents containing the pyrazoline scaffolds are also used for clinical purpose. [21]

However, among several heterocyclic compounds, the isoxazole nucleus are found to play a vital role in a number of natural and pharmacological compounds. Isoxazole unit have found to possess biological properties like fungicidal, antimicrobial, anti-tubercular, anti-viral, and so on.

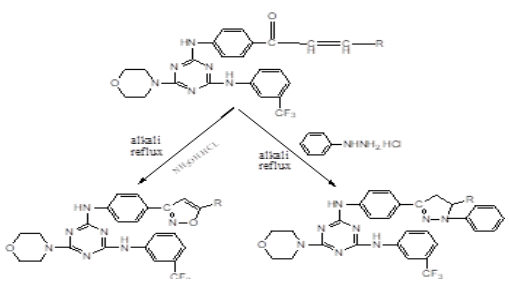


Fig 17

ISSN: 0971-1260
Vol-22-Issue-16-August-2019

A series of S-triazine based chalcones (fig-18) possessing the 1,3-diaryl-2-propen-1-one backbone moiety was reported. The reaction used for this synthesis was Claisen-Schmidt condensation. The compounds were evaluated for anti-oxidant activity by DPPH radical scavenging method and by using the non-enzymatic haemoglobin glycosylation method anti-diabetic were investigated.

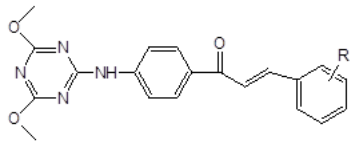


Fig 18

The synthesis of 1,3,5-triazine-chalcone hybrid (fig-19) were reported and screened for their anti-tubercular activity and these compounds showed potency against MTB. [11]

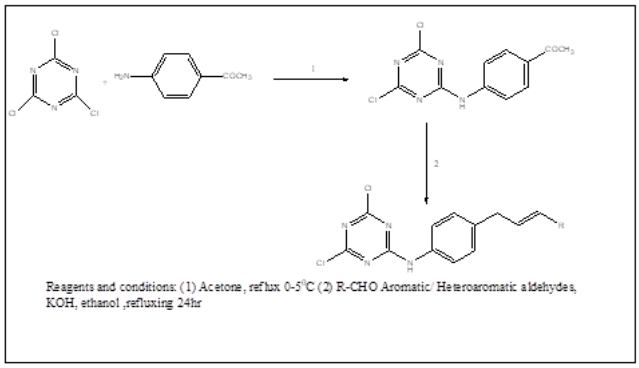


Fig 19

III) BIOACTIVITY OF PYRIMIDINE NUCLEUS:

A series of 2-Amino-4,6-diarylpyrimidines (fig-20) by the reaction of chalcone with guanidine were synthesized. The synthesized pyrimidines were characterised and were evaluated for their biological activities in vitro against a variety of organism. The substituted derivatives were found to be very stable and proved to be beneficial for biological and pharmacological purpose. [8]

Fig 20

ISSN: 0971-1260
Vol-22-Issue-16-August-2019

A novel series of triazine-pyrimidine (fig-21) were synthesized and screened for their in vitro antimalarial activity. In comparison to the standard drug pyrimethamine all the synthesized compounds showed better activity against the chloroquine-resistant strain W2.

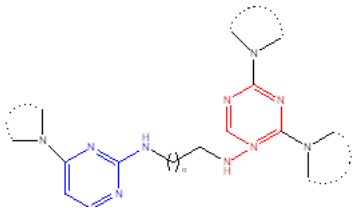


Fig 21

The presence of N-methyl and N-ethyl groups on pyrimidine nucleus and diethyl amino group at triazine nucleus shows the increased bioactivity of synthesized compounds against CQ-sensitive strain of *P. falciparum* and were found to be more potent than other derivatives. [22]

Bioactivity of triazole and their derivatives:

A new series of C-14 1,2,3-triazole-linked dehydroabietic acid derivatives. Antiproliferative activity of most of the hybrids showed good inhibition in a number of cancer cell lines with less IC_{50} values. Compound (Fig 22) was most potent with IC50 values ranging from 0.7 to 1.2µM against a panel of cancer cells, hepatoma prostate (LNCaP), (SMCC-7721) and, breast (SKBR-3), glioma (U251),colon (HCT-116), lung(A549), this also show minor cytotoxicity on normal cells. The compound could induce apoptosis in MDA-MB-231cells and could be developed into an anticancer lead similar to natural product by structural modification. [23]

Fig 22

A sequence of fluorinated thiadiazoles (Figure 23) were prepared to evaluate the effect of fluorine substitution on the aryl ring attached to the thiadiazole nucleus and the various substitutions in the aryl ring attached on the triazole nucleus on the antitumor activity of these compounds. Compounds have been tested for osteosarcoma (SaOS-2), human breast adenocarcinoma (MCF7)and myelogenic leukemia (K562) cell lines. The results showed that penta-fluoro substitution in aryl ring A increases anti-proliferative activity, while structural

ISSN: 0971-1260
Vol-22-Issue-16-August-2019

changes in aryl ring B are detrimental to anti-proliferative potency. As a result, fluorine has been shown to substitute 3,6-diaryl-[1,2,4] triazole[3,4-b][1,3,4] thiadiazole[3,4]

Fig 23

Singh *et al*, synthesized 1,2,3-triazole tethered β-lactam-chalcone bifunctional hybrids (fig 24) on bifunctional moieties with the help of click chemistry. The compound was tested against the four human cancer cell lines known as Caco-2(colon), (leukemia)THP-1, (lung)A-549, (prostate)PC-3. The synthesized compound was almost twice as active against THP-1 cell lines as 5-flouracil. This shows a good activity of compound synthesized by Singh and can be used as screenings [24].

Fig 24

2-triazole derivatives of 5'-O-[N-(salicyl)sulfamoyl] adenosine (Sal-AMS) (Fig 25) were synthesized and tested for their efficacy against *M. tuberculosis.* It was found out that these work by inhibition of Aryl Acid Adenylating Enzymes required for siderophores biosynthesis by *Mycobacterium.*These compounds are active at subanomolar levels.[25]

ISSN: 0971-1260
Vol-22-Issue-16-August-2019

Fig 25

Conclusion:

The presents review presents a brief compilation of various reports on pharmacological activities of heterocyclic nuclei. A comparison of these pharmacophores with their hybrid is made and it could be concluded that hybridisation of active nuclei leads to more potent drugs/molecule. An experimental work could be done to develop new drugs with better activities and less toxicities.

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ISSN: 0971-1260
Vol-22-Issue-16-August-2019

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