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A Mini Review on Antimalarial Activities of Biologically Active Substituted Triazoles Derivatives

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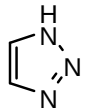
Abstract: *Heterocyclic compounds have paying strong attention interest. Many different derivatives have been prepared and possess various type useful pharmacological activities. A lot of work has been done on five member heterocyclic triazole ring system. Different pharmacological activities of triazole ring and its derivatives have been observed. Triazole derivatives possess a wide range of pharmacological activities such as anticancer, anticonvulsant, antimicrobial, anti-inflammatory, antioxidant, antitubercular, antimalarial, antinociceptive etc. In triazole ring, substitution at 1,4 and 1,3 positions with more electronegative group will possess more active compounds. This review contains various antmalarial activities of triazole compounds and also the landmark for the new research towards this moiety.*

Keywords: *Triazole dervatives, antimalarial, biological activies.*

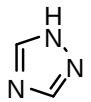
1. INTRODUCTION

Medicinal chemistry is a part of biological, medical and pharmaceutical sciences and concerned with the development, discovery, design and recognition of biologically active drug molecules. It also involves study of metabolism, mode of action at the molecular level and the development of structure activity relationship (SAR) of the active pharmacophore for the discovery and development of new potent agents for treating different diseases or disorders [1]. Inorganic compounds continue to be important in therapy, such as antacids, mineral supplements and radiopharmaceuticals, but organic compounds with increasingly specific biological activities are clearly dominant [2]. Heterocyclic compounds are cyclic compounds with at least two different elements as ring member atoms [3]. Although heterocyclic compounds may be inorganic, most contain at least one carbon atom, and one or more atoms of elements other than carbon within the ring structure, such as sulfur, oxygen or nitrogen. In organic chemistry non carbon atoms which replace carbon atoms are called heteroatoms [4].

Triazole has a basic, five membered, heterocyclic ring containing two carbon and three nitrogen atoms having molecular formula $C_2H_3N_3$. Triazole and its derivatives possess a great significance in medicinal chemistry and numerous heterocyclic compounds containing triazole with different biological activities can be synthesized from them. It forms a pair of isomeric chemical compounds [5].



1, 2, 3-triazole



1, 2, 4-triazole

The 1,2,4-triazoles possess significant and wide variety of activity in comparison to 1,2,3-triazoles. 1,2,3-triazole is considered to be the most stable organic compound in comparison to all other organic compounds possessing three adjacent nitrogen atoms. Aziridine was formed by flash vacuum pyrolysis from 1, 2, 3-triazole at 500°C which leads to loss of molecular nitrogen (N_2). Certain triazoles undergo cleavage very easily due to so called ring-chain tautomerism such as in the Dimroth rearrangement. 1,2,3-triazole is considered to be the most useful component, widely used in research purpose as a building block for complex chemical compounds such as

pharmaceutical drugs like tazobactam [6]. 1,2,4-Triazole and its derivatives posses a wide variety of pharmacological activity such as antibacterial [7-11], antifungal [12-15], antiviral [16] anti-tubercular [17-19], anthelmintic [20-22], analgesic, anti-inflammatory [23,24], cyclooxygenase inhibitor [25], anticancer [26-30], anticonvulsant [31-34], antioxidant [35], anti-malarial and other anticipated activies [36-40]. Some of the marketed preparation which contains triazole ring is fluconazole and itraconazole. The attachment of quinoline ring to triazole ring is responsible for producing anti-bacterial effect and further modifications can be made on it to enhance its pharmacological effect [41]. Substitution at 3rd position may also increase the pharmacological activity of a compound for e.g. 3-Amino-1,2,4 triazole is a competitive inhibitor of the production of HIS3 gene, imidazoleglycerolphosphate dehydratase. It is an enzyme catalyzing the sixth step of the histidine production and is also a non selective systemic triazole herbicide used on non food crop land to control annual grasses and broad leaf and aquatic weeds [42].

There are number of triazoles derivatives reported in this review possessing different biological activity comparable to clinically synthetic compounds. The triazole antifungal drugs include fluconazole, isavuconazole, itraconazole, voriconazole, pramiconazole, and posaconazole. The triazole plant protection fungicides include epoxiconazole, triadimenol, propiconazole, metconazole, cyproconazole, tebuconazole, flusilazole and paclobutrazol. 1,2,3-Triazole is a basic aromatic heterocycle. Substituted 1, 2, 3-triazoles can be produced using the azide alkyne Huisgen cycloaddition in which an azide and an alkyne undergo a 1,3-dipolar cycloaddition reaction. It is a surprisingly stable structure compared to other organic compounds with three adjacent nitrogen atoms. However, flash vacuum pyrolysis at 500 °C leads to loss of molecular nitrogen (N2) to produce aziridine. Certain triazoles are relatively easy to cleave due to so-called ring-chain tautomerism. One manifestation is found in the Dimroth rearrangement. 1,2,3-Triazole finds use in research as a building block for more complex chemical compounds, such as pharmaceutical drugs like tazobactam [43].

2. PHARMACOLOGICAL ACTIVITIES OF TRIAZOLE DERIVATIVES

The synthesis of high nitrogen containing heterocyclic systems has been attracted to many pharmaceutical and agrochemical industries. The triazole nucleus is one of the most important heterocycles which is a feature of natural products and medicinal agents. Triazole nucleus is enjoying their importance as being the center of activity. The nitrogen containing heterocyclics are found in abundance in most of the medicinal compounds. The triazoles are said to be the isosters of imidazoles in which the carbon atom of imidazole is isosterically replaced by nitrogen. Triazole & its derivatives have a wide range of application. The derivatization of Triazole ring is based on the phenomenon of bioisosterism in which replacement of oxygen of oxadiazole nucleus with nitrogen triazole analogue.The triazole derivatives are versatile and have been featured in a number of clinically used drugs. The most relevant and recent studies have revealed that triazole derivatives have a broad spectrum pharmacological activities. Triazoles and its derivatives possess a great importance in medicinal chemistry and can be used for the synthesis of numerous heterocyclic compounds with different biological activities. This review article covers the latest information over active triazoles derivatives having different pharmacological action.

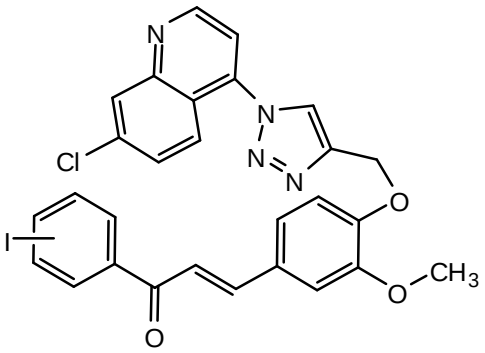
3. ANTIMALARIAL ACTIVITY

A series of chalcone and dienone hybrid compounds **(1a-c)** containing aminoquinoline and nucleoside templates which were then screened for *in-vitro* antimalarial activity. Amongst the synthesized compounds, three compounds were found to be most active that is compounds **1a, 1b** and **1c**, compound **1a** was the most active and potent against D10, Dd2 and W2 strains of *Plasmodium falciparum* compared with the standard drug chloroquine [44].

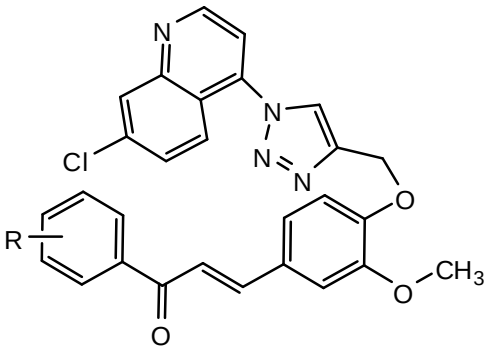
A series of triazolium salts (**2)** has been carried out and found to be highly potent with active conc. in the nanomolar range in *P. falciparum* cultures. It is hypothesized as electron deficient cores that are essential to interact with negatively charged moiety on the parasites merozoite which determine both the potency and selectivity of the compound [45].

Some compounds were evaluated and sensitivity of chloroquine-resistant *P. falciparum* malarial parasite to *in vitro* by using triturated Hypoxanthine incorporation assay. The compounds were tested for antimalarial activity and only one compound that is 3-{4-[4-(4-fluoro-phenyl)-4*H*-[1,2,4]triazol-3-yl-methoxy]-phenyl}-2-phenyl-3*H*-quinazolin-4-one **(3)** was found to be most

active against *P. falciparum* strains and its 50% inhibitory concentration IC50 value was 1.2M [46]. **A** series of novel 1,3-diaryl propenone derivatives **(4)** and their antimalarial activity *in vitro* against asexual blood stages of human malaria parasite, *P. falciparum*. Chalcone derivatives were prepared *via* Claisen-Schmidt condensation of substituted aldehydes with substituted methyl ketones. The chloro-series, 1,2,4-triazole substituted chalcone was found to be the most effective in inhibiting the *in vitro* growth of *P. falciparum in vitro* while pyrrole and benzotriazole substituted chalcones showed relatively less inhibitory activity. This is probably the first report on antiplasmodial activity of chalcones with azoles on acetophenone ring [47]. A structure-based design project to optimise activity, species selectivity and pharmaceutical properties of triazenylpyrimethamine TAB (IC50= 0.17 M; rat liver DHFR IC50/*P.* carinii DHFR IC50=114). This concern led them to design, synthesise and evaluate four new series of pyrimethamine derivatives bearing triazole **(5)** triazolium, triazinium and amino moieties at the 3'-position of parachlorophenyl ring. Such stabilised 'triazene' derivatives address potentially compromised pharmaceutical profile of TAB and the 3'-amine substituted agents afford conformationally flexible substitutes [48]. Phenyl-substituted triazolopyrimidines **(6)** leading to identification of analogs with low predicted metabolism in human liver microsomes and which showed prolonged exposure in mice.The most active single substituted compounds in the series contained para substituents, combinations of para and meta substitutions on phenyl ring attached to triazole nucleus yielded compounds with the best antimalarial activity. One compound containing para-trifluoro methyl phenyl group suppressed growth of *P. berghei* in mice after oral administration [49].



Compound **1a** and 1b



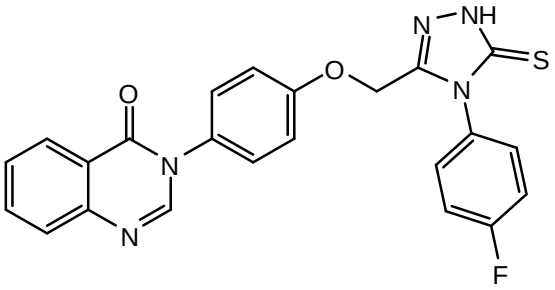
Compound **1a** and **1c**

1a: 2,4-diOCH_3; **1b**: 2,3,4-triOCH_3; **1c**: 2,3,4-triOCH_3

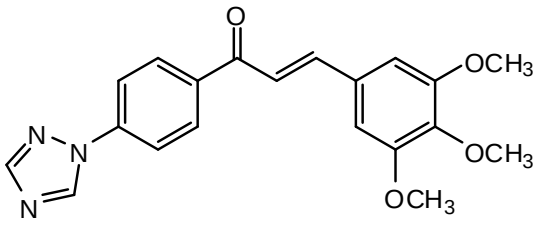
Compound **2**

R_1=C_6H_5, 4-Br-$C_6H_5CH_3$, -$C_6H_5CH_2COCH_3$, -$C_6H_5CH_2CH_2COCH_3$; R_2= -CH_3, -C_6H_5, -H;

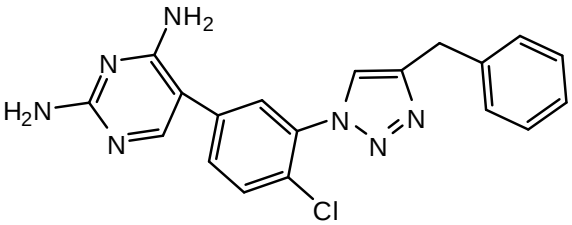
R_3= -C6H5, -CH3; R4= -SCH3, -C6H5,



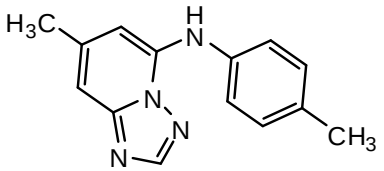
Compound **3**



Compound **4**



Compound **5**



Compound **6**

4. DISCUSSION

Triazoles have attracted considerable attention in the fields of medicine and agrochemical research as well as in materials science, due to their unique structures and properties. Triazole and its derivatives belong to a class of exceptionally active compounds possessing many pharmacological properties. Now a day's research is concentrated towards the introduction of new and safe therapeutic agents of clinical importance. The success of imidazole as an important moiety of number of medicinal agents led to introduction of the triazoles. The triazoles are said to be the isosters of imidazoles in which the carbon atom of imidazole is isosterically replaced by nitrogen. Triazoles nucleus have been incorporated into a wide variety of therapeutically interesting drug candidates including anticonvulsant, antineoplastic, antimalarial, antiviral, antiproliferative,anticancer, analgesic, anti-inflammatory, CNS stimulants, sedatives, antianxiety, antimicrobial, antifungal antioxidant activities etc. They are used as optical brightening agents, corrosion inhibitors and additives with a variety of other functions. Many dye stuffs and pigments have heterocyclic. The importance of triazole derivatives lies in the field that these have good position in heterocyclic chemistry, due to its various biological activities [50-55]. Thus triazole acts as a promising medicinal agent for the scientists working over this field. This review can be helpful to develop various more new compounds possessing triazoles moiety that could be better in terms of efficacy and lesser toxicity. From the above discussions it may be concluded that the modifications in triazole moiety displayed valuable biological activities and these modifications can be utilized to develop potentially active agents for future investigations.

5. CONCLUSION

Triazole is a unique moiety that is responsible for various biological activities. This article highlighted research work of many researchers reported in literature for different pharmacological activities on synthesized triazole compounds. This review has presented comprehensive details of triazole analogues, potent compounds reported for particular pharmacological activity and the method or technique involved in evaluation process. More investigations must be carried out to evaluate more activities of triazole for many diseases whose treatment are difficult in the medical sciences. This has been noticed so far, that modifications on triazole moiety results in the formation of compounds with valuable biological activities. It will be interesting to observe that these modifications can be utilized as potent therapeutic agents in future. Thus many more modifications on triazole moiety can be possible and needs to be continued for the use of mankind.

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