Review Article

Antimalarial Activity of Oxadiazoles - A Review

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ABSTRACT

The oxadiazole nucleus is one of the most important five membered heterocyclic compound with one oxygen and two nitrogen atoms. The compound containing this nucleus have various biological activities like antimalarial, antibacterial, antitubercular, anticoagulant, cytotoxic, antifungal, hypoglycemic, antiallergic, enzyme inhibitor, vasodialatory, hypolipidemia, insecticidal, analgesic, anticancer etc. Due to the broad and potent activity of oxadiazole and their derivatives it is a molecule of interest among medicinal chemist. The review represents a broad view on the antimalarial activity possessed by compounds having oxadiazole nucleus.

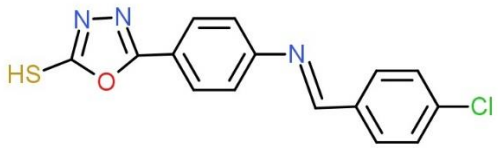
Keywords: Oxadiazole, antimalarial, *Plasmodium falciparum*, pyrazole.

INTRODUCTION

Malaria is an infectious disease caused by the protozoan parasite from the plasmodium parasite like plasmodium falciparum. It is transmitted through the anopheles mosquito and also through the transfusion and contaminated needle. It is one of the major infectious disease in the world affect the human health. According to WHO reports in last year, malaria afflicted 228 million people and killed an estimated 405000, mostly in sub Saharan Africa. More cases are reported in social and economic backward countries. Five different types of plasmodium are involved in the malaria, among them plasmodium falciparum responsible for critical conditions. In humans the erythrocyclic phase of the plasmodium falciparum is responsible for the infection. There for the design of antimalarial drugs it mainly focused on the erythrocyclic phase of the parasite. During this phase the parasite utilise the proteases which cause the hydrolysis of haemoglobin in the acidic food vacuoles. It leads to amino acid formation required for the parasite protein synthesis. The enzyme like falcipain-2 involved in the digestion. So the inhibition of falcipain-2 enzyme causes the accumulation of undigested haemoglobin in the swollen food vacuole, it will block the parasite development.

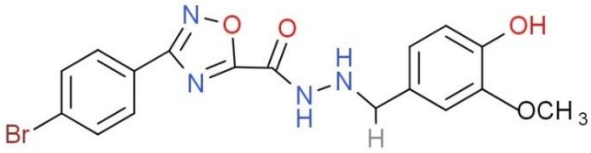
Nowadays the importance of heterocyclic compound is increased in the research field of pharmaceutical industry. This scenario is due to wide range of applications, which include biological and pharmacological properties. The oxadiazole is a heterocyclic compound which belongs to the azole family with molecular formula $C_2H_2N_2O$. Nowadays the oxadiazole and their derivatives are used due to their potent antimalarial activity. The substituents like 1,3,4-oxadiazole, 1,2,5-oxadiazole, 1,2,4- oxadiazole are include in the number of pharmaceutical drugs like valtegravir, discovery programs like antibacterial, antitubercular, anticoagulant, cytotoxic, antifungal, hypoglycemic, antiinflammatory, antiallergic, enzyme inhibitor, vasodialatory, analgesic, hypolipidemia, anticancer, insecticidal activities due to their wide range of applications. They are attracted in medicinal chemistry. Boosters of carboxylic acid, ester and carboxamide contribute to pharmacological activity due to the involvement in hydrogen bonding formation with the receptor. This review mainly aimed at the antimalarial activity of oxadiazol derivatives.

S. S. Thakkar et al describe the antimalarial activity of 1,3,4-oxadiazole analogues by the method of in vitro DHFR (Dihydro folate reductase) enzyme inhibition study. From the different analogues the compound 5-(4-((4-chloro benzylidene) amino) phenyl) -1, 3,4-oxadiazole-2-thiol **SS 9** exhibit highest antimalarial activity. This compound prepared by the treatment of 5-(4-amino phenyl) -1, 3,4-oxadiazole-2-thiol with chlorine, in the presence of acetic acid as a catalyst. The in vitro antimalarial activity of different compounds is studied. From this, the compound **SS 9** exhibit best antimalarial activity due to the presence of 4- cl in phenyl ring. The IC 50 value is 0.301+0.021µg/ml. Chloroquine and pyrimethamine was taken as standard with IC 50 value 0.063+0.009 and 1.005+0.053 respectively. The potent entities of compound **SS 9** active against plasmodium falciparum strain evaluated for inhibitory efficacy against bovine liver DHFR enzyme with IC 50 value of. O450+0.005. In this assay compound **SS 9** were found to be poor inhibitor of enzyme when compared to standard drug chloroquine with IC 50 value 0.063+0.009 µg/ml[1].



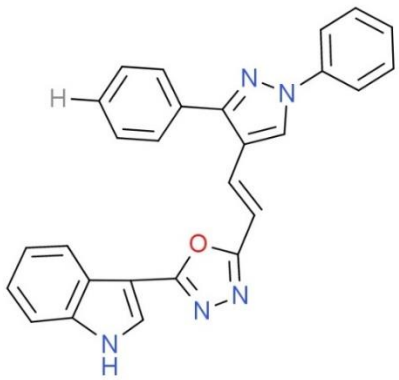
SS 9

Santos filho et al reported the synthesis and antimalarial activity of a series of N-acylhydrazone-1,2,4-oxadiazole derivatives (compound **2**). The compounds were evaluated against chloroquine resistant W2 strain of blood stage of plasmodium falciparum and cytotoxicity against human cell line HepG2.The authors indicated the importance of vanillinyl moiety attached to the iminic structure. The compound **2** show better antimalarial activity with lowest IC50 value 0.07µg/ml similar to that of mefloquine with IC50 value 0.04µg/ml. The mefloquine was taken as standard in the past study[2].



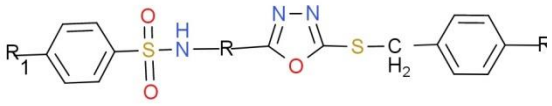
2

G.verma et al reported the synthesis and antimalarial activity of pyrazole acrylic acid based 1, 3, 4-oxadiazole derivatives using schizont maturation inhibition assay. Oxadiazole derivatives prepared by pyrazole acrylic acids were linked to different substituted benzohydrazide in the presence of a cyclization agent pocl3.From this the compound 2-(2-(1,3-diphenyl-1H-pyrazol-4-yl)vinyl)-5-(1H-indol-3-yl)-1,3,4-oxadiazole (compound **6V**) as the most potent antimalarial agent targeting falcipain-2-enzyme.Evaluation of antimalarial activity was done against chloroquine sensitive 3D7 strain of plasmodium falciparum. The compound **6V** having IC50 value 0.245 µg/ml. The chloroquine was taken as standard with IC50 value 0.405µg/ml.[3]



6V

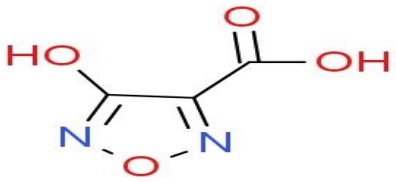
M. Zareef et al reported synthesis and antimalarial activity of novel chiral and achiral benzene sulfonamide bearing 1,3,4-oxadiazole moieties. From the different moieties the compound 2-(4-chlorolphenyl sulfonamido) propane hydrazide is found to be potent inhibitor of the degradation of hemoglobin from plasmodium berghei (ANKA strain with an inhibition value of 54.14%+2.26. It is prepared by treating different amino acid with 4-methyl benzene sulfonyl chloride in alkaline medium to form 4-(4-chlorophenylsulfonamido)alkane hydrazide. From this intermediate different new compound were synthesis like N-[1-(5-(benzyl thio)- 1,3,4-oxadiazole-2-yl)propyl]-4-methyl benzene sulfonamide(**4a**),N-[1-(5-(4-nitro benzyl thio)-1,3,4-oxadiazole-2-yl)propyl]-4-chlorobenzene sulfo namide(**4b**) etc are reported.[4]



3a)R_1 - CH_3 ,R_2 -H

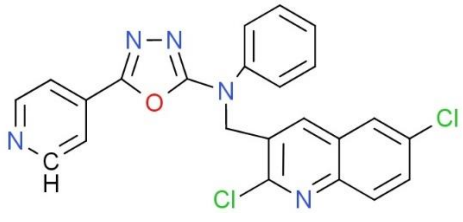
3b)R_1 -Cl ,R_2- NO_2

Angus cameron et al reported a series of azole based compounds with lactate dehydrogenase directed antimalarial activity. The azole based compounds are described that inhibition of plasmodium falciparum LDH at submicro polar concentration (10 m). The concentration about 100 fold lower than required for human lactate dehydrogenase inhibition. The in vitro anti-plasmodial activity determined against plasmodium falciparum 3D7 drug sensitive clone and K1 drug resistant strain. The IC50 value of compound 4-hydroxy -1, 2, 5-oxadiazole-3-carboxylic acid (**compound 5**) was 0.65 M. The modification to or the substitution of the C3 hydroxyl and C4 carboxyl group resulted in the loss of at least two orders of magnitude of activity against plasmodium falciparum LDH.[5]



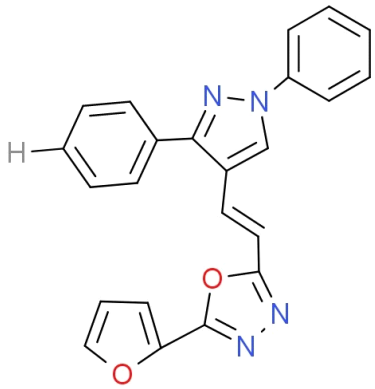
5

G.G.Ladani et al reported the in vitro antimalarial activity of a series of quinoline based 1, 3, 4-oxadiazole derivatives N-((2-chloro-6-(UN) substituted quinolin-3-yl) methyl)-N-phenyl-5-substituted -1, 3, 4-oxadiazole-2-amine against chloroquine and quinine sensitive strain of plasmodium falciparum. These derivatives were synthesized by chloramine coupling reaction approach with different catalyst and solvent. That is the coupling of 2-chloro-3-(chloromethyl)-6-(un) substituted quinoline and N-phenyl-5-substituted-1, 3,4-oxadiazole-2-amine. There of all synthesized compounds the compound N-((2,6-dichloroquinoline-3-yl)methyl)-N-phenyl-5-(pyridin-4-yl)-1,3,4- oxadiazol- 2-amine (**compound 8j**) show excellent activity against plasmodium falciparum strain with IC50 value 0.089 as compared to quinine (IC50=0.826µg/ml). And furthermore it possess moderate activity with chloroquine with IC50 value 0.062 µg/ml.[6]



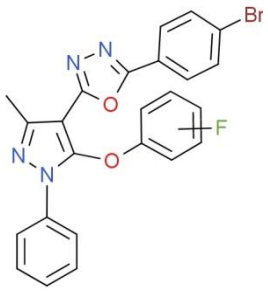
8j

G.verma et al reported the antimalarial activity of pyrazole-1, 3, 4-oxadiazole hybrids by schizont maturation inhibition assay. The compounds was prepared by the acrylic acid derivatives reacted with substituted benzohydrazide derivatives lead to the formation of desired 1,3,4-oxadiazole derivatives in the presence of pocl3.From the different compound synthesized 2-(2-(1,3-diphenyl-1H-pyrazol-4-yl)vinyl)-5-(furan-2-yl)1,3,4-oxadi azole (**compound 5f**) was the most potent compound with IC50 value of 0.248 against 3D7 strain. For this study, chloroquine was taken as standard with IC50 value of 0.405µg/ml. The mode of action of this compound was ascertained using enzyme assay and docking studies.[7]



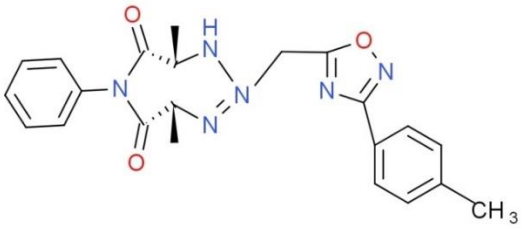
5f

S.C.Karad et al., reported the antimalarial activity of novel series of flouro substituted pyrazole nucleus clubbed with 1, 3, 4-oxadiazole scaffolds against plasmodium falciparum strain using chloroquine and quinine as standard. The compound was synthesized by the reaction of 3-methyl-1-phenyl-1H-pyrazol-5-(4H)-one are using on the final step phenyl iodo diacetate (phI (OAC)2) in dichloromethane at room temperature. From the different compound 2-(4-bromophenyl)-5-(5-(4-fluorophenoxy)-3-methyl-1-phenyl-1H-pyrazol-4-yl)-1,3,4-oxadiazole (**compound 7h**) possess excellent antimalarial activity with IC50 value 0.506 M against the plasmodium falciparum strain as compared to quinine with IC50 value 0.826 µg/ml.[8]



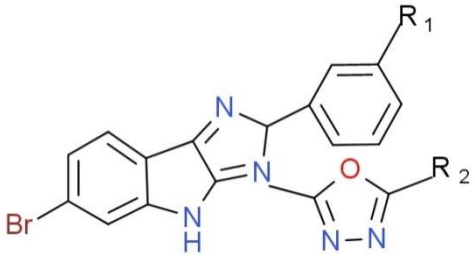
7h

Y.Durust et al reported the synthesis and antimalarial activity of series of novel compound containing both 1,2,4-oxadiazole and 1,2,3-triazole heterocyclic ring determined by modified [H3]-hypoxanthin incorporation assay using chloroquine and pyrimethacine resistant K1 strain. From the different derivatives benznidazole (**compound 5a-k**) show most potent activity against plasmodium falciparum IC50 value 13.2µg/ml.[9]



5a-k

Balaji.k.et al reported the synthesis and antimalarial activity of 20 novel heterocycles bearing imidazole oxadiazole derivatives. The compounds were assayed against chloroquine sensitive NF54 and chloroquine resistant Dd2 strain of plasmodium falciparum. The chloroquine was taken as reference standard. The presence of unsaturation the imidazole ring and bromine atom responsible for the activity of these compounds.2-substituted -5-amino-oxadiazole derivatives were synthesised by refluxing or sonicating the semicarbazide with aromatic acid in concentrated H2SO4 followed by condensation with p-dimethylamino benzaldehyde to form imino derivatives. It is reacting with ammonium acetate and 5-bromosatin to form potentially active imidazole analogue.[10]



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