Green Chemistry Approach for Synthesis of Some 1,3,4-Oxadiazole Derivatives As Potent Antimalarial Agents

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Abstract

Green chemistry incorporates a new approach to the synthesis, processing and application of chemical substances in such manner as to reduce threats to health and environment. An efficient synthesis for the preparation of novel azole derivatives by using both conventional and microwave method has been devised. The result revealed that microwave assisted technique is efficient, eco-friendly and in-expensive which are giving higher yield and reduces the reaction time significantly. The synthesized compound was characterized by means of spectral data and compound code 1c showed significant antimalarial activity.

Keywords: *1,3,4-oxadiazole, Green chemistry Microwave irradiation, Antimalarial activity.*

1. INTRODUCTION

Malaria remains a significant worldwide health problem, with serious social and economic consequences in affected countries[1]. The problem has been worsened by the emergence and spread of parasites that are resistant to well-established antimalarial drugs. The swelling of malaria in the human body is through five different types of protozoan of the genus Plasmodium, but Plasmodium falciparum is responsible for most of the critical cases. However, the appearance of P. falciparum resistance to these drugs is a serious cause for concern[2-3]. To reduce the variety of resistant parasites, the WHO has suggested the combined formulation of artemisinins with traditional antimalarial drugs such as lumefantrine, amodiaquine and mefloquine, and ACT (Artemisinin Combination Therapy) is currently approved in multiple countries[4-5]. For this reason, the development of new, effective, nontoxic, and inexpensive antimalarial drugs is a high priority in medicinal chemistry. Azoles square measure vital as heterocyclic parts of the many natural product, medicine and biologically active molecules.

Consequently, new efficient methodologies for the preparation of azole derivatives provide a valuable tool to synthetic organic chemists[6-7]. Heterocyclic compound having five membered ring containing two carbon atom, one oxygen, two nitrogen and two double bonds such as oxadiazole. 1,3,4-oxadiazole derivatives have played a vital role in the medicinal chemistry it has been synthesized using microwave irradiation and conventional methods. An azole is a class of five-membered nitrogen heterocyclic ring compounds containing at least one other non-carbon atom of either nitrogen, sulfur, or oxygen. The parent compounds are aromatic and have two double bonds; there are successively reduced analogs (azolines and azolidines) with fewer. One, and just one, lone pair of electrons from each heteroatom in the ring is part of the aromatic bonding in an azole[8-11]. The Names of azoles maintain the prefix upon reduction (e.g. pyrazoline, pyrazolidine). The numbering of ring atoms in azoles starts with the heteroatom that's not a part of a covalent bond, then take towards the opposite heteroatom. 1,3,4-Oxadiazoles are an important class of heterocyclic compounds with a wide range of biological activities such as antiviral, antimicrobial, antineoplastic, fungicidal, inhibition of tyrosinase and cathepsin K. The five-membered 1,3,4-oxadiazole heterocycles are also useful intermediates in organic synthesis and widely employed as electron sporting and hole-blocking materials. Oxadiazole based molecular assemblies are an interesting and continuously developing area of research. Conventional methods for different chemical synthesis is very well documented and practiced. The methods for synthesis of organic compounds had continuously modified from the last 10 years. The application of green chemistry principles and practices renders regulation, control, clean-up, and remediation of the environment. In year 1855 Robert Bunsen invented the burner acts as energy source for heating reaction vessel this was latter superseded by isomental, oil bath but the drawback of the heating though method remains the same[12-17]. Microwave Assisted Organic Synthesis had developed in now years which has been considered superior to traditional heating. Microwave assisted organic synthesis has as a new “lead” in the organic synthesis. The technique offers clean, simple, efficient, fast and economic for the synthesis of a number of organic molecules such reaction has new tool in the organic synthesis[18-28]. Important advantage of this technology includes highly accelerated rate of the reaction time with an improvement in yield and quality of product. This technique is considered as important approach toward green chemistry because this technique is more environments friendly and this technology is used in the laboratory and has the potential to have a large impact on the fields of combinatorial

chemistry, screening, medicinal chemistry and drug development. Conventional method of organic synthesis usually requires longer heating time, tedious apparatus setup which result in higher cost of process and the excessive use of solvents or reagents lead to environmental pollution. Computational studies are the crucial steps in the drug designing. Docking study is the computational routine to determine probable binding manners of a ligand to the dynamic site of a receptor. It makes an image of the dynamic site with interaction points known as grid. Then it fits the ligand in the binding site either by grid search or energy search. Due to failure of ADME so it necessary to perform docking studies before pharmacological activity. An outbreak of coronavirus disease (COVID-19) caused by the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) raises an unparalleled challenge in the discovery of appropriate drugs for prevention and treatment. Given the rapid pace of scientific research and clinical data produced by the large number of people quickly infected with SARS-CoV-2, clinicians need reliable proof of successful medical care for this infection as in intial stage with help of molecular docking software it is easy to do in-silico study. The chemical modification of drug delivery system for protein and peptide drugs is important in improving both enzymatic stability and membrane permeations can help to have good biological activity from any heterocyclic compound modification. Someday soon, you might be making your own medicines at home. That's because researchers have tailored a 3D printer to synthesize pharmaceuticals and other chemicals from simple, widely available starting compounds fed into a series[29-39]. These compounds demonstrate interesting luminescent properties, emitting blue to green light with high quantum efficiency depending on the substituents attached to the oxadiazole ring. Given facile synthesis and the possibility of appending different π-conjugated groups new oxadiazole derivatives are intensively investigated for biomedical applications and in polymer field due to their advanced optoelectronic properties. It is known that the introduction of electron-transporting 1,3,4-oxadiazole units (Ox) into the polymer improves their optical properties[40-54].

2. MATERIALS AND METHODS

Chemistry:

All chemicals and solvent procured fromcommercial sources, purified and dried using standard procedures from literature whenever required the reagents were purchasedfromResearch lab,

Mumbai .and issued from storedepartment of Rajarambapu College of Pharmacy, Kasegaon. And solvents were purified bydistillation and residual water was removed. Thetest compounds 1, 3, 4-oxadiazole derivatives 1a-1e were synthesized in our laboratory. Melting pointof synthesized compounds was determined byopen capillary tubes. IR spectra were recordedusing KBr disc on JASCO FTIR-4600. Massspectra were recorded on QP 2010 Shimadzu. H1NMR spectra were performed in $CDCl_3$ solution

I. Conventional method:

Synthesis of substituted ethyl benzoate

Substituted ethyl benzoate was prepared by dissolving 0.01mole of benzoic acid derivatives in absolute ethanol (30 ml).carboxylic acid group is esterified with ethanol and the reaction is processed by refluxing the mixture for 3-5 hours by adding few drops of H_2SO_4, which is act as a catalyst. The final product was obtained as precipitated form which was continued for the next step preparation.

Synthesis of 4-nitrobenzohydrazide

The mixture of compound 1 (0.01mol) and 0.02 Mol 99% hydrazine hydrate was refluxed for 5-6 hours. The reaction mixture was cooled. The solid precipitate was obtained. Dried and recrystallized from ethanol. The completion of reaction was monitored by Thin Layer Chromatography and Infrared Spectrophotometer.

Synthesis of 5-substituted-1,3,4 oxadiazole-2-amine

To a solution of the substituted benzohydrazide (0.01 Mol) in ethanol (30 ml), and cyanogenbromide (1.05g) were added, and the reaction mixture was refluxed and continuously stirring (around 6 h). The residue was dissolved in water and then made basic with sodium bicarbonate solution. The precipitate was filtered off, dried, and crystallized from ethanol, room temp for overnight. The mixture was poured into cold water, filtered, dried and crystallized from ethanol. The completion of reaction was monitored by Thin Layer Chromatography and Infrared Spectrophotometer.

II. Microwave method:

Synthesis of substituted ethyl benzoate

Sub. ethyl benzoate was prepared by dissolving 0.01mole of benzoic acid derivatives in absolute ethanol (20 ml).carboxylic acid group is esterified with ethanol and the reaction is processed by

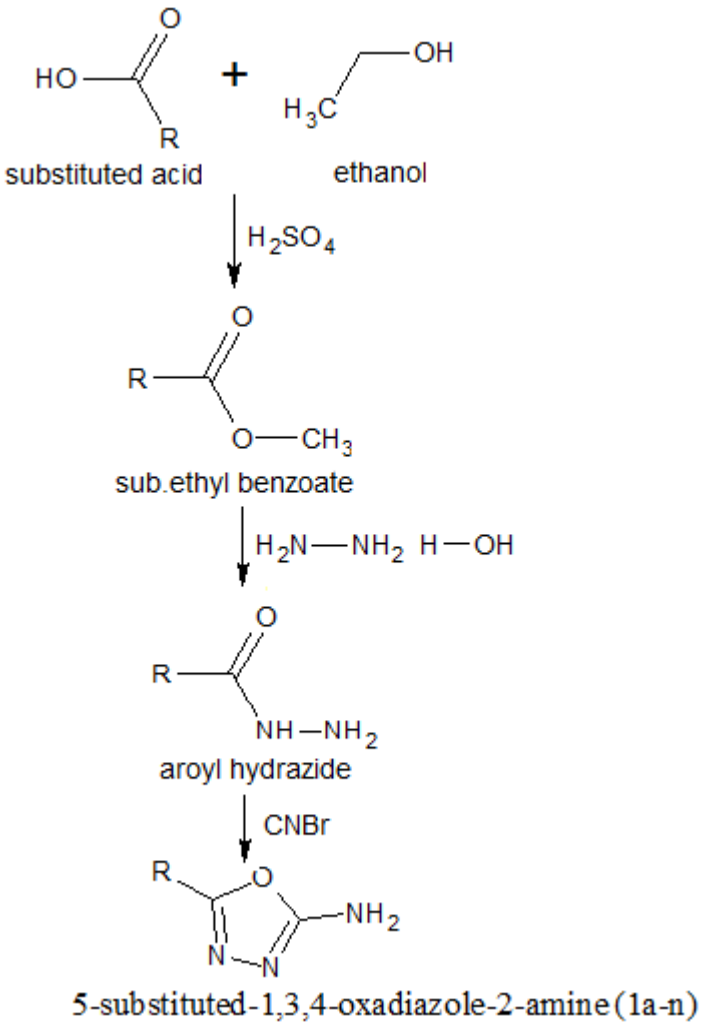
refluxing the mixture for4-6 min by adding few drops of H_2SO_4, which is act as a catalyst. The final product was obtained as precipitated form which was continued for the next step preparation.

Synthesis of 4-nitrobenzohydrazide

The mixture of compound 1 (0.01mol) and 0.02 Mol 99% hydrazine hydrate was refluxed for 6-10 minThe reaction mixture was cooled. The solid precipitate was obtained. Dried and recrystallized from ethanol. The completion of reaction was monitored by Thin Layer Chromatography and Infrared Spectrophotometer.

Synthesis of 5-substituted-1,3,4 oxadiazole-2-amine

To a solution of the substituted benzohydrazide (0.01 Mol) in ethanol (20 ml), and cyanogen bromide (1.01g) were added, and the reaction mixture was refluxed and continuously stirring (around 8-10 min). The residue was dissolved in water and then made basic with sodium bicarbonate solution. The precipitate was filtered off, dried, and crystallized from ethanol, room temp for overnight. The mixture was poured into cold water, filtered, dried and crystallized from ethanol. The completion of reaction was monitored by Thin Layer Chromatography and Infrared Spectrophotometer.



Scheme 1. *Synthetic route for the preparation of the title compound (1a-n)*

Table 1. Synthesized 5-substituted-1,3,4-oxadiazole-2-amine derivatives from benzoic acid and its derivatives

Sr. no	Compounds
1.	5-phenyl-1, 3, 4-oxadiazole-2 amine (1a)
2.	5-(2-hydroxy phenyl)-1, 3, 4-oxadiazole-2 amine (1b)
3.	5-(2-chlorophenyl)-1, 3, 4-oxadiazole-2amine (1c)
4.	5-(4-amino phenyl)-1, 3, 4-oxadiazole-2amine (1d)
5.	5-(4-chlorophenyl)-1, 3, 4-oxadiazole-2amine (1e)

Table 2. Spectral data of the synthesized compound

Compound code	Spectral data
1a	IR(KBr): 3170 (-NH) ,3018 (Ar-CH) ,1609(-C=N),1230(C-O-C str.) 1093(N-N str.)cm^{-1};^{1}HNMR ($CDCl_3$, 300 MHz, ppm): δ 7.42-7.55 (m, 2H, Ar-H), 3.51-3.58 (d, 2H); mass m/z (M^+) 160.
1b	IR(KBr): 3168 (-NH) ,3030 (Ar-CH) ,1650(-C=N),1410(OH),1239(C-O-C str.) 1090(N-N str.) cm^{-1}; ^{1}HNMR ($CDCl_3$, 300 MHz, ppm): δ 7.75-7.84(q, 2H, Ar-H), 3.28-3.32 (d, 2H); mass m/z (M^+) 175.
1c	IR(KBr): 3401 (-NH) ,3023(Ar-CH) ,1620(-C=N),1235(C-O-C str.) 1096(N-N str.),750(C-Cl) cm^{-1};^{1}HNMR ($CDCl_3$, 300 MHz, ppm): δ 7.24-7.31(q, 2H, Ar-H),3.64-3.69 (d, 2H); mass m/z (M^+)195
1d	IR(KBr): 3270 (-NH) ,3018 (Ar-CH) ,1616(-C=N),1230(C-O-C str.) ,1089(N-N str.) cm^{-1} ;^{1}HNMR ($CDCl_3$, 300 MHz, ppm): δ 7.41-7.49 (q, 2H, Ar-H), 3.12-3.18 (d, 2H); mass m/z (M^+)174.
1e	IR(KBr): 3350 (-NH) ,3018 (Ar-CH) ,1590(-C=N),1221(C-O-C str.), 1090(N-N str.),804.17(C-Cl) cm^{-1}; ^{1}HNMR ($CDCl_3$, 300 MHz, ppm): δ 7.84-7.92 (q, 2H, Ar-H), 3.44-3.49 (d, 2H); mass m/z (M^+)194.

Pharmacology:

In-vitro antimalarial activity All the target compounds (1a–e) were screened for their in vitro antimalarial activity against the P. falciparum strain using chloroquine and quinine as the reference compounds. The results of the antimalarial screening are expressed as the drug concentration resulting in 50% inhibition (IC_{50}) of parasite growth and are listed in Table 3.

Biological Evaluation

In-vitro Antimalarial assay

All the synthesized compounds were screened for their antimalarial activity against the P. falciparum strain. The P. falciparum strain was cultivated by a modified method described by Trager and Jensen. The compounds were dissolved in DMSO. The final concentration of DMSO used was not toxic and did not interfere with the assay. The antiparasitic effect of the compounds was measured by growth inhibition percentage as described by Carvalho and Krettli. For experimental purposes, the cultures were synchronized with 5% D-sorbitol when the parasites were at the ring stage.54 The parasitic suspension, consisting of predominately the ring stage parasites, was adjusted to a 1–2% parasitaemia and 2.5% haematocrit in hypoxanthine-free RPMI-1640 culture medium with 10% human plasma and was exposed to 7 concentrations of each compound for a single cycle of parasite growth for 48 h at 37 1C. Positive controls containing the standard antimalarial drugs chloroquine and quinine, in standard concentrations, wereused in each experiment. The stock solutions were additionally diluted in whole medium (RPMI 1640 plus 10% human serum)to each of the used concentrations. The concentration that inhibited 50% of the parasite growth (IC_{50} value) was determined by interpolation using Microcal Origin software. The blood smears used were read blind and each duplicate experiment was repeated three times[55-61].

3. RESULT AND DISCUSSION

Chemistry

4-nitrobenzohydrazide was prepared by mixture of benzoic acid (0.01mol) and 0.02 mol 99% hydrazine hydrate was refluxed for 5-6 hours. The reaction mixture was cooled. The solid precipitate was obtained. Dried and recrystallized from ethanol. The completion of reaction was monitored by Thin Layer Chromatography and Infrared Spectrophotometer. In next step, 5-

substituted-1,3,4 oxadiazole-2-amine was prepared by using substituted benzohydrazide (0.01 Mol) in ethanol, and cyanogenbromide were added, and the reaction mixture was refluxed and continuously stirring. The residue was dissolved in water and then made basic with sodium bicarbonate solution. The precipitate was filtered off, dried, and crystallized from ethanol, room temp for overnight. The mixture was poured into cold water, filtered, dried and crystallized from ethanol. For microwave method half quantity of each chemical were taken and irradiate mixture in microwave. The IR, NMR and mass spectra are fully consistent with the structure.

Table 3. Physicochemical data of synthesized compound

Compound Code	Molecular formula	M.W	% Yield		M.P (^{0}C)	R_f value	M. Phase
			Conventional method	Microwave method			
1a	$C_8H_7N_3O$	161.16	65.27	71.22	220-222	0.79	B:Cl:W 7:2:1
1b	$C_8H_7N_3O_2$	177.16	64.37	69.52	178-180	0.63	B:Cl:W 7:2:1
1c	$C_8H_6ClN_3O$	195.60	64.35	69.79	186-188	0.70	B:Cl:W 7:2:1
1d	$C_8H_8N_4O$	176.17	61.27	68.89	196-198	0.71	B:Cl:W 7:2:1
1e	$C_8H_6ClN_3O$	195.60	63.63	65.65	212-214	0.69	B:Cl:W 7:2:1

Antimalarial activity

All the synthesized compounds (1a–e) were evaluated for their antimalarial activity against a chloroquine and quinine sensitive strain of P. falciparum. All experiments were performed in duplicate and mean values of IC_{50} are reported in Table 2. As shown in Table 2, compounds 1e and 1c were found to have IC_{50} values in the range of 0.091 to 0.905 mM against the P. falciparum strain. These compounds displayed excellent activity against the P. falciparum strain

compared to quinine (IC_{50}= 0.832mM) and (i.e. IC_{50}= 0.065mM) compared to chloroquine. All the remaining compounds were found to be less active against chloroquine sensitive strains of P. falciparum.

Table 4. In-vitro antimalarial activity of the compounds (1a-e)

Entry	IC_{50} (μM)
1a	3.015
1b	1.312
1c	0.905
1d	2.011
1e	0.091
Chloroquine	0.065
Quinine	0.832

3. CONCLUSION

Some magnificent results have been obtained with the oxadiazole hybridized scaffold. Furthermore, this work helps to validate the choice of the 1,3,4-oxadiazole scaffold as a useful template for designing new antimalarial compounds. This synthetic approach allows the inclusion of potent bioactive nuclei in asingle scaffold in an easy way. The majority of the compounds showed excellent activity against P. falciparum strainscompared to quinine. Compound 1e emerged as the most promising antimalarial member of the series, and lower toxicity. Consequently,such a type of compound would represent a fertile matrix for the further development of more biologically potent agents anddeserves further investigation and derivatization in order to discoverthe scope and limitations of its biological activities.

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