International Journal of Science Academic Research
Vol. 04, Issue 11, pp.6531-6533, November, 2023
Available online at http://www.scienceijsar.com

ISSN: 2582-6425

Research Article

AN ECO-FRIENDLY SYNTHESIS OF SOME ANTIMICROBIAL QUINOLINES

***Akkal Dev Mishra**

Central Department of Chemistry, Tribhuvan University, Kathmandu, Nepal

Received 12th September 2023; **Accepted** 15th October 2023; **Published online** 28th November 2023

Abstract

A series of substituted quinolines have been synthesized by the reaction of differentthiadiazolyl/oxadiazolylthiols with halogen substituted quinolines on the solid support of basic alumina using microwaves. The reaction time has been brought down from hours to seconds with improved yield as compared to conventional heating. All the compounds showed promising antibacterial and antifungal activities.

Keywords: Solid support, Thiadiazole, Oxadiazole, Quinoline, Microwaves, Antimicrobial activities.

INTRODUCTION

Quinolines and their derivatives have got importance for their antimicrobial activities.[1] organic compounds with quinoline functionality are reported to show good amoebicidal, bactericidal, fungicidal and antimalarial activities[2]. Among some highly active antimalarial drugs plasmaquin, chloroquin and primaquin have covered broad arena of chemotherapeutics[3]. Various derivatives with 1, 3, 4- thiadiazole and oxadiazole functionalities are pharmacologically important heterocycles[4]. There are some other heterocycles of medicinal importance like quinazolinones, naphthoquinones, pyrazoles, furanose, thioles, etc.[5,6] The derivatives of 1, 4- naphthoquinone have been reported to be associated with diverse biological activities.[7] Similarly, 3-substituted -4- (2H) – quinazolinones are good antibacterial and antifungal drugs. A series of 3, 4- substituted pyrazolinones have been synthesized as excellent antifungal agents.[8] Reactions on solid support without using solvent in microwave oven are currently in use for synthetic chemists to develop an eco-friendly technique.[9] The coupling of microwave irradiation with the use of inexpensive inorganic solid supported reagents is considered as a facile and efficient green methodology in organic synthesis.[10] These solvent free microwave assisted reactions have attracted attention due to their enhanced selectivity, milder reaction condition and associated ease of manipulation among the chemists devoted in synthesis.[11] In addition, they enable organic reactions to occur rapidly at atmospheric pressure thereby circumvent the problems attributed to low boiling solvents in solution phase reactions.[12] Keeping in view the utility of microwave irradiation and pharmacological importance of the quinoline derivatives mentioned above, it is thought desirable to synthesize them under microwave irradiations in dry media followed by screening for their antifungal and antibacterial activities.

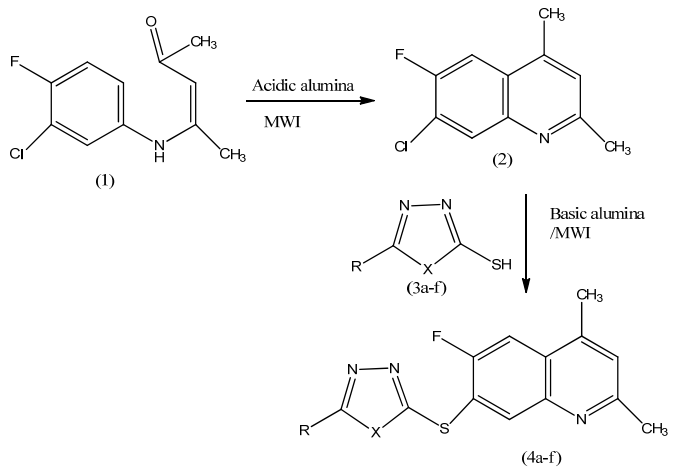
Experimental Methods and Materials

Microwave irradiations were carried out in Kenstar Microwave Oven model no. OM9925E at the frequency 2450 MHz and 800W.

Corresponding Author:** ***Akkal Dev Mishra
Central Department of Chemistry, Tribhuvan University, Kathmandu, Nepal.

IR spectra were recorded on Nicolet 5PC FT-IR spectrometer in KBr pellets and the frequency was measured in cm^{-1}. ^1H NMR spectra were recorded on Brucker DRX-300 FT-NMR spectrometer using tetramethylsilane (TMS) as internal reference at 60 MHz with deutereated chloroform ($CDC1_3$) as solvent and chemical shifts (**δ**) were measured in ppm. Elemental analysis was performed by means of Heraeus CHN-Rapid Analyzer and temperature was measured on Az Mini Gun Non-Contact IR thermometer model no. 8868. Melting points were determined on Thomas Hoover melting point apparatus. The purity of compounds was checked on silica gel G plates using iodine vapour as visualizing agent. Oxytetracycline and Salicylic acid were used as standard drugs for the determination of antibacterial and antifungal activities respectively. All the chemicals were purchased from SD Fine Chemicals Co.Ltd.

Scheme 1



R		X
a.	H	O
b.	H	S
c.	CH_3	O
d.	CH_3	S
e.	CH_3CH_2	O
f.	CH_3CH_2	S

General procedure for the synthesis of 7-chloro-6-fluoro -2,4-dimethylquinoline (2):

Conventional Method

The precursor 4- (3-chloro-4-fluoroaniline) - pent-3-ene-2- one (1), in the amount of 0.01 mole was dissolved in 25 ml of dichloromethane (DCM) and the resulted solution was refluxed for 3 hours. The reaction proceeds through cyclisation accompanied with dehydration. After the completion of reaction the mixture was cooled and the product (2) was obtained in solid state by distillation under reduced pressure. Thus obtained quinoline (2) was purified by recrystallization from ethanol.

Microwave Method

The solution of compound (1) with 0.01 mole in 10 ml of dichloromethane was adsorbed in 20 gm of acidic alumina at room temperature and dried in air in a small beaker. The beaker was then placed in an alumina bathinside the microwave oven followed by irradiation at an interval of 30 seconds for 4 minutes for the completion of reaction[13]. Upon the completion of reaction as indicated by thin layer chromatography (TLC), the mixture was cooled and the product was extracted in DCM (3×15 ml). The solvent was recovered by distillation under reduced pressure to get quinoline (2) as residue which was purified by recrystallization from ethanol.

General procedure for the synthesis of 7-(5-alkly-1',3',4'- thiadiazolyl/ oxadiazoly-2'- thio)-6-fluoro-2,4- dimethylquinolines (4a-f):

Conventional Method

The mixture of quinoline (2) and 5-substituted- 1,3,4-thiadiazole/oxadiazole-2-thiols (3a-f) in the amont of 0.01 mole was dissolved in 25 ml of DCM followed by defluxion for 4-6 hours to complete the reaction. Thus obtained content was then cooled and the solvent was recovered by distillation under reduced pressure. The residue of quinolines (4a-f) was purified by recrystallization from ethanol to afford 70-78% yield.

Microwave Method

An equimolar mixture (0.01 mole each)of quinoline (2) and thiadiazole/oxadiazole - thiols (3a-f) was dissolved in 10 ml of DCM and the resulted solution was adsorbed in 20 gm of basic alumina at room temperature followed by air drying in a small beaker. The beaker was then placed in an alumina bath inside the microwave oven and irradiated with microwaves at an interval of 30 seconds for 5-7 minutes in order to complete the reaction. The completion of the reaction was monitored by TLC. The product (4a-f) was cooled and extracted in DCM (3×15ml). Then the solvent was recovered by distillation under reduced pressure to obtain quinolines (4a-f) in solid state which was recrystallized from ethanol to afford 90-95% yield.

Antimicrobial Evaluation of Quinolines (4a-f)

***In vitro* Antibacterial Activities**

The quinoline derivatives 4a-f were evaluated for their *in vitro* antibacterial activities against pathogenic bacteria *Escherichia coli, Rhizobium Japonicum, Enterobactoraerogenes* and *Bacillus majavensis*by the cup-diffusion method. The nutrient agar medium (Hi media) was used for microbiological evaluation of the compounds. The suspension of each bacteria was thoroughly spreaded on the surface of the agar medium in Petridishes followed by making several cups (cavities) with the help of pre-sterilized stainless steel cylinder of 8 mm diameter. All the synthesized quinoline derivatives 4a-f, in the concentrationof 50 µg/mL were placed in these cavities separately with the help of micropipette and allowed to diffuse for 1 hour. Dimethyl formamide (DMF) was used as the solvent for all the compounds and as a control. These plates were incubated at 37^0C for 48 hours. The zone of inhibition was measured after incubation and percentage inhibition of the compounds was calculated which gives the bio-potentiality of the compounds under evaluation (Table 1).Oxyteracycline was used as standard drug for the study of antibacterial activities.

***In vitro* Antifungal Activities**

All the synthesized quinoline derivatives 4a-f were evaluated for their antifungal activities against *Aspergillusniger* and *Aspergillusflavus* by paper-disc diffusion method. Saburoud's dextrose agar (Hi-media) was used as culture medium in sterilized petridishes. The suspensions of these fungi are spreaded on the surface of the culture medium with the help of sterilized triangular loop. Then the quinoline derivatives were dissolved in DMF with concentration of 50 µg/mL and applied to different paper-discs which were placed on the solid surface of the agar medium. The Petridishes were then incubated for 72 hours at 28^0C. The zones of inhibition around the discs were measured and percentage inhibition of the compounds under experiment were calculated which shows the bio-potentiality of the compounds 4a-f against the tested fungal strains (Table 1). Salicylic acid was used as standard drug for study of antifungal activities.

RESULTS AND DISCUSSION

A series of 7-(5-alkyl-1', 3', 4'- thiadiazolyl/oxadiazolyl-2'-thio) -6-fluoro-2,4- dimethylquinolines 4a-f have been synthesized from 7-chloro-6-fluoro-2,4- dimethylquinoline -2 and 5- substituted-1,3,4- thiadiazole/oxadiazole-2-thioles 3a-f by conventional heating method and the microwave irradiation methods. Thiole group interacts with chlorine atom of the aromatic ring forming a thio- ether linkage between the two reacting molecules. Conventional heating method took 4-6 hours for completion of the reactions yielding 70-78% quinolines. Whereas basic alumina supported microwave irradiation took 5-7 minutes for completion affording 90-95% quinolines with higher degree of purity. Further, microwave irradiation method has shown advantage over conventional heating method in terms of easy work-up, limited use of solvents and elimination of toxic chemicals which are essential principles of green synthesis. Shorter reaction time and high yield makes microwave technology an eco-friendly synthetic tool.

Quinolines obtained by the synthesis are confirmed by different physical characterization and spectral data. In IR spectra C=N absorption appears at 1620-1662 cm^{-1} and C-F linkage appears at 902-918 cm^{-1} in the quinolines 4a-f. Similarly, both inter and intramolecular thioether bond shows absorption band at 607-625 cm^{-1}.IR band at 1202-1221 cm^{-1} indicates the cyclic ether linkage in the compounds. Aromatic protons have appeared at **δ** 7.0-7.3 ppm in ^{1}H NMR spectral analysis.

Table 1. *In vitro* antibacterial and antifungal activities of the compounds 4a-f

Comp.no.	Antibacterial activities				Antifungal activities	
	E. coli	Rhizobium japonicum	Enterobacter aerogenes	Bacillus mojavensis	Aspergillusniger	Aspergillusflavus
4a	+	+	+	++	+	+
4b	+	++	+	++	++	+++
4c	++	++	++	+++	++	++
4d	+	++	++	++	+++	+++
4e	+	+++	+++	++++	+++	++
4f	++	++	+++	++	+++	+++
OTC*& SA**	++++	++++	+++++	++++	++++	+++++

* Oxytetracycline – Reference drug for antibacterial activities:
-: no measurable activity; +:2-4mm; ++: 5-8 mm; +++: 9-14mm; ++++: 15-18 mm; +++++: 19-22 mm.
** Salicylic acid – Reference drug for antifungal activities:
-: no measurable activity; +: 3-7mm; ++: 8-12 mm; +++: 13-18 mm; ++++: 19-21 mm; +++++: 23-28 mm.

The proton in thadiazole ring has shown the signal at 8.0-8.2 in compounds 4a and 4b. All the methyl protons directly linked to aromatic ring have appeared at **δ** 2.2-2.6 ppm in the quinoline derivatives. The protons of ethyl group in compounds 4e and 4f have shown the signal at 2.1-2.3 ppm for CH_2 protons and 1.1-1.2 ppm for CH_3 protons. The variations in IR and ^1H NMR data are justified with the structural differences of the compounds. Quinoline derivatives 4a-f were screened for their antimicrobial activities against different fungal and bacterial strains. They have shown moderate to excellent antimicrobial activities. Quinolines 4a, 4b and 4c have shown excellent antibacterial and antifungal activities and rest of the compounds have shown moderate antimicrobial activities (Table 1).

Conclusion

Some substituted quinoline derivatives with biologically active functionalities have been synthesized from aniline derivatives and thiadiazole derivatives under the solid supported microwave irradiations. Simple, inexpensive and commonly available compounds are converted into chemotherapeutically important heterocycles. Microwave irradiation method took 5-7 minutes for completion of reaction yielding 90-95% quinoline derivatives 4a-f whereas the same reactions took 4-6 hours for completion affording only 70-78% products in conventional heating methods. Microwave assisted synthesis has been proved as rapid, efficient and environmentally benign method for organic synthesis. Harmful and expensive solvents have been eliminated in this method. The use of inorganic solid support as catalyst and reaction media makes this method much beneficial and popular among the chemists devoted to organic synthesis. All the synthesized quinoline derivatives have shown notable antifungal and antibacterial activities against tested fungal and bacterial strains.

Acknowledgement

The author thanks the Central Departments of Chemistry and Microbiology, Tribhuvan University, Kirtipur, Kathmandu for providing laboratory facilities to carryout synthesis and antimicrobial screening of the compounds. Thanks are due to Instrumentation Laboratory, Department Chemistry, University of Delhi, India for spectral analysis of the compounds.

REFERENCES

1. Mullican, M. D., Wilson, M. W., Conner, D. T., Kostlan, C. R., Schrier, D. J., & Dyer, R. D. (1993). Design of 5-(3, 5-di-tert-butyl-4-hydroxyphenyl)-1, 3, 4-thiadiazoles,-1, 3, 4-oxadiazoles, and-1, 2, 4-triazoles as orally active, non ulcerogenic anti inflammatory agents. *Journal of medicinal chemistry*, *36*(8), 1090-1099.
2. Kidwai, M., Bhushan, K. R., Sapra, P., Saxena, R. K., & Gupta, R. (2000). Alumina-supported synthesis of antibacterial quinolines using microwaves. *Bioorganic & medicinal chemistry*, *8*(1), 69-72.
3. Kidwai, M., &Negi, N. (1997). Synthese einiger neuer substituierter Chinolineals stark analgetischwirkende Substanzen. *Monatsheftefür Chemie/Chemical Monthly*, *128*, 85-89.
4. Mishra, A. D. (2011). An Expeditious Route for the Synthesis of Thiadiazolo-Pyrimidin-2-Thiones Using Microwaves. *Tribhuvan University Journal*, *27*(1-2).
5. Caddick, S. (1995). Microwave assisted organic reactions. *Tetrahedron*, *51*(38), 10403-10432.
6. Amir, M., Javed, S. A., & Kumar, H. (2007). Synthesis of some 1, 3, 4-oxadiazole derivatives as potential anti-inflammatory agents.
7. Kamal, A., Reddy, K. S., Prasad, B. R., Babu, A. H., &Ramana, A. V. (2004). Microwave enhanced reduction of nitro and azidoarenes to N-arylformamides employing Zn–HCOONH4: synthesis of 4 (3H)-quinazolinones and pyrrolo [2, 1-c][1, 4] benzodiazepines. *Tetrahedron letters*, *45*(34), 6517-6521.
8. Mishra, A. D. (2009). Microwave-assisted solvent free synthesis of spiro-indole derivative. *Journal of Nepal Chemical Society*, *24*, 49-52.
9. Sharma, L. K., Singh, S., & Singh, R. K. P. (2011). Green synthesis of 2-amino-5-substituted-1, 3, 4-oxadiazoles at the platinum anode in acetic acid.
10. Mishra, A. D. (2010). Solid-supported Synthesis of 3, 4-dihydrobenzo [2, 3-d] pyrimidines. *Nepal Journal of Science and Technology*, *11*, 153-158.
11. Kidwai, M., & Mishra, A. D. (2001). Solid supported synthesis of some lactams. *Pure and Applied Chemistry*, *71*, 147-154.
12. Bakhite, E. A., Al-Sehemi, A. G., & Yamada, Y. (2005). Synthesis of novel pyrido [3′, 2′: 4, 5] thieno [3, 2-d] pyrimidines, pyrido [3 ″, 2 ″: 4′, 5′] thieno [3′, 2′: 4, 5] pyrimido [l, 6-a] benzimidazoles and related fused systems. *Journal of heterocyclic chemistry*, *42*(6), 1069-1077.
13. Dabholkar, V. V., & Mishra, S. K. J. (2006). Efficient synthesis of some novel spiroheterocycles containing thiazole, oxazole, thiadiazole and triazolo-thiadiazole moiety under microwave irradiation. *Heterocyclic Communications*, *12*(3-4), 241-246.

****