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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Conventional and microwave techniques for synthesis and antimicrobial studies of novel 1-[2-(2-chloro(3-quinolyl))-5-(4-nitrophenyl)-(1,3,4-oxadiazolin-3-yl)]-3-(aryl)prop-2-en-1-ones

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Abstract In this article, we have described the conventional and microwave method for the synthesis of 1-[2-(2-chloro(3-quinolyl))-5-(4-nitrophenyl)(1,3,4-oxadiazolin-3-yl)]-3-(aryl)prop-2-en-1-ones (**4a–l**). Through this method, we have achieved reduction in reaction time and better yield than the previously described conventional method. The application of microwave irradiation (MWI) is used for carrying out chemical transformations which are pollution-free and eco-friendly. The structure of the compounds was characterized by spectral data. These compounds (**4a–l**) were evaluated for their in vitro antimicrobial screening on different strains of bacteria and fungi.

Keywords Quinoline-oxadiazole-based chalcones · 2-Chloroquinoline-3-carbaldehyde · Microwave method for quinoline–oxadiazole derivatives

Introduction

Quinoline containing drugs such as doxorubicin and mitoxantrone have been established as one of the most effective class of anticancer agents in clinical use today with broad applications in the treatment of several leukaemia and lymphomas as well as in combination chemotherapy of solid tumours (Wakelin and Waring, 1990). However, toxic dose-related side effects such as myelosuppression and cardiotoxicity, limited their clinical applications (Cheng and Zee-Cheng, 1983; Murray, 2000). The potent anticancer activity as well as toxic effects described for these compounds are normally ascribed, at least, to two main mechanisms: one, which is associated with protein, involves trapping of a protein enzyme–DNA cleavable intermediate, whereas the other, a non-protein-associated mechanism, is related to redox cycling of the quinone moiety, which produces damaging free-radical species (Murray, 2000).

In searching for agents with an improved pharmacokinetic properties, potency or spectrum and lower side effects, a large number of quinoline derivatives and related compounds have been prepared and several of these have shown promise in clinical trials (Lown, 1998). Regarding structural and chemical modifications of this system, one of the most interesting modification has been the introduction of heteroatoms (N, S) into different positions of the chromophore through incorporation of one or more of five or six-members heterocyclic ring to the basic quinoline system (Krapcho *et al.*, 1990, 1994, 1998). These bioisosteres would clearly differ from their carbocyclic counterparts in their interaction with DNA and enzymes, as well as in their reduction potential.

The chemistry of 1,3,4-oxadiazoles have received considerable attention from synthetic organic chemists due to their diverse biological activities (Omar *et al.*, 1996; Hui *et al.*, 2002; Mohan *et al.*, 2004). Several research groups have contributed for the development of methods for the synthesis of 1,3,4-oxadiazoles (Chiba and Mitsuhiro, 1992; Bacu *et al.*, 2003; Bhat *et al.*, 2004). However, these procedures are time consuming and proceed in low yields. Therefore, a more convenient and eco-friendly method for the synthesis of 1,3,4-oxadiazoles is highly desirable.

Chalcones are natural biocides (Geiger and Conn, 1945) and are well known intermediates for synthesizing various heterocycles. Chalcones and their derivatives are also medicinally important. Many chalcone derivatives have

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been reported to possess antimalarial and antimicrobial properties (Katritzky, 1984). Anticancer properties of some simple chalcone derivatives have also been reported in literature (Rezig *et al.*, 2000; Ducki *et al.*, 1996). However, the synthesis of quinolinyl chalcones is scarcely reported in literature. Sayed et al. (1976) and Ibrahim et al. (1996) have synthesized a few quinoline–chalcone derivatives by Claisen–Schmidt condensation reaction.

Dominquez et al. (2001) have reported the synthesis of some quinoline–chalcones and claimed their antimalarial activity. Moussaoui et al. (2002) have also described the synthesis of quinolinyl chalcones and claimed their cytotoxicity in K 562 human leukaemia cell lines.

The formation of heterocyclic rings by cyclocondensation reactions is typically a process well-suited for microwave technology. Many of these condensation reactions require high temperature and conventional reaction conditions very often involve heating the reactants in an oil, metal or sand bath for many hours or even days. An example is the formation of 4-hydroxy-1-*H*-quinoline-2-ones from anilines and malonic esters. The corresponding conventional, thermal protocol involves heating the two components in equimolar amounts in an oil bath at 220–300°C for several hours (without solvent), whereas similar high yields can be obtained by microwave heating at 250°C for 10 min (Kappe, 2004). This prompted us to adopt the MWI method for the synthesis of bio-active heterocyclic molecules.

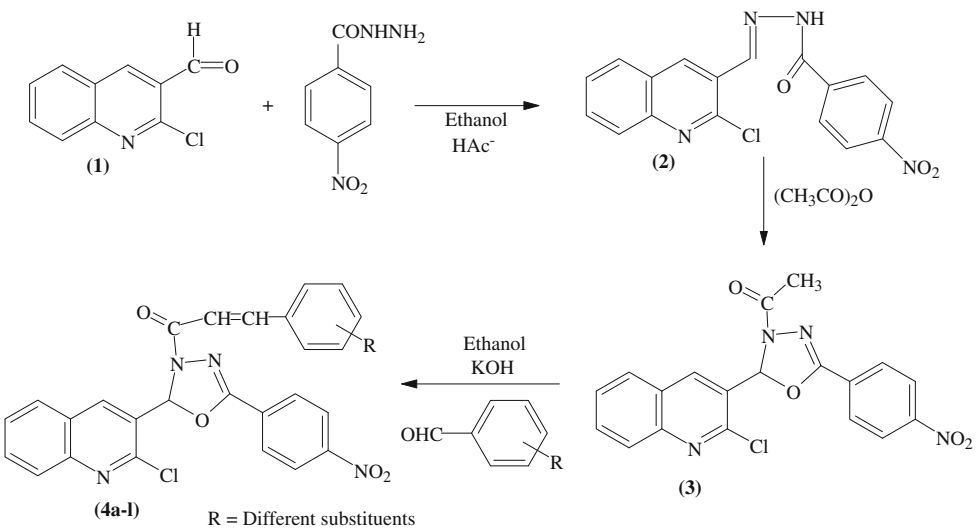
The present study aims at preparing quinoline–oxadiazole–chalcone derivatives. The solvent-free organic reactions assisted by microwave irradiation in organic synthesis can increase the purity of the resulting products, enhance the chemical yield and shorten the reaction time. Solvent-free reaction leads to a clean, eco-friendly and economic technology. Reactions on solid support without using solvent usually with close vessel in Synthos-3000, Anton Paar microwave reaction system is currently popular among the synthetic chemists to create eco-friendly atmosphere (Loupy, 2002; Rana *et al.*, 2009).

Looking at the medicinal importance of quinolines, 1,3,4-oxadiazoles and chalcones, we have designed and synthesized a series of 1-[2-(2-chloro(3-quinolyl))-5-(4-nitrophenyl)(1,3,4-oxadiazolin-3-yl)]-3-(aryl)prop-2-en-1-ones (**4a–l**) (Scheme 1) by conventional and microwave methods. The difference of reaction times and yields are shown in Table 2. The structures of the compounds synthesized were assigned on the basis of IR, ^{1}H NMR, ^{13}C NMR and mass spectral data.

Reaction mechanism of the synthesized compounds (4a–l)

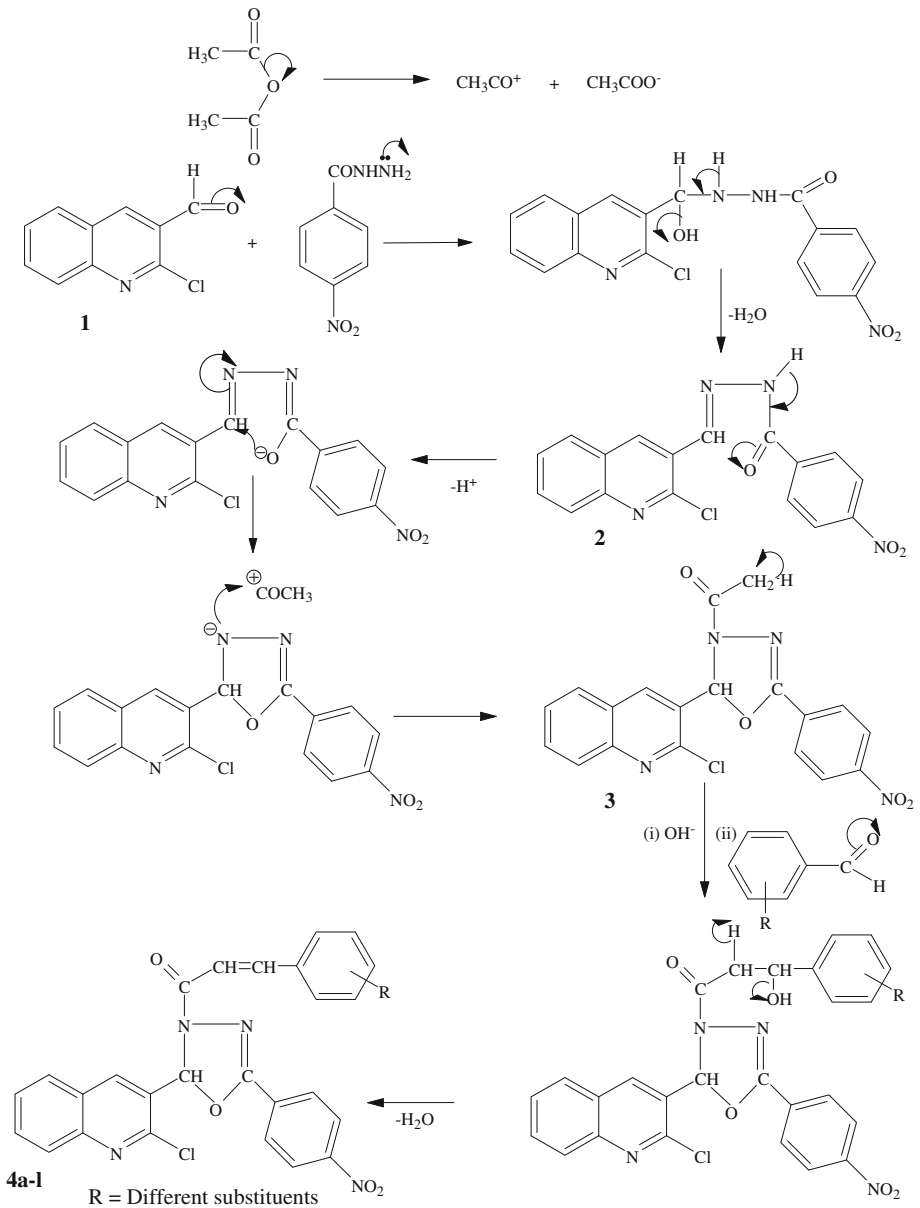
In the first step, acetic anhydride is cleaved to give acetyl carbocation and acetate carbanion, which will be used in the reaction with aroylhydrazone intermediate. The lone pair present over nitrogen atom will attack on the cationic carbon of 2-chloroquinoline-3-carbaldehyde moiety, which will undergo self condensation reaction to form aroylhydrazone derivative. Due to the keto-imine tautomerization, the keto

Scheme 1 Synthesis of 1-[2-(2-chloro(3-quinolyl))-5-(4-nitrophenyl)(1,3,4-oxadiazolin-3-yl)]-3-(aryl)prop-2-en-1-ones (**4a–l**)



Sr. No.	R	Sr. No.	R	Sr. No.	R
4a	-2-Cl	4e	-3-NO_2	4i	-4-OH
4b	-3-Cl	4f	-4-NO_2	4j	-4-CH_3
4c	-4-Cl	4g	-2-OH	4k	-4-OCH_3
4d	-2-NO_2	4h	-3-OH	4l	-3,4,5-$(OCH_3)_3$

Scheme 2 The mechanism of the synthesized compounds **4a–l**



group of aroylhydrazone derivative converts to hydroxyl group. The negatively charged oxygen atom which is formed due to deprotonation of the hydroxyl group will attack on C=N bond to form oxadiazole ring. The nitrogen anion will attack on acetyl carbocation to form acetyl derivative of oxadiazole moiety. Here acetyl group undergoes Claisen–Schmidt condensation reaction which is a well known reaction. The reaction mechanism is described in (Scheme 2) by taking the example of compound (**4a–l**).

Results and discussion

All the reactions (steps-2, 3 and 4) were completed in 6–8 h by conventional method, while under MWI, the same reactions were completed in 3–5 min, and also found in good yield as compared to the conventional method. A comparative study in terms of yield and reaction period is shown in Table 2.

IR-data

The IR spectrum of the title compound **4h** (molecular formula $C_{26}H_{17}ClN_4O_5$, m.w. 500.09) has given vibration at 3,048 cm^{-1} over the range which shows multiple weak absorption peak corresponding to Qu-H and Ar-H stretching vibration absorption peaks. The strong absorption at 1,675 cm^{-1} is due to the C=O stretching vibration and the moderate intensity absorption at 1,611 cm^{-1} corresponds to a C=N stretching vibration and C=C linkage appeared

stretching vibration at 1,595 cm^{-1}. The absorption at 1,354 cm^{-1} is due to the symmetric stretching of $–NO_2$ group while the absorption at 1,533 cm^{-1} is due to the asymmetric stretching of $–NO_2$ group. The high frequency region of the IR spectra of these compounds contain –OH stretching vibration band at 3,429 cm^{-1}. While in oxadiazole nucleus C–O–C linkage appeared in the range of 1,207 cm^{-1}. Methylene (CH=CH) linkage appeared stretching vibration in the range of 3,093 cm^{-1}, while methylene linkage appeared bending vibration in the range of 825 cm^{-1}. The absorption peak at 758 cm^{-1} arises due to the C–Cl group and absorption peak at 764 cm^{-1} indicates that mono substituted benzene ring is present.

H-NMR-data

It can be seen from the chemical structure of compound **4h** that different pairs of carbons, e.g. C-13 and C-17, C-14 and C-16 are attached to chemically equivalent protons, which appeared at $\delta = 8.09$ and 8.34 ppm, respectively. The proton attached to C-7 position appeared as a multiplet at 7.78 ppm due to mutual coupling with C-6 and C-8, while the proton attached to C-6 position also appeared as a multiplet at $\delta = 7.80$ ppm due to mutual coupling with C-5 and C-7. The protons of the C-5 and C-8 appeared as a doublet at 8.06 and 7.83 ppm, respectively. Chemical shift in the aromatic region with a multiplet centered at $\delta = 8.05$ ppm corresponds to C-3, while the C-10 (–CH group) present in the oxadiazole nucleus appeared at $\delta = 6.61$ ppm. The protons, which are present in alkene linkage, C-19 and C-20 gives doublet, C-19 appeared at $\delta = 6.84$ ppm, because of vicinity of carbonyl group at C-18, while the proton of C-20 appeared at $\delta = 7.55$ ppm, because it is directly attached to the phenyl ring. The proton of the –OH group, which is attached to carbon C-23 appeared as a singlet at $\delta = 9.83$ ppm, while four other protons of the phenyl ring attached to carbons C-22, C-24, C-25 and C-26 appeared as a multiplet at $\delta = 6.61$–7.04 ppm.

^{13}C-NMR-data

The final compound **4h** contains three moieties like quinoline, oxadiazole and chalcone. The chemical shifts of the carbons of the final compound **4h** carbons varies from $\delta = 167.0$ to 70.1 ppm. The carbon nuclei under the influence of a strong electronegative environment appeared downfield, e.g. the C-18 carbonyl, which is directly linked to the ring nitrogen has a chemical shift at $\delta = 167.0$ ppm, whereas the C-1 linked to one chlorine and other nitrogen atom, appeared at $\delta = 150.8$ ppm. The chemical shift of the ring carbon at C-9 is affected by the presence of directly attached ring nitrogen atom and appeared at $\delta = 143.5$ ppm. While alkene carbon at C-19 is directly attached to a carbonyl group and then appeared at $\delta = 118.8$ ppm. While alkene carbon at C-20 directly conjugated to the phenyl ring, indicates downfield chemical shift at $\delta = 144.0$ ppm. The carbons of the phenyl ring (C-21, C-22, C-24, C-25, C-26) conjugated to the alkene functionality have chemical shifts in the range $\delta = 115.1$ to 136.6 ppm. While C-23, which is attached to a hydroxyl group appeared at $\delta = 158.4$ ppm, under the strong electron withdrawing influence exerted by the hydroxyl group. While, the carbons which are present in oxadiazole nucleus C-10 and C-11 both are on one side directly attached to oxygen atom and on the other side C-10 is attached to nitrogen with a single bond. Therefore, it gives a chemical shift at $\delta = 70.1$ ppm, while on the other side C-11 is attached to nitrogen atom by a double bond, so, it gives a chemical shift at $\delta = 155.0$ ppm. The carbons of the quinoline ring (C-2, C-3, C-4, C-5, C-6, C-7, C-8) appeared upfield between $\delta = 125.8$ to 136.4 ppm compared to those quinoline ring carbons at C-1 and C-9. The carbon C-12 which is present in phenyl ring and which is attached to oxadiazole nucleus carbon C-11, appeared at 135.9 ppm. The equivalent carbons C-13 and C-17 appeared at $\delta = 130.1$ ppm, while other equivalent carbons C-14 and C-16 appeared at 124.0 ppm. While C-15 which is directly attached to nitro group appeared at 150.2 ppm, respectively. Carbon numbering is described in Fig. 1.

Antimicrobial activity

For the antibacterial activity, the newly synthesized compounds were screened for their antibacterial activity against Gram positive bacteria *Staphylococcus aureus* (MTCC-96) and *Streptococcus pyogenes* (MTCC-442) and Gram negative *Escherichia Coli* (MTCC-443) and *Pseudomonas aeruginosa* (MTCC-1688)]. Antibacterial activity was carried out by serial broth dilution method (Ghalem and Mohamed, 2009; Desai and Trivedi, 1993; Al-Bayati and Al-Mola, 2008). The standard strains used for the antimicrobial activity was procured from Institute of Microbial Technology, Chandigarh. The compounds (**4a–l**) were screened for their antibacterial activity in triplicate against *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas*

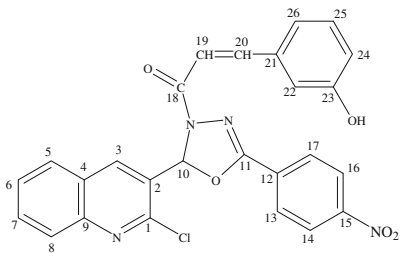


Fig. 1 Carbon numbering of the compound **4h**

Table 1 Antibacterial and antifungal data for the final synthesized compounds (**4a–l**)

S. no.	Compd.	–R	Minimum inhibitory concentration for bacteria μg/ml ± SD				Minimum inhibitory concentration for fungi μg/ml ± SD		
			Gram positive		Gram negative				
			E. coli MTCC-443	*P. aeruginosa* MTCC-1688	*S. aureus* MTCC-96	*S. pyogenes* MTCC-442	*C. albicans* MTCC-227	*A. niger* MTCC-282	*A. clavatus* MTCC-1323
1	**4a**	–2-Cl	500 ± 2.34*	500 ± 3.35*	500 ± 3.6*	500 ± 3.34*	250 ± 4.36*	500 ± 3.50*	500 ± 3.11*
2	**4b**	–3-CI	100 ± 3.65*	200 ± 3.55*	100 ± 4.04*	100 ± 3.43*	100 ± 3.55*	100 ± 2.44*	500 ± 3.20*
3	**4c**	–4-C1	200 ± 3.30*	100 ± 2.13*	1000 ± 3.34*	500 ± 4.13*	100 ± 4.34*	200 ± 3.02*	1000 ± 3.23*
4	**4d**	–2-NO_2	50 ± 3.23*	50 ± 4.57*	500 ± 3.23*	200 ± 2.53*	500 ± 2.48*	500 ± 3.5*	100 ± 3.36*
5	**4e**	–3-NO_2	1000 ± 3.56*	500 ± 2.18*	500 ± 3.04*	100 ± 4.55*	100 ± 4.24*	100 ± 3.4*	500 ± 3.41*
6	**4f**	–4-NO_2	100 ± 4.45*	500 ± 2.58*	100 ± 2.56*	500 ± 2.53*	500 ± 4.25*	1000 ± 3.5*	100 ± 3.31*
7	**4g**	–2-OH	500 ± 3.32*	250 ± 2.69*	500 ± 4.13*	250 ± 3.05*	1000 ± 3.2*	500 ± 2.02*	500 ± 3.25*
8	**4h**	–3-OH	25 ± 3.56*	50 ± 4.57*	200 ± 3.08*	100 ± 4.93*	500 ± 3.4*	200 ± 3.12*	100 ± 3.35*
9	**4i**	–4-OH	250 ± 3.12*	50 ± 2.66*	100 ± 3.45*	500 ± 4.73*	500 ± 3.53*	100 ± 3.55*	500 ± 3.3*
10	**4j**	–4-CH_3	200 ± 4.35*	100 ± 2.42*	200 ± 3.36*	250 ± 3.6*	250 ± 3.75*	100 ± 3.4*	1,000 ± 3.40*
11	**4k**	–4-OCH_3	100 ± 4.24*	500 ± 3.45*	100 ± 3.53*	100 ± 4.02*	500 ± 4.8*	1,000 ± 3.2*	100 ± 2.30*
12	**4l**	–3,4,5-$(OCH_3)_3$	200 ± 4.36*	200 ± 3.55*	500 ± 3.36*	500 ± 3.53*	100 ± 3.43*	100 ± 3.54*	100 ± 4.15*
	Ampicillin		100 ± 4.57*	100 ± 4.12*	250 ± 4.15*	100 ± 3.55*	–	–	–
	Griseofulvin		–	–	–	–	500 ± 2.64*	100 ± 3*	*100 ± 3.46**

±*SD* standard deviation

* $P \leq 0.0001$

aeruginosa and *Streptococcus pyogenes* at different concentrations of 1000, 500, 200, 100, 50, 25, 12.5 μg/ml as shown in Table 1. The drugs which were found to be active in primary screening were similarly diluted to obtain 100, 50, 25, 12.5 μg/ml concentrations. 10 μg/ml suspensions were further inoculated on appropriate media and growth was noted after 24 and 48 h. The lowest concentration, which showed no growth after spot subculture was considered as MIC for each drug. The highest dilution showing at least 99% inhibition is taken as (MIC). The test mixture should contain 10^8 cells/ml. The standard drug used in the present study was 'ampicillin' for evaluating antibacterial activity which showed (100, 100, 250 and 100 μg/ml) MIC against *E. coli*, *P. aeruginosa*, *S. aureus* and *S. pyogenes*, respectively.

While for the antifungal activity, same compounds were tested for antifungal activity in triplicate against *Candida albicans*, *Aspergillus niger* and *Aspergillus clavatus* at various concentrations of 1000, 500, 200 and 100 μg/ml as shown in Table 1. The results were recorded in the form of primary and secondary screening. The synthesized compounds were diluted at 1,000 μg/ml concentration, as a stock solution. The synthesized compounds which were found to be active in this primary screening were further tested in a second set of dilution against all microorganisms. The lowest concentration, which showed no growth after spot subculture was considered as (MIC) for each drug. The highest dilution showing at least 99% inhibition is taken as MIC. The test mixture should contain 10^8 spores/ml MIC. 'Griseofulvin' was used as a standard drug for antifungal activity, which showed (500, 100 and 100 μg/ml) MIC against *C. albicans*, *A. niger* and *A. clavatus*, respectively. The results of antimicrobial evaluation of derivatives (**4a–l**) are collected in (Table 1).

Antibacterial activity

From screening results, it has been observed that final compounds **4b**, **4f** and **4k** possess good activity against *E. coli* while compound **4d** possess very good activity against *E. coli* and compound **4h** possess excellent activity against *E.coli*. Final compounds **4c** and **4j** possess good activity against *P. aeruginosa* and compounds **4d**, **4h** and **4i** possess very good activity against *P. aeruginosa*. Final compounds **4b**, **4f**, **4i** and **4k** possess very good activity against *S. aureus*, while compounds **4c** and **4j** possess excellent activity against *S. aureus*. Final compounds **4b**, **4e**, **4h** and **4k** were considered as good active against *S. pyogenes* and compound **4f** possess very good activity. The remaining compounds of the series possess moderate to poor antibacterial activity. The discussion and comparison of antibacterial activity was given with respect to ampicillin antibiotic.

Antifungal activity

Antifungal screening data showed that final compounds **4d**, **4f**, **4h**, **4i** and **4k** possess good activity against *C. albicans*,

while compound **4j** possess very good activity against *C. albicans* and compounds **4b**, **4c**, **4e** and **4l** possess excellent activity. Compounds **4b**, **4e**, **4i**, **4j** and **4l** possess good activity against *A. niger*. Compounds **4d**, **4f**, **4h**, **4k** and **4l** possess good activity against *A. clavatus*. The remaining compounds of the entire series possess only moderate to poor antifungal activity. The discussion and comparison of antifungal activity was compared with griseofulvin.

Statistical analysis

The standard deviation value is expressed in terms of ±SD. On the basis of the calculated value by using ANOVA method, it has been observed that the differences below 0.0001 level ($P \leq 0.0001$) were considered as statistically significant.

Experimental

Materials and methods

All the required chemicals were purchased from E. Merck. 2-Chloroquinoline-3-carbaldehyde was synthesized by Narine et al. (Meth-Cohn and Narine, 1978) and modified (Kappe *et al.*, 1994; Bawa and Kumar, 2009). IR spectra were recorded on Perkin Elmer FT-IR spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Bruker DPX-40C instrument at 400 MHz. Chemical shifts are reported in ppm referenced to the residual solvent signal. Mass spectra were recorded on JEOL SX-102. Elemental analysis was performed by Perkin-Elmer 2400-CHN analyzer. Melting points were recorded on Gallenkemp apparatus and were uncorrected. Aluminium coated TLC plates 60 F_{245} (E. Merck) were used for monitoring of reaction and purity of compounds. In the conventional method, compounds were synthesized by using Random synthesizer. Bookie Rotavapour was used for distillation, while microwave irradiation was carried out in Synthos-3000 Anton Paar, microwave Reaction System.

Chemical synthesis

The conventional method involves the reaction of 2-chloroquinoline-3-carbaldehyde (**1**) and 4-nitro-hydrazide in the presence of catalytic amount of glacial acetic acid in ethanol to form aroylhydrazone (**2**), the same reaction when performed under the microwave irradiation, same starting material in 1,4-dioxane (5 drops) was subjected to microwave irradiation at 200 W intermittently at 30 s intervals for the specified time to obtained aroylhydrazone (**2**) as a product. In the third step, aroylhydrazone (**2**) was cyclized by refluxing with excessive amount of acetic anhydride for 6 h which resulted in product (**3**), while in microwave irradiation Silica gel (1 g) was added to the mixture of aroylhydrazone (**2**) and acetic anhydride (2 ml) and was irradiated in microwave oven at 400 W intermittently at 30 s interval three to four times to yield (**3**). In the final step, intermediate (**3**) was reacted with substituted aldehydes in the presence of ethanolic-KOH solution for 6 h to furnish the final product 1-[2-(2-chloro(3-quinolyl))-5-(4-nitrophenyl)(1,3,4-oxadiazolin-3-yl)]-3-(aryl)prop-2-en-1-ones (**4a–l**), while the same product is obtained in microwave irradiation at 100 W intermittently at 30 s intervals for the specified time. Thus, the final product (**4a–l**) is obtained.

General procedure for the synthesis of N-[(1E)-1-aza-2-(2-chloro(3-quinolyl))vinyl]-(4-nitrophenyl)carboxamide (**2**)

(A) Conventional method

A mixture of 2-chloroquinoline-3-carbaldehyde (**1**) and 4-nitrophenyl hydrazide was mixed and dissolved in ethanol and a catalytic amount of glacial acetic acid was added and the mixture was refluxed for 5–6 h by using reflux condenser. After cooling, the crystals formed were filtered off and recrystallized from absolute alcohol (99.5%) to give product (**2**).

M.P. 128–130°C; Yield 71%; IR (KBr): $\upsilon = 3034$ (aromatic-H), 1676 (C=O), 1608 (C=N), 1593, 1563, 1432 (C=C and quinoline ring), 1340 (–NO_2 symmetric stretching), 1522 (–NO_2 asymmetric stretching), 761, 774 (C–Cl bond, mono substituted benzene); ^{1}H-NMR: δ 7.51–8.90 (m, 9H, quinoline-H and Ar–H), 10.88 (s, 1H, O=C–N–H), 7.50 (s, 1H, N=C–H); ^{13}C-NMR: δ 124.0, 124.1, 126.4, 126.6, 127.0, 128.4, 132.5, 136.6, 137.2, 140.3, 142.9, 147.8, 151.3, 151.6, 162.9; MS: m/z 354.09 (M^{+}). Anal. calc. For $C_{17}H_{11}ClN_4O_3$: C-57.56; H-3.13; N-15.79. Found: C, 57.61; H. 3.18; N, 15.85%.

(B) Microwave method

A mixture of 2-chloroquinoline-3-carbaldehyde (0.01 mol), 4-nitrophenyl hydrazide (0.01 mol) and 1,4-dioxane (5 drops) was subjected to microwave irradiation at 200 W intermittently at 30 s interval for the specified time (Table 2). On completion of the reaction, it was monitored by TLC. The reaction mixture was cooled and treated with chilled water. The precipitate thus obtained was filtered, washed with water and recrystallized from ethanol to afford **2**.

The progress of the reaction and the purity of the compound were routinely checked on TLC aluminium sheet silica gel 60 F_{245} (E. Merck) using benzene-acetonitrile (4:1 v/v) as an irrigator and was developed in iodine chamber.

Table 2 The compounds (**4a–l**) synthesized by conventional and microwave method

S. no.	–R	Molecular formula	M.P.	Conventional method		Microwave method	
				Yield	Time (in h)	Yield	Time (in min.)
4a	–2Cl	$C_{26}H_{16}Cl_2N_4O_4$	221–223	76	6	77	1.7
4b	–3Cl	$C_{26}H_{16}Cl_2N_4O_4$	201–203	64	5	68	2.5
4c	–4Cl	$C_{26}H_{16}Cl_2N_4O_4$	195–197	73	7.5	78	1.5
4d	$-2NO_2$	$C_{26}H_{16}ClN_5O_6$	187–189	68	7	71	3.5
4e	$-3NO_2$	$C_{26}H_{16}ClN_5O_6$	203–205	62	6.5	65	4.2
4f	$-4NO_2$	$C_{26}H_{16}ClN_5O_6$	238–240	69	5.5	72	3
4g	–2OH	$C_{26}H_{17}ClN_4O_5$	232–234	67	6	70	2.5
4h	–3OH	$C_{26}H_{17}ClN_4O_5$	202–204	65	7	74	3.5
4i	–4OH	$C_{26}H_{17}ClN_4O_5$	197–199	58	6.8	63	2
4j	$-4CH_3$	$C_{27}H_{19}ClN_4O_4$	188–190	70	6.5	73	4
4k	$-4OCH_3$	$C_{27}H_{19}ClN_4O_5$	205–207	75	8	77	2.5
4l	$-3,4,5\text{-}(OCH_3)_3$	$C_{29}H_{23}ClN_4O_7$	218–220	64	7.5	69	3

General procedure for the synthesis 3-acetyl-2-(2-chloro(3-quinolyl))-5-(4-nitrophenyl)-1,3,4-oxadiazoline (**3**)

(A) Conventional method

Acetic anhydride (0.02 mol) was added to aroylhydrazone (**2**) (0.01 mol) and refluxed for 2 h. After cooling, the reaction mixture was poured into ice-cold water. The precipitate was filtered off, washed with water, dried and recrystallized from DMF–ethanol to give product (**3**).

M.P. 185–187°C; Yield 67%; IR (KBr): $\upsilon = 3034$ (aromatic-H), 2958 ($-CH_3$ stretching), 1675 (C=O), 1607 (C=N), 1590, 1563, 1431 (C=C and quinoline ring), 1341 ($-NO_2$ symmetric stretching), 1523 ($-NO_2$ asymmetric stretching), 1454 ($-CH_3$ bending), 1204 (C–O–C linkage), 762, 774 (C–Cl bond, mono substituted benzene); ^{1}H-NMR: δ 7.47–8.34 (m, 9H, quinoline-H and Ar-H), 2.02 (s, 3H, $-CO-CH_3$), 6.61 (s, 1H, N–CH-quinoline ring); ^{13}C-NMR: δ 24.7, 69.8, 124.0,125.8, 126.4, 126.5, 130.1, 130.7, 131.4, 135.6, 135.9, 136.4, 143.5, 150.2, 150.8, 155.0, 168.5; MS: m/z 396.06 (M^+). Anal. calc. For $C_{19}H_{13}ClN_4O_4$: C, 57.51; H, 3.30; N, 14.12. Found: C, 57.57; H, 3.36; N, 14.15%.

(B) Microwave method

Silica gel (1 g) was added to the mixture of aroylhydrazone (0.01 mol) and acetic anhydride (2 ml) at room temperature. The reaction mixture was thoroughly mixed and the absorbed material was dried in air and irradiated in microwave oven at 400 W intermittently at 30 s interval for the specified time (Table 2). The reaction mixture was cooled and the product was extracted from methanol. Dilution of methanol solution with ice-cold water gave the crude product, which was filtered, washed with water and recrystallized from methanol to give product (**3**).

The progress of the reaction and the purity of the compound were routinely checked on TLC aluminium sheet silica gel 60 F_{245} (E.Merck) using benzene–acetonitrile (4:1 v/v) as an irrigator and was developed in iodine chamber.

General synthesis of 1-[2-(2-chloro(3-quinolyl))-5-(4-nitrophenyl)(1,3,4-oxadiazolin-3-yl)]-3-(aryl)prop-2-en-1-ones (**4a–l**)

(A) Conventional method

A mixture of (**3**) (0.01 mol) and different substituted aldehydes (0.01 mol) was stirred in ethanolic potassium hydroxide for 2 h. The yellow crystals formed were filtered off, washed with water and crystallized from ethanol (99.5%).

(B) Microwave method

A mixture of compound (3) (0.01 mol), different substituted aldehydes (0.01 mol), potassium hydroxide and ethanol (95%) (1 ml) was subjected to microwave irradiation at 100 W intermittently at 30 s interval for the specified time (Table 2). On completion of the reaction as monitored by TLC, the reaction mixture was cooled. The precipitate thus obtained was filtered and recrystallized from ethanol (95%) to afford final compound (**4h**).

The progress of the reaction and the purity of the compound were routinely checked on TLC aluminium sheet silica gel 60 F_{245} (E. Merck) using benzene–acetonitrile (4:1 v/v) as an irrigator and was developed in iodine chamber.

Other compounds of the series were prepared by using the same conventional and microwave method.

Physical constants and characterization of 1-[2-(2-Chloro(3-quinolyl))-5-(4-nitrophenyl) (1,3,4-oxadiazolin-3-yl)]-3-(2-chlorophenyl) prop-2-en-1-one (**4a**)

IR (KBr): υ = 3038 (aromatic-H), 3058 (CH=CH group), 1672 (C=O), 1609 (C=N), 1595, 1561, 1433 (C=C, benzene and quinoline ring), 1342 (–NO_2 symmetric stretching), 1543 (–NO_2 asymmetric stretching), 1218 (C–O–C linkage), 760, 771 (C–Cl bond, mono substituted benzene) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 7.06–8.34 (m, 13H, quinoline-H and Ar-H), 6.67 (d, 1H, O=C–C–H), 7.82 (d, 1H, =C–H), 6.61 (s, 1H, N–CH-quinoline ring); ^{13}C-NMR: δ 24.7, 70.1, 118.8, 124.0, 125.8, 126.4, 126.5, 126.8, 127.8, 128.7, 129.4, 130.1, 130.7, 131.1, 131.4, 133.0, 135.6, 135.9, 136.4, 143.5, 150.0, 150.8, 155.0, 167.0; MS: m/z 519.34 (M^+). Anal. calc. For $C_{26}H_{16}Cl_2N_4O_4$, C, 60.13; H, 3.11; N, 10.79%. Found: C, 60.15; H, 3.17; N, 10.85%.

Physical constants and characterization of 1-[2-(2-Chloro(3-quinolyl))-5-(4-nitrophenyl) (1,3,4-oxadiazolin-3-yl)]-3-(3-chlorophenyl) prop-2-en-1-one (**4b**)

IR (KBr): υ = 3052 (aromatic-H), 3063 (CH=CH group), 1682 (C=O), 1614 (C=N), 1583, 1541, 1433 (C=C, benzene and quinoline ring), 1346 (–NO_2 symmetric stretching), 1522 (–NO_2 asymmetric stretching), 1209 (C–O–C linkage), 761, 775 (C–Cl bond, mono substituted benzene) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 7.15–8.34 (m, 13H, quinoline-H and Ar–H), 6.84 (d, 1H, O=C–C–H), 7.55 (d, 1H, =C–H), 6.61 (s, 1H, N–CH-quinoline ring); ^{13}C-NMR: δ 70.1, 118.8, 124.0, 125.8, 126.4, 126.5, 127.8, 128.7, 130.1, 130.7, 131.4, 133.3, 133.5, 135.6, 135.9, 136.4, 143.5, 144.0, 150.2, 150.8, 155.0, 167.0; MS: m/z 519.34 (M^+). Anal. calc. For $C_{26}H_{16}Cl_2N_4O_4$, C, 60.13; H, 3.11; N, 10.79%. Found: C, 60.17; H, 3.16; N, 10.86%.

Physical constants and characterization of 1-[2-(2-Chloro(3-quinolyl))-5-(4-nitrophenyl) (1,3,4-oxadiazolin-3-yl)]-3-(4-chlorophenyl) prop-2-en-1-one (**4c**)

IR (KBr): υ = 3039 (aromatic-H), 3064 (CH=CH group), 1684 (C=O), 1609 (C=N), 1607, 1571, 1443 (C=C, benzene and quinoline ring), 1343 (–NO_2 symmetric stretching), 1521 (–NO_2 asymmetric stretching), 1205 (C–O–C linkage), 757, 778 (C–Cl bond, mono substituted benzene) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 7.15–8.34 (m, 13H, quinoline-H and Ar-H), 6.84 (d, 1H, O=C–C–H), 7.55 (d, 1H, =C–H), 6.61 (s, 1H, N–CH-quinoline ring); ^{13}C-NMR: δ 70.1, 118.8, 124.0, 125.8, 126.4, 126.5, 127.8, 128.7, 130.7, 130.1, 131.4, 133.3, 133.5, 135.6, 135.9, 136.4, 143.5, 144.0, 150.2, 150.8, 155.0, 167.0; MS: m/z 533.37 (M^+). Anal. calc. For $C_{26}H_{16}Cl_2N_4O_4$, C, 60.13; H, 3.11; N, 10.79%. Found: C, 60.14; H, 3.17; N, 10.85%.

Physical constants and characterization of 1-[2-(2-Chloro(3-quinolyl))-5-(4-nitrophenyl) (1,3,4-oxadiazolin-3-yl)]-3-(2-nitrophenyl) prop-2-en-1-one (**4d**)

IR (KBr): υ = 3063 (aromatic-H), 3058 (CH=CH group), 1687 (C=O), 1590 (C=N), 1585, 1545, 1427 (C=C, benzene and quinoline ring), 1219 (C–O–C linkage), 1349 (–NO_2 symmetric stretching), 1516 (–NO_2 asymmetric stretching), 758, 775 (C–Cl bond, mono substituted benzene) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 7.56–8.34 (m, 13H, quinoline-H and Ar-H), 6.91 (d, 1H, O=C–C–H), 8.11 (d, 1H, =C–H), 6.61 (s, 1H, N–CH-quinoline ring); ^{13}C-NMR: δ 70.1, 118.8, 123.8, 124.0, 125.8, 126.4, 126.5, 127.2, 127.3, 128.9, 130.1, 130.7, 131.4, 134.8, 135.6, 135.9, 136.4, 143.5, 144.0, 145.0, 150.2, 150.8, 155.0, 167.0; MS: m/z 529.08 (M^+). Anal. calc. For $C_{26}H_{16}ClN_5O_6$: C, 58.93; H, 3.04; N, 13.22. Found: C, 58.97; H, 3.09; N, 13.28%.

*Physical constants and characterization of 1-[2-(2-Chloro(3-quinolyl))-5-(4-nitrophenyl)(1,3,4-oxadiazolin-3-yl)]-3-(3-nitrophenyl)prop-2-en-1-one (**4e**)*

IR (KBr): υ = 3057 (aromatic-H), 3081 (CH=CH group), 1678 (C=O), 1608 (C=N), 1589, 1558, 1430 (C=C, benzene and quinoline ring), 1219 (C–O–C linkage), 1353 (–NO_2 symmetric stretching), 1524 (–NO_2 asymmetric stretching), 763, 774 (C–Cl bond, mono substituted benzene) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 7.57–8.34 (m, 13H, quinoline-H and Ar-H), 7.09 (d, 1H, O=C–C–H), 7.66 (d, 1H, =C–H), 6.61 (s, 1H, N–CH-quinoline ring); ^{13}C-NMR: δ 24.7, 70.1, 118.8, 120.0, 123.1, 124.0, 125.8, 126.4, 126.5, 129.6, 130.1, 130.7, 131.4, 132.5, 135.6, 135.9, 136.1, 136.4, 143.5, 144.0, 147.8, 150.2, 150.8, 155.0, 167.0; MS: m/z 529.08 (M^+). Anal. calcd. For $C_{26}H_{16}ClN_5O_6$: C, 58.93; H, 3.04; N, 13.22. Found: C, 58.98; H, 3.07; N, 13.28%.

*Physical constants and characterization of 1-[2-(2-Chloro(3-quinolyl))-5-(4-nitrophenyl)(1,3,4-oxadiazolin-3-yl)]-3-(4-nitrophenyl)prop-2-en-1-one (**4f**)*

IR (KBr): υ = 3039 (aromatic-H), 3065 (CH=CH group), 1672 (C=O), 1616 (C=N), 1597, 1561, 1434 (C=C, benzene and quinoline ring), 1216 (C–O–C linkage), 1342 (–NO_2 symmetric stretching), 1523 (–NO_2 asymmetric stretching), 756, 768 (C–Cl bond, mono substituted

benzene) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 7.57–8.34 (m, 13H, quinoline-H and Ar-H), 7.13 (d, 1H, O=C–C–H), 7.69 (d, 1H, =C–H), 6.61 (s, 1H, N–CH-quinoline ring); ^{13}C-NMR: δ 70.1, 118.8, 123.8, 124.0, 125.8, 126.4, 126.5, 127.3, 130.1, 130.7, 131.4, 135.6, 135.9, 136.4, 141.3, 143.5, 144.0, 147.1, 150.2, 150.8, 155.0, 167.0; MS: m/z 529.08 (M^+). Anal. calc. For $C_{26}H_{16}ClN_5O_6$: C, 58.93; H, 3.04; N, 13.22. Found: C, 58.99; H, 3.08; N, 13.26%.

*Physical constants and characterization of 1-[2-(2-Chloro(3-quinolyl))-5-(4-nitrophenyl)(1,3,4-oxadiazolin-3-yl)]-3-(2-hydroxyphenyl)prop-2-en-1-one (**4g**)*

IR (KBr): $\upsilon = 3060$ (aromatic-H), 3420 (aromatic-OH group), 3087 (CH=CH group), 1681 (C=O), 1612 (C=N), 1608, 1565, 1405 (C=C, benzene and quinoline ring), 1212 (C–O–C linkage), 1353 (–NO_2 symmetric stretching), 1468 (C–H bending), 1523 (–NO_2 asymmetric stretching), 756, 768 (C–Cl bond, mono substituted benzene) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 6.68–8.34 (m, 13H, quinoline-H and Ar–H), 6.67 (d, 1H, O=C–C–H), 7.82 (d, 1H, =C–H), 6.61 (s, 1H, N–CH-quinoline ring), 9.82 (s, 1H, aromatic-OH group); ^{13}C-NMR: δ 70.1, 115.5, 116.5, 118.8, 121.3, 124.0, 125.8, 126.4, 126.5, 127.8, 129.4, 130.1, 130.7, 131.4, 135.6, 135.9, 136.4, 143.5, 144.0, 150.2, 150.8, 155.0, 158.3, 167.0; MS: m/z 500.09 (M^+). Anal. calc. For $C_{27}H_{19}ClN_4O_5$: C, 62.34; H, 3.42; N, 11.19. Found: C, 62.39; H, 3.47; N, 11.23%.

*Physical constants and characterization of 1-[2-(2-Chloro(3-quinolyl))-5-(4-nitrophenyl)(1,3,4-oxadiazolin-3-yl)]-3-(3-hydroxyphenyl)prop-2-en-1-one (**4h**)*

IR (KBr): $\upsilon = 3048$ (aromatic-H), 3429 (aromatic-OH group), 3093 (CH=CH group), 1675 (C=O), 1611 (C=N), 1593, 1561, 1425 (C=C, benzene and quinoline ring), 1354 (–NO_2 symmetric stretching), 1533 (–NO_2 asymmetric stretching), 1207 (C–O–C linkage), 758, 764 (C–Cl bond, mono substituted benzene) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 7.57–8.34 (m, 13H, quinoline-H and Ar-H), 6.84 (d, 1H, O=C–C–H), 7.55 (d, 1H, =C–H), 6.61 (s, 1H, N–CH-quinoline ring), 9.82 (s, 1H, aromatic-OH group); ^{13}C-NMR: δ 70.1, 112.1, 115.1, 188.8, 119.0, 124.0, 125.8, 126.4, 126.5, 130.1, 130.7, 131.4, 135.6, 135.9, 136.4, 136.6, 143.5, 144.0, 150.2, 150.8, 155.0, 158.4, 167.0; MS: m/z 500.09 (M^+). Anal. calc. For $C_{27}H_{19}ClN_4O_5$: C, 62.34; H, 3.42; N, 11.19. Found: C, 62.38; H, 3.46; N, 11.24%.

*Physical constants and characterization of 1-[2-(2-Chloro(3-quinolyl))-5-(4-nitrophenyl)(1,3,4-oxadiazolin-3-yl)]-3-(4-hydroxyphenyl)prop-2-en-1-one (**4i**)*

IR (KBr): $\upsilon = 3064$ (aromatic-H), 3429 (aromatic-OH group), 3075 (CH=CH group), 1673 (C=O), 1602 (C=N), 1608, 1564, 1423 (C=C, benzene and quinoline ring), 1341 (–NO_2 symmetric stretching), 1522 (–NO_2 asymmetric stretching), 1219 (C–O–C linkage), 761, 769 (C–Cl bond, mono substituted benzene) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 7.57–8.83 (m, 13H, quinoline-H and Ar-H), 6.67 (d, 1H, O=C–C-H), 7.82 (d, 1H, =C–H), 6.61 (s, 1H, N–CH-quinoline ring), 9.82 (s, 1H, aromatic-OH group); ^{13}C-NMR: δ 70.1, 115.8, 118.8, 124.0, 125.8, 126.4, 126.5, 127.8, 130.1, 130.7, 131.4, 135.6, 135.9, 136.4, 143.5, 144.0, 150.2, 150.8, 155.0, 157.7, 167.0; MS: m/z 500.09 (M^+). Anal. calc. For $C_{26}H_{17}ClN_4O_5$: C, 62.34; H, 3.42; N, 11.19. Found: C, 62.39; H, 3.47; N, 11.24%.

*Physical constants and characterization of 1-[2-(2-Chloro(3-quinolyl))-5-(4-nitrophenyl)(1,3,4-oxadiazolin-3-yl)]-3-(4-methylphenyl)prop-2-en-1-one (**4j**)*

IR (KBr): $\upsilon = 3032$ (aromatic-H), 3072 (CH=CH group), 2892 (C–H stretching), 1681 (C=O), 1605 (C=N), 1579, 1554, 1432 (C=C, benzene and quinoline ring), 1440 (C–H bending), 1345 (–NO_2 symmetric stretching), 1535 (–NO_2 asymmetric stretching), 1209 (C–O–C linkage), 761, 775 (C–Cl bond, mono substituted benzene) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.43 (s, 3H, –CH_3 group), 7.57–8.34 (m, 13H, quinoline-H and Ar-H), 6.84 (d, 1H, O=C–C–H), 7.55 (d, 1H, =C–H), 6.61 (s, 1H, N–CH-quinoline ring); ^{13}C-NMR: δ 24.7, 70.1, 118.8, 124.0, 125.8, 126.3, 126.4, 126.5, 128.9, 130.1, 130.7, 131.4, 132.2, 135.6, 135.9, 136.4, 137.6, 143.5, 144.0, 150.2, 150.8, 155.0, 167.0; MS: m/z 498.11 (M^+). Anal. calc. For $C_{27}H_{19}ClN_4O_5$: C, 62.58; H, 3.92; N, 10.88. Found: C, 62.63; H, 3.98; N, 10.94%.

*Physical constants and characterization of 1-[2-(2-Chloro(3-quinolyl))-5-(4-nitrophenyl)(1,3,4-oxadiazolin-3-yl)]-3-(4-methoxyphenyl)prop-2-en-1-one (**4k**)*

IR (KBr): $\upsilon = 3041$ (aromatic-H), 3068 (CH=CH group), 2833 (Ar-OCH_3), 1673 (C=O), 1609 (C=N), 1611, 1562, 1436 (C=C, benzene and quinoline ring), 1342 (–NO_2 symmetric stretching), 1520 (–NO_2 asymmetric stretching), 1277 (Ar–O–Me, bending), 1209 (C–O–C linkage), 758, 780 (C–Cl bond, mono substituted benzene) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 6.68–8.34 (m, 13H, quinoline-H and Ar-H), 3.85 (s, 3H, –OCH_3 group), 6.84 (d, 1H, O=C–C–H), 7.55 (d, 1H, =C–H), 6.61 (s, 1H, N–CH-quinoline ring); ^{13}C-NMR: δ 55.8, 70.1, 114.2, 118.8, 124.0, 125.8, 126.4, 126.5, 127.4, 127.5, 130.1, 130.7, 131.4, 135.6, 135.9, 136.4, 143.5, 144.0, 150.2, 150.8, 155.0, 159.8, 167.0; MS: m/z 514.10 (M^+). Anal. calc. For $C_{27}H_{19}ClN_4O_5$: C, 62.98; H, 3.92; N, 10.88. Found: C, 62.99; H, 3.98; N, 10.93%.

*Physical constants and characterization of 1-[2-(2-Chloro(3-quinolyl))-5-(4-nitrophenyl)(1,3,4-oxadiazolin-3-yl)]-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**4l**)*

IR (KBr): υ = 3070 (aromatic-H), 3064 (CH=CH group), 2841 (Ar-OCH_3 stretching), 1671 (C=O), 1610 (C=N), 1608, 1570, 1442 (C=C, benzene and quinoline ring), 1343 (–NO_2 symmetric stretching), 1522 (–NO_2 asymmetric stretching), 1284 (Ar-O–Me bending), 1359 (–NO_2 symmetric stretching), 1466 (C–H bending), 1525 (–NO_2 asymmetric stretching), 1209 (C–O–C linkage), 756, 774 (C–Cl bond, mono substituted benzene) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 6.78–8.34 (m, 10H, quinoline-H and Ar-H), 3.71-3.83 (s, 9H, –OCH_3 group) 6.84 (d, 1H, O=C–C–H), 7.55 (d, 1H, =C–H), 6.61 (s, 1H, N–CH-quinoline ring); ^{13}C-NMR: δ 70.1, 56.1, 103.8, 118.8, 124.0, 125.8, 1226.4, 126.5, 129.5, 130.1, 130.7, 131.4, 135.6, 135.9, 136.4, 143.5, 144.0, 150.2, 150.7, 150.8, 155.0, 167.0; MS: m/z 574.13 (M^+). Anal. calc. For $C_{29}H_{23}ClN_4O_7$: C, 60.58; H, 4.03; N, 9.74. Found: C, 60.64; H, 4.07; N, 9.80%.

Conclusion

We have synthesized a variety of quinoline–oxadiazole containing chalcone derivatives under classical and microwave conditions. In general, improvements in rate and yield of reactions were observed in MWI. When organic reactions were carried out under microwave as compared to classical conditions, it may be observed that activation occurs at different temperatures with these techniques and, therefore strict comparisons will require a balance between effectiveness and energy costs. In general, compounds with electron withdrawing groups showed good antibacterial and antifungal activities. These results proved that novel quinoline, oxadiazole and chalcone based heterocyclic compounds are found to be interesting lead molecules for further synthetic and biological evaluation.

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