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Synthesis and evaluation of antifungal activities of (3H)-quinazolin-4-one derivatives against tree plant fungi

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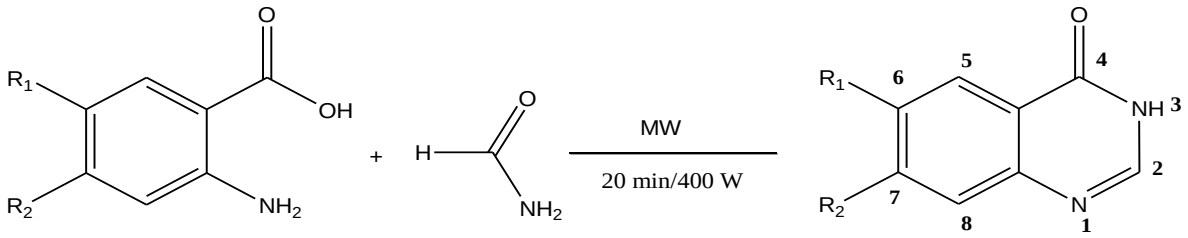
Abstract
A series of Quinazolin-4-(3H)-ones derivatives was prepared under microwave irrradiation, The structural characterization of synthesized products was elucidated by ^{1}H NMR, ^{13}C NMR, mass spectral data, and screened for their in vitro antifungal activity against tree plant fungi; Fusarium oxysporum f. sp.albidinis, Fusarium oxysporum f. sp. canariasis and Verticillium dahliae Kleb. The results revealed that the title compounds **3e, 3d** and **3c** displayed good antifungal activity.

Keyword: *Quinazolin-4-(3H)-ones, microwave irradiation, antifungal activity.*

1. Introduction
Agriculture worldwide has struggled with dramatic economic losses caused by Fungal phytopathogens which cause a severe contaminating food with toxic compounds, reducing yields or lowering product quality.[1-3]. Amongst them are *Fusarium oxysporum* f. sp. *albedinis* that causes the Bayoud disease of date palm in North Africa [4,5], *Fusarium oxysporum* f. sp. *canariensis* that attacks palm of Canary Island and date palm [6] and *Verticillium dahliae Kleb* that causes losses of olive tree in the Mediterranean area [7]. These phytopathogenic fungi that easily infect many crops and ornament plants are hard to control and their management strategies are focused especially on resistant rootstocks, preventive measures; or biological control practices like the use of compost soil amendments [8-11]. But the principal remaining tools are the use of chemicals; as a result, it is necessary to develop novel and effective fungicide or chemical pesticides for increasing levels of crop production and good growth.
Heterocyclic structures are the fundamental elements of many agrochemicals, pharmaceuticals, and veterinary products. One of the heterocyclic compounds that have been shown to exhibit a broad-range of biological activities is the Quinazoline derivatives [12-18]. Fluorinated quinazoline derivatives represent a class of compounds possessing a wide spectrum of biological activity. A number of researches mention their utility as important fungicide [12, 14, 15] thus, their synthesis has been of great interest in the elaboration of biologically active heterocyclic compounds like fluquinconazole which is a fungicide for the control of the agriculture disease [19].
In this study we use a modified route for the rapid laboratory scale preparation of the desired quinazoline derivatives, and then measured their fungicidal activities against *Fusarium oxysporum* f. sp. *albedinis* (*Foa*), *Fusarium oxysporum* f. sp. *canariensis* (*Foc*) and *Verticillium dahliae Kleb* (*Vd*).

2. Experimantal
2.1. Chemistry general
In recent years, various synthetic method have been developed for the construction of (3H)-quinazolin-4-one ring [20-22] among them, the microwave irradiation reaction attracted wide concern with its fast response, less side effects, high yield and easy purification products. [23, 24] (Scheme1).

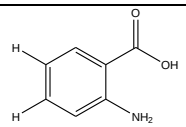
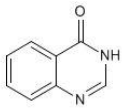
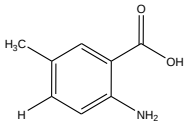
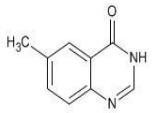
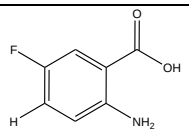
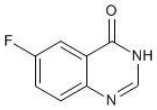
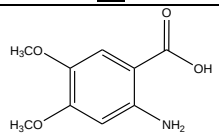
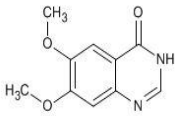
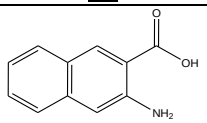
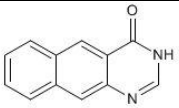
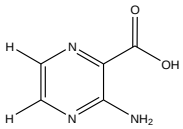
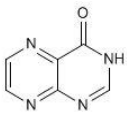


1a-f **2** **3a-f**

R_1 = CH_3, H, F, O-CH_3, (R_1-R_2) phenyl, Pyrazine.
R_2 = H, O-CH_3.

Scheme1. Synthetic route of (3H)-quinazolin-4-one ring derivatives **3a-f**

Table 1: Synthesis of (3H)-quinazolin-4-one ring derivatives (**3a-f**)

Anthranilic acids	Products	Yield % Conventionnal method	Yield % Microwave method
 1a	 3a	43	51
 1b	 3b	56	76
 1c	 3c	46	55
 1d	 3d	41	47
 1e	 3e	27	30
 1f	 3f	31	40

For the synthesis of the compounds **3a-f** two experimental methods were applied conventional method (method A) and the microwave-assisted organic reactions (method B). Physical data of the reactions is shown at Table 1. In our study, the reaction period was 6 h for the conventional method, while it was 20 min for the microwave irradiation method. It was clear that reaction period to obtain the desired compounds was dramatically shortened by microwave irradiation. The yields of the reactions obtained by the conventional method were between 27–56%, while they were between 30–76% for the microwave irradiation method; we can deduce that microwave irradiation can be considered as a good reaction with fast response, less side effects, high yield and easy purification products.

2.1.1. Preparation of quinazolin-4(3H)-one derivatives.
In a 25 ml Erlenmeyer flask: A 1 mmol of benzoic acid derivatives **(1a-f)** dissolved in 1 mmol of formamide. The reaction mixture was irradiated in a microwave oven using 400 W as power level for 20 min.(Scheme 1) The crude products were then purified on a silica gel column I.D.× L (10 mm × 46 cm) with fritted disc; using ethyl acetate as eluant to recover the pure product with a good yield (Table 1).

2.1.2. *General chemistry*
Melting points (mp) were determined using Guna melting point apparatus in open capillaries and are uncorrected; ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 on a Bruker 300 MHz instrument using $SiMe_4$ as internal standard. Chemical shifts (δ) are given in ppm and coupling constants (J) in MHz (Molecules 2014, 19, 3644) (br, broad; m, multiplet; t, triplet; d, doublet; dd, doublet of doublets; and s, singlet). Mass spectra were obtained using ESI/MS. Reactions were carried out in a microwave oven Model AVM510/WP/WH. The reactions were controlled by thin layer chromatography (TLC) on silica gel 60 F254 (Merck, Darmstadt, Germany); UV light was used for visualization of the spots. All products were purified by column chromatography on silica gel (100–200 mesh) Merck.
All microwave-assisted syntheses were carried out in a dedicated CEM-Discover mono-mode microwave apparatus

2.1.3. Analysis of spectra
All the newly synthesized compounds were characterized by NMR and MS spectra. The spectral analyses were in accordance with the assigned structures, and the mass spectra of target compounds showed a major fragment of [M+ H] or [M] according to their molecular formula (Experimental section).

2.2. Antifungal activity assay

2.2.1. Experimental protocol
For all synthesized compounds, we prepared a solution under aseptic and sterilized condition; In 250 mL Erlenmeyer flask,(2.5, 5 and 7.5 μg/mL) each compound were dissolved in 0.1 % dimethyl sulfoxide, added to 100 mL of CZAPECK solid medium at 45 °C and then poured into Petri dishes. The same concentration of Pelt which is systemic fungicide contains 70 % methyl thiophanate: Trademark: PROCIDA GROUPS ROUSSEL UCLAF. Pelt was used as a standard antifungal compound. The control water is also carried out under the same conditions. Mycelial discs of 5 mm diameter, from young cultures of *Fusarium oxysporum* f. sp. *albedinis*, *Fusarium oxysporum* f.sp. *canariensis* and *Verticillium dahliae* which were provided by CRRA Marrakech, Morocco (Centre Regional de Recherche Agronomique) and maintained on CZAPECK medium, were disposed in the center of the petri dishes. Incubation was at 28 °C under continuous light. Each compounds-fungicide was repeated five times. Mycelial growth of colonies was estimated every 2 days for 8 days of incubation by the average of two perpendicular diameters [31].
For the evaluation of sporulation, we used tubes containing 5 mm of slices diameter taken along the diameter of the colony of different fungi at (8 days) in 100 ml of distilled water, two dilutions were prepared 10^{-5} and 10^{-6}. The fungal suspension was then stirred using a vortex for 20 seconds to release spores conidiophores. For each dilution we took 1 mL of the solution being distributed in a Petri dish. These experiments were repeated five times.

2.2.2. Evaluation of mycelial growth
The inhibition rate of mycelial growth of two fungi was calculated using the following formula [32, 35]:

Growth inhibition rate = ((Dco-Dt) / Dco) x100

Where:
Dco = colony diameter of the control (water).
Dt = colony diameter of the test plate.

2.2.3. Evaluation of sporulation.
We proceed to count the total number of spores using a Malassez cell. Values are expressed as the number of spores per unit area (mm^2). The inhibition percentage of the sporulation is calculated using the following formula [32, 35]

Sporulation inhibition rate (%) = ((Nco-Nt) / Nco) x100

Where:
Nco = estimated number of germinated spores of the control (water).
Nt = estimated number of germinated spores of the test plate.

2.2.4. Statistical analysis

The trial was established as a completely randomized experimental design with five replicates. Data were subjected to analyze of variance using SPSS software V17.0. The mean values among treatments were compared by Duncan's multiple range test at a 5 % (p ¼ 0.001) level to determine significant difference between the inhibition rates of various compounds at the same concentration.

3. Results and discussion

3.1. Spectral data for selected compounds

- Quinazolin-4(3H)-one **3a:** litt: [25, 26]

White pounder; Rf=0.6, eluent: Ethyl Acetate, mp = 220-221 °C; ^{1}H NMR (DMSO-d_6) (300 MHz) ; δ (ppm) ; 11.86 (s, 1H, NH); 7.85 (d, 1H, J = 9 Hz, H5); 7.74 (s, 1H, H2) ; 7.71 (Dd, 1H, J = 8.4 Hz , J = 7,1 Hz, H7) ; 7,56 (d, 1H, J = 7.1 Hz, H8) ; 7,42 (dd, 1H, J = 8,4 Hz, J = 9 Hz, H6). ^{13}C NMR: (DMSO-d_6) (300 MHz); δ (ppm); 163.64 (C=O); 145.94 (C2); 134.96 (C7); 127.73 (C6); 127.38 (C8); 126.40 (C5); Anal cal for ($C_8H_6N_2O$) = 146.1484 m/z = ($(M-1)^+$, 145.44, 100 %)

- 6-Methylquinazolin-4(3H)-one **3b**: litt: [27, 28]

White crystals powder, Rf=0.37, eluent: Ethyl Acetate, mp = 260-261 °C; ^{1}H NMR (DMSO-d_6) (300 MHz); δ (ppm); 12.08 (s, 1H, NH); 7.90 (s, 1H, H2); 7.85 (s, 1H, H5); 7.53 (d, ^{1}H, J = 8.1 Hz, H7); 7.53 (d, 1H, J = 8.1 Hz, H8); 2.41 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6) (300 MHz); δ (ppm); 163.54 (C=O); 145.06 (C2); 136.99 (C6); 136.12 (C7); 127.63 (C5); 125.73 (C8); 21.33 (CH_3). ; Anal cal for ($C_9H_8N_2O$) = 160.1752 m/z = ($(M-1)^+$, 159.41, 100 %), (M+,160.31, 20 %)

- 6-Fluoroquinazolin-4(3H)-one **3c**: Litt: [27, 28]

White crystals powder, Rf=0.2, eluent: Ethyl Acetate, mp = 259-261 °C; ^{1}H NMR (DMSO-d_6) (300 MHz); δ (ppm); 12.47 (s, 1H, NH); 7.74 (s, 1H, H2); 7.47 (s, 1H, H5); 7.36 (d, 1H, J = 7.2 Hz, H7); 7.17 (d, 1H, J = 7.2 Hz, H8). ^{13}C NMR (DMSO-d_6) (300 MHz); δ (ppm); 163.47 (C=O); 161. 10 (C6); 146.91 (C2); 115.94 (C8); 115.71 (C7); 113.82 (C5), Anal cal for ($C_8H_5FN_2O$) = 164.1385 m/z= ($(M+H)^+$, 165.50, 100 %)

- 6,7-Dimethoxyquinazolin-4(3H)-one **3d**: Litt: [27, 28]

White powder, Rf=0.67, eluent: Ethyl Acetate, mp = 279-283 °C; ^{1}H NMR (DMSO-d_6) (300 MHz); δ (ppm); 9.94 (s, 1H, NH); 7.89 (s, 1H, H2); 7.22 (s, 1H, H5); 7.14 (s, 1H, H8); 3.68 (s, 3H, O-CH_3). ^{13}C NMR (DMSO-d_6) (300 MHz); δ (ppm); 164.43 (C-O); 160.53 (C7); 149.93 (C2); 146.43 (C6); 105.67 (C8); 104.83 (C5); 56.72 (O-CH_3); Anal cal for ($C_{10}H_{10}N_2O_3$) = 206.2000 m/z = ($(M+H)^+$, 207.07, 10 %) ,(Dimere, 413.18,100 %)

- Benzo[g]quinazolin-4(3H)-one **3e**: Litt: [24, 29]

White powder, Rf=0.40, eluent: Ethyl Acetate, mp = 272-274 °C; ^{1}H NMR (DMSO-d_6) (300 MHz); δ (ppm); 11.90 (s, 1H, NH); 8.74 (s, 1H, H2); 8.10 (s, 1H, H10); 8.01 (d, 1H, J= 7.8 Hz, H9, H6); 7.55 (dd, 1H, J = 7.8 Hz, J = 9.3 Hz, H7, H8); 7,49 (s, 1H, H5). ^{13}C NMR (DMSO-d_6) (300 MHz); δ (ppm); 161.37 (C=O); 145.76 (C2); 129.93 (C5); 129.56 (C6); 128.54 (C8); 127.83 (C9); 126.90 (C7); 120.89 (C10).). Anal cal for ($C_{12}H_8N_2O$) = 196.2082 m/z = ($(M-H)^+$, 195.34, 100 %); (M+,196.90,36 %); ($(M+H)^+$, 197.90, 15 %)

- Pteridin-4(3H)-one **3f**: Litt. [30]

White crystals powder, Rf=0.3, eluent: Ethyl Acetate, mp = 190-193 °C; ^{1}H NMR (DMSO-d_6) (300 MHz); δ (ppm); 11.01 (s, 1H, NH); 9.31 (d, 1H, J = 8.1 Hz, H6, H7); 8.39 (s, 1H, H2). ^{13}C NMR (DMSO-d_6) (300 MHz); δ (ppm); 162.75 (C=O); 143.51 (C2); 142.81 (C7); 140.31 (C6), Anal cal for ($C_6H_4N_4O$) = 148.1246**,** m/z = ($(M+H)^+$, 149.36, 100 %)

Because of their utility as fungicide and herbicide several methods are available for the synthesis of (3H)-quinazolin- 4-ones and their derivatives [36]

Our work was initiated with the reaction between formamide **2** and anthranilic acid **1a,** furthermore to optimize the reaction conditions; the reactants ratio, the reaction time, and the irradiation power were variably studied. As a result we were satisfied to find that the reaction gave quinazolin-4(3H)-one **3a** in 86 % yield after 20 min of irradiation at 400 W with solvent free. Encouraged by this result, the reactivity of anthranilic acid derivatives using the Niementowski reaction was investigated and the results are summarized in Table 1.
Having established the advantages of the microwave irradiation approach for the construction of 2-substituted quinazolin-4-ones **3a-f**, the six products and their anthranilic acid **1a-f** were screened for the antifungal activities against different plant fungi.

3.2. Biological activity

3.2.1. Screening of antifungal activity in Vitro

Compounds **1a-f** and **3a-f** were screened for their *in vitro* antifungal activity against tree phytopathogenic fungi (*Fusarium oxysporum* f. sp. *canariensis* (Foc) and *Fusarium oxysporum* f. sp *albedinis* (Foa) and *Verticillium dahliae* Kleb (Vd) at 2.5 µg/mL, 5 µg/mL and 7.5 µg/mL; by mycelia linear growth rate method and sporulation method. The commercial systemic Fungicide "Pelt" was used as positive control; it contains 70 % methyl thiophanate, the Mean inhibition rates of all tested compounds against the same fungi were compared by Ducan's multiple tests (spss 17). The antifungal activity of the compounds and the reference drug were recorded in (Tables 2; 3 and 4) and (Figures 1 to 6).

Table 2: The antifungal activity of the title compounds against Foc

	Foc					
	Linear growth inhibitory rates (means %)**			Sporulation inhibitory rates (means %)**		
C (µg/mL)	7.5	5	2.5	7.5	5	2.5
1a	6.05 j	2.9 j	-7.23 i	-8.51 i	- 23.37 i	-44.12 j
1b	22.47 i	11.15 i	0.21 h	0.97 h	- 11.75 g	-24.81 h
1c	75.46 d	61.58 d	39.77 e	61.94 b	48.03 c	22.76 d
1d	69.51 f	56.42 e	47.51 d	37.11 d	17.39 d	0.54 f
1e	70.51 e	67.19 c	52.33 c	64.02 b	49.71 c	20.01 d
1f	34.72 h	13.96 i	1.63 h	10.84 g	0.81 f	-32.41 i
3a	37.24 h	25.48 g	17.12 f	19.41 f	3.41 e	-11.59 g
3b	45.42g	17.53 h	4.10 g	28.50 e	-18.68 h	-34.07 i
3c	100 a	100 a	94.11 a	100 a	100 a	81.73 b
3d	89.4 c	69 c	48.27 cd	61.74 b	27.12 d	6.38 e
3e	95.71 b	82.6 b	64.31 b	100 a	83.12 b	51.79 c
3f	62.51 f	29.33f	8.28 g	45.27 c	0.61 f	-13.53 g
PELT	100 a	100 a	96.51 a	100 a	100 a	100 a

Foc: Fusarium oxysporum f. sp. *canariensis* **The differences between data with the different lowercase letters within a column are significant for the same tested fungi ($p < 0.05$)

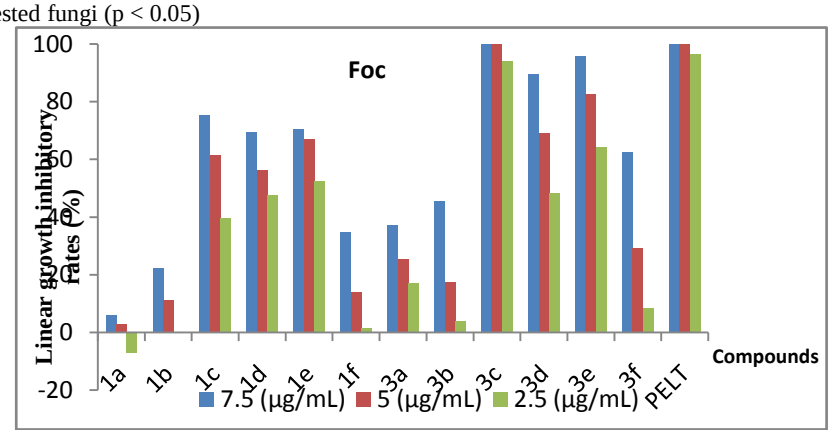


Figure 1: Linear growth inhibitory rate of Foc

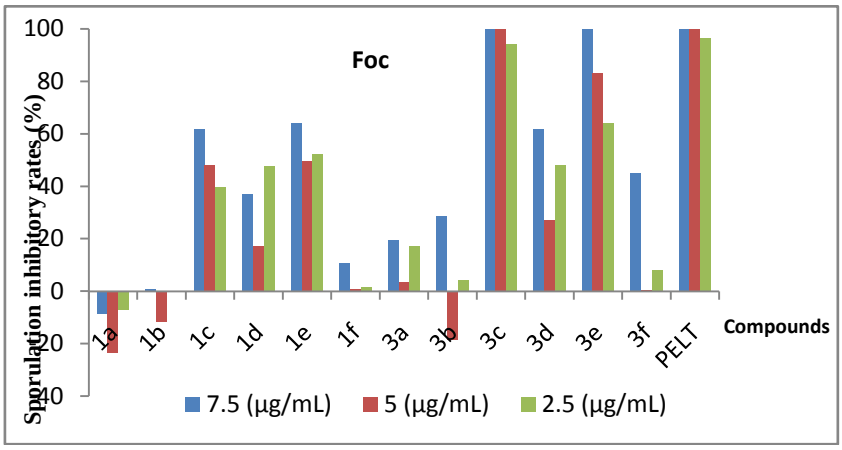


Figure 2: Sporulation inhibitory rate of Foc

Table 3: The antifungal activity of the title compounds against Foa

	Antifungal activity of Foa					
	Linear growth inhibitory rates (means %)**			Sporulation inhibitory rates (means %)**		
Concentrations µg/mL	7.5	5	2.5	7.5	5	2.5
1a	10.65 j	0.61 k	-17.91 k	-10.01 j	-22.37 k	-31.81 j
1b	27.12 i	13.02 j	2.62 j	-3.76 i	-32.09 l	-44.64 k
1c	53.7 e	41.26 f	29.06 e	43.89 e	33.56 d	16.86 d
1d	60.79 d	45.8 e	18.21 f	29.73 f	3.19 i	-9.74 h
1e	32.6 h	18.14 i	6.83 i	21.86 g	9.53 g	-12.65 i
1f	49.02 f	36.1 g	8.91 h	17.07 h	-10.95 j	-43.69k
3a	40.71 g	18.73 i	3.94 j	22.65 g	14.77 e	-2.45 g
3b	52.69 ef	31.33 h	11.78 g	40.06 e	7.32 h	-13.98 i
3c	100 a	87.05 b	71.41 b	100 a	71.41 b	38.18 b
3d	80.65 b	53.63 d	39 d	57.49 d	10.42 f	-0.21 f
3e	81.24 b	73.48 c	54.73 c	89.41 b	45.76 c	29.54 c
3f	77.36 c	44.68 ef	32.07 e	70.82 c	16.19 e	2.28 e
PELT	100 a	100 a	98.2 a	100 a	100 a	92.24 a

Foa: Fusarium oxysporum f. sp. *albedinis* ** The differences between data with the different lowercase letters within a column are significant for the same tested fungi ($p < 0.05$).

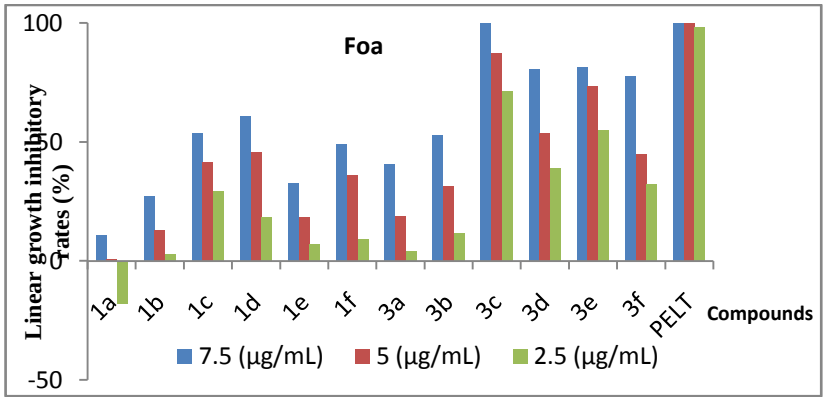


Figure 3: Linear growth inhibitory rate of Foa

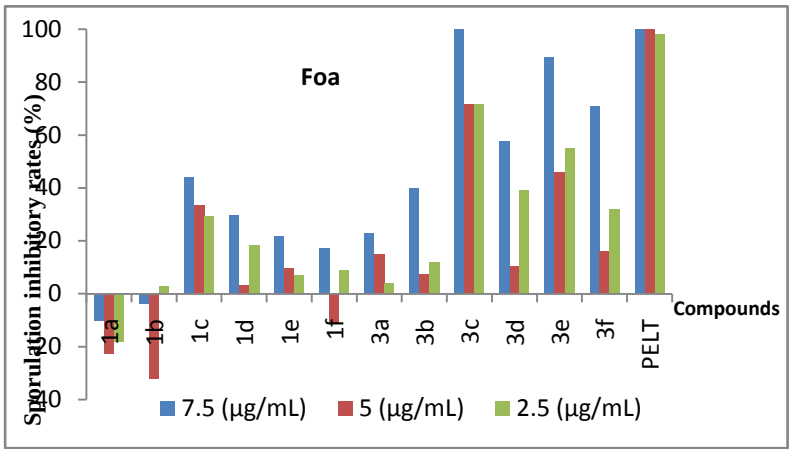


Figure 4: Sporulation inhibitory rate of Foa

Table 4: The antifungal activity of Vd

	Antifungal activity of Vd					
	Linear growth inhibitory rates (means %)**			Sporulation inhibitory rates (means %)**		
C (µg/mL)	7.5	5	2.5	7.5	5	2.5
1a	8.37k	-0.36 j	-23.52 h	-16.47 j	-37.01 j	-50.98 k
1b	14.27 j	9.48 i	-1.72 g	-4.07 i	-17.65 i	-27.30 i
1c	47.28 f	26.1 g	10.03 e	31.73 f	8.40 e	-6.03 f
1d	58.62 e	33.76 f	25.92 d	44.65 e	21.80 cd	0.69 d
1e	28.69 h	10.83 i	3.48 f	16.87 g	2.41 f	-19.03 h
1f	19.57 i	13.05 h	4.16 f	-2.83 i	-19.3 i	-30.64 j
3a	27.61 h	14.37 h	0.23 g	5.28 h	0.12 g	-26.92 i
3b	41.38 g	26.71 g	9.41 e	16.86 g	-9.42 h	-28.79 ij
3c	85.45 b	67.1 b	49.55 b	69.50 c	43.92 b	15.74 b
3d	81.17 c	59.83 c	37.16 c	72.61 b	23.11 c	9.42 c
3e	79.72 c	49.91 d	35.21 c	61.89 d	19.94 d	-10.13 g
3f	70.31 d	41.28 e	26.94 d	58.64 d	8.12 e	-4.81e
PELT	100 a	100 a	82.48 a	100 a	100 a	91.93 a

Vd: Verticillium dahliae ** The differences between data with the different lowercase letters within a column are significant for the same tested fungi ($p < 0.05$).

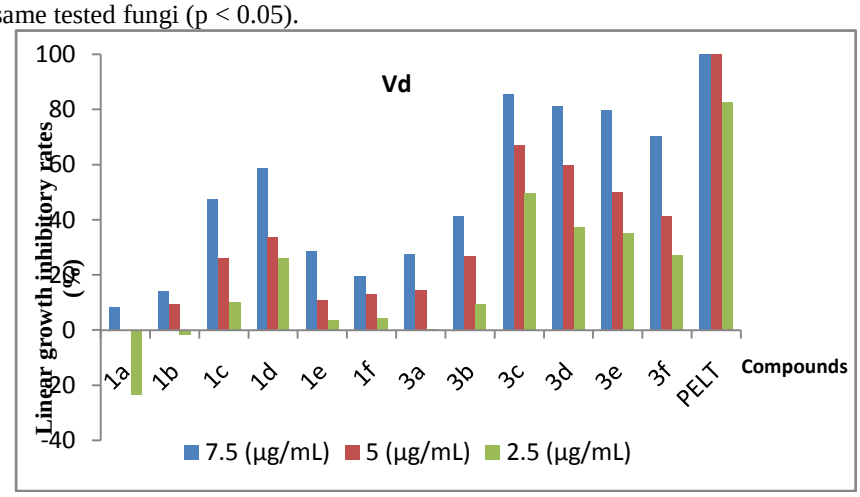


Figure 5: Linear growth inhibitory rate of Vd

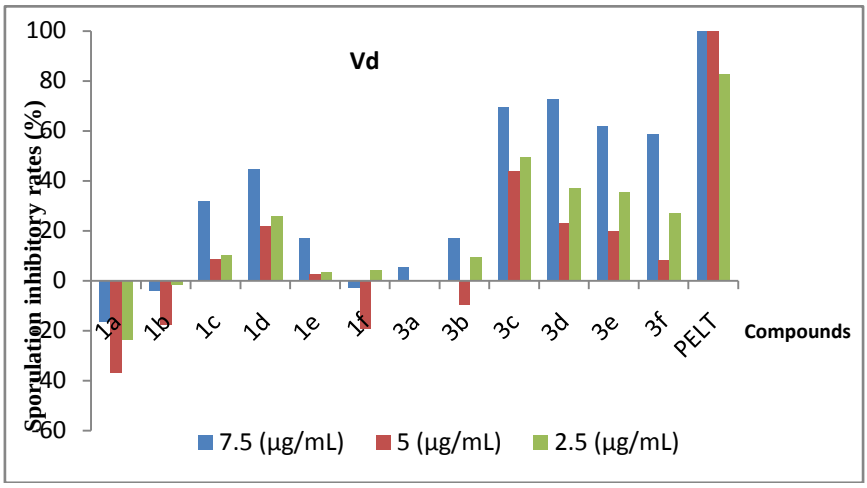


Figure 6: Sporulation inhibitory rate of Vd

Compounds (**1a–f**) and **(3a-f)** were evaluated as inhibitors of tree fungi using reported procedure. Results were reported as percentage of inhibitory values (Tables 2, 3 and 4) and (Figures 1 to 6). The results of preliminary bioassays were compared with commercial agricultural fungicide, "Pelt". As indicated in different tables and figures, most of the synthesized compounds showed certain antifungal activities against the tested fungi.

At 7.5 µg/mL, the compounds **3e, 3d, 3c** inhibited the growth of Foc (Figure 1) at 95.7 %, 89.4 %, 100 %; Foa (Figure 3) at 81.25 %, 80.65 %, 100 % and Vd (Figure 5) at 79.72 %, 81.17 %, 85.45 % respectively. At 5 µg/mL only two compounds **3e** and **3c** showed the highest antifungal activities against Foc with 82.6 % and 100 % respectively: Foa at 73.48 % , 87.05 %, while the highest antifungal activity against Vd was showed by compound **3c** (81.17 %.). Finally at 2.5 µg/mL most of the compound had a weak antifungal activities against the tree fungi, the only compound that showed a remarkable activity was **3c** with 94.11 % against Foc; 71.41 % against Foa and 49.55 % against Vd.

On the other hand the spore germination of all the fungi declined with the increase of the concentration, compound **3c** had a remarkable fungicidal effect against all fungi at different concentrations from 15.74 % (Vd) at 2.5 (µg/mL) to 100 % (Foc) at 7.5 (µg/mL) (Table 2, figure 2), hence **3c** showed a broad-spectrum bioactivity, we also notice that at 2.5 µg/mL most of the compounds showed an increase of spore germination regarding Foa (Table 3, igure 4) and Vd (Table 4, figure 6). The compound **1a** had the lower efficiency against the fungi, most of the compound had a fungiostatic effect, and they are more active in the inhibition of the mycelium growth than the sporulation.

A close examination of the structures of the active compounds revealed that the antifungal activity was confined mainly to the quinazoline derivatives in comparison with their substituted 2-aminobenzoic acid. The result also indicated that most of the compounds are effective against Foc followed by Foa and finally Vd. Starting with **3a**, we set out to investigate the possibility of enhancing the antifungal activity by structurally modifying this scaffold at the 6 and or 7-positions with small substituent. We observe that compounds substituted at position 6 of the quinazoline ring are more active than the other positions. This result was also observed by Al-omar and co-worker[37], they found that antimicrobial activity of the quinazoline ring substituted at position 6 are more active than the other substituted positions -5 or -8. In our study we found that compound **3c** which contain Fluorine in position 6 has the highest antifungal activity in all the tested fungi. In concordance with our result, Guang-Fang Xu and co-worker [38] synthesized a series of novel s-substituted 6-fluoro-4-alkyl(aryl)thioquinazoline derivatives and they studied their antifungal activities , they found that tree of the title compounds have a good antifungal activities especially 4-ethylthio-6-fluoroquinazoline which possess the highest inhibitory effect against *Fusarium oxysporum*. Likewise Fang Liu and Yinjiu Huang [13, 39] revealed that 6-bromo-4-ethoxyethylthio quinazoline possessed remarkable inhibition effects on nine plant pathogenic fungi. Moreover, Wu and co-workers [40, 41] synthesized a series of 6,8-dichloroquinazoline derivatives bearing a sulfide group. These compounds showed good insecticidal activity against Plutella xylostella. In the other hand, number of patents mentions the utility of fluorinated quinazoline as important antifungal, herbicidal, pesticidal [42].

Conclusion

In summary, the present method of formation of 3H-quinazolin-4-ones derivatives under microwave condition offers several advantages such as faster reaction rate and a good yield. It was also found that title compounds **3e**, **3d**, and **3c** displayed good antifungal activity; in particularly **3c** proved to be the most active broad-spectrum antifungal in this study.
Therefore, further investigation requires to be done in the future research through modification of the quinazolin-4-one to design more potent and selective antifungal agent.

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