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Synthesis, characterization and antifungal evaluation of some novel quinoline derivatives derived from ethyl *p*-aminobenzoate

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ABSTRACT

Novel series of quinoline derivatives, compounds ***(4-6),*** *have been synthesized by cyclization of ethyl p-aminobenzoate, formaldehyde, and pyruvic acid which affords****,****6-(ethoxycarbonyl) quinoline-4-carboxylic acid****(1)*** *followed by treatment with ethanol in acidic medium to yield diethyl quinoline 4,6-dicarboxylate* ***(2),*** *then addition of hydrazine hydrate to afford quinoline -4,6-dicarbohydrazide* ***(3).****This compound on condensation with the following: acetaldehyde in acidic medium, acetylacetone, and chloroacetic acid in the presence of anhydrous sodium acetate, furnished : $N^{'4}$,$N^{'6}$-diethylidenequinoline-4,6-dicarbohydrazide* ***(4),*** *quinoline-4,6-diylbis((3,5-dimethyl-1H-pyrazole-1-yl)methanone)* ***(5)****, and 2,2'-(quinoline-4,6-diyl)bis(4,5-dihydro-6H-1,3,4--oxadiazin-6-one)* ***(6)****, respectively. All the compounds were characterized by spectral studies. The synthesized derivatives were screened for their in vitro, antifungal activity against Aspergillus terrus and Aspergillus niger. Compound* ***(1)*** *showed the most potent antifungal activity against A. terreus.*

Keywords: Quinoline, pyrazole, oxadiazine and antifungal activity.

INTRODUCTION

The importance of quinoline nucleus has been well demonstrated as shown by a high number of patents employing such species as chemotherapeutic agents**.**

Quinoline and its derivatives have always attracted both synthetic and medicinal chemist due to its wide chemical and different pharmacological properties. Moreover, quinoline ring system founds in various natural plant products, particularly alkaloids and is used for the design of synthetic compounds with diverse biological activities. There are some natural products containing quinoline skeleton, used as a medicine or employed as a lead molecule for the development newer and potent molecules [1-3].

There are different biological activities associated with quinoline containing compounds, such as anti-inflammatory [4],antiallergic [5],antimalarial [6], antibacterial[7],antiproliferative[8],anticancer[9] and anti parasitic[10] activities. In the present work, a novel series of hydrazide, pyrazole, and oxadiazine, derived from ethyl *p*- aminobenzoate moiety, was reported here. The structures of newly synthesized compounds were elucidated by IR, ^{1}HNMR, and ^{13}CNMR spectral data. All the compounds have been tested for their *antifungal* activity. The reaction sequence for the synthesis of the title compounds is outlined in **Scheme** 1.

MATERIALS AND METHODS

Experimental

All reagents were commercially available and used without any purification. Melting points of all synthesized compounds were determined in open capillary tubes on an electrothermal apparatus and were uncorrected. The progress of the reactions was monitored by thin layer chromatography (TLC) on silica gel coated aluminum plates (Merck) as an adsorbent, and UV light (254 nm) as a visualizing agent. The infrared (IR) spectra were recorded using

(KBr) disc technique on Shimadzu FT- IR-8400S Spectrophotometer in(Al-Musatnsiriyah university-Baghdad), ^{1}H NMR and ^{13}CNMR spectra were recorded on DMSO-d_6 with TMS as an internal standard on Bruker spectrophotometer at 300 MHz and 75 MHz respectively, (chemical shifts in **δ** ppm), the NMR work was done at Al al-Bayt University- Jordan).

General Methods

The title compounds were synthesized by the following steps:

Synthesis of 6-(ethoxycarbonyl) quinoline-4-carboxylic acid (1) [11]

In a (250) ml round bottom flask, prepared with a reflux condenser, the addition of a purified formaldehyde (0.1 mol, 3.1ml), freshly distilled pyruvic acid (0.1 mol, 8.8 ml) and absolute ethanol (100ml), was added slowly. The mixture was heated to the boiling point on a water bath, and a solution of pure ethyl -*p*-aminobenzoate (0.1mol, 16.5 g) in absolute ethanol (100 ml) was added slowly to it, with frequent stirring. The addition lasts about one hr. Then, the mixture was refluxed on a water bath for 3 hrs and then allowed to stand overnight.

The crude quinoline-4- carboxylic acid was filtered off, and crystals were washed with a little ether. The crude product was recrystallized from methanol to give a white compound, m.p.216-218 °C, yield (71%), IR (υ cm^{-1},KBr): 3369.8(OH-str.), 3050 (CH-arom.),1685 (C=O acid str.),1602(C=N quinoline),(C=C arom.); ^{1}HNMR (300MHz, DMSO-d_6, δppm): 12.7 (s,1H,COOH),9.8(s.1H,Ar-H),8.49-8.40 (d,2H, Ar-H), 8.75-7.74 (d,2H,Ar-H), 4.3 (q,2H,CH_2), 1.45 (t,3H,CH_3).

Synthesis of diethyl quinoline-4,6-dicarboxylate (2)

Treatment of 6-(ethoxycarbonyl) quinoline-4-carboxylic acid **(1)**, (0.1mole, 21.9g,) with absolute ethanol (15ml), conc. H_2SO_4(2 ml) and then refluxing the mixture for 6 hrs, to afford compound **(2)**, m.p.122-124 °C , yield (76%); IR(υ cm^{-1},KBr)2983,2935,2904 (CH-aliph. ester),1703,2(C=O ester str.),1604(C=N. quinoline),1521(C=C arom.); ^{1}HNMR (300MHz, DMSO-d_6,δ ppm):8.95(s,1H,Ar-H),8.81(dd,2H,Ar-H),7.3(2H,Ar-H),4.81 (s,4H,$2CH_2$), 1.47 (t,6H,$2CH_3$); ^{13}CNMR (75MHz, DMSO- d_6,δppm):165.4,150.04,149.8,138.6,131.8,129.4,128,9, 127.4, 126.8, 123.2, 60.9, 14.1

Synthesis of quinoline-4,6-dicarbohydrazide (3)

Compound (3) was synthesized by the addition of the hydrazine hydrate (0.1 mol,7 ml), to compound **(2)**, (0.1mol, 27.3ml) in of absolute ethanol (30 ml),then the mixture was refluxed for 5 hrs. After cooling, the product was filtered off and recrystallized by using ethanol, to afford compound **(3)**, m.p.234-236 °C, yield (73%);IR(υcm^{-1},KBr):3350-3219(NH_2andNH-str.),3069(CH-arom.),1631(C=Oamide.),1604(C=N quinoline),1523(C=C arom.); ^{1}HNMR (300MHz, DMSO-d_6, δppm):8.64(t,2H,2CONH), 8.2(s,1H,Ar-H), 8.19(dd,2H,Ar-H), 7.93(dd,2H,Ar-H), 4.26 (t,4H,$2NH_2$); ^{13}CNMR(75MHz,DMSO-d_6,δppm): 167.7, 164.8(2C=O), 153.3, 145.5, 142.8, 137.7, 130.2, 128.8, 128, 3,119.9,118.6

Synthesis of N'^{4}, N'^{6}-diethylidenequinoline-4,6-dicarbohydrazide (4)

A mixture of hydrazide derivative **(3)** ,(0.1 mol, 24.5g) with acetaldehyde (0.2 mol, 8.8 g) in absolute ethanol (50) ml and two drops of glacial acetic acid, was refluxed for 8 hrs. The mixture was cooled to form the precipitate and recrystallized by using methanol, thus, solid obtained,m.p.254-256°C, yield (69%); IR(υcm^{-1},KBr):3223(NH-str.),3085(CH-arom.)2956,2859(CH-aliph.),1683(C=Oamide),1634(C=N str.), 1580(C=Nquinoline),1512(C=Cstr.); ^{1}HNMR (300MHz, DMSO-d_6, δppm):12.03(s,1H,NH), 8.31(s,1H,Ar-H), 7.67(dd,2H,Ar-H), 7.27(q,1H,CH=N), 7.1(dd,2H,Ar-H), 0.89(d,3H,CH_3); ^{13}CNMR: (75MHz, DMSO-d_6,δppm): 165.9(C=O), 160.1(C=O), 159.29 (2CH=N), 145.9,145.6,130.9, 128.6, ,121.1,113.0,19.6

Synthesis of quinoline-4,6-diylbis((3,5-dimethyl-1*H*-pyrazole-1-yl)methanone) (5) [12]

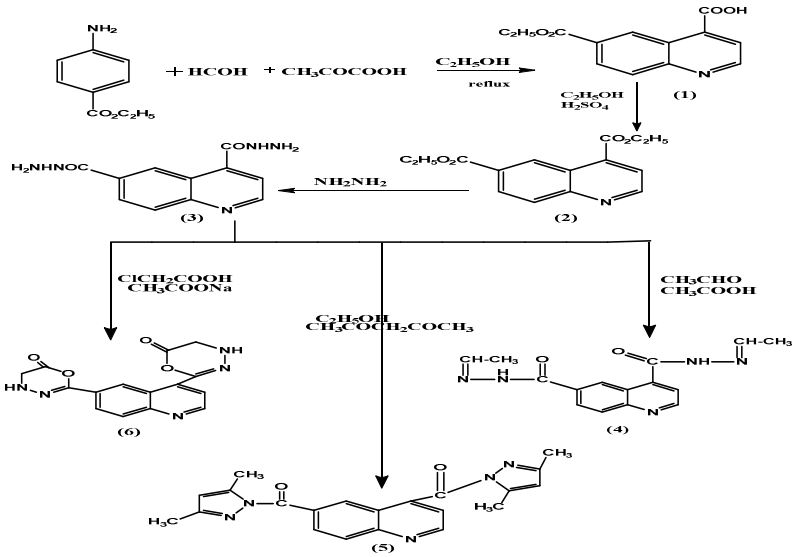
A mixture of carbohydrazide **(3)**,(0.1 mol, 24.5 g) and acetyl acetone (0.2 mol, 20 ml) in absolute ethanol (50) ml was refluxed for 7 hrs. The reaction mixture was cooled and the formed precipitate was filtered off to afford the title compound **(5)**, m.p.268-270 °C, yield (65%); IR (υ cm^{-1},KBr):3037 (CH-arom.),2982,2903 (CH-aliph.), 1687 (C=O amide),1597 (C=N pyrazole),1603(C=N quinoline),1531 (C=C arom.); ^{1}HNMR (300MHz,DMSO-d_6,δppm): 8.05(dd,2H, Ar-H),6.79(dd,2H,Ar-H),6.49(s,1H,Ar-H),6.03 (s,1H,CH-pyrazole),3.14(s,6H,2CH_3), 2.49(s,6H,2CH_3); ^{13}CNMR (75MHz,DMSO-d_6,δppm): 167.28(C=O),163.88(C=O),153.3,145.9, 145.6,129.7, 129.5,121.1,113.0, 19.7,19.4

Synthesis of 2,2'-(quinoline-4,6-diyl)bis(4,5-dihydro-6*H*-1,3,4-oxadiazin--6-one) (6)

A solution of compound **(3)**, (0.1 mol, 24.5 g) and chloroacetic acid (0.2 mol, 18.6g) in the presence of anhydrous sodium acetate (0.2 mol,16.4g) and absolute ethanol (50 ml), was refluxed for (4) hrs., then poured on water, a solid product was obtained, m.p.255-257°C, yield (71%); IR (υ cm^{-1},KBr): 3213 (NH-str),3030(CH-arom.),1728.3 (C=O ester),1612 (C=N quinoline), 1579 (C=C arom.); ^{1}HNMR (300MHz,DMSO-d*6*,δ ppm): 8.86(s,1H,Ar-H),8.31 (dd,2H, Ar-H),8.24 (dd,2H,ArH), 7.52(t,2H,2NH), 3.35(dd,4H,2CH_2); ^{13}CNMR(75MHz,DMSO-d_6,δppm):174.5, 174.2,151.0, 149.4,147.3, 147.2, 135.3, 130.5, 129.1, 128.2,115.7,55.6

Antifungal activity:

All the synthesized compounds **(1-6)** screened *in vitro* for their antifungal activity, by using well diffusion method. The fungi employed for screening are *Aspergillus terreus* and *Aspergillus niger*, at concentration of 250μg/ml in potato dextrose agar (PDA) medium. Fluconazole was used as a standard drug at a concentration of 75 μg/ml. The freshly fungal spores were spread on (PDA) medium in laminar air flow chamber, then were cultured and incubated at 30 °C for 72 hrs. The test compounds were previously dissolved in (DMSO), which is used as a control, the zone of inhibition was measured in (mm), after incubation of plates for 72hrs, for the antifungal test, all the experiments were carried out in triplicate, and the results are demonstrated in **Table 2**.



Scheme 1: Synthesis of title compounds (1-6)

Table 1: Characterization of the synthesized compounds (1-6)

Compound	Formula	M.wt	Yield%	mp (° C)
1	$C_{13}H_{11}NO_4$	245.07	71	216-218
2	$C_{15}H_{15}NO_4$	273.29	76	122-124
3	$C_{11}H_{11}N5O_2$	245.09	73	234-236
4	$C_{15}H_{15}N_5O_2$	297.12	69	254-256
5	$C_{21}H_{19}N_5O_2$	373.42	65	268-270
6	$C_{15}H_{11}N_5O_4$	325.28	71	255-257

Table 2: Antifungal activity of (1-6) derivatives

Compound/Conc. 250µg/ml	Zone of inhibition (mm) *Aspergillus terreus*	Zone of inhibition (mm) *Aspergillus niger*
1	15	9
2	-	3
3	-	-
4	8	-
5	-	6
6	5	-
Fluconazole	20	-
DMSO (control)	-	-

RESULTS AND DISCUSSION

The purity of the synthesized derivatives was checked by performing TLC and by determining the melting points. All the compounds were purified by recrystallization using appropriate solvents. All the compounds were elucidated by IR, ^{1}HNMR, and ^{13}CNMR. The compounds were screened for their antifungal activity by well-diffusion method using two different fungal strains, among the synthesized compounds, **(1)** has shown maximum activity against *Aspergillus terreus*, and the other synthesized compounds were less active when compared to the standard drug.

CONCLUSION

The synthesized new compounds are characterized by spectral data and screened *in vitro* for their antifungal activity, among the synthesized compounds, **(1)** has the most potent antifungal activity by using well-diffusion method against *Aspergillus terreus*. The series of synthesized compounds have given to do more structural modification in pharmacophore replacements, and then screening for an appropriate biological activity.

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