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Solvent-free synthesis of new chalcone derivatives from 3-nitro phthalic acid and evaluation of their biological activities

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Abstract

Synthesis of 2-(4-Acetyl-phenyl)-4-nitro-isoindole-1, 3-dione chalcones were performed by fusion of 3-nitro phthalic anhydride with p-aminoacetophenone. Then the later was grinded with different aromatic aldehydes in the presence of sodium hydroxide to produce new chalcones derivatives A3-10 without using any solvent formation of new N-arylphthailimide chalcones were confirmed by FT-IR,^{1}HNMR, ^{13}CNMR spectroscopy and all final compounds were tested for their antifungal and antibacterial activity some of them showed more biological activity than the standard drugs.

Keywords: Chalcone, 3-nitro phthalic anhydride, biological activity

Introduction

Heterocyclic compounds are found as construction units through some of biological molecules, most of them are molecules which consist of five or six membered rings[1-3].

Chalcones can be produced by biosynthesis, and chemical synthesis [4]. They possess a wide spectrum of biological activities such as amoebicidal [5], antiviral [6], antiprotozoal [7], anticancer [8], antihelmintic [9], antiulcer, insecticidal [10], antioxidative [11], antibacterial [12], and cytotoxic [13]. The relationship between different composition of chalcones with improved good pharmacological properties became rich substance to work for many years ago. In addition to its biological activity, it has industry importance such as food additives and cosmetic formulation ingredients. The aim of this research to create new compounds have five-membered ring fused with a six-membered ring containing chalcone group with a view to find other interesting biological activity with green chemistry method.

Experimental

^{1}H-NMR and ^{13}C-NMR spectra solvent DMSO-d6) was recorded on a 500 MHz spectrometer with TMS as internal standard in Asfahan university/ Iran. Melting points were determined on a Gallen-kamp MFB-600 melting point apparatus and are uncorrected. Analytical thin layer chromatography (TLC) was performed on plates precoated with silica gel (Merck 60 F254, 0.25 mm) and was visualized with ultraviolet light. The biological activity test was performed at the University of Baghdad, College of Science.

1. Preparation of 3-nitro-phthalic anhydride (A1)

3-nitro-phthalic acid (4.5gm, 0.03mole) was put in a Pyrex tube and heated at 200 ^{o}C on the sand bath for about 30 mint. with stirring until the water was evaporated and the resulting product become liquid after that the solid crude product was recrystallized from acetone as white product. m.p163-165 ^{o}C; yield 82%. FT-IR (KBr): 1863 and 1782 cm^{-1} ν (C=O), (1546 and 1355 cm^{-1}) ν (NO_2).

2. Synthesis of 2-(4-Acetyl-phenyl)-4-nitro-isoindole-1,3-dione(A2)

A mixture of 3-nitro- phthalic anhydride (4.5gm, 0.03mole) and p-aminoacetophenone (4g, 0.03mole) was heated at 160C^{o} on sand bath for about 30 mint. with stirring until all mixture become liquid and the vapor of water was evaporated Then the crude product was recrystallized from ethanol as yellow product. m.p190-191 ^{o}C; yield 91% FT-IR (KBr): 1780 and 1733 cm^{-1} ν(C=O) of phthalimide, 1683 cm^{-1}ν(C=O) acetyl group and (1546 and 1355 cm^{-1}) ν NO_2. ^{1}HNMR (ppm): 2.63 (S, 3H,CH_3), 7.61(2H,d,C-2$^{'}$-H), 8.11(2H, d, C-5$^{'}$-H), 8.15(1H,d,C-6-H), 8.27(1H,d,C-7-H), and 8.34(1H, d,C-5-H). ^{13}C-NMR

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(ppm): 26.84(CH_3), 122.86, 127.12, 127.28, 128.48 , 128.84, 133.50 ,135.48,136.21,136.51-144.54(Ar-Cs):164.84 and162.28(C=O) imide, and 197 (C=O, acetyl group).

3. Synthesis of chalcones (A3-10)

A mixture of compound A2 (3.87g, 0.0125mole), respective benzaldehdes (0.0125 mole) and 0.5g of sodium hydroxide was ground in a porcelain mortar at room temperature. After 20 mint the mixture turned to a yellow solid which was treated with cold water(60ml), neutralized with dil. HCl and the formed solid precipitate was filtered, then recrystallization from ethanol to give the desirable compounds. The spectral data of the all chalcone derivatives are given below.

4-Nitro-2-[4-(3-phenyl-acryloyl)-phenyl]-isoindole-1,3-dione[A3]

Pall yellow solid m.p 150-151 ^oC, yield 68%, FT-IR (KBr): 1726 and 1680 cm^{-1} ν (C=O) of phthailimide, 1656 cm^{-1} (C=O) acetyl group (1539 and 1357 cm^{-1}) NO_2. ^{1}H-NMR (ppm): 7.2- 7.8 (8H, m, αH and C-2', 6', 2'', 3'', 4'', 5'', 6''-H), 8.06-8.46 (6H, m, βH and C-5, 6, 7, 3', 5'-H). ^{13}C-NMR(ppm): 118.7, 118.8, 119, 122, 125, 127, 128, 129, 130, 131, 132.6, 132.8,133, 134, 135, 136, 145,147 (Ar-Cs):165.8 and 165.058(2 C=O), 187.7 (C=O, acetyl group) .

4-Nitro-2-[3-(4-nitro-phenyl-acryloyl)-phenyl]-isoindole-1,3-dione (A4)

Brown solid m.p 185-188 ^oC, yield 70%, FT-IR (KBr): 1722 and 1693 cm^{-1} ν (C=O) of phthailimide,1662 cm^{-1} ν (C=O) acetyl group 1525 and 1338 cm^{-1} ν (NO_2).

2-{4-[3-(4-Chloro-phenyl)-acryloyl]-phenyl}-4-nitro-isoindole-1,3-dione(A5)

Yellow solid m.p 170-171 ^oC, yield 63%, FT-IR (KBr):1720 and 1681 cm^{-1} ν (C=O) of phthailimide, 1660 cm^{-1} ν (C=O) acetyl group 1535 and 1323cm^{-1} ν (NO_2). And 761 ν (C-Cl) ^{1}H-NMR (ppm): 7.35-7.35(7H, m, αH and C-2', 6', 2'', 3'', 5'', 6''-H), 8.06-8.39 (6H, m, βH and C-4, 6, 7, 3', 5'-H). ^{13}C-NMR (ppm): 119.05,125.73, 128,128.74, 129.4,129.6,130, 130.7, 131.1, 131.8, 132, 132.8, 136, 137, 143, 146, two signals 165.8 and 166 for (2C=O), and 196.6(C=O, acetyl group).

4-Nitro-2-[4-(5-phenyl-penta-2,4-dienoyl)-phenyl]-isoindole-1,3-dione(A6)

Yellow solid m.p 180-182 ^oC, yield 70%, FT-IR (KBr): 1731as. and 1689 cm^{-1} sym. ν (C=O) of phthalimide, 1630 cm^{-1} ν (C=O) acetyl group and (1526 and 1353 cm^{-1}) ν NO_2**.**

2-[4-(3-Furan-2-yl-acryloyl)-phenyl]-4-nitro isoindole-1,3-dione(A7)

Yellow solid mp. 160-163 °C, yield 60%, FT-IR (KBr): 1733 and 1685 cm^{-1} ν (C=O) of phthailimide, 1650 cm^{-1} ν (C=O) acetyl group (1537and 1377 cm^{-1}) ν NO_2 .

2-{4-[3-(4-methoxy-phenyl)-acryloyl]-phenyl}-4-nitro-isoindole-1,3-dione(A8)

Yellow solid m.p 130-134 ^oC, yield 55%, FT-IR (KBr): 1733 and 1680 cm^{-1} ν (C=O) of phthailimide, 1650 cm^{-1} ν (C=O) acetyl group (1534 and 1376 cm^{-1}) ν NO_2 ,1240 cm^{-1} ν (C-O-C) .

2-{4-[3-(2,4-Dimethoxy-phenyl)-acryloyl]-phenyl}-4-nitro-isoindole-1,3-dione(A9)

Deep yellow solid m.p 100-102 ^oC, yield 50%, FT-IR (KBr): 1733 and 1662 cm^{-1} ν (C=O) of phthailimide,1645 cm^{-1} ν (C=O) acetyl group (1520 and 1338 cm^{-1}) ν NO_2 ,1131 & 1261 cm^{-1} ν (C-O-C).

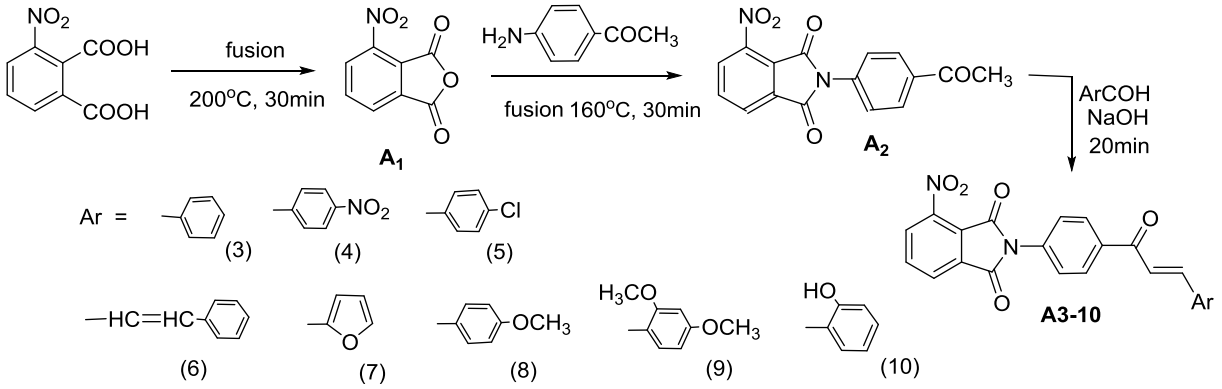
2-{4-[3-(2-hydroxy-phenyl)-acryloyl]-phenyl}-4-nitro-isoindole-1,3-dione(A10)

Yellow solid m.p 210-213^oC, yield 67%, FT-IR (KBr): 1780 and 1733 cm^{-1} ν (C=O) of phthailimide, 1650 cm^{-1} ν (C=O) acetyl group (1521 and 1332 cm^{-1}) ν NO_2 ,and 3301 cm^{-1} ν (OH).

Results and Discussion

In this article formation of N-(acetylphenyl)-3-nitrophthalimide chalcones were carried out by three steps, first step by fusion the 3-nitrophthalic acid at high temperature to produce the 3-nitrophthalic anhydride A1. The FTIR spectrum of the formed compound A1 showed absorption bands at 1863 and 1782 cm^{-1} for asy. and sym. of V(C=O) phthalic anhydride and at 1546 and 1355 cm^{-1} of V(NO_2) [14] than the later compound A1 was fused with *p*-aminoacetophenone to produce N(acetylphenyl)-3-nitrophthalimide A2 as shown in the scheme1.

The FTIR spectrum of the prepared compound A2 showed absorption bands at 1780 and 1733 cm^{-1} for asy. and sym. of V(C=O) phthalimide and bands at 1683 cm^{-1}, 1542 cm^{-1} and 1379 cm^{-1} for V(C=O) of acetyl group, asym. and sym. of V(NO_2) group, respectively Fig1.



Scheme 1. Synthesis of new chalcone derivatives from 3-nitro phthalic acid

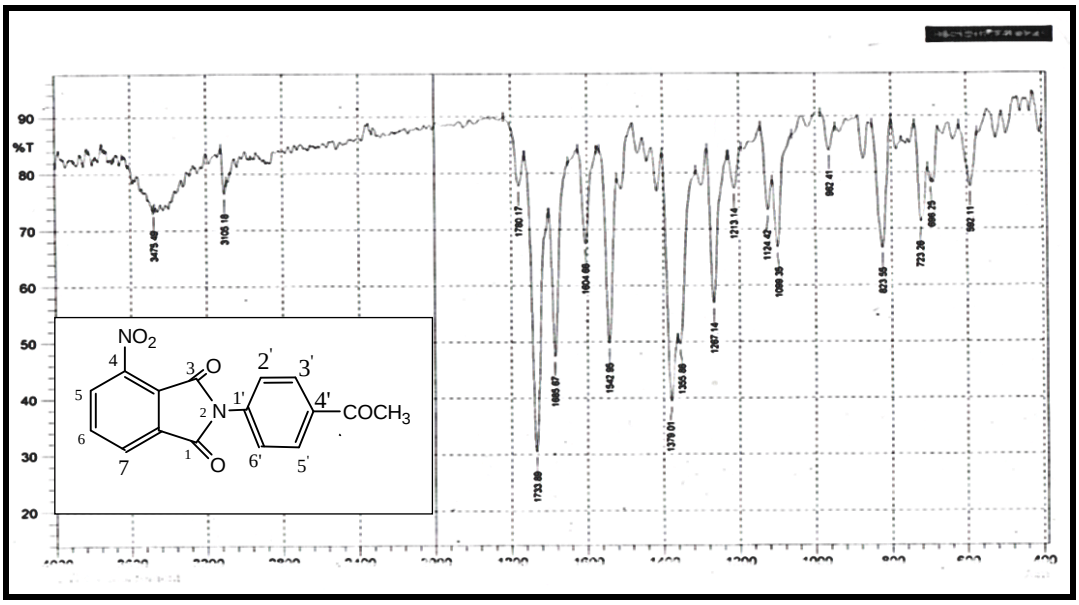


Fig. 1. FT-IR spectrum for compound A2

^{1}H-NMR spectrum for the same compound showed singlet signal at 2.63 ppm for three protons due to CH_3 and signals at 7.61-8.36ppm for aromatic protons. See Fig.2.

While ^{13}C-NMR spectrum for the same compound showed signal at 26.84 ppm for CH_3 group ,signal at 162.28ppm and 164.84ppm for two carbons of carbonyl phthalimide and signal at 197.31ppm for carbon of C=O acetyl group. See Fig.3.

The third step was carried out by the grind the later compound A2 with different substituted aromatic aldehydes in the presence of sodium hydroxide to produce different phthalimide chalcones (3-10). The FTIR spectra of new final compounds showed a shift to lower value absorption bands of carbonyl group at (1662-1630) cm^{-1} due to the conjugation of carbonyl group with the new double bond of chalcone compounds at (1602-1595) cm^{-1}. ^{1}H-NMR spectrum of compound A3 showed signals at 7.2 -7.8 (8H, m, αH and C-2', 6', 2'', 3'', 4'', 5'', 6''-H), 8.06-8.46 (6H, m ,βH and C-5,6,7,3',5'-H). While ^{13}C-NMR spectrum for the same compound A3 showed signal at 118.8ppm for vinilic carbon attached to the carbonyl group (CO<u>CH</u>=) and signals at 165.05ppm and 165.85ppm for two carbon carbonyl groups of phthailimide and 187ppm due to the carbon carbonyl of ketone group. Fig4.

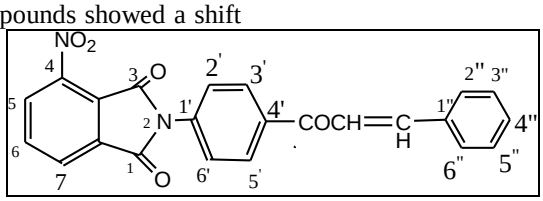


Fig. 4. Compound A3

^{1}H-NMR spectrum of compound A5 showed multi signals at 7.35-7.95ppm for one proton of αH, two protons of (C-2',and 6'-H,) four protons for (C- 2'', 3'', 4'', 5'', 6''-H), and signals at 8.08-8.39ppm for one proton of βH, three aromatic protons of phthalimide ring and two protons of (C-3', 5'-H) for N-phenyl group.

While ^{13}C-NMR spectrum for the same compound showed signal at 119.07ppm for vinilic carbon attached to the carbonyl group (CO<u>CH</u>=) and signals at 165.8ppm and 166ppm for two carbon carbonyl groups of phthalimide and 196.5ppm due to (C=O) carbon of ketone group.

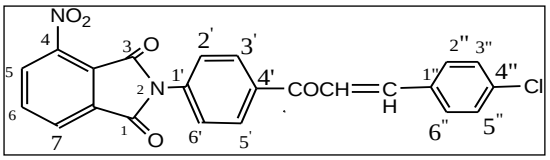


Fig. 5. Compound A5

The Physical properties of new synthesized compounds(A3-A10) are listed in Table 1.

Biological activity

In vitro antifungal studies:

The synthesized compounds were tested for antifungal activity against *candida albicans* by agar well diffusion method (well diameter was 5mm) using DMSO as solvent, Fluconazole was used as stander drug with three replicates and maintained at 37 °C for 3 dayes . Most of the test compounds show a very good antifungal activity except A2 and A3 .Compound A4,A5,A6,A7, A8 and A9 show a very good activity against *Candida albicans* as compare with stander drug while compound A9 was the most activity and better than the stander drug. Table2

In vitro antibacterial studies:

The synthesized compounds (A2-9) were test for antibacterial activity against Escherichia coli (gram-negative bacteria) and staphylococcus aureus (gram-positive bacteria) using cephalexin and Amoxicillin as reference drugs . the compound were dissolved in DMSO as solvent and the incubation was carried out at 27 °C for 24h by agar well disc diffusion method and well diameter was 5 mm the study showed that A9 was found to be most effective against E.coli and better than cephalexin and Amoxicillin against Escherichia coli with a zone of inhibition of 25 mm. against staphylococcus aureus, compound A5 showed more activity than standard drug Cephalexin with a zone of inhibition of 22 mm. Ttable2 Fig.6 and Fig.7.

Table 1: Physical properties of new synthesized compounds(A3-A10)

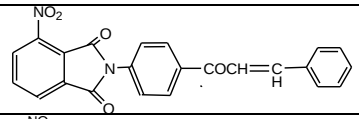
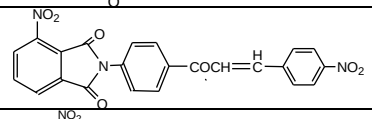
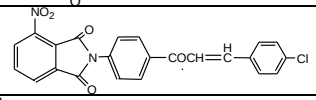
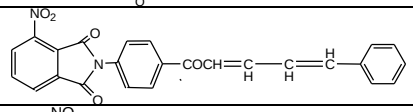
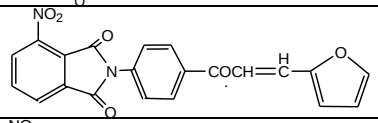
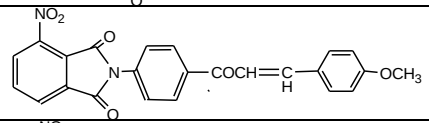
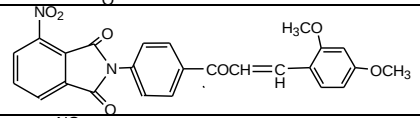
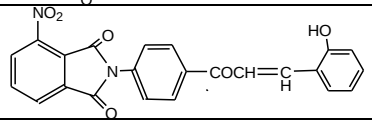
Comp.No.	Compound structures	M.W	m.p °C	Colour	R_f (hexane: Ethyl acetate) 7:3
A3		$C_{23}H_{14}N_2O_5$ 398.37	150-151	Yellow	0.6
A4		$C_{23}H_{13}N_3O_7$ 443.37	185-188	Brown	0.45
A5		$C_{23}H_{13}N_2O_5$ 432.81	170-171	Yellow	0.8
A6		$C_{25}H_{16}N_2O_5$ 424.11	180-182	Yellow	0.6
A7		$C_{21}H_{12}N_2O_6$ 388.33	160-163	Yellow	0.4
A8		$C_{24}H_{16}N_2O_6$ 428.39	130-134	Yellow	0.3
A9		$C_{25}H_{18}N_2O_7$ 458.42	100-102	Deep Yellow	0.7
A10		$C_{23}H_{14}N_2O_6$ 414.09	210-113	Yellow	0.6

Table 2. Antifungal and antibacterial activity for synthesized compounds A1-9 using agar well diffusion method the conc. of compounds is 10 mg/ml with three replicates

Compounds No. the conc. (10 mg/ml)	Diameter of zone of inhibition in mm(MIC) including the diameter of the well (5mm)		
	Candida albicans	*E.Coli*	*S.aureus*
A2	0	11±0.02	10±0.0
A3	0	11±0.0	11±0.19
A4	2.7±0.6	13±0.22	18±0.23
A5	3.0±0.0	25±0.09	22±0.09
A6	3.0±0.0	17±0.54	16±0.32
A7	4.7±0.6	14±0.43	13±0.34
A8	6.7±0.6	16±0.36	18±0.33
A9	9.0±0.0	21±0.42	0
Fluconazole	1.3±0.6	0	23±0.07
Cephalexin	-	22±0.09	20±0.21
Amoxicillin	0	22±0.09	35±0.15
Control (DMSO)	0	0	0

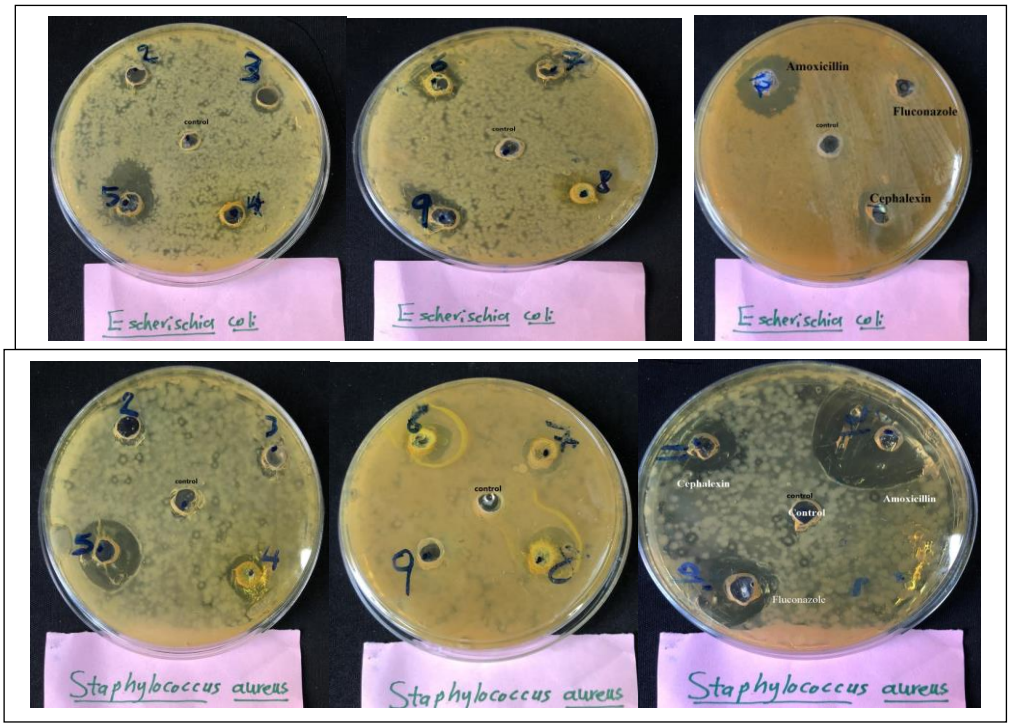


Fig. 7. Effect of compounds A2-9 and standard drugs on staphylococcus aureus

4. Conclusion.

A number of new 3-nitro phthalimide chalcone-derivatives was synthesized by solvent-free methods and all final compounds were tested for their antifungal activity against *candida albicans* and antibacterial activity against *Escherichia coli* and *staphylococcus aureus*, some of them showed good biological activity than the standard drugs. the study also showed that A5 was found to be better than Cephalexin as a standard drug against Escherichia coli and *staphylococcus aureus*. A9 was more antifungal against *candida albicans than* Fluconazole as a standard drug.

Acknowledgments

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فعاليتها البيولوجية تحضير مشتقات جديدة من الجالكونات بدون استخدام مذيب من 3-نايترو فثالك اسد وتقدير

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الخلاصة

تم تخليق 2 -(4-استيل فنيل)-4-نايترو-ايزواندول -1،3-داي اون جالكونات بعملية صهر 3-نايترو فثالك انهدريد مع بارا امينواسيتوفينون والناتج الأخير تم طحنه مع الالديهايدات الاروماتية المختلفة بوجود هيدروكسيد الصوديوم لينتج مشتقات الجالكون A10-A3 بدون استعمال مذيب لتكوين جالكونات من N-اريل فثالايميد التي تم تشخيصها بواسطة مطيافية الأشعة تحت الحمراء ومطيافية الرنين البروتوني المغناطيسي ومطيافية الرنين النووي المغناطيسي للكاربون 13 تم فحص جميع المركبات الناتجة تجاه الفعالية البيولوجية كمضادات للبكتريا ومضادات للفطريات بعض منها أظهرت فعالية بيولوجية افضل من الأدوية القياسية المستعملة.