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Synthesis and Preliminary Biological Activity Evaluation of New N-Substituted Phthalimide Derivatives

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Abstract

A new series of bases of Schiff (**H_2-H_4)** derived from phthalic anhydrideweresynthesized. These Schiff bases were prepared by the reaction of different amines (tyrosine methyl ester, phenylalanine methyl ester, and isoniazid) with the phthalimide derived aldehyde with the aid of glacial acetic acid or triethylamine ascatalysts. All the synthesized compounds were characterized by (FT-IR and ^{1}HNMR) analyses and were *in vitro* evaluated for their antimicrobial activity against six various kinds of microorganisms. All the synthesized compounds had been screened for their antimicrobial activity against two Gram-positive bacteria "*Staph. Aureus, and Bacillus subtilis*", two Gram-negative bacteria "*Escherichia coli*, and *Klebsiella pneumoniae*", and two fungi species "*Candida tropicalis and Candida albicans*" using concentrations of 62.5, 125 and 250 µg\mLof derivative in dimethyl sulfoxide(DMSO). All the synthesized compounds showed no activity at all against Gram-positive bacteria, for Gram-negative bacteria and fungi they showed moderate or no activity except compound **H_1**revealedhigh antifungal activityagainst*Candida tropicalis*at concentrations 125 and 250 µg\ mL.

Keywords: Schiff base, phthalic anhydride, antimicrobial.

تصنيع وتقييم اولي لمركبات دوائية جديدة ناتجة من تعويض جزيئي على موقع ذره النتروجين لمركب الفثالامايد

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الخلاصة

تم تصنيع سلسلة جديدة من قواعد شيف(H_2-H_4) المستمدة من أنهيدريد الفثاليك. تم تحضير هذه القواعد بواسطة تفاعل الأمينات المختلفة (تيروزين ميثيل إستر ، فينيل ألانين ميثيل إستر ، وإيزونيازيد) مع ألدهيد المشتت من الفثاليميد بمساعدة حمض الأسيتيك الجليدي أو تراي إيثيل أمين كعامل مساعد.تشخصت جميع المركبات المركبة بواسطة تحليلات (واستعمال مطياف الاشعة تحت الحمراء ومطيافالرنين النووي المغناطيسي للبروتون) وتم تقييمها في المختبر لنشاطها المضاد للميكروبات ضد ستة أنواع مختلفة من الكائنات الحية الدقيقة. تم فحص جميع المركبات المركبة لنشاطها المضاد للميكروبات ضد اثنين من البكتيريا إيجابية لصبغة الجرام (المكورات العنقودية الذهبية ، والعصية الرقيقة) ، واثنان من البكتيريا سالبة الجرام (*الإشريكية القولونية ، والكلبسيلة الرئوية*) ، ونوعان من الفطريات (*المبيضات المكورنة والمبيضات*) باستخدام تركيزات ٦٢,٥ و ١٢٥ و ٢٥٠ ميكروغرام / مل من مشتق في المذيب ثنائي مثيل السلفوكسايد.لم تظهر جميع المركبات المركبة أي نشاط على الإطلاق ضد البكتيريا إيجابية لصبغة الجرام ، فقد أظهرت نشاطًا معتدلًا أو بلا نشاط ضد بكتريا سلبية لصبغة الجرام والفطريات باستثناء أن المركب **H_1** كشف عن نشاط مضاد للفطريات مرتفع ضد المبيضات المدارية بتركيزات ١٢٥ و ٢٥٠ ميكروغرام / مل.

كلمات مفتاحية: قواعد شيف ، فثالك انهايدرايد، مضاد المكروبات.

Introduction

The development of multidrug microbial resistance is the main challenge that modern scientists have so far been facing in the recent decades. The fact that many pathogenic microorganisms taking charge of numerous human and animal diseases have caused resistance mechanisms to the conventional therapies have encouraged hard work investigations in the fields of natural and synthetic chemistry, to discover new drug classes having many efficient therapeutic profiles[(1)].

Phthalimide derivatives have a structural core (–CO-N(R)- CO-) and an imide ring which confer a biological activity to them. Phthalimides have wide range uses that include as anti-inflammatory agents[(2 ,3)], antidiabetic[(4)], antioxidant [(5)], Anticonvulsant [(6)], HIV-1 Reverse Transcriptase Inhibitor[(7)], as protective agent[(8)], as an antimicrobial agent using Schiff base principle[(9-11)].The structural feature of the five-membered ring shows they are hydrophobic and this enhances their passage across the biological membranes.

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As a result, the Phthalimide subunit has been designed as a hybrid with other molecules to give either synergistic, additive or new biological activity[11,12] .On another hand, it was found that the Schiff bases are of great benefit for the synthesis of various bioactive medicinal compounds from the primary amine. They possess antimalarial, anticancer, antimicrobial, antioxidant, anticonvulsant and anti-inflammatory characters[13]. Schiff bases are the compounds own imine or azomethine (–C=N–) functional group. The nitrogen atom of azomethine may participate in the hydrogen bonding with the active sites of cell components and intervene with normal cell functions[14].

Amino acids Schiff base is of high interest in the research world. Numerous scientists developed new strategies due to the special bioactivity of this design. Zahraa Salim *et al*[15], have studied the anti-acid phosphatase activity of amino acid Schiff base, While Yan Zhang *et al*[16], have investigated the increased herring sperm DNA intercalating of tryptophan vanillin Schiff base. Saroji Kumar *et al*[17], in two separate pieces of research work, have proved the beta-lactamase activity of tryptophan and phenylalanine amino acids Schiff bases with substituted benzaldehyde. Some researchers have linked phthalimide moiety with amino acid either directly proving antimicrobial activity[10]or using a spacer, having no Schiff base structure, with antiviral activity as a result[18].

Similarly, Isoniazid Schiff bases had been of wide attention in medicinal chemistry. Many researchers condensed isoniazid with various aldehydes to produce Schiff bases with enhanced anti-tubercular and antimicrobial activities, For example, S. Syed Tajudeen *et al*[19], produced Schiff base complexes of isoniazid with significantly enhanced antibacterial activity against microbial strains. As well as Joseph N. Yong*e et al*[20], prepare disoniazid's Schiff bases by the reaction of isoniazid with pyridine carboxaldehyde which showed good activity agains tbacteria compared to isoniazid alone. No research work linked isoniazid with phthalimide moiety through Schiff base has been reported.

Experiment

Materials and Methods

Starting material phthalic anhydride and aldehydes were purchased from (Riedel de Haŝen,Germany), tyrosine methyl ester, phenylalanine methyl ester and 4-aminobenzaldehyde from (Hyperchem,China), isoniazid from (Judex,England), acetic acid(BDH,China) ethanol& methanol (Biosolve,Netherland), DMSO&CH_2CL_2 (Romil,UK) and DMF(Thomas Baker, India).

Thin-layer chromatography (TLC) was used to follow up the reaction and to check the purity of synthesized compounds, by using silica gel GF (type 60) pre-coated aluminum sheet from (Merck - Germany), UV-254 lamp was used to visualize the spots, and the elution system used was (Methanol: Ethyl acetate: n-Hexane (0.5: 2: 3)). Stuart SMP3 melting points apparatus was used to measure the melting points, and were uncorrected. IR spectra were made using FT-IR (IR Affinity-1) spectrometer, Shimadzu, Japan at the University of Baghdad - College of Pharmacy. The ^{1}H-NMR spectra were performed at the College of Education for Pure Sciences (Ibn Al-Haitham), University of Baghdad. Instrument Model: NMReady-60 spectrometer, 60 Hz by N analysis Corp., Canada. ^{1}HNMR spectra were obtained on BRUKER model Ultra shield ٤٠٠ MHz spectrophotometer DMSO-d6 used as a solvent for samples measurement; it was performed at Central instrumental lab, School of Chemistry, College of Science, the University of Tehran, Iran.

Chemical synthesis

Synthesis of 4-(1,3-dioxoisoindolin-2-yl)benzaldehyde(H_1)

Compound$H_1$was synthesized by direct mixing equimolar quantities of "phthalic anhydride" with "4-amino benzaldehyde" (16.5 mmol) followed by refluxing in acetic acid 60 mL for 4 hours. After cooling, solid particles were separated out then cold water was added to the resultant mixture and was filtered using Buchner, washed with water several times and dried over silica gel under vacuum. The precipitate was collected by filtration and recrystallized from ethanol to obtain a bright yellow powder[21].

Yield68%; **m.p.**202-204°C;***Rf***=** 0.8;**IR**(*v*, cm^{-1}): 3012: Ar.(C-H) str., 2754: Ald. (C-H) str.,1782, 1697: *asym. &sym.*str. of imide (C=O),1720: aldehyde (C=O) str.,1600-1465: Ar.(C=C) str.,1080, 717: aromatic in plane& out of plane (C-H) bend.;**^{1}HNMR**(δ,ppm)**:**10.06 (1H,s, HCO), 7.7-8.07 (8H, m, Ar-H).

Synthesis of methyl 2-((4-(1,3-dioxoisoindolin-2-yl) benzylidene) amino)-3-(4-hydroxyphenyl) propanoate (H_2)

A mixture of "L-tyrosine methyl ester" (0.5 g, 2.6 mmol) in 100 ml dichloromethane, compound H_1 (0.643 g, 2.55 mmol), and anhydrous magnesium sulfate (0.75 g, 6.25 mmol) was refluxed for 6 hours), Schiff base formation is indicated by conversion of solution into a yellow-color. The solution allowed cooling at room temperature, the precipitated particles (magnesium sulfate) were discarded by filtration. The filtrate solvent was evaporated to obtain a yellow-colored product and was recrystallized from ethanol[22].

Yield =40%; **m.p**209-210°C**;** ***Rf*** = 0.58; **IR**(*v*,cm^{-1}):3394: phenolic (O-H) str.,3024: Ar(C-H) str., 2970& 2873: *asym*. & *sym*. aliphatic (CH_3) str., 2935 & 2854: *asym*. & *sym*. aliphatic (CH_2) str.,1782 &1701: *asym. & sym.* of imide (C=O)

str.,1720:(C=O) str. of ester, 1639: (N=C) Schiff base str.,1600- 1450: Ar-(C=C) str., 1080 & 721: in and out of plane (C-H) bend.; **^{1}H NMR**(δ,ppm):9.18 (1H,s,phenolic OH),7.52-8.14 (8H, m, Ar-H),8.16(1H,s,CH=N),6.62 (2H, d)& 6.67 (2H,d) Ar-H of tyrosine part,4.2 (1H, t, CH),3.63 (3H, s, OCH_3),2.88 & 3.14 (2H, 2d, CH_2).

Synthesis of methyl 2-((4-(1,3-dioxoisoindolin-2-yl) benzylidene) amino)-3-phenylpropanoate (H_3).

An ethanolic solution of 2-phenyl alanine methyl ester hydrochloride (2 g, 9.27 mmol, after stirring for half an hour with triethylamine), was added to hot dry ethanolic solution of compound **H_1** (1.9 g, 7.56 mmol), the mixture refluxed in water bath for 7 hours, a yellow-colored solution indicates Schiff base formation. The mixture was concentrated then allowed to cool. The precipitated Schiff base was filtered, washed with ethanol several times, and dried in the oven at 60 °C. The solid product was then stored under vacuum[23].

Yield70%;**m.p.**207-209 °C;***Rf***= 0.41;**IR**(*v*,cm^{-1}):3055:Ar(C-H) str., 2966 & 2889: *asym*. & *sym*. aliphatic (CH_3) str., 2943 & 2873: *asym*. & *sym*. aliphatic (CH_2) str., 1782 &1701: *asym. & sym.* of imide (C=O) str., 1728: (C=O) str. of ester,1639: (N=C) Schiff base str., 1600- 1450: Ar-(C=C) str., 1080-721: in and out of plane (C-H) bend.; **^{1}HNMR**(δ,ppm):8.14 (1H, s, CH=N), 7.17- 7.90 (13H, m, Ar-H), 4.2 (1H, t, CH), 3.6 (3H, s, OCH_3), 3.02& 3.14 (2H, 2d, CH_2)

Synthesis of N'-(4-(1,3-dioxoisoindolin-2-yl) benzylidene) isonicotinohydrazide (H_4)

A methanolic solution of isoniazid (1.37 g, 10mmol) was added gradually to a hot methanolic solution of compound H_1(1.66 g, 10 mmol, after stirring with 2 drops of glacial acetic acid), after few minutes solid particles appeared and refluxing was continued for 1 hour. The pale yellowish solid separated was filtered, washed several times with methanol,dried and stored over silica gel in a desiccated jar. It was recrystallized from DMF/ Methanol to give a shiny yellow powder[20].

Yield 81%; m.p. 344-346°C; *Rf* = 0.25; IR (*v*, cm^{-1}): 3282: *sec*.amide (N-H) str., 3059: Ar-(C-H) str., 1789 &1701: *asym. & sym.* of imide (C=O) str., 1666: (C=O) amide str., 1604: imine (C=N) str., 1604- 1512: Ar-(C=C) str., 1083 & 717cm^{-1} in and out of plane (C-H) bend.; **^{1}HNMR** (δ, ppm): 12.16 (1H, s,NHCO), 7.48-8.80 (12H, m, Ar-H),8.5 (1H, s, CH=N).

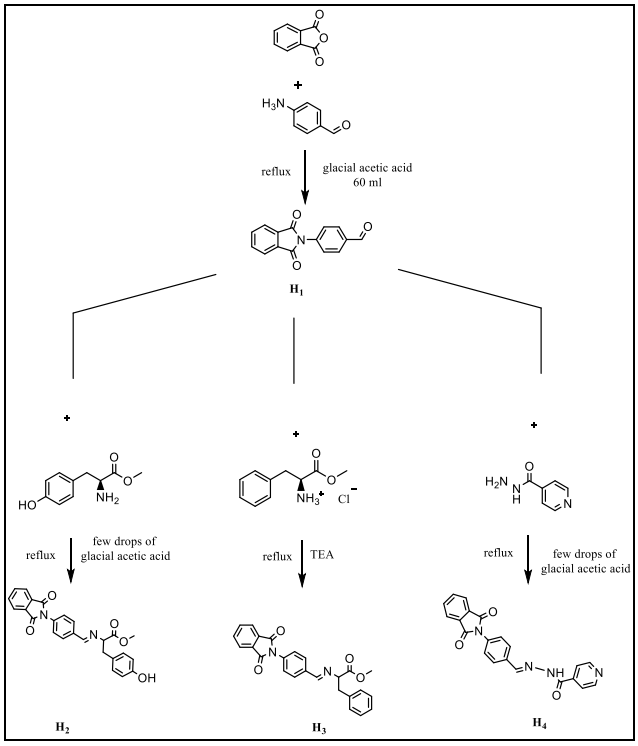
Antimicrobial activity

The Antimicrobial activity was screened using well diffusion methods. Two types of Gram-negative bacteria "*Klebsiella pneumonia*and *Escherichia Coli*" and two types of Gram-positive bacteria "*Staphylococcus aureus* and *Bacillus subtilis*" were used for testing the*in-vitro* antibacterial activity, and two fungi species "*Candida tropicalis and Candida albicans*" for testing the *in-vitro* antifungal activity isolated from a patient in Nahrain Teaching Hospital, Baghdad, Iraq**.** Cefotaxime and Miconazole used as standards against antibacterial and antifungal respectively, and DMSO as a solvent.It was done in "The University of Baghdad, College of Education for Pure Sciences Ibn Al-Haitham, central service laboratory".

Results and Discussion

Chemistry

The pathway for the synthesis of the targeted Schiff bases(H_2-H_4) is depicted in scheme 1.



Scheme 1. General synthetic pathway of the titled compounds.

The synthetic pathway started by the preparation of aldehyde of phthalimide compound **(H_1)** through imide bond formation using glacial acetic acid as solvent and catalyst. This method showed good yield with ease of production. The Schiff baseswereprepared by reaction of compound **(H_1)** with different amines (tyrosine methyl ester, phenylalanine methyl ester and isoniazid with the addition of few drops of "glacial acetic acid or triethylamine". The reaction involves elimination of one water molecule in order to form a carbon-nitrogen double bond (imine or Schiff base).

All the synthesized compounds were characterized and their structures were confirmed by "FTIR and ^{1}HNMR" spectral analyses.

The IR spectra for the parent nucleus **(H_1)**demonstrated characteristic two absorption bands of asymmetrical& symmetrical imide (C=O) stretching displayed at (1782 &1697) cm^{-1}. In

addition, 1720 and 2754 cm^{-1} are accounted for (C=O)&(CH) stretching of aldehyde respectively. For compounds (**H_2)** and (**H_3)**, the disappearance of the characteristic aldehyde band and appearance of the band at 1639 cm^{-1} is a good indication for Schiff base formation i.e. linkage has occurred between the phthalimide core and (tyrosine or phenylalanine methyl ester moiety). Compound (**H_2)** has an obvious band at 3394 cm^{-1} is attributed to phenolic OH group stretching. While Compound **(H4)** shows three important bands one is at 3282 cm^{-1} for secondary NH stretching and the second is at 1666 for amidic carbonyl stretching, and 1604 cm^{-1} for imine band stretching.

The ^{1}HNMR spectra of the synthesized compounds were consistent with the assigned structures. Compound**(H_1)** showed characteristic signals recorded at δ=10.06due to CHO of the aldehyde, besides, the aromatic protons displayed at their expected region as a *multiplate* at δ=7.7- 8.07 ppm. Compound (**H_2**) displayed CH=N peak as a singlet at δ=8.16, while compounds (**H_3**) imine CH=N peak appeared at δ=8.14 ppm.A peak of singlet at δ=9.18 ppm is due to the phenolic group in compound (**H_2**). Two doublet peak in the region of δ=3.٠١ ppm is attributed to the CH_2 group of the amino acid part for (**H_2)** and 3.08 is due to (CH_2) of (**H_3**). Finally, a sharp *singlet* peak integrated for three protons at δ=3.6 ppm is due to the OCH_3 group of both compounds. Compound (**H_4**) Showed characteristic peaks at δ=12.1 ppm, attributed to NHCO, also singlet peak at δ= 8.5 ppm is due to CH=N.

Antibacterial activity

Tables1 and 2 show the antimicrobial activity of the synthesized compounds at concentrations of (62.5, 125 and/or 250 µg\mL).

Table 1. Antibacterial activity of the tested compounds

Compound Name	Conc. µg/mL	*S. aureus*	*B. subtilis*	*E. coli*	*K. pneumoniae*
		Zone of inhibition(mm)			
H_1	62.5	-	-	11	-
	125	-	-	12	-
	250	-	-	12	-
H_2	62.5	-	-	11	10
	125	-	-	12	10
	250	-	-	-	-
H_3	62.5	-	-	-	-
	125	-	-	-	-
	250	-	-	10	-
H_4	62.5	-	-	-	-
	125	-	-	-	-
	250	-	-	10	12
Cefotaxime	100	49	43	51	25
DMSO	-	-	-	-	-

Table 2. Antifungal activity of the tested compounds

Compound Name	Conc. µg/mL	*Candida tropicalis*	*Candida albicans*
		Zone of inhibition(mm)	
H_1	62.5	18	-
	125	24	-
	250	22	-
H_2	62.5	14	-
	125	15	-
	250	-	-
H_3	62.5	-	14
	125	-	-
	250	-	-
H_4	62.5	12	-
	125	13	-
	250	-	-
Miconazole	100	15	23
DMSO	-	-	-

(-) = No activity- slightly active (zone of inhibition between 5-10 mm), moderately active (zone of inhibition between 10-20 mm), highly active (zone of inhibition more Than 20 mm).[24]

The data illustrated in tables1 and 2 reveals that all the synthesized compounds had been screened for their antimicrobial activity against two Gram-positive bacteria "*Staph. aureus, and Bacillus subtilis*", two Gram-negative bacteria "*Escherichia coli*, and *Klebsiella pneumoniae*", and two fungi species "*Candida tropicalis and Candida albicans*" using concentrations of 62.5, 125 and 250 µg\mL of derivatives in DMSO. For antibacterial activity:moderate activity against G-negative "*Escherichia coli*, and *Klebsiella pneumoniae*"appeared at concentrations(62.5 and 125 µg\mL) and250 µg\mL for compounds **(H_2)**and **(H_4),** respectively. Compounds **(H_1**and**H_3)** were moderately active against only E. coli at concentrations (62.5, 125 and 250 µg\mL) and250 µg\mL, respectively. However, all of them exhibited no activity against Gram-positive "*Staph. aureus, and Bacillus subtilis*".

The zero mm inhibition zone at concentration250µg\mL while containing inhibitory zone at lower zones at concentrations62.5 and 125 µg\mL for compound**(H_2)** may be due to at high antimicrobial concentration a small number of bacterial resistant mutants can provide the protection to others by producing signaling molecule to turn on the drug effluxpumps which are transport proteins involved in the extrusion of toxic and antibiotic substrates from within cells into the external environment of bacteria, enhancing the survival capacity of the overall population. [25]

On the other hand, the antifungal activity against *Candida tropicalis* and *Candida albicans* showed that compound **(H_3)** has only moderate activity against *Candida albicans* at a concentration of 62.5 µg\mL. Compounds **(H_2**and**H_4)** were only moderately active against *candida tropicalis*at concentrations 62.5 and 125µg\mL. Finally, the best activity among all the derivatives was obtained from compound **(H_1)** which proved high activity against *Candida tropicalis* at concentrations (125, 250 µg\mL).

Conclusion

New Schiff bases derivatives containing phthalimide core were successfully synthesized and their structures were characterized by "IR and ^{1}HNMR spectral" methods. All the synthesized compounds showed no activity at all against Gram-positive bacteria, for Gram-negative bacteria and fungi they showed moderate or no activity except compound (**H_1**) revealed high antifungal activity against *Candida tropicalis*at concentrations 125 and 250 µg\mL.

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