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Synthesis, Characterization and Study Antimicrobial Activity of Isoniazid Derivatives

Wasan K. Damdoom*,1 and Oday H. R. Al-Jeilawi2

[1] Department of Pharmaceutical Chemistry , College of Pharmacy, University of Thi-Qar , Thi-Qar, Iraq.
[2]Department of Chemistry, College of Sciences, University of Baghdad, Baghdad, Iraq.

***Corresponding Author**

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Abstract

In this study, a series of compounds (B1-B10) containing the (OR-) bond were prepared from nucleophilic substitution reaction of the Schiff base compound containing the (OH) group with different halides (alkyl halides, benzyl halides, benzoyl halides, sulfonyl halides) using the Williamson method. The prepared compounds were identified by FTIR, ^{1}HNMR, and ^{13}CNMR, then their effectiveness was evaluated against positive and negative gram bacterial and fungal and compared with two standard references (Ciprofloxacin, Clotrimazole). Overall, some of prepared compounds showed inhibition zone against Gram-positive and negative bacteria, and some compounds did not show inhibition zone while compound B1 showed a moderate inhibitory activity against all tested bacteria compared to other derivatives. But all the tested compounds showed inhibition zone against fungal Candida albicans except compound B2 had no effect.

Keywords: Antimicrobial activity, Halides, Isonicotinic acid hydrazide, Nucleophilic substitution, Williamson.

Introduction

Williamson is an approved method for the preparation of ethers, which are obtained from the reaction of alcohols and phenols catalyzed by a base with alkyl halides(1). Williamson ether synthesis is a general synthetic method for the formation of ethers from an alcohol and an organic halide, the reaction occurs in the presence of strong bases (2, 3).Ether derivatives have important and wide applications in many fields of the chemical industry. Methods for producing ethers have been developed to produce symmetrical and asymmetrical ethers and to synthesize catalytic reductive alcohol ethers with carbonyl-containing compounds such as aldehydes, ketones, and carboxylic acids (4). Ethers can be intermediates for the preparation of other compounds with medicinal and biological activity, such as amides on other hand obtaining linear compounds of azines that give optical glow in the crystalline and liquid crystal(5, 6).

Most of the ethers were synthesized by the Williamson method, but there are very few selective methods for building a quadruple center that carries an aryloxy part in its structure, and reports have been recorded for the synthesis of optically active ethers(٧).Bicyclic ethers showed good yields this method provides an effective alternative to the known methods for preparing ethers, it is obtained in a one-step method with the use of bicyclic amino alcohol(8). Fluorinated ethers are prepared in different ways from the ethers prepared by the Williamson method, where alcohols are added to alkenes or alkynes, where one of the two components is fluorinated to obtain the target compound(9). Ethers participate in the synthesis of heterocyclic rings by reacting with azide to form triazole derivatives via click chemistry(10, 11).

Heterocyclic compounds are of significant importance as structural sources and are widely recognized as biologically active chemicals (12-15). On the other hand, there is the thioether, which is the chemistry of sulfur, It is an important branch in organic chemistry and shows wide applications in the field of medicine and organic synthesis (16-18). Derivatives containing sulfur-oxygen bonds have anticancer activity against human cells(19).The formation of the etheric bond in the component increases the biological activity(20).Thus, it shows anti-bacterial activity(21, 22) antifungal(23, 24) anticancer(25-27) as well as ethers and thioethers shows corrosion inhibitors(28-30). Our work aims to synthesize new isoniazid derivatives from isonicotinic acid hydrazide via a two-step method. Firstly, condensation between isonicotinic acid hydrazide and 4-hydroxyacetophenone will be

performed to afford the corresponding Schiff base compound. Subsequently, nucleophilic substitution reaction will be performed between the synthesized Schiff bases and different halides to give the desired isoniazid derivatives.

Materials and Methods

Materials: All chemicals and solvents used in this work are from Fluke, BDH companies and were used without purification isonicotinic acid hydrazide, halides (BDH, England), solvents (Fluke). The melting points of the compounds were recorded using Gallen Kamp capillary melting point and were uncorrected. compounds were measured in the infrared spectrum (400 - 600cm^{-1}) Shimadzu device using a KBr disk. The^{1}HNMR and ^{13}CNMR spectra were recorded using Bruker device 400HMz using DMSO-d_6 as a solvent and TMS tetramethyl silane as a reference. TLC thin layer chromatography was used to find out the end point of the reaction, and the eluent was used mixture of ethanol 2: hexane 3, and the spots were shown using iodine. The microbial activity was measured for synthesize compounds.

General procedure to synthesis Schiff base (A) *(31, 32)*.

Reaction (0.4 g,0.003mol) of 4-hydroxy acetophenone with (0.5 g,0.003mol) of iso nicotinic acid hydrazide in 20 ml of ethanol as a solvent in the presence of 3 drops of Con. HCl then the mixture stirs for 3 hours at room temperature. Reaction checked in TLC (2 Ethanol:3Hexane). After the reaction was completed, the formed precipitate is collected, then dried and recrystallized with acetone.

Synthesis of (1-(4-Hydroxyphenyl) ethylidene) isonicotinohydrazide .

Pall yellow (88%), m.p 290-293ºC; FTIR υcm^{-1}:3385(OH) ,3284 (NH) ,3072, 3031 (C-H$_{aromatic}$),2952,2887(C-H$_{aliphatic}$),1654 (C=O),1604(C=N),1566 ,1458(C=C$_{aromatic}$); ^{1}HNMR δ_H (ppm,DMSO-d_6):10.95 (1H,s,NH), 9.89 (1H,s,OH), 8.78-6.83 (8H, m, Ar-H),2.33(3H,s,CH$_3$);^{13}CNMR δ_c (ppm,DMSO-d_6):162 (C=O), 159-115(Ar-C), 150(C=N), 15 (CH$_3$).

General procedure of ethers derivatives (B1-B10) *(3)*.

A mixture (0.3g,0.001mol) of Schiff base (A) and (0.1g,0.001mol) of potassium carbonate in 15 ml of DMF was stirred for 30 minutes at room temperature. Then (0.001mol) of halide derivatives were added and the mixture refluxed for (5-9) hours. The reaction was checked by TLC (2Ethanol:3Hexane), after the reaction was completed, the mixture was poured on crushed ice to obtain a precipitate which was filtered, washed, dried and recrystallized using a suitable solvent.

N-(1-(4-Propoxyphenyl) ethylidene) isonicotino-hydrazide (B1)

Orang(74%),m.p124-126ºC,halide:1-Bromopropane;FTIRυcm^{-1}:3170(NH),3064,3022(C-H $_{aromatic}$),2966, 2877 (C-H $_{aliphatic}$), 1641 (C=O), 1614 (C=N) , 1596,1475 (C=C$_{aromatic}$), 1255(C-O) ;^{1}HNMR δ_H (ppm,DMSO-d_6): 10.98 (1H,s,N<u>H</u>), 8.72-6.95 (8H,m,Ar-<u>H</u>),4.33-4.29 (2H , t , O-C<u>H</u>$_2$), 2.40 (3H, s, N=C-C<u>H</u>$_3$), 1.83-1.73 (2H,m, OCH$_2$-C<u>H</u>$_2$-), 1.03-0.98(3H, t, CH$_2$-C<u>H</u>$_3$);^{13}CNMR δ_c (ppm ,DMSO-d$_6$): 161(C=O), 160-114 (Ar-C), 149 (C=N), 69 (O-<u>C</u>H$_2$) ,22 (-<u>C</u>H$_2$-CH$_3$), 14 (N=C-<u>C</u>H$_3$) , 10 (-CH$_2$<u>C</u>H$_3$).

N-(1-(4-(Allyloxy) phenyl) ethylidene) isonicotinohydrazide (B2)

Dark brown (70%),m.p 195-197ºC , halide :Allyl chloride ;FTIR υcm^{-1}: 3207 (NH), 3089, 3022 (C-H $_{aromatic}$), 2923 ,2885 (C-H $_{aliphatic}$), 1662 (C=O) ,1647 (C=C $_{alkene}$) 1606 (C=N) , 1546 ,1446 (C=C $_{aromatic}$), 1255 (C-O) ;^{1}HNMR δ_H (ppm ,DMSO -d_6) :10.99 (1H ,s, N<u>H</u>), 8.79 -7.02 (8H ,m, Ar-<u>H</u>), 6.07-6.04(1H ,m,-C<u>H</u>=CH$_2$),5.45-5.28 (2H,d,CH=C<u>H</u>$_2$),4.65-4.64 (2H , d , O-C<u>H</u>$_2$), 2.36 (3H, s, N=C-C<u>H</u>$_3$);^{13}CNMR δ_c (ppm ,DMSO-d_6): 162(C=O), 157-114 (Ar-C) 149 (C=N), 68 (O-<u>C</u>H$_2$), 118 (-CH=<u>C</u>H$_2$), 15 (N=C-<u>C</u>H$_3$).

N-(1-(4-P-2-yn-1-yloxy) phenyl) ethylidene) isonicotinohydrazide (B3)

Black(61%),m.p 195-197ºC, halide: Propargyl chloride; FTIR υcm^{-1}:3359(C-H $_{acetylenic}$),3222 (NH), 3060 (C-H $_{aromatic}$), 2980 (C-H $_{aliphatic}$), 2121(C≡C),1664 (C=O) ,1602 (C=N) , 1577 ,1461 (C=C $_{aromatic}$), 1242 (C-O) ;^{1}HNMR δH (ppm ,DMSO -d_6) :10.54 (1H ,s, NH), 8.73 -7.09 (8H ,m, Ar-H), 4.92 (2H , d ,O-C<u>H</u>$_2$) ,3.6٩ -3.65 (1H,t, C≡C<u>H</u>), 2.52 (3H, s, N=C-C<u>H</u>$_3$);^{13}CNMR δc (ppm , DMSO-d_6): 162(C=O),161-115(Ar-C) ,150 (C=N),82 (-<u>C</u>≡CH),79 (-C≡<u>C</u>H), 56 (O-<u>C</u>H$_2$) ,14 (N=C-<u>C</u>H$_3$).

N-(1-(4-(Benzyloxy) phenyl) ethylidene) isonicotinohydrazide (B4)

Orange (69%), m.p 80-83ºC, halide: Benzyl chloride; FTIRυcm^{-1}: 3172(NH), 3064 ,3035 (C-H $_{aromatic}$), 2933 ,2873 (C-H $_{aliphatic}$), 1674 (C=O) ,1612 (C=N), 1591 ,1456 (C=C aromatic), 1247 (C-O).

N-(1-(4-((4-Bromobenzyl) oxy) phenyl) ethylidene) isonicotinohydrazide (B5)

Orange (69%), m.p 155-158ºC, halide: 4-Bromobenzylchloride; FTIRυcm^{-1}: 3290 (NH), 3026 (C-H $_{aromatic}$), 2974 ,2819 (C-H $_{aliphatic}$),1650 (C=O) ,1629 (C=N), 1598 ,1488 (C=C $_{aromatic}$), 1247 (C-O).

N-(1-(4-((4-nitrobenzyl) oxy) phenyl) ethylidene) isonicotinohydrazide (B6)

Yellow (80%),m.p 203-205ºC, halide : 4-Nitrobenzylechloride ;FTIR υcm^{-1}: 3105 (NH), 3078 (C-H $_{aromatic}$), 2952, 2883 (C-H $_{aliphatic}$), 1668 (C=O) ,1645 (C=N) , 1600, 1450 (C=C $_{aromatic}$), 1253 (C-O) ;^{1}HNMR δH (ppm ,DMSO -d$_6$) :10.99

(1H ,s, NH), 8.75 -3.78 (12H ,m, Ar-H), 5.57 (2H , s ,O-CH_2), 2.30 (3H, s, N=C-CH3) ;^{13}CNMR δc (ppm ,DMSO-d_6):162 (C=O), 59-115(Ar-C),147 (C=N), 67 (O-$\underline{C}H_2$),14 (N=C-$\underline{C}H_3$) .

4-(1-(2-Isonicotinoylhydrazineylidene) ethyl) phenyl benzoate (B7)

White (78%), m.p 167-169ºC, halide: Benzoyl chloride; FTIR υcm^{-1}: 3334(NH) ,3064 ,3006(C-H $_{aromatic}$),2889(C-H $_{aliphatic}$), 1735 (C=O ester),1676 (C=O) ,1637(C=N) , 1595 ,1452 (C=C $_{aromatic}$) ,1259 (C-O) ;^{1}HNMR δH (ppm ,DMSO -d_6) :10.88 (1H ,s, NH), 8.77 -7.47 (13H ,m, Ar-H), 2.63 (3H, s, N=C-$\underline{C}H_3$);^{13}CNMR δc (ppm ,DMSO-d_6): 164.7(O-C=O),164.1 (N-C=O),154 -122 (Ar-C), 151(C=N),27 (N=C-$\underline{C}H_3$) .

4-(1-(2-Isonicotinoylhydrazineylidene) ethyl) phenyl furan-2-carboxylate (B8)

White (81%), m.p 120-123ºC, halide:Furan-2-carbonyl chloride; FTIR υcm^{-1}: 3282 (NH) , 3078(C-H $_{aromatic}$),2929,2858(C-H $_{aliphatic}$), 1741 (C=O $_{ester}$),1679 (C=O $_{amide}$) ,1649 (C=N), 1602 ,1573 (C=C $_{aromatic}$),1209 (C-O) ;^{1}HNMR δH (ppm , DMSO -d_6) : 10.44 (1H ,s, NH), 8.79 -6.77 (11H ,m, Ar-H), 2.38 (3H, s, N=C-CH_3);^{13}CNMR δc (ppm ,DMSO-d_6):159 (O-C=O), 156 (N-C=O), 153-112 (Ar-C),149 ($\underline{C}$=N), 22 (N=C-$\underline{C}H_3$) .

4-(1-(2-Isonicotinoylhydrazineylidene) ethyl) phenyl benzenesulfonate (B9)

Pall yellow (56%), m.p 190-192ºC, halide: Benzenesulfonyl chloride; FTIR υcm^{-1}: 3182 (NH), 3002 (C-H $_{aromatic}$), 2914 ,2837 (C-H $_{aliphatic}$),1683 (C=O) ,1612(C=N), 1568 ,1490 (C=C $_{aromatic}$),1353,1159 (SO_2), 1274 (C-O).

4-(1-(2-Isonicotinoylhydrazineylidene) ethyl) phenyl-4-methylbenzenesulfonate (B10)

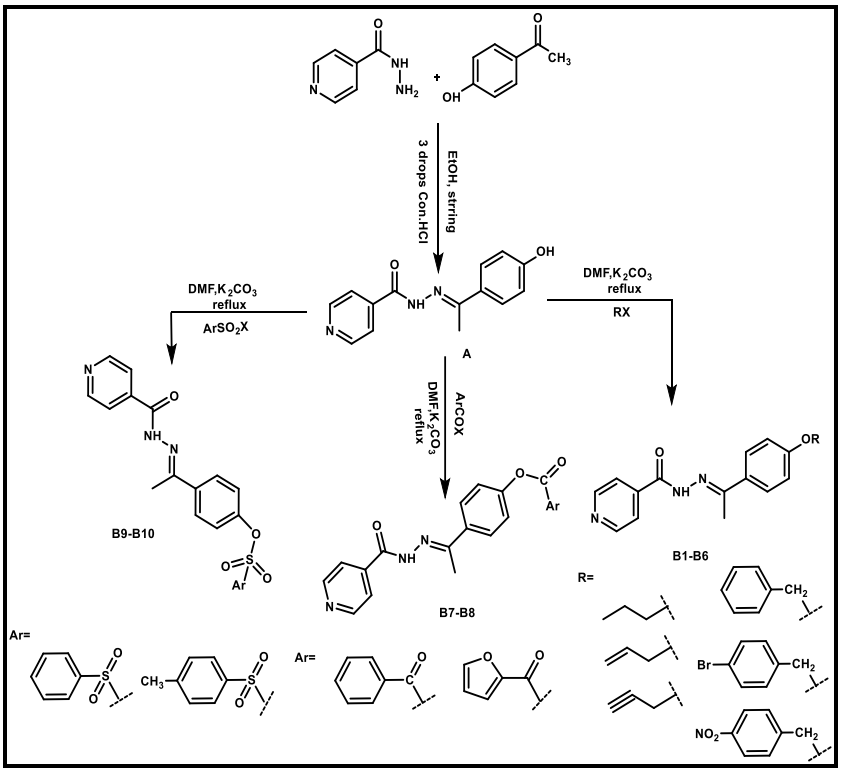
Off white (52%), m.p 150-152ºC, halide: 4-Methylbenzenesulfonyl chloride; FTIR υcm^{-1}: 3280 (NH), 3080,3043 (C-H $_{aromatic}$), 2977 ,2844 (C-H $_{aliphatic}$),1652 (C=O) ,1600(C=N), 1552 ,1463 (C=C $_{aromatic}$),1338,1143(SO_2), 1251 (C-O).

Antimicrobial activity [33]

The antimicrobial activity test of some prepared compounds was performed according to the Agar wells diffusion method. The prepared compounds were evaluated on four bacterial series, two positive and negative bacteria, as well as on a fungal series. Plates were prepared and sterilized, and 0.1 ml was taken from the isolated media and spread on the surface and left to dry for 10 minutes at 37 °C. After drying, 5 mm wells are made with a cork porer. After that, the compounds to be tested is added to the well and incubated at 37 °C for 18 hours. The inhibition zones of evaluated compounds on microorganisms were measured.

Results and Discussion

In this work, ether derivatives were prepared by the Williamson method by a nucleophilic substitution reaction of the hydroxy group in the Schiff base compound prepared in the first step with halides (alkyl, benzyl, benzoyl, sulfonyl). As shown in Scheme (1).



Scheme 1. synthesis of derivatives B1-B10

Schiff base compound (A) were synthesized via the nucleophilic addition reaction of iso nicotinic acid hydrazide with p-hydroxy acetophenone as shown in Scheme1 compound was diagnosed using FTIR, ^{1}HNMR and ^{13}CNMR, the FTIR results showed disappearance of (NH_2) absorption band of isonicotinic acid hydrazide while appearance of a new absorption band belonging to the (C=N) group at 1631cm^{-1}. ^{1}HNMR spectrum showed a signal at 10.9 ppm to the proton of the HN-C=O group and disappearance of singlet signal of (-NH_2) protons, signal at 9.8 ppm to the (OH) group[34].^{13}CNMR spectrum showed signal at 150 ppm to (C=N) group [35].

Derivatives B1-B10 were prepared from the nucleophilic substitution reaction of Schiff base compound A with different halides (alkyl halides, benzyl halides, benzoyl halides, sulfonyl halides). The compounds were identified using FTIR spectra, and some of them were identified by ^{1}HNMR,^{13}CNMR spectra. The FTIR spectrum showed absorbances of 1235-1322 cm^{-1} due to the new bond formed (-OR), the others of the absorptions were previously diagnosed. On the other hand, the spectrum of ^{1}HNMR showed the disappearance of the signal of the OH group and the appearance of signals at certain values, proving the attachment of the alkyl group coming from the different halides used in the reaction. The^{13}CNMR spectrum shows signals at (69,68,56 ,67ppm) due to CH_2O for compounds (B1, B2, B3,B6),The appearance of a signal at (159,164ppm) that belongs to the OC=O group of compounds (B7,B8) [36]. and the appearance of these signals is proof of the formation of derivatives. Other characterize bands have been identified previously.

Biological activity

On two Gram-positive bacteria (***Staphylococcus aureus and Staphylococcus epidermidis***) and two Gram-negative bacteria (***Escherichia coli and Klebsiella sp***.), the biological activity of several compounds produced from the reaction of hydrazine compound with different halides was evaluated. Table 1 shows the data for biological activity. The tested compounds (B1, B8, B9) showed inhibition against (***Staphylococcus aureus and Staphylococcus epidermidis***), while compound B5 show inhibition against only to (***Staphylococcus epidermidis***). on the other hand, all the tested compounds have no inhibition against (***Escherichia coli***) except compound B1. while the compounds have inhibition against to (***Klebsiella Sp.***) (B1, B5, B9, and B10). As for the activity of the prepared compounds against fungal, all the tested compounds showed inhibition against (***Candida albicans***), except for compound B2, which did not give inhibition [37].

Table 1. Result of Antimicrobial test of some prepared compounds.

Comp.100 µg/ml	Staphylococcus aureus	Staphylococcus epidermidis	Escherichia coli	Klebsiella Sp.	Candida albicans
B1	12	12	9	12	9
B2	-	-	-	-	-
B5	-	10	-	11	9
B8	10	11	-	-	8
B9	12	12	-	11	10
B10	-	-	-	9	10

Inhibition Zone :(-) no inhibition ;(6-10) weak;(11-18) moderate;(19-30) strong;(٣٠>) very strong.

Conclusion

In this study, the Williamson method was used to prepare different isoniazid derivatives (B1-B10), the derivatives showed good yields (25-88%) and high purification. Some of compounds showed inhibition zone against Gram-positive and negative bacteria, and some compounds did not show inhibition zone. But all the tested compounds showed inhibition zone against fungal Candida albicans except compound B2.

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Conflicts of Interest

The authors declare that they have no conflict of interest.

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Ethics Statements

There is no need for an ethics committee to approve the research that is synthesized in the lab and evaluated. this declared from authors.

Author Contribution

The author, Oday Hadi Raoof Al-jeilawi, proposed the experiments. The author, Wasan Kareem Damdoom, synthesized compounds and studied their prepared methods. Both authors participated in data processing, contributed to manuscript preparation, and participated in the discussions and share all problems in the manuscript together and dissolve it

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تحضير وتشخيص ودراسة النشاط المضاد للميكروبات لمشتقات الأيزونيازيد

وسن كريم دمدوم[1] وعدي هادي رؤوف الجيلاوي[2]

[1] قسم الكيمياء الصيدلانية، كلية الصيدلة، جامعة ذي قار، ذي قار، العراق.

[2] قسم الكيمياء، كلية العلوم، جامعة بغداد، بغداد، العراق.

الخلاصة

في هذه الدراسة تم تحضير سلسلة من المركبات (B1-B10) التي تحتوي على الاصرة (-OR) من التفاعل التعويضي النيوكليوفيلي لمركب قاعدة شيف الذي يحتوي على مجموعة (OH) مع هاليدات مختلفة (هاليدات الالكيل، هاليدات البنزيل، هاليدات البنزويل، هاليدات السلفونيل) باستخدام طريقة ويليمسون. تم تشخيص المركبات المحضرة بواسطةFTIR ، ^{1}HNMR، و^{13}CNMR، ثم تم تقييم فعاليتها ضد البكتيريا جرام الموجبة والسالبة والفطريات ومقارنتها مع مرجعين قياسيين(Clotrimazole ، Ciprofloxacin) بشكل عام أظهرت بعض المركبات المحضرة منطقة تثبيط ضد البكتريا الموجبة والسالبة لصبغة جرام، ولم تظهر بعض المركبات منطقة تثبيط بينما أظهر المركب B1 نشاط تثبيطي متوسط ضد جميع البكتريا المختبرة مقارنة بالمشتقات الأخرى. لكن جميع المركبات التي تم اختبارها أظهرت منطقة تثبيط ضد فطر Candida albicans ماعدا المركب B2 لم يكن له أي تأثير.

الكلمات المفتاحية: النشاط المضاد للميكروبات، الهاليدات، حامض الايزونيكوتنيك هايدرازايد, التعويض النيوكيلوفيلي, ويليمسون.