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Synthesis and Characterization of New Oxazolidin-4-one Derivatives via the Reaction of Various Some Imines with Glycolic Acid

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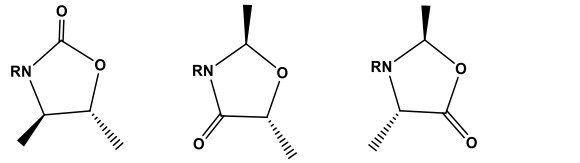
Imines,
Glycolic Acid.

ABSTRACT

New derivatives of 2,3-disubstituted- oxazolidine-4-one were synthesized by cycloaddition reaction of glycolic acid to various imines in anhydrous 1,4-dioxane under dry and reflux conditions. Imines were synthesized by acid–catalyzed thermal condensation of the amino group of aromatic amine and phenylhydrazines with the carbonyl group of aromatic aldehydes and ketones in absolute ethanol. The products were identified by C.H.N content FT-IR and ^{1}HNMR spectra.

1- Introduction:

Oxazolidines are a class of five-membered ring heterocyclic compounds, containing two heteroatoms, oxygen and nitrogen in position 1and 2 in the cyclopentane ring respectively and carbonyl group located at 2,4 or 5 positions with respect the oxygen atom (position 1) and other substituents, (figure1).(1)



1,3-Oxazolidine -2-one 1,3-Oxazoline -4-one 1,3-Oxazolidine -5-one

Figure 1: Chemical structures of oxazolidinones

Oxazolidinones are potent bioactive compounds, and versatile chiral auxiliaries and key intermediates for organic and bioorganic, dyes,agrochemicals and natural products synthesis . They possess a wide area of bioactivities and have been used as :antibacterial, antimicrobial, anticonvulsant, antitumor, antiviral, anti-inflammatory, psychotropic, cardiotonic, antifungal, antihyperglycemic, analagesic, antitbercular, anticoagulant, antidepressant, phospholipase inhibitor, agriculture fungicide,CNS depressants, antithyoid, antiblastic and urinary tract infection agents . (2-7)

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Oxazolidinones, Dup-721 and DuP-105 were discovered by DuPont chemists and scientists and admitted as new antiracial drugs in 1978, (Figure 2) then they were rejected because of their high toxicity . Latterly two new oxazolidinones, Linzolid and Eperezolid (Figure 3) were synthesized and have been approved as potent antibacterial drugs by the Food and Drug Admiration of the United States of America (FDA,USA) in May 2000 under trade name "Zyvox" . The synthetic methods and the chemistry of the key intermediates of these drugs and their analogues in addition to their biological activities have been thoroughly and extensively studied .(8)

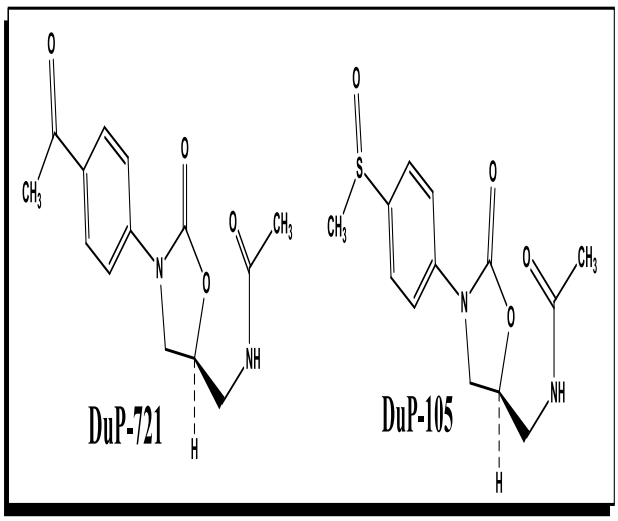


Figure 2: Chemical structures of DuP-721 and DuP-105

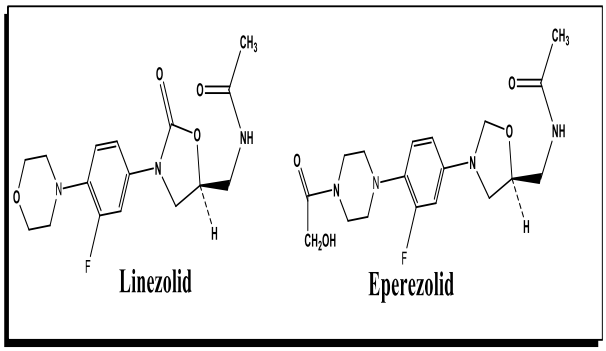


Figure 3:Chemical structures of Linezolid an Eperezolid

The structures biological and pharmacological behaviors, structure - reactivity relationship (SAR) and synthetic methods and precursors, bacteriostatic versus nature of various oxazolidinone drugs such as; Dup-721, U-100592, U100766, Linezolid and thioanalogues (9,10), Ranbenzolidine –RBx7644, PNU-288034, TR-701.Torezolid, Radezolid, DA-7218, MRX-1,PNU-100480, RX-741, Rivaroxaban, Furazolidon, AZD2563, triazol-oxazolidinones,Toloxatone, Goitrin, Famoxadone, Pentizidone, Bay5850, Furaltadone RWJ-416457 and Zolitiptan (ZOL) have been covered by detailed updated review . (11-13)

synthetic of oxazolidinones mainly based on the reactions of commercially available materials such amino acid, amino alcohols, Ethyl carbonate, triphosgene, Urea . azidochloro carbonates, chiral aziridines N-aryl carbamates imines, chloroacetic acid and glycolic acid .These reagents have been used to synthesize various oxazoline -2-one and oxazolidine -5-one derivatives in efficient yield . [14-17]

2. Experimental

2.1. Instrumentation

Melting points were determined in open capillary tubes and are uncorrected. The FT-IR spectra were recorded, an Infrared Spectrophotometer Model Tensor 27 Bruker Co., Germany. The 1HNMR spectra were recorded on a Bruker Ultershield 300MHz NMR Spectrometer, Co., Germany, in DMSO- d6 as a solvent and the chemical shifts are reported as δ values in part per million (ppm) relative to TMS δ=0, as internal standard. The C.H.N. elemental analysis were performed by Euro EA Elemental Analyzer .

2.2 General procedure for synthesis of Schiff's bases 3(a-i).

An equimolar mixture of (18.8 mmole) of aromatic aldehydes (1) and the primary aromatic amines (2) in presence of a few drops of glacial acetic acid as a catalyst in absolute ethanol (40 ml) was refluxed for (2-3) hrs. with continuous stirring The reaction mixture was allowed to cool down in an ice bath, where by a crystalline solid product was separating during cooling. The solid product was filtered off, washed with distilled water, dried and recrystallized from absolute ethanol. The structucture, IR characteristic absorption, yield %, melting point, colors, and the reaction time are given in table (1).

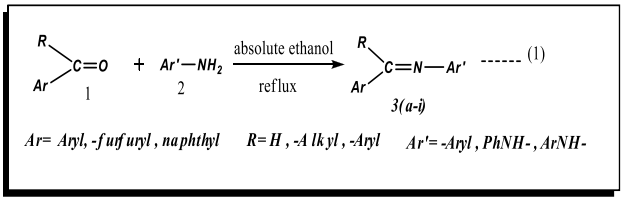
2.3 *General procedure for synthesis of* oxazolidin-4-ones *4(a-i).*

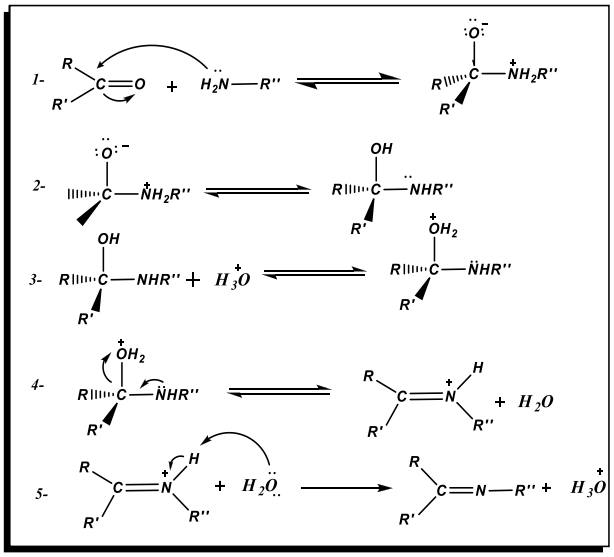
In a well dried 100-ml round- bottom flask equipped with condenser and anhydrous calcium chloride tube guard, a mixture of equimolar amount (13.3mmol) of Schiff's bases 3(a-i) and glycolic acid in anhydrous 1,4-dioxan (50ml) was refluxed for (5-7 hrs). The reaction mixture was allowed to cool down in ice bath, whereupon a crystalline solid product was separating out during cooling. The product was filtered off, washed with distilled water, dried and recrystallized from 1,4- dioxan. The chemical formula, molecular weights, C.H.N %, yield%, melting points, colors, are given in table (2).

3. Result and Discussion

In this paper, the synthesis of 2,3-disubstituted-1,3-oxazolidinone-4-one derivatives from the reaction of glycolic acid as electrophile and various imines (Schiff's bases) as mild nucleophiles in anhydrous 1,4 - dioxane via (3-2) polar cycloaddition is discussed.

Synthesis of imines (Schiff's bases) was achieved by acid-catalyzed thermal condensation reaction of aromatic benzaldehyde and ketones with aromatic primary amines and phenyl hydrazines according to well know literature procedures . [18] The mechanism of imines formation is thoroughly discussed and established by literatures. [19-21]

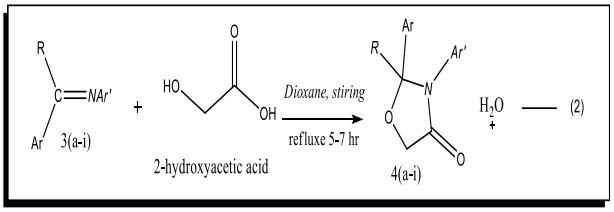




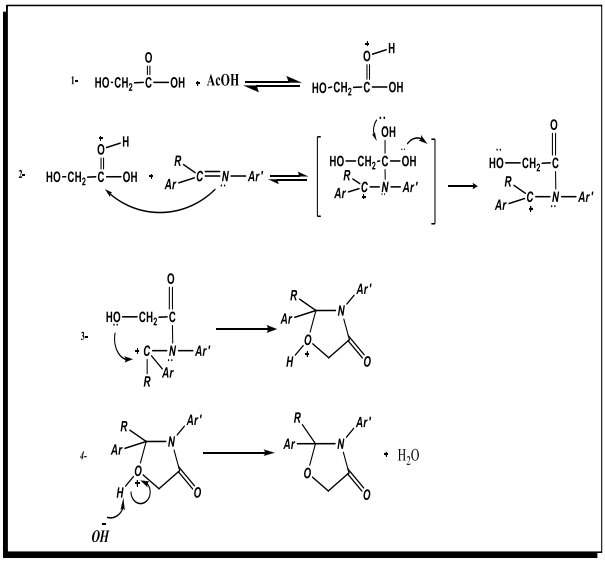
Mechanism of imine formation:Scheme-1

The structure of the synthesized imines were confirmed by their melting points and FTIR spectra,compared with those of the starting compounds . The FTIR spectra of the obtained imines showed significant absorption frequencies of azomethine group (C=N) at (1590-1623) cm^{-1}, and the disappearance of those of the carbonyl groups (C=O) at (1705-1745) cm^{-1} and the the primary amino group ($-NH_2$) at (3300-3500) cm^{-1}, in addition to the appearance of the absorption frequencies of the substituted groups in the precursors.

Imines (Schiff's bases) were reacted with glycolic acid in anhydrous 1,4- dioxane under dry atmosphere and by using calcium chloride tube guard to prevent moisture and reflux.



It is of great importance to understand how the cycloaddition reaction takes place, therefor a plausible mechanism may be suggested as in follow :

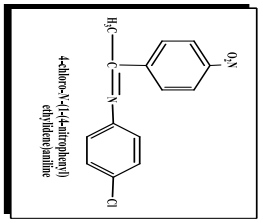
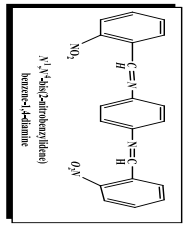
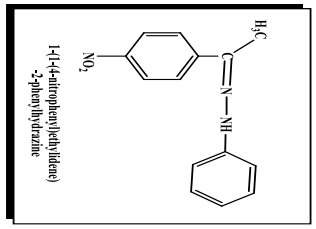
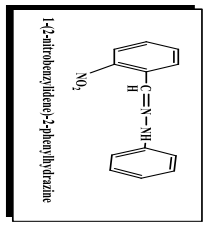


Scheme-2: Mechanism of oxazolidin-4-one formation

Hence, it is inferred that the reaction accrued via addition of the electrophilic, protonated glycolic acid to azomethine nucleophilic moiety by attack of the loan pair of electrons of nitrogen atom on the carbonyl carbon atom to give a dipolar reactive intermediate . Intramolecular cyclic interaction of the resulting intermediate leads to the formation of the protonated oxazolidine -4-one which then deprotonated by the water molecule to give the target molecule .

The products were identified by their melting points compared with those of the reactants, and their FTIR and ^{1}HNMR spectra C.H.N% compared with the calculated percentage in each compound table (2&3) . The FTIR spectra showed significant absorption bands attributed to the stretching vibration of the lactam group at (1590-1684), CH_2 at (2856-2895) $cm^{-1}$and (C-O-C) group at (1158-1384) in addition to the fundamental groups of the substituents which is indicative of formation of the oxazolidione ring , table (3) . In addition, the ^{1}HNMR spectra of the products showed significal signals corresponding to the positions of each proton in the specific structure of each individual compound as given in table (3). Moreover the chemical structure of the products were confirmed by C.H.N content compared with the calculated values of the depicted structures .

Table (1): The structural formula, IR characteristic absorption, yield, melting point, colors, and the reaction time of Schiff's Bases 3(a-j).

Comp.	3a	3b	3c	3d
Molecular *Structure*				
I.R Characteristic Absorption Frequencies, Cm^{-1}	*2963 v_s – CH_3, 3047 v_s C-H Aromatic, 1672 Imine vs C=N, 1579 v_s C=C Aromatic, 1296 v_s C-N,777 δ_w N-H, 674 -H out-of-plane*	*3049 vs C-H Aromatic,1691 Imine vs C=N, 1606 mine vs C=N, 1501 -NO_2, 1521 vs C=C Aromatic, 1259 vs C-N, 1343 C-H bending , 854 -H out-of-plane*	*29643 v_s – CH_3, 311 v_s N-H, 3109 v_s C-H Aromatic, 1691 Imine v_s C=N, 1521 C=C Aromatic, 1242v_s C-N, 13342, v_s N-H, 854 -H out of-plane*	*3429 v_s N-H, 3075 v_s C-H Aromatic,2978 v_s C-H Aliphatic , 1668 Imine v_s C=N, 1585 v_s C=C Aromatic, 1270v_s C-N 889 H out of-plane.*
m.p C°	*122*	*139-140*	*120-123*	*185-188*
Yield %	*72*	62	62	75
Reaction Time (hr.)	*2*	*3*	*3*	*2*
Colour	*white*	*white*	*Red*	*Dark Red*

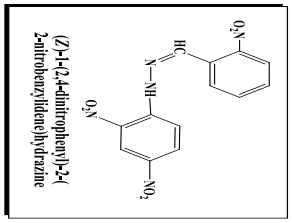
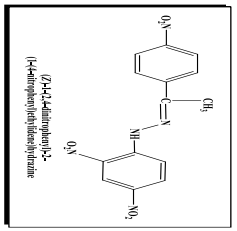
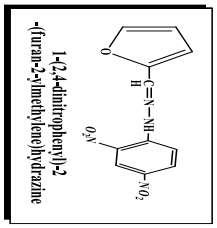
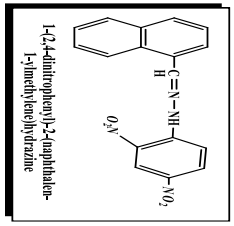
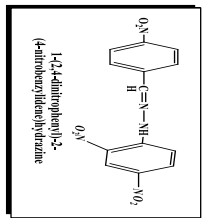
Comp.	3E	3F	3g	3h	3i
Molecular *Structure*					
I.R Characteristic Absorption Frequencies, Cm^{-1}	*3294 v_s N-H, 3034 v_s C-H Aromatic, 1601 Imine v_s C=N, 1572 v_s C=C Aromatic, 1253 v_s C-N, 1358 v_s N-H, 857 H out-of-plane*	*2943 v_s – CH_3, 3276 v_s N-H, 3107 v_s C-H Aromatic, 1691 Imine v_s C=N, 1590 v_s C=C Aromatic,1267 v_s C-N,834-H out-of-plane*	*3278 v_s N-H, 3068 v_s C-H Aromatic1674 v_s Imine C=N, 1574 v_s C=C Aromatic, 1265 v_s C-N,1340 v_s N-H 835 H out-of-plane*	*3279 v_s N-H, 3125 v_s C-H Aromatic, 1615 v_s Imine C=N, 1582 v_s C=C Aromatic, 1265 v_s C-N, 1323 v_s N-H, 834 H out-of-plane*	3279 v_s N-H, 3125 v_s C-H Aromatic, 1615 Imine v_s C=N,1582 v_s C=C Aromatic, 1220 v_s C-N, 1324 v_s N-H, 832 *H out-of-plane*
177-197	*155-157*	*180-183*	*180-183*	*167-170*
63	84	75	66	87
2	*2*	*3*	*4*	*6*
Red	*Red*	*Orange*	*white*	*Red*

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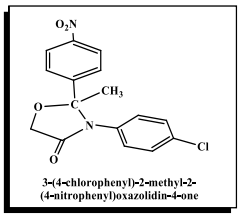
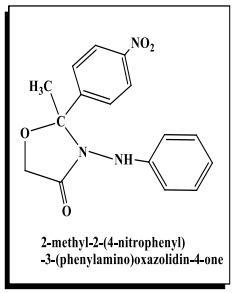
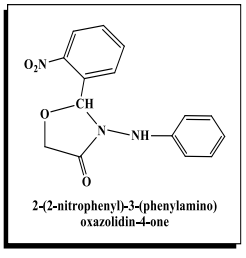
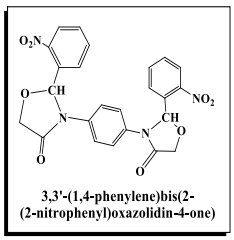
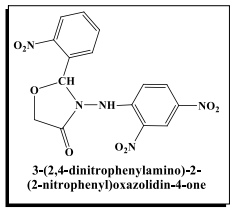
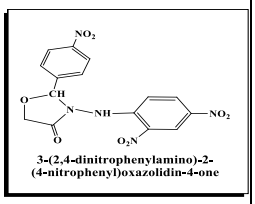
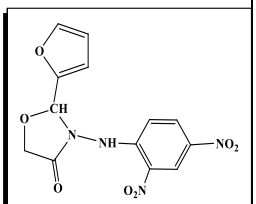
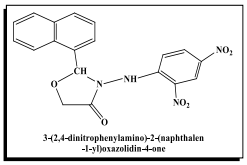
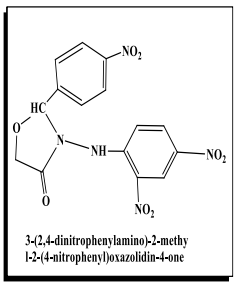
Table (2): The chemical formula, molecular weights, C.H.N %, yield, melting points, colors, and the reaction time, oxazolidin-4-one

Code	4a	4b	4c	4d	4e	4f	4g	4h	4i
Chemical Formula	$C_{16}H_{13}Cl\,N_2O_4$	$C_{16}H_{15}Cl\,N_3O_4$	$C_{15}H_{13}ClN_3O_4$	$C_{24}H_{18}ClN_4O_8$	$C_{15}H_{11}N_5O_8$	$C_{15}H_{11}N_5O_8$	$C_{13}H_{10}N_4O_7$	$C_{19}H_{14}N_4O_6$	$C_{15}H_{11}N_5O_8$
M.wt g\mole	332.06	313.11	299.09	490.42	389.06	389.06	334.05	394.09	389.06
C.H.N Cal.(Found) C%	57.75 (58.04)	61.34 (60.78)	60.20 (59.72)	58.78 (59.27)	46.28 (45.82)	46.28 (45.63)	46.71 (47.07)	57.87 (58.07)	46.65 (45.99)
H%	3.94 (4.13)	4.83 (5.05)	4.38 (4.02)	3.70 (4.02)	2.85 (3.03)	2.85 (2.77)	3.03 (2.93)	3.58 (4.27)	2.85 (3.03)
N%	8.42 (7.79)	13.41 (12.83)	14.04 (13.62)	11.42 (11.29)	17.99 (18.03)	17.99 (18.08)	16.76 (17.02)	14.21 (13.66)	17.99 (18.05)
Yield	65%	88%	65%	77%	82%	91%	90%	80%	80%
M.P	178- 180	123-125	134-137	180-183	100-102	160-162	105-107	90-93	203-206
Color	white	Red	Red	Green	Red	Red	white	white	yellow
Reaction time	6 hr.	7 hr.	4 hr.	6hr.	7 hr.	6hr.	7hr.	7 hr.	6hr.

Table 3: Molecular structure, IR Characteristic Absorption, Chemical Shift δ ppm of oxazolidin-4-one 4(a-i).

Comp. No.	Molecular structure	*I.R Characteristic Absorption Frequencies, Cm^{-1}*	Chemical Shift ppm
4a	 3-(4-chlorophenyl)-2-methyl-2-(4-nitrophenyl)oxazolidin-4-one	*2962 ν_s – CH_3, 2847 ν_s CH_2, 1274 ν_sC-O 3042 ν_s C-H Aromatic, 1643ν_s C=O, 1529 ν_s C=C Aromatic, 1374C-H bending, 823 -H out of-plane*	2.68(s, 3H-CH_3) 3.35 (s,2H-CH_2)7.94-8.60(m, 8H Aromatic Protons)
4b	 2-methyl-2-(4-nitrophenyl) -3-(phenylamino)oxazolidin-4-one	*2938 ν_s CH_3,2856 ν_s CH_2, 1127 ν_sC-O, 3267 ν_s N-H 3098 ν_s C-H Aromatic, 1690 ν_s C=O, 1567 ν_s C=C Aromatic, 1298 ν_s C-N, 1374 δ_w N-H,823 H out of-plane-*	2.73(br,s 3H-CH_3)3.57(s, 2H-CH_2)7.47-9.57(9H Aromatic Protons)11.61-11.94(1H-NH)
4c	 2-(2-nitrophenyl)-3-(phenylamino) oxazolidin-4-one	*2829 ν_s CH_2, 1252 ν_sC-O, 3277.27 ν_s N-H 3091.30 ν_s C-H Aromatic,1601.79 ν_s C=O, 1510.57 ν_s C=C Aromatic, 1263.14 ν_s C-N, 1323.48 C-H bending , 819.57 -H out of-plane*	3.57(s,2H- CH_2) 6.76 (s, 1H-CH) 7.01-8.94(9H Aromatic Protons 11.67-12.75 (1H-NH)

4d	 3,3'-(1,4-phenylene)bis(2-(2-nitrophenyl)oxazolidin-4-one)	***2829 ν_s CH_2, 1283 ν_sC-O, 3294.94 ν_s N-H, 3091.06 ν_s C-H Aromatic, 1611.94 ν_s C=O, 1505.57 ν_s C=C Aromatic, 1325.25 C-H bending , 852.52 -H out of-plane***	**3.57(br,s,4 H- CH_2) 6.69(s,2 H-CH) 7.02-8.97 (12H Aromatic Protons)**
4E	 3-(2,4-dinitrophenylamino)-2-(2-nitrophenyl)oxazolidin-4-one	***2837 ν_s CH_2, 12473 ν_sC-O, 278.79 ν_s N-H, 3037.65 ν_s C-H Aromatic, 1600.86 ν_s C=O, 1572.50 ν_s C=C Aromatic, 1253.07 ν_s C-N,1359.07 C-H bending, 858.12 -H out of-plane.***	**3.57(s,2H –CH_2) 6.69(s,1H –CH) 7.02-8.97 (7H Aromatic Protons) 11.69 - 12.77(s,1H- NH)**
4F	 3-(2,4-dinitrophenylamino)-2-(4-nitrophenyl)oxazolidin-4-one	***2857 ν_s CH_2, 1164 ν_sC-O, 3274.16 ν_s N-H, 3059.98 ν_s C-H Aromatic, 1617.29 ν_s C=O, 1584.00 ν_s C=C Aromatic, 1222.03 ν_s C-N, 1313.63 C-H bending, 884 H out of-plane***	**3.57(br,s,2H-CH_2) 6.69(s, 1H-CH) 7.01-9.84 (7H Aromatic Protons), 11.67-11.67(1H-NH)**
4g	 3-(2,4-dinitrophenylamino)-2-(furan-2-yl)oxazolidin-4-one	***2827 ν_s CH_2, 1183 ν_sC-O, 3268.49 ν_s N-H,3113.57 ν_s C-H Aromatic, 1616.54 ν_s C=O, 1502.00 C=C Aromatic, 1311.17 C-H bending ν_s N-H, 830.17 -H out of-plane .***	----------

4h	 3-(2,4-dinitrophenylamino)-2-(naphthalen-1-yl)oxazolidin-4-one	***2859 ν_s CH_2,1284 ν_sC-O, 3109.02 ν_s C-H Aromatic, 1691.64 ν_s C=O, 1524.87 C=C Aromatic 1384.08 C-H bending 85.15 H out of-plane***	----------
4i	 3-(2,4-dinitrophenylamino)-2-methyl-2-(4-nitrophenyl)oxazolidin-4-one	***2966 ν_s CH_3, 2848 ν_s CH_2,1183 ν_sC-O 3274.62 ν_s- NH 3109.02 ν_s C-H Aromatic, 1691.64 ν_s C=O, 1524.11 ν_s C=C Aromatic, 1259.52 ν_s C-N, 788.15 ν_s N-H, 855.15 H out of-plane***	**3.33(s, 3H-CH_3) 6.82 (s, 1H-CH.)7.11-8.25 (7H Aromatic Protons)11.63-10.89 (1H-NH)**

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تحضير وتشخيص مشتقات اوكسازوليدين -4- اون جديده من تفاعل حامض الكلايكول مع بعض الايمينات

عبيد حسن عبد هاجر حسام

الخلاصة

حضرت مشتقات جديده من اوكسازوليدين -4-اون المعوضة في الموقع 2-,3- من تفاعل الاضافة الحلقية الحامض الكلايكول و الايمينات المختلفة بتصعيدها في ظروف جافه في مذيب دايوكسان الجاف . وقد حضرت الايمينات بالتكثيف الحراري المحفز بالحامض لمجموعة الامينية في الامينات الاروماتية و الهايدرازينات مع مجموعة الكاربونيل في الالديهايدات والكيتونات الاروماتية في الكحول الاثيلي المطلق .وقد شخصت النواتج من خلال درجات الانصهار ونسبه C.H.N% المئوية والاطياف FTIR و^{1}HNMR لهذه المركبات .