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Synthesis and Characterization of Novel Oxazolidinones Via Schiff Base Reactions

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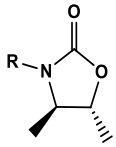
ABSTRACT

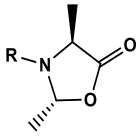
A number of new novel 2,3-disubstituted-1,3-oxazolidine-5-one derivatives were synthesized by the reaction of Schiff's bases with chloroacetic acid in dry banzene with high yields. Schiff bases were synthesized by the reaction of heteroaromatic aldehydes or ketones with primary heterocyclic amines. The products were identified by their melting points and spectral features (FT-IR and UV-Vis-spectra and 1HNMR spectra).

Introduction

Oxazolidinones are a new class of synthetic compounds of pharmacological applications(1-2), antimicrobial(3),antimicrobacterials(4), ntibacterial(5), antibiotics activities(6), an intermediates in organic synthesis(7) and prepartion of natural products(8). Oxazolidinones molecules are heterocyclic five-membered ring systems consist of nitrogen and oxygen atoms with carbonyl group located in the 2- or 5-position and substituted in other positions(9).



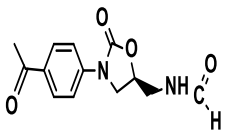
1,3-Oxazolidine-2-one



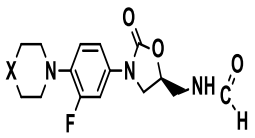
1,3-Oxazolidine-5-one

The first synthrsis of oxazolidinone antimicrobial (DuP-721) was reported in 1978,but it was ignored due to it's toxicity(10). However, numerous new oxazolidinones have been synthesized and several new synthetic methods have been reported(11-12).

As a result of increased need to new antimicrobical agents due to increased bacterial resistance to β-lactam antibiotics, macrolides, quinolones N-[[(SS)-3-(4-amino-3-fluoro phenyl)-2-oxa-1,3-oxazolidine-5yl]-methyl]acetamide and vancomycine N-[[(SS)-3-(4-amino-3-fluorophenyl) -2-oxa-1,3-oxazolidine-5yl]- methyl] hydroxyl acetamide, two new oxazolidinones,Linezolid and Eperezolid have been developed and approved by US FDA in 2000(13-14).



DuP-721



Linezolid X=O

Eperezolid X= N–C(=O)–CH_2OH

The microbical activities and the mechanism of action are thoroughly explained,which show that oxazolidinones inhibiting the very early steps in bacterial protein synthesis(15).

Enantiomerically pure N-(R)-α-methylbenzyl-4(R)-(chloromethyl)-1,3-oxazolidine-2-one were synthesized in one step and high yields from various aziridine-2-methanol by intramolecular cyclization with phosgene(16).And a series of 1,3-oxazolidinone derivatives bearing the five-membered ring nitrogen heterocycles (triazolyl and imidazolyl moieties) were synthesized from the reaction of the key intermediates, 5-methane sulphonate oxazolidinone with acetylenic

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compounds and 5-methylazido oxazolidine or imidazole in presence of NaH(17).

Asymmetric synthesis of N-aryl-(5R)-hydroxymethyl-1,3-oxazolidine-5-one was obtained by alkylation of commercially available (R)-glcidal butyrate with N-lithio-N-aryl carbamates generated by deprotonation of aryl carbamate with n-butyl lithium at -78°C(18).A combination between two substructures into asingle entity to synthesize new oxazolidinone drugs was achieved by converting the key intermediate,N-[[(SS)-3-(4-amino-3-flouro phenyl)-2-oxo-1,3-oxazolidine-5-yl]-methyl]acetamide into the corresponding sulphamide,carboxylic amide and Schiff bases(19). A series of novel N-substituted oxazolidinone phosphonic acid derivatives synthesized efficiently from commercially available L-serine(21).The key intermediate (S)-4-(4-hydroxybenzyl)-1,3-oxazolidine-5-one was synthesized from commercially available L-tyrosine and triphosgen(BTC,Cl3CO)2CO) which is then attached to Merrifield-Cl and Wang-Cl resins by the hydroxyl group of phenol to give new oxazolidinone drugs(20).The hydroxyl group of the 5-(hydroxymethyl)-1,3-oxazolidine-2-one was converted into other derivatives by introducing mesyl or azido groups to obtain new drugs(22).Further works were conducted on synthesis of new Linezolid derivatives by using the key precursor 5-methylazido-3-aryl-1,3-oxazolidine-2-one and commercially available chemicals(23).

Experimental Part

All solvents were distilled and dried on anhydrous $CaCl_2$ immeditely prior to use,and all non-equeous reaction were conducted in dried glassware, the reflux condenser was equipped with anhydrous $CaCl_2$ guard tube .Schiff bases and chloroacetic acid were purified before use.

Melting points were recorded on Electrothermal Melting Point Apparatus (uncorrected).FT-IR spectra were recorded at room temperature from 4000cm^{-1} to 400cm^{-1} with KBr disc on Infrared Spectrophotometer Model Tensor 27 Bruker Co., Germany ,and UV-Vis. spectra were recorded at room temperature from 200nm to 400 nm in absolute ethanol on Shimadzu Double-Beam Spectrophotometer UV-210A .The ^{1}H-NMR spectra were recorded on Bruker Ac-200MHz spectrometer in Jordan.

General Procedure for Synthesis of Schiff bases (K_1-K_9).

A mixture of heterocyclic aldehydes (0.02mol),heterocyclic amine (0.02mol),and trace of glacial acetic acid in absolute ethanol(25ml) was placed in a (100ml)round-bottom flask equipped with condenser and stirbar .The mixture was allowed to react at reflux temperature for 5hr,then allowed to cool down to room temperature,where by a crystalline solid was seprated out.The solid product was washed with 5%HCl solution and then water and recrystallized twice form ethanol.The structural formulas, names, melting points, colours ,and percentage yields for the synthesized Schiff bases are given in table1.

General Procedure for Synthesis of 1,3-Oxazolidinones(A_1-A_9).

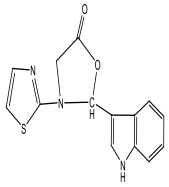
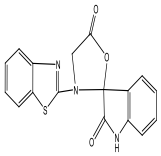
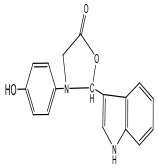
In well dried 100-ml round-bottom flask equipped with condenser and anhydrous calicium chloride tube guard amixture of Schiff bases(0.01mol) and chloroacetic acid (0.01mol) dissolved in(20ml) of benzene, the reaction mixture was refluxed for 5hr and left to stad for 24hr,then solid product was precipitated. The solid product was filtered off and recrystallized form ethanol.The structural formulas,names,melting points ,colours, and percentage yields for the synthesized 1,3-oxazolidinones are given in table2.

Table1. Some Physical and experimental properties of Schiff bases (K1-K9).

Comp. No.	Structural formula	Name	Yield %	m.p. °C	Colour
K1		3-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-ylimino)indolin-2-one	91	152-154	Bright red
K2		3-(pyridin-2-ylimino)indolin-2-one	75	185-194	Red
K3		(E)-3-(thiazol-2-ylimino)indolin-2-one	84	186-192	Dark red
K4		4-(furan-3-ylmethyleneamino)-1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-one	91	212-215	Bright yellow
K5		4-(benzylideneamino) pyrimidin-2(1H)-one	66	260-263.5	White
K6		(E)-3-(naphthalen-1-ylimino)indolin-2-one	80	247.3-250	Red
K7		N-((1H-indol-3-yl)methylene)thiazol-2-amine	68	196-199	Nutty
K8		3-(benzo[d]thiazol-2-ylimino)indolin-	78	139	Dark red
K9		4-((1H-indol-3-yl)methyleneamino)phenol	62	195-198.2	Pale black

Table2. Some Physical and experimental properties of 1,3-oxazolidinone (A1-A9).

Comp. No.	Structural formula	Name	Yield %	m.p. °C	Colour
A1		3'-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)spiro[indoline-3,2'-oxazolidine]-2,5'-dione	91	160-162	Pale orange
A2		3'-(pyridin-2-yl)spiro[indoline-3,2'-oxazolidine]-2,5'-dione	75	196	Dark orange
A3		3'-(thiazol-2-yl)spiro[indoline-3,2'-oxazolidine]-2,5'-dione	84	198-200	Pale red
A4		3-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-2-(furan-3-yl)oxazolidin-5-one	88	164-166	Nutty
A5		3-(2-oxo-1,2-dihydropyrimidin-4-yl)-2-phenyloxazolidin-5-one	82	256-258	White
A6		3'-(naphthalen-1-yl)spiro[indoline-3,2'-oxazolidine]-2,5'-dione	80	250	Orange

A7		**2-(1H-indol-3-yl)-3-(thiazol-2-yl)oxazolidin-5-one**	**78**	**194-196**	**Brown**
A8		**3'-(benzo[d]thiazol-2-yl)spiro[indoline-3,2'-oxazolidine]-2,5'-dione**	**65**	**116**	**While**
A9		**3-(4-hydroxyphenyl)-2-(1H-indol-3-yl)oxazolidin-5-one**	**68**	**180-182**	**Yellow**

Resutls and Discussion

In this work the synthesis of novel 2,3-disubstituted-1,3-oxazolidin-5-ones by direct reaction of several Schiff bases with chloro acetic acid in dry benzene is repoted.

Schiff bases were synthesized from commercially available aldehydes, ketones and primary amines and identified by their melting points, FT-IR and UV-Vis.spectra, tables,(1),(3) and (5). Formation of the products were followed up by the disappearance of both (C=O) absorption bands at (1670-1700) cm-1 and (-NH2) absorption bands at (3340-3420)cm-1 in the FT-IR spectra of starting materials and the appearance of azomethine (C=N-) group at (1612-1660)cm-1 in the FT-IR spectra of the resulting imines. The UV-Vis. Spectra of these imines show absorption maxima at (250-430)nm owing to the electronic transfers π-π* and n-π* characteristic of the structures of the synthesized imines (K1-K9).

The synthesis of novel 2,3-disubstituted-1,3-oxazolidin-5-ones were achieved by the reaction of imines and chloroacetic acid and the resulling products were identified by their melting points, FT-IR and UV-Vis.spectra, tables,(2),(4) and (6). The FT-IR spectra of the products show characteristic absorption band at (1633-1749)cm-1 indicative of C=O (lactone) bond formation beside the characteristic bands of the residual groups in the structure, table,(6). The UV-Vis.spectra show absorption maxima at (205-455)nm owing to the electronic transfers π-π* and n-π* characteristic of the structure of the synthesized 1,3-oxazolidinones, table,(4). The 1HNMR spectrum of compound A4 in D6-dimethyl sulphoxide shows chemical Shiffs,δ(ppm) at:8.22-10.07 (3H,furan ring), 6.64-7.85 (5H,phenyl), 4.23,3.65(1H,2H,oxazolidinone ring), 3.14 (3H,N-CH3), 2.01 (3H,=C-CH3), and spectrum of compound A7 shows chemical shiffs,δ(ppm) at:6.82-10.41(6H,Arom. Het.), 3.36,2.4 (1H,2H,oxazolidinone ring), 2.20 (1H,-N-H).

It may be concluded that the reaction takes place via concerted dipolar cycloaddition mechanism as in the following reaction scheme(24):

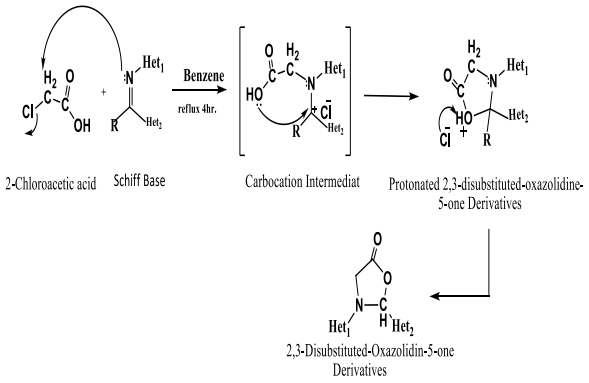


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Table 5: The UV-Visible absorption of the prepared Imines (K_1-K_2)

Comp Cod.	λmax/mn absorbance				
K1	295.0	310.0	415.0	-	-
K2	220.0	250.0	300.0	420.0	-
K3	225.0	300.0	420.0	-	-
K5	205.0	280.0	310.0	-	-
K6	205.0	285.0	305.0	430.0	-
K7	235.0	280.0	325.0	-	-
K8	225.0	250.0	300.0	420.0	-
K9	200.0	255.0	310.0	-	-

Table 6: The UV-Visible absorption of the prepared 2,3-disubstituted-1,3-oxazolidin-5-one (A1-A2)

Comp Cod.	λmax/mn absorbance				
A1	205.5	-	225.0	250.0	310.0
A2	225.0	240.0	250.0	305.0	420.0
A4	210.0	-	270.0	350.0	-
A7	220.0	-	280.0	300.0	330.0
A8	220.0	240.0	250.0	295.0	455.0
A9	235.0	-	250.0	270.0	320.0

Tab 3:The majer FT-IR absorptions bands (cm^{-1}) of (K_1-K_9) the prepared Imines

Comp. Code	K_1	K2	K_3	K_4	K_5	K_6	K_7	K_8	K_9
ν_s N-H Lactam	3471	3445	3445	3452	3444	3451	3445	3415	3340
ν_s C-H Aromatic	3088	3057	3058	3045	3009	3093	3042	3054	3079
ν_s C-H Aliphatic	2967	-	-	2958	-	-	-	-	-
ν_s C=O Lactam	1724	1728	1729	1647	1632	1749	-	1735	-
ν_s C=N Imine	1650	1615	1616	1602	1613	1656	1635	1640	1612
ν_s C=C Aromatic	1584	1483	1483	1575	1520	1506	1521	1537	1504
ν_{sc} C-S	-	-	1201	-	-	-	1243	1254	-
ν_s C-N	1296	1288	1288	1264	1243	1269	1270	1288	1269
δ_w N-H Lactam	738	735	735	760	761	732	759	739	749
C-H bending	1339	1331	1330	1331	1333	1328	1335	1331	1379
C-H out of-plane	884	817	882	879	892	800	789	885	828

Tab 4:The majer FT-IR absorptions bands (cm^{-1}) (A_1-A_9) of the prepared 2,3-disubstituted-1,3-oxazolidin-5-one

Comp. Code	A_1	A_2	A_3	A_4	A_5	A_6	A_7	A_8	A_9
ν_s N-H Lactam	3445	3450	3445	3424	3103	3425	3167	3444	3445
ν_s C-H Aromatic	3054	3058	3058	3045	3008	3055	3041	3060	3043
ν_s C-H Aliphatic	2968	2887	2886	2958	2962	2968	2978	2953	2980
ν_s C=O Lactone	1749	1747	1743	1647	1733	1749	1632	1732	1633
ν_s C=O Lactam	1729	1729	1728	1603	1652	1728	1612	1698	1613
ν_s C=N Imine	-	1617	1616	-	1630	-	-	1619	-
ν_s C=C Aromatic	1574	1483	1483	1546	1496	1549	1520	1464	1497
ν_{sc} C-S	-	-	1201	-	-	-	1224	1246	-
ν_s C-N	1296	1290	1288	1264	1135	1270	1295	1289	1243
δ_w N-H Lactam	738	735	735	760	761	732	759	739	749
C-H bending	1339	1331	1331	1351	1333	1386	1334	1331	1392
C-H out of-plane	884	885	884	879	888	873	884	871	885

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تحضير وتشخيص اوكسازولدينات جديدة من تفاعلات قواعد شف

عبيد حسن عبد , اوس كريم محمد

الخلاصة

تم تحضير عدد من المشتقات الجديدة لمركبات الاوكسازوليدينون, من تفاعل قواعد شف في البنزين الجاف بمنتوج عالي. حضرت قواعد شف من تفاعل الالديهايدات الحلقية غير المتجانسة مع امينات حلقية غير متجانسة. وقد شخصت النواتج بواسطة قياس درجات انصهارها واطياف (FT-IR و UV-Vis وH1NMR) .