Polymerization acryl monomers of 1,3,4-oxadiazole derivatives of cephalexin

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Abstract A novel acryl monomers of cephalexin containing 1,3,4-oxadiazole were synthesized and polymerized by using azobisisobutylronitrile (AIBN) as initiator. The 1,3,4-oxadiazole cephalexin have been synthesized from cephalexin and various chemicals, the synthesized oxadaizole derivatives reacted with acryloyl chloride to give acryl monomers then polymerized to prepare the target polymers. The structure of synthesized compounds have been characterized and confirmed by FT-IR and NMR spectral studies. In-vitro antibacterial activity of some synthesized compounds were tested against gram-positive and gram-negative bacteria and showed good activity against all culture.

Keywords: cephalexin , acryl monomers, acryl polymers ,1,3,4- oxadiazole, antibacterial activity, azobisisobutylronitrile.

1.Introduction

Oxadiazole five member heterocyclic is present in most of the members of vit- B complex, antibiotics, alkaloids, amino acid, drugs, dyes,enzyme & genetic material DNA and having therapeutics use[1].

Oxadiazole is a heterocyclic nucleus and is considered to be derived from furan by replacement of two methane (- CH=) group by two nitrogen (- N=) . There are four possible isomers of oxadiazole (**1, 2, 3, 4**) depending on the position of nitrogen atom inthe ring and are numbered as shown in Figure1 [2].

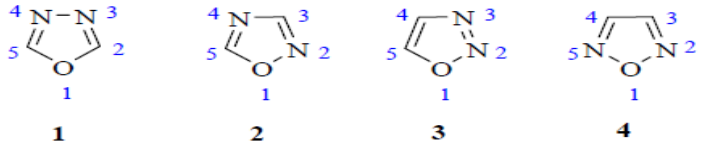

Figure1. Isomers of Oxadiazole

Many researchers have reported excellent biological activity for compounds containing the 1,3,4-oxadiazole core with antimicrobial activity[3],anticonvulsant activity[4],anti-inflammatory activity [5]analgesic activity[6]and antitumor activity[7].

Acrylic polymers and the related compounds are more widely used as polymeric carriers for proteins, enzymes, drugs and other biologically active substances. In the latter case, these polymers can be used for solving two mutually related problems of the chemistry and technology

of biopolymer for medical applications[8].Antimicrobial polymers represent a class of biocides that has become increasingly important as an alternative to existing biocides and in some cases even to antibiotics[9]. Antimicrobial polymers have been known since 1965 described homo and copolymers that kill bacteria[10]. In the 1970s several groups synthesized polymers that showed antimicrobial activity. The most recent review have discussed the parameters that influence on the bactericidal action of antimicrobial polymers, such as molecular weight, type and degree of alkylation[11].

In pharmacology, biological activity or pharmacological activity describes the beneficial or adverse effects of a drug on living matter[12] When a drug is a complex chemical mixture, this activity is exerted by the substance's active ingredient or pharmacophore but can be modified by the other constituents. Among the various properties of chemical compounds, pharmacological/biological activity plays a crucial role since it suggests uses of the compounds in the medical applications[13].

Materials

All chemicals used were available from Aldrich and Fluka Companies and cephalexin standard material was provided from state company for drug industries and medical appliance (SDI) Samaraa – Iraq.

Instruments

Melting points were determined in an open capillary tube . Infrared spectra were recorded on Shimadzu spectrophotometer. ^{1}HNMR were measured in DMSO solution on a Bruker-400 MHz spectrometer .the reactions was monitored by thin layer chromatography (TLC) . The antibacterial activity was determined by Agar-well diffusion method.

Synthesis Methods

Synthesis of Methyl-7-[2-amino-2-phenyl acetamido]-3-methyl-6-oxo-1-thia-5-azabicyclo[4.2.0]oct-3-ene-4-carboxylate(2) [14].

A mixture of drug (cephalexin) (0.05 mole) and an excess of methanol (150 mL) with (2-4) drops of concentrate sulfuric acid was refluxed for (3-4) hrs. The solution was cooled and poured into crushed ice. Sodium bicarbonate was added to remove an excess of acid Precipitate obtained filtered recrystallized from ethanol.

Synthesis of 2-amino-N-[(2-acidhydrazide)-3-methyl-6-oxo-1-thia-5-azabicyclo [4.2.0]oct-3-en-7-yl)]-2- phenylacetamide (3) [15].

A mixture of (0.05mole) ester**(2)**and (0.05mole) hydrazine hydrate were refluxed in (50mL) ethanol for (5-8) hrs. The resultant mixture was concentrated, cooled and poured into crushed ice. The solid mass thus separated out recrystallized from ethanol .

Synthesis of 2-substituted-N[-(2-(4-benzylideneacid hydrazino)-3-methyl-6-oxo-1-thia-5-azabicyclo[4.2.0]oct-3-en-7-yl]acetamide (4-6) [16].

A solution of acid hydrazide**(3)(**0.01 mole) in methanol(50 mL) with aldehyde (0.02 mole) and(3- 5)drops of glacial acetic acid was refluxed for(4-6) hrs. The resultwas allowed to cool and poured into cold water. The solid was collected and recrystallized from ethanol to obtain the pure product.

Synthesis of 2-substuted- N-{3-methyl-6-oxo-4-(5-phenyl-1,3,4-oxadiazol-2-yl}-1-thia-5-azabicyclo[4.2.0]oct-3-en-7-yl]acetamide (7-9) [17]

To compounds **(4-6)** (0.01mole) was added to glacial acetic acid (50 mL)with stirring, lead dioxide (0.01mole)was added to the solution.The mixture was stirred at 25℃ for 1 hr ,ice-water was added and the mixture left to stand for 24 hrs,the precipitate was recrystallized .

Synthesis of acryl monomers of N -[2- substituted- acetyl]-N-{3-methyl-6-oxo-4-(5-phenyl-1,3,4-

oxadiazol-2-yl)-1-thia-5-azabicyclo [4.2.0]oct-3-en-7-yl}] acrylamide (10-12) [18].

(0.002 mole) of hydrazidehydrazones **(7-9)** was dissolved in THF (5mL) and (0.002mole) of Et_3N to

(0.002 mole) acryloyl chloride in THF (5mL) was added drop wise with stirring at 0℃. The reaction was continued at 0℃ for (4-6) hrs.The Et_3N-HCl was precipitated and filtered. The solvent was removed from the filtrate. The residual liquid was poured with stirring into water(100mL)to precipitate the product. recrystallization was carried out in ethanol.

Synthesis of acryl polymers of [N-[2- substuted-acetyl]-N-{3-methyl-6-oxo-4-(5-phenyl-1,3,4-oxadiazol- 2-yl)-1-thia-5-azabicyclo [4.2.0]oct-3-en-7-yl}]acrylamide] (13-15) [19].

(0.001mole) of monomers **(10-12)**dissolve in (5mL) DMF In a screw-capped polymerization bottle,. An amount equal to 0.02% of the monomers wt. of AIBN added. bottle was flushed with nitrogen gas for few minutes . The maintained at (60-70)ºC in constant temperature water bath for (1-2)hrs. Then the solution was poured into about 50mL of water or methanol. The precipitate was filtrate, washed with methanol several time and finally dried.

The physical properties of compounds **(2-15)** are listed in Table1.

Table 1: The physical properties of compound [2-15]

Comp. No.	Compound structure	Compound name	Dec. Point	Yield %	Color
2		Methyl-7-[2-amino-2-phenyl acetamido]-3-methyl-6-oxo-1-thia-5-azabicyclo[4.2.0]oct-3-ene-4-carboxylate	180	91	Off white
3		2-amino-N-[(2-acidhydrazide)-3-methyl-6-oxo-1-thia-5-azabicyclo [4.2.0]oct-3-en-7-yl)]-2-phenylacetamide	156	76	Orange

4		2-[(benzyl ideneamino)(2-phenyl)]-N[-(2-(4-benzylideneacid hydrazino)-3-methyl-6-oxo-1-thia-5-azabicyclo [4.2.0]oct-3-en-7-yl]acetamide	176	68	Dark orange
5		2-[(2-hydroxybenz ylidene)amino)(2-phenyl)-N[-(2-(4-(2-hydroxybenzyl ideneacidhydrazino)-3-methyl-6-oxo-1-thia-5-azabicyclo [4.2.0]oct-3-en-7-yl]acetamide	168	83	Light brown
6		N-[(3-methyl-4-(4-nitrobenzylidene acidhydrazino)-6-oxo-1-thia-5-aza bicyclo[4.2.0]oct-3-en-7-yl)-4-[(4-nitrobenzylidene) amino)(2-phenyl)] acetamide	170	85	Deep Brown
7		2-[{(benzylideneamino) (phenyl)}-N-{3-methyl-6-oxo-4-(5-phenyl-1,3,4-oxadiazol-2-yl}-1-thia-5-azabicyclo[4.2.0]oct-3-en-7-yl]acetamide	118	79	Orange
8		2-[{((2-hydroxybenzylidene) amino)(phenyl)}-N-{4-(5-(2-hydroxy phenyl)-1,3,4-oxadiazol-2-yl}-3-methyl-6-oxo-1-thia-5-azabicyclo [4.2.0]oct-3-en-7-yl] acetamide	106	78	Brown
9		N-{3-methyl-4-(5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl}-6-oxo-1-thia-5-azabicyclo[4.2.0] oct-3-en-7-yl)-2-[{(4-nitrobenzylidene)amino} (phenyl)]acetamide	122	75	Brown
10		N-[2-{(benzylidene amino)(phenyl)} acetyl]-N-{3-methyl-6-oxo-4-(5-phenyl-1,3,4-oxadiazol-2-yl)-1-thia-5-azabicyclo [4.2.0]oct-3-en-7-yl}] acrylamide	166	69	Orange

11	N-[2-{(2-hydroxy benzylidene) amino} (phenyl)acetyl]-N-[4-{5-(2-hydroxyphenyl) -1,3,4-oxadiazol-2-yl} -3-methyl-6-oxo-1-thia-5-azabicyclo [4.2.0]oct-3-en-7-yl] acrylamide	152	66	Radish brown
12	N-[3-methyl-4-{5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl}-6-oxo-1-thia-5-azabicyclo[4.2.0] oct-3-en-7-yl]-N-[2-{(4-nitrobenzylidene)amino}-2-phenylacetyl] acrylamide	156	51	Dark red
13	Poly[N-[2-{(benzylidene amino)(phenyl)}acetyl]-N-{3-methyl-6-oxo-4-(5-phenyl-1,3,4-oxadiazol-2-yl)-1-thia-5-azabicyclo [4.2.0]oct-3-en-7-yl}]acrylamide]	156	69	Light brown
14	Poly[N-[2-{(2-hydroxybenzylidene)amino}(phenyl)acetyl]-N-[4-{5-(2-hydroxyphenyl)-1,3,4-oxadiazol-2-yl}-3-methyl-6-oxo-1-thia-5-azabicyclo[4.2.0]oct-3-en-7-yl] acrylamide]	152	66	Orange
15	Poly[N-[3-methyl-4-{5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl}-6-oxo-1-thia-5-azabicyclo[4.2.0] oct-3-en-7-yl]-N-[2-{(4-nitrobenzyl idene)amino}-2-phenylacetyl] acrylamide]		70	Brown

Result and Discussion

The present work involved preparation of different compounds (2-15)from cephalexin ,Scheme1.

Scheme 1. Preparation of different compounds (2-15)from cephalexin

The compound**(2)** have been synthesized by condensation reaction of drug (cephalexin) with absolute methanol and few drops concentration H_2SO_4,The reaction proceeds by nucleophilic substitution, Fischer mechanism[20].Hyroxami test give (+ve) for present ester , that compound is identified by FT-IR spectrum that show ν(C=O) at (1741)cm^{-1}, ν(C- O)cm-^{1} at (1251)cm^{-1} for ester and disappearance of ν(O-H) at (2781)cm^{-1}, ν(C=O) at (1712)cm^{-1} for -COOH indrug cephalexin .^{1}HNMR spectrum for compound **(2)** show signal at δ(3.49)ppm due to (-$COOCH_3$) protons.

The ester **(2)** was converted to acid hydrazide compound **(3)** via reaction with hydrazine hydrate in ethanol.

The reaction proceeds by nucleophilic substitution and its mechanism involve nucleophilic attack of amino group in hydrazine hydrate on carbonyl in ester followed by eliminate of methanol molecule[21].Hydroxamic test give(-ve)that indicate for not presence any ester**(2)**.FT-IR spectrum of compound **(3)** showed disappearance ν(C=O) and ν(C-O-C) of ester and appearance ν(-NH_2) at (3545,3490)cm^{-1} and ν(NH) at (3208)cm^{-1} for compound**(3)**proving acid hydrazideformation. ^{1}HNMR spectrum of compound**(3)**

showed signal at δ(1.91)ppm due to (NH-NH_2) protons and at δ(8.00)ppm due to (NH-NH_2) proton and

disappearance signal belong to ($COOCH_3$) ester.

Synthesized compound**(3)** treated with different aliphatic and aromatic aldehydes resulted of Schiff's bases

compounds**(4-6).** The mechanism of reaction between the hydrazine compound **(3)**and carbonyl compounds

involved nucleophilic addition of amino group to carbonyl group in the first step then elimination water

molecule in the second step to producing Schiff's bases[22] FT-IR spectra of compounds**(4-6)** showed

disappearance ν(-NH_2) of compound**(3)** and appearance ν(-N=C) at (1609-1624)cm^{-1} that indicate imines

formation.^{1}HNMR spectrum of the compound**(5)** showed disappearance signals belong to (NH-NH_2) hydrazine protons and (-NH_2) amine protons and appearance signals at δ(8.2)ppm due to (CH-N=CH)

proton and δ(8.71) due to (NH-N=CH) proton. Treatment hydrazone**(4-6)** with lead dioxide in glaicial acetic acid affords intramolecular cyclization to give

1,3,4-oxadiazoles**(7-9)**.The mechanism was proposed oxidative cyclization[23].These compounds were

indentified from FT-IR that show appearance ν(C-O-C) between (1219-1229)$cm^{-1,}$

Figure(10).^{1}HNMR spectrum of compound**(9)**showed disappearance signals due to(CH-N=CH) proton and (NH-N=CH) proton,.

Drug-containing monomers**(10-12)**were synthesized by the direct reaction of acryloyl chloride with

compounds **(7-9)**.The reaction between acryloyl chloride and compounds**(7-9)** take place in DMF at

moderate temperatures, in the presence of (Et_3N) as hydrogen chlorideacceptor.

Thisreactionisoftenusedforthesynthesisofvinylmonomersbecauseofthemildconditionswhichallows acylsubstitutionwithoutanydamageofsensitivemolecules[24]. The end point of the reaction was examined by thin layer chromatography (TLC).The mechanism of reaction involves a nucleophilic attack[37] of amide group in compounds**(7-9)** on the carbonyl in acryloyl chloride in presence of a nucleophile such as triethylamine followed by elimination of hydrogen chloride. FT-IR spectra of compounds**(10-12)** showed appearance absorption bands of the ν(C=C) vinyl at (1601-1609). ^{1}HNMR spectrum for compound**(10)** appearance the signals in, δ(5.959)ppm due to (–CH=CH_2) protons and δ(6.468)ppm, due to (-CH=CH_2) proton and disappearance the signals for (N-H) proton.

The polymerization of monomers**(10-12)** were carried out in DMF using AIBN as initiator.The mechanism of reaction involve free radical polymerization[25], and prepared polymers**(13-15)**.All these polymers were identified from FT-IR spectra that show disappearance of ν(C=C) vinylic, Figure(14)**.** The ^{1}HNMR spectrum of polymer**(13)** is shown disappearance signals due to vinylic protons in the monomer**(10)** but when polymerized appearance signals at δ(1.657)ppm due to –(-CH2-CH-)$_n$- protons and signal at δ(2.618)ppm due to–(-CH2-CH-)$_n$- proton which indicate the formation polymer.All details of FT-IR spectra data of compounds**(2-15)** are listed in Table2. Results ^{1}HNMR spectral data of some selected compounds are listed in Table 3.

Table 2. FT-IR spectra data of compounds(2-15)

Comp. No.	FT-IR Spectral data cm^{-1}								
	v(NH2)	v(N-H) Amide	v(C-H) Arom.	v(C-H) Aliph.	v(C=C) Arom	1.azetidinone 2.ester(imide)	v(CH=N)Imine	v(C-O-C)
2	3507 3418	3269	3055	2889 3001	1557 1518	1.1763 2.1741 3.1692		1251
3	3545 3490	3208	3061	2972 2878	1588 1511	1.1770 3.1661		
4		3229	3038	2966 2942	1585 1530	1.1742 3.1674	1611	
5		3242	3038	2976 2936	1580 1489	1.1744 3.1665	1624	
6		3227	3075	2972 2911	1576 1522	1.1752 3.1665	1609	
7		3242	3042	2976 2951	1587 1516	1.1742 3.1668	1616	1227
8		3240	3063	2963 2932	1580 1532	1.1744 3.1668	1622	1229
9		3220	3057	2970 2933	1579 1520	1.1752 3.1668	1619	1228
10			3063	2965 2926	1532 1518	1.1767 2.(1680) 3.1644	1622	1275
11			3062	2961 2928	1584 1514	1.1755 2.(1688) 3.1655	1615	1227
12			3061	2967 2933	1598 1520	1.1749 2.(1695) 3.1659	1616	1224
13			3057	2963 2934	1564 1516	1.1744 2.(1682)	1612	1214
14			3062	2961 2930	1587 1516	1.1745 2.(1655)	1611	1232
15			3074	2968 2924	1568 1520	1.1765 2.(1676)	1617	1230

Table 3. ^{1}HNMR Spectral data δ(ppm) for selected compounds

Comp. No.	^{1}HNMR Spectral data(δppm)
2	7.22-7.51(m,5H,Ar-H); 1.76(s,3H,-CH_3); 3.17(s,2H,S-CH_2); 3.49(s,3H,-CO-OCH_3);

	4.99(s,1H,-CH-NH_2); 5.1(d,1H,-CH-CH-S) .; 5.11(s,2H,-NH_2); 5.45(d,1H,CH-CH-S) Azet.; 8.11(s,1H,-NH).
3	7.31-7.76(m,1H,Ar-H); 1.79(s,3H,-CH_3); 1.91(s,2H,-NH-NH_2); 3.15(s,2HS-CH2); 4.81(s,1H,CH-NH_2); 4.95(d,1H,-CH-CH-S)Azet.; 5.22(s,1H,-CH-NH_2); 5.31(d,1H,-CH-CH-S-)Azet.; 8.00(s,1H,NH-NH2); 8.12(s,1H,-NH)Amide
4	6.88-7.91(m,15H,Ar-H); 1.66(s,3H,-CH_3); 3.33(d,2H,S-CH_2-); 4.87(s,1H,CH-CH-S)Azet.; 5.51(s,1H,-CH-N=CH); 5.61(s,1H,CH-CH-S)Azet.; 8.00(s,1H,-NH-N=CH)Amide; 8.17(s1H,NHAmide); 8.26(s,1H,CH-N=CH); 8.58(s,1H,NHN=CH)
5	6.92-7.67(m,15H,Ar-H); 1.81(s,3H,-CH_3); 3.36(d,2H,S-CH_2-); 5.01(s,1H,CH-CH-S)Azet.; 5.33(s,1H,-OH); 5.39(s,1H,-CH-N=CH); 5.43(s,1H,-CH-CH-S)Azet.; 8.02(s,1H,NH-N=CH); 8.09(s,1H,-NH)Amide; 8.23(s,1H,CH-N=CH); 8.71(s,1H,NHN=CH)
7	6.99-7.88(m,15H,Ar-H); 1.91(s,3H,-CH_3); 3.09(S,2H,S-CH_2); 5.01(s,1H,-CH-CH-S); 5.42(s,1H,-CH-N=CH); 5.48(d,1H,-CH-CH-S)Azet.; 8.06(s,1H,-NH)Amide; 8.26(s,1H,CH-N=CH)
10	7.008-8.003(m,15H,Ar-H); 1.763(s,3H,-CH3); 3.096(s,2H,S-CH2); 5.013(d,1H,-CH-CH-S); 5.297(s,1H,CH-N=CH); 5.355(d,1H,-CH-CH-S); 5.959(s,2H,-CH2=CH-); 6.468(s,1H,CH2=CH-); 8.117(s,1H,-CH-N=CH)
13	7.124-8.003(m,15H,Ar-H); 1.957(s,3H,-CH3); 1.657(d,2H,-(-CH2-CH-)n-); 2.618(t,1H,-(-CH2-CH-)n-); 3.102(s,2H,S-CH2); 5.155(d,1H,-CH-CH-S)Azet; 5.354(s,1H,CH-N=CH); 5.496(d,1H,-CH-CH-S)Azet; 8.117(s,1H,-CH-N=CH)

Antibacterial activity

The antibacterial activity of some synthesized compounds were determined by agar diffusion method at

concentration (1mg), DMSO served as control due to this there was no visible change in bacterial growth,

cephalexin was used a standard drug and the plates were incubated at 37℃for 24 hours. the inhibition zone measured in (mm).

Synthesized compounds**(7-9)**and **(13-15)** were screened antibacterial activity and showed varying degree of inhibition zone against the tested gram positive and gram negative bacteria and observed that gram positive bacteria show better activity than gram negative bacteria, Table 4.

Table4. antibacterial activity of synthesized compounds(7-9) and (13-15)

Comp. Code	*Inhibition zone diameter(mm)*			
	Staphylococcus aurous	***Bacillus subtitles'***	***Escherichia coli***	***Pseudomonas Aeruginosa***
7	13	12	6	-
8	14	12	8	3

9	14	11	7	6
13	13	13	6	-
14	13	12	6	4
15	15	11	5	-
Cephalexin [C]	12	10	5	-
DMSO	-	-	-	-

[Conc.]: 1mg/ml

Zone inhibition: (-) no i**nhibition zone**

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