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Research Article

Synthesis and Antibacterial Activity of 1,3-Oxazepine Derivatives Starting From L-Ascorbic Acid

Rasha Saad Jwad[1] A. J. Kadir[2]

[1] Department of Chemistry,College of Science, Al-Nahrain University,Baghdad,Iraq
[2] Madenat Alelm University College, Baghdad, Iraq

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Abstract

In this work, an aldehyde precursor has been prepared by four subsequent steps starting from L-ascorbic acid. This compound was reacted with different amines namely; phenyl hydrazine, aniline, *p*-toluidine, *p*-methoxyaniline, *p*-acetamidoaniline and 2-aminopyrimidene to afford six imine derivatives. Finally, the cycloaddition of Schiff bases to four separate acid anhydrides; maleic anhydride, 2,3-dichloromaleic anhydride, 3-nitrophthalic anhydride and phthalic anhydride produced 24 oxazepine derivatives. All synthesized compounds were characterized by FT-IR spectroscopy, ^{1}H NMR spectroscopy, micro-elemental analysis and TLC. The antibacterial activity of 1,3-oxazepines against *S. aureus* and *E. coli* were studies using disk diffusion method.

Corresponding Author E-mail : rasha.s.jwad@gmail.com , rasha.saad@nahrainuniv.edu.iq
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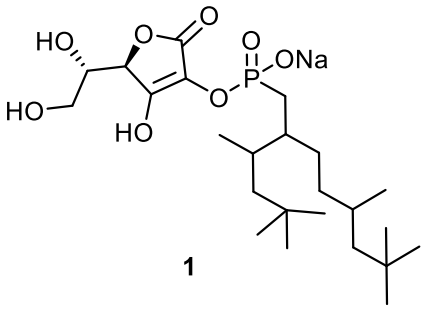
Introduction

Vitamin C is one of the most powerful naturally occurring antioxidant also it is found to have a significant role in various biological processes.[1] L-Ascorbic acid is widely available in fruit and vegetables such as orange, lemon, kiwi, green pepper, broccoli, tomatoes…etc. This compound can be synthetically produced from simple carbohydrate precursors. [2] Moreover, the derivatives of L-ascorbic acid attract great attention because they possess biological activity. [3] A study showed that Zinc salt of L-ascorbic acid exhibited antibacterial activity against *S. aureus* and *E. coli*, and can be utilised in the treatment acne. [4] Tai et al. synthesized 3-O-ethylascorbic acid and studied its effect on the outgrowth of neurite in PC12 cells. [5] The synthesis and in-vitro skin permeability of amphiphilic ascorbic acid derivative isostearyl-2-O-L-ascorbic acid phosphate 1 have been demonstrated by Shibayama *et al*. [6]. This compound showed high thermal stability and skin permeability, which can be used in cosmetics.



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Furthermore, hydrophilic and lipophilic ascorbic acid derivatives such as glycoside and fatty acid derivative are exploited in the synthesis of nanoparticles for drugs formulation. [7] A small library of vitamin C lactone derivatives have been prepared and screened against five types of human cancer cells. However, these lactones did not display anticancer activity. [8] In 2014, a study showed that ascorbic acid-based oxazepine derivatives produced excellent inhibition zone when they are tested against Gram (+ve) and Gram (−ve) bacteria. [9]. Recently, Alrammahi et al. [10] synthesized a library of 1,3-oxazepine derivatives starting from terephthalaldehyde in moderate yields. It has been reported that the addition of cinnamyl-based oxazepine derivatives to PVC films decreases the photodegradation and this can be achieved through the absorption of UV by the seven-membered ring. [11] In this work, a small library of 1,3-oxazepine derivatives are synthesized starting from L-ascorbic acid and the biological activity of these compound against *S. aureus* and *E. coli* have been screened.

Experimental

General

All chemicals are purchased from commercial sources; Sigma-Aldrich, Merk chemicals, Fluka AG and Acros Organics. Melting points were recorded using Electrothermal Melting Point Apparatus IA9000, USA. Thin layer chromatography (TLC) was performed on aluminum plates coated with (0.25mm) layer of silica gel F254 and the spots were detected by either iodine vapor or H_2SO_4 / MeOH solution. Infrared spectra were recorded using Testean Shimadzu FT-IR 8000 series, Japan. Micro-elemental analysis was performed at Al al-Bayt University, Jordan using Elemental Analyzer EA-300 Eurovector 2003, Italy. NMR Ultra Shield 300 MHz, Bruker 2003, Switzerland was utilized to record NMR spectra at Al al-Bayt University, Jordan. Most of the synthesized compounds, unless otherwise mentioned, were purified by column chromatography using silica-gel 60−120 Mesh (250−125µm).

Methods

Synthesis of 5,6-*O*-isopropylidene-L-ascorbic acid (3) [12]

A mixture of L-ascorbic acid (**2**) (10 g, 56.8 mmol) in dry acetone (100 mL) was saturated with HCl gas and stirred at r.t. for 20 min then n-hexane (80 mL) was added, and the mixture was left to settle down before decantation of liquid. The residue filtered under suction and the solid was washed four times with (acetone: n-hexane 4:7) to give com-

pound **3** (11.6 g, 94.5%) as a white solid; m.p (219−222 °C); R_f = 0.68.

Synthesis of 2,3-O-dibenzoyl-5,6-O-isopropylidene-L-ascorbic acid (4)[13]

Benzoyl chloride (15 mL, 107 mmol) was added dropwise to the solution of acetal **3** (10 g, 46 mmol) in pyridine (50 mL) at 0 °C. The resulting mixture was warmed up r.t. and kept at the same temperature for 16 h. After which time, the mixture was poured onto ice-water (200 mL) and stirred for 20 min. The mixture was extracted with DCM (2 × 250 mL) and the combined extracts were washed with water then dried over anhydrous magnesium sulfate, evaporated under reduced pressure and finally co-evaporated with toluene (3 × 50 mL) to give compound **4** (17.9 g, 91.3%) as a pale-yellow syrup; R_f = 0.81.

Synthesis of 2,3-*O*-dibenzoyl-L-ascorbic acid (5)[14]

A solution of compound **4** (10 g, 23.6 mmol) in 65% glacial acetic acid (30 mL) was stirred at r.t. for 12 h. After, which time, TLC showed that the starting material has completely been consumed a new compound was formed. The solution was evaporated under reduced pressure and resulting residue was chromatographed on silica gel (n-hexane → n-hexane / EtOAc 1:2) to yield diol **5**, (7.4 g, 83 %) as a homogenous syrup; R_f = 0.26.

Synthesis of (S)-2-formyl-5-oxo-2,5-dihydrofuran-3,4-diyl dibenzoate (6)[15]

A solution of compound **5** (1.0 g, 2.7 mmol) in absolute ethanol (5 mL) was added to the stirred solution of sodium periodate (0.6 g) in distilled water (3 mL) at 0 °C. After 15 min a drop of ethylene glycol was added and stirring was continued at r.t. for a further 1 h. The mixture was extracted with ethyl acetate (3 × 50 mL), dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was chromatographed on silica gel (n-hexane → n-hexane / EtOAc 3:1) to afford aldehyde **6** (0.68 g, 72%) as white crystals; m.p (79−81 °C); Rf = 0.47. FT-IR ν cm^{-1}: 3070, 2933, 2870, 2745, 1710, 1689, 1601, 1588, 1431, 1377, 1250, 1110, 811, 715. 1H NMR ($CDCl_3$, 300 MHz) δ ppm: 5.77 (d, J = 6.4 Hz, 1H, H5), 7.64 (d, J = 7.2, 5.1 Hz, 4H, H-Ar), 7.82 (m, 2H, H-Ar), 8.16 (dd, J = 7.2, 5.0 Hz, 4H, H-Ar), 9.81 (d, J = 6.3 Hz, 1H, H-aldehyde). CHN for $C_{19}H_{12}O_7$; required C, 64.78; H, 3.43 found C, 64.74; H, 3.39.

General procedure of synthesis of imines 7 a−f[16]

A proper amine (1.42 mmol) was added to the stirred solution of compound **6** (0.5 g, 1.42 mmol) in absolute ethanol (5 mL) and the mixture was refluxed until the TLC showed that the reaction was completed ~ 2 h. The solvent was then removed under reduced pressure and the residue was recrystallized from (*n*-hexane / EtOAc 1:1) to give the corresponding imine.

General procedure of synthesis of 1,3-oxazepine derivatives 8−11[17]

An acid anhydride (1.0 mmol) was added in small portions to a solution of equimolar ratio of Schiff base in toluene (20 mL). The mixture was the refluxed for 5−10 h, filtered, the precipitated was washed with cold mixture of (*n*-hexane / EtOAc 3:1) and dried at 70 °C to afford the proper 1,3-oxazepine derivative.

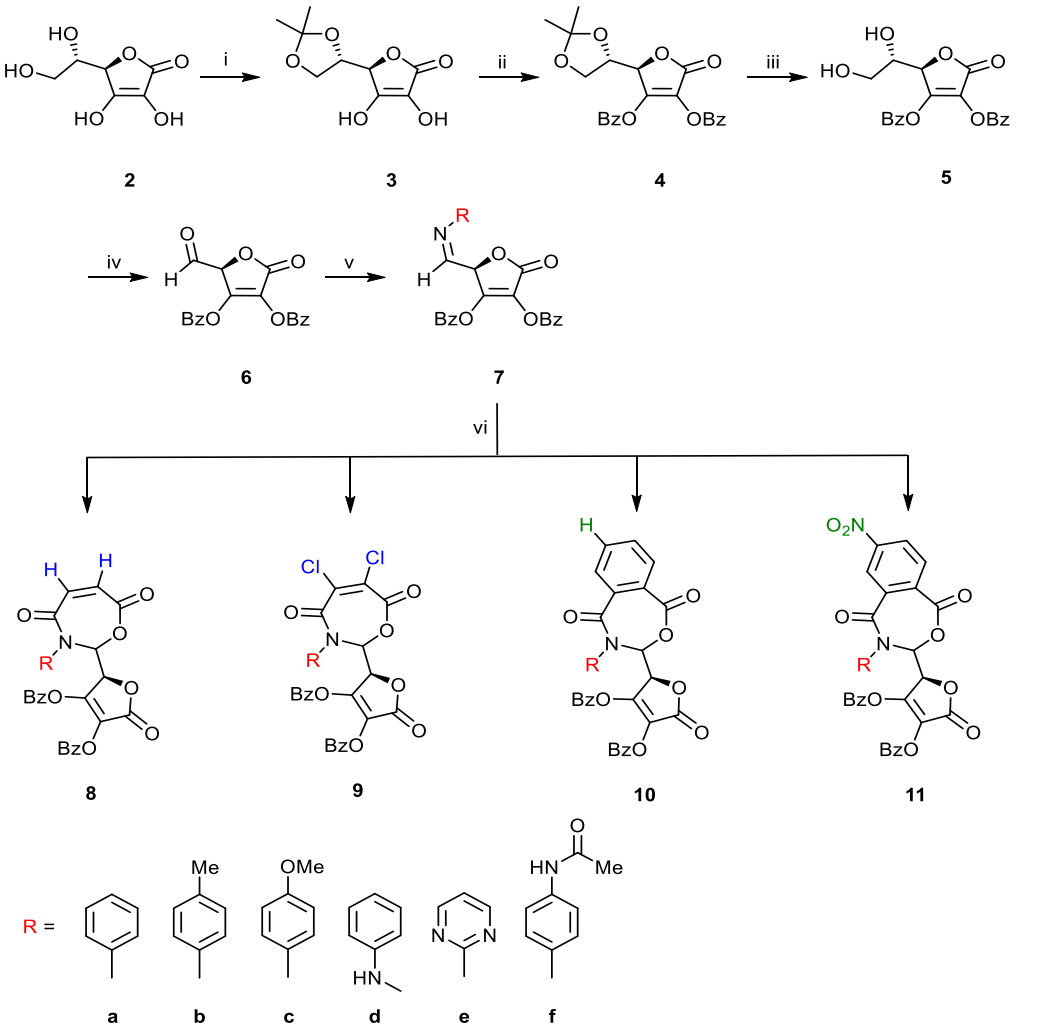
Antibacterial activity[18]

The antibacterial activity was performed using disk diffusion method or Kirby Bauer method on Müeller-Hinton agar. 1,3-Oxazepine derivatives **8−11** were examined against two bacterial species; *S. aureus* and *E. coli*. A solution of each derivative has been prepared in a concentration of (1.0 µg/1.0 mL) in DMSO and Ampicillin was used as a control. The plates were tested after 24 h incubation at 37 °C.

Results and discussion

The first step in synthetic protocol is the preparation of 5,6-isopropylidene-L-ascorbic acid (**3**) from the reaction of L-ascorbic acid (**2**) with acetone in acidic media following modified Solomon [12] method. The FT-IR spectrum of compound **3** showed stretching bands; vinylic O−H at ν 3238 cm^{-1}, aliphatic C−H at 2997 cm^{-1} and 2912 cm^{-1} and the characteristic lactone C=O band at 1750 cm^{-1}.

Compound **3** reacts with excess of benzoyl chloride in dry pyridine to give dibenzoyl derivative **4**. This compound is characterized by the FT-IR spectrum through the disappearance of the vinylic O–H band and the appearance of new benzoyl ester C=O at 1689 cm^{-1}. Moreover, the presence of aromatic C–H and C=C at 3080 cm^{-1} and 1600 cm^{-1} is another evidence of formation of compound **4**. A selective acetal protecting group removal is achieved when dibenzoyl ester **4** is treated with 65% acetic acid at room temperature for 12 h to afford diol **5**. The deprotection is assigned by the appearance of broad O–H stretching bands at 3410 cm^{-1}. Next, diol **5** is shortened by one carbon to give aldehyde **6** via the oxidative cleavage in the presence of $NaIO_4$. The formation of aldehyde **6** is assigned by the appearance of the new aldehyde C=O stretching bands at 1710 cm^{-1} in FT-IR in addition to the presence of the aldehyde proton at 9.81 ppm in ^1H NMR spectrum. Moreover, a positive Tollens' test is observed by the formation silver mirror. After the getting aldehyde **6**, the work proceeds to prepare imines **7a**–**f**. The reflux of compound **6** with an appropriate amine; aniline, *p*-toluidine, *p*-methoxyaniline, phenylhydrazine, 2-aminopyrimidine and *p*-acetamidoaniline in absolute ethanol for two hours gives corresponding imine in very good yields. The overall synthetic route of this work is shown in Scheme 1.



Reagents and conditions: **i**] dry acetone, $HCl_{(g)}$, r.t., 20 min, 94%; **ii**] BzCl, pyridine, 0 °C–r.t.,16 h, 91%; **iii**] AcOH 65%, r.t., 12 h, 83%; iv] $NaIO_4$, H_2O, EtOH, 0 °C–r.t., 90 min, 72%; v] RNH_2, EtOH, reflux, 2 h, 76–89%; vi] acid anhydride, toluene, reflux, 5–10 h, 49–63%.

Scheme 1. Synthesis of 1,3-oxazepine derivatives starting from L-ascorbic acid

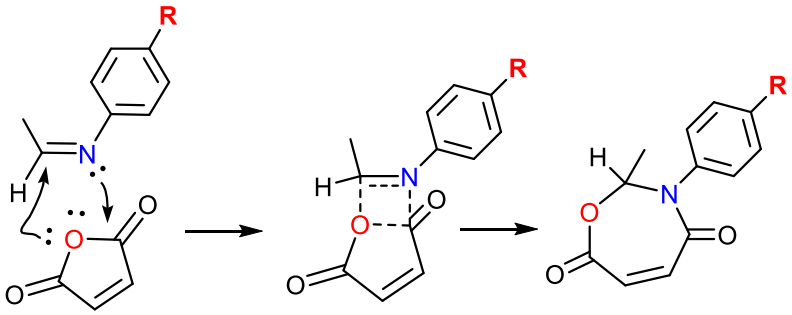
All amine derivatives **7a**–**f** are characterized by FT-IR and ^{1}H NMR. In FT-IR spectra, the aldehyde C=O band at 1710 cm^{-1} disappears and a new imine C=N band appears between 1690 cm^{-1} and 1650 cm^{-1}. Similarly, the aldehyde signal at 9.80 ppm vanishes and new imine proton appears around 8.52 ppm. Table 1 illustrates the typical IR bands, chemical shifts and micro-elemental analysis of imine derivatives **7a**–**f**.

Table 1. Characteristic FT-IR bands cm^{-1}, chemical shifts ppm and micro-elemental analysis of imine derivatives 7a–f

Comp. (Yield)	FT-IR cm^{-1}	Chemical shift ppm (DMSO-d_6)	Formula CHN required (found)
7a (76%)	3073, 2918, 2865, 1689, 1680, 1602, 1576, 1424, 1355, 1204, 1151, 865, 782, 603.	4.92 (d, *J* = 7.1 Hz, 1H, H5), 6.93 (d, *J* = 7.5 Hz, 2H, H-Ar), 7.07 (m, 1H, H-Ar), 7.34 (dd, *J* = 7.5, 5.0 Hz, 2H, H-Ar), 7.62 (d, *J* = 7.3, 4.9 Hz, 4H, H-Ar), 7.81 (m, 2H, H-Ar), 8.15 (dd, *J* = 7.3, 5.0 Hz, 4H, H-Ar), 8.50 (d, *J* = 7.1 Hz, 1H, H-imine)	$C_{25}H_{17}NO_6$ C, 70.25; H, 4.01; N, 3.28 (C, 70.21; H, 3.99; N, 3.24)
7b (83%)	3075, 2928, 2864, 1691, 1682, 1600, 1566, 1421, 1360, 1201, 1153, 853, 789, 601.	2.37 (s, 3H, CH_3), 4.93 (d, *J* = 7.1 Hz, 1H, H5), 7.18 (d, *J* = 7.5 Hz, 2H, H-Ar), 7.20 (d, *J* = 7.4 Hz, 2H, H-Ar), 7.63 (d, *J* = 7.3, 4.9 Hz, 4H, H-Ar), 7.82 (m, 2H, H-Ar), 8.15 (dd, *J* = 7.3, 5.0 Hz, 4H, H-Ar), 8.53 (d, *J* = 7.1 Hz, 1H, H-imine)	$C_{26}H_{19}NO_6$ C, 70.74; H, 4.34; N, 3.17 (C, 70.73; H, 4.31; N, 3.13)
7c (89%)	3083, 2925, 2865, 1690, 1685, 1604, 1566, 1417, 1365, 1202, 1155, 862, 790, 605.	3.85 (s, 3H, OCH_3), 4.92 (d, *J* = 7.1 Hz, 1H, H5), 6.98 (d, *J* = 7.3 Hz, 2H, H-Ar), 7.41 (d, *J* = 7.4 Hz, 2H, H-Ar), 7.61 (d, *J* = 7.1, 4.9 Hz, 4H, H-Ar), 7.83 (m, 2H, H-Ar), 8.16 (dd, *J* = 7.1, 4.9 Hz, 4H, H-Ar), 8.53 (d, *J* = 7.1 Hz, 1H, H-imine)	$C_{26}H_{19}NO_7$ C, 68.27; H, 4.19; N, 3.06 (C, 68.24; H, 4.18; N, 3.03)
7d (80%)	3332, 3080, 2922, 2861, 1691, 1656, 1602, 1512, 1444, 1362, 1200, 1155, 863, 795, 610.	4.93 (d, *J* = 7.0 Hz, 1H, H5), 7.06 (m, 1H, H-Ar), 7.31 (m, 2H, H-Ar), 7.34 (dd, *J* = 7.5, 4.6 Hz, 2H, H-Ar), 7.62 (d, *J* = 7.4, 4.8 Hz, 4H, H-Ar), 7.82 (m, 2H, H-Ar), 8.16 (dd, *J* = 7.3, 4.9 Hz, 4H, H-Ar), 8.50 (d, *J* = 7.0 Hz, 1H, H-imine), 11.64 (broad s, 1H, NH)	$C_{25}H_{18}N_2O_6$ C, 67.87; H, 4.10; N, 6.33 (C, 67.86; H, 4.11; N, 6.34)
7e (83%)	3079, 2928, 2861, 1693, 1681, 1604, 1576, 1415, 1364, 1201, 1158, 861, 793, 613.	4.93 (d, *J* = 7.1 Hz, 1H, H5), 7.61 (d, *J* = 7.2, 4.9 Hz, 4H, H-Ar), 7.83 (m, 2H, H-Ar), 7.86 (m, 1H, H-Ar), 8.14 (dd, *J* = 7.3, 4.9 Hz, 4H, H-Ar), 8.45 (d, *J* = 7.1 Hz, 1H, H-imine), 8.87 (m, 2H, H-Ar).	$C_{23}H_{15}N_3O_6$ C, 64.34; H, 3.52; N, 9.79 (C, 64.32; H, 3.49; N, 9.77)
7f (84%)	3441, 3083, 2929, 2867, 1690, 1653, 1601, 1524, 1437, 1365, 1207, 1153, 861, 777, 603.	2.10 (s, 3H, OCH_3), 4.95 (d, *J* = 7.2 Hz, 1H, H5), 7.44 (d, *J* = 7.1 Hz, 2H, H-Ar), 7.59 (d, *J* = 7.2 Hz, 2H, H-Ar), 7.63 (d, *J* = 7.1, 4.9 Hz, 4H, H-Ar), 7.81 (m, 2H, H-Ar), 8.13 (dd, *J* = 7.1, 4.9 Hz, 4H, H-Ar), 8.55 (d, *J* = 7.2 Hz, 1H, H-imine)	$C_{27}H_{20}N_2O_7$ C, 66.94; H, 4.16; N, 5.78 (C, 66.92; H, 4.15; N, 5.73)

The last step in the synthesis is the cycloaddition of acid anhydrides to the prepared amines **7a**–**f** in toluene at reflux from five to ten hours to produce the corresponding oxazepine derivatives **8**–**11**. The formation of later compounds follows [2 + 5] cycloaddition mechanism that shown in Scheme 2.[19] It is demonstrated that the oxazepine derivatives **9** and **11** formed in shorter time (~ 5–6 hours) when the anhydride contains electron-withdrawing group such as chloro group in 2,3-dichloromaleic anhydride or nitro group 3-nitrophthalic anhydride. These groups increase the electrophilicity of the carbonyl of the anhydride and this will facilitate the attack of the nitrogen lone pair of imine. Whereas other derivatives **8** and **10** require more time (~ 8–10 hours) to be formed.

The structures of oxazepine derivative are firstly confirmed by FT-IR spectra that show two characteristic bands at about 1770 cm^{-1} and 1750 cm^{-1} attributed to the C=O of the seven membered-ring. In addition, ^{1}H NMR spectra reveals the appearance of new doublet at around 7.40 ppm due to the C–H of the oxazepine and the disappearance of the imine proton signal at 8.50 ppm. Tables 2–5 show the characteristic IR bands, chemical shifts, and micro-elemental analysis of the synthesized oxazepine derivatives.



Scheme 2. Mechanism of [2 + 5] cycloaddition

Table 2. Characteristic FT-IR bands cm^{-1}, chemical shifts ppm and micro-elemental analysis of oxazepine derivatives 8a−f

Comp. Yield	FT-IR cm^{-1}	Chemical shift ppm (DMSO-d_6)	Formula CHN required (found)
8a (49%)	3073, 3069, 2917, 2865, 1770, 1753, 1689, 1600, 1575, 1422, 1355, 1204, 1151, 865, 781, 607.	6.14 (d, *J* = 9.2 Hz, 1H, H5), 6.40 (d, *J* = 9.1 Hz, 1H, H-olefine), 6.91 (d, *J* = 9.0 Hz, 1H, H-olefine), 6.93 (d, *J* = 7.5 Hz, 2H, H-Ar), 7.07 (m, 1H, H-Ar), 7.34 (dd, *J* = 7.5, 5.0 Hz, 2H, H-Ar), 7.39 (d, *J* = 9.3 Hz, 1H, H-oxazepine), 7.61 (dd, *J* = 7.3, 4.9 Hz, 4H, H-Ar), 7.81 (m, 2H, H-Ar), 8.14 (dd, *J* = 7.3, 5.0 Hz, 4H, H-Ar)	$C_{29}H_{19}NO_9$ C, 66.29; H, 3.64; N, 2.67 (C, 66.26; H, 3.63; N, 2.66)
8b (54%)	3080, 3072, 2927, 2862, 1775, 1749, 1681, 1601, 1565, 1422, 1360, 1201, 1153, 852, 784, 603.	2.37 (s, 3H, CH_3), 6.12 (d, *J* = 9.1 Hz, 1H, H5), 6.40 (d, *J* = 9.1 Hz, 1H, H-olefine), 6.90 (d, *J* = 9.0 Hz, 1H, H-olefine), 7.04 (m, 1H, H-Ar), 7.18 (d, *J* = 7.5 Hz, 2H, H-Ar), 7.20 (d, *J* = 7.4 Hz, 2H, H-Ar),), 7.37 (d, *J* = 9.2 Hz, 1H, H-oxazepine), 7.63 (d, *J* = 7.3, 4.9 Hz, 4H, H-Ar), 7.82 (m, 2H, H-Ar), 8.15 (dd, *J* = 7.3, 5.0 Hz, 4H, H-Ar)	$C_{30}H_{21}NO_9$ C, 66.79; H, 3.92; N, 2.60 (C, 66.74; H, 3.90; N, 2.57)
8c (58%)	3083, 3066, 2926, 2865, 1772, 1761, 1687, 1601, 1564, 1423, 1355, 1201, 1151, 872, 788, 601.	3.85 (s, 3H, OCH_3), 6.15 (d, *J* = 9.3 Hz, 1H, H5), 6.40 (d, *J* = 9.1 Hz, 1H, H-olefine), 6.93 (d, *J* = 9.0 Hz, 1H, H-olefine), 6.98 (d, *J* = 7.3 Hz, 2H, H-Ar), 7.02 (m, 1H, H-Ar), 7.38 (d, *J* = 9.3 Hz, 1H, H-oxazepine), 7.41 (d, *J* = 7.4 Hz, 2H, H-Ar), 7.61 (d, *J* = 7.1, 4.9 Hz, 4H, H-Ar), 7.83 (m, 2H, H-Ar), 8.16 (dd, *J* = 7.1, 4.9 Hz, 4H, H-Ar)	$C_{30}H_{21}NO_{10}$ C, 64.87; H, 3.81; N, 2.52 (C, 64.86; H, 3.80; N, 2.50)
8d (55%)	3336, 3082, 3073, 2924, 2863, 1780, 1763, 1677, 1601, 1512, 1444, 1362, 1200, 1155, 863, 795, 610.	6.13 (d, *J* = 9.1 Hz, 1H, H5), 6.41 (d, *J* = 9.2 Hz, 1H, H-olefine), 6.92 (d, *J* = 9.1 Hz, 1H, H-olefine), 7.05 (m, 1H, H-Ar), 7.31 (m, 2H, H-Ar), 7.34 (dd, *J* = 7.5, 4.6 Hz, 2H, H-Ar), 7.39 (d, *J* = 9.2 Hz, 1H, H-oxazepine), 7.62 (d, *J* = 7.4, 4.8 Hz, 4H, H-Ar), 7.82 (m, 2H, H-Ar), 8.16 (dd, *J* = 7.3, 4.9 Hz, 4H, H-Ar), 11.64 (broad s, 1H, NH)	$C_{29}H_{20}N_2O_9$ C, 64.45; H, 3.73; N, 5.18 (C, 64.42; H, 3.70; N, 5.16)
8e (59%)	3088, 3079, 2926, 2863, 1778, 1755, 1680, 1602, 1562, 1418, 1361, 1205, 1155, 860, 795, 610.	6.15 (d, *J* = 9.2 Hz, 1H, H5), 6.39 (d, *J* = 9.1 Hz, 1H, H-olefine), 6.93 (d, *J* = 9.1 Hz, 1H, H-olefine), 7.06 (m, 1H, H-Ar), 7.40 (d, *J* = 9.1 Hz, 1H, H-oxazepine), 7.61 (d, *J* = 7.2, 4.9 Hz, 4H, H-Ar), 7.83 (m, 2H, H-Ar), 7.85 (m, 1H, H-Ar), 8.15 (dd, *J* = 7.2, 3.9 Hz, 4H, H-Ar), 8.86 (m, 2H, H-Ar).	$C_{27}H_{17}N_3O_9$ C, 61.48; H, 3.25; N, 7.97 (C, 61.44; H, 3.20; N, 7.94)
8f (58%)	3447, 3086, 3076, 2924, 2861, 1785, 1757, 1657, 1602, 1523, 1423, 1352, 1201, 1156, 875, 776, 605.	2.10 (s, 3H, OCH_3), 6.12 (d, *J* = 9.1 Hz, 1H, H5), 6.38 (d, *J* = 9.1 Hz, 1H, H-olefine), 6.92 (d, *J* = 9.0 Hz, 1H, H-olefine), 7.01 (m, 1H, H-Ar), 7.41 (d, *J* = 9.2 Hz, 1H, H-oxazepine), 7.43 (d, *J* = 7.1 Hz, 2H, H-Ar), 7.58 (d, *J* = 7.2 Hz, 2H, H-Ar), 7.62 (d, *J* = 7.1, 4.7 Hz, 4H, H-Ar), 7.81 (m, 2H, H-Ar), 8.13 (dd, *J* = 7.0, 4.9 Hz, 4H, H-Ar)	$C_{31}H_{22}N_2O_{10}$ C, 63.92; H, 3.81; N, 4.81 (C, 63.88; H, 3.78; N, 4.80)

Table 3. Characteristic FT-IR bands cm^{-1}, chemical shifts ppm and micro-elemental analysis of oxazepine derivatives 9a−f

Comp. Yield	FT-IR cm^{-1}	Chemical shift ppm (DMSO-d_6)	Formula CHN required (found)
9a (57%)	3079, 2916, 2863, 1777, 1754, 1684, 1601, 1560, 1425, 1351, 1209, 1158, 879, 788, 615, 533.	6.13 (d, *J* = 9.1 Hz, 1H, H5), 6.94 (d, *J* = 7.7 Hz, 2H, H-Ar), 7.03 (m, 1H, H-Ar), 7.34 (dd, *J* = 7.6, 4.0 Hz, 2H, H-Ar), 7.38 (d, *J* = 9.2 Hz, 1H, H-oxazepine), 7.63 (dd, *J* = 7.5, 4.0 Hz, 4H, H-Ar), 7.82 (m, 2H, H-Ar), 8.15 (dd, *J* = 7.4, 5.0 Hz, 4H, H-Ar)	$C_{29}H_{17}Cl_2NO_9$ C, 58.60; H, 2.88; Cl, 11.93; N, 2.36 (C, 58.58; H, 2.85; Cl, 11.90; N, 2.32)
9b (59%)	3083, 2922, 2860, 1778, 1758, 1680, 1604, 1556, 1428, 1355, 1203, 1151, 851, 767, 610, 556.	2.39 (s, 3H, CH_3), 6.14 (d, *J* = 9.2 Hz, 1H, H5), 7.05 (m, 1H, H-Ar), 7.19 (d, *J* = 7.4 Hz, 2H, H-Ar), 7.22 (d, *J* = 7.5 Hz, 2H, H-Ar), 7.38 (d, *J* = 9.1 Hz, 1H, H-oxazepine), 7.64 (d, *J* = 7.2, 4.2 Hz, 4H, H-Ar), 7.81 (m, 2H, H-Ar), 8.16 (dd, *J* = 7.3, 4.0 Hz, 4H, H-Ar)	$C_{30}H_{19}Cl_2NO_9$ C, 59.23; H, 3.15; Cl, 11.65; N, 2.30 (C, 59.19; H, 3.09; Cl, 11.61; N, 2.26)
9c (61%)	3079, 2921, 2856, 1780, 1762, 1683, 1600, 1567, 1426, 1365, 1207, 1158, 867, 781, 606, 586.	3.83 (s, 3H, OCH_3), 6.13 (d, *J* = 9.1 Hz, 1H, H5), 6.95 (d, *J* = 7.2 Hz, 2H, H-Ar), 7.04 (m, 1H, H-Ar), 7.39 (d, *J* = 9.1 Hz, 1H, H-oxazepine), 7.42 (d, *J* = 7.2 Hz, 2H, H-Ar), 7.62 (d, *J* = 7.2, 4.1 Hz, 4H, H-Ar), 7.84 (m, 2H, H-Ar), 8.14 (dd, *J* = 7.1, 3.9 Hz, 4H, H-Ar)	$C_{30}H_{19}Cl_2NO_{10}$ C, 57.71; H, 3.07; Cl, 11.36; N, 2.24 (C, 57.67; H, 3.02; Cl, 11.33; N, 2.22)
9d (60%)	3342, 3080, 2921, 2867, 1781, 1765, 1672, 1604, 1515, 1456, 1376, 1209, 1158, 838, 790, 617, 528.	6.15 (d, *J* = 9.2 Hz, 1H, H5), 7.05 (m, 1H, H-Ar), 7.30 (m, 2H, H-Ar), 7.35 (dd, *J* = 7.5, 4.6 Hz, 2H, H-Ar), 7.40 (d, *J* = 9.1 Hz, 1H, H-oxazepine), 7.63 (d, *J* = 7.5, 4.1 Hz, 4H, H-Ar), 7.83 (m, 2H, H-Ar), 8.14 (dd, *J* = 7.5, 4.3 Hz, 4H, H-Ar), 11.60 (broad s, 1H, NH)	$C_{29}H_{18}Cl_2N_2O_9$ C, 57.16; H, 2.98; Cl, 11.64; N, 4.60 (C, 57.15; H, 2.96; Cl, 11.63; N, 4.56)
9e (53%)	3082, 2921, 2865, 1775, 1759, 1680, 1600, 1543, 1418, 1356, 1208, 1150, 867, 746, 602, 537.	6.12 (d, *J* = 9.0 Hz, 1H, H5), 7.02 (m, 1H, H-Ar), 7.38 (d, *J* = 9.0 Hz, 1H, H-oxazepine), 7.62 (d, *J* = 7.5, 4.1 Hz, 4H, H-Ar), 7.82 (m, 2H, H-Ar), 7.87 (m, 1H, H-Ar), 8.13 (dd, *J* = 7.4, 4.0 Hz, 4H, H-Ar), 8.84 (m, 2H, H-Ar).	$C_{27}H_{15}Cl_2N_3O_9$ C, 54.38; H, 2.54; Cl, 11.89; N, 7.05 (C, 54.34; H, 2.51; Cl, 11.87; N, 7.01)
9f (56%)	3441, 3082, 2922, 2866, 1783, 1752, 1657, 1600, 1522, 1420, 1351, 1200, 1153, 871, 771, 621, 525.	2.11 (s, 3H, OCH_3), 6.14 (d, *J* = 9.0 Hz, 1H, H5), 7.04 (m, 1H, H-Ar), 7.38 (d, *J* = 9.1 Hz, 1H, H-oxazepine), 7.44 (d, *J* = 7.2 Hz, 2H, H-Ar), 7.56 (d, *J* = 7.3 Hz, 2H, H-Ar), 7.64 (d, *J* = 7.3, 4.1 Hz, 4H, H-Ar), 7.83 (m, 2H, H-Ar), 8.15 (dd, *J* = 7.1, 3.9 Hz, 4H, H-Ar)	$C_{31}H_{20}Cl_2N_2O_{10}$ C, 57.16; H, 3.09; Cl, 10.88; N, 4.30 (C, 57.12; H, 3.08; Cl, 10.85; N, 4.25)

Table 4. Characteristic FT-IR bands cm^{-1}, chemical shifts ppm and micro-elemental analysis of oxazepine derivatives 10a–f

Comp. Yield	FT-IR cm^{-1}	Chemical shift ppm (DMSO-d_6)	Formula CHN required (found)
10a (51%)	3080, 3075, 2926, 2856, 1773, 1757, 1687, 1601, 1567, 1421, 1351, 1202, 1157, 874, 754, 601.	6.15 (d, *J* = 9.0 Hz, 1H, H5), 6.94 (d, *J* = 7.7 Hz, 2H, H-Ar), 7.08 (m, 1H, H-Ar), 7.34 (dd, *J* = 7.6, 4.0 Hz, 2H, H-Ar), 7.38 (d, *J* = 9.2 Hz, 1H, H-oxazepine), 7.63 (dd, *J* = 7.5, 4.0 Hz, 4H, H-Ar), 7.76 (t, *J* = 8.1 Hz, 1H, H-Ar), 7.81 (t, *J* = 8.2 Hz, 1H, H-Ar), 7.82 (m, 3H, H-Ar), 8.10 (d, *J* = 8.4 Hz, 1H, H-Ar), 8.15 (dd, *J* = 7.4, 5.0 Hz, 4H, H-Ar)	$C_{31}H_{19}N_3O_9$ C, 68.87; H, 3.68; N, 2.43 (C, 68.82; H, 3.65; N, 2.39)
10b (57%)	3085, 3077, 2923, 2865, 1779, 1760, 1681, 1601, 1552, 1422, 1352, 1200, 1154, 851, 762, 614.	2.41 (s, 3H, CH_3), 6.14 (d, *J* = 9.2 Hz, 1H, H5), 7.02 (m, 1H, H-Ar), 7.19 (d, *J* = 7.4 Hz, 2H, H-Ar), 7.22 (d, *J* = 7.5 Hz, 2H, H-Ar), 7.38 (d, *J* = 9.1 Hz, 1H, H-oxazepine), 7.65 (dd, *J* = 7.4, 4.0 Hz, 4H, H-Ar), 7.75 (t, *J* = 8.1 Hz, 1H, H-Ar), 7.82 (t, *J* = 8.2 Hz, 1H, H-Ar), 7.84 (m, 3H, H-Ar), 8.12 (d, *J* = 8.4 Hz, 1H, H-Ar), 8.14 (dd, *J* = 7.4, 5.0 Hz, 4H, H-Ar)	$C_{34}H_{23}NO_9$ C, 69.27; H, 3.93; N, 2.38 (C, 69.25; H, 3.93; N, 2.34)
10c (55%)	3090, 3081, 2927, 2851, 1779, 1761, 1681, 1605, 1563, 1422, 1361, 1203, 1154, 862, 785, 601.	3.85 (s, 3H, OCH_3), 6.13 (d, *J* = 9.1 Hz, 1H, H5), 6.95 (d, *J* = 7.2 Hz, 2H, H-Ar), 7.03 (m, 1H, H-Ar), 7.39 (d, *J* = 9.1 Hz, 1H, H-oxazepine), 7.61 (dd, *J* = 7.5, 4.0 Hz, 4H, H-Ar), 7.75 (t, *J* = 8.1 Hz, 1H, H-Ar), 7.82 (t, *J* = 8.2 Hz, 1H, H-Ar), 7.85 (m, 3H, H-Ar), 8.12 (d, *J* = 8.4 Hz, 1H, H-Ar), 8.16 (dd, *J* = 7.4, 5.0 Hz, 4H, H-Ar)	$C_{34}H_{23}NO_{10}$ C, 67.44; H, 3.83; N, 2.31 (C, 67.41; H, 3.82; N, 2.30)
10d (50%)	3345, 3087, 3078, 2924, 2862, 1783, 1762, 1683, 1601, 1525, 1452, 1375, 1202, 1153, 834, 791, 612.	6.15 (d, *J* = 9.2 Hz, 1H, H5), 7.05 (m, 1H, H-Ar), 7.30 (m, 2H, H-Ar), 7.35 (dd, *J* = 7.5, 4.6 Hz, 2H, H-Ar), 7.40 (d, *J* = 9.1 Hz, 1H, H-oxazepine), 7.63 (dd, *J* = 7.4, 4.0 Hz, 4H, H-Ar), 7.76 (t, *J* = 8.1 Hz, 1H, H-Ar), 7.82 (t, *J* = 8.2 Hz, 1H, H-Ar), 7.84 (m, 3H, H-Ar), 8.12 (d, *J* = 8.4 Hz, 1H, H-Ar), 8.17 (dd, *J* = 7.4, 5.0 Hz, 4H, H-Ar)	$C_{33}H_{22}N_2O_9$ C, 67.12; H, 3.76; N, 4.74 (C, 67.09; H, 3.74; N, 4.73)
10e (54%)	3089, 3077, 2925, 2862, 1777, 1758, 1684, 1604, 1545, 1411, 1353, 1204, 1154, 864, 741, 603.	6.12 (d, *J* = 9.0 Hz, 1H, H5), 7.03 (m, 1H, H-Ar), 7.31 (m, 2H, H-Ar), 7.34 (dd, *J* = 7.5, 4.6 Hz, 2H, H-Ar), 7.38 (d, *J* = 9.0 Hz, 1H, H-oxazepine), 7.61 (dd, *J* = 7.5, 4.0 Hz, 4H, H-Ar), 7.75 (t, *J* = 8.1 Hz, 1H, H-Ar), 7.80 (t, *J* = 8.2 Hz, 1H, H-Ar), 7.84 (m, 3H, H-Ar), 8.10 (d, *J* = 8.4 Hz, 1H, H-Ar), 8.14 (dd, *J* = 7.4, 5.0 Hz, 4H, H-Ar)	$C_{31}H_{19}N_3O_9$ C, 64.47; H, 3.32; N, 7.28 (C, 64.42; H, 3.30; N, 7.25)
10f (51%)	3445, 3082, 8076, 2924, 2863, 1784, 1755, 1657, 1601, 1522, 1420, 1351, 1200, 1153, 878, 777, 623.	2.11 (s, 3H, OCH_3), 6.14 (d, *J* = 9.0 Hz, 1H, H5), 7.04 (m, 1H, H-Ar), 7.38 (d, *J* = 9.1 Hz, 1H, H-oxazepine), 7.61 (dd, *J* = 7.5, 4.0 Hz, 4H, H-Ar), 7.74 (t, *J* = 8.1 Hz, 1H, H-Ar), 7.81 (t, *J* = 8.2 Hz, 1H, H-Ar), 7.86 (m, 3H, H-Ar), 8.12 (d, *J* = 8.4 Hz, 1H, H-Ar), 8.15 (dd, *J* = 7.4, 5.0 Hz, 4H, H-Ar)	$C_{35}H_{24}N_2O_{10}$ C, 66.46; H, 3.82; N, 4.43 (C, 66.46; H, 3.82; N, 4.43)

Table 5. Characteristic FT-IR bands cm^{-1}, chemical shifts ppm and micro-elemental analysis of oxazepine derivatives 11a–f

Comp. No.	FT-IR cm^{-1}	Chemical shift ppm (DMSO-d_6)	Formula CHN required (found)
11a (59%)	3084, 3076, 2922, 2856, 1773, 1757, 1687, 1601, 1567, 1550, 1422, 1353, 1201, 1152, 872, 751, 600.	6.15 (d, *J* = 9.0 Hz, 1H, H5), 6.94 (d, *J* = 7.7 Hz, 2H, H-Ar), 7.08 (m, 1H, H-Ar), 7.34 (dd, *J* = 7.6, 4.0 Hz, 2H, H-Ar), 7.39 (d, *J* = 9.2 Hz, 1H, H-oxazepine), 7.63 (dd, *J* = 7.5, 4.0 Hz, 4H, H-Ar), 7.76 (t, *J* = 8.1 Hz, 1H, H-Ar), 7.81 (t, *J* = 8.2 Hz, 1H, H-Ar), 7.82 (m, 3H, H-Ar), 8.10 (d, *J* = 8.4 Hz, 1H, H-Ar), 8.15 (dd, *J* = 7.4, 5.0 Hz, 4H, H-Ar), 8.45 (d, *J* = 8.3 Hz, 1H, H-Ar), 8.48 (s, 1H, H-Ar), 8.55 (d, *J* = 8.3 Hz, 1H, H-Ar).	$C_{33}H_{20}N_2O_{11}$ C, 63.88; H, 3.25; N, 4.51 (C, 63.86; H, 3.22; N, 4.51)
11b (60%)	3089, 3075, 2922, 2861, 1778, 1763, 1681, 1606, 1552, 1540, 1422, 1352, 1200, 1154, 851, 762, 614.	2.40 (s, 3H, CH_3), 6.14 (d, *J* = 9.2 Hz, 1H, H5), 7.02 (m, 1H, H-Ar), 7.19 (d, *J* = 7.4 Hz, 2H, H-Ar), 7.22 (d, *J* = 7.5 Hz, 2H, H-Ar), 7.38 (d, *J* = 9.1 Hz, 1H, H-oxazepine), 7.62 (dd, *J* = 7.5, 4.0 Hz, 4H, H-Ar), 7.75 (t, *J* = 8.1 Hz, 1H, H-Ar), 7.82 (t, *J* = 8.2 Hz, 1H, H-Ar), 7.85 (m, 3H, H-Ar), 8.10 (d, *J* = 8.4 Hz, 1H, H-Ar), 8.14 (dd, *J* = 7.4, 5.0 Hz, 4H, H-Ar), 8.46 (d, *J* = 8.3 Hz, 1H, H-Ar), 8.49 (s, 1H, H-Ar), 8.57 (d, *J* = 8.3 Hz, 1H, H-Ar).	$C_{34}H_{22}N_2O_{11}$ C, 64.36; H, 3.49; N, 4.41 (C, 64.35; H, 3.45; N, 4.37)
11c (62%)	3092, 3082, 2924, 2852, 1777, 1763, 1680, 1603, 1563, 1551, 1421, 1365, 1201, 1157, 861, 775, 600.	3.83 (s, 3H, OCH_3), 6.13 (d, *J* = 9.1 Hz, 1H, H5), 6.95 (d, *J* = 7.2 Hz, 2H, H-Ar), 7.03 (m, 1H, H-Ar), 7.39 (d, *J* = 9.1 Hz, 1H, H-oxazepine), 7.61 (dd, *J* = 7.5, 4.0 Hz, 4H, H-Ar), 7.75 (t, *J* = 8.1 Hz, 1H, H-Ar), 7.80 (t, *J* = 8.2 Hz, 1H, H-Ar), 7.82 (m, 3H, H-Ar), 8.11 (d, *J* = 8.4 Hz, 1H, H-Ar), 8.16 (dd, *J* = 7.4, 5.0 Hz, 4H, H-Ar), 8.44 (d, *J* = 8.3 Hz, 1H, H-Ar), 8.48 (s, 1H, H-Ar), 8.56 (d, *J* = 8.3 Hz, 1H, H-Ar).	$C_{34}H_{22}N_2O_{12}$ C, 62.77; H, 3.41; N, 4.31 (C, 62.73; H, 3.39; N, 4.30)
11d (61%)	3348, 3087, 3079, 2926, 2866, 1781, 1760, 1681, 1600, 1545, 1525, 1450, 1373, 1201, 1156, 830, 795, 610.	6.15 (d, *J* = 9.2 Hz, 1H, H5), 7.05 (m, 1H, H-Ar), 7.30 (m, 2H, H-Ar), 7.35 (dd, *J* = 7.5, 4.6 Hz, 2H, H-Ar), 7.40 (d, *J* = 9.1 Hz, 1H, H-oxazepine), 7.63 (dd, *J* = 7.5, 4.0 Hz, 4H, H-Ar), 7.74 (t, *J* = 8.1 Hz, 1H, H-Ar), 7.82 (t, *J* = 8.2 Hz, 1H, H-Ar), 7.84 (m, 3H, H-Ar), 8.13 (d, *J* = 8.4 Hz, 1H, H-Ar), 8.16 (dd, *J* = 7.4, 5.0 Hz, 4H, H-Ar), 8.46 (d, *J* = 8.3 Hz, 1H, H-Ar), 8.48 (s, 1H, H-Ar), 8.56 (d, *J* = 8.3 Hz, 1H, H-Ar).	$C_{33}H_{21}N_3O_{11}$ C, 62.37; H, 3.33; N, 6.61 (C, 62.33; H, 3.33; N, 6.58)
11e (59%)	3085, 3073, 2923, 2861, 1779, 1760, 1682, 1604, 1550, 1545,	6.14 (d, *J* = 9.0 Hz, 1H, H5), 7.04 (m, 1H, H-Ar), 7.33 (m, 2H, H-Ar), 7.37 (dd, *J* = 7.5, 4.6 Hz, 2H, H-Ar), 7.39 (d, *J* = 9.0 Hz, 1H, H-oxazepine), 7.63 (dd, *J* = 7.5, 4.0 Hz, 4H, H-Ar), 7.75 (t, *J* = 8.1 Hz, 1H, H-Ar), 7.79 (t, *J*	$C_{31}H_{18}N_4O_{11}$ C, 59.81; H, 2.91; N, 9.00 (C, 59.77; H, 2.90; N, 8.98)

	1421, 1356, 1201, 1153, 861, 745, 599.	= 8.2 Hz, 1H, H-Ar), 7.82 (m, 3H, H-Ar), 8.10 (d, *J* = 8.4 Hz, 1H, H-Ar), 8.13 (dd, *J* = 7.4, 5.0 Hz, 4H, H-Ar), 8.45 (d, *J* = 8.3 Hz, 1H, H-Ar), 8.47 (s, 1H, H-Ar), 8.54 (d, *J* = 8.3 Hz, 1H, H-Ar).	
11f (60%)	3449, 3080, 8070, 2925, 2863, 1782, 1755, 1655, 1601, 1555, 1522, 1421, 1357, 1208, 1158, 899, 789, 620.	2.13 (s, 3H, OCH_3), 6.14 (d, *J* = 9.0 Hz, 1H, H5), 7.04 (m, 1H, H-Ar), 7.33 (m, 2H, H-Ar), 7.38 (d, *J* = 9.1 Hz, 1H, H-oxazepine), 7.63 (dd, *J* = 7.5, 4.0 Hz, 4H, H-Ar), 7.76 (t, *J* = 8.1 Hz, 1H, H-Ar), 7.81 (t, *J* = 8.2 Hz, 1H, H-Ar), 7.82 (m, 3H, H-Ar), 8.10 (d, *J* = 8.4 Hz, 1H, H-Ar), 8.16 (dd, *J* = 7.4, 5.0 Hz, 4H, H-Ar), 8.44 (d, *J* = 8.3 Hz, 1H, H-Ar), 8.47 (s, 1H, H-Ar), 8.56 (d, *J* = 8.3 Hz, 1H, H-Ar).	$C_{35}H_{23}N_3O_{12}$ C, 62.04; H, 3.42; N, 6.20 (C, 62.00; H, 3.41; N, 6.20)

Biological activity

The antibacterial activity of the synthesized oxazepines **8**–**11** were tested against two bacterial species: *S. aureus* and *E. coli* using disk diffusion method. Only chlorinated derivatives **9a**–**9f** showed weak to fair inhibition zones 7, 5, 6, 10, 3 and 11 mm respectively for *S. aureus* only compared to ampicillin 29 mm and exhibited no activity against *E. coli* (Table 6). The main reason of the antibacterial activity of compounds **9a**–**9f** is that the structure activity relationship (SAR) of these molecules is influenced by chlorine and its electron density. [20,21] On the other hand, compounds **9d** and **9f** demonstrated greater inhibition zone compared to other chlorine-containing derivatives. This can be attributed to the presence of the NH moiety which can paly crucial role in the formation of hydrogen bonding and which in turn increase the probability of ligand-receptor interactions.[22,23]

Table 6. Inhibition zone of the chlorinated compounds 9a–9f against *S. aureus* and *E. coli*

Compound	Inhibition zone against *S. aureus* (mm)	Inhibition zone against *E. coli* (mm)
DMSO	-	-
Ampicillin	30	-
9a	7	-
9b	5	-
9c	6	-
9d	10	-
9e	3	-
9f	11	-

Conclusion

New oxazepine derivatives are synthesized starting from L-ascorbic acid via [2 + 5] cycloaddition. It is found that the anhydrides with electron-withdrawing group such as chloro group in 2,3-dichloromaleic anhydride and nitro group 3-nitrophthalic anhydride react more rapidly with amine derivatives because these groups increase the electrophilicity of the carbonyl of the anhydride and this will facilitate the attack of the nitrogen lone pair of imine. The antibacterial activity against *S. aureus* and *E. coli* is performed using disk diffusion method. The chlorinated set of compounds revealed weak to fair activity against *S. aureus* compared to ampicillin.

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