Original Article

Ultrasound Assisted Synthesis, Characterization and Antimicrobial Evaluation of Novel Oxazolidinone-Biphenyl Chalcone Hybrid Derivatives

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ABSTRACT

Objective: The main objective of our present study, is to potentiate the antibacterial activity of biphenyl chalcones and oxazolidinones, thus in order to achieve the potent antibacterial agents, we coupled both derivatives by using green chemistry approach for Buchwald's protocol under ultrasound irradiation. **Methodology:** Ultrasonication technique was used to couple a series of 24 novel bromo-biphenyl-chalcone derivatives and 5-chloromethyl-oxazolidinone in the presence of copper iodide (CuI) (10 mol %) for the amidation of chalcones and (±)-*trans*-1,2-diaminocyclohexane was used to solubilize CuI and potassium carbonate (K_2CO_3) as base, which provided the products in good yields after short reaction times under mild conditions. **Results and Discussion:** Herewith we report the synthesis of 24 novel oxazolidinone-biphenyl chalcone hybrid derivatives (7a-7x). All the synthesized compounds were characterized by spectral data and evaluated for *in vitro* antibacterial and antifungal activities. Antibacterial and antifungal activities were tested using the serial dilution method. From the screening studies it was observed that compounds 7c to 7g have shown significant antibacterial activities against the both the strains of gram-positive and gram-negative bacteria at 3.125 μg/ml when compared to the standard drugs ciprofloxacin and linezolid and were as other compounds showed moderate to weak activities. In case of antifungal studies the compounds 7e-7g showed moderate activities at 12.5 μg/ml compared to standard fluconazole and whereas other compounds showed weak activities. **Conclusion:** We have developed an experimentally simple, efficient, short time and high yielding CuI-mediated N-arylation of oxazolidinones under ultrasound irradiation with a simple set up at room temperature. This approach would be a worthwhile in the development of green chemistry protocols. Compounds 7c to 7g have shown significant antibacterial activities against the both the strains of gram-positive and gram-negative bacteria.

Key words: Buchwald's Protocol, Ultrasound (US) irradiation, Lithium hydroxide monohydrate ($LiOH.H_2O$), Aryl aldehydes, Biphenyl chalcones, 5-chloromethyl-oxazolidinone.

Submission Date: 30-10-2018;
Revision Date: 28-12-2018;
Accepted Date: 18-01-2019

DOI: 10.5530/ijper.53.2.37

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INTRODUCTION

N-Aryloxazolidinones are a novel and promising class of synthetic antibiotics that have recently emerged as important therapeutic agents, active against numerous multidrug-resistant gram-positive organisms.[1] N-Aryloxazolidinones are currently the center of interest in pharmaceutical research and continuous synthetic efforts are necessary to develop more effective antibacterial agents. Linezolid (1) was the first member of this series introduced in the market (Figure-1).[1] The combination of two antibacterial cores or substructures into a single entity to achieve drugs has received considerable attention.[2] Both the oxazolidinones and chalcone drugs exhibit antibacterial

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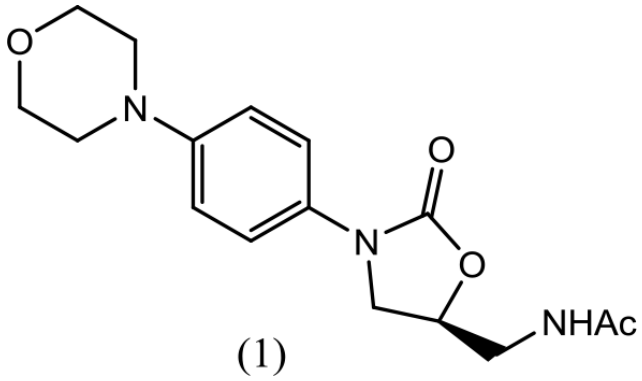


Figure 1: Structural information of linezolid.

activities[3-7] thus, efforts to enhance the spectrum and potency of this class of hybrid antibiotics have been ongoing throughout the pharmaceutical industry.[8]

Recently Selvakumar *et al*.[6] synthesized hybrid compounds possessing both chalcone and oxazolidinone moieties that were tested for antibacterial activity against gram-positive organisms and these hybrid molecules were found to be active. Based on our analysis of the limited data available on published oxazolidinone-chalcone hybrids till date, we decided that the most prudent approach would be to synthesize a novel type of analogs, which embody both the characteristic oxazolidinone core and a biphenyl chalcone fragment.

To date only a few number of synthetic methods have been established towards the synthesis of these hybrid compounds, however few examples were found where coupling of oxazolidinones with aryl halides were achieved in a one-pot process using Buchwald's protocol.[9]

Over the past decades, many catalytic procedures were developed for carbon–nitrogen bond formation, for instance, amination of aryl halides, amidation and hydroamination, have been reported. Nevertheless, further improvements are still possible.[10] Hartwig, Buchwald and Shakespeare have reported that arylation of amines, amides and C-N bond forming cross-coupling reactions of NH-containing substrates has emerged as a powerful methodology.[11]

Landmark innovations from the above groups have continued to inspire researchers to discover milder and more selective conditions for a diverse array of substrates. This has led to the development of various synthetic strategies for many important heterocyclic systems. Traditional synthetic methods of N-arylation of copper-mediated coupling reactions has various limitations, such as high-temperature reaction conditions, moderate yields, use of expensive ligands and stoichiometric amounts of the catalyst.[10] Hence, efforts have been put towards the development of new, eco-friendly, high yielding, inexpensive and green chemistry approach for coupling of aryl halides (bromine containing biphenyl chalcones) with oxazolidinone.

Ultrasonic irradiation leads to the acceleration of numerous catalytic reactions both in homogeneous and heterogeneous systems.[12] The driving force for sono-chemistry is cavitation,[13] in other words, the bubbles are generated at localized sites in the liquid mixture that contain small amounts of dissolved gases. Within the microbubble, the reactants collide with each other and the molecules are fractured, forming highly reactive species, which readily react with the surrounding molecules. Thus, beneficial effects were observed under sonication on the chemical reactivity, such as to accelerate the reaction, to reduce the induction period and to enhance the catalyst efficiency.[12]

In view of the above and in continuation of our research work, we took the advantages of sonochemical method for coupling of 24 bromine containing biphenyl chalcones with 5-chloromethyl-2-oxazolidinone. As far as we are aware there are no reports on any reaction between these above mentioned chemical entities.

MATERIALS AND METHODS

Materials

All the chemicals and reagents were purchased from Sigma Aldrich India, Merck and Molychem India. All the reagents were used without purification and solvents used were of analytical grade.

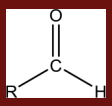
Melting point was checked using capillary method and was uncorrected. The IR spectra of synthesized compounds were taken on Bruker FTIR spectrophotometer. ^{1}H NMR spectra were recorded on Bruker Avance DRX400 (400 MHz, FTNMR) in DMSO and $CDCl_3$ solvents. Chemical shifts were reported as δ (ppm); TMS was taken as internal standard. Coupling constants J are expressed in Hertz. Mass spectra was recorded on Agilent 6410 Triple Quadrupole LC/MS and Agilent 6545 Q-TOF LC/MS. Reaction progress was monitored by TLC, under UV radiation chamber as the visualizing aid. Column chromatography was performed on silica gel (100–200 mesh).Sonication was performed by locating the reaction flask in the maximum energy area in ultrasonic cleaner (with a frequency of 50 Hz and a nominal power 170 W).

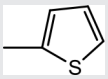
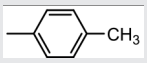
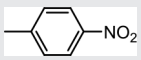
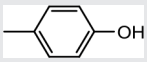
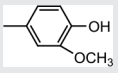
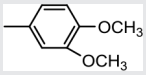
Experimental

General Procedure for Synthesis of Biphenyl Chalcones[7]

A mixture of ketone [4'-(4-bromophenyl)-acetophenone] (2) (1 g, 3.63 mmol) and corresponding aryl aldehydes

Table 1: Corresponding aryl aldehydes used during synthesis of chalcones (3a-3x).



Compound Code	Substitutions at (R)	Compound Code	Substitutions at (R)
3a		3m	
3b		3n	
3c		3o	
3d		3p	
3e		3q	
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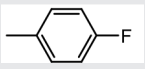
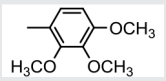
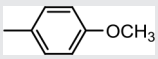
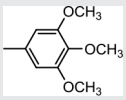
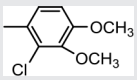
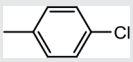
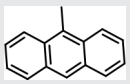
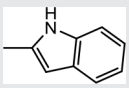
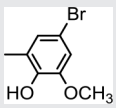
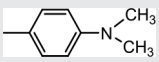
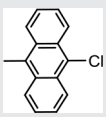
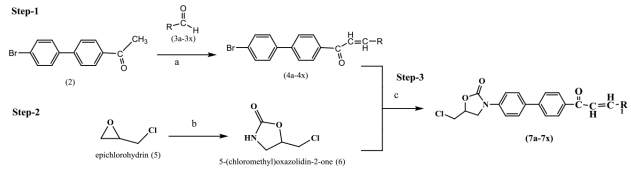
3g		3s	
3h		3t	
3i		3u	
3j		3v	
3k		3w	
3l		3x	

(3a-3x) (shown in Table 1) (3.63 mmol) in ethanol (25 mL) was treated with lithium hydroxide monohydrate ($LiOH \cdot H_2O$) (15 mg, 0.363 mmol). The mixture was irradiated in water bath of an ultrasonic cleaner at room temperature until a precipitate was formed. This reaction mixture was then poured over crushed ice and acidified with dilute HCl (18.5 %). The solid thus obtained was filtered, washed with water and dried over anhydrous sodium sulfate (Na_2SO_4). Further, the



Scheme 1: Reagents and Conditions : a) $LIOH.H_2O$, Ethanol,Sonication, 25 ^{0}C, 1h b) KOCN, Mg_2SO_4, H_2O,Reflux, 15h c) (±)-trans-1,2-Diaminocyclohexane, 1,4-dioxane, CuI, K_2CO_3,Sonication, 25 ^{0}C.

Scheme 1: General procedure for synthesis of oxazolidinone-biphenyl chalcone hybrid derivatives (7a-7x).

residue obtained was purified on column chromatography to afford pure crystals of (4a-4x) (as shown in Scheme-1, step-1).

General Procedure for Synthesis of 5-(chloromethyl)-oxazolidin-2-one (5)[14]

To a stirred solution of epichlorohydrin (5.0 g, 0.054 mol) in water (50 mL), potassium cyanate (8.76 g, 0.108 mol) and magnesium sulfate (13.0 g, 0.108 mol) were added at ambient temperature. The temperature of the reaction mixture was maintained at 100°C and refluxed for 15 hrs. The reaction mixture was filtered to remove solids and the resulted filtrate was extracted with ethyl acetate (2×25 mL). The combined organic layer was washed with saturated sodium chloride solution (25 mL), dried over anhydrous sodium sulfate and the solvent was removed by evaporation under reduced pressure. The solid obtained was purified by column chromatography with n-hexane: ethylacetate (7:3) to afford **5**-(chloromethyl)-oxazolidin-2-one (5) as a white solid (as shown in scheme-1, step-2).

General Procedure for Coupling of 5-(chloromethyl)-oxazolidin-2-one with biphenyl Chalcones[15]

A mixture of corresponding biphenyl chalcones (4a-4x) (1 gm, 2.6 mmol), 5-(chloromethyl)-oxazolidin-2-one (6) (358 mg, 2.6 mmol), copper iodide (49 mg, 0.26 mmol), potassium carbonate (718 mg, 5.2 mmol), (±)-*trans*-1,2-diaminocyclohexane (29 mg, 0.26 mmol) and 2 mL of dry 1,4-dioxane were added using a syringe at room temperature to 25 mL of volumetric flask. The cap of the flask was fitted with a rubber septum and was evacuated, back filled with nitrogen gas by using a balloon and this sequence was repeated twice. The mixture was irradiated in the water bath of an ultrasonic cleaner at the room temperature for 2 to 3hrs. The reaction was quenched by adding ethyl acetate and the resulting solution was filtered through a pad of celite. The filtrate was concentrated and the residue was purified by column chromatography on silica gel (100-200 mesh)

using n-hexane: ethylacetate (7:3) as solvent to afford (7a-7x) (as shown in scheme-1, step-3).

1-(4'-bromo-[1,1'-biphenyl]-4-yl)-3-(thiophen-2-yl) prop-2-en-1-one (4a)

Yield: 85%, mp: 143-145 (°C); IR (KBr) (cm^{-1}): 3014.40 (aromatic =C-H), 1691.88 (C=O), 1597.97 (aromatic –C=C-), 783.35 (-C-Br), ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.93–7.99 (m, 2H), 7.90–7.91 (d, *J* = 15.3 Hz, 1H), 7.76–7.82 (m, 2H), 7.76 (d, 1H), 7.64–7.69 (m, 2H), 7.56–7.67 (m, 3H), 7.50–7.59 (m, 1H), 7.15 (d, 1H).

1-(4'-bromo-[1,1'-biphenyl]-4-yl)-3-(p-tolyl)prop-2-en-1-one (4b)

Yield: 83%, mp: 115-116 (°C); IR (KBr) (cm^{-1}): 2928.74 (aromatic =C-H), 1675.02 (C=O), 1515.98 (aromatic –C=C-), 599.53 (-C-Br), ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.03–8.07 (d, 2H), 7.60–7.69 (m, 5H), 7.50–7.54 (m, 3H), 7.30–7.35 (m, 3H), 7.20 (d, *J* = 15.0 Hz, 1H), 2.65 (s, 3H).

1-(4'-bromo-[1,1'-biphenyl]-4-yl)-3-(2-hydroxyphenyl) prop-2-en-1-one (4c)

Yield: 65%, mp:132-133 (°C); IR (KBr) (cm^{-1}): 3079.51 (aromatic =C-H), 1702.25 (C=O), 1580.79 (aromatic –C=C-), 783.35 (-C-Br), 3426.22 (-OH stretch), ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.21 (s, 1H), 7.93-7.96 (d, *J* = 15.1 Hz, 1H), 7.89–7.91 (d, 2H), 7.79–7.81 (d, 2H), 7.60–7.65 (m, 4H), 7.47–7.50 (d, 2H), 7.33-7.36 (d, 1H), 6.97-7.00 (d, 1H), 6.79-6.81 (dd, 1H).

1-(4'-bromo-[1,1'-biphenyl]-4-yl)-3-(4-hydroxyphenyl)prop-2-en-1-one (4d)

Yield: 72%, mp:135-136 (°C); IR (KBr) (cm^{-1}): 3085.60 (aromatic =C-H), 3442.94 (-OH stretch), 1749.85 (C=O), 1586.08 (aromatic –C=C-), 789.43 (-C-Br), ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.93–7.96 (d, 2H), 7.78–7.81 (d, 2H), 7.75 (s, 1H), 7.63-7.65 (m, 3H), 7.60-7.61 (d, 2H), 7.51–7.53 (m, 2H), 7.38-7.41 (d, 1H), 6.78– 6.80 (m, 2H).

1-(4'-bromo-[1,1'-biphenyl]-4-yl)-3-(2-fluorophenyl)prop-2-en-1-one (4e)

Yield: 78%, mp: 112-113 (°C); IR (KBr) (cm^{-1}): 3570.06 (aromatic =C-H), 1654.94 (C=O), 1590.72 (aromatic –C=C-), 750.01 (-C-Br), 1158.77 (-C-F),^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.87–7.93 (m, 2H), 7.78–7.84 (m, 2H), 7.74–7.75 (d, *J* = 15.0 Hz, 1H), 7.63–7.67 (m, 2H), 7.61–7.62 (d, 2H), 7.58 (d, 1H), 7.39– 7.47 (d, 2H), 7.27–7.28 (d, 1H), 7.13–7.14 (d, 1H).

1-(4'-bromo-[1,1'-biphenyl]-4-yl)-3-(3-fluorophenyl)prop-2-en-1-one (4f)

Yield: 79%, mp: 110-111 (°C); IR (KBr) (cm^{-1}): 3570.06 (aromatic =C-H), 1654.94 (C=O), 1590.72 (aromatic –C=C-), 750.01 (-C-Br), 1158.77 (-C-F), ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.86–7.92 (m, 2H), 7.77–7.84 (m, 2H), 7.72–7.74 (d, *J* = 15.0 Hz, 1H), 7.63–7.67 (m, 4H), 7.62-7.63 (d, 1H), 7.57-7.61 (m, 1H), 7.39–7.47 (m, 2H), 7.18–7.26 (m, 1H).

1-(4'-bromo-[1,1'-biphenyl]-4-yl)-3-(4-fluorophenyl)prop-2-en-1-one (4g)

Yield: 71%, mp: 111-112 (°C); IR (KBr) (cm^{-1}): 3570.06 (aromatic =C-H), 1654.94 (C=O), 1590.72 (aromatic –C=C-), 750.01 (-C-Br), 1158.77 (-C-F), ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.10–8.13 (d, 1H), 8.04–8.06 (d, 1H), 7.81–7.85 (d, *J* = 15.0 Hz ,1H), 7.61–7.72 (m, 6H), 7.50–7.54 (m, 3H), 7.12–7.17 (m, 2H).

1-(4'-bromo-[1,1'-biphenyl]-4-yl)-3-(4-methoxyphenyl)prop-2-en-1-one (4h)

Yield: 82%, mp: 156-157 (°C); IR (KBr) (cm^{-1}): 3509.10 (aromatic =C-H), 1697.69 (C=O), 1575.44 (aromatic –C=C-), 662.61 (-C-Br), ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.08–8.10 (m, 2H), 7.82–7.85 (d, 1H), 7.67–7.69 (d, 2H), 7.52–7.62 (m, 4H), 7.37–7.411 (d, 1H), 6.72–6.75 (d, 2H), 3.12 (s, 3H).

1-(4'-bromo-[1,1'-biphenyl]-4-yl)-3-(2-chlorophenyl)prop-2-en-1-one (4i)

Yield: 91%, mp: 118-119 (°C); IR (KBr) (cm^{-1}): 3561.89 (aromatic =C-H), 1699.52 (C=O), 1553.71 (aromatic –C=C-), 678.59 (-C-Br), ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.20–8.21 (d, 1H), 8.01–8.04 (d, 2H), 7.80–8.00 (d, *J* = 15.0 Hz , 1H), 7.61–7.71 (m, 6H), 7.50–7.54 (m, 3H), 7.12–7.15 (m, 1H).

1-(4'-bromo-[1,1'-bi phenyl]-4-yl)-3-(4-chlorophenyl)prop-2-en-1-one (4j)

Yield: 90%, mp: 116-117 (°C); IR (KBr) (cm^{-1}): 3561.89 (aromatic =C-H), 1699.52 (C=O), 1553.71 (aromatic –C=C-), 678.59 (-C-Br), ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.87–7.92 (m, 2H), 7.78–7.83 (m, 2H), 7.76 (d, *J* = 15.3 Hz, 1H), 7.69–7.75 (m, 2H), 7.62–7.67 (m, 2H), 7.56–7.60 (m, 2H), 7.49–7.55 (m, 2H), 7.39-7.42 (d, 1H).

1-(4'-bromo-[1,1'-biphenyl]-4-yl)-3-(1H-indol-2-yl) prop-2-en-1-one (4k)

Yield: 68%, mp: 182-183 (°C); IR (KBr) (cm^{-1}): 3532.54 (aromatic =C-H), 3374.33 (N-H stretch) 1631.51

(C=O), 1563.80 (aromatic –C=C-), 665.22 (-C-Br), ^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.08 (s, 1H), 8.32–8.34 (d, 1H), 8.03–8.06 (d, 3H), 7.89–7.90 (d, *J* = 1.5 Hz, 1H), 7.60–7.67 (m, 4H), 7.44–7.49 (m, 4H), 7.32–7.34 (m, 2H).

1-(4'-bromo-[1,1'-biphenyl]-4-yl)-3-(4-(dimethylamino)phenyl)prop-2-en-1-one (4l)

Yield: 88%, mp: 162-163 (°C); IR (KBr) (cm^{-1}): 3637.10 (aromatic =C-H), 1650.54 (C=O), 1580.69 (aromatic –C=C-), 684.58 (-C-Br), ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.05–8. 08 (d, 2H), 7.80–7.84 (d, 2H), 7.67–7.68 (d, 3H), 7.56–7.62 (m, 4H), 7.52–7.54 (d, 2H), 7.35–7.39 (d, *J* = 1.5 Hz, 1H), 3.03 (s, 6H).

1-(4'-bromo-[1,1'-biphenyl]-4-yl)-3-(2-nitrophenyl) prop-2-en-1-one (4m)

Yield: 81%, mp: 182-183 (°C); IR (KBr) (cm^{-1}): 3674.52 (aromatic =C-H), 1696.38 (C=O), 1552.44 (aromatic –C=C-),1342.51 (Ar-NO_2), 743.52 (-C-Br), ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.28–8.30 (d, 1H), 8.10–8.12 (d, 2H), 7.82–7.88 (d, 2H), 7.72–7.74 (d, 2H), 7.61–7.67 (m, 4H), 7.52–7.54 (d, 2H).

1-(4'-bromo-[1,1'-biphenyl]-4-yl)-3-(3-nitro phenyl) prop-2-en-1-one (4n)

Yield: 84%, mp: 188-189 (°C); IR (KBr) (cm^{-1}): 3674.52 (aromatic =C-H), 1696.38 (C=O), 1552.44 (aromatic –C=C-),1342.51 (Ar-NO_2), 743.52 (-C-Br), ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.29–8.31 (d, 1H), 8.12–8.14 (d, 1H), 7.84–7.89 (d, 3H), 7.71–7.73 (m, 3H), 7.62–7.68 (m, 4H), 7.53–7.55 (d, 2H).

1-(4'-bromo-[1,1'-biphenyl]-4-yl)-3-(4-nitrophenyl) prop-2-en-1-one (4o)

Yield: 77%, mp: 185-186 (°C); IR (KBr) (cm^{-1}): 3502.10 (aromatic =C-H), 1694.53 (C=O), 1551.63 (aromatic –C=C-),1339.32 (Ar-NO_2), 689.25 (-C-Br), ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.19–8.25 (m, 2H), 7.88–7.94 (m, 2H), 7.74–7.84 (m, 5H), 7.61–7.68 (m, 3H), 7.56–7.60 (m, 2H).

1-(4'-bromo-[1,1'-biphenyl]-4-yl)-3-(4-hydroxy-3-methoxy phenyl)prop-2-en-1-one (4p)

Yield: 66% , mp: 108-109 (°C); IR (KBr) (cm^{-1}): 3664.97 (aromatic =C-H), 3407.81 (-OH stretch), 1641.26 (C=O), 1580.80 (aromatic –C=C-), 690.78 (-C-Br), ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.20 (s, 1H), 7.78–7.83 (d, 2H), 7.65–7.67 (m, 3H), 7.69–7.63 (m, 5H), 7.58–7.60 (d, 2H), 7.43–7.46 (d, *J* = 15.0 Hz, 1H), 3.84 (s, 3H).

1-(4'-bromo-[1,1'-biphenyl]-4-yl)-3-(3,4-dimethoxy phenyl)prop-2-en-1-one (4q)

Yield: 92%, mp: 103-104 (°C); IR (KBr) (cm^{-1}): 3074.57 (aromatic =C-H), 1656.65 (C=O), 1583.65 (aromatic –C=C-), 620.81 (-C-Br), ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.09–8.11 (d, 2H), 7.83–7.86 (d, *J* = 15.0 Hz, 1H), 7.68–7.70 (d, 2H), 7.58–7.63 (m, 4H), 7.52–7.54 (d, 2H), 7.37–7.41 (d, *J* = 15.0 Hz, 1H), 6.71–6.74 (d, 1H), 3.07 (s, 6H).

1-(4'-bromo-[1,1'-biphenyl]-4-yl)-3-(4-bromothiophen-2-yl)prop-2-en-1-one (4r)

Yield: 85%, mp: 128-129 (°C); IR (KBr) (cm^{-1}): 3088.71 (aromatic =C-H), 1655.33 (C=O), 1546.33 (aromatic –C=C-), 680.50 (-C-Br), ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.97–7.99 (m, 2H), 7.84–7.85 (d, 1H), 7.79–7.81 (m, 2H), 7.66–7.68 (m, 2H), 7.60–7.62 (m, 2H), 7.57–7.58 (d, 1H), 7.51–7.53 (d, *J* = 15.0 Hz, 1H), 7.33–7.35 (d, 1H).

1-(4'-bromo-[1,1'-biphenyl]-4-yl)-3-(2,3,4-trimethoxy phenyl)prop-2-en-1-one (4s)

Yield: 95%, mp: 113-114 (°C); IR (KBr) (cm^{-1}): 3072.93 (aromatic =C-H), 1657.21 (C=O), 1585.75 (aromatic –C=C-), 696.87 (-C-Br), ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.02–8.04 (d, 2H), 7.83–7.77 (m, 4H), 7.70–7.63 (m, 3H), 7.63–7.55 (m, 3H), 6.97 (d, *J* = 15.0 Hz, 1H), 3.89 – 3.87 (m, 9H).

1-(4'-bromo-[1,1'-biphenyl]-4-yl)-3-(3,4,5-trimethoxy phenyl)prop-2-en-1-one (4t)

Yield: 95%, mp: 112-113 (°C); IR (KBr) (cm^{-1}): 3561.55 (aromatic =C-H), 1691.29 (C=O), 1554.33 (aromatic –C=C-), 693.42 (-C-Br), ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.75–7.79 (m, 1H), 7.70–7.72 (d, 2H), 7.60–7.67 (m, 4H), 7.47–7.54 (m, 2H), 7.43 (d, *J* = 15.0 Hz, 1H), 6.90 (s, 2H), 3.92 (s, 6H), 3.90 (s, 3H).

1-(4'-bromo-[1,1'-biphenyl]-4-yl)-3-(2-chloro-3,4-dimethoxyphenyl)prop-2-en-1-one (4u)

Yield: 64%, mp: 121-122 (°C); IR (KBr) (cm^{-1}): 3020.02 (aromatic =C-H), 1749.78 (C=O), 1597.60 (aromatic –C=C-), 684.68 (-C-Br), ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.83–7.86 (d, 1H), 7.68–7.70 (d, 2H), 7.58–7.63 (m, 4H), 7.52–7.54 (m, 2H), 7.37–7.41 (d, *J* = 15.3 Hz, 1H), 6.71–6.74 (d, 2H), 3.07 (s, 6H).

3-(anthracen-9-yl)-1-(4'-bromo-[1,1'-biphen yl]-4-yl)prop-2-en-1-one (4v)

Yield: 69%, mp: 168-169 (°C); IR (KBr) (cm^{-1}): 3045.78 (aromatic =C-H), 1639.10 (C=O), 1590.51 (aromatic

–C=C-), 622.97 (-C-Br), ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.84–8.88 (d, *J* = 1.6 Hz, 1H), 8.52–8.54 (d, *J* = 15.3 Hz, 1H), 8.34–8.36 (m, 2H), 8.18–8.20 (d, 2H), 8.06–8.08 (m, 2H), 7.72–7.74 (d, 2H), 7.58–7.64 (m, 3H), 7.52–7.64 (m, 6H).

3-(5-bromo-2-hydroxy-3-methoxyphenyl)-1-(4'-bromo-[1,1'-biphenyl]-4-yl)-prop-2-en-1-one (4w)

Yield: 72%, mp: 124-125 (°C); IR (KBr) (cm^{-1}): 3064.97 (aromatic =C-H), 3407.81 (-OH stretch), 1641.26 (C=O), 1580.80 (aromatic –C=C-), 690.78 (-C-Br), ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.30 (s, 1H), 7.98 (d, *J* = 15.3 Hz, 1H), 7.97–7.91 (m, 2H), 7.84–7.78 (m, 2H), 7.70–7.63 (m, 4H), 7.62–7.58 (m, 2H), 7.05 (d, 1H), 3.88 (s, 2H).

1-(4'-bromo-[1,1'-biphenyl]-4-yl)-3-(10-chloroanthracen-9-yl)prop-2-en-1-one (4x)

Yield: 91%, mp: 152-153 (°C); IR (KBr) (cm^{-1}): 3045.78 (aromatic =C-H), 1639.10 (C=O), 1590.51 (aromatic –C=C-), 622.97 (-C-Br), ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.32–8.25 (m, 2H), 8.18–8.07 (m, 3H), 8.01–7.95 (m, 2H), 7.84–7.79 (m, 2H), 7.70–7.64 (m, 2H), 7.64–7.57 (m, 3H), 7.52–7.44 (m, 4H).

5-(chloromethyl)-oxazolidin-2-one (6)

Yield: 75%, mp: 102-103 (°C); IR (KBr) (cm-1): 3257.86 and 3444.02 (-N-H stretch), 1749.88 (-C=O), 714.46 (-C-Cl stretch), ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 3.536–3.572 (m, 1H), 3.663–3.787 (m, 3H), 4.823–4.887 (m, 1H), 5.60 (s, NH of oxazolidinone ring), ^{13}C NMR (100 MHz, Chloroform-*d*) δ: 43.39, 43.59, 74.70, 159.12, Calculated Mass: 135.01 Found: MS (ESI m/z): 136.12 [M+H]$^+$.

5-(chloromethyl)-3-(4'-(3-(thiophen-2-yl)acryloyl)-[1,1'-biphenyl]-4-yl)-oxazolidin-2-one (7a)

Yield: 75%, mp: 184-185 (°C); IR (KBr) (cm^{-1}): 3088.71 (aromatic =C-H), 1691.86 (C=O), 1597.97 (aromatic –C=C-), 783.35 (C-Cl), ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.06–8.07 (d, 2H), 7.83–7.86 (d, *J* = 15.3 Hz, 1H), 7.68–7.70 (d, 2H), 7.60–7.61 (d, 2H), 7.50–7.52 (d, 2H), 7.35–7.39 (d, 2H), 7.29–7.32 (d, 2H), 4.82–4.88 (m, 1H), 3.73–3.78 (m, 1H), 3.66–3.76 (dd, 2H), 3.52–3.56 (m, 1H), Calculated Mass: 423.91 Found: MS (ESI m/z): 423.80 [M+H]$^+$.

5-(chloromethyl)-3-(4'-(3-(p-tolyl)acryloyl)-[1,1'-biphenyl]-4-yl)oxazolidin-2-One (7b),

Yield: 72%, mp: 133-134 (°C); IR (KBr) (cm^{-1}): 3063.79 (aromatic =C-H), 1672.78 (C=O), 1588.20 (aromatic –C=C-), 776.43 (C-Cl), ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.09–8.11 (d, 2H), 7.81–7.85 (d, 2H), 7.62–7.68 (d, 2H), 7.51–7.62 (m, 6H), 7.24–7.26 (d, 2H), 4.83–4.87 (m, 1H), 3.69–3.78 (m, 2H), 3.53–3.56 (m, 2H), 2.41 (s, 3H), Calculated Mass: 431.92 Found:MS (ESI m/z): 432.00 [M+H]$^+$.

5-(chloromethyl)-3-(4'-(3-(2-hydroxyphenyl) acryloyl)-[1,1'-biphenyl]-4-yl)oxazolidin-2-one (7c),

Yield: 82%, mp: 168-169 (°C); IR (KBr) (cm^{-1}): 3018.97 (aromatic =C-H), 3444.45 (-OH stretch), 1747.20 (C=O), 1487.33 (aromatic –C=C-), 762.78 (-C-Cl), ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.15 (s, 1H), 8.03–8.05 (d, 2H), 7.60–7.67 (dd, 4H), 7.51–7.59 (dd, 6H), 7.48–7.49 (d, 2H), 4.82-4.86 (m, 1H), 3.75-3.79 (m, 2H), 3.70–3.74 (m, 2H), 3.53–3.57 (m, 1H), Calculated Mass: 433.89; Found: MS (ESI m/z): 433.90 [M+H]$^+$.

5-(chloromethyl)-3-(4'-(3-(4-hydroxyphenyl) acryloyl)-[1,1'-biphenyl]-4-yl)oxazolidin-2-one (7d)

Yield: 78%, mp: 161-162 (°C); IR (KBr) (cm^{-1}): 3125.60 (aromatic =C-H), 3434.01 (-OH stretch), 1673.21 (C=O), 1523.54 (aromatic –C=C-), 753.50 (-C-Cl), ^{1}H NMR (400 MHz, Chloroform-*d*) 8.03–8.05 (d, 2H), 7.65–7.67 (d, 2H), 7.60–7.67 (m, 5H), 7.49–7.51 (d, 3H), 4.82–4.86 (m, 1H), 3.75–3.79 (m, 2H), 3.70–3.74 (m, 2H), 3.53–3.57 (m, 1H), Calculated Mass: 433.89; Found: MS (ESI m/z): 433.90 [M+H]$^+$.

5-(chloromethyl)-3-(4'-(3-(2-fluorophenyl) acryloyl)-[1,1'-biphenyl]-4-yl)oxazolidin-2-one (7e)

Yield: 81%, mp: 120-121 (°C); IR (KBr) (cm^{-1}): 3158.40 (aromatic =C-H), 1675.36 (C=O), 1597.60 (aromatic –C=C-), 790.96 (-C-Cl), 1035.81 (-C-F), ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.91–7.97 (m, 2H), 7.69–7.80 (m, 5H), 7.58–7.60 (d, 1H), 7.48–7.55 (m, 3H), 7.41–7.42 (d, *J* = 15.3 Hz, 1H), 7.30–7.32 (d, 2H), 4.82–4.85 (m, 1H), 3.85–3.74 (m, 2H), 3.52–3.54 (m, 2H), Calculated Mass: 435.88; Found: MS (ESI m/z): 436.10 [M+H]$^+$.

5-(chloromethyl)-3-(4'-(3-(3-fluorophenyl) acryloyl)-[1,1'-biphenyl]-4-yl)oxazolidin-2-one (7f)

Yield: 65%, mp: 125-126 (°C); IR (KBr) (cm^{-1}): 3570.76 (aromatic =C-H), 1654.94 (C=O), 1590.72 (aromatic –C=C-), 750.01 (-C-Cl), 1024.56 (-C-F), ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.91–7.97 (m, 2H), 7.69–7.80 (m, 5H), 7.58-7.60 (d, 1H), 7.48–7.55 (m, 3H), 7.41–7.42 (d, *J* = 15.3 Hz, 1H), 7.30–7.32 (d, 2H), 4.82–4.85 (m, 1H), 3.85–3.74 (m, 2H), 3.52–3.54 (m, 2H), Calculated Mass: 435.88; Found: MS (ESI m/z): 436.10 [M+H]$^+$.

5-(chloromethyl)-3-(4'-(3-(4-fluorophenyl) acryloyl)-[1,1'-biphenyl]-4-yl)oxazolidin-2-one (7g)

Yield: 82%, mp: 123-124 (°C); IR (KBr) (cm^{-1}): 3570.76 (aromatic =C-H), 1654.94 (C=O), 1590.72 (aromatic

–C=C-), 750.01 (-C-Cl), 1024.56 (-C-F), ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.70–7.79 (d, *J* = 15.0 Hz, 1H), 7.60–7.68 (m, 6H), 7.53–7.59 (d, 2H), 7.48–7.50 (m, 3H), 7.13–7.14 (d, 2H), 4.82–4.85 (m, 1H), 3.73–3.77 (d, 1H), 3.69–3.71 (m, 2H), 3.51–3.55 (m, 1H), Calculated Mass: 435.88; Found: MS (ESI m/z): 436.10 $[M+H]^+$.

5-(chloromethyl)-3-(4'-(3-(4-methoxyphenyl) acryloyl)-[1,1'-biphenyl]-4-yl)oxazolidin-2-one (7h)

Yield: 74%, mp: 180-181 (°C); IR (KBr) (cm^{-1}): 3081.28 (aromatic =C-H), 1697.69 (C=O), 1575.44 (aromatic –C=C-), 786.32 (-C-Cl), ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.06–8.08 (m, 2H), 7.83–7.87 (d, *J* = 15.0 Hz, 1H), 7.68–7.70 (m, 3H), 7.60–7.62 (m, 3H), 7.50–7.52 (m, 2H), 7.35–7.39 (d, 1H), 7.29–7.32 (m, 2H), 4.83–4.88 (m, 1H), 3.76–3.78 (m, 2H), 3.74 (s, 3H), 3.52–3.73 (m, 2H), Calculated Mass: 447.92; Found: MS (ESI m/z): 448.00 $[M+H]^+$.

5-(chloromethyl)-3-(4'-(3-(2-chlorophenyl) acryloyl)-[1,1'-biphenyl]-4-yl)oxazolidin-2-one (7i)

Yield: 70%, mp: 122-123 (°C); IR (KBr) (cm^{-1}): 3020.02 (aromatic =C-H), 1749.78 (C=O), 1597.60 (aromatic –C=C-), 762.78 (-C-Cl), ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.75–7.89 (d, 2H), 7.62–7.64 (m, 4H), 7.42–7.51 (d, 3H), 7.37–7.42 (m, 3H), 7.30–7.35 (d, *J* = 15.3 Hz, 1H), 7.17–7.18 (d, 1H), 4.83–4.89 (m, 1H), 3.70 – 3.79 (m, 2H), 3.56 – 3.69 (m, 2H), Calculated Mass: 452.33; Found: MS (ESI m/z): 452.20 $[M+H]^+$.

5-(chloromethyl)-3-(4'-(3-(4-chlorophenyl) acryloyl)-[1,1'-biphenyl]-4-yl)oxazolidin-2-one (7j)

Yield: 83%, mp: 128-129 (°C); IR (KBr) (cm^{-1}): 3020.02 (aromatic =C-H), 1749.78 (C=O), 1597.60 (aromatic –C=C-), 762.78 (-C-Cl), ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.75–7.79 (d, 2H), 7.42–7.64 (m, 6H), 7.402–7.406 (d, 1H), 7.35–7.40 (d, 3H), 7.30–7.34 (d, 1H), 7.17–7.18 (d, *J* = 15.0 Hz, 1H), 4.82–4.85 (m, 1H), 3.75–3.77 (d, 1H), 3.66–3.70 (m, 2H), 3.51–3.55 (m, 1H), Calculated Mass: 452.33; Found: MS (ESI m/z): 452.08 $[M+H]^+$.

3-(4'-(3-(1H-indol-2-yl)acryloyl)-[1,1'-biphenyl]-4-yl)-5-(chloromethyl)oxazolidin-2-one (7k)

Yield: 66%, mp: 206-207 (°C); IR (KBr) (cm^{-1}): 3020.03 (aromatic =C-H), 3232.39 (N-H stretch), 1646.99 (C=O), 1522.18 (aromatic –C=C-), 762.67 (-C-Cl), ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.30 (s, 1H), 8.03–8.06 (m, 1H), 7.87–7.88 (d, 2H), 7.65–7.67 (d, 1H), 7.60–7.62 (m, 4H), 7.48–7.52 (m, 5H), 7.32–7.34 (d, 2H), 4.86–4.88 (m, 1H), 3.75–3.80 (m, 2H), 3.54–3.58 (m, 2H), Calculated Mass: 456.93; Found: MS (ESI m/z): 456.90 $[M+H]^+$.

5-(chloromethyl)-3-(4'-(3-(4-(dimethylamino) phenyl)acryloyl)-[1,1'-biphenyl]-4-yl)oxazolid in-2-one (7l)

Yield: 92%, mp: 188-189 (°C); IR (KBr) (cm^{-1}): 3020.03 (aromatic =C-H), 1643.25 (C=O), 1522.16 (aromatic –C=C-), 760.75 (-C-Cl), ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.07–8.10 (d, 2H), 7.81–7.85 (d, 1H), 7.67–7.69 (m, 2H), 7.56–7.62 (m, 4H), 7.51–7.53 (d, 2H), 7.35–7.39 (d, 1H), 6.70–6.72 (d, 2H), 4.84–4.86 (m,1H), 3.71–3.78 (m, 2H), 3.55–3.56 (m, 1H), 3.47–3.52 (m, 1H), 3.06 (s, 6H), Calculated Mass: 460.96 Found: MS (ESI m/z): 460.10 $[M+H]^+$.

5-(chloromethyl)-3-(4'-(3-(2-nitrophenyl)acryloyl)-[1,1'-biphenyl]-4-yl)oxazolidin-2-one (7m)

Yield: 83%, mp: 195-196 (°C); IR (KBr) (cm^{-1}): 3069.50 (aromatic =C-H), 1639.77 (C=O), 1577.99 (aromatic –C=C-),1340.3 (Ar-NO_2), 786.85 (-C-Cl), ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.29–8.31 (d, 2H), 8.12–8.14 (d, 2H), 7.81–7.88 (dd, 3H), 7.71–7.73 (d, 2H), 7.61–7.67 (m, 3H), 7.52–7.54 (d, 2H), 4.84–4.86 (m, 1H), 3.68–3.76 (m, 2H), 3.53–3.57 (m, 2H), Calculated Mass: 462.89; Found: MS (ESI m/z): 463.10 $[M+H]^+$.

5-(chloromethyl)-3-(4'-(3-(3-nitrophenyl)acryloyl)-[1,1'-biphenyl]-4-yl)oxazolidin-2-one (7n)

Yield: 68%, mp: 194-195 (°C); IR (KBr) (cm^{-1}): 3096.24 (aromatic =C-H), 1643.83 (C=O), 1583.28 (aromatic –C=C-),1331.74 (Ar-NO_2), 798.84 (-C-Cl), ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.58–8.59 (d, 1H), 8.14–8.18 (d, 2H), 7.91–7.94 (m, 3H), 7.71–7.79 (m, 5H), 7.59–7.62 (d, *J* = 15.0 Hz, 1H), 7.51–7.54 (d, 2H), 4.84–4.86 (m, 1H), 3.75–3.79 (m, 2H), 3.69–3.72 (m, 1H), 3.54–3.57 (m, 1H), Calculated Mass: 462.89; Found: MS (ESI m/z): 463.10 $[M+H]^+$.

5-(chloromethyl)-3-(4'-(3-(4-nitrophenyl)acryloyl)-[1,1'-biphenyl]-4-yl)oxazolidin-2-one (7o)

Yield: 73%, mp: 199-200 (°C); IR (KBr) (cm^{-1}): 3502.10 (aromatic =C-H), 1694.53 (C=O), 1551.63 (aromatic –C=C-),1339.32 (Ar-NO_2), 778.14 (-C-Cl), ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.22–8.19 (m, 2H), 7.96–8.02 (d, 2H), 7.79–7.82 (m, 2H), 7.76–7.78 (m, 3H), 7.71–7.73 (m, 2H), 7.62–7.65 (d, *J* = 15.0 Hz, 1H), 7.51–7.54 (m, 2H), 4.84–4.86 (m, 1H), 3.68–3.76 (m, 2H),

3.53–3.57 (m, 2H), Calculated Mass: 462.89; Found: MS (ESI m/z): 463.10 $[M+H]^+$.

5-(chloromethyl)-3-(4'-(3-(4-hydroxy-3-methoxyphenyl)acryloyl)-[1,1'-biphenyl]-4-yl) oxazo lidin-2-one (7p)

Yield: 81%, mp: 141-142 (°C); IR (KBr) (cm^{-1}): 3664.97 (aromatic =C-H), 3407.81 (-OH stretch), 1641.26 (C=O), 1580.80 (aromatic –C=C-), 793.28 (-C-Cl), ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.68 (s, 1H), 7.93–7.94 (d, 2H), 7.81–7.84 (d, 1H), 7.77–7.79 (d, 2H), 7.71–7.73 (d, 2H), 7.51–7.54 (d, 2H), 7.43–7.45 (d, *J* = 1.5 Hz, 1H), 7.14–7.15 (d, 1H), 7.00–7.02 (d, 1H), 6.83–6.85 (d, 1H), 4.85–4.82 (m, 1H), 3.95–4.00 (m, 2H), 3.84 (s, 3H), 3.76–3.83 (m, 2H), 3.54–3.56 (m, 1H), Calculated Mass: 463.91; Found: MS (ESI m/z): 464.10 $[M+H]^+$.

5-(chloromethyl)-3-(4'-(3-(3,4-dimethoxyphenyl) acryloyl)-[1,1'-biphenyl]-4-yl)oxazolidin-2-one (7q)

Yield: 65%, mp: 138-139 (°C); IR (KBr) (cm^{-1}): 3074.57 (aromatic =C-H), 1656.65 (C=O), 1583.65 (aromatic –C=C-), 720.81 (-C-Cl), ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.10–8.12 (d, 2H), 7.75–7.79 (d, 1H), 7.70–7.72 (d, *J* = 15.0 Hz, 1H), 7.63–7.66 (d, 2H), 7.60–7.61 (d, 2H), 7.49–7.54 (d, 2H), 7.44–7.416 (d, *J* = 15.0 Hz, 1H), 6.90–6.91 (d, 1H), 4.84–4.88 (m, 1H), 3.95 (s, 6H), 3.67–3.79 (m, 2H), 3.54–3.58 (m, 2H), Calculated Mass: 477.94; Found: MS (ESI m/z): 478.10 $[M+H]^+$.

3-(4'-(3-(4-bromothiophen-2-yl)acryloyl)-[1,1'-biphenyl]-4-yl)-5-(chloromethyl)oxazolidin-2-one (7r)

Yield: 69%, mp: 192-193 (°C); IR (KBr) (cm^{-1}): 3088.71 (aromatic =C-H), 1655.33 (C=O), 1546.33 (aromatic –C=C-), 680.50 (-C-Br),^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.05–8.07 (m, 2H), 7.83–7.86 (d, 1H), 7.68–7.70 (d, 2H), 7.60–7.62 (d, 2H), 7.50–7.52 (d, 2H), 7.24–7.28 (d, *J* = 1.5 Hz, 1H), 7.12–7.13 (d, 1H), 7.07–7.08 (d, 1H), 4.03–4.07 (d, 1H), 3.82–3.88 (dd, 2H), 3.76–3.81 (m, 2H), Calculated Mass: 502.81; Found: MS (ESI m/z): 503.00 $[M+H]^+$.

5-(chloromethyl)-3-(4'-(3-(2,3,4-trimethoxyphenyl) acryloyl)-[1,1'-biphenyl]-4-yl)oxazolidin -2-one (7s)

Yield: 71%, mp: 155-156 (°C); IR (KBr) (cm^{-1}): 3069.50 (aromatic =C-H), 1639.77 (C=O), 1525.51 (aromatic –C=C-), 786.85 (-C-Cl), ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.08–8.10 (d, 2H), 8.00–8.045 (d, 2H), 7.64–7.70 (m, 5H), 7.58–7.62 (d, 2H), 7.49–7.53 (d, *J* = 15.0 Hz, 1H), 4.84–4.88 (m, 1H), 3.90–3.97 (m, 1H), 3.69–3.78 (m, 9H), 3.52–3.56 (m, 3H), Calculated Mass: 507.97; Found: MS (ESI m/z): 508.10 $[M+H]^+$.

5-(chloromethyl)-3-(4'-(3-(3,4,5-trimethoxyphenyl) acryloyl)-[1,1'-biphenyl]-4-yl)oxazolidin-2-one (7t)

Yield: 92%, mp: 158-159 (°C); IR (KBr) (cm^{-1}): 3561.55 (aromatic =C-H), 1691.29 (C=O), 1554.33 (aromatic –C=C-), 739.10 (-C-Cl), ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.10–8.12 (d, 2H), 8.03–8.05 (d, 1H), 7.75–7.79 (d, 1H), 7.70–7.72 (d, 1H), 7.60–7.67 (m, 4H), 7.52–7.54 (d, 2H), 7.43–7.49 (s, 1H), 6.90 (s, 2H), 4.84–4.88 (m, 1H), 3.92–3.95 (s, 6H), 3.90 (s, 3H), 3.70–3.75 (m, 2H), 3.55–3.58 (m, 2H), Calculated Mass: 507.97; Found: MS (ESI m/z): 508.10 $[M+H]^+$.

3-(4'-(3-(2-chloro-3,4-dimethoxyphenyl)acryloyl)-[1,1'-biphenyl]-4-yl)-5-(chloromethyl)oxa- zolidin-2-one (7u),

Yield: 90%, mp: 161-162 (°C); IR (KBr) (cm^{-1}): 3096.24 (aromatic =C-H), 1643.83 (C=O), 1583.28 (aromatic –C=C-), 712.40 (-C-Cl), ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.05–8.08 (d, 1H), 7.96–7.98 (d, 2H), 7.78–7.80 (d, 2H), 7.69–7.71 (d, 2H), 7.53–7.55 (d, 2H), 7.39–7.46 (d, 2H), 6.93–6.94 (d, 1H), 4.84–4.88 (m, 1H), 3.87 (s, 6H), 3.70–3.75 (m, 2H), 3.54–3.58 (m, 2H), Calculated Mass: 512.38; Found: MS (ESI m/z): 512.10 $[M+H]^+$.

3-(4'-(3-(anthracen-9-yl)acryloyl)-[1,1'-biphenyl]-4-yl)-5-(chloromethyl)oxazolidin-2-one (7v),

Yield: 88%, mp: 232-233 (°C); IR (KBr) (cm^{-1}): 3034.15 (aromatic =C-H), 1652.51 (C=O), 1513.45 (aromatic –C=C-), 798.54 (-C-Cl), ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.82–8.86 (d, 1H), 8.50 (s, 1H), 8.32–8.35 (d, 2H), 8.16–8.18 (d, 2H), 8.04–8.07 (m, 2H), 7.70–7.72 (d, 2H), 7.624–7.628 (m, 3H), 7.60–7.51 (m, 6H), 4.84–4.87 (m, 1H), 3.69–3.78 (m, 2H), 3.53–3.56 (m, 2H), Calculated Mass: 518.01; Found: MS (ESI m/z): 518.10 $[M+H]^+$.

3-(4'-(3-(5-bromo-2-hydroxy-3-methoxyphenyl) acryloyl)-[1,1'-biphenyl]-4-yl)-5-(chloro methyl) oxazolidin-2-one (7w)

Yield: 72% , mp: 130-131 (°C); IR (KBr) (cm^{-1}): 3010.15 (aromatic =C-H), 3463.62 (-OH stretch), 1663.14 (C=O), 1524.98 (aromatic –C=C-), 780.78 (-C-Cl), ^{1}H NMR (400 MHz, Chloroform-*d*) δ 11.01 (s, 1H), 9.87 (s, 1H), 8.03–8.05 (d, 2H), 7.65–7.67 (d, 2H), 7.60–7.62 (d, 2H), 7.50–7.52 (d, 2H), 7.333–7.338 (s, 1H), 7.19–7.20 (s, 1H), 4.85–4.90 (m, 1H), 3.94 (s, 3H), 3.75–3.77 (m, 1H), 3.67–3.73 (m, 2H), 3.54–3.58 (m, 1H), Calculated Mass: 542.81; Found: MS (ESI m/z): 543.00 $[M+H]^+$.

3-(4'-(3-(10-chloroanthracen-9-yl)acryloyl)-[1,1'-biphenyl]-4-yl)-5-(chloromethyl) oxazolidin-2-one (7x)

Yield: 91%, mp: 197-198 (°C); IR (KBr) (cm^{-1}): 3019.69 (aromatic =C-H), 1637.16 (C=O), 1568.89 (aromatic –C=C-), ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.231-8.236 (d, 1H), 8.02–8.05 (m, 3H), 7.64–7.67 (m, 6H), 7.58–7.61 (m, 4H), 7.48–7.51 (m, 4H), 4.83–4.86 (m, 1H), 3.69–3.78 (m, 2H), 3.54–3.56 (m, 2H), Calculated Mass: 552.45 Found: MS (ESI m/z): 553.00 $[M+H]^+$.

Antimicrobial Screening

The *in vitro* antibacterial and antifungal screening of newly synthesized 24 novel oxazolidinone-biphenyl chalcone hybrid derivatives were determined using serial dilution method.[16,17]

Antibacterial Screening

The test compounds 7a to 7x were screened for *in vitro* antibacterial activity against three gram-positive bacteria [*Staphylococcus aureus* NCIM 5257, *Bacillus subtilis* NCIM 2097 *and Streptococcus faecalis* NCIM 2080] and three gram-negative bacteria [*Escherichia coli* NCIM 2065, *Pseudomonas aeruginosa* NCIM 5210, *Klebsiella pneumoniae* NCIM 5289] by serial broth dilution method. The above bacterial strains were obtained from NCIM -National Collection of Industrial Microorganisms, Pune, India. Ciprofloxacin and linezolid were used as the standard drugs. The medium used was double strength nutrient broth. Cultures of test organisms were maintained on nutrient agar slants and were sub cultured in Petri dishes prior to activity. The nutrient agar and nutrient broth used for *in vitro* antibacterial studies were procured from Himedia Laboratories, Mumbai.

Stock solutions of the synthesized compounds of different concentrations were prepared in the range of 1000 μg/ml to 1.56 μg/ml, using dimethyl sulfoxide (DMSO) as solvent for antibacterial activity. Water was used as solvent to dissolve the standard drugs ciprofloxacin and linezolid.

To verify that the solvent had no effect on bacterial growth, a control test was performed with test medium employing DMSO at the same dilution as used in the experiments. The minimum inhibitory concentration (MICs) values were the lowest concentration of compounds, which resulted in no visible growth or turbidity in the culture media after 24 h of incubation at 37°C and are listed in Table 4.

Antifungal Screening

The test compounds 7a to 7x were screened for in *vitro* antifungal activity against two standard organisms [*Candida albicans* NCIM 3628 and *Aspergillus niger* NCIM 1317] by two fold serial broth dilution method. Fluconazole was used as the standard. The medium used was double strength malt yeast extract broth. Test compounds and standard drug (Fluconazole) were Dissolved in Dimethyl Sulfoxide (DMSO) to give a concentration range of 1000 μg/ml to 1.56 μg/ml. Minimum Inhibitory Concentration (MIC) of the synthesized compounds was determined. The MIC is the lowest concentration of tested compounds that completely inhibited the growth of the test organisms after 48 h of incubation at 25-27°C and are listed in Table 5.

RESULTS AND DISCUSSION

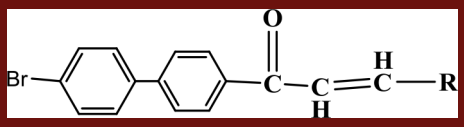
Chemistry

As part of our research to fuse two antibacterial cores or substructures into a single entity to achieve novel hybrid scaffolds of potent antibacterial agents, herewith we attempted to couple both biphenyl chalcone and oxazolidinone cores by using buchwald's protocol under ultrasound irradiation to enhance the spectrum and potency of the newly synthesized hybrid molecules. In this paper, we report the synthesis and antimicrobial activities of 24 novel oxazolidinone-biphenyl chalcone hybrid derivatives (7a-7x). IR, ^{1}H NMR and MS spectral data was collected for the synthesized compounds and the data was found consistent to the assigned structure.

The synthesis of the compounds were carried out in three steps (scheme-1). The first step involves the synthesis of biphenyl chalcones by treating the aryl ketone (4'-(4-bromophenyl)-acetophenone) (5) with corresponding aryl aldehydes in ethanol with lithium hydroxide monohydrate ($LiOH{\cdot}H_2O$) as base catalyst under ultrasound irradiation.[5] The second step involves synthesis of compound 5-(chloromethyl)-oxazolidin-2-one (6) by refluxing epichlorohydrin, potassium cyanate and magnesium sulfate in water at 100°C for 15 hrs until a white solid is formed. The third step involves coupling of corresponding biphenyl chalcones (4a-4x) with 5-(chloromethyl)-oxazolidin-2-one (6), in presence of copper iodide, potassium carbonate (base), (±)-*trans*-1,2-diaminocyclohexane (ligand) under nitrogen gas environment. The mixture was irradiated in the water bath of an ultrasonic cleaner at the room temperature for a period mentioned in the Table 3.

Initially the reaction was carried out in air to know the effect of ultrasonication on percentage yield and time of product formation, but we found that the reactions proceeded very slowly with poor yields (less than 40 percentage). Reactions were thus carried out under nitrogen gas environment (Figure 2), which provided

Table 2: Substitutions at (R) and physicochemical properties of biphenyl chalcones (4a-4x)

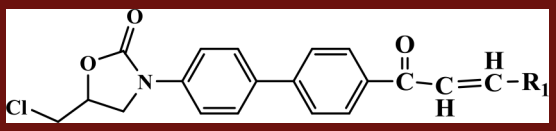


Compound Code	Substitutions at R	Molecular Formula	Molecular Weight	Melting Point (°C)	Percentage (%) yield
4a	Thiophen-2-yl	$C_{19}H_{13}BrOS$	369.28	143-145	85
4b	4-CH3-C6H4	$C_{22}H_{17}BrO$	377.28	115-116	83
4c	2-OH-C_6H_4	$C_{21}H_{15}BrO_2$	379.25	132-133	65
4d	4-OH-C_6H_4	$C_{21}H_{15}BrO_2$	379.25	135-136	72
4e	2-F-C_6H_4	$C_{21}H_{14}BrFO$	381.24	112-113	78
4f	3-F-C_6H_4	$C_{21}H_{14}BrFO$	381.24	110-111	79
4g	4-F-C_6H_4	$C_{21}H_{14}BrFO$	381.24	111-112	71
4h	4-OCH_3-C_6H_4	$C_{22}H_{17}BrO_2$	393.28	156-157	82
4i	2-Cl-C_6H_4	$C_{21}H_{14}BrClO$	397.70	118-119	91
4j	4-Cl-C_6H_4	$C_{21}H_{14}BrClO$	397.70	116-117	90
4k	Indole-2-yl	$C_{23}H_{16}BrNO$	402.29	182-183	68
4l	C_6H_4-N-$(CH_3)_2$	$C_{23}H_{20}BrNO$	406.32	162-163	88
4m	2-NO_2-C_6H_4	$C_{21}H_{14}BrNO_3$	408.25	182-183	81
4n	3- NO_2-C_6H_4	$C_{21}H_{14}BrNO_3$	408.25	188-189	84
4o	4- NO_2-C_6H_4	$C_{21}H_{14}BrNO_3$	408.25	185-186	77
4p	3-OCH_3-4-OH-C_6H_3	$C_{22}H_{17}BrO_3$	409.28	108-109	66
4q	3,4-Di-OCH_3-C_6H_3	$C_{23}H_{19}BrO_3$	423.31	103-104	92
4r	4-bromo-Thiophen-2-yl	$C_{19}H_{12}Br_2OS$	448.17	128-129	85
4s	2,3,4,-tri-OCH_3-C_6H_2	$C_{24}H_{21}BrO_4$	453.33	113-114	95
4t	3,4,5-tri-OCH_3-C_6H_2	$C_{24}H_{21}BrO_4$	453.33	112-113	95
4u	2-Cl-3,4-Di-OCH_3-C_6H_2	$C_{23}H_{18}BrClO_3$	457.75	121-122	64
4v	Anthracen-9-yl	$C_{29}H_{19}BrO$	463.37	168-169	69
4w	2-OH-3-OCH_3-5-Br-C_6H_2	$C_{22}H_{16}Br_2O_3$	488.18	124-125	72
4x	10-Cl-Anthracen-9-yl	$C_{29}H_{18}BrClO$	497.82	152-153	91

good yields (above 65 percentage) with shorter period of time that is less than 5 hrs at normal room temperature when compared to the conventional buchwald's protocol (5-20 hrs at 110°C).

The FT-IR spectra of the synthesized oxazolidinone-biphenyl chalcone hybrids showed the vibration bands at a range of ν 3000-3200 cm^{-1} and bands at 1500-1610 cm^{-1} are assigned to the vibrations of the aromatic =C-H and aromatic –C=C- stretch respectively. The vibration bands at a range of ν 1650-1786 cm^{-1} assigned to C=O stretch of α, β unsaturated ketone nucleus which confirms the formation of chalcones. The ^{1}H NMR of the novel oxazolidinone-biphenyl chalcones suggested two doublets, one at a range of δ 7.15–8.23 ppm (for Hα) and another at a range of δ 7.45–8.07 ppm (for H_β) for vinylic protons nearer the carbonyl group (-C**H**$_\beta$=C**H**$_\alpha$-C=O). Interestingly for all compounds we found the coupling constants value (J) in the range of JHα –Hβ = 15-16 Hz, that confirms the trans configuration of the vinylic system. Further, the aromatic protons of biphenyl ring were observed at a range of δ 6.9–8.1 ppm. The coupling of oxazolidinone ring system with biphenyl chalcones were confirmed by absence of singlet at δ 5.0-6.5 which was assigned to –NH of oxazolidinone ring. ^{1}H NMR spectrum of oxazolidinone ring showed a multiplet of two protons assigned to the methylenic protons of -CH_2-Cl ranging from δ 3.50-3.60, while a methynic proton of oxazolidinone -CH-CH_2- showed a multiplet of one proton ranging from δ 4.80-5.80, the methylenic protons of oxazolidinone -CH-CH_2- showed multiplet of two protons ranging from δ 3.63-4.07. Finally, the molecular ion peaks observed for all the synthesized oxazolidinone-biphenyl chalcone hybrid molecules (7a-7x) by ESI-MS strongly reveals their predicted molecular weights.

Table 3: Substitutions at (R_1) and Physicochemical properties of newly synthesized oxazolidinone-biphenyl chalcone hybrid derivatives (7a-7x).



Compound Code	Substitutions at R_1	Molecular Formula	Molecular Weight	Melting Point (°C)	Ultrasound time (hrs.)	(%) yield
7a	Thiophen-2-yl	$C_{23}H_{18}ClNO_3S$	423.91	184-185	3	75
7b	4-CH3-C6H4	$C_{26}H_{22}ClNO_3$	431.92	133-134	2	72
7c	2-OH-C_6H_4	$C_{25}H_{20}ClNO_4$	433.89	168-169	5	82
7d	4-OH-C_6H_4	$C_{25}H_{20}ClNO_4$	433.89	161-162	5	78
7e	2-F-C_6H_4	$C_{25}H_{19}ClFNO_3$	435.88	120-121	3	81
7f	3-F-C_6H_4	$C_{25}H_{19}ClFNO_3$	435.88	125-126	3	65
7g	4-F-C_6H_4	$C_{25}H_{19}ClFNO_3$	435.88	123-124	3	82
7h	4-OCH_3-C_6H_4	$C_{26}H_{22}ClNO_4$	447.92	180-181	3	74
7i	2-Cl-C_6H_4	$C_{25}H_{19}Cl_2NO_3$	452.33	122-123	2.5	70
7j	4-Cl-C_6H_4	$C_{25}H_{19}Cl_2NO_3$	452.33	128-129	3	83
7k	Indole-2-yl	$C_{27}H_{21}ClN_2O_3$	456.93	206-207	3.5	66
7l	C_6H_4-N-$(CH_3)_2$	$C_{27}H_{25}ClN_2O_3$	460.96	188-189	4.5	92
7m	2-NO_2-C_6H_4	$C_{25}H_{19}ClN_2O_5$	462.89	195-196	4	83
7n	3- NO_2-C_6H_4	$C_{25}H_{19}ClN_2O_5$	462.89	194-195	4.5	68
7o	4- NO_2-C_6H_4	$C_{25}H_{19}ClN_2O_5$	462.89	199-200	4.5	73
7p	3-OCH_3-4-OH-C_6H_3	$C_{26}H_{22}ClNO_5$	463.91	141-142	3	81
7q	3,4-Di-OCH_3-C_6H_3	$C_{27}H_{24}ClNO_5$	477.94	138-139	3	65
7r	4-bromo-Thiophen-2-yl	$C_{23}H_{17}BrClNO_3S$	502.81	192-193	3.5	69
7s	2,3,4,-tri-OCH_3-C_6H_2	$C_{28}H_{26}ClNO_6$	507.97	155-156	4	71
7t	3,4,5-tri-OCH_3-C_6H_2	$C_{28}H_{26}ClNO_6$	507.97	158-159	5	92
7u	2-Cl-3,4-Di-OCH_3-C_6H_2	$C_{27}H_{23}Cl_2NO_5$	512.38	161-162	5	90
7v	Anthracen-9-yl	$C_{33}H_{24}ClNO_3$	518.01	232-233	5	88
7w	2-OH-3-OCH_3-5-Br-C_6H_2	$C_{26}H_{21}BrClNO_5$	542.81	130-131	3.5	72
7x	10-Cl-Anthracen-9-yl	$C_{33}H_{23}Cl_2NO_3$	552.45	197-198	5	91

Different substitutions on the aromatic ring (R) and physicochemical properties of biphenyl chalcones (4a-4x) along with newly synthesized novel oxazolidinone-biphenyl chalcone hybrid compounds (7a-7x) were shown in Table 2 and Table 3 respectively.

Antimicrobial Activity

All the newly synthesized oxazolidinone-chalcone hybrid compounds (7a-7x) were screened for their *in vitro* antibacterial and antifungal activities. The results are produced in Table 4 and Table 5 respectively. The results of antibacterial screening revealed that all the tested compounds showed moderate to good bacterial inhibition against gram positive and gram-negative bacteria compared to standard compounds ciprofloxacin and linezolid. Compounds 7c-7g were found to be active against gram negative strains at 3.125 µg/ml and against gram positive bacteria it was found to be 6.25 µg/ml compared to standard compounds ciprofloxacin and linezolid.

The compounds 7i, 7j and 7p exhibited significant activities against gram-positive bacteria at 6.25 µg/ml while exhibiting moderate activities at 12.5 to 25 µg/ml against gram-negative bacteria compared to standard compounds. The compounds 7p and 7h are moderately active against gram-negative bacteria only.

The corresponding MIC values (µg/mL) of highly active compounds 7c-7g against six bacterial strains, three gram positive- *S. aureus, B. subtilis, S. faecalis* and three gram negative bacteria, *E. coli, P. aeruginosa, K. pneumonia* are presented in Figure 3.

The results of antifungal screening revealed that the tested compounds (7e-7g) showed moderate antifungal inhibition at 12.5 µg/ml against *Candida albicans* and

Table 4: Minimum inhibitory concentration MIC (µg/ mL) of newly synthesized oxazolidinone-biphenyl chalcone hybrid derivatives (7a-7x).

Test Compounds	*S. aureus* (NCIM 5257)	*B. subtilis* (NCIM 2097)	*S. faecalis* (NCIM 2080)	*E. coli* (NCIM 2065)	*P. aeruginosa* (NCIM 5210)	*K. pneumoniae* (NCIM 5289)
7a	50	25	25	50	100	50
7b	6.25	12.5	12.5	25	25	25
7c	3.125	3.125	3.125	6.25	6.25	6.25
7d	3.125	3.125	3.125	6.25	6.25	6.25
7e	3.125	3.125	6.25	6.25	6.25	6.25
7f	3.125	3.125	6.25	6.25	6.25	6.25
7g	3.125	3.125	3.125	3.125	6.25	6.25
7h	25	25	50	12.5	12.5	25
7i	6.25	6.25	6.25	25	25	25
7j	6.25	6.25	6.25	25	25	25
7k	25	25	25	25	25	25
7l	25	25	25	50	50	50
7m	25	25	25	50	50	25
7n	25	25	25	50	25	50
7o	25	25	25	50	50	50
7p	6.25	6.25	6.25	12.5	12.5	12.5
7q	25	25	25	25	25	25
7r	50	50	50	50	50	50
7s	25	25	25	50	50	50
7t	25	25	25	50	50	50
7u	25	25	25	50	50	50
7v	50	25	25	50	50	50
7w	12.5	12.5	12.5	25	25	25
7x	50	25	25	25	25	25
Linezolid	1.56	1.56	1.56	6.25	6.25	6.25
Ciprofloxacin	0.39	0.39	0.78	0.78	0.78	0.78

B. subtilis - Bacillus subtilis, S. aureus -Staphylococcus aureus, S. faecalis-Streptococcus faecalis, E. coli- Escherichia coli, P. aeruginosa- Pseudomonas aeruginosa, K. pneumonia- Klebsiella pneumonia.

Figure 2: Ultrasonication setup to carry out the Buchwald's reactions under nitrogen gas environment.

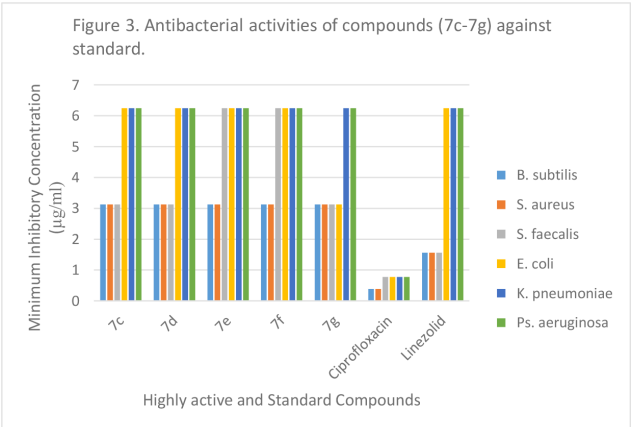


Figure 3: MIC Values of test compounds (7c-7g) and standard.

Table 5: Minimum Inhibitory Concentration (MIC µg/ mL) of Test Compounds (7a to 7x) against *Candida albicans* and *Aspergillus niger*.

Test Compounds	*C. albicans* (NCIM 3628)	*A. niger* (NCIM 1317)
7a	50	50
7b	50	25
7c	25	25
7d	25	25
7e	12.5	12.5
7f	12.5	12.5
7g	12.5	12.5
7h	50	50
7i	25	50
7j	25	25
7k	100	50
7l	100	100
7m	25	25
7n	25	25
7o	25	25
7p	25	25
7q	25	25
7r	25	25
7s	100	100
7t	50	100
7u	50	12.5
7v	100	100
7w	50	25
7x	50	50
Fluconazole	6.25	6.25

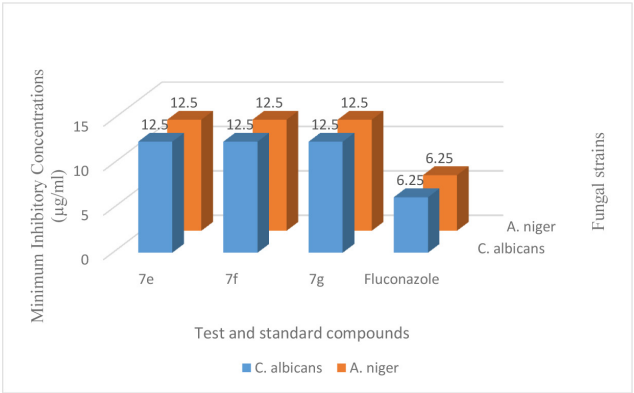


Figure 4: MIC Values of test compounds (7c-7g) and standard.

Aspergillus niger compared to the standard fluconazole, whereas all other compounds showed weak activities against both the fungal strains. It is evident from the literature and from our studies that the oxazolidinones have better antibacterial activity rather than antifungal activity. The MIC values (µg/mL) of newly synthesized oxazolidinone-chalcone hybrids compounds (7e-7g) against two fungal strains are presented in Figure 4.

Structure Activity Relationships (SAR)

The synthesized compounds contains both the combination of Electron With Drawing (EWG) and Electron Donating (EDG) groups at different positions on the ring R_1. Structure activity relationship (SAR) of the screened compounds results suggest that the effect of substitutions on the ring R_1 on antibacterial activity is mostly steric, with only small or linear substituents ($F < Cl < Br < NO_2$ and $OH < CH_3 < OCH_3$) tolerates the ribosomal binding site (oxazolidinones inhibits protein synthesis),[18-19] whereas increase in the bulk of substitution are not tolerated. Substitution with electron with drawing (EWG) groups like fluorine and chlorine derivatives are more active amongst all and are even better than that of hydroxyl derivatives against each strain, that may be attributed to higher lipophilicity of these groups.

CONCLUSION

We have developed an experimentally simple, efficient, short time and high yielding CuI-mediated N-arylation of oxazolidinones using the Buchwald protocol under ultrasound irradiation with a simple set up at room temperature. This approach would be a worthwhile in the development of green chemistry protocols. The antimicrobial activities of novel hybrids (7a-7x) were evaluated against selected strains of bacterial and fungal strains. Among them compounds, 7c to 7g have shown significant antibacterial and moderate antifungal activities when compared to the standard drugs ciprofloxacin, linezolid and fluconazole against bacterial and fungal strains respectively. A systematic SAR study on screened compounds reveals that the effect of substitutions on the ring R_1 on antibacterial activity is mostly steric, with only small or linear substituents ($F < Cl < Br < NO_2$ and $OH < CH_3 < OCH_3$) tolerates the ribosomal binding site, whereas increase in the bulk of substitution are not tolerated. Finally, we hope that our current results will stimulate researchers to further modify the oxazolidinone-chalcone hybrid nucleus and design more potent and selective antibacterial and antifungal agents.

ACKNOWLEDGEMENT

Authors are deeply grateful for GITAM Deemed to be University for providing necessary facilities to carry out this research work. The authors also thank to Dr. S. Murugesan, Associate Professor, BITS Pilani as

well as Dr. M. Murali Krishna form Andhra University for spectral characterization.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

TLC: Thin layer chromatography; **UV:** Ultraviolet spectroscopy; **FT-IR:** Fourier transform infrared spectroscopy; **NMR:** Proton Nuclear Magnetic Resonance; **TMS:** Tetramethylsilane; **$CDCl_3$:** Deuterated chloroform; **MS:** Mass spectrometry; **ESI-MS:** Electrospray ionization-Mass Spectrometer; **Q-TOF:** Quadrupole-Time of flight; **SAR:** Structure Activity Relationships; **MIC:** Minimum Inhibitory Concentration; **EWG:** Electron Withdrawing Groups; **EDG:** Electron Donating Groups; **NCIM:** National Collection of Industrial Microorganisms; **DMSO:** Dimethyl sulfoxide.

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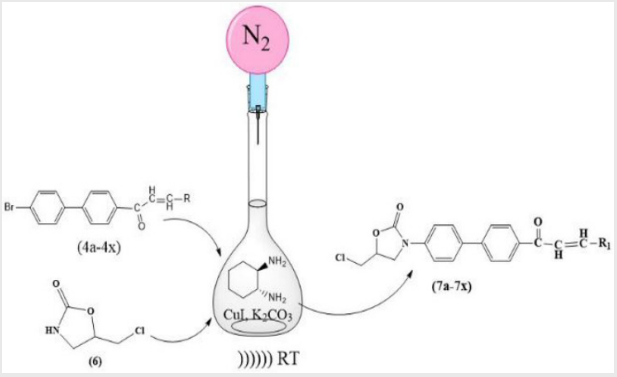
PICTORIAL ABSTRACT



SUMMARY

- An experimentally simple, efficient, short time and high yielding CuI-mediated N-arylation of oxazolidinones using the Buchwald protocol under ultrasound irradiation with a simple set up at room temperature was developed. A novel library of 24 biphenyl chalcone-oxazolidinones hybrids were synthesized, characterized and evaluated for antimicrobial activities. Compounds, 7c to 7g have shown significant antibacterial and moderate antifungal activities when compared to the standard drugs ciprofloxacin, linezolid and fluconazole against bacterial and fungal strains respectively. All other compounds showed moderate to significant antibacterial activities.

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Cite this article: Panigrahi N, Ganguly S, Panda J. Ultrasound Assisted Synthesis, Characterization and Antimicrobial Evaluation of Novel Oxazolidinone-Biphenyl Chalcone Hybrid Derivatives. Indian J of Pharmaceutical Education and Research. 2019;53(2):286-300.