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Design, Synthesis of New Iso-oxazoline Containing Iminothiazolidinone and its Antibacterial Activity

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ABSTRACT

We have synthesized novel 2-(4-(3a,4,5,6,7,7a-hexahydro-4,7-methanobenzo[d]isooxazol-3-yl)phenyl) imino)-3-methylthiazolidin-4-one and its benzilidine derivatives in good yields, by clubbing substituted Isooxazoline and 4-Iminothiazolidinone. All the synthesized compounds were characterized using IR and NMR spectroscopy. The results of the characterization are in agreement with the structures of compounds and tested for its antibacterial and antifungal activity against various strains like Staphylococcus aureus (NCLM 2602), Bacillus subtilis (NCLM 2458), Escherichia coli (NCLM 2809), Aspergillus niger (NCLM 617), Rhizopus ostoyae NCLM 1299) by using antibacterial susceptibility test. All the newly synthesized compounds possess moderate to good antibacterial activity.

Keywords: Isooxazoline, 4-Iminothiazolidinone, Benzilidine derivatives, Antibacterial activity

INTRODUCTION

Among five-member heterocycles, isoxazolines represent a class of compounds of great biological importance. For instance, isoxazolines possess a broad spectrum of biological activity [1,2]. Isoxazoline also serves as an important building block for the synthesis of biologically active molecules [2] and serves as a prodrug for an antiarthritic agent [3]. "Valdecoxib" is an isoxazoline derivative, now widely used in the market as an anti-inflammatory drug [4]. Isoxazoline derivatives have been reported to possess antifungal [5], antibacterial [6], anticonvulsant [7], anti-inflammatory [8], antiviral [9], analgesic [10], antitumor [11], chemotherapy [12] activity. Isoxazoline derivatives also show a good potency in animal models of thrombosis [13]. In addition, isoxazoline derivatives have played a crucial role in the theoretical development of heterocyclic chemistry and are also used extensively in organic synthesis [14,15]. 1,3-Dipolar cycloaddition reactions are useful tools for the construction of biologically potent five-member heterocycles, and nitrile oxides serve as excellent 1,3-dipoles. Cycloaddition of nitrile oxides to olefinic compounds are of synthetic interest, since the resulting isoxazolines are versatile intermediates for the synthesis of bifunctional compounds [16]. Nitrile oxides can be generated by dehydrogenation of aryl aldoximes with mercuric acetate [17], manganese dioxide [18], tert-butyl hypochlorite [19], chloramine-T [20] and N-chlorosuccinamide, triethylamine [21]. As our continuous efforts in search of novel and potent antibacterial and antifungal imino thaiazolidinones [22-24] and biological significance of isooxazoline prompted us to introduce the isooxazoline phenylimino moiety in the 2-imino-thiazolidin-4-ones. We have synthesized novel 2-((4-(3a,4,5,6,7,7a-hexahydro-4,7-methanobenzo[d]isooxazol-3-yl)phenyl)imino)-3-methylthiazolidin-4-one core compound then by using Knovengel condensation reaction with different aromatic aldehydes to form its benzilidine derivatives 8(a-o) and further evaluated for its antibacterial and antifungal activity (Figure 1).

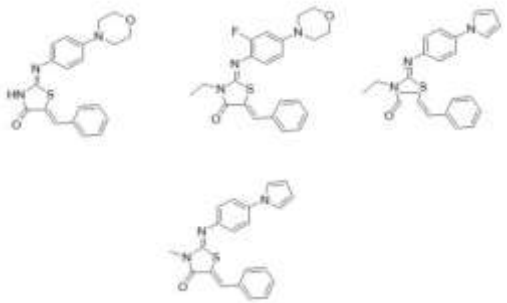

Figure 1: S.G. Patil et al. reported iminothiazolidinones as antibacterial

MATERIALS AND METHODS

Progress of reaction was monitored by silica gel-G coated TLC plates in Ethyl acetate: Hexane system (1:1). The spot was visualized by exposing dry plate in iodine vapors. Melting points were determined by the melting point determination apparatus (TEMPO) in open capillary tubes and are uncorrected. Proton NMR spectra were recorded on Bruker Advance II 400 & 200 NMR Ultra Shield Spectrometer using $CDCl_3$ as a solvent and Tetramethylsilane (TMS) as internal standard. Chemical shift value is expressed in delta parts per million (ppm).

General procedure for 5-benzilidine-2-((4-(3a,4,5,6,7,7a-hexahydro-4,7-methano-benzo[d]isooxazol-3-yl)phenyl)imino)-3-methylthiazolidin-4-one (8a-o)

A mixture 2-((4-(3a,4,5,6,7,7a-hexahydro-4,7-methanobenzo[d]isooxazol-3-yl)phenyl)imino)-3-methylthiazolidin-4-one 7 (1 mmol) in absolute ethanol was added benzaldehyde (1.1 mmol) and diisopropylethylamine (1.5 mmol), reaction mixture was refluxed at 90-95°C for 10 h. After completion of the reaction (TLC check), ethanol was evaporated cold water was added to residue and extracted with ethyl acetate (3 × 20 ml). The combined organic layers were washed with brine and dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was recrystalised using absolute ethanol to get 5-benzilidine-2-((4-(3a,4,5,6,7,7a-hexahydro-4,7-methano-benzo[d]isooxazol-3-yl)phenyl) imino)-3-methylthiazolidin-4-one (8 a-o).

Spectroscopic data of compounds

2-((4-(3a,4,5,6,7,7a-hexahydro-4,7-methanobenzo[d]isooxazol-3-yl)phenyl)imino)-3-methylthiazolidin-4-one (7): Off-white solid; M.P.: 112-114°C; IR (KBr): 2962, 1701, 1630, 1597, 1119, 922 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz), δ=1.19-1.24 (m, 2H), 1.34 (q, 1H), 1.53-1.67 (m, 3H), 2.55 (d, 1H), 2.62 (d, 1H), 3.31 (s, 3H), 3.46 (d, 1H), 3.84 (s, 2H), 4.62 (d, 1H), 6.97-7.01 (m, 2H), 7.68-7.71 (m, 2H). MS (m/z): 342.0 [M^++1].

(2Z,5Z)-5-(benzilidene)-2-((4-(3a,4,5,6,7,7a-hexahydro-4,7-methanobenzo[d]isooxazol-3-yl)phenyl)imino)-3-methylthiazolidin-4-one (8a): Yellow solid; M.P: 173-175°C.; IR (KBr): 2963, 2873, 1712, 1634, 1600, 1509, 1362, 1177, 921 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz), δ=1.25-1.27 (m, 2H), 1.33-1.41 (m, 1H), 1.61-1.67 (m, 3H) 2.60-2.65 (d, 2H), 3.48 (s, 3H), 3.50-3.52 (d, 1H), 4.66-4.68 (d, 1H), 7.04-7.08 (d, 2H), 7.36-7.48 (m, 5H), 7.74-7.77 (d, 2H), 7.79 (s, 1H).; MS (m/z): 430.0 [M^++1].

(2Z,5Z)-5-(4-hydroxy-benzilidene)-2-((4-(3a,4,5,6,7,7a-hexahydro-4,7-methanobenzo[d]isooxazol-3-yl)phenyl)imino)-3-methylthiazolidin-4-one (8b): Yellow solid; M.P: 156-158°C.; IR (KBr): 3447, 3121, 2961, 2871, 1710, 1635, 1600, 1597, 1106, 920 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 400 MHz), δ=1.12-1.17 (m, 1H), 1.36-1.42 (m, 2H), 1.45-1.51 (m, 3H), 2.63-2.65 (t, 2H), 3.32 (s, 3H), 3.36 (d, 1H), 4.6 (d, 1H), 6.81-6.84 (d, 2H), 7.09-7.11 (d, 2H), 7.36-7.38 (d, 2H), 7.67 (s, 1H), 7.73-7.75 (d, 2H).; MS (m/z): 446.0 [M^++1].

(2Z,5Z)-5-(4-bromobenzilidene)-2-((4-(3a,4,5,6,7,7a-hexahydro-4,7-methano-benzo[d]isooxazol-3-yl)-phenyl)imino)-3-methylthiazolidin-4-one(8c): Yellow solid; M.P: 197-199°C.; IR (KBr): 2970, 2871, 1715, 1633, 1596, 1365, 1124 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 400 MHz), δ=1.12-1.23 (m, 2H), 1.29-1.34 (m, 1H), 1.39-1.42 (m, 1H), 1.42-1.55 (m, 2H), 2.49-2.50 (t, 2H), 3.32 (s, 3H), 3.68-3.70 (d, 1H), 4.59-4.61 (d, 1H), 7.09-7.11 (d, 2H), 7.48-7.51 (d, 2H), 7.68-7.69 (d, 2H), 7.70 (s, 1H), 7.73-7.76 (d, 2H).; MS (m/z): 509.9 [M^++1].

(2Z,5Z)-5-(4-phenylbenzilidene)-2-((4-(3a,4,5,6,7,7a-hexahydro-4,7-methanobenzo[d]isooxazol-3-yl)phenyl)imino)-3-methylthiazolidin-4-one (8d): Yellow solid; M.P: 181-183°C; IR (KBr): 3751, 2963, 2872, 1704, 1640, 1598, 1409, 1134 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz), δ=1.16-1.24 (m, 2H), 1.35-1.39 (t, 1H), 1.55-1.62 (m, 3H), 2.59-2.64 (d, 2H), 3.47 (s, 3H), 3.49-3.51 (d, 1H), 4.64-4.66 (d, 1H), 7.05-7.07 (d, 2H), 7.38-7.39 (m, 1H), 7.42-7.46 (t, 2H), 7.52-7.54 (m, 2H), 7.57-7.59 (m, 2H), 7.64-7.66 (m, 2H), 7.74-7.76 (m, 2H), 7.81(s, 1H).; MS (m/z): 506.3 [M^++1].

(2Z,5Z)-5-(3-indollidene)-2-((4-(3a,4,5,6,7,7a-hexahydro-4,7-methanobenzo[d]isooxazol-3-yl)phenyl)-imino)-3-methylthiazolidin-4-one (8e): Yellow solid; M.P: 151-153°C; IR (KBr): 3303, 2958, 2872, 1684, 1634, 1598, 1417, 1130 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz), δ=1.18-1.25 (m, 2H), 1.37-1.41 (t, 1H), 1.57-1.66 (m, 3H), 2.65-2.66 (d, 2H), 3.47 (s, 3H), 3.51-3.53 (d, 1H), 4.66-4.68 (d, 1H), 7.07-7.09 (d, 2H), 7.25-7.33 (m, 2H), 7.43-7.44 (m, 2H), 7.74-7.76 (m, 2H), 7.84-7.86 (d, 1H), 8.14 (s, 1H), 8.88 (bs, 1H).; MS (m/z): 469.5 [M^++1].

(2Z,5Z)-5-(2-furylidine)-2-((4-(3a,4,5,6,7,7a-hexahydro-4,7-methanobenzo[d]isooxazol-3-yl)phenyl)-imino)-3-methylthiazolidin-4-one (8f): Yellow solid; M.P: 164-166°C; IR (KBr): 2952, 1701, 1630, 1421, 1364, 1119 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz), δ=1.21-1.27 (m, 2H), 1.36-1.40 (t, 1H), 1.56-1.67 (m, 3H), 2.60-2.63 (d, 2H), 3.44 (s, 3H), 3.50-3.52 (d, 1H), 4.65-4.67 (d, 1H), 6.51-6.53 (q, 1H), 6.69-6.70 (d, 1H), 7.04-7.08 (d, 2H), 7.54 (s, 1H), 7.58 (d, 1H), 7.73-7.76 (d, 2H).; MS (m/z): 420.2 [M^++1].

(2Z,5Z)-5-(2,4-dimethoxybenzilidene)-2-((4-(3a,4,5,6,7,7a-hexahydro-4,7-methanobenzo[d]isooxazol-3-yl)-phenyl)imino)-3-methylthiazolidin-4-one (8g): Yellow solid; M.P: 147-149°C; IR (KBr): 2975, 1709, 1630, 1597, 1470, 1125 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz), δ=1.09-1.12 (m, 1H), 1.36-1.40 (m, 2H), 1.51-1.60 (m, 3H), 2.48-2.51 (d, 2H), 3.42 (s, 3H), 3.44-3.46 (d, 1H), 3.80 (s, 6H), 4.61-4.63 (d, 1H), 6.68-6.70 (d, 2H), 7.08-7.10 (d, 2H), 7.25-7.28 (m, 1H), 7.68-7.70 (d, 2H), 8.15 (s, 1H).; MS (m/z): 490.2 [M^++1].

(2Z,5Z)-5-(3-bromo,4-flourobenzilidene)-2-((4-(3a,4,5,6,7,7a-hexahydro-4,7-methanobenzo[d]isooxazol-3-yl)phenyl)imino)-3-methylthiazolidin-4-one (8h): Yellow solid; M.P: 207-209°C; IR (KBr): 2967, 1709, 1633, 1596, 1472, 1128 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz), δ=1.12-1.23 (m, 1H), 1.37-1.42 (m, 2H), 1.54-1.62 (m, 3H), 2.58-2.61 (d, 2H), 3.45 (s, 3H), 3.47-3.49 (d, 1H), 4.61-4.63 (d, 1H), 7.05-7.10 (d, 2H), 7.37-7.38 (d, 2H), 7.57-7.59 (d, 2H), 7.67 (s, 1H), 7.77-7.79 (d, 1H).; MS (m/z): 526.5 [M^++1].

(2Z,5Z)-5-(2-methyl-benzilidene)-2-((4-(3a,4,5,6,7,7a-hexahydro-4,7-methanobenzo[d]isooxazol-3-yl)phenyl)-imino)-3-methylthiazolidin-4-one (8i): Yellow solid; M.P: 145-147°C; IR (KBr): 2958, 2873, 1707, 1636, 1598, 1367, 1136 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz), δ=0.90-1.00 (m, 1H), 1.20-1.22 (m, 2H), 1.38-1.42 (m, 3H), 2.40 (s, 3H), 2.58-2.62 (d, 2H), 3.45 (s, 3H), 3.46-3.47 (d, 1H), 4.61-4.63 (d, 1H), 7.05-7.10 (d, 2H), 7.20-7.28 (m, 2H), 7.39-7.40 (d, 1H), 7.76-7.78 (d, 2H), 7.95 (s, 1H); MS (m/z): 446.0 [M^++1].

(2Z,5Z)-5-(3-flouro,4-methoxy-benzylidene)-2-((4-(3a,4,5,6,7,7a-hexahydro-4,7-methanobenzo[d]isooxazol-3-yl)phenyl)imino)-3-methylthiazolidin-4-one (8j): Yellow solid; M.P: 191-193°C; IR (KBr): 3447, 2963, 2873, 1712, 1634, 1600, 1507 cm^{-1}; ^{1}H-NMR ($CDCl^3$, 400 MHz), δ=1.18-1.29 (m, 3H), 1.37-1.43 (m, 3H), 2.58-2.62 (d, 2H), 3.42 (s, 3H), 3.44-3.47 (d,1H), 3.97 (s, 3H), 4.66-4.68 (d, 1H), 6.92 (bs, 1H), 7.01-7.15 (m, 4H), 7.72 (s, 1H), 7.74-7.76 (d, 2H); MS (m/z): 478.5 [M^++1].

(2Z,5Z)-5-(4-methoxybenzilidene)-2-((4-(3a,4,5,6,7,7a-hexahydro-4,7-methanobenzo[d]isooxazol-3-yl)phenyl)imino)-3-methylthiazolidin-4-one (8k): Yellow solid; M.P: 137-139°C; IR (KBr): 3448, 2960, 2873, 1718, 1635, 1597, 1141, 1308 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz),

δ=1.12-1.18 (m, 2H), 1.37-1.41 (m, 1H), 1.54-1.67 (m, 3H), 2.58-2.62 (d, 2H), 3.42 (s, 3H), 3.46-3.48 (d, 1H), 3.82 (s, 3H), 4.63-4.65 (d, 1H), 6.91-6.97 (d, 2H), 7.10-7.14 (d, 2H), 7.41-7.43 (d, 2H), 7.74 (s, 1H), 7.77-7.79 (d, 2H).; MS (m/z): 460.2 [M^++1].

(2Z,5Z)-5-(4-nitro-benzilidene)-2-((4-(3a,4,5,6,7,7a-hexahydro-4,7-methanobenzo[d]isooxazol-3-yl)phenyl)-imino)-3-methylthiazolidin-4-one (8l): Yellow solid; M.P: 176-178°C; IR (KBr): 3853, 2954, 2874, 1718, 1645, 1600, 1308, 1125 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz), δ=1.19-1.27 (m, 2H), 1.37-1.41 (m, 1H), 1.56-1.67 (m, 3H), 2.66-2.67 (d, 2H), 3.50 (s, 3H), 3.52 (d, 1H), 4.67-4.69 (d, 1H), 7.04-7.06 (d, 2H), 7.60-7.62 (d, 2H) 7.76-7.78 (d, 2H), 7.80 (s, 1H), 8.26-8.29 (d, 2H).; MS (m/z): 475.2 [M^++1].

(2Z,5Z)-5-(2-flouro,4-bromobenzilidine)-2-((4-(3a,4,5,6,7,7a-hexahydro-4,7-methanobenzo[d]isooxazol-3-yl)phenyl)-imino)-3-methylthiazolidin-4-one (8m): Yellow solid; M.P.: 183-185°C; IR (KBr): 2954, 2874, 1716, 1630, 1596, 1511, 1382 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz), δ=1.19-1.27 (m, 2H), 1.37-1.41 (m, 1H), 1.56-1.67 (m, 3H), 2.66-2.67 (d, 2H), 3.50 (s, 3H), 3.52 (d, 1H), 4.67-4.69 (d, 1H), 7.06-7.10 (m, 3H), 7.22-7.40 (m, 4H), 7.92 (s, 1H).; MS (m/z): 526.5 [M^++1].

(2Z,5Z)-5-(3,4-diflourobenzilidine)-2-((4-(3a,4,5,6,7,7a-hexahydro-4,7-methanobenzo[d]isooxazol-3-yl)-phenyl)-imino)-3-methylthiazolidin-4-one (8n): Yellow solid; M.P.: 133-134°C; IR (KBr): 2944, 1712, 1632, 1598, 1512, 1363 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz), δ=1.12-1.23 (m, 1H), 1.37-1.42 (m, 2H), 1.54-1.62 (m, 3H), 2.58-2.61 (d, 2H), 3.45 (s, 3H), 3.47-3.49 (d, 1H), 4.61-4.63 (d, 1H), 6.92 (bs, 1H), 7.05-7.10 (d, 2H), 7.37-7.38 (d, 2H), 7.57-7.59 (d, 2H), 7.67 (s, 1H); MS (m/z): 466.5 [M^++1].

(2Z,5Z)-5-(3,4-diflourobenzilidine)-2-((4-(3a,4,5,6,7,7a-hexahydro-4,7-methanobenzo[d]isooxazol-3-yl)phenyl)imino)-3-methylthiazolidin-4-one (8o): Yellow solid; M.P.: 179-181°C; IR (KBr): 2951, 1710, 1635, 1585, 1500, 1360, 1105 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz), δ=1.12-1.23 (m, 1H), 1.37-1.42 (m, 2H), 1.54-1.62 (m, 3H), 2.58-2.61 (d, 2H), 3.45 (s, 3H), 3.47-3.49 (d, 1H), 4.61-4.63 (d, 1H), 6.92 (t, 2H), 7.25-7.28 (d, 2H), 7.41-7.43 (d, 2H), 7.67-7.69 (d, 2H), 7.79 (s, 1H); MS (m/z): 448.5 [M^++1].

Antimicrobial activity

The antimicrobial activity of the compounds was assayed by antimicrobial susceptibility test [25]. 100 µl of 24 h growth of each microorganism was spread on the surface of nutrient agar for bacteria (Mac Conkey's agar for *E. coli*) and potato dextrose agar for fungi, in petri plates (Composition of media is given below). 50 µl compounds at the concentration of 100 µg/ml in Dimethyl Sulfoxide (DMSO) saturated on discs of 6 mm diameter were kept on agar surface. The plates were refrigerated for 2 h to allow pre-diffusion of the compounds from the discs into the seeded agar layer and then incubated at 37°C for 24 h for bacteria and 28°C for 48 h for fungi. Zones of inhibition were measured in millimeter and size of the disc was subtracted from the zone size to measure final activity. DMSO saturated discserved as solvent control or negative control and streptomycin saturated discs (30 µg) for bacteria and nystatin (30 µg) for fungi as reference or positive control. All the synthesized iminothiazolidinone derivatives were tested for their potential to inhibit growth of different bacterial and fungal species at doses of 100 µg/ml in DMSO as a solvent, against bacterial and fungal cultures. All the compounds were found to have antimicrobial activities against different species of bacteria and fungi in our studies.

RESULT AND DISCUSSION

Chemistry

Iso-oxazoline ring was constructed using 1,3-Dipolar cycloaddition [21] reaction of N-hydroxy-4-nitrobenzimidoyl chloride with bicyclo[2.2.1]hept-2-eneindiethylether using triethylamine to get nitrophenyl-4-(3a,4,5,6,7,7a-hexahydro-4,7-methanobenzo[d]isooxazol-3-yl), which is used as key starting material for target compound.

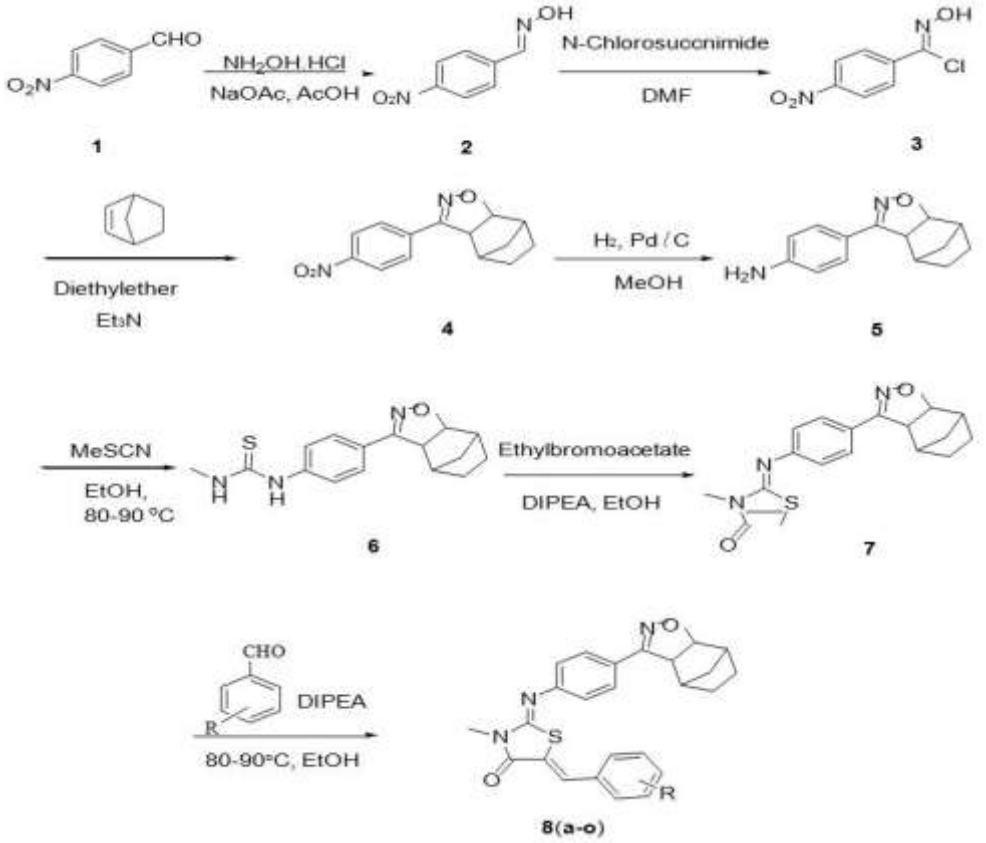

Figure 2: Synthetic strategy for target compound

The nitrophenyl-4-(3a,4,5,6,7,7a-hexahydro-4, 7-methanobenzo[d]isooxazol-3-yl) 4 on catalytic reduction by using H2/Pd/C in methanol afforded 4-(3a,4,5,6,7,7a-hexahydro-4,7-methanobenzo[d]isooxazol-3-yl)-benzamine 5, which was further treated with methyl-isothiocynate in ethanol at 80°C to afford the 4-(3a,4,5,6,7,7a-hexahydro-4,7-methanobenzo[d]isooxazol-3-yl)phenyl)-3-methylthiourea 6 is key intermediate for synthesis of iminothiazolidinone core for further derivatization (Figure 2).

Our core compound 7 was prepared by treating 6 with ethyl bromoacetate in presence of diisopropylethylamine in refluxing ethanol afforded the key intermediate 2-((4-(3a,4,5,6,7,7a- hexahydro-4,7-methanobenzo [d]iso-oxazol-3-yl)phenyl)imino)-3-methylthiazolidin-4-one 7 with 69% yield. The IR spectrum of the compound 7 shows the strong absorption bands at 1630 cm^{-1} (C=O) and at 1701 cm^{-1} (C=N) confirm the presence of C=O and C=N functional groups respectively. The ^{1}H-NMR spectrum of compound **7** showed three multiplates between 1.19-1.24, 1.33-1.37 and 1.53-1.61 ppm each integrating for two, one and three protons respectively was due to the protons of three methylene groups of bicyclic ring. Two broad singlets's each integrating for one proton resonated at and 2.62 ppm was due to methine protons of bicyclic ring. Two doublets each integrating for one proton at 3.46 (=C-CH) and 4.62 (O-CH) ppm with coupling constant 8.4 Hz, were assigned to the methine protons at bicyclic and iso-oxazoline ring fusion. A singlet at 3.31 ppm integrating for three protons was assigned to the protons of methyl group attached to N-atom of iminothiazolidinone ring. Another singlet at 3.84 ppm integrating for two protons was due to the protons of methylene group attached to S-atom of iminothiazolidin-4-one ring. Aromatic protons showed two multiplates between 6.97-7.01 and 7.68-7.71 ppm each integrating for two protons. The mass spectrum showed a peak at m/z=342.0 (M^++1) matches with the molecular formula $C_{18}H_{19}N_3O_2S$.

The synthesis of benzilidine derivativeof 2-((4-(3a,4,5,6,7,7a-hexahydro-4,7-methanobenzo[d]isooxazol-3-yl)phenyl)imino)-3-methylthiazolidin-4-one 8a-o was carried out using our core compound **7** by Knoevengel condensation with different substituted aromatic aldehydes in presence of diisopropylethylamine as a base in absolute ethanol afforded the 5-benzilidene-2-((4-(3a,4,5,6,7,7a-hexahydro-4,7-methanobenzo[d]isooxazol-3-yl)phenyl)imino)-3-methylthiazolidin-4-one 8(a-o) in good yields, The IR spectrum of this compound showed strong absorption bands at 1615 cm^{-1} (C=C), 1635 cm^{-1} (C=O) and at 1710 cm-1 (C=N) confirms the presence of C=C, C=O and C=N functional groups respectively, ^{1}H-NMR spectrum shows, the absence of the signal of methylene protons of thiazolidin-4-one ring of starting compound 7 at 3.84 ppm together with the resonance of the benzilic methine proton at 7.67 ppm confirms the formation of proposed structure 8. Stereochemistry of the C=N imino and C=C exocyclic double bond is reported in literature [18,19]. The Z-configuration of the exocyclic C=C bond was assigned on the basis of ^{1}H NMR spectroscopy. The methine proton deshielded by adjacent C=O, was detected in the range of 7.67-8.30 ppm in the ^{1}H-NMR spectrum as observed for 5-benzilidene-thiazildin-4-one 8(a-o), this values were in agreement with the reported data [26]. In E-iosmer due to lesser deshielding effect such a proton should resonate at lower chemical shift value [27,28]. Literature study reveals that stereochemistry of the C=N exocyclic double bond is also Z [26].

Antibacterial and antifungal activity

The newly synthesized compounds were tested to evaluate their antibacterial and antifungal activity. All these compounds were found to exhibit better antibacterial and antifungal activity against different species of bacteria and fungi from the activity data (Table 1). Compound 8a, 8b, 8c, 8f, 8g and 8k showed good activity against all bacteria. Compound 8b, 8c, 8g and 8k showed good activity against fungi. Among all tested bacteria and fungi compound 8c, 8g, 8k showed excellent activity against *S. aureus, B. subtilis* and *E. coli*. showed good activity against all the bacteria. Compounds 8d, 8h and 8m showed good activity against *Aspergillus niger* and *R. ostoyae* fungi. Among all the compounds 8b, 8g, 8k were found to be most active compounds. Overall results shows Compounds 8(a-o) are showing moderate to good antimicrobial activity.

Table 1: Antimicrobial activity of 5-(benzilidene)-2-((4-(3a,4,5,6,7,7a-hexa-hydro-4,7-methanobenzo[d]isooxazol-3-yl)phenyl)imino)-3-methylthiazolidin-4-one 8(a-o)

Comp. No. 32	Zone of inhibition (mm)				
	Bacteria			Fungi	
	Staphylococcus aureus **(NCLM No.2602)**	***Bacillus subtilis*** **(NCLM No.2458)**	***Escherichia coli*** **(NCLM No.2809)**	***Aspergillus niger*** **(NCLM No.617)**	***Rhizopus ostoyae*** **(NCLM No.1299)**
a	7.1	6.8	7.3	8.0	5.9
b	8.1	8.0	7.1	7.1	7.1
c	11.3	10.5	9.9	8.8	7.5
d	7.6	7.2	6.3	5.9	6.3
e	5.7	6.1	5.4	6.1	4.9
f	9.2	8.1	7.4	6.7	5.9
g	9.13	8.4	7.21	6.19	6.2
h	6.4	6.3	6.9	5.5	5.0
i	8.4	7.9	7.3	5.9	5.2
j	6.5	5.9	5.5	6.1	4.9
k	10.7	9.9	9.7	8.3	7.13
l	9.0	8.8	7.41	8.0	6.5
m	8.8	8.0	8.7	8.0	5.4
n	6.5	5.5	5.5	4.9	4.9
o	5.7	6.1	5.4	6.1	5.2
Standard	12	10	11	10	9

These results are average results of four experiments. These compounds were used at concentration of 100 µg/ml. Streptomycin for bacteria and nystatin for fungi were used as standard at concentration of 30 µg.

CONCLUSION

Conclusively, we have reported Antimicrobial activity of 5-(benzilidene)-2-((4-(3a,4,5,6,7,7a-hexa-hydro-4,7-methanobenzo[d]isooxazol-3-yl)phenyl)imino)-3-methylthiazolidin-4-one derivatives shows moderate to good antibacterial and antifungal activity among all the compounds 8b, 8g, 8k were found to be most active compounds, There is still the further scope to develop iminothiazolidinone derivatives for antibacterial study.

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REFERENCES

[1] R. Huisgen, Angew. *Chem. Int. Ed.* **1963**, 2, 565.
[2] P. Caramella, P. Gruenanger, A. Padwa, 1, 3-Dipolar Cycloaddition Chemistry, Vol. 1,, Wiley Interscience: New York, **1984**; 337.
[3] J.W. Patterson, P.S. Cheung, M.J. Ernest, *J. Med. Chem*., **1992**, 35, 507.
[4] G. Dannhardt, W. Kiefer, G. Kramer, S. Maehrlein, U. Nowe, B. Fiebich, *Eur. J. Med. Chem*., **2000**, 35, 499.
[5] S.S. Korgaokar, P.H. Patil, M.T. Shab, H.H. Parekh, *Indian J. Pharm. Soc*., **1996**, 58, 222.
[6] D. Nauduri, G.B Reddy, *Chem. Pharm. Bull*., **1998**, 46, 1254.
[7] U.H. Kurokawa, M.Y. Masuda, H. Nishimuura, *J. Med. Chem*., **1979**, 22, 180.
[8] B. Shivkumar, L.V. Nargund, *Indian J. Heterocyc. Chem*., **1998**, 8, 27.
[9] G.D. Diana, M.A. Mckinlay, M.J. Otto, V. Akullian, C. Oglesby, *J. Med. Chem*., **1985**, 28, 1905.
[10] K.H. Adachi, J.R Kido, K. Hirose, *J. Med. Chem*., **1967**, 10, 411.
[11] J. Getal, *J. Antibiotic*., **1975**, 28, 91.
[12] S.A. Rajam, M.V.K. Subhash, E. Rajanarendar, *Indian Bot. Report*., **1984**, 3, 38.
[13] J.P.D. Pinto, *J. Med. Chem*., **2001**, 44, 566.
[14] Y.V. Tomilovi, G.P Okonnishnikova, E.V. Shulishov, O.M. Nefedov, *Russ. Chem. Bull*., **1995**, 44, 2114.
[15] E.I. Klimova, M. Marcos, T.B. Klimova, A.T. Cecilio, A.T. Ruben, R.R. Lena, *J. Organomett. Chem*., **1999**, 585, 106.
[16] K.B. Umesha, A. Kumar, K. Rai, M. Lokanatha, *Synth. Commun*., **2002**, 32, 1841.
[17] K. Rai, M. Lokanatha, N. Linganna, A. Hassner, C. Anjanamurthy, *Org. Prep. Proc. Int*., **1992**, 24, 91.
[18] J. Keigiel, M. Poplawaska, J. Jozwik, M. Kosior, J. Jurzak, *Tetrahedron*., **1999**, 40, 5605.
[19] O. Moriya, H. Takenaka, M. Iyoda, Y. Urata, T. Endo, *J. Chem. Soc*., **1994**, 413.
[20] K. Rai, M. Lokanatha, A. Hassner, *Indian J. Chem*., **1997**, 36B, 242.
[21] S. Balachandran, *Biorg. Med. Chem. Lett*., **2009**, 19, 4773.
[22] S.G. Patil, R.R. Bagul, M.S. Swami, N.S. Kotharkar, K. Darade, *Chinese Chem. Lett*., **2011**, 22, 883.
[23] S.G. Patil, R.R. Bagul, M.S. Swami, S.N. Hallale, V.M. Kamble, N.S. Kotharkar, K. Darade, *J. Chem. Pharm. Res*., **2011**, 3(3), 69.
[24] S.G. Patil, D.S. Kadam, R.R. Bagul, D.K. Pagar, N. S. Kotharkar, *J. Chem. Pharm. Res*., **2017**, 9(9), 86-91.
[25] F. Kavangh, *Anal. Microbiol.*, **1963**, 125.
[26] M.H. Bolli, S. Abele, C. Binkert, *J. Med. Chem*., **2010**, 53, 4198.
[27] P. Vicini, A. Geronikaki, K. Anastasia, M. Incerti, F. Zania, *Bioorg. Med. Chem*., **2006**, 14, 3859.
[28] R. Ottana, R. Maccari, M.L. Barreca, G. Bruno, A. Rotondo, A. Rossi, G. Chiricosta, R. Paola, D.L. Sautebin, S. Cuzzocread, M.G. Vigorita, *Bioorg. Med. Chem*., **2005**, 13, 4243.