Synthesis, Characterization and Antimicrobial Activity of Novel 2H-oxazinyl-thiazolidinone-4 and 2H-oxazinyl-3(4H))-4-methylbenzo[h] quinolinone-2(1H)Derivatives

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Abstract

The synthesis of effective biomaterial works as antimicrobial agent. A series of -thiazolidin-4-one and -oxoazetidin-2-yl- derivatives were easily obtained commencing from α-naphthol and ethyl acetoacetate to form coumarin and then converted into -quinolin-2(1H)-one using hydrazine hydrate followed by subsequent reaction of quinolin-2(1H)-one and p-hydroxy benzaldehyde oxazine-6-carbaldehyde Thereafter carbaldehyde and aromatic primary amine were condensed from imines.

Final cyclized derivatives were achieved by the reaction of imine with thioglycollic acid and chloroacetyl chloride. The structure elucidation of all the novel derivatives was accomplished through PMR, Mass and IR studies. The antimicrobial activity was assessed in vitro by serial dilution method. The activity of 5(b,d,g) and 6(b,f,g)derivatives showed noticeable antimicrobial activity against the tested microbes.

Keywords: Ethyl acetoacetate, thioglycollic acid, chloroacetyl chloride, pyridine, hydrazine hydrate, toluene, primary, aromatic amine.

Introduction

The thiazolidine -4-one moiety is utilized as excellent pharmacophoric scaffold for various chemotherapeutic agents such as anti HIV, anti-proliferative, antifungal, antimicrobial, antihistaminic, analgesic, antitubercular, antioxidant, cytotoxic etc. The thiazolidiones are the saturated variety of thiazole with the sulphur positioned at number 1, nitrogen positioned at number 3 and a carbonyl group at 2,4, or 5[3]. They also display antidiarrheal, anticonvulsant, anti-diabetic and antiplatelet activating factor. The 4 thiazolidiones are extensively employed as chemical fertilizer for increasing the crop yields. Their variants are utilized to eliminate the pests. The 4 amino antipyrine also depicts antimicrobial and anti-inflammatory properties besides inhibiting the mild steel corrosion in HCl solution.

Gram- +ve, Gram- -ve and anaerobic bacteria can all be successfully deal with β-lactam antibiotics, which have been found to have a wide range spectrum of activity. β-lactam antibiotics have also been known to controlled urinary tract infections (UTIs), sinusitis, pneumonia, pharyngitis and soft tissues, skin, bloodstream infections. Penicillins, cephalosporins, carbapenems and monobactams are the four types of β-lactam antibiotics, which are distinguished by their four-membered azetidinone ring. The enzymes known as bacterial cell wall transpeptidases, which crosslink cell wall pentapeptides during peptidoglycan production, are the target of these antibiotics.

The synthesis of heterocyclic derivatives has long piqued the interest area for researchers because of their significant antimicrobial activity. Because of their moderate toxicity[2], β-lactam derivatives, which are distinguished by the presence of a 4-membered azetidinenone ring[1], have demonstrated various medical applications. Antimicrobial, antimalarial[4,5], antifungal[6], antidiabetic[7], antitubercular[8], anticancer[9], antiparkinsonian[10], anti-HIV[11] and antitumor[12] medicines are among the many medications in this family that are still widely used[3]. In any case, the widespread use of these drugs has led to the production of several β-lactamases (β-Lases) by the bacteria[13].

Oxazines moeities have been the pillars in the theoretical development of heterocyclic chemistry[14-16]. They have immense deployment in the organic synthesis. Since the advancement of antibiotic resistance is on the rise, the search for new and powerful drug scaffolds is inevitable. Benzo 1,3 oxazine moieties have depicted some interesting biological activities such as antirheumatic, antianginal, antihypertensive, cytotoxic and antiosteoclastic bone resorption phenomenon[17-19].

Efavirenz, a medication that contains trifluromethyl-1-oxazin-2, is very efficient against HIV-1 mutant strains (20–21) because it functions as a non-nucleoside reverse transcriptase inhibitor. Another variant i.e. 1, 3 oxazine derivative acts as progesterone receptor agonist and hence is able to alter a number of metabolic pathways[22-28]. The oxazine compounds can be synthezied using a number of different pathways. They can be synthesized from anthranilic acid and its derivatives through ring closure achieved by acetic anhydride or chloro acetyl, succinic anhydride or by alkyl chloroacetate[29-34]. Another method of preparing the oxazine compounds is by taking amido salicylate which can undergo cyclization by utilizing different reagents like by using Vismeier HAAck reactions[34-36]. The enhancement of the activity of synthesized derivatives is due to presence of three

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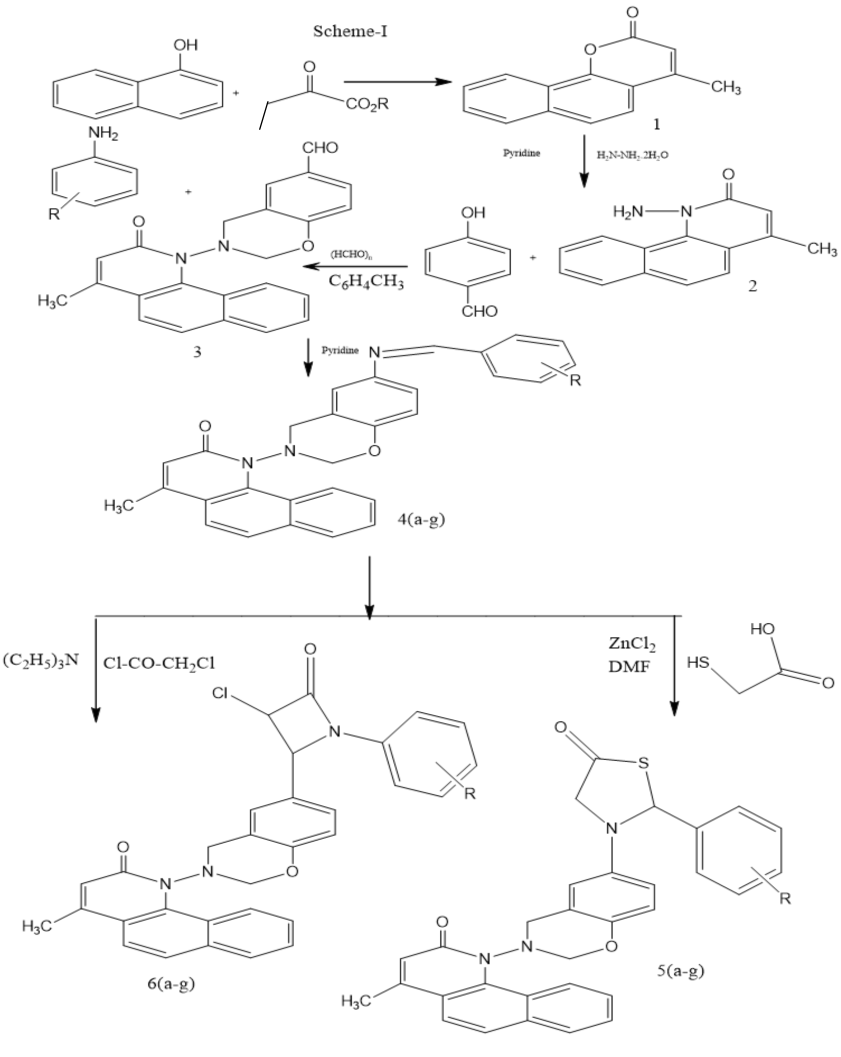
heterocyclic ring as oxazin β-lactam coumarin and oxazin, thiazolidinone and coumarin within tailored molecule.

Chemistry: The synthesized derivatives of 2-(4-substituted-phenyl)-3-(3-(4-methyl-2-oxobenzo [h]quinolinyl -1-)-3,4-dihydro-(2h)-benzo[e,1,3]-2H-oxazinyl-6)thiazolidinone-4 and 1-(6-(3-chloro-1-(substituted/unsubstitutedphenyl)-4-oxoazetidinyl-2)-benzo[e,1,3]-2H-oxazinyl-3,(4H)-4-methylbenzo[h] quinolinone-2(1H) involved four steps. In step 1, the condensation of β naphthol and acetoacetic ester yielded 4-methyl-2H-benzo[h]chromenone-2. The characterization data is: infrared-ν_{max} per cm-KBr: 3025(Aromatic, CH), 2714(C-H, Aldehyde), 1033(C-O), 1767(C=O), PMR-Deuterated chloroform-300 MHz δ in ppm: 7.02-7.36-9Hmultipilate of aromatic ring and 3H at 1.09 ($-CH_3$) confirmed the structure of product 1. The conversion of N-amino-4-methylbenzo[h]quinolinone-2(1H) by reaction of hydrazine hydrates with 4-methyl-2H-benzo[h]chromenone-2 in pyridine took place, with new spectral data corresponding to infrared-ν_{max} per cm-KBr: 3345($-NH_2$), 2912($-CH_3$), 915(N-N) PMR-Deuterated chloroform-300 MHz δ in ppm: 2.45($-NH_2$) respectively.

The condensation product 2 with p-hydroxy benzaldehyde in an excess of chloroform and toluene gave product 3. The characterization data is: infrared-ν_{max} per cm-KBr: CH),1033(C-O), 915(N-N) PMR-Deuterated chloroform-300 MHz δ in ppm: 7.02-7.36(Aromatics), 1.09(-CH3). The synthesis of compound 4 was generated by the reaction of various substituted primary amine and product 3.

The structure was confirmed by the spectral data FTIR-ν_{max}-KBr (per cm): the additional 1252 (C=N) with along 746 (N-N), 1670 (C=O) suggesting the formation of Schiff base PMR-Deuterated chloroform-300 MHz δ in ppm: 5.23 (s,2H, oxazin-ring), 4.5 (s,2H, oxazin-ring), 2 (S,3H,$-CH_3$). The final products 5 (a-g) and 6 (a-g) were obtained by the cyclization of Schiff base 5 through thioglycollic acid -thiazolidin-4-one and chloroacetyl chloride-β lactam.

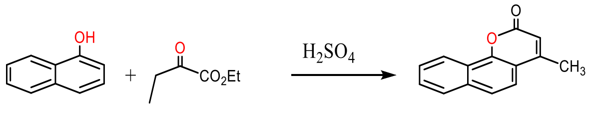
The characterization data of new peak is: FTIR-ν_{max}-KBr (per cm): Infrared-ν_{max} per cm-KBr: 1035 (C-S) and PMR-Deuterated chloroform-300 MHz δ in ppm: 2.05 (s,1H, N-CH-S) the singlet new peaks confirmed the presence of ring structure of thiazol ring and 2.9(s,2H,$-CH_2$-S). Infrared-ν_{max} per cm-KBr: peaks (N-C=O, str.), 670 (C-Cl), and PMR-Deuterated chloroform-300 MHz δ in ppm: the doublet 6.39 (-HC-CH-Cl,) showed the presence of lactam ring.



Material and Methods

The PMR-Deuterated chloroform-300 MHz δ in ppm on Bruker NMR spectrophotometer at 300 MHz's tetramethyl silane was taken as the internal standard and chemical shift PMR-Deuterated chloroform values (δ) are shown as part per million (ppm). The measurement of IR with the Jasco FT-IR-470 spectrophotometer (Shimadzu 8700) KBr with diffuse reflectance method has been used. The melting points of synthesized derivatives were taken by thermoelectric instrument using fused capillary's tube expressed in °C and are uncorrected. The purity and structure of the prepared derivatives were determined by using precoated TLC plates (Merk, 60F-254), iodine vapor as visualizing agent and eluent as 5:2hexane/ethyl acetate).

The synthesis of 4-methyl-2H-benzo[h]chromenone-2:



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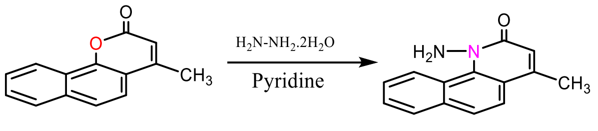
0.01 mole of both α-naphthol and ethyl acetoacetate were used in 40 ml of conc. H_2SO_4 and agitated for 0.5 hour. On cooling, the resultant solution was poured over chunks of shattered ice. The product was filtered out and then repeatedly rinsed down with water and dried at 100°C. The resulting anhydrous coumarins were recrystallized with ethanol. Yield 84%; mp 120–121°C; Mol. Wt:210.23 molecular formula: $C_{14}H_{10}O_2$.

4-methyl-2H-benzo[h]chromen-2-one
Chemical Formula: $C_{14}H_{10}O_2$
Exact Mass: 210.06808
Molecular Weight: 210.23200
m/z: 210.06808 (100.0%), 211.07143 (15.1%), 212.07479 (1.1%)
Elemental Analysis: C, 79.98; H, 4.79; O, 15.22

The synthesis of 1-amino-4-methylbenzo[h]quinolinone-2(1H):



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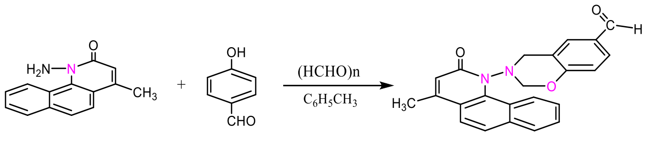
0.01 moles of both 4-methyl-2H-benzo[h]chromenone-2 and hydrazine hydrate in 30 ml pyridine were refluxed on heating mantle for 07 hours. After that, the obtained product was added to 10 milliliters of concentrated hydrochloric acid in ice-cold water. After a solid began to split, it was given an hour to settle. It was removed by filtering and then repeatedly cleaned with water. Using a vacuum desiccator to dry it out, it was separated from ethanol. Yield 71%; mp 87–88°C; Mol. Wt.: 224.26 elemental analysis calculated and found: for $C_{14}H_{12}N_2O$ C, 74.98, N, 12.49 and C, 74.93, N, 12.44.

The synthesis of 3-4-methyl-2-oxobenzo[h]quinolinyl-1(2 H)-3,4-dihydro-2h-benzo[e,1,3] 6-oxazine-carbaldehyde:



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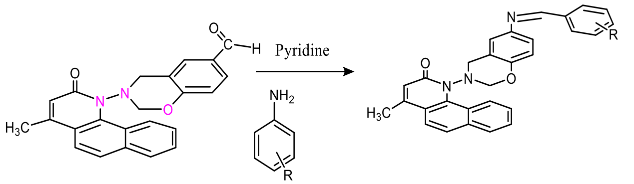
Use 40 ml of toluene and 0.4 moles of aqueous formaldehyde solution in a round bottom flask having three-necked with a stirrer at room temperature and then cooling the reactant up to 5°C with ice, 0.01 mol of 1-amino-4-methylbenzo[h]quinolinone-2(1H) was also added.

Under stirring, 25 ml toluene were added to a flask and the temperature was kept below 5°C. In 35 ml toluene, 0.1 mole of p-hydroxybenzaldehyde was added to the flask with agitated stirring after 0.05 hours at the same temperature. Continuously stir for 2 hours at room temperature. then heat for 7 hours at 95 °C while stirring. Reduced pressure was used to remove the residue and an excess of chloroform was applied to dissolve it. 0.5 cc of an aqueous NaOH solution was used to wash the resultant compound.

Yield 63 %; mp 89-90°C; Mol. Wt: 370.41 elemental analysis calculated and found: for $C_{23}H_{18}N_2O_3$, C, 74.58, N, 7.56 and C, 74.52, N, 7.51; infrared-vmax per cm-KBr: 3025(Aromatic, CH),2714(C-H,Aldehyde), 1634 (C=C, olifins),1033(C-O),1767(C=O),915(N-N) PMR-Deuterated chloroform-300 MHz δ in ppm : 5.23(s,2H,-oxazin-ring-N-CH2), 3.5(s, 2H,- oxazin-ring-N-CH2-O), 2.37 (S,3H, CH3), 6.6-7.9(m,9H,Aro.), 9.73 (s,1H,CHO), 4.32(s,1H,CH3-C= CH).

The Synthesis of 1-(6-(substituted/unsubstituted phenyl) imino)-l3-methyl)-benzo[e,1,3]-2H-oxazinyl-3(4H)-4-methylbenzo[h]quinolinone-2(1H) (schiff base 4a-i):



3

4(a-g)

0.01 mole of each reactant as 3-(4-methyl-2-oxobenzo[h]quinolin-1(2H)-yl)-3,4-dihydro-2h-benzo[e,1, 3]6-oxazine-carbaldehyde, substituted aryl primary amine and 40 mL of absolute ethyl alcohol were refluxed on heating mantle for 9 hours with one milliliter of glacial acetic acid. Reduced pressure was used to remove the excess solvent. After being rinsed in cold water, the resulting yield was recrystallized by ethanol. The following are the characterization details of the newly created heterocyclic derivatives:

a. 1-(6-(4-chlorophenyl)imino)-l3-methyl)-benzo[e,1,3]-2H-oxazinyl-3(4H)-4-methylbenzo[h]quinolinone-2(1H): Yield 66 %; mp 7103-104°C ; Mol. Wt:478.96 elemental analysis calculated and found: for $C_{29}H_{21}ClN_3O_2$, C, 72.72; Cl, 7.40; N, 8.77 and C, 72.67; Cl, 7.36; N, 8.72, FTIR-ν_{max}-KBr (per cm): 3060 (Aromatic, CH), 670 (C-Cl), 1632(C=C, olifins), 2820 (-CH_3), 989(C-O), 1252 (C=N), 746 (N-N), 1670 (C=O) , PMR-Deuterated chloroform-300 MHz δ in ppm: -δ-ppm: 6.7-7.7 (m,14H,Aromatic), 5.25 (s,2H, oxazin-ring-N-methylene), 4.5 (s,2H, oxazin-ring-N-methylene$_2$-O), 2 (s,3H,- methyl).

b. 1-(6-(4-bromophenyl)imino)-l3-methyl)-benzo[e,1,3]-2H-oxazinyl-3(4H)-4-methylbenzo[h]quinolinone-2(1H): Yield 58 %; mp 115-116 °C ; Mol. Wt:523.41 elemental analysis calculated and found: For $C_{29}H_{21}BrN_3O_2$, C, 66.55; Br, 15.27; N, 8.03 and C, 66.50; H, Br, 15.22; N, 8.00, FTIR-ν_{max}-KBr (per cm): 3064 (Aromatic, CH), 620 (C-Br), 1636(C=C, olifins), 2824 (-CH_3), 995 (C-O), 1245 (C=N), 740 (N-N), 1666 (C=O) , PMR-Deuterated chloroform-300 MHz -δ-ppm: 6.69-7.74 (m,14H,Aromatic), 5.21 (s,2H,oxazin-ring-N- methylene), 4.2 (s,2H,oxazin-ring-N-methylene -O), 2.3 (s, 3H, methyl).

c. 1-(6-(4-hydroxyphenyl)imino)-l3-methyl)-benzo [e, 1, 3]-2H-oxazin-yl3(4H)-4-methylbenzo[h]quinolinone -2 (1H): Yield 65 %; mp 127-128 °C ; Mol. Wt:460.51 elemental analysis calculated and found: for $C_{29}H_{22}N_3O_3$C, 75.64; N, 9.12 and C, 75.60; N, 9.07, FTIR-ν_{max}-KBr (per cm): 3052 (Aromatic, CH), 1640(C=C, olifins), 2830 (-CH_3), 3360 (-OH), 980 (C-O), 1248 (C=N), 741 (N-N), 1675 (C=O) , PMR-Deuterated chloroform-300 MHz δ in ppm : 6.77-7.81 (m,14H,Aromatic), 5.29 (s,2H oxazin-ring-N- methylene), 4.7 (s,2H, oxazin-ring-N- methylene -O), 2.1 (s,3H, methyl).

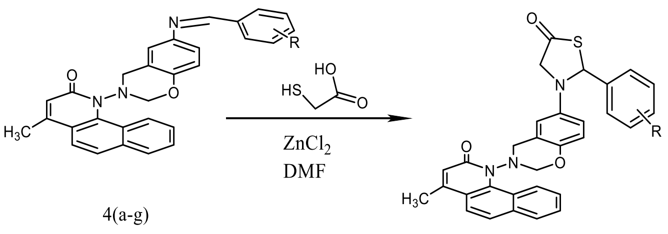
d. 4-methyl-1-(6-(4-nitrophenyl)imino)-l3-methyl)-benzo [e,1,3]-2H-oxazinyl-3(4H)benzo[h]quinolinone-2(1H): Yield 71 %; mp 125-126 °C ; Mol. Wt:489.51 elemental analysis calculated and found: For $C_{29}H_{21}N_4O_4$C, 71.16; N, 11.45 and C, 71.12; N, 11.42, FTIR-ν_{max}-KBr (per cm): 3060 (Aromatic, CH), 1380 (N=O str. sym), 1568 (N=O str. asym), 2825 (-CH_3), 1632(C=C, olifins), 2820 (-CH_3), 989(C-O), 1252 (C=N), 746 (N-N), 1670 (C=O) , PMR-Deuterated chloroform-300 MHz δ in ppm : 6.74-7.67 (m,14H,Aromatic), 5.28 (s,2H, oxazin-ring-N- methylene), 4.1 (s,2H oxazin-ring-N- methylene -O), 2.8 (s,3H, methyl).

e. 1-4-(6-(3-hydroxy-4-methoxyphenyl)imino)-l3-methyl) -benzo[e,1,3]-2H-oxazinyl-3(4H)-4-methylbenzo[h] quinolinone-2(1H): Yield 63 %; mp 95-96 °C ; Mol. Wt:490.54 elemental analysis calculated and found: For $C_{30}H_{24}N_3O_4$ C, 73.46; N, 8.57 and C, 73.42; N, 8.53, FTIR-ν_{max}-KBr (per cm): 3072 (Aromatic, CH), 2810 (-CH_3), 1648 (OCH_3 , p-OCH_3-C_6H_5), 3460 (OH, m-OH-C_6H_5) 1638 (C=C, olifins), 2815 (-CH_3), 983 (C-O), 1255 (C=N), 740(N-N), 1678 (C=O) , PMR-Deuterated chloroform-300 MHz δ in ppm: 6.78-7.60 (m,14H,Aromatic), 5.23 (s,2H, oxazin-ring-N-methylene), 4.4(s,2H, oxazin-ring-N- methylene -O), 2.6 (s,3H, methyl), 3.87 (1H, s, phenyl-3-OH), 2.78 (3H, s, phenyl-4-OCH_3).

f. 4-methyl-1-(6-(phenylimino)-l3-methyl)-benzo[e,1,3]-2H-oxazinyl-3(4H)benzo[h]quinolinone-2(1H): Yield 58 %; mp 104-105 °C ; Mol. Wt:444.51 elemental analysis calculated and found: for $C_{29}H_{22}N_3O_2$, C, 78.36; N, 9.45 and C, 78.32; N, 9.40, FTIR-ν_{max}-KBr (per cm): 3080 (Aromatic, CH), 2820 (-CH_3), 1645(C=C, olifins), 2822 (-CH_3), 970 (C-O), 1262 (C=N), 735 (N-N), 1673 (C=O) , PMR-Deuterated chloroform-300 MHz δ in ppm : 6.69-7.64 (m,14H,Aromatic), 5.25 (s,2H, oxazin-ring-N- methylene), 4.8(s,2H, oxazin-ring-N- methylene -O), 2.7 (s,3H, methyl).

g. 1--6-3-chloro-1-(2-chlorophenyl)-4-oxoazetidinyl-2-benzo[e][1,3]-2H- oxazinyl-3(4H)-4-methylbenzo[h]quinolinone-2(1H): Yield 62 %; mp 108-109 °C ; Mol. Wt: 478.96 elemental analysis calculated and found: for $C_{29}H_{21}ClN_3O_2$, C, 72.72; Cl, 7.40; N, 8.77 and C, 72.68; Cl, 7.40; N, 8.72, FTIR-ν_{max}-KBr (per cm): 3076 (Aromatic, CH), 2815 (-CH_3), 1648 (C=C, olifins), 2830 (-CH_3), 964 (C-O), 1266 (C=N), 740 (N-N), 1677 (C=O) , PMR-Deuterated chloroform-300 MHz δ in ppm : 6.62-7.66 (m,14H,Aromatic), 5.21 (s,2H, oxazin-ring-N- methylene), 4.7 (s,2H, oxazin-ring-N- methylene -O) 3.0 (s,3H, methyl).

The synthesis of 2-(substituted/unsubstitutedphenyl)-3-(3-(4-methyl-2-oxobenzo [h]quinolin-yl-1)-3,4-dihydro-(2H)-benzo[e,1,3]-2H-oxazinyl-6)thiazolidinone-4:



4(a-g)

5(a-g)

For the synthesis of novel thiazolidinone derivatives, 0.01 1-(6-(((4-substituted/unsubstitutedphenyl)imino)-l3-methyl)-2H-benzo[e][1,3]oxazinyl-3(4H)-4-methylbenzo[h] quino linone-2(1H)-one (Schiff base) 4a-g and thioglycollic acid using trace amount of $ZnCl_2$ in 20 ml DMF were refluxed on heating mantle for 12-14 hour. The obtained product was poured onto crushed ice. After fifteen minutes, solidification took place, was filtered off and washed with cold water. Ethanol-based recrystallization produced a pure sample.

a. 2-(4-chlorophenyl)-3-(3-(4-methyl-2-oxobenzo [h] quinolin-yl-1)-3,4-dihydro-(2H)-benzo[e,1,3]-2H-oxazin yl-6)thiazolidinone-4: Yield 60 %; mp 97 °C ; Mol. Wt: 554.06 elemental analysis calculated and found: for

$C_{31}H_{24}ClN_3O_3S$; C, 67.20; Cl, 6.40; N, 7.58; S, 5.79 and C, 67.16; Cl, 6.38; N, 7.54; S, 5.73; Infrared-ν_{max} per cm-KBr: 3080 (Aromatic, CH), 1035 (C-S), 989 (C-N) , 1010 (C-O), 1670 (N-C=O),710(C-Cl), 785(N-N), 1590 (C=C, olifins), 2865(-CH_3); PMR-Deuterated chloroform-300 MHz δ in ppm : 1.49 (s,3H, methyl), 3.5 (s,2H, N-methylene), 2.05 (s,1H, thaizol ring), 2.9(s,2H,-CH_2-S), 6.12 (s,2H,thaizol ring), 6.18-7.48 (m,14H,aromatic).

b. 2-(4-bromophenyl)-3-(3-(4-methyl-2-oxobenzo [h] quinolin-yl-1)-3,4-dihydro-(2H)-benzo[e,1,3]-2H-oxazinyl-6)thiazolidinone-4: Yield 62 %; m.p. 109 °C ; Mol. Wt: 598.52 elemental analysis calculated and found: for $C_{31}H_{24}BrN_3O_3S$ C, 62.21; Br, 13.35; N, 7.02; S, 5.36 and C, 62.17; Br, 13.33; N, 7.00; S, 5.34. Infrared-ν_{max} per cm-KBr: 3088 (Aromatic, CH), 1030 (C-S), 985 (C-N) , 1016 (C-O), 1664 (N-C=O), 689 (C-Br), 790 (N-N), 1585 (C=C, olifins), 2872 (-CH_3), PMR-Deuterated chloroform-300 MHz δ in ppm : 1.38 (s,3H, methyl), 3.47 (s,2H N-methylene), 2.12 (s,1H, thaizol ring), 2.87 (s,2H,-CH_2-S), 6.10 (s,2H, thaizol ring), 6.42-7.51 (m,14H,aromatic).

c. 2-(4-hydroxyphenyl)-3-(3-(4-methyl-2-oxobenzo [h] quinolin-yl-1)-3,4-dihydro-(2H)-benzo[e,1,3]-2H-oxazinyl-6)thiazolidinone-4: Yield 56 %; mp 87 °C ; Mol. Wt:535.62 elemental analysis calculated and found: for $C_{31}H_{25}N_3O_4S$ C, 69.52; N, 7.85; S, 5.99 and C, 69.47; N, 7.82; S, 5.95. Infrared-ν_{max} per cm-KBr: 3088 (Aromatic, CH), 1036 (C-S), 992 (C-N), 1022 (C-O), 1670 (N-C=O), 3310 (-OH), 790 (N-N), 1592 (C=C olifins), 2880 (-CH_3), PMR-Deuterated chloroform-300 MHz δ in ppm : 1.43 (s, 3H, methyl), 3.43 (s,2H, N-methylene), 2.21 (s,1H, thaizol ring), 2.82 (s,2H,-CH_2-S), 6.16 (s,2H, thaizol ring), 6.42-7.58 (m,14H,aromatic).

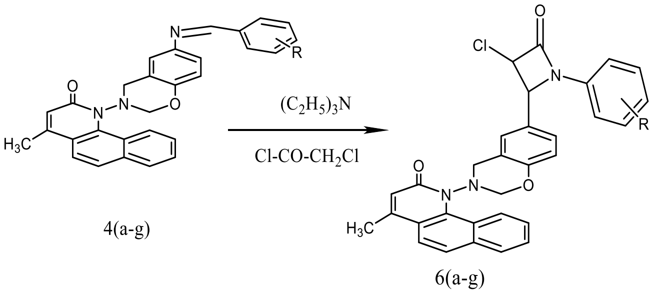
d. 3-(3-(4-methyl-2-oxobenzo[h]quinolinyl-1-3,4-dihydro-(2h)benzo[e,1,3]-2H-oxazinyl-6)-2-(4-nitrophenyl)thiazolidinone-4: Yield 52 %; mp 89-90 °C ; Mol. Wt: 564.62, elemental analysis calculated and found: for $C_{31}H_{24}N_4O_5S$ C, 65.95; N, 9.92; S, 5.68 and C, 65.92; N, 9.88; S, 5.66, Infrared-ν_{max} per cm-KBr: 3096 (Aromatic, CH), 1032 (C-S), 980 (C-N) , 1031 (C-O), 1665 (N-C=O), 794 (N-N), 1585 (C=C, olifins), 2875 (-CH_3), PMR-Deuterated chloroform-300 MHz δ in ppm : 1.45 (s, 3H, methyl), 3.48 (s,2H, N-methylene), 2.24 (s,1H, thaizol ring), 2.87 (s,2H,-CH_2-S), 6.14 (s,2H, thaizol ring), 6.54-7.61 (m,14H,aromatic).

e. 2-(3-hydroxy,4-methoxy-phenyl)-3-(3-(4-methyl-2-oxobenzo [h]quinolin-yl-1)-3,4-dihydro-(2h)-benzo[e,1,3]-2H-oxazinyl-6)thiazolidinone-4: Yield 62 %; mp 127-128 °C ; Mol. Wt: 565.64, elemental analysis calculated and found: for $C_{32}H_{27}N_3O_5S$ C, 67.95; N, 7.43; ; S, 5.67 and C, 67.91; N, 7.39; ; S, 5.64. Infrared-ν_{max} per cm-KBr: 3088 (Aromatic, CH), 1040 (C-S), 982 (C-N), 1038 (C-O), 1654 (N-C=O), 788 (N-N), 1171 (O-C, str. 4-OCH 3 -phenyl), 3462 (O-H, str. 3-OH-yphenyl) 1594 (C=C, olifins), 2882 (-CH_3), PMR-Deuterated chloroform-300 MHz δ in ppm : 1.46 (s,3H, methyl), 3.43(s,2H, N-methylene), 2.28 (s,1H, thaizol ring), 2.81 (s,2H,-CH_2-S), 6.21 (s,2H, thaizol ring), 6.58-7.69 (m,14H, aromatic) 3.76 (s, 3H, Ar-OCH 3) 5.51 (brs, 1H, s, changeable-OH).

f. 3-(3-(4-methyl-2-oxobenzo[h]quinolinyl-1-3,4-dihydro-(2H)-benzo[e,1,3]-2H-oxazinyl-6)-2-phenylthiazolidinone-4: Yield 67 %; mp 109-110 °C; Mol. Wt: 519.62 elemental analysis calculated and found: for $C_{31}H_{25}N_3O_3S$ C, 71.66; N, 8.09; S, 6.17 and C, 71.63; N, 8.03; S, 6.13. Infrared-ν_{max} per cm-KBr: 3096 (Aromatic, CH), 1034 (C-S), 993 (C-N), 1040 (C-O), 1662 (N-C=O), 796 (N-N), 1590 (C=C, olifins), 2890 (-CH_3), PMR-Deuterated chloroform-300 MHz δ in ppm: 1.36 (s,3H,- methyl), 3.41 (s,2H, N-methylene), 2.23 (s,1H, thaizol ring), 2.86 (s,2H,-CH_2-S), 6.24 (s,2H, thaizol ring), 6.62-7.58 (m,14H,aromatic).

g. 2-(2-chlorophenyl)-3-(3-(4-methyl-2-oxobenzo [h]quinolin-yl-1)-3,4-dihydro-(2H)-benzo[e,1,3]-2H-oxazinyl-6)thiazolidinone-4: Yield 55 %; mp 101-102 °C; Mol. Wt: 554.06 elemental analysis calculated and found: Calcd. for $C_{31}H_{24}ClN_3O_3S$ C, 67.20; Cl, 6.40; N, 7.58; S, 5.79 and C, 67.17; Cl, 6.37; N, 7.54; S, 5.76. Infrared-ν_{max} per cm-KBr: 3096 (Aromatic, CH), 1034 (C-S), 993 (C-N), 1040 (C-O), 1662 (N-C=O), 796 (N-N), 1596 (C=, olifins C),695 (C-Cl), 2884 (-CH_3), PMR-Deuterated chloroform-300 MHz δ in ppm: 1.33 (s,3H,-methyl), 3.41 (s,2H, N-methylene), 2.23 (s,1H, thaizol ring), 2.86 (s,2H,-CH_2-S), 6.22 (s,2H, thaizol ring), 6.62-7.58 (m,14H,aromatic).

The synthesis of 1-(6-(3-chloro-1-(substituted/ unsubstitutedphenyl)-4-oxoazetidinyl-2)-benzo[e,1,3]-2H-oxazinyl-3(4H)-4-methylbenzo[h] quinolinone-2(1H):



0.01 1-(6-(((4-substituted/unsubstitutedphenyl)imino)-l3-methyl)-benzo[e][1,3]-2H-oxazin-3(4H)-yl)-4-methylbenzo [h]quinolinone-2(1H) 4 a-g in 50 ml Dixon was added to .02 mole of chloroacetyl chloride and triethylamine at 0°C while stirring vigorously. The reaction was refluxed on heating for 6 to 8 hours after being maintained at room temperature for 5 hours. The remaining solvent was poured onto ice and recrystallized in alcohol after the excess solvent was distilled out.

a. 1-(6-(3-chloro-1-(4-chloro-phenyl)-4-oxoazetidinyl-2)-benzo[e,1,3]-2H-oxazinyl-3(4H)-4-methylbenzo[h] quinolinone-2(1H): Yield 66 %; mp 122 °C; Mol. Wt: 556.44

elemental analysis calculated and found: For $C_{31}H_{23}Cl_2N_3O_3$C, 66.91; Cl, 12.74; N, 7.55 and C, 66.85; Cl, 12.70; N, 7.52; infrared-ν_{max} per cm-KBr: 3026 (Aromatic, CH), 1596 (C=C, olefins),1030 (C-O),1252 (C=N), 1674 (N-C=O, str. lactam ring),890 (N-N),670 (C-Cl), PMR-Deuterated chloroform-300 MHz δ in ppm: 1.6(s,3H, methyl), 3.7 (s,2H, N-methylene), 2.54-2.56(d,1H,CH-CO-N), 6.12(s,2H,O-CH_2-O),3.7(s,1H,CH_3-CH=CH_2),7.26-8.58(m,13H,aromatic), 6.39 (d, 1H, -HC-CH-Cl, lactam ring).

b. 1-(6-(3-chloro-1-(4-bromo-phenyl)-4-oxoazetidinyl-2)-benzo[e,1,3]-2H-oxazinyl-3(4H)-4-methylbenzo[h] quino linone-2(1H): Yield 68 %; mp 129 °C ; Mol. Wt:600.90 elemental analysis calculated and found: for $C_{31}H_{23}BrClN_3O_3$, C, 61.96; Br, 13.30; Cl, 5.90; N, 6.99; and C, 61.92; Br, 13.24; Cl, 5.87; N, 6.96; infrared-ν_{max} per cm-KBr: 3017(Aromatic, CH), 1627(C=C, olefins),1022(O-C),1247 (N=C),1661(C=O, str. lactam ring), 913(N-N),715(-C-Br), PMR-Deuterated chloroform-300 MHz δ in ppm: 1.6 (s,3H, methyl), 3.5(s,2H, N-methylene), 2.541-2.545(d,1H,CH-CO-N),4.19(s,2H,-CH_2-O),3.7(s,1H,CH_3-CH=CH_2),7.26-8.59(m,13H,aromatic), 6.39(d, 1H, -HC-CH-Cl, lactam ring).

c. 1-(6-(3-chloro-1-(4-hydroxy-phenyl)-4-oxoazetidinyl-2)-benzo[e,1,3]-2H-oxazinyl-3(4H)-4-methylbenzo[h] qui nolinone-2(1H): Yield 61%; mp 114-115 °C ; Mol. Wt:538.00 elemental analysis calculated and found: for $C_{31}H_{24}ClN_3O_4$ C, 69.21; Cl, 6.59; N, 7.81; and C, 69.16; Cl, 6.53; N, 7.77; infrared-νmax per cm-KBr: 3028(Aromatic, CH), 1639(C=C, olefins),1032(C-O), 1669(C=O, str. lactam ring),919(N-N),3320(-OH),876(C-Cl), PMR-Deuterated chloroform-300 MHz δ in ppm: 0.86 (s, 3H, methyl),2.168(s,2H, N-methylene),2.54(d,1H,CH-CO-N),3.09(s,2H,-CH_2-O),3.7(s,1H,CH_3-CH=CH_2),4.2(s,2H,-CH_2-O),3.81 (1H, s, Ar-OH) 7.26-8.5(m,13H,aromatic),6.39 (d, 1H, -HC-CH-Cl, lactam ring).

d. 1-(6-(3-chloro-1-(4-nitro-phenyl)-4-oxoazetidinyl-2)-benzo[e,1,3]-2H-oxazinyl-3(4H)-4-methylbenzo[h] quino linone-2(1H): Yield 64 %; mp 122-123 °C ; Mol. Wt: 567.00 elemental analysis calculated and found: for $C_{31}H_{23}ClN_4O_5$C, 65.67; Cl, 6.25; N, 9.88 and C, 65.62; Cl, 6.21; N, 9.84, infrared-ν_{max} per cm-KBr: 3015(Aromatic, CH), 1625(C=C, olefins),1040(C-O),1370 (O=N sym str.) asym 1262 (C=N),1670(C=O, str. lactam ring),925(N-N),860(C-Cl), PMR-Deuterated chloroform-300 MHz δ in ppm: 1.36(s,3H, methyl), 3.16(s,2H, N-methylene), 2.47(d,1H,CH-CO-N),4.228(s,2H,-CH_2-O),3.66(s,1H,CH_3-CH=CH_2),6.82-8.64(m,13H,aromatic), 6.40 (d, 1H, -HC-CH-Cl, lactam ring).

e. 1-(6-(3-chloro-4-oxo-1-(p-tolyl)azetidinyl-2)-benzo[e,1,3]-2H-oxazinyl-3(4H))-4-methylbenzo[h]quinolinone-2(1H): Yield 58 %; mp 131-132 °C; Mol. Wt: 536.03 elemental analysis calculated and found: for $C_{32}H_{26}ClN_3O_3$ C, 71.70; Cl, 6.61; N, 7.84 and C, 71.66; Cl, 6.57; N, 7.81, infrared-ν_{max} per cm-KBr: 3050(Aromatic, CH), 1626(C=C, olefins),1044(C-O),1255 (C=N),1660(C=O, str. lactam ring),935(N-N),860(C-Cl), PMR-Deuterated chloroform-300 MHz δ in ppm: 1.38 (s,3H, methyl), 3.22(s,2H, N-methylene),2.59(d,1H,CH-CO-N),4.41(s,2H,-CH_2-O), 1.42 (3H,CH_3-Ar), 3.3 (s,1H,CH_3-CH=CH_2),6.69-8.72 (m,13H, aromatic), 6.42 (d, 1H, -HC-CH-Cl, lactam ring).

f. 1-(6-(3-chloro,4-oxo-1-arylazetidinyl-2)-benzo[e,1,3]-2H-oxazinyl-3(4H))-4-methylbenzo[h]quinolinone-2(1H): Yield 73%; mp 118°C; Mol. Wt:522.00 elemental analysis calculated and found: for $C_{31}H_{24}ClN_3O_3$, C, 71.33; Cl, 6.79; N, 8.05 and C, 71.31; Cl, 6.73; N, 8.01, infrared-ν_{max} per cm-KBr: 3005(Aromatic, CH), 1624(C=C, olefins),1044(C-O),1245 (C=N),1670(C=O, str. lactam ring),924(N-N),858(C-Cl), PMR-Deuterated chloroform-300 MHz δ in ppm : 1.37 (s,3H, methyl), 3.1(s,2H N-methylene), 2.57(d,1H,CH-CO-N), 4.7 (s, 2H, CH_2-O), 3.7(s,1H, CH_3-CH=CH_2), 6.68-8.9 (m,14H,aromatic),6.43 (d, 1H, -HC-CH-Cl, lactam ring).

g. 1-(6-(3-chloro-1-(2-chloro-phenyl)-4-oxoazetidinyl-2)-benzo[e,1,3]-2H-oxazinyl-3(4H)-4-methylbenzo[h] quino linone-2(1H): Yield 69 %; mp 123 °C ; Mol. Wt: 556.44 elemental analysis calculated and found: for $C_{31}H_{23}Cl_2N_3O_3$ C, 66.91; Cl, 12.74; N, 7.55 and C, 66.88; Cl, 12.72; N, 7.51, infrared-ν_{max} per cm-KBr: 3040(Aromatic, CH), 1625(C=C, olefins),1045(oxazin C-O),1240 (C=N),17655(C=O, str. lactam ring),930(N-N),865(C-Cl), PMR-Deuterated chloroform-300 MHz δ in ppm: 1.35 (s,3H, methyl), 3.4(s,2H N-methylene),2.51(d,1H,CH-CO-N),4.0(s,2H,-CH_2-O), 3.9 (s,1H, CH_3-CH=CH_2), 6.87-8.6(m,13H, aromatic), 6.37(d, 1H, -HC-CH-Cl, lactam ring).

Results and Discussion

Antimicrobial Evaluation: Antibacterial and antifungal *in vitro* activities against *P. aeruginosa* (MTCC 6538), *Proteus mirabilis* (MTCC 743), *Bacillus subtilis* (MTCC 1305), *Corynebacterium striatum* (MTCC 8963) and *Candida albicans* (MTCC227) in contrast with ciprofloxacin and gentamicin have been evaluated for the derivatives of oxoazetidinyl-2 and thiazolidinone-4. The broth microdilution process is used to check the MIC value of synthesized derivatives. Two-fold serial dilutions of the synthesized derivatives have been prepared directly in a microtiter plate filled with Mueller Hinton broth of different concentrations. Each well received a concentration of 5 × 105 CFU/mL after the bacterial inoculum was introduced.

The plates covered with sterile sealer were incubated at 37°C for 24 hours. After that using resazurin to all microtiter plate well, the plate was incubated for 30 minutes at 37°C. The MIC is characterized as the minimum concentration of compounds that breaks off the microbial growth. The MIC value shows the antibacterial activities of oxazin-lactam and oxazin thiazol derivatives against various Gram-ve and Gram+ve bacteria. The compounds tested include different phenyl derivatives and the data shows their effectiveness, calculated in terms of the minimum inhibitory concentration (MIC) values. The strains tested include *Candida albicans* (MTCC 227), *Pseudomonas aeruginosa* (MTCC 6538), *Proteus mirabilis* (MTCC 743), *Bacillus subtilis* (MTCC 1305) and *Corynebacterium striatum* (MTCC 8963).

This breakdown covers the antibacterial activity of various phenyl derivatives on the listed bacteria, showing their effectiveness by the MIC values. For the Gram-negative bacteria, *Pseudomonas aeruginosa* and *Proteus mirabilis*, the phenyl derivatives generally show a range of MIC values, indicating varied efficacy. Similarly, for Gram-positive bacteria, *Bacillus subtilis* and *Corynebacterium striatum*, the activity of the compounds also varies. 4-OH, 3-OCH$_3$-phenyl (6.25 µg per mL) is the most influential compound against *P. aeruginosa*. o-OH-phenyl (12.5 µg per mL) is the puissant against *Proteus mirabilis*.

Other compounds with relatively low MIC values include phenyl, 6a (25 µg/mL), which also shows strong activity though not as potent as o-OH-phenyl. 4-OH, 3-OCH$_3$-phenyl contain both a hydroxyl group (OH) and a methoxy group (OCH$_3$). The methoxy group (OCH$_3$) is an +I effect group, which increases the electron density of the phenyl ring, enhances the reactivity of the compound. This might help it to interact more effectively with bacterial cell walls or enzymes, enhancing its antibacterial activity. o-OH-phenyl, which has a hydroxyl group in the ortho position, could also be more effective as the ability of hydroxyl groups to form hydrogen bonds, potentially disrupting bacterial cell membranes or inhibiting essential enzymes.

The best-performing compounds against *Bacillus subtilis* are o-Cl-phenyl (12.5 µg/mL) and 6f (o-Cl-phenyl), which exhibited 100% activity at 12.5 µg/mL. 4-OH, 3-OCH$_3$-phenyl and 5g (4-OH, 3-OCH$_3$-phenyl) showed 25% activity, which is also relatively potent but not as effective as o-Cl-phenyl. The best-performing compounds against *Corynebacterium striatum* are: p-NO$_2$-phenyl (6.25 µg/mL) with highest effectiveness for *Corynebacterium striatum*. Other highly effective compounds include p-OH-phenyl (12.5 µg/mL) and 6b (p-OH-phenyl), with 100% activity at 12.5 µg/mL.

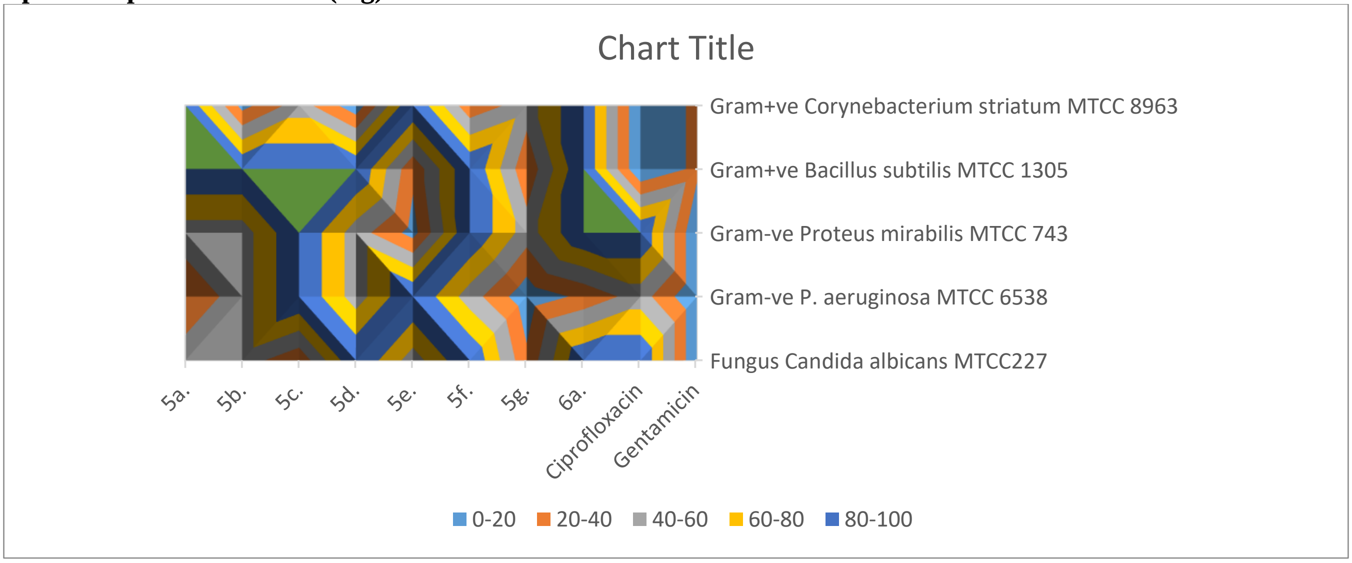
The -I effect of nitro group (NO$_2$) significantly increases the electrophilicity of the aromatic ring. This can enhance the reactivity of the compound, making it more effective in disrupting bacterial membranes, interfering with bacterial enzymes, or disrupting DNA synthesis. The low MIC value (6.25 µg/mL) against *Corynebacterium striatum* suggests that the nitro group is particularly effective in this strain, potentially by weakening the bacterial cell wall or enhancing penetration into the bacterial cell. The chlorine group (Cl) is also an electron-withdrawing group but with a different effect on the molecule.

Chlorine might help increase lipophilicity, which can improve the ability to penetrate the bacterial membrane. The ortho position of the chlorine in o-Cl-phenyl might also lead to favorable interactions with bacterial cell wall components, increasing its antibacterial effectiveness against *Bacillus subtilis*. Chlorine and nitro groups increase the lipophilicity of the phenyl ring. This allows the compound to better penetrate the bacterial cell membrane, which is crucial for targeting intracellular bacterial components. The low MIC values in both *Bacillus subtilis* and *Corynebacterium striatum* suggest that these compounds are able to cross the bacterial membrane effectively and interfere with essential biological functions.

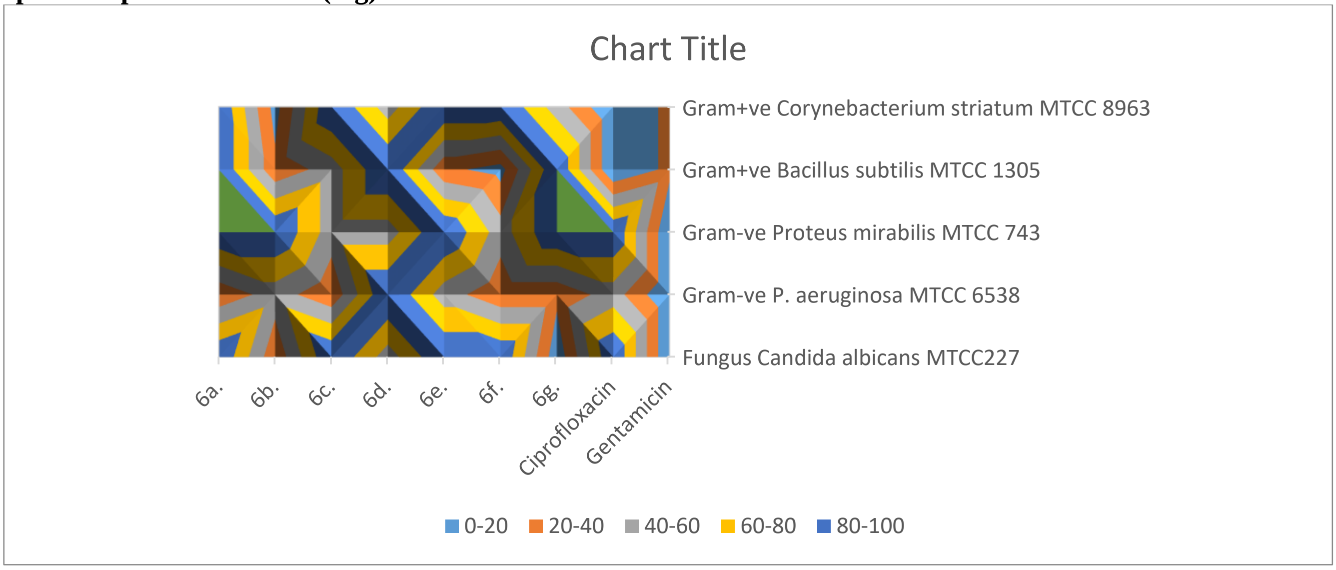
Antimicrobial activity-(MIC µg/mL) of compounds 5a-h and 6a-h:

S.N.		**Fungus**	**Gram-ve**		**Gram+ve**	
	R-with benzene ring	***Candida albicans MTCC227***	***P. aeruginosa MTCC 6538***	***Proteus mirabilis MTCC 743***	***Bacillus subtilis MTCC 1305***	***Corynebacterium striatum MTCC 8963***
5a.	Phenyl	50	25	50	100	100
5b.	p-OH- phenyl	50	50	50	100	12.5
5c.	p-Cl-phenyl	25	100	100	100	50
5d.	p-NO$_2$- henyl	100	50	50	100	6.25
5e.	o-OH-phenyl	50	100	12.5	25	100
5f.	o-Cl-phenyl	100	50	100	100	25
5g.	4-OH,3-OCH$_3$-phenyl	25	6.25	50	25	50
6a.	Phenyl	100	25	100	100	100
6b.	p-OH- phenyl	25	50	100	25	12.5
6c.	p-Cl-phenyl	100	25	50	50	100
6d.	p-NO$_2$-phenyl	50	100	50	100	50
6e.	o-OH-phenyl	100	50	100	25	100
6f.	o-Cl-phenyl	100	25	50	12.5	100
6g.	4-OH,3-OCH$_3$-phenyl	6.25	25	100	100	50
	Ciprofloxacin		50			
	Gentamicin				25	25

Graphical representation of 5(a-g):



Graphical representation of 6(a-g):



Conclusion

Based on the provided data, the lowest activity values (MICs) are observed for p-NO_2-phenyl (100% activity at 50 µg/mL) compound showing the highest level of activity among the phenyl derivatives. o-Cl-phenyl and p-NO_2-phenyl both exhibit 100% activity at relatively moderate concentrations (50 µg/mL). Thus, p-NO_2-phenyl and o-Cl-phenyl show the most potent ant ifungal activity, with p-NO_2-phenyl appearing particularly strong across various tests. The nitro group (p-NO_2) at the para position (as in p-NO_2-phenyl) enhances the antimicrobial activity.

Nitro groups are known for their ability to interfere with microbial cellular processes, such as electron transport and DNA replication, by interacting with cellular structures. The chlorine substituent (as in o-Cl-phenyl) also seems to increase the compound ability to inhibit fungal growth, as halogen groups can disrupt the membrane or have electron-withdrawing effects that increase the overall potency. The p-NO_2 group is an electron-withdrawing group and it typically enhances the electron deficiency of the aromatic ring, which could make the compound more reactive and able to disrupt the *Candida albicans* cell wall or membrane. This increases its antifungal efficacy.

Both p-NO_2-phenyl and o-Cl-phenyl have properties that might increase their lipophilicity, which aid in crossing the fungal cell membrane. This is important because antifungal compounds often need to be able to penetrate the lipid-rich fungal cell membrane to exert their action.

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