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Synthesis, Characterization and Antimicrobial Activity of Schiff Bases of Some Benzimidazole Substituted Thiazoles and Oxazoles as Bioisosteres

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Two series of benzimidazole substituted oxazole and thiazole molecular scaffold containing divalent isosteres viz oxygen and sulphur were synthesized by reacting 2-(methyl amino)-[(3''-phenyl-4''-oxo-(3''H)-quinazolin)-2'-mercaptophenyl-benzimidazol-1'-yl]-acetyl chloride with thiourea/urea in absolute ethanol medium. Then their corresponding Schiff bases were formed by reacting it with different aromatic aldehydes. The chemical structure of newly synthesized compounds was characterized by elemental analysis, IR, ^{1}H-NMR and Mass spectra. The Schiff bases were screened for their antimicrobial activity against four bacterial and two fungal strains. The bacterial strains used were *Escherichia coli, Alcaligenes faecalis, Pseudomonas aeruginosa* and *Klebsiella pneumoniae* and fungal strains used were *Chaetomium globosum* and *Curvularia lunata.* The synthesized compounds were evaluated for qualitative (zone of inhibition) antimicrobial activity by agar cup plate method at three concentrations (500,1000 and 3000ppm). Compound (7d) and (8e) showed good to excellent activity against all the tested strains while others were moderately active.

Key words: Benzimidazole, Thiazole, Oxazole, Schiff bases, Bioisostere, Antibacterial and Antifungal Activities.

The major class of almost all the antibiotics have encountered resistance in clinical applications. [1]Resistance to β-lactam antibiotics, macrolides, quinolones and Vancomycin is specially among most important worldwide health problems.[2-3] The development of resistance upon introduction of a novel antibiotic follows a sigmoid curve. The antibiotic is highly successful in the initial lag phase which is followed by steady, often rapid rise in resistance levels plateauing to equilibrium depending on the organism, its ability to circulate and antibiotic pressure.[4] Thus the increasing antibiotic resistance is becoming a serious problem for human beings.

Apart from this with the emergence of common opportunistic fungal infection which continue to increase rapidly in sizable susceptible population of immuno-compromised patients (including AIDS, Cancer and transplants), and its impact on such patients is life threatening. Chaetomium and Curvularia are some of the opportunistic fungi responsible for these kinds of infections.

In order to overcome this rapid development of drug resistance, new agents

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should preferably consist of chemical characteristics that clearly differ from those of existing agents .In drug designing programs an essential component of search for a new lead is the synthesis of molecules, which is novel yet resembles known biologically active molecules by virtue of the presence of critical structural features. Certain heterocyclic molecules act as highly functionalized scaffolds and are known pharmacophores of number of biologically active and medicinally useful molecules.[5]

Over a last few decade, a variety of oxazole/thiazole derivatives were synthesized and studied. Thiazoles are known to posses a broad range of biological activities such as antitumor,[6] anti-inflammatory,[7] antimicrobial,[8] antifungal,[9] diuretic[10] and anticonvulsant.[11] Some of the thiazole derivatives are also known to posses Acetyl-Co-A carboxylase inhibitors[12] and neuroprotective antioxidant activity[13]. Ritonivar (Fig I), an antiretroviral drug from the protease inhibitor class used to treat HIV infection and AIDS, contains thiazole in its structure.[14]

Oxazoles are found to be associated with various biological activities such as antibacterial,[15] antifungal,[16] antitubercular[17] and anti-inflammatory activity[18]. Calcimycin (Fig: II) a well known antibiotic contains 2- substituted benzoxazole ring in its structure.[19]

On the other hand the related heterocycle benzimidazoles have been proven to be the most important group of fungicides with systemic activity. The benzimidazole nucleus binds to free tubulin, particularly â tubulin at the colchicines binding site, disrupting microtubule formation and thereby inhibiting mitosis leading to enhancement of the biological potential. Thiabendazole (2-(4-thaizolyl)-1H—benzimidazole) which includes benzimidazole and thiazole moiety is well known example for this fungicide class.[20-21]

The modification on thiazole moiety displayed valuable biological activities. It will be interesting to observe that these modifications can be utilized as potent therapeutic agents in future. Thus the quest to explore many more modifications on the thiazole moiety needs to be continued.

Due to such an investigation it was thought worthwhile to synthesize some congeners of thiazole/oxazoles by incorporating the benzimidazole nucleus in a single molecular framework and further asses the pharmacological profile. This approach seems to be useful in view of the fact that it may combine the physiological action of the group with the well known biological activity of both the groups.

EXPERIMENTAL

All the melting points were determined in open capillary tubes and were uncorrected. Spectroscopic data were recorded using following instruments, IR: FTIR RX1 Perkin Elmer Spectrophotometer, ^{1}HNMR: Bruker DRX 300 MHz Spectrophotometer in DMSO-d6 using TMS as internal standard, Mass: JMS-T100 LC, Accu TOF Mass Spectrophotometer (DART).

The general scheme of preparation of all the compounds are given in Scheme I and II.

In the present study 2-mercapto-3-phenylquinazol-4-ones (1) was prepared by reacting 2-aminobenzoic acid with phenylthiourea in accordance with the method described in the literature.[22]

General procedures for synthesis

Synthesis of 2-(3'-phenyl-4'-oxo-(3'H) - quinazolin) - mercapto benzoic acid (2)

A mixture of 2-mercapto-3-phenylquinazol-4-ones (1) (0.01 mol), 4-chloro benzoic acid and 10-12 ml dioxane were taken in a round bottom flask and refluxed for 4-5 hrs. The solution was cooled and poured into crushed ice containing 10% $NaHCO_3$ solution. A solid separated out which was filtered and dried. m.p: 150°C, ir: 1225 (C-N), 1620 (C=N) , 1660 (C=O, Quinazolin) , 1685 (C=O, Carboxy) , ^{1}Hnmr : δ 7.12-7.66 (m, 13H, ArH), 13.01 (s,1H,-OH) , ms (EI):*m/z* 373(M$^+$). *Anal*. Calcd. for $C_{21}H_{14}N_2O_3S$: C, 67.37, H , 3.74 , N, 7.48 .Found : C, 67.13 , H , 3.52 , N, 7.18.

Synthesis of 2-mercaptophenyl - (3'-phenyl-4'-oxo -(3'H)-quinazolin)-benzimidazole (3)

Equimolar mixture of 2-(3'-phenyl-4'-ones-(3'H) - quinazolin)- mercapto benzoic acid (2) , 2-phenylenediamine and 30 ml of 4N HCl were refluxed for 8-9 hrs on sand bath. The solution on cooling gave a precipitate which was filtered dried and recrystallized from ethanol. m.p: 195°C, ir: 1220 (C-N) , 1600 (C=N), 1660 (C=O, Quinazolin), 3250 (NH), ^{1}HNMR: δ 7.01-7.64 (m, 17H, ArH), 8.98 (s, 1H, NH), ms (EI): *m/z* 445(M$^+$). *Anal.* Calcd. for

$C_{27}H_{18}N_4OS$: C , 72.64 , H, 4.03 , N , 12.55 .Found : C, 72.40 ,H , 3.94, N, 12.24.

Synthesis of 1-(methylamino)- 2-mercaptophenyl - (3'-phenyl-4'-oxo -(3'H)-quinazolin)-benzimidazole (4)

0.01M Benzimidazole (**3**), formaldehyde (0.01M) and ammonium chloride (0.01 M) were stirred using a magnetic stirrer. 10-12 ml ethanol was then added and the contents were further refluxed for 5-6 hrs. Excess ethanol was distilled off and the solution was cooled. A solid was obtained which was filtered and recrystallised with ethanol. m.p: 188 °C, ir :1220 (C-N), 1600 (C=N), 1660 (C=O, Quinazolin), 3130 (broad, NH_2), ^{1}HNMR: δ2.51 (s,2H,CH_2) , 5.22 (s,broad,2H,NH_2), 7.14-7.56 (m,17H,ArH) ,ms (EI):*m/z* 474 (M^+). *Anal.* Calcd. for $C_{28}H_{21}N_5OS$: C, 70.73 , H, 4.42, N, 14.73.Found : C, 70.51, H, 4.18, N, 14.59.

Synthesis of 2- (methylamino) - [3' – phenyl - 4' – oxo - (3'H) – quinazolin) - 2' –mercaptophenyl – benzimidazole – 1' – yl] acetyl chloride (5)

0.01M Mannich base (4) in 15 ml ethanol was taken in a round bottom flask and it was magnetically stirred, while the contents were stirred 0.01 M chloroacetyl chloride was added dropwise during first one hour. Reaction mixture was further stirred for 2 hrs and then refluxed for one hour. Thereafter the solution was cooled and then poured into crushed ice. Separated solid was filtered, washed with water and then recrystallized with methanol. m.p: 208 °C , ir: 680 (Cl),1225 (C-N),1600 (C=N),1660 (C=O,Quinazolin) ,1820 (CO, acetyl chloride), 3250 (NH) , ^{1}HNMR: δ2.50 (s,2H,CH_2), 5.17 (s,2H,CH_2Cl), 7.05-7.61 (m, 17H,ArH), 8.23 (s,1H,NH), ms (EI): *m/z* (M^+) 550, (M+2)552. *Anal.* Calcd. for $C_{30}H_{22}N_5O_2SCl$: C, 65.33, H, 3.99, N, 12.70.Found: C, 65.01, H, 3.82, N, 12.49.

Synthesis of 2-(amino/phenyl amino)-[1'-(methylamino)-2'-mercaptophenyl-{3"-phenyl-4"-oxo-(3"H)-quinazolin}-benzimidazol-1'-yl]-thiazole/oxazole (6a-c)

0.002M of (**5**) and 0.0025M of thiourea/ phenylthiourea/urea was refluxed in absolute ethanol (12ml) for 12 hrs. Excess of solvent was distilled off and the solution was cooled, poured into crushed ice. The solid obtained was filtered, washed with 2% $NaHCO_3$ solution follwed by water. It was dried and recrystallized from ethanol.

2-(amino)-[1'-(methylamino)-2'-mercaptophenyl-{3''-phenyl-4''-oxo-(3''H)-quinazolin}-benzimidazol-1'-yl]-thiazole (6a)

m.p: 212°Cc , ir: 1225 (C-N), 1355 (N=C-S), 1155 (C-S-C,cyclic), 1600 (C=N), 1660 (C=O, Quinazolin), 3250 (NH), 3400 (NH_2), ^{1}HNMR: δ 2.54 (s,2H,CH_2), 5.20 (s,broad,2H,NH_2)**,** 7.27 (s, 1H,C_5 thiazole), 7.38-7.89 (m,17H,ArH), 8.24 (s,1H,NH) ms (EI)**:** *m/z*: 572(M^+) . *Anal.* Calcd. for $C_{31}H_{23}N_7OS_2$: C, 64.92, H, 4.01, N, 17.1.Found: C, 64.89, H, 3.86, N, 16.98.

2-(phenyl amino)-[1'-(methylamino)-2'-mercaptophenyl-{3"-phenyl-4"-oxo-(3"H)-quinazolin}-benzimidazol-1'-yl]-thiazole (6b)

m.p: 160 °C , ir :1225 (C-N), 1355 (N=C-S), 1155 (C-S-C, cyclic) , 1600 (C=N) , 1660 (C=O, Quinazolin) , 3250 (NH). ^{1}HNMR δ 2.57 (s,2H,CH_2), 6.90 (s,1H,C_5 thaizole), 7.09-7.96 (m,22H,ArH), 8.19 (s,1H,NH), 8.28 (s,1H,CH_2NH), ms(EI): *m/z* 648 (M^+). *Anal.* Calcd for $C_{37}H_{27}N_7OS_2$: C, 68.41, H, 4.16, N, 15.1, Found: C, 68.11, H , 4.02, N, 14.81.

2-(amino)-[1'-(methylamino)-2'-mercaptophenyl-{3''-phenyl-4''-oxo-(3''H)-quinazolin}-benzimidazol-1'-yl]-oxazole (6c)

m.p: 192°C , ir: 1090 (C-O-C,cyclic) ,1225 (C-N), 1580 (N=C-O), 1600 (C=N) ,1660 (C=O, Quinazolin) ,3280 (NH), 3400 (NH_2). ^{1}HNMR δ 2.54 (s,2H,CH_2) ,5.18 (b,s, 2H, NH_2) ,7.29-7.76 (m,17H,ArH), 7.22 (s, 1H,C_5 oxazole), 8.14 (s,1H,NH) , ms (EI): *m/z* 556 (M^+), *Anal.* Calcd. for $C_{31}H_{23}N_7O_2S$: C, 66.78, H, 4.12, N, 17.59, Found: C, 66.51, H, 3.91, N, 17.36.

Synthesis of 2-(substituted arylimino)-[1'-methylamino-2'-mercaptophenyl-{3"-phenyl-4"-oxo-(3"H)-quinazolin}-benzimidazol-1'-yl]-thiazole/oxazole (7a-d,8a-e)

A mixture of (0.01 M) substituted benzaldehyde , thiazole(**6a**) / oxazole (**6c**) (0.01M) and anhydrous sodium acetate (0.02M) was refluxed in 10-15 ml acetic acid for 4 hrs. After cooling the solution was poured in ice cold water and kept overnight. The resulting precipitate was filtered, washed with water, dried and recrystallized from ethanol.

2-(4'"-nitro benzylideneimino)-[1'-methylamino-2'-mercaptophenyl-{3"-phenyl-4"-oxo-(3"H)-quinazolin}-benzimidazol-1'-yl]-thiazole (7a)

m.p: 180°C , ir: 1225 (C-N), 1355 (N=C-S), 1155 (C-S-C, cyclic), 1540 (NO_2), 1600 (C=N), 1660 (C=O, Quinazolin), 3250 (NH) .^{1}Hnmr δ 2.49 (s, 2H,CH_2), 7.19 (s, 1H,C_5 thiazole) , 7.35-7.96 (m,21H,ArH), 8.15 (s,1H, N=CH), 8.25 (s, 1H,NH)

,ms (EI): *m/z* 673 (M^+), *Anal.* Calcd. for $C_{38}H_{26}N_8OS_2$: C, 67.65, H, 3.85, N, 16.61, Found: C, 67.41, H, 3.72, N, 16.59.

2-(2''',4'''-di chloro benzylideneimino)-[1'-methylamino-2'-mercaptophenyl-{3''-phenyl-4''-oxo-(3''H)-quinazolin}-benzimidazol-1'-yl]-thiazole (7b)

m.p: 203 °C , ir:734 (Cl), 1225 (C-N), 1355 (N=C-S), 1480 (N=CH),1155 (C-S-C, cyclic) , 1600 (C=N), 1660 (C=O, Quinazolin), 3250 (NH). [1]Hnmr δ 2.56 (s, 2H,CH_2), 7.27 (s,1H, C_5 thiazole) , 7.29-7.96 (m, 20H,ArH), 8.07 (s,1H,N=CH), 8.19 (s ,1H,NH)

ms (EI): *m/z* (M^+) 728**,**(M+2) 730. *Anal.* Calcd. for $C_{38}H_{25}N_7OS_2Cl_2$: C, 62.55, H, 3.42, N, 13.44, Found: C, 62.34, H, 3.14, N, 13.21.

2-(4'''-hydroxy benzylideneimino)-[1'-methylamino-2'-mercaptophenyl-{3''-phenyl-4''-oxo-(3''H)-quinazolin}-benzimidazol-1'-yl]-thiazole (7c)

m.p:164 °C , ir: 1225 (C-N), 1355 (N=C-S),1480 (N=CH), 1155 (C-S-C, cyclic),1600 (C=N) , 1660 (C=O, Quinazolin), 3250 (NH) .[1]HNMR δ2.51 (s, 2H,CH_2), 7.27 (s, 1H,C_5 thiazole) , 7.35-7.96 (m,21H,ArH), 8.07 (s,1H, N=CH), 8.17 (s, 1H,NH), 10.28 (s,1H, OH) ,ms (EI) : *m/z* 676 (M^+). *Anal.* Calcd. for $C_{38}H_{27}N_7O_2S_2$: C, 67.35, H, 3.98, N, 14.47. Found : C, 67.16, H, 3.63, N, 14.32.

2-(4'''-hydroxy-3'''-methoxy-benzylideneimino)-[1'-methylamino-2'-mercaptophenyl-{3''-phenyl-4''-oxo-(3''H)-quinazolin}-benzimidazol-1'-yl]-thiazole (7d)

m.p: 182 °C , ir: 1225 (C-N), 1245 (O-C), 1355 (N=C-S),1480 (N=CH), 1155 (C-S-C, cyclic) , 1600 (C=N), 1660 (C=O, Quinazolin), 3250 (NH) ,3760 (OH)[1]Hnmr δ 1.29 (s,3H, CH_3), 2.49 (s, 2H,CH_2), 7.20 (s, 1H,C_5 thiazole), 7.24-7.82 (m,21H,ArH), 8.13 (s,1H, N=CH), 8.07 (s, 1H,NH), 9.90(s,1H,OH) ,ms (EI): *m/z* 692(M^+).*Anal.* Calcd. for $C_{39}H_{29}N_7O_3S_2$: C, 67.53, H, 4.18, N, 12.12 , Found : C, 67.23, H, 3.99, N,11.84.

2-(2''',4'''-di chloro benzylideneimino)-[1'-methylamino-2'-mercaptophenyl-{3''-phenyl-4''-oxo-(3''H)-quinazolin}-benzimidazol-1'-yl]-oxazole (8a)

m.p: 222 °C , ir: 734 ((Cl),1085 (C-O-C, cyclic), 1225 (C-N),1480 (N=CH), 1580 (N=C-O), 1600 (C=N), 1660 (C=O, Quinazolin), 3250 (NH). [1]Hnmr δ 2.52 (s, 2H, CH_2), 7.55 (s, 1H, C_5 oxazole) ,7.21-7.93 (m,21H,ArH), 8.02 (s, 1H,NH), 8.10 (s,1H, N=CH), ms (EI): *m/z* 712(M^+).*Anal.* Calcd. for $C_{38}H_{25}N_7O_2SCl_2$: C, 63.95, H, 3.50, N, 13.74, Found : C, 63.76, H, 3.18, N, 13.57.

2-(4'''-hydroxy-3'''-methoxy-benzylideneimino)-[1'-methylamino-2'-mercaptophenyl-{3''-phenyl-4''-oxo-(3''H)-quinazolin}-benzimidazol-1'-yl]-oxazole (8b)

m.p:200 °C , ir: 1085 (C-O-C, cyclic), 1225 (C-N), 1245 (O-C), 1480 (N=CH), 1580 (N=C-O), 1600 (C=N), 1660 (C=O, Quinazolin), 3250 (NH) , 3680 (OH), [1]Hnmr δ 2.45 (s, 2H,CH_2), 7.28 (s, 1H,C_5 oxazole), 7.34-7.88 (m,21H,ArH), 8.10 (s, 1H,NH), 8.15 (s,1H, N=CH), 9.86 (s,1H,OH)**,** ms (EI): *m/z* 690 (M^+). Anal. Calcd. for $C_{39}H_{29}N_7O_4S$: C, 67.72, H, 4.19, N, 14.18, Found : C, 67.44, H, 4.06, N, 13.92.

2-(2'''-nitro-benzylideneimino)-[1'-methylamino-2'-mercaptophenyl-{3''-phenyl-4''-oxo-(3''H)-quinazolin}-benzimidazol-1'-yl]-oxazole (8c)

m.p:196 °C , ir: 1085 (C-O-C, cyclic), 1225 (C-N),1480 (N=CH), 1537 (NO_2), 1580 (N=C-O), 1600 (C=N), 1660 (C=O, Quinazolin), 3250 (NH).[1]Hnmr δ 2.48 (s, 2H, CH_2), 7.32 (s, 1H,C_5 oxazole), 7.42-7.79 (m,21H,ArH), 8.02 (s,1H, N=CH), 8.13 (s, 1H,NH) ms (EI): *m/z* 699 (M^+). *Anal.* Calcd. for $C_{38}H_{26}N_8O_4S$: C, 66.08, H, 3.76, N, 16.23 , Found : C, 65.98, H, 3.51, N, 16.02.

2-(4'''-hydroxy-benzylideneimino)-[1'-methylamino-2'-mercaptophenyl-{3''-phenyl-4''-oxo-(3''H)-quinazolin}-benzimidazol-1'-yl]-oxazole (8d)

m.p:219 °C ,ir: 1085 (C-O-C, cyclic), 1225 (C-N), 1480 (N=CH), 1580 (N=C-O), 1600 (C=N) , 1660 (C=O, Quinazolin), 3250 (NH) ,3700 (OH), [1]Hnmr δ 2.33 (s, 2H,CH_2), 7.28 (s, 1H,C_5 oxazole), 7.35-7.67 (m,21H,ArH), 8.11 (s,1H, N=CH), 8.20 (s, 1H,NH) ms (EI): *m/z* 660 (M^+). *Anal.* Calcd. for $C_{38}H_{27}N_7O_3S$: C, 68.98, H, 4.08, N, 14.82, Found : C, 68.67, H, 3.79, N, 14.49.

2-(4'''-nitro-benzylideneimino)-[1'-methylamino-2'-mercaptophenyl-{3''-phenyl-4''-oxo-(3''H)-quinazolin}-benzimidazol-1'-yl]-oxazole (8e)

m.p:173 °C , ir: 1085 (C-O-C, cyclic) , 1225 (C-N), 1480 (N=CH), 1537 (NO_2), 1580 (N=C-O) , 1600 (C=N), 1660 (C=O, Quinazolin) , 3250 (NH). [1]Hnmr δ1.26 (s,3H,CH_3) 2.52 (s, 2H,CH_2), 7.40 (s, 1H,C_5 oxazole), 7.47-7.77 (m,21H,ArH) , 8.08 (s,1H, N=CH), 8.24 (s, 1H,NH), 10.08 (s,1H,OH) , ms (EI): *m/z* 699 (M^+). *Anal.* Calcd. for $C_{38}H_{26}N_8O_4S$: C, 66.08, H, 3.76, N, 16.23 , Found: C, 65.86, H, 3.43, N, 16.11.

Antimicrobial activity

The antimicrobial activity of the test

compounds was determined using agar cup plate method[23] and the bacterial strains used were *Escherichia coli, Alcaligenes faecalis* , *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* and fungal strains used were *Chaetomium globosum* and *Curvularia lunata*. The standard drugs used were Ciprofloxacin (for bacteria) and Flucanzole (for fungus).This method is based on diffusion of antibacterial component from the reservoir bore to the surrounding inoculated nutrient agar medium so that growth of microorganism is inhibited as circular zone around the bore. The concentrations used were 3000ppm, 1000ppm and 500 ppm (75, 25, 12.5µg /well). The test samples and standard drugs were placed in a bore made in petridishes which contained different organisms and incubated at 37°C for 24 hrs (bacteria) and 72 hrs (fungus).

RESULTS AND DISCUSSION

The FTIR of Compound (2) gave two characteristic vibrations at 1660 and 1685 cm^{-1} which were identified as the (C=O,Quinazolin) and

Table 1. Antibacterial activity of compounds (6a) and ($7_{a–d,}8_{a-e}$)

S. No.	(Zone inhibition in mm) *E.coli*			*A.faecalis*			*P.areuginosa*			*K.pneumonae*		
	500 Ppm	1000 Ppm	3000 ppm	500 ppm	1000 ppm	3000 ppm	500 ppm	1000 ppm	3000 ppm	500 ppm	1000 ppm	3000 ppm
6a	2	6	2	11	10	11	6	4	1	3	7	8
7a	8	16	7	20	11	12	4	3	8	10	10	12
7b	3	10	5	11	6	14	10	14	11	4	6	9
7c	14	14	7	4	15	12	18	22	18	20	14	13
7d	7	9	5	8	15	17	9	10	9	12	12	14
8a	7	6	6	17	13	1	9	9	13	21	15	12
8b	5	7	9	9	16	10	2	4	5	9	6	8
8c	7	7	21	4	13	14	11	13	9	13	15	17
8d	9	11	7	4	14	12	15	16	15	19	21	24
8e	15	7	3	9	9	7	13	16	16	16	13	15
Std.	14	22	32	18	27	35	18	26	38	20	28	33

Control: DMSO (negative); Reference Standard: Ciprofloxacin

Table 2. Antifungal activity of compounds (6a) and ($7_{a–d,}8_{a-e}$)

S. No.	(Zone inhibition in mm) *C.globosum*			*C.lunata*		
	500 ppm	1000 ppm	3000 ppm	500 ppm	1000 ppm	3000 ppm
6a	7	10	18	19	14	22
7a	2	12	27	12	6	26
7b	13	12	15	14	13	12
7c	7	5	8	22	2	19
7d	17	14	26	16	9	19
8a	13	10	31	28	14	28
8b	19	13	19	22	10	24
8c	26	13	5	25	8	15
8d	24	16	14	10	6	11
8e	19	13	28	19	12	15
Std.	19	24	33	20	25	32

Control: DMSO (negative); Reference Standard: Flucanazole

(C=O,carboxy) respectively. The structure was further supported by NMR which showed a multiplet between 7.12-7.66 integrated for 13 aromatic protons. Cyclization to Benzimidazole(3) was characterized by the appearence of new vibrations at 1220,1600,3250 cm^{-1} which were characterized as C-N,C=N,-NH hence confirming the cyclization. The NMR spectra showed a singlet at 8.98 which integrated for one proton (NH group) of benzimidazole. The Mannich base (4) further formed was confirmed by appearance of vibration at 3130 cm^{-1} of NH_2 group. Further the chloroacetylated product (5) showed a new vibration at 1820 cm^{-1} identified as the carbonyl group vibration attached to the chloro group. The cyclization to Thiazole/Oxazole was confirmed by appearance of characteristic vibrations at 1155,1355 and 1085 cm^{-1} for C-S-C,N=C-S and C-O-C. It was also confirmed by NMR data which showed peaks at 7.27 and 6.90 as a singlet for proton at C_5 of the Thiazole and Oxazole respectively. The free amino group was then blocked with various aromatic aldehydes .The various compounds showed characteristic vibrations at 1480 cm^{-1} which confirmed the presence of (N=CH) linkage. NMR also supported the formation of the Schiff base as a singlet was visible at 8.13 which integrated for one proton and was identified as a methene proton. The mass spectrum gave the molecular ion peak at 372(2), 445(3), 474(4), 572(6a), 648(6b), 556(6c) respectively supporting the molecular weight and molecular formula of these derivatives. The isotopic peaks in (5), (7b) and (8a) confirmed the presence of a halogen as a substituent.

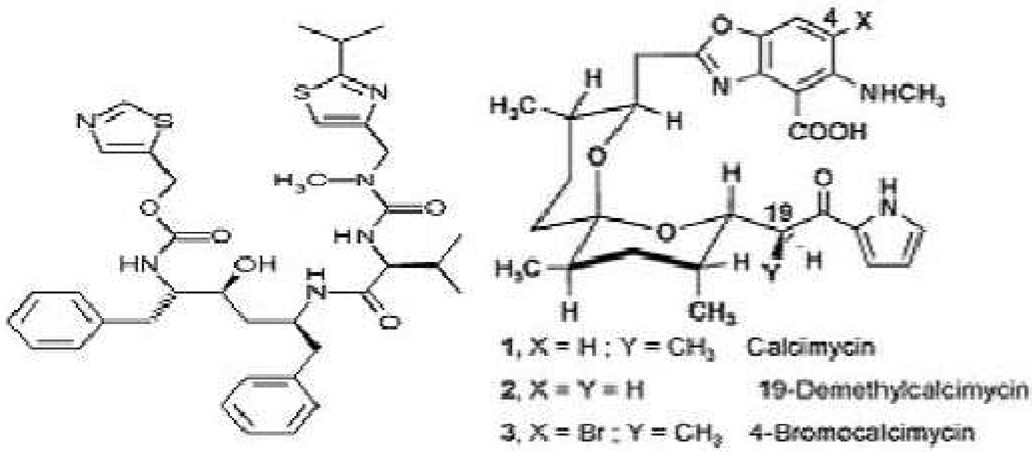
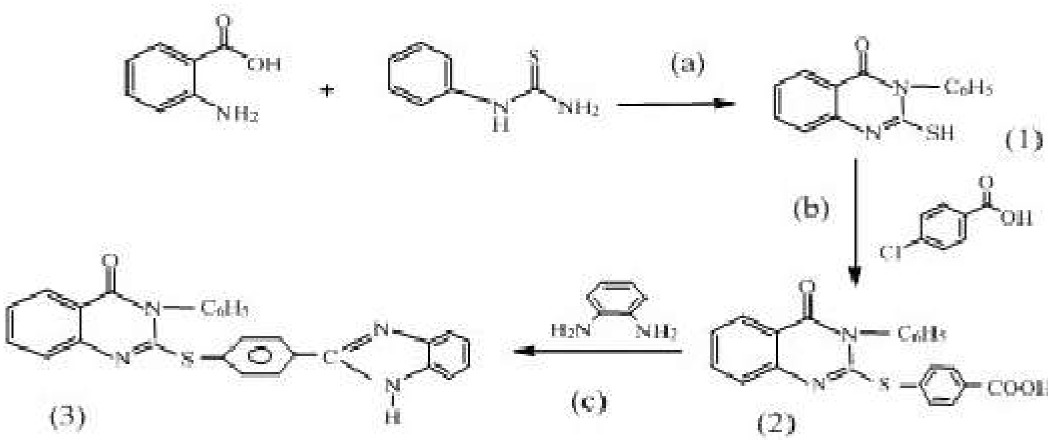


Fig. 1-2. Ritonivar and Calcimycin

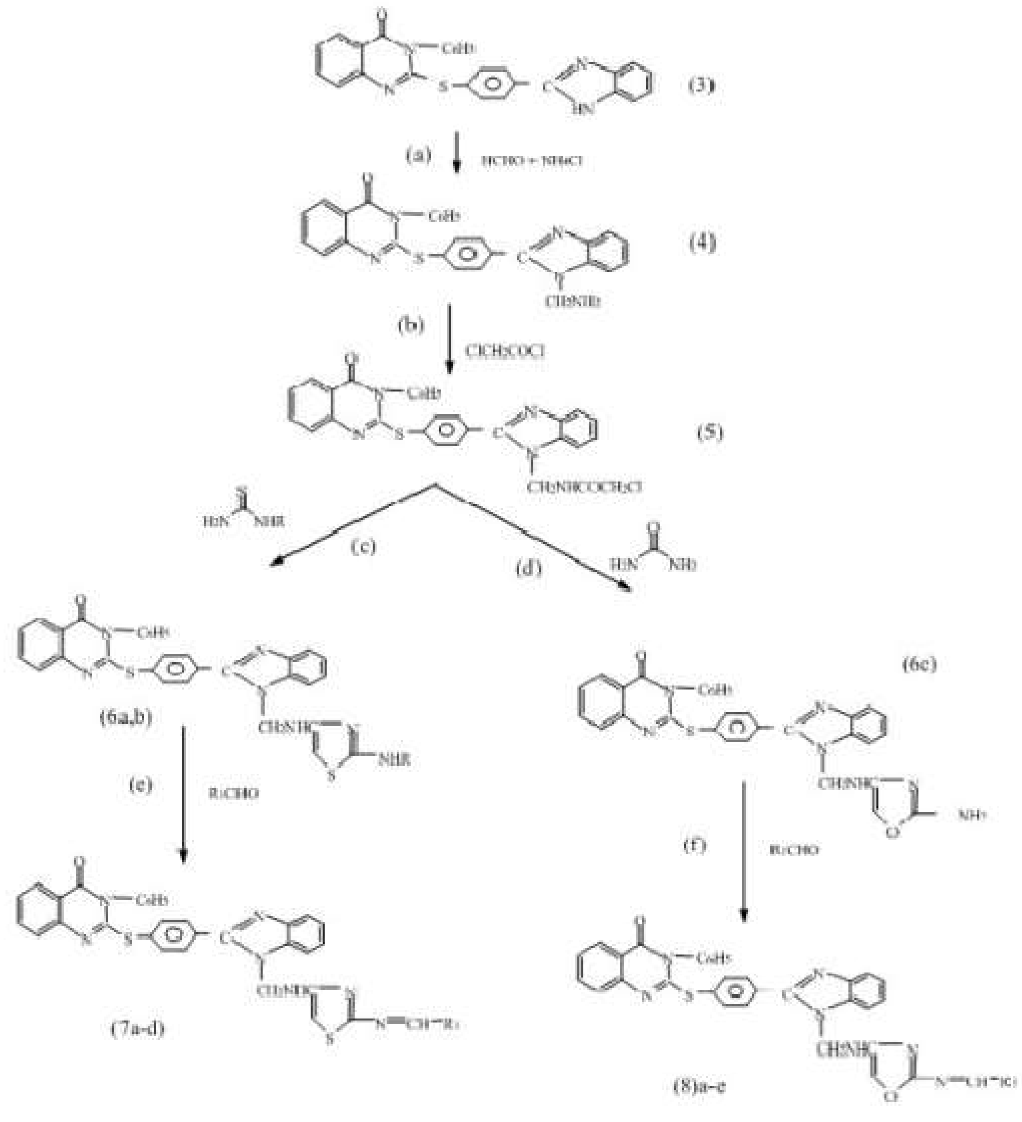


Scheme 1. Synthesis of Benzimidazole nucleus

Antimicrobial activity

The results of antimicrobial activity are shown in Table I and II .The prepared Schiff bases showed significant antibacterial and antifungal activity. The study reveals that 500ppm was the most effective concentration among the chosen ones.

Among the Schiff bases of thiazoles (6a,7a-d), (7c) showed excellent activity against *E. coli, P. aeruginosa , K. pneumoniae* and *C. lunata* while (7a) showed excellent activity against *A. faecalis* and 7d against *C. globosum*. Compounds (7a) and (7d) showed moderate activity against *E. coli* and *K. pneumoniae* while (6a) and (7b) were inactive against these strains. In case of *A. faecalis* (6a) and (7b) were moderately active while (7c) and (7d) were inactive. Only one derivative (7b) was moderately active against *P. aeruginosa* and *C. globosum* while against *C. lunata* all were moderately active.



Where R=H, C_6H_5

R1 =4 OH- C_6H_4, 4-NO_2-C_6H_4, 2,4-Cl- C_6H_4, 3-OCH_3-4-OH- C_6H_4, 2-NO_2- C_6H_4

Scheme 2. Synthesis of Thiazoles and oxazoles

Among the oxazoles (7a) and (7e) showed good inhibition against *E. coli* and *A. faecalis* respectively while others moderately inhibited the growth of *E. coli* .Others showed moderate to good activity against *K. pneumoniae* and *P. areuginosa* with (7b) being inactive . Against both the fungus *C. globosum* and *C. lunata* all the compounds showed moderate activity.

Surprisingly the 4-hydroxy substituted thiazoles (**7c**) showed significant activity against the tested strains. The chloro and nitro group also increased the activity but the compounds containing methoxy group were inactive among the tested strains.

CONCLUSION

In summary, we have synthesized various substituted oxazole analogs (8a-e) and their bioisosteres substituted thiazole analogs (6a, 7a-d) and the yields are found to be good . Oxazole analogs containing various substituted arylimino groups at 2 positions have been synthesized and their bioisostere counterpart thiazole analogs have also been synthesized with similar substitution at the second position and evaluated for their in-vitro antimicrobial activity. In particular oxazole analogs have shown promising antimicrobial activity when compared to their bioisostere counterpart that is the thiazole analogs.

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REFERENCES

1. Lipsitch, M. *Trends Microbiol.*, 2001; **9:** 438.
2. Cunha, B.A. *Drugs Today* **,** 1998; **34**: 691.
3. Cassell, G.H. and Mekalanos, J. *J. Am. Med. Assoc.,* 2001; **285**: 601.
4. Sephala, H., Kkankka, T., Vupio-Varkila, J., Muotiala, A., Helenius, H., Lager, K., Huoviven, P. *N. Eng. J. Med.,* 1997 ; **337**: 441.
5. Silverman, R. B. *Organic chemistry of Drug Desing and Drug Action, Academic press: San Diego,* 1992.
6. Popsavin, M., Spaic, S., Svircev, M., Kojic, V., Bogdanovic, G., Popsavin, V. *Bioorg Med Chem Lett.,* 2007; **17:** 4123.
7. Kumar, A., Rajput, C.S., Bhati, S.K. *Bioorg Med Chem.,* 2007; **15**: 3089
8. Shiradkar, M.R., Murahari, K.K., Gangadasu, H.R., Suresh, T., Kalyan, C.A. Panchal, D., Kaur, R., Burange, P., Ghogare, J., Mokale, V., Raut, M. *Bioorg Med Chem,* . 2007; **15**: 3997.
9. Chimenti, F., Bizzarri, B., Maccioni, E., Secci, D., Bolasco, A., Fioravanti, R., Chimenti, P., Granese, A., Carradori, S., Rivanera, D., Lilli, D., Zicari, A., Distinto, S. *Bioorg Med Chem Lett.* , 2007; **17**: 4635.
10. Andreani, A., Rambaldi, M., Mascellani, G., Rugarli, P. *Eur J Med Chem.,* 1987; **22**: 19.
11. Azam, F., Alkskas, I.A., Khokra, S.L., Prakash, O. *Eur J Med Chem.,* 2009; **44** : 203
12. Clark, R.F., Zhang, T., Wang, X., Wang, R., Zhang, X., Camp, H.S., Beutel, B.A., Sham, H.L., Gu, Y.J. *Bioorg Med Chem Lett.,* 2007; **17**: 1961
13. Koufaki, M., Kiziridi, C., Nikoludaki, F., Alexis, M.N. *Bioorg Med Chem Lett,.* 2007; **17**: 4223.
14. Kempf, D.J., Sham, H.L., Marsh, K.C., Flentge, C.A., Betebenner, D., Green, B.E., McDonald, E., Vasavanonda, S., Saldivar, A., Wideburg, N.E., Kati, W.M., Ruiz, L., Zhao, C., Fino, L., Patterson, J., Molla, A., Plattner, J.J. and Norbeck, D.W. *J. Med. Chem.,* 1998; **41**(4): 602.
15. Tsuji, K. and Ishikawa, H. *Bioorg. Med. Chem. Lett.,* 1994; **4**: 1601.
16. George, C., Martin, N., Ray, R. *J. Med. Chem.,* 1973; **16**: 1402.
17. Anna, C.G., Helena, I.M.B., Scott, G.F., Clifton, E.B., Brent, R.C. *Tetrahedron Lett.,* 2005 ; **46**: 7355.
18. George, C., Michael, J.F. *J. Med. Chem.,* 1971; **14**: 1075.
19. Prudhomme, M., Guyat, J., Jeminet, G. *J. Antibiot.* , 1986; **39**: 934.
20. Goodman-Gilman, A. *The pharmacological basis of therapeutics*, McGraw-Hill company, USA, 2001
21. López-García, B., Veyrat, A., Pérez-Payá, E., González- Candelas, L. and Marcos, J.F. *Int. J. Food Microbiol.,* 2003; **89***:* 63.
22. Dave, G.R., Mewada, G.S and Amin, G.C. *J. In. Chem. Soc.,* 1960; **37**(9).
23. Barry, A.L. *The antimicrobial susceptibility test, Principle and practice*;Ed. By Illus-Lea and Febiger, Philadelphia, PA, USA,1976; p.180.