Available on line www.jocpr.com

Journal of Chemical and Pharmaceutical Research

ISSN No: 0975-7384
CODEN(USA): JCPRC5

J. Chem. Pharm. Res., 2010, 2(5):461-475

Synthesis and biological activity of some novel quinazolinone derivatives

S. Venkataraman[*1], R. Meera[1], Pandiarajan[1], P.Devi[2],

[1]*Department of Pharmaceutical Chemistry, K.M. College of Pharmacy, Uthangudi, Madurai, TamilNadu, India*
[2]*Department of Pharmacognosy, K.M. College of Pharmacy, Uthangudi, Madurai, TamilNadu, India*

ABSTRACT

In this work, an efficient synthesis for the preparation of some novel quinozolinones by 2 steps. In step I , various 2-substituted-3,1-benzoxazin-4-ones are formed by the reaction of anthranilic acid and acetic anhydride / benzoyl chloride / propionic anhydride. In step II , 2-substituted-3,1-benzoxazin-4-ones, which are formed in step I, are condensed with Etoricoxib. The resulting quinazolinone derivatives were characterized by IR, NMR, [13] CNMR and mass spectral analysis. The resulting quinazolinone derivatives PBE 1, PBE 2, PBE 3, PBE 4, PBE 5 were carried out for Anti inflammatory activity and Anti microbial activity. Anti inflammatory activity was determined by carragenan induced paw-odema method for 25, 50 mg/kg derivative compounds. Anti microbial activity was effective against S.aureus and E.coli by using standard drugs like Lincomycin and Cefatazidime. The compounds 6-bromo-2-phenyl-3-{[4-(5-methyl-3-phenyl-4-isoxazolyl) phenyl] sulfonyl4-(3H) quinazolinone and 6,8-dibromo-2-phenyl-3-{[4-(5-methyl-3-phenyl-4-isoxazolyl)phenyl]sulfonyl4-(3H) quinazolinone are promising ones against Staphylococcus aureus. The compounds tested 2-phenyl-3-{[4-(5-methyl-3-phenyl-4-isoxazolyl)phenyl]sulfonyl4-(3H) quinazolinone and 6-bromo-2-phenyl-3-{[4-(5-methyl-3-phenyl-4-isoxazolyl) phenyl sulfonyl 4-(3H) quinazolinone showed better anti-inflammatory activity and 6-bromo-2-methyl-3-{[4-(5-methyl-3-phenyl-4-isoxazolyl)phenyl]sulfonyl4-(3H) quinazolinone showed lesser activity at both the doses tested. There is no significant increase in the activity with increase in the dose (50mg/kg).

Key words: 2-substituted-3,1-benzoxazin-4-one, Etoricoxib ,quinazolinones derivatives, IR, NMR, Mass spectroscopy, Anti inflammatory activity, Anti microbial activity.

INTRODUCTION

Quinazolinone derivatives have been reported for antimalarial[1],diuretic[2],sedative and hypotenstion[3],Monoaminooxidaseinhibitoractivity[4,5,6],antihypertensive[7],antitubercular[8],analgesic[9],antiinflammatory[10],antifibrillatory[11],antihistamine[12],CNSdepresant[13,14],anticonvulsant[15,16],ant

iparkinsonisom[17,18],antibacterial[19,20],antiviral[21],antiallergy[22],anthelmintic[23],anticancer[24],antiHIV[25] ,antitubercular[26] CVS[27],bronchodilator[28].Etoricoxib which is a potent COX-2inhibitor and also contain –SO2NH2 group. This group can condensed with benzoxainone derivatives and the produced novel quinazolinones may show better or additional activities. 4-(4-methyl-3-phenyl-4-isoxazolyl)benzene sulfonamide, empirical formula $C_{16}H_{14}N_2O_3S$, Molecular weight 314.36, white crystalline powder relatively insoluble in ethanol, methanol. Freely soluble in organic solvents and aqueous alkali. Etoricoxib is a nonsteroidal anti inflammatory drug that exhibit anti-inflammatory, analgesic and antipyretic properties, the mechanism of action is believed to be due to inhibition of prostaglandin synthesis primarily through inhibition of cyclo-oxigenase-2(COX-2). At therapeutic plasma concentrations in human . Etoricoxib does not inhibit cyclo-oxygenase-1(COX-1). It was found that when one biodynamic heterocyclic system was coupled with another heterocyclic system enhanced biological activity was produced.

EXPERIMENTAL SECTION

All the melting points were taken in Veego-Vmp 1 melting point apparatus are uncorrected. IR spectra were recorded on Perkin Elmer FT-IR spectrometer. NMR spectra were recorded on Bruker spectrospeir 200MHZ, the chemical shifts referenced to TMS.

Synthesis of compounds[29,30,31,32,33,34]

Synthesis of 2-phenyl-3,1-benzoxazin-4-one PB-1

To a solution of anthranilic acid (1a-c) (0.01mol) in pyridine (30ml)was added benzoylchloride (0.02 mol), and the mixture was shaken for 5 min and then kept aside Room temperature for further 25 min with occasional shaking. The reaction mixture was treated with 5% $NaHCO_3$ solution (15 ml), filtered, washed with water, dried and the crude product was recrystallised from absolute ethanol. The yield and melting point of synthesized PB-1 were shown in the table.

Synthesis of 2-ethyl-3,1-benzoxazin-4-one (PB-2)

A mixture of anthranilic acid(0.mol1) and propionic anhydride(0.2mol) was refluxed for 4 hr under anhydrous conditions. The excess of propionic anhydride was distilled off under reduced pressure and cooled to room temperature. The PB-2 separated as solid mass. The crude drug thus obtained was recrystallized from absolute alcohol. The yield and melting point of synthesized PB-2 were shown in the table.

Synthesis of 6-bromo-2-methyl-3,1-benzoxazin-4-one (PB-3)

A mixture of 5-bromo anthranilic acid(0.mol1) and acetic anhydride(0.2mol) was refluxed for 4 hr under anhydrous conditions. The excess of acetic anhydride was distilled off under reduced pressure and cooled to room temperature. The PB-2 separated as solid mass. The crude drug thus obtained was recrystallized from absolute alcohol. The yield and melting point of synthesized PB-3 were shown in the table.

Synthesis of 6-bromo-2-phenyl-3,1-benzoxazin-4-one (PB-4)

To a solution of 5-bromo anthranilic acid (0.01mol) in pyridine (30ml)was added benzoylchloride (0.02 mol), and the mixture was shaken for 5 min and then kept aside Room temperature for further 25 min with occasional shaking. The reaction mixture was treated with 5% $NaHCO_3$ solution (15 ml), filtered, washed with water, dried and the crude product was

recrystallised from absolute ethanol. The yield and melting point of synthesized PB-4 were shown in the table.

Synthesis of 6-bromo-2-ethyl-3,1-benzoxazin-4-one (PB-5)

A mixture of 5-bromo anthranilic acid(0.mol1) and propionicanhydride(0.2mol) was refluxed for 4 hr under anhydrous conditions. The excess of acetic anhydride was distilled off under reduced pressure and cooled to room temperature. The PB-5separated as solid mass. The crude drug thus obtained was recrystallized from absolute alcohol. The yield and melting point of synthesized PB-5 were shown in the table

Synthesis of 6-bromo-2-methyl-3,1-benzoxazin-4-one (PB-6)

A mixture of 3,5-dibromo anthranilic acid(0.mol1) and acetic anhydride(0.2mol) was refluxed for 4 hr under anhydrous conditions. The excess of acetic anhydride was distilled off under reduced pressure and cooled to room temperature. The PB-6 separated as solid mass. The crude drug thus obtained was recrystallized from absolute alcohol. The yield and melting point of synthesized PB-6 were shown in the table.

Synthesis of 6,8-dibromo-2-phenyl-3,1-benzoxazin-4-one (PB-7)

To a solution of 5-bromo anthranilic acid (0.01mol) in pyridine (30ml)was added benzoylchloride (0.02 mol), and the mixture was shaken for 5 min and then kept aside Room temperature for further 25 min with occasional shaking. The reaction mixture was treated with 5% $NaHCO_3$ solution (15 ml), filtered, washed with water, dried and the crude product was recrystallised from absolute ethanol. The yield and melting point of synthesized PB-7 were shown in the table.

Synthesis of 6,8-dibromo-2-ethyl-3,1-benzoxazin-4-one (PB-8)

A mixture of 3,5-dibromo anthranilic acid(0.mol1) and propionicanhydride(0.2mol) was refluxed for 4 hr under anhydrous conditions. The excess of acetic anhydride was distilled off under reduced pressure and cooled to room temperature. The PB-8separated as solid mass. The crude drug thus obtained was recrystallized from absolute alcohol. The yield and melting point of synthesized PB-8 were shown in the table

Synthesisof2-Phenyl-3-{[4-(5-Methyl-3-Phenyl-4isoxazolyl)-Phenyl]Sulfonyl}4-(3H)Quinazolinone (PBE-1)

An equmolar(0.1mol) mixture of 2-phenyl-3,1-benzoxazin-4-one and Etoricoxib was refluxed for 6 hr with 10 ml of glacial aceticacid. The mixture was cooled to room temperature and poured into crushed ice. Then it was filtered and dried. The solid thus obtained was recrystallised from absolute alcohol. The yield and melting points were given in the table.

Synthesisof2-ethyl-3-{[4-(5-Methyl-3-Phenyl-4isoxazolyl)-Phenyl]Sulfonyl}4-(3H)Quinazolinone (PBE-2)

An equmolar(0.1mol) mixture of 2-ethyl-3,1-benzoxazin-4-one and Etoricoxib was refluxed for 6 hr with 10 ml of glacial aceticacid. The mixture was cooled to room temperature and poured into crushed ice. Then it was filtered and dried. The solid thus obtained was recrystallised from absolute alcohol. The yield and melting points were given in the table.

Synthesisof6-bromo-2-methyl-3-{[4-(5-Methyl-3-Phenyl-4isoxazolyl)-Phenyl]Sulfonyl}-4-(3H)Quinazolinone (PBE-3)

An equmolar(0.1mol) mixture of 6-bromo-2-methyl-3,1-benzoxazin-4-one and Etoricoxib was refluxed for 6 hr with 10 ml of glacial aceticacid. The mixture was cooled to room temperature and poured into crushed ice. Then it was filtered and dried. The solid thus obtained was recrystallised from absolute alcohol. The yield and melting points were given in the table.

Synthesisof6-bromo-2-phenyl-3-{[4-(5-Methyl-3-Phenyl-4isoxazolyl)-Phenyl]Sulfonyl}4-(3H)Quinazolinone (PBE-4)

An equimolar(0.1mol) mixture of 6-bromo-2-phenyl-3,1-benzoxazin-4-one and Etoricoxib was refluxed for 6 hr with 10 ml of glacial aceticacid. The mixture was cooled to room temperature and poured into crushed ice. Then it was filtered and dried. The solid thus obtained was recrystallised from absolute alcohol. The yield and melting points were given in the table.

Synthesisof6-bromo-2-ethyl-3-{[4-(5-Methyl-3-Phenyl-4isoxazolyl)-Phenyl]Sulfonyl}-4-(3H)Quinazolinone (PBE-5)

An equmolar(0.1mol) mixture of 6-bromo-2-ethyl-3,1-benzoxazin-4-one and Etoricoxib was refluxed for 6 hr with 10 ml of glacial aceticacid. The mixture was cooled to room temperature and poured into crushed ice. Then it was filtered and dried. The solid thus obtained was recrystallised from absolute alcohol. The yield and melting points were given in the table

Synthesis of 6,8-dibromo-2-methyl-3-{[4-(5-Methyl-3-Phenyl-4isoxazolyl)-Phenyl] Sulfonyl} -4-(3H)Quinazolinone (PBE-6)

An equmolar(0.1mol) mixture of 6,8-dibromo-2-methyl-3,1-benzoxazin-4-one and Etoricoxib was refluxed for 6 hr with 10 ml of glacial aceticacid. The mixture was cooled to room temperature and poured into crushed ice. Then it was filtered and dried. The solid thus obtained was recrystallised from absolute alcohol. The yield and melting points were given in the table.

Synthesisof6,8-dibromo-2-phenyl-3-{[4-(5-Methyl-3-Phenyl-4isoxazolyl)-Phenyl]Sulfonyl}4-(3H)Quinazolinone (PBE-7)

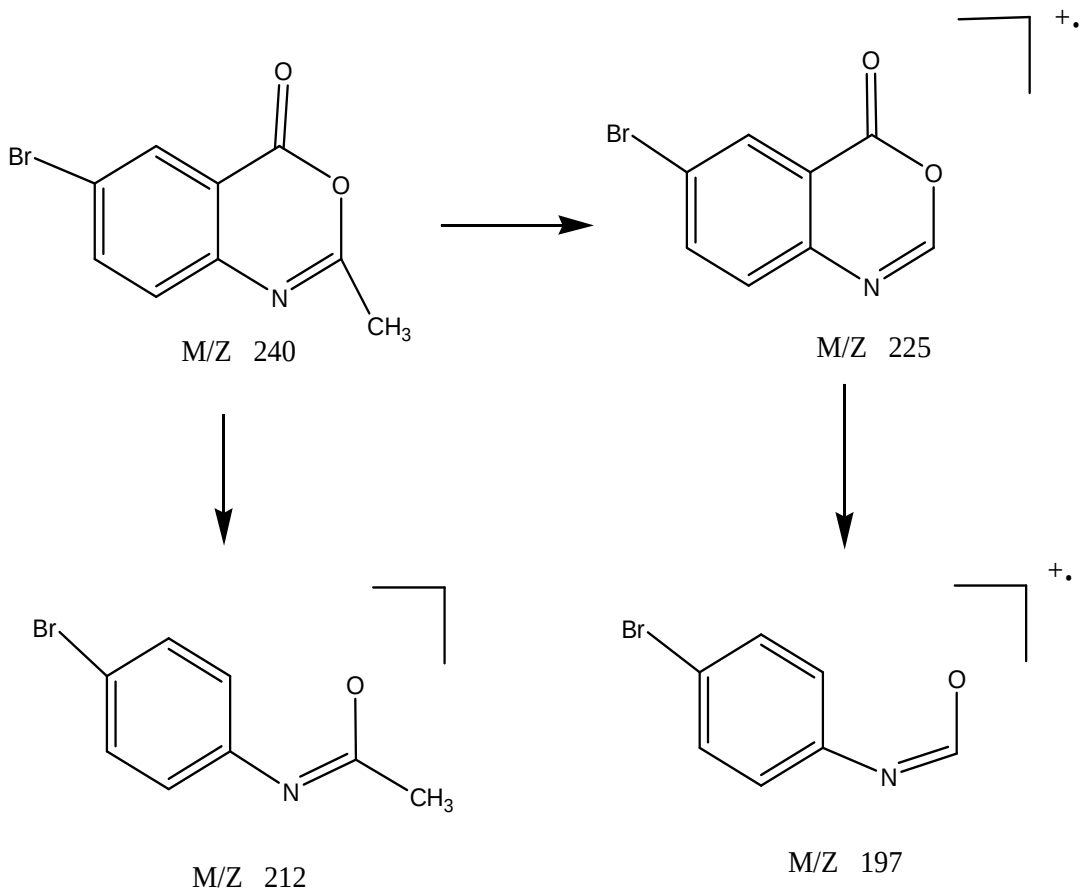
An equmolar(0.1mol) mixture of 6,8-dibromo-2-phenyl-3,1-benzoxazin-4-one and Etoricoxib was refluxed for 6 hr with 10 ml of glacial aceticacid. The mixture was cooled to room temperature and poured into crushed ice. Then it was filtered and dried. The solid thus obtained was recrystallised from absolute alcohol. The yield and melting points were given in the table.

Synthesisof6,8-dibromo-2-ethyl-3-{[4-(5-Methyl-3-Phenyl-4isoxazolyl)-Phenyl]Sulfonyl}-4-(3H)Quinazolinone (PBE-8)

An equmolar(0.1mol) mixture of 6,8-dibromo-2-ethyl-3,1-benzoxazin-4-one and Etoricoxib was refluxed for 6 hr with 10 ml of glacial aceticacid. The mixture was cooled to room temperature and poured into crushed ice. Then it was filtered and dried. The solid thus obtained was recrystallised from absolute alcohol.

Spectral analysis of the compounds:-[33,34,35]

PB-1 IR (Kbr): 1764(C=O str), 1612(C=Nstr) cm^{-1}
PMR (200MHZCDCl$_3$): δ 7.63-8.34(m9H, Ar-H)
PB-2 IR (Kbr): 1685(C=O str), 1640(C=Nstr) cm^{-1}
PB-3 IR (Kbr): 1700(C=O str), 1613(C=Nstr), 530(C-Br str) cm^{-1}
PB-4 IR (Kbr): 1755(C=O str), 1578(C=N str), 560(C-Br str) cm^{-1}
PB-5 IR (Kbr): 1700(C=O str), 1613(C=Nstr), 530(C-Br str) cm^{-1}
PB-6 IR (Kbr): 1712(C=O str), 1598(C=N str), 532 (C-Br str) cm^{-1}
PB-7 IR (Kbr): 1756(C=O str), 1614(C=Nstr), 583,537 (C-Br str) cm^{-1}
PB-8 IR (Kbr): 1774(C=O str), 1579(C=N str), 530,554 (C-Br str) cm^{-1}
PBE-1 IR (Kbr): 1643(C=O str), 1333 and 1150(S=Ostr), 1599 (C=N str) cm^{-1}
PMR (200MHZDMSO): δ 1.54 (s, 3H, CH_3)7.63-8.34(m18H, Ar-H)
PBE-2 IR (Kbr): 1678(C=O str), 1332 and1150(S=O str), 1465 (C=Nstr) cm^{-1}
PMR (200MHZ,DMSO): δ 0.69 (t, 3H, $CH_3.CH_2$) 1.39(q,2HCH_2CH_3),1.85(s,3H,CH_3),6.80-6.95(m13H, Ar-H)
PBE-3 IR (Kbr): 1663(C=O str), 1333 and1150(S=O str), 1578 (C=Nstr) cm^{-1}
PMR (200MHZ CDCl3): δ 1.22 (s,3H,CH_3)1.56(s,3H, CH_3), 6.52-7.51 (m,11H, Ar-H)
PBE-4 IR (Kbr): 1664(C=O str), 1338 and 1156 (S=O str), 1597(C=N str) cm^{-1}
PMR (200MHZDMSO): δ 1.56 (s, 3H, CH_3)6.47-7.77(m17H, Ar-H),
^{13}C-NMR Spectral 11.6, 25.1 (δ) in ppm (2-CH_3 carbons), 114.1, 14.4, 119.2, 122.3, 126.3, 128.4, 128.6, 129.0, 129.9, 130.2, 133.2, 133.5, 136.5, 140.1, 143.5, 160.9, 167.8, 168.8 (18-Aromatics carbons), 187.9 (One carbonyl carbon).
PBE-5 IR (Kbr): 1656(C=O str), 1334 and1150(S=O str), 1502 (C=Nstr) cm^{-1}
PMR (200MHZ DMSO): δ 0.68 (t,3H,$CH_3.CH_2$)1.41(q,2H,$CH_2.CH_3$),1.82(s,3H,CH_3), 6.62-6.92 (m,12H, Ar-H)
PBE-6 IR (Kbr): 1663(C=O str), 1333 and1151(S=O str), 1598 (C=Nstr) cm^{-1}
PMR (200MHZ DMSO): δ 1.20 (s,3H,CH_3)1.55 (s,3H,CH_3), 6.46-7.51 (m,11H, Ar-H)
PBE-7 IR (Kbr): 1662(C=O str), 1332 and1156(S=O str), 1578 (C=Nstr) cm^{-1}
PMR (200MHZCDCl$_3$): δ 1.54 (s, 3H, CH_3)7.63-8.34(m18H, Ar-H)
PBE-8 IR (Kbr): 1656(C=O str), 1334 and1150(S=O str), 1502 (C=Nstr) cm^{-1}
PMR (200MHZ DMSO): δ 0.68 (t,3H,$CH_3.CH_2$)1.41(q,2H,$CH_2.CH_3$),1.82(s,3H,CH_3), 6.62-6.92 (m,12H, Ar-H).

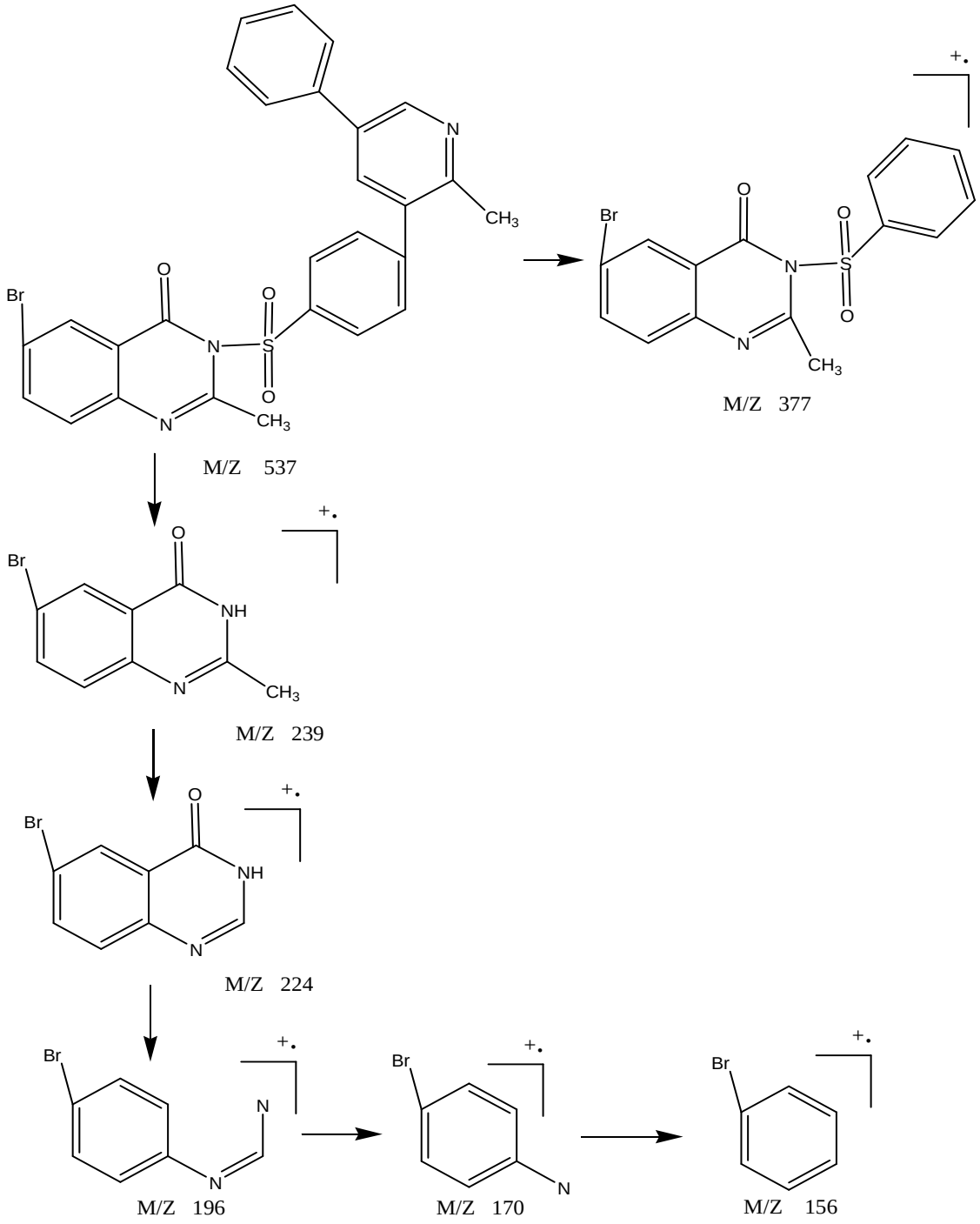


Postulated fragmentation pattern for 6-bromo-2-methyl benzoxazinone (PB-3)

In the mass spectrum of PB-3, though the molecular ion peak is not observed at m /z 240, the peaks at m/z 225, m/z 212,m/z 197 can be accounted by the scheme.

Postulated fragmentation pattern for 6-bromo-2-methyl-3-{[4-(5-methyl-3-phenyl-4-isoxazolyl) phenyl] sulphonyl}4-(3h)-quinazoline (PBV-3)

In the mass spectrum of PB-3, though the molecular ion peak is not observed at m/z 537, the peaks at m/z 239, m/z 224 and m/z 196,m/z 170,m/z 156 can be accounted by the following scheme



Biological activity

Anti inflammatory activity[36,37,38]

Anti inflammatory activity was measured using the Carrageenan induced paw edema in rats. Animals were divided in to different groups each consisting of six animals. Test compounds were administered orally at a dose of 25mg/kg, 50mg/kg as an aqueous suspension in 1% CMC, while the control group was fed with the same volume of 1% CMC suspension. Thirty minutes later, the rats were challenged by subcutaneous injection of 0.05 mo of 1% w/v solution of

Carrageenan into the plantar side of the left hint paw. The paw volume was measured using the mercury displacement technique with the help of a plethysmograph. Paw volume of the test compounds, standard and control groups were measured at 30, 60,120,180, minutes after Carrageenan challenge.

The difference between the mean paw volume of control and standard is considered as 100% and the difference between the mean paw volume of control and the test compounds treated groups were expressed with reference to standard and percentage inhibition was also calculated and tabulated.(Table 1,2)

Antimicrobial activity[39,40,41]

Muller Hinton agar media (Hi media Labs, Mumbai) of 100 ml was prepared as per the composition and sterilized in the autoclave as 15 lbs/in^2 for 20 minutes. When the medium was in warm molten state, 100µl of overnight incubated test culture was seeded. From this, 27 ml was transferred to sterile Petri plates and allowed to solidify. Solution of standard and test samples were prepared as per above mentioned concentration using DMF as solvent in sterile cotton plugged tubes. The filter paper discs (sterile) of 5 mm diameter were soaked in standard and test solutions and in solvent control DMF. After evaporating the solvent in a sterile atmosphere, the drug impregnated discs were placed over seeded agar medium in Petri plates. The plates were refrigerated for 1 hour to arrest the growth and for easier diffusion of test compounds. Then the plates were removed from refrigerator and incubated at 37° C over night in an inverted condition. The zone of inhibition (mm) was measured using graph sheet and tabulated. (Table 3,4)

RESULTS AND DISCUSSION

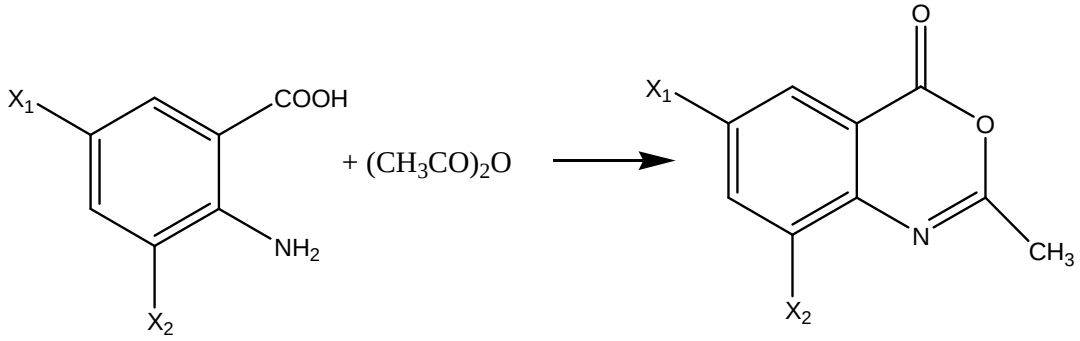
Eight novel quinazolinone derivatives were synthesized and characterized by spectral analysis. The2-phenyl/ethyl,6-bromo2-methyl/6bromo2-phenyl/6bromo2-ethyl and 6,8-dibromo2-methyl/ 6,8-dibromo2-phenyl/6,8-dibromo2-ethyl3-{[4-(5-methyl-3-phenyl-4-isoxazolyl)phenyl] sulfon yl}-4-(3H)quinozolinone were synthesized by refluxing equimolar amount of 2-substituted-3,1-benzoxazin-4-one and Etoricoxib in the presence of glacial acetic acid. The melting point of the synthesized compounds was found out by open capillary tube method and the results were uncorrected. The purity of the co pounds was checked By TLC using silica gel G as an adsorbent, ethyl acetate and chloroform (9.8:0.2) were used as mobile phase. The spot was visualized by iodine vapor or dinitrophenyl hydrazine solution. The structure of the synthesized compounds was characterized by its IR-HNMR and Mass spectral analysis in which it complies with the normal values.

The result of the anti inflammatory activity reveals that all the test compounds protected the rats from carrageenan induced inflammation and the test compounds showed significant anti-inflammatory activity against the control group. All the compounds significantly reduced the inflammation after 3rd hour. Among the compounds tested 2-phenyl-3-{[4-(5-methyl-3-phenyl-4-isoxazolyl)phenyl]sulfonyl4-(3H) quinazolinone and 6-bromo-2-phenyl-3-{[4-(5-methyl-3-phenyl-4-isoxazolyl) phenyl sulfonyl 4-(3H) quinazolinone showed better anti-inflammatory activity and 6-bromo-2-methyl-3-{[4-(5-methyl-3-phenyl-4-isoxazolyl)phenyl]sulfonyl4-(3H) quinazolinone showed lesser activity at both the doses tested. There is no significant increase in the activity with increase in the dose (50mg/kg).

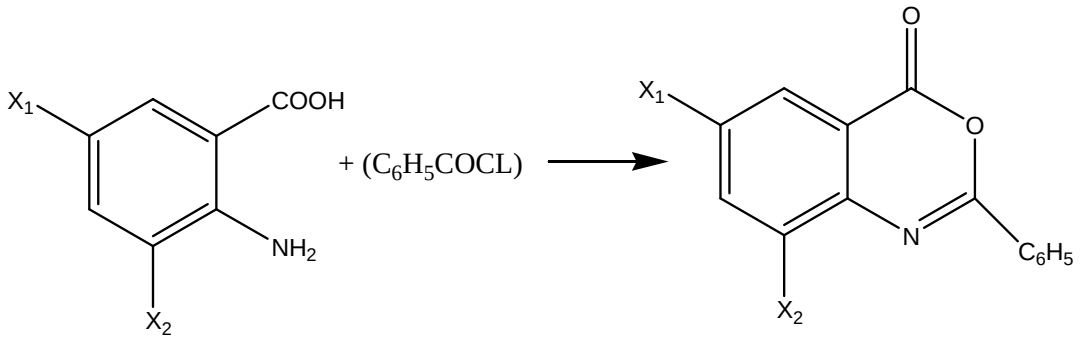
Antibacterial activity of the test compounds in DMF was determined by filter paper disc method at a concentration of 200µg/ml. All the compounds showed comparable activity as that of the standard Lincomycin against *Staphylococcus aureus* (MTCC 96). None of the test compounds could exhibit comparable activity to that of the standard Ceftazidime against *Escherichia Coli* (MTCC 722). The test compounds showed better activity at 200µg/ml concentration against *S. aureus*. Further test can be done using higher concentration is diffusion is not the barrier. The compounds 6-bromo-2-phenyl-3-{[4-(5-methyl-3-phenyl-4-isoxazolyl) phenyl] sulfonyl4-(3H) quinazolinone and 6,8-dibromo-2-phenyl-3-{[4-(5-methyl-3-phenyl-4-isoxazolyl)phenyl] sulfonyl-4-(3H) quinazolinone are promising ones against *Staphylococcus aureus*. The further, some more test organisms of gram positive and gram negative types can be used.

SCHEME

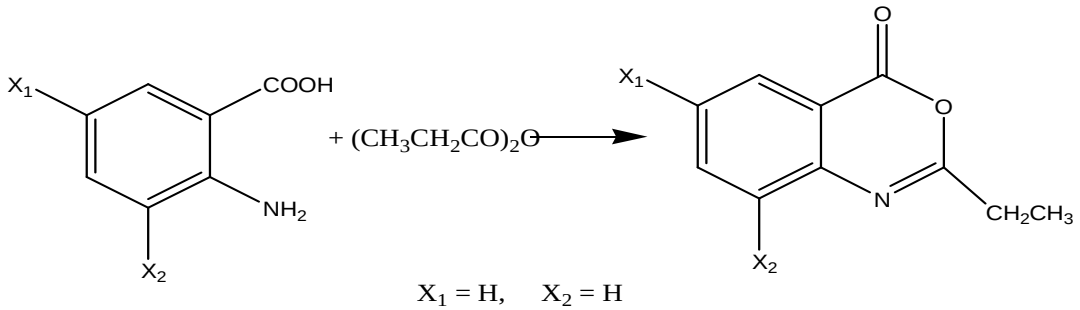
Step – 1 (Synthesis of 2- Substituted – 3,1-benzoxazin-4-one).



X_1 = Br, X_2 = H
X_1 = Br, X_2 = Br



X_1 = H, X_2 = H
X_1 = Br, X_2 = H
X_1 = Br, X_2 = Br



X_1 = H, X_2 = H
X_1 = Br, X_2 = H
X_1 = Br, X_2 = Br

Step -II (Synthesis of various Quinazolinones).

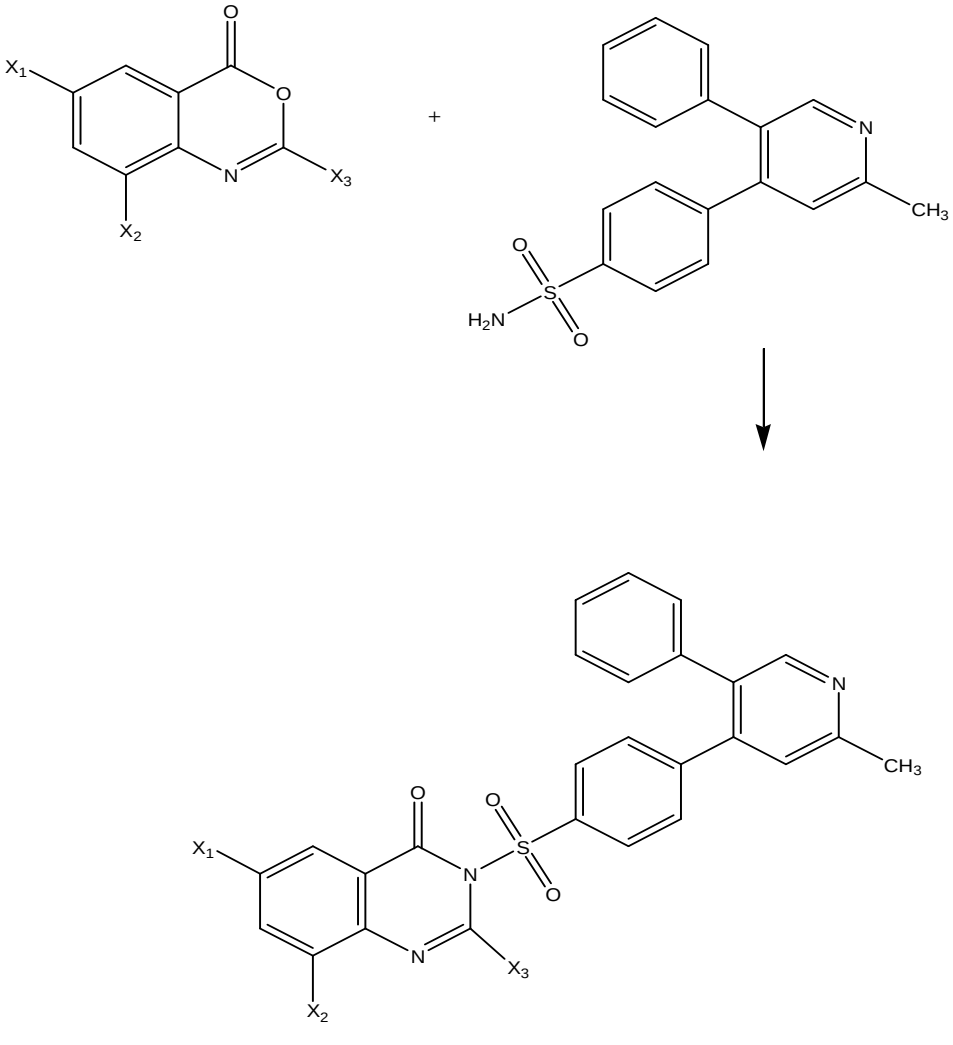


Table 1: Physical data of Synthesized compounds

Sl.No	Code	Molecular formula	Molecular weight	Melting point	%yield	R_f value
1	PB-1	$C_{14}H_9NO_2$	223.233	120°C	89	O.75
2	PB-2	$C_{10}H_9NO_2$	175.188	104°C	74	0.86
3	PB-3	$C_9H_6BrO_2N$	240.57	123°C	55	0.68
4	PB-4	$C_{14}H_8BrNO_2$	302.129	180°C	58	0.87
5	PB-5	$C_{10}H_8BrNO_2$	254.084	190°C	69	0.97
6	PB-6	$C_9H_5Br_2NO_2$	318.953	176°C	61	0.93
7	PB-7	$C_{14}H_7Br_2NO_2$	381.025	153°C	60	0.81
8	PB-8	$C_{10}H_7Br_2NO_2$	332.980	158°C	83	0.85
9	PBE-1	$C_{30}H_{21}N_3O_4S$	519.574	135°C	81	0.70
10	PBE-2	$C_{26}H_{21}N_3O_4S$	471.537	146°C	77	0.68
11	PBE-3	$C_{25}H_{18}BrN_3O_4S$	536.397	157°C	86	0.72
12	PBE-4	$C_{30}H_{20}BrN_3O_4S$	598.467	155°C	94	0.69
13	PBE-5	$C_{26}H_{20}BrN_3O_4S$	550.424	148°C	97	0.84
14	PBE-6	$C_{25}H_{17}Br_2N_3O_4S$	615.293	168°C	80	0.58
15	PBE-7	$C_{30}H_{19}Br_2N_3O_4S$	677.363	160°C	96	0.63
16	PBE-8	$C_{26}H_{19}Br_2N_3O_4S$	629.320	138°C	78	0.71

Table 2: Percentage Inhibition of Test Compounds 25 mg/kg against Carrageenan Induced Paw Edema in Rats

S.no	Drug 25mg/ml	Normal paw volume	Drug administration				Percentage inhibition
			0.5 hr	1 hr	2 hr	3 hr	
1	control	0.49±0.01	0.74±0.08	0.75±0.05	0.74±0.04	0.72±0.001	-------
2	PBE-1	0.46±0.03	0.71±0.01	0.67±0.05	0.65±0.02	0.63±0.02*	50
3	PBE-2	0.48±0.02	0.74±0.05	0.70±0.03	0.68±0.01	0.65±0.01*	38
4	PBE-3	0.46±0.01	0.71±0.01	0.68±0.05	0.68±0.02	0.66±0.05*	33
5	PBE-4	0.50±0.02	0.75±0.03	0.70±0.02	0.65±0.02	0.64±0.02*	44
6	PBE-5	0.47±0.01	0.73±0.05	0.70±0.05	0.67±0.01	0.66±0.01*	44
7	Standard	0.49±0.05	0.75±0.02	0.69±0.01	0.62±0.05	0.54±0.02*	100

**P.0.05 against control at 3rd hour; ONE-WAY ANOVA was used to test significance*

Table 3:Percentage Inhibition of Test Compounds 50 mg/kg against Carrageenan Induced Paw Edema in Rats

s.no	Drug 50mg/ml	Normal paw volume	Drug administration				Percentage inhibition
			0.5 hr	1 hr	2 hr	3 hr	
1	Control	0.48±0.01	0.75±0.02	0.76±0.02	0.76±0.01	0.74±0.002	-------
2	PBE-1	0.50±0.03	0.76±0.03	0.70±0.01	0.63±0.05	0.59±0.05*	60
3	PBE-2	0.48±0.02	0.74±0.05	0.63±0.05	0.60±0.02	0.60±0.03*	48
4	PBE-3	0.46±0.05	0.72±0.01	0.68±0.05	0.68±0.03	0.64±0.02*	40
5	PBE-4	0.49±0.08	0.74±0.01	0.71±0.01	0.64±0.05	0.60±0.04*	56
6	PBE-5	0.47±0.05	0.73±0.05	0.69±0.04	0.69±0.01	0.63±0.01*	44
7	Standard	0.46±0.02	0.73±0.02	0.66±0.03	0.56±0.05	0.49±0.01*	100

**P.0.05 against control at 3rd hour; ONE-WAY ANOVA was used to test significance*

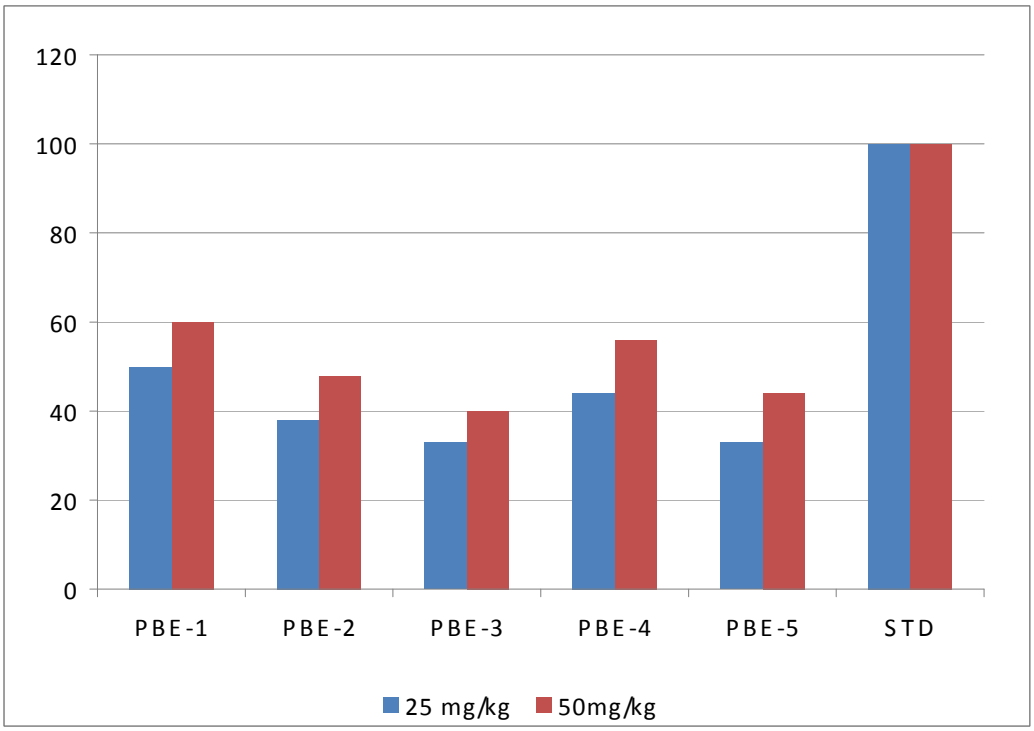


Fig No.1 percentage inhibition of test compounds against carrageenen induced paw edema in rats

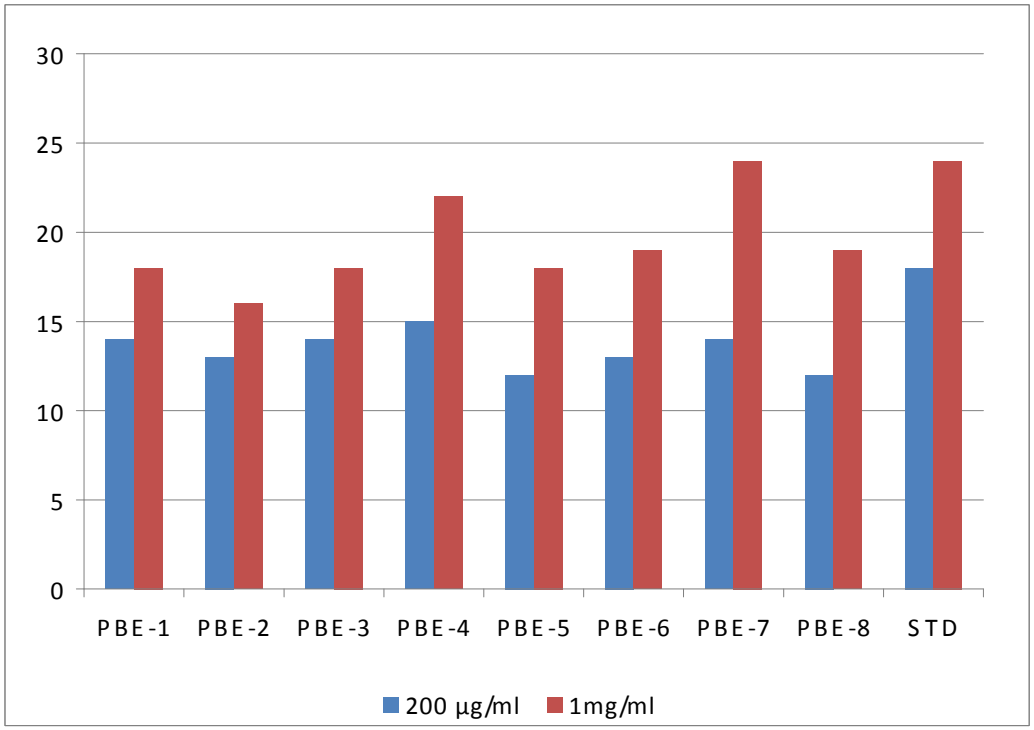


Fig No.2 Anti-bacterial activity of test compounds against *S.aureus* IN COMPARISON TO Lincomyin (10 µg, 50 µg per disc)

Table 4: Anti bacterial activity of test compounds against S.*aureus* in comparison to lincomycin (10µg, 50µg per disc)

Sl. No.	Test compounds	Zone of inhibition in mm	
		200 µg / ml	1 mg / ml
1	PBE - 1	14	18
2	PBE – 2	13	16
3	PBE – 3	14	18
4	PBE – 4	15	22
5	PBE – 5	12	18
6	PBE – 6	13	19
7	PBE – 7	14	24
8	PBE – 8	12	19
9	Standard	18	24

Table 5:Anti bacterial activity of test compounds against *E. coli* in comparison to ceftazidime (10µg, 50µg per disc)

Sl. No.	Test compounds	Zone of inhibition in mm	
		200 µg / ml	1 mg / ml
1	PBE - 1	7	12
2	PBE – 2	8	15
3	PBE – 3	7	14
4	PBE – 4	6	11
5	PBE – 5	10	16
6	PBE – 6	8	15
7	PBE – 7	10	13
8	PBE – 8	7	11
9	Standard	17	27

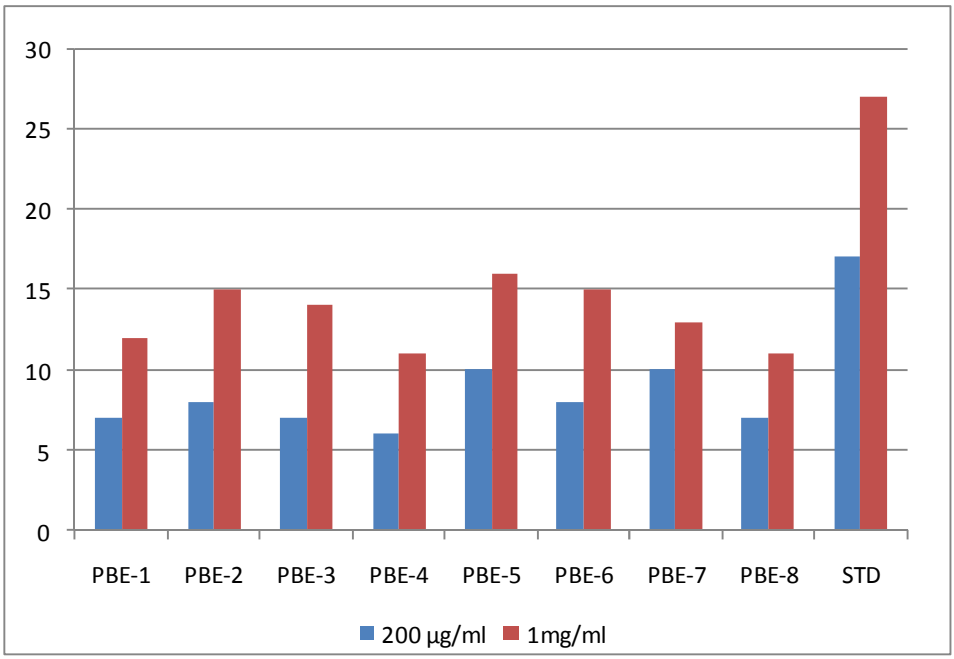


Fig No.3 Anti-bacterial activity of test compounds against *E.coli* in comparison to ceftazidime (10 µg, 50 µg per disc)

REFERENCES

[1] Baker BR, Robert.E.Schaub, Joseph P. Joseph, Francis.J.McEvoy, James H.Williams. *J.Org.Chem*., **1952**,17,149-156.
[2] Elliott Cohen, Betty Klarberg and James R.Vaughan., *J.Am.Chem.Soc*., **1960**, 82, 2731-2735.
[3] Shin Hayao, Herbert J.Havera, Wallace G.Strycker, T. J. Leipzig, Richard A. Kulp and Harold E.Hartzler. *J.Med.chem*., **1965**, 8, 807-811.
[4] Surendra S.Parmar and Arora RC. *Can.J.Chem*.., **1966**, 44, 2100-2102.
[5] Surendra S.Parmar and Arora RC. *J.Med.Chem*., **1967**, 10(6),1182-1183.
[6] Surendra S.Parmar and Arora RC. *Can.J.Chem*., **1968**, 46, 2519-2524.
[7] Hess HJ, Cronin TH and Scriabine A. *J.Med.Chem*., **1968**, 11,130-136.
[8] Surendra S.Parmar, Kumar R. *J.Med.Chem*., **1969**, 11(3), 635-636.
[9] Somaskehara S, Dighe VS , Parikh SH and Gokhale SV . *Indian J.pharm*., **1971**, 33(1) 96-97.
[10] Okumura Oine, Yamada, Hayashi and Nakama, *J.Med.Chem*., **1969**, 11,348-352.
[11] Bonola,Da re,Magistretti,Massarani and Setnikar. *J.Med.Chem*., **1968**, 11, 1136-1139.
[12] Shin Hayao, H.JHavera and W.G.Strycker, *J.Med. Chem*., **1970**, 12, 936-938 .
[13] Kumar R, Gupta TK and Surendra S. Parmar, *Indian J.Pharm*., **1971**, 33(6), 108-110.
[14] Mukerji DD, Nautiyal SR and Prasad CR . *Indian J.Pharm.Sc*., **1978**, 40(2), 44-47.
[15] Nagar S and Surendra S.Parmar. *Indian. J.Pharm*., **1971**,33(4),61-64.
[16] Rastogi VK, Parmar SS , Singh SP and Akers TK. *J.Heterocyclic Chem*., **1978**, 15,497-499.
[17] Surendra S.Parmar and Shiva P. Singh. *J.Heterocyclic Chem*., **1979**, 16,449-452.
[18] Shankar K ,Vijai K .Srivastava, Singh IP ,Sharadha Singh, Gupta MB *Indian J.Phar.Sci*., **1986**, 48(5),133-136.
[19] Sengupta AK, Gupta MM and Anurag Ateet Gupta, *Indian J.chem*., , **1982**,21,600-602.
[20] RaviShankar CH, Devandar Rao A, Jahasena Reddy E and Malla Reddy V. *J. Indian Chem. Soc*., LX, **1983**, 61-63.
[21] Anil K. Sengupta, Tapas Bharracharya, Ashok K. Pandey, H.N.Verma and M.M.Abid Alikhan. *Indian drugs*., **1984**, 17 (2), 435-437.
[22] Nortan P.Peet, Larry E. Baugh, Shyam Sunder, John E.Lewis, Emily H. Mathews, Edward L.Oleberding and Dhiren N. Shah. *J.Med.Chem*., **1986**, 29,2403-2409.
[23] Pandey VK and Punita Garg. *Indian J.pharm.Sci.*, **1987**, 49(5), 172-174.
[24] Jiang JB, Hesson DP, Dusak BA, Dexter DL, Kang GJ and Hamel E. *J.Med.Chem*., **1990**, 33,1721-1728.
[25] Desai NC, Shah BR , Bhatt JJ, Patel HH, Undavia NK, Trivedi PB. *Indian J.Chem*., **1995**, 34,201-208.
[26] Ashok Kumar, Ritu Tyagi,Ekta Bansal,R.sVerma,K.K.Saxena and V.K.Srivastava, *Indian drugs*., **1998**, 35(5), 261-265.
[27] Dhar KL, Sharma SC and Zutshi V. *Indian J.Chem*., 38,814-817, (**1999**).
[28] Bain DI and Smalley RK. *J.Chem.Soc*., **1969**,1593-1597.
[29] Deshmukh MB and Deshmukh DS. *J.Indian Chem.Soc*., **1995**, 72,847-848..
[30] Surendra S.Parmar R.Kumar. *J.Med.Chem*., **1969**, 11(3),635-636.
[31] Pradeep Mishra,P.N.Gupta and AshokK.Shakya. *J.Indian Chem.Soc*., **1991**,68,618-619,
[32] Selvam P, Vanitha K ,Chandramohan M and E.De.Clercq. *Indian J.pharm.Sci.*,**2004**,66(6),82-86.

[33] John R.Dyer Applications of absorption spectroscopy of organic compounds, 1st edition, Prentice-Hall of India (P),New Delhi,**1969**, p. 33-38.
[34] Robert M. Silverstein, Francis X. Webster, Spectrometric identification of organic compounds, John Wiley and sons, Inc.**1998**.
[35] McLafferty FW , Interpretation of mass spectra, 2nd edition, W.A. Benjamin. Inc. Publishers, NewYork ,**1974**.
[36] Kulkarni SK,.. Handbook of experimental pharmacology., **2004**,180.
[37] Gerhard vogel, H.. Drug discovery and evaluation, pharmacological assays, 2nd edition, Springer Publication. **2003**, 759 - 762.
[38] Tripathi , K.D. **2004**. Essentials of Medical pharmacology, 5th edition. 180.
[39] Alagarsamy, V., Pathak, U.S., and Goyal R.K., *Indian J.Pharm.Sci.* **2000**, 62(1),63-66.
[40] Kavanagh.. Analytical microbiology, Academic press, NewYork.. 1963 1: 249.
[41] Mackie and McCartney. Practical medical microbiology. 13th edition, Churchill Livingstone, London. **1978**., 2: 260.