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ORIGINAL ARTICLE

Anti-inflammatory and antibacterial activity study of some novel quinazolinones

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Abstract Anti-inflammatory and antibacterial activities of some novel quinazolinones were determined. Evaluation of anti-inflammatory activity of test compounds was performed using carrageenan induced paw edema in rats. Oral administration of test compounds 25 mg/kg and 50 mg/kg reduced the paw edema significantly ($P < 0.05$) in a dose dependent manner compared to carrageenan induced rats. The test compounds were also screened for their antibacterial activity against the strains of *Staphylococcus aureus* and *Escherichia coli* at the concentrations of 200 μg/ml and 1 mg/ml. The test compounds showed better activity as that of the standard lincomycin at the tested higher concentration against *S. aureus*. None of the compounds exhibit comparable activity to that of the standard ceftazidime against *E. coli*.

1. Introduction

In general, the quinazolones are considered to be important compounds in the fields of pharmacy and biology. Microbial infections often produce pain and inflammation. The compounds possessing anti-inflammatory activity with antibacterial activities are not known. Quinazolinone derivatives exhibit a wide range of biological activities like analgesic, anti-inflammatory, antibacterial (Alagarsamy et al., 2003), antifungal (Anshu et al., 2005), antiviral (Dinakaran et al., 2003), antihistaminic (Lemura et al., 1989), antihypertensive (Samir et al., 1989), anticancer (Anjani et al., 2006), antihyperglycemic (Vishnu et al., 2003) and anti-HIV (Alagarsamy et al., 2003). The tested compounds (See Fig. 1) were synthesised by our earlier reported method (Muthumani et al., 2010). The compounds were tested for antibacterial and anti-inflammatory activities.

2. Materials and methods

2.1. Drugs and chemicals

Carrageenan, carboxy methyl cellulose (CMC) and dimethyl formamide (DMF) were obtained from Merck, Mumbai.

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Table 1 Percentage inhibition of test compounds (25 mg/kg) against carrageenan-induced paw edema in rats.

S. No.	Drug 25 mg/kg	Normal paw volume	Drug administration				Percentage inhibition
			0.5 h	1 h	2 h	3 h	
1	Control	0.49 ± 0.01	0.74 ± 0.08	0.75 ± 0.05	0.74 ± 0.04	0.72 ± 0.01	–
2	PBV-1	0.46 ± 0.03	0.71 ± 0.01	0.67 ± 0.05	0.65 ± 0.02	0.63 ± 0.02*	50
3	PBV-2	0.48 ± 0.05	0.74 ± 0.05	0.70 ± 0.03	0.68 ± 0.01	0.65 ± 0.01*	38
4	PBV-3	0.46 ± 0.01	0.71 ± 0.01	0.68 ± 0.05	0.68 ± 0.02	0.66 ± 0.005*	33
5	PBV-4	0.50 ± 0.02	0.75 ± 0.03	0.70 ± 0.02	0.65 ± 0.02	0.64 ± 0.02*	44
6	PBV-5	0.47 ± 0.01	0.73 ± 0.05	0.70 ± 0.05	0.67 ± 0.01	0.66 ± 0.01*	33
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 the third hour. Values are expressed as mean ± SEM, $n = 6$ rats in each group. The statistical analysis was performed by using Graph pad prism software version 4.03. The level of significance was calculated by One way analysis of variance followed by Dunnet's multiple comparison test.

Table 2 Percentage inhibition of test compounds (50 mg/kg) against carrageenan-induced paw edema in rats.

S. No.	Drug 50 mg/kg	Normal paw volume	Drug administration				Percentage inhibition
			0.5 h	1 h	2 h	3 h	
1	Control	0.48 ± 0.01	0.75 ± 0.02	0.76 ± 0.02	0.76 ± 0.01	0.74 ± 0.002	–
2	PBV-1	0.50 ± 0.03	0.76 ± 0.03	0.70 ± 0.01	0.63 ± 0.05	0.59 ± 0.05*	60
3	PBV-2	0.48 ± 0.02	0.74 ± 0.05	0.63 ± 0.05	0.60 ± 0.02*	0.62 ± 0.03*	48
4	PBV-3	0.46 ± 0.05	0.72 ± 0.01	0.68 ± 0.05	0.68 ± 0.03	0.64 ± 0.02*	40
5	PBV-4	0.49 ± 0.08	0.74 ± 0.01	0.71 ± 0.01	0.64 ± 0.05	0.60 ± 0.04*	56
6	PBV-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 the third hour. Values are expressed as mean ± SEM, $n = 6$ rats in each group. The statistical analysis was performed by using Graph pad prism software version 4.03. The level of significance was calculated by One way analysis of variance followed by Dunnet's multiple comparison test.

Lincomycin and ceftazidime were obtained from Hi-media labs, Mumbai. The standard drug, Valdecoxib was obtained from Lyka hetero healthcare limited, Mumbai.

2.2. Animals

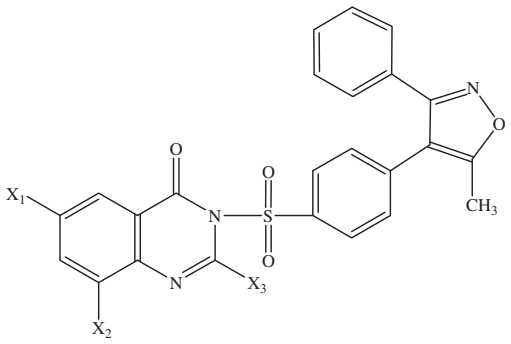
Female Sprague-Dawley rats (150–200 g) were obtained and maintained in the Central Animal house. Animals were housed in polypropylene cages at a room temperature of 21 ± 2 °C with 12 h of light and dark cycles and had free access to water *ad libitum*. Animal experimental protocols have been approved by an institutional animal ethics committee. Antibacterial activity was performed at Vijay labs, Madurai according to the protocol mentioned.

2.3. Anti-inflammatory activity of some novel quinazolinones against carrageenan-induced paw edema in rats

Anti-inflammatory activity was measured using carrageenan-induced paw edema in rats (Winter et al., 1962). Rats were divided into different groups each consisting of six animals and given oral administration of 1% CMC (untreated control), valdecoxib (reference control), and test compounds PBV-1 to PBV-5 were administered at a dose of 25 mg/kg, 50 mg/kg. Thirty minutes later, the rats were challenged by a subcutaneous injection of 0.05 ml of 1% w/v solution of carrageenan into the plantar side of the left hind paw. The paw volume was measured using the mercury displacement technique with the help of plethysmometer (Ugo Basile, Italy). Paw volume of the untreated control, reference control and test compounds was measured at 0.5, 1, 2 and 3 h after carrageenan treatment. The difference between mean paw volume of control and standard is considered as 100% and the difference between the mean paw volume of control and test compounds treated groups was expressed with reference to the standard and percentage inhibition was calculated and tabulated (Tables 1 and 2).

2.4. Antibacterial activity of some novel quinazolinones (Mackie et al., 1978)

Staphylococcus aureus (MTCC 96) and *Escherichia coli* (MTCC 722) were used for this study. Mueller-Hinton agar media of 100 ml was prepared as per the composition and sterilized in an autoclave at 15 lbs/in^2 for 20 min. When the medium was in a warm molten state, 100 µl of over night incubated test culture was seeded. From this, 27 ml was transferred into sterile petri plates and allowed to solidify. Solutions of standard (lincomycin and ceftazidime) and sample (PBV-1 to PBV-8) were prepared (200 µg/ml and 1 mg/ml) using DMF as a solvent in sterile cotton plugged tubes. The filter paper discs of 5 mm diameter were soaked in standard, test solutions and 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 h to arrest the growth and for easier diffusion of test compounds. Then the plates were removed from the refrigerator and incubated at 37 °C over night in an inverted condition and the zone of inhibition was measured and tabulated (Table 3).



Compounds	X_1	X_2	X_3
PBV-1	H	H	C_6H_5
PBV-2	H	H	C_2H_5
PBV-3	Br	H	CH_3
PBV-4	Br	H	C_6H_5
PBV-5	Br	H	C_2H_5
PBV-6	Br	Br	CH_3
PBV-7	Br	Br	C_6H_5
PBV-8	Br	Br	C_2H_5

Figure 1 Structures of title compounds.

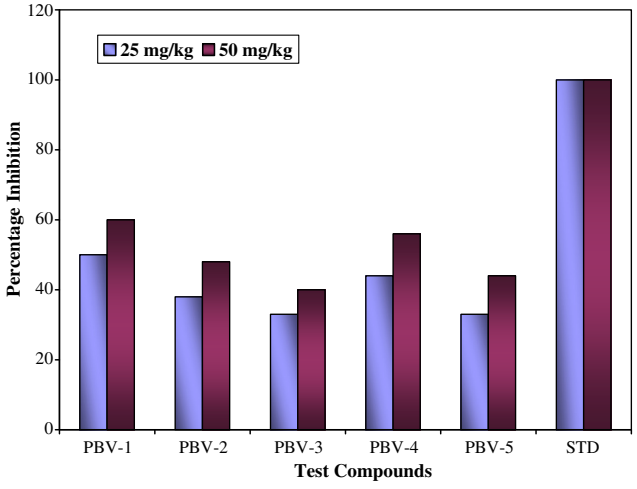


Figure 2 Percentage inhibition of test compounds against carrageenan-induced paw edema in rats.

3. Results and discussion

3.1. Anti-inflammatory activity

The role of test compounds (PBV-1 to PBV-5) on carrageenan-induced acute inflammation model was evaluated at concentrations of 25 mg/kg and 50 mg/kg. Edema was reduced by test compounds in a dose dependent manner till the end of the third hour. In carrageenan administered animals the severe swelling was reached at 1 h and the swelling was maintained until the third hour. The valdecoxib treated groups decreased paw edema significantly throughout the period of study. The swelling was completely reduced during the third hour in valdecoxib treated rats. However, the animals treated with test compounds (50 mg/kg) showed considerable inhibition on swelling as compared to carrageenan administered animals. Similarly the animals treated with test compounds (25 mg/kg) also showed moderate inhibition on swelling as compared to carrageenan induced animals. The results revealed that all the test compounds protected the rats from carrageenan induced inflammation and the test compounds showed a significant anti-inflammatory activity against the control group (see Fig. 2). All the compounds significantly reduced the inflammation after the third hour. Among the compounds tested PBV-1 and PBV-4 showed better anti-inflammatory activity. PBV-2, PBV-3 and PBV-5 showed moderate activity at both the doses tested.

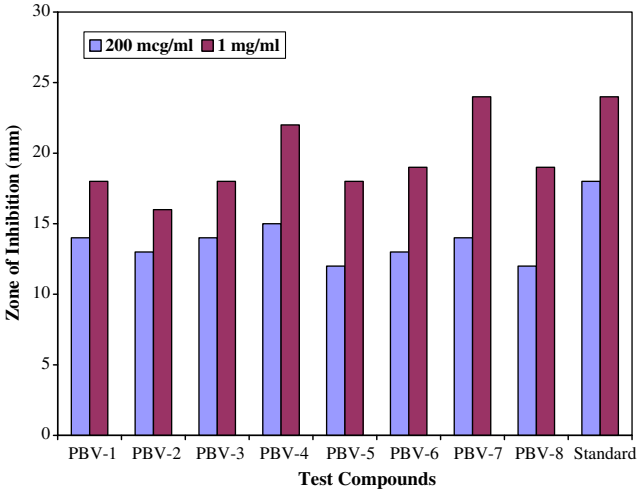


Figure 3 Antibacterial activity of test compounds against *S. aureus*.

Carrageenan-induced paw edema as an *in vivo* model of inflammation has been frequently used to assess the anti-edematous effects, which is known to be sensitive to cycloxygenase (COX) inhibitors and has been used to evaluate the effects of NSAID. Development of edema in the paw of the rat after the injection of carrageenan involves three phases by several inflammatory mediators released in an ordinary sequence. An initial phase during the first 1.5 h is caused by the release of histamine and serotonin, the second phase is mediated by bradykinin-like substances from 1.5 to 2.5 h. The treatment with the COX-1 inhibitor could reduce the first and second phases of paw edema (Siqueira-Junior et al., 2003). Finally, COX-2 is up-regulated only in the third phase, the mediator of which is suspected to be prostaglandins, proteases and lysosymes occur from 2.5 to 6 h after carrageenan injection (Guang-Ming et al., 2010). The results of our *in vivo* study (Tables 1 and 2) indicated that the test compounds were able to effectively inhibit edema in the third phase, suggesting that test compounds inhibited cyclo oxygenase pathway of inflammation.

3.2. Antibacterial activity

The results of the antibacterial screening of the test compounds are presented (see Figs. 3 and 4). Antibacterial activity of the test compounds in DMF was determined by Filter paper disc method at concentrations of 200 μg/ml and 1 mg/ml. All

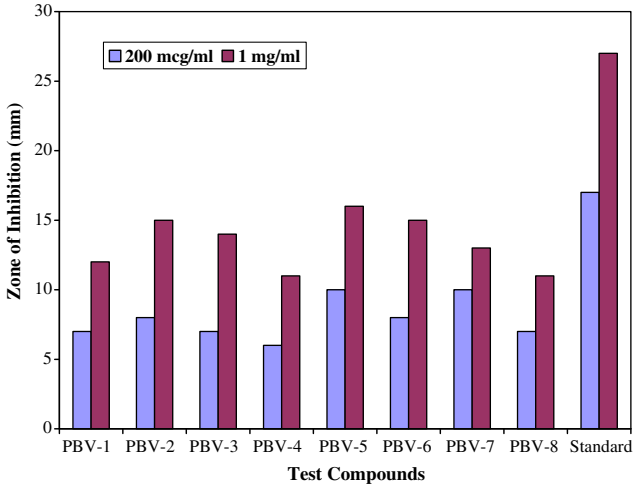


Figure 4 Anti-bacterial activity of test compounds against *E. coli*.

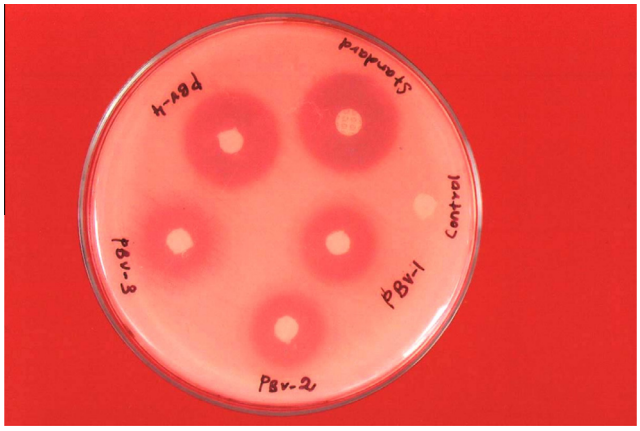


Figure 7 Antibacterial activity against *S. aureus* (1 mg/ml). The zone of inhibition in mm for the test compounds PBV-1 to PBV-4 at the concentration 1 mg/ml against *S. aureus* was found to be 18, 16, 18 and 22, respectively.

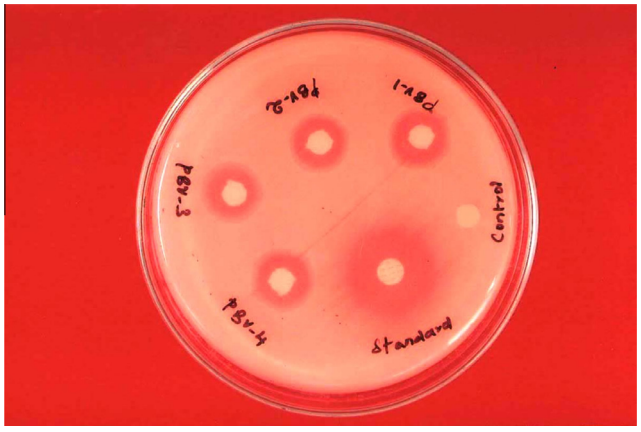


Figure 5 Antibacterial activity against *S. aureus* (200 μg/ml). The zone of inhibition in mm for the test compounds PBV-1 to PBV-4 at the concentration 200 μg/ml against *S. aureus* was found to be 14, 13, 14 and 15, respectively.

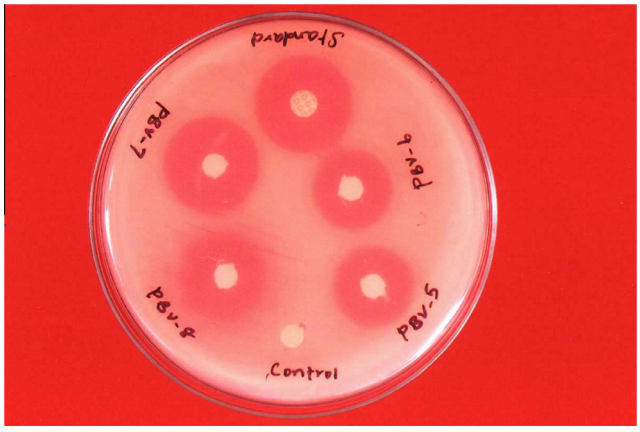


Figure 8 Antibacterial activity against *S. aureus* (1 mg/ml). The zone of inhibition in mm for the test compounds PBV-5 to PBV-8 at the concentration 1 mg/ml against *S. aureus* was found to be 18, 19, 24 and 19, respectively.

Figure 6 Antibacterial activity against *S. aureus* (200 μg/ml). The zone of inhibition in mm for the test compounds PBV-5 to PBV-8 at the concentration 200 μg/ml against *S. aureus* was found to be 12, 13, 14 and 12, respectively.

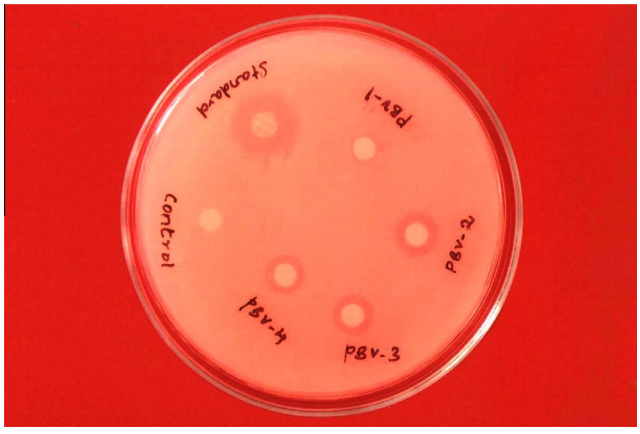


Figure 9 Antibacterial activity against *E. coli* (200 μg/ml). The zone of inhibition in mm for the test compounds PBV-1 to PBV-4 at the concentration 200 μg/ml against *E. coli* was found to be 7, 8, 7 and 6, respectively.

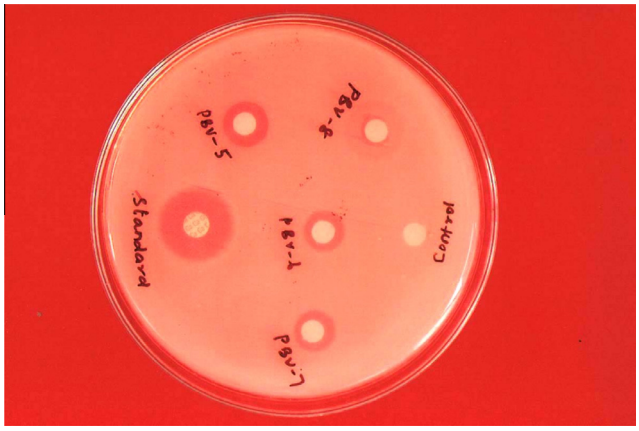


Figure 10 Antibacterial activity against *E. coli* (200 μg/ml). The zone of inhibition in mm for the test compounds PBV-5 to PBV-8 at the concentration 200 μg/ml against *E. coli* was found to be 10, 8, 10 and 7, respectively.

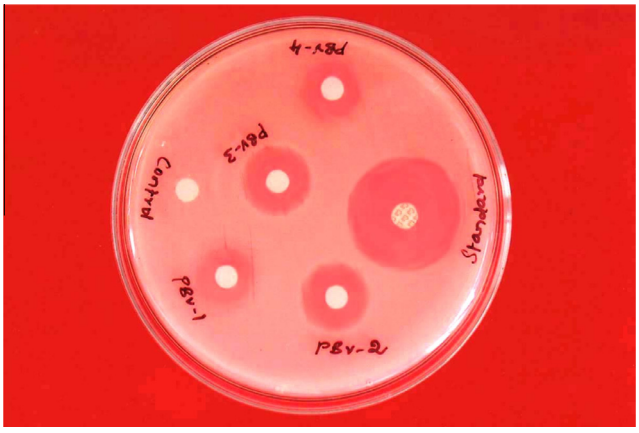


Figure 11 Antibacterial activity against *E. coli* (1 mg/ml). The zone of inhibition in mm for the test compounds PBV-1 to PBV-4 at the concentration 1 mg/ml against *E. coli* was found to be 12, 15, 14 and 11, respectively.

Figure 12 Antibacterial activity against *E. coli* (1 mg/ml). The zone of inhibition in mm for the test compounds PBV-5 to PBV-8 at the concentration 1 mg/ml against *E. coli* was found to be 16, 15, 13 and 11, respectively.

Table 3 Antibacterial activity of test compounds against *S. aureus* and *E. coli*.

Test compounds	Zone of inhibition in mm against *S. aureus*		Zone of inhibition in mm against *E. coli*	
	200 μg/ml	1 mg/ml	200 μg/ml	1 mg/ml
PBV-1	14	18	7	12
PBV-2	13	16	8	15
PBV-3	14	18	7	14
PBV-4	15	22	6	11
PBV-5	12	18	10	16
PBV-6	13	19	8	15
PBV-7	14	24	10	13
PBV-8	12	19	7	11
Standard	18	24	17	27

the compounds showed comparable activity as that of the standard lincomycin against *S. aureus* (MTCC 96) (see Figs. 5–8). None of the test compounds could exhibit comparable activity to that of the standard ceftazidime against *E. coli* (MTCC 722) (see Figs. 9–12). The test compounds showed a better activity at the tested higher concentration (1 mg/ml) than at the lower concentration (200 μg/ml) against *S. aureus*. The compounds PBV-4 and PBV-7 are promising ones against *S. aureus*.

4. Conclusion

The present study results showed the antibacterial and anti-inflammatory activities of the test compounds. As NSAIDs are associated with the side effect of ulcer, the test compounds can be evaluated for their ulcer potential. In antibacterial activity a further test can be done using a higher concentration of more than 1 mg/ml if diffusion is not the barrier. In future, some more test organisms of gram positive and gram negative types can be used. In conclusion we suggest that the future studies on these quinazolones could be useful for the management of bacterial infections and inflammatory diseases.

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