PHARMACOLOGICAL POTENTIAL OF SOME NOVEL QUINAZOLIN-4(3H)-ONES

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Summary

In present study some novel derivatives of 2-(-N-substituted amino) methyl-3-(4-chlorophenyl)-quinazolin-4(3H)-ones have been synthesized by the condensation of respective 6, 8-disubstituted-2-chloromethyl-3-(4-chlorophenyl)-quinazolin-4-(3H) ones with different primary amines in equi molar concentrations. The structures of these compounds have been established on the basis of their spectral data. These compounds were tested for anti-inflammatory and antimicrobial potentials by carrageenan-induced rat paw oedema model and cup-plate method respectively. Compound 3-(4-chlorophenyl)-2-[(3-hydroxy phenyl amino)-methyl]-3h-quinazolin-4-one (QN03) showed comparable anti-inflammatory activity with the standard drug used and also showed good antibacterial activity. Other compounds exhibited mild to moderate antibacterial activity.

Key words: Quinazolin-4(3H)-ones, primary amine, anti-inflammatory activity, antimicrobial activity.

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Introduction

In recent years, the synthesis of quinazolin-4(3H)-ones gained more importance because of their biological activities like anti-inflammatory (1), analgesic (2) , antihypertensive (3), sedative and hypnotic (4), antihistaminic (5), antimicrobial (6), anticonvulsant (7), enzyme inhibition activity (8), antitumor (9) and many other activities.

A number of attempts have been made by various research groups to obtain potent and safe analogs without much success. Multi drug resistance among the pathogens represents a serious challenge for health practitioners in treating both nosocomial and community acquired infections. The continued rise in microbial resistance has called for antimicrobial agents to be developed that are effective against resistant strains.

In view of the above information we initiated a progress of preparing novel quinazolin-4(3H)-ones analogs. Quinazolin-4(3H)-one is 4-oxo-1,3-benzopyrimidine and the chemistry are discussed in the text book of heterocyclic chemistry(10). This work has been focused towards synthesis of 2, 3-disubstituted Quinazolin-4(3H)-ones using 2-chloromethyl-3-(-4-chlorophenyl)-6,8-disubstituted quinazolin-4(3H)-one with primary amines of anti-inflammatory and antimicrobial potentials.

Reaction of anthranillic acid and chloroacetyl chloride in equi molar ratio led to the formation of N-Chloroacetylanthranillic acid which is then refluxed with 4-chloro aniline for 6h in presence of $POCl_3$ in toluene to give 2-chloromethyl-3-(-4-chlorophenyl)-6,8-disubstituted quinazolin-4(3H)-one (11). This quinazolin-4(3H)-one on treatment with different primary amines gives the target compounds 2-(N-substituted amino) methyl-3-(-4-chlorophenyl) quinazolin-4(3H)-ones (12).

All the compounds were obtained in good yield. The compounds were characterized by IR, ^{1}H-NMR and mass spectral analysis. Out of eight synthesized compounds, five compounds were selected for their anti-inflammatory and antimicrobial activity.

Material and methods

Anti-inflammatory activity
Carrageenan induced hind paw edema in rats

The anti-inflammatory activity was determined by carrageenan in rats. Albino rats of *Wistar* strain of either sex, weighing 120-140g, were selected by random sampling technique. The animals were allowed food and water *ad libitum*. Animals were divided into six groups, each comprising of six rats. Indomethacin (200mg/100g) and the five test compounds (200mg/100g) were administered orally 60minutes prior to the administration of carrageenan. In all the groups hind paw oedema was produced by sub planter injection of 0.1ml of freshly prepared 1% suspension of carrageenan in normal saline in the right hind paw of the rats and paw volume was measured plethysmometrically at 0 h and 3h after carrageenan injection (13). The institutional animal ethics committee of kasthurba medical college has approved the experimental protocol (No. IAEC/KMC/05/2004-05).

Test organism and drugs used

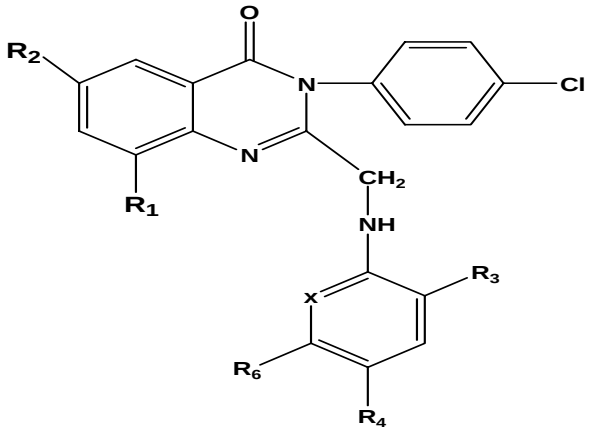
Pure cultures of test organisms *Staphylococcus aureus, Escherichia coli, Proteus vulgaris, Clostridium diptheriae*, *Pseudomonas aeroginosa, Candida albicans* and *Aspergillus niger* were procured from the central drugs laboratory (Kolkata, India). All the organisms were maintained on agar slant stocks and were subsequently sub cultured into newly prepared nutrient agar slants. Gentamycin and Amphotericin B (Dr. Reddy's Lab, Batch no: 1C 666E04, India) were used as a standard in antibacterial and antifungal studies respectively.

Antimicrobial activity

All the synthesized compounds were screened for antimicrobial activity by cup-plate method (14). The antibacterial activity of the compounds (125µg/ml) was tested with *Staphylococcus aureus, Escherichia coli, Proteus vulgaris, Clostridium diptheriae*, *Pseudomonas aeroginosa* using nutrient agar media. The antifungal activity of the compounds was tested against *Aspergillus niger and Candida albicans* using sabouraud dextrose agar media. The sterilized medium was poured in to Petri dishes and allowed to solidify. On the surface of the media microbial suspension was spread with the help of sterilized triangular loop. A stainless steel cylinder of 8mm diameter (pre-sterilized) was used to bore the cavities. All the synthesized compounds were placed serially in the cavities with the help of micropipette and allowed to diffuse for 1h. Dimethylformamide (DMF) was used as a solvent for all compounds and as control. Then the plates were incubated for 24 h and 48 h at 37 ± 1^0C to observe for antibacterial and antifungal activity respectively. The diameter of zone of inhibition against bacteria and fungi were observed. The results were presented in Table 2.

Results and conclusions

The novel 2-(-N-substituted amino) methyl quinazolin-4(3H)-ones were synthesized by the reaction of 2-chloromethyl-3-(-4-chlorophenyl)-6,8-disubstituted quinazolin-4(3H)-one with primary amines under reflux conditions. The structures of the compounds were given in Figure1.



QN 01-08

Cpd code	X	R1	R2	R3	R4	R5
QN01	C	H	H	H	Cl	H
QN02	C	H	H	COOH	H	H
QN03	C	H	H	H	H	OH
QN04	C	Br	Br	H	Cl	H
QN05	C	H	H	COOH	H	H
QN06	C	H	H	H	COOH	H
QN07	C	H	H	H	H	H
QN08	N	H	H	H	H	H

Figure1- General structure of the targeted compounds.

Compound 3-(4-chlorophenyl)-2-[(3-hydroxy phenyl amino)-methyl]-3*H*-quinazolin-4-one (QN03) was found to have anti-inflammatory activity comparable to the standard, having percentage reduction of paw volume of about 74.5%. All other compounds showed mild activity. The activity profile was given in Table-1.

Table 1- Effect of quinazolin-4(3h)-ones on Carrageenan induced rat paw edema at 200mg/100g.

Cpd code	Mean oedema volume ± S.E (0-3h)	Reduction in oedema volume
QN01	0.10±0.04*	50
QN02	0.13±0.026*	35
QN03	0.05±0.028*	74.5
QN04	0.09±0.04*	55
QN05	0.12±0.046*	40
IBF	0.04±0.01	80
Control	0.2±0.05	-

5% allowance value is 0.25 (Scheffe's method), *P<0.05 Vs control. Note: Any two means showing a difference of 0.25 are statistically significant.

The selected compounds were tested in vitro for their antimicrobial activity against seven microorganisms belonging to bacteria and fungi classes. Compound QN03 showed good antibacterial activity. Other compounds exhibited mild to moderate antibacterial activity. All the compounds showed resistance against *A.niger*. Compounds QN01 and QN02 showed moderate antifungal activity against *C.albicans*. Compound QN05 did not show any antimicrobial activity against the strains used. The data was given in table-2.

Table 2- Antimicrobial activity of the selected compounds at 125 µg/ml.

Cpd code	*In vitro* antibacterial activity-Zone of inhibition (mm)						
	S.aureus	*P. vulgaris*	*C. diptheriae*	*P. aeroginosa*	*E.coli*	*C.albicans*	*A.niger*
QN01	10	11	-	10	-	14	-
QN02	9	10	-	-	-	13	-
QN03	9	18	17	10	8	-	-
QN04	9	-	-	-	11	-	-
QN05	-	-	-	-	-	-	-
GM	15	19	17	16	16	-	-
AMP	-	-	-	-	-	20	23
DMF	-	-	-	-	-	-	-

GM Gentamycin; AMP Amphotericin B; DMF Dimethylformamide; '-' indicates resistance

From the data, it was cleared that the substituted aryl group at 2nd and 3rd place have shown increased anti-inflammatory and antibacterial activity. But they did not possess any encouraging antifungal activity.

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