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ANTIMICROBIAL ACTIVITY OF 2-HETEROARYL SUBSTITUTED QUINAZOLONES

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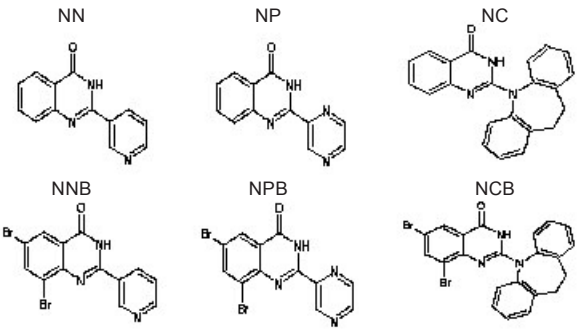
ABSTRACT
2-hetero substituted-4-quinazolone derivatives attract a wide spread interest due to the diverse biological activities. Six novel 2-heterosubstituted quinazolones were synthesized and the structures were assigned on the basis of spectral data. These compounds were screened for their antimicrobial activity. The recorded zone of inhibition showed significant broad spectrum antibacterial activity when compared with standard ciprofloxacin. Antifungal screening indicated that all the synthesized moieties had inhibitory effect against the tested pathogenic fungi.

Keywords: *quinazolone; antimicrobial activity.*

INTRODUCTION
Analogues of the lead nucleus 4-quinazolones were synthesised and analysed to identify structural features, which are important for activity. Changes in structure are usually accompanied with changes in biological activity. The hetero substituted-4-quinazolones form an important class of pharmacophore having wide variety of pharmacological activity. 2or3 substituted-4-quinazolone derivatives are pharmaceutically important as analgesic & anti-inflammatory[1], anticonvulsant[2], antiparkinsonism[3], anthelmintic[4], anti-oxidant & antiamnesic[5] and antimicrobial agents[6]**.** The synthesis, experimental data and spectral data of the said derivatives had already been accepted for publication[7-9].
The hetero compounds synthesized include 2-pyridyl-4-quinazolone(NN), 2-pyrazinyl-4- quinazolone(NP), 2-Carbamazepinyl-4-quinazolone(NC), 6,8-Dibromo-2-pyridyl-4-quinazolone(NNB), 6,8-Dibromo-2-pyrazinyl-4-quinazolone(NPB) and 6,8-Dibromo-2-carbamazepinyl-4-quinazolone(NCB).

Structures of the synthesized compounds are as follows:



EXPERIMENTAL
Antibacterial Activity
All the six synthesized compounds were evaluated for their antimicrobial activity. The various organisms used in the *in-vitro* study include *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhi, Salmonella paratyphi A, Salmonella paratyphiB, Staphylococcus aureus, Coagulase negative staphylococci***.** MIC values of the test compound were determined by dilution technique. The bacteria were subcultured on Muller Hinton Agar Medium. DMF was used as negative control and ciprofloxacin 5µg as standard. Six different concentrations of test solutions (66.66µg/mL, 106.66µg/mL, 160.00µg/mL, 200µg/mL, 320µg/mL, 400µg/mL) were used to determine the MIC [10]**.** Zone of inhibition of the individual compound was studied by antibiotic disc diffusion techniqu[11]. Diameters of the zone of inhibition in mm for the test compounds at MIC were measured and compared with that produced by the standard drug. The results of the study are presented in Table 1 and 2.

Table 1: *Minimum inhibitory concentration of 2-Hetero substituted-4-quinazolones*

S. No	Name of the organism	Minimum inhibitory concentration (in µg/ml)					
		NN	NNB	NP	NPB	NC	NCB
1.	*Escherichia coli*	320	200	320	320	320	320
2.	*Klebsiella pneumoniae*	200	320	200	320	320	320
3.	*Pseudomonas aeruginosa*	160	160	160	160	320	160
4.	*Salmonella typhi*	320	200	320	320	320	320
5.	*Salmonella paratyphi A*	320	320	320	320	320	320
6.	*Salmonella paratyphi B*	200	320	160	160	160	160
7.	*Staphylococcus aureus*	400	320	400	320	400	400
8.	*Coagulase negative staphylococci*	400	400	400	320	400	400

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Table 2: *Antibiotic disc diffusion assay of 2-Hetero substituted-4-quinazolones*

S. No	Name of the organism	Zone of Inhibition (in mm)						
		Ciprofloxacin	NN	NNB	NP	NPB	NC	NCB
1.	*Escherichia coli*	23	32	38	14	26	26	38
2.	*Klebsiella pneumoniae*	24	11	21	19	22	26	12
3.	*Pseudomonas aeruginosa*	24	20	12	26	30	36	40
4.	*Salmonella typhi*	20	25	40	20	32	29	30
5.	*Salmonella paratyphi A*	24	20	12	21	29	34	41
6.	*Salmonella paratyphi B*	20	25	36	9	9	36	31
7.	*Staphylococcus aureus*	26	38	39	25	13	36	21
8.	*Coagulase negative staphylococci*	26	19	14	28	14	28	34

Antifungal Activity

The antifungal activities of tested compounds were studied against the fungi *Aspergillus niger, Microsporum gypseum, Rhizopus spp., and Aspergillus fumigatus.* at 66.66µg/mL, 133.33µg/mL, 166.66µg/mL concentrations. The fungi were subcultured in Sabaroud dextrose agar medium. The fungal susceptibility test was done by comparing the growth of pathogenic control and the test compound containing the said cultures[12]. The fungal study related data are given in Table 3.

Table 3: *Susceptibility tests of 2-hetero-4-quinazolone against pathogenic fungi*

Compound	Concentration (µg/ml)	*M.gypseum*	*A.fumigatus*	*A.niger*	*Rhizopus spp.*
Control		+	+	+	+
NN	66.66	+	+	+	+
	133.00	-	-	-	-
	166.66	-	-	-	-
NNB	66.66	+	+	+	+
	133.00	-	+	+	+
	166.66	-	-	-	-
NP	66.66	+	+	-	+
	133.00	-	-	-	-
	166.66	-	-	-	-
NPB	66.66	+	+	-	+
	133.00	-	-	-	-
	166.66	-	-	-	-
NC	66.66	+	+	+	+
	133.00	-	+	+	+
	166.66	-	-	-	-
NCB	66.66	+	+	+	+
	133.00	-	-	+	+
	166.66	-	-	-	-

Note: (+) indicates growth; (-) no growth

RESULTS AND DISCUSSION

New drugs are needed to fight the diseases for which no cure is available currently or as an alternative to existing drugs with improved safety and efficacy, the two important requirements of drugs and drug therapy. It was observed from the study that the minimal inhibitory concentration for the synthesised 2-hetero substituted-4-quinazolones varied between 160µg/ml to 320µg/ml for all the organisms except for *Staphylococcus aureus* and *Coagulase negative staphylococci* which was between 320 and 400 µg/ml. A comparative study on the zones of inhibition by the antibiotic disc diffusion technique indicated that all the compounds: NN, NNB, NP, NPB, NC and NCB had antibacterial effect on the microorganisms tested. The compound, NN and NNB were very effective against *Escherichia coli, Salmonella typhi, Salmonella paratyphi B, Staphylococcus aureus;* NP was very effective against *Pseudomonas aeruginosa and Coagulase negative staphylococci* whereas NPB was found to be very effective against *Escherichia coli Pseudomonas aeruginosa, Salmonella typhi, and Salmonella paratyphi A;* NC was very effective against all the organisms tested while NCB was effective against all the organisms except *Klebsiella pneumoniae* and *Staphylococcus aureus* .

Thus the synthesised compounds were found effective against most of the micro organisms tested including both gram positive and glass negative. The compounds NP, NPB, NC and NCB were found to be effective against *Pseudomonas aeruginosa.* The results showed that all the synthesised moieties had inhibitory effect against the tested pathogenic fungi. The compounds NN, NP and NPB were effective against *M. gypseum, A. fumigatus, A. niger and Rhizopus spp.* at a concentration of 133.33µg/ml whereas the compounds NNB, NC and NCB were effective at a concentration of 166µg/ml. The inhibitory concentration of all the synthesised compounds against *Candida albicans is* 320µg/ml.

CONCLUSION

The synthesised compounds were found to exhibit both antibacterial and antifungal activity making it an interesting field for further *in vivo* study. At present multi drug resistant strains of *Pseudomonas aeruginosa, are* posing threat and suitable antibacterial agents to combat the resistance has become the need of the day. The compounds NP, NPB, NC and NCB were found to be effective against *Pseudomonas aeruginosa.* This feature could be utilised to combat multi drug resistant *Pseudomonas aeruginosa* strains.

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