Synthesis of some Newer-4 (3H)-Quinazolinones as Antimicrobial agents

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Summary: Twenty eight quinazolinones, incorporating the moieties of N-/4- (aryloxy) / phenyl ureas, and 1-chloroacetyl-3-/ 4-(aryloxy) / phenyl ureas have been synthesised and evaluated for their antibacterial and antifungal properties. Some of them showed significant inhibition.

Quinazolinone derivatives have been reported to exhibit a diverse range of biological activites[1,2] including antibacterial[3] and antifungal[4]. Urea derivatives, too, have been known to possess significant antibacterial and antifungal properties[5,6]. It was therefore thought of interest to synthesis a series of compounds having both quinazolinones as well as substituted urea moieties and to evaluate them for their antibacterial and antifungal activities.

5-Bromo-3,5-dibromoanthranilic acids[7], arylisothiocyanates[8], 2-mercaptoquinazolinones[9-11] (I) and 4-aminodiphenyl ethers (II)[12] were prepared according to the reported methods. N- /4-(aryloxy)/ phenylureas /IIIa,b, table-1/ were synthesised by adopting the methods of Hoffmann[13], wherein reaction between potassium cyanate 4-aminodiphenylethers in acetic acid was carried out. 1-Chloroacetyl-3-/4-(aryloxy) phenylureas /IVa,b table/ were prepared according to the method of Jacobs[14], by the treatment of III(a,b) with chloroacetylchloride in dry benzene. Synthesis of the quinazolinones /Va-Vb'] was carried out by the condensation of IVa,b with 2-mercaptoquinazolinones in presence of ethanolic sodiumhydroxide solution. Structure of all the compounds prepared were supported by their characteristic IR bands at 1660 cm^{-1} (-N-C=O, quinazolonyl), 1640 cm^{-1} (C=O) and 1200 cm^{-1} (Ar-O-Ar). NMR of the compound Vc shows a prominent singlet at 7.55 τ which is due to a methylene group.

Antibacterial activity:

Antibacterial activity of the compounds Va-Vb' was determined by the Agar-plate dissusion technique[15]. Maximum inhibition by the compounds Vk, Vl, Vm, Vw, Wx, Vy, Vz & Vb was observed against *S. aureus*. Few compound viz. Vl, Vm, Vx & Vz, also inhibited *B. subtilis*. In general the quinazolinones were more active against gram positive bacterial than gram negative and also all the quinazolinones having 6 and 8-bormo substituent displayed significant antibacterial activity against gram positive strains.

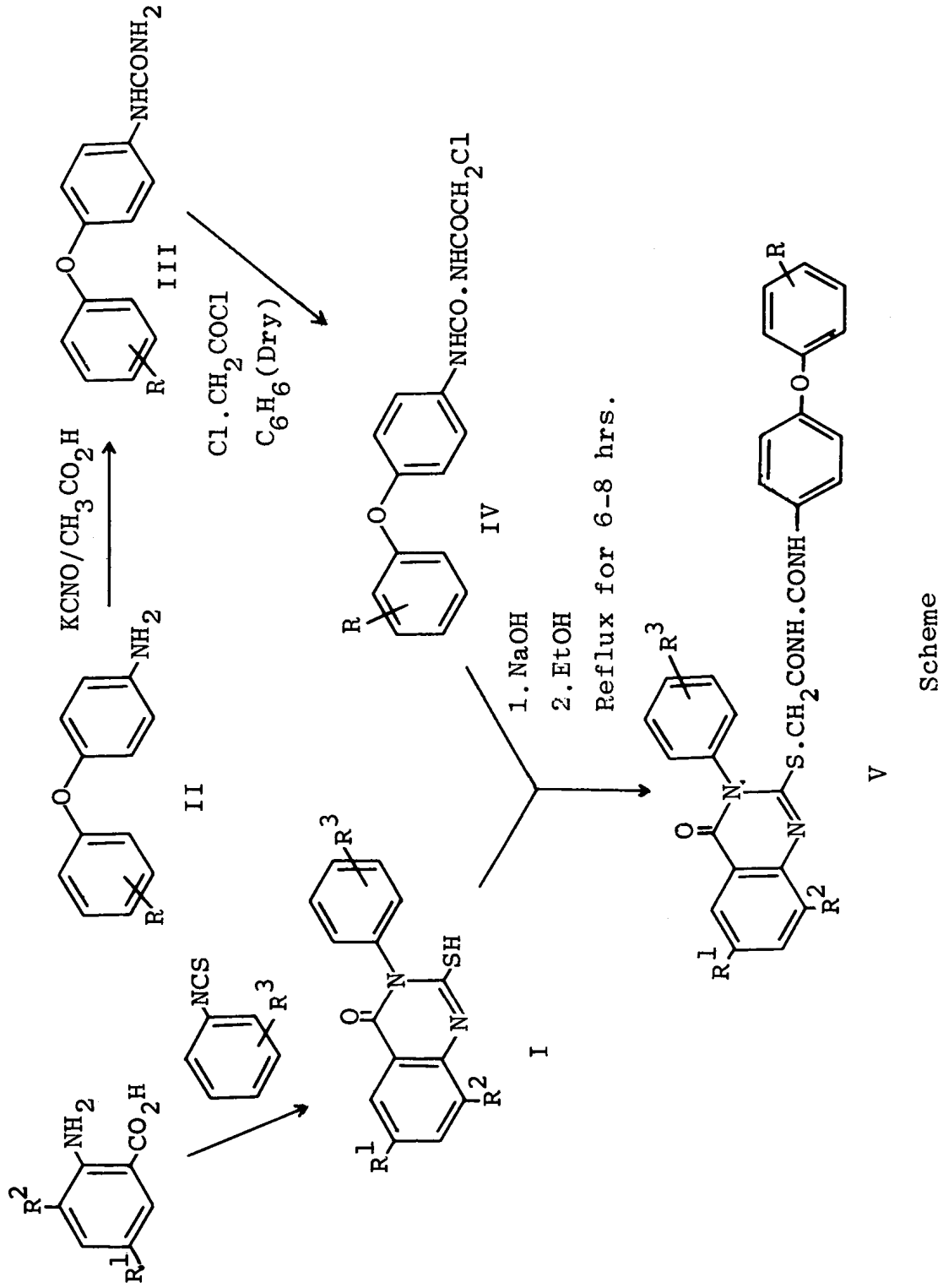
Antifungal activity:

Three compounds Vb, Vo and Vt were evaluated for their antifungal activity against *Aspergillus niger* and *Helminthosporium* spp. by the method of Horshfall[16]. Compounds Vb and Bt exhibited moderate inhibition against both the fungus while marginal inhibition was exhibited by Vo.

Table-1 Physical data of aryloxy phenyl ureas and chloroacetyl aryloxyphenyl ureas

Compound	R	m.p. °C	Molecular formula	% Analyses N	
				Calcd.	Found
IIIa	H	142-144	$C_{13}H_{12}N_2O_2$	12.28	12.57
IIIb	CH_3	154	$C_{14}H_{14}N_2O_2$	11.57	11.21
IVa	H	236-37	$C_{15}H_{13}N_2O_3Cl$	9.21	9.35
IVb	CH_3	165	$C_{16}H_{15}N_2O_3Cl$	8.80	8.53

Compounds were obtained in 80-85% yield.


KCNO/CH3CO2H
II
III
Cl.CH2COCl
C6H6(Dry)
IV
1. NaOH
2. EtOH
Reflux for 6-8 hrs.
I
V

Scheme

Table-2 Physical data of quinazolinones

Compound	R (b)	R^1	R^2	R^3	m.p. °C	Molecular formula	% Analyses N Calcd	Found
Va	H	H	H	H	297	$C_{29}H_{22}N_4O_4S$	10.72	10.23
Vb	H	H	H	4-Cl	305	$C_{29}H_{21}ClN_4O_4S$	10.06	9.57
Vc	H	H	H	4-CH_3	263	$C_{30}H_{24}N_4O_4S$	10.44	10.05
Vd	H	H	H	3-CH_3	283	$C_{30}H_{24}N_4O_4S$	10.44	10.21
Ve	H	H	H	4-OCH_3	232	$C_{30}H_{24}N_4O_5S$	10.14	9.82
Vf	H	Br	H	H	275	$C_{29}H_{21}BrN_4O_4S$	9.31	9.51
Vg	H	Br	H	4-Cl	170	$C_{29}H_{20}BrClN_4O_4S$	8.81	8.69
Vh	H	Br	H	4-CH_3	335	$C_{30}H_{23}BrN_4O_4S$	9.10	9.27
Vi	H	Br	H	3-CH_3	315	$C_{30}H_{23}BrN_4O_4S$	9.10	8.83
Vj	H	Br	H	4-OCH_3	321	$C_{30}H_{23}BrN_4O_5S$	8.87	8.51
Vk	H	Br	Br	H	240	$C_{29}H_{20}Br_2N_4O_4S$	8.23	8.45
Vl	H	Br	Br	4-CH_3	218	$C_{30}H_{22}Br_2N_4O_4s$	8.06	8.17
Vm	H	Br	Br	3-CH_3	205	$C_{30}H_{22}Br_2N_4O_4S$	8.06	8.39
Vn	CH_3	H	H	H	295	$C_{30}H_{24}N_4O_4S$	10.44	10.05
Vo	CH_3	H	H	4-Cl	315	$C_{30}H_{23}ClN_4O_4S$	9.81	9.51
Vp	CH_3	H	H	4-CH_3	260	$C_{31}H_{26}N_4O_4S$	10.18	10.62
Vq	CH_3	H	H	3-CH_3	198	$C_{31}H_{26}N_4O_4S$	10.18	10.25
Vr	CH_3	H	H	4-OCH_3	290	$C_{31}H_{26}N_4O_5S$	9.89	9.75
Vs	CH_3	Br	H	H	310	$C_{30}H_{23}BrN_4O_4S$	9.10	9.38
Vt	CH_3	Br	H	4.Cl	300	$C_{30}H_{22}BrClN_4O_4S$	8.62	8.31
Vu	CH_3	Br	H	4-CH_3	295	$C_{31}H_{25}BrN_4O_4S$	8.90	8.72
Vv	CH_3	Br	H	3-CH_3	230	$C_{31}H_{25}BrN_4O_4S$	8.90	8.85
Vw	CH_3	Br	H	4-OCH_3	313	$C_{31}H_{25}BrN_4O_5S$	8.68	8.96
Vx	CH_3	Br	Br	H	212	$C_{30}H_{22}Br_2N_4O_4S$	8.06	8.42
Vy	CH_3	Br	Br	4-Cl	197	$C_{30}H_{21}Br_2ClN_4O_4S$	7.48	7.41
Vz	CH_3	Br	Br	4-CH_3	210	$C_{31}H_{24}Br_2N_4O_4S$	7.69	7.61
Va′	CH_3	Br	Br	3-CH_3	221	$C_{31}H24Br_2N_4O_4S$	7.69	7.65
Vb′	CH_3	Br	Br	4-OCH_3	175	$C_{31}H_{24}Br_2N_4O_5S$	7.73	7.57

Compounds were obtained in 40-55% yield.

All the melting points were taken in open capillaries and are uncorrected. IR spectra were recorded on Perkin-Elmer Models 137 & 177 in KBr.

N-[4-(aryloxy)] phenyl ureas (IIIa,b-Table-1) - A solution of potassium cyanate (0.1 mole) in 100 ml. of water was added gradually to a suspension of II (0.04 mole) in dilute acetic acid (25 ml gl. acetic acid in 100 ml. water) with constant stirring at room temperature. The pasty solid obtained, after being stirred further for 1 hr and left as such for 4 hr at room temperature when diluted with water and cooled at 0° solidified. In was filtered, washed with water and recrystallised from aqueous ethanol to give IIIa & IIIb.

1-(Chloroacetyl-3 [4-(aryloxy)] phenyl ureas [IVa, b, table -1] A mixture of III (0.05 mole) and chloracetylchloride (0.055 mole) in dry benzene (100 ml) was refluxed on a water bath for 4 hr. The reaction mixture was then distilled under reduced pressure to remove benzene and the crude product, thus obtained, after washing several times with sodium bicarbonate solution to remove excess of chloroacetylchloride, was filtered, washed with water and recrystallised from ethanol to give IVa & IVb.

2-Mercaptoacetyl-N-(4-aryloxy) phenylureido-3-aryl -4-(3H) quinazolinones (Va-Vb′ Table 2). A solution of 2-mercapto-3-phenyl-3-phenyl-4 (3H)-quinazolinone

Table 3. Biological data of quinazolinones

Compound no.	Antibacterial activity against			
	S. aureus	*E. coli*	*B. subtilis*	*S.typhi*
Va	–	–	–	–
Vb	–	–	–	–
Vc	–	++	–	+
Vd	–	–	–	+
Ve	–	–	–	+
Vf	+++	–	–	+
Vg	–	+	–	++
Vh	–	–	–	–
Vi	–	–	–	–
Vj	–	+	–	–
Vk	++++	–	++	++
Vl	++++	–	++++	++
Vm	++++	–	++++	+++
Vn	–	–	–	–
Vo	–	–	–	–
Vp	–	–	–	+
Vq	++	–	–	+
Vr	–	+	–	++
Vs	–	–	–	–
Vt	–	–	–	–
Vu	–	–	++	–
Vv	–	–	–	–
Vw	++++	+	–	–
Vx	++++	–	++++	+
Vy	++++	+++	+++	++
Vz	++++	++	++++	++
Va′	+++	–	+++	++
Vb′	++++	+	++	++

– = no inhibition, + = inhibition zone 6-8 mm; ++ = inhibition zone 9-14 mm; +++ = inhibition zone 15-20 mm ++++ = inhibiton zone more than 20 mm.

(0.005 mole) and sodium hydroxide (0.005 mole) in methanol (23 ml) was refluxed on a steam bath for 30 minutes. To this was added N′-chloroacetyl-N-/4-(phenoxy) / phenyl urea and the reaction mixture, after being heated under reflux for 4 hr, was filtered, diluted with 25 ml water and then acidified with dil acetic acid (pH-7). The solid, thus obtained, was recrystallised from acetone to give Va-Vb′.

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References

1. Zaheer, S.H. Sidhu, G.S., Sattur, P.B., Seth, V.K., Mandreker, S.S. and Seth, V.G., Symposium on CNS drugs, CSIR, New Delhi, 1966, 170.
2. A.B. Sen, and S.K. Gupta, *J. Indian Chem. Soc.*, **39**, 369 (1962).
3. R.S. Varma, *J. Ind. Chem. Soc.*, **52**, 344 (1975).
4. R.C. Gupta, R. Nath, K. Shanker, K.P. Bhargava, and K. Kishor, *J. Ind. Chem. Soc.*, **56**, (2), 219 (1979).
5. O. Rohr, Swiss Pat. 503, 459; *Chem. Abstr.* **75**, 35485 (1971).
6. P. Giroult and G. Hogemang, *Ger. Offer.* **2**, 119, 728; *Chem. Abstr.*, **76**, 45981 f (1972).
7. A.S. Wheeler, and W.M. Oats, *J. Chem. Soc.*, 32, 770 (1910).
8. G.M. Dyson and H.J. George, *J. Chem. Soc.*, **105**, 1704 (1924).
9. G.S. Mewada, G.R. Dave, and G.C. Amin, *J. Sci. Ind. Research*, 20**B**, 299-300 (1961).
10. P.N. Bhargava and R. Lakhan, *Curr. Sci.* **36**, (21), 575 (1967).
11. P.N. Bhargava and M.R. Chaurasia, *J. Med. Chem.* **11**, (2), 404 (1968), 404.
12. Anup, Kapoor, Ph.D. Thesis 1978, Lucknow University.
13. A.W. Hoffmann, *Ann.* **70**, 129 (1849).
14. W.S. Jacobs, M. Heidelberger and I.P. Rofl, *J. Amer. Chem. Soc.*, **41**, 458 (1919).
15. R.S. Verma and S.A. Imam, *Indian J. Microbiol*, **13**, 45 (1973).
16. J.G. Horshfall, *Bot. Rev.*, **5**, 357 (1945).