

Synthesis and Antimicrobial Evaluation of Some New 4 (3H)-Oxoquinazolinyli-thiosemicarbazones

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2,6,8-Trisubstituted-3-thiosemicarbazido-4(3H)-quinazolones(3) and (4), synthesized by the condensation of 3-amino-2,6,8-trisubstituted-4 (3H)-quinazolones (1 and 2) with carbon disulphide and hydrazine hydrate in presence of liquid ammonia, were reacted with arylaldehydes such as 4-dimethylaminobenzaldehyde, 2-furaldehyde and 2-naphthaldehyde to afford corresponding thiosemicarbazones (5-10). All these compounds were characterized by their analytical and spectral data. Some of them were found to possess moderate antibacterial and antifungal properties on evaluation.

4 (3H)-Quinazolones are well known for their wide spectrum of biological and pharmacological properties^{1,2}. Several thiosemicarbazones on the other hand are reported to possess biological potential^{3,4}. Encouraged by these observations and in continuation of our investigations on the synthesis of some new 4 (3H)-quinazolones⁵ of medicinal importance, we report herein the synthesis and antimicrobial activities of arylaldehyde-4-[2,6,8-trisubstituted-4 (3H)-oxoquinazolin-3-yl]-3-thiosemi-carbazones. Synthesis of the title compounds was effected as outlined in Scheme-1.

3-Amino-2,6,8-trisubstituted-4 (3H)-quinazolones (1 and 2)^{6,7}, on reaction with carbon disulphide in liquid ammonia at 10° followed by treatment with hydrazine hydrate gave single product in each case which was purified by recrystallization from ethanol and characterized as 2,6,8-trisubstituted-3-thiosemicarbazido-4 (3H)-quinazolones (3 and 4). IR (KBr) spectrum of compound 3 showed peaks at 3320-3460 (NH-NH₂), 1665 (CO-N), 1602 (C=N), 1340 (C=S) and 722 (C-Br) cm⁻¹, PMR (DMSO-d₆) spectrum exhibited signals for the presence of Ar-CH₃, -NH₂, aromatic -H and 2XNH groups, respectively (Table-2) and the mass spectrum showed strong molecular ion peak at m/z 407 (23%).

* For Correspondence

Condensation of compounds 3 and 4 separately with different arylaldehydes such as, 4-dimethylaminobenzaldehyde, 2-furaldehyde and 2-naphthaldehyde in dry ethanol afforded crystalline solids in reasonably good yields which were purified by recrystallization from water-ethanol (1:1) mixture and characterized as respective arylaldehyde-4-[2,6,8-trisubstituted-4 (3H)-oxoquinazolin-3-yl]-3-thiosemicarbazones (5-10). IR (KBr) spectrum of compound 6 showed characteristic absorptions at 3435 (NH), 1685 (CO-N), 1610 (C=N), 1320 (C=S), 1240 (C-O-C) and 715 (C-Br)cm⁻¹. Its PMR (DMSO-d₆) spectrum displayed characteristic signals for Ar-CH₃, CH=N, Ar-H and 2XNH groups, respectively (Table-2), while its mass spectrum showed molecular ion peak of m/z 485 (15%).

Melting points of the compounds reported are uncorrected, IR spectra were recorded on Perkin-Elmer infracord-283 spectrophotometer, PMR spectra on Varian EM-360 60 MHz spectrophotometer using TMS as the internal reference and mass spectra on Jeol JMS-D 300 double beam spectrophotometer.

3-Amino-6, 8-dibromo-2-methyl and 3-amino-2-phenyl-4(3H)-quinazolones (1 and 2) were prepared by reported methods^{6,7}. 2,6,8-Trisubstituted-3-thiosemicarbazido-4 (3H)-quinazolones (3 and 4) were prepared by slowly adding to a mixture of 3-amino-2,6,8-

Table 1 - Physical and analytical parameters and antimicrobial activity of compounds 3-10

Compd	Substituents			M.P. (°C)	Antibacterial activity*				Antifungal activity*	
	X ¹ &X ²	R	R ¹		B.s	S.a	E.c	P.v	C.a	A.f
3	Br	CH ₃	-	140	9	-	11	6	8	-
4	H	C ₆ H ₅	-	191	12	12	10	11	6	4
5	Br	CH ₃	4-dimethyl-aminophenyl	176	11	14	-	-	-	-
6	Br	CH ₃	furan-2-yl	182	13	6	7	9	19	7
7	Br	CH ₃	naphthalene-2-yl	160	10	-	-	-	8	5
8	H	C ₆ H ₅	4-dimethyl-aminophenyl	184	14	9	7	-	-	-
9	H	C ₆ H ₅	furan-2-yl	143	16	12	10	11	15	-
10	H	C ₆ H ₅	naphthalene-2-yl	203	9	-	-	-	6	4

Yields were between 42-70%. Satisfactory CHN analyses were obtained for all the compounds. IR (KBr) spectra of all the compounds showed characteristic peaks in cm⁻¹ for NH (3290-3470), CO-N (1650-1685), C=N (1600-1620), C=S (1320-1340) and in addition compounds 3&5-7 exhibited characteristic absorptions for C-Br (710-730) while compounds 6&9 showed peaks for C-O-C (1230-1245).

*Zone of inhibition in mm; B.s = *B. subtilis*, S.a = *S. aureus*, E.c = *E. coli*, P.v = *P. vulgaris*, C.a = *C. albicans*, A.f = *A. flavus*.

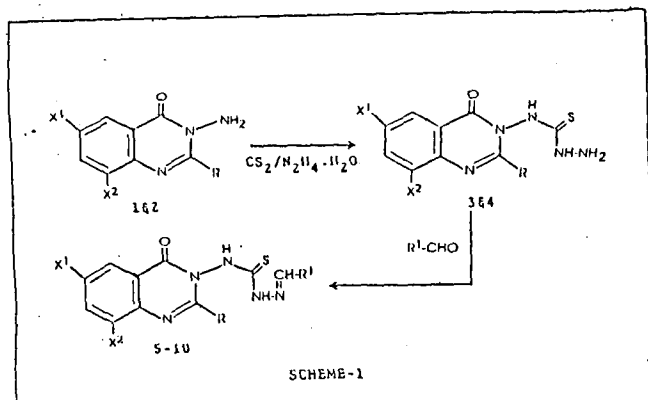
Table 2 - ¹H NMR data of representative compounds

Compd	¹ H NMR (DMSO-d ₆) in δ ppm
3	2.55 (s, 3H, Ar-CH ₃), 5.25 (bs, 2H, NH ₂ , D ₂ O exchangeable), 7.10-7.65 (m, 2H, Ar-H), 8.25 (br, 2H, 2XNH, D ₂ O exchangeable).
4	4.95 (bs, 2H, NH ₂ , D ₂ O exchangeable), 6.90-7.55 (m, 9H, Ar-H), 8.80 (br, 2H, 2XNH, D ₂ O exchangeable).
6	2.63 (s, 3H, Ar-CH ₃), 7.40-8.15 (m, 6H, Ar-H and CH=N), 8.55 (br, 2H, 2XNH, D ₂ O exchangeable).
8	3.18 [s, 6H, N (CH ₃) ₂], 7.15-8.10 (m, 14H, Ar-H and CH=N), 8.92 (br, 2H, 2XNH, D ₂ O exchangeable).

trisubstituted-4 (3H)-quinazolone (0.01 mol) in ethanol (30 ml), a solution of carbon disulphide (0.01 mol) in ammonium hydroxide (30 ml) over 15 minutes with stirring at 10° and the mixture was allowed to stand for 1 h. Then hydrazine hydrate (0.02 mol) was added with thorough stirring. The reaction mixture was then concentrated to half of its original volume and kept overnight. The resultant solid was filtered, washed with cold water and purified by recrystallization from ethanol. The physical and

analytical data of these compounds are presented in Table-1 and Table-2.

Arylaldehyde-4-(2,6,8-trisubstituted-4 (3H)-oxoquinazolin-3-yl)-3-thiosemicarbazones (5-10) were synthesized using the following procedure; An equimolar (0.01 mol) mixture of the corresponding thiosemicarbazide (3 or 4) and appropriate arylaldehyde was refluxed in ethanol (40 ml) for 3 h., cooled and kept overnight at room



temperature. Then the contents were poured onto crushed ice and the product thus resulted was filtered, washed with cold water, dried and purified by recrystallization from water-ethanol (1:1) mixture. Pertinent data of the compounds synthesized adopting this procedure are given in Table-1 and Table-2.

Antibacterial activity of the compounds (in DMF) was determined by Agar cup-plate method⁹ at a concentration of 100 µg/ml against two gram-positive bacteria, *Bacillus subtilis* and *Staphylococcus aureus* and two gram-negative bacteria, *Escherichia coli* and *Proteus vulgaris* employing ampicillin (100 µg/ml) as a reference standard. Antifungal activity was also determined in similar way against *Candida albicans* and *Aspergillus flavus* using amphotericin (100 units/ml) as the standard. The results are presented in Table-1.

It was found that the antibacterial activities of the test compounds were not comparable to that of standard, ampicillin which was effective against *B-subtilis*, *S. aureus*, *E. coli* and *P. vulgaris* with zones of inhibition 25, 27, 29, 30 mm, respectively. However, among the two thiosemicarbazides, the compounds with phenyl substitution showed better activity against all the bacteria em-

ployed. Among the six thiosemicarbazones (5-10), compound 9 exhibited appreciable activity against all the bacteria closely followed by compound 6. Interestingly, all of these compounds could exhibit some degree of inhibition against *B. subtilis*.

Results obtained with antifungal screening revealed that only compound 6 exhibited better antifungal activity while the rest of the compounds produced only moderate to mild antifungal activity. However, none of these compounds could exhibit comparable activity to that of the standard, amphotericin which was effective against *C. albicans* and *A. flavus* with zones of inhibition 28 and 21 mm, respectively.

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