

# Synthesis and Antimicrobial Screening of Pyrazolo-3-Aryl Quinazolin-4(3H)ones

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Deshmukh, *et al.*: Antimicrobial Screening of Quinazolin-4(3H)ones

2-thio-3-aryl quinazolin-4(3H)one (1) was synthesized by reacting anthranilic acid with thiocarbamate salts of substituted aniline and carbon disulphide, which on reflux with excess of hydrazine hydrate to form 2-hydrazino quinazolin-4(3H)one derivatives (2). The reaction of (2) with variously substituted aryl aldehydes gave the corresponding hydrazones (3). Further, the cyclization of compound (3) in acetic anhydride gave tricyclic pyrazoloquinazolinones (4). All newly synthesized compounds have been tested for their antibacterial activity against gram +ve bacteria *B. subtilis*, *S. aureus* and gram -ve bacteria *E. coli*, *P. vulgaris*. The species used for antifungal

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activity are *Aspergillus niger* and *Phytophthora*. Introduction of -OCH<sub>3</sub>, -OH and -Cl groups to the heterocyclic framework enhanced antibacterial and antifungal activities.

**Key words:** Acetic anhydride, hydrazino, hydrazones, pyrazolo-quinazolinones, quinazolinones

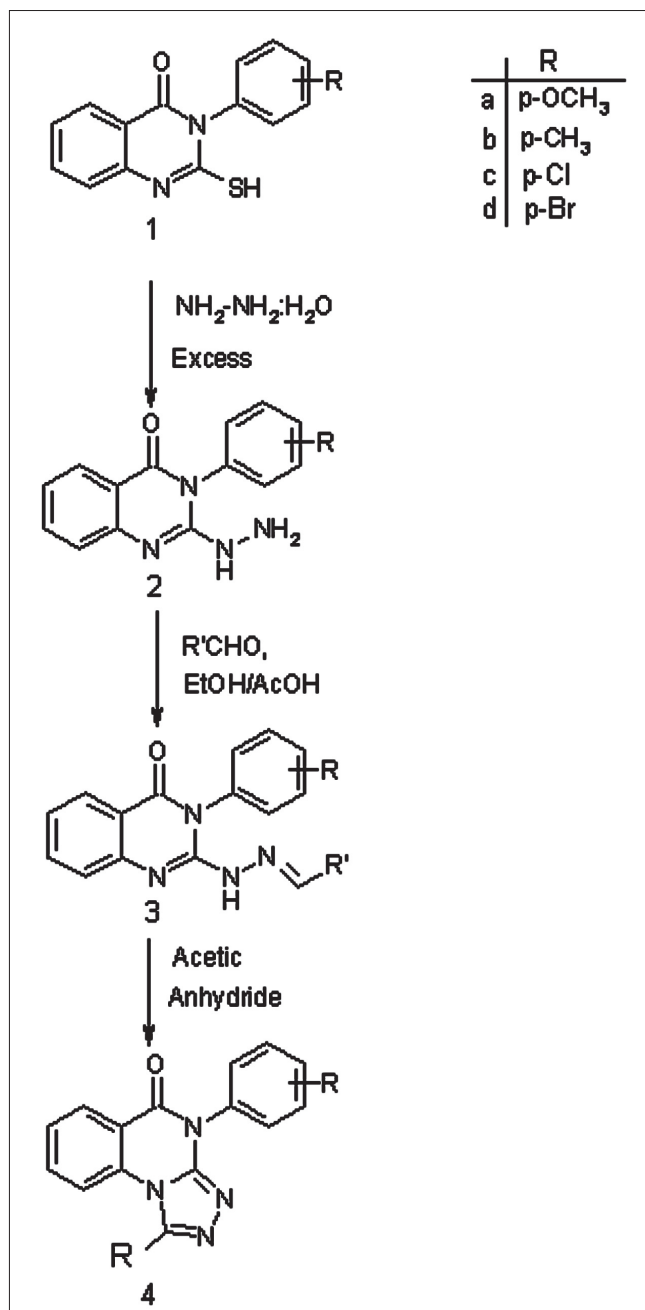
Derivatives quinazolines are of special importance because of their versatile biological activities<sup>[1,2]</sup>, especially antihistaminic<sup>[3]</sup>, antiinflammatory<sup>[4]</sup>, antihypertensive<sup>[5]</sup>, antiHIV<sup>[6]</sup>, antifungal<sup>[6,7]</sup>, antimicrobial<sup>[8,9]</sup>, anticonvulsant<sup>[10]</sup>, antithrombotic<sup>[11]</sup>, antitubercular<sup>[12,13]</sup>, antitumor<sup>[14]</sup>, analgesic<sup>[15]</sup>, antibacterial<sup>[6,15]</sup> and insecticidal<sup>[16]</sup>. In this paper, a new route for the synthesis of pyrazolo quinazolinones is reported.

The strategy employed for the synthesis of desired compounds involved the sequential treatment of anthranilic acid with thiocarbamate salts of substituted aniline and carbon disulphide to give substituted 2-thio-3-aryl quinazol-4(3H)ones (1). The appearance of broad band at 3330-3110 cm<sup>-1</sup> in IR spectrum and a singlet displayed at  $\delta$ , 10-13 ppm in the PMR spectrum due to -SH supports their formation. Compound (1) were refluxed with excess hydrazine hydrate to form 2-hydrazino derivative (2), the formation which has been explained by the appearance of IR band at 3390-3100 cm<sup>-1</sup> due to -NHNH<sub>2</sub> and disappearance of signal observed at  $\delta$ , 10-13 ppm due to -SH and the appearance of two additional singlet between  $\delta$ , 9-11 and  $\delta$ , 2-7 ppm due to -NH and -NH<sub>2</sub> protons, respectively in their PMR spectra. The condensation of (2) with variously substituted aryl aldehydes gave the corresponding hydrazones (3). The appearance -NH and =CH protons at  $\delta$ , 5.1 and  $\delta$ , 8.2 in PMR spectrum and also disappearance of -NH<sub>2</sub> band 3390-3200 cm<sup>-1</sup> in IR spectrum indicated their formation. Further, the cyclization of compound (3) in acetic anhydride gave tricyclic triazolo quinazolones (4). The formation of these compounds have been established by the disappearance of the PMR singlet due to -NH and =CH displayed at  $\delta$ , 5.1 and  $\delta$ , 8.2, respectively in the PMR spectrum of (3). (Scheme 1)

All chemicals used were of AR grade and are used without further purification. Melting points were determined by open capillary method and are uncorrected. <sup>1</sup>H NMR spectra in DMSO-d<sub>6</sub> were scanned on a Bruker A-300 F-NMR spectrometer. IR spectra were recorded on a Perkin-Elmer 783 (FTIR) spectrophotometer. Purity of the products in addition

to the elemental analysis was checked by TLC.

The starting compound (1) was prepared by reported method<sup>[17]</sup>. 2-Hydrazino 3-p-methoxy phenyl quinazolin-4(3H)one (2a) was synthesized as follows;



Scheme 1: Synthetic route for synthesis of Quinazolin-4(3H)One derivatives

TABLE 1: CHARACTERIZATION DATA OF COMPOUNDS 2, 3 AND 4

S. No.	R Groups	M.P.(o)	Yield (%)	Mol. Formula	% C		% H		% N	
					Cal.	Found	Cal.	Found	Cal.	Found
2a	p-OCH <sub>3</sub>	205	76	C <sub>15</sub> H <sub>14</sub> O <sub>2</sub> N <sub>4</sub>	63.82	63.76	5.00	5.10	19.85	19.90
2b	p-CH <sub>3</sub>	215	86	C <sub>15</sub> H <sub>14</sub> ON <sub>4</sub>	67.65	67.59	5.30	5.38	21.04	21.10
2c	p-Cl	218	82	C <sub>14</sub> H <sub>11</sub> ON <sub>4</sub> Cl	58.65	58.58	3.87	4.95	19.54	19.47
2d	p-Br	196	83	C <sub>14</sub> H <sub>11</sub> ON <sub>4</sub> Br	50.78	50.62	3.35	3.40	16.92	16.86
	R <sup>1</sup> groups									
4 <sub>a-1</sub>	p-OCH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	230	83	C <sub>23</sub> H <sub>18</sub> O <sub>3</sub> N <sub>4</sub>	69.34	69.45	4.55	4.41	14.06	13.86
4 <sub>a-2</sub>	o-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	193	78	C <sub>22</sub> H <sub>15</sub> O <sub>4</sub> N <sub>5</sub>	63.92	63.85	3.66	3.70	16.94	16.82
4 <sub>a-3</sub>	3,4,5(OCH <sub>3</sub> ) <sub>3</sub> -C <sub>6</sub> H <sub>2</sub>	211	68	C <sub>25</sub> H <sub>22</sub> O <sub>5</sub> N <sub>4</sub>	65.49	67.00	4.84	4.89	12.22	12.18
4 <sub>a-4</sub>	o-OHC <sub>6</sub> H <sub>4</sub>	216	77	C <sub>22</sub> H <sub>16</sub> O <sub>3</sub> N <sub>4</sub>	68.74	68.80	4.20	4.16	14.58	14.49
4 <sub>a-5</sub>	p-OHC <sub>6</sub> H <sub>4</sub>	239	71	C <sub>22</sub> H <sub>16</sub> O <sub>3</sub> N <sub>4</sub>	68.74	68.65	4.20	4.18	14.58	14.50
4 <sub>a-6</sub>	o-ClC <sub>6</sub> H <sub>4</sub>	241	70	C <sub>22</sub> H <sub>15</sub> O <sub>2</sub> N <sub>4</sub> Cl	65.60	65.60	3.75	3.68	13.91	14.00
4 <sub>a-7</sub>	p-ClC <sub>6</sub> H <sub>4</sub>	235	72	C <sub>22</sub> H <sub>15</sub> ON <sub>4</sub> Cl	65.60	65.58	3.75	3.81	13.91	13.86
4 <sub>a-8</sub>	p-OH,m-OCH <sub>3</sub> -C <sub>6</sub> H <sub>3</sub>	243	78	C <sub>23</sub> H <sub>18</sub> O <sub>4</sub> N <sub>4</sub>	66.66	66.70	4.38	4.40	13.52	13.60
4 <sub>b-1</sub>	p-OCH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	198	86	C <sub>23</sub> H <sub>18</sub> O <sub>2</sub> N <sub>4</sub>	72.24	72.30	4.74	4.81	14.65	14.72
4 <sub>b-2</sub>	o-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	175	81	C <sub>22</sub> H <sub>15</sub> O <sub>3</sub> N <sub>5</sub>	66.49	66.40	3.80	3.75	17.62	17.70
4 <sub>b-3</sub>	3,4,5(OCH <sub>3</sub> ) <sub>3</sub> -C <sub>6</sub> H <sub>2</sub>	203	78	C <sub>25</sub> H <sub>22</sub> O <sub>4</sub> N <sub>4</sub>	67.86	67.70	5.01	5.11	12.66	12.73
4 <sub>b-4</sub>	o-OHC <sub>6</sub> H <sub>4</sub>	218	68	C <sub>22</sub> H <sub>16</sub> O <sub>2</sub> N <sub>4</sub>	71.73	71.62	4.38	4.29	15.21	15.30
4 <sub>b-5</sub>	p-OHC <sub>6</sub> H <sub>4</sub>	221	62	C <sub>22</sub> H <sub>16</sub> O <sub>2</sub> N <sub>4</sub>	71.73	71.66	4.38	4.30	15.21	15.16
4 <sub>b-6</sub>	o-ClC <sub>6</sub> H <sub>4</sub>	216	72	C <sub>22</sub> H <sub>15</sub> ON <sub>4</sub> Cl	68.31	68.40	3.91	3.83	14.48	14.53
4 <sub>b-7</sub>	p-ClC <sub>6</sub> H <sub>4</sub>	235	72	C <sub>22</sub> H <sub>15</sub> ON <sub>4</sub> Cl	68.31	68.39	3.91	4.00	14.48	14.51
4 <sub>b-8</sub>	p-OH,m-OCH <sub>3</sub> -C <sub>6</sub> H <sub>3</sub>	235	81	C <sub>23</sub> H <sub>18</sub> O <sub>3</sub> N <sub>4</sub>	69.34	69.28	4.55	4.49	14.06	14.10
4 <sub>c-1</sub>	p-OCH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	246	86	C <sub>22</sub> H <sub>15</sub> O <sub>2</sub> N <sub>4</sub> Cl	65.60	64.30	3.75	3.81	13.91	13.84
4 <sub>c-2</sub>	o-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	198	82	C <sub>21</sub> H <sub>12</sub> O <sub>3</sub> N <sub>5</sub> Cl	60.37	60.45	2.89	2.81	16.76	16.68
4 <sub>c-3</sub>	3,4,5(OCH <sub>3</sub> ) <sub>3</sub> -C <sub>6</sub> H <sub>2</sub>	261	79	C <sub>24</sub> H <sub>24</sub> O <sub>4</sub> N <sub>4</sub> Cl	62.27	62.32	4.14	4.21	12.10	12.05
4 <sub>c-4</sub>	o-OHC <sub>6</sub> H <sub>4</sub>	232	71	C <sub>21</sub> H <sub>13</sub> O <sub>2</sub> N <sub>4</sub> Cl	64.87	64.91	3.37	3.42	14.41	14.35
4 <sub>c-5</sub>	p-OHC <sub>6</sub> H <sub>4</sub>	222	69	C <sub>21</sub> H <sub>13</sub> O <sub>2</sub> N <sub>4</sub> Cl	64.87	65.00	3.37	3.40	14.41	14.50
4 <sub>c-6</sub>	o-ClC <sub>6</sub> H <sub>4</sub>	248	65	C <sub>21</sub> H <sub>12</sub> ON <sub>4</sub> Cl <sub>2</sub>	61.93	61.85	2.97	3.05	13.76	13.81
4 <sub>c-7</sub>	p-ClC <sub>6</sub> H <sub>4</sub>	242	80	C <sub>21</sub> H <sub>12</sub> ON <sub>4</sub> Cl <sub>2</sub>	61.93	61.86	2.97	3.10	13.76	13.82
4 <sub>c-8</sub>	p-OH,m-OCH <sub>3</sub> -C <sub>6</sub> H <sub>3</sub>	243	65	C <sub>22</sub> H <sub>15</sub> O <sub>3</sub> N <sub>4</sub> Cl	63.09	63.13	3.61	3.53	13.38	13.31
4 <sub>d-1</sub>	p-OCH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	246	86	C <sub>21</sub> H <sub>15</sub> O <sub>2</sub> N <sub>4</sub> Br	59.08	59.10	3.38	3.42	12.53	12.60
4 <sub>d-2</sub>	o-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	198	82	C <sub>21</sub> H <sub>12</sub> O <sub>3</sub> N <sub>5</sub> Br	54.56	54.50	2.62	2.56	15.15	15.10
4 <sub>d-3</sub>	3,4,5(OCH <sub>3</sub> ) <sub>3</sub> -C <sub>6</sub> H <sub>2</sub>	261	79	C <sub>24</sub> H <sub>19</sub> O <sub>4</sub> N <sub>4</sub> Br	56.82	56.89	3.77	3.68	11.04	11.12
4 <sub>d-4</sub>	o-OHC <sub>6</sub> H <sub>4</sub>	232	71	C <sub>21</sub> H <sub>13</sub> O <sub>2</sub> N <sub>4</sub> Br	58.22	58.16	3.02	3.11	12.93	12.84
4 <sub>d-5</sub>	p-OHC <sub>6</sub> H <sub>4</sub>	222	69	C <sub>21</sub> H <sub>13</sub> O <sub>2</sub> N <sub>4</sub> Br	58.22	58.31	3.02	3.12	12.93	12.86
4 <sub>d-6</sub>	o-ClC <sub>6</sub> H <sub>4</sub>	248	65	C <sub>21</sub> H <sub>12</sub> ON <sub>4</sub> ClBr	55.84	55.91	2.68	2.61	12.40	12.32
4 <sub>d-7</sub>	p-ClC <sub>6</sub> H <sub>4</sub>	218	73	C <sub>21</sub> H <sub>12</sub> ON <sub>4</sub> ClBr	55.84	55.80	2.68	2.73	12.40	12.46
4 <sub>d-8</sub>	p-OH,m-OCH <sub>3</sub> -C <sub>6</sub> H <sub>3</sub>	226	78	C <sub>23</sub> H <sub>18</sub> O <sub>4</sub> N <sub>4</sub> Br	57.04	57.12	3.26	3.20	12.09	12.11

The compound (1a) (5.0 g, 0.018 mole) was refluxed with excess of hydrazine hydrate (15 ml) with constant stirring at 100°C for about 1 ½ h, cooled and the solid obtained was filtered and recrystallized from ethanol to furnish (2a), IR(KBr); 3386-3328 (-HNNH<sub>2</sub>), 1664 (cyclic amido C=O) cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ, 3.81(3H,s,Ar-OCH<sub>3</sub>), 6.25(2H,s,-NH<sub>2</sub>), 6.9-7.8(8H,m, Ar-H), 10.9(1H,s, br, -NH).

2-(p-Methoxybenzylidene)hydrazine-3-(p-

methoxyphenyl)quinazolin-4-(3H)one (3a<sub>-1</sub>) was synthesized using following procedure; the mixture of compound (2a) (0.2 g, 0.0007 mole) and p-methoxy benzaldehyde (0.1 g, 0.0007 mole) in ethanol (10 ml) to which two drops of acetic acid were added and the reaction mixture heated on oil bath for 5 h. The separated solid was filtered under vacuum and further recrystallized from DMF, IR(KBr); 3100-3350(-NH), 1665 cm<sup>-1</sup> (cyclic amido >C=O), 1600 cm<sup>-1</sup> (-C=N); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): 3.82 (3H, s, Ar-OCH<sub>3</sub>), 3.84 (3H, s,

TABLE 2: ANTIMICROBIAL SCREENING DATA OF THE DERIVATIVES OF 4

Comp	Bacteria			Fungi		
	<i>E. coli</i>	<i>p. vulgaris</i>	<i>B. subtilis</i>	<i>S. aureus</i>	<i>Aspergillus niger</i>	<i>Phytophthora spp.</i>
4 <sub>a-1</sub>	17	16	12	17	17	15
4 <sub>a-2</sub>	5	7	15	14	5	11
4 <sub>a-3</sub>	20	14	19	14	16	12
4 <sub>a-4</sub>	7	10	7	4	8	1
4 <sub>a-5</sub>	14	5	9	11	13	8
4 <sub>a-6</sub>	16	20	17	15	17	20
4 <sub>a-7</sub>	18	18	17	12	19	18
4 <sub>a-8</sub>	12	15	11	12	12	14
4 <sub>b-1</sub>	20	19	11	16	19	12
4 <sub>b-2</sub>	4	8	9	7	4	8
4 <sub>b-3</sub>	25	20	16	17	20	16
4 <sub>b-4</sub>	9	4	14	4	9	7
4 <sub>b-5</sub>	5	9	12	8	7	9
4 <sub>b-6</sub>	17	11	16	11	19	19
4 <sub>b-7</sub>	16	20	16	13	18	11
4 <sub>b-8</sub>	11	12	14	11	12	12
4 <sub>c-1</sub>	16	20	13	16	20	15
4 <sub>c-2</sub>	9	4	8	4	8	10
4 <sub>c-3</sub>	20	18	17	20	18	20
4 <sub>c-4</sub>	8	6	12	6	8	5
4 <sub>c-5</sub>	5	5	11	7	6	8
4 <sub>c-6</sub>	22	19	18	17	23	16
4 <sub>c-7</sub>	19	22	17	16	24	17
4 <sub>c-8</sub>	11	11	7	12	9	12
4 <sub>d-1</sub>	20	20	11	19	18	11
4 <sub>d-2</sub>	14	14	6	8	12	7
4 <sub>d-3</sub>	22	24	18	25	20	18
4 <sub>d-4</sub>	7	8	11	5	7	7
4 <sub>d-5</sub>	12	12	14	9	13	10
4 <sub>d-6</sub>	25	23	20	16	24	20
4 <sub>d-7</sub>	20	21	25	20	22	24
4 <sub>d-8</sub>	15	12	14	11	15	11

Diameter of zone of inhibition in millimeters

another Ar-OCH<sub>3</sub>), 6.00 (1H, s, br, -NH), 8.21 (1H, s, =CH), 6.8-8.1 (12H, m, Ar-H), 8.20 (=CH) ppm.

3,5'-(p-Dimethoxyphenyl) pyrazolo-[3',4'-a]quinazolin-4(3H)one (4<sub>a-1</sub>) was synthesized as follows; To a solution of compound (3<sub>a-1</sub>) (0.1 g, 0.00025 mole) in acetic anhydride (10 ml) was refluxed for about 2 h then poured in ice-cold water and separated solid was filtered, recrystallized from DMF to get desired tricyclic pyrazolo quinazolinones, IR (KBr): 1665 cm<sup>-1</sup> (cyclic amido > C=O) and 1620 cm<sup>-1</sup> (C=N); <sup>1</sup>H NMR: (DMSO-d<sub>6</sub>): 3.79 (3H, s, Ar-OCH<sub>3</sub>) 3.95(3H, s, another Ar-OCH<sub>3</sub>), 6.8-8.2(12H, m, Ar-H) ppm. (Table 1)

The antimicrobial screening of synthesized compounds was carried out by paper disc diffusion method<sup>[18]</sup>

at 100 ppm against Gram +ve bacteria *B. subtilis*, *S. aureus* and Gram -ve bacteria like *E. coli*, *P. vulgaris*. The antifungal activity of the compounds was assayed using fungal species *Aspergillus niger* and *Phytophthora*. Standard antibacterial streptomycin and antifungal griseofulvin were also screened under similar condition for comparison. (Table 2)

The result indicated that some compounds exhibit good antimicrobial activity against the above mentioned bacterial and fungal species, while some compounds have moderate antimicrobial activity against both Gram +ve and Gram -ve bacterial and fungal species. It was abserved that introduction of -OCH<sub>3</sub> and -Cl groups to the heterocyclic frame work enhanced antibacterial and antifungal activities.

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