

## Exploration of some new Mannich Bases of 6, 8-disubstituted 2-Phenyl-3-Aminoquinazolin-4(3H)-Ones Containing Isatin As an Antimicrobial agents

Dr. Mrityunjay Banerjee<sup>1\*</sup> and Dr. Susant Kumar Sahu<sup>2</sup>

<sup>1</sup>Dept. of Pharmaceutical Chemistry, Institute of Pharmacy & Technology, Salipur, Cuttack, Odisha-754202, India.

<sup>2</sup>University Dept. of Pharmaceutical Science, Utkal University, Vani Vihar, Bhubaneswar, Odisha-751003, India.

### Abstract

A series of novel 3-{(1'-aryl/alkylaminomethyl-2'-oxo-1',2'-dihydroindole-3'-ylidene)amino}-6,8-dibromo-2-phenylquinazolin-4-(3H)-ones (**4a<sub>1-6</sub>**) were synthesized and tested for their antimicrobial activities. Compound **4a<sub>6</sub>** was found to be promising antimicrobial agent. The purity of the compounds was checked by TLC and elemental analyses. Both analytical and spectral data (<sup>1</sup>H NMR, IR and MS) of all the synthesized compounds were in full agreement with the proposed structures.

**Key words:** Quinazolinones, Isatin, Mannich bases, antimicrobial activity

### Introduction

Quinazolin-4(3H)-ones and Schiff's bases of quinazolin-4(3H)-ones are known to exhibit analgesic, anti-inflammatory, antimicrobial activity and anthelmintic activities<sup>1-5</sup>. Certain Schiff's and Mannich bases of isatin have been reported to possess significant analgesic, antipyretic, anti-inflammatory and antimicrobial activities.<sup>6-11</sup> In view of the pharmacological profiles of these two chemical moieties as described above, we considered it interesting to combine two chemically different but pharmacologically compatible molecules in one frame with the aim of obtaining some novel heterocyclic systems with potentially enhanced biological properties. In the present investigation a new series of novel 3-{(1'-aryl/alkylaminomethyl-2'-oxo-1',2'-dihydroindole-3'-ylidene)amino}-6,8-dibromo-2-phenylquinazolin-4-(3H)-ones (**4a<sub>1-6</sub>**) were synthesized as per **Scheme 1** and evaluated for their antimicrobial activities.

### Results and Discussion

#### Chemical synthesis

3-Amino-6,8-dibromo-2-phenylquinazolin-4(3H)-one **2** was prepared according to the literature procedures<sup>12,13</sup> Compound **2** was condensed with isatin in ethanol to afford the corresponding Schiff's bases **3** in 70 % yields (**Table 1**). The N-Mannich bases of the above Schiff's base were synthesized by condensing acidic imino group of isatin with formaldehyde and various secondary amines in 51-74 % yields. All the synthesized compounds were characterized by their elemental analysis, FT-IR, <sup>1</sup>H NMR, and Mass spectroscopy. For example, the IR spectrum of **3** shows an absorption band at 3473 cm<sup>-1</sup> corresponding to the stretching vibration of NH group, while bands at 1671 and 1730 cm<sup>-1</sup> correspond to the characteristic keto group of quinazolinone and isatin, respectively. The IR spectrum of **4a<sub>1</sub>** shows an absorption band at 2816 and 1313 cm<sup>-1</sup> corresponding to the methylene and dialkylaminomethyl groups, respectively present at 1' position of isatin moiety.

The <sup>1</sup>H NMR of **3a** showed the absence of the signal for the NH<sub>2</sub> group, while the isatin imino NH signal appeared as a singlet at 8.55 ppm. Diagnostically important signals in the

nuclear magnetic resonance ( $^1\text{H}$  NMR) spectrum of **4a<sub>1</sub>** were two singlet at 2.52 and 4.41 ppm attributed to the  $\text{N}(\text{CH}_3)_2$  and  $\text{CH}_2$  groups, respectively. Aromatic protons of quinazolinone and isatin moieties all appeared at the expected chemical shifts. The structures of **3** and **4a<sub>1</sub>** were also confirmed by its mass spectrum that shows molecular ion peaks ( $\text{M}^+$ ) at  $m/z$  524 and  $m/z$  581.

### Antimicrobial activity

In the present study, antimicrobial activities of 6 different newly synthesized Schiff's bases were evaluated<sup>14,15</sup> against four human pathogens such as *Staphylococcus aureus*, *Staphylococcus faecalis*, *Escherichia coli* and *Salmonella typhi*. Antifungal activities of these compounds were also tested against *Candida albicans* and *Aspergillus niger* in an *in vitro* condition. The biological screening results of Schiff's bases of quinazoline-4(3H)-ones with 10% DMSO as control for antimicrobial inhibition are presented in **Table 2**. The results obtained clearly indicate that the series of Schiff's bases of quinazoline -4(3H)-ones discussed here have varying degree of antimicrobial activities. Compounds **4a<sub>6</sub>** containing morpholinomethyl group at 1' position of isatin moiety exhibited significant activity against all the tested microorganisms. Compound **4a<sub>5</sub>** exhibited moderate antimicrobial activities against all the pathogens except *Salmonella typhi*. *Staphylococcus faecalis* was found to be sensitive to all the test compounds except **4a<sub>3</sub>** and **4a<sub>4</sub>**.

Among the newer derivatives, compound **4a<sub>6</sub>** showed a promising activity in the entire test. It is conceivable that these derivatives showing antimicrobial can be further modified to achieve potent chemotherapeutic agents.

### Experimental

Melting points were determined on a Tempstar apparatus and are uncorrected. Infrared spectra were recorded on a Jasco (410) FT-infrared spectrophotometer, measured as KBr disks.  $^1\text{H}$  NMR were recorded on a Bruker DPX-300 MHz spectrometer in deuteriochloroform with trimethylsilane as internal standard (chemical shift in  $\delta$  ppm). The mass spectral data were obtained with a Perkin-Elmer Hitachi RMU-6L MS-30 spectrometer at 70 eV and a 90 °C inlet temperature. Purity of all the compounds was checked on silica gel plates and spots were located in iodine vapours. Elemental analysis was performed on EURO EA (Italy) analyzer and the results were within  $\pm 0.4\%$  of calculated values. Physical data of the synthesized compounds are presented in **Table 1**

#### General method for the preparation of Schiff's bases (**3**).

To a solution of isatin (0.005 mol) in ethanol (50 mL) was added the appropriate 3-amino-6,8-dibromo-2-phenylquinazolin-4(3H)-one **2** (0.005 mol) and a few drops of acetic acid. The reaction mixture was refluxed for 17 hrs. on a water bath and then allowed to cool. The separated solid was filtered, washed with aqueous ethanol, and recrystallized from benzene.

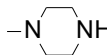
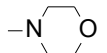
#### 3-**{(2'-Oxo-1', 2'-dihydroindole-3'-ylidene)amino}**-2-phenylquinazolin-4-(3H)-one (**3**).

IR (KBr): 3471 (NH), 3076(Ar-CH), 1730 (C=O), 1670 (C=O), 1606 (C=N), 1575 (C=N), 1302 (CN); MS: ( $m/z$ ) 524( $\text{M}^+$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  : 8.55 (s, 1H, NH), 8.06 (m, 9H, ArH), 6.48-7.72 (m, 4H, ArH);

#### General method for the preparation of Mannich bases (**4a<sub>1-6</sub>**)

To a mixture of **3** (0.005 mol) and 37 % formalin (1mL) in ethanol (20 mL) was added dropwise appropriate secondary amines (0.005 mol) with stirring over 15 min. The stirring was continued for 1hr. at room temperature and the reaction mixture then warmed for 15 min. on a water bath. The mixture was poured into ice-cold water and stored in a refrigerator. The crude product, which separated, was washed with water, dried and recrystallized from ethanol.

**Table 1 Physical data of synthesized compounds 3 and 4a<sub>1-6</sub>**

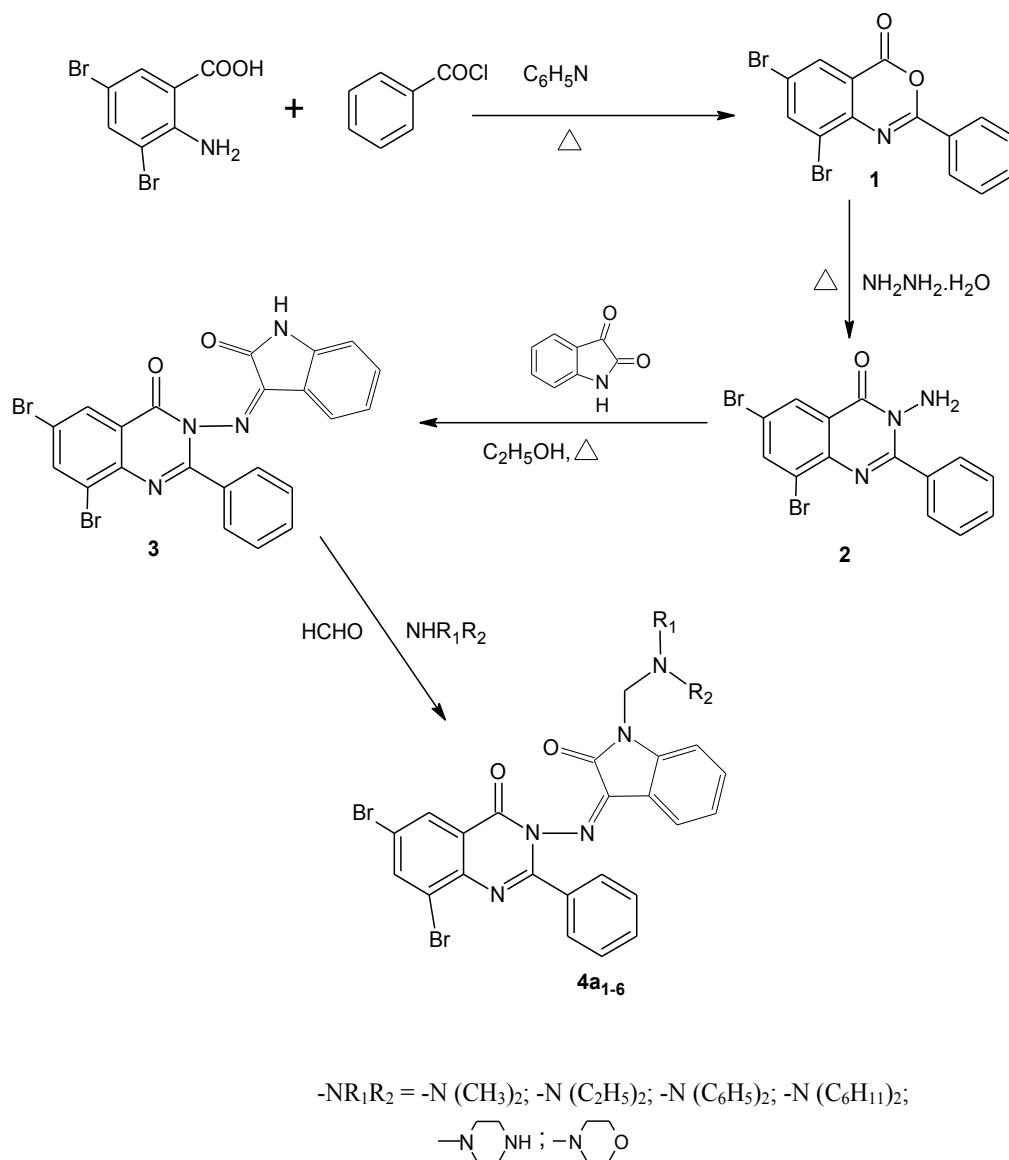
Compd.	-NRR	Molecular Formula	m.p (C <sup>0</sup> )	Yield (%)	% Analysis Calc.(Found)		
					C	H	N
3a	---	C <sub>22</sub> H <sub>12</sub> Br <sub>2</sub> N <sub>4</sub> O <sub>2</sub>	182	70	50.41 50.44	2.31 2.28	10.69 10.35
4a <sub>1</sub>	-N(CH <sub>3</sub> ) <sub>2</sub>	C <sub>25</sub> H <sub>19</sub> Br <sub>2</sub> N <sub>5</sub> O <sub>2</sub>	104	64	51.66 51.89	3.29 3.05	12.05 12.09
4a <sub>2</sub>	-N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	C <sub>27</sub> H <sub>23</sub> Br <sub>2</sub> N <sub>5</sub> O <sub>2</sub>	112	74	53.22 53.61	3.80 3.89	11.49 11.52
4a <sub>3</sub>	-N(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub>	C <sub>35</sub> H <sub>23</sub> Br <sub>2</sub> N <sub>5</sub> O <sub>2</sub>	152	62	59.99 59.76	3.29 3.50	09.93 10.06
4a <sub>4</sub>	-N(C <sub>6</sub> H <sub>11</sub> ) <sub>2</sub>	C <sub>35</sub> H <sub>35</sub> Br <sub>2</sub> N <sub>5</sub> O <sub>2</sub>	148	53	58.59 58.31	4.92 4.59	09.76 09.53
4a <sub>5</sub>		C <sub>31</sub> H <sub>31</sub> Br <sub>2</sub> N <sub>9</sub> O <sub>2</sub>	154	57	51.61 51.42	4.33 4.21	17.47 17.19
4a <sub>6</sub>		C <sub>31</sub> H <sub>27</sub> Br <sub>2</sub> N <sub>7</sub> O <sub>4</sub>	139	51	51.47 51.64	4.04 4.01	13.55 13.32

**Table 2 Antimicrobial screening of compounds 4a<sub>1-6</sub> by cup plate method**

Compd.	<u>Inhibition of zone(mm) 100µg/ml( *</u>					
	<i>S. a</i>	<i>S. f</i>	<i>E. c</i>	<i>S. t</i>	<i>C. a</i>	<i>A. n</i>
<b>4a<sub>1</sub></b>	13	16	15	15	12	17
<b>4a<sub>2</sub></b>	12	16	14	15	13	17
<b>4a<sub>3</sub></b>	16	14	14	15	16	18
<b>4a<sub>4</sub></b>	13	18	16	16	16	17
<b>4a<sub>5</sub></b>	17	16	18	17	18	15
<b>4a<sub>6</sub></b>	20	23	22	23	24	21
Ciprofloxacin	29	31	32	26	--	--
Clotrimazole	--	--	--	--	28	27
10 % DMSO control	--	--	--	--	--	--

Average of three readings\*

*S. a*: *Staphylococcus aureus*; *S. f*: *Staphylococcus faecalis*; *E. c*: *Escherichia coli*; *S. t*: *Salmonella typhi*; *C. a*: *Candida albicans*; *A. n*: *Aspergillus niger*



**Scheme1: 3-((1'-Alkyl/arylamino)methyl-2'-oxo-1',2'-dihydroindole-3'-ylidene)amino-6,8-dibromo-2-phenylquinazolin-4(3H)-ones**

**3-((1'-Dimethylaminomethyl-2'-oxo-1',2'-dihydroindole-3'-ylidene)amino)-2-phenylquinazolin-4(3H)-one (4a<sub>1</sub>).**

IR (KBr) : 3066 (Ar-CH), 2818 (CH<sub>2</sub>), 1730 (C=O), 1675 (C=O), 1603 (C=N), 1560 (C=N), 1314 (CN); MS: m/z 581 (M<sup>+</sup>); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ : 2.53 [s, 6H, N(CH<sub>3</sub>)<sub>2</sub>], 4.41 (s, 2H, CH<sub>2</sub>), 6.40-7.25 (m, 4H, ArH), 7.55-8.23 (m, 9H, ArH).

Compounds 4a<sub>2-6</sub> were prepared similarly.

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