

## Synthesis and Characterization of Carboxamides of 2'-Amino-4'-[3-(2*H*-1-benzopyran-2-one)]thiazole as Antimicrobial Agents

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A series of carboxamides of aminothiazolyl 2*H*-1-benzopyran-2-one were synthesized by treating 2'-amino-4'-[3-(2*H*-1-benzopyran-2-one)]thiazole with acid chlorides. The former compound was obtained by cyclizing 3-bromoacetyl 2*H*-1-benzopyran-2-one with thiourea. The structure of the synthesized compounds have been characterized on the basis of spectral data such as IR, <sup>1</sup>H NMR and mass spectral studies and evaluated for antibacterial activity by agar cup plate method. Out of the compounds tested, few showed significant antibacterial activity.

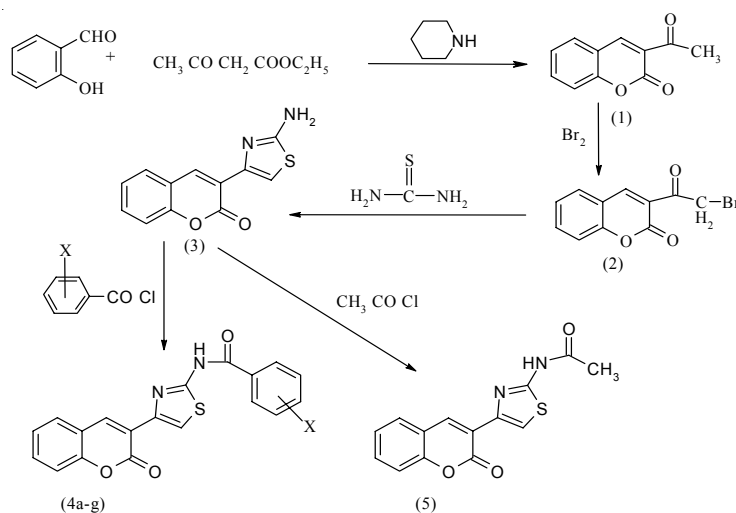
**Key Words:** Carboxamides, Aminothiazolyl 2*H*-1-benzopyran-2-one, Antibacterial activity.

### INTRODUCTION

The large number of 2*H*-1-benzopyran-2-one derivatives are known for their diversified biological activity and easy acceptability have drawn the attention of many researchers. 4-Hydroxycoumarins possess a wide range of biological activities, predominantly anticoagulant<sup>1</sup> and HIV protease inhibition<sup>2,3</sup>, coumadin<sup>®</sup> (sodium warfarin<sup>4</sup>) is the most widely prescribed anti-thrombotic in North America<sup>5</sup>. 4-Methylcoumarins were also known to possess pharmacological activities like analgesic activity<sup>6</sup>. Further, thiazoles<sup>7</sup> and 2*H*-1-benzopyran-2-one derivatives with a heterocyclic system at the 3-position exhibit promising biological activities<sup>8</sup>. This wide range of biological activities prompted us to undertake present work. In continuation of our work on synthesis of some heterocycles containing sulphur and nitrogen for biological activity<sup>9</sup> and synthesis of 3-acetyl 2*H*-1-benzopyran-2-one for concomitant polymorphism<sup>10</sup>, it was thought worthwhile to synthesize and evaluate carboxamides of 2'-amino-4'-[3-(2*H*-1-benzopyran-2-one)]-thiazole for their antibacterial activity.

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The parent amine, 2'-amino-4'-[3-(2*H*-1-benzopyran-2-one)]thiazole (**3**) was prepared by the reaction between 3-bromoacetyl-2*H*-1-benzopyran-2-one<sup>11</sup> (**2**) and thiourea. The former was prepared by bromination of 3-acetyl-2*H*-1-benzopyran-2-one in alcohol free chloroform. 3-Acetyl-2*H*-1-benzopyran-2-one<sup>12</sup> was prepared by mixing appropriate molar quantities of salicylaldehyde and ethylacetoacetate in presence of piperidine as a catalyst. Title compounds (**4a-g**) were obtained by treating parent amine (**3**) with different substituted aromatic acid chlorides in pyridine medium and also the acetyl derivative (**5**) of 2'-amino-4'-(3-2*H*-1-benzopyran-2-one) thiazole was prepared by treating with acetyl chloride (**Scheme-I**).



**Scheme-I**

The structure of the synthesized compounds were characterized on the basis of IR,  $^1\text{H}$  NMR and mass spectral data. The physical data of the synthesized compounds are given in Table-1.

### EXPERIMENTAL

Melting points were determined in open capillary tubes and are found uncorrected. IR spectra were recorded on Fourier Transform IR spectrophotometer (Shimadzu 8700) using (KBr,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ) disc method.  $^1\text{H}$  NMR spectra were recorded in  $\text{CDCl}_3$  and  $\text{DMSO}-d_6$  on AMX-400 liquid state NMR spectrometer using TMS as an internal reference standard, mass spectra were recorded on Jeol JMS DX303 Mass spectrometer with electron impact ionization (EII) at 70 eV and elemental analysis was performed on Thermo Finnigan FLASH EA 1112 CHNS analyzer at Indian Institute of Science, Bangalore. The purity of the test compounds was determined by thin layer chromatography using Merck silica gel 60 F<sub>254</sub> coated aluminium plates of several solvent systems of different polarity. All the chemicals used were of AR grade and were procured from Sigma-Aldrich.

**3-Acetyl-2*H*-1-benzopyran-2-one (1):** A mixture of salicylaldehyde (12.2 g, 0.1 mol) and ethylacetoacetate (12.98 g, 0.11 mol) were taken in a conical flask, stirred and cooled. To this mixture, 1 g of piperidine was added with shaking. The mixture was then maintained at freezing temperature for 2-3 h and a yellow coloured solid mass separated out were broken in cold ethanol and filtered. The solid was washed with cold ethanol and dried to give 3-acetyl-2*H*-1-benzopyran-2-one (18.17 g, 96.64 %). The product was recrystallized from hot glacial acetic acid which yielded needle shaped crystals (m.p. 120 °C). The formation of this compound was confirmed by difference in m.p.,  $R_f$  values and IR peaks ( $\text{cm}^{-1}$ ) at 3042  $\nu(\text{ArC}=\text{C})$ , 1726  $\nu(\text{lactone C}=\text{O})$ , 1682  $\nu(\text{C}=\text{O of } -\text{COCH}_3)$ , 1669, 1554, 1487  $\nu(\text{ArC}=\text{C})$ , 1226  $\nu(\text{C}-\text{O})$ , 851, 763  $\nu(\text{ArC}-\text{H})$ .

**3-Bromoacetyl-2*H*-1-benzopyran-2-one (2):** To a solution of compound **1** (18.0 g, 0.095 mol) in 150 mL of glacial acetic acid, bromine (16 g, 0.1 mol) in 20 mL of glacial acetic acid was added with stirring for 0.5 h at room temperature. The mixture was then warmed to decompose an addition product. The mixture was heated for 15 min on a waterbath to expel most of the hydrogen bromide, cooled and filtered. It was then poured into ice-cold water and the solid (19.6 g, 76.87 %) separated out was filtered, washed with water and dried. The product was washed with ether and recrystallized from chloroform. The formation of this compound was confirmed by difference in m.p.,  $R_f$  values and IR peaks ( $\text{cm}^{-1}$ ) at 3050  $\nu(\text{ArC}=\text{C})$ , 1730  $\nu(\text{lactone C}=\text{O})$ , 1680  $\nu(\text{C}=\text{O of } -\text{COCH}_3)$ , 1613, 1555, 1489  $\nu(\text{ArC}=\text{C})$ , 1227  $\nu(\text{C}-\text{O})$ , 875, 762  $\nu(\text{ArC}-\text{H})$ , 558  $\nu(\text{ArC}-\text{Br})$ .

**Synthesis of 2'-amino-4'-[3-(2*H*-1-benzopyran-2-one)]thiazole (3):** A suspension of compound **2** (15 g, 0.056 mol) in 15 mL of hot ethanol was treated with thiourea (4.56 g, 0.06 mol) a mild exothermic reaction took place, gave a clear solution that soon deposited as crystals. The deposit was removed, washed with ethanol and then boiled with water containing sodium acetate which yielded 10.25 g (74.81 %) of 2'-amino-4'-[3-(2*H*-1-benzopyran-2-one)]thiazole and the product obtained was recrystallized with absolute ethanol, m.p. 222 °C.

IR (KBr,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 3416, 3310 ( $-\text{NH}_2$ ), 3048 (ArC-H), 1712 (lactone C=O), 1628 ( $-\text{NH}_2$  def.), 1609, 1534, 1473 (ArC=C), 1371 ( $-\text{C}-\text{N}-$ ), 1249 ( $-\text{C}-\text{O}-$ ), 816, 788 (ArC-H).  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ): 7.14 (2H,  $\text{NH}_2$ ), 7.40 (Ar-H, 2H), 7.51 (Ar-H, 2H), 7.79 (Ar-H, 1H), 8.51 (Hetero aromatic, 1H). Elemental analysis (%) for  $\text{C}_{12}\text{H}_8\text{N}_2\text{O}_2\text{S}$  Calcd. (found): C 59.01 (58.97), H 3.30 (3.25), N 11.47 (11.44) and S 13.13 (13.12).

**Synthesis of carboxamides of 2'-amino-4'-[3-(2*H*-1-benzopyran-2-one)]thiazole (4a-g) and (5):** Parent compound **3** was dissolved in pyridine and cooled to 10 °C in an ice bath, acetyl chloride (**5**) and different aromatic acid chlorides (**4a-g**) were added dropwise with constant stirring and the stirring was continued upto 1 h. Finally the reaction medium is

poured in to ice water the crude product obtained was filtered, washed with water and recrystallized using aqueous dimethyl sulfoxide as a recrystallizing solvent. The physical data of the newly synthesized compounds is given in Table-1.

TABLE-1  
PHYSICAL DATA OF CARBOXAMIDES OF 2'-AMINO-4'-[3-(2H-1-BENZOPYRAN-2-ONE)]THIAZOLE (**4a-g**) AND (**5**)

Compd.	X	m.f.	m.w.	Yield (%)	m.p. (°C)
<b>1</b>	–	C <sub>11</sub> H <sub>8</sub> O <sub>3</sub>	188	96.64	120
<b>2</b>	–	C <sub>11</sub> H <sub>7</sub> O <sub>3</sub> Br	267	76.87	164
<b>3</b>	–	C <sub>12</sub> H <sub>8</sub> N <sub>2</sub> O <sub>2</sub> S	244	74.81	222
<b>4a</b>	H	C <sub>19</sub> H <sub>12</sub> N <sub>2</sub> O <sub>3</sub> S	348	63.64	230
<b>4b</b>	4-CH <sub>3</sub>	C <sub>20</sub> H <sub>14</sub> N <sub>2</sub> O <sub>3</sub> S	362	93.11	228
<b>4c</b>	4-NO <sub>2</sub>	C <sub>19</sub> H <sub>11</sub> N <sub>3</sub> O <sub>5</sub> S	393	71.00	178
<b>4d</b>	4-OCH <sub>3</sub>	C <sub>20</sub> H <sub>14</sub> N <sub>2</sub> O <sub>4</sub> S	378	69.23	186
<b>4e</b>	2-CH <sub>3</sub>	C <sub>20</sub> H <sub>14</sub> N <sub>2</sub> O <sub>3</sub> S	362	57.97	192
<b>4f</b>	4-Cl	C <sub>19</sub> H <sub>11</sub> N <sub>2</sub> O <sub>3</sub> SCl	382	74.37	244
<b>4g</b>	2-Cl	C <sub>19</sub> H <sub>11</sub> N <sub>2</sub> O <sub>3</sub> SCl	382	62.08	190
<b>5</b>	–	C <sub>14</sub> H <sub>10</sub> N <sub>2</sub> O <sub>3</sub> S	286	55.36	182

**4b**: IR (KBr,  $\nu_{\max}$ , cm<sup>-1</sup>): 3408 (w, N-H), 1726 (s, C=O), 1658 (m, NH-CO), 1371 (m, C-N), 1239 (m, C-O) and 579 (m, Ar C-Br). <sup>1</sup>H NMR (CDCl<sub>3</sub>): 2.41 (s, CH<sub>3</sub>, 3H) 7.25-8.41 (m, Ar-H, 10H), 9.57 (s, N-H, 1H). Elemental analysis (%) for C<sub>20</sub>H<sub>14</sub>N<sub>2</sub>O<sub>3</sub>S Calcd. (found): C 66.28 (66.23), H 3.89 (3.88), N 7.73 (7.75) and S 8.85 (8.89). MS m/z: 362 (M<sup>+</sup>, 100 %), 271, 142 and 64.

**Antibacterial activity**: The antibacterial activity of the test samples (**4a-g**) and (**5**) were determined by agar cup plate method using four organisms such as *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli* and *Klebsiella pneumoniae* and two standard drugs ampicillin and streptomycin. This method was based on diffusion of antibacterial component from reservoir bore to the surrounding inoculated nutrient agar medium, so that the growth of microorganisms was inhibited as circular zone around the bore. The concentration of test compounds was 100 µg/100 µL and was prepared in dimethyl sulfoxide. The test samples and standard drugs were placed in a bore made in petridishes which contains different organisms and incubated at 37 °C for 24 h. The zone of inhibitions around the bore was measured after 24 h. The antibacterial activity was classified as highly active (>21 mm), moderately active (15-21 mm), slightly active (12-15 mm) and less than 12 mm was taken as inactive. All the samples were tested in triplicate. The antibacterial activity data are recorded in Table-2.

TABLE-2  
ANTIBACTERIAL ACTIVITY OF CARBOXAMIDES OF 2'-AMINO-4'-  
(3-2H-1-BENZOPYRAN-2-ONE)THIAZOLE (4a-g) AND (5)

Compd.	Control	<i>Bs</i>	<i>Ec</i>	<i>Sa</i>	<i>Kp</i>
<b>4a</b>	–	+++	+++	++	++
<b>4b</b>	–	+++	+++	++	+++
<b>4c</b>	–	+	+++	+++	+
<b>4d</b>	–	++	+++	++	+
<b>4e</b>	–	+++	++	+	+
<b>4f</b>	–	++	+++	+++	+
<b>4g</b>	–	+	++	++	+
<b>5</b>	–	+	++	–	++
<b>Standard</b>					
Streptomycin	–	++++	++++	++++	++++
Ampicillin	–	++++	++++	++++	++++

+ = Less than 12 mm; ++ = 12-15 mm (slightly active); +++ = 15-21 mm (moderately active); ++++ = > 21 mm (highly active)

*Bs* = *Bacillus subtilis*; *Ec* = *Escherichia coli*;

*Sa* = *Staphylococcus aureus*; *Kp* = *Klebsiella pneumonia*

## RESULTS AND DISCUSSION

Out of eight compounds screened for antibacterial activity compounds such as **4a**, **4b** and **4f** showed significant antibacterial activity against *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli* and *Klebsiella pneumoniae* when compared to that of standard streptomycin and ampicillin. Among all the test samples, only **4b**, which is *p*-methyl derivative of substituted 2'-amino-4'-(3-2H-1-benzopyran-2-one) thiazole, showed activity against all strains of test organisms.

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(Received: 4 November 2006;

Accepted: 22 October 2007)

AJC-6030