SYNTHESIS AND ANTIMICROBIAL EVALUATION OF SOME NOVEL SULFUR INCORPORATED 7-SUBSTITUTED CHROMONES.

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ABSTRACT: We report herein the design and synthesis of five 2-(phenylthio)methylchromone (4a-d and 5), from 2-bromomethylchromones (3) which were obtained on refluxing 2-methylchromone with N-bromosuccinimide in carbon tetrachloride. The title compounds were characterised by spectral data (IR and NMR). All the compounds have been screened for antimicrobial activity.

Keywords: Thiocromones, allylic bromination, antimicrobial.

INTRODUCTION
Chromones are naturally occurring oxygen heterocycles that are widely distributed in plant kingdom. They exhibit a wide spectrum of biological activity. (Cox, et. al., 1970) Some chromone derivatives of medicinal importance are: khellin, a coronary vasodilator, chromone-2-carboxylic acid, a spasmylytic agent and disodium chromoglycate, an antiallergic drug. (Geissmann, et. al., 1951; Clargee, et. al., 1949)

Since, it is well known that organosulfur compounds exhibit a variety of biological activities, it is anticipated that oxygen heterocycles of natural origin incorporating sulfur as sulfide and sulfone moieties may exhibit useful biological properties as in case of 3-arylsulfonylflavones. (Ramesh, et. al., 2006) Further, antiallergic properties of chromone derivatives (Fitsmaerice, et. al., 1966) appear to be largely confined to those compounds which contain a carboxyl group at C-2. These observations prompted us to synthesise 2-(arylthio)methylchromones (Scheme 1) with a view to introduce a new pharmacopore.

MATERIALS AND METHODS
Melting points were determined in open capillary tubes and are uncorrected. The purity of the compounds were checked on a silica gel-G plate and visualised using iodine/UV lamp. IR spectra were recorded on a Schimadzu FT-IR spectrophotometer using KBr pellets. 1H NMR spectra were recorded on a Bruker Avance 300 MHz NMR spectrometer in CDCl3 and DMSO-d6, using TMS as an internal standard. All the chemicals used were purchased from Merck and s.d. fine chemicals.

Experimental Procedures
Synthesis of 2-bromomethylchromone (3)
To a solution of 2-methylchromone (2.0 g) in carbon tetrachloride (20.0 mL), N-bromosuccinimide (2.5 g) and benzoyl peroxide (0.1 g) were added and the mixture was refluxed on a water bath for one hour. The reaction mixture was filtered and the filtrate was evaporated in vacuo and the solid residue that formed was used as such for further reactions.

General procedure for the synthesis of 2-(phenylthio)methylchromones (4 a-d)
To a solution of 2-bromomethylchromone (3.0 g) in dry DMF (10.0 mL) and thiophenol (2.0 mL) as sodium salt in DMF (5.0 mL), the reaction mixture was added and refluxed for 1 hr. The reaction mixture was poured into excess of cold water and separated solid was filtered, washed with water, dried and recrystallised from chloroform-diethyl ether.

2-(phenylthio)methylchromone: (4a). IR (KBr): 1650 (C=O) cm\(^{-1}\); 1H NMR(CDCl3): 3.21 (s, 2H, CH\(_2\)), 6.26 (s, 1H, H-3), 7.29 - 8.08 (m, 9H, Ar-H); Anal. Calcd for C\(_{16}\)H\(_{12}\)O\(_2\)S: C 71.62; H 4.51, found: C 71.60; H 4.52.
7-acetoxy-2(phenylthio)methylchromone: (4b). IR (KBr): 1690 (O-C=O), 1644 (C=O) cm⁻¹; ¹H NMR(CDCl₃): 2.23 (s, 3H, -COCH₃), 3.41 (s, 2H, CH₂), 6.43 (s, 1H, H-3), 7.19-8.03 (m, 8H, Ar-H); Anal. Calcd for C₁₈H₁₄O₄S: C 66.24; H 4.32, found: C 66.23; H 4.34.

7-acetoxy-2-(2-mercaptobenzothiozolyl)methylchromone: (4c). IR (KBr): 1690 (O-C=O), (C=N), (C-O-), 1644 (C=O) cm⁻¹; ¹H NMR (CDCl₃): 2.23 (s, 3H, -COCH₃), 3.61(s, 2H, CH₂), 6.13(s, 1H, H-3), 7.32 - 8.09 (m, 7H, Ar-H); Anal. Calcd for C₃₅H₂₅NO₈S₂: C 64.50; H 3.87, found: C 64.53; H 3.89.

7-methoxy-2-(phenylthio)methylchromone: (4d). IR (KBr): 1650 (C=O), (O-C) cm⁻¹; ¹H NMR(CDCl₃): 3.25 (s, 2H, CH₂), 3.78 (s, 3H, -OCH₃), 6.26 (s, 1H, H-3), 6.71 - 8.01 (m, 8H, Ar-H); Anal. Calcd for C₃₄H₂₅NO₇S₂: C 65.01; H 3.80, found: C 65.03; H 3.81.

**RESULTS AND DISCUSSION**

Compounds 4a-d and 5 shows positive towards the presence of sulfur moiety and the presence of hydroxyl at C-7 of 5 was confirmed by ¹H NMR (δ 9.89). 2-(Arylthio)methylchromones 4 a-d are readily accessible by nucleophilic displacement of bromine from 2-bromomethylchromones 3 by appropriate thiols (Table 1). The required 2-bromomethylchromones are readily prepared by allylic bromination of 2-methylchromones 2 employing NBS and benzoyl peroxide as a radical initiator. It is interesting to note that although, allylic bromination of 4-methylcoumarins is well documented, there is no record of such allylic type of bromination of 2-methylchromones.

The intermediates and the final products have been characterized by their spectral data (¹H NMR & ¹³C NMR). (Scheme 1)
Table. I: Physical characteristics of synthesized compounds 4 a-d & 5.

<table>
<thead>
<tr>
<th>Compd.</th>
<th>R</th>
<th>Ar</th>
<th>mp°C</th>
<th>Yield</th>
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<tbody>
<tr>
<td>4a</td>
<td>H</td>
<td></td>
<td>212</td>
<td>90</td>
</tr>
<tr>
<td>4b</td>
<td>OCOCH₃</td>
<td></td>
<td>193</td>
<td>87</td>
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<tr>
<td>4c</td>
<td>OCOCH₃</td>
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</tr>
<tr>
<td>5</td>
<td>OH</td>
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<td>254</td>
<td>68</td>
</tr>
</tbody>
</table>

Antimicrobial activity

Compounds 4a-d and 5 were screened in vitro for their antimicrobial activity against various bacterial strains (Gram-negative strain - *E. coli* while gram-positive bacterial strain was *S. aureus*). Methanol was used as a solvent. The standard drugs used for comparison were ciprofloxacin and cloxacillin. For each biological activity test, two to three experiments were performed and the average zone of inhibition are shown in Table 2.

Table 2. Inhibitory zone (diameter) mm of synthesized compounds 4(a-d) & 5 against tested bacterial strains by disc diffusion method.

<table>
<thead>
<tr>
<th>Inhibitory zone (diameter) mm at 10 μg / mL</th>
<th>Compounds</th>
<th>Gram-negative bacteria</th>
<th>Gram-positive bacteria</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td><em>S. aureus</em></td>
<td><em>E. coli</em></td>
</tr>
<tr>
<td></td>
<td>4a</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>4b</td>
<td>7</td>
<td>12</td>
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<tr>
<td></td>
<td>4c</td>
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<td>8</td>
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<tr>
<td></td>
<td>4d</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>5</td>
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<td>12</td>
</tr>
<tr>
<td></td>
<td>Ciprofloxacin</td>
<td>9</td>
<td>17</td>
</tr>
</tbody>
</table>
Compounds 4b, 4d and 5 exhibited high activity against both species *S. aureus* as well as *E. coli*. Compounds 4a and 4c showed moderate activity against *S. aureus* and *E. coli*.

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**REFERENCES**

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