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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 Thiochromones, 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 importantce are: khellin, a coronary vasodilator, chromone-2-carboxyclic acid, a spasmolytic 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 detivatives (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. ^{1}H NMR spectra were recorded on a Bruker Avance 300 MHz NMR spectrometer in $CDCl_3$ and DMSO-d_6 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}; ^{1}H NMR($CDCl_3$): 3.21 (s, 2H, CH_2), 6. 26 (s, 1H, H-3), 7.29 - 8.08 (m, 9H, Ar-H); *Anal.* Calcd for $C_{16}H_{12}O_2S$: C 71.62; H 4.51, found: C 71.60; H 4. 52.

7 - acetoxy - 2(phenylthio)methyl - chromone: ***(4b).*** IR (KBr): 1690 (O-C=O), 1644 (C=O) cm^{-1}; ^1H NMR($CDCl_3$): 2.23 (s, 3H,-$COCH_3$), 3.41 (s, 2H, CH_2), 6.43 (s, 1H, H-3), 7.19-8.03 (m, 8H, Ar-H); *Anal.* Calcd for $C_{18}H_{14}O_4S$: 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 ($CDCl_3$): 2.23 (s, 3H, -$COCH_3$), 3.61(s, 2H, CH_2), 6.13(s, 1H, H-3), 7.32 - 8.09 (m, 7H, Ar-H); *Anal.* Calcd for $C_{35}H_{25}NO_8S_2$: 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($CDCl_3$): 3.25 (s, 2H, CH_2), 3.78 (s, 3H, -OCH_3), 6.26 (s, 1H, H-3), 6.71 - 8.01 (m, 8H, Ar-H); *Anal.* Calcd for $C_{34}H_{25}NO_7S_2$: C 65.47; H 4.04, found: C 65. 43; H 4. 01.

Synthesis of 7-hydroxy-2-(phenylthio)methylchromone ***(5)***

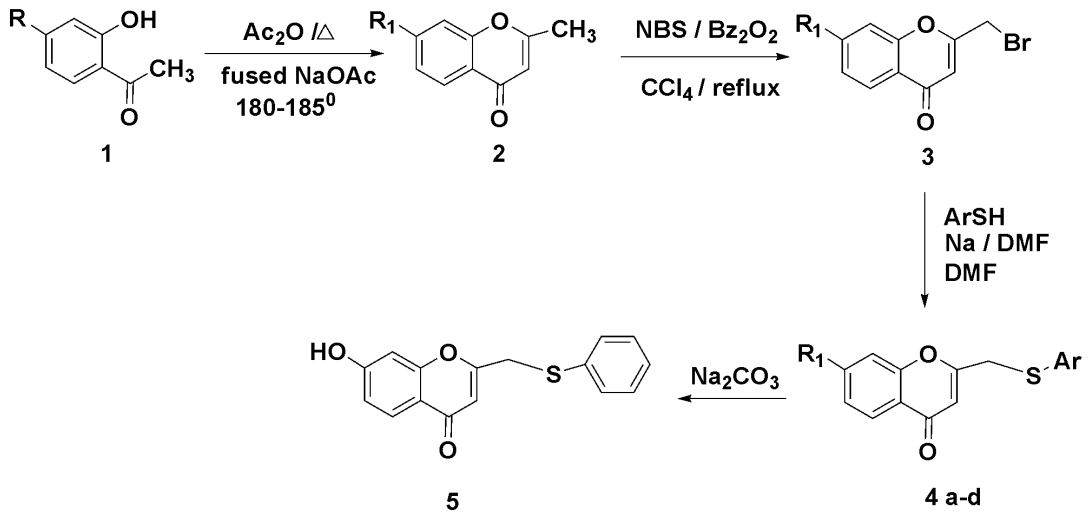
To a solution of 7-acetoxy-2-(phenylthio)methylchromone (3.0 g) in alcohol (50.0 mL) aq. sodium carbonate (10.0 mL, 10%) was added and the clear solution was refluxed for 1hr. The solvent was removed *in vacuo* diluted with water, cooled and neutralized with conc. HCl. The solid that separated was filtered, dried, and recrystallised from methanol.

5: IR (KBr): 1650 (C=O), (O-C) cm^{-1}; ^1H NMR($CDCl_3$): 3.26 (s, 2H, CH_2), 6.31 (s, 1H, H-3), 6.51 - 7.32 (m, 8H, Ar-H), 9.89 (s, 1H, OH); *Anal.* Calcd for $C_{33}H_{23}NO_7S_2$: 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 & ^{13}C NMR). (**Scheme 1**)



Scheme 1

Table. I : Physical characteristics of synthesised compounds 4 a-d & 5.

Compd.	R	Ar	mp°C	Yield
4a	H		212	90
4b	$OCOCH_3$		193	87
4c	$OCOCH_3$		172	78
4d	OCH_3		198	92
5	OH		254	68

Antimicrobial activity

Compounds **4**a-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.

Inhibitory zone (diameter) mm at 10 µg / mL		
Compounds	Gram-negative bacteria	Gram-positive bacteria
	S.aureus	*E.coli*
4a	4	10
4b	7	12
4c	5	8
4d	6	14
5	7	12
Ciprofloxacin	**9**	17

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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