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INTEGRATED
RESEARCH ADVANCES

Synthesis and antibacterial studies of 3-substituted chromone derivatives

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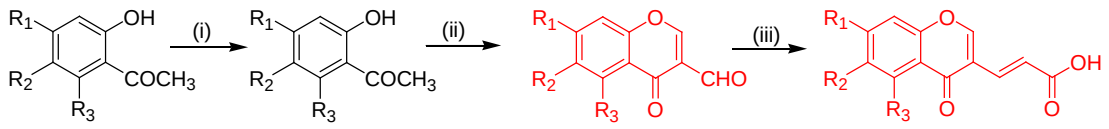
ABSTRACT



4-7 8-11 12-15 16-17

Antibacterial activity Antibacterial activity

$R_1/R_2/R_3$ = H/OH/OCH_3 Rxn conditions: (i) $(CH_3)_2SO_4$, Acetone, K_2CO_3, (ii) $POCl_3$, 55-60 °C, anhyd. DMF,13 h (iii) $CH_2(COOH)_2$, pyr, reflux

A series of 3-substituted chromone derivatives have been synthesized. All of the synthesized compounds have been characterized from their spectral data and were tested for their antibacterial activity against both gram-positive as well as gram-negative bacteria. The activity results revealed that all the compounds examined displayed good activity against all the pathogenic bacterial strains studied with zone of inhibition 16-20 mm and MIC values in the range of 50–100µg/mL as compared to the standard used.

Keywords: Chromone. Vilsmeier-Haack formylation. Antibacterial activity. Zone of Inhibition. MIC.

INTRODUCTION

Chromones represent an unusual group of structurally diverse secondary metabolites that are ubiquitous in nature, mainly in plants. Chromones are oxygen-containing heterocycles with a benzoannelated γ-pyrone ring. Several biological activities have been ascribed to simple chromones and their analogues such as anti-inflammatory,[1] antiplatelet,[2] anticancer,[3] antimicrobial,[4] antiulcers,[5] antioxidants,[6] antiarrhythmic and hypotensive agents,[7] aldose reductase and calpain inhibitors,[8-10] MAO inhibition[11]

Due to potential pharmacological properties, chromones are topic of great interest among a number of research groups. Generally, chromones are synthesized by Vilsmeier-Haack formylation,[12-15] Allan-Robinson synthesis by acylation rearrangement and then cyclisation,[16] Baker-Venkatraman synthesis through internal Claisen condensation of 2-Arylonyl-1-acetyl arenes.[17] Chromone derivatives have also been synthesized by intramolecular ester carbonyl olefination[18] or Pd-catalysed regiospecific carbonylative annulation of acetylenes and o-iodophenol acetates.[19]

The reactivity of 3-substituted chromones is extensively different depending upon the type of substitution present at the position 3 and the reaction conditions. And amongst the 3-substituted chromones, 3-Formyl chromone derivatives are the most widely used synthons in heterocyclic synthesis with diverse biological activities due to (i) availability of three electron deficient sites, the aldehyde carbon, C-2 and C-4 carbon of the carbonyl group (ii) good biological activity (iii) simple synthesis by Vilsmeier-Haack formylation in good yields.[20,21]

In the present study, we report the synthesis of biologically important 3-substituted chromone derivatives for their antibacterial study.

EXPERIMENTAL

Materials and methods

Melting Points were determined by Buchi M-560. The ^{1}HNMR spectra were recorded on Bruker Avance 400 Mhz NMR spectrometerusing TMS as internal standard . The chemical shift values are on δ scale and coupling constant values (J) are in Hz. Analytical TLC were performed on pre-coated Merck silica gel 60 F_{254} plates with fluorescence indicator, the spots were visualised by irradiation with UV light. Column chromatography was carried out using silica gel (100-200 mesh). All chemicals were purchased from Merck, Spectrochem, Sigma-Aldrich and used as supplied without further purification.

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*General procedure for the synthesis of 2,5-Dihydroxyacetophenone (**3**):*

5g of hydroquinone (1) was added to13ml of acetic anhydride and then 2-3ml of conc. H_2SO_4 was added to it. The reaction mixture was poured over ice to obtain white coloured precipitates (7g) of hydroquinone diacetate (2). Then dry hydroquinone diacetate was gently heated with $AlCl_3$ to 100-110°C for 30min, then temperature was raised to 160-165°C and maintained for 4 h. The progress of the reaction was monitored by TLC (PE:EA). Afterwards 300 g of crushed ice and 10 ml of conc. HCl was added in order to decompose excess of $AlCl_3$. The mixture was filtered and recrystallised with 95% ethanol to give 4 g of pure 2,5-Dihydroxy acetophenone as green needles. mp. 205-206°C (Lit. = 202-204 °C). Yield. 80%. Color: Green needles. ^{1}H ($CDCl_3$, 400MHz) δ 2.57 (s, 3H, -$COCH_3$), 6.79 (d, J = 8.1, 1H, H-3), 6.98 (d, J=8.1, 1H, H-4), 7.17 (s, 1H, H-6), 9.17(brs, 1H, *OH*-5), 11.31(brs, 1H, *OH*-2).

General procedure for the synthesis of methoxy derivatives of dihydroxyacetophenone (8-11)

A mixture of 15g (0.098 mol) of dihydroxyacetophenone (5-7), 15 ml of dimethylsulfate (0.148 mol) and 300 ml of acetone were refluxed with 25g of anhydrous K_2CO_3 for approximately 5 h continuously to obtain the corresponding methoxy derivatives (9-11) in 75-85% yield. The progress of the reaction was monitored by TLC (PE:EA::70:30). The mixture was filtered and the filterate was distilled to give the product and purified by Column chromatography.

2-Hydroxy-4-methoxyacetophenone (**9**): Yield. 90%. Color. White needles. mp. 47-48°C (Lit. 45 °C). ^{1}H(400 MHz, $CDCl_3$). δ 2.54 (3H, s, $COCH_3$),3.82 (3H, s, OCH_3), 6.41 (lH, dd, J_m = 2.5and J_o = 4.3 Hz, H-5), 6.44 (lH, d, J = 2.5Hz, H-3), 7.62 (lH, d, J_o = 8.7 Hz, H-6) and 12.72 (lH, s, OH).

2-Hydroxy-5-methoxyacetophenone (**10**): Yield. 90%. Color: White needles. mp. 45-46 °C (Lit. 49°C). ^{1}H(400 MHz, $CDCl_3$). δ 2.60 (3H, s, COCH3),3.80 (3H, s, OCH_3), 6.91 (lH, d, J_o= 9.0 Hz, H-3), 7.09 (lH, dd, J_m= 3.0, J_o=9.0 Hz, H-4), 7.16 (lH, d, J_o = 3.1Hz, 6-H) and 11.85 (lH, s, OH).

2-Hydroxy-6-methoxyacetophenone (**11**): Yield. 88%. Color: Light yellow needles. mp. 50-51°C (Lit. 52 °C). ^{1}H (400 MHz, $CDCl_3$). δ 2.4092 (3H, s, -OCH_3), 3.8259 (3H, s, -$COCH_3$), 6.3272-6.3063 (d, 1H, J_o = 8.36, H-6), 6.5062-6.4830 (m, 1H, J_o = 8.36, H-6) , 7.2917-7.2500 (t, 1H, J = 8.32Hz, H-4), 13.1855 (1H, s, -OH, H-2).

General procedure for synthesis of 4-Oxo-4 H-benzopyran-3-yl-carboxaldehyde derivatives (**12-15**): A solution of methoxy substituted hydroxyacetophenone (0.04 mol) in 21 ml anhydrous DMF and 16 ml of $POCl_3$ was stirred at 55-60°C for 13 h continuously and then poured on crushed ice (100g). The progress of the reaction was monitored by TLC (PE:EA::70:30). The resulting precipitate was filtered and washed with water. The crude product obtained was recrystallized with ethanol.

4-Oxo-4Hbenzopyran-3-yl-carboxaldehyde (**12**): Yield. 80%. Pale yellow Color. mp. 152-153 °C. ^{1}H. (400 MHz, $CDCl_3$). δ 7.48-7.54 (m, 2H, H-6 and H-8), 7.75 (t, 1H, J=8.4, H-7), 8.28 (d, 1H, J = 8.0, H-5), 8.54(s, 1H, H-2) and 10.39 (s, 1H, CHO).

6-Methoxy-4-oxo-4H-benzopyran-3-yl-carboxaldehyde (**13**): Yield. 85%. Color: Reddish brown. mp. 164-166 °C. ^{1}H (400 MHz, $CDCl_3$). δ 3. 8554(s, 3H, -OCH_3), 7.2655-7.2350 (m, 1H, J_o = 9.12 Hz, H-7), 7.4154-7.3925 (d, 1H, J_o = 9.16 Hz, H-8), 7.5758-7.5681 (d, 1H, J_m = 3.08 Hz, H-5), 8.4632 (s, 1H, H-2), 10.3829 (s, 1H, H-3).

7-Methoxy-4-oxo-4H-benzopyran-3-yl-carboxaldehyde (**14**): Yield. 88%. Color: Dark brown. mp. 142-145 °C. ^{1}H (400 MHz, $CDCl_3$). δ 3.9341 (3H, s, H-7), 6.9231-6.9137 (1H, d, J = 3.76 Hz, H-8), 7.0678-7.0396 (1H, dd, J_o= 8.9 Hz, J_m = 2.4 Hz, H-6), 8.2126-8.1902 (1H, d, J = 8.96Hz, H-5), 8.4808 (1H, s, H-2), 10.3841 (s, 1H, H-3).

5-Methoxy-4-oxo-4H-benzopyran-3-yl-carboxaldehyde (**15**): Yield.85. Color: Yellow. mp. 112-114 °C. ^{1}H (400 MHz, $CDCl_3$). δ 3.9324 (s, 3H, H-5), 7.0475-70266 (d, 1H, J = 8.36, H-6), 7.1515-7.1305 (d, 1H, J = 8.4, H-8), 7.7278-7.6857 (t, 1H, J =84, H-7), 8.6348(1H, s, H-2), 10.1376 (1H, s, H-3).

General procedure for the synthesis of 3(4-oxo-4H-chromen-3yl)acrylic acids (16-17):

A mixture of 3-formyl chromone (10 mmol) and malonic acid (20 mmol), in the presenceof pyridine (5ml) was refluxed in 50 ml round bottom flask for 30-45 min with vigorousstirring. After completion of reaction (monitored by TLC), the reaction mixture wascooled to room temperature, the pH was adjusted to 1.0 with conc. HCl and the reactionmass was stirred for 30 min. The yellow coloured solid thus obtained was filtered andwashed with (15 ml x 2) 1N HCl and dried.

(E)-3-(4-Oxo-4H-1- benzopyran-3-yl) propenoic acid (**16**): Yield 85%. Color: Light Yellow. mp. 253-254°C. ^{1}H (400, DMSO). δ 7.10 (d, 1H, J_{trans} = 15.9 Hz, H-2'), 7.40 (d, 1H, J_{trans} = 15.9 Hz, H-1'), 7.52 (t, J = 6.0 Hz, 1H, H-6), 7.67 (d, 1H, J = 6.8 Hz, H-8), 7.82 (t, 1H, J = 7.2 Hz, H-7), 8.10 (d, 1 H, J = 6.9 Hz, H-5), 8.84 (s, 1H, H-2), and δ 12.00-12.50 (bs, 1 H, COOH).

(E)-3-(6-Methoxy-4-oxo-4H-1- benzopyran-3-yl)propenoic acid (**17**): Yield 80%. Color Light Yellow. mp.200-204. ^{1}H (400, DMSO). δ 3.8916 (3H, s, -OCH_3), 7.1540-7.1144 (1H, d, J_{trans} = 15.84 Hz, H-1'), 7.3811-7.3506 (1H, dd, J_o = 9.12 Hz, J_m = 3.08 Hz, H-7), 7.4598-7.4200 (1H, d, J_{trans} = 15.92 Hz, H-2'), 7.5127-7.5050 (1H, d, J_m = 3.08 Hz, H-5), 8.7228 (1H, s, H-

Biology

Pathogens

All the pathogenic strains of bacteria viz. *Bacillus cereus*, *Aeromonas hydrophila*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli* and*Staphylococcus epidermis* were procured from Institute of Microbial Technology, Chandigarh (India).

Materials

Mueller–Hinton agar and Nutrient broth were procured from HiMedia, Mumbai, India. Iodonitrotetrazolium chloride (INT), Gentamicin and DMSO used in the assay were purchased from Sigma-Aldrich Chemicals Pvt. Ltd., USA

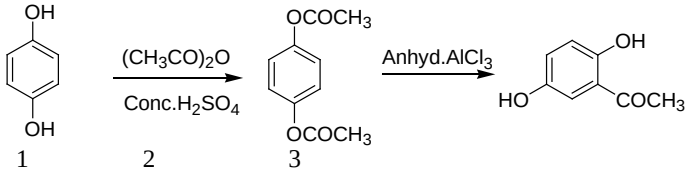
Antibacterial activity assay

Agar well test method was used to determine the inhibitory potential of pathogenic bacterial growth by the synthesized compounds. The minimal inhibitory concentration (MIC) was determined by the broth microdilution method.[22,23] The synthesized compounds were weighed (5 mg) and dissolved in DMSO to prepare the stock solutions of 5mg/mL. The serial dilution from 2000 to 1 µg/mL was made in a 96-well plate. Fifty µL of a bacterial suspension, obtained from a 24 h culture (~106 cfu/mL) was added to each well. The plates were incubated at 35 °C for 24 h. Gentamicin was used as a positive control in the assay. The MIC of the samples was detected by addition of INT dye and incubated at 37 °C for 30 min.

RESULTS AND DISCUSSION

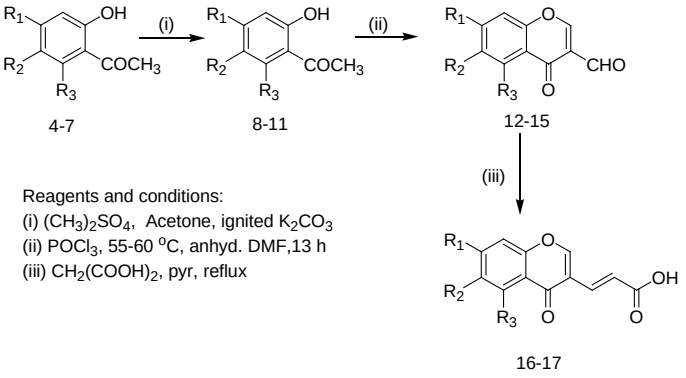
The compounds described in the present work were prepared by simple straight known methods. A series of 4-Oxo-4*H*-benzopyran-3-yl-carboxaldehyde (11-15) and (E)-3-(4-Oxo-4*H*-1-benzopyran-3-yl) propenoic acid derivatives (16-17) have been synthesized. Hydroxyacetophenones were taken as a starting material for synthesis of substituted 4-Oxo-4*H*-benzopyran-3-yl-carboxaldehydes through Vilsmeier-Haack formylation in good yields which in turn condensed with malonic acid to give (E)-3-(4-Oxo-4*H*-1-benzopyran-3-yl) propenoic acidderivatives.

Firstly, 2,5-Dihydroxyacetophenone (3) was synthesized from hydroquinone. In order to synthesize 2,5-Dihydroxyacetophenone, hydroquinone (1) was made to undergo Friedel crafts acylation with acetic anhydride in presence of sulphuric acid as a catalyst to yield hydroquinone diacetate (2). Then dry hydroquinone diacetate was heated gently with anhydrous aluminium chloride to form 2,5-Dihydroxyacetophenone (Scheme1).



Scheme 1. Synthesis 2,5-Dihydroxyacetophenone from hydroquinone.

Afterwards methylation of Dihydroxyacetophenone derivatives was carried out. Compounds (4-7) were refluxed in anhydrous conditions using dimethylsulfate and ignited potassium carbonate to produce methoxy derivatives of dihydroxyacetophenones (8-11) (Scheme 2). All the methoxy derivatives of dihydroxyacetophenones (8-11) were treated with phosphorus oxychloride in dry N,N-Dimethylformamide to give substituted 4-Oxo-4-*H*-benzopyran-3-yl-carboxaldehydes (12-15) in yield ranging from 85-95% (Scheme 2). Various synthesized substituted 4-Oxo-4-*H*-benzopyran-3-yl-carboxaldehydes were then refluxed with malonic acid in the presence of dry pyridine by simple knoevenagel reaction to give 3-(4-Oxo-4*H*-chromen-3yl)acrylic acids (16-17).



Scheme 2. Synthesis of 3-substituted chromone derivatives.

Compd.	R_1	R_2	R_3
4/8/12/16	H	H	H
5	OH	H	H
6	H	OH	H
7	H	H	OH
9/13	OCH_3	H	H
10/14/17	H	OCH_3	H
11/15	H	H	OCH_3

Biology

Antibacterial activity

All the synthesized aldehydes and acid derivatives of chromone (11-17) were evaluated for antibacterial activity analysis against six pathogenic bacterial strains using agar well method.[24] The antibacterial activity was tested for six pathogenic bacterial strains viz. *Bacillus cereus*, *Aeromonas hydrophila*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Staphylococcus epidermis*. All the tested compounds were displayed good antibacterial activity against both gram-positive as well as gram-negative bacteria by showing a zone of inhibition in the range of 15-20 mm (Table 1). For further insights on the antibacterial action, minimum inhibitory concentration (MIC) was

Table 1: Zone of inhibition (mm) of active compounds (12-17) against pathogenic bacterial test strains using gentamicin as positive control.

Compound	*B. cereus*	*S. epidermis*	*A. hydrophila*	*S. aureus*	*E. coli*	*P. aeruginosa*
12	16	18	17	19	18	19
13	18	16	16	20	17	19
14	16	16	17	19	15	15
15	16	18	16	18	19	18
16	16	16	16	18	19	19
17	20	17	18	20	18	19
Gentamicin	30	27	29	31	33	30

Average diameter of well = 8 mm. All the experiments were carried out in triplicate.

determined using broth dilution assay (table 2). According to the antibacterial activity results, all the compounds exhibited good activity against all the six pathogenic bacterial strains when compared to the standard drug gentamicin with MIC value in the range 50-100μg/mL.

Table 2: Minimum inhibitory concentration (μg/ml) of active compounds (12-17) against pathogenic bacterial test strains using gentamicin as positive control.

Compd	*B. cereus*	*S. epidermis*	*A. hydrophila*	*S. aureus*	*E. coli*	*P. aeruginosa*
12	75	50	75	100	50	75
13	50	75	75	50	75	75
14	75	75	50	50	50	75
15	50	75	50	50	50	50
16	75	75	100	75	100	75
17	75	50	75	100	75	75
Gentamicin	0.39	<0.39	1.56	1.5625	1.5625	0.78

All the experiments were in triplicate and the results expressed as average values.

CONCLUSION

To conclude, it was found that chromone-3-carbaldehydes and chromone-3-acrylic acid derivatives have shown good antibacterial activity against both gram-positive (*B. cereus*, *S. epidermis* and *S. aureus*) as well as gram-negative bacterial strains (*P. aeruginosa*, *E. coli* and *A. hydrophila*). The zone of inhibition was found in the range of 15-20 mm and MIC value in the range 50-100 μg/mL. This study can be used in designing of synthesis of compounds with better antibacterial efficacy.

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