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Synthesis and antibacterial activity of substituted 2-phenyl-4-chromones

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ABSTRACT

One of the important classes of flavones is 2-phenyl-4-chromones widely distributed in the plant kingdom. Generally flavonoids are biological pigments have important roles in the growth and development of plants, protection against UV-β radiation forming antifungal barriers, antibacterial activities. The present work deals with the synthesis, characterization and antibacterial activity of substituted 3-hydroxy-2-phenyl-4-chromones. The synthesized compounds were characterized by the IR, ^{1}H-NMR & Mass spectral studies. Out of 10 test compounds evaluated for their antibacterial activities, the test compounds NF-3 & NF-5 showed antibacterial activity against both gram positive & gram negative organisms similar to that of the standard antibiotics used.

Key words: 2-phenyl-4-chromone, chalcone, antibacterial activity.

INTRODUCTION

Chromone-4-ones are a class of naturally occurring low molecular weight compounds[1-2] widely distributed in the plant kingdom. These are of three types namely flavone (2-phenyl-4-chromone), isoflavone & neoflavone. 2-phenyl-4-chromones are generally oxygen containing heterocycles having fused ring system with many biological and pharmacological activities such as antibacterial, anticarcinogenic, anti-inflammatory [3-13] etc. Quercetin and related flavonoids are known to inhibit the growth of tumor cells and potentiates the cytotoxicity of DNA damaging anti-cancer drugs such as cisplatin. The discovery that a variety of flavonoids were protein-tyrosine kinases and angiogenesis inhibitors generated considerable interest in the structural activity relationship [14]. The protein-tyrosine kinase is thought to play a key role in mediating signal transduction from the CD4 receptor during lymphocyte activation and is found to elevate

in certain murine lymphomas and human colon carcinomas [15]. Further in vivo studies are necessary to develop flavonoid-based anticancer strategies. The human body cannot produce bioflavonoids sometimes referred to as Vit 'P'[3] which is supplied in the diet .The dietary intake of flavonoids is estimated to be between 23-1000mg/day. The compounds containing flavonoid structure are also reported to posses antimicrobial, analgesic and anti-inflammatory activity [16]. The aim of the study was to synthesize substituted 2- phenyl-4-chromones and to evaluate them for their antibacterial activity.

MATERIALS AND METHODS

All the chemicals required for the synthesis of the compounds were obtained from Merck and SD Fine chemicals.

Synthesis of 4-chloro-3-methyl phenyl acetate (II)

To a solution of 71 mL (0.5 mole) of 4-chloro-3-methyl phenol **(I)** in 320 mL of 10% sodium hydroxide contained in 1-liter beaker was added 350 g of crushed ice followed by 65 g (60 mL, 0.635 mole) acetic anhydride. The mixture was shaken vigorously for 5 minutes. Separation of the resulting emulsion was facilitated by adding about 20-25 mL of carbon tetrachloride. The organic layer was then washed carefully with dilute sodium bicarbonate solution until the effervescence ceases and distillation of carbon tetrachloride gave the 4-chloro-3-methyl phenyl acetate.

Synthesis of 5-chloro-2-hydroxy-4-methyl acetophenone (III)

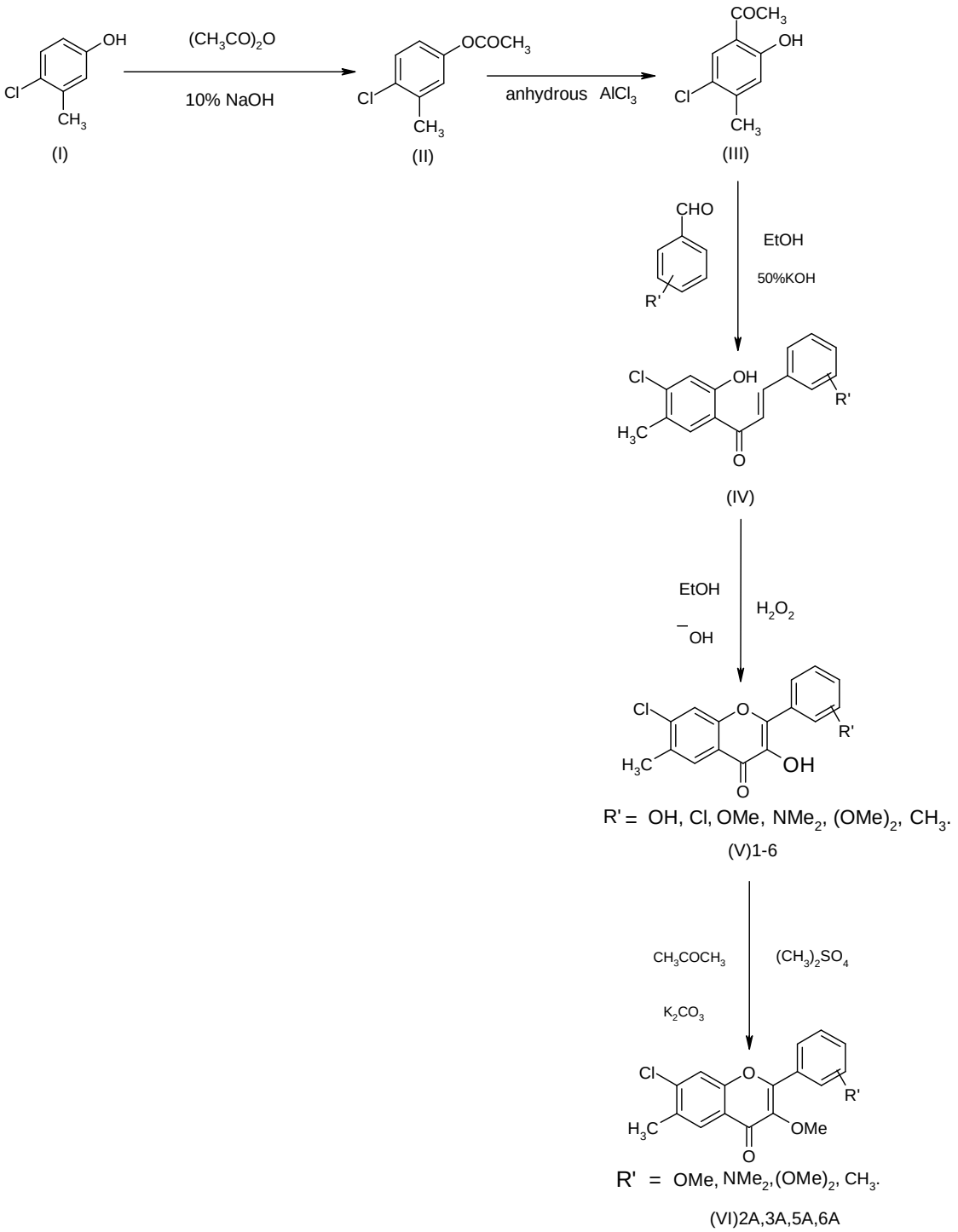
To a solution of 0.5 mole (92 mL) of 4-chloro-3-methyl phenyl acetate **(II)** in a 500 mL round bottom flask, 0.65 mole (87.1 g) of aluminum chloride was added and reflux condenser, provided with calcium chloride guard tube was attached and refluxed at 120 ^{0} C for 15 minutes. The resulting solution was cooled to room temperature followed by addition of ice-cold water and dilute HCl to neutralize excess $AlCl_3$ .The resulting solid was filtered and washed with cold water and was recrystallized from alcohol.

Synthesis of Chalcones (IV)

To a solution of 0.1 mole (18.5 g) of 5-chloro-4-methyl-2-hydroxy acetophenone **(III)** in 152 mL alcohol and 31 mL of 50% potassium hydroxide, 0.12 mole of aldehyde was added and the mixture was refluxed on water bath for 1 hrs and left overnight. The deep red solution was poured into crushed ice and acidified. The yellow precipitate that separated was filtered and recrystallized from aqueous alcohol.

Synthesis of substituted 3-hydroxy 2-phenyl-4-chromones (V) [1-6]

To a suspension of 0.01 mole of chalcone **(IV)** in 85 mL ethanol was added 10 mL of 20% aq.sodium hydroxide with stirring, followed by the careful addition of 18 mL of 30% hydrogen peroxide over a period of 0.5 hrs. The reaction mixture was stirred for 3.0 to 3.5 hrs at 30 ^{o} C and poured into crushed ice containing 5N hydrochloric acid. The precipitate was filtered, washed, dried and recrystallized from ethyl acetate [6].


OH
Cl
CH3
(I)
(CH3CO)2O
10% NaOH
OCOCH3
Cl
CH3
(II)
anhydrous AlCl3
COCH3
OH
Cl
CH3
(III)
CHO
R'
EtOH
50%KOH
Cl
OH
R'
H3C
O
(IV)
EtOH
H2O2
OH
Cl
O
R'
H3C
OH
O
R' = OH, Cl, OMe, NMe2, (OMe)2, CH3.
(V)1-6
CH3COCH3
(CH3)2SO4
K2CO3
Cl
O
R'
H3C
OMe
O
R' = OMe, NMe2,(OMe)2, CH3.
(VI)2A,3A,5A,6A

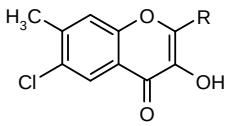
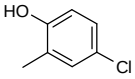
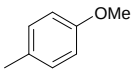
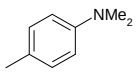
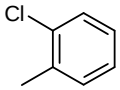
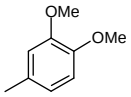
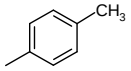
(Scheme-1)

Synthesis of substituted 3-methoxy 2-phenyl-4-chromones (VI) [2A,3A,5A,6A]
0.01 mole of 3-hydroxy flavone was suspended in dry acetone containing powdered anhydrous potassium carbonate (0.03 mole) and dimethyl sulphate (0.02 mole).The suspension was refluxed for 5 hrs. The solvent was evaporated under pressure and the residue diluted with water. The precipitate obtained was filtered, washed, dried and recrystallized from alcohol (Scheme-1) [6]

RESULTS AND DISCUSSION

The Chromone derivatives were synthesized successfully in moderate to good yields. The newly synthesized compounds were identified on the basis of R_f values; melting point range; IR, ^{1}H-NMR, Mass spectral analysis and elemental analysis. All the newly synthesized derivatives were screened for antibacterial activity using agar diffusion method.

Table No.1 Physical properties of various substituted 3-hydroxy 2-phenyl-4-chromones

Compound Code	Structure 'R' 	Chemical Name	Mol. Formula	Mol. Wt	Melting Point	Yield
NF-1		6-chloro-3-hydroxy-7-methyl-2-[(2'-hydroxy,5'-chloro)phenyl]-4-chromone	$C_{16}H_{10}O_4Cl_2$	338	232 ^oC	68%
NF-2		6-chloro-3-hydroxy-7-methyl-2-[(4'methoxy)phenyl]-4-chromone	$C_{17}H_{13}O_4Cl$	316	205-206 ^oC	71%
NF-3		6-chloro-3-hydroxy-7-methyl-2[(4'-dimethylamino) phenyl]-4-chromone	$C_{18}H_{16}O_3NCl$	329	230 ^oC	69%
NF-4		6-chloro-3-hydroxy-7-methyl-2-[(2'-chloro) phenyl]-4-chromone	$C_{16}H_{11}O_3Cl_2$	320	Above 235 ^oC	75%
NF-5		6-chloro-3-hydroxy-7-methyl-2-[(3',4'-dimethoxy)phenyl]-4-chromone	$C_{18}H_{15}O_5Cl$	346	178-181 ^oC	64%
NF-6		6-chloro-3-hydroxy-7-methyl-2-[(4'-methyl) phenyl]-4-chromone	$C_{17}H_{13}O_3Cl$	300	199-201 ^oC	69%

Antimicrobial activity
All the ten test compounds synthesized, purified and characterized were screened for their qualitative antimicrobial activity. They were tested against four species of bacteria namely, *Bacillus subtilis* (Gram-positive), *Escheria coli* (Gram-negative), *Pseudomonas aeruginosa* (gram-negative), *Staphylococcus aureus* (Gram-positive). The technique used was Agar Diffusion Method using 100 µg/0.1 mL of Amoxicillin and Gentamycin as standard. Specified quantity of beef extract, peptone & agar were accurately weight, dissolved in distilled water and sterlised by autoclaving at 121^{o}C for 15 minutes. The plates were prepared with the assay media was cooled to 50 ^{o}C. It was then inoculated with the test organisms. Four bores per plate were made using sterile cork borer. The above operation was carried out under asceptic condition in

sterile area. The following Table-3 indicates the antimicrobial activity of the test compounds synthesized.

Table No. 2 Physical properties of various substituted 3-methoxy -2-phenyl-4-chromones

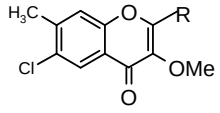
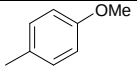
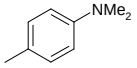
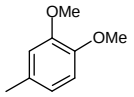
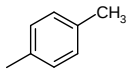
Compound Code	Structure 'R' 	Chemical Name	Mol. Formula	Mol. Wt	Melting Point	Yield
NF-2A		6-chloro-3-methoxy-7-methyl-2-[(4'methoxy) phenyl]- chromone	$C_{18}H_{15}O_4Cl$	330	148-153^o C	69%
NF-3A		6-chloro-3-methoxy-7-methyl-2[(4'-dimethylamino)phenyl]-chromone	$C_{19}H_{18}O_3NCl$	343	150^o C	65%
NF-5A		6-chloro-3-methoxy-7-methyl-2-[(3',4'-dimethoxy)phenyl] chromone	$C_{20}H_{17}O_5Cl$	360	150^o C	64%
NF-6A		6-chloro-3-methoxy-7-methyl-2-[(4'-methyl) phenyl]- chromone	$C_{18}H_{15}O_3Cl$	314	122-124^o C	68%

Table 3: Antimicrobial activity of synthesized molecules

Compound Code	Zone of inhibition (in mm)			
	B.S	*P.a*	*E.c*	*S.a*
Amoxicillin	28	29	35	32
Gentamycin	26	31	29	33
NF-1	14	13	11	12
NF-2	13	14	12	10
NF-2A	11	12	10	09
NF-3	21	20	24	25
NF-3A	21	20	23	22
NF-4	09	07	10	08
NF-5	21	20	19	22
NF-5A	11	06	12	11
NF-6	04	06	10	09
NF-6A	06	07	10	12

Spectral Analysis

6-chloro-3-hydroxy-7-methyl-2-[(2'-hydroxy,5'-chloro)phenyl]-chromone-4-one.(NF-1)

KBr (cm^{-1}): 3251.8 (b, O-H str), 2862.2 (w, C-H str), 1600.8 (s, C=O str), 1554.5,1461.9, 1429.2 (s, Ar C=C str),1118..6 (s, C-O str), 1099.3 (s, C-Cl str), 759.9 (s, Ar =C-H str).

6-chloro-3-hydroxy-7-methyl-2-[(4'-methoxy)phenyl]-chromone-4-one.(NF-2)

KBr (cm^{-1}).3321.2 (b, O-H str), 2997.7, 2842.9 (w, C-H str), 1600.8 (s, C=O str), 1554.5, 1510.2, 1465.8 (s, Ar C=C str), 1112.9 (s, C-O str), 1024.1 (C-Cl str); ^{1} H-NMR(400MHz in $CDCl_3$): 8.19-8.21[d,2H,Ar-H(e), J_{ef} = 9.10 Hz], 8.18[s,1H, Ar-H (b)], 7.47 [s, 1H, Ar-H (c)], 7.03-7.05 [d,2H,Ar-H (f), J_{ef} = 9.08 Hz], 6.89 [s,1H, O-H, (d)], 3.89(s,3H, OCH_3 (g)], 2.52 [s,3H,CH_3 (a)]; MS m/e = 316.

6-chloro-3-methoxy-7-methyl-2-[(4'-methoxy) phenyl]-chromone-4-one.(NF-2A)
KBr (cm^{-1}): 3045.6 (w, Ar C-H str), 2931.6 (C-H str), 1649.0 (s, C=O str), 1558.4, 1508.2, 1450.4 (s, Ar C=C str), 1257. (s, C-O str), 829.3 (s, Ar =C-H str), 102225 (m, C-Cl str). ^{1}H-NMR(400MHz in acetone): 8.11-8.13[d,2H,Ar-H(e), J_{ef} = 9.06 Hz], 8.05[s,1H, Ar-H (b)], 7.69 [s, 1H, Ar-H (c)], 7.11-7.13 [d,2H,Ar-H (f), J_{ef} = 9.05 Hz], 3.91 [s,3H, O-CH_3, (d)], 3.88 [s, 3H,-OCH_3 (g)], 2.52[s,3H, CH_3 (a)]; MS m/e = 330.

6-chloro-3-hydroxy-7-methyl-2-[(4'-dimethylamino)-phenyl]-chromone-4-one.(NF-3)
KBr (cm^{-1}). 3234.4 (b, s O-H str), 3010.7 (w, C-H str), 1596.9 (s, C=O str), 1461.9 (s, Ar C=C str), 1361.7 (s, C-N str), 1201.6 (s, C-O-C str), 1201.6 (m, C-O str), 1070.4 (w, C-Cl str), 777.3 (m, Ar =C-H O.P.B). ^{1} H-NMR(400MHz in $CDCl_3$): 8.16 [s,1H, Ar-H (b)], 8.13-8.15[d,2H,Ar-H(e), J_{ef} = 9.2 Hz],7.42 [s, 1H, Ar-H (C)]6.85 [s,1H, OH (D)], 6.77-6.79 [d, 2H, Ar-H(f), J_{ef} = 9.18 Hz], 3.06 [s,6H, NMe_2 (G)], 2.50[S,3h,CH_3 (a)]; MS m/e = 331(M+2), m/e = 329.

6-chloro-3-methoxy-7-methyl-2-[4'-dimethylzmino)-phenyl]-chromone-4-one.(NF-3A)
KBr (cm^{-1}): 3015.3 (w, Ar C-H str), 2904.6, 2813.9 (m, C-H str), 1602.7 (s, C=O str), 1554.5, 1523.7,1448.4 (s, Ar C=C str), 1359.7 (s, C-N str), 1203.5 (s, C-O str), 1070.4 (m, C-Cl str), 775.3 (s, Ar =C-H str).

6-chloro-3-hydroxy-7-methyl-2-[(2'-chloro) phenyl]-chromone-4-one.(NF-4)
KBr cm^{-1}): 3280.7 (b,s, O-H str), 3074.7 (w, Ar C-H str), 2923.9, 2856.4 (m, C-H str), 1616.2 (s,C=O str), 1554.5, 1452.3 (s, Ar C=C str), 1209.3 (m, C-O str), 1085.8 (m, C-Cl str),754.1 (s, Ar =C-H O.P.B)

6-chloro-3-hydroxy-7-methyl-2-[(3',4'-dimethoxy)phenyl]-chromone-4-one.(NF-5)
KBr (cm^{-1}): 3269.1 (b, s, O-H str), 2931.6, 2835.2 (m, C-H str), 1604.7 (s, C=O str), 1552.6, 1463.9, 1433.0 (s, Ar C=C str), 1110.9 (s, C-O str), 1024.1 (s, C-Cl str).

6-chloro-3-methoxy-7-methyl-2-[(3,4-dimethoxy)-phenyl]-chromone-4-one.(NF-5A)
KBr (cm^{-1}) : 2937.4, 2842.9, (m, C-H str), 1604.7 (s, C=O str), 1556.4, 1517.4, 1456.2 (s, Ar C=C str), 1141.8 (s, C-O str), 1026.1 (m, C-Cl str) 800.4 (m, Ar =C-H O.P.B).

6-chloro-3-hydroxy-7-methyl-2-[(4'-methyl)-phenyl-chromone -4-one. (NF-6)
KBr (cm^{-1}): 3280.7 (b, s, O-H str), 2960.2 (w, C-H str), 1604.7 (s, C=O str), 1554.5, 1460.0 (m, Ar C=C str), 1209.3 (s, C-O str), 1116.7 (m, C-Cl str), 823.5 (m, Ar =C-H O.P.B).

6-chloro-3-methoxy-7-methyl-2-[(4'-methyl)-phenyl]-chromone-4-one.NF-6A)
(KBr cm^{-1}): 2978.8, 2928.9 (m, C-H str), 1625.9 (s, C=O str), 1556.4, 1508.2, (s, Ar C=C str), 1209.3 (s, C-O str), 1020.3 (s, C-Cl str), 746.4 (m, Ar =C-H O.P.B).

CONCLUSION

From the antibacterial screening data it was concluded that the compounds NF-3, NF-5 showed activity against both gram positive and gram negative bacteria and were found to have zones of inhibition value at 21 mm and 21 mm respectively against *Bacillus subtilis;* 21 mm and 20 mm respectively against *Pseudomonas aeruginosa;* 24 mm and 19 mm respectively against

Escherichia coli; 25 mm and 22 mm respectively against *Staphylococcus aureus* as shown in the experimental studies.

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