International Journal of Knowledge Engineering
ISSN: 0976-5816 & E-ISSN: 0976-5824, Volume 3, Issue 1, 2012, pp.-148-150.
Available online at http://www.bioinfo.in/contents.php?id=40

SYNTHESIS AND BIOLOGICAL EVALUATION OF 3-HYDROXY-2-PHENYL-4*H*-CHROMEN-4 ONES

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Received: February 28, 2012; Accepted: March 06, 2012

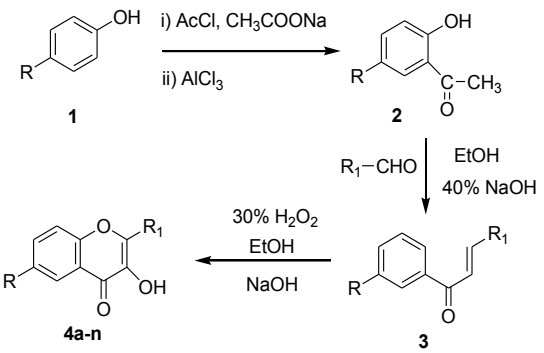
Abstract- 33-Hydroxy-2-phenyl-4*H*-chromen-4-ones (4a-n) have been synthesised from appropriate 1-(2-hydroxyphenyl)-3-phenylprop-2-en -1-one (3a-n). All compounds were evaluated for antimicrobial activity against *S. Aureus, B. Subtilis, E. Coli* and *P. Aerugenosa* as well as fungi e.g. *C. Albicans* and *A. Niger* and good results were obtained as in comparison with the standards. These compounds have been characterized on the basis of IR, ^{1}H NMR, Mass spectrometry and elemental analysis.
Keywords- Chalcones, flavones, antimicrobial activity

Citation: Mangesh Gharpure, et al (2012) Synthesis and Biological evaluation of 3-hydroxy-2-phenyl-4*H*-chromen-4 ones. International Journal of Knowledge Engineering, ISSN: 0976-5816 & E-ISSN: 0976-5824, Volume 3, Issue 1, pp.-148-150.

Introduction

Chromones constitute one of the major class of naturally occurring compounds, and interest in their chemistry continues unabated because of their usefulness as biologically active agents. Some of the biological activities attributed to chromone derivatives include cytotoxic (anticancer), neuroprotective, HIV-inhibitory, antimicrobial, antifungal and antioxidant activity, due to their abundance in plants and their low mammalian toxicity, chromone derivatives are present in large amounts in the human diet. The synthesis of chromone derivatives is a research field of great interest and has long history. Flavonoids (2-phenyl chromone derivatives) are phenolic compounds widely distributed in the plant kingdom. They are known to exhibit antioxidant, anti-inflammatory, antimicrobial, antihypertensive, antiplatelet, gastroprotective, antitumor, antiallergic, etc activies. Flavonoids and iso-flavonoids, which are natural components of plants with antifungal properties, have been investigated. Consideration has been given to increase the understanding of the mode of action of these natural fungicides and of improving their effectiveness through substitutions. These vast literatures prompted us to modify the benzopyrone ring to explore the biological activities associated with this nucleus.[1-8]
In the present work, 3-Hydroxy-2-phenyl-4*H*-chromen-4-ones (2-Aryl/heteryl-3-hydroxy chromones) have been synthesized and explored for antimicrobial activities.

Results and Discussion



Scheme 1. Synthesis of 3-Hydroxy-2-phenyl-4*H*-chromen-4-ones (4a-n)

Acetylation (esterification) of phenols followed by Fries migration gave 2-hydroxy acetophenones, reaction of 2-hydroxy acetophenones with different aromatic aldehydes produced 1-(2-hydroxyphenyl)-3-phenylprop-2-en-1-one (chalcones) (3a-n), which on cyclization in alkaline H_2O_2 yielded 2-aryl/heteryl-3-hydroxychromones (flavones) (4a-n) in excellent yield (Scheme (1)).

The IR spectrum of 4a shows a broad peak at 3222 (Ar-OH), due to presence of phenolic –OH group, 3033, 3075 (aromatic str.), 1611 (C=O pyrone ring). ^{1}H NMR δ 7.02 (s, 1H, OH), 7.26-8.27 (m, 9H, Ar-H). All the compounds (4a-n) gave satisfactory IR, NMR, Mass spectra and Elemental analysis data correlation with the assigned structure.

Biological Activity

Antibacterial activity

The synthesized compounds were screened for their antibacterial activities against pathogenic bacteria such as *E. Coli*, *S. Aureus*, *B. Subtilis* and *P. Aeruginosa* using the cup plate diffusion method. The test compounds were dissolved in dimethyl sulphoxide at a concentration of 100 µg/mL using Ciprofloxacin and Sulphacetamide as a standard drug. All the inoculated plates were incubated at 35 °C and the results were evaluated after 24 h of incubation.

Antifungal activity

The synthesized compounds were also screened for their antifungal activity against *A. Niger* and *C. Albicans* using the cup plate diffusion method. The test compounds were dissolved in dimethyl sulphoxide at a concentration of 100µg/mL. The zone of inhibition was observed after 7 days at 25 ^{0}C and it was compared with Gentamycin and Clotrimazole as standard drugs as shown in Table 1.

Table 1- Biological activity of 3-Hydroxy-2-phenyl-4H-chromen-4-ones (4a-n).

Zone of Inhibition[b] (mm)						
	Antibacterial Activity				Antifungal Activity	
Compd	Gram-positive		Gram-negative			
	SA	BS	EC	PA	CA	AN
4a	18	18	19	18	17	16
4b	16	17	18	16	15	13
4c	19	16	17	16	17	16
4d	18	19	20	18	18	16
4e	15	16	16	15	14	15
4f	16	18	18	17	15	17
4g	15	16	16	14	14	15
4h	17	16	15	12	13	-
4i	19	21	21	20	19	17
4j	21	22	19	20	18	21
4k	16	15	17	17	16	18
4l	15	16	16	14	15	17
4m	17	18	18	15	16	19
4n	16	15	17	11	14	-
Std1	33	29	34	22	21	25
Std2	31	26	29	21	23	24

Key to symbols; SA= S. Aureus, BS= B. Subtilis, EC=E. Coli, PA= P. Aeruginosa, CA=C. Albicans and AN=A. Niger
b = average zone of inhibition in mm,
for antibacterial activity: Std. 1 = Ciprofloxacin and Std. 2= Sulphacetamide, for antifungal activity:
Std. 1 = Gentamycin and Std. 2 = Clotrimazole

Experimental

All the chemicals and solvents were obtained from Merck (LR grade) and were used without further purification. Melting points were taken in an open capillary tube and are uncorrected. FT-IR spectra were recorded (KBr disk) on a Shimadzu 8101A FT-IR spectrophotometer. ^{1}H-NMR were obtained from Bruker Avance II 400MHz spectrophotometer using tetramethylsilane as an internal standard in $CDCl_3$. Mass spectra were recorded on water Micromass Q-T of Micro spectrometer equipped with an ESI source. All the elemental analyses were done using Perkin Elmer 2400 CHN analyzer. The reactions were monitored on pre-coated TLC plates (Silica gel 60 F254, Merck), using iodine vapor as visualizing agent.

General procedure for the preparation of 3-hydroxy-2-phenyl-4*H*-chromen-4-one (**4a**). The mixture of 1-(2-hydroxyphenyl)-3-phenylprop-2-en-1-one **3** (2.24 gm, 0.01 mol), ethanol (50 mL), NaOH (10%, 56 mL) and H_2O_2 (30%, 13 mL) was stirred vigorously for 30 minutes and kept for 4 hrs at ice cold condition. It was poured on to cold 5N, 80 mL HCl. The solid was filtered, washed with water, dried and crystallised from alcohol (yield 66%); mp 170 °C; FT-IR (KBr): 3222 (Ar-OH), due to presence of phenolic –OH group, 3033, 3075 (aromatic str.), 1611 (C=O pyrone ring) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.02 (s, 1H, OH), 7.26-8.27 (m, 9H, Ar-H) ppm; MS-EI, m/z = $(M)^+$ = 238. Anal. Calcd for $C_{15}H_{10}O_3$: C, 75.62; H, 4.23%. Found: C, 75.71; H, 4.13%. Similarly, other flavones (**4b-n**) were synthesized using this method and spectral data of these compounds are given as follows.

3-hydroxy-2-*p*-tolyl-4*H*-chromen-4-one (4b): Yield 69%; mp 206 °C; FT-IR (KBr): 3218 (Ar-OH), 1615 (C=O pyrone ring) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.35 (s, 3H, CH_3), 7.02 (s, 1H, OH), 7.26-8.27 (m, 8H, Ar-H) ppm; MS-EI, m/z = 252 $(M)^+$. Anal. Calcd for $C_{16}H_{12}O_3$: C, 76.18; H, 4.79%. Found: C, 76.11; H, 4.85%.

3-hydroxy-2-(3,4-dimethoxyphenyl)-4*H*-chromen-4-one (4c): Yield 68%; mp 210 °C; FT-IR (KBr): 3212 (Ar-OH), 1622 (C=O pyrone ring) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.95 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 7.02 (s, 1H, OH), 7.00-8.25 (m, 7H, Ar -H) ppm; MS-EI, m/z = $(M)^+$ = 298. Anal. Calcd for $C_{17}H_{14}O_5$: C, 68.45; H, 4.73%. Found: C, 68.53; H, 4.67%.

6-chloro-3-hydroxy-2-(3,4-dimethoxyphenyl)-4*H*-chromen-4-one (4d). Yield 67%; mp 262 °C; FT-IR (KBr): 3226 (Ar-OH), 1618 (C=O pyrone ring) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.95 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 7.02 (s, 1H, OH), 7.00-8.25 (m, 6H, Ar -H) ppm; MS-EI, m/z = $(M)^+$ = 332. Anal. Calcd for $C_{17}H_{13}ClO_5$: C, 61.36; H, 3.94%. Found: C, 61.42; H, 3.99%.

2-(4-chlorophenyl)-3-hydroxy-4H-chromen-4-one (4e). Yield 65%; mp 192 °C; FT-IR (KBr): 3202 (Ar-OH), 1619 (C=O pyrone ring) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.02 (s, 1H, OH), 7.26-8.27 (m, 8H, Ar-H) ppm; MS-EI, m/z = $(M)^+$ = 272. Anal. Calcd for $C_{15}H_9ClO_3$: C, 66.07; H, 3.33%. Found: C, 66.14; H, 3.29%.

6-chloro-2-(4-chlorophenyl)-3-hydroxy-4*H*-chromen-4-one (4f). Yield 66%; mp 232 °C; FT-IR (KBr): 3212 (Ar-OH), 1608 (C=O pyrone ring) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.02 (s, 1H, OH),

7.26-8.27 (m, 7H, Ar-H) ppm; MS-EI, m/z = $(M)^+$ = 306. Anal. Calcd for $C_{15}H_8Cl_2O_3$: C, 58.66; H, 2.63%. Found: C, 58.72; H, 2.69%.

6-chloro-3-hydroxy-2-phenyl-4*H*-chromen-4-one (4g). Yield 68%; mp 169 °C; FT-IR (KBr) : 3227 (Ar-OH), 1616 (C=O pyrone ring) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.02 (s, 1H, OH), 7.26-8.27 (m, 8H, Ar-H) ppm; MS-EI, m/z = $(M)^+$ = 272. Anal. Calcd for $C_{15}H_9ClO_3$: C, 66.07; H, 3.33%. Found: C, 66.19; H, 3.45%.

6-chloro-2-(4-(dimethylamino)phenyl)-3-hydroxy-4*H*-chromen-4-one (4h). Yield 66%; mp 242 °C; FT-IR (KBr): 3215 (Ar-OH), 1632 (C=O pyrone ring) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.06 (s, 6H, $N(CH_3)_2$), 6.89 (s, 1H, OH), 6.87-8.24 (m, 7H, Ar-H) ppm; MS-EI , m/z = $(M)^+$ = 315. Anal. Calcd for $C_{17}H_{14}ClNO_3$: C, 64.67; H, 4.47; N, 4.44%. Found: C, 64.71; H, 4.39; N, 4.48%.

2-(furan-2-yl)-3-hydroxy-4*H*-chromen-4-one (4i). Yield 64%; mp 151 °C; FT-IR (KBr): 3218 (Ar-OH), 1617 (C=O pyrone ring) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 11.22 (s, 1H, OH), 5.11-8.16 (m, 7H, Ar-H) ppm; MS-EI, m/z = $(M)^+$ = 228. Anal. Calcd for $C_{13}H_8O_4$: C, 68.42; H, 3.53%. Found: C, 68.47; H, 3.59%.

6-chloro-2-(furan-2-yl)-3-hydroxy-4*H*-chromen-4-one (4j). Yield 64%; mp 212 °C; FT-IR (KBr): 3229 (Ar-OH), 1615 (C=O pyrone ring) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 11.22 (s, 1H, OH), 5.11-8.16 (m, 6H, Ar-H) ppm; MS-EI, m/z = $(M)^+$ = 262. Anal. Calcd for $C_{13}H_7ClO_4$: C, 59.45; H, 2.69%. Found: C, 59.55; H, 2.63%.

2-(4-fluorophenyl)-3-hydroxy-4*H*-chromen-4-one (4k). Yield 63%; mp 162 °C; FT-IR (KBr): 3220 (Ar-OH), 1614 (C=O pyrone ring) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.02 (s, 1H, OH), 7.26-8.27 (m, 8H, Ar-H) ppm; MS-EI, m/z = $(M)^+$ = 256. Anal. Calcd for $C_{15}H_9FO_3$: C, 70.31; H, 3.54%. Found: C, 70.44; H, 3.51%.

6-chloro-2-(4-fluorophenyl)-3-hydroxy-4*H*-chromen-4-one (4l). Yield 65%; mp 215 °C; FT-IR (KBr): 3221 (Ar-OH), 1613 (C=O pyrone ring) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.02 (s, 1H, OH), 7.26-8.27 (m, 7H, Ar-H) ppm; MS-EI, m/z = $(M)^+$ = 290. Anal. Calcd for $C_{15}H_8ClFO_3$: C, 61.98; H, 2.77%. Found: C, 61.92; H, 2.83%.

6-chloro-3-hydroxy-2-(4-methoxyphenyl)-4*H*-chromen-4-one (4m). Yield 68%; mp 219 °C; FT-IR (KBr): 3225 (Ar-OH), 1617 (C=O pyrone ring) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.95 (s, 3H, (OCH_3), 7.02 (s, 1H, OH), 7.00-8.25 (m, 7H, Ar-H) ppm; MS-EI, m/z = $(M)^+$ = 302. Anal. Calcd for $C_{16}H_{11}ClO_4$: C, 63.48; H, 3.66%. Found: C, 63.40; H, 3.74%.

2-(4-(dimethylamino)phenyl)-3-hydroxy-4*H*-chromen-4-one (4n). Yield 62%; mp 196 °C; FT-IR (KBr): 3227 (Ar-OH), 1621 (C=O pyrone ring) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.06 (s, 6H, $N(CH_3)_2$), 6.89 (s, 1H, OH), 6.87-8.24 (m, 8H, Ar-H) ppm; MS-EI, m/z = $(M)^+$ = 281. Anal. Calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98%. Found: C, 72.70; H, 5.25; N, 5.03%.

Conclusions

3-Hydroxy-2-phenyl-4*H*-chromen-4-ones were synthesized with good yield as well as purity. The compounds 4i and 4j were more active in reducing microbial growth than the other corresponding compounds. The present study demonstrates that the antimicrobial potential of certain flavonoids increases significantly by a simple chemical modification.

Acknowledgments

The authors are thankful to the Head, Department of Chemistry and Head, Department of Pharmacy, R.T.M. Nagpur University, India for providing necessary facilities. Thanks are due to SAIF Chandigarh, India for providing spectral analysis.

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