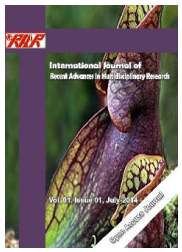

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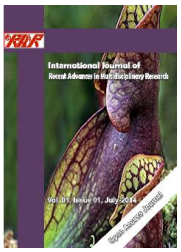

Research Article

SYNTHESIS, CHARACTERIZATION AND EVALUATION OF ANTIMICROBIAL PROFILE OF SOME NOVEL FLAVANOID DERIVATIVES

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ABSTRACT

The objective of the present work was the synthesis of 2- (2, 3, 4, and 5 substituted phenyl) 3-hydroxy-4H-Chromen-4-one and evaluation of *in-vitro* antimicrobial activity. Based on this a new series of compound had been planned to synthesize by reacting 2-hydroxy acetophenone and various aromatic aldehydes in the presence of potassium hydroxide, methanol and 30% hydrogen peroxide. The synthesized compounds were characterized by IR, NMR, and Mass spectroscopy. The *in-vitro* antimicrobial profile of newly synthesized compounds were carried out by using agar diffusion method using bacterial cultures of *Staphylococcus aureus* (*ATCC 9144*) and *Escherichia coli* (*ATCC 25922*) and fungal culture of *Aspergillus niger* (*ATCC 9029*). By observing it was found that most of the synthesized compounds executed moderate to good antimicrobial activity against the tested micro-organisms. The most of the synthesized compounds were active against all the tested micro-organisms for antimicrobial activity with an MIC range of 15-40µg/ml. The MIC values for the synthesized compounds were found to be 4B (MIC of 15 µg / ml), 4J(MIC of 16 µg / ml), and 4E (MIC of 17) against *Staphylococcus aureus* (*ATCC 9144*) and 4B (MIC of 16 µg / ml), 4J (MIC of 19 µg / ml), and 4E (MIC of 18) against *Escherichia coli* (*ATCC 25922*) and 4A (MIC of 16 µg / ml), 4C (MIC of 19 µg / ml), and 4E MIC of 18 µg / ml) against *Aspergillus niger* (*ATCC9029*).

INTRODUCTION

Flavanoids belong to a large group of abundant plant secondary metabolites, which can be found in vascular plants like ferns, conifers and flowering plants (Di Carlo *et al*., 1999; Middleton *et al*., 2000). These natural compounds are generally divided into various classes on the basis of their molecular structures including chalcones, flavones, flavanones, flavanols, and anthocyanidins. Approxymately, 4000 varieties of flavanoids have been identified and many of these are intense pigments, providing a spectrum of yellow, red and blue colours in flowers, fruits and leaves (Middleton *et al*., 2000; Trossel, 1997). Besides their contribution to plant colour, flavanoids have several pharmacological benefits such as anticancer, anti inflammatory, anti-allergic and are known as effective anti oxidants, metal chelators and free radical scavengers (Middleton *et al*., 2000; Pick *et al*., 2090-2102; Amaral *et al*., 2009; Burda *et al*., 2001; Ollis and Neoflavanoids, 1966).

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Natural and synthetic flavanoids are therefore of considerable interest in the development of novel therapeutic agents for various diseases and are generally believed to be non-toxic compounds since they are widely distributed in the human diet (Rackova *et al*., 2005; Harborne and Williams, 2000).

Chalcones: Chalcones, 1, 3-diphenylpropenones constitute one of the major classes of flavanoids with widespread distribution in vegetables, fruits, tea and soy (Middleton *et al*., 2000; Nowakowska, 2007). Prehistoric therapeutic applications of chalcones can be associated with the thousand-year old use of plants and herbs for the treatment of different medical disorders (Burlando *et al*., 2010). Contemporary studies report a generous variation of significant pharmacological activities of chalcones including antiproliferative, antioxidant, anti inflammatory and anti cancer effects (Nowakowska, 2007; Dimmock *et al*., 1999 and Bandgar *et al*., 2010). The chromone ring system, 1-benzopyran-4-one, is the core fragment in several flavanoids such as flavones, flanols and isoflavones (Ananthanarayan and Paniker's, 2006).

MATERIALS AND METHODS

The all chemicals used for the synthesis were of laboratory grade and analytical grade. The progress of the reaction was monitored by TLC using solvent systems of different polarities. TLC plates are pre-coated silica gel (HF254-200 mesh) aluminium and spots were visualized under U.V chamber. The melting point of newly synthesized flavanoid compounds were determined by open capillary method. The IR spectra of synthesized compounds were recorded by ABB Bomen FT-IR spectrometer MB 104 IR spectra recorder with KBr pellets**.** The H^1-NMR spectra of synthesized compounds were obtained from Bruker Avance II 400 MHz spectrometer using TMS as an internal standard in $CDCl_3$. All the Mass spectra (MS, HR-MS) of synthesized compounds were recorded on a LTQ-orbitrap linear ion trap high resolution mass spectrometer. The IR, H^1-NMR and Mass spectra were assigned to elucidate the structure of synthesized compounds (4A-4J).

General procedure for the synthesis of target compounds (Dajun Zhang, 2012)

2-hydroxy acetophenone [**(1),** 1.36gm, 0.01mol] and benzaldehyde [**(2),** 1.06gm, 0.01mol) were added to a solution of potassium hydroxide (1.12gm, 0.02 mol) in methanol (50 ml) at 0-5^oC. The reaction mixture was stirred over night at room temperature and then poured over crushed ice and acidified to P^H 6 with 2M Hcl.

The resulting yellow solid was filtered and the filter cake washed with water to give the crude product that either be crystallized from ethanol to afford pure 2-hydroxy chalcones 3A or used directly in the next reaction without further purification. 30% hydrogen peroxide (10 ml) was added to a well stirred solution of 3A (1.57gm, 0.007 mol) and 20% (w/w) aqueous potassium hydroxide (10 ml) in methanol (20 ml) at 0-5^oC in a drop wise manner over 1 hour.

The resulting reaction mixture was stirred for 10 hours and then poured on crushed ice and neutralized with 2M Hcl. Ethyl aceto acetate (50 ml) was added and the organic layer was washed successfully with water, a saturated solution of sodium bicarbonate, water and brine and then dried over anhydrous magnesium sulphate. The solvent was removed in vacuum and the residue was purified by column chromatography on silica gel (ACOEt/ n-hexane = 1/3 to 1/1) to give the title compound 4A as a white solid.

Synthetic scheme

[1] = 2-Hydroxy acetophenone
[2]=Various aromatic aldehydes
[A]=KOH, CH_3OH
[B]= KOH, CH_3OH, 30% H_2O_2

Spectral data

COMPOUND 4A: 2-(4-aminophenyl) 3-hydroxy-4H-Chromen-4-one

M.F: $C_{15}H_{11}NO_3$, M.W : 253.252, M.P-180^Oc, R_f-0.55, Yield-68.9%, FT-IR (KBr) : 3212 cm^{-1} (Ar-OH), 1622 cm^{-1} (C=O , Pyrone ring), ^{1}H-NMR (400MHz, $CDCl_3$) : δ (ppm) : 3.91 (s, H, $-NH_2$), 7.01 (s, 1H, OH), 7.00-8.25 (m, 7H, Ar-H), MS(ESI^+)m/z : 253.2 $(M+H)^+$, HR-MS(ESI^+)m/z: 253.07 $(M+H^+)$.

COMPOUND 4B: 2-(4-dimethylaminophenyl) 3-hydroxy-4H-Chromen-4-one

M.F: $C_{17}H_{15}NO_3$, M.W : 281.105, M.P-175^Oc, R_f-0.45, Yield-65.9%, FT-IR (KBr) : 3213 cm^{-1} (Ar-OH), 1625 cm^{-1} (C=O , Pyrone ring), ^{1}H-NMR (400MHz, $CDCl_3$) : δ (ppm) : 3.06 [s, 6H, $-N(CH_3)_2$], 6.87 (s, 1H, OH), 6.84-8.27 (m, 7H, Ar-H), MS(ESI^+)m/z : 281.3 $(M+H)^+$, HR-MS(ESI^+)m/z: 281.105 $(M+H^+)$.

COMPOUND 4C: 2-[4-dimethylaminophenol) 2-hydroxy phenyl] 3-hydroxy-4H-Chromen-4-one

M.F: $C_{17}H_{15}NO_4$, M.W : 297.1000, M.P-181^Oc, R_f-0.47, Yield-63.9%, FT-IR (KBr) : 3218 cm^{-1} (Ar-OH), 1618 cm^{-1} (C=O , Pyrone ring), ^{1}H-NMR (400MHz, $CDCl_3$) : δ (ppm) : 3.07 [s, 6H, $-N(CH_3)_2$], 6.88 (s, 1H, OH), 6.56 (s, 1H, OH), 6.87-8.27 (m, 7H, Ar-H), MS(ESI^+)m/z : 297.3 $(M+H)^+$, HR-MS(ESI^+)m/z: 297.1000 $(M+H^+)$.

COMPOUND 4D: 2-(4-aminopheno-2-hydroxyphenyl) 3-hydroxy-4H-Chromen-4-one

M.F: $C_{15}H_{11}NO_4$, M.W : 269.068, M.P-172^Oc, R_f-0.39, Yield-68.5%, FT-IR (KBr) : 3224 cm^{-1} (Ar-OH), 1617 cm^{-1} (C=O , Pyrone ring), ^{1}H-NMR (400MHz, $CDCl_3$) : δ (ppm) : 3.93 [s, 2H, $-NH_2$], 6.88 (s, 1H, OH), 6.59 (s, 1H, OH), 6.83-8.22 (m, 7H, Ar-H), MS(ESI^+)m/z : 269.2 $(M+H)^+$, HR-MS(ESI^+)m/z: 269.06 $(M+H^+)$.

COMPOUND 4E: 3-hydroxy-2-(4-hydroxy-3-methyl-phenyl)-4H-Chromen-4-one

M.F: $C_{16}H_{12}O_4$, M.W : 268.073, M.P-181^Oc, R_f-0.45, Yield-66.2%, FT-IR (KBr) : 3213 cm^{-1} (Ar-OH), 1620 cm^{-1} (C=O , Pyrone ring), ^{1}H-NMR (400MHz, $CDCl_3$) : δ (ppm) : 3.92 (s, 3H, $-OCH_3$), 7.02 (s, 1H, OH), 6.44 (s, 1H, OH), 6.81-8.21 (m, 7H, Ar-H), MS(ESI^+)m/z : 268.07 $(M+H)^+$, HR-MS(ESI^+)m/z: 268.26 $(M+H^+)$.

COMPOUND 4F: 2-(3,4-dimethoxyphenyl) 3-hydroxy-4H-Chromen-4-one

M.F: $C_{17}H_{14}O_5$, M.W : 298.084, M.P-174^Oc, R_f-0.48, Yield-62.9%, FT-IR (KBr) : 3225 cm^{-1} (Ar-OH), 1617 cm^{-1} (C=O , Pyrone ring), ^{1}H-NMR (400MHz, $CDCl_3$) : δ (ppm) : 3.94 (s, 3H, $-OCH_3$), 3.96 (s, 3H, $-OCH_3$), 7.03 (s, 1H, OH), 7.00-8.24 (m, 7H, Ar-H), MS(ESI^+)m/z : 298, $(M+H)^+$, HR-MS(ESI^+)m/z: 298.2 $(M+H^+)$.

COMPOUND 4G: 3-hydroxy-2-(3,4,5-trimethoxyphenyl)-4H-Chromen-4-one

M.F: $C_{17}H_{14}O_5$, M.W : 328.09, M.P-179^Oc, R_f-0.47, Yield-69.9%, FT-IR (KBr) : 3225 cm^{-1} (Ar-OH), 1617 cm^{-1} (C=O , Pyrone ring), ^{1}H-NMR (400MHz, $CDCl_3$) : δ (ppm) : 3.94 (s, 3H, $-OCH_3$), 3.96 (s, 3H, $-OCH_3$), 3.99 (s, 3H, $-OCH_3$), 7.03 (s, 1H, OH), 7.00-8.24 (m, 7H, Ar-H), MS(ESI^+)m/z : 328, $(M+H)^+$, HR-MS(ESI^+)m/z: 328.3 $(M+H^+)$.

Table 1. Zone of Inhibition of Tested Microorganisms by the Synthesized Compounds

Compounds	Bacteria						Fungi		
	S.aureus			*E.coli*			A.niger		
	Concentration (µgm/ml)								
	50	100	150	50	100	150	50	100	150
4A	18	21	25	19	21	25	19	21	24
4B	22	24	29	22	25	29	20	22	23
4C	23	27	31	18	21	24	23	25	28
4D	17	19	23	15	18	20	19	21	28
4E	25	29	32	23	27	29	22	25	31
4F	20	24	27	19	21	24	18	21	24
4G	23	25	27	24	28	31	23	26	31
4H	20	24	28	18	21	25	20	24	27
4I	17	19	22	19	22	24	22	25	29
4J	24	28	32	23	27	31	20	21	24
Tetracyclin (100 µg/ml)		38			38			–	
Griseofulvin (100 µg/ml)		–			–			38	

Table 2. For the Minimum Inhibitory Concentration of the Synthesized Compounds

Compounds	Mnimum Inhibitory Concentration (µg/ml)		
	Bacteia		Fungi
	S.aureus	E.coli	A.niger
4A	36	31	38
4B	15	16	16
4C	33	35	19
4D	38	40	33
4E	17	18	18
4F	34	37	25
4G	20	21	17
4H	35	35	40
4I	31	33	23
4J	16	19	25
Tetracyclin	0.2	0.3	-
Griseofulvin (100 µg/ml)	-	-	6.1

Table 3. Various flavanoid derivatives

3	R1	R2	R3	R4	4	R1	R2	R3	R4
3A	H	H	$-NH_2$	H	4A	H	H	H	$-NH_2$
3B	H	H	$N-(CH_3)_2$	H	4B	H	H	$N-(CH_3)_2$	H
3C	OH	H	$N-(CH_3)_2$	H	4C	OH	H	$N-(CH_3)_2$	H
3D	OH	H	$-NH_2$	H	4D	OH	H	$-NH_2$	H
3E	H	$-CH_3$	OH	H	4E	H	CH_3	OH	H
3F	H	$-OCH_3$	$-OCH_3$	H	4F	H	$-OCH_3$	$-OCH_3$	H
3G	H	$-OCH_3$	$-OCH_3$	$-OCH_3$	4G	H	$-OCH_3$	$-OCH_3$	$-OCH_3$
3H	H	$-OCH_3$	OH	$-OCH_3$	4H	H	$-OCH_3$	OH	$-OCH_3$
3I	OH	Cl	H	Cl	4I	H	Cl	Cl	H
3J	OH	H	H	$-NH_2$	4J	OH	H	H	$-NH_2$

COMPOUND 4H: 3-hydroxy-2-(4-hydroxy-3,5-dimethoxyphenyl)-4H-Chromen-4-one

M.F: $C_{17}H_{14}O_6$, M.W : 314.079, M.P-177^{O}c, R_f-0.46, Yield-67.9%, FT-IR (KBr) : 3224 cm^{-1} (Ar-OH), 1617 cm^{-1} (C=O , Pyrone ring), ^{1}H-NMR (400MHz, $CDCl_3$) : δ (ppm) : 3.94 (s, 3H, $-OCH_3$), 3.99 (s, 3H, $-OCH_3$), 6.03 (s, 1H, OH), 7.02 (s, 1H, OH), 7.00-8.24 (m, 7H, Ar-H), MS(ESI^+)m/z : 314, $(M+H)^+$, HR-MS(ESI^+)m/z: 314.2 $(M+H^+)$.

COMPOUND 4I: 2-(3,5-dichloro-2-hydroxyphenyl)-3-hydroxy-4H-Chromen-4-one

M.F: $C_{16}H_{10}Cl_2O_3$, M.W: 320, M.P-175^{O}c, R_f-0.44, Yield-62.2%, FT-IR (KBr) : 3224 cm^{-1} (Ar-OH), 1617 cm^{-1} (C=O , Pyrone ring), ^{1}H-NMR (400MHz, $CDCl_3$) : δ (ppm) : 6.03 (s, 1H, OH), 7.02 (s, 1H, OH), 7.00-8.24 (m, 7H, Ar-H), MS(ESI^+)m/z : 321.1, $(M+H)^+$, HR-MS(ESI^+)m/z: 320 $(M+H^+)$.

COMPOUND 4J: 2-(5-amino-2-hydroxyphenyl)-3-hydroxy-4H-Chromen-4-one

M.F: $C_{15}H_{11}NO_4$, M.W : 269.06, M.P-174^{O}c, R_f-0.47, Yield-63.6%, FT-IR (KBr) : 3222 cm^{-1} (Ar-OH), 1617 cm^{-1} (C=O , Pyrone ring), ^{1}H-NMR (400MHz, $CDCl_3$) : δ (ppm) : 3.93 [s, 2H, $-NH_2$], 6.03 (s, 1H, OH), 7.02 (s, 1H, OH), 7.00-8.24 (m, 7H, Ar-H), MS(ESI^+)m/z : 269, $(M+H)^+$, HR-MS(ESI^+)m/z: 269.2 $(M+H^+)$.

Evaluation of Antimicrobial Activity by paper disc diffusion method (Ananthanarayan and Paniker's, 2006; Vibhor *et al*., 2010 and Gaud and Gupta, 2004)

The sterilized (autoclaved at 120^{o}C for 30 min) medium was inoculated (1mL/100mL of medium) with the suspension [10^5 cfu m/l (colony forming unit per milliliter)] of the microorganism (matched to McFarland barium sulphate standard) and poured in Petri dish to give a depth of 3-4mm. The paper impregnated with the test compounds (50, 100,150 µg/ml in dimethylformamide) was placed on the solidified medium. The plates were pre-incubated for 1hr at RT and incubated at 37 ^{o}C for 24 hr for anti-bacterial and antifungal activities respectively. Tetracyclin (100 µg/disc) and Griseofulvin (100 µg/disc) were used as a standard drugs.

Determination of MIC by agar streak dilution method (Hawkey and Lewis, 1994)

MIC of the synthesized compounds was determined by agar streak dilution method. A stock solution of the synthesized compounds (100µg/ml) in Dimethyl formamide was prepared and graded quantities of the test compounds were incorporated in specified quantities of molten nutrient agar medium. A specified quantity of the medium containing the compounds was poured into a Petri dish to give a depth of 3-4mm and allowed to solidify. Suspension of the micro-organism were prepared to contain approximately10^5 cfu m/l and applied to plates with serially diluted compounds in Dimethyl formamide to be tested and incubated at 37^{o}C for 24hr. for bacteria and fungi. The MIC was considered to be the lowest concentration of the test substance exhibiting no visible growth of bacteria on the plate.

RESULTS AND DISCUSSION

Chemistry

The synthesis of target compounds (4A-4J) 2-(2, 3, 4, and 5 substituted phenyl) 3-hydroxy-4H-Chromen-4-one were carried out by reacting 2-hydroxy acetophenone and various aromatic aldehydes in the presence of potassium hydroxide, methanol and 30% hydrogen peroxide. The synthesized compounds were characterized by IR, NMR, and Mass spectroscopy. The progress of the reaction was monitored by TLC using solvent systems of different polarities. TLC plates are pre-coated silica gel (HF254-200 mesh) aluminium and spots were visualized under U.V chamber and the proposed structures of the synthesized compounds were ascertained by spectral data.

Antimicrobial Screening

The synthesized compounds were (50, 100 and 150 µg/ml) screened for antimicrobial activity by paper disc diffusion method. The experimental data had shown that most of the synthesized compounds executed moderate to good antimicrobial activity against the tested micro-organisms. When compared to standard drug (Tetracyclin) compounds 4B, 4E, 4G and 4J were found to exhibit good Anti-bacterial activity. When compared to standard drug (Griseofulvin) compounds 4C, 4E, 4G and 4I were found to exhibit good Anti-fungal activity. The MIC of synthesized compounds was screened by agar streak dilution method.

The experimental data had shown that most of the synthesized compounds executed moderate to good antibacterial and antifungal activity with an MIC range of 15-40µg/ml. The MIC values for the synthesized compounds were found to be 4B (MIC of 15 µg / ml), 4J (MIC of 16 µg / ml), and 4E (MIC of 17) against *Staphylococcus aureus (ATCC 9144)* and 4B (MIC of 16 µg / ml), 4J (MIC of 19 µg / ml), and 4E (MIC of 18) against Escherichia coli *(ATCC 25922)* and 4A (MIC of 16 µg / ml), 4C (MIC of 19 µg / ml), and 4E MIC of 18 µg / ml) against *Aspergillus niger(ATCC9029).*

Conclusion

By observing it was found that most of the newly synthesized compounds exhibited moderate to good antimicrobial activity against the tested micro-organisms. The synthesized compounds were active against all the tested micro-organism for antibacterial activity with an MIC range of 15-40µg/ml against *Staphylococcus aureus (ATCC 9144)* and *Escherichia coli (ATCC 25922)* and for antifungal activity with an MIC range of 15-40µg/ml against *Aspergillus niger(ATCC9029).*

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