Original Article

SYNTHESIS CHARACTERISATION AND BIOLOGICAL EVALUATION OF BIS-CHALCONES BASED ON RESORCINOL

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Abstract

The biogenetic antecedents of flavonoids and isoflavonoids, which are abundant in plants, are chalcones. They have antimitotic, antimutagenic, and antitumor-promoting properties, as well as antibacterial, antiviral, anti-inflammatory, and hepatoprotective properties.

Claisen condensation of 1:2 moles of 2,4-Diacetyl Resorcinol (DAR) and substituted aldehydes yielded novel bis-chalcones, which were characterized by 1HNMR, and 13C NMR. To determine whether these compounds have antibacterial activity, the disk diffusion method was performed. Microorganisms are Gram-positive and Gram-negative.

Keywords: Bis-Chalcones. 2, 4-Diacetyl Resorcinol (DAR). Claisen-Schmidt Condensation. FT-IR. 1HNMR. 13CNMR. Biological activity.

1. INTRODUCTION

Higher plants' biogenetic predecessors of flavonoids are unsaturated ketones (Chalcones). They're also known as chalcones since they're open-chain flavonoids that have two aromatic rings connected by a three-carbon chain. [1]

Chalcones have cytotoxicity against cancer cell lines,[2] antiviral activity,[3] and hepatoprotective action,[4] among other pharmacological activities. Transformability Hydroxyl group to phenoxy highlight via the hydrogen atom transfer process,. chalcones embrace hydroxyl substitution, which could significantly improve the antioxidant activity of chalcones.[5] The consequences on the central. nervous system (CNS) is, however, poorly understood. There is a wide range of human degenerative disorders,.antioxidants have been shown to provide prevention and treatment advantages, and Reactive oxygen.species (ROS) have been linked to several degenerative illnesses in humans.[6,7] In this study, novel bis-chalcone compounds were created by mixing 1,4-diacetyl benzene with various aldehydes in basic circumstances. Cyanopyridine derivatives were created by reacting cyanopyridine with ethyl cyanoacetate in the presence of ammonium acetate.

Using 2,4-dinitrophenyl hydrazine, bis-chalcones were cyclized to pyrazole analogs, in good yields.[8] Chalcones (pharmacophore1,3-diaryl.heteroaryl-2-propene-1) are a prominent pharmacophore found in the natural.sources..[9] 3-Methoxy hydroxyl oncocarpin.(NADH:.ubiquinone oxidoreductase activity inhibitor), xanthohumol (ant-oxidant), and flavonoid chalcone are instances of approved prescription medications that include this chemical framework (anticancer agents). There are also a variety of functionalized derivatives.

Four ranges of bis-chalcone compounds were created and synthesized, with core parts built on benzyl piperidinone, tetrahydrothiopyranone, pyridine, or biphenyl., allowing the development of a large number of bis-chalcones with different central cores, substitution patterns (Ortho, Meta, Para-positions), and perivascular substituent groups (aromatic rings substituted by pyridine).

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Chalcones contain a 1,3-diaryl propenone skeleton and are anti-inflammatory,[10,11] antiparasitic (antimalarial, antileishmanial),[11-13] antituberculosis,[14] antioxidant,[15,16] antimitotic,[17] anti-invasive,[11] and anticancer.[12-15] P-glycoprotein-mediated multidrug resistance control is also possible.[10] As part of our ongoing research into this important category of biologically active chemicals, we present the synthesis and in vitro biological evaluation of recognized [19, 20] bis-chalcones as NO production inhibitors and cytotoxic agents. The most frequent technique of synthesis is Claisen-Schmidt.condensation in a basic or acidic media under uniform conditions with diverse catalysts.[23-27]

Claisen-Schmidt Condensation was used to synthesize Bis-Chalcone derivatives. Considerable yields of bis-chalcone derivatives were obtained by treating 1,4-diacetyl benzene with substituted benzaldehyde.[28]

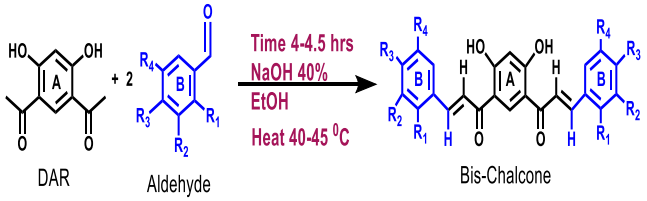
2. Experimental section

2.1 Apparatus and Chemicals

The Fisher-Johns melting point device was used to determine the uncorrected melting points. Using precoated TLC plates, the purity of the compounds was evaluated (Merck, 60F-254). 1H-NMR and 13CNMR spectra were recorded by Bruker Ascend 400 NMR spectrometer

2.2 Synthesis of 1, 1-(4,.6-dihydroxy-1,3- Arylene)bis(3-Aryl prop-2-en-1-one):

Diacetyl resorcinol (DAR) (0.01 mole) was added to 10 ml of 40 percent sodium hydroxide and 15 ml of pure ethanol. After being poured into a 100 ml round bottom flask, the mixture was stirred for 30 minutes before being added (0.02 moles) of a substituted aldehyde; the crude was neutralized with 50% HCl and recrystallized with ethanol after refluxing at (40-45) 0C on a water bath for (4-5 hours).



1. R_1 =H, R_2 = R_3 = R_4 = OCH_3
2. R_1 = R_2 = R_4 =H, R_3 =OH
3. R_1 = R_4=H, R_2 =NO_2, R_3 =OH
4. R_1 = R_2 = R_4 =H,R_3 =Cl
5. R_1 = R_4 = H,R_2 =OCH_3, R_3 =OH
6. R_1 =Cl, R_2 = R_3 =R_4=H

2.3 Method

1. 1,1-(4,6-dihydroxy-1,3-phenylene)bis(3-phenyl prop-2-en-1-)one():Chemical Formula: C24H18O4; yield 78.5%; m.p. 114-116 °C ; 1H NMR (499 MHz, acetone) δ 13.09 (s, 2H), 7.85 (d, J = 8.8 Hz, 2H), 7.47 (d, J = 12.6 Hz, 2H), 7.15 – 7.01 (m, 10H), 6.55 – 6.35 (m, 2H). 13C NMR (499MHz, CDCl3): d 205.28, 168.65, 147.87, 143.13, 137.81, 131.85, 124.61, 117.88, 113.45, 103.67.

2. 3-(4-hydroxyphenyl)-1-{5-[3-(4hydroxyphenyl)-2-propenoyl]-2,4-dihydroxyphenyl}-2-propen-1-one:. Chemical Formula C24H18O6;Yield 79 %; m.p. 169°C; 1H NMR (499 MHz, acetone) δ 13.73 (s, 2H,-OH), 8.98 (s, 2H,-OH), 7.94 (d, 2H), 7.58 (d, 2H), 7.43 (m, 8H), 6.43 (m, 2H).13C NMR (125MHz, CDCl3): d 203.84, 182.21, 168.65, 152.51, 137.81, 135.61, 133.44, 113.45, 107.45, 103.67.

3. 1,1'-(4,6-dihydroxy-1,3-phenylene)bis(3-(4-hydroxy-3-nitrophenyl)prop-2-en-1-one): Chemical Formula: C24H16N2O10.Yield 76 %; m.p. 169.°C; 1H NMR (499 MHz, acetone) δ 13.56 (s, 2H,-OH), 9.76 (s, 2H,-OH), 7.80 (d, J = 8.6 Hz, 2H),7.28(d, J =8.6,2H) 7.12-6.80 (m, 6H), 6.74-6.68 (m, 2H). 13C NMR (125MHz, CDCl3): d 205.71, 166.67, 144.11, 137.75, 136.80, 132.35, 131.37, 126.99, 116.03, 115.50, 113.96, 104.03.

4. 3-(2,4-Dichlorophenyl)-1-{5[3(2,4Dichlorophenyl)-2-propenoyl]-2,4dihydroxyphenyl}-2-propen-1-one: Chemical Formula: C24H14Cl4O4 Yield 81-83%; m.p. 164 °C; 1H NMR (499 MHz, acetone) δ 13.20 (s, 2H), 7.92 (d, J = 15.1 Hz, 2H), 7.66 (d, J = 18.0 Hz, 2H), 7.45 – 7.21 (m, 6H), 6.48 – 6.27 (m, 2H). 13C NMR (125MHz, CDCl3): d 205.35, 166.00, 142.68, 131.44, 131.31, 129.76, 129.36, 129.06, 128.71, 128.17, 127.31, 103.68.

5. 3-(4-hydroxy-3-methoxyphenyl)-1-{5-[3-(4-hydroxy-3-methoxyphenyl)-2-propenoyl]-2,4-dihydroxyphenyl}-2-propen-1-one:Chemical Formula: C26H22O8 Yield 84 %; m.p. °C; 1H NMR (499 MHz, acetone) δ 13.93 (s, 2H), 9.19 (s, 2H), 7.78 (d, J = 7.4 Hz, 2H), 7.44 (d, J = 12.3 Hz, 2H), 7.19 – 6.92 (m, 6H), 6.54 – 6.27 (m, 2H), 4.65 (s, 6H). 13C NMR (125MHz, CDCl3): d 206.14, 187.76, 166.00, 161.45, 157.53, 148.10, 142.28, 131.75, 128.17, 123.13, 122.53, 117.33, 113.68.

6. 1,1-(4,6-dihydroxy-1,3-phenylene).bis.(3-(2-chlorophenyl)prop-2-en-1-one): Chemical Formula: C24H16Cl2O4 Yield 79 %; m.p. 169°C; 1H NMR (499 MHz, acetone) δ 13.89 (s, 2H), 7.83 (d, J = 15.9 Hz, 2H), 7.68 (d, J = 15.9 Hz, 2H), 7.44-7.28 (m, 8H), 6.67-6.50 (m, 2H). 13C NMR (499MHz, CDCl3): d 205.27, 184.01, 168.66, 137.82, 128.72, 124.72, 116.73,114,87, 113.46, 112.42, 103.67, 97.68.

2.4 Antibacterial activity

At a dosage of 100µg/ ml,.antibacterial activity against Escherichia coli bacteria, as well as Gram-positive and Gram-negative Staphylococcus aureus bacteria, were tested in the samples. Freshly produced liquid agar media (20 mL/Petri dish) was used to fill each Petri dish, which was then dried in an incubator at 37 C for 1 hour. An L-shaped spreader was then used on each Petri plate to disperse a homogenous microbial culture. With an agar punch, 6 mm wells were punched out, and each one of them was labeled. The study even included a controlled experiment (solvent).

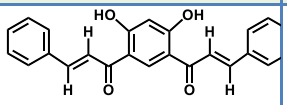
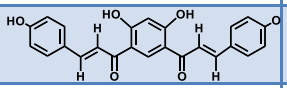
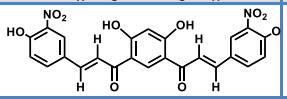
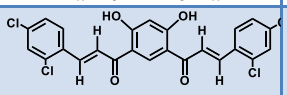
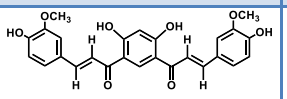
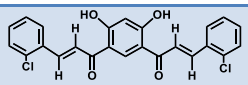
In acetone, the test chemical and the standard medicament

solutions (100g/mL) were made separately and applied to each well, with the Petri plates kept aseptically for 1 hour to allow the sample to diffuse. After diffusion, All Petri plates underwent a 24-hour incubation period at 37°C before the millimeter-scale diameter of the zone of inhibition was recorded. (Table 1).

Table 1 Antibacterial activity (MIC, 100µg/ ml) of bis Chalcones

Aryl group		Antibacterial activity mm	
		S.aureus	E. coli
C1	Phenyl	9	10
C2	4-hydroxy phenyl	12	15
C3	3-nitro-4-hydroxy phenyl	12	15
C4	2,4-di chloro phenyl	18	15
C5	4-hydroxy-3-methoxy phenyl	17	20
C6	2-Chloro phenyl	15	16
7	Standard-1	6.25	6.25
8	Standard-2	nt	nt
9	Standard-3	> 100	> 100

Table 2: The physical properties and FT-IR spectral data cm-1 of synthesized bis-Chalcones (C1-C8)

Symbols	physical properties				Major FT-IR absorption cm^{-1}		
	Structure compounds of	Color	M.P. ^{O}C	Yield %	υ(C=O)	υ(C=C)	Other Bands
C1		Beige	114.3-116	67	1623.20	1586.62	-
C2		brown	167-169.5	77	1633.47	1591.08	-
C3		Olive	141.2-144	74	1623.47	1588.27	υ(N-O) 1489.59
C4		Dark brow	160.5-162	75	1635.74	1577.23	υ(C-Cl) 865.48 814.46
`C5		Yellow	141.3-143.5	82	1623.63	1585.38	υ(C-O) ether
C6		Faint yellow	192.3-194.4	86	1624.95	1587.55	υ(C-Cl) 838.05

Indicates minimal activity; nt stands for "not tested"; Ciprofloxacin is Standard 1, Griseofulvin is Standard 2, and Quercetin is Standard 3. MIC stands for minimum inhibitory concentration, which is the lowest concentration at which microbial growth can be inhibited, according to evidence from the literature. [29]

Cell viability assay in MCF-7 Cells (MTT):

Cells were separated at 37°C using 0.25 percent trypsin and 0.1 percent ethylenediaminetetraacetic acid in PBS. After that, the cells were reconstituted in DMEM containing 10% FBS and 1% PSF. Before the studies, cells were seeded onto the 96-well plates at a density of 5000 cells per well and incubated for 24 hours. PBS (phosphate-buffered saline, pH 7.4) was used to wash the cells afterward, and they were subsequently cultured for 72 hours in fresh media containing

various sample concentrations (1000, 500, 250, 125, and 0 g/ml). The 3-(4, 5dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) dye reduction test was used to conduct the cell viability assay. The cytotoxic effects of the compounds at varying doses were assessed using MTT. MTT (0.5 mg/mL in PBS) was applied to each well after 72 hours of incubation at 37°C, 5% CO2, and in an atmosphere that was humid. The plate was then left to stand for a further four hours at 37°C. The formazan's absorbance at 570 nm was determined using an ELISA reader after being gently shaken at 37°C and dissolved in 100 l of DMSO. Three different trial results were combined to present the final product. Then, the IC50 values—concentrations of materials that result in a 50% reduction in cell viability were determined.

Table 3: Show the MTT assay of synthesized compounds (C1-C6)

Synthesized compounds		IC_{50} values µg/mL
Symbol	Aryl group	
C1	**Phenyl**	1329.049
C2	**4-hydroxy phenyl**	972.1166
C3	**3-nitro-4-hydroxy phenyl**	933.6702
C4	**2,4-di chloro phenyl**	644.3925
C5	**4-hydroxy-3-methoxy phenyl**	
C6	**2-Chloro phenyl**	1022.727

3. Result and discussion

The Claisen-Schmidt reaction was used to create the bis-chalcones, which were then produced by condensing various aryl aldehydes in the presence of potassium hydroxide. In the majority of usual solvents, the chemicals are only weakly soluble. By crystallizing the solid byproducts in the proper concentrations of ethyl alcohol/benzene, they were purified in small amounts. By using 1H NMR and 13CNMR to confirm the structures of the synthesized compounds, additional testing for their antibacterial properties was conducted. When two doublets appeared at 7.3 ppm and 7.9 ppm, respectively, as two doublets integrating for two CH- and two CH-protons, the 1H NMR spectra of bis-chalcones (C1-C6) showed the presence of two -CH=CH- groups. The newly synthesized compounds' antibacterial effectiveness was tested against S.aureus and E. coli bacteria. At a concentration of 100g/mL, the initial evaluation was carried out, and the compounds that were determined to be active were then investigated further to seek out their MIC. Compounds 4 and 5 demonstrated high antibacterial activity in preliminary antibacterial data compared with Ciprofloxacin, Griseofulvin, and Quercetin (a natural antimicrobial flavonoid) in Table 1. MTT assay was performed to determine the cytotoxic effect of bis-chalcones (C1-C6) at various concentrations, for each cell line, the median inhibitory concentration (IC50) values were calculated in Table 2. The investigated substances (C1-C6) were discovered to be considerably cytotoxic to MCF-7 cell lines due to their anticancer activities. The outcomes also showed that C4 is superior to the other generated chemicals in their effectiveness against cancer.

4. Conclusions:

Synthesized bis-chalcones structures with better 1HNMR, 13CNMR, and FT-IR results demonstrated C4 and C5's antibacterial effectiveness against S. aureus and E. coli. Derivative C4 has the highest anticancer efficacy when compared to the other synthesized chemicals in Table 2 and is significantly cytotoxic to MCF-7 cell lines by the anticancer activity.

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