Heterocyclic Letters
Vol. 14| No.1|65-72|Nov-Jan|2024
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL ACTIVITY OF NOVEL CHALCONE DERIVATIVES HAVING 1-[4-(BENZYLOXY)-3 CHLOROPHENYL] ETHANONE MOEITY.

Shreekant Prajapati[a], Sanjay .S. Shah[b], Saddam .S. Sipai[c]

[a]Ph.D. Scholar, Department of Chemistry, H. N. G. U, Patan
[b]Professor, Department of Chemistry, Shri U P Arts, Smt. M. G.Panchal Science &V.L.ShahCommerce College,Pilvai, Gujarat, India
[c]Research Assistant, Department of Chemistry, Shri U P Arts, Smt. M. G. Panchal Science & V.L. Shah Commerce College, Pilvai, Gujarat, India
Corresponding Author Email: shreekant12041991@gmail.com

ABSTRACT:
Chalcone, a widely employed compound globally for pharmaceutical and medicinal applications, serves as the focal point of investigation in this research paper. The study explores into the synthesis of 1-[4-(benzyloxy)-3-chlorophenyl] ethanone compounds, denoted as 2C1 to 2C4, achieved through coupling with aldehydes bearing aromatic substitutions. This paper aims to elucidate the production process and assess the antimicrobial properties inherent to 1-[4-(benzyloxy)-3-chlorophenyl] ethanone. The synthesized compounds undergo comprehensive characterization through various analytical techniques, including infrared spectroscopy (IR), mass spectrometry (Mass), proton nuclear magnetic resonance spectroscopy (^{1}HNMR), and carbon-13 nuclear magnetic resonance spectroscopy (^{13}C NMR).

KEYWORDS: Chalcone, Pharmaceutical, Antimicrobial activity, Medicinal, Spectroscopy

INTRODUCTION:

Chalcones, classified within the flavonoid family[(i)], constitute a group of natural compounds abundantly present in various edible plants. These unique compounds are identified as α β-unsaturated ketones, specifically trans-1,3-diaryl-2-propen-1-ones, characterized by their distinctive structure comprising two aromatic rings connected by an α β-unsaturated carbonyl[(ii)] system, often featuring a diverse array of substituents. Notably, the α-β-unsaturated carbonyl system stands as a defining hallmark of chalcones, setting them apart from other molecules in the chemical landscape. The synthesis of chalcones typically involves an aldol condensation reaction between benzaldehyde and acetophenone. This reaction pathway has been well-established and widely employed for chalcone production. Chalcones exhibit a wide range of biological effects, including antiviral[(iii-v)],antibacterial[(vi-viii)], anti-inflammatory[(ix-xiii)], antifungal[(xiv,xv)], anticancer[(xvi-xix)], antioxidant[(xx,xxi)], analgesic[(xxii)], antiulcer[(xxiii)], antimalarial [(xxiv-xxvii)], and antihelmintic[(xxviii)] activities. This diverse array of properties highlights their

significant therapeutic potential in various fields.. These multifaceted characteristics make them valuable compounds in the realm of pharmaceutical research and development. To elucidate the structures of these newly synthesized compounds, the research team employed a comprehensive set of analytical techniques, including infrared (IR) spectroscopy, proton nuclear magnetic resonance (1H NMR) spectroscopy, carbon-13 nuclear magnetic resonance (13C NMR) spectroscopy, and mass spectrometry. These analytical methods provided valuable insights into the molecular compositions and structural arrangements of the BCE and Chalcones. Additionally, antimicrobial screening assays were performed to assess the potential bioactivity of these compounds. These screening assays utilized dimethyl sulfoxide (DMSO) as the solvent, and the results were meticulously documented. This phase of the research aimed to evaluate the effectiveness of the compounds against various microbial strains, offering insights into their potential as antimicrobial agents. Following this assessment, the resulting product underwent a recrystallization process in ethanol, a critical step in improving the purity and crystalline structure of the synthesized compounds. This ensured their suitability for further investigations and potential applications. The research conducted here represents a substantial contribution to the field, offering a comprehensive exploration of the synthesis, characterization, and potential bioactivity of the newly developed BCE and Chalcones.

EXPERIMENTAL:

In our experimental procedures, we exclusively utilized analytical-grade chemicals. The determination of uncorrected melting points was achieved using the open capillary technique, while the assessment of purity was conducted via thin-layer chromatography (TLC). For spectroscopic analysis, Fourier-transform infrared (FTIR) spectra and proton nuclear magnetic resonance (^{1}H NMR) spectra were acquired using a Varian 400MHz spectrometer. $CDCl_3$ was employed as the solvent, and tetramethylsilane (TMS) served as the reference standard. Elemental analysis was performed using a Thermofinigan Flash EA instrument (Italy), with sulfur and halogen content calculated using specific methods. To assess antibacterial and antifungal activity, our research team conducted Broth Dilution method tests against a diverse range of both Gram-positive and Gram-negative bacteria, as well as fungi, as outlined in Table 1.

GENERAL PROCEDURE:

Synthesis of 1-[4-(benzyloxy)phenylethan-1-one

In a chemical experiment, a solution was created by combining 100ml of Acetone with 0.1 moles of 1-(4-hydroxyphenyl)ethanone, 0.1 moles of Benzyl bromide, and 0.1 moles of potassium carbonate. This mixture was heated to a temperature between 50°C and 60°C and stirred for a period of 7 hours. After the reaction time, the mixture was allowed to cool at room temperature and then treated with 100ml of cold water to stop the reaction. The resulting product, 1-(4-(benzyloxy)phenyl)ethanone, was separated by filtration and washed with water. To further purify the product, it was recrystallized using ethanol

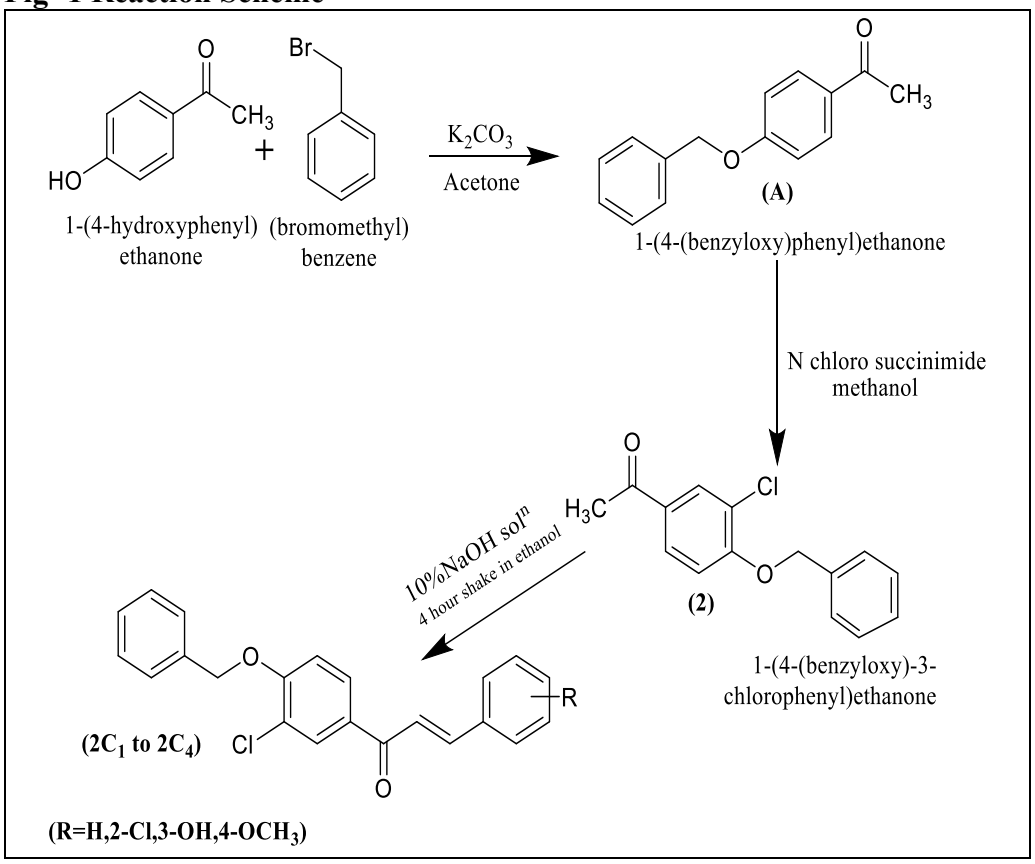
(1)Synthesis of 1-(4-(benzyloxy)-3-chlorophenyl)ethanone (BCE) (2)

A solution was prepared by combining 100ml of acetic acid with 0.1 moles of 1-(4-(benzyloxy)phenyl)ethanone. In a separate step, NCS (N-chlorosuccinimide) was dissolved in a small quantity of DMF. These two solutions were gently mixed at room temperature for a period of 5 to 6 hours. To terminate the reaction, 200ml of cold water was added to the mixture. The resulting product, 1-(4-(benzyloxy)-3-chlorophenyl)ethanone, was separated via filtration and subsequently rinsed with distilled water. To further purify the synthesized material and eliminate any remaining impurities, it underwent a crystallization process in ethanol.

Synthesis of1-[4-(benzyloxy)-3-chlorophenyl]-4-phenylbut-2-en-1-one (2C1 to 2C4)
General Procedure:

A solution was prepared by dissolving 0.01 moles of 1-[4-(benzyloxy)-3-chlorophenyl] ethanone and 0.01 moles of substituted aromatic aldehydes in 25 ml of ethanol. To this mixture, a 10% sodium hydroxide solution was added slowly while stirring continuously. The reaction progress was monitored using thin-layer chromatography (TLC). After stirring for 4 hours, the reaction mixture was poured into 400 ml of cold water with constant agitation.To neutralize the solution, a 10% hydrochloric acid solution was carefully added. The resulting mixture was then left undisturbed overnight in a refrigerator. The precipitate that formed was subsequently separated by filtration, thoroughly washed, and subjected to recrystallization using ethanol as the solvent.

Fig -1 Reaction Scheme



Characterization of BCE and chalcone derivatives

1-(4-(benzyloxy)-3-chlorophenyl)ethanone (BCE) (2)

Product- 66.30% **, M.P** 105^0 107^0C **, LC-MS: m/z-**261

FT-IR(KBr Cm^{-1}): 2923 (C-H Str.Vib) 3050 (Aromatic C-H) 1559,1591 (C=C strVib), 1054 C-O-C str.vib, 1666 (-C=O str.vib),695 (C-Fstr.vib)

^{1}HNMR(400MHz,$CDCl_3$): 5.234(s,2H,O-CH_2-),2.542(s,3H,$COCH_3$), 7.0-7.7(m,8H,Aromatic)

^{13}CNMR(400MHz,$CDCl_3$):26.51(1C,-CO$\underline{C}H_3$),71.30(1C,O-CH_2),110-175(12C Aeromatic),196.95(1C,-CO-)

Theoretical for $C_{15}H_{13}ClO_2$,C-69.10, H- 5.03

Obtained:C-69.09, H- 5.00

1-(4-(benzyloxy)-3-chlorophenyl)-3-phenylprop-2-en-1-one [2-C-1]
Product- 59.23 % **, M.P** 143^0 -145^0C **, LC-MS: m/z-** 349
FT-IR(KBr Cm$^{-1)}$: 3061(Aromatic C-H), 1557,1498(C=C strVib), 1056(C-O-C str.vib), 1655(-C=O str.vib), 974(CH=CH bending,760(C-Clstr.vib)
^{1}HNMR(400MHz,$CDCl_3$): 5.242(s,2H,O-CH_2-), 7.55-8.0(m,2H,CH=CH)
7.0-7.8(m,13H,Aromatic).
^{13}CNMR(400MHz,$CDCl_3$):71.063(1C,O-CH_2),110-175(18C,Aeromatic),187.766(1C,-CO-),100-150(2C,CH=CH)
Theoretical for $C_{22}H_{17}ClO_2$C-75.75, H-4.91
Obtained: C-75.71, H-4.89

1-(4-(benzyloxy)-3-chlorophenyl)-3-(2-chlorophenyl)prop-2-en-1-one [2-C-2]
Product-63.00% , M.P 148^0-150^{0}C , LC-MS: m/z 383
FT-IR(KBr Cm$^{-1)}$: 3063(Aromatic C-H), 1499,1411(C=C strVib), 1659(-C=Ostr.vib),977(CH=CHbending, ,1057(C-O-Cstr.vib),754(C-Clstr.vib).
^{1}HNMR(400MHz,$CDCl_3$): 5.240-5.262(s,2H,O-CH_2-), 7.55-8.0(m,2H,CH=CH)
7.0-7.8(m,12H,Aromatic).
^{13}CNMR(400MHz,$CDCl_3$):70.836(1C,O-CH_2),110-175(18C,Aeromatic),187.583(1C,-CO-),100-150(2C,CH=CH)
Theoretical for $C_{22}H_{16}Cl_2O_2$C- 68.94,H- 4.21
Obtained: C- 68.91,H- 4.18

1-(4-(benzyloxy)-3-chlorophenyl)-3-(3-hydroxyphenyl)prop-2-en-1-one [2-C-3]
Product- 66.32% ,M.P -112^0 -114^{0}C , LC-MS: m/z 364.83
FT-IR(KBr Cm$^{-1)}$:3037(Aromatic C-H), 1562,1499(C=C strVib), 1081(C-O-C str.vib), 1667(-C=O str.vib), 971(CH=CH bending,734(C-Clstr.vib),3595(C-OH str.vib)**.**
^{1}HNMR(400MHz,$CDCl_3$): 5.242-5.263(s,2H,O-CH_2-), 7.55-8.0(m,2H,CH=CH)
7.0-7.8(m,12H,Aromatic),4.00-7.00 (s,1H,-OH)
^{13}CNMR(400MHz,$CDCl_3$):71.102(1C,O-CH_2),110-175(18C,Aeromatic),187.932(1C,-CO-),100-150(2C,CH=CH)
Theoretical for $C_{22}H_{17}ClO_3$ C- 72.43,H-4.70
Obtained: C- 72.45, H-4.73

1-(4-(benzyloxy)-3-chlorophenyl)-3-(4-methoxyphenyl)prop-2-en-1-one [2-C-4]
Product- 64.81% , M.P 118^{0-}120^{0}C ,LC-MS: m/z 378.85
FT-IR(KBr Cm$^{-1)}$: 3035(Aromatic C-H), 1455,1410(C=C strVib), 1054(C-O-C str.vib), 1666(-C=O str.vib), 976(CH=CH bending,691(C-Clstr.vib)
^{1}HNMR(400MHz,$CDCl_3$): 5.241(s,2H,O-CH_2-), 7.55-8.0(m,2H,CH=CH)
7.0-7.8(m,12H,Aromatic).3.863(s,3H,-O-CH_3)
^{13}CNMR(400MHz,$CDCl_3$):71.063(1C,O-CH_2),110-175(18C,Aeromatic),187.697(1C,-CO-),100-150(2C,CH=CH),
55.387(1C,-O-CH_3)
Theoretical for $C_{23}H_{19}ClO_3$C-72.92, H-5.05
Obtained: C-72.92, H-5.02

RESULTS AND DISCUSSION

Table 1 – Result of Antimicrobial activity of BCE and it's chaclone derevitives.

MINIMAL INHIBITION CONCENTRATION [MICROGRAM/ML]				
SR. No	**CODE. No**	**E.COLI**	**S.AUREUS**	**C.ALBICANS**
		MTCC 443	**MTCC 96**	**MTCC 227**
1	2	100	100	250
2	2C1	100	125	500
3	2C2	100	100	1000
4	2C3	100	250	250
5	2C4	62.5	250	>1000
Standard drug	**CHLORAMPHENICOL**	**50**	**50**	
	CIPROFLOXACIN	**25**	**50**	
	GRESEOFULVIN			**500**

Antimicrobial activity

The antimicrobial activity of synthesized compounds 2, 2C1, 2C2, 2C3, 2C4 was determined invitroagainst bacterial strains S.aureus, E.coliand one fungal strains C.ALBICANS. The antimicrobial Activity of compounds against test fungi and bacteria by using Broth Dillution Method. Chloramphenicol and Ciprofloxacin used as reference drug for bacterial strain and Greseofulvin for fungi

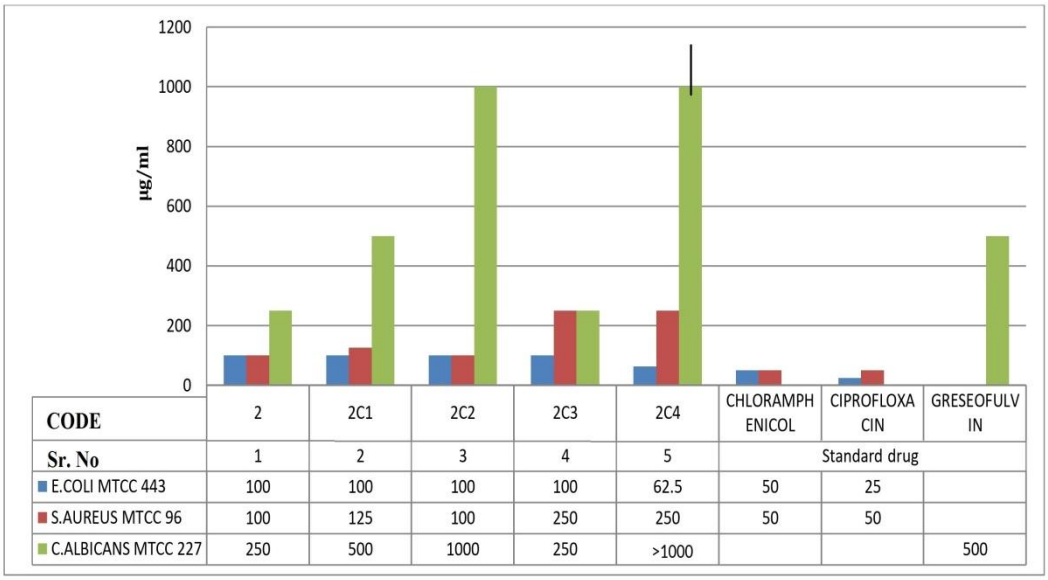


Fig- 2 Histogram of antimicrobial activity of derivatives

CONCLUSION:

In the concluding section of the study, the researcher presents a straightforward, highly efficient, and cost-effective protocol for synthesizing chalcone using the clasian Schmidt condensation method. This method allows chalcone synthesis at room temperature within a 72-hour timeframe. Significantly, chalcones derived from aromatic aldehydes demonstrated stability and the potential for easy transformation into heterocyclic compounds. The research

innovatively applied a synthetic process to produce chalcone from 1-[4-(benzyloxy)-3-chlorophenyl] ethanone, utilizing aromatic substituted aldehydes.The study explored novel BCE and chalcones compounds, with Compound 2, 2C1, 2C2, 2C3, and 2C4 exhibiting limited antibacterial efficacy against E.Coli and S.Aureus. However, Compound 2 and 2C3 displayed noteworthy antifungal properties, demonstrating strong activity against C.albicans fungi at a concentration of 250 µg/mL, comparable to or even superior to Greseofulvin. Compound 2C2, at a concentration of 500µg/mL, exhibited effectiveness comparable to Greseofulvin. These recently discovered compounds exhibit promising potential against fungal strains. Medicinal chemists can leverage these novel compounds to develop and advance chalcones derivatives as potential lead compounds in drug discovery efforts.

ACKNOWLEDGEMENT:

I am thankful to Dr S. S. Shah and Dr S. S. Sipai for their valuable guidance and is also obliged to the Department of Chemistry, Shri U P Arts, Smt. M. G. Panchal Science & V.L.Shah Commerce College Pilvai, Gujarat, India for providing needed facilities for the research work. I am also thankful to the Baroda analytical lab and Spark lab Hyderabad for providing the necessary spectral data.

REFERENCES:

i Veitch NC.; Grayer R.; Chalcones, dihydrochalcones and aurones;In: Andersen QM, Markham KR, editors;Flavonoids chemistry, biochemistry and applications: CRC Press.; 2006, 1003-1070.

ii Alam M. S..;Rahman S. M..; Lee D. U.; Synthesis, biological evaluation, quantitative-SAR and docking studies of novel chalcone derivatives as antibacterial and antioxidant agents. Chem. Papers.;2015, **69 (8)**, 1118–1129.

iii Bernini R.;Mincione E.; Coratti A.; Fabrizi G.; Battistuzzi G.;Epoxidation of chromonesand flavonoids in ionic liquids Tetrahedron.;2004,**60**, 967-971, 2004.

iv Zhao LM.; Jin HS.; Sun LP.; Piao HR.; Quan ZS.; Synthesis and evaluation of antiplatelet activity of trihydroxychalcone derivatives. Bioorg Med ChemLett.;2005,**15**,5027-5029.

v Campos-Buzzi F.; Campos JP.; Tonini PP.; Correa R.; Yunes RA.; Boeck P.; Cechinel- Filho V. Antinociceptive effects of synthetic chalcones obtained from Xanthoxyline. Arch Pharm Chem Life Sci.;2006,**339**, 361- 365

vi Nielsen SF.; Boesen T.; Larsen M.; KristianSchonning K, Kromann H. Antibacterial chalcones-bioisosteric replacement of the 4′-hydroxy group. Bioorg Med Chem,;2004,**12**,3047-3054.

vii Nowakowska, Z.; Structural assignment of stilbenethiols and chalconethiols and differentiation of their isomeric derivatives by means of 1H- and 13C-NMR spectroscopy, SpectroscLett;2005,**38**,477- 485.

viii Selvakumar N.; Kumar GS.; Azhagan.; AM, Rajulu G G.; Sharma S.; Kumar MS.; Das J.; Iqbal J.; Trehan S.; Synthesis, SAR and antibacterial studies on novel Chalconeoxazolidinone hybrids. Eur J Med Chem.,;2007,**42 (4)**,538-543.

vix Herencia F.; Ferrandiz ML.; Ubeda A, Dominguez J, Charris JE.; Lobo GM.; AlcarazMJ.Synthesis and anti-inflammatory activity of chalcone derivatives. Bioorg Med ChemLett.;1998,**8**,1169-1174.

x Xia Y.; Yang ZY.; Xia P.; Bastow KF, Nakanishi Y.; Lee KH.; Antitumor agents.

Part 202: Novel 2′-amino chalcones: Design, synthesis and biological evaluation. Bioorg Med ChemLett,;2000,**10**, 699- 701.

xi Phrutıvorapongkul A.; Lıpıpun V.; Ruangrungsı N.; Kırtıkara K, Nıshıkawa K.; Maruyama S.; Watanabe T.; Ishıkawa T.; Studies on the chemical constituents of stembark of Millettialeucantha: isolation of new chalcones with cytotoxic, anti-herpes simplex virus and antiinflammatory activities. Chem Pharm Bull,;2003,**51 (2)**,187- 190.

xii Viana GSB.; Bandeira MAM.; Matos FJA.; Analgesic and antiinflammatory effects
of chalcones isolated from MyracrodruonurundeuvaAllemão. Phytomedi-cine,;2003,**10**: 189-195.

xiii Climent MJ.; Corma A.; Iborra S.;Velty A.; Activated hydrotalcites as catalysts for
the synthesis of chalcones of pharmaceutical interest. J Catal,;2004,**221**, 474- 482.

xiv Lopez SN.; Castelli MV,.;Zacchino SA.; Domınguez JN.; Lobo G.; Charris-Charris J.; Cortes JCG.; Ribas JC.; Devia C.; Rodrıguez AM.; Enriz RD.; In vitro antifungal evaluation and structure-activity relationships of a new series of chalcone derivatives
and synthetic analogues, with inhibitory properties against polymers of the fungal cell wall. Bioorg Med Chem,;2001,**9**,1999-2013.

xv Batovska D.; Parushev ST.; Slavova A.; Bankova V.; Tsvetkova I.; Ninova M.; Najdenski H.; Study on the substituents' effects of a series of synthetic chalcones against the yeast Candida albicans. Eur J Med Chem,;2007,**42**,87-92.

xvi Ducki S.; Forrest R.; Hadfield JA.; Kendall A.; Lawrence NJ.; Mcgown AT.; Rennison D.; Potent antimitotic and cell growth inhibitory properties of substituted Chalcones, Bioorg Med ChemLett,;1998,**8**, 1051- 1056.

xvii Boumendjel A.; Pietro AD.; Dumontet C.; Barron D.; Recent advances in the discovery of flavonoids and analogs with high-affinity binding to P-Glycoprotein Responsible for cancer cell multidrug resistance; Med Res Rev,;2002, **22 (5)**,512-529.

xviii Meric B.; Kerman K.; Ozkan D.; Kara P.; ArzumErdem A.; Kucukoglu O.; Erciyas
E.; Ozsoz M.; Electrochemical biosensor for the interaction of DNA with the alkylating agent 4,4'-dihydroxy chalcone based on guanine and adenine signals. J PharmaceutBiomed,;2002,**30**, 1339-1346.

xix Akihisa T.; Tokuda H.; Ukiya M, Lizuka M.; Schneider S.; Ogasawara K.;Mukainaka T.; Iwatsuki K.; Suzuki T.; Nishino H. Chalcones, coumarins, and flavanones from the exudate of Angelica keiskei and their chemopreventive effects. CancerLett,;2003, 201, 133-137.

xx Mathıesen L.;Malterud KE.; Sund RB.; Hydrogen bond formation as basis for radical scavenging activity: A structure-activity study of C-methylated dihydrochalcones from Myrica gale and structurally related acetophenones.Free Radical Bio Med,;1997, **22 (1/2)**,307-311.

xxi Cuendet M.; Potterat O.; Salvi A.; Testa B.; Hostettmann K.; A stilbene and dihydrochalcones with radical scavenging activities from Loiseleuriaprocumbens. Phytochemistry,;2000,**54**,871-874.

xxii Anuradha V.; Srinivas P.;Rao R, Manjulatha K, Purohit MG.; Rao JM. Isolation and synthesis of analgesic and anti-inflammatory compounds from Ochnasquarrosa L. Bioorg Med Chem,;2006,**14**,6820-6826.

Tanaka H.; Nakamura S.; Onda K.; Tazaki T.; Hirano T.; Sofalcone, an anti-ulcer

xxiii chalcone derivative, sup presses inflammatory crosstalk between macrophages and adipocytes and adipocyte differentiation: im plication of heme-oxygenase-1 induction. BiochemBiophys Res Commun,;2009,**381**, 566-571.

xxiv Ram VJ.; Saxena AS.; Srivastava S.; Chandra S.; Oxygenated chalcones and bischalcones as potential antimalarial agents. Bioorg Med ChemLett,; 2000,**10**,2159- 2161.

xxv Liu M.; Wilairat P.; Go ML. Antimalarial alkoxylated and hydroxylatedchalcones: Structure-activity relationship analysis.J Med Chem.;2001,**44 (25)**, 4443-4452.

xxvi Wu X.; Wilairat P.; Go ML.; Antimalarial activity of ferrocenylchalcones. Bioorg\ Med ChemLett,;2002,**12,**2299-2302.

xxvii Kumar A.; Katiyar SB.; Agarwal A.;Chauhan PMS. Perspective in antimalarial chemotherapy. Curr Med Chem,;2003,**10**: 1137-1150.

xxviii Nielsen SF.;Kharazmi A.; Christensen SB. Modifications of the a,b-double bond in chalcones only marginally affect the antiprotozoal activities; Bioorg Med Chem,;1998,**6**, 937-945,1998.

Received on October 12, 2023.