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VITAMIN B1PROMOTED GREEN SYNTHESIS OF BENZOFURAN CHALCONES: PROMISING SCAFFOLDS FOR DRUG DEVELOPMENT IN ANTIMICROBIAL

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ABSTRACT

Objective: To develop metal free and environmentally benign synthetic method for the synthesis of chalcones bearing benzofuran scaffolds.
Materials and Methods: Starting material chloroacetone,anhydrous potassium carbonate, different aromatic aldehydes, ethanol and vitamin B1 of AR grade wereused for synthesis.Various chalcones were synthesized byClaisen-Schmidt condensation.The structure of the synthesized compounds was confirmed by elemental analysis, IR,^{1}H NMR and mass spectra.

Results: In this context we have tried new metal free and environmentally benign synthetic method for synthesis of the pharmaceutically important molecule 1-(4-substituted-1-benzofuran-2-yl) substituted chalcones and its derivatives and it was screened for their antimicrobial activity.Most of the compounds exhibited the good to moderate activity.

Conclusion: Herein we have tried a highly efficient protocol for the synthesis of chalconesa good result with variety of functionalities, a high yield of products, and the recoverability of this catalyst.Vitamin B1 as a catalyst has been developed using green solvent EtOH.

Keywords: Benzofuran, chalcones, vitamin B1catalyst and antimicrobial property.

INTRODUCTION

Benzofuran chalconesis one of the most important classes of synthetic or biogenetic precursors with general manifestation in fruits, vegetables, spices and soya based foodstuffs, which have impressive array of biological and pharmacological activities [1]. In addition, benzofuran chalcones derivatives occur in a number of natural products and its ring system is a common structural element that appears in a large number of important compounds [2], used in cosmetics and medicinal industry [3,4].Recently, there are many studies related to the cytotoxic activity of chalconesderivatives in various cancer cell lines [5-7].Chalcones were first isolated from flavonoid biosynthesis in plants [8] and since then many studies have focused on structuralmodifications of the chalcones scaffold and the variety of its biological activities [9].Chalcones consist of two aromatic rings connected by α,β-unsaturated carbonyl group[10]. A number of synthetic modifications, such as heterocyclic infused [11], biphenyl based [12], coumarin based chalcones [13]have also been reported to affect the biological activities including anticancer activities of chalcones [14-21].

Material and Methods: Melting points were determined in open capillaries in sulfuric acid bath and are uncorrected. TLC analysis wasperformed on silica gel-G and spotting was done using iodine or UV light. IR spectra were recorded on Perkin -Elmer model 446 instruments in KBrp phase. ^{1}H NMR was recorded in $CDCl_3$/DMSO-d6 using 400 MHz Varian Gemini spectrometer and mass spectra were recorded on LCMSspectrometer.**2.1 Synthesis of 2-acetyl-5-chloro benzofuran (1):**In a 250 mL four necked round bottom flask fitted with overhead mechanical stirrer, a dropping funnel, a thermometer and condenser with child water circulation, 2-hydroxy-5-chlorobenzaldehyde (0.01 mole), chloroacetone (0.011 mole) and anhydrous potassium carbonate (1.5gm) were refluxed in dry acetone (7.5 mL) for12 h. Potassium salts were filtered off, the filtrate on removal of solvent and on trituration with ethanol gave the pale yellow crystals of 2-acetyl-5-chloro benzofuran(1). The sample was purified by recrystallized from absolute ethanol. MP = 92 °C, Yield = 68%

Compound 1IR (KBr, λmax): 3109cm^{-1} (Ar-H str.), 2921cm^{-1} (-CH str.), 1674 cm^{-1} (C=O str. in ketone), 1086-1170 cm^{-1} (C-O-C), 1515 cm^{-1} (C=C str. in Ar), 1443 & 1359 cm^{-1} (CH_3 def.), **^{1}HNMR**:(400MHz,$CDCl_3$,δppm):8.03(s,1H,ArH),7.57(dd,1H,ArH,J=7.60Hz),7.48(t,2H,ArH,J=6.80Hz),2.61(s,3H,-CH_3).**MS:**m/z195.3(M+1).

GeneralProcedure for the Synthesis of compounds (2a–l):

(2E)-1-(5-Chloro-1-benzofuran-2-yl)-3-(3-substitutedphenyl)prop-2-en-1-one:A solution of substituted benzaldehyde (4 mmol), 2-acetyl-5-chloro benzofuran(4mmol), and vitamin B1 (202mg, 0.6mmol, and 30 mol%) in EtOH (20 mL) was stirred for 09 h at reflux. After cooling to room temperature, the mixture was concentrated in a vacuum;during this process a precipitate was formed.The product was dissolved in EtOH, and the catalyst was dissolved in water. The EtOH was removed under reduced pressure, and the water was left. This precipitate was then filtered off and washed with more water.The crude product was purified by column chromatography (AcOEt/PE) to give corresponding chalcone derivatives.

Reaction Scheme

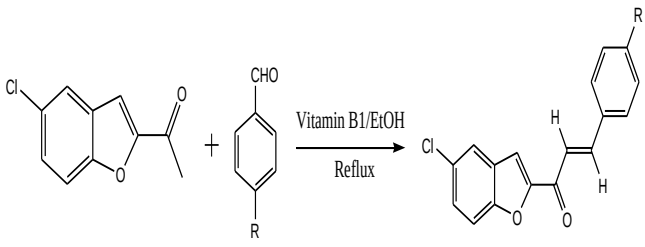
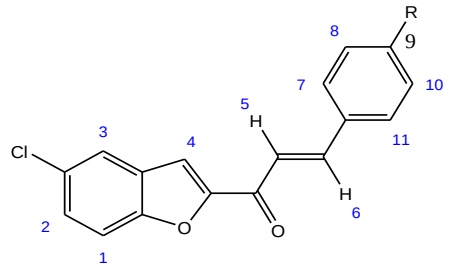


Table1:Analytical data for synthesized (2E)-1-(5-chloro-1-benzofuran-2-yl)-3-(3-substituted phenyl) prop-2-en-1-one.

Entry	R	Molecular formula	M.Pt.	Yield %	Elemental analysis C % (obs.)	H% (obs.)	N% (obs.)	X% (obs.)
2a	H	$C_{17}H_{11}ClO_2$	140	71	72.22 (72.98)	3.92(4.09)	-----	12.54(12.77)
2b	Cl	$C_{17}H_{10}BrClO_2$	123	81,81, 79,78	64.38 (63.91)	3.18(3.41)	-------	22.36(22.87)
2c	Br	$C_{17}H_{10}Cl_2O_2$	156	79	56.46 (56.83)	2.79(2.67)	-------	22.10&9.80(21.82 & 9.54)
2d	I	$C_{17}H_{10}ClO_2$	103	71	49.97 (50.07)	2.47(2.85)	------	8.68&31.06 (8.97&31.15)
2e	CH_3	$C_{18}H_{13}ClO_2$	179	68	72.85 (73.04)	4.42(4.88)	------	11.95(10.93)
2f	OCH_3	$C_{18}H_{13}ClO_3$	109	64	69.13 (69.05)	4.19(4.65)	------	11.34(11.88)
2g	NO_2	$C_{17}H_{10}ClNO_4$	203	88	62.30(62.88)	3.08(2.98)	4.27(4.62)	10.82(10.32)
2h	C_6H_5	$C_{23}H_{15}ClO_2$	196	59	76.99 (77.34)	4.21(4.44)		9.88(9.76)
2i	OH	$C_{17}H_{11}ClO_3$	134	76	68.35 (68.74)	3.71(3.32)	-------	11.87(11.43)
2j	C_2H_5	$C_{19}H_{15}ClO_2$	164	65	73.43 (73.88)	4.86(4.98)	------	11.41(11.78)

Characterization



1]*(2E)-1-(5-chloro-1-benzofuran-2-yl)-3-phenylprop-2-en-1-one(2a)*FT-IR(KBr,cm^{-1}):1655(C=O),1599(C=C);^{1}H-NMR(400MHz,DMSO-d6),δppm:8.78(s,1H,5-H),7.99(s,1H,7-H),7.62-7.94(m,4H,H-13,H-17,H-11,H-10)7.44-7.85(m,2H,H-2,H-3),7.65–7.40(m,3H,14-H,15-H,16-H).**2]*(2E)-1-(5-chloro-1-benzofuran-2-yl)-3-(3-bromophenyl)prop-2-en-1-one(2b)*.**FT-IR(KBr,cm^{-1}):1654(C=O),1604(C=C);^{1}H-NMR(400MHz,DMSO-d6),ppm:7.91(s,1H,H-5),8.44(s,1H,H-7),8.11-7.85(m,8H,H-3,H-2,H-17,H-16,H-14,H-13,H-10,H-11)**3]*(2E)-1-(5-chloro-1-benzofuran-2-yl)-3-(3-chlorophenyl)prop-2-en-1-one(2c)*.**

FT-IR(KBr,cm^{-1}):1676 (C=O),1647 (C=C);^{1}H-NMR (400MHz,DMSO-d6), ppm: 8.12 (s,1H,5-H),8.23(s,1H,7-H),8.07-7.78(m,8H,3-H,2-H,17-H,16-H,14-H,13-H,10-H,11-H)**4]*(2E)-1-(5-chloro-1-benzofuran-2-yl)-3-(3-iodophenyl)prop-2-en-1-one(2d)***.FT-IR (KBr,cm^{-1}):1698 (C=O),1657 (C=C);^{1}H-NMR(400MHz,DMSO-d6), ppm: 8.01(s,1H, 5-H),8.12(s,1H,7-H),7.87-6.68(m,8H,3-H,2-H,17-H,16-H,14-H,13-H,10-H,11-H) **5]*(2E)-1-(5-chloro-1-benzofuran-2-yl)-3-(3-methylphenyl)prop-2-en-1-one(2e)***FT-IR(KBr,cm^{-1}):1654 (C=O),1632 (C=C);^{1}H-NMR (400MHz,DMSO-d6), ppm: 7.81 (s,1H, 5-H),7.82(s,1H,7-H), 2.31(s,3H,9-H)7.87-6.68 (m, 8H, 3-H,2-H,17-H,16-H,14-H,13-H,10-H,11-H) **6]*(2E)-1-(5-chloro-1-benzofuran-2-yl)-3-(3-nitrophenyl)prop-2-en-1-one(2g)***FT-IR (KBr,cm^{-1}): 1679 (C=O), 1643(C=C);^{1}H-NMR (400MHz,DMSO-d6), ppm: 8.92 (s,1H, H-5), 8.67-8.57 (m,H-13, H-15,H-17),7.98(s,1H,H-7), 8.32(d,1H, *J* = 15.6Hz,H-11),8.04(d,1H, *J* = 16Hz,H-10), 7.84-7.68 (m, 3H, H-3, H-2, H-16).

7]*(2E)-1-(5-chloro-1-benzofuran-2-yl)-3-(3-hydroxyphenyl)prop-2-en-1-one(2i)*FT-IR (KBr, cm^{-1}): 1636 (C=O),1549 (C=C);^{1}H-NMR (400MHz,DMSO-d6), ppm: 7.11 (s,1H, 5-H),7.32(s,1H,7-H), 11.02(s,1H,-OH)7.46-6.28 (m, 8H, 3-H,2-H,17-H,16-H,14-H,13-H,10-H,11-H)**3.Resultsand discussion:3.1Optimization of the reaction conditions.** To check and enhance the yield and to optimize the reaction conditions thisClaisen-Schmidt condensation reaction was carried out under different conditions and results are tabulated in table II,along with this we have checked the recyclable character of Vitamin B1 and the desired product was isolated by a simple filtration technique. Next, the filtered solution having the catalyst was again treated with the reactants, and the yields of the desired product as illustrated in the entry (2b) were 81,81,79 and 78 after 4 runs, respectively, indicating the catalyst could be reused without considerable loss of activity.Based on the above reaction conditions, the effect of the amount of Vitamin B1 from 10 to 40 mol% was checked. As shown in Table II, we observed that the catalyst amount could be reduced to 30 mol% without a decrease of the yield (Table II,entry 3).

Table 2: The optimization of the amount of catalyst#

Entry	Vitamin B1(mol%)	Time (h)	Yield of 2b* (%)
1	10	9	78
2	20	9	79
3	**30**	**9**	**81**
4	40	10	81

Reaction conditions: 4.0 mmol of substituted benzaldehyde, 4.0 mmol of 2-acetyl-5-chloro benzofuranand 20 mL,ofEtOH at a reflux temperature.*-Isolated yields..**3.3The Scope of the Substrates:** Inorder to check the scope and limitation of the process, we applied the optimized reaction conditions to a variety of substrates in the presence of 30 mol% Vitamin B1 in EtOH as solvent at a reflux temperature (Table-I).We discovered that aromatic aldehydes carrying strong electron-withdrawing groups afforded relevant high yields (81-88%). Most interestingly, aromatic aldehydes carrying hydroxyl groups, which arebase-sensitive functional groups, worked well to give high yields of products without a significant difference.

StructuralCharacterization*:* In the FT-IR spectra of 1-(5-chloro-1-benzofuran-2-yl)ethanone,C=O stretching vibration was observed at 1678 cm^{-1}. The synthetic chalcones 2a-2j

showed characteristic bands between 1666 and 1679 cm^{-1}(C=O stretching at chalcone) and between 1586 and 1628 cm^{-1}(C=C stretching at chalcone).The most characteristic signals in ^{1}H-NMR spectra ofthe benzofuran substituted chalcones were observed at 8.29–8.03 ppm and at 7.80–7.40 ppm(*α*-H and *β*-H of chalcone moiety) with a coupling constantabout 15-16 Hzwhich characterizes the transconfiguration of thealkene moiety in chalcones.**3.5 Antimicrobial activity**

All the synthesized compounds were dissolved in dimethyl formamide (DMF) to prepare stock solution at the concentration of 1 mg/mL. The antimicrobial activity was carried out by the agar-well diffusion method [22]. Each microorganism was suspended in nutrient broth and diluted approximately colony forming unit (cfu) per mL. They were 'flood-inoculated' onto the surface of nutrient agar and then dried. Five-millimeter diameter wells were cut from the agar using a sterile cork-borer; 50 µL and 100 µL of the test compound solution were delivered into the wells. The plates were incubated for 32 h at 35 °C. Antimicrobial activity was evaluated by measuring the zone of inhibition against the test organisms.All the synthesized compounds were screened for their antibacterial and antifungal activities at two different concentrations and the results are shown in Table 1. The results revealed that most of the synthesized compounds showed variable degrees of inhibition against the tested microorganisms.

Table 3: Antimicrobial activity data (Zone of inhibition in mm).

Entry No.	*S. aureus*		*K. pneumonia*		*P. aeruginosa*		*E. Coli*		*A. Niger*	
	50 µL	100 µL	50 µL	100 µL	50 µL	100 µL	50 µL	100 µL	50 µL	100 µL
2a	12	16	09	16	08	12	12	16	10	12
2b	20	27	16	22	18	25	15	18	19	22
2c	20	24	06	09	12	19	10	12	22	26
2d	18	22	12	18	–	08	15	22	14	20
2e	14	17	06	16	12	14	18	20	06	12
2f	18	22	–	10	14	18	16	20	08	12
2g	08	10	13	18	–	–	–	–	14	16
2h	23	28	13	18	18	24	12	16	08	10
2i	15	23	06	14	12	18	16	20	06	08
2j	18	22	12	18	–	12	15	22	23	26
Ampicillin	24	30	28	32	20	28	28	31	–	–
Flucanozole	–	–	–	–	05	–	–	–	28	34

Antibacterial activity

Compounds **2b** and **2h** showed an excellent effect at both the tested concentrations against *S. aureus* and *P. aeruginosa* whereas the same compounds revealed moderate activity against *Klbesillapneumonia* and *E. coli*,Compounds2d and **2j** showed excellent activity against *S. aureus* and *E. coli.* On the other hand other compounds displayed moderate activity against all bacterial species.

Antifungal activity

Antifungal activity was carried against two human pathogen fungal species *A.Niger* and *TrichodermaVirdae*. The results obtained from the present study recorded a remarkable difference in the antifungal effect of all tested compounds at both the concentrations, Compounds **2b**, **2c** and **2g** showed excellent activities against both the tested organisms whereas compounds **2d** and **2h** showed moderate activity and compounds **2a**, **2e**, **2f**, **2h** and **2j** showed weak antifungal activity against both the tested organisms.

CONCLUSION

Recently we have tried a metal-free and highly efficient protocol for the synthesis of chalcones byClaisen-Schmidt condensation using recoverableVitamin B1 as a catalyst has been developed. Thus, the methodis characterized by the use of a convenient source of Vitamin B1 and a green solvent EtOHto enable it to have these advantages including a tolerance for base-sensitive functional groups(hydroxy), high yields, and no side reactions.

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