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MICROWAVE ASSISTED SYNTHESIS, PHYSICOCHEMICAL PROPERTIES AND ANTIMICROBIAL ACTIVITIES OF SOME NOVEL BARBITONE MOIETY LINKED BY BENZIMIDAZOLE CHALCONES

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ABSTRACT

Introduction: The benzimidazole nucleus exhibits wide range of biologic activities. The aim of our research was incorporate a barbitone pharmacophore to the benzimidazole chalcone by means of a C=C bond and improve its bioactive nature. Materials and Methods: The benzimidazole chalcones (4a–f) were prepared by reacting 2-acetyl benzimidazole with appropriate aldehydes in the presence of a base by Claisen-Schmidt condensation. The condensation of benzimidazole chalcones (4a-f) with barbituric acid in acetic acid gave the titled derivatives. (5a-f).The structures of the final derivatives were established on the basis of IR,[1]HNMR and mass. The physicochemical properties of the derivatives were established from ChemDraw Ultra 11.0 software. The final compounds were screened for their antimicrobial studies. All the compounds showed a good activity towards Gram-positive bacteria and less activity towards Gram-negative bacteria. Some of the derivatives showed a moderate activity against tested fungi. Result and Discussion: IR spectrum of the 5-[(2E)-1-(1H-benzimidazol-2-yl)-3-phenylprop-2-en-1-ylidene] pyrimidine-2,4,6(1H, 3H, 5H)-trione showed a strong absorption band at 3232cm^{-1} corresponding to benzimidazole NH absorption at 2910 and 2878 cm^{-1} corresponds to pyrimidine NH/NH.A sharp absorption at 1678 cm^{-1} corresponds to carbonyl stretching and 771 cm^{-1} due to aryl chloride. The [1]HNMR spectra showed the singlet peak at δ 8.4 and 8.6 were assigned to pyrimidine NH/NH.The singlet peak at δ 8.9 corresponding to benzimidazole NH.The doublet for vicinal protons has seen along with the aromatic multiplet between 6.4 and 8.3 ppm.Mass spectrum of compound 5b revealed the molecular ion peak [M+2] at *m/z* 394 corresponding to the molecular mass of the compound. Out of the synthesized derivatives 5d, 5c and 5 b showed good activity against Gram-positive bacteria. Conclusion: SAR of the final candidates revealed a correlation between CLogP and antimicrobial studies. The higher the value of Molar refractivity favors the activity ratio.

KEYWORDS: Benzimidazole chalcone, Barbituric acid, Molar refractivity.

INTRODUCTION

Benzimidazole is a bicyclic heteroaromatic compound. The acidic and basic nature of nitrogen atoms are assigned in a position of 1&3 respectively. Benzimidazole is regarded as the most promising bioactive heterocyclic compounds in the heterocyclic compounds. The derivatives belong to this nucleus are effective against various strains of microorganisms [1].Benzimidazoles are regarded as a promising class of biologically active agents. The benzimidazole nucleus exhibit a wide range of biological profile such as, antimicrobial [3-5], anti-tubercular [6, 7], anticancer [8], angiotensin II receptor antagonists [9] and anti-HIV [10, 11].Our research was concentrated on the reactivity of ketone group in the benzimidazole chalcone. The carbonyl group in an alpha, beta unsaturated ketone has a tendency to react with an acidic hydrogen present in the methylene unit of barbituric acid is already reported [12, 13].This finding promoted as the synthesis of a novel candidates of benzimidazole chalcone linked by barbitone moiety via a carbon-carbon double bond. Our research also made a new pathway for the formation of a C=C from a ketone and acidic hydrogen on methylene group by a microwave assisted approach. All the final compounds were screened for their antimicrobial activities.

MATERIALS AND METHODS

All the solvents and chemicals were purchased from MERCK, Nice chemicals and SD Fine Chemicals. Melting points were determined by using melting point apparatus MP-DS TID 2000 V and the values were uncorrected. Reactions were monitored by thin layer chromatography (TLC) on pre coated silica gel G plates using iodine vapour as visualizing agent.IR spectra were recorded on JASCO FT/IR-140 spectrophotometer by using KBr pellets technique.PMR spectra were recorded using BRUCKER FT-NMR-500MHz spectrophotometer by using DMSO as solvent and TMS as internal standard. The chemical shift was expressed in δ ppm.Mass spectra were recorded on a JEOL GCmate mass spectrometer. The physicochemical properties like CLogP and molar refractivity of the final derivatives were established from ChemDraw Ultra 11.0 software.

Chemistry

The synthesis of 5-[(2*E*)-1-(1*H*-benzimidazol-2-yl)-3-substituted phenylprop-2-en-1-ylidene] pyrimidine-2, 4, 6(1*H*, 3H, 5H)-trione (**5a–g**) described in this study are outlined in Figure 1.

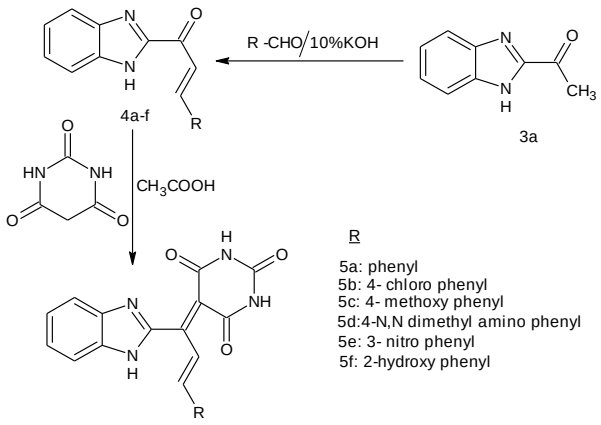

Figure 1. Synthetic scheme of the compounds **(5a-f)**

General Synthesis of (2E)-1-(1H-benzimidazol-2-yl)-3-phenylprop-2-en-1-one (4a-f) (1)

2-Acetyl benzimidazole (0.01 mol) and appropriately substituted aromatic aldehydes (0.012 mol) were mixed in ethanol (20 ml) containing 10% aq. KOH (8 ml) and magnetically stirred the solution constantly at room temperature for 10 hrs.The whole mixture was transferred in to 100 ml ice cold water and acidified with dil.HCl. The solid formed was washed, filtered and dried, recrystallized from absolute ethanol [7].The physical data of the derivatives were shown in Table 1.

Table 1. Physical Characterization of the final derivatives (5a-f)

Compound	Colour	MP (°C)	% Yield	R_f
5a	brownish	255-258	77	0.69
5b	yellowish	265-267	77	0.82
5c	pale green	225-228	67	0.58
5d	brownish	210-213	76	0.79
5e	brownish	239-240	66	0.71
5f	yellowish	200-203	61	0.88

Micro wave assisted Synthesis of (2E)-1-(1H-benzimidazol-2-yl)-3-phenylprop-2-en-1-one (4a-h) (2)

2-Acetyl benzimidazole (0.01 mol) is taken in 10ml of ethanol in a beaker and stir well. To this add 4ml of 10% KOH with aldehydes (0.012).The whole mixture stirs vigorously for 20 minutes. Then it becomes viscous and that subjected to a domestic microwave oven at 60% power over a

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period of 2-3mins.The resultant product cooled and diluted with cold water and neutralized with dil.HCl [14].

General Synthesis of 5-[(2*E*)-1-(1*H*-benzimidazol-2-yl)-3-substituted phenylprop-2-en-1-ylidene] pyrimidine-2, 4, 6(1*H*, 3H, 5H)-trione (5a-f) (3)

To a solution of (**4a-g**) (0.01 mol) was suspended in 7ml acetic acid. To this barbituric acid (0.01 mol) was added with constant stirring. The reaction mixture was then refluxed for 7 hours with occasional stirring. The resultant contents were poured in to in to crushed ice. The crude product was filtered and recrystallized from methanol.

Microwave assisted synthesis of 5-[(2*E*)-1-(1*H*-benzimidazol-2-yl)-3-substituted phenylprop-2-en-1-ylidene] pyrimidine-2, 4, 6(1*H*, 3H, 5H)-trione (5a-f) (4)

Barbituric acid (0.01mol) was added to a mixture of chalcone (4a-g) (0.01 mol) in acetic acid. The reaction mixture was irradiated for 2-3 minutes at 60%microwave power with 30 seconds interval using a domestic microwave oven. The reaction progress was monitored by TLC. The resultant contents were poured in to in to crushed ice with constant stirring. The isolated product was recrystallized from methanol.

Table 2. Spectral characterization of the final derivatives **(5a-f)**

Compd	FT-IR (KBr,$V_{max}cm^{-1}$)	^{1}HNMR (DMSO-d_6),δppm	m/z
5a	3230(NHstr),1693 (C=O),1587(C=N)	9.1(1H,s,NHbenzimidazole),8.0-8.4(2H,s,pyrimidineNH)6.48.1(11H,m,9ArH, 2CH=CH)	359.21 (M^++1)
5b	3232(NHstr),1678 (C=O),1581(C=N), 771 (Ar-Cl)	8.9(1H,s,NHbenzimidazole), 8.4-8.6(2H,s,pyrimidineNH),6.4-8.3(10H,m,8ArH,2CH=CH)	394.1 (M^++2)
5c	3239(NHstr),1681 (C=O), 1576(C=N)	8.9(1H,s,NHbenzimidazole),8.4-8.6(2H,s,pyrimidineNH),6.48.3(10H,m,8ArH,2CH=CH), 3.3(3H,s,OCH_3)	390.06 (M^+1)
5d	3227 (N-H str), 1678 (C=O), 1569(C=N)	8.9(1H,s,NHbenzimidazole), 8.5-8.7(2H,s,pyrimidineN),6.3-8.4 (10H,m,8ArH,2CH=CH), 3.3(6H,s,N(CH_3)$_2$)	402.56 (M^+1)
5e	3227 (NHstr), 1678(C=O), 1569(C=N), 1310(Ar-NO_2)	8.5(1H,s,NHbenzimidazole),8.2-8.4(2H,s,pyrimidine NH),6.4-8.4(10H,m,8ArH,2CH=CH)	405.56 (M^+2)
5f	3379(ArOH),3231 (NHstr), 1680(C=O),1562(C=N)	9.1(1H,s,NHbenzimidazole),8.4-8.8(2H,s,pyrimidineNH)6.4-8.5(10H,m,8ArH,2CH=CH),5.62(1H,s,ArO-H)	375.65 (M^+1)

Table 3. Physicochemical Properties the final derivatives (5a-f)

Compd	C logP	MR	MW	No. H-bond donors	No. Hbond acceptors	No. rotatable bond	No. of violation
5a	2.38	100.64	358.35	3	7	3	0
5b	2.41	105.40	392.79	3	7	3	0
5c	2.44	107.30	388.37	3	8	4	0
5d	2.99	114.96	401.41	3	8	4	0
5e	1.97	107.10	403.34	3	10	4	1
5f	2.17	102.50	374.34	4	8	3	0

Antimicrobial screening

The antimicrobial screening of the synthesized derivatives were evaluated against two Gram-positive bacteria viz., *Bacillus subtilis, Staphylococcus aureus*, two Gram-negative bacteria viz. *Escherichia coli*, *Klebsiella pneumoniae* and two fungi viz. *C.albicans,A.niger* using streptomycin,benzyl penicillin and amphotericin B respectively as standard drugs respectively by the Cup-plate method using DMSO as the solvent.

RESULT AND DISCUSSION

In our present research, we have synthesized a series of 5-[(2*E*)-1-(1*H*-benzimidazol-2-yl)-3-phenylprop-2-en-1-ylidene] pyrimidine-2, 4, 6(1*H*, 3H, 5H)-trione derivatives from benzimidazole chalcone and barbituric acid. The above benzimidazole chalcone is obtained from the reaction between 2-acetyl benzimidazole and different aromatic aldehydes compounds. The final compounds were screened for their antimicrobial studies. The physicochemical properties of the derivatives were calculated from computational tools. This proposal suggested a good correlation between molar refractivity and CLogP to the antimicrobial studies.

Compound code	*B. subtilis*	*S. aureus*	*E. coli*	*K. pneumoniae*	*C. albicans*	*A. niger*
5a	12	11	06	08	08	02
5b	14	14	11	11	03	-
5c	13	12	6	09	05	-
5d	15	16	10	11	04	01
5e	10	8	12	06	05	-
5f	11	06	11	12	08	06
Streptomycin	-	-	16	16	-	-
Benzyl Penicillin	18	17	-	-	-	-
Amphoteracin B	-	-	-	-	22	24

Table 4. Antimicrobial screening of the final derivatives **(5a-f)**

Chemistry

The highly reactive acidic hydrogen present in the barbituric acid has a tendency to react with ketone group in the, β unsaturated carbonyl system in presence of an acetic acid medium is the key of our study. The structures of the final candidates were confirmed on the basis of spectral studies. All the newly synthesized compounds were characterized by IR,^{1}HNMR and mass spectroscopic data.IR spectrum of the 5-[(2E)-1-(1H-benzimidazol-2-yl)-3-phenylprop-2-en-1-ylidene] pyrimidine-2,4,6(1H, 3H, 5H)-trione 5b showed a strong absorption band at 3232 cm^{-1} corresponding to benzimidazole NH,absorption at 2910 and 2878 cm^{-1} corresponds to pyrimidine NH/NH.A sharp absorption at 1678 cm^{-1} corresponds to carbonyl stretching and 771 cm^{-1} due to aryl chloride. The ^{1}HNMR spectra showed the singlet peak at δ 8.4 and 8.6 were assigned to pyrimidine NH/NH.The singlet peak at δ 8.9 corresponds to benzimidazole NH.The doublet for vicinal protons has seen along with the aromatic multiplet between 6.4 and 8.3 ppm.Mass spectrum of compound 5b revealed the molecular ion peak [M+2] at *m/z* 394 corresponding to the molecular mass of the compound.

Antimicrobial screening

All the compounds showed a good activity towards Gram-positive bacteria and less activity towards Gram-negative bacteria. Some of the derivatives showed a moderate activity against tested fungi. The diameters zone of inhibition for the final derivatives were measured in mm.Out of the synthesized derivatives **5d, 5c and 5b** showed good activity against Gram-positive bacteria. Compound **5a** and **5f** showed moderate activity against *C.albicans.*

CONCLUSION

The present study described the synthesis of novel derivatives of 5-[(2*E*)-1-(1*H*-benzimidazol-2-yl)-3-substituted phenylprop-2-en-1-ylidene] pyrimidine-2, 4, 6(1*H*, 3H, 5H)-trione (**5a–f**) by both conventional and microwave assisted. Here the establishment of the physicochemical descriptor is a good tool for the prediction of antimicrobial activities. In this skeleton introduction of electron donating group in the para or ortho position of the aromatic nucleus increases the calculated logP value. It is believed that strong lipophilic character of the molecule plays an essential role in producing antimicrobial effect. These properties are seen as an important parameter related to membrane permeation in biological system [15].It has been concluded that higher value of the molar refractivity favors the activity ratio.

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