Research Article

Synthesis and antimicrobial evaluation of some novel bis-heterocyclic chalcones from cyclic imides under microwave irradiation

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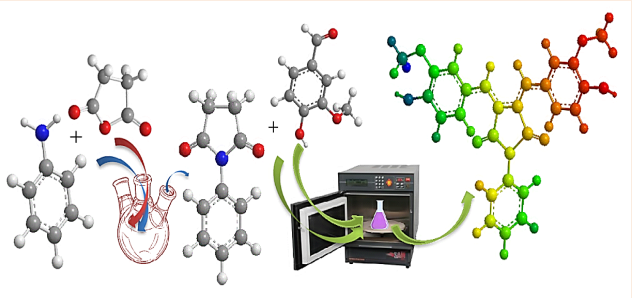
Abstract

Synthesis of a new series of bis-heterocyclic chalcone derivatives has been reported. The condensation proceeded by the one pot reaction of N-phenyl succinimides and 4-hydroxy-3-methoxy benzaldehyde in presence of neutral alumina under microwave irradiation. The advantages of this method are high yield, shorter reaction time and simple workup procedure. Most of the synthesized compounds have shown moderate to significant antimicrobial activity against different microbial strains.

Keywords: N-phenyl succinimides, bis-chalcones, antimicrobial activities



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Introduction

Chalcones and cyclic imides perform a significant title role in the heterocyclic synthesis containing oxygen, nitrogen and sulphur groups. Cyclic imides [1] like succinimides [2] [3] [4], maleimides [5], glutarimide [6], itaconimide[7] and phthalimides[8] showed the defensive antibacterial [9], antifungal activities. Cyclic imides exhibited the CNS anxiolytic and anti-depressive [10], brain metabolism [11], nephrotoxic [12], antiviral [13], anticonvulsant [14] electroshocks [15], muscle relaxant [16], anti-mutagenic [17], analgesic [18], anxiety and depression [19], myeloperoxidase induction [20], anti-proliferative [21], seedling growth [22] activities. The substituted heterocyclic imides were developed from cyclic anhydrides [23], formamide [24], trifluoroacetylation [25], triethylamine [26], hydroxylamine [27], thalidomide biotin [28], pyrolidine triones [29] reagents and bis-heterocyclic analogs [30] by microwave synthesis.

Bis-chalcones are the pioneer flavonoids of heterocycle ancestor containing carbon stuck between α, β-unsaturated aromatic rings and carbonyl carbons. These are prepared by the condensation [31] of the substituted ketones and aldehyde groups [32] [33]. The chalcone showed significant cytotoxic activities against antimicrobial [34], cell line and breast cancer [35], anti-oxidant [36], bovine lens aldose reductase [37], tumor-genesis activities [38]. The chalcones are synthesized by utilizing a number of synthetic routes like solid phase Claisen-Schemdit, Cross-Aldol condensation, acid catalyst [39], coupling reaction [40], Knoevenagel condensation [41] and microwave assisted synthesis.

Experimental:

Materials and Reagents

Melting points of all the synthesized compounds were recorded in an open glass capillaries and were uncorrected. IR spectra in (KBr pallets) were chronicled on Shimadzu FTIR-8400S and ATR Brucker alpha FT-IR spectrophotometer. ^{1}H NMR spectra were recorded on 400 MHz and 500.13 MHz by Brucker spectrophotometer. The reaction was monitored by TLC which was accomplished by using pre-coated silica gel aluminium plates with the mixture of diethyl ether and ethyl acetate 7:3 proportion or benzene. Commercially purchased succinic anhydride, substituted anilines, acetyl chloride, benzene, 4-hydroxy-3-methoxy benzaldehyde (vanillin), neutral alumina (Al_2O_3) and ethanol were used for the preparation.

Preparation of substituted bis-heterocyclic chalcones:
The N-substituted Phenylpyrrolidine-2, 5-diones or N-phenyl succinimides are conventionally synthesized by succinic anhydride and substituted anilines. Then afforded succinimides were employed for the preparation of bis-chalcone derivatives by microwave synthesis. The experimental method of conventional to microwave synthesis is schematically represented in **figure 1**;

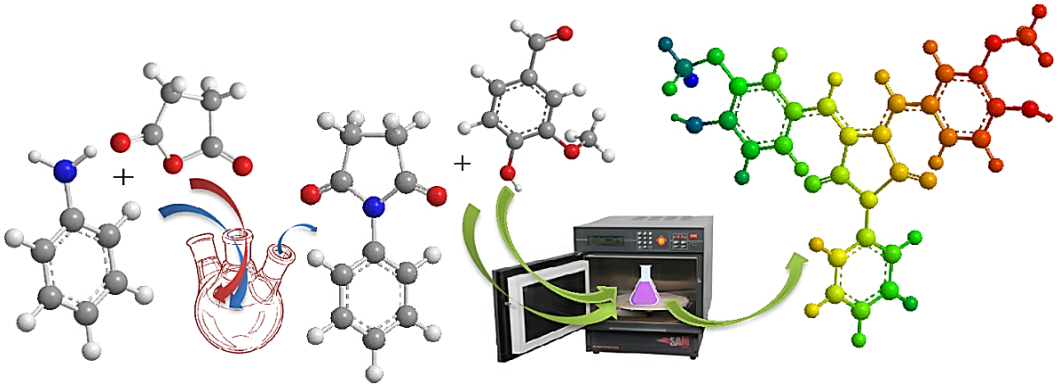
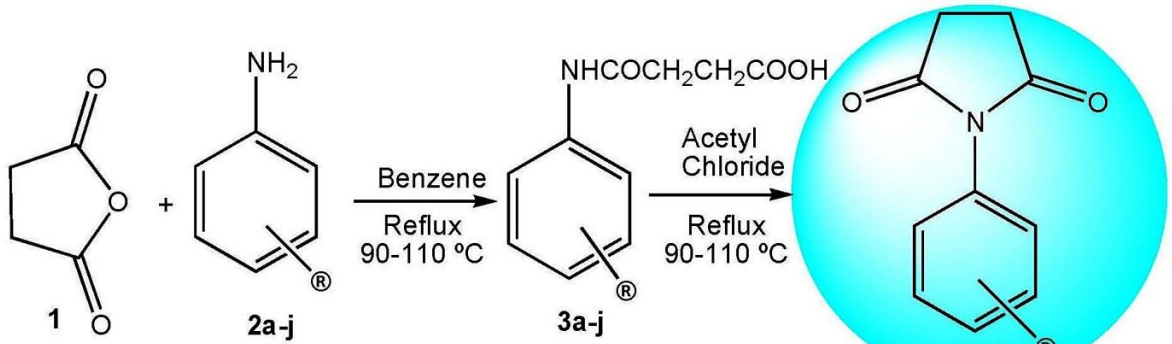


Figure 1 Experimental design of conventional to microwave method

General Procedure for the Synthesis of N-phenyl-pyrrolidine-2, 5-dione or N-Phenyl Succinimides:

To accomplish the work succinic anhydride (0.1 moles) benzene was added and heated under reflux with constant stirring for 15 to 20 min till the solution becomes clear. Into this solution the primary aromatic amines (0.2 moles) in 5 ml benzene was slowly poured with constant stirring for 15- 20 min till the solution becomes homogenized. On the vaporization of benzene amorphous powder of 3-(N-phenyl) propanoic acid was obtained. Further the mixture of 3-(N-phenyl) propanoic acid and acetyl chloride (0.9 moles) was reflux for 15-20 min by thoroughly evolution of HCl fumes. The reaction mixture was cooled at room temp the solid product was obtained and recrystallized by ethanol as shown in the **scheme 1**.



Scheme 1 Synthesis of N-phenyl Succinimides (4a-j)

Phenylpyrrolidine-2, 5-dione (4a):
White Shaped Crystals; M. F.: $C_{10}H_9NO_2$; Percent Yield: 79.91%; M. W.: 175.06; Melting Point (ºC): 154-156 ºC; FTIR: >C=O (2-Peaks): 1708 cm^{-1} and 1774 cm^{-1}, cyclic CH_2-CH_2: 2937 cm^{-1}, cyclic imines 1291 cm^{-1}, aromatic ring (3-Peaks): 1457 cm^{-1}, 1502 cm^{-1} and 1595 cm^{-1}

(4-bromophenyl) pyrrolidine-2, 5-dione (4b):
Whitish Brown Crystals; M. F.: $C_{10}H_8BrNO_2$; Percent Yield: 89.78%; M. W.: 254.08; Melting Point (ºC): 174-176 ºC; FTIR: >C=O (2-Peaks): 1707 cm^{-1} and 1766 cm^{-1}, cyclic CH_2-CH_2: 2998 cm^{-1}, cyclic imines 1295 cm^{-1}, aromatic ring (3-Peaks): 1455 cm^{-1}, 1488 cm^{-1} and 1588 cm^{-1}, Ar-Br: 1070 cm^{-1}

1-(4-chlorophenyl) pyrrolidine-2, 5-dione (4c):
Whitish Crystals; M. F.: $C_{10}H_8ClNO_2$; Percent Yield: 76.60%; M. W.: 209.63; Melting Point (ºC): 159-161 ºC; FTIR: >C=O (2-Peaks): 1711 cm^{-1} and 1773 cm^{-1}, cyclic CH_2-CH_2: 2985 cm^{-1}, cyclic imines 1302 cm^{-1}, aromatic ring (3-Peaks): 1495 cm^{-1}, 1527 cm^{-1} and 1589 cm^{-1}, Ar-Cl: 1093 cm^{-1}

1-p-tolylpyrrolidine-2, 5-dione (4d):
Cream White Crystals; M. F.: $C_{11}H_{11}NO_2$; Percent Yield: 62.73%; M. W.: 189.21; Melting Point (ºC): 150-152 ºC; FTIR: >C=O (2-Peaks): 1710 cm^{-1} and 1774 cm^{-1}, cyclic CH_2-CH_2: 2995 cm^{-1}, cyclic imines 1288 cm^{-1}, aromatic ring (3-Peaks): 1450 cm^{-1}, 1519 cm^{-1} and 1589 cm^{-1}

1-(4-methoxyphenyl) pyrrolidine-2, 5-dione (4e):
Whitish Crystals; M. F.: $C_{11}H_{11}NO_3$; Percent Yield: 78.91%; M. W.: 205.21; Melting Point (ºC): 160-162 ºC; FTIR : >C=O (2-Peaks): 1708 cm^{-1} and 1770 cm^{-1}, cyclic CH_2-CH_2: 2963 cm^{-1}, cyclic imines 1302 cm^{-1}, aromatic ring (3-Peaks): 1476 cm^{-1}, 1512 cm^{-1} and 1606 cm^{-1}, Ar-OCH_3: 1178 cm^{-1}

1-(4-fluorophenyl) pyrrolidine-2, 5-dione (4f):
White Crystals; M. F.: $C_{10}H_8FNO_2$; Percent Yield: 62.90%; M. W.: 193.17; Melting Point (ºC): 176-178 ºC; FTIR: >C=O (2-Peaks): 1712 cm^{-1} and 1767 cm^{-1}, cyclic CH_2-CH_2: 3000 cm^{-1}, cyclic imines 1290 cm^{-1}, aromatic ring (3-Peaks): 1456 cm^{-1}, 1513 cm^{-1} and 1604 cm^{-1}, Ar-F: 1178 cm^{-1}; Elemental Anal: C, 62.38; H, 4.09; N, 6.87; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.16-7.36 (m, 4H, Ar-H), 2.94 (s, 4H, imide)

1-(4-nitrophenyl) pyrrolidine-2, 5-dione (4g):
Pale Yellow Solid; M. F.: $C_{10}H_8N_2O_4$; Percent Yield: 88.86%; M. W.: 220.18; Melting Point (ºC): 219-221 ºC; FTIR: >C=O (2-Peaks): 1617 cm^{-1} and 1679 cm^{-1}, cyclic CH_2-CH_2: 2883 cm^{-1}, cyclic imines 1300 cm^{-1}, aromatic ring (3-Peaks): 1501 cm^{-1}, 1564 cm^{-1} and 1596 cm^{-1}, Ar-NO_2: 1501 cm^{-1}

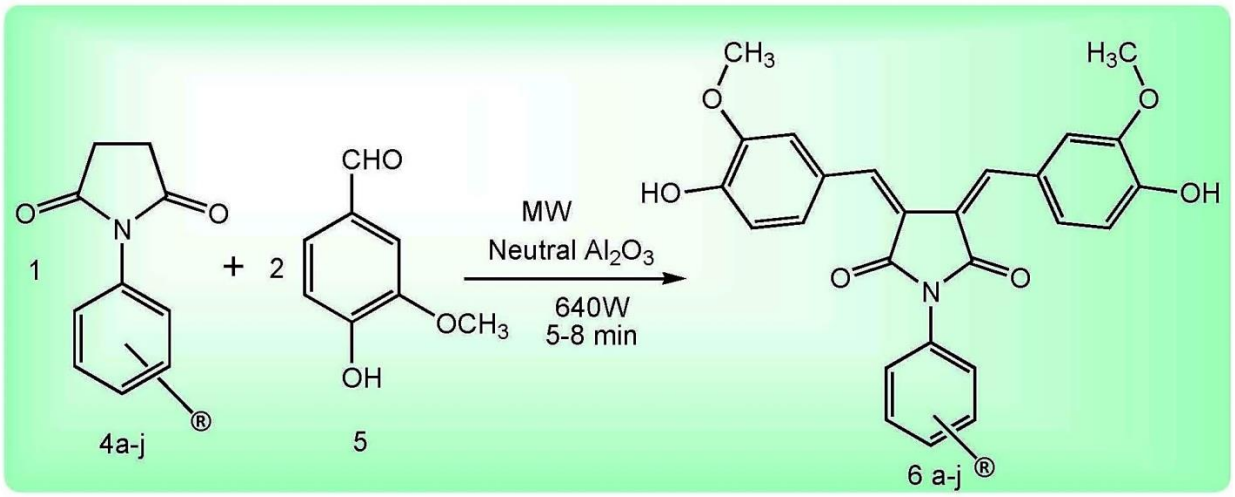
1-(naphthalen-4-yl) pyrrolidine-2, 5-dione (4h):
Whitish Solid; M. F.: $C_{14}H_{11}NO_2$; Percent Yield: 99.11%; M. W.: 225.24; Melting Point (ºC): 148-150 ºC; FTIR: >C=O (2-Peaks): 1700 cm^{-1} and 1776 cm^{-1}, cyclic CH_2-CH_2: 2939 cm^{-1}, cyclic imines 1291 cm^{-1}, aromatic ring (3-Peaks): 1463 cm^{-1}, 1509 cm^{-1} and 1595 cm^{-1}; Elemental Anal: C, 75.04; H, 3.89; N, 6.26; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.30-8.03 (m, 7H, napthyl), 3.06 (s, 4H, imide)

1-(3-chloro-4-fluorophenyl) pyrrolidine-2, 5-dione (4i):
Pure White Solid; M. F.: $C_{10}H_7ClFNO_2$; Percent Yield: 79.91%; M. W.: 227.62; Melting Point (ºC): 158-160 ºC; FTIR: >C=O (2-Peaks): 1698 cm^{-1} and 1776 cm^{-1}, cyclic CH_2-CH_2: 2937 cm^{-1}, cyclic imines 1294 cm^{-1}, aromatic ring (3-Peaks): 1490 cm^{-1}, 1502 cm^{-1} and 1595 cm^{-1}, Ar-Br: 1070 cm^{-1}, Ar-*p*-F: 1173 cm^{-1} and *m*-Cl: 1059 cm^{-1}; Elemental Anal: C, 53.01; H, 3.32; N, 6.20; ^{1}H NMR (500.13 MHz, $CDCl_3$, δ ppm): 7.25-7.44 (m, 3H, Ar-H), 2.92 (s, 4H, imide)

1-(2, 4, 5-trichlorophenyl) pyrrolidine-2, 5-dione (4j):
White Solid; M. F.: $C_{10}H_6Cl_3NO_2$; Percent Yield: 75.56%; M. W.: 278.52; Melting Point (ºC): 196-198 ºC; FTIR: >C=O (2-Peaks): 1660 cm^{-1} and 1700 cm^{-1}, cyclic CH_2-CH_2: 2993 cm^{-1}, cyclic imines 1356 cm^{-1}, aromatic ring (3-Peaks): 1454 cm^{-1}, 1508 cm^{-1} and 1570 cm^{-1}, Ar-2,4,5 Cl_3: 1072 cm^{-1}; Elemental Anal: C, 43.04; H, 3.01; N, 5.27; ^{1}H NMR (500.13 MHz, $CDCl_3$, δ ppm): 7.28-7.57 (m, 2H, Ar-H), 2.27 (s, 4H, imide)

General procedure for the synthesis of bis-chalcones derived from N-phenyl succinimides:

The bis-chalcones **(6a-j)** derivatives were synthesized by the mixture of 0.1 moles of N-phenyl succinimides **(4a-j)** and 0.2 mole of 4-hydroxy-3-methoxy benzaldehyde in 2 gm of neutral Al_2O_3 under microwave supported solvent free condition on 640W power for 5-8 min. The developed compounds were recrystallized from ethanol **(Scheme 2)**



® , a = -H, b = -4Br, c = -4Cl, d = -4CH_3, e = -4OCH_3,
f = -4F, g = -4NO_2, h = -phenyl, i = -3Cl,-4F, j = -2,4,5Cl

Scheme 2 (3Z,4Z)-3,4-bis(4-hydroxy-3-methoxybenzylidene)-N-phenylpyrrolidine-2,5-dione (6a-j)

(3Z,4Z)-3,4-bis(4-hydroxy-3-methoxybenzylidene)-1-phenylpyrrolidine-2,5-dione (6a):
Yellowish Needle Shaped Crystals; M.W.: $C_{26}H_{21}NO_6$; Percent Yield: 84.56%; M. W.: 443.45; Melting Point (ºC): 112-114 ºC; FTIR: >C=O (2-Peaks): 1661 cm^{-1} and 1700 cm^{-1}, =C-H: 3000 cm^{-1}, aromatic ring (3-Peaks): 1453 cm^{-1}, 1501 cm^{-1} and 1590 cm^{-1}, Ar-OCH_3: 1296 cm^{-1}, Ar-OH: 3400 cm^{-1}; Elemental Anal: C, 69.85; H, 4.50; N, 3.34; ^{1}H NMR: 6.80-7.42 (m, 8H, Ar-H and =CH), 9.77 (s, 1H, -OH), 3.86 (s, 3H, -OCH_3)

(3Z,4Z)-3,4-bis(4-hydroxy-3-methoxybenzylidene)-1-(4-bromophenyl) pyrrolidine - 2 , 5-dione (6b):
Whitish Granular Crystals; M. F.: $C_{26}H_{20}BrNO_6$; Percent Yield: 97.59%; M. W.: 522.34; Melting Point (ºC): 91-93 ºC; FTIR: >C=O (2-Peaks): 1689 cm^{-1} and 1739 cm^{-1}, =C-H: 2923 cm^{-1}, aromatic ring (3-Peaks): 1480 cm^{-1}, 1536 cm^{-1} and 1624 cm^{-1}, Ar-OCH_3: 1235 cm^{-1}, Ar-OH: 3503 cm^{-1}, Ar-Br: 1048 cm^{-1}; Elemental Anal: C, 60.17; H, 3.79; N, 2.50

(3Z,4Z)-3,4-bis(4-hydroxy-3-methoxybenzylidene)-1-(4-chlorophenyl) pyrrolidine-2,5-dione (6c):
Whitish Pink Granular Crystals; M. F.: $C_{26}H_{20}ClNO_6$; Percent Yield: 94.93%; M. W.: 477.89; Melting Point (ºC): 109-111 ºC; FTIR: >C=O (2-Peaks): 1710 cm^{-1} and 1745 cm^{-1}, =C-H: 2924 cm^{-1}, aromatic ring (3-Peaks): 1462 cm^{-1}, 1540 cm^{-1} and 1618 cm^{-1}, Ar-OCH_3: 1187 cm^{-1}, Ar-OH: 3590 cm^{-1}, Ar-Cl: 1109 cm^{-1}; Elemental Anal: C, 66.04; H, 4.50; N, 2.75

(3Z,4Z)-3,4-bis(4-hydroxy-3-methoxybenzylidene)-1-p-tolylpyrrolidine-2,5-dione (6d):
Yellowish Needle Shaped Crystals; M. F.: $C_{27}H_{23}NO_6$; Percent Yield: 68.28%; M. W.: 457.47; Melting Point (ºC): 99-101 ºC; FTIR: >C=O (2-Peaks): 1707 cm^{-1} and 1774 cm^{-1}, =C-H: 3042 cm^{-1}, aromatic ring (3-Peaks): 1459 cm^{-1}, 1517 cm^{-1} and 1589 cm^{-1}, Ar-OCH_3: 1185 cm^{-1}, Ar-OH: 3617 cm^{-1}; Elemental Anal: C, 71.02; H, 4.86; N, 3.10

(3Z,4Z)-3,4-bis(4-hydroxy-3-methoxybenzylidene)-1-(4-methoxyphenyl) pyrrolidine-2,5-dione (6e):
Whitish Needle Shaped Flakes; M. F.: $C_{27}H_{23}NO_7$; Percent Yield: 71.48%; M. W.: 473.47; Melting Point (ºC): 108-110 ºC; FTIR: >C=O (2-Peaks): 1668 cm^{-1} and 1710 cm^{-1}, =C-H: 3027 cm^{-1}, aromatic ring (3-Peaks): 1460 cm^{-1}, 1512 cm^{-1} and 1590 cm^{-1}, Ar-OCH_3: 1167 cm^{-1}, Ar-OH: 3500 cm^{-1}, Ar-OCH_3: 1298 cm^{-1}; Elemental Anal: C, 69.09; H, 4.95; N, 3.03; ^{1}H NMR: 6.25-7.30 (m, 5H, Ar-H and =CH), 9.87 (s, 1H, -OH), 3.86 (s, 3H, -OCH_3)

(3Z,4Z)-3,4-bis(4-hydroxy-3-methoxybenzylidene)-1-(4-fluorophenyl) pyrrolidine-2,5-dione (6f):
Yellow Granular Crystals; M. F.: $C_{26}H_{20}FNO_6$; Percent Yield: 64.62%; M. W.: 461.44; Melting Point (ºC): 148-150 ºC; FTIR: >C=O (2-Peaks): 1674 cm^{-1} and 1711 cm^{-1}, =C-H: 3079 cm^{-1}, aromatic ring (3-Peaks): 1460 cm^{-1},

1513 cm^{-1} and 1594 cm^{-1}, Ar-OCH_3: 1187 cm^{-1}, Ar-OH: 3279 cm^{-1}, Ar-F: 1218 cm^{-1}; Elemental Anal: C, 68.00; H, 4.48; N, 2.98

(3Z,4Z)-3,4-bis(4-hydroxy-3-methoxybenzylidene)-1-(4-nitrophenyl)pyrrolidine-2,5-dione (6g):
Yellow Granular Crystals; M. F.: $C_{26}H_{20}N_2O_8$; Percent Yield: 84.42%; M. W.: 488.45; Melting Point (ºC): 152-154 ºC; FTIR: >C=O (2-Peaks): 1681 cm^{-1} and 1719 cm^{-1}, =C-H: 3101 cm^{-1}, aromatic ring (3-Peaks): 1460 cm^{-1}, 1565 cm^{-1} and 1595 cm^{-1}, Ar-OCH_3: 1299 cm^{-1}, Ar-OH: 3279 cm^{-1}, Ar-NO_2: 1510 cm^{-1}; Elemental Anal: C, 64.01; H, 4.25; N, 5.69

(3Z,4Z)-3,4-bis(4-hydroxy-3-methoxybenzylidene)-1-(naphthalen-4-yl) pyrrolidine-2,5-dione (6h):
Brownish Solid; M. F.: $C_{30}H_{23}NO_6$; Percent Yield: 83.26%; M. W.: 493.51; Melting Point (ºC): 89-91 ºC; FTIR: >C=O (2-Peaks): 1707 cm^{-1} and 1776 cm^{-1}, =C-H: 3055 cm^{-1}, aromatic ring (3-Peaks): 1463 cm^{-1}, 1511 cm^{-1}, 1547 cm^{-1}, 1589 cm^{-1} and 1665 cm^{-1}, Ar-OCH_3: 1186 cm^{-1}, Ar-OH: 3549 cm^{-1}; Elemental Anal: C, 72.91; H, 4.79; N, 3.05

(3Z,4Z)-3,4-bis(4-hydroxy-3-methoxybenzylidene)-1-(3-chloro-4-fluorophenyl) pyrrolidine-2,5-dione (6i):
Whitish Solid; M. F.: $C_{26}H_{19}ClFNO_6$; Percent Yield: 74.39%; M. W.: 495.88; Melting Point (ºC): 98-100 ºC; FTIR: >C=O (2-Peaks): 1695 cm^{-1} and 1776 cm^{-1}, =C-H: 3031 cm^{-1}, aromatic ring (3-Peaks): 1460 cm^{-1}, 1511 cm^{-1} and 1589 cm^{-1}, Ar-OCH_3: 1266 cm^{-1}, Ar-OH: 3600 cm^{-1}, Ar-F: 1172 cm^{-1}, Ar-Cl: 1028 cm^{-1}; Elemental Anal: C, 63.10; H, 4.03; N, 3.01

(3Z,4Z)-3,4-bis(4-hydroxy-3-methoxybenzylidene)-1-(2,4,5-trichlorophenyl) pyrrolidine-2,5-dione (6j):
Pinkish Needle Shaped Crystals; M. F.: $C_{26}H_{18}Cl_3NO_6$; Percent Yield: 71.06%; M. W.: 546.78; Melting Point (ºC): 137-139 ºC; FTIR: >C=O (2-Peaks): 1667 cm^{-1} and 1704 cm^{-1}, =C-H: 3032 cm^{-1}, aromatic ring (3-Peaks): 1460 cm^{-1}, 1512 cm^{-1} and 1589 cm^{-1}, Ar-OCH_3: 1266 cm^{-1}, Ar-OH: 3269 cm^{-1}, Ar-2,4,5Cl: 1027 cm^{-1}; Elemental Anal: C, 57.30; H, 3.51; N, 2.77; ^{1}H NMR: 6.23-7.51 (m, 5H, Ar-H and =CH), 9.87 (s, 1H, -OH), 4.01 (s, 3H, -OCH_3)

Result and Discussion:

Chemistry:

The starting compounds of bis-chalcones **6a-j** were prepared by the reaction of substituted N-phenyl-pyrrolidine-2, 5-dione **4a-j** using 4-hydroxy-3-methoxy benzaldehyde. The series of 3,4-bis(4-hydroxy-3-methoxy benzylidene)-N-phenylpyrrolidine-2,5-diones **6a-j** were synthesized in reasonable yields by the microwave irradiation of cyclic imides **4a-j** with vanillin in presence of neutral alumina in solvent free condition. The structure of bis-chalcones was confirmed by IR, ^{1}H NMR and elemental analysis.

Antimicrobial activities (4a-j and 6a-j):

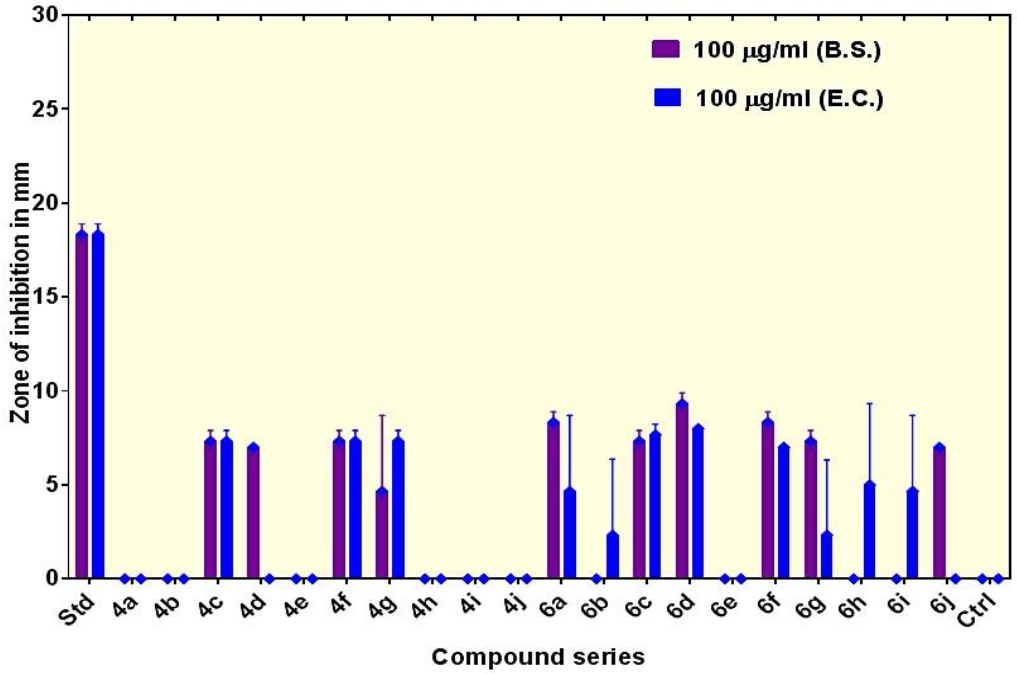
All the synthesized compounds **4a-j** and **6a-j** were screened for their antibacterial activity against gram positive bacteria *Bacillus subtilis* (MCMB-310) and gram negative bacteria *Escherichia coli* (MCMB-301) using DMF solvent as shown in the graph -1. And antifungal activities against *Candida albicans* (NCIM-3471) and *Aspergillus niger* (NCIM- 545) strains using DMSO solvent revealed in the graph - 2. All the results of the synthesized compounds were carried out by the triplicate format N=3 with Mean ± SD. The statistical significance was carried out by one way ANOVA and confirmed by Dunnett multiple comparisons test performed the standard drugs against synthesized compounds. P value < 0.05 was considered as statistically significant remarked by *p<0.05, **p<0.01, ***p<0.001 compared to standard groups.

The calculated data were tabulated as shown below;

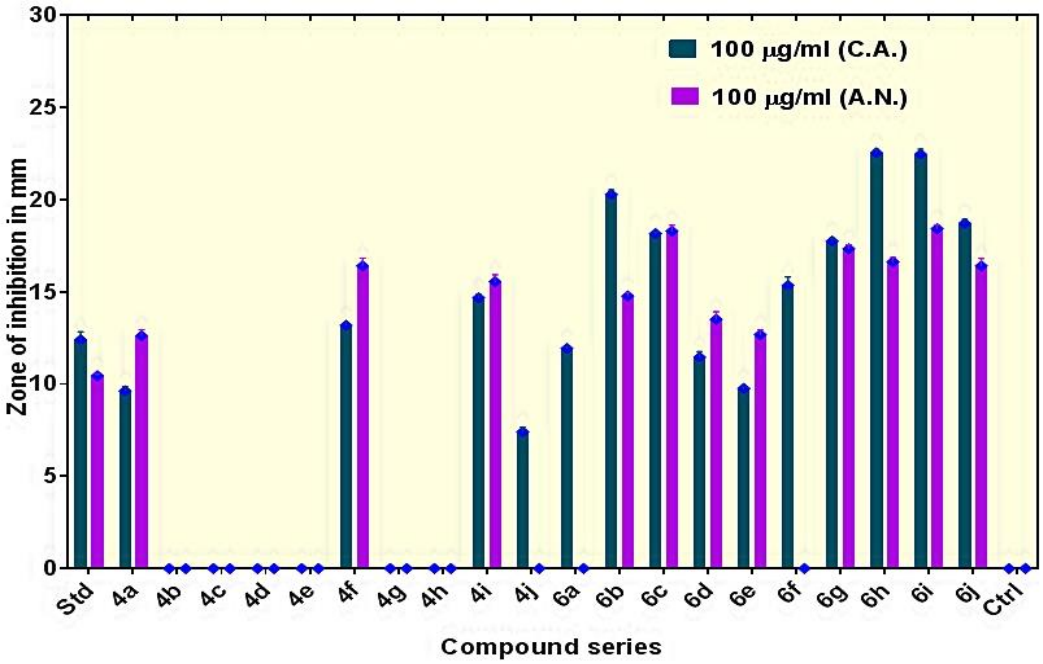
Table 1 Antimicrobial activities of Bis-chalcones

Compd Code	Zone diameter calculated in mm and tabulated by (Mean±S.D.)			
	Bacillus subtilis	***Escherichia coli***	***Candida albicans***	***Aspergillus niger***
	100 µg/ml	**100 µg/ml**	**100 µg/ml**	**100 µg/ml**
4a	--	--	9.63 ± 0.23 **	12.62 ± 0.33 **
4b	--	--	--	--
4c	7.33±0.57 **	7.33±0.57 **	--	--
4d	7±0 **	--	--	--
4e	--	--	--	--
4f	7.33±0.57 **	7.33±0.57 **	13.19 ± 0.15 *	16.41 ± 0.42 **
4g	4.66±4.04 **	7.33±0.57 **	--	--
4h	--	--	--	--
4i	--	--	14.68 ± 0.18 **	15.56 ± 0.37 **
4j	--	--	7.41 ± 0.27 **	--
6a	8.33±0.57 **	4.66±4.04 **	11.94 ± 0.09 ns	--
6b	--	2.33±4.04 **	20.28 ± 0.25 **	14.78 ± 0.19 **
6c	7.33±0.57 **	7.66±0.57 **	18.16 ± 0.06 **	18.29 ± 0.33 **
6d	9.33±0.57 **	8±0 **	11.46 ± 0.30 **	13.51 ± 0.41 **
6e	--	--	9.77 ± 0.08 **	12.68 ± 0.26 **
6f	8.33±0.57 **	7±0 **	15.35 ± 0.47 **	--
6g	7.33±0.57 **	2.33±4.0 **	17.75 ± 0.16 **	17.34 ± 0.22 **
6h	--	5±4.34 **	22.54 ± 0.19 **	16.63 ± 0.23 **
6i	--	4.66±4.04 **	22.46 ± 0.28 **	18.43 ± 0.21 **
6j	7±0 **	--	18.71 ± 0.22 **	16.41 ± 0.40 **
Ctrl	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0
Std	18.33±0.57	18.33±0.57	12.40 ± 0.43	10.45 ± 0.11

Keynote: *Zone of inhibition measured in mm (Mean±S.D.) (N=3) ('--' means no zone)*



Graph 1 Antibacterial activities of 4a-j and 6a-j (B.S. and E.C.) Mean±SD



Graph 2 Antifungal activities of 4a-j and 6a-j (C.A. and A.N.) Mean±SD

Conclusion

An entire new series of bis-heterocyclic chalcones containing 4-hydroxy-3-methoxy benzylidene nucleus have been synthesized in one pot and facile manner from cyclic imides in good yield. A good number of the synthesized bis-chalcone **6a-j** showed noticeable synergistic antifungal activities against *Candida albicans* and *Aspergillus niger* fungal strains.

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