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Microwave assisted solvent free synthesis and antifungal evaluation of3, 5-bis-(4-hydroxy-3-methoxybenzylidene)-N-phenylpiperidine-2, 6-dionederived from N-phenyl glutarimides

Ravindra S. Dhivare[1]*, S. S. Rajput[2]

[1]Department of General Science, J.S.P.M., JayawantraoSawant polytechnic, Hadapsar, Pune, India
[2]Department of Chemistry, SVS's DadasahebRawal College, Dondaicha, Maharashtra, India

Abstract: An efficient microwave supported solvent free synthesis of 3,5-bis-(4-hydroxy-3-methoxybenzylidene-N-phenylpiperidine-2,6-diones described with the subsequent condensation of N-phenyl glutarimides with 4-hydroxy-3methoxy-benzaldehyde inpresence neutral alumina. The afforded compounds exhibited good and remarkable antifungal activities.
Keywords: Bis-chalcones, N-phenyl glutarimides, antifungal actions.

Introduction:

Heterocyclic nitro[1] derivative provides the great opportunities for the development of novel and potent medicinal drugs. Heterocyclic imides such as succinimides[2-4], glutarimides[5, 6] and their malononitriles[7]and chalcone[8]centered pyrazolies[9], pyrimidines[10, 11] derivatives plays a very important role in the synthesis of organic compounds. Chalcones are the usefulprecursors of heterocycle family having a carbon bridge between α-β-unsaturated aromatic rings and carbonyl carbons. These are prepared by the condensation [12] of the substituted ketones and aldehyde groups[13, 14]. The chalcones are synthesized by using the several types of synthetic routes like solid phase claisenschemdit, cross aldol condensation, acid catalyst, coupling reaction [15], knoevanogel condensation [16] and microwave assisted synthesis. On the other hand, the chalcone showed significant cytotoxic activities against cell line, hepatocellular and lung carcinoma and breast cancer [17] and also potent microbial agents [18]. The clalcone based five membered pyrazoles are prepared by hydrazine hydrate or aromatic hydrazines in presence of sodium acetate [19], acetic acid [20,21], amberlyst[22]catalysts by conventional and microwave [23-25], facile grinding [26], chromine ring opening [27], solvent free [28], one pot tandem [29] and regio-selective [30] methods so on. The pyrazolinederivatives state the reasonable antibacterial [31], antifungal [32] activities.

Experimental:

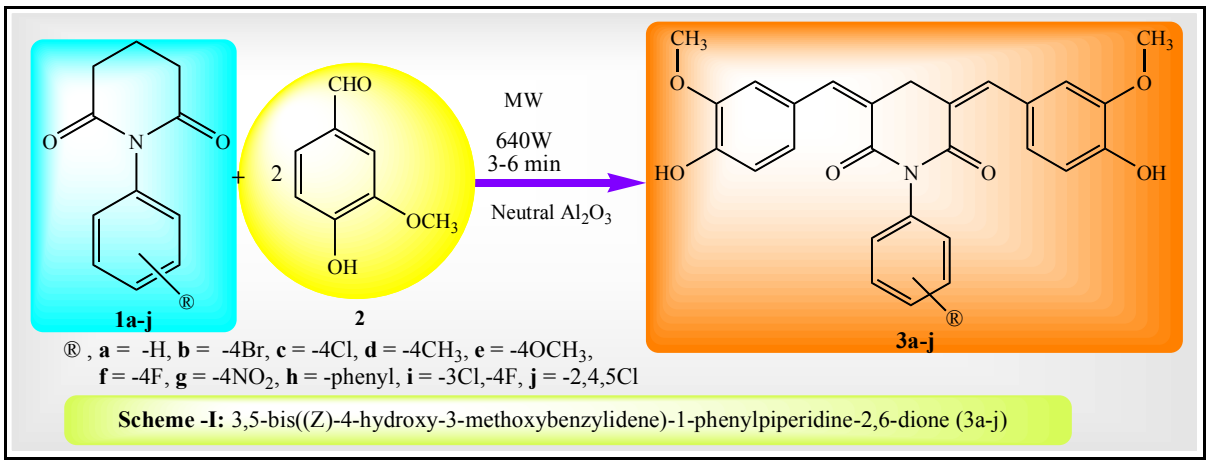
Material method

All the Melting points of synthesized compounds were recorded and uncorrected by using open glass capillaries. IR spectra in (KBr pallets) were verifiedby Shimadzu FTIR-8400S and ATR Brucker alpha FT-IR spectrophotometer. ^{1}HNMR spectra were recorded on 400 MHz and 500.13 MHz by Brucker

spectrophotometer. The reaction was monitored by TLC which was accomplished by using precoated silica-gel aluminiumsheets with the mixture of diethyl ether and ethyl acetate 7:3 proportion. Commercially purchased succinic anhydride, substituted anilines, acetyl chloride, benzene, vanillin, neutral Al_2O_3 and ethanol were used for the preparation.

General Procedure for Synthesis of Bis-chalcones by using N-Phenyl Glutarimides:

The bis-chalcones**(3a-j)** are synthesized by the mixture of 5 mmole of N-phenyl substituted glutarimides**(1a-j)** and 10 mmole of 4-hydroxy-3-methoxy-benzaldehyde **(2)** in 2 gm of neutral Al_2O_3 under microwave assisted solvent free conditions take place on 640W powers for 3-6 minutes. The afforded coloured compounds were recrystallized by ethanol as shown in the **scheme – I**and the physical standards were interpreted in the table-1.



Scheme -I: 3,5-bis((Z)-4-hydroxy-3-methoxybenzylidene)-1-phenylpiperidine-2,6-dione (3a-j)

Table-1: Physical standard of the compounds (3a-j)

Compd Code	Molecular Formula	M.Wt.	Yield %	Melting Point (ºC)	Colour
3a	$C_{27}H_{23}NO_6$	457.47	79.91	78-80 ºC	Yellowish White Solid
3b	$C_{27}H_{22}BrNO_6$	536.37	94.37	94-96ºC	Dark Yellow Crystals
3c	$C_{27}H_{22}ClNO_6$	491.92	82.25	76-78 ºC	Yellow Solid
3d	$C_{28}H_{25}NO_6$	471.5	83.98	95-97 ºC	Yellow Crystals
3e	$C_{28}H_{25}NO_7$	487.5	69.41	68-70 ºC	Yellow Crystals
3f	$C_{27}H_{22}FNO_6$	475.47	90.84	85-87 ºC	Yellow Crystals
3g	$C_{27}H_{22}N_2O_8$	502.47	78.33	93-95 ºC	Pale Yellow Crystals
3h	$C_{31}H_{25}NO_6$	507.53	91.74	88-90 ºC	Whitish Brown Solid
3i	$C_{27}H_{21}ClFNO_6$	509.91	82.23	74-76 ºC	Dark Yellow Solid
3j	$C_{27}H_{20}Cl_3NO_6$	560.81	83.03	103-105 ºC	Pinkish White Crystals

3,5-bis((Z)-4-hydroxy-3-methoxybenzylidene)-1-phenylpiperidine-2,6-dione(3a):

Molecular Formula: $C_{27}H_{23}NO_6$, Yellowish White AmorphousSolid, Percent Yield: 79.91%,Molecular Weight: 457.47, Melting Point (ºC): 78-80 ºC, C, H, N AnalObserved: C, 71.06; H, 6.98; N, 3.24, FTIR (KBr): >C=O (2-Peaks): 1595 cm^{-1} and 1672 cm^{-1}, =C-H: 2968 cm^{-1}, aromatic ring (3-Peaks): 1455 cm^{-1}, 1513 cm^{-1} and 1541 cm^{-1}, Ar-OCH_3: 1157 cm^{-1}, Ar-OH: 3320 cm^{-1}, ^{1}H NMR-(200.13 MHz; $CDCl_3$; δ ppm): 7.40-6.26 (m, 8H, Ar-H and =CH), 9.87 (s, 1H, -OH), 3.70 (s, 3H, -OCH_3), 2.46 (s, 2H, -CH_2) .

1-(4-bromophenyl)-3,5-bis((Z)-4-hydroxy-3-methoxybenzylidene)piperidine-2,6-dione(3b):Molecular Formula: $C_{27}H_{22}BrNO_6$, Dark Yellow Granular Crystals, Percent Yield: 94.37%, Molecular Weight: 536.37, Melting Point (ºC): 94-96 ºC, C, H, N AnalObserved: C, 60.88; H, 4.25; N, 2.75, FTIR (KBr): >C=O (2-Peaks):

1667 cm^{-1} and 1689 cm^{-1}, =C-H: 3032 cm^{-1}, aromatic ring (3-Peaks): 1462 cm^{-1}, 1514 cm^{-1} and 1590 cm^{-1}, Ar-OCH_3: 1172 cm^{-1}, Ar-OH: 3294 cm^{-1}, Ar-Br: 1072 cm^{-1}.

1-(4-chlorophenyl)-3,5-bis((Z)-4-hydroxy-3-methoxybenzylidene)piperidine-2,6-dione(3c):Molecular Formula: $C_{27}H_{22}ClNO_6$, Yellow Solid, Percent Yield: 82.25%, Molecular Weight: 491.92, Melting Point (ºC): 76-78 ºC, C, H, N AnalObserved: C, 66.42; H, 4.68; N, 2.99, FTIR (KBr): >C=O (2-Peaks): 1667 cm^{-1} and 1742 cm^{-1}, =C-H: 3030 cm^{-1}, aromatic ring (3-Peaks): 1462 cm^{-1}, 1512 cm^{-1} and 1590 cm^{-1}, Ar-OCH_3: 1170 cm^{-1}, Ar-OH: 3287 cm^{-1}, Ar-Cl: 1026 cm^{-1}.

3,5-bis((Z)-4-hydroxy-3-methoxybenzylidene)-1-(p-tolyl)piperidine-2,6-dione(3d):

Molecular Formula: $C_{28}H_{25}NO_6$, Yellow Granular Crystals, Percent Yield: 83.98%, Molecular Weight: 471.5, Melting Point (ºC): 95-97 ºC, C, H, N AnalObserved: C, 71.86; H, 5.73; N, 3.55, FTIR (KBr): >C=O (2-Peaks): 1594 cm^{-1} and 1675 cm^{-1}, =C-H: 2946 cm^{-1}, aromatic ring (3-Peaks): 1459 cm^{-1}, 1514 cm^{-1} and 1596 cm^{-1}, Ar-OCH_3: 1171 cm^{-1}, Ar-OH: 3280 cm^{-1}, ^{1}H NMR-(500.13 MHz; DMSO-d^6; δ ppm): 7.48-6.97 (m, 5H, Ar-H and =CH), 9.78 (s, 1H, -OH), 3.70 (s, 3H, -OCH_3), 2.71 (s, 2H, -CH_2) .

3,5-bis((Z)-4-hydroxy-3-methoxybenzylidene)-1-(4-methoxyphenyl)piperidine-2,6-dione(3e):Molecular Formula: $C_{28}H_{25}NO_7$, Yellow Granular Crystals, Percent Yield: 69.41%, Molecular Weight: 487.5, Melting Point (ºC): 68-70 ºC, C, H, N AnalObserved: C, 69.09; H, 5.72; N, 3.20, FTIR (KBr): >C=O (2-Peaks): 1596 cm^{-1} and 1677 cm^{-1}, =C-H: 2971 cm^{-1}, aromatic ring (3-Peaks): 1460 cm^{-1}, 1514 cm^{-1} and 1596 cm^{-1}, Ar-OCH_3: 1171 cm^{-1}, Ar-OH: 3466 cm^{-1}.

1-(4-fluorophenyl)-3,5-bis((Z)-4-hydroxy-3-methoxybenzylidene)piperidine-2,6-dione(3f):Molecular Formula: $C_{27}H_{22}FNO_6$, YellowGranular Crystals, Percent Yield: 90.84%, Molecular Weight: 475.47, Melting Point (ºC): 85-87 ºC, C, H, N AnalObserved: C, 68.81; H, 4.93; N, 3.33, FTIR (KBr): >C=O (2-Peaks): 1594 cm^{-1} and 1672 cm^{-1}, =C-H: 3089 cm^{-1}, aromatic ring (3-Peaks): 1426 cm^{-1}, 1513 cm^{-1} and 1594 cm^{-1}, Ar-OCH_3: 1158 cm^{-1}, Ar-OH: 3316 cm^{-1}, Ar-F: 1126 cm^{-1}.

3,5-bis((Z)-4-hydroxy-3-methoxybenzylidene)-1-(4-nitrophenyl)piperidine-2,6-dione(3g):Molecular Formula: $C_{27}H_{22}N_2O_8$, Pale Yellow Granular Crystals, Percent Yield: 78.33%, Molecular Weight: 502.47, Melting Point (ºC): 93-95 ºC, C, H, N AnalObserved: C, 64.76; H, 4.65; N, 5.85, FTIR (KBr): >C=O (2-Peaks): 1668 cm^{-1} and 1711cm^{-1}, =C-H: 3078 cm^{-1}, aromatic ring (3-Peaks): 1460 cm^{-1}, 1512 cm^{-1} and 1590 cm^{-1}, Ar-OCH_3: 1170 cm^{-1}, Ar-OH: 3269 cm^{-1}, Ar-NO_2: 1512 cm^{-1}.

3,5-bis((Z)-4-hydroxy-3-methoxybenzylidene)-1-(naphthalen-1-yl)piperidine-2,6-dione(3h):Molecular Formula: $C_{31}H_{25}NO_6$, Whitish Brown Solid, Percent Yield: 91.74%, Molecular Weight: 507.53, Melting Point (ºC): 88-90 ºC, C, H, N AnalObserved: C, 73.79; H, 5.02; N, 2.98, FTIR (KBr): >C=O (2-Peaks): 1667 cm^{-1} and 1704 cm^{-1}, =C-H: 3078 cm^{-1}, aromatic ring (3-Peaks): 1429 cm^{-1}, 1460 cm^{-1}, 1511 cm^{-1}, 1589 cm^{-1} and 1667 cm^{-1}, Ar-OCH_3: 1172 cm^{-1}, Ar-OH: 3178 cm^{-1}.

1-(3-chloro-4-fluorophenyl)-3,5-bis((Z)-4-hydroxy-3-methoxybenzylidene)piperidine-2,6-dione (3i):Molecular Formula: $C_{27}H_{21}ClFNO_6$, Dark Yellow Solid, Percent Yield: 82.23%, Molecular Weight: 509.91, Melting Point (ºC): 74-76 ºC, C, H, N AnalObserved: C, 63.91; H, 4.69; N, 2.86, FTIR (KBr): >C=O (2-Peaks): 1595 cm^{-1} and 1674 cm^{-1}, =C-H: 3027 cm^{-1}, aromatic ring (3-Peaks): 1459 cm^{-1}, 1511 cm^{-1} and 1544 cm^{-1}, Ar-OCH_3: 1172 cm^{-1}, Ar-OH: 3309 cm^{-1}, Ar-F: 1172 cm^{-1}, Ar-Cl: 1056 cm^{-1}.

3,5-bis((Z)-4-hydroxy-3-methoxybenzylidene)-1-(2,4,5-trichlorophenyl)piperidine-2,6-dione(3j):Molecular Formula: $C_{27}H_{20}Cl_3NO_6$, Pinkish White Granular Crystals, Percent Yield: 83.03%, Molecular Weight: 560.81, Melting Point (ºC): 103-105 ºC, C, H, N AnalObserved: C, 58.58; H, 3.84; N, 2.87, FTIR (KBr): >C=O (2-Peaks): 1669 cm^{-1} and 1694 cm^{-1}, =C-H: 3027 cm^{-1}, aromatic ring (3-Peaks): 1459 cm^{-1}, 1512 cm^{-1} and 1580 cm^{-1}, Ar-OCH_3: 1170 cm^{-1}, Ar-OH: 3276 cm^{-1}, Ar-2,4,5Cl: 1078 cm^{-1}, ^{1}H NMR-(500.13 MHz; DMSO-d^6; δ ppm): 8.07-6.96 (m, 5H, Ar-H and =CH), 9.77 (s, 1H, -OH), 3.70 (s, 3H, -OCH_3), 2.30 (s, 2H, -CH_2).

Result and discussion:

Chemistry

The target molecules of bis-chalcones 3a-j were synthesized by the reaction of N-phenyl piperidine-2, 6-diones with 4-hydroxy-3-methoxy benzaldehyde in presence of neutral alumina. IR, ^{1}H NMR spectra and elemental anal of the afforded derivatives were confirmed. IUPAC naming of the final compounds were determined by Perkins Elmer Chemdraw software.

Antifungal Protocol

Antimicrobial susceptibility testing of chemically synthesized compounds was qualitatively assessed by disc diffusion assay. The yeast *Candida albicans*was cultured using a malt extract, glucose yeast extract peptone agar medium (MGYP medium). For fungi *Aspergillusniger*potato dextrose agar medium was used. After autoclaving, respective media were allowed to attain temperature 50℃ . Then 50 mL, corresponding agar medium was poured into sterile square petri-plate (120 mm x 120 mm) which formed uniform layer of agar medium (16 mm). Then petri plates were allowed to cool at room temp and refrigerateit on 2 to 8 °C until further use. A sterile cotton mop was submerged into the fungal suspension. The mop was gyrated a number of times and pushed firmly on the inner-wall of the tube above runny-level. The corresponding agar medium plate was inoculated by zipping the mopfinishes the whole surface of agar. This procedure was frequently run through 2-4 times streaking on spinning plate.After spreading of suspensions, sterile disc (6 mm) was dipped in stock solution (100 µg) and placed on surface of agar medium. Inoculated petri plates were kept in the refrigerator 8 °C. After 15-30 min, petri-plates with yeast strain were incubated at 30 °C while petri plates inoculated with fungal strain were incubated at 28 °C.After appropriate incubation period, each plate was examined. The diameters of the zones of inhibition were measured using digital vernier caliper from the back side of the petri plate as shown in the figure -1.

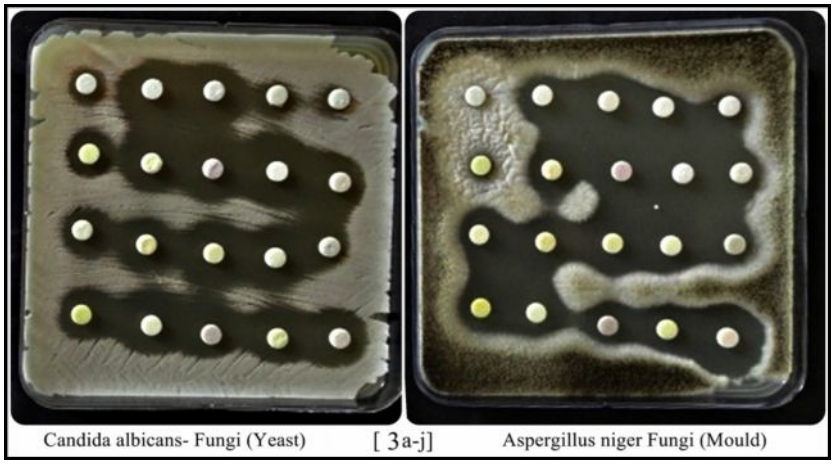


Figure-1: Antifungal activities of bis-chalcones(3a-j)

Stock solution of the synthesized compounds:

Stock solutions (1000 µg/ml) of each compound were prepared in Dimethylsulfoxide (DMSO) solvent. Assay carried out by taking concentration 100 microgram per disk. Hi-media antibiotics disk: Amphotericin-B (100 units/disk) moistened with DMSO was used as standard. All the compounds result shown in the table-2

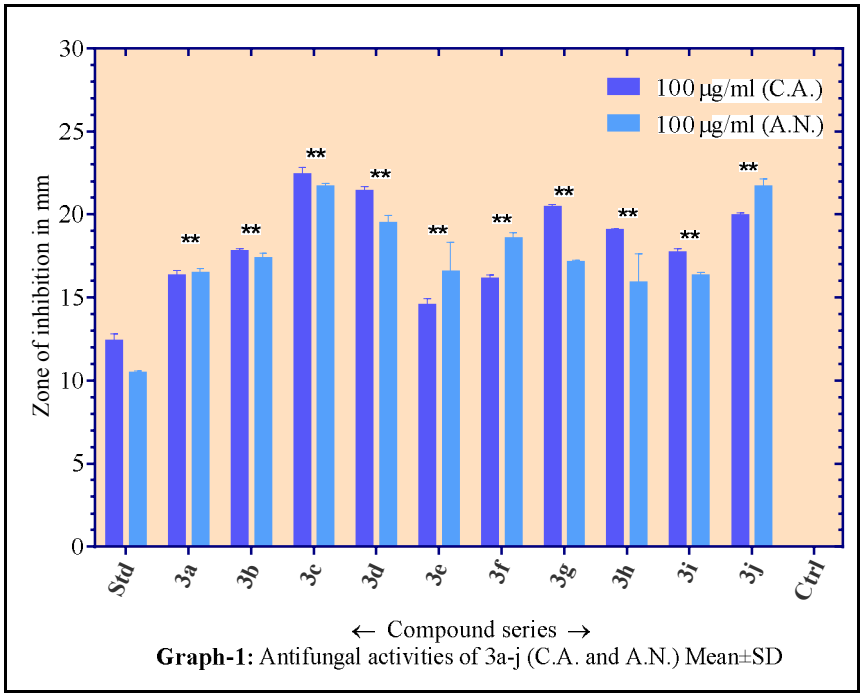
Table-2: Antifungal activities of bis-chalcones(3a-j)

	100µg/ml	**100µg/ml**
3a	16.31 ± 0.33**	16.46 ± 0.27 **
3b	17.80 ± 0.16**	17.36 ± 0.31 **
3c	22.42 ± 0.39**	21.69 ± 0.18 **
3d	21.41 ± 0.25**	19.50 ± 0.45 **

3e	14.53 ± 0.41**	16.56 ± 1.75 **
3f	16.15 ± 0.22**	18.57 ± 0.32 **
3g	20.43 ± 0.16**	17.12 ± 0.12 **
3h	19.04 ± 0.08**	15.89 ± 1.72 **
3i	17.71 ± 0.22**	16.31 ± 0.22 **
3j	19.94 ± 0.15**	21.67 ± 0.48 **
Ctrl	0.0±0.0	0.0±0.0
Std	12.40 ± 0.43	10.45 ± 0.11

Statistical Analysis:

All the results of the synthesized compounds **3a-j** were carried out by the triplicate practice N=3 with Mean ± SD shown in the graph-1. The statistical tests were executed by using GraphPad prism-6 and GraphPadInStat 3.10 version software. The statistical significance was calculated by one way ANOVA ensured by Dunnett multiple comparisons test will performed by standard drug against synthesized compounds. p value < 0.05 were considered as statistically significant and stated by *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 compared to standard groups.



Graph-1: Antifungal activities of 3a-j (C.A. and A.N.) Mean±SD

Conclusion:

Bis-chalcones (3a-j) has been prepared by the treatment of substituted N-phenyl glutarimides and vanillin with neutral alumina in microwave supported solvent free method. All the synthesized compounds were characterized by their physical, spectral as well as antifungal analysis. Almost all the synthesized compounds showed the superior activities against *Candida albicans*and *Aspergillusniger* fungal strains. The ecofriendly microwave method can be used for the preparation of different substituted heterocyclic synthones.

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