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Microwave Assisted Synthesis and Antimicrobial activities of 3,4-bis-(4-hydroxy-3-methoxybenzylidene)-7-(N-phenyl)-3,3a,3b,4,5,7-hexahydro-2*H*-pyrrolo[2,3-c,5,4-c] di pyrazole

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A B S T R A C T

The novel pyrazole derivatives were synthesized by reacting substituted bis-chalcones with 4-hydroxy-3-methoxy benzaldehyde to get 3,4-bis-(4-hydroxy-3-methoxybenzylidene)-7-(N-phenyl)-3,3a,3b,4,5,7-hexahydro -2*H*-pyrrolo [2,3-c,5,4-c] dipyrazole using solvent-free microwave method. All these derivatives were screened for antimicrobial activities.

Keywords: bis-chalcones, bis-pyrazoles, antimicrobial activities

A R T I C L E I N F O

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1. Introduction

Over the previous years has remains the brilliant acceptance in the practice of microwave energy source to enhance the synthetic chemical conversions. Currently the eco-friendly manner of the green chemistry is crucial in the synthesis of heterocyclic components for superior and expedient product systems. In this manner the microwave energy is a very effective means of dynamic chemical reactions. The clalcone [1] [2] centered pyrazoles [3] are prepared by hydrazine hydrate [4] or aromatic hydrazines in presence of sodium acetate [5], acetic acid [6] catalysts by conventional

and microwave [7], grinding [8], chromine ring opening [9], solvent free [10], tandem [11] and regio-selective [12] methods so on. The newer techniques of pyrazole synthesis by using eco-friendly one pot multicomponent, solvent free, solid support, microwave [13] and ultrasound synthetic methods are more useful than that of the conventional methods [14]. The chalconic pyrazoles and pyrazolones are significant anticancer [15], anti-breast cancer [16], antipyretic [17], α-reductase inhibitors [18], anti-oxidant [19], anti-inflammatory [20], anti-mycobacterial [21] and good antimicrobial [22] [23], antifungal [24] agents.

Pyrazoles are heterocyclic five membered ring structure having three carbon atoms and two nitrogen atoms fixed at first and third position. Most of the pyrazole derivatives have been developed for different antimicrobial, medicinal, biological actions. Hence it has been synthesized the different substituted pyrazole by using microwave assisted clean and efficient reactions in a recent way to get better yield by eco-friendly reaction [25]. At this instant the researcher has undertaken the di-substituted aromatic aldehyde used for the synthesis of chalcones to pyrazoles. These are developed through the substituted phenyl succinimides [26] [27] in the solvent free microwave assisted method.

2. Materials and Methods

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,ATR Brucker alpha FT-IR spectrophotometer. ^{13}C NMR and ^{1}H NMR spectra were recorded on 125.77 MHz, 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 mixture of diethyl ether and ethyl acetate 7:3 proportion or benzene. All the compounds **3a-j** was synthesized in the microwave oven in hours from 4-hydroxy-3-methoxy benzaldehyde (vanillin), hydrazine hydrate, neutral alumina (Al_2O_3) and ethanol.

Preparation of substituted bis-pyrazole derivatives (3a-j): The previously prepared bis-chalcones were used for the preparation of novel pyrazole derivatives by microwave synthesis. The experimental method of microwave assisted synthesis is diagrammatically shown in fig.01

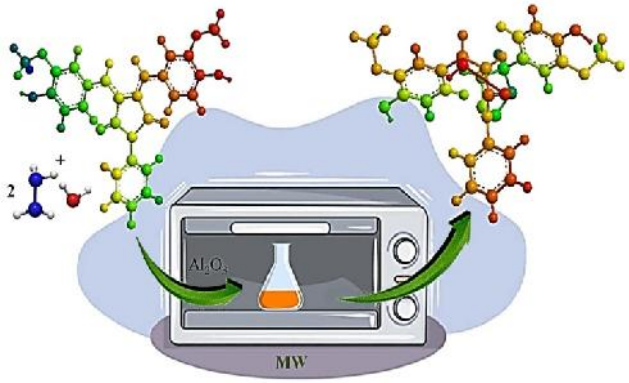
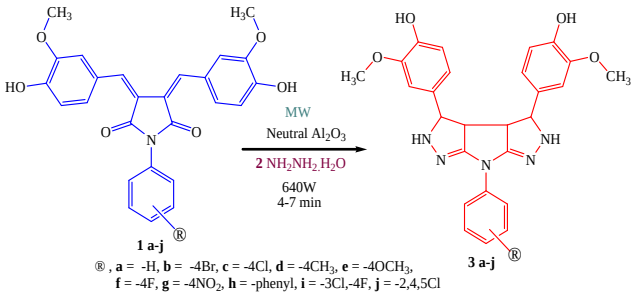


Figure 1: Microwave synthesis of pyrazole derivatives

2.2.1 General procedure for the synthesis of pyrazoles derived from bis-chalcones:

The bis-pyrazole **(3a-j)** derivatives were synthesized by the mixture of 2 mmole of bis-chalcones **(1a-j)** and 4 mmole of hydrazine hydrate in 2 gm of neutral Al_2O_3 under microwave supported solvent-less condition on 640W power for 4-7 min. The afforded coloured compounds were recrystallized from ethanol **(Scheme – 01)**



® , **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 -01: (3Z,4Z)-3,4-bis-(4-hydroxy-3-methoxybenzylidene)-7-(N-phenyl)-3,3a,3b,4,5,7-hexahydro-2H-pyrrolo[2,3-c,5,4-c] dipyrazole (3a-j)

(3Z,4Z)-3,4-bis-(4-hydroxy-3-methoxybenzylidene)-7-(1-phenyl)-3,3a,3b,4,5,7-hexahydro-2H-pyrrolo[2,3-c,5,4-c] dipyrazole (3a):

Yellow Solid, Percent yield (91.48%), M. P.: 172-174 ºC, M. F.: $C_{26}H_{25}N_5O_4$, Mol. Wt.: 471.51; Calculated Anal: C, 66.38; H, 5.44; N, 14.79; IR (KBr): 3292, 1507, 1597, 1643, 1271, 3600 cm^{-1}; ^{1}H NMR (DMSO-d^6, δ ppm): 7.57-6.39 (m, 8H, Ar-H), 8.56 (s, 1H, -NH), 9.93 (s, 1H, -OH), 3.34 (d, 1H, -CH), 2.32-2.23 (d, 1H, -CH), 3.74 (s, 3H, -OCH_3)

(3Z,4Z)-3,4-bis-(4-hydroxy-3-methoxybenzylidene)-7-(4-bromophenyl)-3,3a,3b,4,5,7-hexahydro-2H-pyrrolo[2,3-c,5,4-c] dipyrazole (3b):

Brownish Yellow Solid, Percent yield (60.36%), M. P.: 207-209 ºC, M. F.: $C_{26}H_{24}BrN_5O_4$, Mol. Wt.: 550.4; IR (KBr): 3246, 1513, 1599, 1649, 1280, 3482, 1033 cm^{-1}

(3Z,4Z)-3,4-bis-(4-hydroxy-3-methoxybenzylidene)-7-(4-chlorophenyl)-3,3a,3b,4,5,7-hexahydro-2H-pyrrolo[2,3-c,5,4-c] dipyrazole (3c):

Muddy Yellow Solid, Percent yield (95.61%), M. P.: 194-196 ºC, M. F.: $C_{26}H_{24}ClN_5O_4$, Mol. Wt.: 505.95; IR (KBr): 3294, 1513, 1599, 1649, 1280, 3486, 1033 cm^{-1}

(3Z,4Z)-3,4-bis-(4-hydroxy-3-methoxybenzylidene)-7-(p-tolyl)-3,3a,3b,4,5,7-hexahydro-2H-pyrrolo[2,3-c,5,4-c] dipyrazole (3d):

Yellow Solid, Percent yield (78.83%), M. P.: 197-199 ºC, M. F.: $C_{27}H_{27}N_5O_4$, Mol. Wt.: 485.53; IR (KBr): 3292, 1514, 1600, 1646, 1287, 3486 cm^{-1}

(3Z,4Z)-3,4-bis-(4-hydroxy-3-methoxybenzylidene)-7-(4-methoxyphenyl)-3,3a,3b,4,5,7-hexahydro-2H-pyrrolo [2,3-c,5,4-c] dipyrazole (3e):

Yellowish Brown Solid, Percent yield (67.87%), M. P.: 179-181 ºC, M. F.: $C_{27}H_{27}N_5O_5$, Mol. Wt.: 501.53; IR (KBr): 3242, 1512, 1602, 1656, 1277, 3485 cm^{-1}

(3Z,4Z)-3,4-bis-(4-hydroxy-3-methoxybenzylidene)-7-(4-fluorophenyl)-3,3a,3b,4,5,7-hexahydro-2H-pyrrolo[2,3-c,5,4-c] dipyrazole (3f): Brownish Yellow Solid, Percent yield (88.88%), M. P.: 202-204 ºC, M. F.: $C_{26}H_{24}FN_5O_4$, Mol. Wt.: 489.5; IR (KBr): 3292, 1512, 1602, 1656, 1267, 3617, 1121 cm^{-1}

(3Z,4Z)-3,4-bis-(4-hydroxy-3-methoxybenzylidene)-7-(4-nitrophenyl)-3,3a,3b,4,5,7-hexahydro-2H-pyrrolo[2,3-c,5,4-c] dipyrazole (3g):

Yellowish Brown Solid, Percent yield (92.63%), M. P.: 173-175 ºC, M. F.: $C_{26}H_{24}N_6O_6$, Mol. Wt.: 516.51; IR (KBr): 3276, 1602, 1619, 1649, 1267, 3617, 1511cm^{-1}

(3Z,4Z)-3,4-bis-(4-hydroxy-3-methoxybenzylidene)-7-(naphthalen-4-yl)-3,3a,3b,4,5,7-hexahydro-2H-pyrrolo [2,3-c,5,4-c] dipyrazole (3h):

Whitish Brown Solid, Percent yield (96.52%), M. P.: 128-130 ºC, M. F.: $C_{30}H_{27}N_5O_4$, Mol. Wt.: 521.57; Calculated Anal: C, 68.78; H, 5.49; N, 13.82; IR (KBr): 3271, 1427, 1459, 1512, 1599, 1648, 1280, 3486 cm^{-1}; ^{1}H NMR (500.13 MHz, DMSO-d^6, δ ppm): 7.91-6.71 (m, 8H, Ar-H), 8.60 (s, 1H, -NH), 9.73 (s, 1H, -OH), 3.02 (d, 1H, -CH), 2.51-2.20 (d, 1H, -CH), 3.84 (s, 3H, -OCH_3)

(3Z,4Z)-3,4-bis-(4-hydroxy-3-methoxybenzylidene)-7-(3-chloro-4-fluorophenyl)-3,3a,3b,4,5,7-hexahydro-2H-pyrrolo[2,3-c,5,4-c] dipyrazole (3i):

Pale Yellow Solid, Percent yield (76.15%), M. P.: 177-179 ºC, M. F.: $C_{26}H_{23}ClFN_5O_4$, Mol. Wt.: 523.94; Calculated Anal: C, 59.87; H, 4.90; N, 13.54; IR (KBr): 3261, 1512, 1603, 1650, 1280. 3482, 1166, 1033 cm^{-1}; ^{1}H NMR (500.13 MHz, DMSO-d^6, δ ppm): 7.92-6.81 (m, 6H, Ar-H), 8.58 (s, 1H, -NH), 9.72 (s, 1H, -OH), 2.78 (d, 1H, -CH), 1.98-1.84 (d, 1H, -CH), 3.81 (s, 3H, -OCH_3)

(3Z,4Z)-3,4-bis-(4-hydroxy-3-methoxybenzylidene)7-(2,4 5-trichlorophenyl)-3,3a,3b,4,5,7-hexahydro-2H- pyrrolo [2,3-c,5,4-c] dipyrazole (3j):

Yellow Solid, Percent yield (84.66%), M. P.: 169-171 ºC, M. F.: $C_{26}H_{22}Cl_3N_5O_4$, Mol. Wt.: 574.84; Calculated Anal: C, 54.80; H, 3.97; N, 12.26; FTIR (KBr): 3233, 1459, 1511, 1601, 1279, 3485, 1033 cm^{-1}; ^{1}H NMR (500.13 MHz, DMSO-d^6, δ ppm): 8.10-6.89 (m, 5H, Ar-H), 8.58 (s, 1H, -NH), 9.72 (s, 1H, -OH), 3.39 (d, 1H, -CH), 2.13-2.05 (d, 1H, -CH), 3.39 (s, 3H, -OCH_3); ^{13}C NMR (125.77 MHz, DMSO-d^6, δ ppm): (55.99, 110.55, 115.95, 123.91, 125.97, 130.88, 148.45, 150.33 and 161.03)

3. Results and discussions

Chemistry:

The starting compounds of bis-chalcones **1a-j** were prepared by the reaction of substituted N-phenyl succinimides using di-substituted aromatic aldehyde i.e. vanillin. The series of pyrazoles **3a-j** were synthesized in reasonable yields by the cyclization of bis-chalcones **1a-j** with hydrazine hydrate in presence of neutral Al_2O_3 in microwave solvent free condition. Formation of bis-pyrazoles was confirmed by IR, ^{13}C NMR, ^{1}H NMR and elemental analysis.

Antimicrobial activities (3a-j):

All the synthesized compounds **3a-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. And antifungal activities against *Candida albicans* (NCIM-3471) and *Aspergillus niger* (NCIM- 545) strains using DMSO solvent. Temperate to good antibacterial activities shown by *Bacillus Subtilis* and *Escherichia coli* and the compound **3c** and **3i** has given good antifungal activities against *Candida albicans* and *Aspergillus niger* strains. Ampicillin was used as a standard drug for antibacterial activities and Amphotericin-B used for antifungal activities as a standard. The calculated readings are put into a table.1.

Statistical Analysis:

All the results of the synthesized compound series **3a-j** were carried out by the triplicate format N=3 with Mean ± SD. The statistical tests were performed by using the GraphPad prism-6 trial version and GraphPad InStat 3.10 demo version software. 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.

Table 1: Antimicrobial activities of pyrazole derivatives

Compd Code	Zone diameter calculated in mm and tabulated by Mean ± SD			
	Bacillus subtilis	***Escherichia coli***	***Candida albicans***	***Aspergillus niger***
	100 µg/ml	**100 µg/ml**	**100 µg/ml**	**100 µg/ml**
3a	7.33±0.57 **	7.33±0.57 **	--	--
3b	7.33±0.57 **	4.66±4.04 **	--	--
3c	8.66±0.57 **	8±0 **	--	10.15 ± 0.29 **
3d	7.66±1.52 **	7.66±0.57 **	--	--
3e	7±0 **	2.33±4.04 **	--	--
3f	8.33±1.15 **	8±1 **	--	--
3g	7.66±0.57 **	2.66±4.61 **	--	--
3h	7±1 **	2.66±4.61 **	--	--
3i	7.66±1.52 **	4.66±4.04 **	10.92 ± 0.09 **	--
3j	7.66±0.57 **	7.66±0.57 **	--	--
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)*

4. Conclusion

A method for synthesis of bis-pyrazoles **3a-j** has been developed in good yield obtained by the treatment of substituted bis-chalcones and hydrazine hydrate with neutral Al_2O_3 by microwave method. All these compounds were characterized by their spectral analysis. Most of the compound showed moderate to good activity against *Bacillus Subtilis* and *Escherichia coli.* The compound **3c** and **3i** exhibited good antifungal activities against *Candida albicans* and *Aspergillus niger*. The synthesized compounds may be used for preparation of various heterocyclic systems as well as the microwave centered green method might be used for the synthesis of the heterocyclic synthones.

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