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Microwave Assisted Synthesis of Novel Aryl and Heteroaryl hydrazinocurcumins

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ABSTRACT

In the present study, convenient method for the synthesis of aryl and heteroarylhydrazinocurcumins using curcumin, hydrazine and acetic acid under microwave condition is reported. In this method, the yields are high compared to conventional methods. The reaction duration also reduced considerably.

Keywords : aryl and heteroarylhydrazinocurcumins, curcumin, hydrazine and acetic acid.

INTRODUCTION

In modern synthetic chemistry, Microwave Assisted Organic Reaction (MAOS) offers promising alternative to the conventional methods, especially the MAOS is extremely helpful in reducing the reaction time, temperature and improving the yield as well [1-2].

The arylhydrazinocurcumin shows many biological activities were synthesized from curcumin using conventional methods. The yields of these reactions were very low from 5% to 65% [3-10]. The reaction durations of these reactions were too long i.e., from 6 h to 48 h.

In the present work, we report a facile synthesis of aryl and heteroarylhydrazinocurcumin from curcumin in good yield as well as extremely reduced reaction duration.

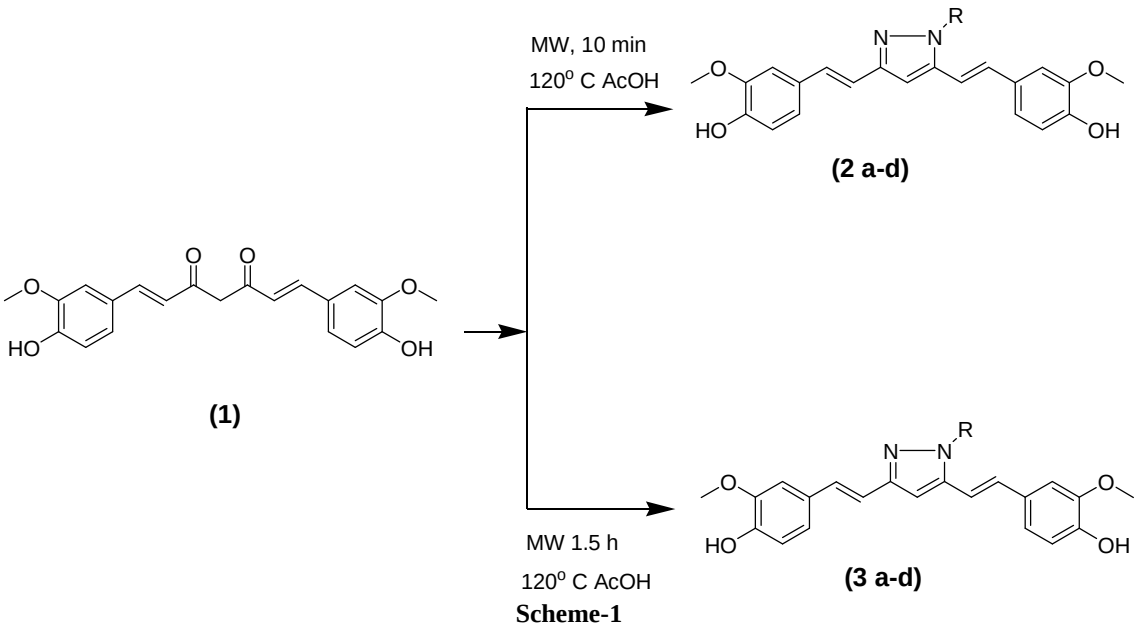
MATERIALS AND METHODS

^{1}H NMR and ^{13}C NMR spectra were recorded using Bruker 400 spectrophotometer using DMSO-D6, TMS as the internal reference. All the LCMS were recorded using Agilent LCMS system.TLC using silica gel G60 (Merck, Germany).

Isolation of Curcumin [11]:
The rhizome of *curcuma longa* was dried in sun shade and finely powdered. The dried powder was washed with petroleum ether to remove the fat material. The fine powder was extracted with Methanol. The crude extract was purified by coloumn chromatography using Methanol : DCM system to get crude curcuminoid mixture i.e., curcumin, demethoxycurcumin (DMC) and bisdemethoxycurcumin (BDMC). Then curcumin was purified using preparative TLC plate using 3% Methanol:dichlormethane system.

General procedure for the synthesis of arylhydrazinocurcumins (2a-d)
To a solution of curcumin (**1**) (1 eq) in glacial acetic acid 5 volume, added 1.2 eq of aryl hydrazine. The reaction mixture was heated to 120°C in microwave for 10 minutes. TLC compiled shows clear formation of polar spot. The excess acetic acid evaporated to dryness, purified by preparative TLC plate.

General procedure for the synthesis of heteroarylhydrazinocurcumins (3a-d)
To a solution of curcumin (**1**) (1 eq) in glacial acetic acid 5 volume, added 1.2 eq of heteroarylhydrazine. The reaction mixture was heated to 120°C in microwave for 1.5 h. TLC compiled shows clear formation of polar spot. The excess acetic acid evaporated to dryness, purified by preparative TLC plate.



Scheme-1

Curcumin (1)
^{1}H NMR (400 MHz, D^{6}-DMSO) 6.06 (s, 1H), 6.73 (d, J = 16 Hz, 2H), 6.82 (d, J = 16 Hz, 2H), 7.14 (m, 2H), 7.32 (d, J = 1.6 Hz, 2H), 7.53 (d, J = 16 Hz, 2H), 9.65 (s, 2H); ^{13}C NMR (100 MHz) δ 56.17, 101.26, 111.85, 116.18, 121.55, 123.57, 126.79, 141.15, 148.47, 148.85, 183.66; LCMS (m/z):369.2 [M^{+}];

4-((E)-2-(5-((E)-4-hydroxy-3-methoxystyryl)-1H-pyrazol-3-yl)vinyl)-2-methoxyphenol (2a)
^{1}H NMR (400 MHz, CD_3OD) δ 3.92 (s, 6H), 6.65 (s, 1H), 6.80 (d, J = 8.0 Hz, 2H), 6.88 (m, 2H), 6.99 (d, J = 7.6 Hz, 2H), 7.08 (m, 4H); ^{13}C NMR (100 MHz, D6-DMSO) δ 56.9, 98.8, 110.9,

113.81, 116.72, 117.4, 122.65,122.89, 130.03, 136.61, 137.84, 148.21, 148.33,151.43, 151.84; LCMS (m/z): 365.2 [M^+].

4-((E)-2-(5-((E)-4-hydroxy-3-methoxystyryl)-1-phenyl-1H-pyrazol-3-yl)vinyl)-2-methoxyphenol (2b)
^{1}H NMR (400 MHz, CD_3OD) δ 3.81 (s, 3H), 3.88 (s, 3H), 6.61 (d, J = 16.4 Hz, 1H), 6.75 (m, 2H), 6.86 (m, 5H), 7.08 (m, 3H), 7.46 (m, 3H), 7.55 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 56.41, 101.22, 110.49, 110.99, 113.31, 116.41, 116.53, 117.95, 121.54, 126.83, 129.44, 129.93, 130.47, 130.58, 132.83, 134.1, 140.61, 144.58, 148.09, 148.62, 149.26, 153.11; LCMS (m/z): 441.6 [M^+].

4-((E)-2-(5-((E)-4-hydroxy-3-methoxystyryl)-1-(2-nitrophenyl)-1H-pyrazol-3-yl)vinyl)-2-methoxy phenol (2c)
^{1}H NMR (400 MHz, CD_3OD) δ 3.82 (s, 3H), 3.89 (s, 3H), 6.49 (d, 1H), 6.73 (m, 2H), 6.85 (m, 2H), 6.99 (m, 3H), 7.09 (t, 3H), 7.64 (d, 1H), 7.73 (t, 1H), 7.85 (t, 3H), 8.14 (d,1H); ^{13}C NMR (100 MHz, CD_3OD) δ 56.33, 56.46, 68.41, 101.31, 110.41, 110.49, 110.94, 111.03, 111.03, 111.80, 116.51, 117.59, 121.68, 126.55, 129.57, 130.40, 131.11, 131.38, 133.45, 134.95, 135.71, 145.89, 147.86, 148.24, 148.96, 149.28, 154.35; LCMS (m/z): 485.9 [M^+].

4-((E)-2-(5-((E)-4-hydroxy-3-methoxystyryl)-1-(3-bromophenyl)-1H-pyrazol-3-yl)vinyl)-2-methoxy phenol (2d)
1H NMR (400 MHz, CD_3OD) δ 3.85 (s, 3H), 3.91 (s, 3H), 6.67 (d, J = 16.0 Hz,1H), 6.77 (m, 2H), 6.92 (m, 5H), 7.01 (m, 3H), 7.46 (m, 2H), 7.63 (m, 1H), 7.65 (s, 1H); ^{13}C NMR (100 MHz, CD3OD) δ 56.43, 66.89, 101.83, 110.53, 110.86, 112.99, 116.41, 116.53, 117.74, 121.60, 121.77, 123.60, 125.22, 129.42, 129.81, 130.47, 131.96, 132.18, 133.23, 135.14, 141.87, 144.71, 148.21, 148.80, 149.30, 153.66; LCMS (m/z): 519.2 [M+].

4-((E)-2-(5-((E)-4-hydroxy-3-methoxystyryl)-1-(pyridin-2-yl)-1H-pyrazol-3-yl)vinyl)-2-methoxy phenol (3a)
^{1}H NMR (400 MHz, CD_3OD) δ 3.90 (s, 3H), 3.93 (s, 3H), 6.80 (m, 2H), 6.96 (m, 4H), 7.09 (d, J = 1.6 Hz, 1H), 7.15 (m,3H), 7.42 (dd, J = 6.8, 5.2 Hz, 1H), 7.57 (d, J = 16.4 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 8.00 (dd, J = 7.8,1.4 Hz, 1H), 8.56 (s, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 56.42, 102.53, 110.52, 111.03, 115.34, 116.40, 116.48, 117.93, 118.84, 121.59, 123.45, 130.38, 130.48, 133.50, 134.19, 140.33, 145.64, 148.21, 148.47, 149.12, 149.23, 149.28, 153.84, 154.20; LCMS (m/z): 442.2 [M^+].

4-((E)-2-(5-((E)-4-hydroxy-3-methoxystyryl)-1-(2-methylpyridin-4-yl)-1H-pyrazol-3-yl)vinyl)-2-methoxyphenol (3b)
^{1}H NMR (400 MHz, CD_3OD) δ 2.57 (s, 3H), 3.81 (s, 3H), 3.84 (s, 3H), 6.80 (dd, J = 8.0, 1.6 Hz, 2H), 7.02 (m, 3H), 7.11 (m,1H), 7.19 (m, 3H), 7.49 (m, 1H), 8.69 (s, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 20.01, 56.39, 100.99, 110.37, 110.89, 111.59, 116.39, 116.59, 117.39, 121.54, 121.72, 123.74, 129.05, 130.10, 132.98, 133.31, 135.57, 145.37, 147.16, 148.37, 149.05, 149.18, 149.27, 149.42, 153.27, 153.98; LCMS (m/z): 456.2 [M^+].

4-((E)-2-(5-((E)-4-hydroxy-3-methoxystyryl)-1-(3-methylpyridin-4-yl)-1H-pyrazol-3-yl)vinyl)-2-methoxyphenol (3c)
^{1}H NMR (400 MHz, CD_3OD) δ 2.25 (s, 3H), 3.84 (s, 3H), 3.93 (s, 3H), 6.42 (d, J = 16.4 Hz, 1H), 6.75 (d, J = 8.4 Hz, 1H), 6.81 (d, J = 8.0 Hz, 1H), 6.90 (m, 1H), 6.97 (m, 4H), 7.15 (m, 3H),

7.44 (d, J = 5.2 Hz, 1H), 8.61 (d, J = 5.2 Hz, 1H), 8.69 (s, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 15.04, 56.41, 100.91, 110.48, 111.00, 111.70, 116.50, 116.70, 117.50, 121.65, 121.83, 123.85, 129.16, 130.21, 133.07, 133.42, 135.68, 145.59, 147.38, 148.59, 149.27, 149.40, 149.49, 149.64, 153.49, 154.20; LCMS (m/z): 456.2 [M^+].

4-((E)-2-(5-((E)-4-hydroxy-3-methoxystyryl)-1-(7-chloroquinolin-4-yl)-1H-pyrazol-3-yl)vinyl)-2-methoxyphenol (3d)

^{1}H NMR (400 MHz, D^6-DMSO) δ 3.80 (s, 3H), 3.94 (s, 1H), 6.54(d, J = 16 Hz, 1H), 6.75 (d, J = 7.6 Hz, 1H), 6.84 (d, J = 8.0 Hz, 1H), 6.88 (d, J = 8.4 Hz, 1H), 7.07 (m, 4H), 7.66 (d, J = 4.8 Hz, 2H), 7.71 (dd, J = 9.2, 2.0 Hz, 1H), 7.90 (d, J = 9.2 Hz, 2H), 8.24 (d, J = 2.0 Hz, 2H), 9.12 (d, J = 4.4 Hz, 1H); ^{13}C NMR (100 MHz, D^6-DMSO) δ 56.40, 100.83, 110.50, 111.01, 115.32, 116.42, 116.45, 117.90, 118.81, 121.56, 123.40, 130.38, 130.48, 133.50, 134.19, 140.33, 145.61, 148.17, 148.37, 149.12, 149.23, 149.28, 151.21, 153.84, 154.20, 155.11; LCMS (m/z): 526.2 [M^+].

Table 1: Reaction time and yields of aryl and heteroarylhydrazinocurcumins (2 and 3)

S. No	Compound No.	R	Mol. Wt.	Molecular formula	Yield (%)		Reaction time	
					Actual	Lit.	Actual	Lit.
1	**2a**	H	364.39	$C_{21}H_{20}N_2O_4$	80	71	10 min	8h [12]
2	**2b**	Phenyl	440.49	$C_{27}H_{24}N_2O_4$	83	65	10 min	8h [12]
3	**2c**	2-NO_2-phenyl	485.49	$C_{27}H_{23}N_3O_6$	79	-	10 min	-
4	**2d**	3-Br-phenyl	519.39	$C_{27}H_{23}BrN_2O_4$	92	-	10 min	-
5	**3a**	2-pyridyl	441.48	C26H23N3O4	87	-	1.5 h	-
6	**3b**	2-Me-4-pyridyl	455.51	C27H25N3O4	78	-	1.5 h	-
7	**3c**	3-Me-4-pyridyl	455.51	C27H25N3O4	77	-	1.5 h	-
8	**3d**	7-chloroquinolin-4-yl	491.18	C30H25N3O4	84	-	1.5 h	-

RESULTS AND DISCUSSION

The microwave assisted synthesis of novel heteroarylhydrazinocurcumin opens the new class of curcumin derivatives which can be synthesized rapidly. On the other hand, the synthesis of arylhydrazinocurcumin was became accelerated microwave synthesis. The yield of the reactions were excellent i.e., 79%-92%. In total, the synthesis of these compounds becomes easier, faster and cheaper due to the advantages of microwave.

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