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Article

Synthesis of Nitrogen Containing Curcumin Analogs by Green Protocol

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ABSTRACT

Synthesis of curcumin pyrazole analogs and curcumin isoxazole analogs from curcumin and substituted hydrazine and hydroxyl amine hydrochloride, respectively, in MWI technique with the help of green solvent like PEG-400 and 2–3 drops of acetic acid as an acid catalyst for development of time reducing and efficient methodology.

Key words: Curcumin analogue, Green technique, Hydrazine hydrate, MWI, PEG 400

1. INTRODUCTION

Heterocyclic molecules are well established for their therapeutic properties. Almost two-third compounds are heterocyclic among all reported drugs. Curcumin heterocyclic analogs are reported for their outstanding biological activity. Pyrazole analogs are curcumin and were synthesized and reported for various biological activities. To improve biological activity of curcumin, medicinal chemists have exploited total four site for chemical transformation consisting aryl side chain, central diketones functionality, carbon-carbon unsaturated bond, and central acidic methylene group. Heterocyclic modifications mainly involved with one or two keto groups. Molecular modeling was tried and obtained improved antimalarial curcumin analogues [1]. As pyrazole heterocyclic analogs have been already proven as molecules with excellent anticancer property [2-6]. Curcumin-pyrazole is well known for their pharmaceutical significance, such as antiproliferative [7], antimicrobial [8], anticancer [9], and antibacterial activity [10].

2. MATERIALS AND METHODS

2.1. General

The commercial sample of curcumin was purchased from S. D. Fine Chemical Limited, Mumbai, Maharashtra. Solvents were used during experimentation that was of analytical grade purchased from Spectrochem of Loba, India and used further without purification.

Starting materials were check by thin layer chromatography (TLC) for their purity purpose. Separation or formation of products was initially confirmed by TLC techniques. Mobile phase selected by trial and error method. Silica plate was used TLC Silica gel 60G, F_{254} Plates by Merck. IR was recorded for compounds synthesized in the laboratory and for validation of isolated curcumin from curcuminoides. Absorption spectra recorded in the range of 400–4000 cm^{-1} with KBr pallets, JASCO-8000 FT-IR spectrophotometer. Recorded spectra further substantiated by matching with reported values.

Compounds synthesized during laboratory experimental work analyzed using proton NMR and carbon NMR. Deuterated solvents mostly used as DMSO-d_6, unless it is mention. Tetra Methyl Silane was used as internal standard. Actual scanning was done by Burker Advance DRX 300 FT-NMR.

2.2. Experimental

2.2.1. Experimental procedure for synthesis of curcumin pyrazole analogs

Curcumin (1; 1 eq.) and substituted hydrazine hydrate (2; 1.5 eq.) were taken in PEG-400 and stirred for 10 min at room temperature to become a homogenous mixture. Catalytic amount of acetic acid was added, and irradiate in microwave oven (800W; 3–5 min), progress of reaction was monitor by TLC check, and on completion of reaction mixture was poured to ice cold water and left overnight. Solid obtained was filter, washed with water for several time, and thus obtained crude products which further purified by column chromatography. (EtOAc: n-Hexane; 4:6) reaction scheme depicted in Scheme 1.

2.2.2. Experimental procedure for synthesis of curcumin isoxazole analogs

Curcumin (1; 1 eq.) and hydroxylamine hydrochloride salt (2; 1.5 eq.) were taken in PEG-400 and stirred for 10 min at room temperature to become a homogenous mixture. Catalytic amount of acetic acid was added, and irradiate in microwave oven (800W; 3 min), progress of reaction was monitor by TLC check, and on completion of reaction mixture was poured to ice cold water and left overnight. Solid obtained was filter and washed with water for several time to obtained crude product finally purified by column chromatography. (EtOAc: n-Hexane; 4:6) Reaction depicted in Scheme 2.

3. RESULTS AND DISCUSSIONS

Model reaction strategy was used to optimize reaction condition for synthesis of curcumin-pyrazole analogs. Curcumin (1 eq.) and hydrazine hydrate (1.2 eq.) were taken with fix mention stoichiometry, with single drops of acetic acid. Excess of hydrazine was used to ensure complete transformation of curcumin to curcumin-pyrazole as

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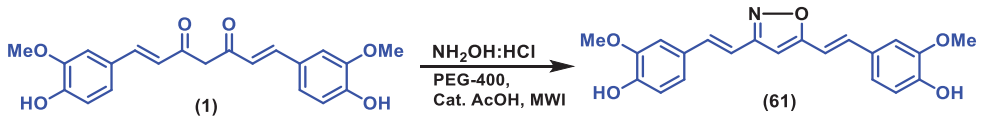
Scheme 1: Synthesis of Curcumin pyrazole analogs from curcumin and substituted hydrazine.



Scheme 2: Synthesis of curcumin isoxazole analogs from curcumin and hydroxyl amine hydrochloride.

product. Various polar as well as non-polar solvents initially used at Microwave irradiation power 600W. Obtained results were shown in Table 1.

Among used solvents, polar solvents such as PEG-400, Dimethyl Formamide, and alcohol offer better result than non-polar toluene (Table 1; Entry 6). PEG-400 emerged as best solvent and used further for optimization of microwave irradiation power.

Various MWI power ranges from 300W to 800W were applied and found that 800W for 3 min emerged as best reaction condition. Further investigation to 4 min (Table 2; Entry 7) did not found fruitful, black sticky mass was observed at the end of irradiation. During irradiation care was taken to avoid overheating of reaction mixture by 10 s interval after successive 1 min irradiation. Occasional mechanical stirring was applied throughout series of reaction. Stoichiometry of reaction was also optimized by varying amount of hydrazine hydrate from 1.2 equivalents to 3 equivalents.

For further derivatization of curcumin-pyrazole with substituted (aromatic) hydrazine used reaction condition was finalized as, curcumin (1eq.) substituted hydrazine (1.5 eq.) PEG (7–8 ml) catalytic amount of acetic acid and MWI power 800 Watt for 3 min (10 s interval after each successive 1 min's irradiation). This used for preparation of pyrazole analogues depicted in Figure 1 and 2 (52–60) as well as single isoxazole-curcumin derivative (61) as shown in Table 3.

3.1. Spectral Analysis of Synthesized Compounds

3.1.1. 1H-pyrazole-3,5-diyl)bis(ethene-2,1-diyl))bis(2-methoxyphenol) (52)

IR: (KBr) $cm^{-1:}$ 3545, 3328, 3087, 1634, 1566, 1456, 1370, 1322, 990, 910; ^{1}H NMR (300 MHz, DMSO): δ 7.10–6.98 (m, 6 H), 6.83–6.56 (m, 4 H, J = 12.6 Hz), 6.50 (s, 1H), 4.61 (s, 2 H), 3.87 ppm (s, 6H); ^{13}C NMR (75MHz, DMSO): δ 56.1, 56.5, 105.6, 109.3, 116.1, 116.8, 122.8, 130.5, 131.2, 147.8, 148.1 ppm., MS: m/z [M+H] calcd for $C_{21}H_{20}N_2O_4$ is 364.14, found: 364.16.

3.1.2. (1-phenyl-1H-pyrazole-3,5-diyl)bis(ethene-2,1-diyl)) bis(2-methoxyphenol) (53)

IR: (KBr) $cm^{-1:}$ 3610, 3346, 3056, 1613, 1557, 1439, 1310, 1247, 991, 909; ^{1}H NMR (300 MHz, DMSO): δ 7.46–7.31 (m, 5 H), 7.00–6.97 (d, 2 H, *J* = 15.7 Hz), 6.93–6.83 (m, 6H), 6.80–6.69 (m, 3H), 5.55 (s, 2 H), 3.86 (s, 3 H), 3.84 ppm (s, 3H); ^{13}C NMR (75MHz, DMSO): δ 56.3, 56.5, 109.1, 110.3, 116.2, 116.8, 122.9, 123.5, 126.2, 126.3, 129.3, 130.6, 139.6, 139.9, 147.9, 149.1, 154.9 ppm., MS: m/z [M+H] calcd for $C_{27}H_{24}N_2O_4$ is 440.17, found: 440.16.

3.1.3. 1-(2-nitrophenyl)-1H-pyrazole-3,5-diyl)bis(ethene-2,1-diyl))bis(2-methoxyphenol) (54)

IR: (KBr) $cm^{-1:}$ 3588, 3374, 3147, 1658, 1573, 1487, 1410, 1364, 1042, 932; ^{1}H NMR (300 MHz, DMSO): δ 9.36 (s, 1H), 9.91 (s, 1H), 8.18 (d, 1H, J = 7.7 Hz), 7.60–7.90 (m, 3H), 7.45 (d, 2H, J = 12.8 Hz),

Table 1: Optimization of solvent for synthesis of (52) and with respect to yield

S. No.	Reaction condition[b]	Time in second	Yield[a] of products
1.	DMF	120	41
2.	EtOH	120	37
3.	MeOH	120	32
4.	Water	120	N.R.*
5.	PEG-400	120	66
6.	Toluene	120	Trace

[a]Isolated yield, [b]MWI 600W, *TLC Check

Table 2: Optimization of MWI power for synthesis of (52) and with respect to yield

S. No.	MWI (in Watt)	Time in Sec.	Yield[a] of products
1.	300	300	22
2.	400	300	35
3.	500	300	47
4.	600	240	61
5.	700	180	60
6.	800	180	82
7.	800	240	Black mass
8.	800	120	63

[a]Isolated yield

Table 3: Synthesis of various analogs of curcumin-pyrazole with optimized reaction condition

Entry	Product No.	Yield[a] (in %)	Melting point
1.	(52)	82	214–215°C
2.	(53)	85	128–129°C
3.	(54)	88	194–195°C
4.	(55)	86	114–115°C
5.	(56)	90	215–216°C
6.	(57)	91	208–209°C
7.	(58)	94	200–201°C
8.	(59)	89	203–204°C
9.	(60)	77	135–136°C
10.	(61)*	90	116–119°C

[a]Isolated yield, *Curcumin-isoxazole

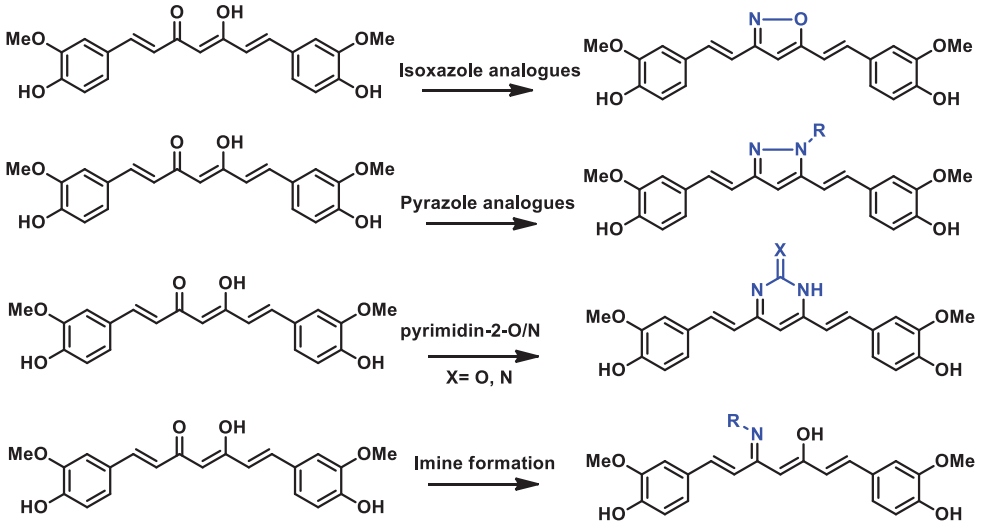


Figure 1: General synthetic strategy for nitrogen containing curcumin analogs.

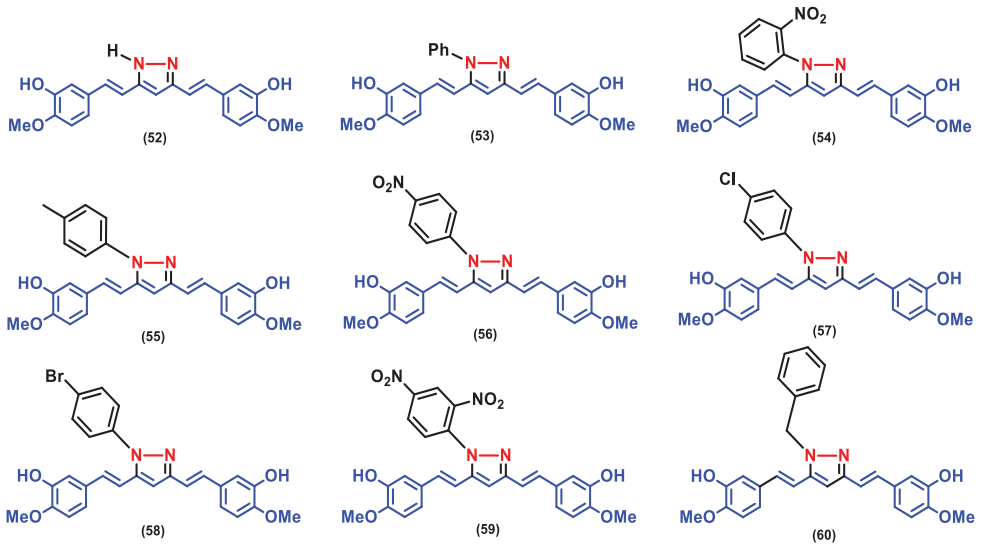


Figure 2: Structures of Curcumin pyrazole analogs.

7.21–7.38 (m, 2H), 6.95–7.10 (m, 4H), 6.89 (d, 2H, J = 12.8 Hz), 6.65 (s, 1H), 3.85 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (75MHz, DMSO): δ 56.7, 57.9, 109.1, 110.4, 116.1, 116.8, 117.9, 123.5, 125.6, 127.3,130.5, 131.2, 135.4, 147.8, 155.3 ppm., MS: m/z [M+H] calcd for $C_{27}H_{23}N_3O_6$ is 485.16, found: 485.191.

3.1.4. 4,4'-((1E,1'E)-(1-(p-tolyl)-1H-pyrazole-3,5-diyl) bis(ethene-2,1-diyl)) bis(2methoxyphenol) (55)

IR: (KBr) cm$^{-1:}$ 3611, 3384, 3024, 1684, 1531, 1446, 1371, 1322, 997, 922; ^{1}H NMR (300 MHz, DMSO): δ 7.35–7.28 (m, 4 H), 7.00–6.91 (d, 2 H, J = 15.3 Hz), 6.9–6.79 (m, 6H), 6.80–6.69 (m, 3H), 5.48 (s, 2 H), 3.81 (s, 3 H), 3.77 ppm (s, 3H), 2.39 (s, 3H); ^{13}C NMR (75MHz, DMSO): δ 21.5, 56.3, 56.5, 109.2, 110.3, 116.1, 116.8, 122.9, 123.6, 130.5, 131.2, 147.8, 155.7 ppm., MS: m/z [M+H] calcd for $C_{28}H_{26}N_2O_4$ is 454.19, found: 454.20.

3.1.5. 4,4'-((1E,1'E)-(1-(4-nitrophenyl)-1H-pyrazole-3,5-diyl) bis(ethene-2,1-diyl)) bis(2methoxyphenol)(56)

IR: (KBr) cm$^{-1:}$ 3589, 3321, 3090, 1635, 1542, 1444, 1330, 1384, 962, 900; ^{1}H NMR (300 MHz, DMSO): δ 9.88 (s, 1H), 10.34 (s, 1H), 8.56 (d, 1H, J = 7.9 Hz), 7.72–7.94 (m, 3H), 7.56 (d, 2H, J = 12.6 Hz), 7.28–7.35 (m, 2H), 6.91–7.24 (m, 4H), 6.82 (d, 2H, J = 13.2 Hz), 6.65 (s, 1H), 3.91 (s, 3H), 3.87 (s, 3H); ^{13}C NMR (75MHz, DMSO): δ 56.2, 56.3, 109.3, 110.7, 116.2, 116.7, 118.5, 122.8, 130.5, 131.2,139.6, 145.1,145.8, 148.1, 155.3 ppm., MS: m/z [M+H] calcd for $C_{27}H_{23}N_3O_6$ is 484.16, found: 484.167.

3.1.6. (1-(4-chlorophenyl)-1H-pyrazole-3,5-diyl)bis(ethene-2,1-diyl))bis(2methoxyphenol) (57)

IR: (KBr) cm$^{-1:}$ 3583, 3321, 3041, 1635, 1551, 1479, 1341, 1310, 997, 916; ^{1}H NMR (300 MHz, DMSO): δ 9.39 (s, 1H), 9.31 (s, 1H), 7.79 (d, 2H, J = 8.5 Hz), 7.53 (d, 2H, J = 8.5 Hz), 6.99–7.24 (m, 8H, J = 15.4 Hz), 6.79 (m, 3H), 3.84 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (75MHz, DMSO): δ 56.3, 56.9, 109.3, 110.1, 116.1, 116.8, 122.8, 130.5, 131.2, 147.8, 148.1, 157.3 ppm., MS: m/z [M+H] calcd for $C_{27}H_{23}ClN_2O_4$ is 474.13, found: 474.15.

3.1.7. (1-(4-bromophenyl)-1H-pyrazole-3,5-diyl)bis(ethene-2,1-diyl))bis(2methoxyphenol) (58)

IR: (KBr) cm$^{-1:}$ 3545, 3328, 3087, 1634, 1566, 1456, 1370, 1322, 990, 910; ^{1}H NMR (300 MHz, DMSO): δ 9.30 (s, 1H), 9.22 (s, 1H), 7.74 (d, 2H, J = 8.5 Hz), 7.48 (d, 2H, J = 8.5 Hz), 6.95–7.19 (m, 8H, J = 15.4 Hz), 6.73 (m, 3H), 3.81 (s, 3H), 3.74 (s, 3H);^{13}C NMR (75MHz, DMSO): δ 56.3, 56.5, 109.7, 110.3, 116.1, 116.8, 118.6, 120.4, 122.8, 123.6, 130.5, 131.2, 138.5, 139.7, 147.8, 148.1, 155.9 ppm., MS: m/z [M+H] calcd for $C_{27}H_{23}BrN_2O_4$ is 518.10, found: 518.13.

3.1.8. (1-(2,4-dinitrophenyl)-1H-pyrazole-3,5-diyl)bis(ethene-2,1-diyl))bis(2methoxyphenol) (59)

IR: (KBr) $cm^{-1:}$ 3601, 3351, 3057, 1613, 1537, 1483, 1320, 1280, 957, 890; ^{1}H NMR (300 MHz, D_6 -DMSO): δ 9.38(s, 1H), 9.26(s, 1H), 8.96 (d, 1H, J = 8.7 Hz), 8.71(d, 1H, J = 8.7Hz), 8.03(d, 1H), 7.19 (m, 5H), 7.01 (m, 2H), 6.91 (d, 1H), 6.82 (m, 3H), 3.87 (s, 3H), 3.82 (s, 3H); ^{13}C NMR (75MHz, DMSO): δ 53.2, 56.5, 109.2, 116.1, 116.8, 120.5, 122.8, 130.5, 131.2, 148.1, 149.5, 156.8 ppm., MS: m/z [M+H] calcd for $C_{27}H_{22}N_4O_8$ is 530.14, found: 530.18.

3.1.9. (1-benzyl-1H-pyrazole-3,5-diyl)bis(ethene-2,1-diyl)) bis(2-methoxyphenol) (60)

IR: (KBr) $cm^{-1:}$ 3588, 3365, 3030, 1643, 1555, 1459, 1373, 1319, 994, 900; ^{1}H NMR (300 MHz, D_6 -DMSO): δ 9.18 (s,1H), 9.11(s, 1H), 7.35–7.39 (m, 2H), 7.22–7.28 (m, 5H), 7.09(d, 1H, J = 5.6 Hz), 7.01(d, 1H, J = 12.3 Hz), 6.95–6.97 (m, 4H), 6.89 (m, 1H), 6.77(dd, 2H, J_1 = 8 Hz, J_2 = 5.6 Hz,), 5.51 (s, 2H), 3.81 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (75MHz, DMSO): δ 56.1, 56.2, 59.6, 105.6, 109.3, 116.1, 116.8, 122.8, 130.5, 131.2, 138.4 147.8, 149.3, 153.4 ppm., MS: m/z [M+H] calcd for $C_{28}H_{26}N_2O_4$ is 454.19, found: 454.199.

4. CONCLUSION

In brief, we concluded here, for synthesis of various analogs of curcumin-pyrazole and curcumin-isoxazole in a green solvent like PEG 400 with the help of catalytic amount of acetic acid under microwave irradiation method for good to better yield in very small amount of time span.

5. ACKNOWLEDGMENT

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***Bibliographical Sketch**

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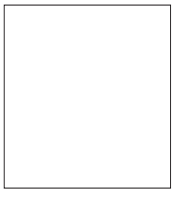

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