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Simple and efficient microwave assisted PEG mediated synthesis of Pyrazole analogues of Curcumin

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ABSTRACT

Pyrazole Curcumin was synthesized by using Microwave irradiation technique in Polyethylene Glycol-400 (PEG-400) as solvent. One mole of Curcumin and 1.5 moles of substituted hydrazine when irradiate corresponding curcumin pyrazole derivatives were obtained in good yield. This method is eco friendly, time saving, productive and easy to workup.

Keywords: Curcumin, pyrazole, Curcumin analogues, Claisen-Schmidt condensation, PEG-400, Microwave

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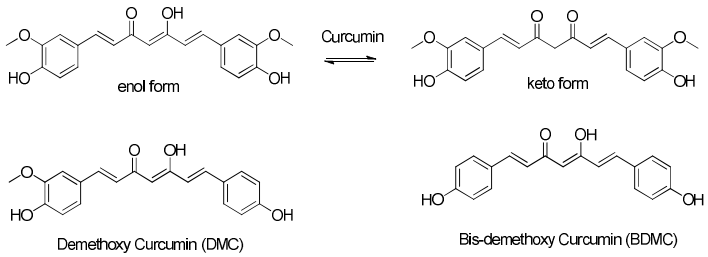
INTRODUCTION

Curcumin (5-hydroxy-1, 7-bis (4-hydroxy-3-methoxyphenyl) hepta-1, 4, 6-trien-3-one) isolated from rhizomes of Curcumin longa, with a mixture of other two isomers (Fig. 1). Curcumin known for its versatile medicinal properties, and has been used in various Asian countries like India and China. Naturally isolated molecules exhibit various biological properties, due to traditional history of curcumin [1] it attracts attention of modern science. Modern science now authenticated curcumin as very good anti-oxidant [2-3], anti-cancer properties [4] during the progress of research curcumin reveals that it also exhibits, anti-inflammatory [5], anti-malarial properties [6-8]. Recent study of curcumin underlines wide spectrum of biological activity and importance of curcumin by reporting its inhibitory effect in the formation of β-amyloids (Alzheimer disease) [9-10] and against integrase enzymes of HIV-I. [11]

Curcumin with such surprising wide range of biological activity, on the other hand has poor metabolic property [12-14]. Due to low solubility of curcumin, potential impact at cellular level is limited. Attempt was made for the synthesis of curcumin analogues to overcome this limitation [15-20]. Altering curcumin structure by introducing five member heterocyclic rings, like pyrazole and isoxazole, which are well known established chemical moieties for its pharmacokinetic properties. Here we reported a simple, efficient, ecofriendly and productive method for synthesis of curcumin pyrazole.

Fig. 1 Structure of Curcumin

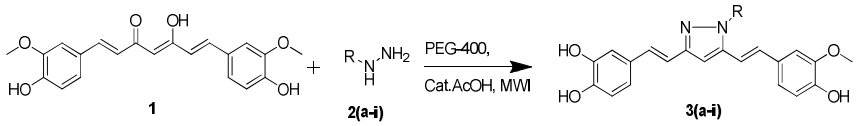


MATERIALS AND METHODS

Experimental Section

All the compounds used in synthesis were purchase of analytical grade, the melting points of the compounds were determined in open head capillary in paraffin bath and are uncorrected. The IR spectra of the compounds were recorded in the region of 4000-400 cm^{-1} by using KBr pallet on FT-IR Perkin spectrophotometer. H^1 NMR spectra were recorded on a DRX-400 Bruker FT-NMR spectrophotometer in D^6-DMSO. The values of chemical shift are expressed in δ ppm as a unit. All the compounds were checked for purity by thin layer chromatography (TLC).

Reaction Scheme 1



General Experimental Procedure (3a-i)

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 min.), on completion of (TLC) reaction, mixture was poured to ice cold water and left overnight. Solid obtained was filter, washed with water and purified by column chromatography. (EtoAc: n-Hexane; 4:6)

3a. 4, 4'-((1E,1'E)-(1H-pyrazole-3,5-diyl)bis(ethene-2,1-diyl))bis(2-methoxyphenol)
^{1}H NMR (400 MHz, D^6-DMSO): 7.10– 6.98 (m, 6 H), 6.83–6.56 (m, 4H), 6.50 (s, 1H), 4.61 (s, 2 H), 3.87 ppm (s, 6H)

3b. 4,4'-((1E,1'E)-(1-phenyl-1H-pyrazole-3,5-diyl)bis(ethene-2,1-diyl))bis(2-methoxyphenol)
^{1}H NMR (400 MHz, D^6-DMSO): 7.46–7.41 (m, 3H), 7.34–7.31 (m, 2 H), 7.00–6.97 (m, 2 H), 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)

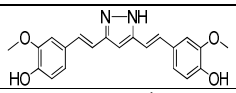
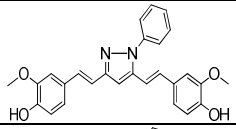
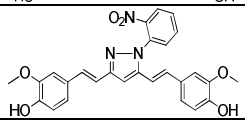
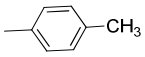
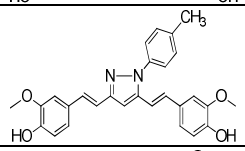
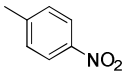
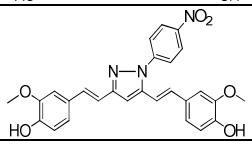
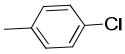
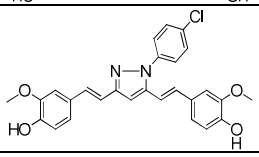
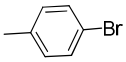
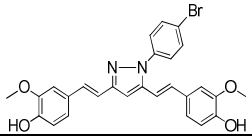
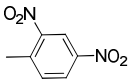
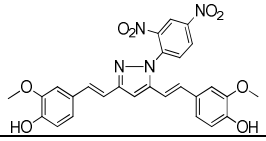
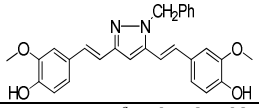
3c. 4,4'-((1E,1'E)-(1-(2-nitrophenyl)-1H-pyrazole-3,5-diyl)bis(ethene-2,1-diyl))bis(2-methoxyphenol)
^{1}H NMR (400 MHz, D^6-DMSO) 9.35(s, 1H), 9.23(s, 1H), 8.18(d, 1H), 7.95-7.81(m, 3H), 7.29-7.18(m, 5H), 6.99-6.93(m, 3H), 6.78(d, 2H)

3d. 4,4'-((1E,1'E)-(1-(p-tolyl)-1H-pyrazole-3,5-diyl)bis(ethene-2,1-diyl))bis(2-methoxyphenol)
^{1}H NMR (400 MHz, D^6-DMSO) 9.33(s, 1H), 9.20(s, 1H), 7.43(m, 4H), 7.22(m, 3H), 7.08(m, 3H), 6.90(m, 2H), 6.83(d, 2H), 6.81(m, 1H), 3.77(s, 3H), 3.73(s, 3H)

3e. 4,4'-((1E,1'E)-(1-(4-nitrophenyl)-1H-pyrazole-3,5-diyl)bis(ethene-2,1-diyl))bis(2-methoxyphenol) ^{1}H NMR (400 MHz, D^6-DMSO) 9.35(s, 1H), 9.27(s, 1H), 8.46(d, 2H), 7.88(d, 2H), 7.26(m, 5H), 7.05(m, 4H), 6.82(d, 2H), 3.88(s, 3H), 3.84(s, 3H)

3f. 4,4'-((1E,1'E)-(1-(4-chlorophenyl)-1H-pyrazole-3,5-diyl)bis(ethene-2,1-diyl))bis(2-methoxyphenol) ^{1}H NMR (400 MHz, D^6-DMSO): 7.89-7.76 (m, 4H), 7.35-7.29 (m, 6H), 6.81-6.78 (m, 5H) 3.76(s, 3H), 3.73(s, 3H)

Table 1. Structure and Yield and Melting of curcumin pyrazole (3a-3i)

Sr.N	R	Structure of Products	Mol. Weight	M.P. (°C)	Yield[a]
3a	-H		364.39	214-215	82%
3b			440.49	128-129	85%
3c			485.49	194-195	88%
3d			454.52	114-115	86%
3e			485.49	215-216	90%
3f			474.94	208-209	91%
3g			519.39	200-201	94%
3h			530.49	203-204	89%
3i			454.52	135-136	77%

[a] *isolated yield*

3g. 4,4'-((1E,1'E)-(1-(4-bromophenyl)-1H-pyrazole-3,5-diyl)bis(ethene-2,1-diyl))bis(2-methoxyphenol) ^{1}H NMR (400 MHz, D^6-DMSO) 8.40(d, 2H), 7.81(d, 2H), 7.19(m, 5H), 6.91(m, 4H), 6.71(d, 2H), 3.64(s, 3H), 3.57(s, 3H).

3h. 4,4'-((1E,1'E)-(1-(2,4-dinitrophenyl)-1H-pyrazole-3,5-diyl)bis(ethene-2,1-diyl))bis(2-methoxyphenol) ^{1}H NMR (400 MHz, D^6-DMSO) 9.38(s, 1H), 9.26(s, 1H), 8.96(d, 1H), 8.71(dd, 1H), 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).

3i. 4,4'-((1E,1'E)-(1-benzyl-1H-pyrazole-3,5-diyl)bis(ethene-2,1-diyl))bis(2-methoxyphenol) ^{1}H NMR (400 MHz, D^6-DMSO) 9.18(s,1H), 9.11(s, 1H), 7.37(d, 2H), 7.25(m, 5H), 7.09(d, 1H), 7.01(d, 1H), 6.97(m, 4H), 6.89(m, 1H), 6.77(d, 2H), 5.51(s, 2H), 3.81(s, 3H), 3.80(s, 3H).

RESULTS AND DISCUSSION

Microwave irradiation methods are useful due to its unique ability to transfer higher energy to reaction within no time. This method allows overcoming high energy barriers and gives smooth chemical transformation. This reaction opens various possibilities in the field of synthesis of pyrazole curcumin analogues by green pathways. During the reaction procedure it is observed that pouring reaction mixture overnight is an important condition for obtaining good yield (Table 1). Attempt was made to performed reaction without catalytic acetic acid, which drops yield of reaction and multiple spots appears on TLC. In conclusion, this is facile, time saving and productive method of synthesis of pyrazole analogues of Curcumin.

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