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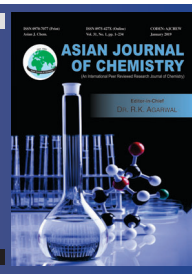

Synthesis of New Dihydropyrazoles of Designed Curcumin Analogues

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Present work demonstrates a facile synthesis of a series of 20 dihydropyrazole derivatives from well designed curcumin analogues by reaction of chalcone derivatives with phenylhydrazine. All the synthesized compounds were characterized by spectroscopic (^{1}H and ^{13}C NMR, IR spectra), spectrometric (Mass spectra) data and elemental analysis. Synthesized dihydropyrazoles have diversity points on attached phenyl ring. Effect of substituent on reactivity was explained on the basis of electronic effect generated due to groups on phenyl ring. Presence of dd (double doublet) in ^{1}H NMR spectrum of dihydropyrazoles was also explained due to presence of optically active carbon of pyrazole ring.

Keywords: Dihydropyrazoles, Curcumin, Heterocycles, Phenylhydrazine, Chacone.

INTRODUCTION

Pyrazoles constitutes one of the representative classes of heterocycles and remains an attractive target for chemists in the field of heterocyclic chemistry. After the first synthesis of pyrazoles proposed by Buchner in 1889 *via* decarboxylation of pyrazole-3,4,5-tricarboxylic acid, a number of methods have been reported for their synthesis in literature [1]. Particularly the importance of pyrazoles scaffolds are not only due to their structural simplicity, but also because many natural products, many drugs and many dyes belong to this group [2,3]. They are crucial due to their theoretical implications, the diversity of its synthetic procedures and the physiological as well as industrial significance of heterocyclic compounds [4-6]. Pyrazole containing molecules posses an essential place in the drug discovery domain because it is known to be most abundant pharmacophore in synthetic as well as natural bioactive molecules. These heterocycles continue to attract extensive attention due to the broad range of biological activities they possess. Pyrazoles are reported as potent bioactive molecules [7-11] and are known to exhibit a wide range of pharmaceutical activities such as CNS depressant, neuroleptic, tuberculostatic, antihypertensive, antileishmanial, analgesic, antidiabetic, antitumor and antimicrobial [12-14]. Fig. 1 represents several molecules bearing pyrazole nucleus which are used in clinics for treatment of various health problems. Apart from their crucial role in medicinal chemistry pyrazoles have a great significance in organometallic chemistry as ligands as well as in catalysis. Their metal coordination complexes are also reported to show anticancer and antimicrobial properties [15].

Being an essential pharmcophore in therapeutically important molecules pyrazole moiety attached with some other biologically important molecule create a new chemical space in medicinal chemistry and drug discovery. Due to this reason and in an attempt to get better biological profile several research groups were interested in preparation of pyrazole analogues of many biologically active natural compounds and investigating their biological potential. Moreover, pyrazole derivatives of curcumin were synthesized and investigated for lipoxygenase inhibitory activity [16], cytotoxic activity [17,18] and antioxidant activity [19]. In addition to this curcumin has been shown to have synergistic effects with artemisinin against *Plasmodium berghei* [20,21]. Among the different drug molecules as illustrated in Fig. 1 pyrazole nucleus is known to be a crucial factor for showing biological activity. Furthermore, the presence of enone function of chalcone moiety with pyrazole ring also reported to get the enhanced the biological activity. Our group have previously reported the synthesis of fabricated curcumin based chalcone analogues and their biological activity [22]. In continuation of the work this time we hypo-

thesize that the incorporation of the essential structural features of pyrazoles with a curcumin moiety could provide new derivatives with better biological activities since several curcumin derivatives have already been shown to be active as potent anticancer agents [23-25]. Prompted by all these observations, here in we report the synthesis of dihydropyrazoles derivative of curcumin based chalcones by utilizing condensation reaction between chalcones and phenyl hydrazine. All the synthesized heterocycles were characterized by ^{1}H and ^{13}C NMR, IR spectra, mass spectra as well as elemental analysis measurements.

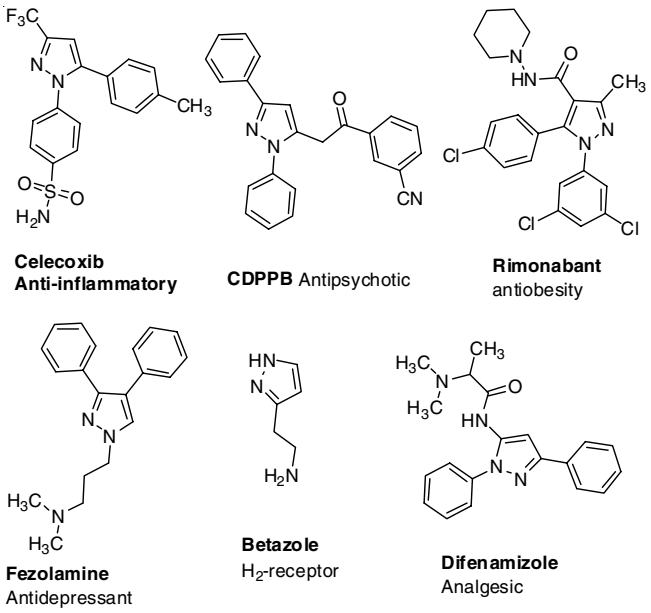


Fig. 1. Structures of some representative pyrazole containing drug molecules

EXPERIMENTAL

Unless otherwise specified all the reagents and catalysts were purchased from Sigma-Aldrich and were used without further any purification. The common solvents were purchased from Ranbaxy. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Reactions were monitored by thin-layer chromatography (TLC) on 0.25 mm silica gel plates visualized under UV light, iodine or $KMnO_4$ staining. ^{1}H and ^{13}C NMR spectra were recorded on a Brucker DRX-200 MHz Spectrometer. Chemical shifts (δ) are given in ppm relative to TMS and coupling constants (*J*) in Hz. IR spectra were recorded on a FTIR spectrophotometer Shimadzu 8201 PC and are reported in terms of frequency of absorption (cm^{-1}). Mass spectra (ESIMS) were obtained by micromass quattro II instrument.

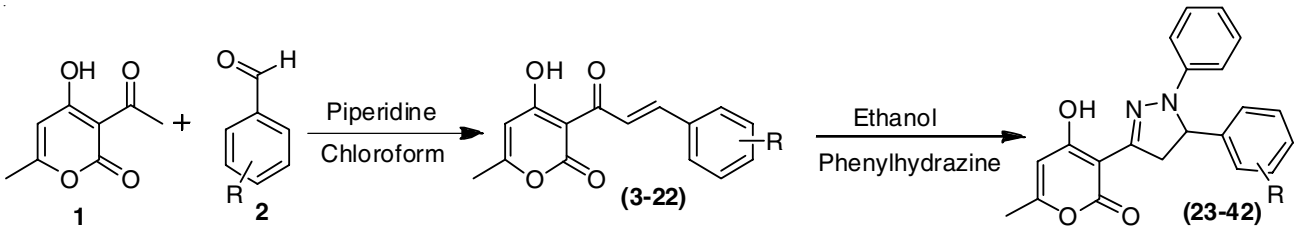
General procedure for synthesis of dihydropyrazoles (23-42): Chalcone analogues (1 mmol) and phenyl hydrazine (1.5 mmol) were mixed with 10 mL of ethanol in a 100 mL round bottom flask. To this solution catalytic amount of acetic acid (10 mol %) was added followed by stirring under refluxing condition upto completion of reaction. Progress of reaction was monitored by thin layer chromatography. After completion of reaction solvent was evaporated under the reduced pressure in rotavapour. Solid residue was poured in ice water under stirring and filtered off. After filtration the solid residue was recrystallized with ethanol and dried under vacuum to afford the pure dihydropyarazole derivatives (**23-42**) (**Scheme-I**), which were further characterized by spectroscopic data.

Analytical data for compounds (23-42)

3-(1,5-Diphenyl-4,5-dihydro-1*H*-pyrazol-3-yl)-4-hydroxy-6-methyl-2*H*-pyran-2-one (23): Yellow solid; m.p. 153 °C; IR (KBr, ν_{max}, cm^{-1}): 3452, 3022, 1640, 1526, 1216, 1022; ^{1}H NMR ($CDCl_3$, 300 MHz): 7.29-7.13 (m, 5H); 6.92-6.78 (m, 3H); 6.71-6.67 (m, 2H); 5.20 (dd, *J* = 8 Hz, *J* = 12 Hz); 4.17 (dd, *J* = 12 Hz, *J* = 18 Hz); 3.48 (dd, *J* = 8 Hz, *J* = 22 Hz); 2.26 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 192.4, 183.7, 167.4, 153.6, 151.1, 136.1, 133.2, 131.1, 129.2, 126.4, 122.1, 116.4, 101.3, 98.4, 51.6, 33.8, 20.6. MS (ES): *m/z* (%) = 347 (100) $[M+1]^+$; Anal. calcd. (%) for $C_{21}H_{18}N_2O_3$: C, 71.82; H, 5.24; N, 8.09; Found (%): C, 71.78; H, 5.21; N, 8.12.

4-Hydroxy-3-(5-(4-methoxyphenyl)-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)-6-methyl-2*H*-pyran-2-one (24): Yellow solid; m.p. 164 °C; IR (KBr, ν_{max}, cm^{-1}): 3452, 3022, 1640, 1526, 1216, 1022; ^{1}H NMR ($CDCl_3$, 300 MHz): 7.23-7.16 (m, 5H); 6.91 (d, *J* = 8.4 Hz, 2H); 6.86-6.81 (m, 2H); 6.04 (s, 1H); 5.22 (dd, *J* = 8.4 Hz, *J* = 12 Hz, 1H); 4.26 (dd, *J* = 12.2 Hz, *J* = 19 Hz, 1H); 3.91 (s, 3H); 3.48 (dd, *J* = 8.4 Hz, *J* = 12 Hz, 1H); 2.28 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 192.7, 181.1, 169.0, 168.3, 153.7, 153.5, 141.4, 131.6, 129.3, 124.2, 123.9, 118.7, 113.3, 113.5, 101.4, 56.1, 20.6. MS (ES): *m/z* (%) = 377 (100) $[M+1]^+$; Anal. calcd. (%) for $C_{22}H_{20}N_2O_4$: C, 70.20; H, 5.36; N, 7.44; Found (%): C, 70.16; H, 5.30; N, 7.50.

4-Hydroxy-3-(5-(3-methoxyphenyl)-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)-6-methyl-2*H*-pyran-2-one (25): Yellow solid; m.p. 173 °C; IR (KBr, ν_{max}, cm^{-1}): 3452, 3022, 1640, 1526, 1216, 1022; ^{1}H NMR ($CDCl_3$, 300 MHz): 7.41-7.21 (m, 5H); 6.93-6.86 (m, 3H); 6.85-6.83 (m, 1H); 6.06 (s, 1H); 5.18 (dd, *J* = 8.2 Hz, *J* = 11 Hz, 1H); 4.26 (dd, *J* = 11.2 Hz, *J* = 18 Hz, 1H); 3.89 (s, 3H); 3.48 (dd, *J* = 8.0 Hz, *J* = 18 Hz, 1H); 2.26 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 192.9, 182.4, 169.2, 167.2, 151.4, 150.5, 143.4, 132.6, 130.1, 128.2, 123.9, 115.4, 111.3, 103.6, 101.4, 56.4, 20.6. MS (ES): *m/z* (%) = 377 (100) $[M+1]^+$; Anal. calcd. (%) for $C_{22}H_{20}N_2O_4$: C, 70.20; H, 5.36; N, 7.44; Found (%): C, 70.16; H, 5.30; N, 7.50.



Scheme-I: Synthesis of heterocyclic curcumin analogues and corresponding pyrazoles

3-(5-(3,4-Dimethoxyphenyl)-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)-4-hydroxy-6-methyl-2*H*-pyran-2-one (26): Yellow solid; m.p. 168 °C; IR (KBr, ν_{max}, cm^{-1}): 3430, 3022, 2922, 1630, 1485, 1216; ^1H NMR ($CDCl_3$, 300 MHz): 13.4 (s, 1H); 7.22-7.19 (m, 3H); 6.92-6.83 (m, 5H); 6.06 (s, 1H); 5.07 (dd, *J* = 8.5 Hz, *J* = 12.1 Hz, 1H); 4.17 (dd, *J* = 12.1 Hz, *J* = 18.9 Hz, 1H); 3.86 (s, 3H); 3.84 (s, 3H); 3.50 (dd, *J* = 8.4 Hz, *J* = 18.9 Hz, 1H); 2.28 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 190.8, 184.2, 168.2, 162.4, 158.7, 142.7, 133.6, 128.4, 123.6, 122.9, 121.8, 112.1, 103.3, 99.8, 62.4, 56.0, 20.6. MS (ES): *m/z* (%) = 407 (100) $[M+1]^+$; Anal. calcd. (%) for $C_{23}H_{22}N_2O_5$: C, 67.97; H, 5.46; N, 6.89; Found (%): C, 67.94; H, 5.41; N, 6.92.

4-Hydroxy-6-methyl-3-(5-(4-nitrophenyl)-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)-2*H*-pyran-2-one (27): Yellow solid; m.p. 164 °C; IR (KBr, ν_{max}, cm^{-1}): 3406, 2880, 1717, 1590, 1418, 1353, 1173; ^1H NMR ($CDCl_3$, 300 MHz): 8.23-8.19 (m, 2H); 7.51-7.47 (m, 2H); 7.26-7.18 (m, 2H); 6.91-6.79 (m, 3H); 6.06 (s, 1H); 5.24 (dd, *J* = 7.9 Hz, *J* = 19.1 Hz, 1H); 4.24 (dd, *J* = 12.4 Hz, *J* = 19 Hz, 1H); 3.51 (dd, *J* = 7.9 Hz, *J* = 18.9 Hz, 1H); 2.27 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 191.8, 183.6, 167.8, 153.4, 151.2, 144.3, 136.1, 130.7, 129.5, 126.2, 122.2, 116.2, 101.3, 98.7, 51.3, 33.4, 20.7. MS (ES): *m/z* (%) = 392 (100) $[M+1]^+$; Anal. calcd. (%) for $C_{21}H_{17}N_3O_5$: C, 64.45; H, 4.38; N, 10.74; Found (%): C, 64.40; H, 4.33; N, 10.77.

4-Hydroxy-6-methyl-3-(5-(2-nitrophenyl)-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)-2*H*-pyran-2-one (28): Yellow solid; m.p. 144 °C; IR (KBr, ν_{max}, cm^{-1}): 3452, 3022, 1640, 1526, 1216, 1022; ^1H NMR ($CDCl_3$, 300 MHz): 8.20-8.17 (m, 2H); 7.48-7.44 (m, 2H); 7.17-7.06 (m, 2H); 6.90-6.82 (m, 3H); 6.05 (s, 1H); 5.18 (dd, *J* = 8 Hz, *J* = 18.6 Hz, 1H); 4.24 (dd, *J* = 11 Hz, *J* = 18.1 Hz, 1H); 3.51 (dd, *J* = 8 Hz, *J* = 18.4 Hz, 1H); 2.25 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 192.8, 185.6, 166.3, 158.8, 153.6, 142.4, 134.6, 131.2, 129.4, 124.7, 121.3, 116.5, 112.4, 103.8, 56.3, 37.4, 21.6. MS (ES): *m/z* (%) = 392 (100) $[M+1]^+$; Anal. calcd. (%) for $C_{21}H_{17}N_3O_5$: C, 64.45; H, 4.38; N, 10.74; Found (%): C, 64.40; H, 4.33; N, 10.78.

3-(5-(4-(Dimethylamino)phenyl)-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)-4-hydroxy-6-methyl-2*H*-pyran-2-one (29): Yellow solid; m.p. 171 °C; IR (KBr, ν_{max}, cm^{-1}): 3406, 2880, 1717, 1590, 1418, 1353, 1173; ^1H NMR ($CDCl_3$, 300 MHz): 7.29-7.13 (m, 4H); 6.92-6.78 (m, 3H); 6.71-6.67 (m, 3H); 5.07 (dd, 1H, *J* = 8 Hz, *J* = 12 Hz); 4.12 (dd, 1H, *J* = 12 Hz, *J* = 18 Hz); 3.50 (dd, 1H, *J* = 8 Hz, *J* = 22 Hz); 2.93 (s, 6H); 2.26 (s, 3H).^{13}C NMR ($CDCl_3$, 75 MHz): δ 191.2, 183.3, 168.4, 159.6, 144.3, 132.6, 130.3, 128.7, 119.4, 104.6, 100.2, 98.9, 52.1, 35.4, 20.5 MS (ES): *m/z* (%) = 390 (100) $[M+1]^+$; Anal. calcd. (%) for $C_{23}H_{23}N_3O_3$: C, 70.93; H, 5.95; N, 10.79; Found (%): C, 70.89; H, 5.91; N, 10.82.

3-(5-(3-Chlorophenyl)-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)-4-hydroxy-6-methyl-2*H*-pyran-2-one (30): Yellow solid; m.p. 157 °C; IR (KBr, ν_{max}, cm^{-1}): 3452, 3022, 1640, 1526, 1216, 1022; ^1H NMR ($CDCl_3$, 300 MHz): 7.26-7.11 (m, 5H); 7 61 (d, *J* = 6.4 Hz, 1H); 6.91-6.80 (m, 4H); 6.06 (s, 1H); 5.44 (dd, *J* = 7.4 Hz, *J* = 12.0 Hz); 4.17 (dd, *J* = 12.0 Hz, *J* = 18 Hz); 3.42 (dd, *J* = 7.4 Hz, *J* = 18 Hz); 2.25 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 192.6, 184.2, 167.4, 153.7, 151.2, 144.9, 136.3, 130.5, 129.1, 126.2, 122.6, 116.5, 101.5, 98.6, 51.3, 33.4, 20.4. MS (ES): *m/z* (%) = 381 (100) $[M+1]^+$; Anal. calcd. (%) for $C_{21}H_{17}N_2O_3Cl$: C, 66.23; H, 4.50; N, 7.36; Found (%): C, 66.18; H, 4.46; N, 7.38.

3-(5-(4-Chlorophenyl)-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)-4-hydroxy-6-methyl-2*H*-pyran-2-one (31): Yellow solid; m.p. 148 °C; IR (KBr, ν_{max}, cm^{-1}): 3406, 2880, 1717, 1590, 1418, 1353, 1173; ^1H NMR ($CDCl_3$, 300 MHz): 7.23-7.16 (m, 5H); 6.89-7.81 (m, 4H); 6.05 (s, 1H); 5.12 (dd, *J* = 8 Hz, *J* = 12 Hz, 1H); 4.17 (dd, *J* = 12.2 Hz, *J* = 19 Hz, 1H); 3.51 (dd, *J* = 8.0 Hz, *J* = 11.9 Hz, 1H); 2.26 (s, 3H).^{13}C NMR ($CDCl_3$, 75 MHz): δ ^{13}C NMR: δ 191.4, 183.1, 166.8, 162.3, 158.2, 142.1, 133.4, 128.4, 123.3, 121.7, 120.6, 112.1, 103.3, 99.8, 61.5, 56.2, 20.8; MS (ES): *m/z* (%) = 381 (100) $[M+1]^+$; Anal. calcd. (%) for $C_{21}H_{17}N_2O_3Cl$: C, 66.23; H, 4.50; N, 7.36; Found (%): C, 66.18; H, 4.46; N, 7.38.

3-(5-(3,5-Dichlorophenyl)-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)-4-hydroxy-6-methyl-2*H*-pyran-2-one (32): Yellow solid; m.p. 143 °C; IR (KBr, ν_{max}, cm^{-1}): 3430, 3022, 2922, 1630, 1485, 1216; ^1H NMR ($CDCl_3$, 300 MHz): 13.25 (s, 1H); 8.26 (d, *J* = 8.1 Hz, 2H) 7.54 (d, *J* = 8.2 Hz, 2H); 7.29-7.22 (m, 3H); 6.93-6.83 (m, 3H); 6.09 (s, 1H); 5.27 (dd, *J* = 8.07 Hz, *J* = 12.3 Hz, 1H); 4.27 (dd, *J* = 12.7 Hz, *J* = 19.2 Hz, 1H); 3.49 (dd, *J* = 7.5 Hz, *J* = 18.9 Hz, 1H); 2.27 (s, 3H).^{13}C NMR ($CDCl_3$, 75 MHz): δ 191.6, 183.5, 168.2, 167.2, 163.1, 158.8, 144.6, 136.4, 135.3, 128.1, 121.9, 121.1, 113.4, 104.1, 99.6, 58.4, 37.6, 20.4. MS (ES): *m/z* (%) = 415 (100) $[M+1]^+$; Anal. calcd. (%) for $C_{21}H_{16}Cl_2N_2O_3$: C, 60.74; H, 3.88; N, 6.75; Found (%): C, 60.70; H, 3.83; N, 6.79.

4-Hydroxy-3-(5-(4-hydroxy-3-methoxyphenyl)-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)-6-methyl-2*H*-pyran-2-one (33): Yellow solid; m.p. 153 °C; IR (KBr, ν_{max}, cm^{-1}): 3328, 2917, 1684, 1597, 1423, 1270, 1127; ^1H NMR ($CDCl_3$, 300 MHz): 13.39 (s, 1H); 7.21-7.19 (m, 3H); 7.17 (t, *J* = 8.2 Hz, 2H); 6.91-6.79 (m, 3H); 6.05 (s, 1H); 5.03 (dd, *J* = 8 Hz, *J* = 12 Hz, 1H); 4.31 (s, 1H); 4.16 (dd, *J* = 8 Hz, *J* = 12.4 Hz, 1H); 3.84 (s, 3H); 3.49 (dd, *J* = 12.2 Hz, *J* = 19 Hz, 1H); 2.27 (s, 3H).^{13}C NMR ($CDCl_3$, 75 MHz): δ 190.4, 184.6, 168.8 167.2, 162.6, 156.7, 148.2, 146.3, 138.3, 135.4, 127.3, 121.9, 122.2, 113.0, 103.8, 99.4, 57.6, 37.3, 20.6. MS (ES): *m/z* (%) = 393 (100) $[M+1]^+$; Anal. calcd. (%) for $C_{22}H_{20}N_2O_5$: C, 67.34; H, 5.14; N, 7.14; Found (%): C, 67.29; H, 5.11; N, 7.41.

4-Hydroxy-3-(5-(3-hydroxyphenyl)-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)-6-methyl-2*H*-pyran-2-one (34): Yellow solid; m.p. 168 °C; IR (KBr, ν_{max}, cm^{-1}): 3561, 3157, 1732, 1628, 1346, 1268; ^1H NMR ($CDCl_3$, 300 MHz): δ 10.04 (1H, s), 7.47-7.26 (m, 4H); 6.99-6.76 (m, 3H); 6.62-6.62 (m, 2H); 5.96 (1H, s), 5.26 (dd, *J* = 6 Hz, *J* = 14.2 Hz); 4.18 (dd, *J* = 14.2 Hz, *J* = 16 Hz); 3.44 (dd, *J* = 6 Hz, *J* = 22 Hz); 2.26 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 189.8, 182.3, 163.2, 162.1, 150.6, 147.2, 136.4, 134.3, 129.8, 127.9, 126.7, 123.8, 114.1, 112.3, 111.5, 103.2, 97.6, 21.1; MS (ES): *m/z* (%) = 363 (100) $[M+1]^+$; Anal. calcd. (%) for $C_{21}H_{18}N_2O_4$ C, 69.60; H, 5.01; N, 7.73,; Found (%): C, 69.55; H, 4.98; N, 7.78.

4-Hydroxy-3-(5-(4-hydroxyphenyl)-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)-6-methyl-2*H*-pyran-2-one (35): Bright yellow solid; m.p. 153 °C; IR (KBr, ν_{max}, cm^{-1}): 3541,

3167, 1724, 1658, 1346, 1268; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 10.04 (1H, s), 7.46-7.29 (m, 4H); 6.98-6.74 (m, 3H); 6.68-6.61 (m, 2H); 5.98 (1H, s), 5.24 (dd, *J* = 6 Hz, *J* = 14.2 Hz); 4.16 (dd, *J* = 14.2 Hz, *J* = 16 Hz); 3.42 (dd, *J* = 6 Hz, *J* = 22 Hz); 2.27 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 189.3, 182.2, 163.4, 162.4, 150.2, 147.6, 136.4, 134.2, 129.8, 127.3, 126.4, 123.2, 114.2, 112.6, 111.5, 103.2, 97.6, 21.0; MS (ES): *m/z* (%) = 363 (100) $[M+1]^+$; Anal. calcd. (%) for $C_{21}H_{18}N_2O_4$ C, 69.60; H, 5.01; N, 7.73,; Found (%): C, 69.57; H, 4.97; N, 7.77.

3-(5-(4-Fluorophenyl)-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)-4-hydroxy-6-methyl-2*H*-pyran-2-one (36): Yellow solid; m.p. 126 °C; IR (KBr, ν_{max}, cm^{-1}): 3406, 2880, 1717, 1590, 1418, 1353, 1173; ^{1}H NMR ($CDCl_3$, 300 MHz): 13.31 (s, 1H); 7.31-7.18 (m, 4H); 7.07-7.02 (m, 2H); 6.89-6.85 (m, 3H); 6.07 (s, 1H); 5.15 (dd, *J* = 8.1 Hz, *J* = 12.2 Hz, 1H); 4.12 (dd, *J* = 12 Hz, *J* = 14 Hz, 1H); 3.50 (dd, *J* = 7.9 Hz, *J* = 17.1 Hz, 1H); 2.28 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 192.0, 184.1, 167.5, 154.1, 150.5, 144.6, 136.3, 131.6, 129.8, 127.5, 123.21 116.1, 101.4, 98.9, 51.4, 34.7, 20.7 MS (ES): *m/z* (%) = 365 (100) $[M+1]^+$; Anal. calcd. (%) for $C_{21}H_{17}N_2O_3F$: C, 69.22; H, 4.70; N, 7.69; Found (%): C, 69.18; H, 4.67; N, 7.85.

4-Hydroxy-3-(5-(2-methoxyphenyl)-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)-6-methyl-2*H*-pyran-2-one (37): Yellow solid; m.p. 161 °C; IR (KBr, ν_{max}, cm^{-1}): 3452, 3022, 1640, 1526, 1216, 1022; ^{1}H NMR ($CDCl_3$, 300 MHz): 13.4 (s, 1H); 7.28-7.11 (m, 4H); 6 93 (d, *J* = 8.2 Hz, 1H); 6.92-6.83 (m, 4H); 6.04 (s, 1H); 5.49 (dd, *J* = 7.28 Hz, *J* = 12.3 Hz, 1H); 4.17 (dd, *J* = 12.3 Hz, *J* = 19.1 Hz, 1H); 3.93 (s, 3H); 3.42 (dd, *J* = 7.6 Hz, *J* = 19.1 Hz, 1H); 2.27 (s, 3H).^{13}C NMR ($CDCl_3$, 75 MHz): δ 192.9, 183.3, 168.3, 161.3, 159.1, 141.7, 132.6, 129.5, 123.7, 122.9, 120.8, 112.2, 102.5, 99.4, 55.5, 20.6. MS (ES): *m/z* (%) = 377 (100) $[M+1]^+$; Anal. calcd. (%) for $C_{22}H_{20}N_2O_4$: C, 70.20; H, 5.36; N, 7.44; Found (%): C, 70.16; H, 5.30; N, 7.50.

3-(5-(2-Chlorophenyl)-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)-4-hydroxy-6-methyl-2*H*-pyran-2-one (38): Yellow solid; m.p. 151 °C; IR (KBr, ν_{max}, cm^{-1}): 3452, 3022, 1640, 1526, 1216, 1022; ^{1}H NMR ($CDCl_3$, 300 MHz): 8.20-8.02 (m, 5H); 7.31-7.20 (m, 4H); 6.04 (s, 1H); 5.24 (dd, *J* = 7.4 Hz, *J* = 18.1 Hz, 1H); 4.18 (dd, *J* = 11 Hz, *J* = 19 Hz, 1H); 3.49 (dd, *J* = 7.4 Hz, *J* = 18.1 Hz, 1H); 2.26 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 192.2, 184.1, 167.6, 153.4, 151.5, 144.7, 136.1, 130.7, 129.2, 126.8, 122.1, 116.4, 101.5, 98.7, 51.3, 33.4, 20.6. MS (ES): *m/z* (%) = 381 (100) $[M+1]^+$; Anal. calcd. (%) for $C_{21}H_{17}N_2O_3Cl$: C, 66.23; H, 4.50; N, 7.36; Found (%): C, 66.18; H, 4.46; N, 7.38.

3-(5-(4-Bromophenyl)-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)-4-hydroxy-6-methyl-2*H*-pyran-2-one (39): Yellow solid; m.p. 148 °C; IR (KBr, ν_{max}, cm^{-1}): 3452, 3022, 1640, 1526, 1216, 1022; ^{1}H NMR ($CDCl_3$, 300 MHz): 13.25 (s,1H); 7.36-7.17 (m, 5H); 7.08-7.01 (m, 2H); 6.86-6.80 (m, 3H); 6.06 (s, 1H); 5.32 (dd, *J* = 8.4 Hz, *J* = 11.9 Hz); 4.08 (dd, *J* = 11.9 Hz, *J* = 14 Hz); 3.51 (dd, *J* = 7.9 Hz, *J* = 17.1 Hz); 2.26 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 191.8, 183.7, 167.2, 153.5, 148.4, 144.7, 136.2, 130.8, 129.2, 126.5, 122.1, 116.4, 101.5, 98.6, 51.7, 33.4, 20.5. MS (ES): *m/z* (%) = 425 (100) $[M+1]^+$; Anal. calcd. (%) for $C_{21}H_{17}N_2O_3Br$: C, 59.31; H, 4.03; N, 6.59; Found (%): C, 59.27; H, 3.98; N, 6.62.

3-(5-(2,5-Dimethoxyphenyl)-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)-4-hydroxy-6-methyl-2*H*-pyran-2-one (40): Yellow solid; m.p. 146 °C; IR (KBr, ν_{max}, cm^{-1}): 3468, 3121, 1725, 1629, 1316, 1252; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 10.10 (1H, s); 7.47-7.26 (m, 5H); 7.50-7.24 (2H, m); 7.21-6.86 (2H, m), 5.94 (1H, s); 5.27 (dd, *J* = 8 Hz, *J* = 19 Hz); 4.18 (dd, *J* = 19 Hz, *J* = 18 Hz); 3.44 (dd, *J* = 8 Hz, *J* = 21 Hz); 3.89 (s, 3H), 3.86 (s, 3H); 2.31 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 192.1, 183.4, 166.3, 161.9, 150.6, 147.3, 133.8, 131.8, 128.7, 126.6, 124.6, 123.2, 121.2, 116.4, 114.8, 112.5, 111.6, 103.8, 98.6, 56.4, 21.3; MS (ES): *m/z* (%) = 407 (100) $[M+1]^+$; Anal. calcd. (%) for $C_{23}H_{22}N_2O_5$: C, 67.97; H, 5.46; N, 6.89; Found (%): C, 67.93; H, 5.42; N, 6.92.

4-Hydroxy-6-methyl-3-(1-phenyl-5-(2,3,5-trimethoxyphenyl)-4,5-dihydro-1*H*-pyrazol-3-yl)-2*H*-pyran-2-one (41): Orange solid; m.p. 161 °C; IR (KBr, ν_{max}, cm^{-1}): 3436, 3148, 1718, 1658, 1350, 1261; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.84 (1H, s), 8.16 (1H, d, *J*= 15 Hz), 8.04 (1H, d, *J*= 15 Hz), 7.47-7.26 (m, 5H); 7.24 (1H, s), 7.13 (1H, s), 5.91 (1H, s), 5.28 (dd, *J* = 9 Hz, *J* = 16 Hz); 4.18 (dd, *J* = 16 Hz, *J* = 18 Hz); 3.44 (dd, *J* = 9 Hz, *J* = 22 Hz); 4.28 (3H, s), 4.19 (3H, s), 3.86 (3H, s,), 2.27 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 190.8, 181.4, 168.4, 162.1, 153.2, 147.4, 136.8, 133.6, 132.8, 130.4, 129.7, 128.4, 126.5, 124.2, 116.8, 114.3, 112.4, 103.1, 96.5, 56.4, 21.0; MS (ES): *m/z* (%) = 437 (100) $[M+1]^+$; Anal. calcd. (%) for $C_{24}H_{24}N_2O_6$ C, 66.04; H, 5.54; N, 6.42; Found (%): C, 66.00; H, 5.491; N, 6.45.

4-Hydroxy-6-methyl-3-(5-(3-nitrophenyl)-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)-2*H*-pyran-2-one (42): Yellow solid; m.p. 166 °C; IR (KBr, ν_{max}, cm^{-1}): 3452, 3022, 1640, 1526, 1216, 1022; ^{1}H NMR ($CDCl_3$, 300 MHz): 8.20-8.09 (m, 2H); 7.48-7.40 (m, 2H); 7.21-7.08 (m, 2H); 6.93-6.82 (m, 3H); 6.05 (s, 1H); 5.41 (dd, *J* = 8.4 Hz, *J* = 18 Hz); 4.24 (dd, *J* = 12.4 Hz, *J* = 18 Hz); 3.51 (dd, *J* = 8.4 Hz, *J* = 16 Hz); 2.24 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 192.6, 185.6, 166.2, 158.8, 153.4, 142.1, 134.5, 131.2, 129.4, 124.7, 121.8, 116.5, 112.3, 103.8, 56.3, 37.4, 21.4. (ES): *m/z* (%) = 392 (100) $[M+1]^+$; Anal. calcd. (%) for $C_{21}H_{17}N_3O_5$: C, 64.45; H, 4.38; N, 10.74; Found (%): C, 64.41; H, 4.33; N, 10.78.

RESULTS AND DISCUSSION

In this work, we developed a facile synthesis of a series of 20 substituted dihydropyrazoles. Dihydropyrazole analogues were synthesized by reaction of various curcumin based chalcones having nitro, methoxy, chloro, bromo, flouro, benzyloxy, methyl, amino functional groups at phenyl ring with phenylhydrazine. Designing and synthesis of curcumin based chalcone analogues were reported [22,25]. Reaction of phenylhydrazine with chalcone under neutral conditions leads to the formation of corresponding dihydropyrazoles. The synthesis of designed analogue is shown in **Scheme-I**. Chalcone analogues (**3-22**) were synthesized from dehydroacetic acid (**1**) and substituted benzaldehydes (**2**) *via* condensation reaction as earlier reported procedure.

Further in an attempt to prepare corresponding dihydropyrazole derivatives the chalcone analogues were reacted with

phenyl hydrazine in refluxing condition to afford dihydropyrazole derivatives. First we made our attempt in search of optimum solvents and reaction conditions for this reaction. To achieve this we selected reaction of unsubstituted chalcone and phenyl hydrazine as model reaction and checked the feasibility of various table solvents as methanol, ethanol, dichloromethane, chloroform, THF and DMF for the reaction and results are summerized in Table-1. It is found that the use of ethanol provides the desired heterocycle in best yield and minimum time (Table-2). Hence we had chosen ethanol as solvent for synthesis of dihydropyrazole nucleus.

TABLE-1
SOLVENT OPTIMIZATION FOR SYNTHESIS OF DIHYDROPYRAZOLE NUCLEUS

Entry No.	Solvent	Time (h)	Yield (%)
1	THF	8	55
2	DMF	8	55
3	Methanol	6	76
4	Ethanol	4	93
5	Dichloromethane	8	65
6	Chloroform	8	67
7	Acetonitrile	9	50
8	1,4-Dioxane	8	50

TABLE-2
SYNTHESIS OF CORRESPONDING PYRAZOLES

Compd.	R	Time (h)	Yield (%)	m.p. (°C)
23	H	7	84	167
24	4-OCH_3	6	87	155
25	3- OCH_3	6	85	152
26	3,4-$(OCH_3)_2$	6	85	150
27	4-NO_2	7	84	200
28	2-NO_2	7	89	205
29	N,N-$(CH_3)_2$	9	82	180
30	3-Cl	4	87	141
31	4-Cl	4	87	130
32	3,5-Cl_2	4	86	162
33	3-OH,4-OCH_3	7	81	158
34	3-OH	5	85	164
35	4-OH	5	86	162
36	4-F	4	91	138
37	2-OCH_3	6	84	157
38	2-Cl	4	87	153
39	4-Br	7	80	149
40	2,5-$(OCH_3)_2$	4	88	161
41	2,3,5-$(OCH_3)_3$	6	84	166
42	3-NO_2	7	85	145

After optimizing the best solvent for reaction we synthesized a 20 dihydropyrazoles by reacting phenyl hydrazine and chalcone analogues under neutral conditions to yield desired heterocycle in satisfactory yields. Progress of reaction was monitored on silica TLC by using suitable mobile phase and after completion dihydropyrazoles were precipitated in reaction medium. Precipitate was filtered off from reaction mass and dihydropyrazole derivatives were further recrystallized in absolute ethanol. Isolated pure dihydropyrazoles were also evaluated for their melting points. All synthesized derivatives were found to have their melting points above 100 °C. All the synthesized dihydropyrazoles were characterized and confirmed by spectroscopic (^{1}H NMR and ^{13}C NMR) and spectrometric (mass) data. Prepared dihydropyrazole derivatives were characterized by presence of an asymmetric carbon adjacent to methylene carbon. Presence of optically active centre adjacent to methylene carbon it made both the methylene protons magnetically non-equivalent in nature which results in presence of three different double doublets (dd) in proton NMR spectra for each of three protons. Prepared dihydropyrazole derivatives also shown characteristic peaks in ^{13}C NMR at 192 ppm corresponding to carbonyl carbon in dihydropyrazole structure. All of the prepared heterocycles shown characterstic (M+1) peak in ESI mass spectra. In the process of preparation of dihydropyrazoles library we have observed a great deal of substituent effect on the rate and yield of reaction. We have noticed that electron withdrawing substituent like nitro and chloro groups reaction was taking longer time for completion while with the substituent like methoxy and *N,N*-dimethyl amino aromatic ring reaction time was short. We have also noticed that dihydropyrazoles with nitro substitution on phenyl ring were found to have poor solubility in organic solvents. Possible explanation for this substituent effect may be electronic displacement effect of substituent attached with phenyl ring.

Conclusion

In summary, we have reported an efficient synthesis of newly designed dihydropyrazoles. Synthetic methodology was further established by synthesizing a series of 20 substituted heterocyclic dihydropyrazoles. Structures of prepared heterocycles were established by all the spectroscopic, spectrometric and elemental analysis data. Appearance of double doublet (dd) was also explained due to presence of asymmetric carbon atom. The reported synthesis is an important finding in the field of synthesis of heterocyclic compounds, which may be useful for future drug discovery programme.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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