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ARTICLE

Synthesis and Antifungal Activity of New Dihydropyrazoles of Designed Curcumin Analogues

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ABSTRACT

A library of new dihydropyrazole derivatives have been synthesized 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. Dihydropyrazoles exhibited characteristic dd (double doublet) due to presence of optically active carbon of pyrazole ring. All the synthesized compounds were also evaluated for their antifungal potential against six different fungal starins. Evaluated heterocyles showed potent inhibitory property against tested fungal strains with minimum inhibitory concentration (MIC) values upto 3.12 µg/mL. Heterocyles with nitro and methoxy substitutions were showing best antifungal activities. Among 20 different derivatives tested for biological activity SAR has been developed between the various substitutions at phenyl ring of synthesized heterocycles.

KEYWORDS

Dihydropyrazoles, Curcumin, Antifungal activity.

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INTRODUCTION

The heterocyclic compounds constitute one of the most complex branches in chemistry of organic chemistry. In particular, the heterocyclic compounds have been comprehensively studied not only for their intrinsic interest, but also because of many natural products, many drugs and medicines and many dyes belong to this group [1,2]. Pyrazole constitutes an important family of the heterocyclic compounds which are having special place in chemistry as well as medicinal chemistry. Pyrazole nucleus was first reported by Ludwig Knorr in 1883 [3]. It is equally interesting for its theoretical implications, the diversity of its synthetic procedures and the physiological as well as industrial significance of heterocyclic compounds [4-6]. These heterocycles have been studied for over a century as an important class of heterocyclic compounds and continue to attract considerable interest due to the broad range of biological activities they possess. Pyrazoles are of interest as potent bioactive molecules [7-11]. They are known to exhibit pharmaceutical activities such as CNS depressant, neuroleptic, tuberculostatic, antihypertensive, antileishmanial, analgesic, antidiabetic, anti-tumor and antimicrobial [12-15]. Fig. 1 shows

several mole-cules bearing pyrazole nucleus which are used in clinics for treatment of various health problems. Moreover, pyrazole analogues of curcumin were synthesized and investigated for lipoxygenase inhibitory activity [16], cytotoxic activity [17,18] and antioxidant activity [19]. Recently, curcumin has been shown to have synergistic effects with artemisinin against *Plasmodium berghei in vivo* [20,21]. Among the different drug molecules illustrated in Fig. 1 pyrazole nucleus is considered as active pharmacophore due to its intrinsic activity. Further-more, the presence of enone function of chalcone moiety with pyrazole ring also enhanced the biological activity. We have previously reported the synthesis of fabricated curcumin based chalcone analogues [22]. This time we hypothesize the incor-poration of the essential structural features of pyrazoles with a curcumin moiety could provide new derivatives with unex-pected and/or enhanced biological activities since several curcumin derivatives have already been shown to be active against a number of tumors [23,24]. Prompted by all these observations, we report here the synthesis of curcumin based chalcones and corresponding dihydropyrazoles by utilizing condensation reaction between chalcones and phenyl hydrazine. Curcumin based chalcones previously reported by our group were used for synthesis of dihydropyrazoles [25]. All the synthe-sized hetrocycles were characterized by ^{1}H and ^{13}C NMR, IR spectra, mass spectra as well as elemental analysis measure-ments.

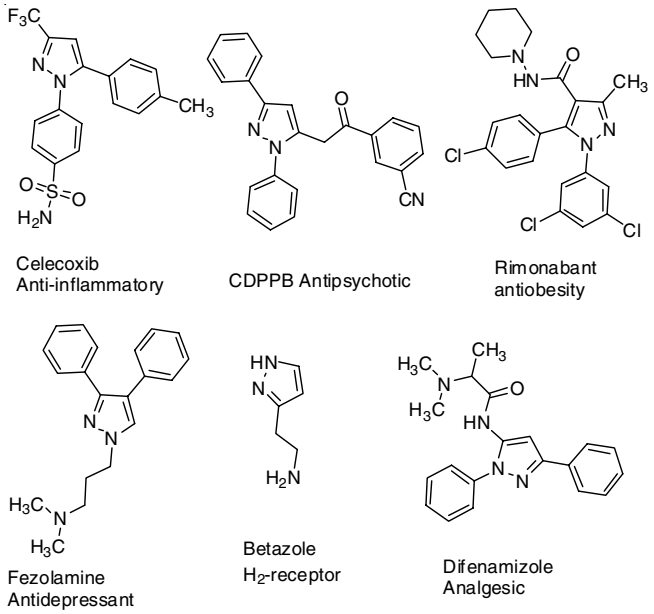


Fig. 1. Some pyrazoles based drug molecules

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 India. 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 dihydro pyrazoles (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 up to 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 dihydro pyarazole derivatives (**23-42**), which were further characterized by spectroscopic and spectrometric 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) $[M+1]^+$; Ana. 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) $[M+1]^+$; Ana. 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) $[M+1]^+$; Ana. 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-(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; ^{1}H 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) $[M+1]^+$; Ana. 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; ^{1}H 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) $[M+1]^+$; Ana. 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; ^{1}H 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) $[M+1]^+$; Ana. 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; ^{1}H 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) $[M+1]^+$; Ana. 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; ^{1}H 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) $[M+1]^+$; Ana. calcd. for $C_{21}H_{17}ClN_2O_3$: 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; ^{1}H 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): ^{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) $[M+1]^+$; Ana. calcd. for $C_{21}H_{17}ClN_2O_3$: 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; ^{1}H 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) $[M+1]^+$; Ana. 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; ^{1}H 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) $[M+1]^+$; Ana. 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; ^{1}H 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) $[M+1]^+$; Ana. 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) $[M+1]^+$; Ana. 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) $[M+1]^+$; Ana. 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) $[M+1]^+$; Ana. 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) $[M+1]^+$; Ana. 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) $[M+1]^+$; Ana. 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) $[M+1]^+$; Ana. 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) $[M+1]^+$; Ana. 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) $[M+1]^+$; Ana. 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 %.

Antifungal activity: Minimum inhibitory concentration (MIC) and IC_{50} values are determined using standard broth microdilution technique as per NCCLS guidelines. The activity of compounds was determined as per NCCLS protocol using Mueller Hinton broth (Becton Dickinson, USA) in 96-well tissue culture plates. Proper growth control, drug control and the negative control were adjusted onto the plate. The fungal strains are grown in Sabouraud Dextrose Agar slants at 35 °C. For yeast like fungi (*e.g. Candida* sp.) the cells are suspended in normal saline after 24 h growth (in case of sporulating mycelial fungi 3-7 days old slant cultures are used) and approximately 1.0-2.0 × 10^6 cells/mL by matching with 0.5 McFarland standards. This suspension serves as stock fungal cell suspension. The activity of compounds is determined by two-fold microbroth dilution method using RPMI 1640 (1.04 g/100 mL) buffered with MOPS (3.47 g per 100 mL RPMI) for fungus. Compounds were dissolved in DMSO at a concentration of 1 mg/mL (synthetic compound) or 10 mg/mL (natural extract) and 20 µL of this was added to each well of 96-well tissue culture plate having 180 µL Mueller Hinton broth. From here the solution was serially diluted resulting in two fold dilution of the test compounds in subsequent wells. 100 µL of McFarland matched bacterial or fungal suspension was diluted in 10 mL of media and then 100 µL of it was added in each

well and kept for incubation. The maximum concentration of compounds tested was 500 µg/mL. The micro-titer plates were incubated at 35 °C in a moist, dark chamber and MICs were recorded visually.

RESULTS AND DISCUSSION

In present, we have demonstrated the synthesis of 20 member library of substituted dihydropyrazoles and tried to evaluate their antifungal property. Dihydropyrazole analogues were synthesized by reaction of various curcumin based chalcones bearing nitro, methoxy, chloro, bromo, benzyloxy, *N,N*-dimethyl, amino functional groups at phenyl ring with phenylhydrazine. Reaction of phenylhydrazine with chalcone under neutral conditions leads to the formation of corresponding dihydropyrazoles. Synthetic scheme for 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 by earlier reported procedure [25].

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 solvents for the reaction and results are summarized in Table-1. It is found that the use of ethanol provides the desired heterocycle in best yield and minimum time. Hence we had chosen ethanol as solvent for synthesis of dihydropyrazole nucleus.

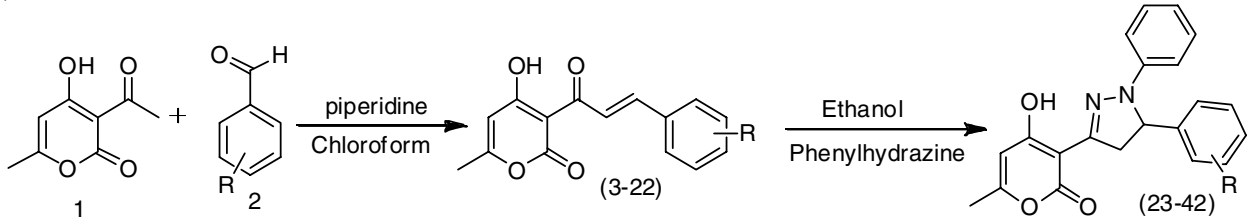
TABLE-1
SOLVENT OPTIMIZATION FOR SYNTHESIS OF DIHYDROPYRAZOLE NUCLEUS

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

After optimizing the solvent for reaction we synthesized a library of dihydropyrazoles by reacting phenyl hydrazine and chalcone analogues 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. All the synthesized derivatives (Table-2) were found to have their melting points above 100 °C. All the 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 doublet in proton NMR spectra for each of three protons. All the 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 characteristic (M+1) peak in ESI mass spectra. In the process of preparation of dihydropyrazole library we have observed a great deal of substituent effect on the rate and yield of reaction. It is noticed that the 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. It is also noticed that the dihydropyrazoles with nitro substitution on phenyl ring were found to have poor solubility in organic solvents. One of the possible explanation for this substituent effect is the electronic displacement effect of substituent attached with phenyl ring.

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	4-OH, 3-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



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

All the synthesized dihydropyrazoles (**3**-**24**) were screened for their antifungal activity against six different fungal strains *Candida albicans, Cryptococcus neoformans, Sporothrix schenckii, Trichophyton mentagrophyte, Aspergillus fumigates* and *Candida parapsilosis*. As shown in Table-3, all the compounds exhibited concentration dependent antifungal activities, inhibitory values are reported in form of minimum inhibitory concentration (MIC) values against tested cell lines. Among all the compounds tested for antifungal property compounds **26**, **27** were exhibited excellent antifungal property by showing the lower MIC values against tested antifungal strains. Compound **26** having 3,4-dimethoxy substitution on phenyl ring exhibited MIC value of 6.25 µg/mL for *Candida albicans*, 6.25 µg/mL for *Cryptococcus neoformans*, 12.5 µg/mL for *Sporothrix schenckii*, 25 µg/mL for *Trichophyton mentagrophyte*, 25 µg/mL *Aspergillus fumigates* and 12.5 µg/mL *Candida parapsilosis*. While Compound **27** with 4-nitro substitution at phenyl ring exhibited MIC values of 6.25, 3.12, 6.25, 12.5, 25 and 12.5 µg/mL in *Candida albicans*, *Cryptococcus neoformans, Sporothrix schenckii*, *Trichophyton mentagrophyte*, *Aspergillus fumigates*, *Candida parapsilosis* strains respectively. These two compounds were found to be selective to show good inhibition for *Cryptococcus neoforman* fungal strain. Compound **28** with 2-nitro group on phenyl ring exhibited moderate antifungal activity with MIC values of 25, 12.5, 50, 50, 50 and 25 µg/mL against *Candida albicans*, *Cryptococcus neoformans, Sporothrix schenckii*, *Trichophyton mentagrophyte*, *Aspergillus fumigates*, *Candida parapsilosis* strains respectively. Compound **41** having 2,3,5-trimethoxy substitution was also showing MIC values of 50, 25, 12.5 and 50 µg/mL against *Candida albicans*, *Sporothrix schenckii*, *Trichophyton mentagrophyte*, *Aspergillus fumigates* strains respectively. On having closure observation of all the biological activity we have developed SAR (structure activity relationship) between the antifungal activity of evaluated dihydropyrazoles and groups attached with the phenyl ring of dihydropyrazole analogues. Interestingly compounds having nitro substitution (**27** and **28**) and methoxy substitution (**24**, **26** and **41**) were showing excellent antifungal potential against all the evaluated antifungal strains, whereas compounds with halogens substituted on phenyl ring were showing no inhibitory potential against fungal cell lines. One of the compounds containing *N,N*-dimethyl substitution on phenyl ring (**29**) was showing moderate activity with MIC value of 50 µg/mL against *Candida albicans*, *Sporothrix schenckii* fungal strains.

TABLE-3
ANTIFUNGAL ACTIVITY OF SYNTHESIZED PYRAZOLES

Compd. No.	Minimum inhibitory concentration (MIC) in µm against various fungal strains					
	1	2	3	4	5	6
23	50	50	50	50	> 50	> 50
24	50	50	50	50	> 50	> 50
25	> 50	> 50	> 50	> 50	> 50	> 50
26	6.25	6.25	12.5	25	25	12.5
27	6.25	3.12	6.25	12.5	25	12.5
28	25	12.5	50	50	50	50
29	50	50	> 50	> 50	> 50	> 50
30	50	50	50	> 50	> 50	> 50
31	> 50	> 50	> 50	> 50	> 50	> 50
32	> 50	> 50	> 50	> 50	> 50	> 50
33	> 50	> 50	> 50	> 50	> 50	> 50
34	> 50	> 50	> 50	> 50	> 50	> 50
35	> 50	> 50	> 50	50	> 50	> 50
36	> 50	> 50	> 50	> 50	> 50	> 50
37	50	> 50	> 50	> 50	> 50	> 50
38	50	> 50	> 50	50	> 50	> 50
39	50	> 50	> 50	50	> 50	> 50
40	> 50	> 50	> 50	> 50	> 50	> 50
41	50	> 50	25	12.5	50	> 50
42	> 50	> 50	> 50	> 50	> 50	> 50

1 = *Candida albicans*, 2 = *Cryptococcus neoformans,* 3 = *Sporothrix schenckii*, 4 = *Trichophyton mentagrophyte*, 5 = *Aspergillus fumigates*, 6 = *Candida parapsilosis*

Conclusion

In summary we have reported an easy and facile method for synthesis of new curcumin based dihydropyrazole library. All the synthesized compounds were characterized by spectroscopic and spectrometric techniques. ^{1}H NMR clearly shows double doublets for methylene protons. All dihydrpyrazoles were also screened for their antifungal activity. Two compounds with nitro substitutions were exhibited excellent antifungal property against evaluated atrains. The work reported by us in the manuscript is of great interest from chemistry as well as biological perspective and could be of great interest in drug discovery programme in near future.

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