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Research Article

Chemistry for New drug discovery

Design, Synthesis and Antibacterial Evaluation of Hybrid Curcumin Based Pyrazole Derivatives

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Abstract: Present work demonstrates synthesis and antibacterial property of new pyrazole derivatives. A series of new Curcumin based dihydropyrazoles has been synthesized with an objective to evaluate their antibacterial property. Dihydropyrazoles analogues were synthesized using Curcumin based chalcones and differently substituted phenylhydrazine derivatives. We used the previously designed Curcumin based chalconesto react with phenylhydrazine derivatives in ethanol in a catalyst free medium to afford new dihydropyrazole derivatives. Effect of substituent on reactivity was also studied. All the synthesized pyrazole analogues were characterized using proton and carbon NMR, Mass spectroscopy and IR techniques. 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 proton NMR spectrum of Dihydropyrazoles was also explained due to presence of optically active carbon of pyrazole ring. The synthesized library was screened for their inhibitory activity against 4 different bacterial strains 1. *E. Coli* (ATCC 9637), 2. *Pseudomonas aeruginosa* (ATCC BAA-427), 3. *Staphylococcus aureus* (ATCC 25923) and 4. *Klebsiella pneumonia* (ATCC 27736). Out of all the compounds evaluated, the compounds that exhibited IC_{50} value greater than 50µM, were considered to be inactive. We established an important SAR based on the structure dependent inhibitory potential of screened dihydropyrazoles. Two compounds 4e and 4t having nitro and benzyl substitution respectively were showing the best inhibitory potential against Gram Positive bacterial strain *Staphylococcus aureus* with MIC value of 1.56 µg/ml. Compounds having Chloro and Methoxy substitution were found to be less effective against screened bacterial strains. Compounds 4a and 4b were selective towards *Staphylococcus aureus* species with the MIC value of 1.56 µg/ml for each. These pyrazole analogues were not showing inhibitory potential against other screened bacterial strains.

Keywords: Antibacterial, Chalcones, Pyrazole, Phenyl hydrazine, Curcumin, Dihydropyrazole, Heterocyclics.

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1. INTRODUCTION

Infectious diseases are one of the biggest public health threats globally specially for the developing countries which results in millions of deaths worldwide.[1-3]The emergence of resistance towards existing representative antibiotic drugs makes this situation more serious. Bacterial genome is known to be capable of adapting themselves according to the applied antibiotics and generates resistance towards it, consequently these weapons become inactive.[4-5]The main hurdle behind the difficulty to develop an ideal antibiotic is the bacterial first line of defence the cell wall. Situation becomes more and more difficult in case of gram positive bacteria due to presence of thick cell wall.[6] Hence there is an urgent need of developing novel molecules to tackle this alarming situation. Medicinal chemists around the globe are under the burden of synthesizing new and safe antimicrobial molecules. Curcumin is an active ingredient present in turmeric and well known for its various pharmacological effects.[7-9] Chemically Curcumin is a β-diketone moiety which is connected with substituted phenyl ring at both the ends.[10] Literature is full of reports which reveal the anticancer[11], antimicrobial[12], anti-inflammatory[13], antioxidant[14], and anti-angiogenic[15] properties of Curcumin. It is also traditional medicine for liver disease, indigestion, urinary tract disease and rheumatoid arthritis [16-19]. We are working in field of developing small heterocycles of therapeutic importance.[20-21] Previously we have reported several natural product mimetic molecules which exhibited excellent medicinal properties.[22-23] We earlier published the anticancer property of Curcumin mimic chalcones analogues and converted them to corresponding pyrazoles.[24-25] Pyrazoles are an important class of heterocycles in synthetic chemistry and is an attractive target for medicinal chemists due to its presence in various drug molecules and medicinally active compounds. So in extension of our work and inspired by the various beneficial effects of Curcumin we designed and synthesized our molecule consisting of active β-diketone moiety of Curcumin from dehydroacetic acid and benzaldehyde as shown in Figure 1.

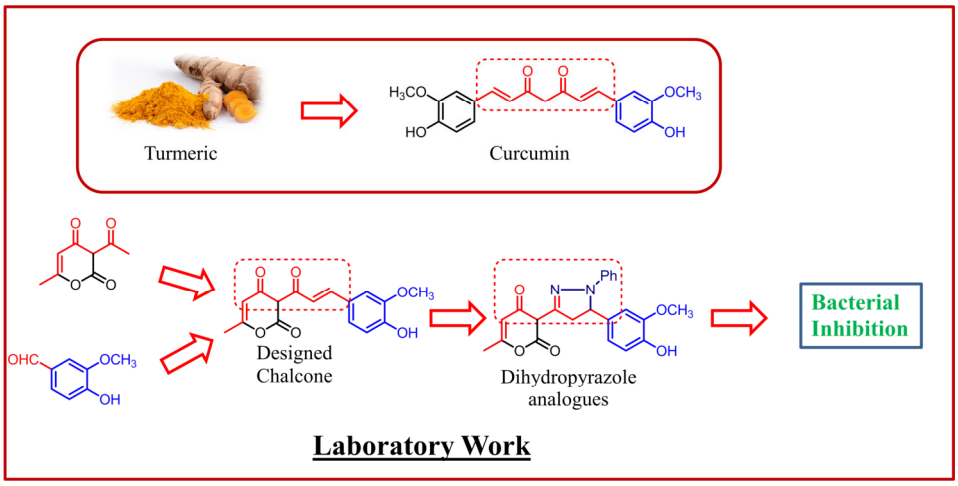


Fig 1. Designing of our synthesized molecule

2. MATERIALS AND METHODS

All the reactions were carried out as specified in their protocol. All the reagents were purchased from Sigma-Aldrich Chemical Co, and were used directly without further purification. NMR spectra were obtained using the Bruker DRX 300MHz spectrometer. Chemical shifts (δ) are given in ppm relative to TMS, coupling constants (*J*) in Hz. IR spectra were taken on VARIAN FT-IR spectrometers as KBr pellets (when solid). Elemental analysis was performed using a Perkin Elmer Auto system XL Analyzer. Melting points were measured using a COMPLAB melting-point apparatus. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates visualized with UV light.

2.1 General procedure for synthesis of pyrazoles(4a-v)

Chalcone analogues (1 mmol) were dissolved in 10 ml of ethanol in a 100 ml round bottom flask. Phenyl hydrazine (1.5 mmol) was added to it. Acetic acid (10 mol%) was added as a catalyst. Reaction mixture was allowed to reflux upto completion of reaction. Progress of reaction was monitored by thin layer chromatography. After completion of reaction solvent was evaporated under the reduced pressure. Solid residue was poured in ice water and filtered out. After filtration the solid residue was recrystallised with ethanol to get the pure pyrazole derivatives (4a-4u)

2.2 Analytical data for compounds (4a-v)

2.2.1 3-(1,5-diphenyl-4,5-dihydro-1H-pyrazol-3-yl)-4-hydroxy-6-methyl-2H-pyran-2-one (4a)

Yellow solid; mp 153^{0}C; ν_{max}(KBr) 3452, 3022, 1640, 1526, 1216, 1022 cm^{-1}; ^{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 = 18Hz); 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%.

2.2.2 4-hydroxy-3-(5-(3-methoxyphenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-6-methyl-2H-pyran-2-one (4b)

Yellow solid; mp 173^{0}C; ν_{max}(KBr) 3452, 3022, 1640, 1526, 1216, 1022 cm^{-1}; ^{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 = 8.2Hz, J = 11 Hz, 1H); 4.26 (dd, J = 11.2Hz, J = 18Hz,

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%.

2.2.3 4-hydroxy-3-(5-(4-methoxyphenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-6-methyl-2H-pyran-2-one (4c)

Yellow solid; mp 164^{0}C; ν_{max}(KBr) 3452, 3022, 1640, 1526, 1216, 1022 cm^{-1}; ^{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 = 8.4Hz, J = 12 Hz, 1H); 4.26 (dd, J = 12.2Hz, J = 19Hz, 1H); 3.91 (s, 3H); 3.48 (dd, J = 8.4Hz, J = 12Hz, 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%.

2.2.4 3-(5-(3,4-dimethoxyphenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-4-hydroxy-6-methyl-2H-pyran-2-one (4d)

Yellow solid; mp 168^{0}C; ν_{max}(KBr) 3430, 3022, 2922, 1630, 1485, 1216 cm^{-1}; ^{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 = 8.4Hz, 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%.

2.2.5 4-hydroxy-6-methyl-3-(5-(4-nitrophenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-2H-pyran-2-one (4e)

Yellow solid; mp 164^{0}C; ν_{max}(KBr) 3406, 2880, 1717, 1590, 1418, 1353, 1173 cm^{-1}; ^{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 = 12.4Hz, J = 19Hz, 1H); 3.51 (dd, J = 7.9Hz, J = 18.9Hz, 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%.

2.2.6 4-hydroxy-6-methyl-3-(5-(2-nitrophenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-2H-pyran-2-one (4f)

Yellow solid; mp 144^{0}C; ν_{max}(KBr) 3452, 3022, 1640, 1526, 1216, 1022 cm^{-1}; ^{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 = 11Hz, J = 18.1 Hz, 1H); 3.51 (dd, J = 8Hz, 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%.

2.2.7 3-(5-(3-chlorophenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-4-hydroxy-6-methyl-2H-pyran-2-one (4g)

Yellow solid; mp 157^{0}C; ν_{max}(KBr) 3452, 3022, 1640, 1526, 1216, 1022 cm^{-1}; ^{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%.

2.2.8 3-(5-(4-chlorophenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-4-hydroxy-6-methyl-2H-pyran-2-one (4h)

Yellow solid; mp 148^{0}C; ν_{max}(KBr) 3406, 2880, 1717, 1590, 1418, 1353, 1173 cm^{-1}; ^{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 = 8Hz, J = 12 Hz, 1H); 4.17 (dd, J = 12.2Hz, J = 19Hz, 1H); 3.51 (dd, J = 8.0Hz, J = 11.9Hz, 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) $[M+1]^+$; 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%.

2.2.9 3-(5-(4-(dimethylamino)phenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-4-hydroxy-6-methyl-2H-pyran-2-one (4i)

Yellow solid; mp 171^{0}C; ν_{max}(*K*Br) 3406, 2880, 1717, 1590, 1418, 1353, 1173 cm^{-1}; ^{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 = 8Hz, J = 12Hz); 4.12 (dd, 1H, J = 12Hz, J = 18Hz); 3.50 (dd, 1H, J = 8Hz, J = 22Hz); 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%.

2.2.10 4-hydroxy-3-(5-(3-hydroxyphenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-6-methyl-2H-pyran-2-one (4j)

Yellow solid; mp 168^{0}C; ν_{max}(KBr) 3561, 3157, 1732, 1628, 1346, 1268 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ10.04 (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 %.

2.2.11 4-hydroxy-3-(5-(4-hydroxy-3-methoxyphenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-6-methyl-2H-pyran-2-one (4k)

Yellow solid; mp 153^{0}C; ν_{max}(KBr) 3328, 2917, 1684, 1597, 1423, 1270, 1127 cm^{-1}; ^{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 = 8Hz, J = 12 Hz, 1H); 4.31 (s, 1H); 4.16 (dd, J = 8Hz, J = 12.4Hz, 1H); 3.84 (s, 3H); 3.49 (dd, J = 12.2Hz, 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%.

2.2.12 *3-(5-(3,5-dichlorophenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-4-hydroxy-6-methyl-2H-pyran-2-one (4l)*

Yellow solid; mp 143^{0}C; ν_{max}(KBr) 3430, 3022, 2922, 1630, 1485, 1216 cm^{-1}; ^{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 = 8.07Hz, J = 12.3 Hz, 1H); 4.27 (dd, J = 12.7 Hz, J = 19.2Hz, 1H); 3.49 (dd, J = 7.5Hz, 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%.

2.2.13 *4-hydroxy-3-(5-(4-hydroxyphenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-6-methyl-2H-pyran-2-one (4m)*

Bright yellow solid; mp 153^{0}C; ν_{max}(KBr) 3541, 3167, 1724, 1658, 1346, 1268 cm^{-1}; ^{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 %.

2.2.14 *3-(5-(4-fluorophenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-4-hydroxy-6-methyl-2H-pyran-2-one (4n)*

Yellow solid; mp 126^{0}C; ν_{max}(KBr) 3406, 2880, 1717, 1590, 1418, 1353, 1173 cm^{-1}; ^{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 = 12Hz, J = 14Hz, 1H); 3.50 (dd, J = 7.9Hz, J = 17.1Hz, 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 $C_{21}H_{17}FN_2O_3$: C, 69.22; H, 4.70; N, 7.69 Found: C, 69.18; H, 4.67; N, 7.85%.

2.2.15 *4-hydroxy-3-(5-(2-methoxyphenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-6-methyl-2H-pyran-2-one (4o)*

Yellow solid; mp 161^{0}C; ν_{max}(KBr) 3452, 3022, 1640, 1526, 1216, 1022 cm^{-1}; ^{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 = 19.1Hz, 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%.

2.2.16 *3-(5-(2,5-dimethoxyphenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-4-hydroxy-6-methyl-2H-pyran-2-one (4p)*

Yellow solid; mp 146^{0}C; ν_{max}(KBr) 3468, 3121, 1725, 1629, 1316, 1252 cm^{-1}; ^{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 %.

2.2.17 *3-(5-(2-chlorophenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-4-hydroxy-6-methyl-2H-pyran-2-one (4q)*

Yellow solid; mp 151^{0}C; ν_{max}(KBr) 3452, 3022, 1640, 1526, 1216, 1022 cm^{-1}; ^{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 = 11Hz, 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 $C_{21}H_{17}ClN_2O_3$: C, 66.23; H, 4.50; N, 7.36 Found: C, 66.18; H, 4.46; N, 7.38%.

2.2.18 *3-(5-(4-bromophenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-4-hydroxy-6-methyl-2H-pyran-2-one (4r)*

Yellow solid; mp 148^{0}C; ν_{max}(KBr) 3452, 3022, 1640, 1526, 1216, 1022 cm^{-1}; ^{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 = 14Hz); 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 $C_{21}H_{17}BrN_2O_3$: C, 59.31; H, 4.03; N, 6.59 Found: C, 59.27; H, 3.98; N, 6.62%.

2.2.19 *4-hydroxy-6-methyl-3-(1-phenyl-5-(2,3,5-trimethoxyphenyl)-4,5-dihydro-1H-pyrazol-3-yl)-2H-pyran-2-one (4s)*

Pale yellow solid; mp 176^{0}C, ν_{max}(KBr) 34436, 3137, 1717, 1658, 1354, 1259 cm^{-1} NMR ($CDCl_3$, 300 MHz): δ 10.14 (1H, s); 7.48-7.24 (m, 5H); 7.51-7.22 (2H, m); 7.20-6.84 (2H, m), 5.92 (1H, s); 5.28 (dd, J = 8 Hz, J = 19 Hz); 4.17(dd, J = 19 Hz, J = 18 Hz); 3.43 (dd, J = 8 Hz, J = 21 Hz); 3.91 (s, 3H), 3.89-3.82 (m, 6H); 2.30 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz):

δ 192.4, 183.8, 166.2, 161.7, 151.1, 147.8, 133.8, 131.8, 128.7, 126.5, 124.6, 123.2, 120.4, 116.4, 114.8, 112.5, 111.2, 103.6, 98.6, 56.1, 21.4. 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%.

2.2.20 *4-hydroxy-6-methyl-3-(5-(3-nitrophenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-2H-pyran-2-one (4t)*

Orange solid; mp 161^{0}C; ν_{max}(KBr) 3436, 3148, 1718, 1658, 1350, 1261 cm^{-1}; ^{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 (%) = 392 (100) $[M+1]^+$; Ana. calcd. for $C_{21}H_{17}N_3O_5$ C, 66.45; H, 4.38; N, 10.71; Found: C, 66.43; H, 4.41; N, 10.69%.

2.2.21 *4-hydroxy-6-methyl-3-(5-(3-nitrophenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-2H-pyran-2-one (4u)*

Yellow solid; mp 166^{0}C; ν_{max}(KBr) 3452, 3022, 1640, 1526, 1216, 1022 cm^{-1}; ^{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 = 12.4Hz, 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%.

2.2.22 *3-(5-(4-(benzyloxy)-3-methoxyphenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-4-hydroxy-6-methyl-2H-pyran-2-one (4v)*

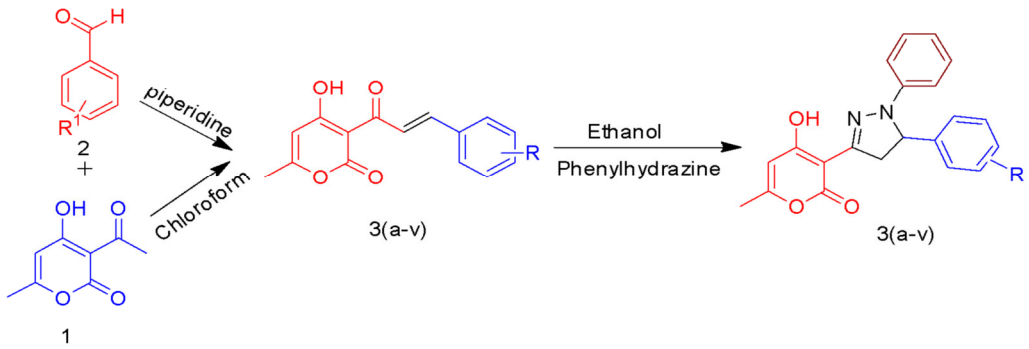
Light brown solid; mp 59^{0}C; ν_{max}(KBr) 3700, 3325, 3062, 2968, 1722, 1656, 1265 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.84 (1H, s), 7.46-7.35 (5H, m), 7.34-7.21 (m, 5H), 7.19-7.01 (m, 2H); 7.01 (1H, d, *J*= 8.4Hz, 1H), 5.92 (1H, s), 5.27 (2H, s); 5.25 (dd, J = 6 Hz, J = 20 Hz); 4.16 (dd, J = 19 Hz, J = 20 Hz); 3.42 (dd, J = 6 Hz, J = 21 Hz); 3.97 (3H, s), 2.26 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 192.1, 181.8, 167.4, 163.6, 150.8, 148.6, 136.4, 133.9, 132.8, 130.3, 128.4, 126.4, 127.8, 127.1, 123.4, 121.9, 121.1, 118.2, 116.5, 115.3, 114.3, 112.5, 111.8, 103.1, 98.9, 58.4, 56.4, 21.3; 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, 5.51; N, 6.47 %.

2.3. *Antimicrobial Assay*

Minimum inhibitory concentration (MIC) and IC_{50} values are determined using standard broth micro dilution technique as per NCCLS guidelines. The bacterial strains were grown on nutrient agar at 37^{0}C. After 24 h of incubation, bacterial cells were suspended in normal saline containing Tween 20 at 0.05% at a concentration of approximately 1.0–2.0 X 107 cells/mL by matching with 0.5 McFarland standards. 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.

3. RESULTS AND DISCUSSION

In continuation of our work to fulfil our objective of investigating antimicrobial properties of dihydropyrazoles, we started our work by synthesizing a series of dihydro pyridines. We designed the dihydropyrazole analogues keeping in mind the Curcumin structure in order to incorporate the better pharmacological properties in desired compounds. Pyrazole analogues were prepared by reacting Curcumin based chalcones (3a-v) and substituted phenyl hydrazine derivatives as shown in scheme **1**. The chalcone analogues were synthesized by our earlier reported procedure[26] using dehydroacetic acid and substituted benzaldehyde derivatives as depicted in figure 1.



Scheme 1. Synthesis of Dihydropyrazole analogues.

These synthesized chalcone analogues are subjected to react under heating conditions with phenyl hydrazine derivatives to afford dihydropyrazole analogues in excellent yields. During the reaction progress was monitored at regular time interval by thin layer chromatography of silica and in the course of reaction we observed that the substrate with nitro substituent were taking longer time (more than 6 hrs.) for completion of reaction, while in case of substrates with alkyl substitution the reaction time was short (3-4 hrs). This observation made us conclude that electron withdrawing substrates on phenyl rings slowed down the reaction while electron donating substrates increased the rate of reaction. The newly prepared pyrazole analogues were fully characterized by 1H NMR, 13C NMR, ESMS and elemental analysis data. Formation of the dihydropyrazole ring was signified by appearance of double doublets (dd) in 1H NMR

spectrum. The appearance of dd in proton NMR was attributed due to presence of chiral centre in the molecule which we have reported in our earlier article.[27] Except the N,N-dimethyl derivatives most of the compounds were purified without any chromatographic purification. All the synthesized dihydropyrazoles were screened for their in vitro antimicrobial activity on 4 different bacterial cell lines 1. *E. Coli* (ATCC 9637), 2. *Pseudomonas aeruginosa* (ATCC BAA-427), 3. *Staphylococcus aureus* (ATCC 25923) and 4.*Klebsiella pneumonia* (ATCC 27736) in DMSO. Inhibitory Potential of screened dihydropyrazoles was reported in the form of MIC value of corresponding compound. MIC Values were reported in µg/ml. Screened compounds have shown very selective and excellent antibacterial activity. Results are summarized in tabular format in Table **2**. Results are depicted in the form of their MIC values against the evaluated strains. Out of all the compounds evaluated, most of the compounds exhibited MIC value greater than 50µM, that compounds were considered to be inactive.

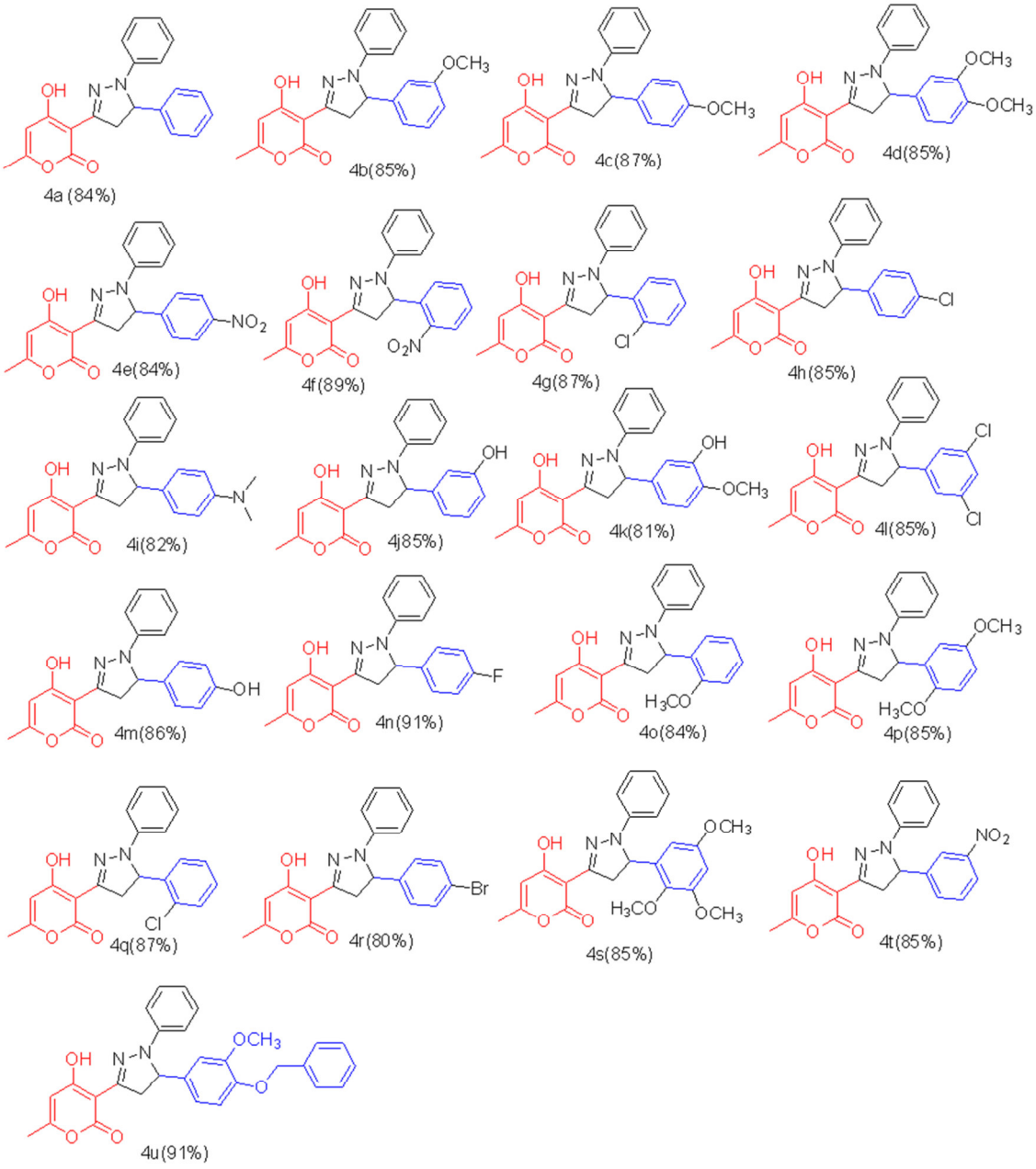


Fig 2. Synthesized Dihydropyrazole Library

Two compounds 4e and 4t have shown excellent inhibitory activity against Gram Positive bacterial strain *Staphylococcus aureus* with MIC value of 1.56 µg/ml. But 23 and 24 do not exhibit any promising activity against Gram negative bacterial strains like *E. Coli*. Compounds 4e and 4t were having nitro and benzyl substitution respectively, while compounds having Chloro and Methoxy substitution were found to be less effective against screened bacterial strains. Moreover compounds 4n and 4r were showing moderate activity with MIC value of 50µg/ml. Most of the compounds were found to be less effective. A minute observation of Table 1 reveals that Nitro substitution in the phenyl ring was showing promising inhibitory activity against gram positive as well as gram negative bacterial strain.

Table 1.Antibacterial activity of Synthesized Pyrazoles.

S.No.	C.No.	MIC (Minimum Inhibitory Concentration) in µg/ml			
		E. Coli	*P. aeruginosa*	*S. aureus*	*K. pneumoniae*
1	4a	**50**	>50	**1.56**	>50
2	4b	**50**	>50	**1.56**	>50
3	4c	>50	>50	>50	>50
4	4d	>50	>50	>50	>50
5	4e	>50	>50	**>1.56**	**>1.56**
6	4f	>50	>50	>50	>50
7	4g	>50	>50	>50	>50
8	4h	>50	>50	>50	>50
9	4i	>50	>50	>50	>50
10	4j	>50	>50	>50	>50
11	4k	>50	>50	>50	>50
12	4l	>50	>50	>50	>50
13	4m	>50	>50	>50	>50
14	4n	>50	>50	**50**	**50**
15	4o	>50	>50	>50	>50
16	4p	>50	>50	>50	>50
17	4q	>50	>50	>50	>50
18	4r	>50	>50	**50**	**50**
19	4s	>50	>50	>50	>50
20	4t	>50	>50	**>1.56**	**>1.56**
21	4u	**50**	**50**	>50	>50
22	4v	**50**	**50**	>50	>50

None of the synthesized compounds has shown inhibitory activity against K. pneumoniae bacterial strain.

4. CONCLUSION

In summary we have designed and synthesized Curcumin mimic chalcones which were further converted to dihydropyrazoles. Synthesized pyrazole analogues after in vitro screening against four different gram positive as well as gram negative bacterial strains were found to possess' very good antibacterial property in which two analogues were found to be very selective against gram positive strains. SAR reveals that compounds with Nitro substitution were found to be active against screened bacterial strains. In vivo screenings of active compounds are underway. The result of our work is very important from a medicinal chemistry perspective and can generate an opportunity for medicinal chemists in the field of antibacterial drug discovery.

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6. AUTHORS CONTRIBUTION STATEMENT

Dr. A. M. Jha worked for planning and execution of all the work and Md. M. Alam contributed to drafting the manuscript.

7. CONFLICT OF INTEREST

Conflict of interest declared none.

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