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Synthesis and antimicrobial screening of pyrano[3,2-*c*]chromene derivatives of 1*H*-pyrazoles

Research Article

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Abstract: A new series of twenty four derivatives of pyrano[3,2-c]chromene **IVa-x** bearing 1*H*-pyrazole were synthesized by a one pot, base-catalyzed cyclocondensation reaction of 1*H*-pyrazole-4-carbaldehyde **Ia-l**, malononitrile **II** and 4-hydroxycoumarin **IIIa-b**. All the synthesized compounds were characterized by elemental analysis, FT-IR, ^{1}H NMR and ^{13}C NMR spectral data. All the synthesized compounds were screened against six bacterial pathogens, namely *B. subtilis, C. tetani, S. pneumoniae, S. typhi, V. cholerae, E. coli* and for antifungal activity against two fungal pathogens, *A. fumigatus* and *C. albicans* using the broth microdilution MIC method. Some of the compounds were found to be equipotent or more potent than commercial drugs against most of employed strains, as evident from the screening data.

Keywords: *Chromene • MCR • Pyrazole-4-carbaldehyde • Antimicrobial activity*

1. Introduction

The steadily increasing microbial resistance to existing first drugs is a serious problem in antimicrobial cure and necessitates continuing research into new classes of antimicrobials [1]. Moreover, the progression of drug-resistant strains has contributed to the inefficiency of antimicrobial therapy. This has led to enormous interest in antibacterial research, and we strongly believe that there is an urgent call for development of new drugs with diverse and unique structures and with novel mechanisms of action from that of existing first line drugs. Consequently, this area of research is significant and attracts much attention of an increasing number of medicinal chemists.

Recently, we have been particularly interested in the synthesis of *N*-arylpyrazole and 4*H*-chromene incorporating structures for antimicrobial evaluation [2] on the premise that *N*-arylpyrazole is a chemically useful synthon bearing diverse biological activities like antimicrobial [3-5], anti-inflammatory (COX-2 inhibitor and ulcerogenic activity) [4], antitubercular [5], antitumor [6,7], antiangiogenesis [7], anti-parasitic [8], antiviral [9], analgesic and anxiolytic activity [10]. Moreover, the 4*H*-pyrano[3,2-*c*]chromene nucleus is a fertile source of biologically important molecules possessing a wide spectrum of pharmacological activities, such as antimicrobial [11], antiviral [12], mutagenicity [13], antiproliferative [14], sex pheromone [15], antitumor [16], cancer therapy [17] and central nervous system activity [18].

Despite their importance from pharmacological and synthetic point of views, comparatively few modified methods for the preparation of 4-aryl-4*H*-pyrano[3,2-*c*]chromene derivatives [19] have been reported using piperidine, morpholine, K_2CO_3, diammonium hydrogen phosphate, $H_6[P_2W_{18}O_{62}]\cdot 18H_2O$, tetrabutylammonium bromide or water using various aromatic/heterocyclic aldehydes, wherein not a single reference have been found where 3-methyl-5-aryloxy-1-aryl-1*H*-pyrazole-4-carbaldehyde is used. Thus, in view of the biological significance of 4*H*-chromene, a modification of the 4-position on 4*H*-pyrano[3,2-*c*]chromene by 3-methyl-5-phenoxy-1-phenyl-1*H*-pyrazole is undertaken to check whether it may bring significant changes in the bioactivities of 4*H*-chromene derivatives. As a part of our current studies in developing new antimicrobial agents *via* combination of two therapeutically active moieties

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[20], we have prepared and report herein pyrano[3,2-*c]chromene* **IVa-x** derivatives *via* MCR approach. The identity of all the products was confirmed using elemental analysis, FT-IR, ^{1}H NMR and ^{13}C NMR spectrometry. The compounds were subjected to an *in vitro* antimicrobial screening against a representative panel of eight human pathogens, of which three Gram-positive bacterial pathogens *Streptococcus pneumoniae*, *Clostridium tetani*, *Bacillus subtilis*, three Gram-negative bacterial pathogens *Salmonella typhi*, *Vibrio cholerae*, *Escherichia coli* and two fungal pathogens *Aspergillus fumigatus* and *Candida albicans*, using broth microdilution MIC (Minimum Inhibitory Concentration) method [21].

2. Experimental Procedure

2.1. Chemistry

Solvents used were of analytical grade. Phenyl hydrazine was distilled before used; all other reagents were commercially available and used without further purification. All melting points were taken in open capillaries and are uncorrected. Thin-layer chromatography (TLC, on aluminium plates precoated with silica gel, $60F_{254}$, 0.25 mm thickness) (Merck, Darmstadt, Germany) was used for monitoring the progress of all reactions, purity and homogeneity of the synthesized compounds; eluent-hexane:ethyl acetale 6:4. UV radiation and/or iodine were used as the visualizing agents. Elemental analysis (% C, H, N) was carried out by a Perkin-Elmer 2400 series-II elemental analyzer (Perkin-Elmer, USA) and all compounds were within ±0.4% of calculation. The IR spectra were recorded in KBr on a Perkin-Elmer Spectrum GX FT-IR Spectrophotometer (Perkin-Elmer, USA), and only the characteristic peaks were reported in cm^{-1}. ^{1}H-NMR and ^{13}C-NMR spectra were recorded in DMSO- d_6 on a Bruker Avance 400F (MHz) spectrometer (Bruker Scientific Corporation Ltd., Switzerland) using solvent peak as internal standard at 400 MHz and 100 MHz respectively. Chemical shifts were reported in parts per million (ppm). Mass spectra were scanned on a Shimadzu LCMS 2010 spectrometer (Shimadzu, Tokyo, Japan).

2.2. General procedure for the synthesis of 1-aryl-5-chloro-3-methyl-1H-pyrazole-4-carbaldehyde

1-Aryl-5-chloro-3-methyl-1*H*-pyrazole-4-carbaldehydes were prepared, according to literature procedure [22], by Vilsmeier-Haack reaction of 3-methyl-1-aryl-1*H*-pyrazol-5(4*H*)-one (Scheme 1).

2.3. General procedure for the synthesis of 3-methyl-5-aryloxy-1-aryl-1H-pyrazole-4-carbaldehyde(Ia-l)

3-Methyl-5-aryloxy-1-aryl-1*H*-pyrazole-4-carbaldehydes **Ia-l** were prepared, according to literature procedure [23], by nucleophilic reaction of 1-Aryl-5-chloro-3-methyl-1*H*-pyrazole-4-carbaldehyde and the respective phenol in presence of basic catalyst (K_2CO_3) (Scheme 1).

2.4. General procedure for the synthesis of 4-hydroxy-6-substituted-2H-chromen-2-one(IIIa-b)

4-Hydroxy-6-(substituted)-2*H*-chromen-2-one was synthesized, according to literature procedure [24] by the solid phase reaction of malonic acid and phenol in phosphorous oxychloride in the presence of zinc chloride (Scheme 1).

2.5. General procedure for the synthesis of 2-amino-9-(un)substituted-4-(5-(4-(un)substitutedaryloxy)-1-(3/4-(un) substitutedaryl)-3-methyl-1H-pyrazol-4-yl)-5-oxo-4,5-dihydropyrano[3,2-c] chromene-3-carbonitrile(IVa-x)

A mixture of the appropriate 1*H*-pyrazole-4-carbaldehyde **Ia-l** (30 mmol), malononitrile **II** (30 mmol) and 4-hydroxy coumarin **IIIa-b** (30 mmol) in ethanol (20 mL) containing a catalytic amount of piperidine was stirred and refluxed for 1-1.5 h. Upon completion of the reaction as determined by TLC (ethyl acetate:hexane::1:1), the reaction mixture was cooled to room temperature. The solid separated was filtered and washed with ethanol to obtain the pure compounds **IVa-x.** Physical, analytical and spectroscopic characterization data of the synthesized compounds **Ia-l** and **IVa-x** are given below:

2.6. Spectral data of compounds Ia-l and IVa-x

3-Methyl-5-phenoxy-1-phenyl-1*H*-pyrazole-4-carbaldehyde (Ia): Yield: 92%; m.p.: 115-116 °C; IR (KBr, v, cm^{-1}): 2995 (ArC-H str.), 1695 (-C=O str.), 1200 (C-O-C ether str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 2.57 (s, 3H, CH_3), 7.03-7.62 (m, 10H, Ar-H), 9.62 (S, 1H, CHO). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 14.56 (Ar-CH_3), 108.92, 116.21, 122.81, 124.65, 128.01, 129.24, 130.25, 136.90, 150.83, 152.52, 157.04 (Ar-C), 183.09 (C=O); Anal. Calcd. for $C_{17}H_{14}N_2O_2$ (279.31 gm/mole): C, 73.37; H, 5.07; N, 10.07%. Found: C, 73.43; H, 5.22; N, 10.13%.

3-Methyl-5-(4-methylphenoxy)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (Ib): Yield: 82%; m.p.: 124-126 °C; IR (KBr, v, cm^{-1}): 3005 (ArC-H str.), 1715 (-C=O str.), 1205 (C-O-C ether str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 1.98 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 7.08-7.67 (m, 9H, Ar-H), 9.60 (S, 1H, CHO). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 14.35, 20.43 (Ar-CH_3), 108.77, 116.33, 123.02, 124.44, 127.97, 129.25, 130.63, 137.01, 150.78, 152.64, 157.06 (Ar-C), 182.27 (C=O); Anal. Calcd. for $C_{18}H_{16}N_2O_2$ (292.33 gm/mole): C, 73.95; H, 5.52; N, 9.58%. Found: C, 74.05; H, 5.45; N, 9.37%.

3-Methyl-5-(4-chlorophenoxy)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (Ic): Yield: 88%; m.p.: 118-119 °C; IR (KBr, v, cm^{-1}): 2975 (ArC-H str.), 1690 (-C=O str.), 1200 (C-O-C ether str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 2.18 (s, 3H, CH_3), 6.95-7.52 (m, 9H, Ar-H), 9.57 (S, 1H, CHO). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 14.08 (Ar-CH_3), 108.90, 116.33, 122.67, 124.42, 128.03, 129.54, 130.33, 137.05, 150.73, 152.58, 157.09 (Ar-C), 182.01 (C=O); Anal. Calcd. for $C_{17}H_{13}ClN_2O_2$ (312.75 gm/mole): C, 65.29; H, 4.19; N, 8.96%. Found: C, 65.38; H, 4.27; N, 9.15%.

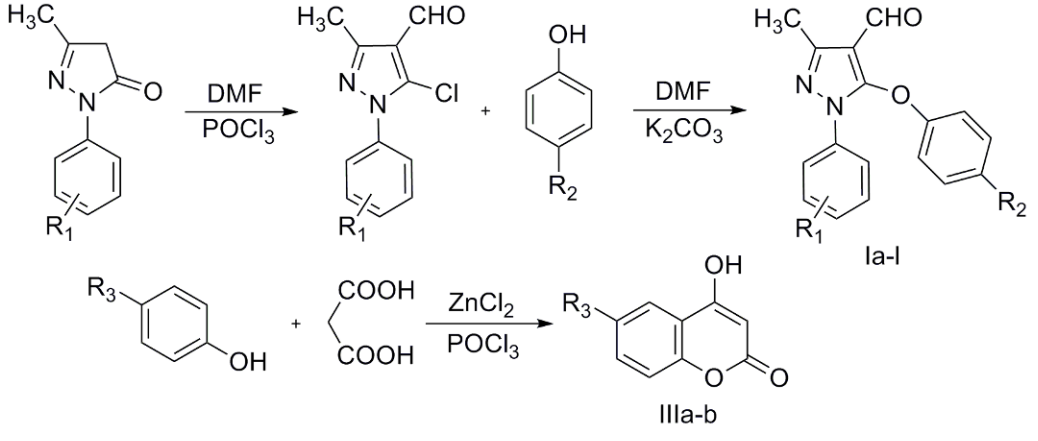
3-Methyl-5-(4-methoxyphenoxy)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (Id): Yield: 95%; m.p.: 148-150 °C; IR (KBr, v, cm^{-1}): 3020 (ArC-H str.), 1720 (-C=O str.), 1195 (C-O-C ether str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 1.82 (s, 3H, CH_3), 3.37 (s, 3H, OCH_3), 6.92-7.54 (m, 9H, Ar-H), 9.58 (S, 1H, CHO). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 14.37 (Ar-CH_3), 54.15 (Ar-OCH_3), 108.88, 116.33, 122.87, 124.84, 128.09, 129.33, 130.26, 137.03, 151.03, 152.55, 157.09 (Ar-C), 183.88 (C=O); Anal. Calcd. for $C_{18}H_{16}N_2O_3$ (308.33 gm/mole): C, 70.12; H, 5.23; N, 9.09%. Found: C, 70.27; H, 5.18; N, 8.93%.

3-Methyl-5-phenoxy-1-(4-methylphenyl)-1*H*-pyrazole-4-carbaldehyde (Ie): Yield: 78%; m.p.: 132-134 °C; IR (KBr, v, cm^{-1}): 3025 (ArC-H str.), 1705 (-C=O str.), 1210 (C-O-C ether str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 2.27 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 7.01-7.70 (m, 9H, Ar-H), 9.62 (S, 1H, CHO). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 14.19, 20.79 (Ar-CH_3), 108.87, 116.32, 122.45, 124.55, 128.23, 129.34, 130.67, 136.88, 150.87, 152.61, 157.06 (Ar-C), 184.25 (C=O); Anal. Calcd. for $C_{18}H_{16}N_2O_2$ (292.33 gm/mole): C, 73.95; H, 5.52; N, 9.58%. Found: C, 74.14; H, 5.36; N, 9.64%.

3-Methyl-5-(4-methylphenoxy)-1-(4-methylphenyl)-1*H*-pyrazole-4-carbaldehyde (If): Yield: 93%; m.p.: 127-128 °C; IR (KBr, v, cm^{-1}): 2955 (ArC-H str.), 1730 (-C=O str.), 1205 (C-O-C ether str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 2.10 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 7.09-7.72 (m, 8H, Ar-H), 9.60 (S, 1H, CHO). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 14.60, 20.28, 20.80 (Ar-CH_3), 108.99, 115.93, 122.81, 124.67, 128.08, 129.87, 131.03, 137.05, 150.64, 152.67, 157.13 (Ar-C), 184.45 (C=O); Anal. Calcd. for $C_{19}H_{18}N_2O_2$ (306.36 gm/mole): C, 74.49; H, 5.92; N, 9.14%. Found: C, 74.52; H, 6.16; N, 9.01%.

3-Methyl-5-(4-chlorophenoxy)-1-(4-methylphenyl)-1*H*-pyrazole-4-carbaldehyde (Ig): Yield: 85%; m.p.: 110-111 °C; IR (KBr, v, cm^{-1}): 3010 (ArC-H str.), 1715 (-C=O str.), 1210 (C-O-C ether str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 2.19 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 7.03-7.63 (m, 8H, Ar-H), 9.59 (S, 1H, CHO). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 14.40, 20.82 (Ar-CH_3), 108.66, 116.86, 122.67, 124.34, 128.22, 129.44, 130.65, 137.17, 151.05, 153.02, 157.01 (Ar-C), 183.92 (C=O); Anal. Calcd. for $C_{18}H_{15}ClN_2O_2$ (326.78 gm/mole): C, 66.16; H, 4.63; N, 8.57%. Found: C, 66.35; H, 4.43; N, 8.33%.

3-Methyl-5-(4-methoxyphenoxy)-1-(4-methylphenyl)-1*H*-pyrazole-4-carbaldehyde (Ih): Yield: 79%; m.p.: 147-148 °C; IR (KBr, v, cm^{-1}): 2990 (ArC-H str.), 1695 (-C=O str.), 1210 (C-O-C ether str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 2.30 (s, 3H,



Scheme 1. Synthetic pathway for the compounds **Ia-l** and **IIIa-b**.

CH_3), 2.34 (s, 3H, CH_3), 3.42 (s, 3H, OCH_3), 6.94-7.65 (m, 8H, Ar-H), 9.63 (S, 1H, CHO). ^{13}C NMR (100 MHz, DMSO-*d_6*) δ_C (ppm): 14.22, 20.80 (Ar-CH_3), 54.85 (Ar-OCH_3), 108.97, 116.90, 123.05, 124.52, 128.14, 129.29, 130.41, 137.04, 150.57, 152.88, 157.15 (Ar-C), 183.07 (C=O); Anal. Calcd. for $C_{19}H_{18}N_2O_3$ (322.36 gm/mole): C, 70.79; H, 5.63; N, 8.69%. Found: C, 70.94; H, 5.44; N, 8.78%.

3-Methyl-5-phenoxy-1-(3-chlorophenyl)-1*H*-pyrazole-4-carbaldehyde (Ii): Yield: 77%; m.p.: 153-155 °C; IR (KBr, v, cm^{-1}): 3015 (ArC-H str.), 1700 (-C=O str.), 1195 (C-O-C ether str.); ^{1}H NMR (400 MHz, DMSO-*d_6*) δ_H (ppm): 2.45 (s, 3H, CH_3), 6.90-7.68 (m, 9H, Ar-H), 9.56 (S, 1H, CHO). ^{13}C NMR (100 MHz, DMSO-*d_6*) δ_C (ppm): 14.18 (Ar-CH_3), 108.88, 116.33, 119.22, 121.99, 123.89, 127.84, 129.42, 130.25, 137.03, 142.57, 150.81, 151.92, 157.07 (Ar-C), 183.14 (C=O); Anal. Calcd. for $C_{17}H_{13}ClN_2O_2$ (312.75 gm/mole): C, 65.29; H, 4.19; N, 8.96%. Found: C, 65.40; H, 4.05; N, 9.16%.

3-Methyl-5-(4-methylphenyloxy)-1-(3-chlorophenyl)-1*H*-pyrazole-4-carbaldehyde (Ij): Yield: 90%; m.p.: 160-162 °C; IR (KBr, v, cm^{-1}): 2965 (ArC-H str.), 1710 (-C=O str.), 1200 (C-O-C ether str.); ^{1}H NMR (400 MHz, DMSO-*d_6*) δ_H (ppm): 2.33 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 7.10-7.55 (m, 8H, Ar-H), 9.64 (S, 1H, CHO). ^{13}C NMR (100 MHz, DMSO-*d_6*) δ_C (ppm): 14.27, 20.29 (Ar-CH_3), 108.95, 116.55, 119.13, 122.87, 124.43, 128.11, 129.24, 130.37, 136.88, 142.12, 151.04, 152.02, 157.10 (Ar-C), 182.33 (C=O); Anal. Calcd. for $C_{18}H_{15}ClN_2O_2$ (326.78 gm/mole): C, 66.16; H, 4.63; N, 8.57%. Found: C, 66.39; H, 4.29; N, 8.41%.

3-Methyl-5-(4-chlorophenoxy)-1-(3-chlorophenyl)-1*H*-pyrazole-4-carbaldehyde (Ik): Yield: 87%; m.p.: 142-144 °C; IR (KBr, v, cm^{-1}): 3015 (ArC-H str.), 1685 (-C=O str.), 1215 (C-O-C ether str.); ^{1}H NMR (400 MHz, DMSO-*d_6*) δ_H (ppm): 2.37 (s, 3H, CH_3), 7.03-7.61 (m, 8H, Ar-H), 9.61 (S, 1H, CHO). ^{13}C NMR (100 MHz, DMSO-*d_6*) δ_C (ppm): 14.12 (Ar-CH_3), 108.88, 116.33, 119.47, 122.67, 124.61, 128.22, 129.63, 130.48, 136.96, 142,27, 150.97, 153.01, 157.07 (Ar-C), 183.67 (C=O); Anal. Calcd. for $C_{17}H_{12}Cl_2N_2O_2$ (347.20 gm/mole): C, 58.81; H, 3.48; N, 8.07%. Found: C, 59.07; H, 3.71; N, 7.93%.

3-Methyl-5-(4-methoxyphenoxy)-1-(3-chlorophenyl)-1*H*-pyrazole-4-carbaldehyde (Il): Yield: 80%; m.p.: 131-132 °C; IR (KBr, v, cm^{-1}): 2985 (ArC-H str.), 1725 (-C=O str.), 1210 (C-O-C ether str.); ^{1}H NMR (400 MHz, DMSO-*d_6*) δ_H (ppm): 2.20 (s, 3H, CH_3), 3.41 (s, 3H, OCH_3), 7.02-7.62 (m, 8H, Ar-H), 9.60 (S, 1H, CHO). ^{13}C NMR (100 MHz, DMSO-*d_6*) δ_C (ppm): 14.42 (Ar-CH_3), 54.40 (Ar-OCH_3), 108.72, 116.24, 118.97, 123.99, 124.69, 127.94, 129.31, 131.55, 137.23, 141.98, 150.74, 152.88, 157.05 (Ar-C), 184.02 (C=O); Anal. Calcd. for $C_{18}H_{15}ClN_2O_3$ (342.78 gm/mole): C, 63.07; H, 4.41; N, 8.17%. Found: C, 63.28; H, 4.13; N, 8.28%.

2-Amino-4-(3-methyl-5-phenoxy-1-phenyl-1*H*-pyrazol-4-yl)-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (IVa): Yield: 80%; m.p.: 250-251 °C; IR (KBr, v, cm^{-1}): 3380 & 3170 (asym. & sym. str. of -NH_2), 2205 (-C≡N str.), 1700 (-C=O str.); ^{1}H NMR (400 MHz, DMSO-*d_6*) δ_H (ppm): 1.88 (s, 3H, CH_3), 4.42 (s, 1H, H4), 6.38-7.54 (m, 16H, NH_2+Ar-H). ^{13}C NMR (100 MHz, DMSO-*d_6*) δ_C (ppm): 13.07 (Ar-CH_3), 26.50 (C4), 56.16 (C-CN), 103.08, 110.21, 112.48, 114.25, 116.86, 119.57, 120.94, 122.55, 124.40, 126.95, 129.31, 130.21, 132.18, 132.88, 137.86, 146.03, 148.39, 152.16, 153.43, 153.89, 158.48 (Ar-C), 160.11 (C=O); Anal. Calcd. for $C_{29}H_{20}N_4O_4$ (488.49 gm/mole): C, 71.30; H, 4.13; N, 11.47%. Found: C, 71.52; H, 4.36; N, 11.22%.

2-Amino-4-(3-methyl-1-phenyl-5-(4-methylphenoxy)-1*H*-pyrazol-4-yl)-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (IVb): Yield: 78%; m.p.: 230-223 °C; IR (KBr, v, cm^{-1}): 3450 & 3150 (asym. & sym. str. of -NH_2), 2200 (-C≡N str.), 1680 (-C=O str.); ^{1}H NMR (400 MHz, DMSO-*d_6*) δ_H (ppm): 1.76 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 4.43 (s, 1H, H4), 6.30-7.52 (m, 15H, NH_2+Ar-H). ^{13}C NMR (100 MHz, DMSO-*d_6*) δ_C (ppm): 13.06, 20.23 (Ar-CH_3), 26.54 (C4), 56.11 (C-CN), 102.29, 110.48, 112.69, 113.69, 116.56, 119.97, 121.54, 122.70, 124.50, 127.05, 129.65, 130.11, 132.16, 132.78, 138.06, 145.83, 148.19, 152.26, 153.43, 153.80, 158.58 (Ar-C), 160.07 (C=O); Anal. Calcd. for $C_{30}H_{22}N_4O_4$ (502.52 gm/mole): C, 71.70; H, 4.41; N, 11.15%. Found: C, 71.52; H, 4.36; N, 10.98%.

2-Amino-4-(5-(4-chlorophenoxy)-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (IVc): Yield: 75%; m.p.: 208-210 °C; IR (KBr, v, cm^{-1}): 3400 & 3200 (asym. & sym. str. of -NH_2), 2180 (-C≡N str.), 1710 (-C=O str.); ^{1}H NMR (400 MHz, DMSO-*d_6*) δ_H (ppm): 2.10 (s, 3H, CH_3), 4.40 (s, 1H, H4), 6.40-7.59 (m, 15H, NH_2+Ar-H). ^{13}C NMR (100 MHz, DMSO-*d_6*) δ_C (ppm): 13.05 (Ar-CH_3) 26.52 (C4), 55.90 (C-CN), 102.17, 110.34, 112.47, 113.86, 115.56, 119.77, 120.34, 122.38, 123.51, 126.15, 128.55, 131.01, 132.26, 132.88, 137.26, 144.85, 148.09, 152.14, 153.43, 154.21, 158.52 (Ar-C), 160.17 (C=O); Anal. Calcd. for $C_{29}H_{19}ClN_4O_4$ (522.94 gm/mole): C, 66.61; H, 3.66; N, 10.71%. Found: C, 66.70; H, 3.46; N, 10.98%.

2-Amino-4-(5-(4-methoxyphenoxy)-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (IVd): Yield: 77%; m.p.: 262-263 °C; IR (KBr, v, cm^{-1}): 3340 & 3150 (asym. & sym. str. of -NH_2), 2190 (-C≡N str.),

1680 (-C=O str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 1.96 (s, 3H, CH_3), 3.39 (s, 3H, OCH_3), 4.45 (s, 1H, H4), 6.38-7.55 (m, 15H, NH_2+Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 13.02 (Ar-CH_3), 26.58 (C4), 54.30 (Ar-OCH_3), 55.85 (C-CN), 103.48, 111.08, 112.19, 113.66, 115.86, 118.99, 121.44, 122.66, 124.59, 126.95, 128.61, 130.31, 132.16, 132.88, 138.02, 144.83, 147.49, 152.22, 153.44, 154.13, 158.61 (Ar-C), 160.15 (C=O); Anal. Calcd. for $C_{30}H_{22}N_4O_5$ (518.52 gm/mole): C, 69.49; H, 4.28; N, 10.81%. Found: C, 69.61; H, 4.36; N, 10.97%.

2-Amino-4-(3-methyl-5-phenoxy-1-(4-methylphenyl)-1*H*-pyrazol-4-yl)-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (IVe): Yield: 68%; m.p.: 221-222 °C; IR (KBr, v, cm^{-1}): 3420 & 3195 (asym. & sym. str. of -NH_2), 2210 (-C≡N str.), 1715 (-C=O str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 2.15 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 4.43 (s, 1H, H4), 6.42-7.59 (m, 15H, NH_2+Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 13.09, 20.85 (Ar-CH_3), 26.55 (C4), 56.03 (C-CN), 103.59, 110.98, 111.96, 113.68, 116.55, 119.07, 120.94, 122.77, 124.55, 127.04, 129.15, 130.21, 131.76, 132.75, 138.16, 145.23, 148.49, 152.28, 153.43, 153.88, 158.59 (Ar-C), 160.05 (C=O); Anal. Calcd. for $C_{30}H_{22}N_4O_4$ (502.52 gm/mole): C, 71.70; H, 4.41; N, 11.15%. Found: C, 71.55; H, 4.56; N, 10.99%.

2-Amino-4-(3-methyl-1-(4-methylphenyl)-5-(4-methylphenoxy)-1*H*-pyrazol-4-yl)-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (IVf): Yield: 65%; m.p.: 257-259 °C; IR (KBr, v, cm^{-1}): 3415 & 3145 (asym. & sym. str. of -NH_2), 2185 (-C≡N str.), 1725 (-C=O str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 1.92 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 4.47 (s, 1H, H4), 6.38-7.50 (m, 14H, NH_2+Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 13.03, 20.21, 20.82 (Ar-CH_3), 26.51 (C4), 56.09 (C-CN), 102.99, 111.38, 112.45, 114.28, 115.76, 119.33, 121.83, 121.96, 123.51, 127.15, 129.32, 130.11, 132.23, 132.80, 138.34, 145.82, 148.48, 152.27, 153.15, 153.43, 158.44 (Ar-C), 160.11 (C=O); Anal. Calcd. for $C_{31}H_{24}N_4O_4$ (516.55 gm/mole): C, 72.08; H, 4.68; N, 10.85%. Found: C, 72.32; H, 4.46; N, 10.66%.

2-Amino-4-(5-(4-chlorophenoxy)-3-methyl-1-(4-methylphenyl)-1*H*-pyrazol-4-yl)-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (IVg): Yield: 62%; m.p.: 215-216 °C; IR (KBr, v, cm^{-1}): 3395 & 3195 (asym. & sym. str. of -NH_2), 2200 (-C≡N str.), 1690 (-C=O str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 2.28 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 4.49 (s, 1H, H4), 6.42-7.45 (m, 14H, NH_2+Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 13.07, 20.79 (Ar-CH_3), 26.49 (C4), 56.19 (C-CN), 102.89, 110.84, 112.44, 112.99, 116.26, 119.43, 120.57, 121.84, 124.34, 126.15, 129.03, 130.41, 132.17, 132.88, 138.36, 145.82, 147.29, 152.66, 153.44, 153.21, 158.39 (Ar-C), 160.13 (C=O); Anal. Calcd. for $C_{30}H_{21}ClN_4O_4$ (536.97 gm/mole): C, 67.10; H, 3.94; N, 10.43%. Found: C, 67.40; H, 3.76; N, 10.25%.

2-Amino-4-(5-(4-methoxyphenoxy)-3-methyl-1-(4-methylphenyl)-1*H*-pyrazol-4-yl)-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (IVh): Yield: 65%; m.p.: 274-275 °C; IR (KBr, v, cm^{-1}): 3375 & 3210 (asym. & sym. str. of -NH_2), 2195 (-C≡N str.), 1730 (-C=O str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 2.32 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 3.43 (s, 3H, OCH_3), 4.47 (s, 1H, H4), 6.33-7.58 (m, 14H, NH_2+Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 13.02, 20.75 (Ar-CH_3), 26.53 (C4), 55.01 (Ar-OCH_3), 56.17 (C-CN), 102.36, 110.12, 111.06, 113.33, 116.16, 119.72, 121.31, 121.98, 123.51, 127.21, 128.95, 130.18, 132.36, 132.88, 137.56, 144.33, 147.29, 152.36, 153.52, 154.35, 158.56 (Ar-C), 160.03 (C=O); Anal. Calcd. for $C_{31}H_{24}N_4O_5$ (532.17 gm/mole): C, 69.92; H, 4.54; N, 10.52%. Found: C, 70.12; H, 4.33; N, 10.59%.

2-Amino-4-(1-(3-chlorophenyl)-3-methyl-5-phenoxy-1*H*-pyrazol-4-yl)-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (IVi): Yield: 72%; m.p.: 225-227 °C; IR (KBr, v, cm^{-1}): 3345 & 3180 (asym. & sym. str. of -NH_2), 2190 (-C≡N str.), 1695 (-C=O str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 2.40 (s, 3H, CH_3), 4.45 (s, 1H, H4), 6.46-7.54 (m, 15H, NH_2+Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 13.05 (Ar-CH_3), 26.46 (C4), 55.98 (C-CN), 103.20, 111.02, 112.57, 115.81, 116.68, 119.70, 119.84, 121.16, 122.59, 124.80, 126.99, 127.53, 129.88, 131.46, 133.20, 134.05, 138.90, 145.44, 148.33, 151.20, 152.21, 154.57, 157.96 (Ar-C), 160.09 (C=O); Anal. Calcd. for $C_{29}H_{19}ClN_4O_4$ (522.94 gm/mole): C, 66.61; H, 3.66; N, 10.71%. Found: C, 66.39; H, 3.73; N, 10.83%.

2-Amino-4-(1-(3-chlorophenyl)-3-methyl-5-(4-methylphenoxy)-1*H*-pyrazol-4-yl)-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (IVj): Yield: 65%; m.p.: 245-247 °C; IR (KBr, v, cm^{-1}): 3445 & 3205 (asym. & sym. str. of -NH_2), 2185 (-C≡N str.), 1700 (-C=O str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 2.32 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 4.40 (s, 1H, H4), 6.41-7.49 (m, 14H, NH_2+Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 13.08, 20.25 (Ar-CH_3), 26.51 (C4), 55.92 (C-CN), 102.49, 110.38, 112.07, 114.87, 117.08, 119.36, 119.85, 120.56, 121.99, 124.30, 126.03, 127.55, 129.17, 130.66, 133.28, 134.48, 138.70, 144.40, 146.92, 151.28, 152.77, 154.47, 158.51 (Ar-C), 160.14 (C=O); Anal. Calcd. for $C_{30}H_{21}ClN_4O_4$ (536.97 gm/mole): C, 67.10; H, 3.94; N, 10.43%. Found: C, 67.35; H, 4.09; N, 10.22%.

2-Amino-4-(5-(4-chlorophenoxy)-1-(3-chlorophenyl)-3-methyl-1*H*-pyrazol-4-yl)-5-oxo-4,5-

dihydropyrano[3,2-*c*]chromene-3-carbonitrile (IVk): Yield: 63%; m.p.: 238-240 °C; IR (KBr, v, cm^{-1}): 3400 & 3200 (asym. & sym. str. of -NH_2), 2200 (-C≡N str.), 1710 (-C=O str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 2.39 (s, 3H, CH_3), 4.45 (s, 1H, H4), 6.48-7.58 (m, 14H, NH_2+Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 13.05 (Ar-CH_3), 26.47 (C4), 55.83 (C-CN), 102.19, 111.35, 112.57, 115.81, 116.68, 119.70, 119.84, 121.16, 122.59, 124.80, 126.99, 127.53, 129.88, 131.46, 133.20, 134.05, 138.90, 145.44, 148.96, 152.20, 153.57, 154.42, 158.61 (Ar-C), 160.01 (C=O); Anal. Calcd. for $C_{29}H_{18}Cl_2N_4O_4$ (557.38 gm/mole): C, 62.49; H, 3.26; N, 10.05%. Found: C, 62.34; H, 3.09; N, 9.88%; MS *m/z*: 558.6 $[M+1]^+$.

2-Amino-4-(1-(3-chlorophenyl)-5-(4-methoxyphenoxy)-3-methyl-1*H*-pyrazol-4-yl)-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (IVl): Yield: 69%; m.p.: 277-279 °C; IR (KBr, v, cm^{-1}): 3385 & 3180 (asym. & sym. str. of -NH_2), 2210 (-C≡N str.), 1690 (-C=O str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 2.23 (s, 3H, CH_3), 3.40 (s, 3H, OCH_3), 4.47 (s, 1H, H4), 6.44-7.51 (m, 14H, NH_2+Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 13.07 (Ar-CH_3), 26.52 (C4), 53.70 (Ar-OCH_3), 55.93 (C-CN), 103.66, 111.93, 112.14, 115.77, 117.05, 119.34, 119.96, 121.34, 122.41, 124.47, 125.92, 127.31, 129.07, 131.33, 132.89, 134.13, 138.16, 143.99, 147.06, 151.97, 153.49, 154.63, 158.37 (Ar-C), 160.06 (C=O); Anal. Calcd. for $C_{30}H_{21}ClN_4O_5$ (552.96 gm/mole): C, 65.16; H, 3.83; N, 10.13%. Found: C, 65.35; H, 4.09; N, 9.91%.

2-Amino-4-(3-methyl-5-phenoxy-1-phenyl-1*H*-pyrazol-4-yl)-9-methyl-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (IVm): Yield: 73%; m.p.: 254-256 °C; IR (KBr, v, cm^{-1}): 3395 & 3195 (asym. & sym. str. of -NH_2), 2196 (-C≡N str.), 1700 (-C=O str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 2.35 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 4.41 (s, 1H, H4), 6.36-7.40 (m, 15H, NH_2+Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 13.08, 20.90 (Ar-CH_3), 26.54 (C4), 56.04 (C-CN), 102.72, 110.87, 112.18, 114.13, 114.99, 116.01, 118.15, 120.62, 122.38, 127.45, 130.33, 133.01, 133.52, 136.92, 145.72, 147.23, 149.27, 150.72, 152.58, 155.38, 158.45 (Ar-C), 160.12 (C=O); Anal. Calcd. for $C_{30}H_{22}N_4O_4$ (502.52 gm/mole): C, 71.70; H, 4.41; N, 11.15%. Found: C, 71.95; H, 4.55; N, 10.97%.

2-Amino-4-(3-methyl-1-phenyl-5-(4-methylphenoxy)-1*H*-pyrazol-4-yl)-9-methyl-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (IVn): Yield: 74%; m.p.: 242-243 °C; IR (KBr, v, cm^{-1}): 3355 & 3175 (asym. & sym. str. of -NH_2), 2205 (-C≡N str.), 1715 (-C=O str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 1.99 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 4.46 (s, 1H, H4), 6.45-7.59 (m, 14H, NH_2+Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 13.04, 20.22, 20.85 (Ar-CH_3), 26.55 (C4), 56.14 (C-CN), 103.45, 111.52, 112.97, 114.33, 114.92, 116.68, 118.73, 121.35, 122.88, 126.13, 128.42, 133.78, 134.12, 137.76, 146.17, 148.25, 149.72, 151.34, 153.01, 154.75, 158.40 (Ar-C), 160.17 (C=O); Anal. Calcd. for $C_{31}H_{24}N_4O_4$ (516.55 gm/mole): C, 72.08; H, 4.68; N, 10.85%. Found: C, 72.37; H, 4.40; N, 10.60%.

2-Amino-4-(5-(4-chlorophenoxy)-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-9-methyl-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (IVo): Yield: 69%; m.p.: 218-220 °C; IR (KBr, v, cm^{-1}): 3375 & 3200 (asym. & sym. str. of -NH_2), 2210 (-C≡N str.), 1705 (-C=O str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 2.05 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 4.40 (s, 1H, C4), 6.47-7.53 (m, 14H, NH_2+Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 13.01, 20.97 (Ar-CH_3), 26.49 (C4), 56.01 (C-CN), 102.01, 110.92, 112.33, 113.87, 114.54, 116.21, 119.02, 121.45, 123.08, 127.02, 129.53, 133.61, 133.71, 138.12, 146.12, 148.75, 149.83, 150.68, 152.25, 153.95, 158.32 (Ar-C), 160.16 (C=O); Anal. Calcd. for $C_{30}H_{21}ClN_4O_4$ (536.97 gm/mole): C, 67.10; H, 3.94; N, 10.43%. Found: C, 67.32; H, 4.15; N, 10.61%.

2-Amino-4-(5-(4-methoxyphenoxy)-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-9-methyl-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (IVp): Yield: 72%; m.p.: 271-273 °C; IR (KBr, v, cm^{-1}): 3430 & 3165 (asym. & sym. str. of -NH_2), 2200 (-C≡N str.), 1725 (-C=O str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 2.36 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 3.37 (s, 3H, OCH_3), 4.41 (s, 1H, H4), 6.35-7.54 (m, 14H, NH_2+Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 13.08, 20.92 (Ar-CH_3), 26.57 (C4), 55.29 (Ar-OCH_3), 56.04 (C-CN), 102.23, 110.39, 112.47, 114.62, 114.77, 116.32, 119.99, 121.54, 122.27, 127.03, 129.66, 133.65, 133.87, 138.12, 146.09, 148.13, 149.68, 150.45, 153.39, 154.90, 158.63 (Ar-C), 160.20 (C=O); Anal. Calcd. for $C_{31}H_{24}N_4O_5$ (532.55 gm/mole): C, 69.92; H, 4.54; N, 10.52%. Found: C, 70.18; H, 4.29; N, 10.68%.

2-Amino-4-(3-methyl-5-phenoxy-1-(4-methylphenyl)-1*H*-pyrazol-4-yl)-9-methyl-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (IVq): Yield: 68%; m.p.: 211-213 °C; IR (KBr, v, cm^{-1}): 3400 & 3100 (asym. & sym. str. of -NH_2), 2190 (-C≡N str.), 1730 (-C=O str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 2.20 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 4.40 (s, 1H, H4), 6.42-7.40 (m, 14H, NH_2+Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 13.04, 20.83, 20.88 (Ar-CH_3), 26.52 (C4), 56.14 (C-CN), 102.27, 110.34, 112.51, 114.08, 116.41, 119.97, 121.64, 122.21, 122.85, 129.69, 130.05, 133.65, 133.91, 135.68, 136.50, 145.38, 147.71, 150.44, 153.45, 156.02, 158.60 (Ar-C), 160.15 (C=O); Anal. Calcd. for $C_{31}H_{24}N_4O_4$ (516.55 gm/mole):

C, 72.08; H, 4.68; N, 10.85%. Found: C, 72.33; H, 4.47; N, 10.68%; MS *m/z*: 517.2 $[M+1]^+$.

2-Amino-4-(3-methyl-1-(4-methylphenyl)-5-(4-methylphenoxy)-1*H*-pyrazol-4-yl)-9-methyl-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (IVr): Yield: 67%; m.p.: 269-270 °C; IR (KBr, v, cm^{-1}): 3385 & 3190 (asym. & sym. str. of $-NH_2$), 2180 (-C≡N str.), 1690 (-C=O str.); ^1H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 2.10 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 4.48 (s, 1H, H4), 6.44-7.49 (m, 13H, NH_2+Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 13.05, 20.24, 20.85, 20.99 (Ar-CH_3), 26.57 (C4), 56.18 (C-CN), 102.39, 110.38, 112.03, 113.91, 117.21, 119.42, 121.19, 122.13, 122.83, 128.28, 130.19, 132.72, 133.42, 135.12, 136.54, 144.78, 147.79, 150.21, 154.03, 156.14, 158.62 (Ar-C), 160.19 (C=O); Anal. Calcd. for $C_{32}H_{26}N_4O_4$ (530.57 gm/mole): C, 72.44; H, 4.94; N, 10.56%. Found: C, 72.18; H, 4.73; N, 10.76%.

2-Amino-4-(5-(4-chlorophenoxy)-3-methyl-1-(4-methylphenyl)-1*H*-pyrazol-4-yl)-9-methyl-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (IVs): Yield: 74%; m.p.: 229-230 °C; IR (KBr, v, cm^{-1}): 3365 & 3170 (asym. & sym. str. of $-NH_2$), 2210 (-C≡N str.), 1710 (-C=O str.); ^1H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 1.92 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 4.49 (s, 1H, H4), 6.32-7.49 (m, 13H, NH_2+Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 13.07, 20.77, 20.89 (Ar-CH_3), 26.51 (C4), 56.13 (C-CN), 102.31, 110.65, 112.13, 114.13, 116.32, 118.42, 121.38, 122.19, 122.87, 128.32, 130.02, 133.46, 133.74, 134.18, 136.44, 144.98, 146.11, 151.14, 153.33, 156.35, 158.29 (Ar-C), 160.18 (C=O); Anal. Calcd. for $C_{31}H_{23}ClN_4O_4$ (550.99 gm/mole): C, 67.57; H, 4.21; N, 10.17%. Found: C, 67.78; H, 4.45; N, 10.35%.

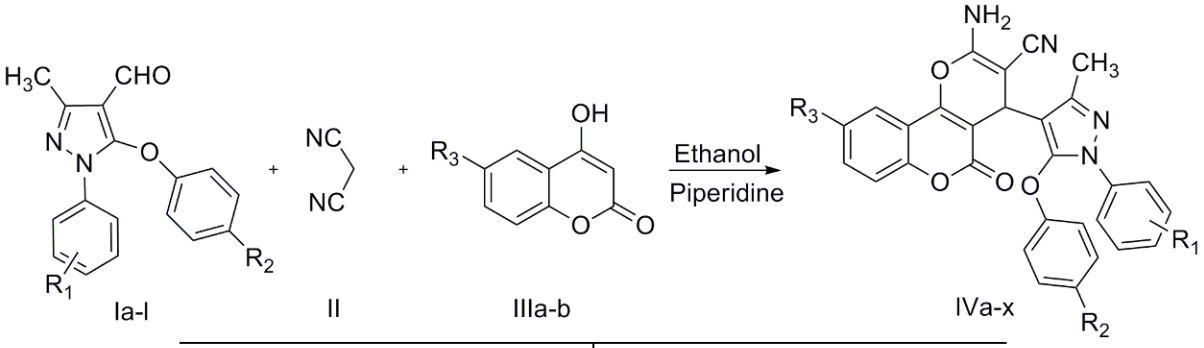
2-Amino-4-(5-(4-methoxyphenoxy)-3-methyl-1-(4-methylphenyl)-1*H*-pyrazol-4-yl)-9-methyl-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (IVt): Yield: 62%; m.p.: 283-285 °C; IR (KBr, v, cm^{-1}): 3450 & 3155 (asym. & sym. str. of $-NH_2$), 2200 (-C≡N str.), 1680 (-C=O str.); ^1H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 2.17 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 3.36 (s, 3H, OCH_3), 4.44 (s, 1H, H4), 6.40-7.50 (m, 13H, NH_2+Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 13.01, 20.86, 20.96 Ar-CH_3), 26.45 (C4), 53.90 (Ar-OCH_3), 56.19 (C-CN), 103.03, 111.12, 112.78, 114.66, 117.41, 119.45, 121.37, 122.46, 122.92, 129.21, 130.18, 132.31, 133.43, 135.13, 136.88, 145.19, 147.83, 150.40, 153.03, 156.23, 158.55 (Ar-C), 160.14 (C=O); Anal. Calcd. for $C_{32}H_{26}N_4O_5$ (546.57 gm/mole): C, 70.32; H, 4.79; N, 10.25%. Found: C, 70.48; H, 4.55; N, 10.54%.

2-Amino-4-(1-(3-chlorophenyl)-3-methyl-5-phenoxy-1*H*-pyrazol-4-yl)-9-methyl-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (IVu): Yield: 72%; m.p.: 235-236 °C; IR (KBr, v, cm^{-1}): 3395 & 3140 (asym. & sym. str. of $-NH_2$), 2205 (-C≡N str.), 1695 (-C=O str.); ^1H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 2.34 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 4.45 (s, 1H, H4), 6.46-7.55 (m, 14H, NH_2+Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 13.06, 21.01 (Ar-CH_3), 26.48 (C4), 55.89 (C-CN), 102.62, 111.12, 112.62, 115.72, 117.04, 119.19, 119.64, 121.29, 122.32, 124.91, 126.85, 127.14, 129.67, 131.31, 133.48, 134.56, 138.78, 144.32, 148.13, 152.38, 153.28, 154.31, 158.44 (Ar-C), 160.07 (C=O); Anal. Calcd. for $C_{30}H_{21}ClN_4O_4$ (536.97 gm/mole): C, 67.10; H, 3.94; N, 10.43%. Found: C, 67.27; H, 4.15; N, 10.62%.

2-Amino-4-(1-(3-chlorophenyl)-3-methyl-5-(4-methylphenoxy)-1*H*-pyrazol-4-yl)-9-methyl-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (IVv): Yield: 71%; m.p.: 248-249 °C; IR (KBr, v, cm^{-1}): 3410 & 3160 (asym. & sym. str. of $-NH_2$), 2180 (-C≡N str.), 1700 (-C=O str.); ^1H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 2.16 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 4.41 (s, 1H, H4), 6.41-7.59 (m, 13H, NH_2+Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 13.08, 20.27, 20.95 (Ar-CH_3), 26.54 (C4), 55.97 (C-CN), 103.02, 110.92, 112.72, 115.37, 116.91, 118.94, 119.72, 121.47, 122.62, 124.77, 126.84, 127.42, 129.57, 131.14, 133.37, 134.18, 138.75, 145.32, 148.62, 152.11, 153.48, 154.31, 158.38 (Ar-C), 160.02 (C=O); Anal. Calcd. for $C_{31}H_{23}ClN_4O_4$ (550.99 gm/mole): C, 67.57; H, 4.21; N, 10.17%. Found: C, 67.35; H, 4.09; N, 9.92%.

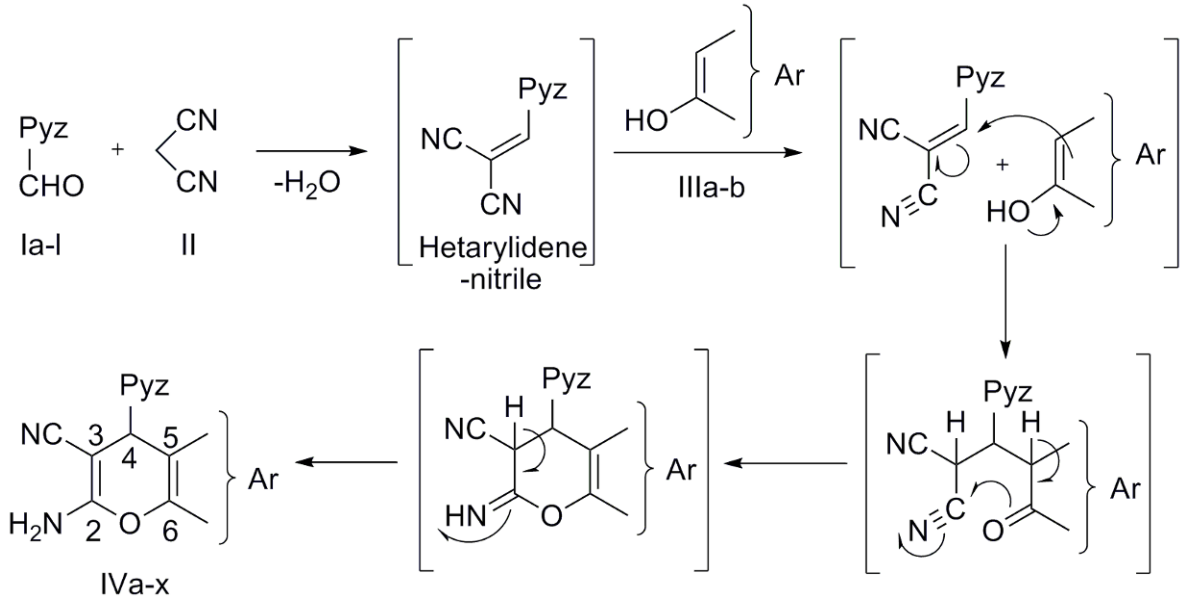
2-Amino-4-(5-(4-chlorophenoxy)-1-(3-chlorophenyl)-3-methyl-1*H*-pyrazol-4-yl)-9-methyl-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (IVw): Yield: 79%; m.p.: 266-268 °C; IR (KBr, v, cm^{-1}): 3435 & 3205 (asym. & sym. str. of $-NH_2$), 2195 (-C≡N str.), 1690 (-C=O str.); ^1H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 2.03 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 4.43 (s, 1H, H4), 6.42-7.60 (m, 13H, NH_2+Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 13.03, 21.05 (Ar-CH_3), 26.55 (C4), 56.15 (C-CN), 102.37, 111.42, 112.71, 114.92, 116.32, 119.62, 119.79, 120.97, 122.31, 124.62, 126.87, 127.62, 129.94, 131.21, 133.91, 134.17, 138.49, 144.33, 148.30, 152.35, 153.31, 154.52, 158.34 (Ar-C), 160.12 (C=O); Anal. Calcd. for $C_{30}H_{20}Cl_2N_4O_4$ (571.41 gm/mole): C, 63.06; H, 3.53; N, 9.81%. Found: C, 62.85; H, 3.79; N, 9.92%.

2-Amino-4-(1-(3-chlorophenyl)-5-(4-methoxyphenoxy)-3-methyl-1*H*-pyrazol-4-yl)-9-methyl-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (IVx): Yield: 68%; m.p.: 280-281 °C; IR (KBr, v, cm^{-1}): 3370 & 3180 (asym. & sym. str. of $-NH_2$), 2200 (-C≡N str.), 1720 (-C=O str.); ^1H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 2.33 (s, 3H, CH_3), 2.36 (s, 3H,



Compd.	R_1	R_2	R_3	Compd.	R_1	R_2	R_3
IVa	H	H	H	IVm	H	H	Me
IVb	H	Me	H	IVn	H	Me	Me
IVc	H	Cl	H	IVo	H	Cl	Me
IVd	H	OMe	H	IVp	H	OMe	Me
IVe	4-Me	H	H	IVq	4-Me	H	Me
IVf	4-Me	Me	H	IVr	4-Me	Me	Me
IVg	4-Me	Cl	H	IVs	4-Me	Cl	Me
IVh	4-Me	OMe	H	IVt	4-Me	OMe	Me
IVi	3-Cl	H	H	IVu	3-Cl	H	Me
IVj	3-Cl	Me	H	IVv	3-Cl	Me	Me
IVk	3-Cl	Cl	H	IVw	3-Cl	Cl	Me
IVl	3-Cl	OMe	H	IVx	3-Cl	OMe	Me

Scheme 2. Synthetic Pathway for the title compounds 4*H*-pyrano[3,2-c]chromene derivatives of 1*H*-pyrazole **IVa-x**.



Pyz-CHO = 3-methyl-5-aryloxy-1-aryl-1*H*-pyrazole-4-carbaldehyde
Ar = 4-hydroxy-6-substituted-2*H*-chromen-2-one

Scheme 3. Plausible mechanistic pathway for the title compounds 4*H*-pyrano[3,2-c]chromene derivatives of 1*H*-pyrazole **IVa-x**.

CH_3), 3.45 (s, 3H, OCH_3), 4.42 (s, 1H, H4), 6.38-7.53 (m, 13H, NH_2+Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 13.08, 20.86 (Ar-CH_3), 26.55 (C4), 55.20 (Ar-OCH_3), 55.16 (C-CN), 103.02, 111.91, 112.53, 115.42, 117.01, 119.82, 119.99, 121.50, 122.31, 124.72, 126.99, 127.53, 129.81, 131.53, 133.18, 134.17, 138.90, 145.32, 148.93, 152.23, 153.71, 154.35, 158.46 (Ar-C), 160.06 (C=O); Anal. Calcd. for $C_{31}H_{23}ClN_4O_5$ (566.99 gm/mole): C, 65.67; H, 4.09; N, 9.88%. Found: C, 65.35; H, 4.23; N, 9.92%.

2.7. Antimicrobial Activity

The *in vitro* antimicrobial activity of all the synthesized compounds and standard drugs were assessed against three representative of Gram-positive bacteria *viz*. *Streptococcus pneumoniae* (MTCC 1936), *Clostridium tetani* (MTCC 449), *Bacillus subtilis* (MTCC 441), three Gram-negative bacteria *viz*. *Salmonella typhi* (MTCC 98), *Vibrio cholerae* (MTCC 3906), *Escherichia coli* (MTCC 443) and two fungi *viz*. *Aspergillus fumigatus* (MTCC 3008) and *Candida albicans* (MTCC 227) by the Broth Microdilution MIC method recommended by the National Committee for Clinical Laboratory Standards (NCCLS) [21]. The strains employed for the activity were procured from (MTCC – Micro Type Culture Collection) Institute of Microbial Technology, Chandigarh. Inoculum size for test strain was adjusted to 10^8 CFUmL^{-1} (Colony Forming Unit per milliliter) by comparing the turbidity (turbidimetric method). Mueller Hinton Broth was used as nutrient medium to grow and dilute the compound suspension for the test bacteria. Sabouraud Dextrose Broth was used for fungal nutrition. Ampicillin, Chloramphenicol, Ciprofloxacin, Gentamicin and Norfloxacin were used as standard antibacterial drugs, whereas griseofulvin and nystatin were used as standard antifungal drugs. DMSO was used as a diluent / vehicle to obtain the desired concentration of synthesized compounds and standard drugs to test upon standard microbial strains. Serial dilutions were prepared in primary and secondary screenings. Each synthesized compound and standard drug was diluted obtaining 2000 μg mL^{-1} concentration, as a stock solution. In primary screening 1000, 500, and 250 μg mL^{-1} concentrations of the synthesized drugs were used. The active synthesized compounds found in this primary screening were further diluted to obtain 200, 100, 62.5 and 50 μg mL^{-1} concentrations for secondary screening to test in a second set of dilution against all microorganisms. The control tube containing no antibiotic is immediately subcultured [before inoculation] by spreading a loopful evenly over a quarter of plate of medium suitable for the growth of the test organism. The tubes are then put for incubation at 37°C for 24 h for bacteria and 48 h for fungi. The highest dilution (lowest concentration) preventing appearance of turbidity is considered as minimal inhibitory concentration (MIC, μg mL^{-1}) i.e. the amount of growth from the control tube before incubation (which represents the original inoculum) is compared. A set of tubes containing only seeded broth and the solvent controls were maintained under identical conditions so as to make sure that the solvent had no influence on strain growth. The result of this is much affected by the size of the inoculum. The test mixture should contain 10^8 CFU mL^{-1} organisms. The protocols are summarized in Table 1 as the minimal inhibitory concentration (MIC, μg mL^{-1}).

3. Results and Discussion

In continuation of our interest on synthesizing biologically potent antimicrobials [20], we report herein a new series of dihydropyrano[3,2-*c*]chromene derivatives **IVa-x** *via* a one pot, three component, base-catalyzed cyclocondensation reaction of 3-methyl-5-aryloxy-1-ary-1*H*-lpyrazole-4-carbaldehyde **Ia-l**, malononitrile **II** and 4-hydroxycoumarin **IIIa-b** in ethanol. The required starting material, 1-aryl-5-chloro-3-methyl-1*H*-pyrazole-4-carbaldehydes were prepared by Vilsmeier-Haack reaction of 3-methyl-1-aryl-1*H*-pyrazol-5(4*H*)-one, which leads to chloroformylation to afford 1-aryl-5-chloro-3-methyl-1*H*-pyrazole-4-carbaldehyde according to literature procedure [22]. 1-Aryl-5-chloro-3-methyl-1*H*-pyrazole-4-carbaldehyde undergoes a nucleophilic substitution reaction with the respective phenol at refluxing temperature for 4 h in the presence of a base catalyst (K_2CO_3) in DMF to yield the desired 3-methyl-5-aryloxy-1-aryl-1*H*-pyrazole-4-carbaldehyde **Ia-l** (Scheme 1) [23]. 4-Hydroxycoumarin (4-hydroxy-6-substituted-2*H*-chromen-2-one) was synthesized according to literature method by the solid phase reaction of malonic acid and phenol in phosphorous oxychloride in the presence of zinc chloride (Scheme 1) [24].

To obtain the title pyrano[3,2-*c*]chromene derivatives of 1*H*-pyrazole, according to literature procedure, the reaction was carried out in aqueous media and under neutral conditions but failed to proceed even with prolonged refluxing. The reaction was also attempted under microwave irradiation but was not successful. The reaction proceeded in acetonitrile, methanol, benzene or DMF in the presence of morpholine or K_2CO_3, but required prolonged refluxing and resulted only in poor yield. Finally, refluxing the reaction mixture in ethanol for 1-1.5 h in the presence of piperidine as a basic catalyst gave moderate to good yield (62–80%) (Scheme 2). Hence, these conditions were considered as the most optimized conditions for the synthesis of the title derivatives.

Table 1. Antibacterial and antifungal activity of compounds **IVa-x**.

Compds	Minimum Inhibitory Concentration (MIC, μg mL^{-1})							
	Gram-positive bacteria			Gram-negative bacteria			Fungi	
	S.P. MTCC 1936	C.T. MTCC 449	B.S. MTCC 441	S.T. MTCC 98	V.C. MTCC 3906	E.C. MTCC 443	A.F. MTCC 3008	C.A. MTCC 227
IVa	250	250	250	250	250	200	500	250
IVb	200	500	100	500	200	250	1000	1000
IVc	250	1000	500	200	100	200	>1000	>1000
IVd	250	200	200	100	200	100	500	500
IVe	100	500	250	250	1000	250	>1000	>1000
IVf	100	500	200	100	1000	100	>1000	>1000
IVg	200	100	250	100	100	62.5	>1000	>1000
IVh	200	500	200	500	500	200	250	250
IVi	200	500	250	200	200	250	500	500
IVj	250	500	500	250	500	500	500	250
IVk	250	500	150	250	100	100	500	1000
IVl	200	100	100	200	200	100	1000	500
IVm	500	500	500	250	500	250	1000	500
IVn	62.5	100	200	200	200	100	500	250
IVo	100	200	500	500	200	500	>1000	>1000
IVp	200	100	500	250	200	500	1000	1000
IVq	200	200	250	200	200	100	>1000	>1000
IVr	500	500	250	250	100	200	500	500
IVs	250	200	500	200	250	62.5	250	250
IVt	200	250	100	100	250	200	500	250
IVu	100	500	100	250	250	100	250	100
IVv	250	100	250	200	250	200	500	250
IVw	250	250	200	200	200	200	500	500
IVx	250	200	250	200	250	100	500	500
Ampicillin	100	250	250	100	100	100	-	-
Chlormphenicol	50	50	50	50	50	50	-	-
Ciprofloxacin	50	100	50	25	25	25	-	-
Gentamycin	0.5	5	1	5	5	0.05	-	-
Griseofulvin	-	-	-	-	-	-	100	500
Nystatin	-	-	-	-	-	-	100	100

B.S.: Bacillus subtilis; C.T.: Clostridium tetani; S.P.: Streptococcus pneumoniae; E.C.: Escherichia coli; S.T.: Salmonella typhi; V.C.: Vibrio cholerae; A.F.: Aspergillus fumigatus; C.A.: Candida albicans

A mechanism for the formation of the chromene derivatives **IVa-x** is outlined in Scheme 3. The reaction may proceed via an *in situ* initial formation of the hetarylidenenitrile, containing the electron-poor C=C double bond, from a Knoevenagel condensation. Finally, Michael addition of **3** to the initially formed unsaturated nitrile, *i.e.*, nucleophilic attack of hydroxyl moiety to the cyano olefins afforded cyclized pyrano[3,2-*c*]chromene derivatives **IVa-x**.

The structures of all the newly synthesized compounds were established by ^{1}H-NMR, ^{13}C-NMR and FT-IR spectral data, and the molecular weight of some selected compounds were confirmed by mass spectrometry. ^{1}H-NMR (DMSO-d_6) spectrum of **IVa-x** exhibited a singlet peak around δ 4.40-4.50 stands for H4 of the pyran ring. Amine and aromatic protons of **IVa-x** resonate as multiplets at δ 6.30–7.60 ppm. A singlet around δ 1.75-2.40 ppm stands for methyl of the pyrazole ring. ^{13}C-NMR of **IVa-x** exhibited distinctive signals around δ 13.01-13.10 and δ 26.40-26.60 ppm stands for methyl of pyrazole ring and C4 of the pyran ring respectively. All the aromatic carbons of **IVa-x** showed signals around δ 102.15–158.70 ppm in the ^{13}C-NMR spectra. Moreover, distinctive signals around δ 55.50-56.60 and δ 160.01-160.15 ppm represent the C-CN and carbonyl carbon respectively. The IR spectrum of compound **IVa-x** exhibited characteristic absorption bands around 3450-3140 cm^{-1} and 2210-2180 cm^{-1} are inidicative of the (asym. & sym. str.) –NH_2 and -CN functional groups, respectively. The characteristic absorption band of carbonyl carbon is found around 1730-1680 cm^{-1} supports the formation of pyran derivative **IVa-x**. Further, the structure of selected compounds **IVk** and **IVq** were confirmed by its mass spectral studies.

The mass spectra detected the expected molecular ion signals corresponding to respective molecular formula of synthesized compounds. Similarly, all these compounds were characterized on the basis of above spectral studies. All spectroscopic and physicochemical data have been given in experimental section. All the compounds were screened for their antibacterial and antifungal activity and results are shown in the form of MIC μg mL^{-1}.

3.1. Antibacterial screening

The examination of the data (Table 1) reveals that most of the compounds showed excellent antibacterial and antifungal activity when compared with standard drugs Ampicillin and Griseofulvin respectively. Against Gram-positive bacteria *S. pneumoniae*, compounds **IVn** (R_1=H, R_2=CH_3, R_3=CH_3) (MIC = 62.5 μg mL^{-1}) was found to be more potent whereas, **IVe** (R_1=CH_3, R_2=H, R_3=H), **IVf** (R_1=CH_3, R_2=CH_3, R_3=H), **IVo** (R_1=H, R_2=Cl, R_3=CH_3) and **IVu** (R_1=Cl, R_2=H, R_3=CH_3) (MIC = 100 μg mL^{-1}) shows comparable activity, to Ampicillin (MIC = 100 μg mL^{-1}). The compounds **IVd** (R_1=H, R_2=OCH_3, R_3=H), **IVg** (R_1=CH_3, R_2=Cl, R_3=H), **IVl** (R_1=Cl, R_2=OCH_3, R_3=H), **IVn** (R_1=H, R_2=CH_3, R_3=CH_3), **IVo** (R_1=H, R_2=Cl, R_3=CH_3), **IVp** (R_1=H, R_2=OCH_3, R_3=CH_3), **IVq** (R_1=CH_3, R_2=H, R_3=CH_3), **IVs** (R_1=CH_3, R_2=Cl, R_3=CH_3), **IVv** (R_1=Cl, R_2=CH_3, R_3=CH_3) and **IVx** (R_1=Cl, R_2=OCH_3, R_3=CH_3) (MIC < 250 μg mL^{-1}) found to be more efficient whereas, **IVa** (R_1=R_2=R_3=H), **IVt** (R_1=CH_3, R_2=OCH_3, R_3=CH_3) and **IVw** (R_1=Cl, R_2=Cl, R_3=CH_3) (MIC = 250 μg mL^{-1}) were found equally potent to Ampicillin (MIC = 250 μg mL^{-1}), towards *C. tetani*. The compounds **IVb** (R_1=H, R_2=CH_3, R_3=H), **IVd** (R_1=H, R_2=OCH_3, R_3=H), **IVf** (R_1=CH_3, R_2=CH_3, R_3=H), **IVh** (R_1=CH_3, R_2=OCH_3, R_3=H), **IVk** (R_1=Cl, R_2=Cl, R_3=H), **IVl** (R_1=Cl, R_2=OCH_3, R_3=H), **IVn** (R_1=H, R_2= CH_3, R_3=CH_3), **IVt** (R_1=CH_3, R_2=OCH_3, R_3=CH_3), **IVu** (R_1=Cl, R_2=H, R_3=CH_3) and **IVw** (R_1=Cl, R_2=Cl, R_3=CH_3) (MIC < 250 μg mL^{-1}) shows better activity whereas, **IVa** (R_1=R_2=R_3=H), **IVe** (R_1=CH_3, R_2=H, R_3=H), **IVg** (R_1=CH_3, R_2=Cl, R_3=H), **IVi** (R_1=Cl, R_2=H, R_3=H), **IVq** (R_1=CH_3, R_2=H, R_3=CH_3), **IVr** (R_1=CH_3, R_2= CH_3, R_3= CH_3), **IVv** (R_1=Cl, R_2=CH_3, R_3=CH_3) and **IVx** (R_1=Cl, R_2=OCH_3, R_3= CH_3) (MIC = 250 μg mL^{-1}) found equally potent, to Ampicillin (MIC = 250 μg mL^{-1}), against *B. subtilis*. Towards Gram-negative strain *S. typhi*, compounds **IVd** (R_1=H, R_2=OCH_3, R_3=H), **IVf** (R_1=CH_3, R_2=CH_3, R_3=H), **IVg** (R_1=CH_3, R_2=Cl, R_3=H) and **IVt** (R_1=CH_3, R_2=OCH_3, R_3=CH_3) (MIC = 100 μg mL^{-1}) were equally active to Ampicillin (MIC = 100 μg mL^{-1}). The Compounds **4c** (R_1=H, R_2=Cl, R_3=H), **IVg** (R_1=CH_3, R_2=Cl, R_3=H), **IVk** (R_1=Cl, R_2=Cl, R_3=H) and **IVr** (R_1= CH_3, R_2= CH_3, R_3= CH_3) (MIC = 100 μg mL^{-1}) found equipotent to Ampicillin (MIC = 100 μg mL^{-1}) against *V. cholerae*. The compound **IVg** (R_1= CH_3, R_2=Cl, R_3=H) and **IVs** (R_1= CH_3, R_2=Cl, R_3= CH_3) (MIC < 100 μg mL^{-1}) shows better and **IVd** (R_1=H, R_2= OCH_3, R_3=H), **IVf** (R_1= CH_3, R_2= CH_3, R_3=H), **IVk** (R_1=Cl, R_2=Cl, R_3=H), **IVl** (R_1=Cl, R_2= OCH_3, R_3=H), **IVn** (R_1=H, R_2= CH_3, R_3= CH_3), **IVq** (R_1= CH_3, R_2=H, R_3= CH_3), **IVu** (R_1=Cl, R_2=H, R_3= CH_3) and **IVx** (R_1=Cl, R_2= OCH_3, R_3= CH_3) (MIC = 100 μg mL^{-1}) were found to exhibit comparable activity to Ampicillin (MIC = 100 μg mL^{-1}) towards *E. coli*.

3.2. Antifungal screening

Against fungal pathogen *C. albicans*, compound **IVa** (R_1=R_2=R_3=H), **IVh** (R_1= CH_3, R_2= OCH_3, R_3=H), **IVj** (R_1=Cl, R_2= CH_3, R_3=H), **IVn** (R_1=H, R_2= CH_3, R_3= CH_3), **IVs** (R_1= CH_3, R_2=Cl, R_3= CH_3), **IVt** (R_1= CH_3, R_2= OCH_3, R_3= CH_3), **IVu** (R_1=Cl, R_2=H, R_3= CH_3) and **IVv** (R_1=Cl, R_2= CH_3, R_3= CH_3) (MIC < 500 μg mL^{-1}) found better activity whereas, **IVd** (R_1=H, R_2= OCH_3, R_3=H), **IVi** (R_1=Cl, R_2=H, R_3=H), **IVl** (R_1=Cl, R_2= OCH_3, R_3=H), **IVm** (R_1=H, R_2=H, R_3= CH_3), **IVr** (R_1= CH_3, R_2= CH_3, R_3= CH_3), **IVw** (R_1=Cl, R_2=Cl, R_3= CH_3) and **IVx** (R_1=Cl, R_2= OCH_3, R_3= CH_3) (MIC = 500 μg mL^{-1}) were found to be equipotent compared to Griseofulvin (MIC = 500 μg mL^{-1}). The remaining compounds showed moderate to good activity to inhibit the growth of bacterial pathogens and are all less effective than standard drugs. From the antimicrobial study of the title derivatives, it is interesting to note that a minor alteration in the molecular configuration of the investigated compounds may have a pronounced effect on antimicrobial activity.

4. Conclusions

A new series of substituted pyrano[3,2-*c*]chromene **IVa-x** derivatives have been synthesized *via* MCR approach. This synthetic strategy allows the construction of relatively complicated nitrogen and oxygen containing fused heterocyclic systems, as well as the introduction of various (hetero)aromatic substitutents onto the 4-position of the chromene system. It can be concluded from antimicrobial screening (Table 1) that compound **Ivn,** which bears two methyl groups, is the most efficient antimicrobial amongst all the synthesized derivatives. Antifungal activity of the compounds shows that most of the compounds wre found to be more potent against *C. albicans* compared to *A. fumigatus*. It is worth mentioning that minor changes in the molecular configuration of these compounds profoundly influences the activity.

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