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Design, synthesis and *in vitro* evaluation of the antibacterial and antifungal activity of some new dihydropyrano[3,2-c]chromene derivatives

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ABSTRACT

An efficient synthesis of some new dihydropyrano[3,2-c]chromene derivatives 4a-r by the cyclocondensation reaction of corresponding 2-thio(oxo)-1,2-dihydroquinoline-3-carbaldehyde - 1a-f, ethylcynoacetate 2a and 4-hydroxy-2H-chromen-2-one 3a-c using piperidine as a catalyst in refluxing ethanol *via* a MCRs approach was used. The structures of new compounds have been characterized on the basis of elemental analysis, FT-IR, ^{1}H-NMR and ^{13}C-NMR spectral data. Some of the synthesized compounds exhibit excellent antimicrobial activity.

Keywords: *MCRs, dihydropyrano[3,2-c]chromene, cyclocondensation, bio-potential.*

1. INTRODUCTION

A major challenge of modern drug discovery is the design of highly efficient chemical reaction sequences that provide maximum structural complexity and diversity with a minimum number of synthetic steps to assemble compounds with interesting properties [1-4]. In the past decade there has been tremendous development in three- and four- component reactions. Recently multicomponent reactions (MCRs) have emerged as a highly valuable tool and have occupied a unique place in modern drug discovery and organic synthesis. MCRs, by virtue of their convergent character [5-9], atom economy, productivity, the simplicity of a one-pot procedure, the possible structural variations, the accessible complexity of the molecules and generally produces high yields of products, have thus attracted considerable attention from the point of view of combinatorial chemistry [10-22]. So, great efforts are on to developing new MCRs [23-29]. The quinolone moiety possesses wide range of biological activities. Several substituted quinolones have been shown to possess anti-inflammatory, CNS depressant, antimicrobial and antifertility activities. Quinolones constitute one of the most active class of the compounds possessing diversified therapeutic activities such as antifungal, anti-allergic agents. In addition, 3,2-Dihydropyrano[c]chromenes and its derivatives are a class of important heterocycles with a wide range of biological properties and pharmacological properties [30-32] such as spasmolytic, diuretic, anticoagulant, anti-cancer, anti-anaphylactic activity and potassium channel activators [33-37]. Moreover they can be used as cognitive enhancers, for the treatment of neurodegenerative diseases, including Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease, Huntington's disease, AIDS associated dementia and Down's syndrome as well as for the treatment of schizophrenia and myoclonus [38]. In addition, aminochromene derivatives exhibit a wide spectrum of biological activities including antihypertensive and anti-ischemic behavior [39-40]. Above observations contemplated us to

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synthesize some dihydropyrano[3,2-c]chromene derivatives containing 2-thio(oxo)-1,2-dihydroquinoline-3-carbaldehyde, ethylcynoaceatate and 4-hydroxy-2H-chromen-2-one *via* a MCRs approach.

2. EXPERIMENTAL SECTION

All the reagents were obtained from commercial sources and used with further purification. The monitoring of the progress of all reactions and homogeneity of the synthesized compounds was carried out by TLC. TLC was runned using TLC aluminum sheets silica gel 60 F_{254} (Merck). Elemental analysis (% C, H, N) was carried out by Perkins Elmer 2400 CHN elemental analyzer. IR spectra were recorded on a shimadzu FT-IR 8401 spectrophotometer in KBr. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Advance 400 MHz spectrometer using solvent peak as internal standard.

2.1. General procedure for the synthesis of 2-chloroquinoline-3-carbaldehyde. 2-chloroquinoline-3-carbaldehyde were prepared, according to literature procedure [41]. In this process dimethylformamide (0.250 mole) was cooled in a three-necked round-bottomed flask to 0^{o}C, to it phosphorous oxychloride (0.70 mole) was added drop wise with stirring at 0-10^{o}C. In this mixture, 4-substituted acetanilide (0.10 mole) was added and the mixture was heated under reflux for 6 hours at 75^{o}C. The reaction mass then cooled to room temperature and poured in crushed ice with mechanical stirring. The product isolated was filtered and washed with water till neutral. The solid was crystallized from ethyl acetate to give pure 2-chloro-3-formylquinoline.

2.2. General procedure for the synthesis of 2-oxo-1,2-dihydroquinoline-3-carbaldehyde 1(a-d)

For the synthesis of compounds 1(a-d), 2-chloro-3-formylquinoline (0.005 mole) and 70% glacial acetic acid were charged in a round bottom flask equipped with mechanical stirrer and condenser. The reaction mixture was slowly heated and reflux for 5-6 hours. After the completion of reaction (checked by TLC), the product was filtered and washed with ethanol. The crude product was purified by leaching in (10:10 v/v) mixture of methanol and chloroform to obtain pure solid sample. Compound 1(e-f) prepared by stirring mixture of 2-chloro-3-formylquinoline (0.5 mole) and sodium sulphide (0.0075 mole) in dry dimethyl formamide for 2 hours with a mechanical stirrer. On completion of reaction (monitored by TLC), the reaction mixture was poured in ice-water and made acidic with acetic acid. The product was filtered off, washed well with water, dried and pure for further use. The product was filtered off, washed well with water. The crude product was purified by leaching in (10:10 v/v) mixture of methanol and chloroform to obtain pure solid sample.

2.3. Synthesis of 4-hydroxy-6,8-(un)substituted-2H-chromen-2-one. A mixture of appropriate phenol (0.2 mole), malonic acid (0.2 mole), anhydrous zinc chloride (0.6 mole) and phosphorous oxychloride (0.4 mole) was heated in a round bottom flask attached with a reflux condenser with stirring at 60-65 °C for 35 hours. The yellow coloured mixture was cooled and decomposed with water and left overnight. The resulting crude 4-hydroxy-6,8-(un)substituted-2H-chromen-2-one was filtetered out, washed with water and dried. This crude product was purified by dissolving it in 10 % sodium bicarbonate solution, filtering and reprecipitating by adding dil. HCl solution. The product was separated out as a yellowish-white solid. This was filtered out, washed with water, dried and recrystallized from ethanol-water.

2.4. Synthesis of ethyl 2-amino-5-oxo-4-(2-oxo-1,2-dihydroquinolin-3-yl)-4,5-dihydropyrano [3,2-c]chromene-3-carboxylate (4a). 2-oxo-1,2-dihydroquinoline-3-carbaldehyde (0.005 mole), 4-hydroxy-2H-chromen-2-one (0.005 mole), ethylcynoacetate (0.005 mol), piperidine (0.00025 mole)

and ethanol (15 mL) were charged in 100 mL round bottom flask with mechanical stirrer and condenser. The reaction mixture was slowly heated and refluxed for 2-3 hr. On completion of reaction, monitored by TLC using 1:1 n-hexane/ethyl acetate as eluent, the reaction mixture was cooled to room temperature and solid separated was filtered and washed with mixture of chloroform and methanol (1:1) to obtain the pure compound. All other compounds were prepared similarly taking the respective 2-(thio)oxo-1,2-dihydroquinoline-3-carbaldehyde derivatives **1(a-f)** and respective 4-hydroxy-6,8-(un)substituted-2H-chromen-2-ones **3(a-c)**.

2.4.1. ethyl 2-amino-5-oxo-4-(2-oxo-1,2-dihydroquinolin-3-yl)-4,5-dihydropyrano[3,2-c] chromene-3-carboxylate (4a): pale yellow solid, m.p. 263-265 ^{0}C, yield, 89 %; Elemental analysis of $C_{24}H_{18}N_2O_6$; calcld C, 66.97; H, 4.22; N, 6.51; found C, 66.87; H, 4.18; N, 6.39. IR (KBr, cm^{-1}): 3396 & 3326 (asym. & sym. str. of NH_2), 1706, 1658 (C=O str.), 1224 (C-O str.) cm^{-1}. ^{1}H NMR: δ_H 1.04-1.08 (t, 3H, CH_3), 3.96-4.01 (q, 2H, CH_2), 5.38 (s, 1H, pyran H4), 7.19 (s, 2H, NH_2), 7.15-7.95 (m, 9H, Ar-H), 11.62 (s, 1H, quinolone N-H) ppm. ^{13}C NMR: δ_c 14.59 (CH_3), 34.45 (C-4, pyran), 59.44 (CH_2), 102.79 (C-CH), 113.62, 115.38, 117.14, 119.62, 119.93, 122.37, 122.93, 125.11, 128.36, 130.56, 133.02, 133.24, 138.25, 138.92, 152.65, 159.21, 159.67, 160.29 (C=O, quinolone), 161.13 (C=O, coumarin) 165.67 (C=O ester) ppm.

2.4.2. ethyl 2-amino-4-(6-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carboxylate (4b): pale yellow solid, m.p. 272-274 ^{0}C, yield, 87 %; Elemental analysis of $C_{25}H_{20}N_2O_6$; calcld C, 67.56; H, 4.54; N, 6.30; found C, 67.47; H, 4.45; N, 6.21. IR (KBr, cm^{-1}): 3391 & 3324 (asym. & sym. str. of NH_2), 1701, 1667 (C=O str.), 1221 (C-O str.) cm^{-1}. ^{1}H NMR: δ_H 1.06 (t, 3H, CH_3), 2.32 (s, 3H, CH_3), 3.91-4.05 (q, 2H, CH_2), 5.33 (s, 1H, pyran H4), 7.18 (s, 2H, NH_2), 7.11-7.94 (m, 8H, Ar-H), 11.84 (s, 1H, quinolone N-H) ppm. ^{13}C NMR: δ_c 14.52 (CH_3), 20.84 (CH_3), 32.51 (C-4, pyran), 59.57 (CH_2), 101.43 (C-CH), 115.12, 115.85, 116.92, 117.51, 119.35, 123.01, 124.16, 125.22, 127.95, 128.28, 128.52, 129.65, 136.32, 138.18, 152.83, 159.52, 160.47, 160.79 (C=O, quinolone), 161.9 (C=O, coumarin) 165.62 (C=O ester) ppm.

2.4.3. ethyl 2-amino-4-(6-methoxy-2-oxo-1,2-dihydroquinolin-3-yl)-5-oxo-4,5-dihydropyrano [3,2-c]chromene-3-carboxylate (4c): pale yellow solid, m.p. 276-278 ^{0}C, yield, 85 %; Elemental analysis of $C_{25}H_{20}N_2O_7$; calcld C, 65.21; H, 4.38; N, 6.08; found C, 65.09; H, 4.24; N, 5.95. IR (KBr, cm^{-1}): 3397 & 3329 (asym. & sym. str. of NH_2), 1708, 1652 (C=O str.), 1229 (C-O str.) cm^{-1}. ^{1}H NMR: δ_H 1.03-1.07 (t, 3H, CH_3), 3.83 (s, 3H, OCH_3), 3.95-4.01 (q, 2H, CH_2), 5.37 (s, 1H, pyrane H4), 7.17 (s, 2H, NH_2), 7.21-7.92 (m, 8H, Ar-H), 11.89 (s, 1H, quinolone N-H) ppm. ^{13}C NMR: δ_c 14.58 (CH_3), 32.61 (C-4, pyran), 56.36 (OCH_3), 59.55 (CH_2), 101.23 (C-CH), 115.31, 115.65, 116.02, 117.86, 119.22, 123.87, 124.42, 125.17, 127.51, 128.34, 128.76, 129.83, 136.57, 138.72, 152.45, 159.92, 160.11, 160.54 (C=O, quinolone), 162.41 (C=O, coumarin) 165.68 (C=O ester) ppm.

2.4.4. ethyl 2-amino-4-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)-5-oxo-4,5-dihydropyrano [3,2-c]chromene-3-carboxylate (4d): pale yellow solid, m.p. 283-285 ^{0}C, yield, 80 %; Elemental analysis of $C_{24}H_{17}ClN_2O_6$; calcld C, 62.01; H, 3.69; N, 6.03; found C, 61.95; H, 3.54; N, 5.96. IR (KBr, cm^{-1}): 3401 & 3332 (asym. & sym. str. of NH_2), 1707, 1659 (C=O str.), 1226 (C-O str.) cm^{-1}. ^{1}H NMR: δ_H 1.01-1.05 (t, 3H, CH_3), 3.94-4.02 (q, 2H, CH_2), 5.33 (s, 1H, pyran H4), 7.10 (s, 2H, NH_2), 7.28-7.90 (m, 8H, Ar-H), 11.91 (s, 1H, quinolone N-H) ppm. ^{13}C NMR: δ_c 14.56 (CH_3), 32.83 (C-4, pyran), 59.54 (CH_2), 101.63 (C-CH), 115.17, 115.31, 116.24, 117.38, 119.53, 123.17, 124.23, 124.91, 127.36, 128.12, 128.42, 129.75, 136.32, 138.67, 152.11, 159.58, 160.31, 160.74 (C=O, quinolone), 162.93 (C=O, coumarin), 164.69 (C=O ester) ppm.

2.4.5. ethyl 2-amino-5-oxo-4-(2-thioxo-1,2-dihydroquinolin-3-yl)-4,5-dihydropyrano[3,2-c] chromene-3-carboxylate (4e): pale yellow solid, m.p. 288-290 ^{0}C, yield, 77 %; Elemental analysis of $C_{24}H_{18}N_2O_5S$; calcld C, 64.56; H, 4.06; N, 6.27; found C, 64.47; H, 4.01; N, 6.19. IR (KBr, cm^{-1}): 3392 & 3321 (asym. & sym. str. of NH_2), 1708, 1653 (C=O str.), 1227 (C-O str.), 1191 (C=S str.) cm^{-1}. ^{1}H NMR: δ_H 1.02-1.06 (t, 3H, CH_3), 3.95-4.06 (q, 2H, CH_2), 5.36 (s, 1H, pyran H4), 7.12 (s, 2H, NH_2) 7.23-7.96 (m, 9H, Ar-H), 11.87 (s, 1H, quinolone N-H) ppm. ^{13}C NMR: δ_c 14.53 (CH_3), 32.41 (C-4, pyran), 59.57 (CH_2), 101.72 (C-CH), 115.27, 115.62, 116.31, 117.47, 119.24, 123.87, 124.12, 125.57, 128.19, 128.41, 128.79, 129.12, 136.93, 138.18, 152.62, 159.01, 160.25, 161.71 (C=O, coumarin), 164.67 (C=O ester), 188.13 (C=S, quinolone) ppm.

2.4.6. ethyl 2-amino-4-(6-methyl-2-thioxo-1,2-dihydroquinolin-3-yl)-5-oxo-4,5-dihydropyrano [3,2-c]chromene-3-carboxylate (4f): pale yellow solid, m.p. 293-295 ^{0}C, yield, 75 %; Elemental analysis of $C_{25}H_{20}N_2O_5S$; calcld C, 65.20; H, 4.38; N, 6.08; found C, 65.06; H, 4.29; N, 6.02. IR (KBr, cm^{-1}): 3389 & 3323 (asym. & sym. str. of NH_2), 1703, 1651 (C=O str.), 1226 (C-O str.), 1195 (C=S str.) cm^{-1}. ^{1}H NMR: δ_H 1.03-1.07 (t, 3H, CH_3), 2.38 (s, 3H, CH_3), 3.92-4.04 (q, 2H, CH_2), 5.31 (s, 1H, pyran H4), 7.14 (s, 2H, NH_2), 7.22-7.91 (m, 8H, Ar-H), 11.82 (s, 1H, quinolone N-H) ppm. ^{13}C NMR: δ_c 14.52 (CH_3), 21.61 (CH_3), 32.16 (C-4, pyran), 59.52 (CH_2), 101.36 (C-CH), 115.01, 115.45, 116.62, 117.75, 119.17, 123.69, 124.92, 125.33, 127.19, 128.15, 128.53, 129.37, 136.52, 138.37, 152.82, 159.31, 160.15, 161.52 (C=O, coumarin), 164.63 (C=O ester), 188.46 (C=S, quinolone) ppm.

2.4.7. ethyl 2-amino-7-methyl-5-oxo-4-(2-oxo-1,2-dihydroquinolin-3-yl)-4,5-dihydropyrano [3,2-c]chromene-3-carboxylate (4g):

pale yellow solid, m.p. 271-273 ^{0}C, yield, 86 %; Elemental analysis of $C_{25}H_{20}N_2O_6$; calcld C, 67.56; H, 4.54; N, 6.30; found C, 67.49; H, 4.48; N, 6.19. IR (KBr, cm^{-1}): 3390 & 3325 (asym. & sym. str. of NH_2), 1706, 1653 (C=O str.), 1226 (C-O str.) cm^{-1}. ^{1}H NMR: δ_H 1.01-1.04 (t, 3H, CH_3), 2.43 (s, 3H, CH_3), 3.95-4.08 (q, 2H, CH_2), 5.38 (s, 1H, pyran H4), 7.19 (s, 2H, NH_2), 7.17-7.92 (m, 8H, Ar-H), 11.82 (s, 1H, quinolone N-H) ppm. ^{13}C NMR: δ_c 14.55 (CH_3), 21.13 (CH_3), 32.71 (C-4, pyran), 59.57 (CH_2), 101.22 (C-CH), 115.26, 115.51, 116.87, 117.62, 119.24, 123.17, 124.62, 125.17, 127.72, 128.04, 128.47, 129.12, 136.48, 138.22, 152.56, 159.82, 160.41, 160.65 (C=O, quinolone), 162.48 (C=O, coumarin), 165.51 (C=O ester) ppm.

2.4.8. ethyl 2-amino-7-methyl-4-(6-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carboxylate (4h):

pale yellow solid, m.p. 273-275 ^{0}C, yield, 84 %; Elemental analysis of $C_{26}H_{22}N_2O_6$; calcld C, 68.11; H, 4.84; N, 6.11; found C, 68.05; H, 4.79; N, 6.02. IR (KBr, cm^{-1}): 3392 & 3328 (asym. & sym. str. of NH_2), 1709, 1653 (C=O str.), 1224 (C-O str.) cm^{-1}. ^{1}H NMR: δ_H 1.06-1.09 (t, 3H, CH_3), 2.13 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 3.94-4.06 (q, 2H, CH_2), 5.35 (s, 1H, pyran H4), 7.04 (s, 2H, NH_2), 7.13-7.94 (m, 7H, Ar-H), 11.85 (s, 1H, quinolone N-H) ppm. ^{13}C NMR: δ_c 14.57 (CH_3), 20.74 (CH_3), 21.51 (CH_3), 32.96 (C-4, pyran), 59.57 (CH_2), 101.14 (C-CH), 115.12, 115.37, 116.93, 117.47, 119.73, 123.05, 124.41, 125.64, 127.12, 128.46, 128.62, 129.31, 136.23, 138.45, 152.31, 159.55, 160.37, 160.98 (C=O, quinolone), 162.13 (C=O, coumarin), 165.53 (C=O ester) ppm.

2. 4. 9. ethyl 2-amino-4-(6-methoxy-2-oxo-1,2-dihydroquinolin-3-yl)-7-methyl-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carboxylate (4i):

pale yellow solid, m.p. 278-279 ^{0}C, yield, 80 %; Elemental analysis of $C_{26}H_{22}N_2O_7$; calcld C, 65.82; H, 4.67; N, 5.90; found C, 65.70; H, 4.54; N, 5.81. IR (KBr, cm^{-1}): 3395 & 3332 (asym. & sym. str. of NH_2), 1702, 1656 (C=O str.), 1223 (C-O str.) cm^{-1}. ^{1}H NMR: δ_H 1.03-1.07 (t, 3H, CH_3), 2.11 (s,

3H, CH_3), 3.83 (s, 3H, OCH_3), 3.91-4.03 (q, 2H, CH_2), 5.32 (s, 1H, pyran H4), 7.17 (s, 2H, NH_2), 7.17-7.89 (m, 7H, Ar-H), 11.78 (s, 1H, quinolone N-H) ppm. ^{13}C NMR: δ_c 14.51 (CH_3), 21.82 (CH_3), 32.65 (C-4, pyran), 55.29 (OCH_3), 59.10 (CH_2), 101.33 (C-CH), 114.97, 115.10, 116.63, 117.25, 119.42, 123.84, 124.51, 125.13, 127.37, 128.23, 128.48, 129.83, 136.15, 138.62, 152.26, 159.72, 160.17, 160.72 (C=O, quinolone), 162.51 (C=O, coumarin), 165.62 (C=O ester) ppm.

2. 4. 10. ethyl 2-amino-4-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)-7-methyl-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carboxylate (4j)

pale yellow solid, m.p. 281-283 ^{0}C, yield, 76 %; Elemental analysis of $C_{25}H_{19}ClN_2O_6$; calcld C, 62.70; H, 4.00; N, 5.85; found C, 62.65; H, 3.91; N, 5.74. IR (KBr, cm^{-1}): 3397 & 3331 (asym. & sym. str. of NH_2), 1711, 1657 (C=O str.), 1235 (C-O str.) cm^{-1}. ^{1}H NMR: δ_H 1.02-1.09 (t, 3H, CH_3), 2.34 (s, 3H, CH_3), 3.93-4.05 (q, 2H, CH_2), 5.36 (s, 1H, pyran H4), 7.08 (s, 2H, NH_2), 7.23-7.95 (m, 7H, Ar-H), 11.84 (s, 1H, quinolone N-H) ppm. ^{13}C NMR: δ_c 14.53 (CH_3), 21.22 (CH_3), 32.34 (C-4, pyran), 59.51 (CH_2), 101.13 (C-CH), 114.72, 115.34, 116.52, 117.56, 119.13, 122.76, 124.32, 125.06, 127.17, 127.72, 128.15, 129.62, 135.85, 138.32, 152.14, 159.52, 160.04, 160.42 (C=O, quinolone), 162.78 (C=O, coumarin), 165.61 (C=O ester) ppm.

2. 4. 11. ethyl 2-amino-7-methyl-5-oxo-4-(2-thioxo-1,2-dihydroquinolin-3-yl)-4,5-dihydropyrano[3,2-c]chromene-3-carboxylate (4k)

pale yellow solid, m.p. 287-289 ^{0}C, yield, 74 %; Elemental analysis of $C_{25}H_{20}N_2O_5S$; calcld C, 65.20; H, 4.38; N, 6.08; found C, 65.03; H, 4.25; N, 6.01. IR (KBr, cm^{-1}): 3392 & 3324 (asym. & sym. str. of NH_2), 1711, 1657 (C=O str.), 1240 (C-O str.), 1193 (C=S str.) cm^{-1}. ^{1}H NMR: δ_H 1.04-1.09 (t, 3H, CH_3), 2.38 (s, 3H, CH_3), 3.95-4.06 (q, 2H, CH_2), 5.33 (s, 1H, pyran H4), 7.15 (s, 2H, NH_2), 7.21-7.88 (m, 8H, Ar-H), 11.86 (s, 1H, quinolone N-H) ppm. ^{13}C NMR: δ_c 14.59 (CH_3), 21.62 (CH_3), 32.64 (C-4, pyran), 59.53 (CH_2), 101.84 (C-CH), 115.47, 115.62, 116.47, 117.32, 119.83, 123.61, 124.45, 125.62, 127.25, 127.82, 128.25, 129.97, 136.79, 138.52, 152.82, 159.25, 160.44, 161.91 (C=O, coumarin), 165.58 (C=O ester), 188.74 (C=S, quinolone) ppm.

2. 4. 12. ethyl 2-amino-7-methyl-4-(6-methyl-2-thioxo-1,2-dihydroquinolin-3-yl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carboxylate (4l)

pale yellow solid, m.p. 294-296 ^{0}C, yield, 71 %; Elemental analysis of $C_{26}H_{22}N_2O_5S$; calcld C, 65.81; H, 4.67; N, 5.90; found C, 65.72; H, 4.59; N, 5.81. IR (KBr, cm^{-1}): 3398 & 3325 (asym. & sym. str. of NH_2), 1709, 1663 (C=O str.), 1227 (C-O str.), 1195 (C=S str.) cm^{-1}. ^{1}H NMR: δ_H 1.03-1.08 (t, 3H, CH_3), 2.19 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 3.91-4.04 (q, 2H, CH_2), 5.35 (s, 1H, pyran H4), 7.04 (s, 2H, NH_2), 7.16-7.99 (m, 7H, Ar-H), 11.81 (s, 1H, quinolone N-H) ppm. ^{13}C NMR: δ_c 14.58 (CH_3), 20.61 (CH_3), 21.85 (CH_3), 32.52 (C-4, pyran), 59.55 (CH_2), 101.54 (C-CH), 115.32, 115.84, 116.52, 117.74, 119.51, 123.27, 124.12, 125.44, 126.82, 128.67, 128.92, 129.26, 136.02, 138.89, 152.61, 159.75, 160.12, 162.46 (C=O, coumarin), 165.62 (C=O ester), 188.94 (C=S, quinolone) ppm.

2. 4. 13. ethyl 2-amino-9-methyl-5-oxo-4-(2-oxo-1,2-dihydroquinolin-3-yl)-4,5-dihydropyrano [3,2-c]chromene-3-carboxylate (4m)

pale yellow solid, m.p. 270-272 ^{0}C, yield, 87 %; Elemental analysis of $C_{25}H_{20}N_2O_6$; calcld C, 67.56; H, 4.54; N, 6.30; found C, 67.46; H, 4.48; N, 6.18. IR (KBr, cm^{-1}): 3393 & 3321 (asym. & sym. str. of NH_2), 1708, 1661 (C=O str.), 1235 (C-O str.) cm^{-1}. ^{1}H NMR: δ_H 1.04-1.07 (t, 3H, CH_3), 2.42 (s, 3H, CH_3), 3.94-4.08 (q, 2H, CH_2), 5.37 (s, 1H, pyran H4), 7.12 (s, 2H, NH_2), 7.14-7.84 (m, 8H, Ar-H), 11.85 (s, 1H, quinolone N-H). ppm ^{13}C NMR: δ_c 14.52 (CH_3), 21.32 (CH_3), 32.85 (C-4, pyran), 59.57 (CH_2), 101.35 (C-CH), 115.12, 115.34, 116.76, 117.43, 119.98, 123.73, 124.35, 125.92,

127.64, 128.27, 128.33, 129.47, 136.63, 138.07, 152.72, 159.15, 160.31, 160.74 (C=O, quinolone), 162.52 (C=O, coumarin), 165.66 (C=O ester) ppm.

2. 4. 14. ethyl 2-amino-9-methyl-4-(6-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carboxylate (4n)

pale yellow solid, m.p. 274-276 ^{0}C, yield, 81 %; Elemental analysis of $C_{26}H_{22}N_2O_6$; calcld C, 68.11; H, 4.84; N, 6.11; found C, 68.03; H, 4.75; N, 6.01. IR (KBr, cm^{-1}): 3391 & 3329 (asym. & sym. str. of NH_2), 1706, 1664 (C=O str.), 1243 (C-O str.) cm^{-1}. ^{1}H NMR: δ_H 1.04-1.05 (t, 3H, CH_3), 2.15 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 3.95-4.06 (q, 2H, CH_2), 5.34 (s, 1H, pyran H4), 7.09 (s, 2H, NH_2), 7.11-7.96 (m, 7H, Ar-H), 11.83 (s, 1H, quinolone N-H) ppm. ^{13}C NMR: δ_c 14.55 (CH_3), 20.51 (CH_3), 21.25 (CH_3), 32.38 (C-4, pyran), 59.59 (CH_2), 101.57 (C-CH), 115.22, 115.48, 116.32, 117.85, 119.62, 123.14, 124.26, 125.42, 127.38, 128.62, 128.89, 129.62, 136.13, 138.35, 152.52, 159.46, 160.22, 161.17 (C=O, quinolone), 162.38 (C=O, coumarin), 165.73 (C=O ester) ppm.

2. 4. 15. ethyl 2-amino-4-(6-methoxy-2-oxo-1,2-dihydroquinolin-3-yl)-9-methyl-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carboxylate (4o)

pale yellow solid, m.p. 275-277 ^{0}C, yield, 80 %; Elemental analysis of $C_{26}H_{22}N_2O_7$; calcld C, 65.82; H, 4.67; N, 5.90; found C, 65.76; H, 4.56; N, 5.82. IR (KBr, cm^{-1}): 3391 & 3334 (asym. & sym. str. of NH_2), 1703, 1665 (C=O str.), 1228 (C-O str.) cm^{-1}. ^{1}H NMR: δ_H 1.01-1.04 (t, 3H, CH_3), 2.14 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 3.95-4.03 (q, 2H, CH_2), 5.31 (s, 1H, pyran H4), 7.03 (s, 2H, NH_2) , 7.22-7.94 (m, 7H, Ar-H), 11.81 (s, 1H, quinolone N-H) ppm. ^{13}C NMR: δ_c 14.56 (CH_3), 21.32 (CH_3), 33.16 (C-4, pyran), 55.02 (OCH_3), 59.56 (CH_2), 101.73 (C-CH), 115.58, 115.83, 116.45, 117.42, 119.94, 123.26, 124.71, 125.25, 127.67, 128.33, 128.52, 129.56, 136.32, 138.85, 152.14, 159.52, 160.06, 160.32 (C=O, quinolone), 162.42 (C=O, coumarin), 165.64 (C=O ester) ppm.

2. 4. 16. ethyl 2-amino-4-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)-9-methyl-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carboxylate (4p)

pale yellow solid, m.p. 283-285 ^{0}C, yield, 75 %; Elemental analysis of $C_{25}H_{19}ClN_2O_6$; calcld C, 62.70; H, 4.00; N, 5.85; found C, 62.59; H, 3.89; N, 5.73. IR (KBr, cm^{-1}): 3392 & 3329 (asym. & sym. str. of NH_2), 1701, 1661 (C=O str.), 1236 (C-O str.) cm^{-1}. ^{1}H NMR: δ_H 1.02-1.06 (t, 3H, CH_3), 2.31 (s, 3H, CH_3), 3.95-4.02 (q, 2H, CH_2), 5.33 (s, 1H, pyran H4), 7.05 (s, 2H, NH_2), 7.27-7.91 (m, 7H, Ar-H), 11.86 (s, 1H, quinolone N-H) ppm. ^{13}C NMR: δ_c 14.58 (CH_3), 21.62 (CH_3), 31.95 (C-4, pyran), 59.52 (CH_2), 101.46 (C-CH), 114.93, 115.65, 116.32, 117.86, 119.22, 122.52, 124.04, 125.13, 127.46, 127.52, 128.25, 129.72, 135.47, 138.18, 152.43, 159.36, 160.12, 160.65 (C=O, quinolone), 162.21 (C=O, coumarin), 165.55 (C=O ester) ppm.

2. 4. 17. ethyl 2-amino-9-methyl-5-oxo-4-(2-thioxo-1,2-dihydroquinolin-3-yl)-4,5-dihydropyrano[3,2-c]chromene-3-carboxylate (4q)

pale yellow solid, m.p. 291-293 ^{0}C, yield, 73 %; Elemental analysis of $C_{25}H_{20}N_2O_5S$; calcld C, 65.20; H, 4.38; N, 6.08; found C, 65.06; H, 4.24; N, 5.94. IR (KBr, cm^{-1}): 3393 & 3327 (asym. & sym. str. of NH_2), 1703, 1672 (C=O str.), 1238 (C-O str.), 1192 (C=S str.) cm^{-1}. ^{1}H NMR: δ_H 1.04-1.07 (t, 3H, CH_3), 2.36 (s, 3H, CH_3), 3.91-4.01 (q, 2H, CH_2), 5.35 (s, 1H, pyran H4), 7.02 (s, 2H, NH_2), 7.20-7.93 (m, 8H, Ar-H), 11.88 (s, 1H, quinolone N-H) ppm. ^{13}C NMR: δ_c 14.51 (CH_3), 21.43 (CH_3), 32.16 (C-4, pyran), 59.55 (CH_2), 101.32 (C-CH), 115.31, 115.93, 116.15, 117.52, 119.46, 123.83, 124.14, 125.32, 127.52, 127.65, 128.42, 129.95, 136.92, 138.34, 152.62, 159.51, 160.35, 161.82 (C=O, coumarin), 165.57 (C=O ester), 188.51 (C=S, quinolone) ppm.

2. 4. 18 ethyl 2-amino-9-methyl-4-(6-methyl-2-thioxo-1,2-dihydroquinolin-3-yl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carboxylate (4r):

pale yellow solid, m.p. 293-295 ^{0}C, yield, 70 %; Elemental analysis of $C_{26}H_{22}N_2O_5S$; calcld C, 65.81; H, 4.67; N, 5.90; found C, 65.69; H, 4.57; N, 5.76. IR (KBr, cm^{-1}): 3391 & 3328 (asym. &

sym. str. of NH_2), 1706, 1669 (C=O str.), 1239 (C-O str.), 1196 (C=S str.) cm^{-1}. ^1H NMR: δ_H 1.03-1.08 (t, 3H, CH_3), 2.16 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 3.96-4.05 (q, 2H, CH_2), 5.32 (s, 1H, pyran H4), 7.08 (s, 2H, NH_2), 7.17-7.86 (m, 7H, Ar-H), 11.84 (s, 1H, quinolone N-H) ppm ^{13}C NMR: δ_c 14.52 (CH_3), 20.34 (CH_3), 21.67 (CH_3), 32.83 (C-4, pyran), 59.54 (CH_2), 101.12 (C-CH), 115.15, 115.57, 116.72, 117.35, 119.82, 123.06, 124.21, 125.62, 126.25, 128.37, 128.78, 129.52, 136.24, 138.92, 152.36, 159.62, 160.17, 162.32 (C=O, coumarin), 165.65 (C=O ester), 188.64 (C=S, quinolone) ppm.

3. RESULTS SECTION

A series of dihydropyrano[3,2-c]chromene derivatives 4(a-r) were synthesized by one pot cyclocondensation reaction of 2-(thio)oxo-1,2-dihydroquinoline-3-carbaldehyde 1(a-f), substituted 4-hydroxy-6,8-(un)substituted-2H-chromen-2-one 3(a-c) and ethylcynoacetate 2a refluxing under ethanol (15 mL) in the presence of piperidine as catalyst gives good yield (90–70 %).

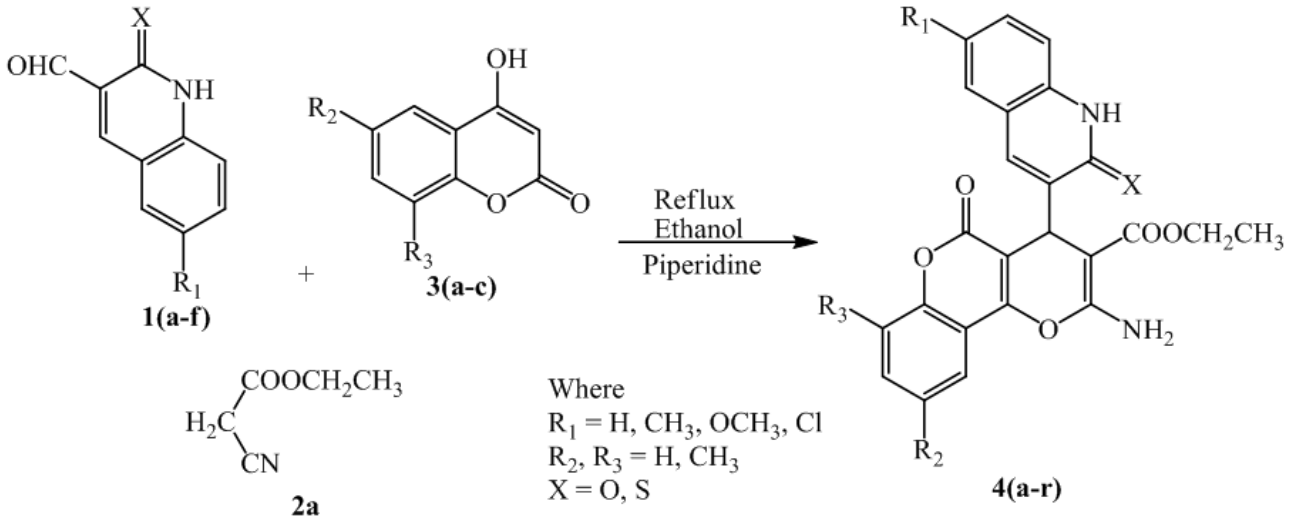

Figure 1: Synthetic procedure of compound 4(a-r)

A mechanism for the formation of pyran derivatives is outlined in (Figure 2). The reaction occurs via an in situ initial formation of the heterylidenenitrile containing the electron poor C=C double bond, from the Knoevenagel condensation between 2-(thio)oxo-1,2-dihydroquinoline-3-carbaldehyde and ethylcynoacetate by lose of water molecule. Finally, Michael addition of 4-hydroxy-6,8-(un)substituted-2H-chromen-2-one to the initially formed unsaturated nitrile, i.e. The methylene of 4-hydroxy-6,8-(un)substituted-2H-chromen-2-one reacts with the initially formed unsaturated nitrile and then nucleophilic attack of hydroxyl moiety to the cyano moiety affords cyclized pyranochromene derivatives 4(a-r). The structure of all the new synthesized compounds were characterized by their elemental analysis, IR, ^1H NMR and ^{13}C NMR spectral studies. The IR spectrum of compound 4a exhibited characteristic absorption band in the region of 3391 and 3324 cm^{-1} (asym. & sym. str.) for $–NH_2$ group, 1706 and 1658 cm^{-1} for C=O str. of carbonyl group and 1224 cm^{-1} for C-O stretching. NMR spectroscopy is especially useful to elucidate the structures of products i.e. ^1H NMR spectrum of compound 4a exhibit a sharp singlet at δ 5.38 ppm (s, 1H, -CH) for methyne proton at C-4 position of quinoline ring and δ 7.19 ppm for NH_2 of pyran ring. Aromatic protons of 4a resonates as multiplets at around δ 7.15-7.95 ppm and absence of singlet at δ 9.82–9.92 ppm (s, 1H, -CHO) indicated starting material 2-(thio)oxo-1,2-dihydroquinoline-3-carbaldehyde totally consumed. Furthermore the ^{13}C NMR spectrum showed a sharp signal at δ 34.45 ppm (C-H) (aliphatic region) ppm, which confirms the formation of fused pyranochromene derivatives by

cyclization. All the aromatic carbon of **4a** showed signals around δ 113.62-159.67 ppm in the ^{13}C NMR spectra. The signals at δ 160.29, 161.13 and 165.67 ppm assigned to carbonyl carbon of quinolone, coumarin and ester respectively. Similarly, all these compounds were characterized on the basis of spectral studies. All spectroscopic data have been given in experimental section. All the compounds were screened for their antibacterial and antifungal activities using Gentamycin, Ampicillin, Chloramphenicol, Ciprofloxacin, Norfloxacin, Nystatin and Griseofulvin as standard drugs.

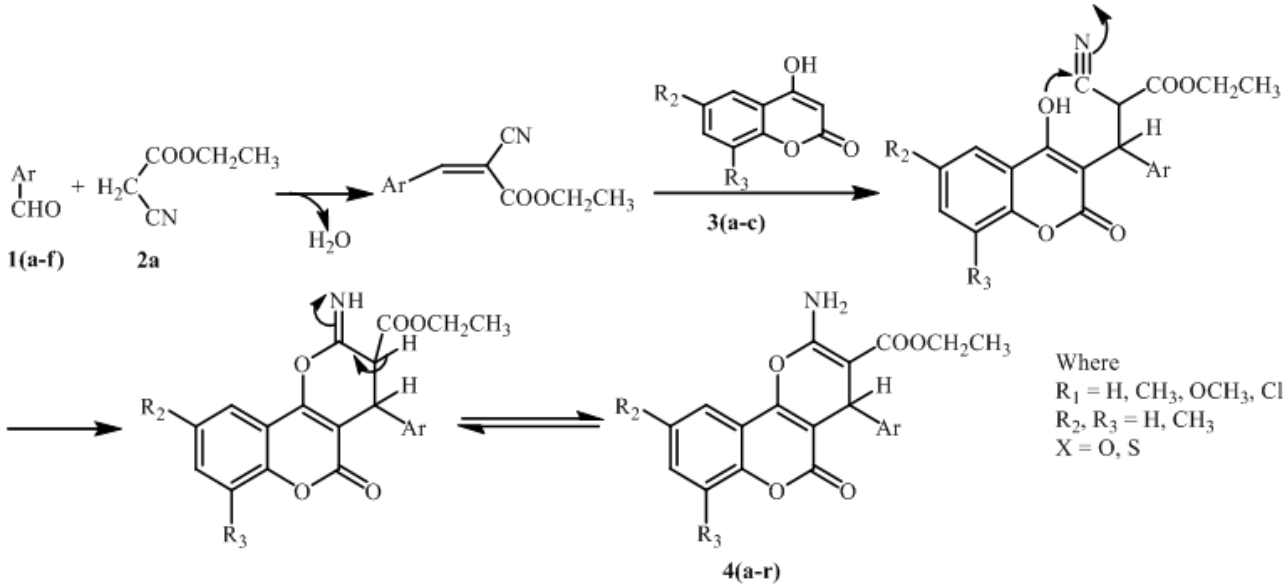

Figure 2: Possible mechanism pathway for the compound 4(a-r)

The antimicrobial activity of the synthesized dihydropyrano[3,2-c]chromene derivatives 4(a-r) was screened *in vitro* against eight pathogenic strains, of which three Gram positive bacterial strains *Streptococcus pneumoniae*, *Clostridium tetani*, *Bacillus subtilis*, three Gram negative *Salmonella typhi*, *Vibrio cholerae*, *Escherichia coli* and two fungi *Aspergillus fumigatus* and *Candida albicans*, using broth microdilution MIC method [42]. Bearing in mind that the spread of resistant strains reduces the number of available chemotherapeutic agents, the minimum inhibitory concentration (MIC) of the synthesized compounds were tested against the bacterial strains by broth dilution method. Gentamycin, Ampicillin, Chloramphenicol, Ciprofloxacin and Norfloxacin were used as reference antibacterial agents. The examination of the data (Table 1) reveals that most of the tested compounds showed excellent antibacterial and antifungal activity when compared with the standard drugs Ampicillin and Griseofulvin. Against the Gram positive strain *S. pneumoniae*, the compounds 4c, 4e and 4l (MIC = 100 μg/mL) were equally active to Ampicillin (MIC = 100 μg/mL). The compounds 4a, 4f, 4h, 4m and 4r (MIC = 250 μg/mL) were found equally potent to Ampicillin (MIC = 250 μg/mL), whereas, compounds 4c, 4i-j, 4l and 4o (MIC = 200 μg/mL) show excellent activity compared to ampicillin, towards *B. substilis*. Compounds 4d, 4p and 4q (MIC = 100 μg/mL) were found as equally potent to Norfloxacin (MIC = 100 μg/mL) and compound 4n (MIC = 50 μg/mL) showed excellent activity compared to Ampicillin and Norfloxacin, but, equally potent compared to Chloramphenicol (MIC = 50 μg/mL) and Ciprofloxacin (MIC = 50 μg/mL) towards *B. substilis*. The Compounds 4c, 4f, 4j-k, 4q and 4r (MIC = 200 μg/mL) were found to be more efficient, whereas, 4n and 4p (MIC = 250 μg/mL) were equipotent to Ampicillin (MIC = 250 μg/mL) against *C. tetani*.

Compounds 4d and 4g-I (MIC = 100 μg/mL**)** found equally potent to Ciprofloxacin (MIC = 100 μg/mL**)** and more efficient compared to Ampicillin against *C. tetani*.

Table 1: Antimicrobial activity of the compounds 4(a-r)

Compds	Minimum Inhibitory Concentration (MIC, $\mu g mL^{-1}$)							
	Gram positive bacteria			Gram negative bacteria			Fungi	
	S. p. **MTCC (*1936*)**	***B. s.*** **MTCC (*441*)**	***C. t.*** **MTCC (*449*)**	***E. c.*** **MTCC (*443*)**	***S. t.*** **MTCC (*98*)**	***V. c.*** **MTCC (*3906*)**	***C. a.*** **MTCC (*227*)**	***A. f.*** **MTCC (*3008*)**
4a	250	250	500	100	500	250	1000	1000
4b	500	500	500	500	250	500	1000	500
4c	100	200	200	250	250	200	500	>1000
4d	500	100	100	200	250	250	500	1000
4e	100	500	500	500	150	100	500	1000
4f	200	250	200	100	250	500	100	500
4g	500	500	100	100	250	50	500	500
4h	500	250	100	100	500	500	500	200
4i	200	200	100	100	500	1000	200	>1000
4j	250	200	200	500	200	250	500	1000
4k	200	500	200	125	25	200	500	1000
4l	100	200	100	100	200	100	500	500
4m	500	250	500	50	150	250	>1000	>1000
4n	250	50	250	250	150	500	200	1000
4o	200	200	500	100	250	500	1000	1000
4p	250	100	250	100	125	250	500	>1000
4q	500	100	200	500	200	200	500	1000
4r	250	250	200	250	100	50	250	500
Genta.	0.5	1	5	0.05	5	5	-	-
Ampi.	100	250	250	100	100	100	-	-
Chlora.	50	50	50	50	50	50	-	-
Cipro.	50	50	100	25	25	25	-	-
Nor.	10	100	50	10	10	10	-	-
Nyst.	-	-	-	-	-	-	100	100
Grise.	-	-	-	-	-	-	500	100

Genta.: Gentamicin, Ampi.: Ampicillin, Chlora.: Chloramphenicol, Cipro.: Ciprofloxacin, Nor: Norfloxacin, Nyst.: Nystatin, Grise.: Griseofulvin

B. s.: Bacillus subtilis, S. t.: Salmonella typhi, V. c.: Vibrio cholerae, S. p.: Streptococcus pneumoniae, E. c.: Escherichia coli, C. t.: Clostridium tetani, C. a.: Candida albicans, A. f.: Aspergillus fumigatus

MTCC—Microbial Type Culture Collection

Towards *E. coli*, compounds 4a, 4f-i, 4l and 4o-p (MIC = 100 μg/mL) exhibited an activity comparable to Ampicillin (MIC = 100 μg/mL) and compound 4m (MIC = 50 μg/mL) was more efficient than Ampicillin and equally potent to Chloramphenicol (MIC = 50 μg/mL). The compound 4r (MIC = 100 μg/mL) was equally potent to Ampicillin (MIC = 100 μg/mL), whereas, compound 4k (MIC = 25 μg/mL) proved to be more active than Ampicillin and Chloramphenicol (MIC = 50 μg/mL), and equally active to Ciprofloxacin (MIC = 25 μg/mL), towards *S. typhi*. The compounds 4e and 4l (MIC = 100 μg/mL) were found equally potent where as 4g and 4r (MIC = 50 μg/mL) showed better activity to Ampicillin (MIC = 100 μg/mL) have been equally potent to Chloramphenicol (MIC = 50 μg/mL), against *V. cholerae*. All the compounds were also tested against two fungal strains (*Candida albicans* and *Aspergillus fumigatus*) using Nystatin and Griseofulvin as reference antifungal agents. Against *C. albicans*, compounds 4i, 4n (MIC = 200 μg/mL) and 4r (MIC = 250 μg/mL**)** exhibited better activity whereas, 4c-e, 4g-h, 4j-l and 4p-q (MIC = 500 μg/mL) were found

to be equipotent compared to Griseofulvin (MIC = 500 $\mu g/$mL). Compound 4f (MIC = 100 $\mu g/$mL) showed better activity compared to Griseofulvin and was equipotent to Nystatin (MIC = 100 $\mu g/$mL**)**. The remaining compounds showed moderate to good activity being all less effective than standard drugs.

4. CONCLUSIONS

A new series of dihydropyrano[3,2-c]chromene derivatives has been synthesized by one pot cyclocondensation reaction of 2-(thio)oxo-1,2-dihydroquinoline-3-carbaldehyde, substituted 4-hydroxy-6,8-(un)substituted-2H-chromen-2-one and ethylcynoacetate in presence of piperidine as a catalyst and characterized by elemental as well as spectral analysis. It can be concluded from antimicrobial screening, against a panel of bacterial and fungal strains that most of the synthesized dihydropyrano[3,2-c]chromene derivatives were found to be highly active against the bacterial strains compared to standard drugs. Among them, many compounds were found to be the most active against *B. subtilis* and *C. tetani* when compared to the rest of the tested species. Antifungal activity of the compounds showed that the most of the compounds found to be more potent against *C. albicans* when compared to *A. fumigatus*. It is worth mentioning that combination of two biologically active moieties profoundly influences the biological activity.

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