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A Greener Approach for Synthesis of Quinoline-3-carboxylate Building Block and their Biological Screening

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ABSTRACT

The analogs of nitrogen-based heterocycles occupy an exclusive position as a value of more than 75% of drugs approved by the FDA and currently available in the market are nitrogen-containing heterocyclic moieties. Among many N-containing heterocycles, quinolines have become important due to their variety of applications in medicinal, synthetic organic chemistry as well as in the field of industrial chemistry. Present work gives information about the green and clean synthesis using multicomponent reactions (MCRs) methods and *L*-proline and ammonium acetate as a catalyst for the synthesis of quinoline derivatives. Synthesized quinoline derivatives undergo spectroscopic analysis and their biological evaluation.

KEYWORDS

Green synthesis, Biginelli reactions, Quinolines, Biological activities.

INTRODUCTION

Heterocyclic compounds are organic compounds with a ring structure that contains in the cycle at least one carbon atom and at least one other element, such as N, O, or S. Fused heterocycles are structurally important motifs and represent one of the abundant classes in organic chemistry, which have extensive applications [1,2]. Among the nitrogen heterocycles, quinoline and its derivatives have always attracted both synthetic and biological chemists because of its diverse chemical and pharmacological properties [3]. In medicinal and material chemistry, the number of novel N-heterocyclic moieties with significant physiological properties and promising applications in medicinal chemistry is ever-growing. In this work, we report on novel nitrogen-containing hetero-cycles and their distinct biological activities [4] especially, nitrogen-fused poly heterocyclic compounds [5,6] are diverse widely in natural products and pharmaceutical agents. The recent study quinoline motifs explained enriched with progressive findings of the synthesis and pharmacological views of quinoline and its derivatives [4]. Quinoline and its derivatives tested with diverse biological activity constitute an important class of compounds for new drug development. The quinoline bearing some novel derivatives with the efficient and convenient synthesis protocol for

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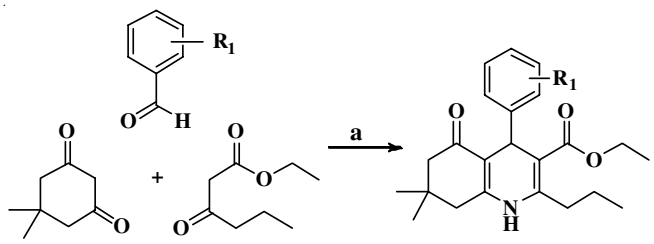
the development of newer fused heterocyclic scaffold through the combination of different pharmacophores in a molecular framework is of considerable interest due to a wide variety of such molecules showing promising biological activities. Some reported quinoline derivatives have been found to possess various biological activities like antimalarial, antibacterial, antifungal, antiasthmatic, antihypertensive, anti-inflammatory and antiplatelet activities [7]. They also exhibit immune depressing activities and antitubercular [8]. There are a few promising compounds with the quinoline ring system, like pamaquine, chloroquine, tafenoquine, bulaquine, quinine and mefloquine as an antimalarial agents and amodiaquine as an antimalarial and anti-inflammatory agent [9,10].

In this work, a new series of quinoline-3-carboxylate derivatives were synthesized *via* Biginelli [11] one-pot multicomponent reactions (MCRs) of different aromatic aldehydes, urea and substituted diketo compounds, using different molecular ratios and different reaction conditions [12]. Herein, we followed a green synthesis approaches towards the mild, non-hazardous conditions and non-metallic catalyst. Small amino acid molecules like *L*-proline was used as a potent catalyst for organic transformation for the Biginelli (MCRs).Thus, synthesis of quinoline-3-carboxylates (**YUG-201** to **YUG-210**) was accomplished by a one-pot multicomponent reaction of dimedone, an appropriate 1,3-bifunctional synthon, appropriate aldehydes, ammonium acetate and *L*-proline using ethanol as a solvent. The products were characterized by FT-IR, mass spectra, ^{1}H NMR, ^{13}C NMR and elemental analysis. The newly synthesized compounds were subjected to evaluate the various biological activities *viz.*, antimicrobial, antiviral antimycobacterial and anticancer activities.

EXPERIMENTAL

The entire chemicals, solvents and reagents were purchased from Spectrochem, Sigma-Aldrich, Loba Chemi and used without further purification. Monitoring of reaction was carried out with silica gel GF_{254} (Merck) TLC plates. Melting points determined by open glass capillary method and are uncorrected. The FT-IR spectra were recorded on a Shimadzu-8200 infinity IR spectrophotometer with KBr pellet method, ^{1}H & ^{13}C spectra were obtained on a Bruker AVANCE-III 400 MHz spectrometer, using TMS used as an internal reference. Mass (EI) spectra were recorded on a SHIMADZU QP-2010 mass spectrometer. Elemental analysis of all the synthesized compounds was carried out on the Elemental Vario EL III Carlo Erba 1108 model and the results were in agreement with the structures assigned.

General procedure for the synthesis of ethyl 1,4,5,6,7,8-hexahydro-7,7-dimethyl-5-oxo-4-(aryl)-2-propylquinoline-3-carboxylate (YUG-201 to YUG-210): A round bottom flask charged with the mixture of dimedone (0.01 mol), ethyl 3-oxohexanoate (0.01 mol) and an appropriate aromatic aldehyde (0.01 mol), ammonium acetate (0.01 mol) and *L*-proline (0.001 mol) in 8-10 mL of EtOH was stirred for 30 to 40 min. After completion of the reaction, the reaction mass was poured into crushed ice and desired solid product was precipitated out. The solid product was isolated by simple vacuum filtration, washed with hexane. The products were recrystallized from ethanol (**YUG-201** to **YUG-210**) (**Scheme-I**).



(YUG 201-210)

Reagents & conditions: (a) NH_4OAc; *L*-proline; EtOH, Stirring, 30-40 min (for R_1 see Table-1)

Scheme-I: General synthetic scheme for quinoline-3-carboxylate and 3-carboxamide derivatives

Spectral data

Ethyl,1,4,5,6,7,8-hexahydro-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-2-propylquinoline-3-carboxylate (YUG-201): Yield: 80%; m.p.: 188-190 ºC; R_f: 0.55; IR (KBr, ν_{max}, cm^{-1}): 3279 (N-H stretching of pyridine ring), 3088 (C-H stretching of aromatic ring), 2883 (C-H stretching of alkane), 1697 (C=O stretching of carbonyl group of ester), 1649 (C=O stretching of carbonyl group of cyclohexanone), 1606 (N-H deformation pyridine ring), 1259 (C-O-C- stretching of ester) 1085 (C-H in plane bending of aromatic ring), 852 (C-H out of plane bend-ing for 1,4-disubstituted aromatic ring); ^{1}H NMR (DMSO-d_6) δ ppm: 0.89 (s, 3H), 0.93-0.97 (t, 3H,), 1.04 (s, 3H), 1.17-1.20 (t, 3H), 1.55-1.62 (m, 2H), 1.98-2.02 (d, 1H), 2.13-2.17 (d, 1H), 2.13-2.17 (d, 1H), 2.35-2.39 (d, 1H), 2.62-2.70 (m, 2H), 3.69 (s, 1H), 3.97-4.02 (q, 2H), 4.84 (s, 1H), 6.67-6.70 (dd, 2H, *J* = 9.74 Hz), 7.09-7.11 (dd, 2H, *J* = 8.68 Hz), 8.77 (s, 1H); MS: *m/z* 397; Anal. calcd. (found) % for $C_{24}H_{31}NO_4$ (*m.w.* 397): C, 72.52 (72.49); H, 7.86 (7.82); N, 3.52 (3.48).

Ethyl 1,4,5,6,7,8-hexahydro-7,7-dimethyl-5-oxo-2-propyl-4-*p*-tolylquinoline-3-carboxylate (YUG-202): Yield: 78%; m.p.: 218-220 ºC; R_f: 0.51; IR (KBr, ν_{max}, cm^{-1}): 3273 (N-H stretching of pyridine ring), 3088 (C-H stretching of aromatic ring), 2885 (C-H stretching of alkane), 1699 (C=O stretching of carbonyl group of ester), 1629 (C=O stretching of carbonyl group of cyclohexanone), 1608 (N-H deformation pyridine ring), 1259 (C-O-C- stretching of ester) 1085 (C-H in plane bending of aromatic ring), 850 (C-H out of plane bending for 1,4-disubstituted aromatic ring); ^{1}H NMR (DMSO-d_6) δ ppm: 0.89 (s, 3H), 0.93-0.97 (t, 3H), 1.05 (s, 3H), 1.17-1.21 (t, 3H), 1.56-1.61 (m, 2H), 1.97-2.02 (d, 1H), 2.13-2.17 (d, 1H), 2.22 (s, 3H), 2.28-2.40 (m, 2H), 2.62-2.70 (m, 2H), 3.97-4.02 (q, 2H), 4.85 (s, 1H), 6.93-6.95 (d, 2H, *J* = 7.92 Hz), 7.06-7.08 (d, 2H, *J* = 8.04 Hz), 8.75 (s, 1H); MS: *m/z* 381; Anal. calcd. (found)% for $C_{24}H_{31}NO_3$ (*m.w.* 381): C, 75.56 (75.53); H, 8.19 (8.15); N, 3.67 (3.63).

Ethyl 4-(4-fluorophenyl)-1,4,5,6,7,8-hexahydro-7,7-dimethyl-5-oxo-2-propyl-quinoline-3-carboxylate (YUG-203): Yield: 81%; m.p.: 162-164 ºC; R_f: 0.61; IR (KBr, ν_{max}, cm^{-1}): 3273 (N-H stretching of pyridine ring), 3088 (C-H stretching of aromatic ring), 2889 (C-H stretching of alkane), 1703 (C=O stretching of carbonyl group of ester), 1649 (C=O stretching of carbonyl group of cyclohexanone), 1606 (N-H deformation pyridine ring), 1282 (C-O-C- stretching of ester) 1084 (C-H in plane bending of aromatic ring), 854 (C-H out

of plane bending for 1,4-disubstituted aromatic ring); ^{1}H NMR (DMSO-d_6) δ ppm: 0.86 (s, 3H), 0.93-0.97 (t, 3H), 1.04 (s, 3H), 1.14-1.18 (t, 3H), 1.54-1.64 (m, 2H), 1.97-2.01 (d, 1H), 2.13-2.18 (d, 1H), 2.27-2.31 (d, 1H), 2.36-2.40 (d, 1H), 2.61-2.74 (m, 2H), 3.95-4.03 (m, 2H), 4.88 (s, 1H), 6.86-6.91 (t, 2H, *J* = 8.84 Hz), 7.16-7.20 (dd, 2H, *J* = 6.56 Hz), 8.88 (s, 1H); MS: *m/z* 385; Anal. calcd. (found) % for $C_{23}H_{28}NO_3F$ (*m.w.* 385): C, 71.66 (71.63); H, 7.32 (7.28); N, 3.63 (3.60).

Ethyl 4-(4-chlorophenyl)-1,4,5,6,7,8-hexahydro-7,7-dimethyl-5-oxo-2-propyl-quinoline-3-carboxylate (YUG-204): Yield: 72%; m.p.: 128-130 ºC; R_f: 0.57; IR (KBr, ν_{max}, cm^{-1}): 3273 (N-H stretching of pyridine ring), 3088 (C-H stretching of aromatic ring), 2872 (C-H stretching of alkane), 1703 (C=O stretching of carbonyl group of ester), 1649 (C=O stretching of carbonyl group of cyclohexanone), 1606 (N-H deformation pyridine ring), 1282 (C-O-C- stretching of ester) 1084 (C-H in plane bending of aromatic ring), 842 (C-H out of plane bending for 1,4-disubstituted aromatic ring); ^{1}H NMR (DMSO-d_6) δ ppm: 0.86 (s, 3H), 0.93-0.97 (t, 3H), 1.04 (s, 3H), 1.14-1.18 (t, 3H), 1.57-1.60 (m, 2H), 1.97-2.01 (d, 1H), 2.13-2.18 (d, 1H), 2.27-2.31 (d, 1H), 2.36-2.41 (d, 1H), 2.65-2.69 (m, 2H), 3.96-4.01 (q, 2H), 4.86 (s, 1H), 7.16 (d, 4H, *J* = 1.00 Hz), 8.92 (s, 1H); ^{13}C NMR (DMSO-d_6) δ ppm: 13.67, 13.95, 21.83, 26.48, 29.16, 32.02, 32.95, 35.61, 50.25, 58.94, 103.08, 109.61, 127.35, 129.11, 130.25, 146.44, 149.33, 149.60, 166.28, 194.05; MS: *m/z* 401; Anal. calcd. (found) % for $C_{23}H_{28}NO_3Cl$ (m.w. 401): C, 68.73 (68.69); H, 7.02 (7.00); N, 3.48 (3.44).

Ethyl 4-(3-chlorophenyl)-1,4,5,6,7,8-hexahydro-7,7-dimethyl-5-oxo-2-propyl-quinoline-3-carboxylate (YUG-205): Yield: 78%; m.p.: 216-219 ºC; R_f: 0.48; IR (KBr, ν_{max}, cm^{-1}): 3275 (N-H stretching of pyridine ring), 3086 (C-H stretching of aromatic ring), 2872 (C-H stretching of alkane), 1701 (C=O stretching of carbonyl group of ester), 1649 (C=O stretching of carbonyl group of cyclohexanone), 1608 (N-H deformation pyridine ring), 1280 (C-O-C- stretching of ester) 1084 (C-H in plane bending of aromatic ring); ^{1}H NMR (DMSO-d_6) δ ppm: 0.88 (s, 3H), 0.94-0.98 (t, 3H), 1.04 (s, 3H), 1.15-1.19 (t, 3H), 1.55-1.65 (m, 2H), 1.99-2.03 (d, 1H), 2.15-2.19 (d, 1H), 2.30-2.37 (d, 1H), 2.37-2.41 (d, 1H), 2.63-2.74 (m, 2H), 3.94-4.06 (q, 2H), 4.89 (s, 1H), 7.07 (d, 2H, *J* = 1.88 Hz), 7.11-7.16 (m, 2H), 7.18 (, 1H), 8.94 (s, 1H); ^{13}C NMR (DMSO-d_6) δ ppm: 13.64, 13.91, 21.82, 26.46, 29.12, 32.04, 32.97, 36.05, 50.24, 58.99, 102.93, 109.44, 125.36, 125.88, 127.52, 129.10, 132.42, 149.51, 149.76, 149.82, 166.23, 194.09; MS: *m/z* 401; Anal. calcd. (found) % for $C_{23}H_{28}NO_3Cl$ (*m.w.* 401): C, 68.73 (68.68); H, 7.02 (7.01); N, 3.48 (3.45).

Ethyl 4-(4-bromophenyl)-1,4,5,6,7,8-hexahydro-7,7-dimethyl-5-oxo-2-propyl-quinoline-3-carboxylate (YUG-206): Yield: 86%; m.p.: 86-88 ºC; R_f: 0.60; IR (KBr, ν_{max}, cm^{-1}): 3275 (N-H stretching of pyridine ring), 3086 (C-H stretching of aromatic ring), 2872 (C-H stretching of alkane), 1701 (C=O stretching of carbonyl group of ester), 1649 (C=O stretching of carbonyl group of cyclohexanone), 1608 (N-H deformation pyridine ring), 1280 (C-O-C- stretching of ester) 1084 (C-H in plane bending of aromatic ring), 842 (C-H out of plane bending for 1,4-disubstituted aromatic ring); ^{1}H NMR (DMSO-d_6) δ ppm: 0.87 (s, 3H), 0.94-0.97 (t, 3H), 1.04 (s, 3H), 1.15-1.19 (t, 3H), 1.56-1.62 (m, 2H), 1.98-2.02 (d, 1H), 2.14-2.18 (d, 1H), 2.27-2.31 (d, 1H), 2.36-2.40 (d, 1H), 2.64-2.71 (m, 2H), 3.96-4.02 (q, 2H), 4.87 (s, 1H), 7.11-7.14 (m, 2H), 7.27-7.30 (m, 2H), 8.88 (s, 1H); ^{13}C NMR (DMSO-d_6) δ ppm: 13.66, 13.93, 21.82, 26.51, 29.16, 32.01, 32.99, 35.73, 50.26, 58.94, 103.08, 109.59, 118.63, 129.53, 130.23, 146.87, 149.31, 149.61, 166.30, 194.12; MS: *m/z* 445; Anal. calcd. (found) % for $C_{23}H_{28}NO_3Br$ (m.w. 445): C, 61.89 (61.85); H, 6.32 (6.28); N, 3.14 (3.11).

Ethyl 4-(2-chlorophenyl)-1,4,5,6,7,8-hexahydro-7,7-dimethyl-5-oxo-2-propyl-quinoline-3-carboxylate (YUG-207): Yield: 76%; m.p.: 88-90 ºC; R_f: 0.52; IR (KBr, ν_{max}, cm^{-1}): 3290 (N-H stretching of pyridine ring), 3080 (C-H stretching of aromatic ring), 2870 (C-H stretching of alkane), 1701 (C=O stretching of carbonyl group of ester), 1645 (C=O stretching of carbonyl group of cyclohexanone), 1604 (N-H deformation pyridine ring), 1280 (C-O-C- stretching of ester) 1080 (C-H in plane bending of aromatic ring); ^{1}H NMR (DMSO-d_6) δ ppm: 0.87 (s, 3H), 0.93-0.97 (t, 3H), 1.03 (s, 3H), 1.11-1.14 (t, 3H), 1.53-1.63 (m, 2H), 1.92-1.97 (d, 1H), 2.11-2.15 (d, 1H), 2.26-2.30 (d, 1H), 2.36-2.40 (d, 1H), 2.51-2.74 (m, 2H), 3.95-3.97 (q, 2H), 5.24 (s, 1H), 7.04-7.09 (m, 1H), 7.10-7.13 (m, 1H), 7.16-7.09 (m, 1H), 7.30-7.32 (m, 1H), 8.88 (s, 1H); ^{13}C NMR (DMSO-d_6) δ ppm: 13.72, 13.95, 21.73, 26.46, 29.16, 31.84, 32.92, 34.96, 50.33, 58.82, 103.30, 109.41, 126.17, 126.78, 128.79, 131.34, 132.03, 145.08, 148.78, 149.83, 166.47, 193.81; MS: *m/z* 401; Anal. calcd. (found) % for $C_{23}H_{28}NO_3Cl$ (*m.w.* 401): C, 68.73 (68.68); H, 7.02 (7.01); N, 3.48 (3.45).

Ethyl 4-(2-bromophenyl)-1,4,5,6,7,8-hexahydro-7,7-dimethyl-5-oxo-2-propyl-quinoline-3-carboxylate (YUG-208): Yield: 80%; m.p.: 168-172 ºC; R_f: 0.62; (KBr, ν_{max}, cm^{-1}): 3286 (N-H stretching of pyridine ring), 3065 (C-H stretching of aromatic ring), 2870 (C-H stretching of alkane), 1699 (C=O stretching of carbonyl group of ester), 1645 (C=O stretching of carbonyl group of cyclohexanone), 1604 (N-H deformation pyridine ring), 1280 (C-O-C-stretching of ester) 1078 (C-H in plane bending of aromatic ring); ^{1}H NMR (DMSO-d_6) δ ppm: 0.87 (s, 3H), 0.93-0.97 (t, 3H), 1.03 (s, 3H), 1.11-1.15 (t, 3H), 1.54-1.64 (m, 2H), 1.92-1.96 (d, 1H), 2.11-2.15 (d, 1H), 2.26-2.31 (d, 1H), 2.36-2.41 (d, 1H), 2.52-2.72 (m, 2H), 3.97-4.00 (q, 2H), 5.20 (s, 1H), 6.92-6.96 (m, 1H), 7.14-7.18 (m, 1H), 7.28-7.31 (m, 1H), 7.35-7.38 (m, 1H), 8.90 (s, 1H); ^{13}C NMR (DMSO-d_6) δ ppm: 13.72, 14.09, 21.71, 26.54, 29.13, 31.85, 32.89, 37.07, 50.37, 58.78, 103.80, 109.75, 122.37, 126.93, 127.04, 131.27, 132.11, 147.02, 148.47, 149.72, 166.50, 193.80; MS: *m/z* 445; Anal. calcd. (found) % for $C_{23}H_{28}NO_3Br$ (*m.w.* 445): C, 61.89 (61.85); H, 6.32 (6.29); N, 3.14 (3.10).

Ethyl 1,4,5,6,7,8-hexahydro-4-(3,4-dimethoxyphenyl)-7,7-dimethyl-5-oxo-2-propylquinoline-3-carboxylate (YUG-209): Yield: 88%; m.p.: 180-182 ºC; R_f: 0.50; IR (KBr, ν_{max}, cm^{-1}): 3268 (N-H stretching of pyridine ring), 3071 (C-H stret-ching of aromatic ring), 2882 (C-H stretching of alkane), 1689 (C=O stretching of carbonyl group of ester), 1657 (C=O stret-ching of carbonyl group of cyclohexanone), 1585 (N-H defor-mation pyridine ring), 1270 (C-O-C- stretching of ester) 1068 (C-H in plane bending of aromatic ring); ^{1}H NMR (DMSO-d_6) δ ppm: 0.87 (s, 3H), 0.91-0.94 (t, 3H), 1.03 (s, 3H), 1.16-1.19 (t, 3H), 1.52-1.58 (m, 2H), 2.02-2.06 (d, 1H), 2.31-2.33 (d, 1H), 2.25-2.29 (d, 1H), 2.33-2.37 (d, 1H), 2.41-2.48 (m,

2H), 2.77 (s, 3H), 2.80 (s, 3H), 3.98-4.01 (m, 2H), 5.02 (s, 1H), 6.51-6.54 (m, 1H), 6.66-6.78 (d, 1H, *J* = 8.88 Hz), 6.73-6.74 (d, 1H, *J* = 3.12 Hz), 8.72 (s, 1H); MS: *m/z* 427; Anal. calcd. (found) % for $C_{25}H_{33}NO_5$ (*m.w.* 427): C, 70.23 (70.20); H, 7.78 (7.74); N, 3.28 (3.24).

Ethyl 1,4,5,6,7,8-hexahydro-4-(2,5-dimethoxyphenyl)-7,7-dimethyl-5-oxo-2-propylquin-oline-3-carboxylate (YUG-210): Yield: 77%; m.p.: 182-184 ºC; R_f: 0.56; IR (KBr, ν_{max}, cm^{-1}): 3279 (N-H stretching of pyridine ring), 3074 (C-H stretching of aromatic ring), 2899 (C-H stretching of alkane), 1699 (C=O stretching of carbonyl group of ester), 1647 (C=O stretching of carbonyl group of cyclohexanone), 1597 (N-H deformation pyridine ring), 1280 (C-O-C- stretching of ester) 1082 (C-H in plane bending of aromatic ring); ^{1}H NMR (DMSO-d_6) δ ppm: 0.89 (s, 3H), 0.92-0.95 (t, 3H), 1.04 (s, 3H), 1.15-1.19 (t, 3H), 1.52-1.59 (m, 2H), 1.93-1.97 (d, 1H), 2.11-2.14 (d, 1H), 2.24-2.28 (d, 1H), 2.34-2.38 (d, 1H), 2.43-2.50 (m, 2H), 2.73 (s, 3H), 2.74 (s, 3H), 3.95-3.98 (m, 2H), 5.05 (s, 1H), 6.56-6.59 (m, 1H), 6.68-6.70 (d, 1H, *J* = 8.88 Hz), 6.74-6.75 (d, 1H, *J* = 3.12 Hz), 8.70 (s, 1H); MS: *m/z* 427; Anal. calcd. (found) % for $C_{25}H_{33}NO_5$: C, 70.23 (70.19); H, 7.78 (7.75); N, 3.28 (3.23).

RESULTS AND DISCUSSION

The quinoline-3-carboxylates (**YUG-201** to **YUG-210**) was synthesized with the reaction of aromatic aldehyde, ketone and ester *via* one-pot MCRs reaction using ammonium acetate and *L*-proline as catalyst and co-catalyst, respectively. The most viable reaction conditions, it was observed that without the use of *L*-proline in the reaction less progressed. But with the combination of catalyst and co-catalyst reactions get faster. For further investigations, the reaction methodology against various aromatic aldehyde and ester substrate were also checked and the reaction was successfully conducted without any problem. All substrates were sufficient pure and had a moderate yield.

Antimicrobial activity: All the synthesized compounds (**YUG-201** to **YUG-210**) were tested for their antibacterial and antifungal activity (MIC) *in vitro* by broth dilution method [13] with two Gram-positive bacteria *Staphylococcus aureus* MTCC-96, *Streptococcus pyogenes* MTCC 442, two Gram-negative bacteria *Escherichia coli* MTCC 443, *Pseudomonas aeruginosa* MTCC 424 and three fungal strains *Candida albicans* MTCC 227, *Aspergillus niger* MTCC 282, *Aspergillus clavatus* MTCC 1323 taking ampicillin, chloramphenicol, ciprofloxacin, norfloxacin, nystatin and griseofulvin as standard drugs. The standard strains were procured from the microbial type culture collection (MTCC) and Gene Bank, Institute of Microbial Technology, Chandigarh, India.

The minimal inhibitory concentration (MIC) values for all the newly synthesized compounds, defined as the lowest concentration of the compound preventing the visible growth, were determined by using the microdilution broth method according to NCCLS standards [14]. Serial dilutions of the test compounds and reference drugs were prepared in Mueller-Hinton agar. Drugs (10 mg) were dissolved in 1 mL of DMSO. Further progressive dilutions with melted Mueller-Hinton agar were performed to obtain the required concentrations. In primary screening 1000, 500 and 250 μg mL^{-1} concentrations of the synthesized drugs were taken. The active synthesized drugs found in this primary screening were further tested in the second set of dilutions at 125, 100, 62.5, 50, 25, 12.5 and 6.25 μg mL^{-1} concentration against all microorganisms. The tubes were inoculated with 10^8 cfu mL^{-1} at 37 ºC for 24 h. The MIC was the lowest concentration of the tested compound that yields no visible growth (turbidity) on the plate. To ensure that the solvent did not affect the bacterial growth, a control was performed with the test medium supplemented with DMSO at the same dilutions as used in the experiments and it was observed that DMSO did not affect the microorganisms in the concentrations studied. The results obtained from antimicrobial susceptibility testing are depicted in Table-1.

Conclusion

In summary, a simple and efficient protocol for the synthesis of quinoline-3-carboxylate by *L*-proline catalyzed

TABLE-1
ANTIBACTERIAL AND ANTIFUNGAL ACTIVITY OF THE SYNTHESIZED COMPOUND

Compounds	R_1	Minimum inhibition concentration (μg mL^{-1})						
		Gram-positive		Gram-negative		Fungal species		
		Staphylococcus aureus	*Streptococcus pyogenes*	*Escherichia coli*	*Pseudomonas aeruginosa*	*Candida albicans*	*Aspergillus niger*	*Aspergillus clavatus*
YUG-01	4-OCH_3	62.5	100	62.5	62.5	100	100	125
YUG-02	4-CH_3	100	100	62.5	62.5	100	100	100
YUG-03	4-F	62.5	62.5	100	100	100	100	125
YUG-04	4-Cl	100	100	250	250	100	100	250
YUG-05	3-Cl	62.5	62.5	100	100	100	100	100
YUG-06	4-Br	100	125	100	100	100	100	125
YUG-07	2-Cl	62.5	62.5	100	100	100	100	100
YUG-08	2-Br	62.5	100	50	62.5	100	100	125
YUG-09	3,4-OCH_3	64.5	125	50	62.5	100	100	100
YUG-10	2,5-OCH_3	65	120	55	60	100	100	125
Ampicillin		250	100	100	100	–	–	–
Chloramphenicol		50	50	50	50	–	–	–
Ciprofloxacin		50	50	25	25	–	–	–
Norfloxacin		10	10	10	10	–	–	–
Nystatin		–	–	–	–	100	100	100
Griseofulvin		–	–	–	–	500	100	100

condensation of diketone compounds, ammonium acetate and aldehydes under non-toxic as well as greener synthesis conditions provided an efficient, eco-friendly and much-improved modification of classical Biginelli reaction. The present procedure will find the easiest and important applications in the synthesis of quinoline motifs to fulfil the requirement of academia as well as pharmaceutical industries.

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