Microwave Assisted Regioselective Synthesis and Biological Evaluation of Pyrano[2,3-c]Pyridine Derivatives Utilizing DMAP as a Catalyst

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Abstract: Regioselective facile production of pyrano[2,3-c]pyridine through multicomponent reaction of aromatic aldehydes, ethyl cyanoacetate or malononitrile and C-H activated compound of 3-hydroxy picolinic acid in the occurrence of smaller amount of DMAP catalyst utilizing microwave apparatus, which is green and simple environmentally with high yield, recyclability catalyst. Totally the products were partitioned for antimicrobiogical action; it was detected that were active in contrast to S. pneumonia, E. coli and Candida albicans such as equated to typical drugs. Compounds of pyrano[2,3-c]pyridine-8-carboxylic acid derivatives 4i, 4e, 4p and 4p demonstrated effective development inhibitory activities. Additionally, the manufactured products were partitioned for in vitro-antioxidant action by DPPH analysis. Products of pyrano[2,3-c]pyridine 4o and 4p were worthy free radical scavenging action through IC$_{50}$ values of 252.52 and 223.2 µM; respectively.

Keywords: Multicomponent Reactions (MCR), 4-Dimethylaminopyridine (DMAP), Pyrano[2,3-c]Pyridine, Antimicrobial and Antioxidant Activity

Introduction

Multicomponent Reactions (MCR) have attempted extensive thought in combinatorial and biological chemistry (Thomas, 2017; Zhu, 2003; Zhu and Bienayme, 2005; Dömling, 2006; Dömling and Ugi, 2000). We established successfully numerous catalytic agent in organic synthesis exhausting MCR approach (Karnakar et al., 2015). The catalyst attractiveness is decrease of solvents ratios (Khan et al., 2008; 2010a; Khan 2010b and Khan, 2011) and furthermore performance role in the yield of the product. This would be inexpensive, mild and environmentally friendly for attention to the synthetic organic researcher. Dimethyl Amino Pyridine (DMAP) is a catalyst of outstanding effectiveness in a variation group-transfer reactions and considered for applications in stereo selective catalysis (Armand et al., 2014).

Pyrane and fused 4H-pyrene derivatives have concerned of interest (Dean, 1963) outstanding to their varied physiological activities. (Feuer, 1974) Earlier studies have presented that pyran derivatives possess pronounced chemical and biological activities, such antimicrobial activity, (Bonsignore et al., 1993; Ashraf, 2012) anti-coagulant, (Akbar et al., 2015; Dinesh et al., 2017) anti-tumor and anti-HIV. Additionally, their besides valuable for the neurodegenerative disorder behavior, for instance Alzheimer, lateral amyotrophic sclerosis, Huntington's and Parkinson diseases (Fan et al., 2010). Moreover, they are similarly used as cosmetics, (Vyas et al., 2009) pigments, doze and useful as photoactive fabric (Nandakumar et al., 2010). In recent times, a limited approaches have been informed by hiring three-constituent responses exhausting different catalyst like as DBU (1,8-Diazabicyclo[5.4.0]undec-7-ene) (Wen et al., 2001), TBAB(Tetra-n-butylammonium bromide) (Yusuke et al., 2016), ammonium phosphate (Saeed et al., 2015; 2007; Jitender and Ankita, 2012) hetero-poly supermans (Brahmachari et al., 2014). However, these procedures informed through, others are relatively beneficial, stable, there is auxiliary opportunity to improve innovative approach exhausting inexpensive catalyst above mild reaction stipulation and appropriate to a widespread variety of substrates.

Materials and Methods

General Instruments

Gallenkamp melting point apparatus were used for measuring the melting points. Furthermore the instrument
Shimadzu FT-IR 8101 PC infrared spectrophotometer was used to record the IR spectrum. The ¹H-NMR and ¹³C-NMR signals were evaluated in Deuterated Chloroform (CDCl₃) or DEUTERATED DIMETHYL SULFOXIDE (DMSO-d₆) at 300 MHz on a Varian Mercury-VX 300 NMR spectrometer (¹H at 300 MHz, ¹³C at 75MHz) exhausting Trimethylsilane (TMS) as an internal signal. Shimadzu GCMS-QP 1000 EX mass spectrometer was used for detect the mass spectra at 70 eV. Elemental analyses were supported through Micro-analytical Center of Cairo University, Giza, Egypt. CEM Discover™ microwave instrument used for Microwave experiments.

Material and Reagents

3-hydroxypicolinicacid, benzaldehyde, 4-methylbenzaldehyde, 4-chlorobenzaldehyde, 4-methoxybenzaldehyde, formaldehyde, isonicotine aldehyde from Aldrich Chemical CO. Ethanol and petroleum ether; chloroform where BDH chemical reagents.

Synthesis

Thermal Method

Different of aromatic aldehydes (1mmol) and malononitrile, ethyl cyanoacetate (1mmol) in 4ml of ethanol was supplementary the catalyst DMAP (0.025g, 0.2mmol) and reserved magnificent at room tempeture. The obtained participation was formed instantaneous ly take 30-45 min in case of ethyl cyanoacetate while in malononitrile take few minutes and checked via Thin Layer Chromatography (TLC) and formerly allowable to the precipiced product approached out underneath hot condition. Then Recrystallization from suitable solvent.

Microwave Method

Solution of aromatic aldehydes (1mmol) and malononitrile, ethyl cyano-acetate (1mmol) in 4ml of ethanol was additional the catalyst DMAP (0.025g, 0.2mmol) were diversified in Plus process vessel HP-500. The vessel was persevered accurately and irradiated through microwave underneat under pressure environments (17.2 bar, 100°C) (Elham et al., 2014; Salem et al., 2015) assumed for 1-5 min with or without stirring After 5 min one-time the reaction mix was transformed to pure solution, the precipiced product approached out underneat hot condition at the required period mention in Table 2 (tested by TLC), The reaction mix was transported to typical temperature and formed precipitated was strained off to acquire the preferred products 4a-4p.

2-Amino-3-Cyano-4-Phenyl-4H-Pyrano[2,3-c]Pyridine-8-Carboxylic Acid (4b)

C₁₉H₁₈N₂O₃ (329.32), Dark brown (225-226°C), Elemental analysis: C: 63.53(63.55), H: 4.74(4.75), N: 8.23(8.22), IR (KBr) $\nu_{max}$ cm⁻¹: 3410(OH), 3100-3290(NH₂) 1755(C = O), ¹HNMR (DMSO-d₆): $\delta$ 1.42(t, 3H, H₃, J = 3.1Hz), 4.23 (q, 2H, H₂C, J = 3.1Hz), 4.65 (s,1H, HC), 6.72 (s, 2H, H₂N D₂O exchangeable), 7.21-7.33(m, 5H, HC aromatic), 8.10 (d, 1H, HC, J = 12Hz), 8.58(d, 1H, HC aromatic, J = 12Hz), 12.025(s, 1H, HO acid, D₂O-exchangeable), ¹³C NMR (DMSO-d₆): $\delta$ 14.2 (CH₂), 43.2 (CH), 62.3 (CH₂), 79.2 (CH), 126.1 (CH), 129.6(CH), 133.5(CH), 136.55(CH), 138.6(CH), 158.8(CH), 168(C = O), 170(C = O) MS (m/z, aband.%): 340(M⁺, 100%), 263(35.5%), 255(44.2%), 77(11.2%).

2-Amino-3-(Ethoxycarbonyl)-4-(P-Tolyl)-4H-Pyrano[2,3-c]Pyridine-8-Carboxylic Acid (4d)

C₁₉H₁₉N₂O₃ (354.12), Dark brown (233-235°C), Elemental analysis: C: 64.40(64.38), H: 5.12(5.14), N: 7.91(7.92), IR (KBr) $\nu_{max}$ cm⁻¹: 3510(OH), 1715(C = O), 136.55(136.53), 125.6(125.62), 118(118), 91(91). ¹HNMR (DMSO-d₆): $\delta$ 1.22 (t, 3H, H₃, J = 7.2Hz), 2.19(s, 3H, HC), 3.98 (q, 2H, H₂C J = 3.1Hz), 4.65(s, 1H, HC), 6.81(s, 2H, H₂N D₂O-exchangeable), 7.1-7.38(m, 4H, HC aromatic), 8.05(d, 1H, HIC, J = 12Hz), 8.58(d, 1H, HC aromatic, J = 12Hz), 12.51(s,1H, HO acid, D₂O-exchangeable), ¹³C NMR (DMSO-d₆): $\delta$ 15.2(15.2), 21.2(CH₂), 42.3(CH), 60.2(CH) 78.9(CH), 125.6(CH), 128.2(CH), 129.6(CH), 133.5(CH), 136.55(CH), 138.6(CH), 159.5(CH), 168(C = O), 170(C = O) MS (m/z, aband.%): 354(M⁺, 100%), 281(12.3%), 275(52.3%), 91(14.3%).

2-Amino-3-Cyano-4-(P-Tolyl)-4H-Pyrano[2,3-c]Pyridine-8-Carboxylic Acid (4h)

C₁₉H₁₉N₂O₃ (307.31), Reddish brown (245-247°C), Elemental analysis: C: 66.44(66.43), H: 4.26(4.28), N: 13.67(13.69), IR (KBr) $\nu_{max}$ cm⁻¹: 3489(OH), 3310-3250(NH₂) 2230(C = N). ¹HNMR (DMSO-d₆): $\delta$ 2.3(s, 3H, H₂C), 4.51(s,1H, HC), 6.62(s, 2H, H₂N D₂O exchangeable), 7.1-7.38(m, 4H, HC aromatic), 7.98(d, 1H, HC, J = 7.2Hz), 8.23(d, 1H, HC aromatic, J = 7.5Hz), 12.02(s, 1H, HO acid, D₂O-exchangeable), ¹³C NMR (DMSO-d₆): $\delta$ 21.2(CH₂), 30.2(CH), 60.2(CH)
118 (CN), 128.2 (CH), 129.6 (CH), 133.5 (CH), 136.55 (CH), 138.6 (CH), 157.2 (CH), 166 (C = O), 176 (CH-O) MS (m/z, aband.%) : 307 (M⁺, 100%), 203 (38.4%), 241 (10.3%).

2-Amino-4-(4-Chlorophenyl)-3-(Ethoxycarbonyl)-4H-Pyrano[2,3-c]Pyridine-8-Carboxylic Acid (4e)

C₁₉H₁₈ClN₂O₅ (374.07), red (287-289°C), Elemental analysis: C: 57.69(57.67), H: 4.03 (4.07), N: 7.47(7.45), Cl: 9.49 (9.51); IR (KBr) ν max/cm⁻¹: 3523(OH), 3423-3352(NH₂), 1702 (C = O), 1HNMR (DMSO-d₆): δ 1.15(t, 3H, J = 3.1Hz), 4.02(q, 2H, H, J = 2.1Hz), 8.41(s, 1H, H, J = 3.1Hz), 8.58(d, 1H, H, J = 7.5Hz), 12.55(s, 1H, HO acid, D₂O-exchangeable), 13C NMR (DMSO-d₆): δ 35.1 (CH₂), 133.5 (CH), 138.5 (CH), 138.6 (CH), 160.2 (CH), 168 (C=O), 170 (C = O), MS (m/z, aband.%) : 374 (M⁺, 100%), 301 (12.5%), 272 (35.62%), 111.2 (18.2%).

2-Amino-4-(4-Chlorophenyl)-3-Cyano-4H-Pyrano[2,3-c]Pyridine-8-Carboxylic Acid (4f)

C₁₉H₁₆ClN₂O₆ (372.72), red (275-277°C), Elemental analysis: C: 58.64(58.65), H: 3.08(3.10), N: 12.82(12.1), Cl: 10.85(10.80), IR (KBr) ν max/cm⁻¹: 3455(OH), 3320-3150(NH₂) 2245(C = N). 1HNMR (DMSO-d₆): δ 4.86(s, 1H, H, J = 3.1Hz), 6.54(s, 2H, H, J = O acid, D₂O-exchangeable), 7.22-7.38(m, 4H, H, J = 3.1Hz), 8.20(d, 1H, H, J = 7.5Hz), 8.85(d, 1H, H, J = 7.5Hz), 12.5(s, 1H, HO acid, D₂O-exchangeable), 13C NMR (DMSO-d₆): δ 28.2 (CH), 61.2(CH), 118 (C = N), 124.5(CH), 131.2 (CH), 133.5 (CH), 136.5(CH), 138.6 (CH), 157.2 (CH), 166 (C = O), 176 (CH-O) MS (m/z, aband.%) : 327 (M⁺, 100%), 216 (40.2%), 138 (50.01%).

2-Amino-4-(4-Bromophenyl)-3-(Ethoxycarbonyl)-4H-Pyrano[2,3-c]Pyridine-8-Carboxylic Acid (4g)

C₁₉H₁₆BrN₂O₅ (418.02), Reddish yellow (290-292°C), Elemental analysis: C: 51.57(51.58), H: 3.61(3.63), N: 6.68(6.70), Br: 19.06(19.08), IR (KBr) ν max/cm⁻¹: 3523(OH), 3423-3352(NH₂), 1702 (C = O), 1HNMR (DMSO-d₆): δ 8.101(t, 3H, J = 3.1Hz), 4.02(q, 2H, H, J = 2.1Hz), 8.41(s, 1H, H, J = 3.1Hz), 8.57(d, 2H, H, J = 2.1Hz), 12.5(s, 1H, H, J = O acid, D₂O-exchangeable), 13C NMR (DMSO-d₆): δ 34.15 (CH₂), 42.3 (CH), 61.9 (CH₂), 77.9 (CH), 118.2 (CH), 131.2 (CH), 133.2 (CH), 136.2 (CH), 138.6 (CH), 157.5 (CH), 168.6 (C = O), 170 (C = O) MS (m/z, aband.%) : 418 (M⁺, 100%), 202 (38.2%), 185 (23.6%).
\text{Pyrano[2,3-\text{c}]Pyridine-8-Carboxylic Acid (4l)}

\text{C}_{12}\text{H}_{10}\text{N}_{4}\text{O}_{5} (338.07), \text{Dark yellow (281-283°C)}, \text{Elemental analysis: C} = 58.61(58.63), \text{H} = 2.98(2.96), \text{N} = 16.56(16.57), \text{IR (KBr)}: 3510(\text{OH}), 3320-3200(\text{NH}), 1699(\text{C = O}).

\text{1H NMR (DMSO-d6):} \delta 4.70(2H, \text{CH}), 6.83(2H, \text{H}_2\text{N D}_2\text{O-exchangeable}), 7.65-7.96(\text{m}, 4\text{H}, \text{HC aromatic}), 8.05(\text{d}, 1\text{H}, \text{HC}, \text{J} = 12\text{Hz}), 8.57(\text{d}, 1\text{H}, \text{HC aromatic}, \text{J} = 12\text{Hz}), 12.5(\text{s}, 1\text{H}, \text{HO acid}, \text{D}_2\text{O-exchangeable}).

\text{13C NMR (DMSO-d6):} \delta 28.7(\text{CH}_2), 58.6(\text{CH}), 118.1(\text{CH}), 124.3(\text{CH}), 124.1(\text{CH}), 128.9(\text{CH}), 133.2(\text{CH}), 136.2(\text{CH}), 142.1(\text{CH}), 145.1(\text{CH}), 158(\text{CH}), 167.9(\text{C}=\text{O}), \text{MS (m/z, aband.%):} 330(\text{M}^+, 100\%), 244(43.3\%), 122(36.2\%).

\text{2-Amino-3-(Ethoxycarbonyl)-4-(Furan-2-yl)-4H-Pyrano[2,3-c]Pyridine-8-Carboxylic Acid (4m)}

\text{C}_{12}\text{H}_{12}\text{N}_{4}\text{O}_{6} (330.09), \text{brown (244-245°C)}, \text{Elemental analysis: C} = 58.18(58.19), \text{H} = 4.27(4.29), \text{N} = 8.48(8.46), \text{IR (KBr)}: 3530(\text{OH}), 3320-3225(\text{NH}), 1699(\text{C}=\text{O}). \text{1H NMR (DMSO-d6):} \delta 1.22(3\text{H}, \text{HC}, \text{J} = 3.1\text{Hz}), 3.98(2\text{H}, \text{HC}, \text{J} = 3.1\text{Hz}), 4.82(2\text{H}, \text{HC}), 6.22(1\text{H}, \text{HC furan}, \text{J} = 1.2\text{Hz}), 6.51(1\text{H}, \text{HC furan}, \text{J} = 3.1\text{Hz}), 6.81(1\text{H}, \text{H}_2\text{N D}_2\text{O-exchangeable}), 7.50(\text{d}, 1\text{H}, \text{HC furan}, \text{J} = 1.2\text{Hz}), 8.05(1\text{H}, \text{HC}, \text{J} = 7.2\text{Hz}), 8.58(1\text{H}, \text{HC aromatic}, \text{J} = 7.2\text{Hz}), 12.56(1\text{H}, \text{HO acid}, \text{D}_2\text{O-exchangeable}). \text{13C NMR (DMSO-d6):} \delta 14.2(\text{CH}_2), 32.2(\text{CH}), 62.3(\text{CH}), 79.1(\text{CH}), 107(\text{CH}), 110(\text{CH}), 133.2(\text{CH}), 136.2(\text{CH}), 158(\text{CH}), 167(\text{C}=\text{O}), \text{MS (m/z, aband.%):} 330(\text{M}^+, 100\%), 288(12.3\%), 257(48.2\%).

\text{Results and Discussion}

\text{Chemistry}

\text{Green synthesis one-pot of pyrano[2,3-c]pyridine annulated heterocyclic compound via three-constituent condensation mixture reaction of aldehydes, ethyl cyanoacetate or malononitrile and 3-hydroxy picolinic acid have been accomplished by microwave irradiation (Mady et al., 2015) and thermal heating utilizing 4-Dimethylaminopyridine (DMAP) as displayed in Scheme 1.}
For this study, an intermixture of aromatic benzaldehydes (1mmol) and ethyl cyanoacetate or malononitrile (1mmol) in ethyl alcohol was preserved with DMAP (0.1mmol) at a typical temperature. Subsequently, the initial aldehyde as examined via thin layer chromatography, 3-hydroxy picolinic acid was supplementary to the reaction combination and reserved for a magnificent further down the heat for 1 min in microwave irradiation. Subsequently the accomplishment of the reaction examined via thin layer chromatography, the reaction combination was acquired to typical temperature and the formed precipitate was riddled off. Product 4a, was achieved in 85% yield in microwave irradiation, which was characterized by 1H NMR, 13C NMR, besides through elemental examination as displayed in Figure 1.

The optimized reaction was exhausting different accelerator for attaining the excellent concern of 4a are summarized in Table 1. That one was distinguished that (20%) mol of DMAP in ethanol consequences from the greatest yield and time, the income obtained about (71%) in thermal heating. Subsequently the reaction optimization condition was comprehensive to a variability of aromatic aldehydes with dissimilar components.

The compounds 4a-4p were associated with those of conventional heating and microwave irradiation. It was demonstrated high yield properties of microwave compounds than thermal performance. The microwave was high yield and in a few minutes as shown in Table 2.

The formation of pyrano[2,3-c]pyridine-8-carboxylic acid derivatives can be reorganized as tracks. Initially, the Knoevenagel condensation of an aldehyde and alkyl nitrile to form acrylonitrile derivative I using DMAP catalyst, which responded to produce carbonian from activated 3-hydroxypicolinic acid to give the intermediate II, which cyclized to IV in the occurrence of DMAP. As a final point, IV tautomerized to provide preferred product 4 as presented in Scheme 2.
Table 1: Reaction condition optimization

| Catalyst | Solvent | Catalytic amount (mol %) | MW time (min) | Yield (%) | Heating time (h) | Yield (%) |
|----------|---------|-------------------------|---------------|-----------|-----------------|-----------|
| 1        | Piperidine | EtOH | 20 | 5 min | 52 | 4h | 43 |
| 2        | DMAP     | Neat | 20 | 5 min | 66 | 4h | 45 |
| 3        | DMAP     | MeOH | 20 | 5 min | 68 | 4h | 55 |
| 4        | DMAP     | H$_2$O | 20 | 10 min | 60 | 6h | 55 |
| 5        | DMAP     | EtOH | 10 | 5 min | 77 | 5h | 65 |
| 6        | DMAP     | EtOH | 20 | 2 min | 85 | 4h | 71 |
| 7        | DMAP     | EtOH | 30 | 1 min | 80 | 4h | 68 |

*Isolated yield*

Table 2: Preparation of pyrano[2,3-c]pyridine-8-carboxylic acid derivatives utilizing aromatic aldehydes, ethyl cyanoacetate or malononitrile and 3-hydroxyphenolic acid through DMAP

| Aromatic aldehydes | Product | MW time | Yield a (%) | Heating time | Yield (%) |
|--------------------|---------|---------|-------------|--------------|-----------|
| 1 C$_6$H$_5$       | 4a      | 1 min   | 85%         | 4h           | 68%       |
| 2 C$_6$H$_5$       | 4b      | 1 min (stirring) | 77%          | 30 min (stirring) | 68%       |
| 3 4-CH$_3$C$_6$H$_4$ | 4c     | 1 min   | 65%         | 5h           | 52%       |
| 4 4-CH$_3$C$_6$H$_4$ | 4d     | 1 min (stirring) | 67%         | 30 min (stirring) | 57%       |
| 5 4-CIC$_6$H$_4$   | 4e      | 1 min   | 77%         | 6h           | 63%       |
| 6 4-CIC$_6$H$_4$   | 4f      | 1 min (stirring) | 75%         | 35 min (stirring) | 59%       |
| 7 4-BrC$_6$H$_4$   | 4g      | 1 min   | 81%         | 6h           | 65%       |
| 8 4-BrC$_6$H$_4$   | 4h      | 1 min (stirring) | 79%         | 35 min (stirring) | 64%       |
| 9 4-CH$_3$OC$_6$H$_4$ | 4i    | 1 min | 63%         | 5h           | 45%       |
| 10 4-CH$_3$OC$_6$H$_4$ | 4j    | 1 min (stirring) | 67%         | 30 min (stirring) | 63%       |
| 11 4-NO$_2$C$_6$H$_4$ | 4k    | 1 min | 74%         | 7h           | 66%       |
| 12 4-NO$_2$C$_6$H$_4$ | 4l    | 1 min (stirring) | 72%         | 40 min (stirring) | 65%       |
| 13 2-Furanyl       | 4m      | 1 min   | 63%         | 5h           | 55%       |
| 14 2-Furanyl       | 4n      | 1 min (stirring) | 68%         | 45 min (stirring) | 57%       |
| 15 Picolinaldehyde | 4o      | 1 min | 71%         | 8h           | 63%       |
| 16 Picolinaldehyde | 4p      | 1 min (stirring) | 73%         | 45 min (stirring) | 59%       |

Scheme 2: Possible mechanism for development of pyrano[2,3-c]pyridine-8-carboxylic acid derivatives
Biological Activity

In vitro Cytotoxic Activity

Antimicrobial activity was accomplished at The Regional Center for Mycology and Biotechnology (RCMB), Al-Azhar University, Cairo, Egypt. Inhibition zones of bacterial evolution premeditated for the manufactured products and standard drugs utilizing Hole-plate dispersal procedure. Six intermediate (1 cm diameter) holes were finished consuming sterile cork borer in (MHA) Mullere Hinton agar sterile plates (16×16 cm), which remained before establishing bacterial separates. Holes were occupied with 100 ml of the established product concentration (100mmol disbanded in 1 ml DMSO) (Sunita and Mahendra, 2008; Andrews, 2001; Abdou et al., 2014). Subsequently, the dish protected for 24 h at 37°C. Subsequently maturation, the antimicrobial action of every regular product was estimated through determining the inhibition region diameters in contrast to examine bacteria and associated with typical region ranges of their standard sulfa medication. The experimentation was accomplished in triplicate and the regular region of inhibition was premeditated. Primarily, totally manufactured products and standard drugs Amphotericin B, Ampicillin and Gentamicin were estimated in vitro for their antimicrobial action, through the inhibition region procedure, exhausting three Gram(+) bacteria: S. pneumonia (RCMB 010010), Enterococcus faecalis (RCMB 010068) and S. aureus (RCMB 010028) through the accumulation of three Gram(-) bacteria: E. coli (RCMB 010052) and Salmonella typhimurium (RCMB 010072) and Pseudomonas aeruginosa (RCMB 010043), also were estimated in vitro for their antifungal action through the inhibition region procedure in contrast to Candida albicans (RCMB 05079) and Aspergillus fumigatus (RCMB 02568).

Inhibition region diameter acquired for resultant products recommends that totally manufactured products retain noteworthy antimicrobial action in contrast to greatest examined organisms used in these evaluates (Table 3), Compounds 4e, 4f, 4g, 4k, 4l, 4o and 4p demonstrated higher antibacterial and antifungal. In addition, Compounds 4d, 4h, 4m and 4n showed moderate activity. For the optimization purpose, the most active agents 4o, 4p, 4e, 4f, 4g and 4h to all strains was designated for further modification, anticipating increasing the antimicrobial along with the antimycobacterial activities due to withdrawing group or a heterocyclic group. Contrariwise, compounds 4k, 4l, 4m and 4n are exactly consuming the same activity. It is value mentioning that interaction of electron withdrawing group or heterocyclic groups in 4e, 4f, 4g, 4o and 4p manufactured a high antimicrobial activity than electron donating group. Compounds 4a, 4b, 4c, 4d, 4i and 4j exhibited moderate activities alongside all strains; these results designate that additional donating group’s substituents reduces the antimicrobial activity. Nevertheless, the highest activity obtained from 2-amino-4-(4-chlorophenyl)-3-(methoxy carbonyl)-4H-pyrano[2,3-c]pyridine-8-carboxylic acid (4e) and 2-amino-3-cyano-4-(pyridin-4-yl)-4H-pyrano[2,3-c]pyridine-8-carboxylic acid (4p) and 2-amino-3-cyano-4-(4-nitrophenyl)-4H-pyrano[2,3-c]pyridine-8-carboxylic acid (4i) groups highest against S. pneumonia and higher also against Aspergillus fumigatus.

Free Radical Scavenging Action

The radical scavenging action of the manufactured products was confirmed by DPPH technique. Free radical (DPPH) is admitted one electron or hydrogen radical to come to be established diamagnetic fragment. DPPH in methanol appears a characteristic band at 517 nm (dependent of pH beginning 5.0 to 6.5) and the solution performs to be bottomless violet color. For instance, DPPH radical is going through the donation hydrogen from the antioxidant, the point of staining designates the searching potential of the antioxidant products. Temporarily, different solution concentration (100, 200, 300, 400, 500 µg ml⁻¹) of the examine products and ascorbic acid (standard) were organized in methanol and supplementary (1.5 ml) to the methanolic solution of DPPH (1.5 ml, 200 µM) (Abu-Hashem et al., 2011; Mohamed et al., 2012 and Shu et al 2007). The mix was stunned forcefully and permitted to attitude for 30 min in the dark. Subsequently, this, the absorbance was tested at 517 nm. Methanol (1.5 ml) was diversified with DPPH solution (1.5 ml, 200 µM). The scavenging action percentage was designed exhausting formulation:

\[
\text{%Inhibition} = \left(\frac{A_c - A_t}{A_c}\right)\times 100
\]

Where, the Ac = observance control (1.5 ml of each of methanol and the 200µM DPPH solution), At = absorption test compound/ascorbic acid.

The inhibition percentage (%) curvatures for ascorbic acid and compounds were strategized in contrast to the concentration, from which IC₅₀ values of the inhibition percentage of DPPH via ascorbic acid and samples were considered exhausting regression equation.

The synthesized samples were selected for in-vitro antioxidant action by DPPH technique. The data achieved are represented in Table 4 as IC₅₀ (µM) values and supplementary to those of ascorbic acid as typical.
Improved observance of the samples with concentration exposes that products retain the radical scavenging action. Analysis of the results in Table 4. The manufactured products were selected for in vitro antioxidant action through DPPH technique. The data acquired are represented in Table 4 as IC$_{50}$ (µM) values and paralleled with those of ascorbic acid as typical.

Absorbance increasing of the products with concentration exposes that products retain radical scavenging action. Analysis of the results in Table 2 which indicated the insertion of electron donating CH$_3$ and OCH$_3$ groups, as 4c, 4d, 4i and 4j reduced the radical scavenging activity and the electron withdrawing Cl, Br and NO$_2$, as in 4e, 4f, 4g, 4h, 4k and 4l increase the radical scavenging, moreover, pyrano[2,3-c]pyridine group of 4m, 4n, 4o, 4p encourages an growth in the antioxidant property. Among the products experienced 4o and 4p demonstrated effective free radical scavenging action with IC$_{50}$ standards of 252.52 and 223.2 µM, respectively (Morimoto et al., 1995).

The indication of the data obtained in Table 3 and 4 exposed that, generally pyrano[2,3-c]pyridine accompanying to heterocyclic were further active than those enclosing aromatic rings. Further studies are desirable to be supported out to invention association between IC$_{50}$ of the evaluated pyrano[2,3-c]pyridine and their molecular descriptors, for instance electronic, lipophilic and steric parameters.

### Table 3: Antimicrobial activity (mg/ml) of compounds 4a-p

| Compound | S. pneumonia (RCMB 010010) | Enterococcus faecalis (RCMB 010068) | S. aureus (RCMB 010028) | E. coli (RCMB 010052) | Salmonella typhimurium (RCMB 010072) | Pseudomonas aeruginosa (RCMB 010043) | Candida albicans (RCMB 05079) | Aspergillus fumigates (RCMB 02568) |
|----------|-----------------|-------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| 4a       | 19.7±0.25       | NA*                           | 10.2±0.51       | 8.3±0.58        | 11.3±0.36       | NA              | 11.3±0.25       | 12.5±0.19       |
| 4b       | 17.7±0.19       | 12.5±0.44                     | 9.2±0.32        | 11.6±0.42       | NA              | 10.3±0.37       | 12.7±0.44       | 14.6±0.37       |
| 4c       | 12.0±0.25       | 10.6±0.37                     | 10.3±0.55       | 11.8±0.57       | 15.9±0.44       | 11.9±0.25       | 11.4±0.34       | 12.6±0.37       |
| 4d       | 18.9±0.25       | 16.8±0.19                     | 10.5±0.54       | 12.3±0.21       | 15.9±0.44       | 14.9±0.58       | 13.2±0.37       | 18.7±0.37       |
| 4e       | 23.5±0.4        | 19.5±0.44                     | 14.3±0.25       | 16.8±0.22       | 16.9±0.36       | 16.8±0.58       | 15.4±0.19       | 20.6±0.19       |
| 4f       | 21.5±0.25       | 18.7±0.58                     | 16.3±0.15       | 17.3±0.49       | 15.2±0.44       | 14.8±0.37       | 16.3±0.25       | 18.8±0.44       |
| 4g       | 20.3±0.27       | 17.3±0.58                     | 18.3±0.25       | 19.3±0.25       | 16.2±0.58       | 15.2±0.25       | 19.4±0.44       | 19.3±0.44       |
| 4h       | 17.5±3.7        | 19.3±0.44                     | 16.3±0.25       | 17.4±0.31       | 14.3±0.25       | 16.4±0.25       | 19.4±0.44       | 15.8±0.44       |
| 4i       | 14.3±0.58       | 15.3±0.63                     | 7.3±0.42        | 15.3±0.28       | 13.7±0.42       | 14.8±0.19       | 17.8±0.63       | 14.6±0.37       |
| 4j       | 14.9±0.25       | 11.7±0.37                     | 10.3±0.35       | 14.3±0.37       | 14.2±0.37       | 11.4±0.25       | 11.7±0.19       | 12.9±0.19       |
| 4k       | 23.4±0.37       | 19.1±0.25                     | 11.3±0.37       | 20.9±0.58       | 15.6±0.58       | 17.8±0.25       | 20.9±0.25       | 19.8±0.19       |
| 4l       | 22.3±0.44       | 17.2±0.19                     | 12.3±0.4        | 15.8±0.19       | 12.6±0.42       | 13.3±0.25       | 14.7±0.58       | 16.2±0.44       |
| 4m       | 19.8±0.25       | NA*                           | 12.3±0.25       | 13.6±0.52       | 13.7±0.44       | NA              | 11.3±0.25       | 14.5±0.41       |
| 4n       | 19.3±0.19       | 17.8±0.44                     | 12.4±0.28       | 16.7±0.58       | 14.8±0.37       | 16.8±0.58       | 18.7±0.44       | 20.6±0.19       |
| 4o       | 20.5±0.25       | 0.37±0.12                     | 17.2±0.19       | 17.8±0.23       | 13.8±0.63       | 17.3±0.37       | 17.7±0.44       | 15.3±0.25       |
| 4p       | 22.3±0.25       | 0.19±0.17                     | 12.6±0.25       | 18.3±0.25       | 16.2±0.44       | 14.9±0.58       | 19.2±0.37       | 18.7±0.37       |
| **Amphotericin B** | 25.4±0.1 | 28.7±0.2 | 19.7±0.2 | 23.7±0.1 | - | - | - | - |
| **Amoxicillin** | - | - | - | - | - | - | - | - |
| **Gentamicin** | - | - | - | - | 17.3±0.1 | 19.9±0.3 | - | - |

NA*: No Action, ± Standard Deviation

### Table 4: Free radical scavenging action of the manufactured products utilizing DPPH technique

| Compound | Inhibition | IC$_{50}$±SE$^{a}$ (µM) |
|----------|------------|-------------------------|
| 4a       | 58.23%     | 863.22±4.8              |
| 4b       | 61.25%     | 789.08±6.8              |
| 4c       | 45.36%     | 652.42±7.85             |
| 4d       | 52.3%      | 587.23±6.7              |
| 4e       | 77.68%     | 409.23±5.86             |
| 4f       | 78.66      | 509.26±3.32             |
| 4g       | 82.52      | 423.52±6.37             |
| 4h       | 79.68%     | 512.17±5.11             |
| 4i       | 43.22%     | 815.71±3.01             |
| 4j       | 58.23%     | 958.06±8.09             |
| 4k       | 68.91%     | 574.2±3.88              |
| 4l       | 66.23%     | 479.18±6.23             |
| 4m       | 67.9%      | 385.32±3.32             |
| 4n       | 65.23%     | 362.55±4.5              |
| 4o       | 83.3%      | 252.53±5.82             |
| 4p       | 88.6%      | 223.2±3.88              |
| **Ascorbic acid** | 90.20% | 100.2±9.60 |

$^{a}$IC$_{50}$ values represent as mean ± SD of three determinations
Conclusion

We require conceived a green and effective simple technique for the production pyran[2,3-c]pyridine derivatives beneath DMAP catalyst exhausting microwave and conventional irradiation. The investigational ease, short reaction periods, extraordinary incomes, easy workup procedures, prevention of organic solvents and consumption of an expensive and freely obtainable and wastefully smart to synthesis these compounds. The improvement of DMAP in contrast to recognized catalyst is (i) cheap, (ii) eco-friendly and (iii) no essential chromatographic separation. The manufactured compounds exhibited moderate to good in vitro antimicrobial and antioxidant activities when associated with standard drugs. Compounds 4e, 4o and 4p demonstrated high potency against antimicrobial or antioxidant due to incorporated two heterocyclic moieties.

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Ethics:

Author declared no conflict of interests.

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