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SYNTHESIS AND MICROBIAL STUDY OF SOME NOVEL CYANOPYRANS AND CYANOPYRIDINES CONTAINING IMIDAZOLE NUCLEUS

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ABSTRACT

The desired fused ring system cyanopyrans **4** were synthesized by the reaction of chalcones **3** with malononitrile in pyridine while chalcones **3** on reaction with malononitrile in presence of ammonium acetate in methanol yielded cyanopyridines **5**. Their IR, ^{1}H NMR, mass spectral data and elemental analyses were in accord with assigned structures.

Key words: Chalcones, Cyanopyran, Cyanopyridine, Antimicrobial activity.

INTRODUCTION

Many naturally occurring and synthetic compounds containing cyanopyran and cyanopyridine scaffold possess interesting pharmacological properties including anticancer[1], antimicrobial[2-6], cardiovascular[7], anticancer[8], anthelminitics[9]. Looking to these multifold properties exhibited by them, we have reported here the synthesis and antimicrobial activities of some new Cyanopyrans **4** and Cyanopyridines **5** derivatives. In the present study, we used this strategy for the synthesis of these compounds in the hope that they may possess different biological activities.

The synthesis of cyanopyran and cyaopyridine from chalcones was performed shown in Scheme 2. In the initial step chalcones **3** were synthesized by the reaction of 1-(4-mthoxybenzyl)-2-butyl-4-chloro-1*H*-imidazole-5-carbaldehyde **2** with various aryl ketones in presence of 40% NaOH in methanol at room temperature[10-16], Compounds **3** on cyclocondensation with malononitrile in pyridine afforded corresponding Cyanopyrans **4**[17-19],

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while **3** on reaction with malononitrile in presence of ammonium acetate in methanol yielded Cyanopyridines **5**[20-23].

The structures of the synthesized compounds were assigned on the basis of elemental analyses such as IR, ^{1}H NMR and mass spectral data. All the synthesized compounds were screened for their antimicrobial activity against various microbes under identical conditions. The standard antibiotics were used for comparison purpose like Ampicillin, Chloramphenicol and Norfloxacin against bacterial strains and Greseofulvin against *Aspergillus niger*.

EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. Thin layer chromatography using silica gel G (E. Merck) plates was used to access the reactions and purity of the synthesized compounds. All the products have been characterized by elemental analysis, IR, ^{1}H NMR and mass spectral study. IR spectra were recorded on Shimadzu FTIR-8400 spectrophotometer in KBr disc and noteworthy absorption levels (cm^{-1}) are listed. ^{1}H NMR spectra were recorded on Bruker spectrometer (400 MHz) using TMS as an internal standard, chemical shift in δ ppm. Mass spectra were determined using direct inlet probe on a GCMS-QP2010 mass spectrometer, Elemental analysis were performed on a Carlo Erba EA 1108 elemental analyzer.

Sythesis of (E)-3-(1-(4-methoxybenzyl)-2-butyl-4-chloro-1*H*-imidazol-5-yl)-1-(4-methoxyphenyl)prop-2-en-1-one (1c)

Dissolve 1–(4–mthoxybenzyl)–2–butyl–4–chloro–1*H*–imidazole–5–carbaldehyde (10 mmol) and 4-methoxy acetophenone (10 mmol) in methanol (25 mL) was stirred at room temperature for 6 hr in presence of catalytic amount of 40% NaOH. The reaction was monitored on TLC by using n-Hexane (7): Ethyl acetate (3) as mobile phase. The resulting solution was poured onto crushed ice, thus the separated solid was filtered and crystallized from ethanol. Yellow solid, yield: 67%, m.p.: 150-156^{o}C; IR (KBr, cm^{-1}): 2999, 2729, 1666, 1614, 1514, 1487, 1451, 1379, 1360, 1278, 1261, 1170, 1157, 1033; ^{1}H NMR (400 MHz $CDCl_3$+DMSO-d6, δ/ppm): 0.95 (3H, m, CH_3), 1.32 (2H, m, CH_2), 1.72 (2H, m, CH_2), 2.64 (2H, t, CH_2), 3.78 (3H, s, -OCH_3). 3.87 (3H, s, -OCH_3), 4.97 (2H, s, Ar-CH_2), 6.76 (3H, t, Ar-H), 7.02 (3H, m, Ar-H), 7.41 (1H, dd, -CH=CH-), 7.71 (1H, dd, -CH=CH-), 7.92 (2H, d, Ar-H); MS: m/z 439 (M^+). Anal. Calcd. for $C_{25}H_{27}ClN_2O_3$: C, 68.41; H, 6.20; N, 6.38 Found: C, 68.40; H, 6.18; N, 6.36. The other chalcones **1** were prepared by the similar procedure.

General method for synthesis of cyanopyrans (4a-l)

A mixture of 3-(1-(4-methoxybenzyl)-2-butyl-4-chloro-1*H*-imidazol-5-yl-1-aryl-prop-2-en-1-one (10 mmol) and malononitrile (10 mmol) in pyridine (20 mL), was heated under reflux for 16 hrs. on oil bath. The progress of reaction was monitored by TLC. The reaction mixture was cooled and poured on to crushed ice. The product was neutralized with 10% HCl, where upon a solid separated out, which was filtered dried and crystallized from ethanol.

(4a) 4-(1-(4-methoxybenzyl)-2-butyl-4-chloro-1*H*-imidazol-5yl)-2-amino-6-phenyl-4*H*-pyran-3-carbonitrile, Off white solid; yield 58%, m.p :122-125^{o}C; IR (KBr, cm^{-1}): 3284, 2880, 2387, 2190, 1878, 1633, 1590, 1568, 1556, 1444, 1404, 1371, 1359, 1336, 1282, 1265, 1228, 813, 773; ^{1}H NMR (400 MHz, $CDCl_3$, δ/ppm): 0.81 (3H, t, CH_3), 1.25 (2H, m, CH_2), 1.54 (2H, m, CH_2), 2.40 (2H, t, CH_2), 3.73 (3H, s, OCH_3), 3.78 (1H, d, pyran), 4.91 (2H, s, Ar-CH_2), 6.64 (4H, d, Ar-H), 6.94 (1H, s, pyran), 7.16 (5H, d, Ar-H), 9.68 (2H, s, NH_2). ^{13}C NMR (100 MHz, CDCl3, δ/ppm): 15.71, 26.66, 34.08, 57.41, 93.07, 116.75, 123.11, 135.20, 143.30, 155.31, 163.56. MS: m/z 475 (M^+). Anal. Calcd for $C_{27}H_{27}ClN_4O_2$: C, 68.27; H, 5.73; N, 11.80. Found: C, 68.25; H, 5.70; N, 11.77

(4b) 4-(1-(4-methoxybenzyl)-2-butyl-4-chloro-1*H*-imidazol-5-yl)-2-amino-6-(4-methyl phenyl)-4*H*-pyran-3-carbonitrile, Off white solid, yield 78%, m.p. : 185-189^{o}C; IR (KBr, cm^{-1}) : 3301, 2829, 1608, 1568, 1500, 1487, 1438, 1386, 1348, 1303, 1250, 1178, 734, 784, 725; ^{1}H NMR (400 MHz, $CDCl_3$, δ/ppm): 0.85 (3H, t, CH_3), 1.31 (2H, m, CH_2), 1.58 (2H, m, CH_2), 2.38 (3H, s, Ar-CH3), 2.44 (2H, m, CH_2), 3.73 (3H, s, OCH_3), 4.18 (1H, d, pyran), 5.25 (2H, s, Ar-CH2), 6.38 (4H, d, Ar-H), 7.12 (1H, s, pyran), 7.23 (4H, d, Ar-H), 9.89 (2H, s. NH_2). ^{13}C NMR (100 MHz, CDCl3, δ/ppm): 15.71, 22.60, 26.66, 32.40, 56.09, 91.50, 113.40, 124.00, 129.14, 141.60, 158.10, 160.40. MS (m/z): 489 (M^+). Anal. Calcd for $C_{28}H_{29}ClN_4O_2$: C, 68.77; H, 5.98; N, 11.46. Found: C, 68.75; H, 5.95; N, 11.44

(4c) 4-(1-(4-methoxybenzyl)-2-butyl-4-chloro-1*H*-imidazol-5-yl)-2-amino-6-(4-methoxy phenyl)-4*H*-pyran-3-carbonitrile, Yellow solid, yield 82%, m.p: 153-155^{o}C; IR (KBr, cm^{-1}): 3388, 2875, 2220, 1721, 1622, 1546, 1505, 1449, 1434, 1365, 1324, 1245, 807; ^{1}H NMR (400 MHz, $CDCl_3$, δ/ppm); 0.80 (3H, t, CH_3), 1.28 (2H, m, CH_2), 1.56 (2H, m, CH_2), 2.40 (2H, t, CH_2), 3.73 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 4.71 (1H, d, pyran), 5.23 (2H, s, Ar-CH_2), 6.63 (4H, d, Ar-H), 6.84 (2H, d, Ar-H), 7.19 (1H, s, pyran), 7.36 (2H, d, Ar-H), 9.81 (2H, s, NH_2). ^{13}C NMR (100 MHz, CDCl3, δ/ppm): 13.90, 21.87, 25.70, 36.11, 55.90, 92.03, 114.20, 122.70, 128.60, 140.80, 158.10. MS (m/z): 505 (M^+). Anal. Calcd for $C_{28}H_{29}ClN_4O_3$: C, 66.59; H, 5.79; N, 11.09. Found: C, 66.55; H, 5.75; N, 11.06.

(4d) 4-(1-(4-methoxybenzyl)-2-butyl-4-chloro-1*H*-imidazol-5-yl)-2-amino-6-(2-hydroxyphenyl)-4*H*-pyran-3-carbonitrile, Yellow solid, yield 52%, m.p.: 170-173^{o}C; IR (KBr, cm^{-1}): 3200, 2800, 2300, 1790, 1680,1640, 1575, 1495, 1440, 1290, 1222, 1145, 1090, 873, 787; ^{1}H NMR (400 MHz, $CDCl_3$, δ/ppm); 0.77 (3H, t, CH_3), 1.30 (2H, m, CH_2), 1.60 (2H, m, CH_2), 2.36 (2H, t, CH_2), 3.87 (3H, s, OCH_3), 4.66 (1H, d, pyran), 5.17 (2H, s, Ar-CH_2), 6.66 (4H, d, Ar-H), 6.88 (2H, d, Ar-H), 7.22 (1H, s, pyran), 7.44 (2H, d, Ar-H), 8.67 (1H, s, OH), 9.88 (2H, s, NH_2). ^{13}C NMR (100 MHz, CDCl3, δ/ppm): 14.10, 22.30, 25.10, 33.21, 41.00, 56.01, 92.11, 111.21, 120.90, 127.80, 130.10, 140.60, 158.30. MS m/z: 491(M^+). Anal. Calcd for $C_{27}H_{27}ClN_4O_3$: C, 66.05; H, 5.94; N, 11.41. Found: C, 66.02; H, 5.91; N, 11.39.

(4e) 4-(1-(4-methoxybenzyl)-2-butyl-4-chloro-1*H*-imidazol-5-yl)-2-amino-6-(4-hydroxyphenyl)-4*H*-pyran-3-carbonitrile, yellow solid, yield 66%, m.p.: 190-192^{o}C; IR (KBr, cm^{-1}): 3330, 3050, 2730, 2140, 1800, 1710, 1690,1587, 1545, 1430, 1390, 1290, 787; ^{1}H NMR (400 MHz, $CDCl_3$, δ/ppm); 0.74 (3H, t, CH_3), 1.38 (2H, m, CH_2), 1.66 (2H, m, CH_2), 2.40 (2H, t, CH_2), 3.88 (3H, s, OCH_3), 4.69 (1H, d, pyran), 5.07 (2H, s, Ar-CH_2), 6.60 (4H, d, Ar-H), 6.80 (2H, d, Ar-H), 7.20 (1H, s, pyran), 7.40 (2H, d, Ar-H), 8.65 (1H, s, OH), 9.86 (2H, s, NH_2). ^{13}C NMR (100 MHz, CDCl3, δ/ppm): 14.58, 22.00, 25.45, 33.41, 40.80, 55.90, 92.00, 115.10, 121.12, 128.20, 130.21, 140.40, 158.70. MS: m/z 491 (M^+). Anal. Calcd for $C_{27}H_{27}ClN_4O_3$: C, 66.05; H, 5.94; N, 11.41. Found: C, 66.00; H, 5.92; N, 11.37.

(4f) 4-(1-(4-methoxybenzyl)-2-butyl-4-chloro-1*H*-imidazol-5-yl)-2-amino-6-(4-chloro phenyl)-4*H*-pyran-3-carbonitrile, yellow solid, yield 53%, m.p.: 143-146^{o}C; IR (KBr, cm^{-1}): 3691, 2966, 2830, 1720, 1615, 1496, 1399; ^{1}H NMR (400 MHz, $CDCl_3$, δ/ppm); 0.90 (3H, t, CH_3), 1.26 (2H, m, CH_2), 1.54 (2H, m, CH_2), 2.37 (2H, t, CH_2), 3.67 (3H, s, OCH_3), 4.70 (1H, d, pyran), 4.97 (2H, s, Ar-CH_2), 6.48 (6H, d, Ar-H), 7.36 (1H, s, pyran), 7.54 (2H, d, Ar-H), 8.84 (2H, s, NH_2). ^{13}C NMR (100 MHz, CDCl3, δ/ppm): 13.90, 21.89, 23.87, 32.01, 39.79, 55.00, 91.50, 114.75, 122.50, 130.00, 133.10, 139.90, 159.47. MS: m/z 509 (M^+). Anal. Calcd for $C_{27}H_{26}Cl_2N_4O_2$: C, 63.66; H, 5.14; N, 11.00. Found: C, 63.63; H, 5.12; N, 10.98.

(4g) 4-(1-(4-methoxybenzyl)-2-butyl-4-chloro-1*H*-imidazol-5-yl)-2-amino-6-(4-bromo phenyl)-4*H*-pyran-3-carbonitrile, yellow solid, yield 60%, m.p.: 202-205^{o}C; IR (KBr, cm^{-1}): 3688, 2823, 1722, 1610, 1496, 1385. 789; ^{1}H NMR (400 MHz, $CDCl_3$, δ/ppm); 0.86 (3H, t, CH_3), 1.24 (2H, m, CH_2), 1.46 (2H, m, CH_2), 2.40 (2H, t, CH_2), 3.87 (3H, s, OCH_3), 4.67 (1H, d, pyran), 4.90 (2H, s, Ar-CH_2), 6.88 (6H, d, Ar-H), 7.24 (1H, s, pyran), 7.68 (2H, d, Ar-H), 8.77 (2H, s, NH_2). ^{13}C NMR (100 MHz, $CDCl_3$, δ/ppm): 15.01, 22.45, 23.00, 30.90, 39.60, 55.72, 89.79, 115.50, 123.76, 131.60, 132.90, 140.30, 160.07. MS: m/z 554

(M^+). Anal. Calcd for $C_{27}H_{26}BrClN_4O_2$: C, 58.55; H, 4.73; N, 10.12. Found: C, 58.53; H, 4.71; N, 10.10.

(4h) 4-(1-(4-methoxybenzyl)-2-butyl-4-chloro-1*H*-imidazol-5-yl)-2-amino-6-(4-fluoro phenyl)-4*H*-pyran-3-carbonitrile, white solid, yield 71%, m.p.: 164-166°C; IR (KBr, cm^{-1}): 3670, 2980, 2850, 1730, 1625, 1476, 1369 ;^{1}H NMR (400 MHz, $CDCl_3$, δ/ppm); 0.88 (3H, t, CH_3), 1.28 (2H, m, CH_2), 1.54 (2H, m, CH_2), 2.64 (2H, t, CH_2), 3.88 (3H, s, OCH_3), 4.40 (1H, d, pyran), 5.01 (2H, s, Ar-CH_2), 6.24 (3H, d, Ar-H), 6.40 (3H, d, Ar-H), 7.36 (1H, s, pyran), 7.88 (2H, d, Ar-H), 9.21 (2H, s, NH_2). ^{13}C NMR (100 MHz, CDCl3, δ/ppm): 14.10, 22.00, 23.76, 32.50, 40.10, 53.89, 90.10, 114.78, 122.90, 132.50, 133.60, 138.90, 159.90. MS: m/z 493 (M^+). Anal. Calcd for $C_{27}H_{26}FClN_4O_2$: C, 65.78; H, 5.32; N, 11.37. Found: C, 65.76; H, 5.29; N, 11.34.

(4i) 4-(1-(4-methoxybenzyl)-2-butyl-4-chloro-1*H*-imidazol-5-yl)-2-amino-6-(3-amino phenyl)-4*H*-pyran-3-carbonitrile, white solid, yield 45%, m.p.: 187-190°C; IR (KBr, cm^{-1}): 3692, 2968, 2833, 1723, 1610, 1492, 1395; ^{1}H NMR (400 MHz, $CDCl_3$, δ/ppm); 0.77 (3H, t, CH_3), 1.36 (2H, m, CH_2), 1.58 (2H, m, CH_2), 2.44 (2H, t, CH_2), 3.70 (3H, s, OCH_3), 4.21 (1H, d, pyran), 5.09 (2H, s, Ar-CH_2), 6.42 (3H, d, Ar-H), 6.66 (3H, d, Ar-H), 7.14 (1H, s, pyran), 7.46 (2H, d, Ar-H), 9.01 (4H, s, NH_2). ^{13}C NMR (100 MHz, CDCl3, δ/ppm): 14.60, 22.50, 23.90, 33.10, 39.78, 55.10, 91.40, 112.80, 120.89, 128.01, 133.00, 140.50, 157.50. MS: m/z 490 (M^+). Anal. Calcd for $C_{27}H_{28}ClN_5O_2$: C, 66.18; H, 5.76; N, 14.29. Found: C, 66.14; H, 5.73; N, 14.26.

(4j) 4-(1-(4-methoxybenzyl)-2-butyl-4-chloro-1*H*-imidazol-5-yl)-2-amino-6-(4-amino phenyl)-4*H*-pyran-3-carbonitrile, white solid, yield 43%, m.p: 200-203°C; IR (KBr, cm^{-1}): 3587, 2878, 2833, 1763, 1670, 1445, 1225; ^{1}H NMR (400 MHz, $CDCl_3$, δ/ppm); 0.76 (3H, t, CH_3), 1.33 (2H, m, CH_2), 1.55 (2H, m, CH_2), 2.47 (2H, t, CH_2), 3.77 (3H, s, OCH_3), 4.28 (1H, d, pyran), 5.11 (2H, s, Ar-CH_2), 6.38 (3H, d, Ar-H), 6.55 (3H, d, Ar-H), 7.27 (1H, s, pyran), 7.44 (2H, d, Ar-H), 9.22 (4H, s, NH_2). ^{13}C NMR (100 MHz, CDCl3, δ/ppm): 14.20, 22.33, 23.78, 33.00, 39.70, 55.00, 91.20, 112.60, 120.86, 128.08, 133.20, 140.00, 157.30. MS: m/z 490 (M^+). Anal. Calcd for $C_{27}H_{28}ClN_5O_2$: C, 66.18; H, 5.76; N, 14.29. Found: C, 66.16; H, 5.75; N, 14.27.

(4k) 4-(1-(4-methoxybenzyl)-2-butyl-4-chloro—1*H*-imidazol-5-yl)-2-amino-6-(3-nitro phenyl)-4*H*-pyran-3-carbonitrile, yellow solid, yield 68%, m.p.: 156-159°C; IR (KBr, cm^{-1}): 3373, 3072, 2895, 2828, 1694, 1635, 1482, 1343, 1298; ^{1}H NMR (400 MHz, $CDCl_3$, δ/ppm); 0.90 (3H, t, CH_3), 1.28 (2H, m, CH_2), 1.65 (2H, m, CH_2), 2.36 (2H, t, CH_2), 3.65 (3H, s, OCH_3), 4.11 (1H, d, pyran), 5.04 (2H, s, Ar-CH_2), 6.44 (6H, d, Ar-H), 6.97 (1H, s, pyran), 7.62 (2H, d, Ar-H), 9.64 (2H, s, NH_2). ^{13}C NMR (100 MHz, CDCl3, δ/ppm): 13.90,

21.78, 22.08, 31.89, 40.14, 53.98, 90.89, 114.40, 122.16, 126.48, 132.88, 139.90, 160.00. MS: m/z 520 (M^+). Anal. Calcd for $C_{27}H_{26}ClN_5O_4$: C, 62.37; H, 5.04; N, 13.47. Found: C, 62.33; H, 5.03; N, 13.43.

(4l) 4-(1-(4-methoxybenzyl)-2-butyl-4-chloro-1*H*-imidazol-5-yl)-2-amino-6-(4-nitro phenyl)-4*H*-pyran-3-carbonitrile, yellow solid, yield 53%, m.p.:172-174°C; IR (KBr, cm^{-1}): 3439, 3007, 2928, 2808, 1599, 1462, 1327, 1255; ^{1}H NMR (400 MHz, $CDCl_3$, δ/ppm); 0.86 (3H, t, CH_3), 1.24 (2H, m, CH_2), 1.62 (2H, m, CH_2), 2.30 (2H, t, CH_2), 3.62 (3H, s, OCH_3), 4.17 (1H, d, pyran), 5.10 (2H, s, Ar-CH_2), 6.40 (6H, d, Ar-H), 6.94 (1H, s, pyran), 7.66 (2H, d, Ar-H), 9.60 (2H, s, NH_2). ^{13}C NMR (100 MHz, CDCl3, δ/ppm): 13.60, 21.70, 22.00, 31.80, 40.10, 53.95, 90.84, 114.38, 122.12, 126.42, 132.84, 139.85, 159.90. MS: m/z 520 (M^+). Anal. Calcd for $C_{27}H_{26}ClN_5O_4$: C, 62.37; H, 5.04; N, 13.47. Found: C, 62.35; H, 5.02; N, 13.45.

General procdure for the synthesis of cyanopyridines (5a-l)

A mixture of 3-(1-(4-methoxybenzyl)-2-butyl-4-chloro-1*H*-imidazol-5-yl-1-aryl-prop-2-en-1-one (10 mmol) and malononitrile (10 mmol) and ammonium acetate (12 mmol) in methanol (25 mL), was heated under reflux condition till reaction complies on TLC. The reaction mixture was cooled to room temperature and poured on to crushed ice. where upon a solid separated out, which was filtered dried and crystallized from methanol/ethanol. The reaction time as well as the yield varies depending on the corresponding reagents.

(5a) 4-(1-(4-methoxybenzyl)-2-butyl-4-chloro-1*H*-imidazol-5-yl)-2-amino-6-phenyl-pyridin-3-carbonitrile, light yellow solid, yield 57%, m.p.: 168-173°C; IR (KBr, cm^{-1}): 3250, 2758, 2240, 1677, 1647, 1490, 1433, 1384, 1295, 703; ^{1}H NMR (400 MHz, $CDCl_3$, δ/ppm): 0.88 (3H, t, CH_3), 1.34 (2H, m, CH_2), 1.66 (2H, m, CH_2), 2.64 (2H, t, CH_2), 3.87 (3H, s, OCH_3), 5.17 (2H, s, Ar-CH_2), 6.86 (4H, d, Ar-H), 7.26 (1H, s, pyridine), 7.54 (5H, m, Ar-H), 9.34 (2H, s, NH_2). ^{13}C NMR (100 MHz, CDCl3, δ/ppm): 14.10, 22.60, 26.00, 33.00, 40.01, 55.40, 85.90, 114.40, 123.11, 130.02, 148.00, 157.70, 160.95. MS: m/z 472 (M^+). Anal. Calcd for $C_{27}H_{26}ClN_5O$: C, 68.71; H, 5.55; N, 14.84. Found: C, 68.68; H, 5.50; N, 14.80.

(5b) 4-(1-(4-methoxybenzyl)-2-butyl-4-chloro-1*H*-imidazol-5-yl)-2-amino-6-(4-methyl phenyl)-pyridin-3-carbonitrile, white solid, yield 62%, m.p.: 201-203°C; IR (KBr, cm^{-1}): 3309, 2852, 2204, 1640, 1554, 1460, 1400, 1364, 1290, 1261, 767; ^{1}H NMR (400 MHz, $CDCl_3$, δ/ppm); 0.91 (3H, t, CH_3), 1.39 (2H, m, CH_2), 1.72 (2H, m, CH_2), 2.36 (3H, s, Ar-CH_3), 2.68 (2H, m, CH_2), 3.77 (3H, s, OCH_3), 4.99 (2H, s, Ar-CH_2), 6.86 (4H, d, Ar-H), 7.01 (1H, s, pyridine), 7.58-7.85 (4H, d, Ar-H), 9.19 (2H, s, NH_2). ^{13}C NMR (100 MHz,

CDCl3, δ/ppm): 14.40, 22.20, 25.70, 33.40, 39.82, 55.00, 85.70, 114.60, 122.90, 129.78, 147.70, 158.05, 161.10. MS: m/z 486 (M^+). Anal. Calcd for $C_{28}H_{28}ClN_5O$: C, 69.20; H, 5.81; N, 14.41. Found: C, 69.17; H, 5.78; N, 14.38.

(5c) 4-(1-(4-methoxybenzyl)-2-butyl-4-chloro-1*H*-imidazol-5-yl)-2-amino-6-(4-methoxyphenyl)-pyridin-3-carbonitrile, off white solid, yield 82%, m.p.: 153-155^{o}C; IR (KBr, cm^{-1}) : 3063, 2929, 2335, 1944, 1666, 1597, 1575, 1492, 1448, 1406, 1330, 1284, 685; ^{1}H NMR (400 MHz, $CDCl_3$, δ/ppm): 0.88 (3H, t, CH_3), 1.28 (2H, m, CH_2), 1.56 (2H, m, CH_2), 2.45 (2H, t, CH_2), 3.76 (6H, s, OCH_3), 4.71 (2H, s, Ar-CH_2), 6.65 (4H, d, Ar-H), 7.27 (1H, s, pyridine), 7.29 (4H, m, Ar-H), 9.74 (2H, s. NH_2). ^{13}C NMR (100 MHz, CDCl3, δ/ppm): 14.71, 23.00, 24.01, 33.00, 40.70, 54.92, 84.90, 113.90, 123.40, 130.70, 147.00, 157.89, 159.96. MS: m/z 502 (M^+). Anal. Calcd for $C_{28}H_{28}ClN_5O_2$: C, 66.99; H, 5.62; N, 13.95. Found: C, 66.97; H, 5.59; N, 13.92.

(5d) 4-(1-(4-methoxybenzyl)-2-butyl-4-chloro-1*H*-imidazol-5-yl)-2-amino-6-(2-hydroxyphenyl)-pyridin-3-carbonitrile, white solid, yield 48%, m.p.:156-160^{o}C; IR (KBr, cm^{-1}) : 3155, 3090, 2937, 2875, 1697, 1687, 1575, 1523, 1443, 1274, 785; ^{1}H NMR (400 MHz, $CDCl_3$, δ/ppm): 0.90 (3H, t, CH_3), 1.30 (2H, m, CH_2), 1.66 (2H, m, CH_2), 2.40 (2H, t, CH_2), 3.78 (3H, s, OCH_3), 4.90 (2H, s, Ar-CH_2), 6.79 (4H, d, Ar-H), 7.40 (1H, s, pyridine), 7.66 (4H, m, Ar-H), 8.94 (2H, s. NH_2), 9.78 (1H, s, OH). ^{13}C NMR (100 MHz, CDCl3, δ/ppm): 15.05, 22.75, 32.47, 39.90, 54.98, 85.40, 112.54, 122.11, 129.01, 146.56, 156.76, 160.20. MS: m/z 488 (M^+). Anal. Calcd for $C_{27}H_{26}ClN_5O_2$: C, 66.46; H, 5.37; N, 14.35. Found: C, 66.44; H, 5.33; N, 14.30.

(5e) 4-(1-(4-methoxybenzyl)-2-butyl-4-chloro-1*H*-imidazol-5-yl)-2-amino-6-(4-hydroxy phenyl)-pyridin-3-carbonitrile, yellow solid, yield 73%, m.p.:187-192^{o}C; IR (KBr, cm^{-1}): 3200, 3076, 2961, 2863, 1645, 1542, 832; ^{1}H NMR (400 MHz, $CDCl_3$, δ/ppm): 0.86 (3H, t, CH_3), 1.34 (2H, m, CH_2), 1.60 (2H, m, CH_2), 2.36 (2H, t, CH_2), 3.87 (3H, s, OCH_3), 4.96 (2H, s, Ar-CH_2), 6.76 (4H, d, Ar-H), 7.44 (1H, s, pyridine), 7.70 (4H, m, Ar-H), 8.90 (2H, s. NH_2), 9.74 (1H, s, OH). ^{13}C NMR (100 MHz, CDCl3, δ/ppm): 15.15, 22.50, 32.40, 39.70, 55.01, 85.35, 112.50, 122.40, 129.20, 146.40, 156.70, 160.00. MS: m/z 488 (M+). Anal. Calcd for $C_{27}H_{26}ClN_5O_2$: C, 66.46; H, 5.37; N, 14.35. Found: C, 66.42; H, 5.35; N, 13.32.

(5f) 4-(1-(4-methoxybenzyl)-2-butyl-4-chloro-1*H*-imidazol-5-yl)-2-amino-6-(4-chloro phenyl)-pyridin-3-carbonitrile, yellow solid, yield 45%, m.p.:171-174^{o}C; IR (KBr, cm^{-1}): 3300, 3087, 2988, 2867, 1616, 1558, 1467, 720; ^{1}H NMR (400 MHz, $CDCl_3$, δ/ppm): 0.91 (3H, t, CH_3), 1.44 (2H, m, CH_2), 1.65 (2H, m, CH_2), 2.56 (2H, t, CH_2), 3.65 (3H, s, OCH_3), 5.01 (2H, s, Ar-CH_2), 6.26 (6H, d, Ar-H), 7.36 (1H, s, pyridine), 7.88 (2H, m, Ar-

H), 8.86 (2H, s. NH_2). ^{13}C NMR (100 MHz, CDCl3, δ / ppm): 14.09, 23.10, 33.33, 40.01, 53.10, 83.90, 111.90, 123.57, 131.00, 145.11, 156.55, 159.70. MS: m/z 506 (M^+). Anal. Calcd for $C_{27}H_{25}Cl_2N_5O$: C, 64.03; H, 4.98; N, 13.83. Found: C, 64.00; H, 4.96; N, 13.81.

(5g) 4-(1-(4-methoxybenzyl)-2-butyl-4-chloro-1*H*-imidazol-5-yl)-2-amino-6-(4-bromo phenyl)-pyridin-3-carbonitrile, yellow solid, yield 62%, m.p.:193-197°C; IR (KBr, cm^{-1}): 3440, 3082, 2946, 2864, 1609, 1579, 878; ^1H NMR (400 MHz, $CDCl_3$, δ/ppm): 0.76 (3H, t, CH_3), 1.40 (2H, m, CH_2), 1.67 (2H, m, CH_2), 2.66 (2H, t, CH_2), 3.86 (3H, s, OCH_3), 5.11 (2H, s, Ar-CH_2), 6.66 (6H, d, Ar-H), 7.24 (1H, s, pyridine), 7.64 (2H, m, Ar-H), 8.90 (2H, s. NH_2). ^{13}C NMR (100 MHz, CDCl3, δ/ppm): 14.40, 25.21, 35.45, 39.75, 56.01, 85.15, 112.70, 128.55, 133.06, 143.70, 153.28, 160.40. MS: m/z 551 (M^+). Anal. Calcd for $C_{27}H_{25}BrClN_5O$: C, 58.87; H, 4.57; N, 12.71. Found: C, 58.85; H, 4.54; N, 12.68.

(5h) 4-(1-(4-methoxybenzyl)-2-butyl-4-chloro-1*H*-imidazol-5-yl)-2-amino-6-(4-fluoro phenyl)-pyridin-3-carbonitrile, white solid, yield 47%, m.p.: 136-139°C; IR (KBr, cm^{-1}): 3190, 3090, 2961, 2853, 1614, 1546, 720, 832; ^1H NMR (400 MHz, $CDCl_3$, δ/ppm): 0.81 (3H, t, CH_3), 1.31 (2H, m, CH_2), 1.44 (2H, m, CH_2), 2.27 (2H, t, CH_2), 3.75 (3H, s, OCH_3), 5.09 (2H, s, Ar-CH_2), 6.43 (6H, d, Ar-H), 7.33 (1H, s, pyridine), 7.80 (2H, m, Ar-H), 9.17 (2H, s. NH_2). ^{13}C NMR (100 MHz, CDCl3, δ/ppm): 14.00, 23.98, 33.45, 40.05, 55.90, 86.00, 113.24, 126.01, 134.44, 145.50, 151.90, 158.70. MS: m/z 490 (M^+). Anal. Calcd for $C_{27}H_{25}FClN_5O$: C, 66.19; H, 5.14; N, 14.29. Found: C, 66.14; H, 5.11; N, 14.65.

(5i) 4-(1-(4-methoxybenzyl)-2-butyl-4-chloro-1*H*-imidazol-5-yl)-2-amino-6-(3-amino phenyl)-pyridin-3-carbonitrile, white solid, yield 58%, m.p.: 177-179°C; IR (KBr, cm^{-1}): 3300, 3190, 2897, 2875, 2312, 1697, 1687, 1575, 1523, 1443, 785; ^1H NMR (400 MHz, $CDCl_3$, δ/ppm): 0.88 (3H, t, CH_3), 1.36 (2H, m, CH_2), 1.56 (2H, m, CH_2), 2.69 (2H, t, CH_2), 3.88 (3H, s, OCH_3), 5.17 (2H, s, Ar-CH_2), 6.64 (6H, d, Ar-H), 7.24 (1H, s, pyridine), 7.66 (2H, m, Ar-H), 9.89 (4H, s. NH_2). ^{13}C NMR (100 MHz, CDCl3, δ/ppm): 14.40, 22.70, 33.60, 40.40, 55.70, 85.70, 113.01, 124.78, 136.40, 144.60, 149.90, 159.89. MS: m/z 487 (M^+). Anal. Calcd for $C_{27}H_{27}ClN_6O$: C, 66.59; H, 5.59; N, 17.26. Found: C, 66.54; H, 5.57; N, 17.23.

(5j) 4-(1-(4-methoxybenzyl)-2-butyl-4-chloro-1*H*-imidazol-5-yl)-2-amino-6-(4-amino phenyl)-pyridin-3-carbonitrile, yellow solid, yield 81%, m.p.:129-131°C; IR (KBr, cm^{-1}): 3240, 2990, 2732, 2710, 2252, 1700, 1657, 1590, 1442, 865; ^1H NMR (400 MHz, $CDCl_3$, δ/ppm): 0.76 (3H, t, CH_3), 1.40 (2H, m, CH_2), 1.54 (2H, m, CH_2), 2.60 (2H, t, CH_2), 3.80 (3H, s, OCH_3), 5.07 (2H, s, Ar-CH_2), 6.66 (6H, d, Ar-H), 7.30 (1H, s, pyridine), 7.74

(2H, m, Ar-H), 9.91 (4H, s. NH_2). ^{13}C NMR (100 MHz, CDCl3, δ/ppm): 14.36, 22.55, 33.44, 40.36, 55.66, 85.64, 113.11, 124.75, 136.44, 144.57, 149.94, 159.85. MS: m/z 487 (M^+). Anal. Calcd for $C_{27}H_{27}ClN_6O$: C, 66.59; H, 5.59; N, 17.26. Found: C, 66.54; H, 5.57; N, 17.23.

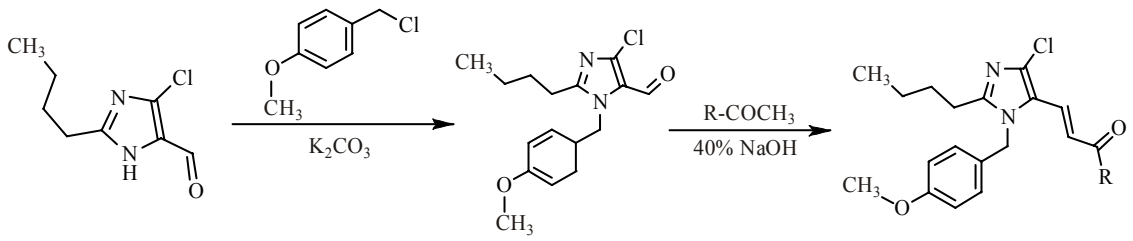
(5k) 4-(1-(4-methoxybenzyl)-2-butyl-4-chloro-1*H*-imidazol-5-yl)-2-amino-6-(3-nitro phenyl)-pyridin-3-carbonitrile, yellow solid, yield 71%, m.p.: 187-190^oC; IR (KBr, cm^{-1}): 3500, 3087, 2973, 2851, 1600, 1587, 1446, 763; ^1H NMR (400 MHz, $CDCl_3$, δ/ppm): 0.77 (3H, t, CH_3), 1.38 (2H, m, CH_2), 1.67 (2H, m, CH_2), 2.34 (2H, t, CH_2), 3.65 (3H, s, OCH_3), 4.97 (2H, s, Ar-CH_2), 6.26 (4H, d, Ar-H), 6.67 (2H, d, Ar-H), 7.12 (1H, s, pyridine), 7.36 (2H, m, Ar-H), 9.88 (2H, s. NH_2). ^{13}C NMR (100 MHz, CDCl3, δ/ppm): 13.90, 23.17, 34.04, 38.87, 54.92, 86.20, 114.03, 123.90, 135.76, 143.46, 151.70, 160.40. MS: m/z 517 (M^+). Anal. Calcd for $C_{27}H_{25}ClN_6O_3$: C, 62.71; H, 4.87; N, 16.26. Found: C, 62.69; H, 4.84; N, 16.23.

(5l) 4-(1-(4-methoxybenzyl)-2-butyl-4-chloro-1*H*-imidazol-5-yl)-2-amino-6-(4-nitro phenyl)-pyridin-3-carbonitrile, yellow solid, yield 52%, m.p.:165-169^oC; IR (KBr, cm^{-1}): 3310, 2987, 2873, 2845, 1643, 1590, 1299, 1163, 780. ^1H NMR (400 MHz, $CDCl_3$, δ/ppm): 0.81 (3H, t, CH_3), 1.43 (2H, m, CH_2), 1.56 (2H, m, CH_2), 2.46 (2H, t, CH_2), 3.77 (3H, s, OCH_3), 4.90 (2H, s, Ar-CH_2), 6.44 (4H, d, Ar-H), 6.71 (2H, d, Ar-H), 7.24 (1H, s, pyridine), 7.44 (2H, m, Ar-H), 9.01 (2H, s. NH_2). ^{13}C NMR (100 MHz, CDCl3, δ/ppm): 14.00, 23.10, 33.97, 39.07, 54.86, 86.00, 113.90, 124.01, 135.70, 143.40, 151.64, 160.35. MS: m/z 517 (M^+). Anal. Calcd for $C_{27}H_{25}ClN_6O_3$: C, 62.71; H, 4.87; N, 16.26. Found: C, 62.67 H, 4.82; N, 16.24.

RESULTS AND DISCUSSION

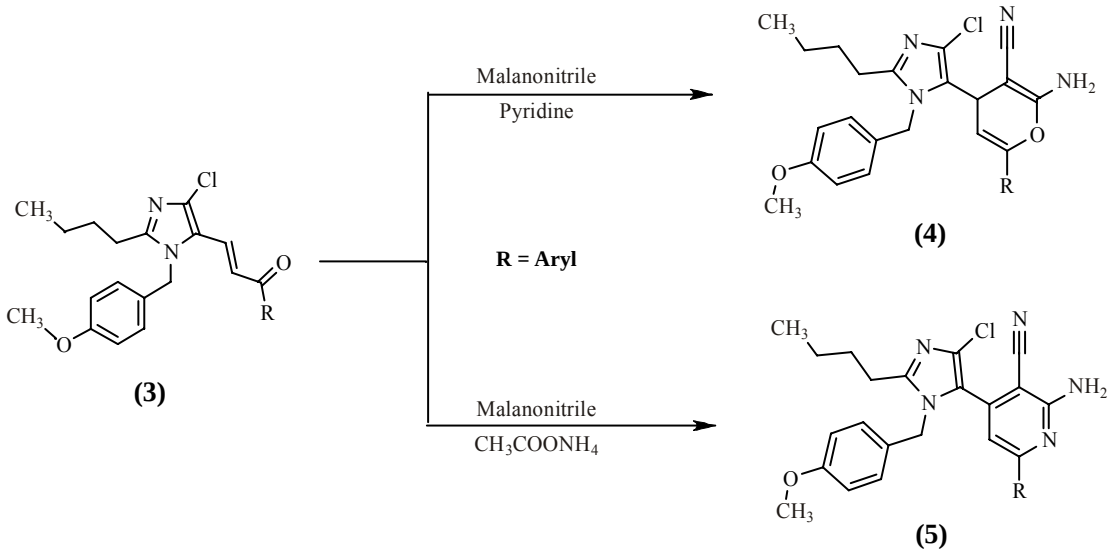
Chemistry of compounds 2-5

The 2-butyl-4-chloro-1-(4-methoxybenzyl)-1*H*-imidazole-5-carbaldehyde **(2)** was prepared by the reaction of 2-butyl-4-chloro-1*H*-imidazole-5-carbaldehyde **(1)** with 1-(chloromethyl)-4-methoxybenzene in presence of base like K_2CO_3. The chalcones **(3)** were synthesized by the reaction of 2-butyl-4-chloro-1-(4-methoxybenzyl)-1*H*-imidazole-5-carbaldehyde (**2)** with aryl ketones in the presence of 40% NaOH at room temperature **(Scheme 1)**. The reaction time as well as the yield varies depending on the corresponding reagents. Compound **(3)** was reacted with malononitrile in presence of pyridine and ammonium acetate in methanol at reflux temperature to get the Cyanopyran **(4)** and Cyanopyridine **(5)** respectively **(Scheme 2)**.



(1) **(2)** **(3)**

Scheme 1



Scheme 2

Where R = (a) Phenyl, (b) 4-methyl phenyl, (c) 4-methoxy phenyl, (d) 2-hydroxy phenyl
(e) 4-hydroxy phenyl, (f) 4-chloro phenyl, (g) 4-bromo phenyl,
(h) 4-fluoro phenyl, (i) 3-amino phenyl, (j) 4-amino phenyl,
(k) 3-nitro phenyl, (l) 4-nitro phenyl

Antimicrobial activity

The antimicrobial activity was assayed by using the cup-plate agar diffusion method[24,25] by measuring the one of inhibition in mm. The antimicrobial activity was compared with standard drugs ampicillin, chloramphenicol, norfloxacin and antifungal activity was compared with greseofulvin. The purified compounds were screened for their antibacterial activity using cup plate agar diffusion method. The nutrient agar broth prepared by the usual was dispensed in 50 mL quantities in different conical flasks. Then, the 0.5 mL

culture of each bacteria (*Bacillus megaterium, Salmonella typhimurium, Staphylococcus, Escherichia coli*) in nutrient agar broth was added and inoculated at 37°C for 24 h. The nutrient agar was melted at 100°C and after cooling to 56°C, poured into Petri plates of 13 cm diameter in quantities of 20 mL, and left on a flate surface to solidify and the surface of the medium was dried at 37°C. Then, above subcultures of each bacteria were pipette in to the nutrient agar plate. The cups (10 mm diameter) were formed by the help of borer in agar medium and filled with 0.05 mL (50 µg) solution of sample in DMF. The plates were incubated at 37°C for 24 h and the control was also maintained with 0.04 mL of DMF in a similar manner. After completion of incubation period, the zone of inhibition of growth in the form of diameter in mm was measured (Table 1).

Table 1: Antimicrobial screening results of compounds 4a-l and 5a-l

Compound	R	Zone of inhibitionin mm				
		Antibacterial activity				Antifungal activity
		B. mega	***S. typhi***	***E. coli***	***S. aureus***	***A. niger***
4a	$C_{25}H_{26}ClN_5O$	10	13	12	21	16
4b	$C_{26}H_{28}ClN_5O$	22	18	22	21	20
4c	$C_{26}H_{28}ClN_5O_2$	08	12	11	10	10
4d	$C_{25}H_{26}ClN_5O_2$	12	07	09	14	09
4e	$C_{25}H_{26}ClN_5O_2$	21	19	22	21	20
4f	$C_{25}H_{25}Cl_2N_5O$	08	12	10	16	15
4g	$C_{25}H_{25}BrClN_5O$	21	07	13	12	21
4h	$C_{25}H_{25}FClN_5O$	08	12	21	07	19
4i	$C_{25}H_{27}ClN_6O$	15	09	12	11	21
4j	$C_{25}H_{27}ClN_6O$	17	19	15	22	12
4k	$C_{25}H_{25}ClN_6O_3$	09	10	11	07	10
4l	$C_{25}H_{25}ClN_6O_3$	12	14	16	09	08
5a	$C_{25}H_{25}ClN_4O_2$	08	11	14	00	10

Cont…

Compound	R	Zone of inhibitionin mm				
		Antibacterial activity				Antifungal activity
		B. mega	***S. typhi***	***E. coli***	***S. aureus***	***A. niger***
5b	$C_{26}H_{27}ClN_4O_2$	11	00	10	00	00
5c	$C_{26}H_{27}ClN_4O_3$	22	10	00	22	07
5d	$C_{25}H_{25}ClN_4O_3$	10	09	08	08	09
5e	$C_{25}H_{25}ClN_4O_3$	00	14	10	11	22
5f	$C_{25}H_{24}Cl_2N_4O_2$	21	11	15	14	13
5g	$C_{25}H_{24}BrClN_4O_2$	10	20	11	10	11
5h	$C_{25}H_{24}FClN_4O_2$	12	12	22	13	00
5i	$C_{25}H_{26}ClN_5O_2$	13	16	18	14	13
5j	$C_{25}H_{26}ClN_5O_2$	21	19	21	22	21
5k	$C_{25}H_{24}ClN_5O_4$	17	00	00	21	12
5l	$C_{25}H_{24}ClN_5O_4$	00	10	00	14	22
Ampiciline	-	22	19	22	22	--
Chlorom-phenicol	-	22	23	25	22	--
Norfloxacin	-	22	22	23	23	--
Gresofulvin	-	--	--	--	--	22

Antifungal activity

Asperigillus niger was employed for testing antifungal activity using cup-plate ager diffusion method. The culture was maintained on sabourauds agar slants, sterilized sabourauds agar medium was inoculated with 72 h old 0.5 mL suspension of fungal spores in a separate flask.

The sabourauds agar was melted at 100°C and after cooling to 56°C, was poured into Petri plates of 13 cm diameter in quantities of 20 mL, and left on a flat surface to solidify

and the surface of the medium was dried at 37°C. Then, the above subculture of fungi was pipette in to the sabourauds agar plate. The cups (10 mm diameter) were form by the help of borer in agar medium and filled with 0.05 mL of DMF in a similar manner. After completion of incubation period, the zone of inhibition of growth in the form of diameter in mm was measured (Table 1).

Evaluation of newly synthesized compounds **(4b)**, **(4e)**, **(4g)**, **(5c)**, **(5f)** and **(5j)** were active against *B. megaterium*. Similarly, compounds **(4b)**, **(4e)**, **(4j)**, **(5g)** and **(5j)** were potent aginst *Salmonella taphimurium*. Also compounds **(4b), (4e), (4h), (5h)** and **(5j)** were most active against *E. coli*. Compounds **(4a)**, **(4b)**, **(4e)**, **(4j)**, **(5c)**, **(5j)** and **(5k)** were highly potent against *S. aureus*. Against *A. niger* compounds **(4b)**, **(4e)**, **(4g)**, **(4i)**, **(5e)**, **(5j)** and **(5l)** were active. Remaining compounds did not show any promising activity against tested bacteria and fungi.

CONCLUSION

In summary, we have synthesized and evaluated a series of novel substituted cyanopyran and cyanopyridine derivatives for their antibacterial and antifungal activity. The synthesis of targeted compounds were achieved via chalcones followed by treatment with malonitrile in pyridine and malononitrile with ammonium acetate in methanol as a binary solvent. The biological evaluation revealed that several derivatives possessed significant antimicrobial activity against various gram positive and negative strains.

The structure-activity relationship studies revealed that compound (4b) and (4e) containing OCH_3 and OH at position 4 were active against all bacteria as well as fungi, while compound (5j) containing NH_2 group at the position 4 was active against all bacteria as compared to those with NH_2 group at the position 3. In case of compound (4e) containing OH at position 4 was active against all bacteria as compared to those with OH group at position 3.

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