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Green Synthesis and Antimicrobial Activity of Some Novel *N*-Arylimidazo[1,2-*a*]pyrazine-2-Carboxamide Derivatives

BOGGAVARAPU JYOTHI[1] and NANNAPANENI MADHAVI[2,*]

[1]Department of Chemistry, Swarna Bharathi Institute of Science and Technology, Khammam-507002, India
[2]P.G. Department of Chemistry, J.K.C. College, Guntur-522006, India

*Corresponding author: E-mail: madhavijkcchempg@gmail.com

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The article deals with the synthesis of some novel *N*-arylimidazo[1,2-*a*]pyrazine-2-carboxamides (**7a-l**) by condensation reaction of imidazo[1,2-*a*]pyrazine-2-carboxylic acid (**5**) with different aliphatic/aromatic amines (**6a-l**) by using 1-methylimidazole, Mukaiyama's reagent and 2-chloro-1-methylpyridinium iodide under microwave irradiation conditions. A new series of compounds **7** have been prepared from 2-iodopyrazine (**1**). Compound **1** on purged with ammonia gas in the presence of Cu_2O and K_2CO_3 furnishes pyrazin-2-amine (**2**), which is treated with ethyl 3-bromo-2-oxopropanoate (**3**) to produce ethyl imidazo[1,2-*a*]pyrazine-2-carboxylate (**4**), which on hydrolysis with NaOH yields imidazo[1,2-*a*]pyrazine-2-carboxylic acid (**5**). The structures of the newly synthesized compounds have been elucidated on the basis of spectral (IR, ^{1}H and ^{13}C NMR and MS) and analytical data. Compounds **7a-l** have also been screened for their antimicrobial activity. Some of the compounds exhibit promising antimicrobial activity.

Keywords: Pyrazine, Imidazole, Carboxamide, Ionic liquid, Mukaiyama's reagent, Microwave irradiation.

INTRODUCTION

Nitrogen containing heterocyclic compounds have attracted prime interest because of their widespread applications in bioactive pharmaceuticals, agrochemicals and functional materials [1-6]. The development of efficient methods to synthesize *N*-heterocycles with structural diversity was one of the active areas of research for modern synthetic organic chemists [7,8]. Among them, imidazole derivatives have attracted much attention, because they were often found in natural and pharmaceutical products and because of their wideranging structural variations [9,10]. In particular, compounds containing a fused imidazole nucleus have been used as antibacterial [11], antifungal [12] and antitumor [13] agents. They were also important building blocks found in naturally occurring compounds [14] and were versatile precursors for the synthesis of new fused *N*-heterocycles. On the basis of these important properties, several methodologies have been described for the preparation of imidazole derivatives [15]. Pyrazine moiety was probably the most well known heterocycle and it was a common and important feature of a variety of medicinal agents [16-18].

Literature survey reveals that when one biodynamic heterocyclic system was fused with another, a molecule with enhanced biological activity was produced. The chemistry of these fused bi-heterocycles has been a fascinating field of investigation in medicinal chemistry, as they have been found to exhibit enhanced biological profile. The newly designed architecture can lead to compounds having improved affinity and effaces than the parent compounds with reduced side effects, while retaining the desired characteristics of original template. The functionalization of imidazole and pyrazine was a valuable chemical transformation in organic synthesis, since derivatives of these aromatic heterocycles can display extremely potent biological, chemical and pharmaceutical properties such as antiviral [19], antiulcer [20], hypo-glycemic activity [21], antileishmanial activity, cytotoxicity [22], antiproliferative activity [23], anticancer activity, *etc*. [24-27].

Microwave assisted organic reactions accelerate chemical reactions from hours to minutes and minutes to seconds because of selective absorption of microwave energy by the polar molecules. In microwave synthesis the environmental heat loss was avoided as compared to conventional heating methods [28-30].

Amide bonds play a major role in the elaboration and composition of biological systems, representing for example the main chemical bonds that link amino acid building blocks together to give proteins. Amide bonds are not limited to biological systems and were indeed present in a huge array of molecules, including major marketed drugs. For example, atorvastatin, the top selling drug worldwide since 2003, blocks the production of cholesterol and contains an amidebond [31], as do lisinopril (inhibitor of angiotensin converting enzyme) [32], valsartan (blockade of angiotensin-II receptors) [33] and diltiazem (calcium channel blocker) used in the treatment of angina and hypertension [34].

This paper was inspired by the resemblance of the original Mukaiyama's reagent [35-39] with ionic liquids. Ionic liquids were ionic salts that were liquids at low temperatures (< 100 °C), many of which are room-temperature ionic liquids (RTILs). Typical ionic liquids produce little vapour pressure, by this means, they were 'greener' solvents in contrast to traditional volatile organic compounds. During the past ten years, ionic liquids have attracted tremendous attention as solvents or co-catalysts in a variety of synthetic reactions [40-44].

Based on the above findings, we were interested to construct imidazole-pyrazine compounds. We, herein, report the green synthesis of *N*-aryl imidazo[1,2-*a*]pyrazine-2-carboxamides (**7a-l**).

EXPERIMENTAL

Melting points were determined using a cintex melting point apparatus and these were uncorrected. The completion and purity of the reactions were monitored by TLC, performed on silica gel aluminium 60 F-254 thin layer plates procured from Merck and visualization on TLC was achieved by UV light and iodine indicator. Column chromatography was performed by using silica gel (particle size 100-200 mesh). IR spectra (KBr) were recorded on a Perkin-Elmer BX series FTIR spectrometer. ^{1}H NMR spectra were recorded on a Bruker AMX 400 MHz spectrometer. Chemical shift values were given in ppm (δ) with TMS as an internal standard. Mass spectra were determined on Agilent LC-1100 (LC-MS) series instrument. Elemental analyses were performed on a Carlo Erba 106 and Perkin Elmer model 240 analyzers. 1-Methylimidazole and Mukaiyama's reagent, 2-chloro-1-methylpyridinium iodide were commercially available. All the chemicals and reagents used in present investigation were purchased from Sigma Aldrich and the solvents from Merck and were used without further purification.

Synthesis of pyrazin-2-amine (2): To a stirred solution of 0.1 equiv. of Cu_2O in dioxane (20 mL) was added 3.0 equiv. of K_2CO_3. To the resulting suspension added 1.0 equiv. of 2-iodopyrazine and ammonia gas was purged 150 psi. The resulting reaction mixture was allowed to reflux for 16 h at 140 °C. After completion of the reaction, the reaction mixture cooled to room temperature and filter using celite-pad. Filtrate was extracted with 30 % ethylacetate–hexane (10 mL × 3). The organic layer was washed with brine and dried over sodium sulphate and concentrated in vacuum to get pure pale brown pyrazin-2-amine (**2**), yield: 92 %; m.p. 112-113 °C. IR (KBr, ν_{max}, cm^{-1}): 3355, 3290, 3057, 2936, 1638, 1501, 1455, 1373, 1291; ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.36 (brs, 2H, NH_2), 7.64 (s, 1H, C_5-H of pyrazine), 7.84 (s, 2H, C_3-H and C_6-H of pyrazine); LC-MS: *m/z* 96.25 $[M+H]^+$. Anal. calcd. (%) for $C_4H_5N_3$: C 50.52, H 5.30, N 44.18. Found (%): C 50.64, H 5.31, N 44.20.

Synthesis of ethyl imidazo[1,2-*a*]pyrazine-2-carboxylate (4): A mixture of pyrazin-2-amine (**2**) (1.0 equiv.) and ethyl 3-bromo-2-oxopropanoate (**3**) (1.5 equiv.) in ethanol (15 mL) was exposed to microwave irradiation at 200 W intermittently at 10 s intervals for 30 min at 150 °C. On completion of reaction as indicated by TLC, the reaction mixture was cooled, concentrated and treated with cold water. Reaction mass was concentrated completely under reduced pressure. Obtained crude was purified by column chromatography on 100-200 silica gel by eluting 50 % ethyl acetate in *n*-hexane, to get off pale brown compound **4**, yield: 90 %; m.p. 151-153 °C. IR (KBr, ν_{max}, cm^{-1}): 3352, 3081, 3009, 2959, 2918, 1748, 1612, 1426, 1426, 1353, 1276, 1254, 903, 813; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.28 (t, 3H, CH_3), 3.85 (q, 2H, CH_2), 4.62 (brs, 1H, NH); LC-MS: *m/z* 192.06 $[M+H]^+$. Anal. calcd. (%) for $C_9H_9N_3O_2$: C 56.54, H 4.74, N 21.98. Found (%): C 56.65, H 4.76, N 22.03.

Synthesis of imidazo[1,2-*a*]pyrazine-2-carboxylic acid (5): To a solution of ethyl imidazo[1,2-*a*]pyrazine-2-carboxylate (**4**) in THF (25 mL) and ethanol (50 mL) was added a solution of sodium hydroxide (3.0 equiv.) in water (15 mL). The mixture was stirred at room temperature for 16 h. The progress of the reaction was monitored by TLC. The reaction mixture was then concentrated at 40 °C in vaccum, the mixture was acidified with 1 N HCl and pH maintained at 2.0-3.0. The precipitate was washed with ice cold water and then the solid thus obtained was collected by filtration and recrystallized from ethanol to give pale brown solid. Yield: 85 %; m.p. 171-172 °C. IR (KBr, ν_{max}, cm^{-1}): 3439, 3119, 3046, 2909, 2819, 1710, 1617, 1525, 1477, 1440, 1289, 1224, 1152, 1030; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.95 (s, 1H, C_5-H of pyrazine), 8.58 (s, 2H, C_3-H and C_6-H of pyrazine), 9.14 (s, 1H, imidazole ring proton), 13.14 (brs, 1H, -COOH); LC-MS: *m/z* 164.9 $[M+H]^+$. Anal. calcd. (%) for $C_7H_5N_3O_2$: C 51.54, H 3.09, N 25.76. Found (%): C 51.67, H 3.11, N 25.79.

Synthesis of *N*-arylimidazo[1,2-*a*]pyrazine-2-carboxamides (7a-l): Imidazo[1,2-*a*]pyrazine-2-carboxylic acid (**5**) (1.0 equiv.) Mukaiyama's reagent and 2-chloro-1-methylpyridinium iodide (1.2 equiv.) were suspended in DMF (5.0 mL) under nitrogen atmosphere. Into the reaction mixture, aliphatic/aromatic amines (**6a-l**) (1.0 equiv.) and 1-methylimidazole (2.0 equiv.) were added. A homogeneous solution was formed after a gentle stirring. The reaction mixture was sealed in a microwave glass reactor and then irradiated by microwave oven at a constant temperature of 80 °C with continuous stirring (1 min ramp, 15 min reaction time). After the reaction was completed, the solvent was removed through a rotary evaporator and the resulting residue was extracted by a biphasic system of 45 mL diethyl ether and 45 mL water. After the layer separation, the ether layer was dried by anhydrous sodium sulphate, followed by an evaporation of ether to get compounds **7a-l** (**Scheme-I**).

Spectral data

***N*-Phenylimidazo[1,2-*a*]pyrazine-2-carboxamide (7a):** Pale brown solid. IR (KBr, ν_{max}, cm^{-1}): 3407, 3048, 2974, 2784, 1642, 1596, 1555, 1515, 1461, 1386, 1344, 1233, 1199, 1088, 967; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.09 (t, 1H, Ar-H), 7.34 (t, 2H, Ar-H), 7.90 (d, 2H, Ar-H), 7.99 (s, 1H, C_5-H of pyrazine), 8.66 (s, 2H, C_3-H and C_6-H of pyrazine), 9.19 (s, 1H, imidazole ring proton), 10.47 (brs, 1H, NH); LC-MS: *m/z* 239.0 $[M+H]^+$. Anal. calcd. (%) for $C_{13}H_{10}N_4OF_3$: C, 65.54, H, 4.23; N, 23.52. Found (%): C, 65.67, H, 4.22; N, 23.54.

***N*-(3-Chlorophenyl)imidazo[1,2-*a*]pyrazine-2-carboxamide (7b):** Pale brown solid. IR (KBr, ν_{max}, cm^{-1}): 3454, 2851, 1640, 1469, 1409, 1358, 1194, 1139; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.22 (t, 1H, Ar-H), 7.41 (d, 1H, Ar-H), 7.56 (d, 1H, Ar-H), 8.02 (s, 1H, Ar-H), 8.25 (d, 1H, C_5-H of pyrazine), 8.64 (d, 1H, C_6-H of pyrazine), 8.72 (s, 1H, C_3-H of pyrazine), 9.24 (s, 1H, imidazole ring proton), 10.01 (brs, 1H, NH); LC-MS: *m/z* 272.0 $[M]^+$. Anal. calcd. (%) for $C_{13}H_9N_4OCl$: C, 57.26, H, 3.33; N, 20.55. Found (%): C, 57.35, H, 3.34; N, 20.58.

***N*-(3-Bromophenyl)imidazo[1,2-*a*]pyrazine-2-carboxamide (7c):** Pale brown solid. IR (KBr, ν_{max}, cm^{-1}): 3420, 2953, 2811, 2763, 1630, 1597, 1507, 1479, 1447, 1412, 1351, 1296, 991; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.20 (t, 1H, Ar-H), 7.40 (d, 1H, Ar-H), 7.54 (d, 1H, Ar-H), 8.04 (s, 1H, Ar-H), 8.23 (d, 1H, C_5-H of pyrazine), 8.62 (d, 1H, C_6-H of pyrazine), 8.70 (s, 1H, C_3-H of pyrazine), 9.18 (s, 1H, imidazole ring proton), 9.88 (brs, 1H, NH); LC-MS: *m/z* 316.0$[M]^+$. Anal. calcd. (%) for $C_{13}H_9N_4OBr$: C, 49.23, H, 2.86; N, 17.67. Found (%): C, 49.33, H, 2.88; N, 17.80.

***N*-(3-Iodophenyl)imidazo[1,2-*a*]pyrazine-2-carboxamide (7d):** Pale brown solid. IR (KBr, ν_{max}, cm^{-1}): 3353, 3079, 2836, 2792, 1678, 1597, 1464, 1394, 1303, 1106, 982, 720; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.18 (t, 1H, Ar-H), 7.98 (d, 1H, Ar-H), 8.17 (d, 1H, Ar-H), 8.35 (s, 1H, Ar-H), 8.62 (d, 1H, C_5-H of pyrazine), 8.75 (d, 1H, C_6-H of pyrazine), 9.21 (s, 1H, C_3-H of pyrazine), 9.90 (s, 1H, imidazole ring proton), 9.88 (brs, 1H, NH); LC-MS: *m/z* 365.23 $[M+H]^+$. Anal. calcd. (%) for $C_{13}H_9N_4OI$: C, 42.88, H, 2.49; N, 15.39. Found (%): C, 42.99, H, 2.47; N, 15.41.

***N*-(4-Chlorophenyl)imidazo[1,2-*a*]pyrazine-2-carboxamide (7e):** Pale brown solid. IR (KBr, ν_{max}, cm^{-1}): 3454, 3234, 2851, 1640, 1469, 1409, 1358, 1194, 1023, 740; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.67 (d, 2H, Ar-H), 7.76 (d, 2H, Ar-H), 8.01 (d, 1H, C_5-H of pyrazine), 8.64-8.67 (m, 2H, C_6-H, C_3-H of pyrazine), 9.19 (s, 1H, imidazole ring proton), 10.66 (brs, 1H, NH); LC-MS: *m/z* 272.0$[M]^+$. Anal. calcd. (%) for $C_{13}H_9N_4OCl$: C, 57.26, H, 3.33; N, 20.55. Found (%): C, 57.37, H, 3.32; N, 20.57.

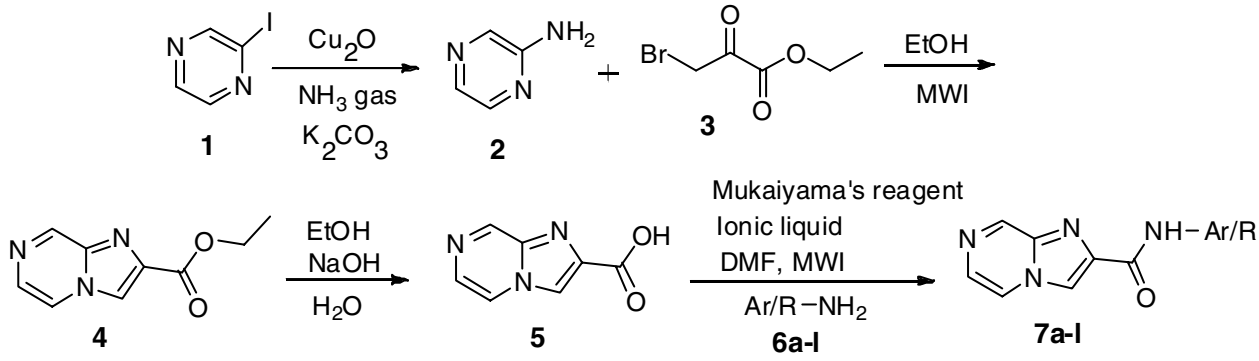
***N*-(4-Bromophenyl)imidazo[1,2-*a*]pyrazine-2-carboxamide (7f):** Pale brown solid. IR (KBr, ν_{max}, cm^{-1}): 3428, 3267, 3180, 3072, 1604, 1525, 1477, 1412, 1130, 920; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.80-7.89 (m, 2H, 2H, C_6-H, C_3-H of pyrazine), 7.91-7.64 (d, 2H, Ar-H), 8.05-8.13 (d, 2H, Ar-H), 8.40 (m, 2H, C_5-H of pyrazine, imidazole ring proton), 10.12 (brs, 1H, NH); LC-MS: *m/z* 316.0$[M]^+$. Anal. calcd. (%) for $C_{13}H_9N_4OBr$: C, 49.23, H, 2.86; N, 17.67. Found (%): C, 49.33, H, 2.88; N, 17.80.

***N*-(4-Iodophenyl)imidazo[1,2-*a*]pyrazine-2-carboxamide (7g):** Pale brown solid. IR (KBr, ν_{max}, cm^{-1}): 3362, 3269, 3188, 1613, 1600, 1570, 1534, 1509, 1476, 1447, 1417, 1346, 1127, 921; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.45-7.60 (m, 4H, Ar-H), 7.62-7.69 (m, 2H, C_6-H, C_3-H of pyrazine), 7.92 (s, 1H, C_5-H of pyrazine), 9.06 (s, 1H, imidazole ring proton), 9.42 (brs, 1H, NH); LC-MS: *m/z* 365.28 $[M+H]^+$. Anal. calcd. (%) for $C_{13}H_9N_4OI$: C, 42.88, H, 2.49; N, 15.39. Found (%): C, 42.99, H, 2.47; N, 15.41.

***N*-(Pyridin-2-yl)imidazo[1,2-*a*]pyrazine-2-carboxamide (7h):** Pale brown solid. IR (KBr, ν_{max}, cm^{-1}): 3228, 2930, 1638, 1592, 1401, 1232, 1161, 1084; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.19 (t, 1H, pyridine-H), 7.88 (t, 1H, pyridine-H), 8.01 (d, 1H, pyridine-H), 8.20 (d, 1H, pyridine-H), 8.38 (s, 1H, C_5-H of pyrazine), 8.64 (s, 1H, C_3-H of pyrazine), 8.75 (s, 1H, C_6-H of pyrazine), 9.22 (s, 1H, imidazole ring proton), 9.92 (brs, 1H, NH); LC-MS: *m/z* 240.11 $[M+H]^+$. Anal. calcd. (%) for $C_{12}H_9N_5O$: C, 60.25, H, 3.79; N, 29.27. Found (%): C, 60.36, H, 3.81; N, 29.28.

***N*-(4-Methoxyphenyl)imidazo[1,2-*a*]pyrazine-2-carboxamide (7i):** Pale brown solid. IR (KBr, ν_{max}, cm^{-1}): 3382, 2932, 2853, 1626, 1562, 1477, 1436, 1414, 1314, 1111, 1010, 817; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.40 (s, 3H, OCH_3), 6.87 (s, 1H, imidazo[1,2-*a*]pyrazine-H), 6.90 (m, 1H, imidazo[1,2-*a*]pyrazine-H), 7.05 (m, 1H, NH, imidazo[1,2-*a*]pyrazine-H), 7.15 (s, 1H, imidazo[1,2-*a*]pyrazine-H), 7.28 (d, 2H, Ar-H), 7.48 (d, 2H, Ar-H), 9.55 (brs, 1H, NH); LC-MS: *m/z* 269.2 $[M+H]^+$. Anal. calcd. (%) for $C_{14}H_{12}N_4O_2$: C, 62.68, H, 4.51; N, 20.88. Found (%): C, 62.78, H, 4.52; N, 20.90.

***N*-(3-Ethynylphenyl)imidazo[1,2-*a*]pyrazine-2-carboxamide (7j):** Pale brown solid. IR (KBr, ν_{max}, cm^{-1}): 3457, 3346, 3184, 3125,2358, 1672, 1589, 1549, 1481, 1421, 1359, 1216; ; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.19 (s, 1H, ethynyl-



Scheme-I

H), 7.20 (d, 1H, Ar-H), 7.36 (t, 1H, Ar-H), 7.92 (d, 1H, Ar-H), 8.01 (d, 1H, C_5-H of pyrazine), 8.08 (1s 1H, Ar-H), 8.64-8.68 (m, 2H, C_6-H, C_3-H of pyrazine), 9.20 (s, 1H, imidazole ring proton), 10.68 (brs, 1H, NH); LC-MS: *m/z* 263.10 $[M+H]^+$. Anal. calcd. (%) for $C_{15}H_{10}N_4O$: C, 68.69, H, 3.84; N, 21.36. Found (%): C, 68.80, H, 3.85; N, 21.39.

***N*-(2,6-Dioxopiperidin-3-yl)imidazo[1,2-*a*]pyrazine-2-carboxamide (7k):** Black solid. IR (KBr, ν_{max}, cm^{-1}): 3424, 2923, 2860, 1630, 1583, 1439, 1359, 1326, 1255, 1187, 1121, 1040; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.98 (m, 1H, dioxopiperidin-H), 2.24 (m, 1H, dioxopiperidin-H), 2.52 (m, 1H, dioxopiperidin-H), 2.75 (m, 1H, dioxopiperidin-H), 4.76-4.83 (m, 1H, dioxopiperidin-H), 7.97 (d, 1H, C_5-H of pyrazine), 8.56 (s, 1H, C_3-H of pyrazine), 8.61 (d, 1H, C_6-H of pyrazine), 9.15 (s, 1H, imidazole ring proton), 9.15 (brs, 1H, NH of dioxopiperidine), 10.85 (brs, 1H, NH); LC-MS: *m/z* 274.89 $[M+H]^+$. Anal. calcd. (%) for $C_{12}H_{11}N_5O_3$: C, 52.75, H, 4.06; N, 25.63. Found (%): C, 52.85, H, 4.04; N, 25.66.

***N*-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)imidazo[1,2-*a*]pyrazine-2-carboxamide (7l):** Pale brown solid. IR (KBr, ν_{max}, cm^{-1}): 3424, 2923, 2860, 1611, 1583, 1439, 1359, 1326, 1255, 1121, 1040, 850; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.21 (s, 4H, [1,4]dioxine), 6.79 (d, 1H, Ar-H), 7.33 (d, 1H, Ar-H), 7.50 (s, 1H, Ar-H), 7.98 (d, 1H, C_5-H of pyrazine), 8.62 (d, 1H, C_6-H of pyrazine), 9.17 (s, 1H, C_3-H of pyrazine), 10.38 (brs, 1H, NH); LC-MS: *m/z* 297.32 $[M+H]^+$. Anal. calcd. (%) for $C_{15}H_{12}N_4O_3$: C, 60.81, H, 4.08; N, 18.91. Found (%): C, 60.93, H, 4.09; N, 18.95.

Antimicrobial activity

Antibacterial activity: *in vitro* Screening of antibacterial activities of compounds **7a-l** in dimethyl sulfoxide were performed by the broth dilution method using nutrient agar against Gram-negative bacteria *Pseudomonas aeruginosa*, *Klebsiella aerogenes*, *Chromobacterium violaceum* and Gram-positive bacteria *Bacillus subtilis*, *Bacillus sphaericus* and *Staphylococcus aureus* at 100 µg/mL concentration. The minimum inhibitory concentration (MIC) was done by the broth dilution method [45]. The ready made nutrient broth medium (HiMedia, 25 g) was suspended in distilled water (100 mL) and heated until it dissolved completely. The medium and test tubes were autoclaved at a pressure of 15 lb/inc^2 for 25 min. A set of sterilized test tubes with nutrient broth medium was capped with cotton plugs. The test compound was dissolved in dimethyl sulfoxide at a concentration of 100 µg/mL and added to the first test tube, which was serially diluted. A fixed 0.5 mL volume of overnight culture was added to all the test tubes and then incubated at 35 °C for 24 h. After 24 h, these tubes were measured for turbidity. Ciprofloxacin and trimethoprim were used as standards for comparison.

Antifungal activity: Antifungal activities of compounds **7a-l** were determined by using the agar cup bioassay method [46] with clotrimazole as the standard. The compounds were tested for their antifungal activity against five test organisms, *Aspergillus niger*, *Chrysosporium tropicum*, *Rhizopus oryzae, Fusarium moniliforme* and *Curvularia lunata* using the agar cup bioassay method at 100 µg/mL concentrations.

The ready-made nutrient broth medium (HiMedia, 40 g) was suspended in distilled water (1000 mL) and heated until it dissolved completely. The medium and petri dishes were autoclaved at a pressure of 15 lb/inc^2 for 20 min. The medium was poured into sterile petri dishes under aseptic conditions in a laminar flow chamber. When the medium in the plates solidified, 0.5 mL of culture of the test organism was inoculated and uniformly spread over the agar surface with a sterile L-shaped rod. Solutions were prepared by dissolving plant extract in dimethyl sulfoxide at a concentration of 100 µg/mL. Agar inoculation cups were scooped out with a 6 mm sterile cork borer and the lids of the dishes were replaced. To each cup, (100 µg/mL) of the test solution was added. Controls were maintained with DMSO and clotrimazole (100 µg/mL). The treated and controls were kept at room temperature for 72-95 h. Inhibition zones were determined and diameter was calculated in millimetre. Three to four replicates were maintained for each treatment.

RESULTS AND DISCUSSION

In this work, some novel *N*-arylimidazo[1,2-*a*]pyrazine-2-carboxamides (**7a-l**) were synthesized in multicomponent steps. Firstly, 2-iodopyrazine and ammonia gas was purged 150 psi then refluxed for 16 h at 140 °C to afford pyrazin-2-amine (**2**). A solution of pyrazin-2-amine (**2**) (1.0 equiv.) and ethyl 3-bromo-2-oxopropanoate (**3**) (1.5 equiv.) in ethanol (250 mL) was exposed to microwave irradiation at 200 W intermittently at 10 s intervals for 3.0 min to get off ethyl imidazo[1,2-*a*]-pyrazine-2-carboxylate (**4**). To a solution of compound **4** in THF (25 mL) and ethanol (50 mL) was added a solution of sodium hydroxide (3.0 equiv.) in water (15 mL). The mixture was stirred at room temperature for 16 h to give imidazo[1,2-*a*]pyrazine-2-carboxylic acid (**5**). Compound **5** (1.0 equiv.), Mukaiyama's reagent and 2-chloro-1-methylpyridinium iodide (1.2 equiv.) were suspended in DMF (5.0 mL) under nitrogen atmosphere. To this reaction mixture, aliphatic/aromatic amines (**6a-l**) (1.0 equiv.) and 1-methylimidazole (2.0 equiv.) were added and irradiated by microwave oven at a constant temperature of 80 °C with continuous stirring (1 min ramp, 15 min reaction time) to afford compounds **7a-l**.

The newly synthesized pyrazin-2-amine (**2**) in its IR spectrum exhibited a strong two absorption bands at 3355 and 3290 cm^{-1} due to NH_2 functional group stretching vibrations respectively. ^{1}H NMR spectrum of compound **2** showed broad singlet at δ 6.36 due to NH_2 protons, which are D_2O exchangeable. The mass spectrum of **2** displayed the molecular ion $[M+H]^+$ peak at *m/z* 96.25, which agrees with the proposed structure.

The infrared spectrum of ethyl imidazo[1,2-*a*]pyrazine-2-carboxylate (**4**) did not show the absorption bands at 3355 and 3290 cm^{-1} due to NH_2 functional group which were present in its precursor **2** confirming the cyclization. The ^{1}H NMR spectra of compound **4** in DMSO-d_6 showed the presence of methyl and methylene protons by displaying as a triplet at δ 5.79 and a quartet at δ 5.79. This indicates the presence of ethyl group. The disappearance of NH_2 protons signals at δ 6.36, which were present in its precursor confirming the cyclization. The mass spectrum of compound **4** showed the molecular ion $[M+H]^+$ peak at 192.06, which is in agreement with the proposed structure. Data from the elemental analyses further confirmed the assigned structure of compound **4**.

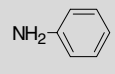
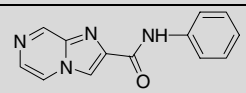
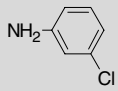
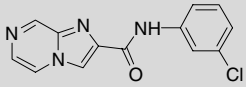
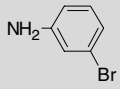
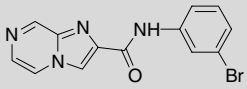
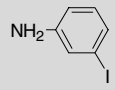
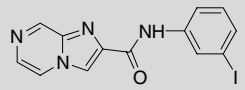
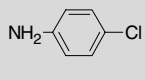
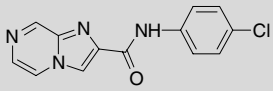
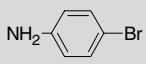
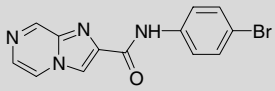
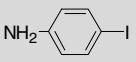
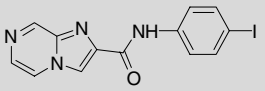
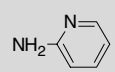
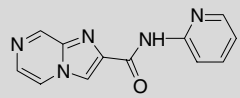
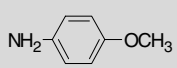
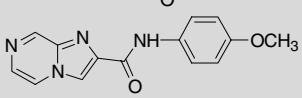
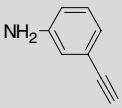
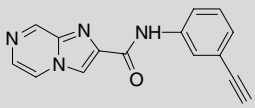
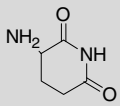
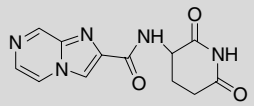
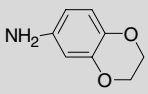
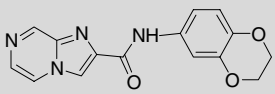
Infrared spectra of compound **5** revealed the presence of strong absorption bands at 3439, 1710 and 1617 cm^{-1} for -OH, C=O and C=N functions respectively. The ^1H NMR spectra of compound **5** displayed a broad singlet at δ 13.14 corresponding to carboxylic acid protons, which are D_2O exchangeable. The mass spectra of compound **5** exhibited the molecular ion $[M+H]^+$ peak at *m/z* 164.9 supporting ester hydrolysis.

The structure of **7a** was supported by IR, ^1H NMR and mass spectral data. The IR spectrum of **7a** exhibited strong absorption at 3407 cm^{-1} due to NH stretching. The absorption due to amide carbonyl appeared at 1642 cm^{-1}. ^1H NMR spectrum of **7a** displayed a broad singlet at δ 10.47 due to NH proton confirming the condensation. Mass spectrum of **7a** showed $[M+H]^+$ at *m/z* 239.

Comparison of microwave and conventional heating: We conducted the amide reactions under reflux or microwave heating at the same temperature (66 °C). The microwave irradiation was more effective than the conventional heating. In addition, the reflux method has a limitation on the reaction temperature. It cannot go beyond the boiling point of the reaction mixture, which was a main reason of low yields (< 40 %) at 66 °C even under microwave irradiation. However, when we conducted the reaction at 80 °C in the microwave oven at 200 W, the amides yield (87-91 %) considerably increased (Table-1).

Antibacterial activity: From Table-2, it appears that compounds **7a-l** showed better antibacterial activity may be due to presence of the imidazo[1,2-*a*]pyrazine ring. The activity was expressed in terms of minimum inhibitory concentration (MIC). Screening results of the compounds **7e**, **7f**, **7h**, **7i** and **7k** exhibited better activity against all the tested microorganisms, as compared to the standard drugs, while compound **7k** showed excellent activity. As far as the structure activity relationship was concerned, compounds **7a-l** displays enhanced activity with the presence of *p*-chloro, *p*-bromo, pyridinyl, *p*-nitro and 2,6-dioxopiperidine substituents than the other substituted compounds (Table-2). They can be utilized as bactericides (**7e**, **7f**, **7h**, **7i** and **7k**) after detailed study.

TABLE-1
PHYSICAL DATA OF SYNTHESIZED *N*-ARYLIMIDAZO[1,2-*a*]PYRAZINE-2-CARBOXAMIDE DERIVATIVES (**7a-l**)

Amine	Product	m.p. (°C)	Reflux		Microwave	
			Time (h)	Yield (%)	Time (h)	Yield (%)
		198	3.5	79	15.0	85
		174	3.0	81	15.0	87
		252	3.5	80	15.0	86
		175	4.0	78	15.0	88
		212	3.5	76	15.0	92
		274	3.0	80	15.0	90
		151	3.5	78	15.0	87
		174	3.0	75	15.0	87
		151	3.5	78	15.0	88
		169	3.0	81	15.0	91
		152	4.0	79	15.0	87
		234	3.5	77	15.0	85

*Isolated yield after column purification

TABLE-2
ANTIBACTERIAL ACTIVITY OF SYNTHESIZED *N*-ARYLIMIDAZO[1,2-*a*]PYRAZINE-2-CARBOXAMIDE DERIVATIVES (**7a-l**)

Compound	MIC[a,b]					
	Gram-positive			Gram-negative		
	B. substilis	*B. sphaerius*	*S. aureus*	*P. aeruginosa*	*K. aerogenes*	*C. violaceum*
7a	23	27	26	32	25	26
7b	25	24	28	34	24	27
7c	24	25	30	35	26	27
7d	19	21	18	31	22	24
7e	18	20	19	24	20	21
7f	19	22	20	23	21	23
7g	23	26	24	32	24	25
7h	20	21	19	26	24	23
7i	19	21	18	26	19	24
7j	17	20	19	28	25	23
7k	17	19	18	22	19	20
7l	24	28	24	35	27	25
Ciproflaxacin	20	25	20	30	25	25
Trimethoprim	21	23	21	28	22	25

Notes: [a]Negative control (DMSO)-no activity; [b]Concentration 100 µg/mL.

Antifungal activity: The antifungal activity results indicated that these compounds **7a-l** were significantly toxic towards all five fungi and they were lethal even at 100 µg/mL concentration (Table-3). The compounds **7e**, **7f**, **7h**, **7i** and **7k** are highly active, because the activity is considerably affected by the presence of *p*-chloro, *p*-bromo, pyridinyl, *p*-nitro and 2,6-dioxopiperidine groups as substituents on benzene ring, besides the presence of basic skeleton. The antifungal activity of these compounds compared with the standard drugs clotrimazole and fluconazole, which demonstrated that they have promising activity. It is noteworthy that compounds **7e**, **7f**, **7h**, **7i** and **7k** displayed better activity, when compared with the standard drugs clotrimazole and fluconazole, hence, they may be exploited for control of wilt diseases of different crops as fungicides after further studies.

Conclusion

A new efficient catalyst was developed for the synthesis of imidazo[1,2-*a*]pyrazine-2-carboxamides (**7a-l**). The products were obtained in good yields and excellent purities. This method offers several advantages including quite simple, time saving, high yielding and most importantly an eco-friendly reaction procedure. The amide formation reaction was greatly enhanced by using 1-methylimidazole (ionic liquid) as the base instead of conventional toxic tertiary amines and by using DMF. Overall, the method described is effective and greener. Imidazo[1,2-*a*]pyrazine-2-carboxamides (**7a-l**) have moderate to excellent activity towards the bacteria and fungi under investigation. Some of them, particularly compounds **7e** and **7k** can be exploited for formulation of bactericide and fungicide after detailed study.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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TABLE-3
ANTIFUNGAL ACTIVITY OF SYNTHESIZED N-ARYLIMIDAZO[1,2-*a*]PYRAZINE-2-CARBOXAMIDE DERIVATIVES (**7a-l**)

Compound	Zone of inhibition[a,b]				
	A. niger	*C. tropicum*	*R. oryzae*	*F. moniliformae*	*C. lunata*
7a	25	20	18	17	22
7b	27	23	20	17	20
7c	27	24	21	18	25
7d	24	21	19	16	21
7e	28	28	22	23	31
7f	26	25	25	21	25
7g	22	21	17	18	20
7h	27	24	21	17	25
7i	25	24	20	15	20
7j	28	26	21	19	20
7k	29	30	29	26	32
7l	23	20	17	15	18
Clotrimazole	30	29	23	20	28
Fluconazole	28	30	27	24	30

Notes: [a]Negative control (DMSO)-no activity; [b]Concentration 100 µg/mL.

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