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Synthesis and antibacterial activity of novel imidazo[1,2-a]pyrimidine and imidazo[1,2-a]pyridine chalcones derivatives

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ABSTRACT

*The chalcone derivatives or 1,3-diphenyl-2-propen-1- ones are known for their multiple anti-infective activities, they may prevent or delay inactivation, degradation and excretion of anti-infective drugs. The wide variety of pharmacological activities reported for these compounds include antimalarial, anti-inflammatory, cytotoxic, anticancer, and antioxidant properties etc. The imidazopyridine nucleus and like chalcone derivatives possesses many anti-infective properties including antibacterial, antiviral, antiprotozoal,anthelmintic. Similarly, imidazo pyrimidine nucleus possesses important therapeutics such as calcium antagonists, anticancer agents, antifungal activity anti-inflammatory and analgesic activity. The present paper describes the synthesis of new chalcones carrying this imidazopyridine/imidazopyrimidine heterocyclic core from commercially available 2-aminopyrimidine and 2-aminopyridine as starting materials. The chalcones (**4a-4f** and **10a -10f**) thus derived (**Scheme 1 and Scheme 2**) have been evaluated for their antimicrobial activities against Escheria.Coli, Pseudomonas.aeruginosa, Staphylococcus.aureus and Streptococus .pyogenes, while using Ciprofloxacin as the reference drug (**Table 1**). In general it is observed that imidazo[1,2-a]pyrimidine chalcone (**4a**, **4b**, **4c**, **4e** and **4f**) derivatives showed excellent activity to good activity when compared to imidazo[1,2-a] pyridine chalcone derivatives **(10a – 10f)** towards the tested bacterial strains.*

Keywords: Chalcones, imidazopyridine, imidazo pyrimidine, 2-amino pyridine, 2-amino pyrimidine, Gram positive and Gram negative bacteria.

INTRODUCTION

The multidrug resistance both in the community and hospitals has been the major concerns to public health and scientific community worldwide [1-4]. The development of antimicrobial agents to treat infectious diseases has been one of the most notable achievements of the past century. The increased use of antimicrobial agents available in the market has resulted in the development of resistance to the commonly used drugs with important implications for morbidity, mortality [5,6] and health care costs. In spite of a large number of antibiotics and chemotherapeutics available for medical use, the antimicrobial resistance has created a substantial need for design of new class of antimicrobials and this field will always remain an area of immense significance.

The chalcone derivatives or 1,3-diphenyl-2-propen-1- ones are known for their multiple anti-infective activities [7, 8]. Several studies have shown that these compounds are active on infectious germs by inhibiting certain enzymes having thiol function, such as glutathione S-transferase [9, 10]. They may prevent or delay inactivation, degradation and excretion of anti-infective drugs (11, 4]. Moreover, their action could also delay or even prevent emergence of new drug-resistant strains of parasites [12,13]. The wide variety of pharmacological activities reported for these compounds include antimalarial, anti-inflammatory, cytotoxic, anticancer, and antioxidant properties [14–18], recently, the antitumor agents [19], antimicrobial agents [20], as inhibitors of breast cancer [21] were also reported.
The imidazopyridine nucleus and like chalcone derivatives possesses many anti-infective properties including antibacterial [22, 23, 24], antiviral [25,26], antiprotozoal [27], anthelmintic [28], as potent MCHR1antagonist [29] and as inhibitors of 5-LO [30]. Similarly, imidazo pyrimidine nucleus possess important therapeutics such as calcium antagonists [31], anticancer agents [32], antifungal activity [33], antiinflammatory and analgesic activity [34] and as as antitumor agents [35]. The present paper describes the synthesis of new chalcones carrying this imidazo[1,2-a]pyridine/imidazo[1,2-a]pyrimidine heterocyclic core from commercially available 2-aminopyrimidine and 2-aminopyridine as starting materials. The chalcones thus derived have been evaluated for their antimicrobial activities against *Escheria.Coli*, *Pseudomonas.aeruginosa*, *Staphylococcus.aureus* and *Streptococus .pyogenes*, while using Ciprofloxacin, as the reference drug.

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MATERIALS AND METHODS

The solvents were purified according to standard procedures prior to use, and all commercial chemicals were used as received. For thin-layer chromatography (TLC) analysis, Merck precoated Plates (silica gel 60 F254) were used and eluting solvents are indicated in the procedures. Merck silica gel 60 (230-400 mesh) was used for flash column chromatography. Melting point (mp) determinations were performed by using Mel-temp apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian Unity instrument at room temperature at 400MHz. Chemical shifts are reported in δ parts per million (ppm) downfield from tetramethylsilane (TMS) with reference to internal solvent and coupling constants in Hz. The mass spectra were recorded on Agilent ion trap MS. Infrared (IR) spectra were recorded on a Perkin Elmer FT-IR spectrometer. All the carboxylic acids used for the preparation of **6a-6k** were purchased from commercial sources.

Experimental methods

2-(dichloromethyl)imidazo[1,2-a]pyrimidine (**2)**

To a mixture of 2-aminopyrimidine (5g, 52.57 mmol), sodium bicarbonate (11.34 g, 105.14 mmol) in ionic liquid 1-n-butyl-3-methylimidazolium tetrafluoroborate-BMImBF$_4$ (20 mL) was added 1,1,3-trichloro acetone (12.70 g, 78.85 mmol) and stirred at room temperature for 10 h. After completion of the reaction (monitored by TLC), the mixture was poured into ice-water (30 mL) with vigorous stirring to precipitate the product 2-(dichloromethyl)imidazo[1,2-a]pyrimidine **2,** which was utilized in the next step without further purification. After filtration of the product, the filtrate ionic liquid was evaporated to remove the water under reduced pressure for recycling.

imidazo[1,2-a]pyrimidine-2-carbaldehyde (**3)**

A mixture of compound **2** (1g, 4.95 mmol) $CaCO_3$ (5g, 24.75 mmol) in water (30 mL) was refluxed for 1h. The reaction mixture was cooled to room temperature and extracted with 2-MeTHF and evaporated under reduced pressure to obtain the crude compound **3,** which was purified by column chromatography (silica gel: 60 – 120 mesh, eluent: 1% MeOH / $CHCl_3$) to afford compound **3** as a pale yellow solid. Yield: 60%; m.p 209- 210 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.96 (s,1H), 9.66 (q, *J* = 6.8 Hz, 1H), 8.88 (q, *J* = 4.0 Hz, 1 H), 8.70 (s, 1H), 7.43 (q, *J* = 6.4 Hz, 1 H). EI-MS: m/z (rel.abund.%) 148.2 (M^+,100).

ethyl 3-bromo-2-oxo-4-phenylbutanoate (**6)**

ethyl 2-oxo-4-phenylbutanoate **5** (5g, 24.27 mmol) was suspended in water (80 mL) and the flask was covered with aluminium foil. A 48% aqueous solution of HBr (4.10 mL, 1.0 mol equiv) and 30% aqueous solution of 30 %H_2O_2 (5.5 mL, 2.0 mol equiv) were added in one portion and the mixture was stirred at room temperature. The progress of the reaction was monitored by TLC. After 48 h, the reaction mixture was dissolved in 50 mL of a mixture of hexane and ethylacetate (20 : 1), then solid $NaHSO_3$ was added to reduce un reacted Br_2 and H_2O_2 and the solution was dried over anhydrous Na_2SO_4. The insoluble material was filtered off and the organic solvent evaporated under reduced pressure to obtain crude compound **6** and was utilized in the next step without further purification. Yield:

6g, 86%. Yellow oil; 1H-NMR ($CDCl_3$) δ : 7.44 - 7.32 (m, 5 H, Ph); 5.36 (m, 1 H, CH); 4.45 (q, *J* = 7.1 Hz, 2H, CH_2); 3.62 (m, 1H, m, AB system, CH_2); 3.33 (m, 1H, AB system, CH_2); 1.46 (t, *J* = 7.23 Hz, 3 H,CH_3).

ethyl 3-benzylH-imidazo [1,2-a]pyridine-2-carboxylate (**7)**
To a mixture of 2-aminopyridine (2.20 g, 33.66 mmol), sodium bicarbonate (67.20 mmol) in ionic liquid 1-n-butyl-3-methylimidazolium tetrafluoroborate- $BMImBF_4$) (15 mL) was added compound **6** (8g, 28.05 mmol) and stirred at room temperature for 7 h. After completion of the reaction (monitored by TLC), the mixture was poured into ice-water (30 mL) with vigorous stirring to precipitate the product ethyl 3-benzylH-imidazo [1,2-a]pyridine-2-carboxylate **7**, which was utilized in the next step without further purification. After filtration of the product, the filtrate ionic liquid was evaporated to remove the water under reduced pressure for recycling. Pale yellow solid; Yield: (51%); m.p. 88 °C; 1H-NMR ($CDCl_3$) δ : 7.85 (d, *J* = 6.8 Hz, 1 H); 7.72 (d, *J* = 9.0 Hz, 1H,); 7.31-7.23 (m, 6 H); 6.81 (t, *J* = 6.8 Hz ,1H); 4.79 (s, 2 H); 4.57 (q, *J* = 7.1 Hz, 2 H); 1.50 (t, *J* = 7.1 Hz, 3H); EI-MS: m/z (rel.abund.%) 281.2 (M+, 100).

(3-benzylH-imidazo [1,2-a]pyridin-2-yl)methanol (**8)**
To a stirred mixture of lithium aluminum hydride (0.8g, 21.4 mmol) in 2-MeTHF (20 mL), cooled to -10 °C, was added a premixed solution of compound **3** (3g, 10.71 mmol) in 2-MeTHF (10 mL) over a period of 15min. The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with sat; Na_2SO_4 solution at 0°C, and the inorganic salts were filtered and washed with isopropyl acetate (50 mL). The filtrate was evaporated to obtain brown residue. The residue was dissolved in isopropyl acetate and washed with water (2 x 30 mL) followed by brine solution (20 mL). The organic layer was separated, dried over Na_2SO_4, filtered and evaporated under reduced pressure to obtain compound **8.** Brown solid; Yield: 70%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, *J* = 16.0 Hz, 1H), 7.58 (d, *J* = 16.0 Hz, 1H), 7.40 – 7.20 (m, 3 H), 7.18 – 7.02 (m, 3 H), 6.70 (t, *J* = 8.2 Hz, 1H), 4.92 (s, 2 H), 4.35 (s, 2 H), 3.98 (br.s, 1 H). EI-MS: m/z (rel.abund.%) 239.3 (M+, 100).

3-benzylH-imidazo[1,2-a]pyridine-2-carbaldehyde **(9)**
To a stirred solution of IBX (2.99 g, 1.13 mmol) in DMSO (18 mL), cooled to 0°C, was added a premixed solution of compound **9** (1.8 g, 7.56 mmol) in DCM (36 mL) over a period of 10 min. The reaction mixture was stirred at room temperature for 4 h. The reaction mixture was filtered and the insolubles were washed with DCM followed by cold water. The organic layer was separated and washed with water followed by brine solution, dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain compound **9.** Yellow solid; Yield: 57%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.40 (s, 1H), 7.86 (d, *J* = 16.0 Hz, 1H), 7.68 (d, *J* = 16.0 Hz, 1H), 7.30 – 7.22 (m, 4 H), 7.14 (d, *J* = 16.0 Hz, 2 H), 6.82 (t, *J* = 8.0 Hz, 1H), 4.78 (s, 2 H). EI-MS: m/z (rel.abund.%) 237.3 (M+, 100).

General Experimental Procedure for the Preparation of imidazo[1,2-a]pyridine/imidazo[1,2-a]pyrimidine derivatives 4a – 4e and 10 a – 10 e
A mixture of acetophenones (R = a – e, **Table 1**) and respective aldehydes **3**/**9**, solid NaOH was grounded by pestle and mortar at room temperature for 5–10 min. The reaction mixture was diluted with cold water and the precipitated solids were filtered and dried at the pump to afford respective chalcone derivatives **4a – 4e** and **10 a – 10** e in 52-88% yield.

(2E)-3-(imidazo[1,2-a]pyrimidin-2-yl)-1-phenylprop-2-en-1-one **4a**: Yellow solid, m.p.87 – 88 ^{o}C; Yield: 87%
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.45 (dd, *J* = 2.2, 6.8 Hz, 1H), 8.70 (s, 2 H), 8.20-8.10 (m, 3 H), 8.0 (d, *J* = 17.8 Hz, 1H), 7.70-7.58 (m, 3 H), 7.28 (dd, *J* = 2.4, 7.2 Hz); EI-MS: m/z (rel.abund.%) 250.1 (M+, 100).

(2E)-3-(imidazo[1,2-a]pyrimidin-2-yl)-1-(4-methoxyphenyl)prop-2-en-1-one **4b**: Yellow solid, m.p.112-113 ^{o}C; Yield: 67%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.41 (dd, *J* = 2.2,9.6 Hz, 1H), 8.68 (s, 2 H), 8.20 (d, *J* = 8.8 Hz, 2 H), 8.10 (d, *J* = 16.2 Hz, 1H), 7.98 (d, *J* = 16.4 Hz, 1H), 7.07 (d, *J* = 8.8 Hz, 3H), 3.88 (s, 3H); EI-MS: m/z (rel.abund.%) 280.2 (M+, 100).

(2E)-3-(imidazo[1,2-a]pyrimidin-2-yl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one **4c**: Yellow solid, m.p.109-111 ^{o}C; Yield: 59%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.43 (dd, *J* = 2.0,7.2 Hz, 1H), 8.70 (s, 1 H), 8.68 (dd, *J* = 2.0, 4.8 Hz, 2 H), 8.13 (d, *J* = 15.6 Hz, 1H), 7.98 (d, *J* = 15.2 Hz, 1H), 7.43 (s, 2H), 7.22 (dd, *J* = 2.4, 6.8 Hz, 1H), 3.88 (s, 6H), 3.77 (s, 3H); ^{13}C NMR (100 MHz,$CDCl_3$): δ 56.2 (2C), 56.5, 107.4 (2C), 111.6, 120.9, 127.4, 129.2, 132.2, 135.3, 136.0, 145.0, 148.8, 151.3 (2C), 157.2, 189.7; EI-MS: m/z (rel.abund.%) 340.1 (M+, 100).
(2E)-1-(3-bromophenyl)-3-(imidazo[1,2-a]pyrimidin-2-yl)prop-2-en-1-one **4d**:

Yellow solid, m.p.89-91 ^{o}C; Yield: 78%;; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.44 (dd, *J* = 2.0,7.2 Hz, 1H), 8.71 (s, 1 H), 8.68 (dd, *J* = 2.2,6.8 Hz,1H), 8.33 (s, 1 H), 8.15 (m, 2 H), 7.98 (m, 2 H), 7.60 (t, *J* = 8.4 Hz, 1H), 7.28 (dd, *J* = 4.4, 6.60 Hz, 1H); EI-MS: m/z (rel.abund.%) 328 (M+, 100).

(2E)-1-(4-bromophenyl)-3-(imidazo[1,2-a]pyrimidin-2-yl)prop-2-en-1-one **4e**:
Yellow solid, m.p.130-131 ^{o}C; Yield: 88%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.44 (dd, *J* = 2.0,5.2 Hz, 1H), 8.68 (s, 2 H), 8.12 (m, 3H), 7.92 (d, *J* = 15.2 Hz, 1H), 7.80 (d, *J* = 19.2 Hz, 2 H), 7.28 (dd, *J* = 4.4, 6.8 Hz, 1H); EI-MS: m/z (rel.abund.%) 328 (M+, 100).

(2E)-1-(3-bromo-4-fluorophenyl)-3-(imidazo[1,2-a]pyrimidin-2-yl)prop-2-en-1-one **4f**:
Yellow solid, m.p.97-99^{o}C; Yield: 88%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.44 (dd, *J* = 1.8,7.2 Hz, 1H), 8.70 (s, 1 H), 8.68 (dd, *J* = 2.2, 6.8 Hz, 1 H), 8.50 (dd, *J* = 2.2, 7.0 Hz, 1H), 8.26-8.21 (m, 1H), 8.15 (d, *J* = 20 Hz, 1H), 7.96 (d, *J* = 20 Hz, 1 H), 7.58 (t, *J* = 8.6 Hz, 1H), 7.28 (m, 1H); EI-MS: m/z (rel.abund.%) 346 (M+, 100).

(2E)-3-(3-benzylH-imidazo[1,2-a]pyridin-2-yl)-1-phenylprop-2-en-1-one **10a**:
Orange solid, m.p. 121-122 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18-8.13 (m, 3 H), 8.06 (d, *J* = 15.2 Hz, 1H), 7.73 (d, *J* = 10.8 Hz, 1H), 7.64 (d, *J* = 10.2 Hz, 1H), 7.60-7.50 (m, 1H), 7.52 (t, *J* = 16.0 Hz, 1 H), 7.32-7.18 (m, 5 H), 7.14 (d, *J* = 16.2 Hz, 2H), 6.71 (t, J = 15.8 Hz, 1 H), 4.45 (s, 2 H). EI-MS: m/z (rel.abund.%) 339.2 (M+, 100).

(2E)-3-(3-benzylH-imidazo[1,2-a]pyridin-2-yl)-1-(4-methoxyphenyl)prop-2-en-1-one **10b**:
Yellow solid, 131-132 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18-8.13 (m, 3 H), 8.06 (d, *J* = 15.4 Hz, 1H), 7.72 (d, *J* = 10.4 Hz, 1H), 7.63 (d, *J* = 10.6 Hz, 1H), 7.30-7.18 (m, 4 H), 7.12 (d, *J* = 15.8 Hz, 2 H), 6.98 (d, *J* = 11.8 Hz, 2 H), 6.70 (d, *J* = 15.6 Hz, 2H), 4.45 (s, 2 H), 3.88 (s, 3H); EI-MS: m/z (rel.abund.%) 369.2 (M+, 100).

(2E)-3-(3-benzylH-imidazo[1,2-a]pyridin-2-yl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one **10c**:
Yellow solid, m.p.106-107 ^{o}C; Yield: 77%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, *J* = 6.8 Hz, 1H), 7.52 (d, *J* = 8.8 Hz, 1H), 7.22-7.20 (m, 5 H), 7.18 (s, 2 H), 7.02 (d, *J* = 17.8 Hz, 2H), 7.08 (t, *J* = 8.8 Hz, 1 H), 6.62 (t, *J* = 8.8 Hz, 1H), 4.42 (s, 2 H), 3.88 (s, 6 H), 3.86 (s, 3H). EI-MS: m/z (rel.abund.%) 429.2 (M+, 100).

(2E)-3-(3-benzylH-imidazo[1,2-a]pyridin-2-yl)-1-(3-bromophenyl)prop-2-en-1-one **10d**:
Yellow solid, m.p.90-91 ^{o}C; Yield: 80%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (t, *J* = 2.0 Hz, 1H), 8.18-8.09 (m, 2 H), 8.05 (d, *J* = 16.0 Hz, 1H), 7.74 (d, *J* = 18.2 Hz, 1H), 7.68 (d, *J* = 16.2 Hz, 1 H), 7.36 (t, *J* = 12.0 Hz, 1H), 7.32-7.28 (m, 4 H), 7.15 (d, *J* = 16.0 Hz, 2H), 6.75 (t, *J* = 8.0 Hz, 1H), 6.47 (s, 2 H); EI-MS: m/z (rel.abund.%) 417.0, (M+, 100).

(2E)-3-(3-benzylH-imidazo[1,2-a]pyridin-2-yl)-1-(4-bromophenyl)prop-2-en-1-one **10e**:
Yellow solid, m.p.116-117 ^{o}C; Yield: 77%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, *J* = 15.2 Hz, 1H), 8.04 (d, *J* = 11.4 Hz, 1H), 7.44 (d, *J* = 7.2 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 3 H), 7.31-7.18 (m, 5 H), 7.12 (d, *J* = 6.8 Hz, 2H), 6.75 (t, J = 13.6 Hz, 1H), 4.45 (s, 2 H); EI-MS: m/z (rel.abund.%) 417.1 (M+, 100).

(2E)-3-(3-benzylH-imidazo[1,2-a]pyridin-2-yl)-1-(3-bromo-4-fluorophenyl)prop-2-en-1-one **10f:**
Yellow solid, m.p. 115-117^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (dd, *J* = 1.2, 6.2 Hz, 1H), 8.14-8.06 (m. 3 H), 7.44 (d, *J* = 11.2 Hz, 1H), 7.63 (d, *J* = 11.4 Hz, 3 H), 7.31-7.20 (m, 5 H), 7.14 (d, *J* = 16.2 Hz, 2 H), 6.72 (t, *J* = 11.8 Hz, 1H), 4.45 (s, 2 H); EI-MS: m/z (rel.abund.%) 435.1 (M+, 100).

Antibacterial Bioassay

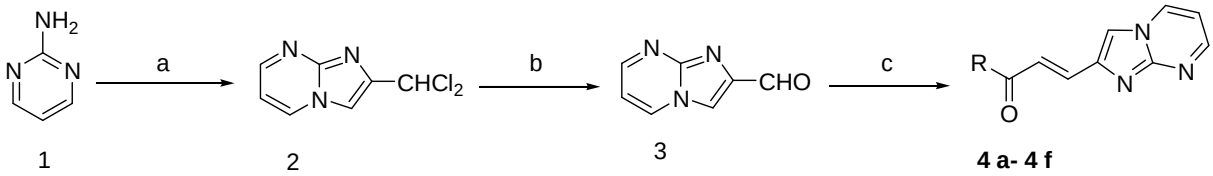
Compounds **4a–4f** and **10a -10f** were tested against two Gram negative strains viz., i) *Escherichia coli* (MTCC443), *(ii) Pseudomonas aeruginosa* (MTCC424), and two Gram positive *Staphylococcus aureus* strains *viz. i). Streptococcus pyogenes* (MTCC442), *and ii)* (MTCC96) using agar well diffusion method according to the literature protocol [36]. Amide derivatives (**4a–4f / 10a-10f**) were dissolved in dimethyl sulphoxide at 50 µg/mL concentration. The composition of nutrient agar medium was Bactotryptone (10 g), yeast extract (5 g), NaCl (10 g), final pH 7.4. After 18 h the exponentially growing cultures of the six bacteria in nutrient broth at 37 ^{o}C were diluted in sterile broth. From each of these diluted cultures, 1mL was added to 100 mL sterilized and cooled nutrient agar media to give a final bacterial count of 1 x 10^6 cell/ml. The plates were set at room temperature and later dried at 37 ^{o}C for 20h. Paper discs (6mm, punched from whatmann no 41 paper) were ultraviolet sterilized and used for the assays. Discs were soaked in different concentration of the test solution and placed on the inoculated agar media at

regular intervals of 6-7 cm, care was taken to ensure that excess solution was not on the discs. All the samples were taken in triplicates. The plates were incubated at 37 ^{o}C in an inverted fashion. Activity was determined by zones showing complete inhibition (mm). Growth inhibition was calculated with reference to positive control.

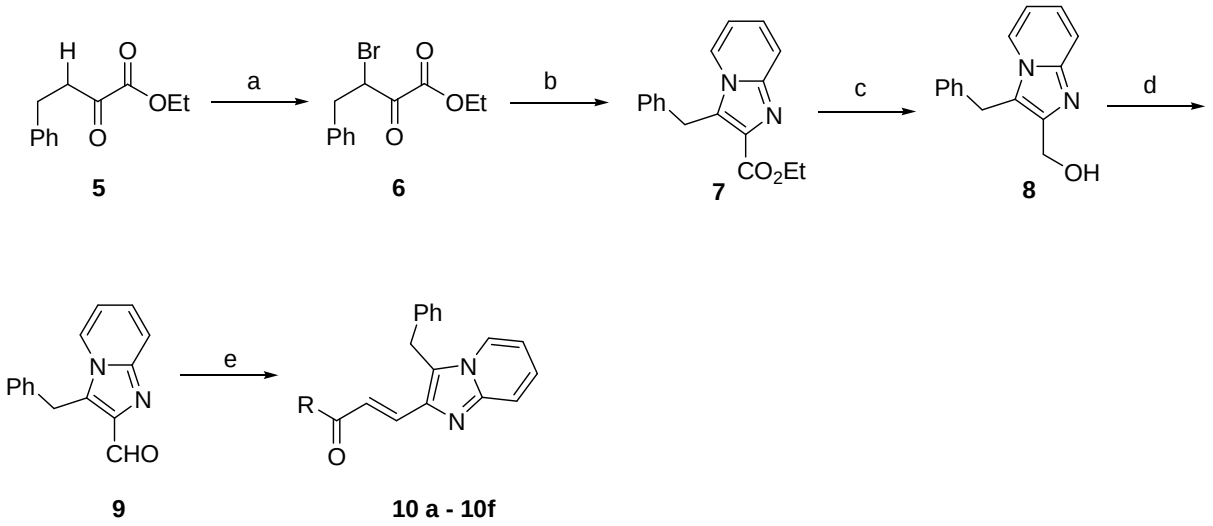
RESULTS AND DISCUSSION

Chemistry

We describe here in the synthesis of imidazo[1,2-a]pyrimidine chalcones **4a-4f** and imidazo[1,2-a]pyridine chalcones **10a-10f** (depicted in **Scheme 1** and **Scheme 2)** utilization greener solvents/green reagents in some of the steps. The cyclocondensation reactions of 1,1,3-trichloro acetone with 2-aminopyrimidine **1** to 2-(dichloromethyl)imidazo[1,2-a]pyrimidine **2** was carried out using room temperature ionic liquid (RTILs), n-butyl-3-methylimidazolium tetrafluoroborate ($BMImBF_4$) as solvent at room temperature for 10 h. RTILs is used as a green recyclable alternative to conventional solvent. Dichloromethyl imidazo[1,2-a]pyrimidine **2** was treated with $CaCO_3$ in water at reflux for 1h to produce imidazo[1,2-a]pyrimidine-2-carbaldehyde **3**, water is being used as a green solvent avoiding the use of organic solvents. Claisen schmidt condensation of aldehyde **3** with acetophenones (**a –f**) was carried out under solvent free conditions using solid NaOH as catalyst at room temperature [37] for 5-10 min to afford chalcones **4 a-4 f** in 75 -83% yield (**Scheme 1**). The advantage of the reaction is, it is carried out under solvent free condition, short reaction time and has a minimum environmental impact. The synthesis of imidazo[1,2-a]pyridine chalcones **10a-10f** is presented in **Scheme 2**. Bromination of ethyl 2-oxo-4-phenylbutanoate **5** was carried out in water using 48% aqueous solution of HBr in presence of 30 % aqueous solution H_2O_2 at room temperature [38] for 48 h resulted in bromide intermediate **6**. The ‘‘green’’ feature in this protocol include the use of inexpensive reagents and a lower impact on the environment, since bromine is generated in situ from H_2O_2 and HBr. The use of H_2O_2 as a ‘‘green’’ oxidant produces water as the only by-product of the reaction [38].



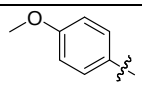
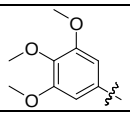
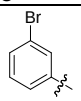
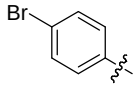
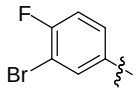
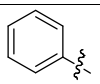
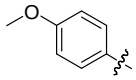
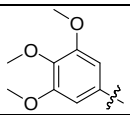
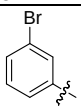
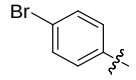
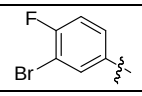
Scheme-1: Synthesis of imidazo[1,2-a] pyrimidine chalcone derivatives; Reagents and Conditions: a) 1,1,3-trichloro acetone, Na_2CO_3, $BMImBF_4$, r.t., 10 h; b) $CaCO_3$, water, reflux, 1 h; c) acetophenones (R = a – f), NaOH, r.t., 5- 10 min.



Scheme-2: Synthesis of imidazo[1,2-a] pyridine chalcone derivatives; Reagents and Conditions: a) 48% aq; HBr, water, 30% H_2O_2, room temperature, 48 h ; b) 2-amino pyridine, ethanol, Na_2CO_3, $BMImBF_4$, r.t., 7 h; c) $LiAlH_4$, 2Me-THF, -10^{o} C – rt, 2 h; d) IBX, DMSO:DCM (1:2), rt, 4 h; e) acetophenones (R = a – f), NaOH, r.t., 5- 10 min.

Transformation of compound **6** to imidazo[1,2-a] pyridine ethylester intermediate **7** was carried out utilizing the procedure used for the preparation of imidazo[1,2-a] pyrimide **2** (**Scheme 1**). 1H NMR data of compound **6** and compound **7** is in agreement with the reported literature data [39]. Lithium aluminum hydride reduction of ethylester intermediate **7** in presence of 2-MeTHF at room temperature produced alcohol intermediate **8**. Oxidation of alcohol **8** in presence of IBX in DMSO:DCM (1:2) resulted in the formation of aldehyde **9**. Claisen schmidt condensation of aldehyde **9** with acetophenones (**a –f**) was carried out similar to the preparation of imidazo[1,2-a]pyrimidine chalcone derivatives. In general the IR spectral data of all the chalcone derivatives **4a-4f** and **10a-10f** indicated the presence of distinctive functional groups such as –C=O, -CH=CH, C=N, C-N str in the range 1700-1640 and 1644-1618, 1610-1590, 1230-1020 cm^{-1}.

Table 1: Results of Antibacterial Bioassay of Compounds 4a-4e and 10 a – 10 e;

Compound no.	R	*Gram negative bacteria*		*Gram positive bacteria*	
		***E. coli* MTCC 443**	***P. aeruginosa* MTCC 424**	***S.aureus* MTCC 96**	***S.poygenes* MTCC 442**
4a		25	23	19	18
4b		28	23	22	21
4c		28	22	20	19
4d		16	14	12	11
4e		24	20	18	17
4f		28	23	21	20
10a		22	20	17	15
10b		21	20	17	18
10c		21	19	17	16
10d		--	--	--	--
10e		20	18	16	17
10f		26	21	19	18
SD* Ciprofloxacin (Conc. 50 µg/mL)	SD* Ciprofloxacin	28	24	21	21

--: No activity

Antibacterial Activity

The antibacterial activity of the analogues (50 µg/mL concentration) was compared with standard drug Ciprofloxacin and the results of investigation have been presented in **Table 1.** Based on the test results it is evident that the synthesized chalcone derivatives possess excellent to good activity against the Gram +ve and Gram –ve bacteria. In general it is observed that imidazo[1,2-a]pyrimidine chalcones (**4a**, **4b**, **4c, 4e** and **4f**) showed excellent to good activity when compared to imidazo[1,2-a]pyridine chalcone **(10a – 10f)** towards the tested bacterial strains. Among the imidazo[1,2-a]pyrimidine chalcones, compounds **4b** with 4-methoxy moiety, **4c** with 3,4,5-trimethoxy and compound **4f** with bromo,fluro substituent displayed equivalent activity and compounds **4a** and **4e** exerted good activity with reference to the standard drug Ciprofloxacin. Imidazo[1,2-a]pyridine chalcones **10a**, **10b**, **10c, 10e** and **10f** indicated similar trends when tested against all the bacterial strains. It is observed that compound **4d** with meta-bromo substituent (imidazo[1,2-a] pyrimidine derivative) displayed weak activity against all the tested bacterial strains where as compound **10d** (imidazo[1,2-a]pyridine derivative) did not show any activity towards any of the tested bacteria.

CONCLUSION

In conclusion, we have synthesized novel imidazo[1,2-a] pyrimidine chalcones (**4a-4f**) and imidazo[1,2-a] pyridine chalcones (**10a-10f**) derivative utilizing starting materials 2-amino-pyrimidine and 2-amino pyridine. The chalcones thus derived have been evaluated for their antimicrobial activities against *Escheria.Coli, Pseudomonas.aeruginosa, Staphylococcus.aureus* and *Streptococus .pyogenes*, while using Ciprofloxacin, as the reference drug. In general it is observed that imidazo[1,2-a]pyrimidine chalcone (**4a**, **4b**, **4c, 4f** and **4e**) derivatives showed excellent activity when compared to imidazo[1,2-a]pyridine chalcone derivatives **(10a – 10f)** towards the tested bacterial strains.

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