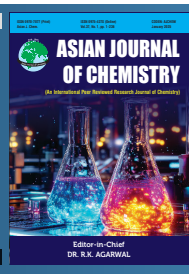
Asian Journal of Chemistry; Vol. 37, No. 5 (2025), 1039-1043

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2025.33461



Design and Synthesis of Novel 2-Chloro-5-(chloromethyl)pyridine Bioactive Derivatives by Rapid and Efficient Continuous Flow Reaction Module

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Received: 1 February 2025; *Accepted*: 6 March 2025; *Published online*: 30 April 2025; AJC-21967

This study explores the synthesis of new bioactive compounds from the key intermediate 2-chloro-5-(hydrazinylmethyl)pyridine by reacting with various aromatic aldehydes. The process started with 2-chloro-5-(chloromethyl)pyridine, which was used in a flow reactor for a continuous and efficient reaction. The key intermediate, 2-chloro-5-(hydrazinylmethyl)pyridine, was synthesized *via* a straightforward method and then reacted with aromatic aldehydes under mild conditions to form hydrazone compounds. The compounds were characterized with FTIR, NMR and mass spectroscopic techniques. Preliminary testing showed the promising biological activities, including potential antimicrobial and anti-malarial effects, suggesting their utility in the drug development.

Keywords: Pyridine derivatives, Flow reactor module, Continuous reaction, Medicinal chemistry, Pharmacological potential.

INTRODUCTION

Heterocycles serve as crucial scaffolds in the development of pharmaceuticals and exert many effects on biological organisms, including combating bacteria, viruses, cancer and inflammation [1,2]. Nitrogen containing pyridine derivatives are significant due to their efficacy in biological environments and their ability to interact with many compounds [3]. In the similar manner, sulfur-containing rings like thiophene, thiazole and benzothiophene have special chemical qualities that make them also effective in the biological applications [4]. The combination of nitrogen and sulfur atoms within the same heterocyclic structure often leads to enhanced or novel biological activities, making these compounds of particular interest in developing new pharmaceuticals [5].

Recent developments in the synthetic techniques, especially flow chemistry, facilitate a more efficient, controlled and scalable generation of these bioactive compounds, opening fields for the identification of novel therapeutic agents with enhanced characteristics [6]. Typically, the production of some unique chemical compounds has been carried out in multi-steps, which can be quite time-consuming and challenging to scale up. Flow chemistry has transformed the synthesis of organic molecules, offering numerous advantages over conventional batch techniques. Flow chemistry is a process where chemicals move continuously through a machine called a reactor. This usually happens at specific temperatures, pressures and mixing speeds. This approach facilitates improved control of reaction specifics, reaction efficiency, safety and the scalability of reactions [7]. Flow chemistry is more automated, which means it can make products in a steady way and is easier to increase production than batch processing [8-10]. Minimizing liquid and chemical usage in the flow processes makes them safer. The chemicals have a low environmental impact and may expand the processes without altering anything [11].

The special features of flow reactors like better mixing and more surface area compared to their volume, offer chances to discover new chemical reactions. The development of novel compounds to combat resistant bacteria and fungi has become a crucial focus of research, as several strains are developing resistance to existing medications, presenting a significant global challenge [12]. Therefore, we have undertaken a study on the synthesis of the starting material 2-chloro-5-(chloromethyl)-pyridine, which is subjected to a reaction with hydrazine hydrate to form the intermediate 2-chloro-5-(hydrazinylmethyl)pyridine. This intermediate is then further reacted with a series of aromatic aldehydes under controlled conditions in a flow reactor module. The flow reactor setup ensures the optimal reaction control,

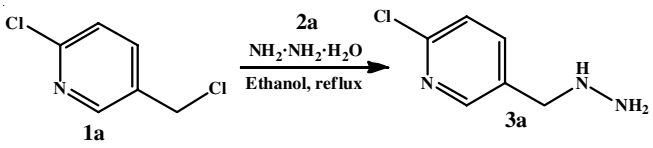
improved reaction efficiency and greater safety compared to the traditional batch methods, particularly when dealing with the reactive intermediates such as hydrazine derivatives [13-15].

EXPERIMENTAL

All the solvents and chemicals were of LR grade and purchased from Avra Synthesis, Spectrochem and SD fine chemicals, India. For reaction at the flow conditions were used the Asia pressurized input store, Asia syringe pump, Asia reagent injector, Asia tube reactor (1.6 mm OD, 0.5 mm ID, VR = 16 mL) and the Asia pressure controller. The purity of starting materials and progress of the reaction were performed by TLC on Merck silica gel G F_{254} plates. The ^{1}H NMR spectra were recorded on the MR400 Agilent Technology NMR spectrometer.

General procedure

Synthesis of 2-chloro-5-(hydrazinylmethyl)pyridine in batch process: An aqueous solution of hydrazine hydrate (50.06 g, 0.85 mol) dissolved in 200 mL of ethanol was heated to reflux. Then, 2-chloro-5-chloromethyl pyridine (95%, 18 g, 0.1056 mol) was added dropwise over a period of 1 h and the reaction mixture was maintained at reflux for an additional 2-3 h. Completion of the reaction was monitored by thin layer chromatography (TLC). Excess ethanol was removed using a rotary evaporator and the residue was dissolved in ethyl acetate. The solution was then washed with brine followed by distilled water. The organic layer was dried and the solvent (ethyl acetate) was removed by distillation to afford 2-chloro-5-(hydrazinylmethyl)pyridine (**3a**) (**Scheme-I**) (yield: 11.6 g, 0.0738 mol, 70%).



Scheme-I

Synthesis of 2-chloro-5-(hydrazinylmethyl)pyridine by using flow reactor: 2-Chloro-5-(chloromethyl)pyridine (**1a**, 35%) was fed into the 16 mL reactor through the first dosing line using pump (P1) at a rate of 1.95 mL/min (1.91 g/min, 1 mol equiv.). Then 80% solution of hydrazine hydrate (**2a**) was fed through the second dosing line using pump (P2) at a rate of 1.26 mL/min (1.3 g/min, 5.0 mol equiv.). Both dosing lines discharged their contents into the reaction region, which was maintained at 50-90 ºC. The desired product, 2-chloro-5-(hydrazinylmethyl)pyridine (**3a**) was formed with 77% selectivity within a residence time of 5 min at 90 ºC. Similarly, when using 6, 7 and 8 mol of compound **2a**, the results at the optimum temperature of 90 ºC were 85.6%, 95% and 98.7% selectivity, respectively, as shown in Table-1.

Completion of the reaction was monitored by thin layer chromatography (TLC). The reaction mixture collected for 8 min and was quenched in water and the product was extracted with toluene. The organic layer was dried over anhydrous sodium sulfate and evaporated under vacuum to yield the final product **3a**. For 8 min collection, subtrate **1a** was taken (7.72 g, 0.0167 mol/8 min) and produced (2.24 g, 0.0142 mol/8 min). The purity of the product was 99.3% and the yield was 85%. The obtained product was identified by ^{1}H NMR spectroscopy.

TABLE-1
OPTIMIZED CONDITIONS FOR COMPOUND **3a** WITH VARIABLE MOLE RATIO OF COMPOUND **2a** AT 90 ºC

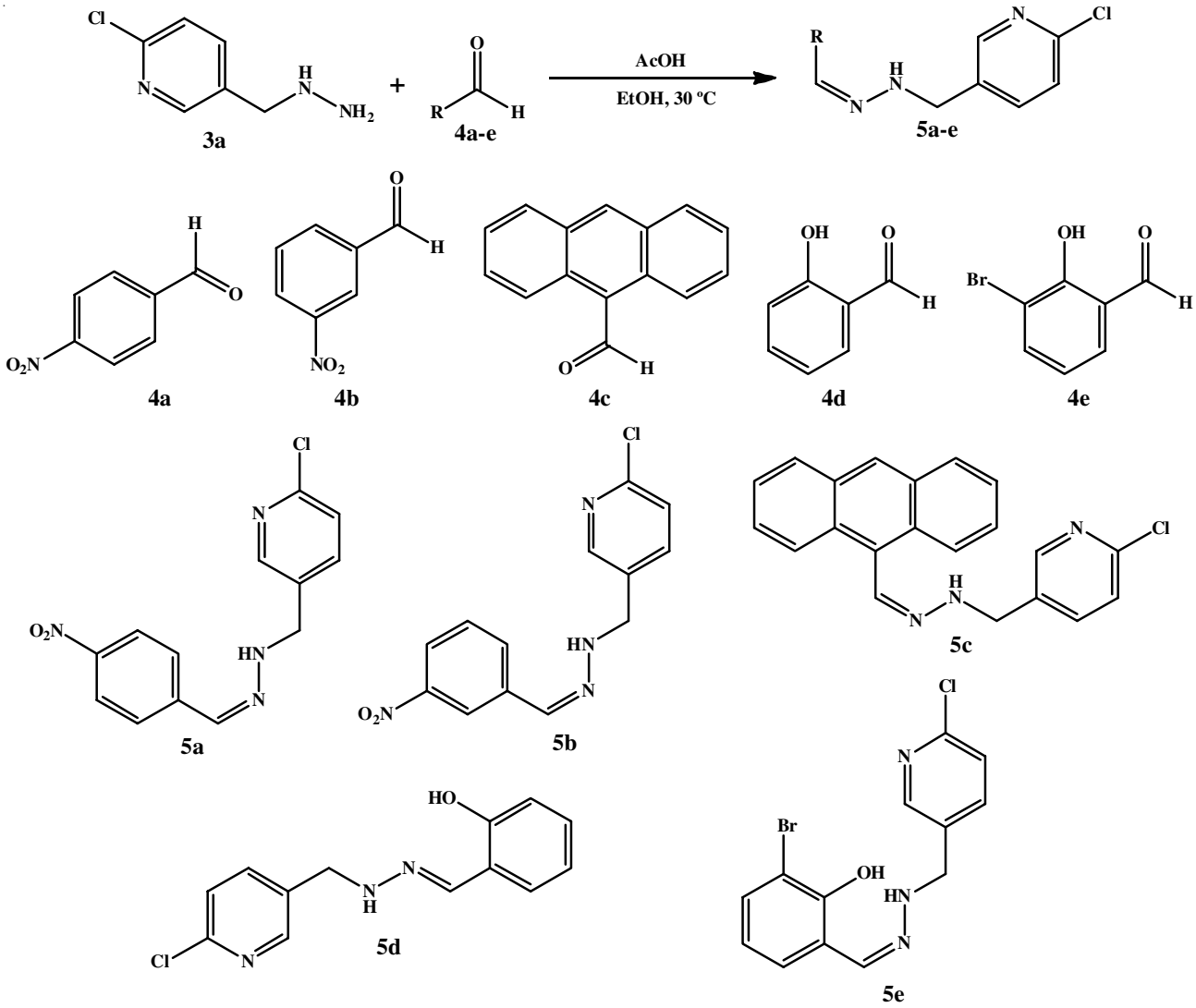
Entry	Residence time (min)	Mole ratio (**1a**:**2a**)	Yield (%) of **3a**
1	8	1:6	85.6
2	8	1:7	95.0
3	8	1:8	98.7

General procedure for the synthesis of a novel derivative of 2-chloro-5-(hydrazinylmethyl)pyridine by flow reactor: Initially, a 50% solution of 2-chloro-5-(hydrazinylmethyl)-pyridine (**3a**) was fed into the reactor through the first dosing line using pump (P1) at a rate of 1.772 mL/min (1.729 g/min, 0.005486 mol/min). Then, 50% solution of 4-nitrobenzaldehyde (**4a**) and acetic acid was fed through the second dosing line using pump (P2) at a rate of 1.428 mL/min (1.657 g/min, 0.005486 mol/min) at 30 ºC. The flow rate was adjusted at the mole ratio of 1:1:0.14 (**3a**:**4a**:acetic acid). The completion of the reaction was monitored by thin-layer chromatography (TLC). The reaction mixture collected for 5 min was quenched in cold water and the solid was filtered to obtain the final product. The product, 2-chloro-5-((2-(4-nitrobenzylidene)hydrazinyl)methyl)pyridine (**5a**) was formed within a residence time of 5 min (**Scheme-II**). Similarly, the other compounds **5b-e** were synthesized by following the same experimental flow process.

2-Chloro-5-((2-(4-nitrobenzylidene)hydrazinyl)methyl)-pyridine (5a): Yellow crystalline solid, yield: 90% (exact mass: 290.06). Residence time: 5 min; IR (KBr, ν_{max}, cm^{-1}): 3302 (N-H *str.*), 3094 (C–H *str.*), 1597 (C=N); ^{1}H NMR (400 MHz, DMSO) δ ppm: 8.50 (t, *J* = 4.6 Hz, 1H,), 8.41 (d, *J* = 2.3 Hz, 1H), 8.14 (d, *J* = 8.9 Hz, 2H), 7.82 (dd, *J* = 8.2, 2.4 Hz, 1H), 7.66 (dd, *J* = 8.9, 1.6 Hz, 3H), 7.48 (d, *J* = 8.2 Hz, 1H), 4.46 (s, 2H); ^{13}C NMR (126 MHz, DMSO) δ ppm: 149.27 (d, *J* = 5.8 Hz), 148.85 (s), 145.57 (s), 143.07 (s), 139.26 (d, *J* = 4.7 Hz), 133.54 (d, *J* = 6.7 Hz), 131.34 (d, *J* = 7.4 Hz), 125.29 (d, *J* = 3.9 Hz), 123.84 (d, *J* = 7.1 Hz), 48.08 (d, *J* = 22.8 Hz).

2-Chloro-5-((2-(3-nitrobenzylidene)hydrazinyl)methyl)-pyridine (5b): Yellow crystalline solid, yield: 85% (exact mass: 290.06). Residence time: 6 min; IR (KBr, ν_{max}, cm^{-1}): 3376 (N-H *str.*), 3084 (C–H *str.*), 1591 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.41-8.28 (m, 2H), 8.07 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.82 (d, *J* = 7.7 Hz, 1H), 7.68 (dd, *J* = 8.2, 2.3 Hz, 1H), 7.60 (s, 1H), 7.47 (t, *J* = 8.0 Hz, 1H), 7.31 (d, *J* = 8.2 Hz, 1H), 6.03 (s, 1H), 4.47 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm: 149.46 (s), 138.79 (s), 137.57 (s), 134.94 (s), 132.81 (s), 131.39 (s), 129.56 (s), 124.47 (d, *J* = 10.3 Hz), 123.30 (s), 122.82 (s), 122.63 (s), 120.66 (s), 50.38 (s).

5-((2-Anthracen-9-ylmethylene)hydrazinyl)methyl)-2-chloropyridine (5c): Dark yellow crystalline solid, yield: 88% (exact mass: 345.1). Residence time: 4 min; IR (KBr, ν_{max}, cm^{-1}): 3376 (N-H *str.*), 3080 (C–H *str.*), 1580 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.65 (s, 1H), 8.49 (d, *J* = 1.7 Hz, 1H), 8.37 (dd, *J* = 15.2, 11.3 Hz, 3H), 7.98 (dd, *J* = 5.5, 4.0 Hz, 2H), 7.77 (dd, *J* = 8.1, 2.2 Hz, 1H), 7.47 (d, *J* = 6.1 Hz, 4H),



Scheme-II

7.34 (d, *J* = 8.2 Hz, 1H), 6.06 (s, 1H), 4.58 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm: 150.68 (s), 149.58 (s), 139.06 (s), 137.22 (s), 133.36 (s), 131.45 (d, *J* = 13.9 Hz), 129.93 (s), 129.31 (d, *J* = 18.5 Hz), 128.95 (s), 128.30 (s), 127.94 (s), 127.57 (s), 127.53-127.17 (m), 126.84 (d, *J* = 7.2 Hz), 126.46-126.15 (m), 125.82 (d, *J* = 8.6 Hz), 125.61 (s), 125.40-124.78 (m), 124.34 (s), 123.61 (s), 50.65 (s).

2-((2-((6-Chloropyridin-3yl)methyl)hydrazinyl)-methyl)phenol (5d): White crystalline solid, yield: 90% (exact mass: 261.07). Residence time: 5 min; IR (KBr, ν_{max}, cm^{-1}): 3268 (N-H *str.*), 3089 (C–H *str.*), 1617 (C=N); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.81 (s, 1H), 8.30 (s, 1H), 7.69 (s, 1H), 7.61 (dd, *J* = 8.2, 2.5 Hz, 1H), 7.25 (d, *J* = 8.2 Hz, 1H), 7.19 (s, 1H), 7.15-7.09 (m, 1H), 6.99 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.84 (d, *J* = 8.2 Hz, 1H), 6.78 (td, *J* = 7.5, 1.1 Hz, 1H), 4.31 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm: 157.27 (s), 150.80 (s), 149.30 (s), 143.29 (s), 138.77 (s), 132.35 (s), 129.94 (s), 129.44 (s), 124.36 (s), 119.28 (s), 118.42 (s), 116.48 (s), 50.48 (s).

2-Bromo-6-((2-((6-chloropyridin-3yl)methyl)hydrazinyl)methyl)phenol (5e): Off-white crystalline solid, yield: 90% (exact mass: 338.98). Residence time: 5 min; IR (KBr, ν_{max}, cm^{-1}): 3186 (N-H *str.*), 3097 (C–H *str.*), 1616 (C=N); ^{1}H NMR (400 MHz, DMSO) δ ppm: 10.95 (s, 1H), 8.40 (s, 1H), 8.00 (s, 1H), 7.83 (d, *J* = 7.4 Hz, 2H), 7.50 (d, *J* = 8.2 Hz, 2H), 7.22 (d, *J* = 8.6 Hz, 1H), 6.76 (d, *J* = 8.6 Hz, 1H), 4.37 (s, 2H). ^{13}C NMR (126 MHz, DMSO) δ ppm: 154.97 (s), 149.54 (s), 148.97 (s), 139.53 (s), 135.91 (s), 133.78 (s), 130.81 (s), 129.39 (s), 124.05 (s), 122.50 (s), 118.00 (s), 110.24 (s), 48.34 (s).

Antimicrobial activity: All the synthesized compounds (**5a-e**) were evaluated for their *in vitro* antibacterial activity against *S. aureus* (MTCC 96), *S. pyogenes* (MTCC 442), *E. coli* (MTCC 443) and *P. aeruginosa* (MTCC 1688) strains as well as their *in vitro* antifungal activity against *C. albicans* (MTCC 227), *A. niger* (MTCC 282) and *A. clavatus* (MTCC 1323) strains using the micro broth dilution method [16]. The standard strains used for screening antibacterial and antifungal activities were procured from the Microbial Type Culture Collection (MTCC), Institute of Microbial Technology, Chandigarh, India. Mueller–Hinton broth was used as the nutrient medium to grow and dilute the drug suspension for the test bacteria. The minimum inhibitory concentration (MIC) was determined using the following formula:

$$\text{MIC } (\%) = \frac{A_c - A_t}{A_c} \times 100$$

where A_c is the average of six replicates of light absorption values of the negative controls; A_t is the average of six replicates of light absorption values of the tested compound. The MIC (μg/mL) values for the synthesized derivatives **5a-e** and standard antibiotics (gentamycin, ampicillin, chloramphenicol, ciprofloxacin, norfloxacin) as well as antifungal agents (nystatin and griseofulvin).

Antimalarial activity: All the synthesized chloropyridine derivatives (**5a-e**) were screened for their antimalarial activity against *P. falciparum* strain. The *in vitro* antimalarial assay was performed in 96-well microtiter plates according to the micro-assay protocol of Rieckmann *et al*. [17], with minor modifications. The *P. falciparum* cultures were maintained in RPMI-1640 medium supplemented with 25 mM HEPES, 0.23% sodium bicarbonate, 1% D-glucose and 10% heat-inactivated human serum. Quinine and chloroquine were used as positive controls. All experiments were performed in duplicate and the screening results were expressed as the concentration of drug (μg/mL) required to inhibit 50% of parasite growth (IC_{50}).

RESULTS AND DISCUSSION

The batch reaction requires a longer reaction time to achieve complete conversion to the desired product **3a**. Since the temperature is crucial for complete conversion; however, the presence of solvent at reflux temperature and the extended reaction time led to the formation of additional side products, resulting in a lower yield. However, flow chemistry outperforms batch processes in terms of safety, efficiency, scalability and reaction control. While it may not be ideal for many reactions, notably those involving solids or requiring flexible, small-scale manufacturing, it offers a potent option for continuous, high-throughput, controlled chemical synthesis. In the typical approach of switching from batch chemistry to flow processes, the initial trials commenced with small-scale batch experiments, closely monitored using HPLC. This not only offered insights into the reaction rate but also enabled to evaluate the uniformity of the reaction and monitor the conversion process.

A set of screening experiments was performed using Syrris coil equipment, where a 35% compound **1a** was used as one inlet stream and 80% aqueous solution of compound **2a** was used as the second inlet stream. The screening experiments quickly revealed that a residence time (RT) of only 8 min and a slightly higher mole ratio of compound **2a** were necessary to achieve near-complete conversion (Table-1). When the flow reactor temperature was varied, while maintaining a constant mole ratio and residence time, higher conversion of product **3a** was observed at the optimal high temperature of up to 90 ºC, with a 1:5 mole ratio of **1a** to **2a**. The reaction conditions were further optimized to evaluate the effects of temperature and residence time on the reaction conversion (Table-2, entries 1-6).

It was observed that at the optimum temperature of 90 ºC, the conversion of compound **3a** was high. Therefore, the reaction was further optimized by varying the residence time and the mole ratio of **2a**, while maintaining the constant optimum temperature of 90 ºC (Table-1, entries 1-3).

TABLE-2
OPTIMIZED CONDITIONS FOR COMPOUND **3a** USING A 16 mL PFA COIL WITH QUENCHING IN COLD WATER AT DIFFERENT TEMPERATURES*

Entry	RT (min)	Temp. (ºC)	Mole ratio (**1a**:**2a**)	Yield (%) (**3a**)
1	5	50	1:5	23.7
2	5	60	1:5	30.7
3	5	70	1:5	43.8
4	5	80	1:5	71.5
5	5	90	1:5	77.2
6	5	100	1:5	74.4

*Reaction monitoring samples analysis done by HPLC.

The outlet stream was quenched by immersing it directly in cold water and the initial toluene layer was discarded. The resultant product was collected by separating the aqueous layer, which was then adjustesd to pH 6 using 35% HCl. The aqueous layer was further extracted with fresh toluene. The combined toluene layers were evaporated to yield the final product, 2-chloro-5-(hydrazinylmethyl)pyridine (**3a**). The yield of compound **2a** was improved to 85%, with a purity of 99.32% as determined by HPLC.

The next step was to implement the synthesis of novel derivative **5a** in a continuous process. A stream of 50% solution of **3a** was mixed with aromatic substituted aldehyde **4a** and then pimped into the flow reactor, where the reaction occurred to afford the final desired product **5a**.

Antimicrobial activity: The results (Table-3) indicated that the synthesized chloropyridine derivatives (**5a-e**) exhibit variable inhibitory effects on the growth of bacterial and fungal strains. Compounds **5b**, **5c** and **5e** showed moderate antibacterial activity against *E. coli* strain compared to the positive control, chloramphenicol. Compound **5c** exhibited moderate antibacterial activity against *P. aeruginosa* strain compared to the standard chloramphenicol. Compound **5d** demonstrated antibacterial activity against *S. aureus* strain compared to the standards chloramphenicol and ciprofloxacin. Against *S. pyogenes*, compound **5b** showed inhibitory action similar to the standards chloramphenicol and ciprofloxacin.

The antifungal activity of the synthesized chloropyridine derivatives was also studied against three fungal strains, namely *C. albicans*, *A. niger* and *A. clavatus*. However, only compounds **5a** and **5d** exhibited significant antifungal activity showed excellent results against *C. albicans* strain; in comparison with the standard drug griseofulvin. Remaining chloropyridine derivatives (**5b**, **5c** and **5e**) exhibited moderate antifungal activities against these three strains.

Antimalarial activity: All the tested compounds exhibited moderate antimalarial activity, with their IC_{50} values ranging from 0.48-1.76 μg/mL. Among all the derivatives, compounds **5b** and **5c** displayed activity comparable to the standard drug quinine (Table-3).

Conclusion

In conclusion, the synthesis of new derivative of 2-chloro-5-(hydrazinyl methyl)pyridine with an aromatic aldehyde using flow chemistry has many benefits compared to batch method. The continuous flow system maintains a steady temperature,

TABLE-3
In vitro ANTIMICROBIAL AND ANTIMALARIAL ACTIVITIES OF SYNTHESIZED CHLOROPYRIDINE DERIVATIVES (**5a-e**)

Compounds	Antibacterial activity MIC (µg/mL) [S.D. = ±5]				Antifungal activity MIC (µg/mL) [S.D. = ±10]			Antimalarial activity IC_{50} in µg/mL [S.D. = ±0.005]
	E. coli	*P. aeruginosa*	*S. aureus*	*S. pyogenus*	*C. albicans*	*A. niger*	*A. clavatus*	*P. falciparum*
5a	125	250	100	125	250	500	1000	0.98
5b	62.5	100	125	62.5	500	>1000	>1000	0.73
5c	50	62.5	100	100	1000	500	1000	0.69
5d	100	100	62.5	125	250	1000	1000	0.96
5e	62.5	100	125	100	500	500	500	0.77
Gentamycin	0.05	1	0.25	0.5	–	–	–	–
Ampicillin	30	-	40	25	–	–	–	–
Chloramphenicol	50	50	50	50	–	–	–	–
Ciprofloxacin	25	25	50	50	–	–	–	–
Norfloxacin	10	10	10	10	–	–	–	–
Nystatin	–	–	–	–	100	100	100	–
Griseofulvin	–	–	–	–	500	100	100	–
Chloroquine	–	–	–	–	–	–	–	0.020
Quinine	–	–	–	–	–	–	–	0.268

Bold values indicate significant activities as compared to standards; S.D. = Standard Deviation
*All calculations are performed from GraphPad prism (http://www.graphpad.com/scientific-software/prism/)

enhances mixing and dissipates heat more effectively. This can result in quicker reactions and better results. The anitmicrobial activity of these new derivatives showed the excellent to moderate activity, moreover also have moderate activity against *P. falciparum* strain.

ACKNOWLEDGEMENTS

The authors are grateful to Smt. P.K. Kotecha Mahila Mahavidyalaya, Bhusawal and Bhusawal Arts, Science and P. O. Nahata Commerce College, Bhusawal, India for their support in this work. The authors would also like to express their sincere gratitude to Mr. Dinesh Purohit, Head of Syrris Scientific Equipment Pvt. Ltd., India, for providing the instruments necessary to carry out the experiments.

CONFLICT OF INTEREST

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

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