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Der Pharma Chemica, 2012, 4(6):2259-2264
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

Synthesis and biological studies of novel chlorophenyl-(pyridinyl)-methylamine hydrochloride derivatives

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ABSTRACT

*A series of novel chlorophenyl-(pyridinyl)-methylamine hydrochloride salts **[1a-1c, 2a-2c, 3a-3c]** are synthesized by the reduction of chlorophenyl-(pyridinyl)-methanone oxime derivatives **[8a-8c]** using zinc in acetic acid. Nucleophilic addition of chlorophenyl magnesium bromide **[5a-5c]** to pyridine carboxaldehyde **[4a-4c]** in dry THF using Grignard's protocol provided corresponding chlorophenyl-(pyridinyl)-methanol derivatives **[6a-6c]** and former chlorophenyl-(pyridinyl)-methanone derivatives **[7a-7c]** are obtained by the oxidation using with chromium trioxide in acetic acid followed reaction with hydroxylamine hydrochloride to afford the chlorophenyl-(pyridinyl)methanoneoxime derivatives **[8a-8c]**. The structures of these newly synthesized **[1a-1c, 2a-2c, 3a-3c]** compounds were characterized by spectral data. The prepared compounds have been screened in vitro for their antibacterial activity using agar diffusion method.*

Key Words: Pyridine derivatives, **p**yridinyl methylamine, chlorophenyls, chlorophenyl-(pyridinyl) methanone oxime, antibacterial activity,

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INTRODUCTION

The first pyridine was obtained from the isolation of bone oil and from coal tar in 1846 by Anderson Korner and Dewar, in 1869. Pyridine, played a pivotal role in the development of different medical agents and has an interesting application to the field of medicine. Activity of pyridine derivatives recently stimulated extensive interest in the synthesis and chemistry of these compounds. During the last two decades, a large number of substituted pyridines have been claimed to have several biological activities[1-11] such as antimicrobial, anticancer, antitubercular activity. It is always been challenging for treating infections due to microorganisms and the bacteria and other microorganisms have developed resistance to the existing line of drugs. This gives us a challenge and ample scope for further investigating new molecules as anti-infective. Further literature study reveals that substituted pyridine analogues were synthesized by various synthetic methodologies.[12-15]

Hence it was thought worthwhile to synthesize some substituted chlorophenyl pyridinyl methylamine moieties in a single molecular frame work. Moreover, customized libraries of primary amines could be used as inputs for the preparation of further libraries. The present work deals with the efficient synthesis of the title compounds in excellent yields followed by their antimicrobial screening.

MATERIALS AND METHODS

Solvents were purified by standard procedures before use. Column chromatography was conducted by using silica gel with different solvent systems as elutes. T.L.C analyses were performed on precoated silicagel (E-Merck Kieselgel 60F254) plates and visualization was done by exposing to iodine vapor. IR Spectra were recorded in KBr

on Perkin-Elmer Spectrum BX series FT-IR spectrometer. ^{1}H-NMR spectrum were recorded on Bruker spectrophotometer 400MHz spectrometers using TMS as internal standard (chemical shifts in δ ppm). ^{13}C-NMR Spectra were recorded on a Brucker 100MHz spectrometer. Mass spectra were scanned on a varian MATCH-7 and Jeol JMSD-300 mass spectrometer. All the chemicals used in the present investigation were purchased from Aldrich chemicals.

Experimental

Stage-1: General method of synthesis of chlorophenyl-(pyridinyl)-methanol derivatives [6a-6c]

A flame dried round bottom flask flushed with nitrogen was charged with magnesium turnings (2.2 mol), one iodine crystal and anhydrous THF (200 ml). The above mixture was heated to 40^{o}C. Added a solution of bromo substituted chlorobenzene **[5a-5c]** (50 ml) drop-wise, which was drawn from the solution of bromo substituted chlorobenzene (1.86 mol) was dissolved in dry THF (650 ml). Once the initiation was observed for Grignard reaction heating bath was removed and remaining portion of the solution of bromo substituted chlorobenzene was added slowly, vigorous exothermicity was observed. When the initial exothermicity ceased the reaction mass was refluxed for 1 hr and then allowed to cool to ambient temperature followed by cooled to 0^{o}C. To this added a solution of pyridinecarboxaldehyde **[4a-4c]** (0.47 mol) dissolved in dry THF (250 ml). The reaction mass was allowed to warm to ambient temperature and stirred for 2hr. After completion of the reaction it was cooled, diluted with water (250 ml) and extracted with ethyl acetate (4x1000 ml). Combined organic layer was washed with saturated brine solution, dried over sodium sulphate and filtered. The solvent is removed under reduced pressure to give crude product as a brown viscous mass. Crude compound was purified by silica gel (100-200 mesh) column chromatography using the solvent mixtures ethyl acetate and n-hexane to afford the pure compound **[6a-6c].**

Stage-2: General method of synthesis of chlorophenyl-(pyridinyl)-methanone derivatives [7a-7c]

To a round bottom flask was charged with compound **[6a-6c]** (0.237 mol), water (364 ml), glacial acetic acid (364 ml) and cooled in an ice bath. Added chromium trioxide (0.356 mol) in portion-wise followed by the reaction mass was allowed to warm to ambient temperature and stirred for overnight. After completion, acetic acid was removed from the reaction mixture under reduced pressure. The residual mass was cooled and slowly quenched with saturated sodium bicarbonate solution, extracted with ethyl acetate (5x500 mL). Combined organic layer was washed with water (2x300 mL), dried over sodium sulphate and filtered. Solvent was removed under reduced pressure to afford the pure compound **[7a-7c]** as viscous liquid which was enough pure to use for the next step without further purification.

Stage-3: General method of synthesis of chlorophenyl-(pyridinyl)-methanoneoxime derivatives [8a-8c]

To a solution of compound **[7a-7c]** (0.18 mol), dissolved in solvent mixture pyridine:ethanol (1:3) was added hydroxylamine hydrochloride (0.64 mol) in small portions. Reaction mixture was heated to reflux for 6 hr and the solvent was removed under reduced pressure, water (200 ml) was added to the residue, separated solid was filtered and dried at 60^{o}C in a vacuum oven to afford the pure compound **[8a-8c]** which was enough pure to use for the next step without further purification.

Stage-4: General method of synthesis of chlorophenyl-(pyridinyl)-methylamine hydrochloride derivatives [1a-1c, 2a-2c, 3a-3c]

To an ice cold solution of compound **[8a-8c]** in ethanol (165 ml) was added acetic acid (264 ml) and zinc (0.49 mol) in portion-wise over a period of 30 min. Reaction mixture was stirred for 16 hr at ambient temperature and cooled to room temperature. It was filtered and the residue was washed with ethanol and the filtrate was evaporated under reduced pressure. Crude mass was diluted with water (500 ml), basified with saturated sodium bicarbonate solution and extracted with ethyl acetate (5x500 ml). Combined organic layer was dried over sodium sulphate, filtered and evaporated the solvent to afford the pure free base as a light brown colored liquid. This was dissolved in methanol (150 ml), cooled in an ice bath and acidified to p^{H} 1-2 with saturated methanolic HCl solution. Methanol was removed completely under reduced pressure and the residue was triturated with n-hexane, filtered the solid and dried under nitrogen atmosphere to afford the hydrochloride salt form of chlorophenyl-(pyridinyl)-methylamines **[1a-1c, 2a-2c, 3a-3c]** as off-white solid to white color solids.

ANTIBACTERIAL ACTIVITY:

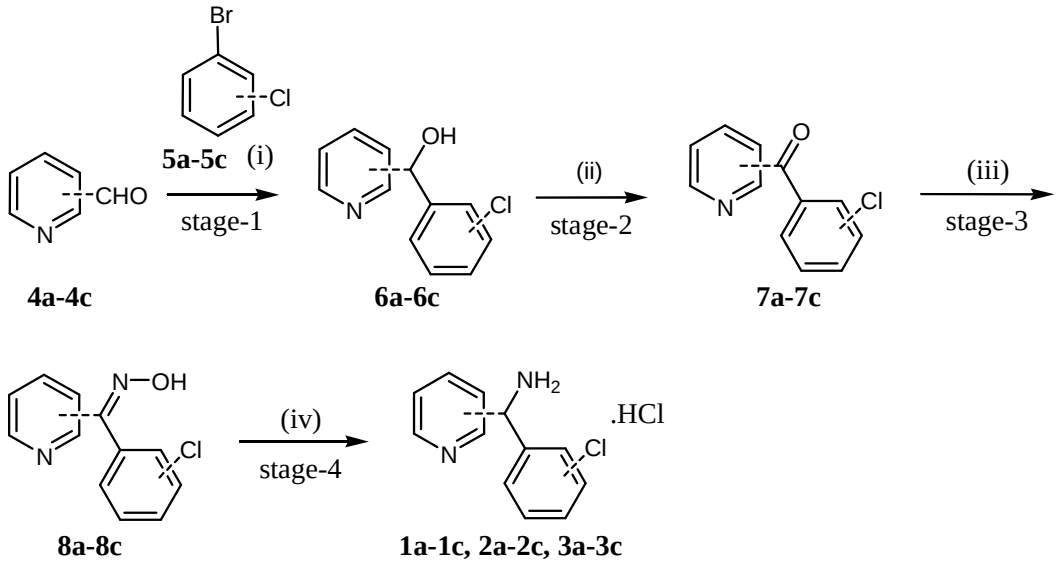
Study of antibacterial activity by agar diffusion method:

The chlorophenyl-(pyridinyl)methylamine hydrochloride derivatives **[1a-1c, 2a-2c, 3a-3c]** were screened in vitro for their antibacterial activity against Gram-negative organisms (*Escherichia coli, Pseudomonas aeruginosa)* and Gram-positive organisms (*Bacillus subtilis, Staphylococcus aureus)* by the cylinder-plate (agar-cup plate) method[16] and the results are discussed below **(Table-II)**.

RESULTS AND DISCUSSION

The reaction sequence employed for the synthesis of title compounds are depicted in **Scheme-I**. Nucleophilic addition of chlorophenyl magnesium bromide **[5a-5c]** to pyridine carboxaldehyde **[4a-4c]** in dry THF using the Grignard's protocol[17-20] to afford the corresponding chlorophenyl-(pyridinyl)methanol[21] derivatives **[6a-6c]** in 80-90% yield. Compound **6a-6c** were oxidized with chromium trioxide in acetic acid[22-23] at room temperature to give corresponding chlorophenyl-(pyridinyl)methanones[17] **[7a-7c]** in quantitative yield. Compound **[7a-7c]** were further treated with hydroxylamine hydrochloride[24-25] in the mixture of pyridine and ethanol under reflux condition to obtain the chlorophenyl-(pyridinyl)methanoneoxime derivatives **[8a-8c]** in quantitative yield. Finally, target compounds were afforded by the reduction of oxime derivatives **[8a-8c]** using with zinc in acetic acid[26-27] in ice cooling to afford the chlorophenyl-(pyridinyl)methanamine[28] hydrochloride derivatives **[1a-1c, 2a-2c, 3a-3c]** in 60-70% yield (**Table-I**). The structures of all the compounds were characterized by ^{1}H-NMR, ^{13}C-NMR, Mass and IR data. All the synthesized compounds exhibited satisfactory spectral data consistent with their structures.

Scheme-I



*Reagents & conditions: (i) Br-PhCl **5a-5c**, Mg, THF, rt, 2 h, 80-90%; (ii) Cr_2O_3, AcOH, rt, over night, 99%; (iii) $NH_2OH.HCl$, pyridine, EtOH, reflux, 6 h, 99%; (iv) Zn, AcOH, EtOH, rt, 16 h, 60-70%.*

Spectral data:

The compounds **[1a-1c, 2a-2c, 3a-3c]** were well characterized by their spectral data such as ^{1}H-NMR, ^{13}C-NMR, LCMS & IR spectrophotometer.

(2-Chlorophenyl)(pyridin-2-yl)methanamine hydrochloride (1a)

Yield 62%; IR (KBr, ν_{max} in cm^{-1}): 3449 (N-H *str*), 3056 (Ar-H *str*), 1601 (C=N *str*), 827 (C-Cl *str*); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 5.93-5.94 (d, 1H, CH of benzylic), 7.37-7.41 (m, 1H, Ar-H), 7.44-7.47 (m, 1H, Ar-H), 7.62-7.64 (d, 2H, Ar-H), 7.89-7.92 (m, 1H, py-H), 8.48-8.50(d, 1H, py-H),8.81-8.82 (d, 1H,py-H), 9.05 (s, 1H,py-H),9.59(bs, 3H, $NH_3^+Cl^-$, D_2O *exch.*); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 53.9, 127.1, 127.7, 128.9, 129.0, 136.3, 137.8, 141.3, 142.1, 144.5; LCMS: m/z 219.2 $(M+1)^+$.

(3-Chlorophenyl)(pyridin-2-yl)methanamine hydrochloride (1b)

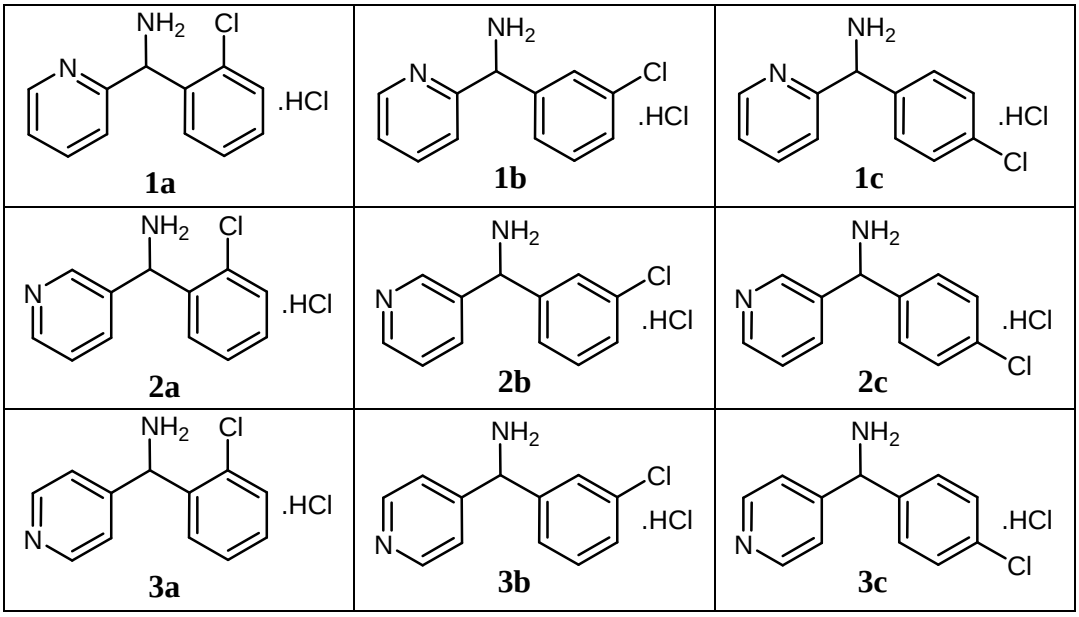
Yield 66%; IR (KBr, ν_{max} in cm^{-1}): 3436 (N-H *str*), 3044 (Ar-H *str*), 1586 (C=N *str*), 829 (C-Cl *str*); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 5.79-5.80 (d, 1H, CH of benzylic), 7.42-7.50 (m, 5H, Ar-H, py-H), 7.67 (s, 1H, py-H), 7.85-7.89 (m, 1H, py-H), 8.67-8.68 (d, 1H, py-H), 9.06 (bs, 3H, $NH_3^+Cl^-$, D_2O *exch.*); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 56.3, 122.7, 123.7, 126.6, 127.7, 128.7, 130.6, 133.1, 137.9, 139.5, 148.7, 155.7; LCMS: m/z 219.0 $(M+1)^+$.

(4-Chlorophenyl)(pyridin-2-yl)methanamine hydrochloride (1c)

Yield 70%; IR (KBr, ν_{max} in cm^{-1}): 3449 (N-H *str*), 3050 (Ar-H *str*), 1597 (C=N *str*), 851 (C-Cl *str*); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 5.78-5.79 (d, 1H, CH of benzylic), 7.41-7.46 (m, 2H, Ar-H), 7.49-7.56 (m, 4H, Ar-H, py-

H), 7.84-7.88 (m, 1H, py-H), 8.65-8.67 (d, 1H, py-H), 9.02 (bs, 3H, $NH_3^+Cl^-$, D_2O *exch.*); ^{13}C NMR (DMSO-d_6, 100 MHz): d 56.3, 122.8, 123.8, 128.6, 129.9, 133.3, 136.1, 138.4, 148.3, 155.7; LCMS: m/z 219.3 $(M+1)^+$.

Table-I



(2-Chlorophenyl)(pyridin-3-yl)methanamine hydrochloride (2a)
Yield 61%; IR (KBr, ν_{max} in cm^{-1}): 3436 (N-H *str*), 3044 (Ar-H *str*), 1586 (C=N *str*), 829 (C-Cl *str*); ^1H NMR (DMSO-d_6, 400 MHz): δ 5.79-5.80 (d, 1H, CH of benzylic), 7.42-7.50 (m, 5H, Ar-H, py-H), 7.67 (s, 1H, py-H), 7.85-7.89 (m, 1H, py-H), 8.67-8.68 (d, 1H, py-H), 9.06 (bs, 3H, $NH_3^+Cl^-$, D_2O *exch.*); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 56.3, 122.7, 123.7, 126.6, 127.7, 128.7, 130.6, 133.1, 137.9, 139.5, 148.7, 155.7; LCMS: m/z 219.0 $(M+1)^+$.

(3-Chlorophenyl)(pyridin-3-yl)methanamine hydrochloride (2b)
Yield 67%; IR (KBr, ν_{max} in cm^{-1}): 3436 (N-H *str*), 3044 (Ar-H *str*), 1586 (C=N *str*), 830 (C-Cl *str*); ^1H NMR (DMSO-d_6, 400 MHz): δ 6.00 (bs, 1H, CH of Benzylic), 7.46-7.51 (m, 2H, Ar-H), 7.62-7.66 (m, 1H, Ar-H), 7.82 (s, 1H, Ar-H), 7.94-7.97 (m, 1H, py-H), 8.57-8.59 (d, 1H, py-H), 8.84-8.86 (m, 1H, py-H), 9.10 (s, 1H, py-H), 9.75 (bs, 3H, $NH_3^+Cl^-$, D_2O *exch.*); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 53.4, 126.4, 126.9, 127.6, 128.8, 130.9, 133.5, 136.9, 138.6, 141.9, 142.7, 143.8; LCMS: m/z 219.1 $(M+1)^+$.

(4-Chlorophenyl)(pyridin-3-yl)methanamine hydrochloride (2c)
Yield 69%; IR (KBr, ν_{max} in cm^{-1}): 3450 (N-H *str*), 3045 (Ar-H *str*), 1593 (C=N *str*), 846 (C-Cl *str*); ^1H NMR (DMSO-d_6, 400 MHz): δ 6.02 (bs, 1H, CH of benzylic), 7.52-7.54 (d, 2H, Ar-H), 7.68-7.70 (d, 2H, Ar-H), 7.96-8.00 (m, 1H, py-H), 8.59-8.61 (d, 1H, py-H), 8.86-8.87 (d, 1H, py-H), 9.11 (s, 1H, py-H), 9.76 (bs, 3H, $NH_3^+Cl^-$, D_2O *exch.*); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 53.4, 126.6, 129.0, 129.7, 133.6, 135.4, 136.8, 142.6, 143.1, 143.3; LCMS: m/z 219.1 $(M+1)^+$.

(2-Chlorophenyl)(pyridin-4-yl)methanamine hydrochloride (3a)
Yield 64%; IR (KBr, ν_{max} in cm^{-1}): 3059 (Ar-H *str*), 1587 (C=N *str*), 838 (C-Cl *str*); ^1H NMR (DMSO-d_6, 400 MHz): δ 4.42 (bs, 1H, CH of Benzylic), 7.46-7.54 (m, 2H, Ar-H), 7.57-7.59 (m, 1H, Ar-H), 8.06-8.10 (m, 3H, Ar-H, py-H), 8.94-8.95 (d, 2H, py-H), 10.02 (bs, 3H, $NH_3^+Cl^-$, D_2O *exch.*); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 53.2, 126.0, 128.1, 129.4, 130.1, 131.1, 132.2, 133.0, 142.8, 153.9; LCMS: m/z 219.0 $(M+1)^+$.

(3-Chlorophenyl)(pyridin-4-yl)methanamine hydrochloride (3b)
Yield 66%; IR (KBr, ν_{max} in cm^{-1}): 3436 (N-H *str*), 3044 (Ar-H *str*), 1586 (C=N *str*), 829 (C-Cl *str*); ^1H NMR (DMSO-d_6, 400 MHz): δ 5.99 (bs, 1H, CH of Benzylic), 7.47-7.49 (m, 2H, Ar-H), 7.62 (m, 1H, Ar-H), 7.81 (m, 1H, Ar-H), 8.08-8.09 (d, 2H, py-H), 8.85-8.90 (d, 2H, py-H), 9.79 (bs, 3H, $NH_3^+Cl^-$, D_2O *exch.*); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 55.3, 124.4, 126.7, 127.9, 129.0, 130.9, 133.5, 138.4, 144.6, 153.1; LCMS: m/z 218.9 $(M+1)^+$.

(4-Chlorophenyl)(pyridin-4-yl)methanamine hydrochloride (3c)
Yield 70%; IR (KBr, ν_{max} in cm^{-1}): 3436 (N-H *str*), 3044 (Ar-H *str*), 1586 (C=N *str*), 839 (C-Cl *str*); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 5.99 (bs, 1H, CH of Benzylic), 7.47-7.49 (m, 2H, Ar-H), 7.62 (m, 1H, Ar-H), 7.81 (m, 1H, Ar-H), 8.08-8.09 (d, 2H, py-H), 8.85-8.90 (d, 2H, py-H), 9.79 (bs, 3H, $NH_3^+Cl^-$, D_2O *exch.*); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 55.3, 124.4, 126.7, 127.9, 129.0, 130.9, 133.5, 138.4, 144.6, 153.1; LCMS: m/z 218.9 $(M+1)^+$.

ANTIBACTERIAL ACTIVITY of [1a-1c, 2a-2c, 3a-3c]
The cylinder-plate method depends upon diffusion of the test compound from a vertical cylinder through a solidified agar layer in a petri plate to such an extent that the growth of the added microorganism is prevented entirely in a zone around the cylinder containing a solution of the test sample of desired concentration. The zone of inhibition (in mm) is a measure of antibacterial activity[28-33] of chlorophenyl-(pyridinyl)-methylamine hydrochlorides at different concentrations (500, 200 and 50 µg/0.05 mL) and the results are presented in the following **Table-II**.

Table-II

Compd.	Conc. µg/ 0.05 ml	*E. coli*	*P. aeruginosa*	*B. subitlis*	*S. aureus*
1a	500	—	12.0	10.0	—
	200	—	12.0	9.0	—
	50	—	11.5	—	—
1b	500	9.0	8.5	9.0	8.5
	200	9.0	8.5	9.0	8.5
	50	8.5	8.0	9.0	8.0
1c	500	8.5	—	8.5	—
	200	8.5	—	8.5	—
	50	—	—	—	—
2a	500	—	10.0	10.0	9.5
	200	—	10.0	9.5	9.5
	50	—	10.0	9.0	9.0
2b	500	12.0	15.0	11.5	9.0
	200	10.0	11.0	9.5	9.0
	50	—	—	—	—
2c	500	11.0	12.0	10.0	10.0
	200	11.0	11.0	10.0	10.0
	50	10.0	11.0	9.0	9.0
3a	500	11.0	11.0	11.0	9.5
	200	10.0	11.0	11.0	9.5
	50	10.0	10.0	10.0	9.5
3b	500	14.0	15.0	13.0	8.0
	200	13.0	12.0	12.0	8.0
	50	11.0	11.0	11.0	—
3c	500	11.0	10.0	10.0	9.5
	200	11.0	10.0	9.5	9.5
	50	10.0	10.0	9.0	9.0

— *No significant antibacterial activity*

The study revealed that the antibacterial activity of chlorophenyl-(pyridinyl)-methylamine hydrochlorides **[1a-1c, 2a-2c, 3a-3c]** is significant with **2b** and **3b** exhibited strongest antibacterial activity (15.0 mm) against the gram-negative organism *P. aeruginosa* at 500 µg/0.05 mL of concentration.

CONCLUSION

It may be concluded that this study describes the general method for the synthesis of new chlorophenyl-(pyridinyl)-methylamine hydrochloride salts. It is noteworthy that the reactions could be easily scaled up to produce good yields. Experimental protocols are easily accessible on multi-gram scale with cheap and readily available staring compounds. The significant antibacterial activities were provided by the chlorophenyl-(pyridinyl)-methylamine hydrochloride salts.

Acknowledgments
We are thankful to Prof. Ch. Appa Rao, department of biochemistry, SV University, Tirupati for carrying out the microbial studies.

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