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Synthesis of Highly Substituted Functionalized Piperidine Derivatives via Oximation Reaction and its Anti-Microbial Activity

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ABSTRACT

The synthesis of Nitrogen base heterocycles particularly highly substituted piperidine are very important structural motif which is present in numerous natural alkaloids including piperine, nicotine, coniine etc and non-natural substances too. The piperidine is extracted from black pepper[1,2], *Psilocaulon absimile* (Aizoaceae)[3] and *Petrosimonia monandra*[4]. The functionalized piperidine derivatives are ubiquitous building block in synthesis of pharmaceuticals and fine chemicals, consequently it attract interest, both for their synthetic challenges,[5] and also their value in synthetic chemistry[6] and diverse biological activity.[7] The present work includes the synthesis of highly functionalized piperidine derivatives using the Oximation of Michael adducts (scheme 3). The target product was oxime for further reaction but instead of the required oxime as product the side product with six member heterocylic product was formed as major product. The yield of side product was depends on time and thermodynamic conditions. Owing to the new results which were confirmed by singe crystal X-rays and NMR data, we have developed this methodology which gives easy access to the synthesis of highly substituted piperidine (Scheme 3). This strategy is very simple and efficient to have 2,3,4,6 substituted nitrogen containing heterocycle as Piperidine.

Keywords: Piperidine, Heterocyclic compound, Oximation, Michel adduct.

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INTRODUCTION

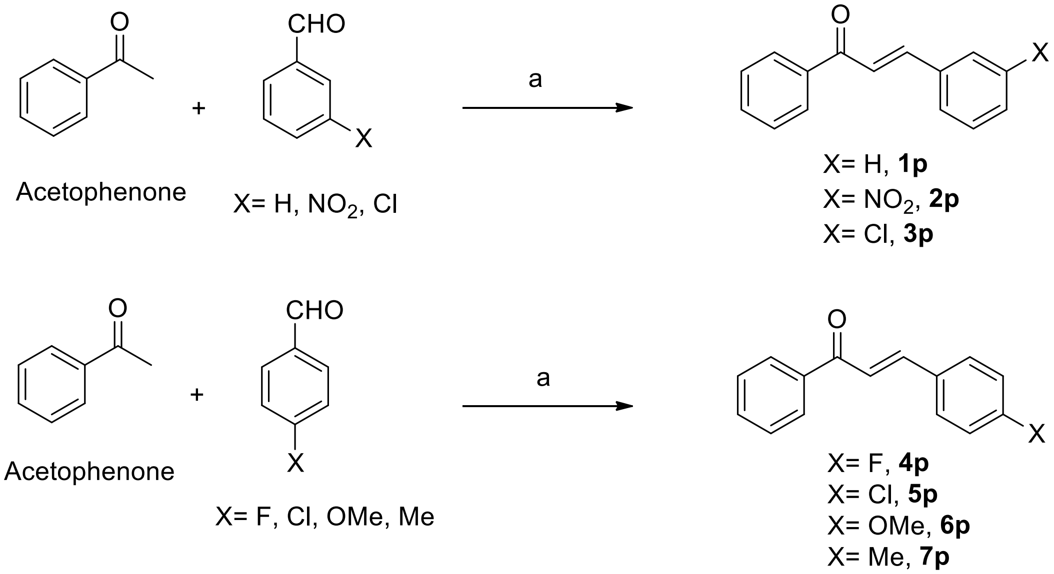
Nucleophilic substitutions, reductive amination, reaction of amines with alkenes and alkynes, ring closing metathesis, radical cyclisation, cycloaddion and Dieckman cyclisation strategies have been broadly used to have synthesis of substituted piperidines[8], activated metal-mediated[9] and organocatalytic[10] ring closing strategies have been reported in the recent years. There are many examples of pre-existing nitrogen heterocycles as pyridine has been successful hydrogenated to piperidines[8].

In our approach the synthesis of substituted Piperidines has been achieved from the cascade reaction as condensation insitu followed by cyclisation of substituted chalcone Michael adducts with ethyl cyanoacetate and $NH_2OH.HCl$ in ethanol as solvent under reflux condition[10]. This methodology gives varies of substitution pattern on 2,3,4,6 positions of the piperidines by using required chalcone adduct (Scheme 3). This strategy have greener synthetic outcome and worked out as a simple and easy one-pot approach for the synthesis nitrogen containing heterocycle as substituted piperidines.

MATERIALS AND METHOD

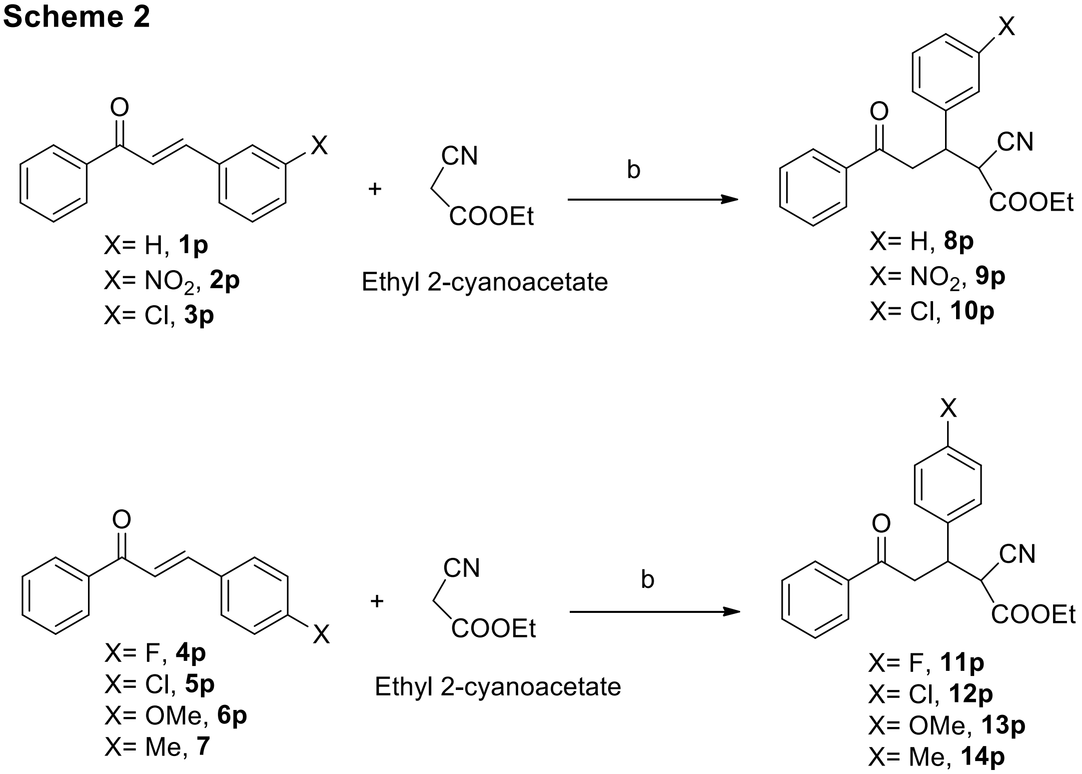
All the Chemicals used in the synthesis of the compounds were obtained from Merck, Sigma-Aldrich and were of analytical grade. Purity of the compounds was checked by Thin Layer Chromatography using silica gel as stationary phase and combination of Ethyl acetate: Petrol as mobile phase. The IR, NMR spectra of the synthesized compounds were recorded for the characterization from the University of Mumbai, Indian Institute of Technology (IIT) Mumbai, TIFR Mumbai and NCL pune. All the synthesized compounds were screened for their antimicrobial activities by drug diffusion method by preparing the discs of the drug.

Scheme 1



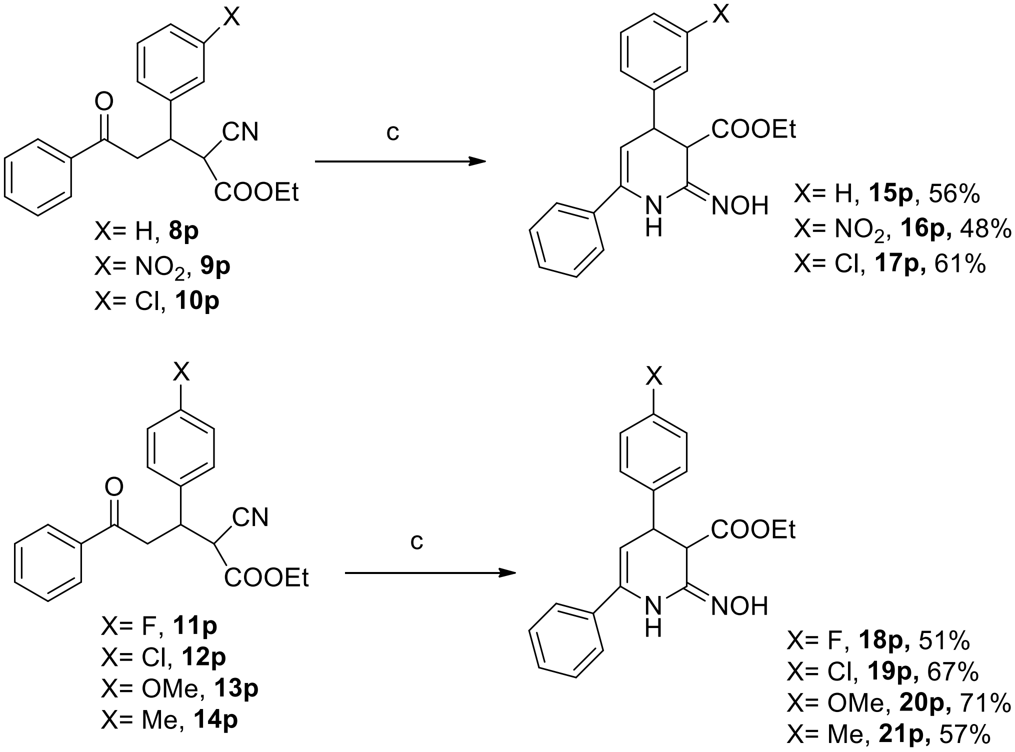
Reagents and Conditions : a) aq KOH in Ethanol stirred at rt for 5-12hrs.

Scheme 2



Reagents and Conditions : b) K_2CO_3 in DCM reflux for 10-15hrs.

Scheme 3



Reagents and Conditions : c) 2 eq. $NH_2OH.HCl$, 3 eq. Et_3N in ethanol reflux for 10hrs.

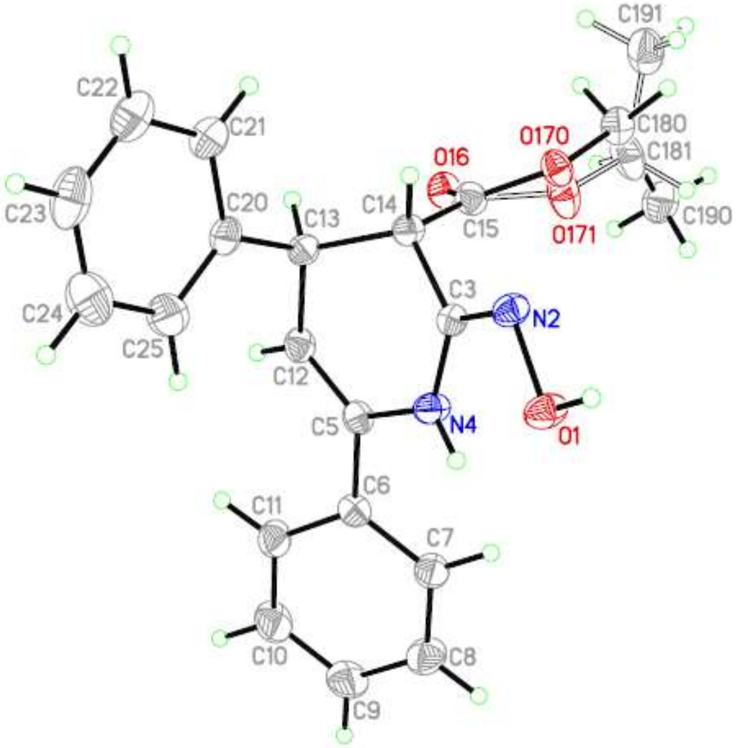


Figure 1: Single crystal X-ray structure of 15P

RESULTS AND DISCUSSION

General Procedure:

In a stirring solution of Michael adduct of substituted chalcone and ethyl cyanoacetate in ethanol as solvent was treated with hydroxylamine hydrochloride ($NH_2OH.HCl$) and triethylamine was added slowly to the reaction mixture which was then stirred under reflux condition overnight. The reaction progress was monitored by TLC and the reaction mixture was pour in to water and product was extracted by ethyl acetate and dried over brine and anhydrous Na_2SO_4, concentration of the organic layer gave the crude product, which was purified by Column chromatography (eluting with ethyl acetate: petrol) to afford the product.

Synthesis of ethyl 2-(hydroxyimino)-4,6-diphenyl-1,2,3,4 tetrahydro-pyridine-3-carboxylate. (15p, Scheme 3)

When **8p** (200mg, 0.62 mmol) was treated with $NH_2OH.HCl$ (64mg, 0.93 mmol), TEA (125mg, 1.24 mmol) in EtOH (5mL) heated to reflux for 10hrs and the reaction progress was monitored by TLC. After completion of reaction the product **15p** was obtained by chromatography purification. **15p** (117mg, 56%) as a pale yellow crystals; m.p. = 92-94 °C; R_f = 0.30 (EtOAc: petrol, 4:6); υ_{max}(film)/cm^{-1} 3423, 3074, 2985, 1735, 1607, 1476, 1248, 1026, 910, 762, 698; δ_H(400 MHz; $CDCl_3$; Me_4Si) 1.16 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 2.06 (1H, bs, O*H*), 3.57 (1H, d, *J* 7.1 Hz, (C3)*H*), 4.14 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 4.22 (1H, dd, *J* 7.1, 4.6 Hz, (C4)*H*), 5.29 (1H, d, *J* 4.6 Hz, (C5)*H*), 7.22-7.54 (10H, m, 2 x Ar*H*), 8.06 (1H, bs, N*H*); δ_C(100 MHz; $CDCl_3$; Me_4Si) 14.1 (OCH_2CH_3), 41.8 (*C*4), 49.7 (*C*3), 61.5 (OCH_2CH_3), 102 (*C*5), 125.4-128.9 (Ar*C*), 135.6, 136.5 (quaternary Ar*C*), 141.5 (*C*5), 145.9 (*C*2), 169.7 (*C*OO).

Synthesis of ethyl 2-(hydroxyimino)-4-(3-nitrophenyl)-6-phenyl-1, 2,3,4-tetrahydro- pyridine-3-carboxylate (16p, Scheme 3)

When **9p** (153mg, 0.42 mmol) was treated with $NH_2OH.HCl$ (43mg, 0.63 mmol), TEA (85mg, 0.84 mmol) in EtOH (5mL) heated to reflux overnight and the reaction progress was monitored by TLC. After completion of reaction the product **16p** was obtained by chromatography purification. **16p** (76mg, 48%) as a pale yellow solid; m.p. = 96-99 °C; R_f = 0.2 (EtOAc: petrol, 4:6); υ_{max}(film)/cm^{-1} 3425, 3076, 2988, 1740, 1600, 1576, 1456, 1240, 1026, 910, 769, 740; δ_H(400 MHz; $CDCl_3$; Me_4Si) 1.1 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 2.1 (1H, bs, O*H*), 3.6 (1H, d, *J* 7.1 Hz, (C3)*H*), 4.2 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 4.23 (1H, dd, *J* 7.0, 4.7 Hz, (C4)*H*), 5.3 (1H, d, *J* 4.6 Hz, (C5)*H*), 7.2-8.1 (9H, m, 2 x Ar*H*), 8.48 (1H, bs, N*H*); δ_C (100 MHz; $CDCl_3$; Me_4Si) 14.1

(OCH$_2$*C*H$_3$), 41.8 (*C*4), 49.7 (*C*3), 61.5 (O*C*H$_2$CH$_3$), 102 (*C*5), 125.4-128.9 (Ar*C*), 135.6, 136.5 (quaternary Ar*C*), 141.5 (*C*5), 145.9 (*C*2), 148.3 (Ar*C*-NO$_2$), 170 (*C*OO).

Synthesis of ethyl 4-(3-chlorophenyl)-2-(hydroxyimino)-6-phenyl-1,2,3,4-tetrahydro-pyridine-3-carboxylate (17p, Scheme 3).

When **10p** (120mg, 0.33 mmol) was treated with NH$_2$OH.HCl (35mg, 0.50 mmol), TEA (67mg, 0.66 mmol) in EtOH (3mL) heated to reflux overnight and the reaction progress was monitored by TLC. After completion of reaction the product **17p** was obtained by chromatography purification. **17p** (76mg, 61%) as a pale yellow solid; m.p. = 103-107°C; R_f = 0.2.5 (EtOAc:petrol, 6:4); υ_{max}(film)/cm^{-1} 3426, 3070, 2950, 1742, 1600, 1242, 1023, 910, 769, 740; δ_H(400 MHz; CDCl$_3$; Me$_4$Si) 1.2 (3H, t, *J* 7.1 Hz, OCH$_2$C*H*$_3$), 2.1 (1H, bs, O*H*), 3.6 (1H, d, *J* 7.1 Hz, (C3)*H*), 4.1 (2H, q, *J* 7.1 Hz, OC*H*$_2$CH$_3$), 4.3 (1H, dd, *J* 7.1, 4.6 Hz, (C4)*H*), 5.4 (1H, d, *J* 4.6 Hz, (C5)*H*), 7.2-8.3 (9H, m, 2 x Ar*H*), 8.48 (1H, bs, N*H*); δ_C(100 MHz; CDCl$_3$; Me$_4$Si) 14 (OCH$_2$*C*H$_3$), 42 (*C*4), 49.8 (*C*3), 61.5 (O*C*H$_2$CH$_3$), 102 (*C*5), 125.4-128.9 (Ar*C*), 135.6, 136.5 (quaternary Ar*C*), 141.5 (*C*5), 145.9 (*C*2), 147 (Ar*C*-Cl), 172 (*C*OO).

Synthesis of ethyl 4-(4-fluorophenyl)-2-(hydroxyimino)-6-phenyl-1,2,3,4-tetrahydro-pyridine-3-carboxylate (18p, Scheme 3).

When **11p** (200mg, 0.59 mmol) was treated with NH$_2$OH.HCl (61mg, 0.88 mmol), TEA (119mg, 1.18 mmol) in EtOH (5mL) heated to reflux overnight and the reaction progress was monitored by TLC. After completion of reaction the product **18p** was obtained by chromatography purification. **18p** (106mg, 51%) as a pale yellow solid; m.p. = 93-96°C; R_f = 0.32 (EtOAc:petrol, 1:1); υ_{max}(film)/cm^{-1} 3427, 3072, 2951 1740, 1600, 1400, 1242, 1020, 910, 769, 745; δ_H(400 MHz; CDCl$_3$; Me$_4$Si) 1.2 (3H, t, *J* 7.1 Hz, OCH$_2$C*H*$_3$), 2.1 (1H, bs, O*H*), 3.6 (1H, d, *J* 7.1 Hz, (C3)*H*), 4.1 (2H, q, *J* 7.1 Hz, OC*H*$_2$CH$_3$), 4.3 (1H, dd, *J* 7.1, 4.6 Hz, (C4)*H*), 5.4 (1H, d, *J* 4.6 Hz, (C5)*H*), 7.2-8.3 (9H, m, 2 x Ar*H*), 8.48 (1H, bs, N*H*); δ_C(100 MHz; CDCl$_3$; Me$_4$Si) 14 (OCH$_2$*C*H$_3$), 42 (*C*4), 49.8 (*C*3), 61.5 (O*C*H$_2$CH$_3$), 102 (*C*5), 125.4-128.9 (Ar*C*), 135.6, 136.5 (quaternary Ar*C*), 141.5 (*C*5), 145.9 (*C*2), 158 (Ar*C*-F), 172 (*C*OO).

Synthesis of ethyl 4-(4-chlorophenyl)-2-(hydroxyimino)-6-phenyl-1,2,3,4-tetrahydro-pyridine-3-carboxylate (19p, Scheme 3).

When **12p** (97mg, 0.27 mmol) was treated with NH$_2$OH.HCl (28mg, 0.41 mmol), TEA (54mg, 0.54 mmol) in EtOH (2mL) heated to reflux overnight and the reaction progress was monitored by TLC. After completion of reaction the product **19p** was obtained by chromatography purification. **19p** (68mg, 76%) as a pale yellow solid; m.p. = 107-110°C; R_f = 0.3 (EtOAc:petrol, 1:1); υ_{max}(film)/cm^{-1} 3426, 3002, 2931 1745, 1600, 1240, 1027, 916, 769; δ_H(400 MHz; CDCl$_3$; Me$_4$Si)

1.2 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 2.1 (1H, bs, O*H*), 3.6 (1H, d, *J* 7.1 Hz, (C3)*H*), 4.1 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 4.3 (1H, dd, *J* 7.1, 4.6 Hz, (C4)*H*), 5.4 (1H, d, *J* 4.6 Hz, (C5)*H*), 7.2-8.3 (9H, m, 2 x Ar*H*), 8.5 (1H, bs, N*H*); δ_C(100 MHz; $CDCl_3$; Me_4Si) 14 (OCH_2CH_3), 42 (*C*4), 49.8 (*C*3), 61.5 (OCH_2CH_3), 102 (*C*5), 125.4-129 (Ar*C*), 135.6, 136.5 (quaternary Ar*C*), 141.5 (*C*5), 145.9 (*C*2), 147 (Ar*C*-Cl), 171 (*C*OO).

Synthesis of ethyl 2-(hydroxyimino)-4-(4-methoxyphenyl)-6-phenyl-1,2,3,4-tetrahydropyridine-3-carboxylate (20p, Scheme 3).

When **13p** (156mg, 0.44 mmol) was treated with $NH_2OH.HCl$ (46mg, 0.66 mmol), TEA (133mg, 1.32 mmol) in EtOH (3mL) heated to reflux overnight and the reaction progress was monitored by TLC. After completion of reaction the product **20p** was obtained by chromatography purification. **20p** (115mg, 71%) as a pale yellow solid; m.p. = 123-127°C; R_f = 0.3 (EtOAc:petrol, 1:1); υ_{max}(film)/cm^{-1} 3420, 2939 1741, 1600, 1200, 1040, 900, 850, 750; δ_H(400 MHz; $CDCl_3$; Me_4Si) 1.2 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 2.1 (1H, bs, O*H*), 3.6 (1H, d, *J* 7.1 Hz, (C3)*H*), 4.1 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 4.3 (1H, dd, *J* 7.1, 4.6 Hz, (C4)*H*), 4.5 (3H, s, OCH_3), 5.5 (1H, d, *J* 4.6 Hz, (C5)*H*), 7.2-8.5 (9H, m, 2 x Ar*H*), 8.6 (1H, bs, N*H*); δ_C(100 MHz; $CDCl_3$; Me_4Si) 14 (OCH_2CH_3), 42 (*C*4), 49.8 (*C*3), 61.5 (OCH_2CH_3), 64 (OCH_3), 103 (*C*5), 125.4-130 (Ar*C*), 135.6, 136.5 (quaternary Ar*C*), 141.5 (*C*5), 145.9 (*C*2), 156 (Ar*C*-OMe), 174 (*C*OO).

Synthesis of ethyl 2-(hydroxyimino)-6-phenyl-4-(p-tolyl)-1,2,3,4-tetrahydropyridine-3-carboxylate (21p, Scheme 3).

When **14p** (198mg, 0.59 mmol) was treated with $NH_2OH.HCl$ (61mg, 0.88 mmol), TEA (119mg, 1.18 mmol) in EtOH (5mL) heated to reflux overnight and the reaction progress was monitored by TLC. After completion of reaction the product **21p** was obtained by chromatography purification. **21p** (117mg, 57%) as a pale yellow solid; m.p. = 97-100°C; R_f = 0.4 (EtOAc: petrol, 1:1); υ_{max}(film)/cm^{-1} 3426, 2900, 1741, 1600, 1242, 1023, 910, 850, 769; δ_H(400 MHz; $CDCl_3$; Me_4Si) 1.2 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 2.1 (1H, bs, O*H*), 2.3 (CH_3), 3.6 (1H, d, *J* 7.1 Hz, (C3)*H*), 4.1 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 4.3 (1H, dd, *J* 7.1, 4.6 Hz, (C4)*H*), 5.4 (1H, d, *J* 4.6 Hz, (C5)*H*), 7.2-8.3 (9H, m, 2 x Ar*H*), 8.5 (1H, bs, N*H*); δ_C(100 MHz; $CDCl_3$; Me_4Si) 14 (OCH_2CH_3), 25 (CH_3), 42 (*C*4), 49.8 (*C*3), 61.5 (OCH_2CH_3), 102 (*C*5), 125.4-129 (Ar*C*), 135.6, 136.5 (quaternary Ar*C*), 138 (Ar*C*-Me), 141.5 (*C*5), 145.9 (*C*2), 170 (*C*OO).

Antimicrobial Activity

All the synthesized 2,3,4,6 substituted piperidine derivatives including 15P, 16P, 17P, 18P, 19P, 20P, 21P were tested for their antimicrobial activities[11] by drug diffusion method by preparing the discs of the drug. The activity was tested with *Staphylococcus aureus* (Gram positive), *Salmonella* *typhi* and *Escherichia coli* (Gram negative) bacterial strains taking Streptomycin, Ciprofloxacin and Cloxacillin as standard drugs. Further all antimicrobially active compounds were tested to find their minimal inhibitory concentration (MIC); using (50 µg/ml), (100µg/ml), (150µg/ml), (200µg/ml) concentrations.

Table 1: Antibacterial activity of compounds 15P, 16P, 17P, 18P, 19P, 20P, 21P.

Compd No.	**Zone of inhibition in mm**											
	E. coli				***S. typhi***				***S. aureus***			
	50 µg	**100 µg**	**150 µg**	**200 µg**	**50 µg**	**100 µg**	**150 µg**	**200 µg**	**50 µg**	**100 µg**	**150 µg**	**200 µg**
15P	14	19	25	28	15	17	19	21	12	15	19	22
16P	14	18	24	27	14	17	20	22	13	15	18	20
17P	15	20	27	33	14	18	21	26	15	16	19	25
18P	16	19	24	32	13	17	19	25	14	17	19	25
19P	15	18	23	31	14	16	19	27	13	17	20	27
20P	13	17	21	26	14	17	18	20	14	18	19	22
21P	14	18	20	27	13	15	18	21	17	18	20	22

Disc size: 6.35 mm; standard: streptomycin; control: DMSO; duration: 24hr resistant (< 11 mm), intermediate (14 mm), sensitive (>15 mm).

CONCLUSION

This is the efficient method for the synthesis of 2,3,4,6 highly substituted piperdines derivatives and the antibacterial screening data concluded that the all compounds 15P-21P showed activity against gram negative microorganisms as well as gram positive organisms. The compounds having the chloro- and flouro- as substituent on ortho- and meta- position of phenyl as substituent showed little more activity as compared to the other. The zones of inhibition were found to at 33 mm, 27 mm and 27 mm as the highest inhibition zone against *E. coli*, *S.typhi and S. aureus* with concentration 200µg with 17P, 18P and 19P.

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