

Synthesis, characterization and anti-bacterial study of fluorine containing N-benzyl substituted piperidine and pyrrolidine derivatives

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Abstract : Piperidine was reacted with 2-fluorobenzylchloride, 3-fluorobenzylchloride, 4-fluorobenzyl chloride, 3-trifluoromethylbenzylchloride, 4-trifluoromethylbenzylchloride, 2-fluorobenzylbromide, 3-fluoro benzyl bromide, 3-trifluoromethylbenzylbromide and 4-trifluoromethylbenzylbromide in the presence of triethylamine in benzene at reflux temperature for 24 hrs to form corresponding mono-(2-fluorobenzyl)piperidine, mono-(3-fluorobenzyl)piperidine, mono-(4-fluorobenzyl)piperidine, mono-(3-trifluoromethylbenzyl)piperidine and mono-(4-trifluoromethylbenzyl)piperidine in ~60% yields, respectively. In analogous reactions, pyrrolidine reacted smoothly with these fluorine containing benzylchlorides and bromides to form monosubstituted fluorine containing derivatives in moderate yields. The derivatives of piperidine and pyrrolidine are stable and soluble in CHCl_3 , CH_3CN , CH_2Cl_2 , THF and DMSO. These compounds have been characterised by using IR, ^1H and ^{19}F NMR spectroscopy, MS and elemental analysis. These derivatives of pyrrolidine and piperidine have been found bio-active.

Keywords: Fluorine-containing piperidine and pyrrolidine, bio-active

Introduction

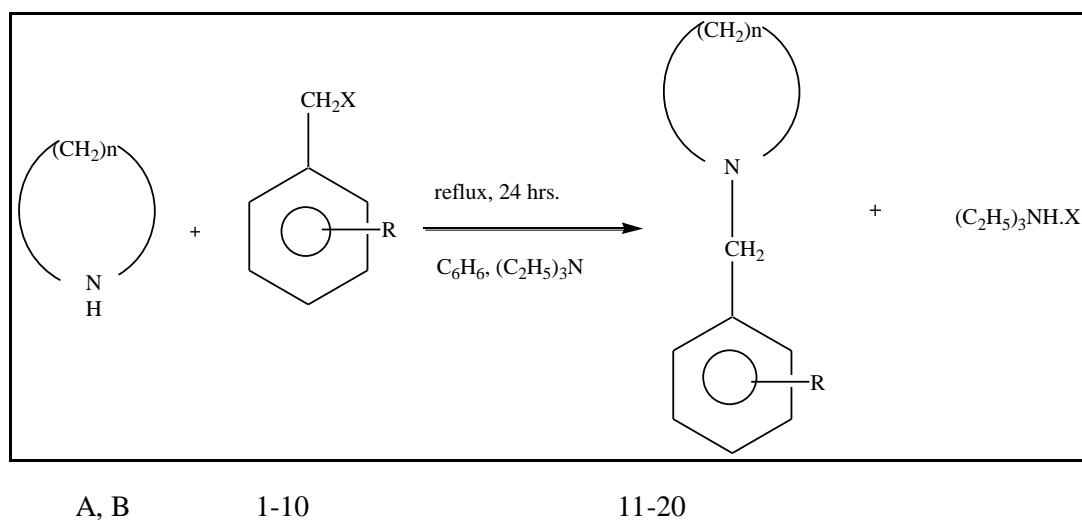
Fluorine containing heterocycles are widely recognized as important organic molecules showing interesting biological activities with a potential for applications in medicine and agriculture¹⁻⁷. Fluorine uniquely affects the properties of organic molecules through strong polar interactions due to the high electronegativity and small size. The introduction of fluorine into pharmaceuticals can make them more bioavailable, lipophilic and metabolically stable, and can increase the strength of a compound's interactions with a target protein⁸. This is mainly due to the fact that the replacement of hydrogen with fluorine often gives rise to drastic changes in biological activity due to the altered electronic distribution and changes in conformational properties^{9,10}. The research dealing with the synthesis of fluorine containing six-membered saturated nitrogen containing heterocyclic compounds has intensified considerably during the last decade and has resulted in new synthetic approaches and new commercial applications. In particular piperidine and pyrrolidine substituted with fluorobenzyl or trifluoromethyl benzyl groups have become increasingly popular as building blocks towards bioactive compounds. The variation of substituents on nitrogen atoms of these moieties plays an important role in selectivity and potency against biological targets. Piperidine and pyrrolidine occupied a unique place in the realm of pharmacological activities¹¹⁻¹⁴.

In the view of these facts and as continuation of our research on pharmaceutically important piperidine and pyrrolidine, here we report the synthesis of a new series of fluorine containing piperidine and pyrrolidine derivatives (Scheme-1). We are prompted for building block approach, and synthesised fluorine containing organic halo substituents into piperidine and pyrrolidine heterocyclic ring via metathesis.

Results and Discussion

The benzylation of piperidine and pyrrolidine heterocycles by using fluorine containing benzylchloride (1-5) and benzylbromide (6-10) has been described. The general procedure consists of heating the heterocycles A and B with compounds (1-10) in the presence of a base using benzene as solvent and isolating the products from the reaction mixture by using silica gel (60A^o) column chromatographic separation with hexane-ethylacetate(70:30) as the eluent. The reaction of piperidine (A) with various benzylchloride (1-5) and benzylbromide (6-10) in benzene that contained stoichiometric amount of triethylamine gave mono(2-fluorobenzyl)-piperidine (11), mono-(3-fluorobenzyl)piperidine (12), mono-(4-fluorobenzyl)piperidine (13), (3-trifluoromethylbenzyl)piperidine (14) and (4-trifluoromethylbenzyl)piperidine (15) respectively (Scheme-1). A similar treatment of pyrrolidine (B) with halo compounds (1-10) resulted in the formation of N-substituted products.

The benzylation reactions with piperidine (A) occurred slightly slower than those with pyrrolidine (B) but the benzylation reaction of chloro compounds (1-5) with piperidine (A) and pyrrolidine (B) occurred more slowly than those with bromo compounds (6-10) which may be due to the weaker bromo-carbon bond than chloro-carbon bond. The mass spectra of the products showed the molecular ion peak and characteristic fragmentation pattern.



Scheme 1

n = 5: Piperidine (A)	X=Cl	X= Br	n= 5	n=4
4: Pyrrolidine (B)	R=1: o-F	6: o-F	R=11: o-F	16: o-F
	2: m-F	7: m-F	12: m-F	17: m-F
	3: p-F	8: p-F	13: p-F	18: p-F
	4: m-CF ₃	9: m-CF ₃	14: m-CF ₃	19: m-CF ₃
	5: p-CF ₃	10: p-CF ₃	15: p-CF ₃	20: p-CF ₃

The substitution occurred smoothly in pyrrolidine with chlorides/bromides (1-10) and forming N-substituted products (16-20) in reasonably good yields as thick oils. The reactions of chlorides (1-5) with pyrrolidine (B) were slower than bromides (6-10) with pyrrolidine (B).

The formation of N-C bond was confirmed by the ¹H NMR spectra of the compounds. The singlet peak at δ 3.4-3.7 ppm in the spectrum of derivatives of piperidine (11-15) and pyrrolidine (16-20), shows the presence of -CH₂ in between nitrogen of piperidine and phenyl ring and similarly between nitrogen of pyrrolidine (B) and phenyl ring. The Two groups of multiplets at δ2.57-2.43 ppm and δ1.82-1.73 ppm were due to the two -N(CH₂)₂ and two -CH₂ farther from N respectively of pyrrolidine ring.

Experimental section

Materials:

Piperidine (A), pyrrolidine (B), 2-fluorobenzylchloride (1), 3-fluorobenzylchloride (2), 4-fluorobenzyl chloride (3), 3-trifluoromethylbenzylchloride (4),4trifluoromethylbenzylchloride(5), 2-fluoro benzylbromide

(6), 3-fluorobenzylbromide (7), 4-fluorobenzylbromide (8), 3-trifluoromethylbenzylbromide (9) and 4-trifluoromethylbenzylbromide (10), were obtained from ACROS and used as received. Triethylamine and benzene were obtained from Aldrich and used after drying with 4 Å molecular sieves.

General Procedure:

¹H NMR spectra were run in 5mm NMR tubes in CDCl₃ and the peak positions were measured relative to residual CHCl₃ and reported relative to Me₄Si. ¹⁹F NMR spectra were obtained on a Bruker DRX 300MHz NMR spectrometer with CFC1₃ as internal reference. Infrared spectra were obtained on a Shimadzu 8400s FTIR spectrometer using KBr disc for volatile liquids and KBr pellets for solids. All the melting points were determined in open capillary on electronic apparatus and are uncorrected. Thin layer chromatography was performed on Aluminium plates coated with silica gel-G using appropriate mobile phase systems and spots were visualized under UV radiations. All synthesized compounds were subjected to elemental analysis and the results obtained are in acceptable range.

General synthetic procedure for target compounds

Fluorine-containing piperidine derivatives and pyrrolidine derivatives were synthesized by refluxing fluorine containing organic halo compounds with piperidine (A) and pyrrolidine (B) in presence of triethylamine according to metathesis.

(A) Synthesis of fluorine containing piperidine derivatives

A mixture of piperidine (1.0 mmol) and fluoro benzylchloride (1.0mmol) were dissolved in benzene (30ml) and added triethylamine (1.0mmol) and refluxed for 24 hrs at 80°C. After completion of reaction as followed by t.l.c. examination, the reaction mixture was filtered; the solvent was removed from the filtrate by rotoevaporator. The resulted reaction mixture was purified with a column chromatography on silica gel by using hexane-ethylacetate (70:30) as eluent.

1-(2-fluorobenzyl)-piperidine (11). Yield: 86%, oil; IR (KBr disc, cm⁻¹): 3035(s), 2830(w), 1630(s), 1470(w), 1435(w), 1345(s), 1295(b), 1185(s), 1130(s), 1060(w), 1025(w), 825(s), 750(s). ¹H NMR (300 MHz, CDCl₃) δ (ppm): 7.05-6.91(m, 4H), 3.62(s, 2H), 2.24-2.20(m, 4H), 1.50-1.54(m, 6H); ¹⁹F NMR (282MHz, CDCl₃) δ (ppm): -119.40(s, 1F); MS (m/z): 194.2(M⁺+1); Elemental analysis for C₁₂H₁₆NF, Found (Calcd)%: C, 74.67(74.57); H, 8.38(8.34), N, 7.26(7.24).

1-(3-fluorobenzyl)-piperidine (12). Yield: 78%, oil; IR (KBr disc, cm⁻¹): 3030(w), 2850(w), 1580(s), 1480(s), 1370(s), 1280(w), 1165(s), 1095(w), 795(s), 730(s). ¹H NMR (300 MHz, CDCl₃) δ (ppm): 7.20-6.84 (m, 4H), 3.67(s, 2H), 2.46-2.48(m, 4H), 1.49-1.51(m, 6H); ¹⁹F NMR (282MHz, CDCl₃) δ (ppm): -117.93(s, 1F); MS (m/z): 194.8(M⁺+1); Elemental analysis for C₁₂H₁₆NF, Found (Calcd)%: C, 74.59(74.57); H, 8.36(8.34), N, 7.28(7.24).

1-(4-fluorobenzyl)-piperidine (13). Yield: 73%, oil; IR (KBr disc, cm⁻¹): 3045(w), 2830(s), 1710(s), 1500(w), 1450(w), 1350(s), 1225(b), 1125(s), 920(s), 870(w), 760(s). ¹H NMR (300 MHz, CDCl₃) δ (ppm): 7.08-6.70 (m, 4H), 3.62(s, 2H), 2.42-2.45(m, 4H), 1.52-1.55(m, 6H); ¹⁹F NMR (282MHz, CDCl₃) δ (ppm): -127.03(s, 1F); MS (m/z): 194.3(M⁺+1); Elemental analysis for C₁₂H₁₆NF, Found (Calcd)%: C, 74.60(74.57); H, 8.39(8.34), N, 7.27(7.24).

1-(3-trifluoromethylbenzyl)-piperidine (14). Yield: 84%, oil; IR (KBr disc, cm⁻¹): 3065(s), 2850(s), 1460(s), 1340(w), 1175(w), 1125(b), 1010(s), 880(s), 870(s), 710(s). ¹H NMR (300 MHz, CDCl₃) δ (ppm): 7.0-6.67 (m, 4H), 3.66(s, 2H), 2.44-2.47(m, 4H), 1.50-1.53(m, 6H); ¹⁹F NMR (282MHz, CDCl₃) δ (ppm): -62.4 (s, 1F); MS (m/z): 244.4(M⁺+1); Elemental analysis for C₁₃H₁₆NF₃, Found (Calcd)%: C, 64.20(64.18); H, 6.66(6.62), N, 5.78(5.75).

1-(4-trifluoromethylbenzyl)-piperidine (15). Yield: 76%, oil; IR (KBr disc, cm⁻¹): 3060(s), 2860(s), 1630(w), 1460(s), 1425(b), 1330(s), 1070(s), 1025(s), 1020(w), 910(s), 815(s). ¹H NMR (300 MHz, CDCl₃) δ(ppm): 7.04-6.98(m, 4H), 3.66(s, 2H), 2.62-2.64(m, 4H), 1.48-1.50(m, 6H); ¹⁹F NMR (282MHz, CDCl₃) δ (ppm): -60.48 (s, 1F); MS (m/z) : 244.6(M⁺+1); Elemental analysis for C₁₃H₁₆NF₃, Found (Calcd)%: C, 64.24(64.18); H, 6.64(6.62), N, 5.80(5.75).

(B) Synthesis of fluorine containing pyrrolidine derivatives

A mixture of pyrrolidine (1.0 mmol) and fluoro benzylchloride (1.0 mmol) were dissolved in benzene (30ml) and added triethylamine (1.0 mmol) and refluxed for 24 hrs at 80°C. After completion of reaction as followed by t.l.c. examination, the reaction mixture was filtered; the solvent was removed from the filtrate by rotoevaporator. The resulted reaction mixture was purified with a column chromatography on silica gel by using hexane-ethyl acetate (60:40) as eluent.

4-(2-Fluorobenzyl)-pyrrolidine (16). Yield: 88%, oil; IR (KBr disc, cm^{-1}): 3030(w), 2870(s), 2350(b), 1600(s), 1500(s), 1450(w), 1230(s), 1030(w), 950(s), 750(w). ^1H NMR (300 MHz, CDCl_3) δ (ppm): 7.4-6.9(m, 4H), 3.6(s, 2H), 2.57-2.55(m, 4H), 1.82-1.73(m, 4H); ^{19}F NMR (282MHz, CDCl_3) δ (ppm): -119.04(s, 1F); MS (m/z): 180.3(M^+ +1); Elemental analysis for $\text{C}_{11}\text{H}_{14}\text{NF}$, Found (Calcd)%: C, 73.74(73.71); H, 7.89(7.87); N, 7.83(7.81).

4-(3-Fluorobenzyl)-pyrrolidine (17). Yield: 79%, oil; IR (KBr disc, cm^{-1}): 3060(w), 2975(b), 2800(s), 1620(w), 1590(s), 1450(s), 1350(w), 1250(s), 1140(b), 940(s), 890(s), 750(s). ^1H NMR (300 MHz, CDCl_3) δ (ppm): 7.2-6.8(m, 4H), 3.5(s, 2H), 2.54-2.42(m, 4H), 1.8-1.7(m, 4H); ^{19}F NMR (282MHz, CDCl_3) δ (ppm): -113.80 (s, 1F); MS (m/z): 180.9(M^+ +1); Elemental analysis for $\text{C}_{11}\text{H}_{14}\text{NF}$, Found (Calcd)%: C, 73.73(73.71); H, 7.90(7.87); N, 7.85(7.81).

4-(4-Fluorobenzyl)-pyrrolidine (18). Yield: 83%, oil; IR (KBr disc, cm^{-1}): 2880(b), 2370(s), 1590(w), 1490(w), 1460(s), 1370(s), 1230(s), 1030(w), 950(s), 750(s). ^1H NMR (300 MHz, CDCl_3) δ (ppm): 7.4-6.9(m, 4H), 3.6(s, 2H), 2.5(b, 4H), 1.8-1.7(m, 4H); ^{19}F NMR (282MHz, CDCl_3) δ (ppm): -118.20(s, 1F); MS (m/z): 180(M^+ +1); Elemental analysis for $\text{C}_{11}\text{H}_{14}\text{NF}$, Found (Calcd)%: C, 73.75(73.71); H, 7.89(7.87); N, 7.83(7.81).

4-(3-Trifluoromethylbenzyl)-pyrrolidine (19). Yield: 90%, oil; IR (KBr disc, cm^{-1}): 2960(s), 2780(w), 1450(b), 1340(s), 1160(w), 1125(b), 1025(s), 870(s), 710(w). ^1H NMR (300 MHz, CDCl_3) δ (ppm): 7.6-7.3(m, 4H), 3.7(s, 2H), 2.5-2.4(m, 4H), 1.7-1.6(m, 4H); ^{19}F NMR (282MHz, CDCl_3) δ (ppm): -62.51(s, 1F); MS (m/z): 230.3(M^+ +1); Elemental analysis for $\text{C}_{12}\text{H}_{14}\text{NF}_3$, Found (Calcd)%: C, 62.89(62.87); H, 6.19(6.15); N, 6.15(6.11).

4-(4-Trifluoromethylbenzyl)-pyrrolidine (20). Yield: 86%, oil; IR (KBr disc, cm^{-1}): 2950(b), 2760(s), 1435(w), 1250(b), 1180(s), 1025(s), 890(s), 850(w), 710(s). ^1H NMR (300 MHz, CDCl_3) δ (ppm): 7.6-7.4(m, 4H), 3.6(s, 2H), 2.5-2.4(m, 4H), 1.7-1.6(m, 4H); ^{19}F NMR (282MHz, CDCl_3) δ (ppm): -67.23(s, 1F); MS (m/z): 230(M^+ +1); Elemental analysis for $\text{C}_{12}\text{H}_{14}\text{NF}_3$, Found (Calcd)%: C, 62.90(62.87); H, 6.18(6.15); N, 6.16(6.11).

3. Antibacterial activity:

A Piperidine (A) and pyrrolidine (B) nucleus has the several important biological activities but in present work, the antimicrobial activity of new synthesized compounds has been investigated against bacteria (**Table No. 1**). The antibacterial activities of the compounds were assayed by agar disc-diffusion method. The method was based on diffusion of antibacterial compound from reservoir disc to the microorganism was inhibited as circular zone around the disc. The antimicrobial activity was tested for four bacteria (two gram negative and two gram positive). Gram positive micro organisms were *Staphylococcus aureus*, and *Bacillus subtilis*, and gram negative micro organisms were *Escherichia coli*, and *Pseudomonas aeruginosa*. The antibacterial activities were screened in DMSO, using standard amoxicillin/ ciprofloxacin/ streptomycin (1mg/ml) concentration. The compounds with trifluoromethyl showed moderate or low biological activities. This is possibly because fluorine atom is a lipophilic group, and the introduction of poly-fluorine atom excessively decreases the hydrophilicity of molecule and further influenced the bioactivities.

Table No. 1: Antibacterial activity: Inhibition zone (mm) of fluorine containing derivatives of piperidine (11-15) and pyrrolidine (16-20) against different microbial strains

Compounds (11-20)	Bacterial strain-Zone of inhibition (mm) and Minimum inhibition concentration of compound Test (10 µg/ml)			
	Gram positive		Gram negative	
	<i>S.aureus</i>	<i>B.subtillis</i>	<i>E. coli</i>	<i>P.aeruginosa</i>
11	18(08)	10(08)	14(12)	10(12)
12	16(08)	06(06)	16(08)	12(08)
13	20(10)	00(00)	18(12)	14(14)
14	16(08)	12(08)	08(08)	16(08)
15	18(10)	00(00)	10(02)	14(14)
16	20(12)	10(08)	14(12)	10(12)
17	18(10)	06(06)	16(08)	12(08)
18	14(08)	00(00)	18(12)	14(14)
19	22(14)	12(08)	08(08)	16(08)
20	18(10)	00(00)	10(02)	14(14)
Streptomycin	24(20)	20(20)	20(20)	22(20)

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