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An efficient ecofriendly protocol for the synthesis of novel fluoro isoxazoline and isoxazolidines using *N*-benzyl fluoro nitrone via cycloaddition reactions

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ABSTRACT

1-Butyl-3-methylimidazolium based ionic liquids are found to accelerate significantly the intermolecular 1,3-dipolar cycloaddition of *N*-benzyl fluoro nitrones derived in situ from aldehydes and benzylhydroxylamine, with electron deficient alkynes to afford enhanced rates and improved yields of isoxazolines while with enals exclusively *endo* isoxazolidines are obtained with high selectivity. Synthetic potentiality of the novel isoxazolines and nitrones has also been tested successfully.

The 1,3-dipolar cycloaddition reactions represent the favourite method for the construction of five-membered heterocycles, the important frameworks of various natural products.[1] In particular the 1,3-dipolar cycloadditions of nitrones with alkenes and alkynes afforded isoxazolidines and isoxazolines which are interesting intermediates for the synthesis of β-amino alcohols and alkaloids.[2,3] Isoxazoline and isoxazolidines possess medicinal activities such as antibacterial, anticonvulsant, antibiotic, antitubercular and antifungal.[4,5] Despite their potential utility, many of these procedures require high temperature and prolonged reaction times (drastic experimental conditions) and also suffer from poor regioselectivity and lack of simplicity. In a few cases, the yields and selectivities reported are far from satisfactory due to the occurrence of several side reactions.[6]

In recent times, ionic liquids have emerged as green solvents with desirable properties such as good solvating ability, wide liquidious range, tunable polarity, high thermal stability, negligible vapour pressure and ease of recyclability.[7] Therefore, classical organic reactions can be performed in these media with great advantages (yield and selectivity) as compared to conventional conditions. They are referred to as 'designer solvents' as their properties such as hydrophilicity, hydrophobicity, Lewis acidity, viscosity and density can be altered by the fine-tuning of parameters such as the choice of organic cation, inorganic anion and the length of alkyl chain attached to an organic cation (Fig. 1).

These structural variations offer flexibility to the chemist to devise the most idealized solvent, catering to the needs of any particular process. Since ionic liquids are entirely composed of non-coordinating ions, they can provide an ideal reaction medium for reactions that involve reactive ionic intermediates. Due to the stabilization of charged intermediates by ionic liquids, they can promote unprecedented selectivities and enhanced reaction rates. Consequently, ionic liquids are being used as recyclable solvents for the immobilization of transition metal based catalysts, Lewis acids and enzymes.[8] As a result of their green credentials and potential to enhance reaction rates and selectivities, ionic liquids are finding increasing applications in organic synthesis[9] with an ever-increasing quest for exploration of newer reactions in ionic liquids.[10]

It is known that introduction of fluorine atom into a specific position of organic molecule may cause significant changes in the stability, lipophilicity and biological activities of the resulting molecules.[11] This has been attributed to the high electro negativity of the halogen, the strong C–F bond and the similar size of the

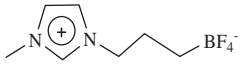

Figure 1. Chemical structure of ionic liquid.

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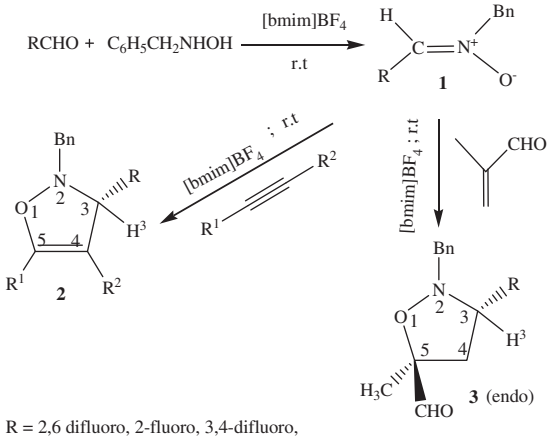
halogen and hydrogen atoms. For these reasons great efforts have been placed on the development and evaluation of biologically active fluorinated materials.[12] The biological properties of multifluorine containing compounds have been recently investigated. Owing to their unique properties, such as high thermal stability and lipophilicity, fluoro-organic compounds have been frequently used as biorelated material, medicine and agrochemicals.[13] The presence of a fluoro group (C–F group) due to low polarizability and high lipophilicity induces a relative metabolic stability and improves the bioavailability of the modified heterocycles compared to its hydrocarbon analogues.[14,15]

In continuation of our effort to establish green methodologies in nitrone cycloaddition reactions,[16–20] herein we wish to report the use of ionic liquids as recyclable solvents for 1,3-dipolar cycloaddition reactions of *N*-benzyl fluoro nitrone (having vast synthetic potentials) with electron deficient alkynes and alkenes (enals) to produce novel isoxazoline and isoxazolidine derivatives in a one-pot operation (Scheme 1).

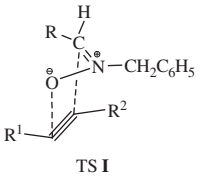
Compared to conventional conditions the cycloaddition reactions performed in ionic liquids are much faster and selective. As



R = 2,6 difluoro, 2-fluoro, 3,4-difluoro,
4-fluoro, 2-hydroxy, 4-hydroxy benzene/ phenyl
$R^1 = C_6H_5$; $R^2 = COOCH_3$
$R^1 = COOCH_3$; $R^2 = COOCH_3$
$R^1 = R^2 = COOH$
Bn = Benzyl

Scheme 1.

an example, the reaction between **1** and alkynes, afforded the cycloaddition derivative **2** after 17 h in CH_2Cl_2 in 67% yield and 93% yield (entry 1) in $[bmim]BF_4$ at room temperature after 26 min respectively. In a typical procedure 1 mmol of nitrone was mixed with 1 equiv of alkynes in $[bmim]BF_4$ (2 ml) under stirring, at room temperature. After the development of nitrone (monitored by TLC), 1 mmol of dipolarophile was added and the progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was washed with diethyl ether (3×10 ml). The combined ether extracts were concentrated in vacuo and the resulting product was directly charged on silica gel column and eluted with a mixture of ethyl acetate:*n*-hexane (1:8) to afford pure isoxazoline. The rest of the viscous ionic liquid was further washed with diethyl ether and dried at 80 °C under reduced pressure to retain its activity in subsequent runs and was reused up to five times without loss of activity or selectivity after five cycles. We have intentionally stopped the recycle at the fifth cycle, however we are convinced that this process may be carried on many more times. Several butylmethylimidazolium based ILs, [bmim]X, with varying anions ($X = PF_6^-$, Br^-, BF_4^-) were screened for this reaction. Evidently, $[bmim]BF_4$ was found to be superior in terms of yield (93%) and reaction time (26 min) as compared with $[bmim]PF_6$ (84%; 43 min; entry 1). For optimizing the conditions, we used the substrates in different ratios. It was found that best results were obtained using 1:1 reactant ratio. The reaction in $[bmim]BF_4$ was also conducted at elevated temperatures for optimizing the conditions and no significant improvements were observed in yields and reaction times. We examined the reaction under neat condition also, without using IL, to demonstrate the catalytic ability of $[bmim]BF_4$ This result clearly indicates that $[bmim]BF_4$ has significant catalytic role in this reaction (Table 1). The addition of nitrone **1** to alkynes and alkenes (enals) can be rationalized by an *exo* and *endo* approach of the nitrone which has the Z configuration (transition state **I** and **II**).[21]



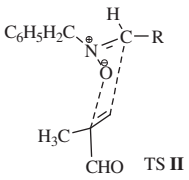


Table 1
1,3-Dipolar cycloaddition reactions of *N*-benzyl fluoro nitrone with alkynes in ionic liquid.

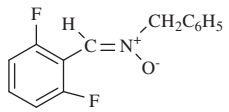
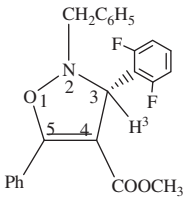
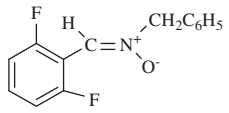
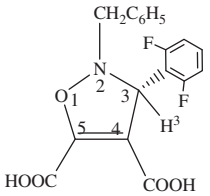
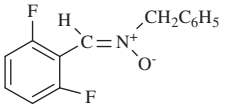
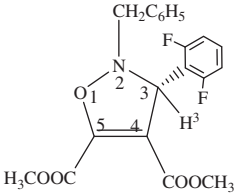
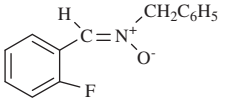
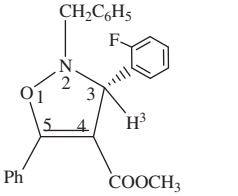
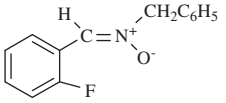
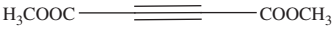
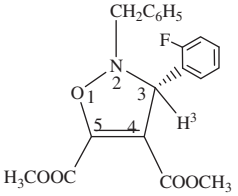
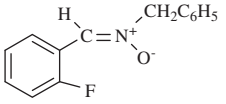
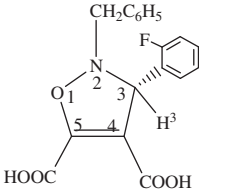
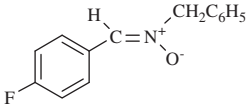
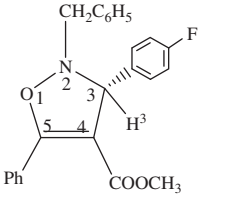
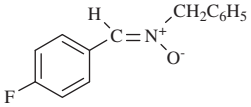
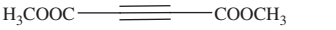
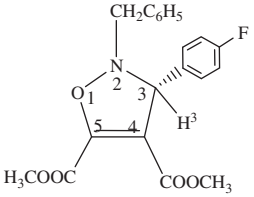
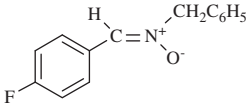
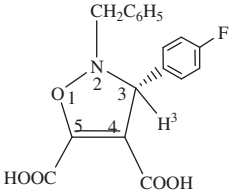
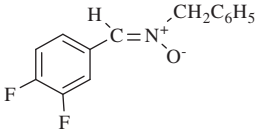
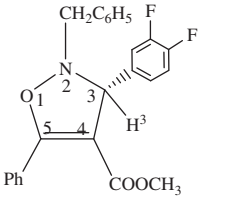
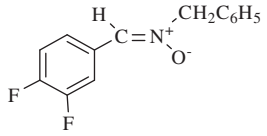
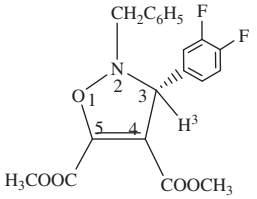
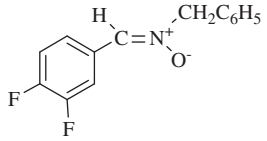
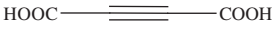
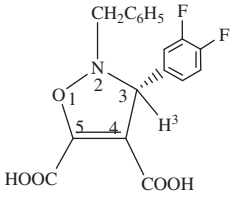
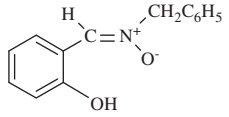
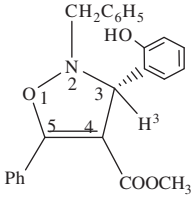
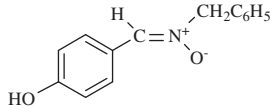
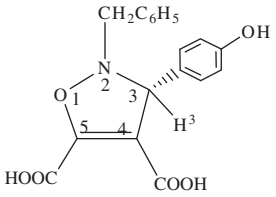
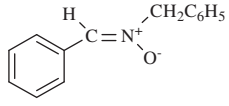
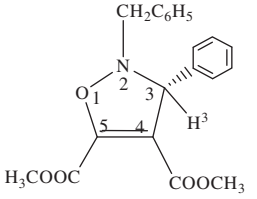
Entry	Nitrone[a]	Alkyne	Product[b] (**2**)	Time (min)	Yield[c] (%)
1				26 (1020)	93 (67)
2				35 (1080)	91 (64)

Table 1 (*continued*)

Entry	Nitrone[a]	Alkyne	Product[b] (**2**)	Time (min)	Yield[c] (%)
3				28 (1080)	89 (63)
4				28 (1140)	90 (66)
5				33 (1140)	93 (62)
6				35 (1260)	90 (61)
7				32 (1200)	88 (61)
8				24 (1320)	92 (62)
9				35 (1260)	90 (59)
10				36 (1380)	88 (57)

(*continued on next page*)

Table 1 (*continued*)

Entry	Nitrone[a]	Alkyne	Product[b] (**2**)	Time (min)	Yield[c] (%)
11				36 (1320)	89 (57)
12				27 (1380)	85 (55)
13				25 (960)	92 (66)
14				23 (900)	90 (67)
15				40 (1200)	87 (62)

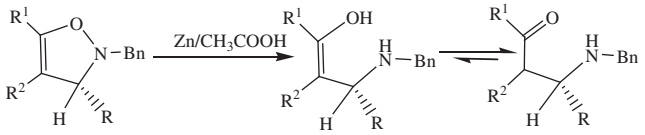
[a] Reaction conditions: nitrone (1 mmol), alkynes (1 equiv), [bmim]BF_4 (2 ml), N_2 atmosphere, rt.
[b] All products were characterized by IR, ^{1}H NMR, ^{13}C NMR and MS spectral data.
[c] Isolated yield after purification. Figures in parentheses indicate reactions performed in conventional methods.

Furthermore, the novel isoxazoline derivatives (**2**) are found to have vast synthetic potential as they could be converted into 1,3 difunctional amino alcohols (Scheme 2). Studies are in progress.

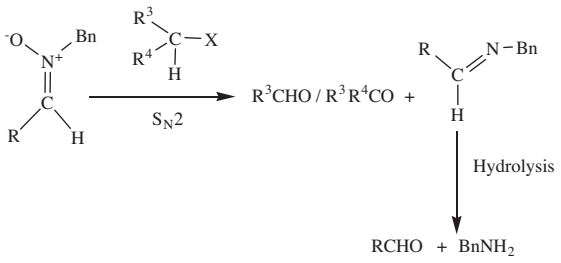
Nitrone **1** may also be used as an oxidizing reagent in the conversion of alkyl halides to aldehydes and ketones (Scheme 3) following a pattern of atom efficient reactions reported by our group.[16] We have already reported the synthesis of various aldehydes and ketones from alkyl halides using α-chloro nitrones in atom efficient reactions.[16,22]

To explore the potential of this procedure we have extended the protocol, with activated alkenes (enals) and to *N*-benzyl–*C*-phenyl nitrones (with fluoro and hydroxy derivatives in phenyl ring) for the synthesis of exclusively *endo* isoxazolidine and isoxazolines in rather good conversions and yields (Tables 1 and 2).

Treatment of *N*-benzyl fluoro nitrone with methacrolein in [bmim]BF4 for 28 min gave the corresponding 5-substituted *endo* isoxazolidine (entry 1, product **3**) in 90% yield with excellent regioselectivity (Table 2, entry 1). However, in the absence of ionic liquids, the reaction did not yield any product even after a long reaction time (30 h). Under conventional conditions (CH_2Cl_2 as solvent, rt, 42 h), the products were obtained as a mixture of *endo* and *exo*-isomers (80:20) favouring the *endo*-diastereomer. Signals for the *endo* and *exo* diastereomers were assigned by ^{1}H NMR analysis.[23] Nitrones bearing benzyl groups on the nitrogen atom are ex-

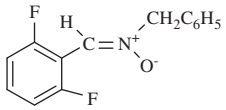
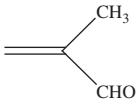
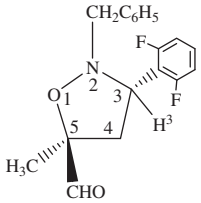
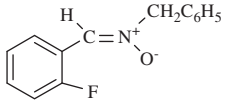
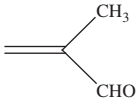
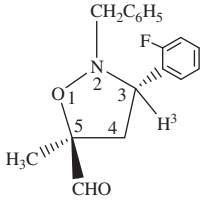
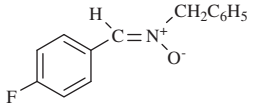
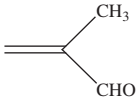
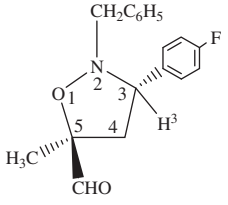
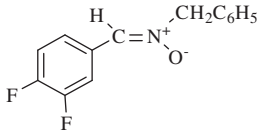
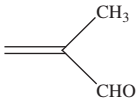
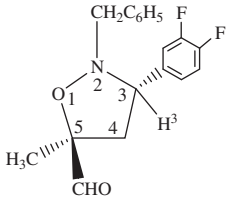


Scheme 2.



Scheme 3.

Table 2
1,3-Dipolar cycloaddition reactions of *N*-benzyl fluoro nitrone with alkenes (enals) in ionic liquid.

Entry	Nitrone[a]	Alkyne	Product[b] (**3**)	Time (min)	Yield[c] (%)
1				28 (2520)	90 (62)
2				30 (2640)	88 (60)
3				33 (2640)	88 (57)
4				32 (2640)	84 (57)

[a] Reaction conditions: nitrone (1 mmol), methacrolein (1 equiv), [bmim]BF4 (2 ml), N_2 atmosphere, rt.
[b] All products were characterized by IR, ^{1}H NMR, ^{13}C NMR and MS spectral data.
[c] Isolated yield after purification. Figures in parentheses indicate reactions performed in conventional methods.

tremely valuable for applications in synthesis as these moieties act as versatile protecting groups. We are pleased to find that the *N*-benzyl fluoro nitrones afforded the expected *endo* substituted isoxazolidines (**3**) with high yields. The anticipated 1,3-dipoles exhibit enhanced reactivity in ionic liquid thereby reducing the reaction times and improving the yields significantly. Furthermore, the ionic liquids were found to give better regioselectivity than organic solvents. In addition, these molten salts could be easily recovered on work-up. Since the products are fairly soluble in ionic media; they could be easily extracted with ether. The rest of the ionic liquids was further washed with ether and recycled in three to four subsequent runs without loss of activity. Enhanced reaction rates, excellent yields and high *cis*-selectivity are the features observed in these ionic solvents. All products were characterized by ^{1}H NMR, IR and mass spectroscopic data.

In conclusion, we have shown that 1,3-dipolar cycloadditions of fluoro nitrones with alkene and alkynes may be conveniently carried out in RTILs with the obtainment of corresponding novel fluoro isoxazolidine and isoxazolines in good conversions and yields[24,25] with high synthetic potentials. The ionic liquid may be recycled several times without loss of activity or selectivity.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.11.111.

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24. *Representative experimental procedure for nitrone and fluoro isoxazoline synthesis* (Table 1; *entry 1*): 2,6-Difluoro benzaldehyde (1 mmol) and *N*-benzylhydroxylamine (1 equiv) were added to [bmim]BF_4 (2 mL) in a 10 mL conical flask, mixed thoroughly and stirred at rt for 2 h. The formation of nitrone was monitored by TLC (R_f = 0.40). The nitrone was isolated as a white crystalline solid (mp 42 °C, uncorrected) following the methodology as adopted in the following cycloaddition reactions. As the nitrone decomposes on keeping at room temperature, in situ reactions were performed with alkynes. Methyl phenyl propiolate (1 mmol) was added at the time of development of nitrone and the reaction mixture was further stirred at room temperature for an appropriate time (Table 1). After completion of reaction, as indicated by TLC (R_f = 0.58), the reaction mixture was washed with diethyl ether (3 × 10 mL). The combined ether extracts were concentrated in vacuo and the resulting product was directly charged on silica gel column and eluted with a mixture of ethyl acetate:*n*-hexane (1:8) to afford pure isoxazoline **2** (Table 1, entry 1, 93%). The rest of the viscous ionic liquid was further washed with ether and dried at 80 °C under reduced pressure to retain its activity in subsequent runs. Spectroscopic data for nitrone 1: UV λ_{max} 238 nm; IR (KBr): ν_{max} 2965 (m), 1610 (s), 1440 (m), 1154 (m), 784 (s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.96–7.79 (m, 3H, $C_6H_3F_2$), 7.67–7.35 (m, 5H, $C_6H_5CH_2$), 6.98 (s, 1H, –CH=N^+), 3.37 (s, 2H, $C_6H_5CH_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.04 (CH=N^+), 134.80, 134.34, 134.12, 133.93, 131.60, 130.00, 129.55, 129.46, 128.67, 128.22 (aromatic carbons). Spectroscopic data for isoxazoline **2** (entry 1): IR (KBr): ν_{max} 3010 (m), 2246 (m), 1813 (m), 1774 (s), 1610 (s), 1480 (s), 1324 (s), 1215 (s), 1105 (s), 993 (m), 782 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.87–7.80 (m, 3H, $C_6H_3F_2$), 7.68–7.21 (m, 2 × 5H, C_6H_5), 3.38 (s, 3H, –$COOCH_3$), 2.68 (s, 2H, $C_6H_5CH_2$), 1.25 (s, 1H, C_3H). ^{13}C NMR ($CDCl_3$): δ 168.52 (–$COOCH_3$), 137.20, 137.04, 136.87, 136.66, 135.65, 135.48, 135.20, 134.93, 132.77, 132.35, 132.08, 131.78, 130.80, 129.90 (aromatic carbons), 88.16 (C_5), 73.60 (C_3), 58.45 (C_4), 45.17 (–$COOCH_3$), 36.80 (benzylic carbon). FAB-MS (*m*/*z*): 407 (M^+), 330, 294, 211 (bp), 203, 105, 91, 77. Anal. Calcd. for $C_{24}H_{19}O_3F_2N$: C, 70.76; H, 4.66; N, 3.43%. Found: C, 70.63; H, 4.61; N, 3.35%.
25. *Representative experimental procedure for fluoro isoxazolidine synthesis* (Table 2; *entry 1*): 2,6-Difluoro benzaldehyde (1 mmol) and *N*-benzylhydroxylamine (1 equiv) were added to [bmim]BF_4 (2 mL) in a 10 mL conical flask, mixed thoroughly and stirred at rt for 2 h. The formation of nitrone was monitored by TLC (R_f = 0.40). Methacrolein (1 mmol) was added dropwise, by syringe, at rt at the time of development of nitrone and the reaction mixture was further stirred at room temperature for an appropriate time (Table 2). After completion of reaction, as indicated by TLC (R_f = 0.50), the reaction mixture was washed with diethyl ether (3 × 10 ml). The combined ether extracts were concentrated in vacuo and the resulting product was directly charged on silica gel column and eluted with a mixture of ethyl acetate:*n*-hexane (1:8) to afford pure isoxazolidine **3** (Table 2, entry 1, 90%). The rest of the viscous ionic liquid was further washed with ether and dried at 80 °C under reduced pressure to retain its activity in subsequent runs. Spectroscopic data for isoxazolidine **3** (entry 1): IR (KBr): ν_{max} 2994 (m), 2970 (m), 1730 (s), 1615 (s), 1462 (s), 1324 (s), 1145 (s), 980 (m), 788 (s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 9.82 (s, 1H, CHO), 8.13–7.86 (m, 3H, $C_6H_3F_2$), 7.64–7.33 (m, 5H, C_6H_5), 3.89 (dd, 1H, *J* = 5.20, 5.60 Hz, C_4H), 3.71 (dd, 1H, *J* = 5.26, 5.60 Hz, C_4H, *endo*), 2.95 (s, 2H, $C_6H_5CH_2$), 1.60 (s, 3H, CH_3), 1.27 (t, 1H, *J* = 5.14 Hz, C_3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.24 (–CHO), 134.53, 134.38, 134.28, 134.17, 132.12, 132.04, 131.95, 131.90, 131.86, 131.72 132 (aromatic carbons), 80.57(C_5), 74.22 (C_3), 55.40 (C_4), 34.90 (benzylic carbon), 23.17 (CH_3). FAB-MS (*m*/*z*): 317 (M^+), 226, 204, 113 (bp), 83, 91, 77. Anal. Calcd. for $C_{18}H_{17}O_2F_2N$: C, 68.11; H, 5.39; N, 4.41%. Found: C, 68.02; H, 5.21; N, 4.28%.