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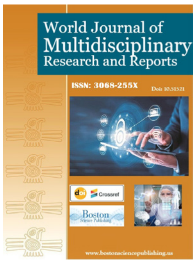

Mechanochemical Synthesis and Potential Anticancer Activities of Fluoro Isoxazolidine & Isoxazoline Derivatives Derived from *N*-Substituted-4-(Trifluoromethyl)-*C*-Phenyl Nitrones

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ABSTRACT

The present study reports solid phase synthesis of some N-Substituted-4-(Trifluoromethyl)-C-phenyl isoxazolidine and isoxazoline derivatives following green chemistry protocol and screened for anticancer activity against a panel of four human cancer cell lines. Among newly synthesized molecules, molecule 2 and 4 have shown IC50 of 0.01, 0.5 and 0.3 µM against HeLa, MDA-MB-231, MCF-7, A549 respectively. The isoxazolidine derivative 4 has also found to be concentration dependent inhibitory activity against NF-kB (nuclear factor kappa-light-chain-enhancer of activated B-cells) with 55% inhibition in 24 hr at 10 µM. This solvent free mechanochemical procedure procedure with the addition of sodium bicarbonate showed remarkably faster reaction rate and enhanced workup process as well as yields of the reported fluoronitrones and fluoro cycloadducts compared to microwave and coventional cycloaddition procedures.

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Introduction

One of the leading causes of death worldwide is due to *cancer* and recent study reports that about 9.8 million deaths (nearly 21% of all deaths) in 2024. Lung cancer has been recognized to be one of the leading causes of death among all cancers with 24% of adulthood cancer deaths. Breast cancer is the most commonly diagnosed malignant tumor in women and is found in approximately 28% of all female cancers followed by cervical cancer, a slow growing cancer cell *carcinoma* caused by human papillomavirus (HPV), that affects women after breast cancer. Though timely detection and treatment provides 100% cure but the mortality rate of cervical cancer is high. Literature and study reflect cytotoxic chemotherapeutic agents are often used to inhibit cell growth and to induce cancer cell apoptosis. In recent years (2018-2025), synthesis of N-O bonded heterocycles [1] especially isoxazolidine and isoxazoline derivatives have attracted tremendous interest among medicinal chemistry researchers due to their potential applications in medicinal chemistry. Even a small molecule containing isoxazolidine moiety is capable of activating the regulatory network which controls gene-specific transcription. These functionalized isoxazolidine derivatives are known to possess various biological activities including antitumor activity [2-4].

Perhaps nitrones are one of the most important reaction intermediates in synthetic organic chemistry as far as the constructions of 5-membered oxygen-nitrogen heterocyclic molecules are concerned [1]. Many new approaches in this chemistry are widely known but greener synthesis and cycloaddition reactions of fluoro nitrones and fluoro cycloadducts have been scarcely reported [5-7]. The introduction of fluorine atom or atoms in a particular position of an organic molecule can significantly change the stability and the bioactivity of the molecule [8]. Three important factors or properties of fluorine atom are expected to play the crucial role for this significant change and bioactivity. These are the high electronegativity of the fluorine, the strong C-F bonding and the same size of the halogen and hydrogen atoms respectively. Hence fluorinated isoxazolidine and isoxazoline derivatives are point of attraction not only to synthetic organic chemists but also in the field of pharmacology as well [9]. The reported works in literature reveals that fluorinated isoxazolidine derivatives are capable of exhibiting excellent bioactive properties [10,11] including the development of new *cancer drugs* [12].

A variety of environment friendly (green chemistry) procedures in the synthesis of isoxazolidine and isoxazoline derivatives and further applications of these molecules including broad spectrum antimicrobial activities have been already reported by our group [13-20]. CF_3 as substituent plays vital role in synthesis and also, we have found its many applications in CF_3 substituted isoxazolidine and isoxazoline derivatives [10,11,12]. In this research article, we would like to report synthesis of some important new stable fluoro isoxazolidine & isoxazoline derivatives using mechanochemical procedure and potential anticancer activities of few isoxazolidine and isoxazoline derivatives. (Scheme 1; Table 1, 2 & 3) [21,22]. Scheme **1** describes reaction pathways for the synthesis of fluoro nitrones, fluoro isoxazolidines and fluoro isoxazoline derivatives respectively. Table **1** and **2** represents comparative studies of the yields of the products obtained in mechanochemical procedure with other methods and the descriptions of reaction condition, time required and *enantiomeric excess* (*ee*) in the footnote. Table **3** describes *anti carcinogenic activities* of few new molecules synthesized with selected human cells and the details of this study are going on at present.

We have found significant acceleration in reaction rate and yield of the cycloadducts in mechanochemical procedure compared with microwave irradiation (MWI) and conventional methodologies. Mechanochemical procedures involving ball-milling technique are very popular in today's

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scenario for its many environmental friendly aspects and hence attracted the attention of mainly synthetic organic chemists [21,22]. Like majority of usual nitrones, fluoro nitrones synthesized in our laboratory are stable (melting points ranges between 68^0C to 85^0C, therefore utilization of these nitrones in the synthesis of isoxazolidine derivatives via cycloaddition reaction becomes very easy. Hence, these fluoro-nitrones may be regarded as an important precursor for the synthesis of new *anticancer drugs* which could attract organic and medicinal chemists in research.

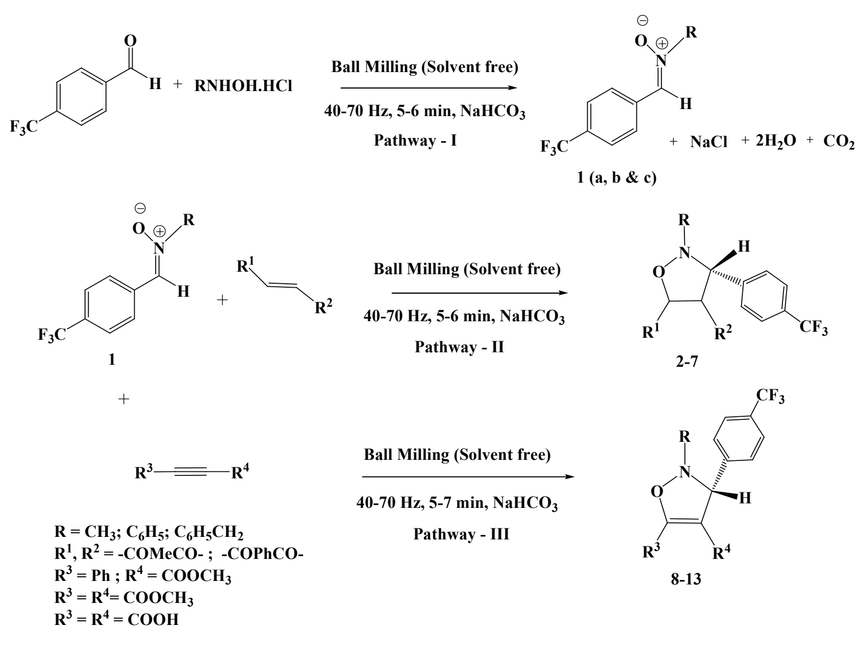
Results & Discussion

Chemistry: In the present study, for the synthesis of *N*-substituted-4-(Trifluoromethyl)-*C*-phenyl nitrone (**1**), we have conducted the reactions taking one equivalent each of 4-(Trifluoromethyl)-benzaldehyde and *N*-substitutedhydroxylaminehydrochloride along with one equivalent of sodium bicarbonate for the synthesis of 1a-1c (Scheme **1;** R = Me, Ph, Bz). The synthesized fluoro nitrones have been used for cycloaddition reactions without further purification. 4-Trifluoromethyl benzaldehyde derived fluoro nitrones were stable (m.p: 68^0C to 85^0C) and cycloaddition reactions were performed with dipolarophiles in 1:1 ratio. We have observed in ball-milling procedure, slight heat and pressure is developed in the reaction vessel. In our study, best results have been obtained when 1:1 ratio of starting materials were used but we have also observed incomplete conversion to molecules when tried with different (1:2 and 2:1) ratios of starting materials. We added sodium bicarbonate in the reaction mixture in the synthesis of fluoro nitrones because we had observed that it could activate the *N*-substitutedhydroxylamines. The probable reason could be due to the addition of sodium bicarbonate the reaction mixture becomes faintly alkaline and the liberated HCl is neutralized.

In mechanochemistry, the development of nitrone has been found to be fast and therefore it becomes easy for conducting *in situ* cycloaddition reactions if researchers desire so. But in our study, we wanted to study the stability and characterize the fluoro nitrones; therefore, we had conducted intermolecular cycloaddition reactions of the fluoro nitrones with various activated double bonded dipolarophiles (maleimides) as well as electron deficient dipolarophiles (alkynes) respectively. After successful study using various reaction conditions and trials, finally we decided to run the cycloaddition reactions in ball-milling process at a frequency of 40-70Hz and found excellent development of fluoro isoxazolidine and isoxazoline derivatives in 5-7 minutes of ball-milling. The yields of fluoro cycloadducts using mechanochemical procedure were also compared (Table **1** & **2**) with "microwave irradiation" (MWI) technique under solvent-free conditions [23,24]. Microwave methodology, for the synthesis of fluoro nitrones and fluoro isoxazolidines required high temperature (120-130^0C) and average time required for the synthesis of fluoro nitrones and fluoro isoxazolidines were found to be 40 – 60 minutes respectively and yields of fluoro isoxazolidine & isoxazolines were found to be 75-80% which was regarded as poor in comparison with ball-milling process.

^{1}H MR spectroscopy technique was mainly used for the confirmation of the structures of newly synthesized molecules (fluoro isoxazolidine & isoxazoline derivatives) and fluoro nitrones [25,26,27]. In addition, ^{13}C NMR, Mass (MS) & IR spectroscopic techniques also have been used successfully. ^{1}H NMR spectrum of the fluoro isoxazolidine and isoxazoline derivatives (2-7 & 8-13) reveals that the structures are expected to be symmetrical in nature. Nitrone 1(a, b &c) exists exclusively in *Z* configuration and *syn* cycloadducts are believed to develop from *Z* nitrone via an *exo* transition state geometry. While comparing *exo* vs *endo* transition state as intermediates in our cycloaddition reactions, we have observed that in the *endo* transition state, substituents on the dipolarophile may experience unfavorable steric interactions with the substituents of 1,3-dipole. These interactions will increase the activation energy if the cycloaddition reaction proceeds through *endo* pathway. On the other hand, the *exo* transition state avoids these steric interactions, as the substituent of the 1,3-dipole is pointing away from the larger ring system and thus leading to a lower activation energy as well as faster reaction rate. Also, secondary orbital interactions are not as prominent in the *exo* transition state like *endo* and often make it the more favorable pathway. Though we have not studied DFT study regarding this issue but literature shows computational studies using density functional theory (DFT) often show that the activation energy for the *exo* transition state is lower than that of the *endo* transition state, which is very much consistent with our experimental observations. The configurations of C_3, C_4, C_5 protons of the fluoro isoxazolidines are expected to be *syn* in nature because the coupling constant ($J \sim 2.00$-3.00Hz, for C_4-C_5 & $J \sim 2.00$-3.00 Hz, for C_3-C_4) values are in good agreement with reported values in our previously published research articles and in literature [25,26,28] as well. Therefore, we may assume from these *J* values that the dipolarophiles with *syn* configuration produced *syn* fluoro cycloadducts and the addition of fluoro nitrones to electron rich alkenes (maleimides) are stereospecifically *syn* in nature. In maleimide cycloadducts, 3-H, 4-H protons are *syn* orientated and are *enantioselective* in nature. The coupling constant (*J*) values of 3-H, 4-H protons ($J_{3,4} \sim 2.00$ Hz) [25,26,29] are also in good agreement in favour of *cis* oriented structure. Due to the absence of 4-H protons, in case of fluoro isoxazoline derivatives, exact geometry could not be determined.

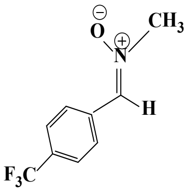
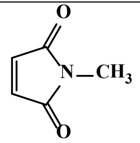
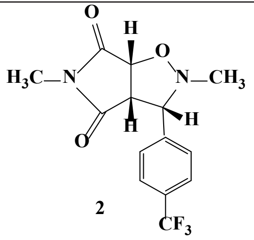
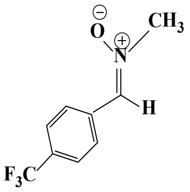
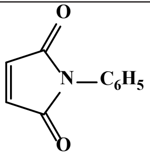
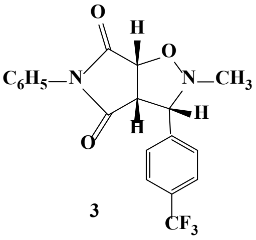
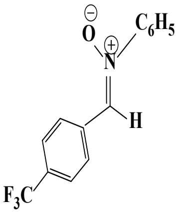
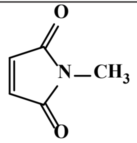
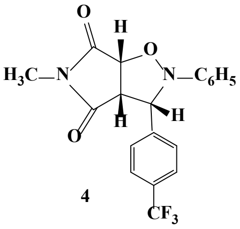
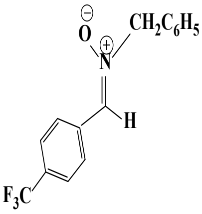
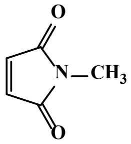
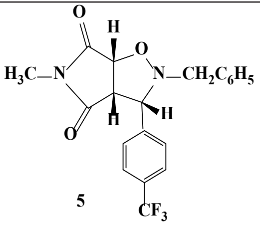
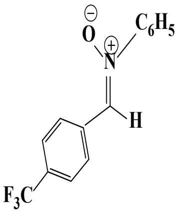
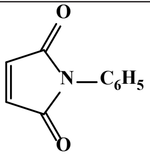
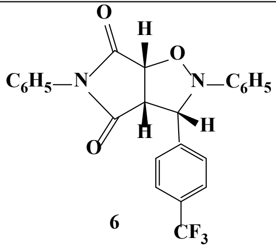
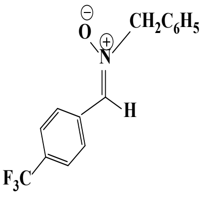
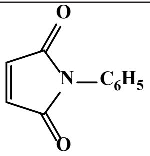
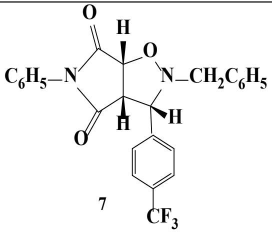
We have observed and obtained expected fragmentation peaks in the mass spectrum including molecular ion (M^+) and base peaks (BP) in all the fluoro isoxazolidine derivatives. In case of fluoro isoxazoline derivatives in addition to M^+ other prominent peaks are also obtained. This is due



Scheme 1: Pathway - I : Synthesis of *N*-Substituted-4-(Trifluoromethyl)-*C*-phenyl fluoro nitrones (1)
Pathway - II : Synthesis of *N*-Substituted-4-(Trifluoromethyl)-*C*-phenyl fluoro isoxazolidines (2-7)
Pathway - III : Synthesis of *N*-Substituted-4-(Trifluoromethyl)-*C*-phenyl fluoro isoxazolidines (8-13)

Bhaskar Chakraborty & Sushma Tamang Pradhan (2025) Mechanochemical Synthesis and Potential Anticancer Activities of Fluoro Isoxazolidine & Isoxazoline Derivatives Derived from N-Substituted-4-(Trifluoromethyl)-C-Phenyl Nitrones. World J Multidiscip Res Rev, 3(2);01-08.*

Table 1: Synthesis of new *N*-substituted-4-(*Trifluoromethyl*)-*C-phenyl-isoxazolidine* derivatives (2-7).

Entry	Nitrone (1)	Dipolarophile[a]	Time (min)	Cycloadduct[b] (2-7)	ee[c]	Yield[d] (%)
1			5 (40)	 2	90	95 (82)
2			5 (45)	 3	88	94 (80)
3			6 (45)	 4	83	93 (76)
4			5 (40)	 5	83	92 (76)
5			6 (45)	 6	84	91(70)
6			5 (50)	 7	84	91 (68)

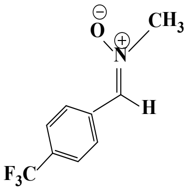
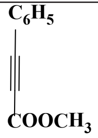
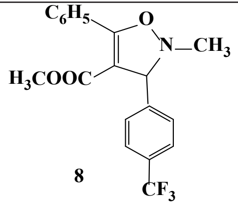
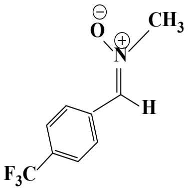
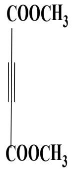
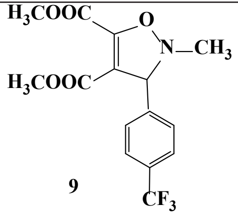
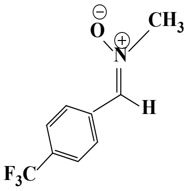
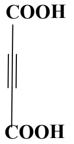
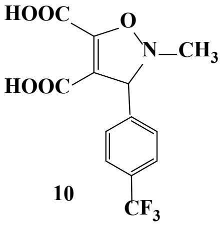
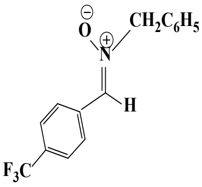
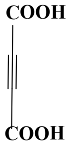
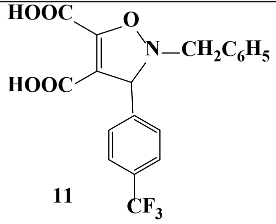
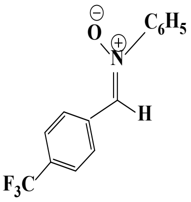
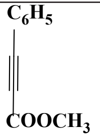
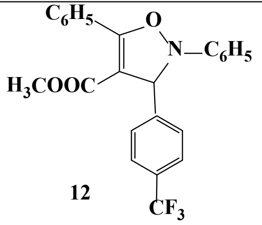
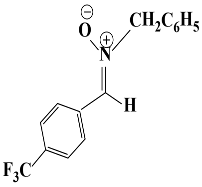
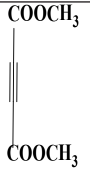
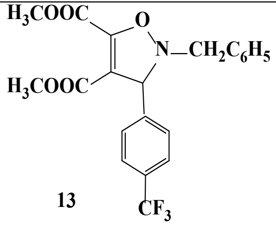
[a] Reaction conditions: nitrone (1 mmol), dipolarophiles (1 equivalent), ball-milling, (40-70Hz)

[b] All products were characterized by IR, ^{1}H NMR, ^{13}C NMR and MS spectral data.

[c] Enantiomeric excess.

[d] Isolated yield after purification. Figures in parentheses indicate yields obtained under MWI.

Table 2: Synthesis of new *N-substituted-4-(Trifluoromethyl)-C-phenyl-isoxazoline* derivatives (8-13).

Entry	Nitrone (1)	Dipolarophile[a]	Time(min)	Cycloadduct[c] (8-13)	ee[c]	Yield[d] (%)
1			6 (50)	 8	NA	95 (82)
2			6 (50)	 9	NA	94 (80)
3			7 (55)	 10	NA	93 (76)
4			6 (60)	 11	NA	92 (78)
5			6 (60)	 12	NA	91(70)
6			7 (60)	 13	NA	90 (68)

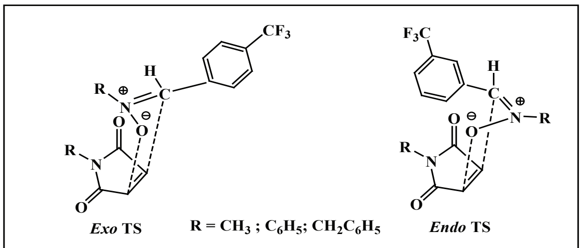
[a]Reaction conditions: nitrone (1 mmol), dipolarophiles (1 equivalent), ball-milling, (40-70Hz)

[b]All products were characterized by IR,^{1}H NMR, ^{13}C NMR and MS spectral data.

[c]Enantiomeric excess; [d]Isolated yield after purification. Figures in parentheses indicate yields obtained under MWI.

Table 3: IC_{50} values (μM) of various *fluoro isoxazolidine* and *isoxazoline* derivatives.

Compound (μg mL^{-1})	HeLa (Cervical)	MDA-MB-231 (Breast)	MCF-7 (Breast)	A549 (Lung cancer)
2	98	85	97	95
3	55	93	82	56
4	84	94	60	80
5	38	80	32	18
8	73	67	48	20
9	60	08	42	17
Doxorubicin (Standard)	0.8	2.00	0.4	0.6
Epirubicin	1.1	1.48	0.7	0.3



Exo/endo approach of the nitrone 1 to the maleimides in cycloaddition reactions

the fragmentations of $COOCH_3$, Ph and COOH groups respectively which subsequently undergoes development of *aziridine* derivatives. Though we have not studied theoretical concepts and studies on fluoro nitrones and fluoro-cycloadducts but recent studies by B. Rachid and coworkers [30] reveals that "*Conceptual Density Function Theory*" (CDFT) calculations favours *exo* isoxazolidines compared to *endo* isoxazolidines as *exo* approach is kinetically and thermodynamically more favoured. While studying ^1H NMR of the fluoro isoxazolidine and isoxazoline derivatives we have obtained almost correct peaks as expected in specified low and high field zones of the spectrum but in case of ^{13}C NMR spectrum of many new molecules we have not obtained markings of the absorptions of couplings of C and F atoms though we have received signals in the spectrum which is in between 100 – 119 MHz. It could be due to very weak couplings of Carbon and Fluorine atoms.

Biology (Anticancer study)

Majority of the newly synthesized isoxazolidine & isoxazoline derivatives have been screened for cancer studies [12,31] as their probability to act as *anticancer drugs* are very high. Cytotoxicity of the compounds were determined on the basis of measurement of *in vitro* growth inhibition of tumor cell lines [31,32], *viz* A549 derived from human alveolar adenocarcinoma epithelial cells (ATCC No.CCL-180), HeLa derived from human cervical cancer cells (ATCC No. CCL-14), MDA-MB-167 derived from human breast adenocarcinoma cells (ATCC No. HTB-35) and MCF7 derived from human breast adenocarcinoma cells (ATCC No. HTB-40) respectively using the MTT assay. The IC_{50} values (50% inhibitory concentration in μM) are expressed as the average of two independent experiments. The effect of cycloadducts (**2-13**) on the growth of cancer cell lines were determined following the general procedure used by the National Cancer Institute for *in vitro* anticancer drug study. The procedure uses the protein-binding dye Sulphorhodamine B for the estimation of cell growth [33,34]. In due course of time, the growth of the cells was counted (95 cells per well in 100 mL medium) in 90 microtitre plates. The study has been conducted keeping the cells for incubation for 40 hrs at 20^0C. The experimental set-up of three different wells was conducted where the cells were kept for 36 hrs. This was followed by reacting the cells with 30% cold (5-10^0C) TCA. It was left for 2 hrs at 20^0C and then washed, dried in air. All the cells were stained with Sulphorhodamine B dye. The dye was dissolved in tris-buffer solution. The plates under study were taken in shaker and kept for 20-30 minutes. The cell growth was calculated using optical density (OD) study and the results were reported in terms of IC_{50} values. Doxorubicin was considered as standard reference. One more standard reference Epirubicin has been recently tried in comparing with anti-cancer activities of our molecules (Table **3**). Since studies are going on we shall be able to try with other references in due course of time. The reported results are preliminary information's only.

From the study of IC_{50} values, it has been found that six (6) newly synthesized cycloadducts showed significant cytotoxicity against human alveolar adenocarcinoma epithelial cells, human cervical cancer cells, human breast adenocarcinoma cells and human breast adenocarcinoma cells respectively. Among all the tested cycloadducts (**2-13**), **2** & **4** showed comparatively more potent IC_{50} value against (ATCC No.CCL-180), HeLa derived from human cervical cancer cells (ATCC No. CCL-14), MDA-MB-167 derived from human breast adenocarcinoma cells (ATCC No. HTB-35) and MCF7 derived from human breast adenocarcinoma cells (ATCC No. HTB-40) as compared to other fluoro cycloadducts. Based upon the study, two most potent fluoro isoxazolidine derivatives **2** and **4** were taken for cell cycle analysis. The isoxazolidine derivative **4** has also found to exhibit concentration dependent inhibitory activity against NF-kB (nuclear factor kappa-light-chain-enhancer of activated B-cells), p65 with 55% inhibition in 24 hr at 10 μM. Phenyl substituted and methyl substituted O-N five membered heterocycles are capable of producing free radical faster and phenyl radicals are involved in polycyclic aromatic hydrocarbons which are known as carcinogens. Methyl radicals are capable of damaging DNA and promote cancer development. Based on this known facts, we have chosen fluoro isoxazolidine derivatives **2** and **4** for cell cycle analysis. The process is going on at present.

Experimental Data

Unless otherwise stated, all reagents were obtained from commercial sources and used without further purification. Progress of all the reactions were monitored by TLC using 0.25 mm silica gel plates (Merck $60F_{254}$, UV indicator). Column chromatography was performed with silica gel (E. Merck, Germany) with 60–200 mesh. All other reagents and solvents were purified before starting reactions or column chromatography. ^1H NMR spectra were recorded on a Bruker DRX 300 (300 Hz) spectrometer at ambient temperature.^{13}C NMR spectra were recorded on a Bruker DRX 300 (75 Hz) spectrometer at ambient temperature. The coupling constants (*J*) were expressed in Hz. Infra-red spectra were recorded on a Perkin-Elmer RX 1-881 machine as a film or KBr pellets. Mass-spectrometry data was recorded using a Joel SX-102 (FAB). The ball mill used was a Retsch MM500 mixer mill digital GmbH, 42781Haan, Germany. All the reactions were carried out using stainless steel jars in a 25 mL steel vessel and 15 mm diameter balls which were purchased from Retsch, Germany.

General procedure 1– General procedure for the synthesis of *N*-substituted-4-(Trifluoromethyl)-*C*- phenyl nitrone (1a) in ball-milling procedure

N-methylhydroxylamine hydrochloride (1 mmol), 4-(Trifluoromethyl) benzaldehyde (1 equivalent), and $NaHCO_3$ (1.0 equivalent) were mixed together and ball-milled at 40 Hz for 5 min. After the completion of reaction, the reaction mixture was taken in CH_2Cl_2. It was filtered on cotton for the removal of NaCl. The filtrate was evaporated under vacuum to afford *N*-methyl-4-(Trifluoromethyl)-*C*- phenyl nitrone **1a** as yellowish white crystalline solid with high purity (90%, m.p; 74^0 C). Same methodology was used for the synthesis of other fluoro nitrones (**1b** & **1c**).

1a: *N*-methyl-4-(Trifluoromethyl)-*C*- phenyl nitrone

Spectroscopic data for nitrone 1a: White crystals. M.P: 74^0C. UV λ_{max} 235 nm; IR (KBr): υ_{max} 3030 (m), 2230 (m), 1680 (m), 1620 (s), 1440 (m), 1150 (m), 786 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.58-7.20 (m, 4H, phenyl protons), 2.34 (s, 3H, CH_3), 1.55 (s, 1H, -$CH=N^+$); ^{13}CNMR ($CDCl_3$): δ 142.1 ($CH=N^+$), 134.8, 134.3, 134.1, 133.9 (phenyl carbons), 30.5 (CH_3), 24.5 (CF_3); Calculated for $C_9H_8F_3ON$: C 52.42, H 3.88, N 6.79%; Found: C 52.37, H 3.80, N 6.64%.

1b: *N*-benzyl-4-(Trifluoromethyl)-*C*- phenyl nitrone

Spectroscopic data for nitrone **1b:** White crystals. M.P: 82^0C. UV λ_{max} 234nm; IR (KBr): υ_{max} 3010 (m), 2215 (m), 1670 (m), 1625 (s), 1430 (m), 782 (s) cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 7.90-7.40 (m, 5H), 7.39-6.96 (m, 4H), 3.36 (s, 2H, CH$_2$Ph), 1.48 (s, 1H, -CH=N$^+$); ^{13}CNMR (CDCl$_3$): δ 143.0 (CH=N$^+$), 134.7, 133.8, 133.5, 133.2 (C-phenyl carbons), 130.6, 130.4, 130.3, 129.8, 128.7 (phenyl carbons of benzyl group), 26.0 (CF$_3$), 24.1 (CH$_2$Ph); Calculated for C$_{15}$H$_{12}$F$_3$ON: C 64.28, H 4.28, N 5.00%; Found: C 64.17, H 4.15, N 4.86%.

1c: *N*-phenyl-4-(Trifluoromethyl)-*C*- phenyl nitrone

Spectroscopic data for nitrone **1c:** White crystals. M.P: 88^{0}C. UV λ_{max} 238nm; IR (KBr): υ_{max} 3036 (m), 2220 (m), 1660 (m), 1635 (s), 1436 (m), 1200 (m), 780 (s) cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 7.82-7.20 (m, 5H & m, 4H merged signals of phenyl ring protons), 1.78 (s, 1H, -CH=N$^+$); ^{13}CNMR (CDCl$_3$): δ 141.8 (CH=N$^+$), 137.6, 137.4, 137.2, 136.9, 134.5, 134.4, 134. 1, 133.9, 133.7 (two phenyl carbons), 26.5 (CF$_3$); Calculated for C$_{14}$H$_{10}$F$_3$ON: C 62.04, H 3.73, N 5.22%; Found: C 61.90, H 3.66, N 5.16%.

2 General procedure II–Mechanochemical syntheses of fluoro isoxazolidine & isoxazolidine derivatives from *N*-substituted-4-(Trifluoromethyl)-*C*- phenyl nitrone (1) (Table 1; entry 1)

N-methyl-4-(Trifluoromethyl)-*C*-phenyl nitrone (**1a**; 1 equivalent), *N*-methyl maleimide (1 equivalent) and NaHCO$_3$ (1 equivalent) were mixed together and ball-milled at 40 Hz for 5 min. After the completion of reaction, the reaction mixture was taken in CH$_2$Cl$_2$. It was filtered on cotton for the removal of NaCl. The filtrate was evaporated under vacuum to afford crude fluoro isoxazolidine derivative as white crystals (95%). The crude product was directly charged on silica gel column and eluted with a mixture of ethyl acetate: *n*-hexane (1:8) resulting pure isoxazolidine **2** (entry **1**, Table **1, Scheme 1**). Same methodology was adopted for the synthesis of other fluoro isoxazolidine & isoxazoline derivatives (**3-13).**

(3*S*)-2-methyl-3-(4-trifluoromethyl)-dihydro-5-methyl-2*H*-pyrrolo[3,4-*d*]isoxazole-4,6(5*H*,6a-*H*)-dione, 2

White crystals. M.P 126^{0}C; Yield 95%; R$_f$= 0.62; IR (KBr): υ_{max} 3310 (m), 2940 (m), 2830 (m), 1760 (s), 1670 (s), 1485 (m), 1320 (m), 780 (s) cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 7.76 – 7.28 (m, 4H, aromatic protons), 6.38 (d, 1H, *J* = 2.00 Hz, C$_5$H), 6.34 (d, 1H, *J* = 2.00 Hz, C$_3$H), 3.40 (s, 6H, 2XCH$_3$), 2.24 (dd, 1H, *J* = 2.00, 2.00 Hz, C$_4$H); ^{13}C NMR (CDCl$_3$): δ 169.0 (carbonyl carbons), 138.4, 138.1, 137.2, 131.4, 130.8. 128.1 (aromatic carbons carbons), 85.4 (C$_5$), 76.8 (C$_3$), 62.2 (C$_4$), 30.2, 28.0 (CH$_3$ carbons), 24.5 (CF$_3$); FAB-MS: *m/z* 314 (M^{+}), 245, 169 (BP, 100%), 145, 69; Calculated for C$_{14}$H$_{13}$F$_3$O$_3$N$_2$: C 53.48, H 4.16, N 8.91%; Found: C 53.34, H 4.06, N 8.70%.

(3*S*)-2-phenyl-3-(4-trifluoromethyl)-dihydro-5-methyl-2*H*-pyrrolo[3,4-*d*]isoxazole-4,6(5*H*,6a-*H*)-dione, 3

White solid. M.P 140^{0}C; Yield 92%; R$_f$= 0.60; IR (KBr): υ_{max} 3236 (m), 2980 (m), 2775 (m), 1760 (s), 1685 (s), 1440 (s), 1262 (m), 784 (s) cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 7.68 – 7.20 (m, 5H; m, 4H merged signals of phenyl ring protons), 6.42 (d, 1H, *J* = 2.10 Hz, C$_5$H), 6.36 (d, 1H, *J* = 2.10 Hz, C$_3$H), 3.36 (s, 3H, N-CH$_3$), 2.34 (dd, 1H, *J* = 2.00, 2.00 Hz, C$_4$H); ^{13}C NMR (CDCl$_3$): δ 170.5, 170.0 (carbonyl carbons), 134.6, 134.3, 134.2, 134.0, 130. 4, 130.2, 129.0, 128.5, 128.3, 127.4 (phenyl carbons), 85.5 (C$_5$), 77.5 (C$_3$), 61.0 (C$_4$), 28.3 (N-CH$_3$), 23.5 (CF$_3$); FAB-MS: *m/z* 376 (M$^+$),361, 307, 299, 231 (BP, 100%), 231, 77, 69; Calculated for C$_{19}$H$_{15}$F$_3$O$_3$N$_2$: C 60.14, H 3.98, N 7.38%; Found: C 60.02, H 3.85, N 7.27%.

(3*S*)-2-methyl-3-(4-trifluoromethyl)-dihydro-5-phenyl-2*H*-pyrrolo[3,4-*d*]isoxazole-4,6(5*H*,6a-*H*)-dione, 4

White crystals. M.P 136^{0}C; Yield 91%; R$_f$= 0.58; IR (KBr): υ_{max} 3230 (m), 2975 (m), 2770 (m), 1760 (s), 1680 (s), 1440 (s), 1260 (m), 780 (s) cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 7.68 – 7.20 (m, 5H; m, 4H merged signals of phenyl ring protons), 6.42 (d, 1H, *J* = 2.10 Hz, C$_5$H), 6.36 (d, 1H, *J* = 2.10 Hz, C$_3$H), 3.36 (s, 3H, N-CH$_3$), 2.34 (dd, 1H, *J* = 2.00, 2.00 Hz, C$_4$H); ^{13}C NMR (CDCl$_3$): δ 170.5, 170.0 (carbonyl carbons), 134.6, 134.3, 134.2, 134.0, 130. 4, 130.2, 129.0, 128.5, 128.3, 127.4 (phenyl carbons), 85.0 (C$_5$), 76.5 (C$_3$), 60.0 (C$_4$), 28.5 (N-CH$_3$), 23.0 (CF$_3$); FAB-MS: *m/z* 376 (M$^+$),361, 307, 299, 231 (BP, 100%), 231, 77, 69; Calculated for C$_{19}$H$_{15}$F$_3$O$_3$N$_2$: C 60.14, H 3.98, N 7.38%; Found: C 60.05, H 3.70, N 7.20%.

(3*S*)-2-methyl-3-(4-trifluoromethyl)-dihydro-5-benzyl-2*H*-pyrrolo[3,4-*d*]isoxazole-4,6(5*H*,6a-*H*)-dione, 5

White solid. Yield 92%; R$_f$= 0.60; IR (KBr): υ_{max} 3310(m), 2910 (m), 2840 (m), 1765 (s), 1678 (s), 1460 (s), 1330 (m), 785 (s) cm^{-1};^{1}H NMR (CDCl$_3$): δ 7.67 – 7.23 (m, 5H & m, 4H,merged phenyl ring protons), 6.42 (d, 1H, *J* = 2.00 Hz, C$_5$H), 6.24 (d, 1H, *J* = 2.00 Hz, C$_3$H), 3.38 (s, 3H, N-CH$_3$), 2.38 (dd, 1H, *J* = 2.00, 2.00 Hz, C$_4$H), 1.20 (s,2H, CH$_2$); ^{13}C NMR (CDCl$_3$): δ 170.0, 168.2 (carbonyl carbons), 138.0, 137.8, 137.2, 136.8, 130.5, 130.1, 129.8, 127.6, 126.3 (phenyl carbons), 80.1 (C$_5$), 77.2 (C$_3$), 60.2 (C$_4$), 28.5 (N-CH$_3$), 25.0 (CF$_3$), 22.5 (CH$_2$); FAB-MS: *m/z* 390 (M$^+$),284, 245 (BP, 100%), 145, 106, 91, 77; Calculated for C$_{20}$H$_{17}$O$_3$F$_3$N$_2$: C 61.51%, H 4.39%, N 7.18%. Found C 61.32%, H 4.26%, N 7.04%.

(3*S*)-2-phenyl-3-(4-trifluoromethyl)-dihydro-5-phenyl-2*H*-pyrrolo[3,4-*d*]isoxazole-4,6(5*H*,6a-*H*)-dione, 6

Yellow solid. M.P 117^{0}C; Yield 91%; R$_f$= 0.66; IR (KBr): υ_{max} 3250 (m), 2960 (m), 2835 (m), 1760 (s), 1685 (s), 1460 (s), 1360 (m), 782 (s) cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 7.68 – 7.20 (m, 2x5H; m, 4H, merged phenyl ring protons), 6.42 (d, 1H, *J* = 2.00 Hz, C$_5$H), 6.24 (d, 1H, *J* = 2.00 Hz, C$_3$H), 2.34 (dd, 1H, *J* = 2.00, 2.00 Hz, C$_4$H); ^{13}C NMR (CDCl$_3$): δ 170.2, 169.5 (carbonyl carbons), 135.9, 135.7, 135.3, 135.0, 134.8, 134.0, 133.7, 133.4, 133.2, 132.7, 131.6, 131.3, 130.2, 129.5, 128.4, 128.1 (phenyl ring carbons), 82.6 (C$_5$), 75.6 (C$_3$), 55.5 (C$_4$), 24.0 (CF$_3$); FAB-MS: *m/z* 441 (M$^+$), 364, 287, 256 (BP,100%), 145, 77; Calculated for C$_{24}$H$_{17}$F$_3$O$_3$N$_2$: C 65.02, H 3.88, N 6.35%; Found : C 64.90, H 3.66, N 6.13%.

(3*S*)-2-benzyl-3-(4-trifluoromethyl)-dihydro-5-phenyl-2*H*-pyrrolo[3,4-*d*]isoxazole-4,6(5*H*,6a-*H*)-dione, 7

Brown crystals. M.P 108^{0}C; Yield 91%; R$_f$= 0.60; IR (KBr): υ_{max} 3240 (m), 2940 (m), 2830 (m), 1760 (s), 1680 (s), 1462 (s), 1366 (m), 786 (s) cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 7.76 – 7.20 (m, 2x5H; m, 4H, merged phenyl ring protons), 6.40 (d, 1H, *J* = 2.00 Hz, C$_5$H), 6.32 (d, 1H, *J* = 2.00 Hz, C$_3$H), 2.34 (dd, 1H, *J* = 2.00, 2.00 Hz, C$_4$H), 1.24 (s, 2H, CH$_2$); ^{13}C NMR (CDCl$_3$): δ 171.3, 168.5 (carbonyl carbons), 136.8, 135.8, 135.3, 135.1, 134.8, 134.2, 133.7, 133.2, 133.0, 132.4, 131.9, 131.3, 130.2, 128.5, 128.4, 128.0 (phenyl ring carbons), 80.5 (C$_5$), 74.6 (C$_3$), 57.5 (C$_4$), 26.0 (CH$_2$), 24.0 (CF$_3$); FAB-MS: *m/z* 455 (M$^+$), 364, 287, 219 (BP,100%), 145, 91, 77; Calculated for C$_{25}$H$_{19}$F$_3$O$_3$N$_2$: C 65.93, H 4.18, N 6.15%; Found : C 65.75, H 4.06, N 6.05%.

(*S*)-methyl-2-methyl-3-(4-trifluoromethyl)-2,3-dihydro-5-phenylisoxazole-4-carboxylate, 8

Red thick liquid. Yield 91%; R$_f$= 0.70; IR (KBr): υ_{max} 3380 (m), 2250 (m), 1760 (s), 1700 (s), 1680 (s),14820(s),1210 (s), 780 (s) cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 7.80 – 7.30 (m, 5H), 7.30-7.20 (m, 4H), 3.88 (s, 3H, -COOCH$_3$), 2.64 (s, 3H, N-CH$_3$), 1.26 (s, 1H, C$_3$H); ^{13}C NMR (CDCl$_3$): δ 170.0 (-$\underline{\text{CO}}$OCH$_3$), 138.4, 138.0, 137.4 137.1, 136.4, 136.3, 135.7, 135.2 (phenyl carbons), 90.0 (C$_5$), 79.4 (C$_3$), 63.0 (C$_4$), 30.0 (-COO$\underline{\text{CH}_3}$), 26.2 (N-CH$_3$), 24.0 (CF$_3$); FAB - MS (*m/z*): 363 (M$^+$), 304, 286, 218 (BP), 145, 77, 59; Calculated for C$_{19}$H$_{16}$F$_3$O$_3$N: C 62.27, H 4.40, N 3.82%; Found : C 62.13, H 4.10, N 3.66%.

(*S*)-dimethyl-2-methyl-3-(4-trifluoromethyl)-2,3-dihydroisoxazole-4,5-dicarboxylate, 9

Red liquid. Yield 92%; R$_f$= 0.60; IR (KBr): υ_{max} 3290 (m), 2180 (m), 1740 (s), 1670 (s), 1620 (s), 1260 (s), 870 (m), 776 (s) cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 7.76 – 7.24 (m, 4H, phenyl protons), 3.84 (s, 6H, 2X -COOCH$_3$), 1.84 (s, 3H, N-CH$_3$), 1.28 (s, 1H, C$_3$H); ^{13}C NMR (CDCl$_3$): δ 172.0, 170.0 (-$\underline{\text{CO}}$OCH$_3$, carbonyl carbons of the ester group), 134.0, 133.4, 130.0, 129.5, 79.0 (C$_5$H), 66.5 (C$_3$H), 54.5 (C$_4$H), 32.0 (N-CH$_3$), 26.5 (CF$_3$); FAB - MS (*m/z*): 345 (M$^+$), 330, 296, 200 (BP), 145, 59; Calculated for C$_{15}$H$_{14}$F$_3$O$_5$N: C 51.72, H 4.02, N 4.12%; Found : C 51.60, H 3.90, N 3.97%.

10. (*S*)-2-methyl-3-(3-trifluoromethyl)-2,3-dihydroisoxazole-4,5-dicarboxylic acid, 10

Colourless thick liquid. Yield 91%; R$_f$= 0.64; IR (KBr): υ_{max} 3180 (m), 2990 (br), 1760 (s), 1485 (s), 1360 (s), 1210 (s), 790 (s) cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 10.00 (s, 2H, 2XCOOH), 7.68 – 7.40 (m, 4H, phenyl protons), 2.36 (s, 1H, C$_3$H), 1.24 (s,3H, N-CH$_3$); ^{13}C NMR (CDCl$_3$): δ 173.2, 172.5 (carboxyl carbons), 138.5, 137.0, 135.0, 134.5, 130. 0 (phenyl carbons), 79.5 (C$_5$), 56.0 (C$_3$), 46.8 (C$_4$), 28.0 (N-CH$_3$ carbon), 25.0 (CF$_3$); FAB - MS (*m/z*): 317 (M$^+$), 302, 272, 172 (BP), 145, 45; Calculated for C$_{13}$H$_{10}$F$_3$O$_5$N: C 48.74, H 3.14, N 4.37%; Found: C 48.58, H 3.07, N 4.18%.

11. (*S*)-2-benzyl-3-(3-trifluoromethyl)-2,3-dihydroisoxazole-4,5-dicarboxylic acid, 11

Colourless thick liquid. Yield 90%; R$_f$= 0.68; IR (KBr): υ_{max} 3280 (m), 2980 (br), 1760 (s), 1485 (s), 1350 (s), 1220 (s), 780 (s) cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 10.02 (s, 2H, 2XCOOH), 7.70 – 7.20 (m, 5H & m, 4H, merged phenyl protons), 2.36 (s,1H, C$_3$H), 1.26 (s,2H, CH$_2$); ^{13}C NMR (CDCl$_3$): δ 170.0, 160.0 (carboxyl carbons), 137.5, 137.0, 136.5, 135.5, 135.0, 134.0, 133.5, 130.0, 128.5 (phenyl carbons), 77.0 (C$_5$), 64.0 (C$_3$), 54.0 (C$_4$), 29.0 (CH$_2$ carbon), 27.0 (CF$_3$); FAB - MS (*m/z*): 396 (M$^+$), 305, 160 (BP), 145, 91,

Bhaskar Chakraborty & Sushma Tamang Pradhan (2025) Mechanochemical Synthesis and Potential Anticancer Activities of Fluoro Isoxazolidine & Isoxazoline Derivatives Derived from N-Substituted-4-(Trifluoromethyl)-C-Phenyl Nitrones. World J Multidiscip Res Rev, 3(2);01-08.*

77; Calculated for $C_{19}H_{14}F_3O_5N$: C 57.57, H 3.53, N 3.53%; Found : C 57.450, H 3.40, N 3.34%.

12. (*S*)-2-phenyl-3-(4-trifluoromethyl)-2,3-dihydro-5-phenylisoxazole-4-carboxylate, 12

Red thick liquid. Yield 92%; R_f = 0.66; IR (KBr): υ_{max} 3230 (m), 2240 (m), 1740 (s), 1715 (s), 1680 (s), 1320 (s), 780 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.87 – 7.40 (m, 2x5H, phenyl protons), 7.39-7.20 (m, 4H, phenyl protons), 3.86 (s, 3H, $-COOCH_3$), 1.25 (s,1H, C_3H); ^{13}C NMR ($CDCl_3$): δ 168.5 ($-\underline{CO}OCH_3$), 137.0, 136.0, 135.0, 134.3, 134.00, 132.0, 131.0, 130.5, 127.0, 126.5, 125.0, 123.7 (phenyl carbons), 82.5 (C_5), 66.0 (C_3), 55.0 (C_4), 31.0 ($-COO\underline{CH_3}$), 28.0 (CF_3); FAB - MS (*m/z*): 425 (M^+), 348, 280 (BP), 271, 154, 77; Calculated for $C_{24}H_{18}F_3O_3N$: C 67.28, H 4.20, N 3.27%; Found : C 67.07, H 4.05, N 3.13%.

13. (*S*)-dimethyl-2-benzyl-3-(4-trifluoromethyl)-) 2,3-dihydroisoxazole-4,5-dicarboxylate, 13

Yellow liquid. Yield 91%; R_f = 0.70; IR (KBr): υ_{max} 3310 (m), 2190(m), 1740 (s), 1680 (s), 1660 (s), 1440 (s), 1265(s), 1220 (s), 788 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.68 – 7.30 (m, 5H & m, 4H, merged signals of phenyl protons), 3.88 (s, br, 2X3H, $-COOCH_3$), 1.70 (s, 3H, C_3H), 1.25 (s,2H, CH_2); ^{13}C NMR ($CDCl_3$): δ 172.0, 162.0 ($-\underline{CO}OCH_3$, carbonyl carbons of the ester group), 136.0, 134.0 133.5, 133.0, 132.5, 131.5, 130.0 129.0 (phenyl carbons), 82.5 (C_5), 74.0 (C_3), 58.0 (C_4), 29.0 (CH_2), 26.5 (CF_3) ; FAB - MS (*m/z*): 421 (M^+), 344, 330, 276 (BP), 91, 77; Calculated for $C_{21}H_{18}F_3O_5N$: C 59.43, H 4.24, N 3.30%; Found : C 59.26, H 4.10, N 3.15%.

Conclusion

We have adopted one of the most favourable green chemistry methodology (mechanochemistry: ball-milling) in a solid phase for the synthesis of few *N*-substituted-4-(Trifluoromethyl)-*C*-phenyl isoxazolidine and isoxazoline derivatives with excellent yields in a minimum time frame. We believe this simple, cost efficient and time saving methodology will be adopted by many more researchers in synthetic organic chemistry and medicinal chemistry. Finally, we have found promising *anticancer activities* in couple of newly synthesized fluoro isoxazolidines and we are hopeful in near future we shall be able to establish these molecules as "*anti-cancer drugs*" after proper applications of cancer screening.

Conflicts of interest: There are no conflicts to declare.

Data Statement: All data are available in the manuscript, Supplementary Information, and from the corresponding author upon request.

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