Greener synthesis of some new isoxazolidine and isoxazoline derivatives via 1,3-Dipolar cycloaddition reactions and studies of biological activities of the cycloadducts

A Thesis submitted to the University of North Bengal

For the Award of

Doctor of Philosophy
in
Chemistry

By

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July 2017

DECLARATION

I declare that the thesis entitled "*Greener synthesis of some new isoxazolidine and isoxazoline derivatives via 1,3-Dipolar cycloaddition reactions and studies of biological activities of the cycloadducts"* has been prepared by me under the guidance's of

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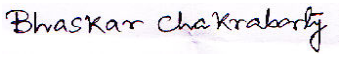
This is also to certify that the research work is *original and completely new*.

I wish him all the success in completion of his *Ph.D programme*.



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"This Ph.D dissertation is dedicated to ***Late Dr.***

Aloranjan Ghosh, *Department of Chemistry,*

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Preface

The nitrones may be regarded as a 3 centered dipolar 4π system, which enables 1,3-dipolar cycloaddition reactions with different dipolarophilic reagents to occur. 1,3-dipolar cycloadditions are susceptible to both electronic and steric influences. 1,3-dipolar cycloaddition reaction between a nitrone and an olefinic dipolarophile is an efficient method for the synthesis of isoxazolidine systems.

The question regarding reactivity and substituent effects in 1,3-dipolar cycloaddition reaction has been rationalized successfully using Fukui's *frontier molecular orbital theory* which provides relative interaction energies of frontier orbitals between 1,3-dipole and dipolarophiles. The electron attracting or electron releasing moiety influences the atomic orbital coefficients and has a significant influence on the regioselectivity of the reaction.

Further more, the cycloadducts (fluoro isoxazolidine, isoxazoline derivatives and bisisoxazolidine, bisisoxazoline derivatives) synthesized from fluoro nitrone and bisnitrones respectively have found numerous applications in synthesis through reductive cleavage of the N – O bond to give a variety of γ-amino alcohols and aziridine derivatives as well. In addition fluoro nitrones may be employed as a good oxidizing reagent in the synthesis of aldehydes and ketones. Asymmetric induction in nitrone olefin cycloaddition has been achieved through the incorporation of chirality in both the dipole and the dipolarophiles. *Greener approaches* in the synthesis and cycloaddition reactions have made this chemistry much more attractive nowadays. *Use of water* as the solvent has been found to *influence the rate, regioselectivity and stereoselectivity* in cycloaddition reactions remarkably.

The present dissertation entitled **"***Greener synthesis of some new isoxazolidine and isoxazoline derivatives via 1,3-Dipolar cycloaddition reactions and studies of biological activities of the cycloadducts***"** reports synthesis and 1,3-dipolar cycloaddition reactions of fluoro nitrone and two different variety of bisnitrones. The cycloaddition reactions have been executed with these nitrones and a variety of olefins and alkynes leading to the generation of regio and stereoselective cycloadducts and their further applications to synthetically more important molecules as well. Significant biological activity of the newly synthesized cycloadducts and aziridines has also been noticed.
The following chapters fulfill these ideas:-

Chapter I This chapter deals with the general theoretical approach and basic concepts of different kinds of 1,3-dipoles. The chapter also explains their stabilities and general nature of intra, inter molecular 1,3-dipolar cycloaddition reactions of nitrones. Special importance has been given on HOMO – LUMO approach in this regard. Attempts have been made in this chapter to cover a comprehensive review of the literature and latest developments up to March, 2017.

Chapter II This chapter deals with the most important experimental section. In this section, the method of synthesis of different bisnitrones (derived from glyoxal and terepthalaldehyde respectively) and fluoro nitrones has been discussed. 1,3-dipolar cycloaddition reactions of these nitrones with different olefins and alkynes have been studied using *green chemistry methodologies* like *aqueous phase synthesis, ionic liquid mediated synthesis* and *solvent less solid phase reactions* (*using microwave irradiations*). Some useful synthetic applications of the new cycloadducts have been also performed successfully for their conversion into the synthesis of *amino alcohols* and *aziridine derivatives* as well. This chapter also describes how fluoro nitrones may be utilized as an oxidizing reagent in the synthesis of aldehydes and ketones. The chapter also deals with *biological study* of the new cycloadducts.

Chapter III This chapter deals with results and discussion and the new achievements of the work done. Spectral interpretation *viz.* ^{1}H NMR, ^{13}C NMR, MS, IR, HRMS and elemental analysis has been discussed in detail for the confirmation of structures of the new molecules. The chapter also explains in detail how the stereoselectivity of the new cycloadducts have been assigned.

Chapter IV This chapter is focused on the future perspectives of the work done and also opens new dimensions of further research in this chemistry.

Acknowledgement

I would like to express deep regards and gratitude towards my supervisor Dr. Bhaskar Chakraborty, Associate Professor in Chemistry and Head of Department, Sikkim Government College, Gangtok who has been an integral part in shaping these four years in research into a unique and rewarding experience for me. Throughout the period of research work I have received expert criticism, valuable comment and above all his best loving care. His unique creativity has had a significant impact on my research, and his passion for his work has in turn provided me with a wealth of opportunities and for which I am highly grateful. I am also equally grateful to Dr. Pranab Ghosh, Professor of Chemistry, University of North Bengal for guiding me with his advices.

I am also fortunate that I could interact with faculty members at Department of Chemistry, University of North Bengal and Indian Association for the Cultivation of Science, Jadavpur over the course of my PhD career. My heartfelt thanks go to Prof. B. Basu and Dr. A.K Nanda, Department of Chemistry, University of North Bengal for their constructive ideas and for providing NMR spectra of some of the vital compounds related to my present work. I would also like thank Prof. B. C. Ranu and Prof. A. Dey of Indian Association for the Cultivation of Science, Jadavpur for their valuable suggestions relating to the research work. Thanks are also due to Dr. (Mrs.) Lily Alley Principal, Sikkim Government College, Tadong and also former principals of our institution viz, Dr. M. P Kharel, Dr. C. B. Sunwar for their enthusiastic support, constant co-operation and for providing research facilities. I am equally grateful to scientist in-charge, SAIF, CDRI, Lucknow for providing IR, NMR, MS Spectral data.

I would like to express my personal appreciation of the assistance given by Dr. Prawin Kumar Sharma Dr.Manjit Singh Chhetri, Dr. Saurav Kafley, Chiran Devi Sharma, Neelam Rai and Esmita Chhetri, Department of Chemistry, Sikkim Government College in this work. I am equally thankful to Prof. Amalesh Samanta of Jadavpur University, Kolkata for helping in finding out the biological aspects of the entire work. Without their support my research work would not have been completed.

I would also like to express my thanks to Mr. Denlock Lepcha, Mr.Bijay Prakash Rai, Mr. Royal Karthak, Mr. Arun Thapa, staff members of Chemistry Department, Sikkim Government College for their continuous support. I also would like to express my heartfelt thanks to Mrs. Malini Chakraborty for her continuous encouragement. Finally, I would like to express my deep gratitude towards my parents. Their affection ever encouraged me for the entire research work. Lastly, all the people who rendered valuable support in direct and indirect ways in bringing this research work to completion are sincerely acknowledged.

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Abstract

Introduction

Nitrones are known as versatile synthetic intermediates and excellent spin trapping reagents. They are prepared either by condensation of aldehyde and ketones with hydroxyl amines or by oxidation of the corresponding *N,N*-disubstitutedhydroxylamines[1]. The 1,3-dipolar cycloaddition reaction between a nitrone and an olefinic dipolarophile is an important method for the synthesis of the isoxazolidine ring system[2]. 1,3-dipolar cycloaddition reactions are an integral and weighty part of organic chemistry in pedagogy and research as well. The wealthy literature on cycloaddition reactions of nitrone and for the syntheses of novel isoxazolidine, isoxazoline derivatives and also their further applications has been widely illustrated. The 1,3-dipolar cycloaddition reaction has a singular capability of establishing large number of stereo-chemical centres in one synthetic step.

The present work entitled **"***Greener synthesis of some new isoxazolidine and isoxazoline derivatives via 1,3-Dipolar cycloaddition reactions and studies of biological activities of the cycloadducts***"** reports synthesis and cycloaddition reactions of two (2) different classes of nitrones viz, *N-Benzyl fluoro nitrone*[3] *& N-Phenyl/Methyl bisnitrones*[4] following *green chemistry* methodologies and their further applications. Evidence of stereoselectivity and regioselectivity was observed in the 1,3-dipolar cycloaddition reactions of *N-benzyl fluoro nitrone* with olefins and alkynes. Majority of these reactions have been carried out in ionic liquid, water and under microwave irradiation. High yield and short reaction time was the major advantage in these protocols of synthesis of *cycloadducts* (both fluoro isoxazolidine & isoxazoline derivatives and bisisoxazolidine & bisisoxazoline derivatives) compared with the reactions performed in conventional solvents[2]. *Bisisoxazoline derivatives* have been also successfully converted into synthetically more important *bisaziridine* derivatives[4]. This may be considered as one of most important applications in this chemistry. Fluoro isoxazoline derivatives have been successfully converted into 1,3-amino alcohols while fluro nitrones have been used as potential oxidizing reagents in the synthesis aldehyde and ketones[3]. Majority of the cycloadducts have been screened for biological activities and are found to have good to excellent potential biological activities[5].

General nature of cycloaddition reaction and review of earlier work

1,3-dipolar cycloaddition reactions of *nitrones* are not only regioselective but also stereoselective in nature. The relative configurations of C_3, C_4, C_5 (*chiral centres*) protons of the isoxazolidines are *syn* in most of the cases since most of the nitrones exist

exclusively in the *Z* configuration. Therefore the isoxazolidines are formed from *Z* nitrone through an *exo*-transition state geometry. The stereochemistry of the isoxazoline derivatives are difficult to assign due to the absence of hydrogen atoms at C_4, C_5 positions. The C-C bond of the isoxazolidine ring is more developed in the transition state then C-O bond. In 1,3-dipolar cycloaddition reaction of nitrone with olefins, the latter approaches the nitrone exclusively from the side opposite to the C_3-substituent. This approach controls stereochemistry at C_3 position.

A comprehensive review on nitrone cycloaddition reactions was conducted as a part of our present research work in this dissertation. This review work was conducted to understand the gravity of nitrone cycloaddition reactions and their applications, contributions to the fraternity of synthetic organic chemists. This review work also helped us to define and understand the work to be presented for this dissertation and especially how to reach the final target.

From the review work it has been found that in the majority of the publications nitrones are generated *in situ*. Because of their instability, 1,3-dipolar cycloaddition reactions are carried out mainly by trapping the nitrones with suitable dipolariphiles at the time of their synthesis. Dimerization of the nitrone can be controlled in this fashion and the yield of the cycloadducts is also extremely high.

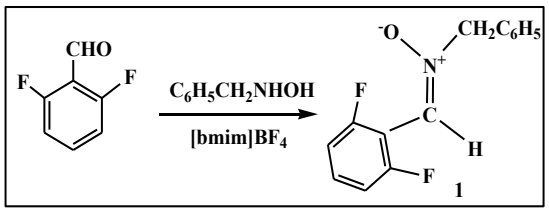
In this dissertation, for the synthesis and 1,3-dipolar cycloaddition reaction of nitones, we have employed the following methodologies of "*Green Chemistry Techniques*".

- *Ionic liquid mediated synthesis and 1,3-dipolar cycloaddition reactions of fluoro nitrones*
- *Aqueous phase synthesis and 1,3-dipolar cycloaddition reactions of bisnitrones*
- *Microwave assisted (solid phase) synthesis and 1,3-dipolar cycloaddition reactions of bisnitrones*
- *To utilize products in further reactions (atom efficiency)*

In majority of these reactions, mild reaction conditions (room temperature, short reaction times, avoiding oil bath heating etc), easy work up in isolation of the compounds have made these protocols more attractive.

Laboratory experimental work with results

Synthesis of N-benzyl fluoro nitrone in ionic liquid

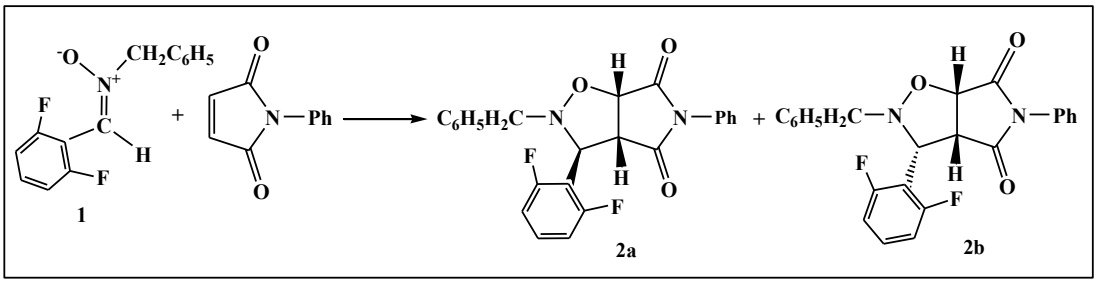


***Spectral data of N-benzyl fluoro nitrone* :**

White crystalline solid (m.p 42^{0}C, uncorrected). UV λ_{max} 238 nm; IR (KBr): υ_{max} 3025 (m), 2235 (m), 1680 (m), 1610 (s), 1440 (m), 1154 (m), 784 (s) cm^{-1}. ^{1}H NMR ($CDCl_3$): 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}CNMR ($CDCl_3$): δ 142.04 (CH=N$^+$), 134.80, 134.34, 134.12, 133.93 (phenyl carbons), 131.60, 130.00, 129.55, 129.46, 128.67, 128.22 (2,6 difluoro phenyl carbons).

It was observed that the nitrone decomposes if kept at RT for a period of 6-8 hrs. Therefore, we have studied *in situ* reactions of the nitrone with various activated alkene and alkynes.

General procedure for the synthesis of fluoro isoxazolidine derivatives using N-benzyl fluoro nitrone (1)



To a stirred solution of 2,6-difluoro benzaldehyde (1 mmol) and [bmim]BF_4 (2 mL) in a 10 mL conical flask, *N*-benzylhydroxylamine (1 mmol;1 equivalent) was added at RT. It was mixed thoroughly and stirred at RT (20^{0}C) for 1 hr. The development of nitrone was monitored by TLC (ethyl acetate: hexane =1:10; R_f=0.45). Added *N*-phenyl maleimide (1 equivalent) *in situ* during the development of fluoro nitrone **1** and the reaction mixture was again stirred at RT for an appropriate time (26 min). The completion of the reaction was monitored by TLC (R_f = 0.52, 0.62) and the reaction mixture was washed with diethyl ether (3x10mL). The ether extracts were concentrated *in vacuo* and the crude product mixture was directly charged on a silica gel column.The column was eluted with a mixture of ethyl acetate and n-hexane (1:8) to furnish pure isoxazolidines **2a** (66%) & **2b** (22%) as white crystals (88%). The remaining ionic liquid was washed with ether and dried at 80 ^{0}C under reduced pressure in order to keep its activity for other reactions.

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

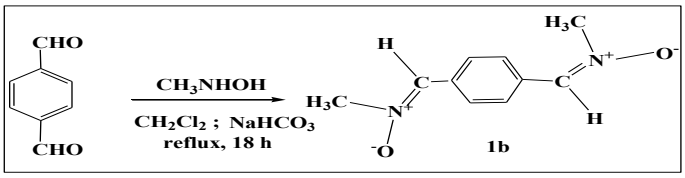
White crystals. Yield 66%; R_f= 0.52; υ_{max} 3020 (m), 2920 (m), 2835 (m), 1758 (s), 1690 (s), 1480 (m), 1346 (m), 805 (s), 770 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.74 – 7.68 (m, 3H, $C_6H_3F_2$), 7.12 – 6.83 (m, 2X5H, C_6H_5 protons), 5.84 (d, 1H, *J* = 6.70 Hz, C_5H), 3.40 (dd, 1H, *J* = 6.06, 6.16 Hz, C_4H), 3.54 (s, 2H, $C_6H_5CH_2$), 2.95 (d, 1H, *J* = 6.32 Hz, C_3H);

^{13}C NMR ($CDCl_3$): δ 173.42, 173.10 (carbonyl carbons), 138.10, 138.06, 138.02, 137.97, 136.86, 136.81, 136.78, 136.75 (phenyl carbons), 134.34, 134.14, 134.06, 133.76, 133.65, 133.45 (2,6 difluoro phenyl carbons), 85.22 (C_5), 77.20 (C_3), 58.46 (C_4), 39.55 ($\underline{CH_2}C_6H_5$); EI-MS: *m/z* 420 (M^+,100%), 343, 329, 306, 252, 216 (B.P), 113, 91, 77; Anal. Calcd. for $C_{24}H_{18}O_3N_2F_2$: C, 68.57; H, 4.28; N, 6.66%. Found: C, 68.44; H, 4.19; N, 6.52.

(3*R*)-2-Benzyl-3-(2,6-difluorophenyl)-dihydro-5-phenyl-2*H*-pyrrolo[3,4-*d*]isoxazole-4,6(5*H*,6 a-*H*)-dione, 2b

White crystals. Yield 22%; R_f = 0.62 IR (KBr): υ_{max} 3010 (m), 2915 (m), 2830 (m), 1764 (s), 1685 (s), 1486 (m), 1340 (m), 864 (s), 783 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.70 – 7.66 (m, 3H, $C_6H_3F_2$), 7.30 – 7.12 (m, 2X5H, C_6H_5 protons), 5.76 (d, 1H, *J* = 2.24 Hz, C_5H), 3.63 (dd, 1H, *J* = 2.26, 2.14 Hz, C_4H), 3.28 (s, 2H, $C_6H_5CH_2$), 3.06 (d, 1H, *J* = 3.04 Hz, C_3H); ^{13}C NMR ($CDCl_3$): δ 172.40, 172.24 (carbonyl carbons), 137.80, 137.74, 137.72, 137.57, 137.36, 136.34, 136.26, 136.18 (phenyl carbons), 134.80, 134.60, 134.44, 134.22, 134.13, 134.06 (2,6 difluoro phenyl carbons), 80.65 (C_5), 76.52 (C_3), 57.90 (C_4), 41.24 ($\underline{CH_2}C_6H_5$); EI-MS: *m/z* 420 (M^+,100%), 343, 329, 306, 216 (B.P), 113, 91, 77; Anal. Calcd. for $C_{24}H_{18}O_3N_2F_2$: C, 68.57; H, 4.28; N, 6.66%. Found: C, 68.49; H, 4.17; N, 6.50.

1. ***Synthesis of bisnitrone from terepthalaldehyde using microwave irradiation***



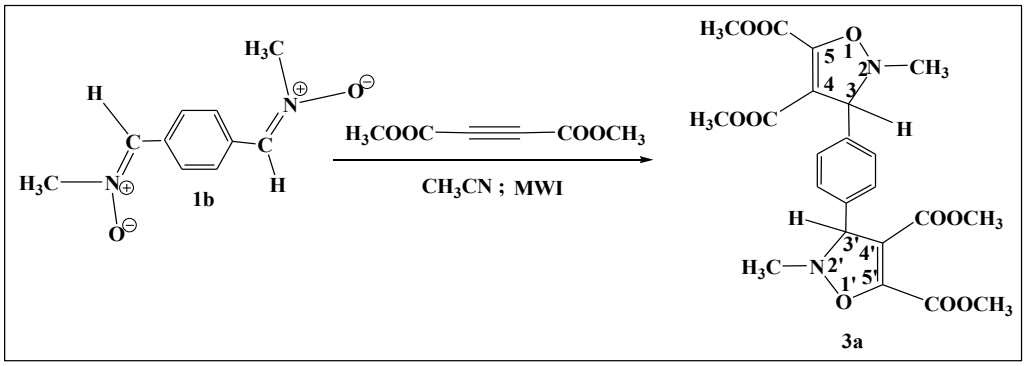
Terephthalaldehyde (1.34 g, 10 mmol) was added to a stirred solution of *N*-methylhydroxylamine hydrochloride (2.09 g, 25 mmol) in CH_2Cl_2 (20 ml) in a 50 ml R.B flask. $NaHCO_3$ (2.52 g, 30 mmol) was added and the mixture was heated at reflux for 18 hr. The reaction was monitored by TLC (R_f = 0.50). The solution was filtered in hot condition and the inorganic solid washed with warm $CHCl_3$. The bisnitrone crystallized from the filtrate as a white solid and was collected at the vacuum pump (74%, m.p > 250 ^{0}C).

Spectroscopic data for bisnitrone 1b

R_f = 0.50; FT-IR (KBr): υ_{max} 3130 (s), 3010 (m), 2970 (m), 2246 (m), 1690 (s), 1630 (s), 1610 (s), 1515 (s), 1310 (m), 1176 (s), 1150 (s), 782 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): 8.24 (s, 4H, Ar-H), 7.40 (s, 2H, 2 x CH=N^+), 3.89 (s, 6H, 2 x CH_3); ^{13}C NMR ($CDCl_3$): δ 134.66 (2 x CH=N^+), 131.81, 130.54, (1,4 Ar-C), 128.29, 127.52 (2,6 & 3,5 Ar-C), 54.58 (2 x CH_3); EI-MS (*m/z*): 192 (M^+), 176 (M-O), 134 (M-CHNOCH$_3$);

Anal.Calcd. for $C_{10}H_{12}O_2N_2$: C, 62.47; H, 6.30; N, 14.58. Found: C, 62.33; H, 6.24; N, 14.35%.

Synthesis of bis (isoxazoline) derivatives (3a)



Bisnitrone **1b** (0.41 mmol, 80 mg) and dimethyl acetylene dicarboxylate (0.82 mmole, 116 mg) was dissolved in acetonitrile (10 mL) and was heated in a sealed vessel at 115 ^{0}C during 5 min under microwave irradiation (400 W, temperature-controlled mode). The progress of the reaction was monitored by TLC (R_f = 0.58).The resulting reaction mixture was concentrated under vacuum and the crude material was directly purified by column chromatography on silica gel (ethyl acetate/hexane) to afford pure bisisoxazoline **3a** (92%) as a colourless gummy mass. Same methodology was adopted for the synthesis of other bisisoxazoline derivatives.

Spectroscopic data for bis (isoxazoline) 3a

FT-IR (KBr): υ_{max} 3036 (s), 2255 (m), 1760 (s), 1710 (s), 1600 (s), 1520 (s), 1440 (s), 1324 (m), 1314 (s), 1260 (m), 1170 (s), 780 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 6.60 (s, 4H, Ar-H), 5.20 (s, 2H, 2 x 3-H), 3.80 (s, 12H, 4 x -$COOCH_3$), 2.52 (s, 6H, 2 x N-CH_3); ^{13}C NMR ($CDCl_3$): δ 172.54 (2 x $\underline{CO}OCH_3$), 171.13 (2 x $\underline{CO}OCH_3$), 134.28, 133.87 (1,4 Ar-C; phenyl ring carbons linked with isoxazoline rings), 131.13, 130.45 (2,6 & 3,5 Ar-C; phenyl ring carbons linked with isoxazoline rings), 88.62 (2 x 5-C), 77.43 (2 x 3-C), 59.79 (2 x 4-C), 52.20 (2 x CH_3), 38.58 (2 x -$COO\underline{CH_3}$), 36.62 (2 x -$COO\underline{CH_3}$); EI - MS (*m/z*): 476 (M^+), 460, 400, 386, 276, 185 (B.P), 75, 59; Anal. Calcd. for $C_{22}H_{24}O_{10}N_2$: C, 55.44; H, 5.07; N, 5.88. Found: C, 55.39; H, 5.02; N, 5.74%.

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4. Chakraborty B.; Luitel G.P.; Chettri M.S, *J. Heterocyclic Chem*, **2017**, *54*, 1611-1618.
5. Chakraborty B.; Samanta A.; Luitel G.P.; Khatun N, *Indian J Chem,* **2013,** *52B*, 1342-1351.

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APPENDIX A

LIST OF PUBLICATIONS

1. "*Synthesis of some novel class of bis(isoxazoline) and bis (aziridine) derivatives*"

Bhaskar Chakraborty*, Manjit Singh Chhetri & Govinda Prasad Luitel, *Journal of Heterocyclic Chemistry* (Wiley), New York, USA, **2017**, *54*, 1611-1618. Impact Factor: 1.220 ; ISSN : 1943-5193; UGC approved journal Sr.No: 20872.

2. *"Synthesis of some novel class of peptides from α-amino nitrones and their potential biological activities"*

Bhaskar Chakraborty*, Amalesh Samanta, Govinda Prasad Luitel, Neelam Rai, Debmalya Mitra, *Journal of Heterocyclic Chemistry* (Wiley), New York, USA, **2016**, *53*, 1222-1230. Impact Factor: 1.220 ; ISSN : 1943-5193; UGC approved journal Sr.No: 20872.

3. "*Microwave assisted synthesis of some novel class of bisisoxazoline derivatives and their further applications*"

Bhaskar Chakraborty*, Manjit Singh Chhetri & Govinda Prasad Luitel, *CSIR-Indian Journal of Chemistry, Section B, Organic including Medicinal,* **2016**, *55B*, 1259-1266. Impact Factor: 0.700; ISSN: 0975-0983; UGC approved journal Sr.No: 15549/15551/1552

4. *"Synthesis of Some Novel Bisisoxazolidine Derivatives from Glyoxal-derived Bisnitrones via Simultaneous Double Cycloaddition Reactions in Water"*

Bhaskar Chakraborty*, Govinda Prasad Luitel, *Journal of Heterocyclic Chemistry* (Wiley), New York, USA, **2015**, *52*, 726 – 731. Impact Factor: 1.220 ; ISSN : 1943-5193 UGC approved journal Sr.No: 20872

5. *"Synthesis of some bisisoxazolidine derivatives via 1,3-dipolar cycloaddition reactions in water"*

Bhaskar Chakraborty*, Govinda Prasad Luitel, *CSIR-Indian Journal of Chemistry, Section B, Organic including Medicinal,* **2014**, *53B*, 1436-1441.Impact Factor: 0.700 ; ISSN: 0975-0983; UGC approved journal Sr.No: 15549/15551/1552

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

Bhaskar Chakraborty* & Govinda Prasad Luitel, *Tetrahedron Letters* (Elsevier), UK, **2013**, *54*, 765-770. Impact Factor: 2.376 ; ISSN : 0040-4039; UGC approved journal Sr.No: 35674

7. *"Synthesis of some novel fluoro isoxazolidine and isoxazoline derivatives using N-Benzyl fluoro nitrone via cycloaddition reaction in ionic liquid"*

Bhaskar Chakraborty* and Govinda Prasad Luitel, *Journal of Chemical Sciences* (Springer), USA, **2013**, *125 (5),* 1071-1077. Impact Factor: 1.126 ; ISSN : 0973-7103; UGC approved

journal Sr.No: 19615.

8. *"Ionic liquid mediated synthesis of some novel fluoro isoxazolidine and isoxazoline derivatives using N-Benzyl-fluoro nitrone via cycloaddition reaction and their antimicrobial activities"*

Bhaskar Chakraborty*, Amalesh Samanta, Govinda Prasad Luitel & Nasima Khatun, *CSIR-Indian Journal of Chemistry, Section B, Organic including Medicinal,* **2013**, *52B*, 1342-1351.Impact Factor: 0.700 ; ISSN: 0975-0983; UGC approved journal Sr.No: 15549/15551/1552

APPENDIX B

SEMINARS & CONFERENCES

1. Presented "*Poster" entitled "Green protocol for the synthesis of α-chloro nitrone and isoxazolidine derivatives"* by the authors : Bhaskar Chakraborty*, **Govinda Prasad Luitel**, Prawin Kumar Sharma & Manjit Singh Chhetri at the **104th Indian Science Congress** held at Shri Venkateswara University, Tirupati, Andhra Pradesh 3rd January – 7th January, **2017.**

2. Presented "*Poster" entitled "Synthetic potentiality of α*-amino nitrones in the synthesis of novel class of peptides" by the authors : Bhaskar Chakraborty*, **Govinda Prasad Luitel**, Prawin Kumar Sharma & Esmita Chhetri at the **103nd Indian Science Congress** held at Mysore University, Mysuru of from 3rd January – 7th January, **2016.**

3. Presented "*Poster" entitled "Synthesis of some novel fluoro isoxazolidine and isoxazoline derivatives using N-Benzyl fluoro nitrone in ionic liquid via cycloaddition reaction and their antibacterial activities"* by the authors : Bhaskar Chakraborty*, **Govinda Prasad Luitel**, Prawin Kumar Sharma & Esmita Chhetri at the **102nd Indian Science Congress** held at University of Mumbai from 3rd January – 7th January, **2015.**

4. Presented "*Poster" entitled* "*Green synthesis of novel α-chloral nitrone and isoxazolidines : one pot convenient cycloaddition reactions in water*" by the authors: Bhaskar Chakraborty*, Prawin Kumar Sharma & **Govinda Prasad Luitel**, at the **100th Indian Science Congress** held at University of Calcutta from 3rd January – 7th January, **2013.**

5. As a member of the organizing committee, has taken part actively in the "***Science Academie's Lecture Workshop****"* at *Sikkim Government College*, Tadong, Gangtok, Sikkim sponsored by *Indian Academy of Sciences, Bangalore, National Academy of Science, Allahabad and Indian National Science Academy, New Delhi* from 12th April – 13th April **2013.**

6. As a member of the organizing committee, has taken part actively in the "***Science Academie's Lecture Workshop****"*at *Sikkim Government College*, Tadong, Gangtok, Sikkim sponsored by *Indian Academy of Sciences, Bangalore, National Academy of Science, Allahabad and Indian National Science Academy, New Delhi* from 22nd February – 23rd February **2014.**

CHAPTER I

Theoretical approach and Review work

General

The term "*1,3-dipole*", $a^{+}-b-c^{-}$ may be defined as such that atom "a" possesses an electron sextet, that is an incomplete valence shell combined with a formal positive charge and the atom c, the negatively charged center, has an unshared electron pairs and undergoes 1,3- dipolar cycloaddition to a multiple bond system called "*dipolarophile*".

Since compounds with 6 electrons in the outer shell of an atom are usually not stable, therefore, the a-b-c system is actually canonical form of a resonance hybrid for which at least one other structure may be drawn e.g.

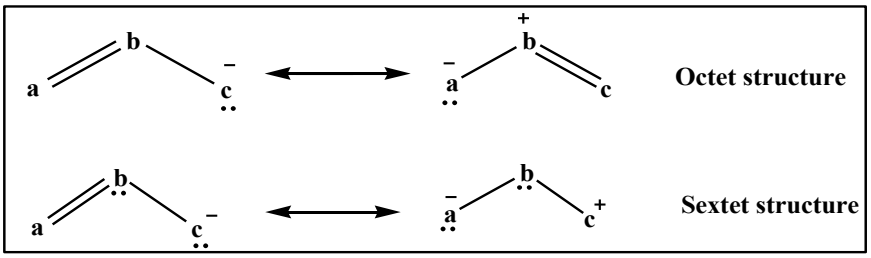


Figure 1

1,3-Dipoles can be further stabilized by internal octet stabilization. 1,3-dipolar compounds can be divided into two major types:

(1) Propargyl - Allenyl type

In this type, the dipolar canonical form has a double bond on the sextet atom and other canonical form has a triple bond on that atom.

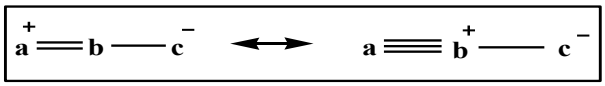


Figure 2

(2) Allyl type

In allyl type, the dipolar canonical form has a single bond on the sextet atom and the other cannonical form has a double bond.

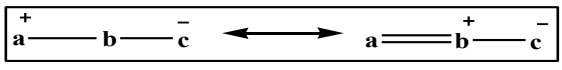


Figure 3

1, 3-Dipoles can be represented as shown in **Figure 3**. In this 1, 3-dipoles, the central atom is never a carbon atom. If the central atom is a carbon function then internal octet stabilization is prevented by lack of an available free pair of electrons. Such systems are therefore extremely reactive and short lived in nature. Examples of this type are unsaturated carbenes and azenes.

1, 3-Dipole

1, 3-dipole participates in the [3+2] cycloaddition reactions which form 5-membered ring systems, in a silmilar way to the Diels-Alder reaction which forms 6 membered rings. The reactive partners in this reaction are 1, 3-dipoles and dipolarophiles (diene and dienophile in Diels-Alder reaction). It is a 4π+2π process as well.

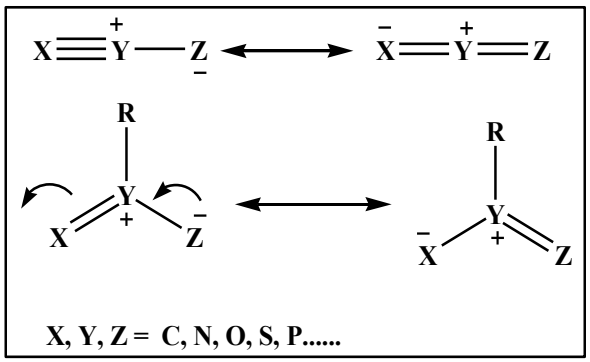


Figure 4

1, 3-dipoles vary in stability greatly. Some can be isolated and stored while others are relatively stable, but are usually made in the same day for their use.

There are two general classes of dipole and are referred to as sp^2 and *sp* hybridized dipoles.

sp-dipole (linear dipoles like the propargyl anion type)

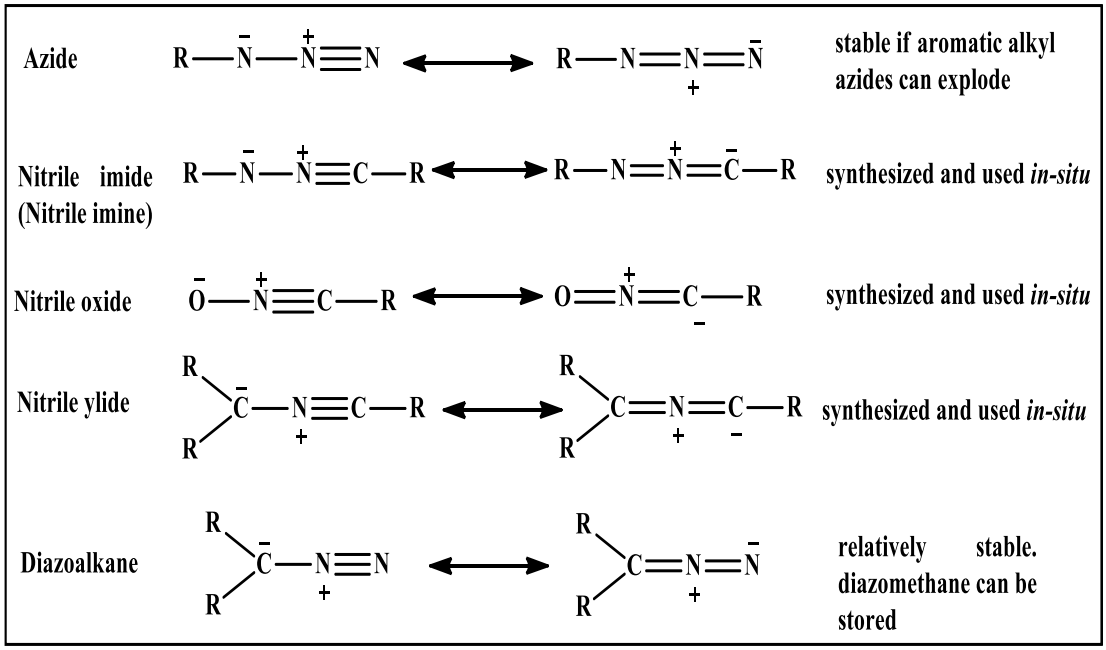


Figure 5

sp^2 hybridised (bent dipoles like the allyl anion type)

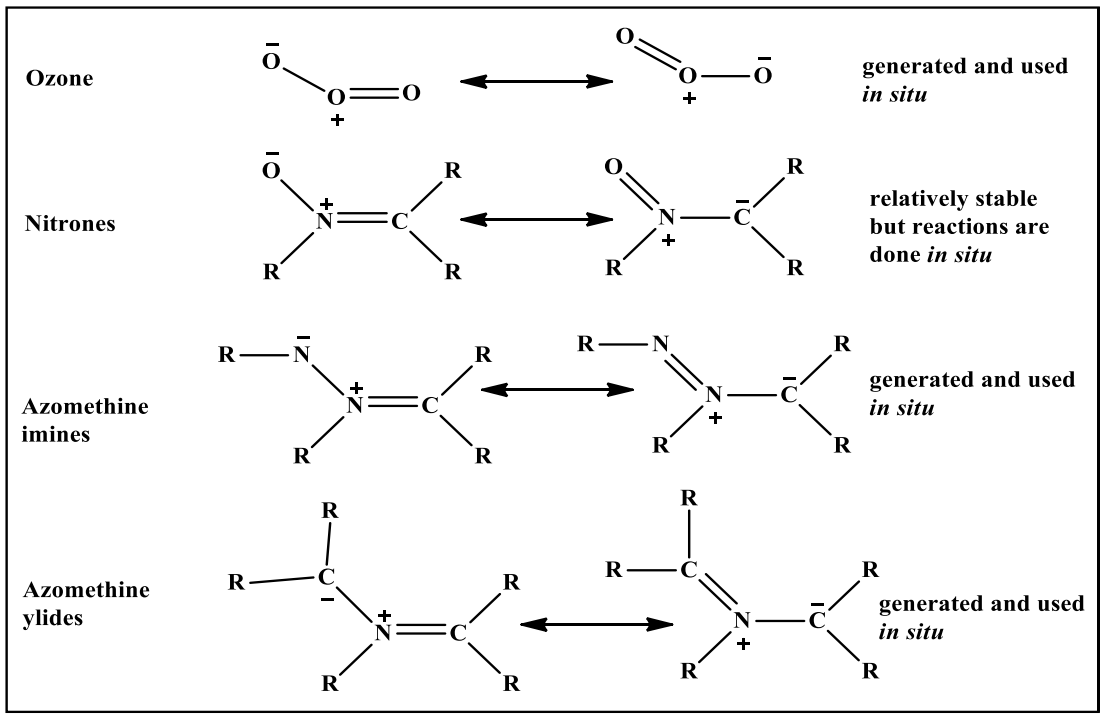


Figure 6

Reactivity profile of 1, 3-dipoles

The reaction between dipoles and dipolarophiles follow the following general profile:

(a) It is generally accepted that cycloadditions are concerted processes *i.e*. they have no distinct intermediates but the bond formation may be asynchronous.

(b) The reaction rates are not influenced much by solvent polarity indicating small change in polarity between reactants and transition state.

The reaction rate between dipoles and dipolarophiles vary considerably. It can be explained by Fukui's Frontier Molecular Orbital Theory (FMO approach) which considers the interaction between molecular orbitals of the dipole and dipolarophiles.

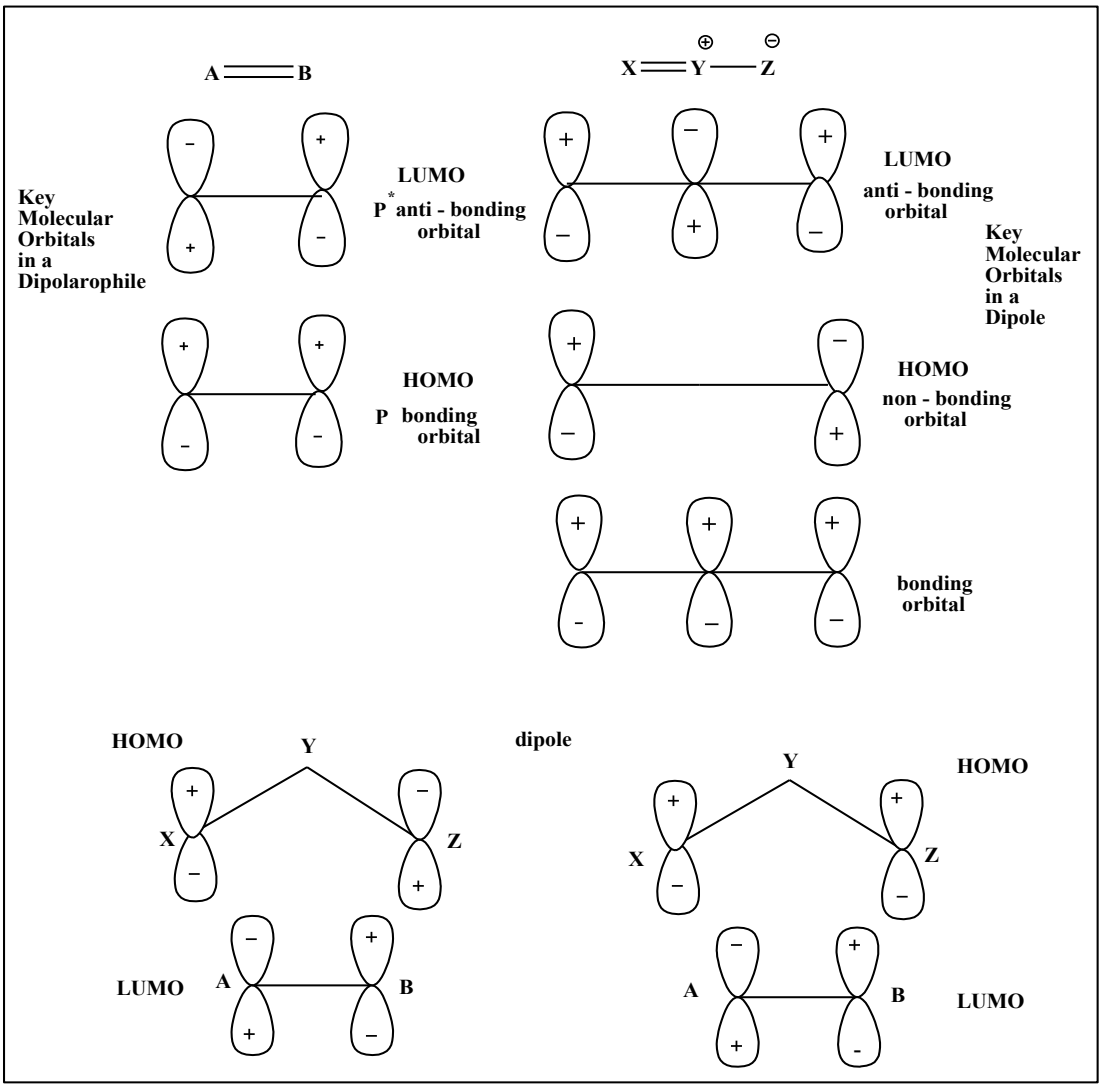


Figure 7

The term "*nitrone*" was introduced by Pfeiffer in 1916 from nitrogen ketone (azomethine oxide) in order to keep its resemblance to the carbonyl group in its several reactions[1].

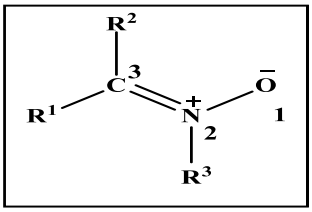
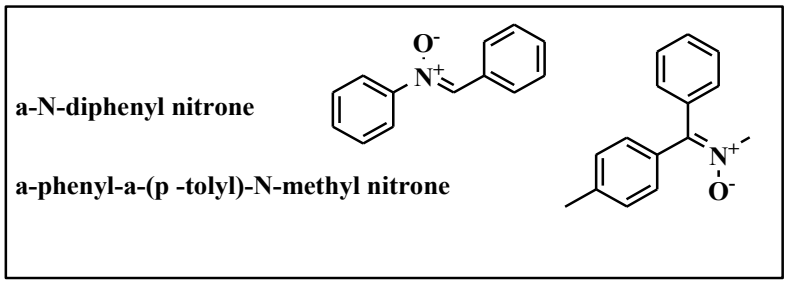


Figure 8

Nomenclature

The nitrones were known since 1887. The nomenclature employed by the chemical abstract is as follows.



The cyclic nitrones are named accordingly to the parent heterocyclic systems e.g. 2,4–dimethyl–Δ^1-pyrolidine-*N*-oxide, Δ^1–tetrahydropyridine-*N*-oxide etc. later, nitrones were named as *C*-cyclopropyl-*N*-methyl ketone, *C*-dicyclopropyl-*N*-methyl nitrone etc. The general term *aldonitrone* and *ketonitrone* has been employed occasionally. *Aldonitrones* contain a proton on the α-carbon atom.

$$\mathbf{RCH = N^{+} (O^{-}) R^{1}}$$

While the *ketonitrones* contain the α-carbon fully substituted with alkyl or aryl group.

$$\mathbf{R, R^{1} C = N^{+} (O^{-}) R^{2}}$$

Geometrical isomerism

Nitrones may exhibit geometrical isomerism due to the presence of the double bond in nitrone molecule.

Figure 9

The existing geometrical isomerism was first reported in 1918 for α-phenyl-α-(*p* -tolyl)-*N*-methyl nitrone[2]. The configuration of the isomers was established using dipole moment studies. The *cis* and *trans* forms were readily converted into the *trans* form by heating. Generally *aldonitrones* exist in stable *trans* isomeric form and this has been established by UV, IR, ^{1}H NMR studies[3]. The only example of geometrical isomerism is known for α-phenyl-*N*-tertiary butyl nitrone[4]. Therefore, in such cases where geometrical isomerism is possible, *E* / *Z* notation can be employed for naming.

The role of a nitrone is a 1,3-dipole in 1, 3-dipolar cycloaddition reactions. It reacts with olefines to form ***Isoxazolidines*** and the scheme has been shown as follows.

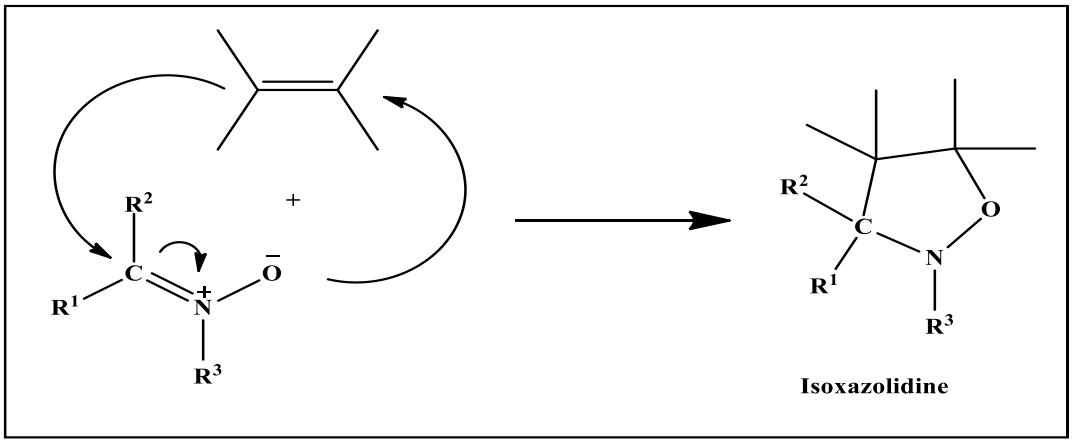


Figure 10

Similarly, a nitrone can react as 1,3-dipole with alkynes in 1,3-dipolar cycloaddition reaction to form ***Isoxazolines***.

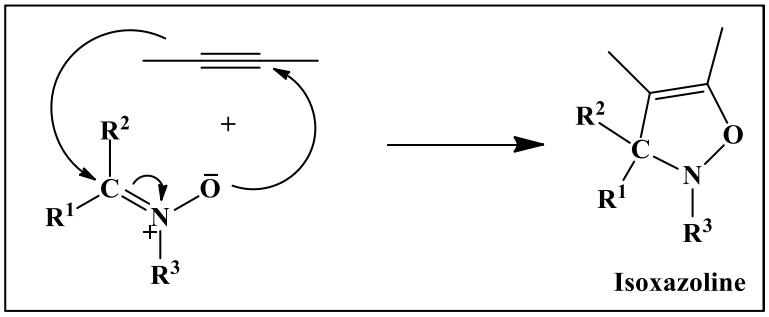


Figure 11

In allyl type 1,3-dipole, if we restrict the atom a,b,c to carbon, nitrogen and oxygen, the *nitrone* results.

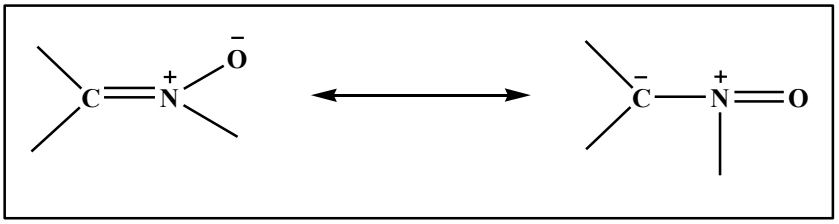
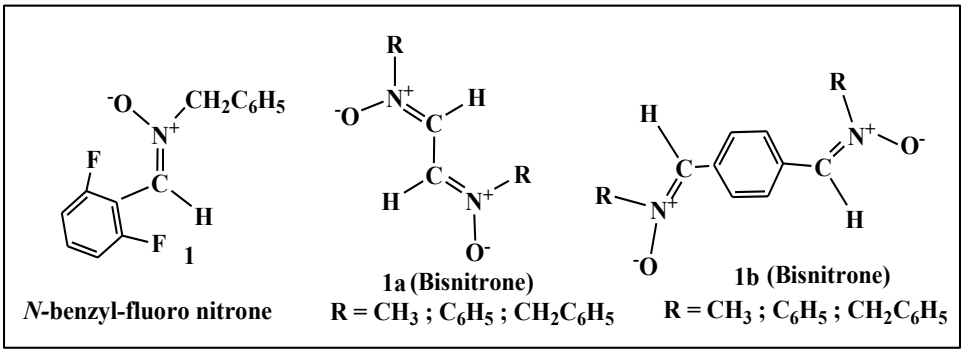


Figure 12

The nitrones of our present study in this dissertation are *N*-benzyl-fluoro nitrone (**1**), glyoxal derived bisnitrone (**1a**) and terepthalaldehyde derived bisnitrone (**1b**) respectively. In general, nitrones are HOMO-LUMO controlled 1,3-dipoles skewing towards LUMO controlled side.



Synthesis of nitrones

The chemistry and the synthesis of the nitrones have been reviewed many times. The general methods of synthesis of the nitrones are briefly discussed here.

By the oxidation of *N*, *N*-substituted hydroxylamines

$$R - N(OH) - CHR^1R^2 \longrightarrow R - N^+(O^-) = CR^1R^2$$

Both cyclic and acyclic nitrones can be prepared by this method. Different oxidizing agents are used viz, yellow mercuric oxide[5], active lead oxide[6], potassium ferricyanide[7], hydrogen peroxide[8], potassium permanganate[9], diammine silver nitrate[10].

The development of the nitrone salt was reported from the reaction between *p*-benzoquinone and 1-hydroxyl piperidine[11].

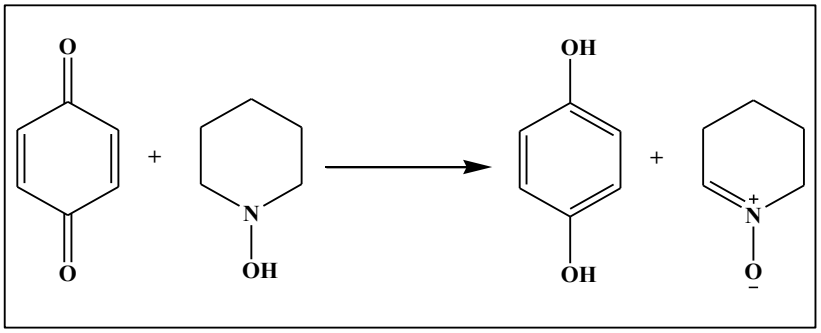


Figure 13

The development of nitrone from *N,N*-disubstituted and *N*-substituted hydroxylamines using palladium catalyst were also reported[12]. Recently a four membered cyclic nitrone was also reported by the oxidation of 1-OH-azetidines with PbO_2[13].

Some other oxidative methods are also known e. g. diammino silver nitrate has been used as the reagent for the preparation of α-styryl-α-benzyl-*N*-phenyl nitrone from corresponding hydroxylamine[14]. Photolysis of *N*-hydroxylamines in presence of 1, 4 – dicyano naphthalene (DCN) as an electron acceptor give high yields of nitrone[15].

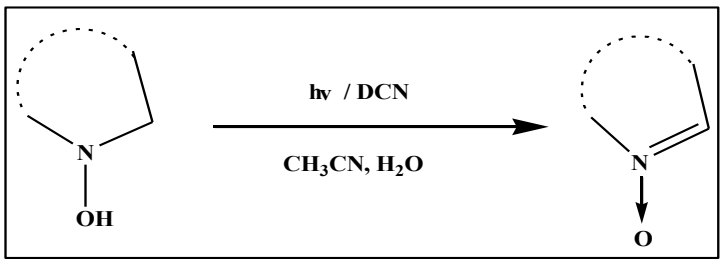


Figure 14

From oximes

The alkylation of the oximes was first reviewed in 1938[16]. Disadvantage of this method was that nitrones were produced along with oxime ether.

$$R^1 R^2 C = N - OH + XR \longrightarrow R^1 R^2 C = NOR + R^1 R^2 C = N^+ (O^-)$$

Li, Na and K or tetramethyl ammonium oxime salts did not alter the product ratio of oxime ether to nitrone significantly. Electron withdrawing group in the *para*, *ortho*-disubstituted benzophenone oxime salts remarkedly promoted the formation of nitrones while electron donating group favours the development of nitrone whereas longer side chain favours oxime – ether formation.

Heptanal oximes when treated with benzyl chloride in solution of ethanol and sodium ethoxide yielded 77% of α-hexyl-*N*-benzyl nitrone[17]. DMSO has been employed in the various keto-oxime alkylations. *C,C*-dicyclopropyl-*N*-methyl nitrone has been prepared by this method[18].

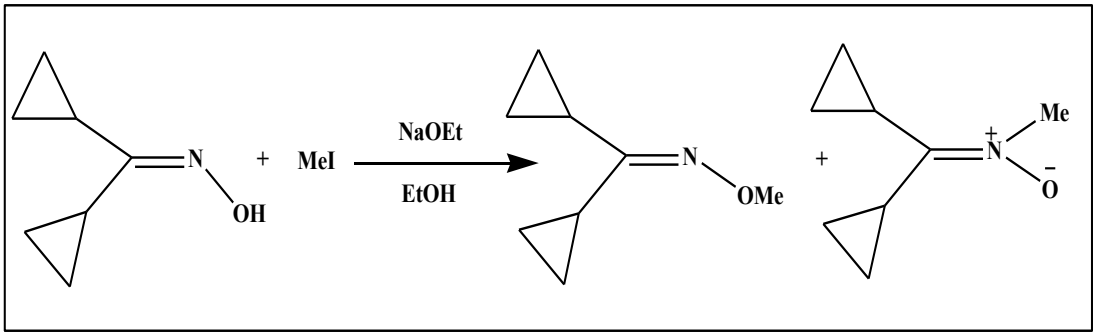


Figure 15

Development of nitrones was also reported by the intramolecular Michael addition of aldoximes and ketoximes to electronegative olefins[19].

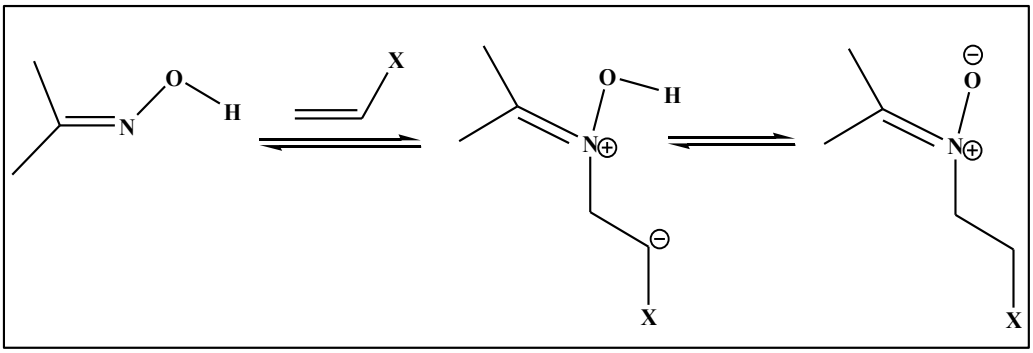


Figure 16

Recently oxime-*O*-allyl ether has been converted into the corresponding *N*-allyl nitrones on treatment with 10 mole % of $PdCl_2$ ($MeCN_2$) by a formal [2+3] sigmatropic shift[20]. Formation of cyclic *N*–vinyl nitrones have been also reported from δ-alkenyl oximes by a concerted 2n + 2π + 2δ 1, 3 – azprotio cyclotransfer reaction[21]. Both the reaction proceeds smoothly and high yields are reported. This is one of the best methods for the preparation of *aldonitrones*. *N*-phenylhydroxylamine has been treated with a variety of aldehydes and ketones[21] for the synthesis of *N*-phenyl nitrones. *N*-cyclohexyl methylene nitrone[22] similar to *N*-phenyl methylene nitrone[23] may be prepared by passing formaldehyde gas through *N*-cyclohexylhydroxylamine in methylene chloride and anhydrous $MgSO_4$.

From aromatic nitroso compounds

Aromatic nitroso compounds react with a variety of compounds to develop nitrones. 2, 4, 6-trinitro toluene, 9-methyl acridine with sufficiently active methylene group can react with aromatic nitroso compound to form nitrones[24,25]. The reaction is usually catalysed by trace amounts of base (e.g. pyridine). One of the examples of this kind of reaction is shown in the following way.

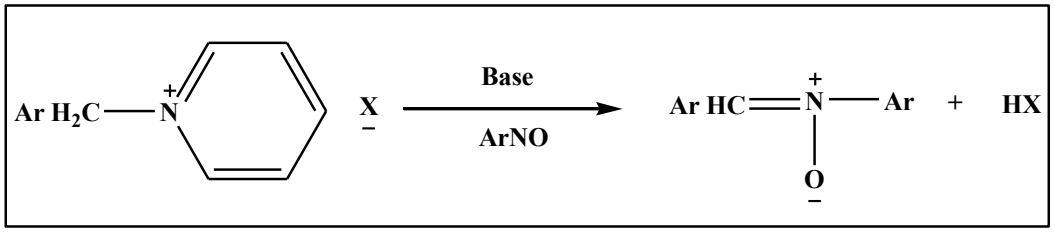


Figure 17

Aromatic nitroso compounds may react with benzyl derivatives such as benzyl chloride in presence of some suitable base to yield nitrones[26,27].

Some other miscellaneous methods

Quinones may yield dinitrones upon treatment with nitrosobenzene[28].

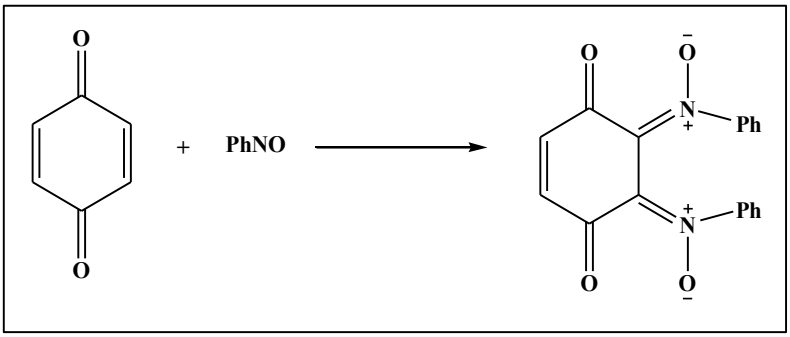


Figure 18

N–methyl nitrones may be generated in good to excellent yields from aldehyde and ketone with stoichiometric amount of *N*-Me, *N-bis* (trimethyl silyl) hydroxylamines[29]. Nitrones can also be isolated in pure state from D – glucose oximes and benzaldehyde without employing any protection of the hydroxyl group[30].

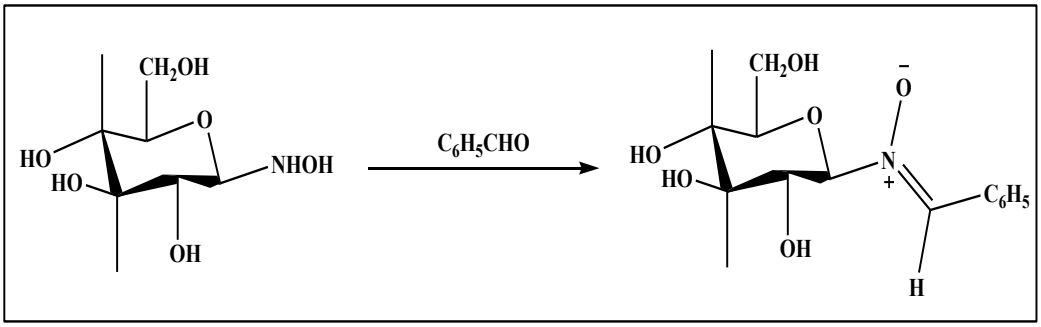


Figure 19

Nitrones can also be obtained by the treatment of trimethyl silyl chloride and triethyl amine on nitroalkanes[31].

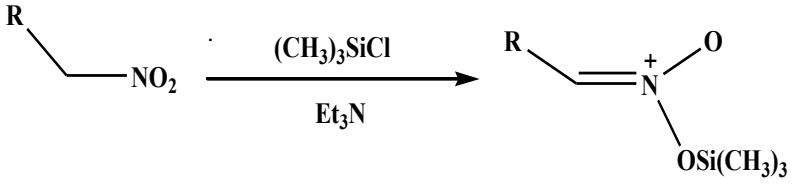


Figure 20

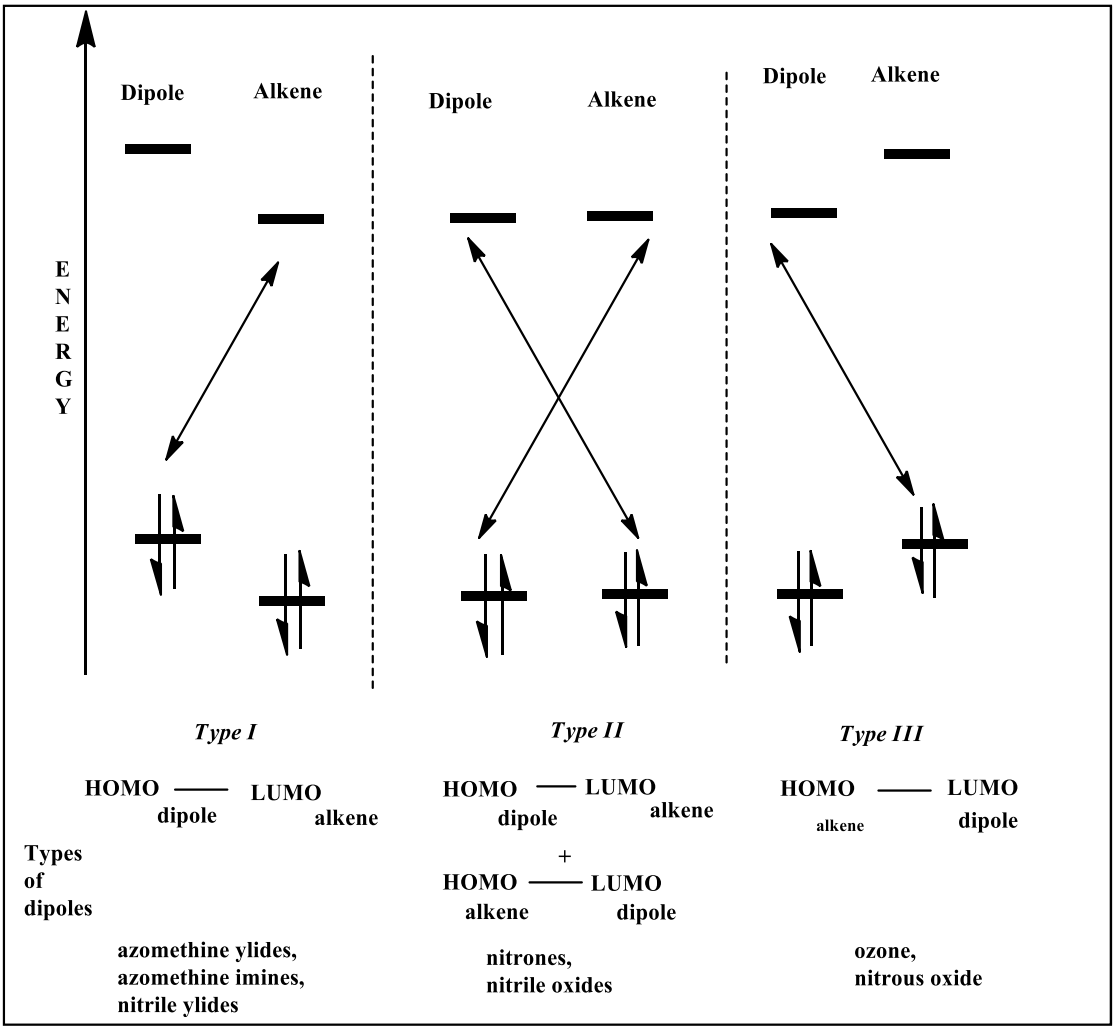
1,3-Dipolar cycloaddition reaction

1,3-dipolar cycloaddition reactions are an integral and important part of organic chemistry in pedagogy and research as well. The 1,3-dipolar cycloaddition reactions represent the favourite method for the synthesis of five-membered heterocycles.These heterocycles constitutes important frameworks of many natural products. The reaction mainly proceeds in a concerted manner, which means that all bonds are created simultaneously, but not necessarily to the same extent at a certain time. Consequently, the stereochemistry of the dipolarophile is conserved in final product.

1,3-dipolar cycloaddition reaction of nitrones with alkenes and alkynes results isoxazolidines and isoxazoline derivatives. They may also serve as important intermediates for their conversion into *β*-amino alcohols and alkaloids. Majority of the isoxazoline and isoxazolidine derivatives are found to exhibit medicinal activities such as *antibacterial, antifungal, anticonvulsant, antibiotic and antitubercular activity.*

K. N. Houk etal[32]on the basis of mechanistic investigations have shown that cycloadditions of 1,3-dipole to alkenes are stereospecifically suprafacial, solvent polarity has a little effect on reaction rates and small activation enthalpies. These facts along with reactivity and regioselectivity have been considered fully compatible with concerted five centered mechanism. Orbital symmetry considerations have provided permissive though not obligatory, theoretical evidence for the concerted mechanism and the observation of [4 π's and 6 π's] cycloaddition but not [4 π's + 4 π's] cycloaddition of 1,3-dipoles to diene has provided further evidence for the concerted mechanism. But the experimentally observed regioselectivity of most of the 1,3-dipolar cycloaddition reaction has been the most difficult phenomenon to explain.

Houk etal[32] solved this problem with the use of generalized frontier molecular orbitals of 1,3-dipoles and dipolarophiles within the frame work of frontier molecular orbital theory. Whether 1,3-dipolar cycloaddition reaction is allowed or forbidden may be judged according to the symmetry properties of the HOMO and LUMO orbitals of the dienes and the dipolarophiles as proposed by Sustman[33].



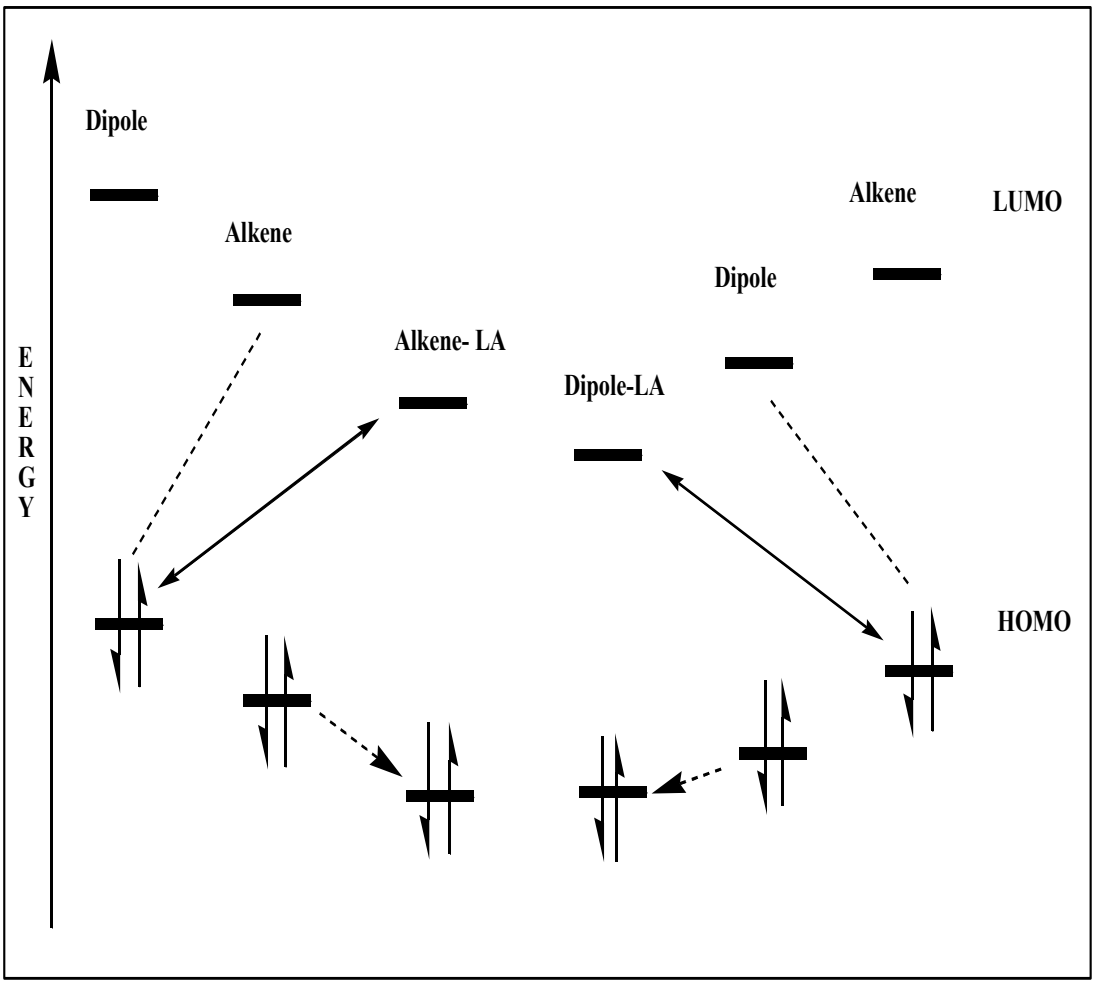
Type I: This involves dominant interaction between HOMO (dipole)–LUMO (dipolarophiles).

Type II: It involves LUMO (dipole)-HOMO (dipolarophiles). But in type II, both LUMO (dipole)-HOMO (dipolarophiles) and HOMO (dipole)-LUMO (dipolarophiles) are important in determining reactivity and regioselectivity. Type I dipoles are those having high lying HOMO's and LUMO's and referred to as HOMO controlled or nucleophilic 1,3-dipoles. It is referred to as HUMO-LUMO controlled dipoles.

Type III: This has low lying FMO's and referred to as LUMO controlled or electrophilic dipoles.

Molecular orbital theory behind 1,3-dipolar cycloaddition reactions

Lewis acid activation



Coordination of LA to either dipole or alkene results in LUMO lowering and a faster reaction rate

Houk[32] has treated all common 1,3-dipoles according to this simple model and have shown that the prediction satisfactorily explains all the experimental results. The nitrile ylides, diazoalkanes and azomethine ylides are HOMO controlled 1,3 dipoles, reacting readily with alkenes having one or more electron withdrawing substituents. The nitrile imines, azides and azomethyne imines are HOMO-LUMO controlled dipoles which react rapidly with both electron rich as well as electron deficient dipolarophiles. The nitrile oxides and nitrones are also HOMO-LUMO controlled dipoles, but these species are skewed towards the LUMO controlled side. Finally, species with several electro negative atoms are LUMO controlled 1,3 dipoles, *e.g.* – nitrous oxide and ozone.

Depending on the nature of the dipole and the dipolarophile, the 1,3-dipolar cycloaddition reaction is controlled either by a LUMO(dipolarophile)-HOMO(dipole)-or a LUMO(dipole)-HOMO(dipolarophile) interaction but in some cases a combination of both the interactions are involved. The interaction of the dipole LUMO with dipolarophile HOMO favours the formation of the product with the substituent on carbon adjacent to z while the opposite frontier orbital interaction favours opposite regioisomers. The HOMO's of the 1,3 dipolar system generally have larger terminal co-efficient on the group z while the LUMO's have larger co-efficient at the opposite terminus. The HOMO's and LUMO's of 1,3 dipoles are quantitatively similar to those of allyl anion. The greater differences in terminal co-efficient occur when the two terminals differs greatly in electronegativity.

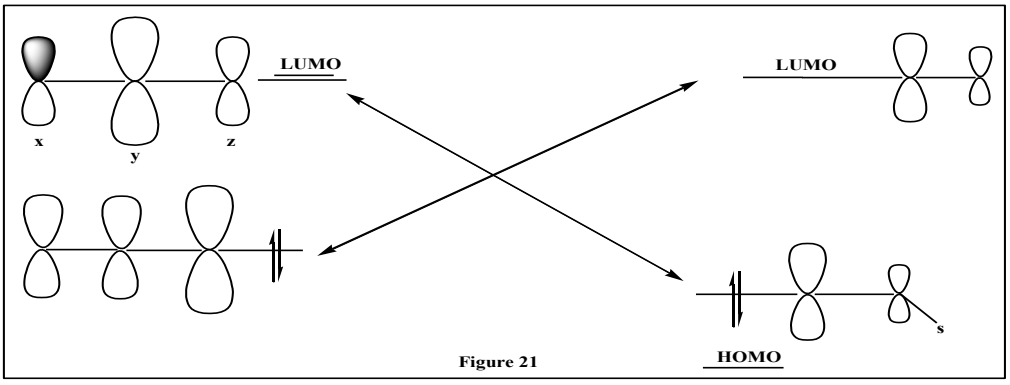


Figure 21

Nitrile oxides and nitrones react to give mainly the five substituted adduct with weakly electron deficient olefins like acrylonitrile and ethyl acrylate. The HOMO's and LUMO's of these electron deficient olefines both interact fairly with the LUMO's and HOMO's of the nitrile oxides and nitrones so that the orientation is influenced by both the interactions. The experimental results shows that the dipole LUMO – dipolarophile HOMO has more influence on regioselectivity. Huisgen[34] observed that acetylenic dipolarophiles are less reactive then expected on basis of their ionization potentials. Since alkynes have large HOMO – LUMO gap then alkenes, it is expected that during interactions with alkyne, LUMO plays the most significant part and hence alkynes are less reactive than expected. However, the reactivity of nitrones with both electron deficient alkynes and alkenes are actually determined by dipole (HOMO)-dipolarophiles (LUMO) interactions and the regiochemistry. The former case is still controlled by dipole (LUMO) and in case of alkyne, the dipole (HOMO)-dipolarophile (LUMO) interactions become very important and dominates the reaction for the formation of 4-substituted adducts. When both the dipole and the dipolarophile are nonsymmetric, regioisomeric adducts may be formed.

Stereoselectivity in nitrone cycloaddition reactions

Addition of nitrones is generally *cis* to dipolarophiles, so the relative stereochemistry at C_4 and C_5 protons is always determined by the geometrical relationship of the substituents on the olefin. *Syn* and *anti* isomers of dipole (stability and therefore proportion of each depends on steric considerations and hydrogen bonding etc.) can lead to diastereoisomeric products depending on approach of dipole and dipolarophiles. *Exo / endo* approach of dipolarophiles needs to be considered. Secondary orbital interactions are not relevant, as in Diels-Alder reactions, steric interactions are important. So the *exo* product is the more stable product.

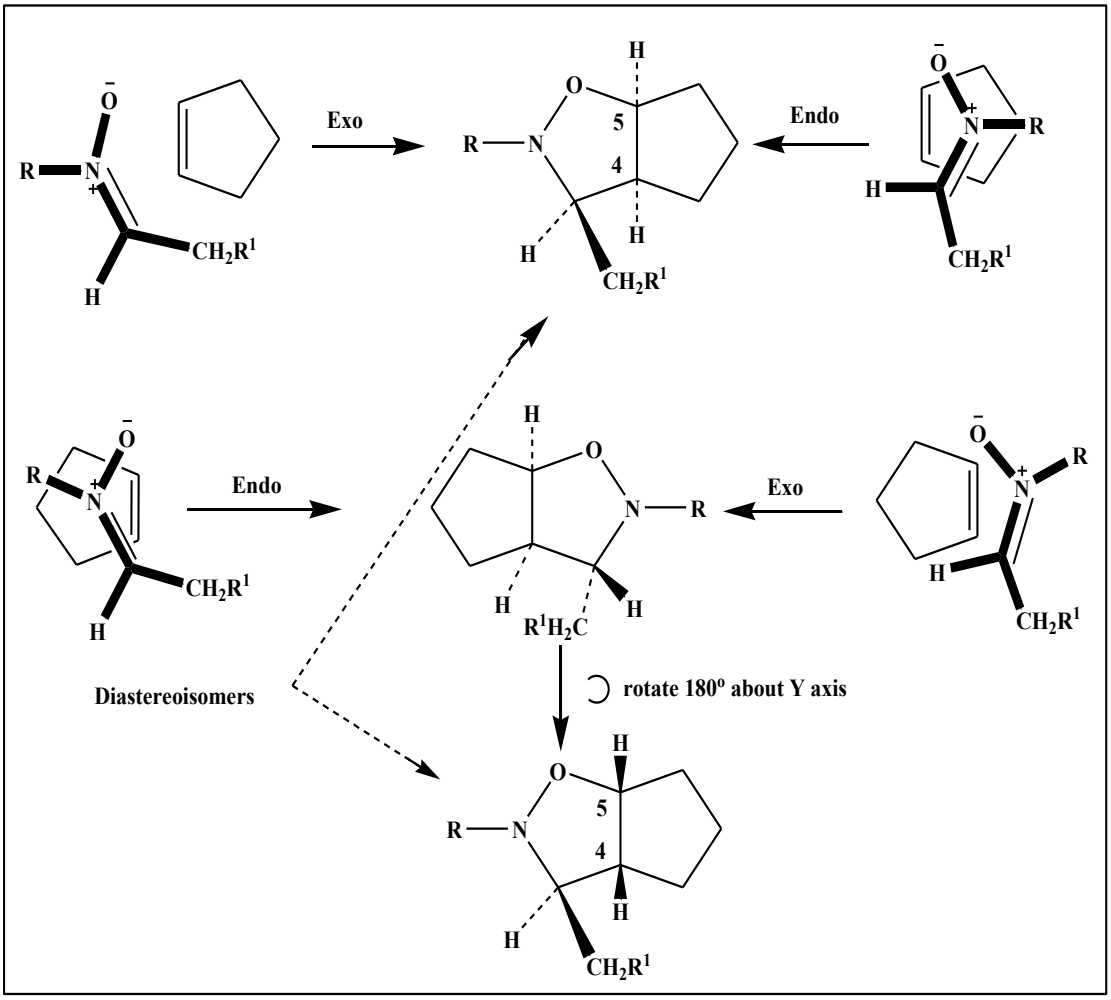


Figure 22

Two pairs of *regioisomeric* and *diastereoisomeric* products can result in any nitrone- olefin cycloaddition reactions. These arise from the nitrone and olefin approaching each other in either of two regiochemical senses, and in either an *endo*- or *exo*-fashion[35] (**Figure 22a**).

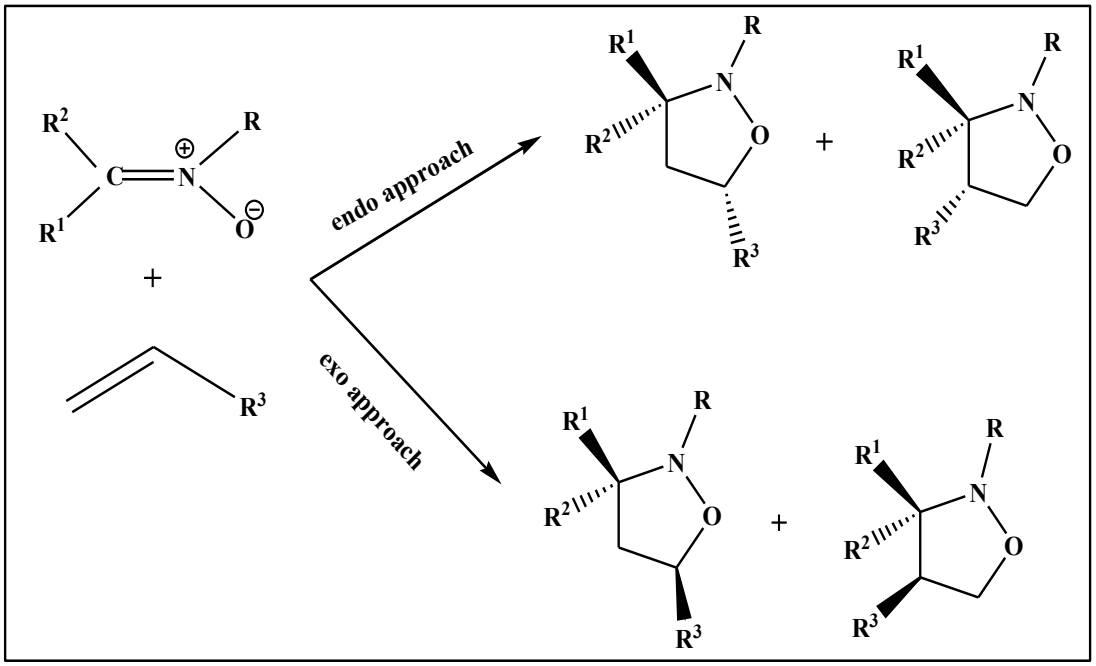


Figure 22a

Therefore, much effort has been focused on the development of regioselective and stereoselective inter and intramolecular nitrone-olefin cycloaddition reactions. The nomenclature *endo* and *exo* is well known from the Diels-Alder reaction[36]. The *endo* isomer arises from the reaction in which the nitrogen atom of the dipole points in the same direction as the substituent of the alkene. However, the *endo* transition state in the Diels-Alder reaction is stabilized by the secondary π-orbital interactions and the actual interaction of the *N*-nitrone p_z orbital with a vicinal p_z-orbital on the alkene, and thus the stabilization, is small[37]. The *endo/exo* selectivity in the 1,3-dipolar cycloaddition reaction is therefore primarily controlled by the structure of the substrates or by the presence of catalyst. It should be noticed that for reactions in which the nitrone can undergo *Z/E*-interconversion, the *endo/exo* assignment of the products is misleading and therefore *cis* or *trans* should be used instead.

Regioselectivity in nitrone cycloaddition reactions

The regioselectivity is controlled by both steric and electronic effects[38]. However, the steric effect may be sometimes weaker compared with strong electronics effects[39]. The 5-substituted isomer of the cycloaddition reaction results where electron-rich or electron-neutral alkenes react with nitrones. The reaction is primarily controlled by the *lowest unoccupied molecular orbital* (LUMO) dipole and the *highest occupied molecular orbital* (HOMO) dipolarophile interaction. The nitrone and alkene combine in a regioselective manner to give the 5-isoxazolidine because the LUMO (dipole) has the largest coefficient at the carbon atom and the HOMO alkene has the largest coefficient at the terminal carbon atom. This is obviously supported by steric factors. For alkenes with an electron withdrawing group (EWG) the reaction is primarily controlled by the HOMO (dipole) - LUMO (dipolarophile) interaction. In this case the HOMO (dipole) has the largest coefficient at the oxygen atom, whereas the LUMO (dipolarophile) has the largest coefficient at the terminal carbon atom. This situation favours for the development of 4-isomers, but since steric effect factors oppose this, a mixture of regioisomers is often obtained[40]. However, the steric factor is eliminated in the reaction of nitrones with 1,2- disubstituted olefines bearing an electron- withdrawing group and leading to the frontier molecular orbitals (FMO) controlled regioselectivity of the reaction with the 4-EWG substituted isomer as the sole product (**Figure 23**)

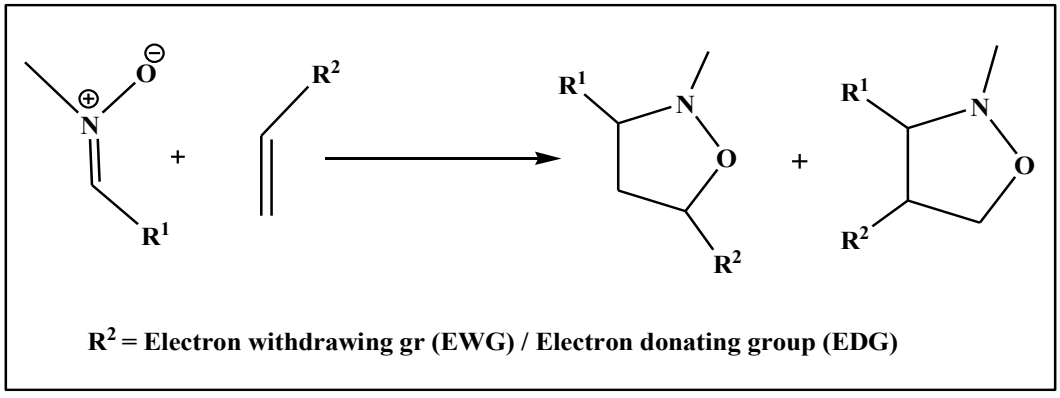


Figure 23

Review on some of the outstanding contributions in nitrone cycloaddition reactions

A comprehensive review on nitrone cycloaddition reactions has been conducted as a part of our present research work in this dissertation. This review work was needed to understand the gravity of nitrone cycloaddition reactions and their further applications, contributions to the community of synthetic organic chemists. This review work helped us to define and understand the work undertaken for this dissertation and especially how to reach the final target.

From the review work it has been found that in the majority of the publications nitrones are generated *in situ*. Due to their instability, 1,3-dipolar cycloaddition reactions are performed mainly by trapping the nitrones with suitable dipolariphiles at the time of their generation. Dimerization of nitrone can be controlled in this fasion and the yield of the cycloadducts is also extremely high.

Current literature survey

The recent reviews (from **January 2000 – March 2017**) reveals that emphasis has been given nowadays to the synthesis and cycloaddition reactions of nitrones following "*Green Chemistry*" methodologies[41].Environment friendliness and sustainable development is being the need of the hour, instead of using conventional solvents like benzene, dichloromethane, tetrahydrofuran etc. Synthesis of the nitrone and their cycloaddition reactions are mainly performed by following the methodologies as under nowadays:

- *Aqueous phase 1,3-dipolar cycloaddition reactions*
- *Microwave assisted (solid phase) synthesis of nitrones and cycloaddition reactions*
- *Ionic liquid (RTIL) mediated 1,3-dipolar cycloaddition reactions*
- *To utilize side products in further reactions (atom efficiency)*

In majority of the reactions, mild reaction conditions (room temperature, short reaction times, avoiding oil bath heating etc), easy work up and isolation of the compounds has made these protocols much more attractive.

Aqueous phase 1,3-dipolar cycloaddition reactions

Organic reactions in water have received increased attention primarily because of their environmental acceptability, abundance and low cost[42,43,44]. However, water also exhibits unique reactivity and selectivity which cannot be attained in conventional organic solvents[45,46,47]. Thus, the development of efficient procedures for useful chemical transformations in water without any catalyst is highly accepted and appreciated.

Pedro de Armas et al[48] explored the first example of a regioselective organocatalyzed 1,3-dipolar cycloaddition reaction between conjugated alkynoates and nitrones ‘‘*on water*’’ (**Figure 24**).

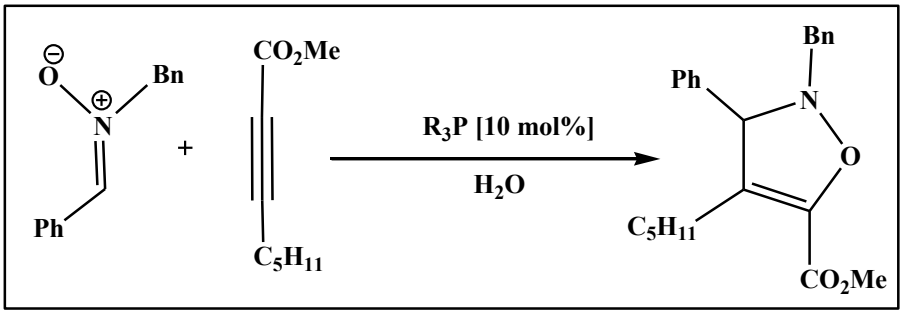


Figure 24

Butler et al[49] showed the great importance of water in nitrone cycloaddition reactions in their research work "*The Influence of Water on the Rates of 1,3-Dipolar Cycloaddition Reactions: Trigger Points for Exponential Rate Increases in Water-Organic Solvent Mixtures. Water-Super versus Water-Normal Dipolarophiles".*

A very interesting example of synthesis of nitrone (a water exclusion reaction) in aqueous media using surfactant and subsequent cycloaddition reaction in the same pot has been described by P.K Bhattacharya et al[50]. This is a new approach of the synthesis of nitrone using green chemistry methodology. The control of regioselectivity favours the formation of *trans*-5-substituted isoxazolidine. This work not only leads to an environmentally benign system but also will provides a new aspect of cycloaddition reactions in water (**Figure 25**).

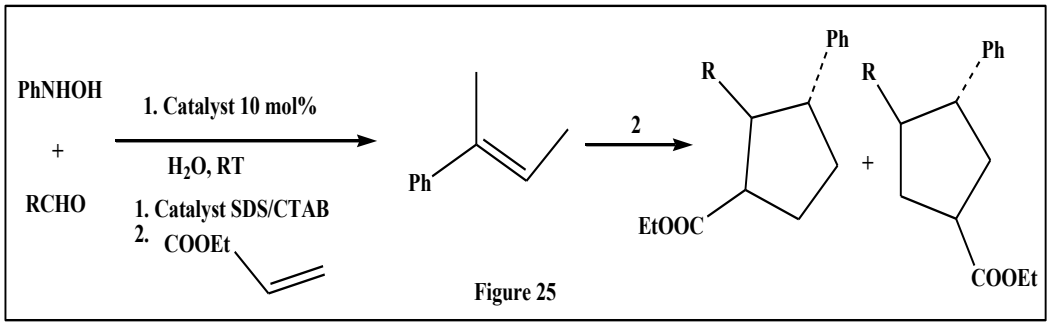
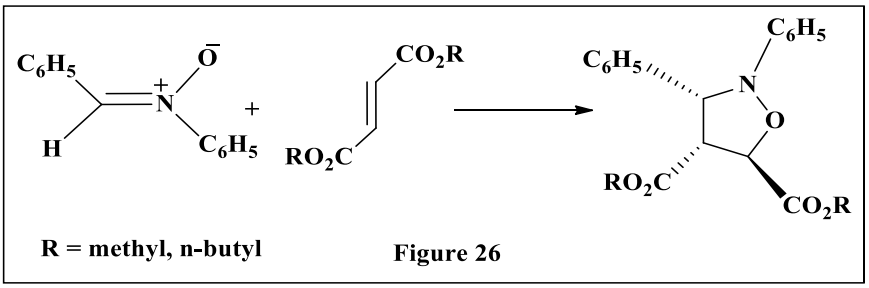


Figure 25

Gholami et al[51] reported 1,3-dipolar cycloaddition reactions of C,*N*-diphenylnitrone with di-*n*-butyl fumarate and dimethyl fumarate in water and other solvents (**Figure 26**). The reaction rates of cycloaddition reaction between nitrone and dimethyl fumarate were found higher than those with di-*n*-butyl fumarate, a fact imputed to steric effects.

They also observed that the reaction rate decreased with increasing polarity of the organic solvent; the rates in *n*-hexane were eight- to 10-fold than that in ethanol. But with water, which has the highest polarity, the rates were unexpectedly 13 and 125 times higher than that in ethanol respectively, pointing to the fact that the solvent polarity was not an important issue for the reaction rate in aqueous solutions.



R = methyl, n-butyl

Figure 26

Shaoqun Zhu et al[52] reported new route of oxidative cycloaddition reaction of *N*-substituted hydroxylamines with alkenes under visible light photoredox catalysis. The highly reactive nitrone is trapped with olefines in water to furnish isoxazolidines (**Figure 27**). This novel protocol provides a rapid, mild, and efficient procedure to valuable five-membered ring isoxazolidine heterocycles in a concise fashion.

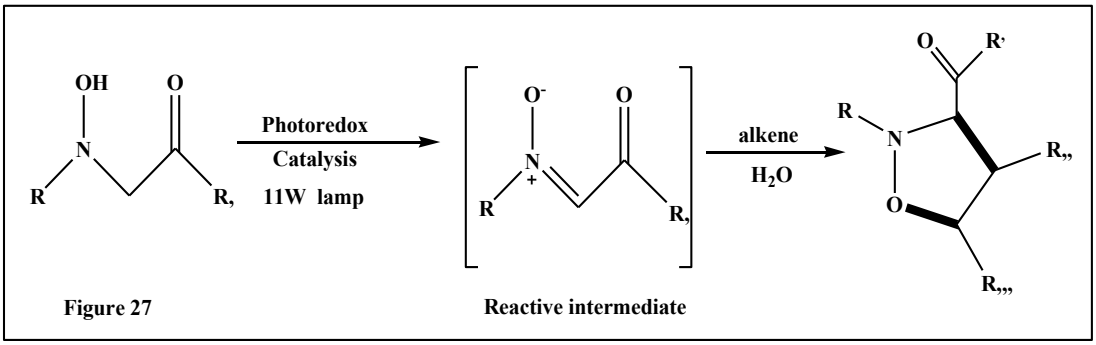


Figure 27 **Reactive intermediate**

Microwave assisted (solid phase) synthesis of nitrones and cycloaddition reactions

The use of microwaves in organic synthesis has increased dramatically within the past decade and received widespread acceptance and thereby becoming an indispensable tool[53]. Nowadays, microwave technology has become a powerful tool in organic synthesis, since by employing this technology it is generally possible to prepare organic compounds very fast with high purity and better yields compared with other more conventional methods[54]. Moreover, the technique is also considered as an important approach towards '*Green Chemistry'* because of its eco-friendly nature. Microwave irradiation can be used as a facile and general method for the synthesis of variety of isoxazolidine and isoxazoline derivatives where considerably shortened reaction time is involved[53].

Pineiro Melo et al[55] in their exclusive review on "*Microwave-Assisted 1,3-Dipolar Cycloaddition: an Eco-Friendly Approach to Five-Membered Heterocycles*" stated that this non conventional energy source is not only reduce chemical reaction times, but increase yields and in some cases can lead to different outcomes from those obtained with conventional heating.

Loupy et al[56] first reported microwave induced nitrone cycloaddition reaction, where they showed the utility of focussed microwaves as energy source in the 1,3-dipolar cycloaddition of *N*-methyl-α-phenyl nitrone with fluorinated dipolarophile under solvent-free condition leading to isoxazolidine derivatives having biological activities. Under classical heating, reactions were performed with refluxing with toluene (110^0C) with limited yields after long times. Both the yields and experimental conditions were improved in solvent-free conditions and even more under microwave. (**Figure 28**). This is also interesting to mention that regio and stereoselectivities remain unchanged irrespective of the experimental condition[57]. Loupy et al also reported an interesting change in yield for the synthesis of fluoro cycloadducts (**Figure 29**).

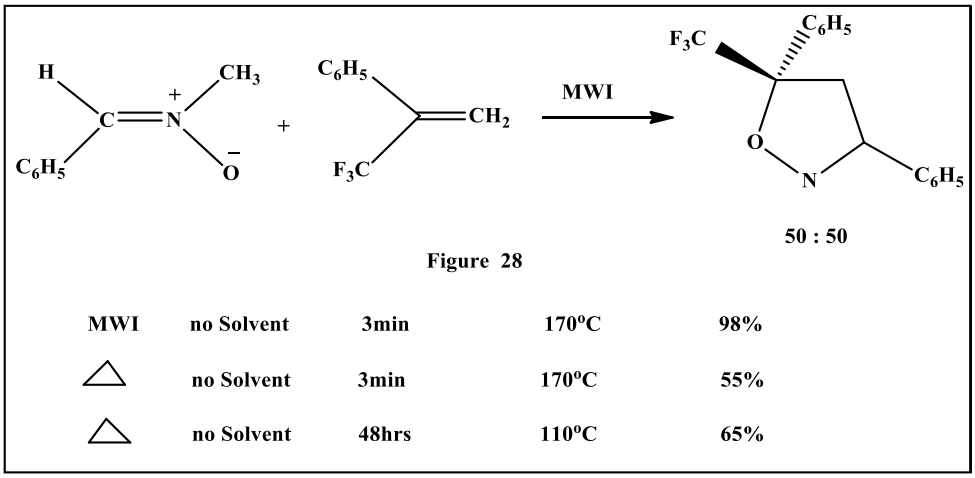


Figure 28

MWI	no Solvent	3min	170°C	98%
△	no Solvent	3min	170°C	55%
△	no Solvent	48hrs	110°C	65%

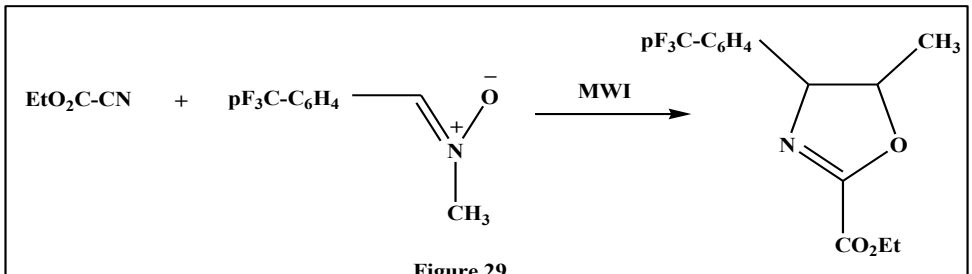
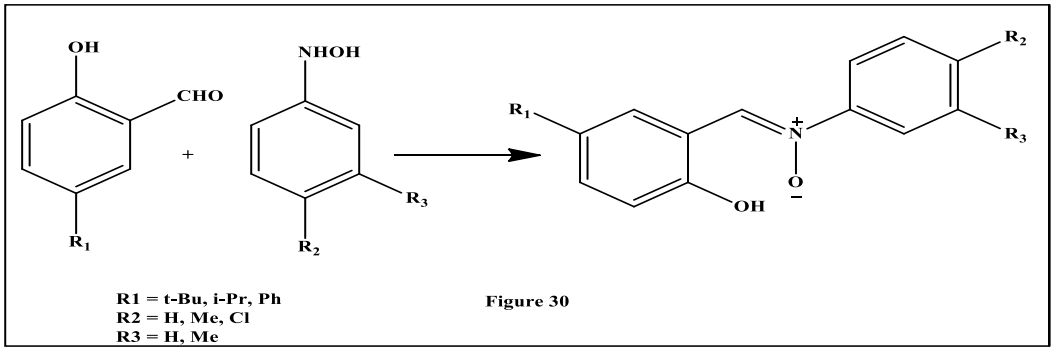


Figure 29

MW	50%
△	17%

An informative review[58] on microwave induced 1,3-dipolar cycloaddition reaction was reported by Muthusubramaniun et al. They have reported synthesis of α-(5-substituted-2-hydroxyaryl)-*N*-aryl nitrones and showed that in microwave assisted reaction the required time for the cycloaddition is much less and the yield is much higher than that of conventional methods.



R1 = t-Bu, i-Pr, Ph
R2 = H, Me, Cl
R3 = H, Me

Figure 30

Antonio de la Hoz et al[59] reported in their review "*Cycloadditions under Microwave Irradiation Conditions: Methods and Applications"* that microwave induced cycloaddition reactions are capable of exploring new dimensions not only in the changes in *chemo*, *regio* and s*tereoselectivity* but also in the transition states of the reactions as well. Heterocyclic compounds have been synthesized by cycloaddition reactions, or have been observed to react as dienes and dipoles under microwave irradiation conditions. Even those heterocyclic systems that are very reluctant to participate in cycloaddition reactions, such as pyrazoles, can be induced to react under microwave irradiation conditions. The application of this method to the chemistry of *[60] fullerene* has permitted derivatization of this system while avoiding the problems of poly cycloaddition and cycloreversion. In most cases, wonderful accelerations and great improvements in yields and reaction conditions are observed. These changes have been connected with the absolute hardness of the transition state, with the harder state being favored using microwave irradiation conditions. Microwave chemistry thus opens new possibilities for modifying the result of competitive reactions by considering the relative hardness of the transition states.

Dujardin et al[60] reported a highly efficient solvent free 1,3-dipolar cycloaddition reaction of *N*-substituted dipolarophiles and nitrones. New isoxazolidine derivatives were synthesized in good to excellent yields by 1,3-dipolar cycloaddition reactions of *N*-vinyl amide dipolarophiles and nitrones. Strikingly solvent free condition gave high conversion and yields in shortened reaction time and minimized degradation products (**Figure 31**).

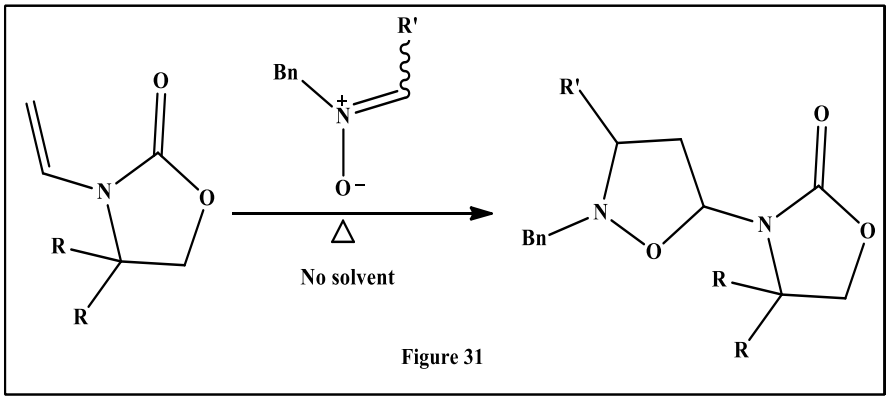


Figure 31

Ionic liquid (RTIL) mediated 1,3-dipolar cycloaddition reactions

It has been observed that, ionic liquids are nowadays used widely as green solvents with excellent properties like high solvating ability, wide liquidious range, tunable polarity, high thermal stability, negligible vapour pressure and for its capability of recyclability[61]. Hence majority of classical organic reactions may be performed in ionic liquid with great advantages especially in yield and selectivity compared with conventional conditions. Ionic liquids are also referred as 'designer solvents' due to their properties like hydrophilicity, hydrophobicity and Lewis acidity[62]. The viscosity and density of IL's can be altered by the fine-tuning of certain parameters like the choice of organic cation, inorganic anion and also the length of alkyl chain attached to an organic cation (**Figure 32**).

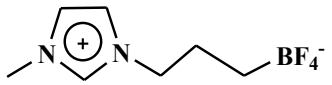


Figure 32- Chemical structure of ionic liquid

Due to the wide scope of structural variations in IL's, a synthetic chemist gets an opportunity to plan for most suitable solvent for a particular reaction. As the ionic liquids are mainly composed of non-coordinating ions, therefore, they can provide a suitable reaction medium for reactions which involve reactive ionic intermediates. The ionic liquids can promote unprecedented stereoselectivities and also increase reaction rates due to the stabilization of charged intermediates. The ionic liquids may be used as recyclable solvents for the immobilization of transition metal based catalysts, Lewis acids and enzymes[62]. Because of their green credentials and potential to increase reaction rates and selectivities, ionic liquids are finding lot of applications in organic synthesis[63] with an ever-increasing interest for exploration of newer synthesis in ionic liquids[64].

Bortolini et al[65] have shown that 1,3-dipolar cycloaddition reaction of nitrones with alkenes afforded the corresponding isoxazolidine derivatives in ionic liquids in the presence of $Er(OTf)_3$. The ionic liquid and the catalyst are recycled up to four times without any specific treatment or loss of activity (**Figure 33**).

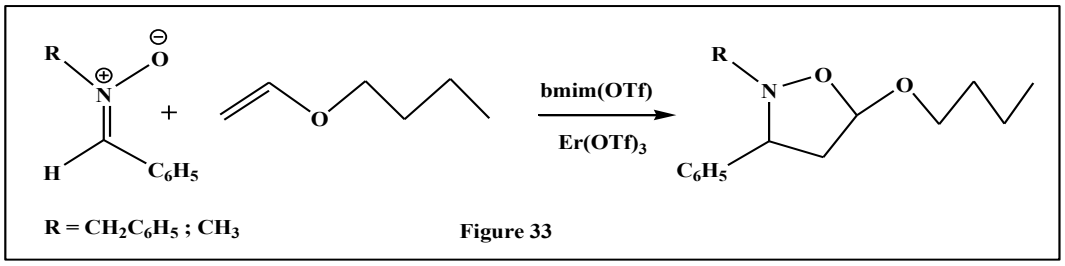


Figure 33

Yadav et al[66] have shown that *1-Butyl-3-methylimidazolium based ionic liquids* are found to accelerate significantly the intermolecular 1,3-dipolar cycloaddition reaction of nitrones derived *in situ* from aldehydes and phenyl hydroxylamine, with electron deficient alkenes to afford enhanced rates and improved yields of isoxazolidine derivatives with high regio and diastereoselectivity (**Figure 34**).

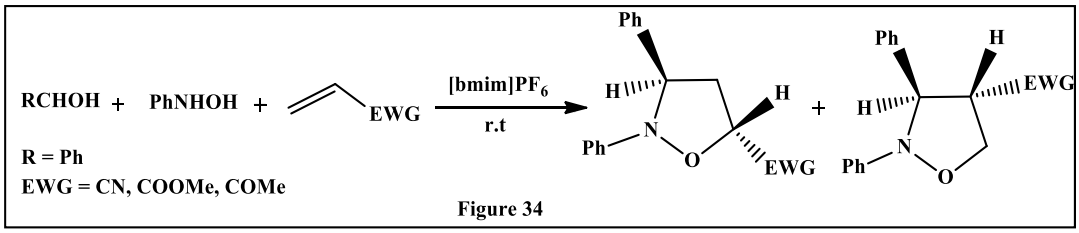


Figure 34

Bazureau et al[67] have reported 1,3-dipolar cycloaddition reactions between a nitrone derived from 2-ethoxy benzaldehyde and electron withdrawing dipolarophiles in various *air and moisture stable ionic liquids.* Significant rate enhancements and improved yields at 70^0 C have been noticed with [emim][BF_4] and [emim][NfO] ionic liquids.

Dinparast et al[68] have reported the importance of RTIL's in the efficient synthesis of isoxazoline derivatives via *N*-Phenyl-C-aryl nitrone with dimethyl acetylene dicarboxylate (**Figure 35**).

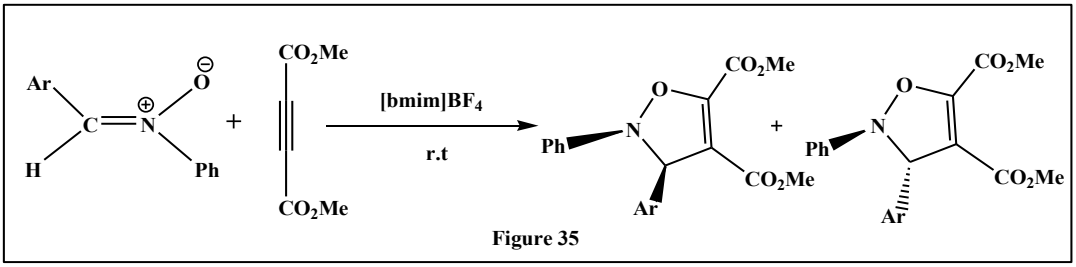
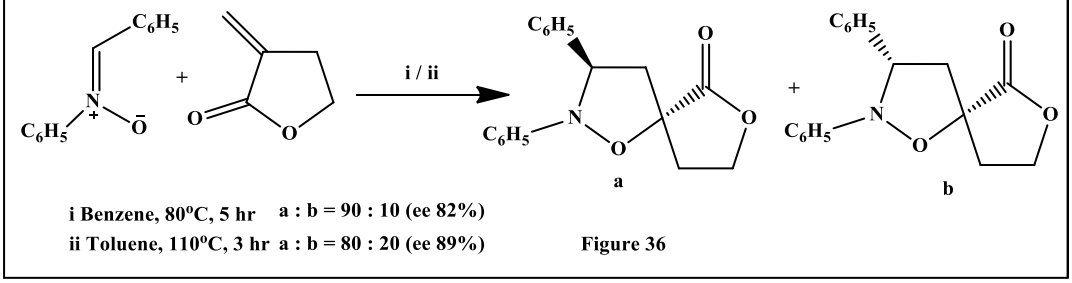


Figure 35

Some other important contributions in the synthesis and cycloaddition reactions of nitrones (may not be adopting "Green Chemistry" methodologies)

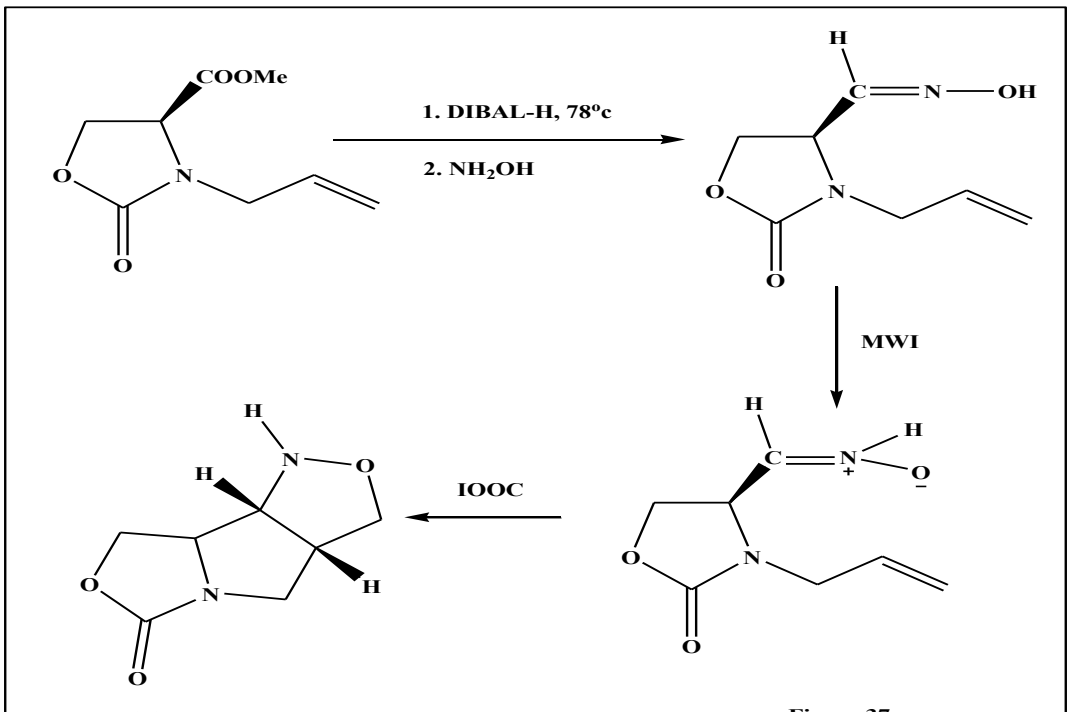
Goti et al[69] have reported cycloaddition reactions of *C*, *N*-diphenyl nitrone with butyrolactones as dipolarophiles. The cycloaddition reactions are found to be highly stereoselective in nature giving both the enantiomers with high yield (**Figure 36**).



i Benzene, 80°C, 5 hr a : b = 90 : 10 (ee 82%)
ii Toluene, 110°C, 3 hr a : b = 80 : 20 (ee 89%)

Figure 36

Cheng et al[70] reported highly stereoselective intramolecular cycloaddition reactions of unsaturated *N*-substituted oximes, nitrones and azomethyne ylides on the surface of the silica gel without a solvent in good yields. These reactions have been conducted under microwave irradiation to produce tricyclic isoxazolidines fused with pyrroline or piperidine ring (**Figure 37**)..



IOOC = Intramolecular oxime-olefin cycloaddition

Figure 37

A series of unexpected cycloadducts along with expected cycloadducts have been reported by Abhijit Banerjee and his group[71] using 1,3-dipolar cycloaddition reaction of 3,4-dihydro morpholine *N*-oxide with piperidine amides of cinnamic acid and *p*-substituted cinnamic acids. Since unexpected cycloadducts are very rare therefore this work has great interest for the researchers working on nitrone cycloaddition reactions (**Figure 38**).

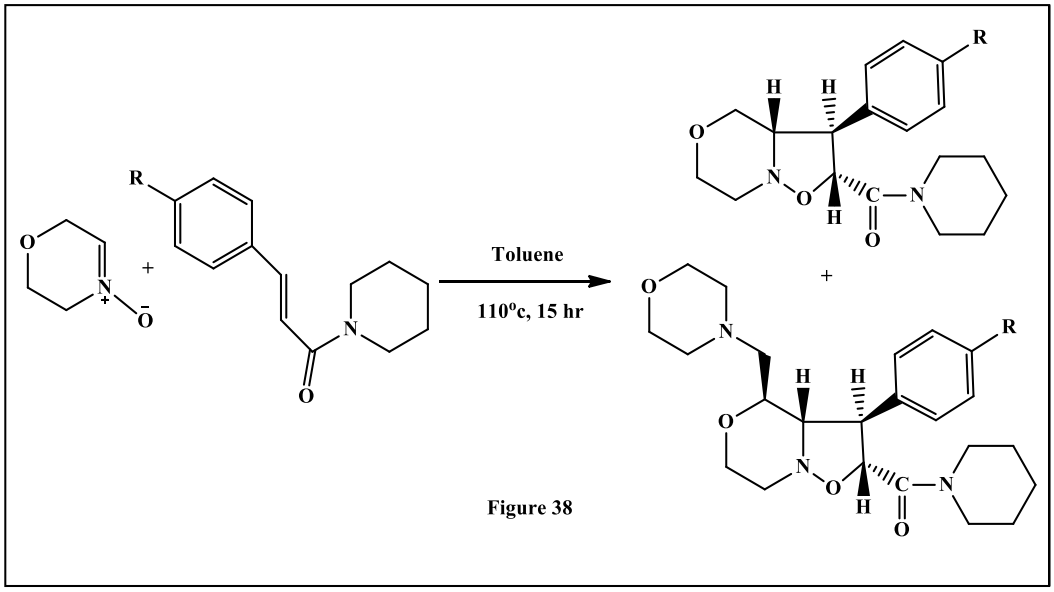


Figure 38

One of the pioneering works on the synthesis and 1,3-dipolar cycloaddition reaction on *bisnitrone* and subsequently *bisisoxazolidines* was reported by Francis Heaney et al[72]. The reactions were reported as highly diastereoselective in nature. This was the first reported synthesis of bisnitrones (**Figure 39**).

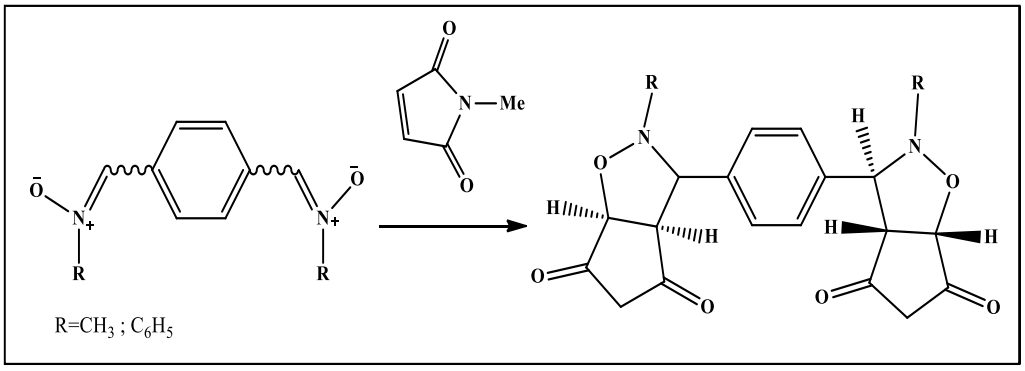


Figure 39

Recently, Patridge and his group[73] reported development of *N*-sulphonyl nitrones and their cycloaddition reactions from *oxaziridines*. The research work has a new approach, as far as the generation of nitrone is concerned (**Figure 40**).

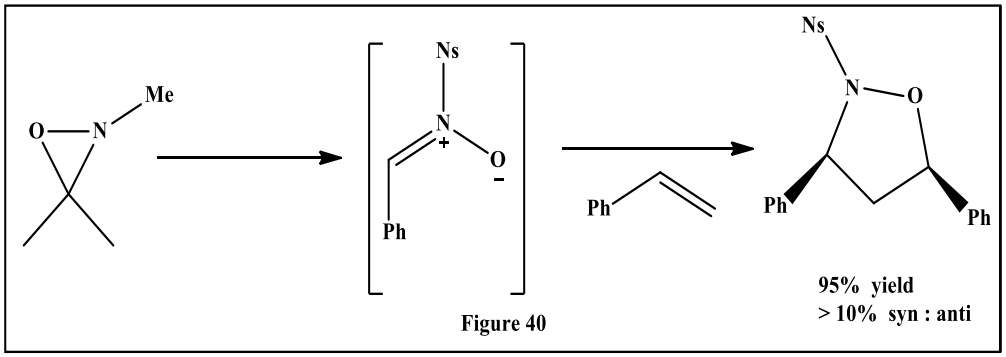


Figure 40

Sheikh Ali and his group[74] reported a new stereochemical approach for 1,3-dipolar cycloaddition reaction of internally H-bonded chiral methylene nitrones. Their contributions in this chemistry are regarded as one of the pioneering research works in nitrone cycloaddition reactions (**Figure 41**).

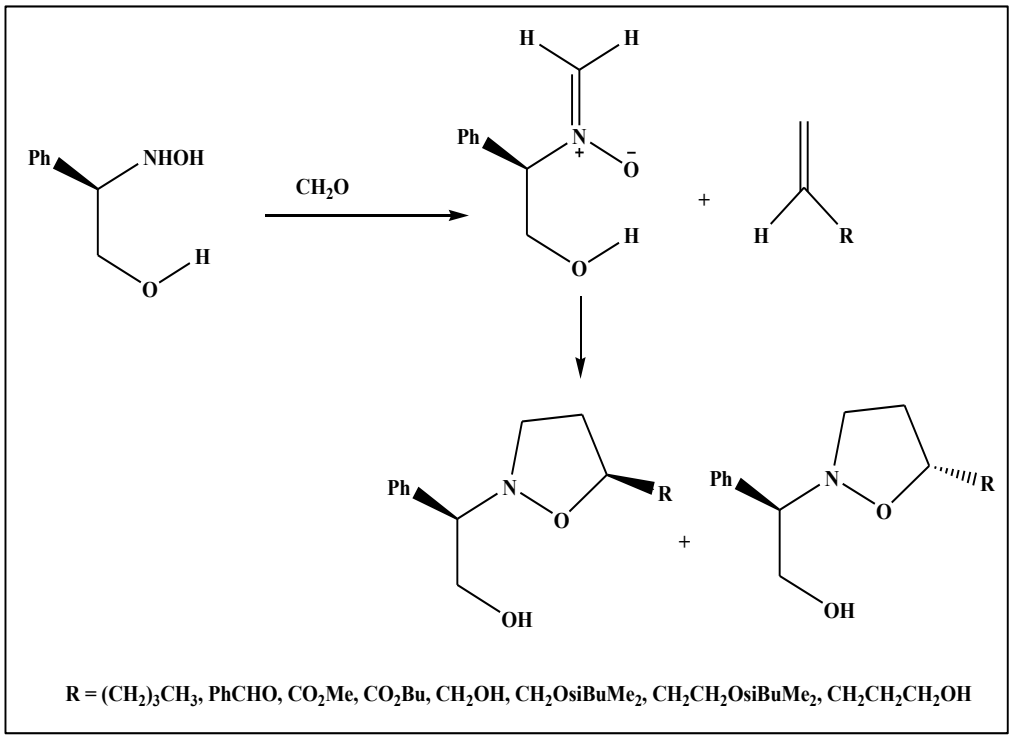


Figure 41

Lubor Fisera and his group[75] reported few novel cycloaddition reactions in 2009 where the nitrones were derived from sugars. Their outstanding contribution is actually diastereoselective synthesis of isoxazolidinyle nucleosides using 1,3-dipolar cycloaddition reaction of chiral sugar derived nitrones (**Figure 42**)..

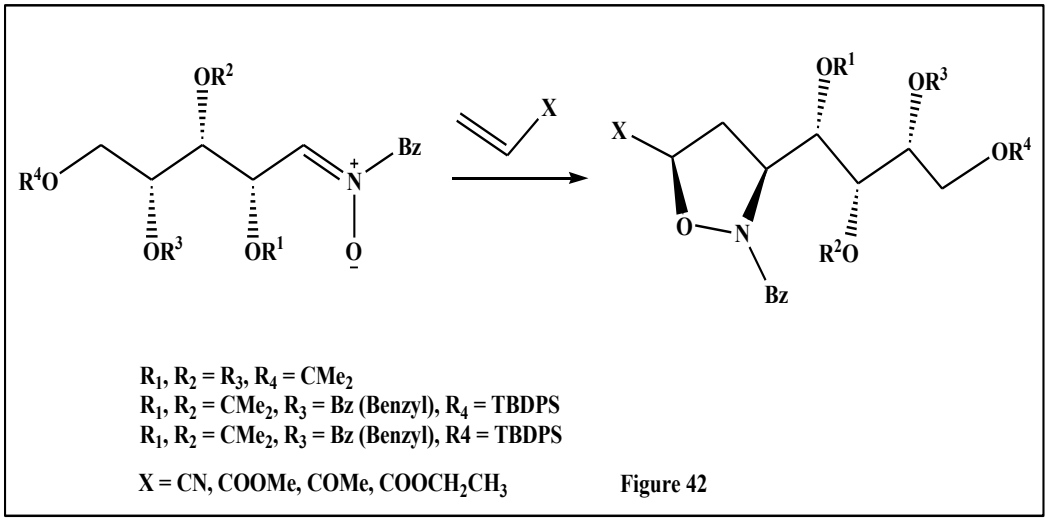


Figure 42

Obijalska et al[76] reported very recently (**2014**) that fluorinated nitrones derived from fluoral and difluoro acetaldehyde may react with thioketones via [3 + 2] cycloaddition reaction yielding 1,4,2-oxathiazolidines in a regioselective manner. It was further reported that, cycloaliphatic thioketones reacted faster than aromatic thioketones and in presence of a fluorinated alkyl group. The cycloadducts display a remarkable stability and do not decompose at room temperature in the crystalline form nor in solution (**Figure 43**).

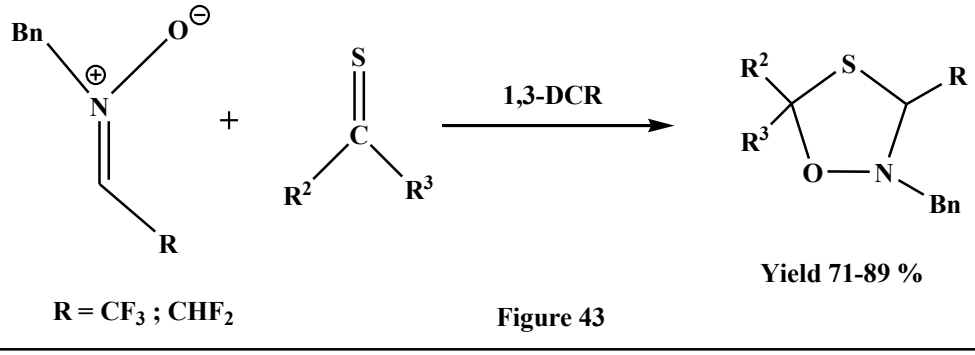


Figure 43

Mekheimer et al[77] reported a new technique of cycloaddition reaction involving the reaction between nitrones and acetonitrile derivatives *under solar heating* efficiently leading to *isoxazolidines* which further underwent rearrangement to *unexpected 3-aryl-2-cyanothioacrylamide* and *3-aryl-2-(hetaryl)acrylonitrile* derivatives. The procedure has significant advantages over conventional methodologies viz, *greener approach,* high yielding and simple work-up procedure (**Figure 44**).

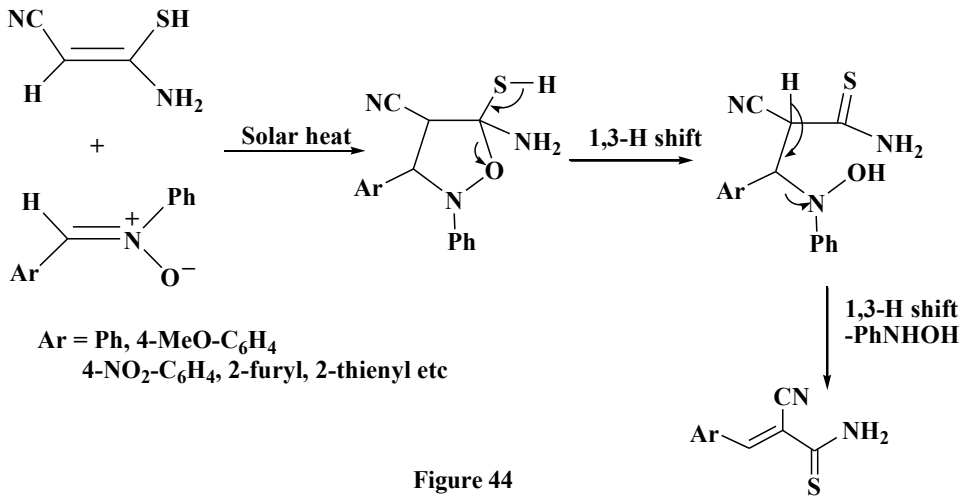


Figure 44

Serkan Yavuz et al[78] reported a simple, fast, efficient and eco-friendly protocol for the synthesis of alkyl and aryl-*N*-methyl nitrones. The corresponding nitrones of aromatic aldehydes, aliphatic aldehydes and alicyclic carbonyl compounds have been prepared from *N*-methylhydroxylaminehydrochloride and Na_2CO_3-Na_2SO_4 by simply grinding at room temperature and also without using a solvent (**Figure 45**).

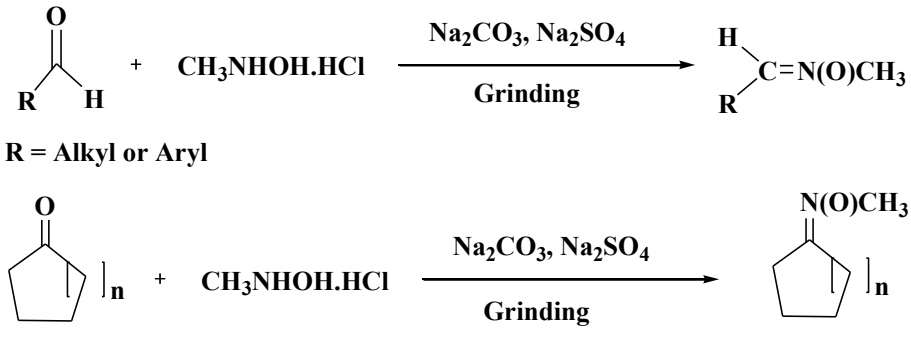


Figure 45

Savinkov et al[79] reported some new class of 1,3-dipolar cycloaddition reactions of dialkyl-substituted 2-benzylidenecyclopropane-1,1-dicarboxylates and a number of C-carbamoyl nitrones having high efficiency and selectivity with the formation of single isomeric spiro[cyclopropane-1,4-isoxazolidine] cycloadducts. Obtained cycloadducts may easily undergo cyclopropyl ring opening and cyclization to form new *β-lactams* fused with isoxazolidine ring in high yields. They demonstrated for the first time a new class of biologically active *β-lactam antibiotics* containing *azeto[2,3- d]isoxazolidine core*. They may be obtained by new base promoted cyclization and cyclopropane ring opening reaction of cycloadducts of 2-arylmethylidene cyclopropane dicarboxylates and C-carbamoyl nitrones (**Figure 46**).

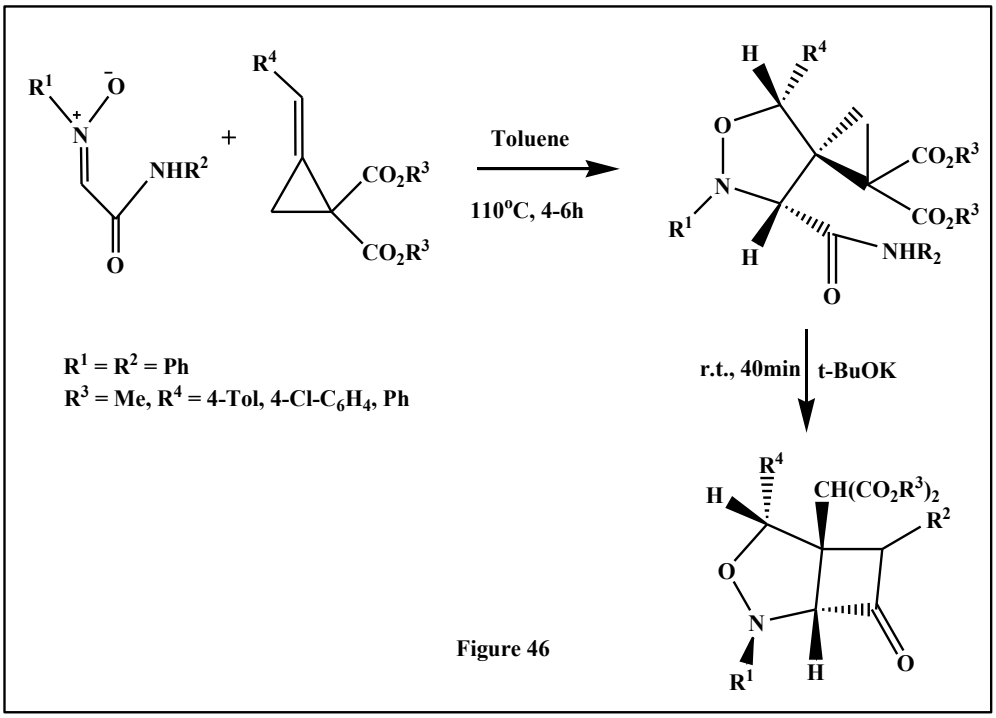


Figure 46

Sandip Hota et al[80] reported an efficient synthetic route to the development of *cis*-fused chromano[4,3-c]isoxazoles via dehydrative intramolecular 1,3-dipolar nitrone cycloaddition reaction in organized aqueous media in presence of a surfactant (viz. CTAB) as catalyst. The reactions were reported as an example of *green and sustainable* methodologies with the additional advantage of easy isolation of products (**Figure 47**).

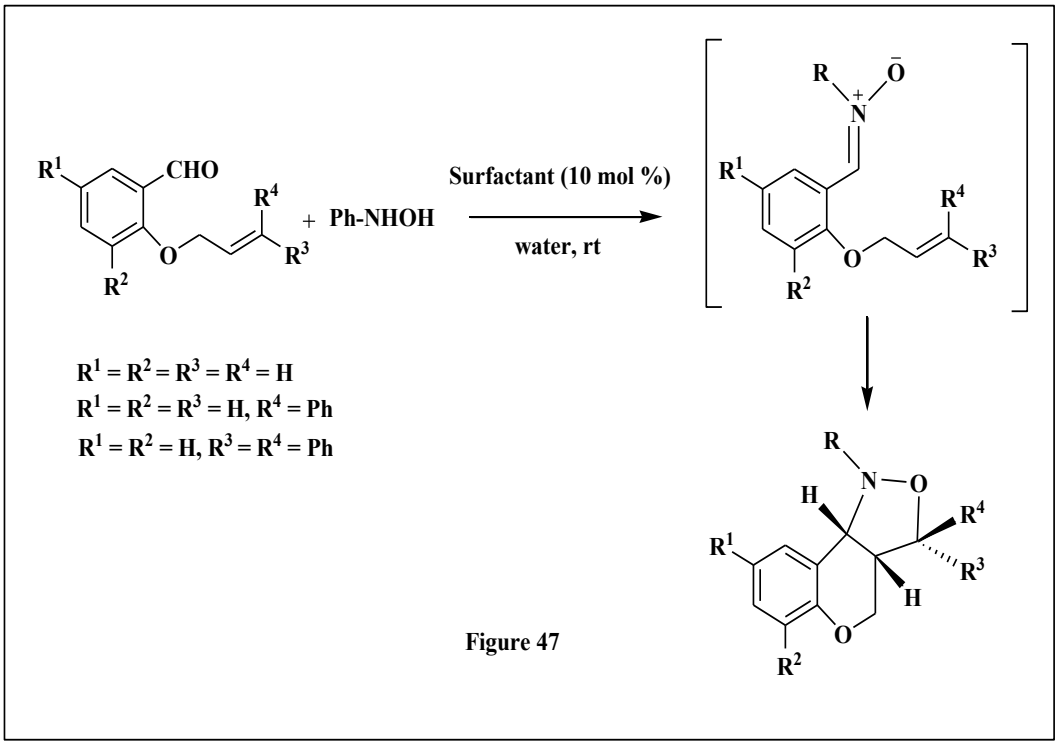


Figure 47

Stepakov et al[81] reported the first example of 1,3-dipolar cycloaddition reactions of nitrones with allene derivatives containing cyclopropane moiety for the synthesis of vinylidene cyclopropanes. The nitrone reacts with the C1'–C2' double bond of vinylidene cyclopropanes to give the corresponding 4-cyclopropylidene-isoxazolidines. The high regioselectivity has been observed in these 1,3-dipolar cycloaddition reactions and was explained from two point of views: (1) steric interactions between the substituents on the reactants and (2) atomic orbital coefficients of HOMO (nitrone)–LUMO (vinylidene cyclopropane) favoured the expected interaction for this type of cycloaddition (**Figure 48**).

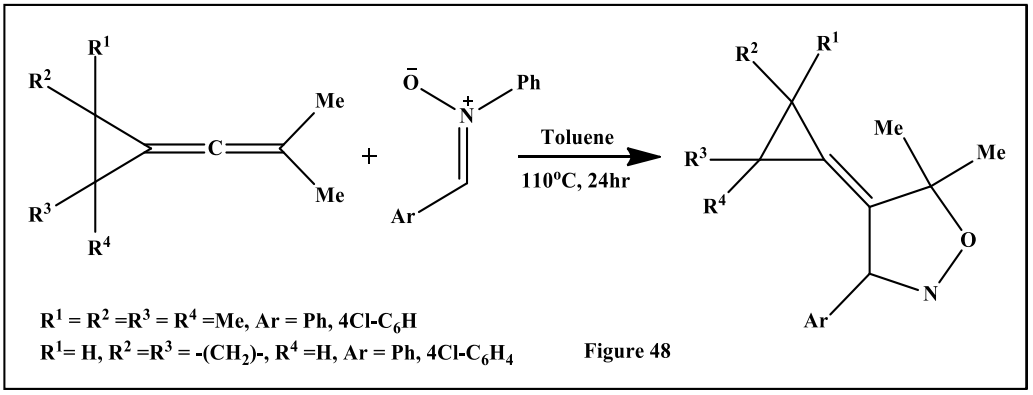
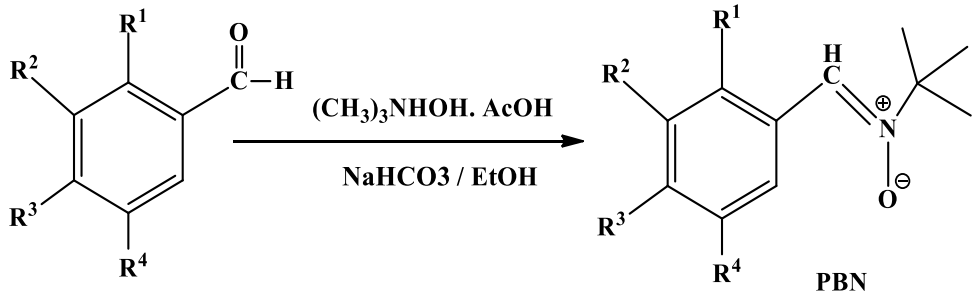


Figure 48

Daniel Perez et al[82] reported the synthesis of hydroxy phenyl nitrones by the reaction of the corresponding hydroxy benzaldehyde with *N*-tert-butyl hydroxylamine under microwave irradiation. Hydroxyphenyl nitrones, derivatives of nitrone, α-phenyl-*N*-tert-butylnitrone (PBN), were synthesized and their *antioxidant*, *anti-inflammatory* and *neuro protective activity* in neural cells were evaluated. The hydroxy phenyl nitrones synthesized showed *anti-inflammatory activity* modulating nitrite production in primary neural cell cultures of astrocytes and microglia treated with lipopolysaccharide (LPS), a potent inflammatory agent. These experimental data recommends a *potential therapeutic use* of these hydroxyl phenyl nitrones against oxygen and nitrogen reactive species involved in neuro degenerative pathology such as *Parkinson's disease* (**Figure 49**).

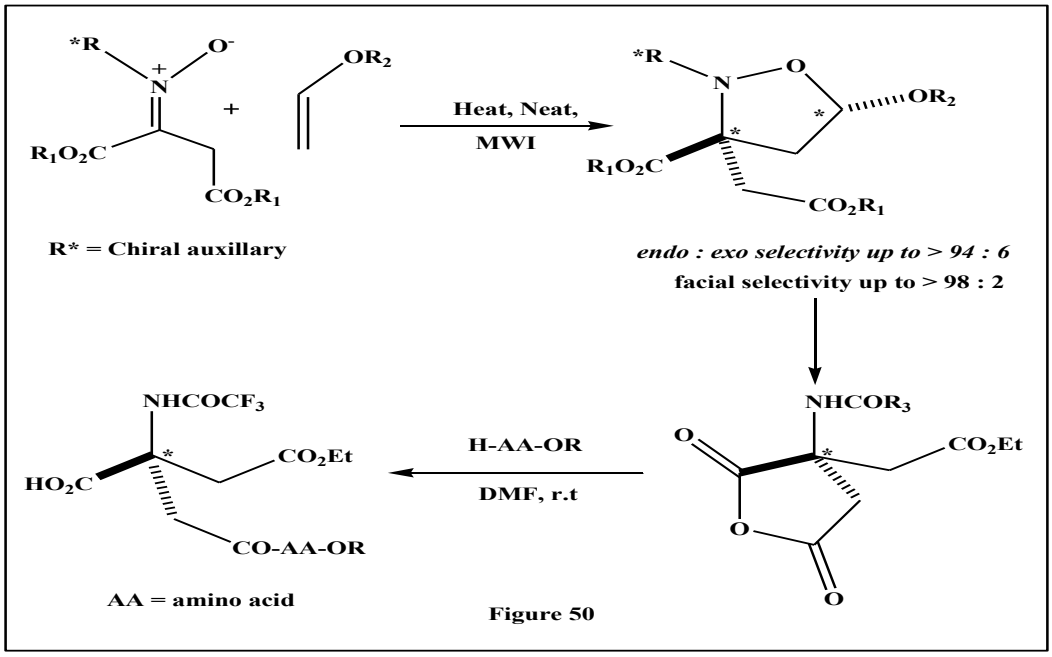


1. R^1, R^2, R^3, R^4 = H
2. R^2, R^3, R^4 = H, R^1 = OH
3. R^1, R^2, R^4 = H, R^3 = OH
4. R^1 = H, R^3 = OH, R^2, R^4 = $(CH_3)_3$

Figure 49

5
6
7

Pascale Cividino et al[83] reported the synthesis of acyclic (*E*)-α,α-dialkyl keto nitrones containing a chiral auxiliary on the nitrogen atom and they have successfully conducted the asymmetric synthesis of *α,α-disubstituted amino acids* using regio- and stereo controlled 1,3-dipolar cycloaddition reactions with vinyl ethers. *α,α-disubstituted amino acids* (DAA, quaternary amino acids) are highly valuable building blocks for the synthesis of many kinds of peptidomimetics (**Figure 50**).



Yong Qian et al[84] reported synthesis of a series of new *cyclometalated iridium hydrides* derived from the C−H bond activation of *aromatic nitrones* and also the biological evaluation of these iridium hydrides as *antitumor agents*. The nitrone *ligands* were based on the structure of a popular antioxidant, *α-phenyl-N-tert-butylnitrone (PBN)*. The author's claimed that compared to *cisplatin*, the *iridium hydrides* exhibit excellent *antitumor activity* and this activity was *remarkebly superior* to that of *cisplatin*. These results recommand for the first time, that metal hydrides could be a new type of *metal-based antitumor agent* (**Figure 51**).

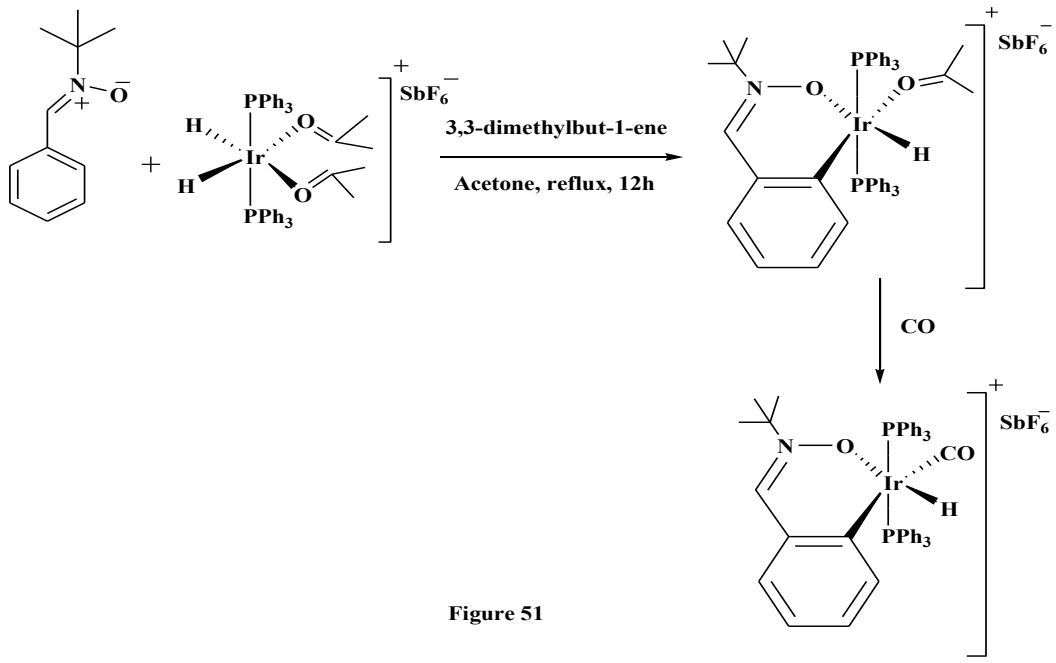


Figure 51

Albert Padwa[85] and K Jorgensen[86] in their respective reviews based upon a variety of isoxazoline derivatives have shown that they may be excellent precursors to a variety of highly useful synthetic intermediates (**Figure 52**).

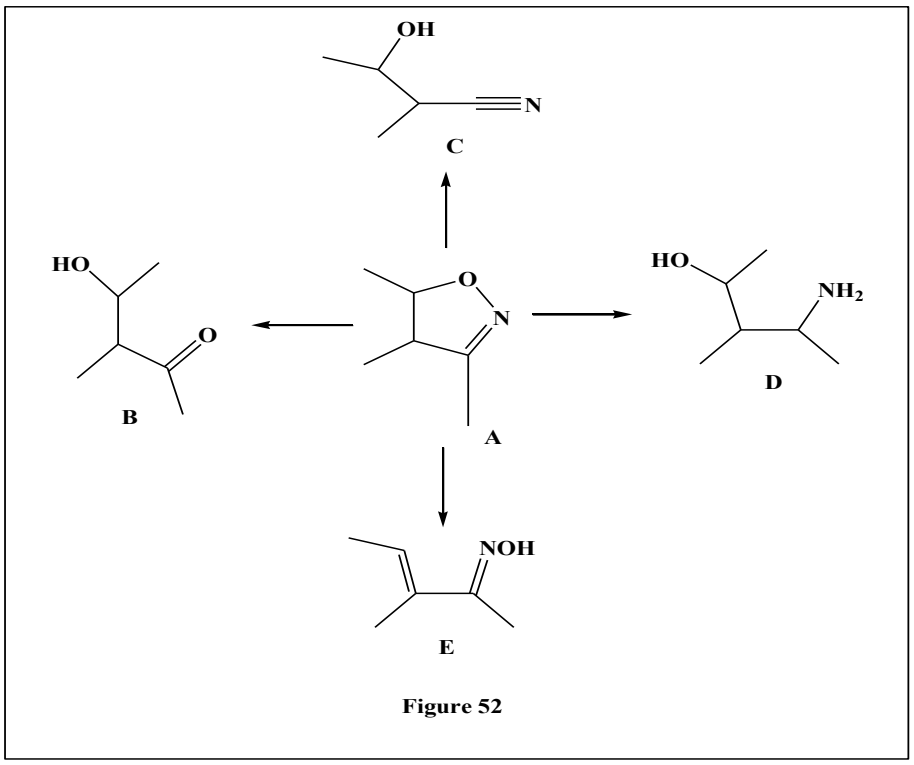
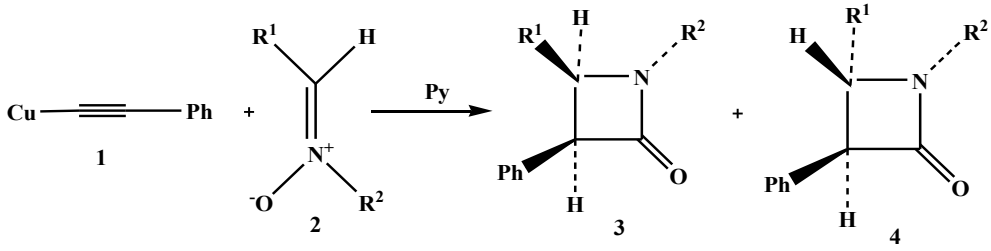


Figure 52

The N-O bond cleavage of isoxazoline (A) followed by hydrolytic workup provides β-hydroxy ketone (B) and therefore provides an alternate route to an aldol product. The dehydrogenation of intermediate imino alcohol arising from N-O bond cleavage affords β-hydroxy nitrile (C).Complete reduction of the isoxazoline ring delivers γ-amino alcohol (D). Base mediated ring opening provides α,β-unsaturated oxime (E). All the above hydroxyl compounds may be easily dehydrated or the other functional group may be transferred further to obtain synthetically useful molecules of biological interest.

Recently, the applications of nitrone cycloaddition reactions in the synthesis of *β-lactam* and further reactions has been reviewed and the gravity of this synthetic procedure has been explored[87,88]. Few examples of these reactions are depicted.

Nitrone cycloaddition reactions are found to be a versatile method for the synthesis of a wide variety of *β*-lactam derivatives. The reaction is commonly known as "Kinugasa reaction". A simple example of Kinugasa reaction is the reaction of copper (I) phenylacetylide with nitrones to produce *β*-lactams (**Figure 53**)[89]. The reaction was performed in anhydrous pyridine at room temperature under nitrogen atmosphere in a short reaction time (from 30 min to 1 h).



4a :R^1= Ph, $OMeC_6H_4$, O-ClC_6H_4

4b : R^2= Ph, O-ClC_6H_4

Figure 53 Synthesis of beta lactam by Kinugasa reaction

Basak et al[90] reported an outstanding contribution in this synthesis i.e, an asymmetric version of the Kinugasa reaction using Evans's oxazolidinone as an asymmetric auxiliary (**Figure 54**).

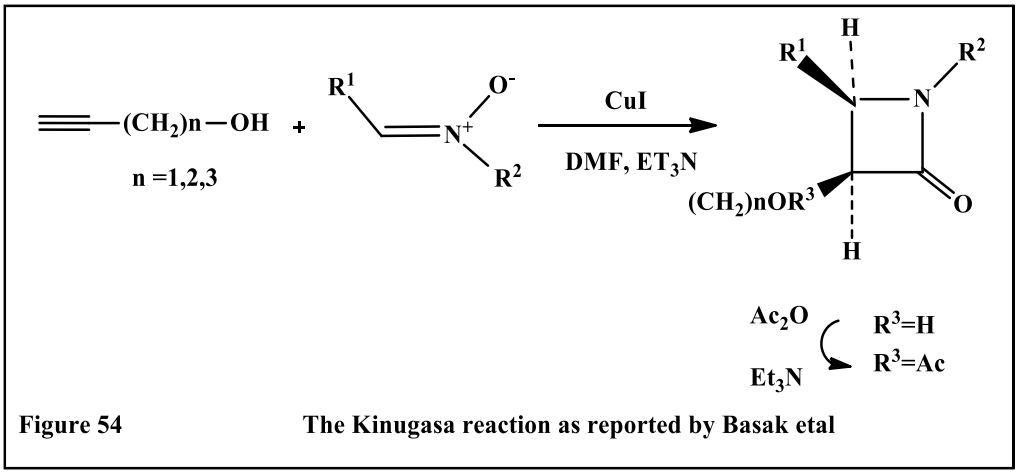


Figure 54 **The Kinugasa reaction as reported by Basak etal**

Keeping in mind the importance of "*Green ChemistryTechniques*" in today's scenario and the valuable flow chart suggested by Paul Anastas and J Warnar[41] (**Figure 55**) our research group has also contributed some important syntheses (**I – VI ; Figure 56-61**) based on nitrone cycloaddition reactions to the fraternity of synthetic organic chemistry.

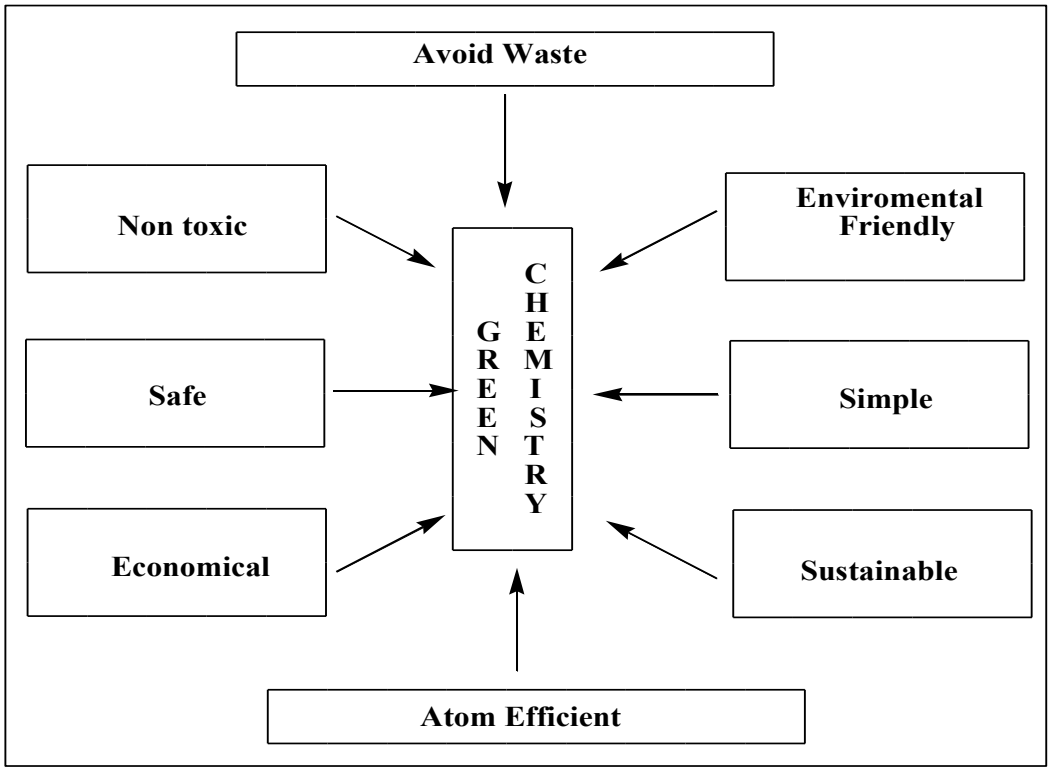


Figure 55

Recent contributions from our research group (I-VI)

I. *Synthesis of some novel class of peptides from α-amino nitrones and their potential biological activities*[91] (**Figure 56**).

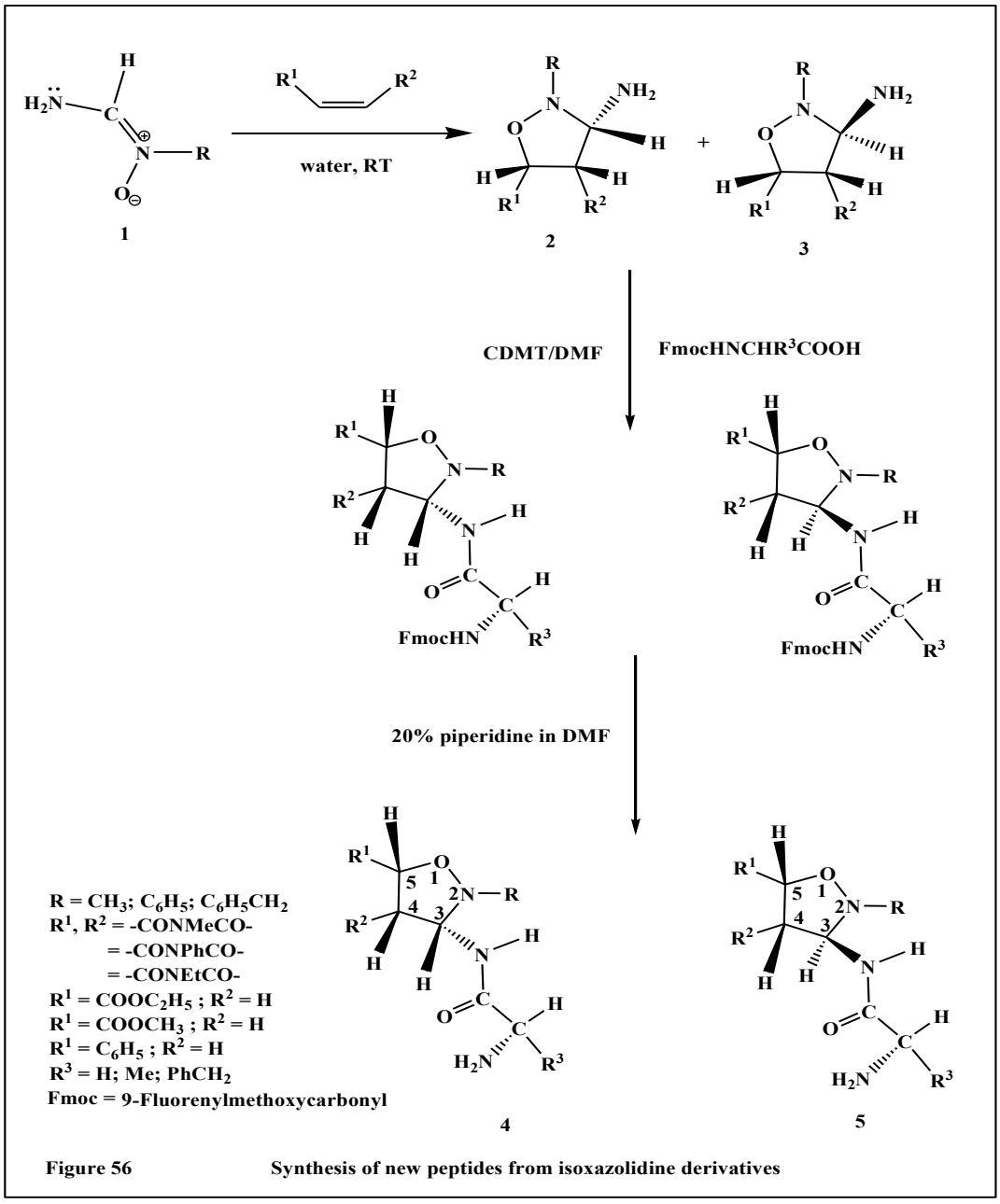
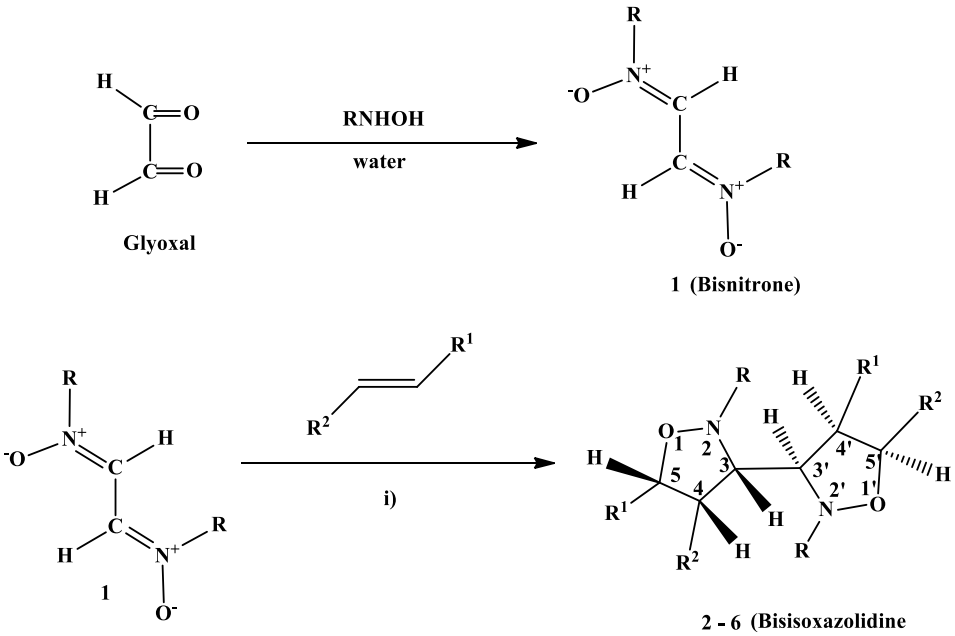


Figure 56 **Synthesis of new peptides from isoxazolidine derivatives**

II. *Synthesis of Some Novel Bisisoxazolidine Derivatives from Glyoxal-derived Bisnitrones via Simultaneous Double Cycloaddition Reactions in Water*[92] (**Figure 57**).



i) water, RT, 3-5 hr, N_2 atmosphere

R = CH_3 ; C_6H_5 ; $CH_2C_6H_5$

2 : R_1, R_2 = -CONMeCO-

3 : R_1, R_2 = -CONPhCO-

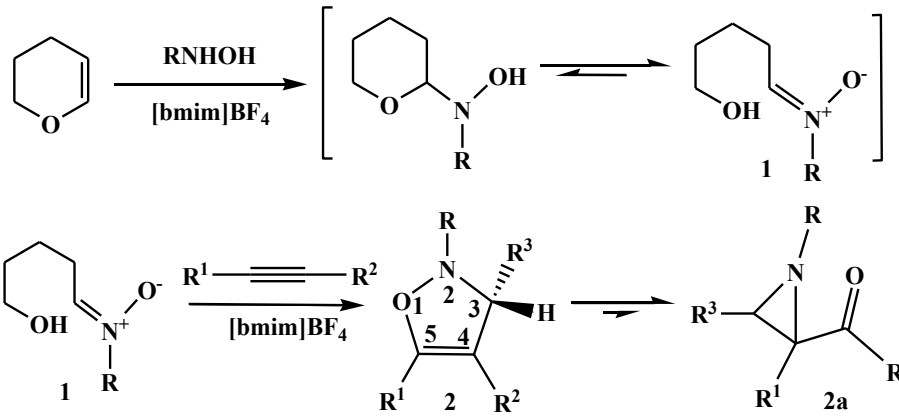
4 : R_1, R_2 = -CONCyCO-

5 : R_1 = H ; R_2 = $-CO_2CH_3$

6 : R_1 = H ; R_2 = $-C_6H_5$

Figure 57 Synthesis of bisnitrones and bisisoxazolidine derivatives from glyoxal

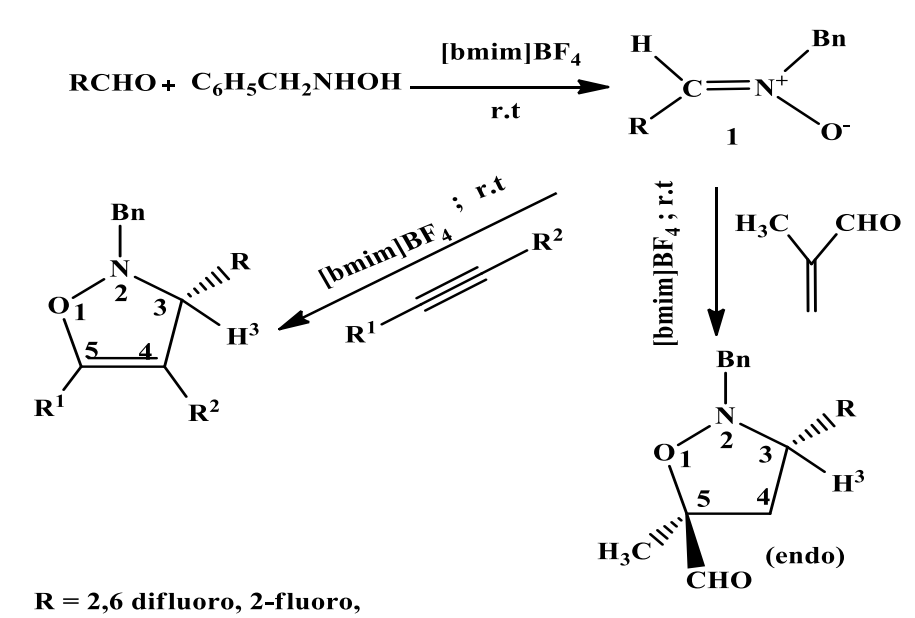
III. *A new route to the synthesis of isoxazoline derivatives from dihydropyran via cycloaddition reaction in ionic liquid*[93] (**Figure 58**).



R = $CH_3/C_6H_5/C_6H_{11}/ C_6H_5CH_2/4\text{-}HOC_6H_4/2\text{-}HOC_6H_4$
R^1 = Ph ; R^2 = $COOCH_3$
R^1 = R^2 = $COOCH_3$
R^1 = R^2 = COOH
R^3 = $-(CH_2)_4OH$

Figure 58

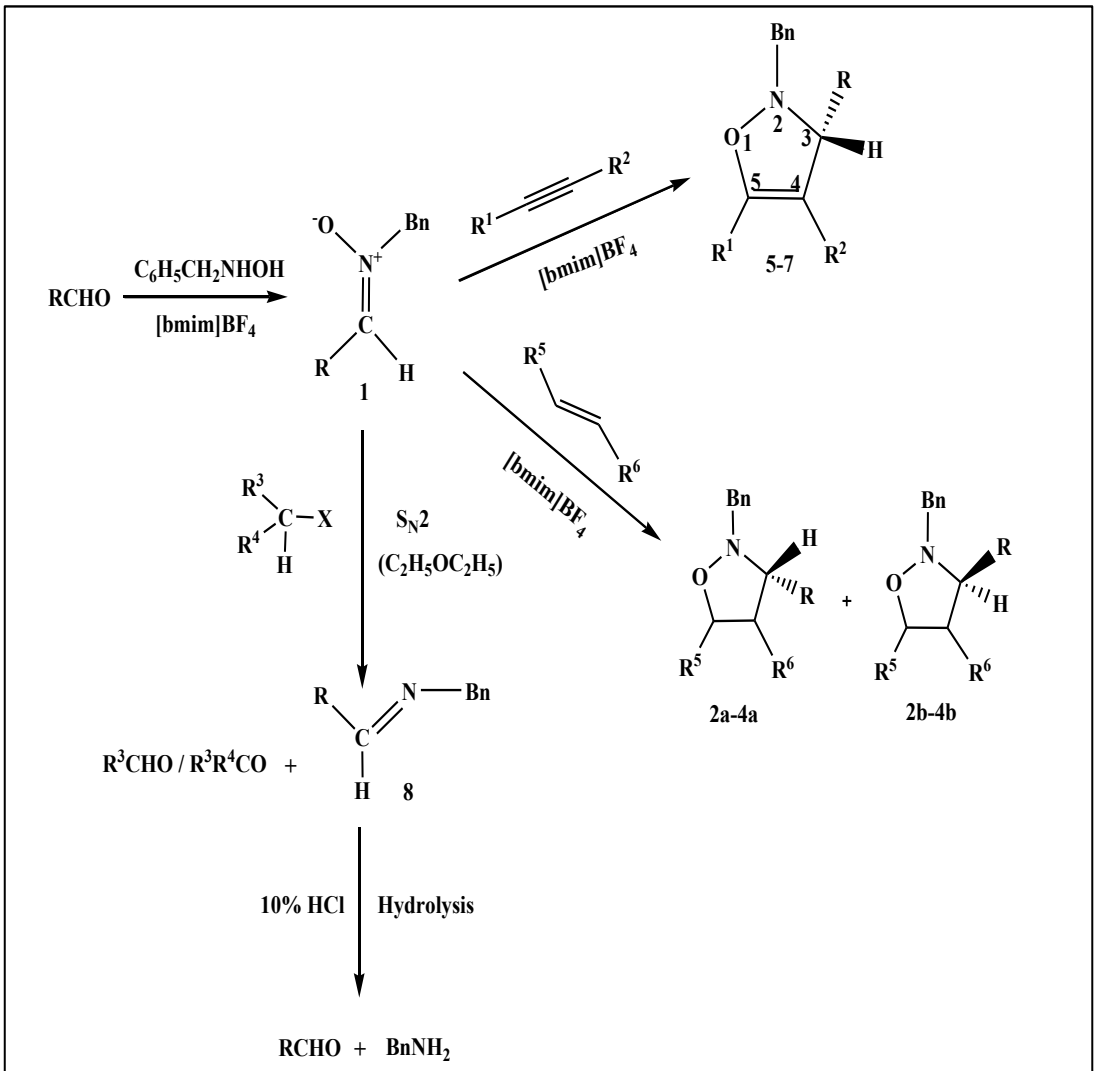
IV. *An efficient ecofriendly protocol for the synthesis of novel isoxazoline and isoxazolidines using N-benzyl fluoro nitrone via cycloaddition reactions*[94] (**Figure 59**).



R = 2,6 difluoro, 2-fluoro,
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

Figure 59

V. *Ionic liquid mediated synthesis of some novel fluoro isoxazolidine and isoxazoline derivatives using N-Benzyl fluoro nitrone via cycloaddition reaction and their antimicrobial activities*[95] (**Figure 60**).



R = 2,6 difluro benzene ; Bn = $C_6H_5CH_2$
R^1 = Ph ; R^2 = $COOCH_3$
R^1 = R^2 = $COOCH_3$
R^1 = R^2 = COOH
R^3 = Et ; Ph ; R^4 = H etc
R^3 = R^4 = Ph ; R^3 = Me ; R^4 = Ph
R^5,R^6 = -COPhCO- ; -COMeCO- ; -COCyCO-

Figure 60- Synthesis of fluoro isoxazoline & isoxazolidine derivatives using fluoro nitrone and application of the nitrone in atom efficient aldehyde & ketone synthesis

VI. *Synthesis of some novel class of bis(isoxazoline) and bis (aziridine) derivatives*[96] (**Figure 61**)

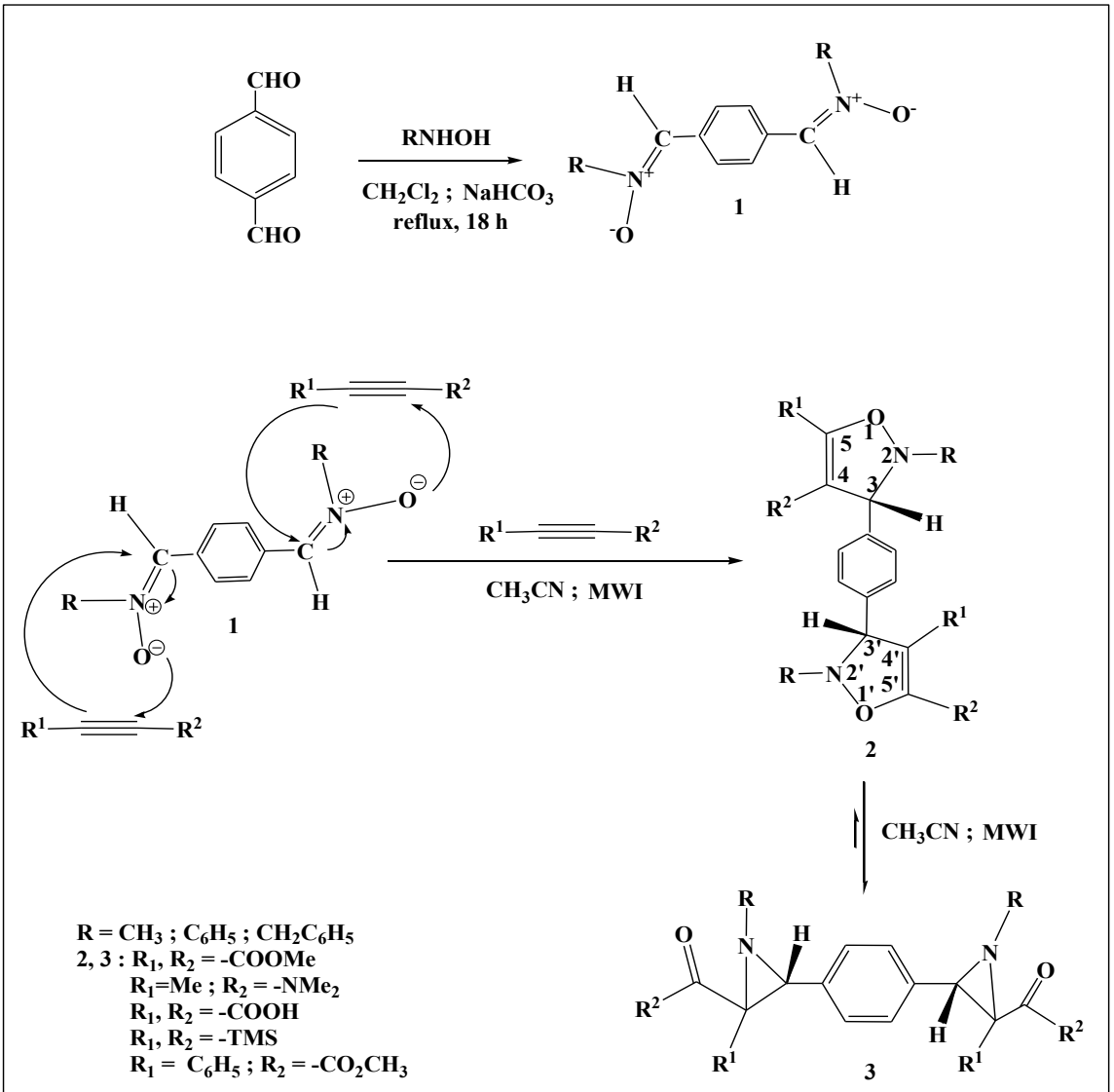


Figure 61. Synthesis of bisisoxazoline and bisaziridine derivatives

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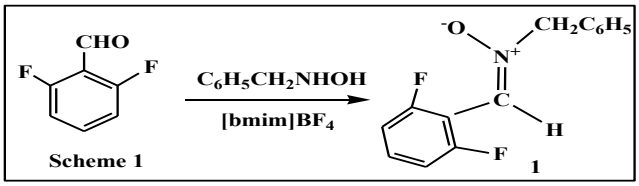
CHAPTER II

Experimental Section

All the melting points were determined in open capillary tube and were uncorrected. ^{1}H NMR spectra were recorded with a Bruker–Avance DPX 400 spectrometer (400MHz, FT NMR) using tetramethylsilane as internal standard. ^{13}C NMR spectra were recorded on the same instrument at 100 MHz. The coupling constants (*J*) are given in hertz (Hz). Chemical shift values are given in δ ppm with tetramethylsilane as internal standard. IR spectra were obtained with a Perkin–Elmer RX 1881 machine as film for all the products. MS and HRMS spectra were recorded with a Jeol–SX 102 (EI) instrument. Elemental analysis (C,H,N) were performed with a Perkin–Elmer 2400 series CHN analyzer. Analytical thin layer chromatography (TLC) was performed on both Fluka silica gel and E. Merck precoated silica gel plates (60 F_{254}). Ethyl acetate and Toluene (1:10) was used as solvent. Microwave studies were carried out in Discover Bench Mate system (Make: CEM-USA) producing continuous irradiation at 2445MHz and infrared control system. Microwave experiments were carried out in sealed vessels with an effective magnetic stirring and reflux (which avoids all problems of non homogeneity in temperature).Visualization was done by exposing to iodine vapour. *N*-Benzylhydroxylamine and *N*-methylhydroxylamine was purchased from Aldrich Chemical Company and was used as received. *N*-phenylhydroxylamine was prepared following the standard methods available in the literature. *1-Butyl-3-methylimidazoliumtetrafluoroborate* ([bmim]BF_4) and *1-butyl-3-methylimidazolium hexafluorophosphate* ([bmim]PF_6) ionic liquids were prepared according to the procedures reported in the literature[1].

All the chemicals and reagents along with common solvents were purified after receiving from commercial suppliers. Ionic liquid mediated reactions, aqueous phase synthesis and Microwave synthesis methodology was adopted following general methodology available in literature[2-4, 5-10]. The microorganisms used in this study include 15 bacterial strains of both gram positive & gram negative varieties. These were obtained from Division of Microbiology, Dept of Pharmaceutical Technology, Jadavpur University, Kolkata. Bacterial strains are *Escherichia coli* 25938, *Salmonella typhi* 62, *Vibrio cholerae* 20, *Klebsiella pneumoniae* 10031, *Shigella dysenteriae* 1, *Pseudomonas* AMRI 100, *Salmonella typhimurium* NTCC 74, *Staphylococcus aureus* 29737, *Bacillus cereus* 11778, *Bacillus subtilis* 6633, *Streptococcus epidermidis* 12228, *Micrococcus luteus* 10240, *Pseudomonas aeruginosa* 25619, *Bacillus pumilus* 14884 and *Bordetella bronchiseptica* 4617 respectively.

***General procedure of synthesis of N-Benzyl fluoro nitrone (1) in ionic liquid*[11,12]**



Scheme 1 — 1

To a stirred solution of 2,6-difluoro benzaldehyde (1 mmol) and [bmim]BF_4 (2 mL) in a 10 mL conical flask, *N*-benzylhydroxylamine (1 mmol;1 equivalent) was added at room temprature. It was mixed thoroughly and stirred at RT (20^0C) for 1 hr. The development of nitrone was monitored by TLC (ethyl acetate: hexane =1:10; R_f=0.45). Following usual workup, the reaction mixture was washed with diethyl ether and the combined ether layer was concentrated *in vacuo* to furnish fluoro nitrone **1** as white crystalline solid (m.p 42^0C, uncorrected). It was observed that the fluoro nitrone **1** decomposes if kept at room temperature for few hours. Therefore, *in situ* reactions were performed with various activated alkene and alkynes.

Spectroscopic data of fluoro nitrone **1** UV λ_{max} 238 nm; IR (KBr): υ_{max} 3025 (m), 2235 (m), 1680 (m), 1610 (s), 1440 (m), 1154 (m), 784 (s) cm^{-1}. ^{1}H NMR ($CDCl_3$): 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}CNMR ($CDCl_3$): δ 142.04 (CH=N^+), 134.80, 134.34, 134.12, 133.93 (phenyl carbons), 131.60, 130.00, 129.55, 129.46, 128.67, 128.22 (2,6 difluoro phenyl carbons).

*Synthesis of new fluoro isoxazolidine and isoxazoline derivatives have been studied using N-Benzyl fluoro nitrone (**1**) with various activated dipolarophiles in ionic liquid. The details of these experimental procedures are described as under:*

Reaction Type - I

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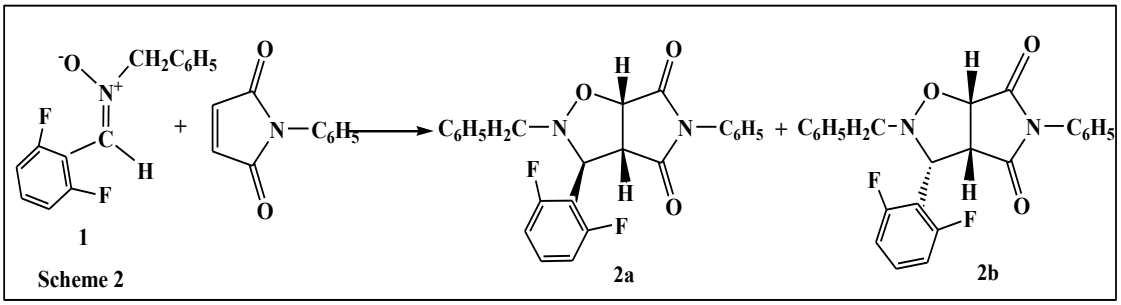
*General procedure for the synthesis of new fluoro isoxazolidine derivatives (**2-5**) using N-benzyl fluoro nitrone (**1**) in ionic liquid*[12]

In a 10 ml of conical flask 2,6-difluoro benzaldehyde (1 mmol) and *N*-benzylhydroxylamine (1 equivalent) and 2ml of *1-Butyl-3-methylimidazoliumtetrafluoroborate* ([bmim]BF_4) were added the reaction was stirred at room temperature for 1 hour the progress of the reaction was monitered by TLC, after the formation of nitrone one equivalent of dipolarophiles (*N-substituted maleimides, methacrolein)* were added and further stirred for 30 minutes, the progress of the reaction was monitored by TLC. The formation of product was indicated by TLC, the reaction mixture was washed with diethyl ether. The reaction mixture was concentrated *in vacuo* and the resulting product was directly charged on silica gel column and eluted with 1:8 ethyl acetate:*n*-hexane ratio to form pure fluoro isoxazolidines. The remaning viscous ionic liquid was washed further with diethyl ether and dried upto 80 °C under reduced pressure to retain its activity for subsequent runs.

This methodology was adopted for the synthesis of novel fluoro isoxazolidine derivatives (**2-5**) and the the substrates used in these reactions are listed as under:

- *N*-phenyl maleimide
- *N*-methyl maleimide
- *N*-cyclohexyl maleimide
- Methacrolein

2. *N-phenyl maleimide cycloadducts*



Scheme 2

To a stirred solution of 2,6-difluoro benzaldehyde (1 mmol) and [bmim]BF_4 (2 mL) in a 10 mL conical flask, *N*-benzylhydroxylamine (1 mmol;1 equivalent) was added at RT. It was mixed thoroughly and stirred at room temprature (20^0C) for 1 hr. The development of nitrone was monitored by TLC (ethyl acetate: hexane =1:10; R_f=0.45). *N*-phenyl maleimide (1 equivalent) was added *in situ* during the development of fluoro nitrone **1** and the reaction mixture was again stirred at RT for an appropriate time (26 min). The completion of the reaction was monitored by TLC (R_f = 0.52, 0.62) and the reaction mixture was washed with diethyl ether . The ether extracts were concentrated *in vacuo* and the crude product mixture was directly charged on a silica gel column.The column was eluted with a mixture of ethyl acetate and *n*-hexane (1:8) to furnish pure isoxazolidines **2a** (66%) **& 2b** (22%) as white crystals (88%). The remaining ionic liquid was washed with diethyl ether and dried at 80 °C under reduced pressure in order to keep its activity for other reactions.

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

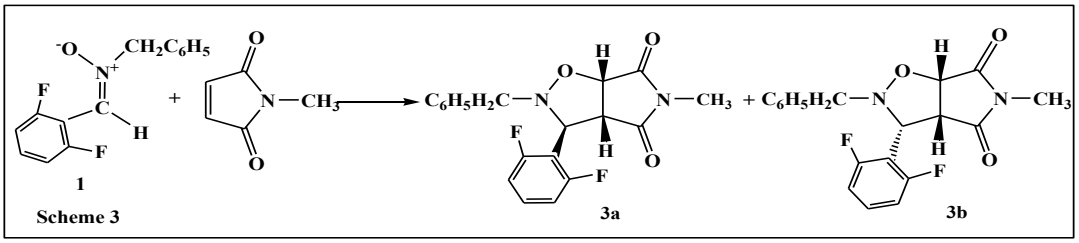
White crystals. Yield 66%; R_f = 0.52; υ_{max} 3020 (m), 2920 (m), 2835 (m), 1758 (s), 1690 (s), 1480 (m), 1346 (m), 805 (s), 770 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.74 – 7.68 (m, 3H, $C_6H_3F_2$), 7.12 – 6.83 (m, 2X5H, C_6H_5 protons), 5.84 (d, 1H, *J* = 6.70 Hz, C_5H), 3.40 (dd, 1H, *J* = 6.06, 6.16 Hz, C_4H), 3.54 (s, 2H, $C_6H_5CH_2$), 2.95 (d, 1H, *J* = 6.32 Hz, C_3H);

^{13}C NMR ($CDCl_3$): δ 173.42, 173.10 (carbonyl carbons), 138.10, 138.06, 138.02, 137.97, 136.86, 136.81, 136.78, 136.75 (phenyl carbons), 134.34, 134.14, 134.06, 133.76, 133.65, 133.45 (2,6 difluoro phenyl carbons), 85.22 (C_5), 77.20 (C_3), 58.46 (C_4), 39.55 ($\underline{CH_2}C_6H_5$); EI-MS: *m/z* 420 (M^+,100%), 343, 329, 306, 252, 216 (B.P), 113, 91, 77; Anal. Calcd. for $C_{24}H_{18}O_3N_2F_2$: C, 68.57; H, 4.28; N, 6.66%. Found: C, 68.44; H, 4.19; N, 6.52.

(3*R*)-2-Benzyl-3-(2,6-difluorophenyl)-dihydro-5-phenyl-2*H*-pyrrolo[3,4-*d*]isoxazole-4,6(5*H*,6 a-*H*)-dione, 2b

White crystals. Yield 22%; R_f = 0.62 IR (KBr): υ_{max} 3010 (m), 2915 (m), 2830 (m), 1764 (s), 1685 (s), 1486 (m), 1340 (m), 864 (s), 783 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.70 – 7.66 (m, 3H, $C_6H_3F_2$), 7.30 – 7.12 (m, 2X5H, C_6H_5 protons), 5.76 (d, 1H, *J* = 2.24 Hz, C_5H), 3.63 (dd, 1H, *J* = 2.26, 2.14 Hz, C_4H), 3.28 (s, 2H, $C_6H_5CH_2$), 3.06 (d, 1H, *J* = 3.04 Hz, C_3H); ^{13}C NMR ($CDCl_3$): δ 172.40, 172.24 (carbonyl carbons), 137.80, 137.74, 137.72, 137.57, 137.36, 136.34, 136.26, 136.18 (phenyl carbons), 134.80, 134.60, 134.44, 134.22, 134.13, 134.06 (2,6 difluoro phenyl carbons), 80.65 (C_5), 76.52 (C_3), 57.90 (C_4), 41.24 ($\underline{CH_2}C_6H_5$); EI-MS: *m/z* 420 (M^+,100%), 343, 329, 306, 216 (B.P), 113, 91, 77; Anal. Calcd. for $C_{24}H_{18}O_3N_2F_2$: C, 68.57; H, 4.28; N, 6.66%. Found: C, 68.49; H, 4.17; N, 6.50.

3. *N-methyl maleimide cycloadducts*



Scheme 3

To a stirred solution of 2,6-difluoro benzaldehyde (1 mmol) and $[bmim]BF_4$ (2 mL) in a 10 mL conical flask, *N*-benzylhydroxylamine (1 mmol;1 equivalent) was added at roo temprature. It was mixed thoroughly and stirred at room temprature (20^0C) for 1 hr. The development of nitrone was monitored by TLC (ethyl acetate: hexane =1:10; R_f=0.45). *N*-methyl maleimide (1 equivalent) was added *in situ* during the development of fluoro nitrone **1** and the reaction mixture was again stirred at room temperature for 35 minutes. The completion of the reaction was monitored by TLC (R_f= 0.55, 0.61) and the reaction mixture was washed with diethyl ether (3x10mL). The ether extracts were concentrated *in vacuo* and the crude product mixture was directly charged on a silica gel column.The column was eluted with a mixture of ethyl acetate and n-hexane (1:8) to furnish pure isoxazolidines **3a** (68%) & **3b** (20%) as white crystals (88%). Same procedure was followed for the purification and reuse of the ionic liquid used in this study for other reactions.

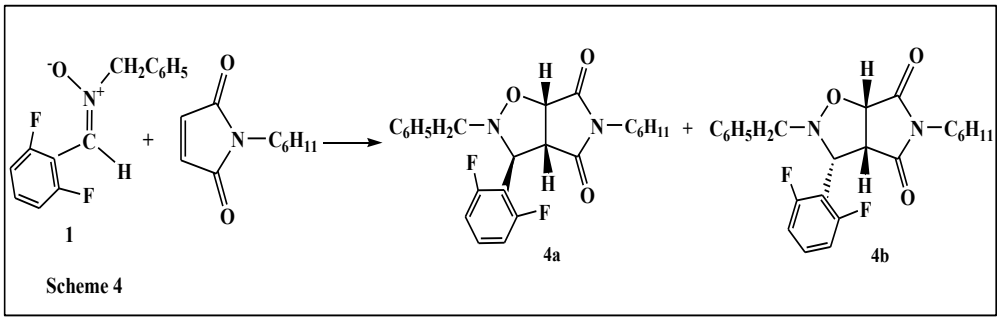
(3*S*)-2-Benzyl-3-(2,6-difluorophenyl)-dihydro-5-methyl-2*H*-pyrrolo[3,4-*d*]isoxazole-4,6(5*H*,6 a-*H*)-dione, 3a

White solid. Yield 68%; R_f = 0.55; IR (KBr): υ_{max} 3005 (m), 2935 (m), 2820 (m), 1760 (s), 1675 (s), 1465 (s), 1340 (m), 814 (s), 778 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.89 – 7.86 (m, 3H, $C_6H_3F_2$), 7.64 – 7.46 (m, 5H, C_6H_5 protons), 6.56 (d, 1H, *J* = 6.10 Hz, C_5H), 3.89 (s, 2H, $C_6H_5CH_2$), 3.79 (dd, 1H, *J* = 6.00, 5.90 Hz, C_4H), 3.49 (s, 3H, N-CH_3), 2.95 (d, 1H, *J* = 6.76 Hz, C_3H); ^{13}C NMR ($CDCl_3$): δ 170.58, 170.50 (carbonyl carbons), 136.44, 136.40, 136.32, 136.25 (phenyl carbons), 132.70, 132.64, 132.51, 132.43, 132.18, 132.06 (2,6 difluoro phenyl carbons), 82.98 (C_5), 76.66 (C_3), 59.70 (C_4), 39.60 ($\underline{CH_2}C_6H_5$), 37.54 (N-CH_3); EI-MS: *m/z* 358 (M^+,100%), 345, 267, 252, 244, 154 (B.P), 113, 91; Anal. Calcd. for $C_{19}H_{16}O_3N_2F_2$: C, 63.68; H, 4.46; N, 7.82%. Found: C, 63.49; H, 4.36; N, 7.57.

(3*R*)-2-Benzyl-3-(2,6-difluorophenyl)-dihydro-5-methyl-2*H*-pyrrolo[3,4-*d*]isoxazole-4,6(5*H*,6 a-*H*)-dione, 3b

White solid. Yield 20%; R_f = 0.61; IR (KBr): υ_{max} 3015 (m), 2905 (m), 2828 (s), 1760 (s), 1680 (s), 1460 (s), 1355 (m), 820 (s), 783 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.88 – 7.84 (m, 3H, $C_6H_3F_2$), 7.60 – 7.49 (m, 5H, C_6H_5 protons), 6.52 (d, 1H, *J* = 3.22 Hz, C_5H), 3.84 (s, 2H, $C_6H_5CH_2$), 3.76 (dd, 1H, *J* = 1.96, 2.12 Hz, C_4H), 3.47 (s, 3H, N-CH_3), 2.96 (d, 1H, *J* = 1.96 Hz, C_3H); ^{13}C NMR ($CDCl_3$): δ 171.34, 171.27 (carbonyl carbons), 135.98, 135.94, 135.82, 135.75 (phenyl carbons), 133.12, 133.04, 132.91, 132.83, 132.77, 132.62 (2,6 difluoro phenyl carbons), 84.08 (C_5), 73.80 (C_3), 54.95 (C_4), 41.42 ($\underline{CH_2}C_6H_5$), 39.05 (N-CH_3); EI-MS: *m/z* 358 (M^+,100%), 345, 267, 252, 154 (B.P), 113, 91, 77; Anal. Calcd. for $C_{19}H_{16}O_3N_2F_2$: C, 63.68; H, 4.46; N, 7.82%. Found: C, 63.42; H, 4.32; N, 7.62.

3. *N-cyclohexyl maleimide cycloadducts*



Scheme 4

In a 10 ml conical flask 2ml of [bmim]BF_4, 2,6-Difluoro benzaldehyde (1 mmol) and *N*-benzylhydroxylamine (1 equiv) were added and mixed thoroughly and stirred at room temperature for 1hr.

The formation of nitrone was monitored by TLC (R_f = 0.45). *N*-cyclohexyl maleimide (1 equivalent) was added *in situ* at the time of development of nitrone **1** and the reaction mixture was stirred further at room temperature for 40 minutes. The completion of reaction was indicated by TLC (R_f = 0.52, 0.67), the reaction mixture was washed with diethyl ether. The reaction mixture were concentrated *in vacuo* and the resulting product was charged on silica gel column and eluted with 1:8 (ethyl acetate:*n*-hexane) ratio to form pure fluoro isoxazolidines **4a** (64%) **& 3b** (21%) as yellowish white crystals (85%). The remaning viscous ionic liquid was washed further with diethyl ether and dried upto 80^0C under reduced pressure to retain its activity for subsequent runs.

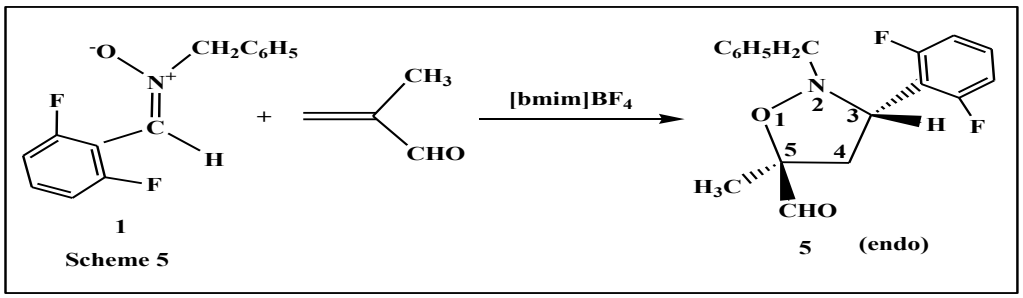
(3*S*)-2-Benzyl-5-cyclohexyl-3-(2,6-difluorophenyl)-dihydro-2*H*-pyrrolo[3,4-*d*]isoxazole-4,6(5*H*,6 a-*H*)-dione, 4a

Yellow crystal Yield 64% R_f = 0.52; IR (KBr): υ_{max} 3015 (m), 2900 (s), 2840 (m), 1760 (s), 1674 (br, s), 1470 (s), 1330 (m), 805 (s), 786 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.60 – 7.56 (m, 3H, $C_6H_3F_2$), 7.17 – 7.06 (m, 5H, C_6H_5 protons), 6.30 (d, 1H, *J* = 6.74 Hz, C_5H), 3.60 (s, 2H, $C_6H_5CH_2$), 3.42 (dd, 1H, *J* = 6.20, 6.10 Hz, C_4H), 2.83 (d, 1H, *J* = 6.76 Hz, C_3H), 1.95-1.52 (m, 11H, cyclohexyl protons); ^{13}C NMR ($CDCl_3$): δ 168.54, 168.50 (carbonyl carbons), 131.66, 131.60, 131.55, 131.50 (phenyl carbons), 129.15, 129.06, 128.80, 128.73, 128.68, 128.43 (2,6 difluoro phenyl carbons), 83.60 (C_5), 74.55 (C_3), 58.24 (C_4), 38.78 ($\underline{CH_2}C_6H_5$), 27.40, 27.29, 26.87, 26.70, 26.58, 26.46 (cyclohexyl carbons); EI-MS: *m/z* 426 (M^+,100%), 343, 335, 312, 252, 222 (B.P), 113, 91, 83; Anal. Calcd. for $C_{24}H_{24}O_3N_2F_2$: C, 67.60; H, 5.63; N, 6.57%. Found: C, 67.46; H, 5.35; N, 6.37.

(3*R*)-2-Benzyl-5-cyclohexyl-3-(2,6-difluorophenyl)-dihydro-2*H*-pyrrolo[3,4-*d*]isoxazole-4,6(5*H*,6 a-*H*)-dione, 4b

Yellow crystals. Yield 21%, R_f = 0.67; IR (KBr): υ_{max} 3010 (m), 2905 (s), 2835 (m), 1764 (s), 1675 (s), 1466 (s), 1336 (m), 815 (s), 783 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.52 – 7.85 (m, 3H, $C_6H_3F_2$), 7.25 – 7.14 (m, 5H, C_6H_5 protons), 6.14 (d, 1H, *J* = 1.88 Hz, C_5H), 3.55 (s, 2H, $C_6H_5CH_2$), 3.38 (dd, 1H, *J* = 2.08, 2.04 Hz, C_4H), 2.80 (d, 1H, *J* = 1.80 Hz, C_3H), 1.90-1.38 (m, 11H, cyclohexyl protons); ^{13}C NMR ($CDCl_3$): δ 169.88, 169.83 (carbonyl carbons), 130.54, 130.49, 130.45, 130.32 (phenyl carbons), 128.77, 128.68, 128.56, 128.53, 128.48, 128.30 (2,6 difluoro phenyl carbons), 80.44 (C_5), 77.50 (C_3), 58.97 (C_4), 37.05 ($\underline{CH_2}C_6H_5$), 25.30, 25.22, 25.17, 25.06, 24.88, 24.76 (cyclohexyl carbons); EI-MS: *m/z* 426 (M^+,100%), 343, 312, 252, 222 (B.P), 113, 91, 83, 77; Anal. Calcd. for $C_{24}H_{24}O_3N_2F_2$: C, 67.60; H, 5.63; N, 6.57%. Found: C, 67.37; H, 5.40; N, 6.33.

4. ***Methacrolein cycloadduct***



Scheme 5

In a 10 ml conical flask 2ml of [bmim]BF_4, 2,6-Difluoro benzaldehyde (1 mmol) and *N*-benzylhydroxylamine (1 equiv) were added and mixed thoroughly and stirred at RT for 1 hr. The formation of nitrone was monitored by TLC (R_f = 0.45). Methacrolein (1 equivalent) was added dropwise by syringe at the time of development of nitrone **1** and the reaction mixture was stirred further at room temperature for 32 minutes. The completion of reaction was indicated by TLC (R_f= 0.52), the reaction mixture was washed with diethyl ether. The reaction mixture were concentrated *in vacuo* and the resulting product was charged on silica gel column and eluted with 1:8 (ethyl acetate:*n*-hexane) ratio to form pure fluoro isoxazolidines **5** (90%) as yellow gummy mass. The remaning viscous ionic liquid was washed further with diethyl ether and dried upto 80 °C under reduced pressure to retain its activity for subsequent runs.

(*S*)-2-benzyl-3-(2,6-difluorophenyl)-5(*S*)-methylisoxazolidine-5-carbaldehyde, **5**

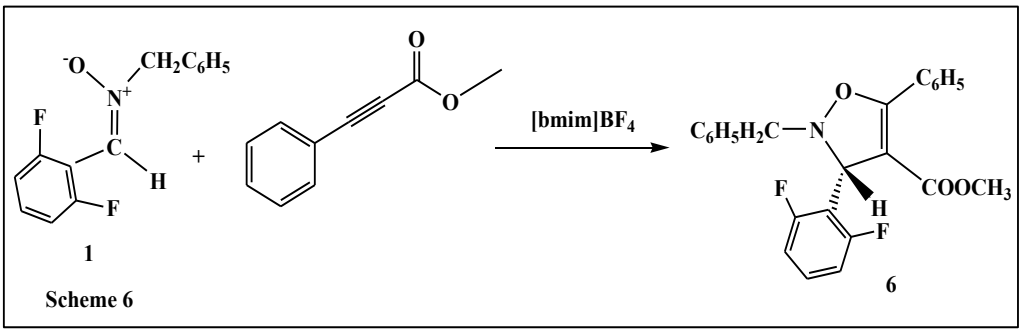
IR (KBr): υ_{max} 2995 (m), 2971 (m), 1732 (s), 1614 (s), 1461 (s), 1325 (s), 1146 (s), 982 (m), 786 (s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 9.81 (s, 1H, CHO), 8.12 – 7.85 (m, 3H, $C_6H_3F_2$), 7.65-7.34 (m, 5H, C_6H_5), 3.88 (dd, 1H, *J* = 5.22, 5.62 Hz, C_4H), 3.72 (dd, 1H, *J* = 5.25, 5.62 Hz, C_4H, *endo*), 2.94 (s, 2H, $C_6H_5CH_2$), 1.61 (s, 3H, CH_3), 1.28 (t, 1H, *J* = 5.15 Hz, C_3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.25 (-CHO), 134.54, 134.37, 134.30, 134.18, 132.10, 132.05, 131.96, 131.92, 131.85, 131.73, 132.10 (aromatic carbons), 80.56(C_5), 74.24 (C_3), 55.41 (C_4), 34.92 (benzylic carbon), 23.18 (CH_3). EI-MS (*m/z*): 317 (M^+), 226, 204, 113 (B.P), 83, 91, 15. Anal. Calcd. for $C_{18}H_{17}O_2F_2N$: C, 68.12; H, 5.38; N, 4.42. Found: C, 68.03; H, 5.22; N, 4.27%.

***General procedure of synthesis of new fluoro isoxazoline derivatives (6-8) in ionic liquid*[11]**

In a 10 ml conical flask 2ml of [bmim]BF_4, 2,6-Difluoro benzaldehyde (1 mmol) and *N*-benzylhydroxylamine (1 equiv) were added and mixed thoroughly and stirred at room temprature for 1 hr. The formation of nitrone was monitored by TLC (R_f = 0.45).

- Alkynes (1 equivalent) was added at the time of development of fluro nitrone **1** and the reaction mixture was stirred further at room temperature for 30 minutes. The completion of reaction was indicated by TLC (R_f = 0.67), the reaction mixture was washed with diethyl ether. The reaction mixture were concentrated *in vacuo* and the resulting product was charged on silica gel column and eluted with 1:8 (ethyl acetate:*n*-hexane) ratio to form pure fluoro isoxazoline **6** (87%) as dark red mass. The remaning viscous ionic liquid was washed further with diethyl ether and dried upto 80 °C under reduced pressure to retain its activity for subsequent runs. This same methodology was adopted for the synthesis of novel fluoro isoxazoline derivatives (**6-8**) using the substrates listed as under:
- Methyl phenyl propiolate
- Dimethyl acetylene dicarboxylate
- Acetylene dicarboxylic acid

5. ***Methyl phenyl propiolate cycloadduct***



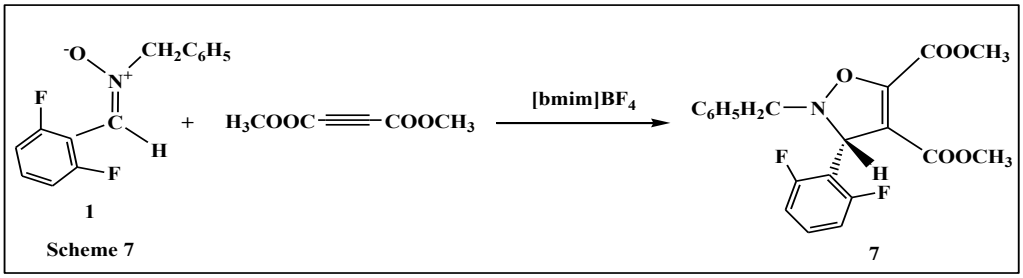
Scheme 6

(*S*)-methyl-2-benzyl-3-(2,6-difluorophenyl-2,3-dihydro-5-phenylisoxazole-4-carboxylate, 6 At the time of development of fluro nitrone **1,** one equivalent of Methyl phenyl propiolate was added and the reaction mixture was stirred further at room temperature for 27minute. The completion of reaction was indicated by TLC (R_f = 0.65) and the reaction mixture was washed with diethyl ether. The reaction mixture was concentrated *in vacuo* and the resulting product was charged on silica gel column and was eluted with 1:8(ethyl acetate:*n*-hexane) ratio to form pure fluoro isoxazoline **6** as dark red thick liquid (87%). The remaning viscous ionic liquid was washed further with diethyl ether and dried upto 80°C under reduced pressure to retain its activity in subsequent runs.

Dark red thick liquid. Yield 87%; R_f = 0.65; IR (KBr): υ_{max} 3010 (m), 2246 (m), 1740 (s), 1710 (s), 1690 (s), 1610 (s), 1480 (s), 1324 (s), 1215 (s), 810 (m), 782 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.87 – 7.80 (m, 3H, $C_6H_3F_2$), 7.68-7.31 (m, 2x5H, 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 (-$\underline{CO}OCH_3$), 137.20, 137.04, 136.87, 136.66, 135.65, 135.48, 135.20, 134.93 (aromatic carbons), 132.77, 132.35, 132.08, 131.78, 130.80, 129.90 (2,6 difluoro phenyl carbons), 88.16 (C_5), 73.60 (C_3), 58.45 (C_4), 45.17 (-$COO\underline{CH_3}$), 36.80 (benzylic carbon); EI - MS (*m/z*): 407 (M^+), 330, 294, 211 (B.P), 203, 113, 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%.

6. *Dimethyl acetylene dicarboxylate cycloadduct*

At the time of development of fluro nitrone **1,** one equivalent of Dimethyl acetelene dicarboxylate was added *in situ* and the reaction mixture was stirred further at room temperature for 35 minutes. The completion of reaction was indicated by TLC (R_f= 0.63) and the reaction mixture was washed with diethyl ether. The reaction mixture was concentrated *in vacuo* and the resulting product was charged on silica gel column and was eluted with 1:8 (ethyl acetate:*n*-hexane) ratio to form pure fluoro isoxazoline **7** as dark red thick liquid (87%). The remaning viscous ionic liquid was washed further with diethyl ether and dried upto 80°C under reduced pressure to retain its activity in subsequent runs



Scheme 7

(*S*)-dimethyl-2-benzyl-3-(2,6-difluorophenyl)-2,3-dihydroisoxazole-4,5-dicarboxylate, 7

Red viscous liquid. Yield 87%; R_f= 0.63; IR (KBr): υ_{max} 3016 (m), 2251 (m), 1726 (s), 1686 (s), 1612 (s), 1442 (s), 1259 (s), 1224 (s), 806 (m), 778 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.45 – 7.35 (m, 3H, $C_6H_3F_2$), 7.12-6.97 (m, 5H, C_6H_5), 3.32 (s, 3H, -$COOCH_3$), 3.25 (s, 3H, -$COOCH_3$), 2.56 (s, 2H, $C_6H_5CH_2$), 1.73 (s,1H, C_3H); ^{13}C NMR ($CDCl_3$): δ 169.75, 169.59 (-$\underline{CO}OCH_3$, carbonyl carbons of the ester group), 135.78, 135.74, 135.55, 135.48 (aromatic carbons), 133.31, 133.29, 133.25, 133.16, 133.13, 133.06 (2,6 difluoro phenyl carbons),

EI - MS (*m/z*): 389 (M^+), 358, 330, 302, 276, 271 (B.P), 185, 113, 91, 77; Anal. Calcd. for $C_{20}H_{17}O_5F_2N$: C, 61.68; H, 4.36; N, 3.58. Found: C, 61.59; H, 4.25; N, 3.36%.

7. ***Acetylene dicarboxylic acid cycloadduct***

Scheme 8

At the time of development of nitrone **1,** one equivalent of Acetylene dicarboxylic acid was added *in situ* and the reaction mixture was stirred further at room temperature for 35 minute. The completion of reaction was indicated by TLC (R_f = 0.60) and the reaction mixture was washed with diethyl ether. The reaction mixture was concentrated *in vacuo* and the resulting product was charged on silica gel column and was eluted with 1:8(ethyl acetate:*n*-hexane) ratio to form pure fluoro isoxazoline **8** as colourless thick liquid (82%). The remaning viscous ionic liquid was washed further with diethyl ether and dried upto 80°C under reduced pressure to retain its activity in subsequent runs

(*S*)-2-Benzyl-3-(2,6-difluorophenyl)-2,3-dihydroisoxazole-4,5-dicarboxylic acid, 8

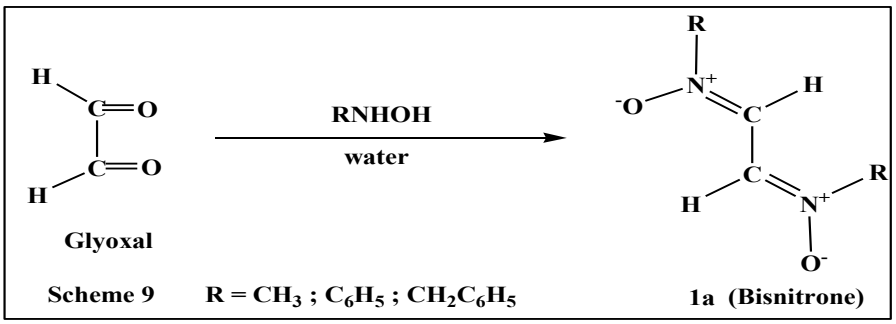
Colourless thick liquid. Yield 82%; R_f = 0.60; IR (KBr): υ_{max} 3012 (m), 2996 (br), 2245 (m), 1762 (s), 1608 (s), 1482 (s), 1325 (s), 1216 (s), 1106 (s), 802 (m), 780 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 10.01 (s, 2H, 2XCOOH), 7.91– 7.86 (m, 3H, $C_6H_3F_2$), 7.65-7.45 (m, 5H, C_6H_5), 2.92 (s,2H, $C_6H_5CH_2$), 2.87 (s,1H, C_3H); ^{13}C NMR ($CDCl_3$): δ 173.68, 172.05 (carboxyl carbons), 138.51, 138.45, 138.36, 138.25 (aromatic carbons), 135.45, 135.41, 135.27, 134.92, 134.86, 134.74 (2,6 difluoro phenyl carbons), 88.22 (C_5), 74.42 (C_3), 58.61 (C_4), 37.86 (benzylic carbon); FAB - MS (*m/z*): 361 (M^+), 344, 316, 288, 271 (B.P), 248, 157, 113, 91, 77. Anal.Calcd. for $C_{18}H_{13}O_5F_2N$: C, 59.84; H, 3.61; N, 3.86. Found: C, 59.74; H, 3.41; N, 3.57%.

Reaction Type II

*General Procedure for the synthesis of new bisisoxazolidine derivatives (**9-13**) using glyoxal derived bisnitrone (**1a**) in water*[13,14]

*Synthesis of new bisisoxazolidine derivatives have been studied using glyoxal derived bisnitrone (**1a**) with various activated dipolarophiles in water. The details of these experimental procedures are described as under:*

General procedure of synthesis of bisnitrone (1a) in water

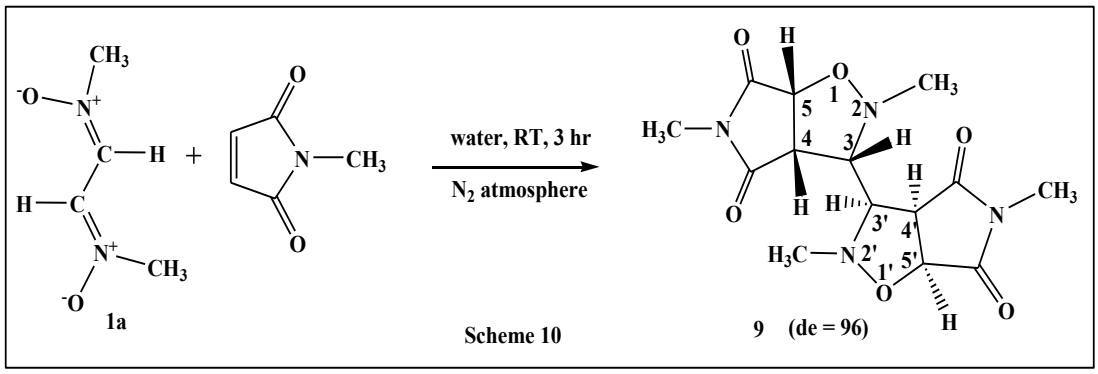


To a solution of glyoxal (309mg, 5.3 mmole) in diethyl ether (20 mL) *N*-methylhydroxylamine (500mg, 2 equivalent) and anhydrous $MgSO_4$ (2 gms) was added. The reaction mixture was kept at RT with constant stirring with a magnetic stirrer under N_2 atmosphere for 8 hr. The formation of bisnitrone was monitored by TLC (R_f = 0.36). The reaction mixture was filtered and the filtrate on concentrated *in vacuo* furnished *N*-methyl bisnitrone as white crystals (86%; m.p: 78^0C). Same methodology was followed for the synthesis of other bisnitrones (R = C_6H_5 ; $CH_2C_6H_5$). All the bisnitrones were found stable and were reacted with various activated alkenes in 1,3-dipolar cycloaddition reactions in water at room temperature.

Spectroscopic data for bisnitrone **1a** (**R = CH_3**): UV λ_{max} 233 nm. IR (KBr): υ_{max} 1635 (m), 1610 (s) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.45 (d, 1H, *J* = 3.22 Hz, -CH=N^+), 6.23 (d, *J* = 3.22 Hz, -CH=N^+), 3.84 (s, 6H, 2xCH_3, N^+-CH_3); ^{13}CNMR (75 MHz, $CDCl_3$): δ 141.60 (CH=N^+), 140.94 (CH=N^+), 24.74, 24.70 (N^+-CH_3).

General procedure of synthesis of diastereoselective bisisoxazolidine derivatives (9-11) in water (Cycloaddition reaction of methylbisnitrone with N-methyl maleimide)

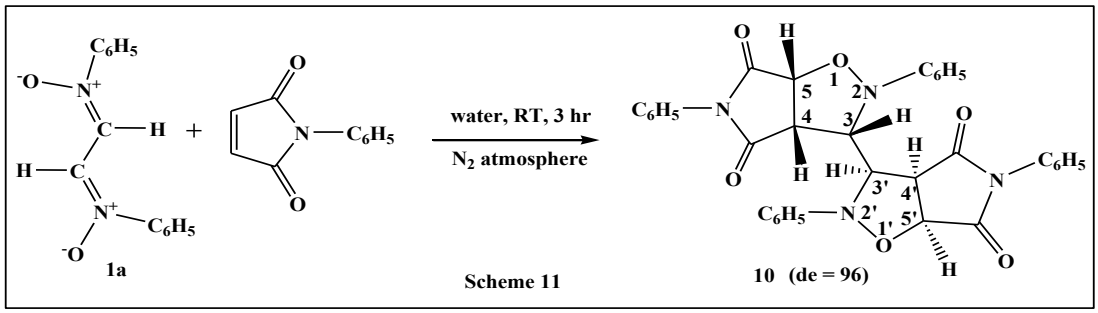
8. *N*-methylmaleimide (2 equivalent) was added to a solution of methylbisnitrone (1 equivalent ; **R = CH_3**) in water (15 mL) and the reaction mixture was stirred at RT for an appropriate time (3 hr). After completion of reaction, as indicated by TLC (R_f= 0.68, 0.62), the reaction mixture was extracted with diethyl ether (3x10mL), the organic layer was washed with saturated brine (2x15mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The resulting crude products were directly charged on silica gel column and eluted with a mixture of ethyl acetate and *n*-hexane (1:6) to afford pure bisisoxazolidines **9** (94% & 6% respectively) as yellowish white crystals. Same methodology was adopted for the substrates like *N*-phenyl maleimide.



(*3R*, 3a*R*, 6a*S*)-dihydro-3-((3'*S*, 3'a*S*, 6a*R*)-hexahydro-2,5-dimethyl-4,6-dioxo-2*H*-pyrrolo[3,4-*d*]isoxazol-3-yl)-2', 5'-dimethyl-2*H*-pyrrolo[3,4-*d*]isoxazole-4,6(5*H*, 6a*H*) dione 9

Yellowish white crystals, Yield 94%; R_f= 0.68; FT-IR (KBr): υ_{max} 2822 (m), 1762 (s), 1674 (s), 1464 (m), 1230 (m), 1126 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.31 (d, 2H, *J* = 4.06 Hz, 2xC_5H), 3.11 (s, 6H, 2x$ONCH_3$), 2.98 (s, 6H, 2x$(O=C)NCH_3$), 2.85 (d, 2H, *J* = 4.22 Hz, 2xC_3H), 2.50 (dd, br, 2H, 2xC_4H); ^{13}C NMR ($CDCl_3$): δ 174.79, 173.11 (carbonyl carbons), 75.82 (C_5, $C_{5'}$), 69.95 (C_3, $C_{3'}$), 56.78 (C_4, $C_{4'}$), 26.62, 26.57 (methyl carbons); EI - MS (*m/z*): 338 (M^+), 169, 168, 154. Calcd. for $C_{14}H_{18}O_6N_4$: C, 49.67; H, 5.35; N, 16.55%. Found: C, 49.52; H, 5.26; N, 16.43%.

9. *Cycloaddition reaction of phenylbisnitrone with N-phenyl maleimide*

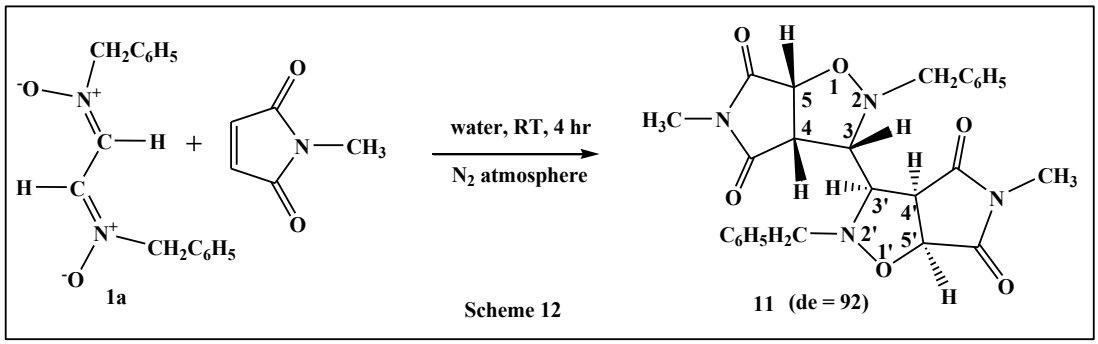


N-phenyl maleimide (2 equivalent) was added to a solution of phenylbisnitrone (1 equivalent ; **R = C_6H_5**) in water (15 mL) and the reaction mixture was stirred at RT for an appropriate time (3 hr). After completion of reaction, as indicated by TLC (R_f= 0.66, 0.60), the reaction mixture was extracted with diethyl ether (3x10mL), the organic layer was washed with saturated brine (2x15mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The resulting crude products were directly charged on silica gel column and eluted with a mixture of ethyl acetate and *n*-hexane (1:6) to afford pure bisisoxazolidines **10** (91% & 9% respectively) as yellow crystals.

(*3R*, 3a*R*, 6a*S*)-dihydro-3-((3'*S*, 3'a*S*, 6a*R*)-hexahydro-4,6-dioxo-2,5-diphenyl-2*H*-pyrrolo[3,4-*d*]isoxazol-3-yl)-2', 5'-diphenyl-2*H*-pyrrolo[3,4-*d*]isoxazole-4,6(5*H*, 6a*H*)dione 10

Yellow crystals, Yield 91%; R_f= 0.66; FT-IR (KBr):): υ_{max} 3026 (m), 2832 (m), 1765 (s), 1662 (s), 1484 (m), 1346 (m), 785 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.35-7.25 (m, 10H, 2x(O=C)NC_6H_5), 6.61-6.51 (m, 10H, 2xONC_6H_5), 2.11 (dd, br, 2H, 2xC_4H), 1.85 (d, 2H, *J* = 6.00 Hz, 2xC_5H), 1.67 (d, 2H, *J* = 6.10 Hz, 2xC_3H); ^{13}C NMR ($CDCl_3$): δ 172.42, 172.25 (carbonyl carbons), 138.82, 138.13, 137.95, 137.72, 129.75, 129.71, 129.34, 129.05 (aromatic carbons), 76.16 (C_5, $C_{5'}$), 66.48 (C_3, $C_{3'}$), 55.82 (C_4, $C_{4'}$); EI - MS (*m/z*): 586 (M^+), 293, 292, 216, 77. Calcd. for $C_{34}H_{26}O_6N_4$: C, 69.61; H, 4.45; N, 9.56%. Found: C, 69.51; H, 4.37; N, 9.50%.

10. *Cycloaddition reaction of benzylbisnitrone with N-methyl maleimide*



Scheme 12

N-methylmaleimide (2 equivalent) was added to a solution of benzylbisnitrone (1 equivalent ; **R = $CH_2C_6H_5$**) in water (15 mL) and the reaction mixture was stirred at RT for an appropriate time (4 hr). After completion of reaction, as indicated by TLC (R_f= 0.62, 0.60), the reaction mixture was extracted with diethyl ether (3x10mL), the organic layer was washed with saturated brine (2x15mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The resulting crude products were directly charged on silica gel column and eluted with a mixture of ethyl acetate and *n*-hexane (1:6) to afford pure bisisoxazolidines **11** (91% & 9% respectively) as white crystals.

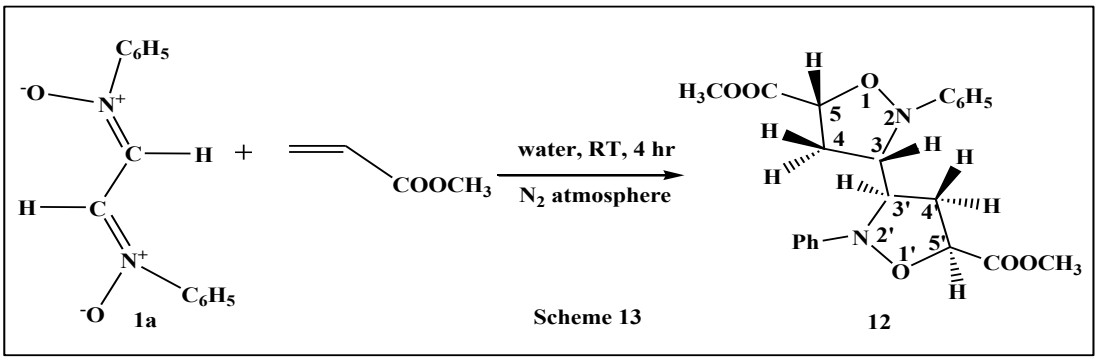
(*3R*, 3a*R*, 6a*S*)-2-benzyl-3-((3'*S*, 3'a*S*, 6a*R*)-2'-benzyl-hexahydro-5-methyl-4,6-dioxo-2*H*-pyrrolo[3,4-*d*]isoxazol-3-yl)-dihydro-5-methyl-2*H*-pyrrolo[3,4-*d*]isoxazole-4,6(5*H*, 6a*H*)dione 11

White crystals, Yield 91%; R_f= 0.62; FT-IR (KBr): υ_{max} 3010 (m), 2900 (m), 1760 (s), 1660 (s), 1482 (m), 1340 (m), 780 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.46-7.26 (m, 10H, 2x$CH_2\underline{C_6H_5}$), 4.37 (d, 2H, *J* = 7.16 Hz, 2xC_5H), 3.24 (d, 2H, *J* = 7.14 Hz, 2xC_3H),

2.89 (dd, br, 2H, 2xC_4H), 2.60 (s, 6H, 2xN-CH_3 protons), 2.15 (s, 4H, 2x$\underline{CH_2}C_6H_5$); ^{13}C NMR ($CDCl_3$): δ 177.18, 177.04 (carbonyl carbons), 133.22, 133.12, 132.90, 132.70 (aromatic carbons), 73.67 (C_5, $C_{5'}$), 64.80 (C_3, $C_{3'}$), 53.77 (C_4, $C_{4'}$), 32.05, 31.94 (benzyl carbons), 28.70, 28.58 (N-Me carbons); EI - MS (*m/z*): 490 (M^+), 245, 244, 154, 77. Calcd. for $C_{26}H_{26}O_6N_4$: C, 63.64; H, 5.34; N, 11.42%. Found: C, 63.57; H, 5.26; N, 11.35%.

General procedure of synthesis of regioselective bisisoxazolidine derivatives (12 & 13) in water (Cycloaddition reaction of phenylbisnitrone with methyl acrylate)

Methyl acrylate (2 equivalent) was added to a solution of phenylbisnitrone (1 equivalent ; **R = C_6H_5**) in water (15 mL) and the reaction mixture was stirred at RT for an appropriate time (4 hr). After completion of reaction, as indicated by TLC (R_f = 0.76), the reaction mixture was extracted with diethyl ether (3x10mL), the organic layer was washed with saturated brine (2x15mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The resulting crude product was directly charged on silica gel column and eluted with a mixture of ethyl acetate and *n*-hexane (1:6) to afford pure bisisoxazolidine **12** (88%) as colourless liquid. Same methodology was followed for styrene.

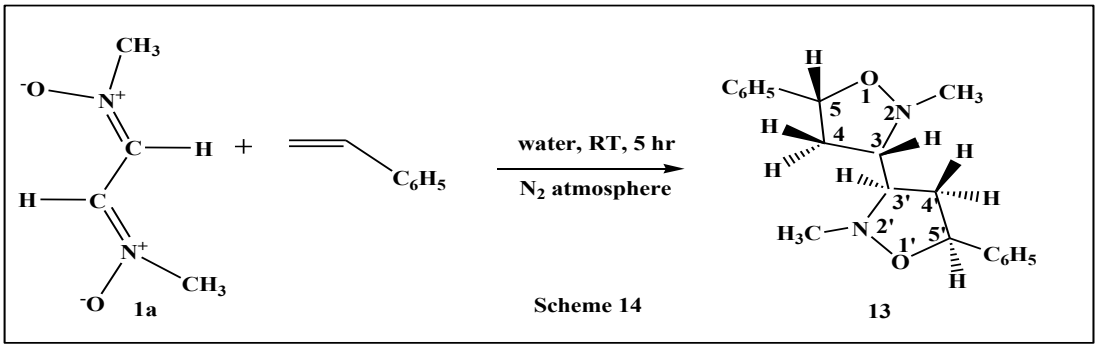


Scheme 13

(*3S*,5*S*)-methyl-3-(((5'*R*)-5-(methoxycarbonyl)-2-phenylisoxazolidine-3-yl)methyl)-2'-phenyl isoxazolidine-5'-carboxylate 12

Colorless gummy liquid, Yield 88%; R_f = 0.76; FT-IR (KBr): υ_{max} 3025 (m), 2890 (m), 1762 (s), 1665 (s), 1484 (m), 784 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.06-8.02 (m, 5H, C_6H_5), 7.51-7.46 (m, 5H, C_6H_5), 3.72 (dd, 2x1H, *J* = 5.44, 5.42 Hz, C_4H, *endo*), 3.44 (s, 2x3H, -$COOCH_3$), 2.96 (d, 2H, *J* = 6.32 Hz, 2xC_5H), 2.59(d, 2H, *J* = 6.30 Hz, 2xC_3H), 1.25 (ddd, 2x1H, *J* = 2.80, 2.82 Hz, C_4H); ^{13}C NMR ($CDCl_3$): δ 170.25, 170.16 (carbonyl carbons), 129.46, 129.37, 129.26, 129.18 (aromatic carbons), 70.45(C_5, $C_{5'}$), 60.55 (C_3, $C_{3'}$), 52.48 (C_4, $C_{4'}$), 17.21, 17.06 (ester methyl carbons); EI-MS (*m/z*): 412 (M^+), 206, 205, 147, 129, 77, 59. Calcd. for $C_{22}H_{24}O_6N_2$: C, 64.04; H, 5.85; N, 6.78%. Found: C, 63.96; H, 5.75; N, 6.71%.

Cycloaddition reaction of methylbisnitrone with styrene



1a Scheme 14 13

Styrene (2 equivalents) was added to a solution of methylbisnitrone (1 equivalent; **R = CH_3**) in water (15 mL) and the reaction mixture was stirred at RT for an appropriate time (5 hr). After completion of reaction, as indicated by TLC (R_f = 0.52), the reaction mixture was extracted with diethyl ether (3x10mL), the organic layer was washed with saturated brine (2x15mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The resulting crude product was directly charged on silica gel column and eluted with a mixture of ethyl acetate and *n*-hexane (1:6) to afford pure bisisoxazolidine **13** (83%) as colourless liquid.

(*3S*,5*S*)-2-methyl-3-(((5'*R*)-2'-methyl-5-phenylisoxazolidin-3-yl)methyl)-5'-phenylisoxazolidine 13

Greenish thick liquid, Yield 83%; R_f= 0.52; FT-IR (KBr): υ_{max} 3215 (m), 2905 (m), 2245 (s), 1484 (m), 780 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.88-7.73 (m, 5H, C_6H_5), 7.50-7.44 (m, 5H, C_6H_5), 3.60 (ddd, 2x1H, *J* = 6.24, 6.22 Hz, C_4H, *endo*), 2.76 (d, 2H, *J* = 6.06 Hz, 2xC_5H), 2.62 (d, 2H, *J* = 6.28 Hz, 2xC_3H), 2.30 (s, 2x3H, N-Me protons), 1.70 (dd, 2x1H, *J* = 3.66, 3.62 Hz, C_4H); ^{13}C NMR ($CDCl_3$): δ 136.67, 136.58, 136.52, 136.38, 131.80, 131.72, 131.55, 131.23 (aromatic carbons), 73.60 (C_5, $C_{5'}$), 58.45 (C_3, $C_{3'}$), 55.37 (C_4, $C_{4'}$), 36.64, 35.21 (N-Me carbons); EI-MS (*m/z*): 324 (M^+), 246, 161, 147, 77; Calcd. for $C_{20}H_{24}O_2N_2$: C, 74.03; H, 7.45; N, 8.64%. Found: C, 73.95; H, 7.33; N, 8.59%.

Reaction Type III

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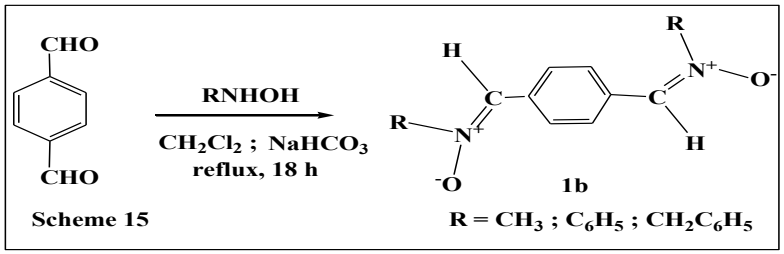
*Synthesis of new bisisoxazoline derivatives (**14-18**) have been studied using terepthalaldehyde derived bisnitrone (**1b**) using microwave irradiation (MWI) with various activated dipolarophiles (alkynes). The details of these experimental procedures are described as under:*

***General procedure of synthesis of bisnitrone (1b)*[15,16]**



Scheme 15 **R = CH_3 ; C_6H_5 ; $CH_2C_6H_5$**

Terephthalaldehyde (1.34 g, 10 mmol) was added to a solution of *N*-methylhydroxylamine (2.09 g, 25 mmol; R = CH_3) in CH_2Cl_2 (20 ml) in a 50 ml R.B flask. $NaHCO_3$ (2.52 g, 30 mmol) was added and the mixture was heated and reflux for 18 hr. The reaction was monitored by TLC (R_f = 0.50). The solution was filtered in hot condition and the inorganic solid washed with warm $CHCl_3$. The bisnitrone crystallized from the filtrate as a white solid and was collected at the vacuum pump (74%, m.p > 250 ^{0}C).

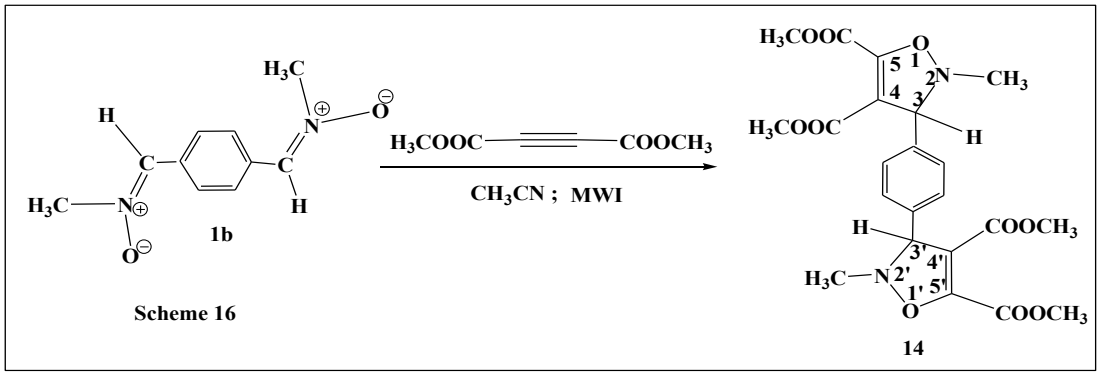
Spectroscopic data for bisnitrone 1b (R = CH_3): N-Methyl(4-{[methyl(oxido)iminio]methyl{phenyl)methylideneamine N-oxide

Yeild 74%; R_f = 0.50; FT-IR (KBr): υ_{max} 3130 (s), 3010 (m), 2970 (m), 2246 (m), 1690 (s), 1630 (s), 1610 (s), 1515 (s), 1310 (m), 1176 (s), 1150 (s), 782 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): 8.24 (s, 4H, Ar-H), 7.40 (s, 2H, 2 x CH=N^+), 3.89 (s, 6H, 2 x CH_3); ^{13}C NMR ($CDCl_3$): δ 134.66 (2 x CH=N^+), 131.81, 130.54, (1,4 Ar-C), 128.29, 127.52 (2,6 & 3,5 Ar-C), 54.58 (2 x CH_3); EI-MS (*m/z*): 192 (M^+), 176 (M-O), 134 (M-$CHNOCH_3$); Anal.Calcd. for $C_{10}H_{12}O_2N_2$: C, 62.47; H, 6.30; N, 14.58%. Found: C, 62.33; H, 6.24; N, 14.35%

***General experimental procedure for the synthesis of bisisoxazoline derivatives (14-18) under microwave irradiation*[15,16]**

Cycloaddition reaction of bisnitrone* (1b; R=CH_3) *with dimethyl acetylene dicarboxylate

Bisnitrone **1b** (0.41 mmol, 80 mg) and dimethyl acetylene dicarboxylate (0.82 mmole, 116 mg) was dissolved in acetonitrile (10 mL) and was heated in a sealed vessel at 115 ^{0}C for 5 minutes under microwave irradiation (400 W, temperature-controlled mode). The progress of the reaction was monitored by TLC (R_f = 0.58).The resulting reaction mixture was concentrated under vacuum and the crude material was directly purified by column chromatography on silica gel (ethyl acetate:n-hexane =1:6) to afford pure bisisoxazoline **14** (92%) as a colourless gummy mass. Same methodology was adopted for the synthesis of other bisisoxazoline derivatives **15-18**.



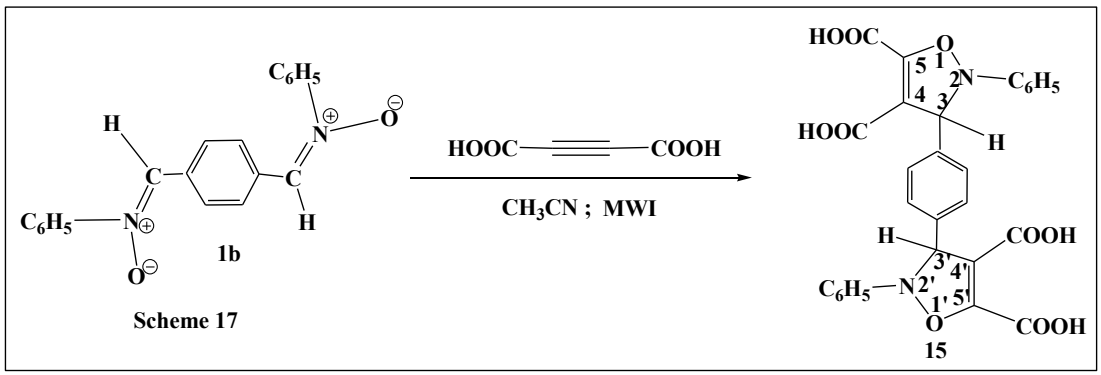
Scheme 16

***Spectroscopic data for bisisoxazoline**: (3R,3'R)-tetramethyl 3,3'-(1,4-phenylene)bis(2-methyl-2,3-dihydroisoxazole-4,5-dicarboxylate* **14**

FT-IR (KBr): υ_{max} 3036 (s), 2255 (m), 1760 (s), 1710 (s), 1600 (s), 1520 (s), 1440 (s), 1324 (m), 1314 (s), 1260 (m), 1170 (s), 780 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.60 (s, 4H, Ar-H), 5.20 (s, 2H, 2 x 3-H), 3.80 (s, 12H, 4 x -$COOCH_3$), 2.52 (s, 6H, 2 x N-CH_3); ^{13}C NMR ($CDCl_3$): δ 172.54 (2 x $\underline{CO}OCH_3$), 171.13 (2 x $\underline{CO}OCH_3$), 134.28, 133.87 (1,4 Ar-C; phenyl ring carbons linked with isoxazoline rings), 131.13, 130.45 (2,6 & 3,5 Ar-C; phenyl ring carbons linked with isoxazoline rings), 88.62 (2 x 5-C), 77.43 (2 x 3-C), 59.79 (2 x 4-C), 52.20 (2 x CH_3), 38.58 (2 x -$COO\underline{CH_3}$), 36.62 (2 x -$COO\underline{CH_3}$); EI - MS (*m/z*): 476 (M^+), 460, 400, 386, 276, 185 (B.P), 75, 59; Anal. Calcd. for $C_{22}H_{24}O_{10}N_2$: C, 55.44; H, 5.07; N, 5.88. Found: C, 55.39; H, 5.02; N, 5.74%.

Cycloaddition reaction of bisnitrone* (1b; R=C_6H_5) *with acetylene dicarboxylic acid

Bisnitrone **1b** (0.41 mmol) and acetylene dicarboxylic acid (0.82 mmole) was dissolved in acetonitrile (10 mL) and was heated in a sealed vessel at 110 ^{0}C for 5 minutes under microwave irradiation (400 W, temperature-controlled mode). The progress of the reaction was monitored by TLC (R_f = 0.54).The resulting reaction mixture was concentrated under vacuum and the crude material was directly purified by column chromatography on silica gel (ethyl acetate: n-hexane =1:6) to afford pure bisisoxazoline **15** (88%) as a colourless liquid.



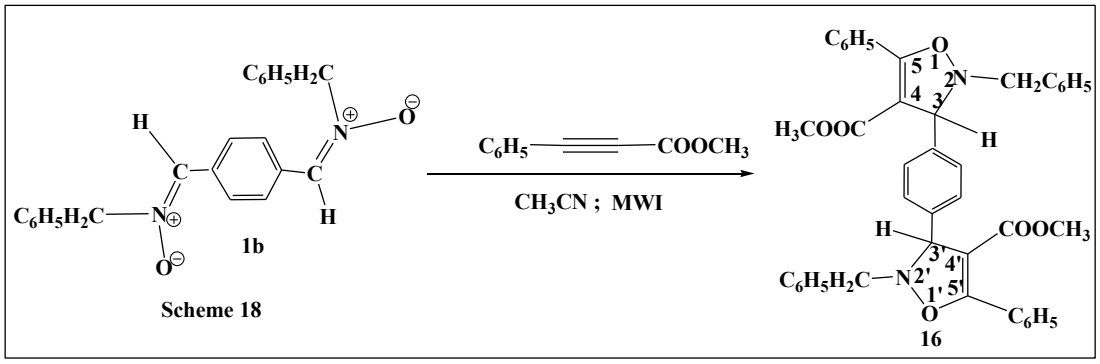
Scheme 17

***Spectroscopic data for bisisoxazoline**: (3R,3'R)-3,3'-(1,4-phenylene)bis(2-phenyl-2,3-dihydroisoxazole-4,5-dicarboxylic acid* **15**

Gray gummy liquid (88%), FT-IR (KBr): υ_{max} 3285 (s), 3080 (s), 2250 (m), 1760 (s), 1685 (s), 1585 (s), 1545 (s), 1360 (m), 1285 (m), 1015 (m), 880 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 10.13 (s, 2H, 2 x -COOH), 10.06 (s, 2H, 2 x -COOH), 7.05 (s, 4H, Ar-H), 6.84-6.68 (m, 10H, 2 x Ar-H), 5.42 (s, 2H, 2 x 3-H); ^{13}C NMR ($CDCl_3$): δ 174.27 (2 x COOH), 173.45 (2 x COOH), 136.54, 135.42 (1,4 Ar-C; phenyl ring carbons linked with isoxazoline rings), 133.25, 132.72 (2,6 & 3,5 Ar-C; phenyl ring carbons linked with isoxazoline rings), 129.44, 128.70 (2 x 1,4 Ar-C; N-phenyl carbons), 128.12, 127.83 (2 x 2,6 & 3,5 Ar-C; N-phenyl carbons), 85.71 (2 x 5-C), 78.32 (2 x 3-C), 57.14 (2 x 4-C); EI - MS (*m/z*): 544 (M^+), 467, 466, 310, 234, 77; Anal.Calcd. for $C_{28}H_{20}O_{10}N_2$: C, 61.75; H, 3.70; N, 5.14. Found: C, 61.63; H, 3.57; N, 5.03%.

Cycloaddition reaction of bisnitrone* (1b; R=$CH_2C_6H_5$) *with methyl phenyl propiolate

Bisnitrone **1b** (0.46 mmol) and methyl phenyl propiolate (0.92 mmole) was dissolved in acetonitrile (10 mL) and was heated in a sealed vessel at 110 ^{0}C for 6 minutes under microwave irradiation (400 W, temperature-controlled mode). The progress of the reaction was monitored by TLC (R_f = 0.58).The resulting reaction mixture was concentrated under vacuum and the crude material was directly purified by column chromatography on silica gel (ethyl acetate:n-hexane =1:6) to afford pure bisisoxazoline **16** (88%) as colourless liquid.



Scheme 18

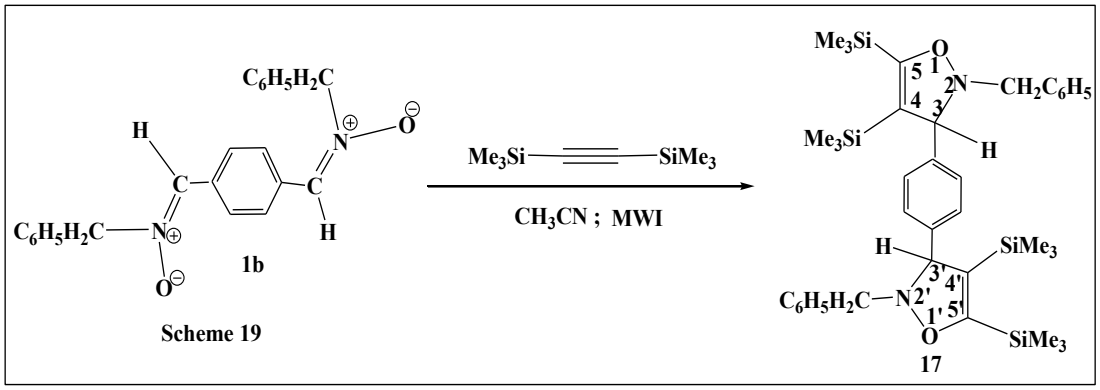
***Spectroscopic data for bisisoxazoline**: (3R,3'R)-dimethyl 3,3'-(1,4-phenylene)bis(2-benzyl-5-phenyl-2,3-dihydroisoxazole-4-carboxylate* **16**

Colourless liquid. Yield 88%; FT-IR (KBr): υ_{max} 3065 (s), 1740 (s), 1660 (s), 1590 (s), 1490 (m), 1480 (m), 1355 (m), 1290 (m), 1020 (m), 830 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.80 (s, 4H, Ar-H), 7.54-7.35 (m, 10H, 2 x Ar-H, phenyl protons linked with C_5 & $C_{5'}$ carbons),

7.12-6.94 (m, 10H, 2 x $CH_2C_6H_5$), 5.13 (s, 2H, 2 x 3-H), 3.74 (s, 4H, 2 x $CH_2C_6H_5$), 3.30 (s, 6H, 2 x –$COOCH_3$); ^{13}C NMR ($CDCl_3$): δ 174.54 (2 x $\underline{CO}OCH_3$), 134.07, 133.85 (1,4 Ar-C; phenyl ring carbons linked with isoxazoline rings), 133.14, 133.03 (2,6 & 3,5 Ar-C; phenyl ring carbons linked with isoxazoline rings), 130.92, 130.64 (2 x 1,4 Ar-C; phenyl carbons linked with C_5 & $C_{5'}$ carbons), 129.75, 129.57 (2 x 2,6 & 3,5 Ar-C; phenyl carbons linked with C_5 & $C_{5'}$ carbons), 128.77, 128.64 (2 x 1,4 Ar-C; phenyl carbons linked with benzyl carbons), 128.15, 127.97 (2 x 2,6 & 3,5 Ar-C; phenyl carbons linked with benzyl carbons), 83.80 (2 x 5-C), 74.46 (2 x 3-C), 59.32 (2 x 4-C), 32.16 (2 x $\underline{CH_2}C_6H_5$), 28.12 (2 x -$COO\underline{CH_3}$); EI-MS (*m/z*): 664 (M^+), 587, 559, 370, 294, 91, 77; Anal. Calcd. for $C_{42}H_{36}O_6N_2$: C, 75.87; H, 5.45; N, 4.21. Found: C, 75.79; H, 5.38; N, 4.23%.

***Cycloaddition reaction of bisnitrone* (1b; R=$CH_2C_6H_5$) *with bis-(trimethylsilyl) acetylene* (BTMSA)**

Bisnitrone **1b** (0.46 mmol) and bis-(trimethylsilyl) acetylene (0.92 mmole) was dissolved in acetonitrile (10 mL) and was heated in a sealed vessel at 110 ^{0}C for 5 minutes under microwave irradiation (400 W, temperature-controlled mode). The progress of the reaction was monitored by TLC (R_f = 0.52).The resulting reaction mixture was concentrated under vacuum and the crude material was directly purified by column chromatography on silica gel (ethyl acetate:n-hexane =1:6) to afford pure bisisoxazoline **17** (87%) as yellow sticky liquid.



Scheme 19

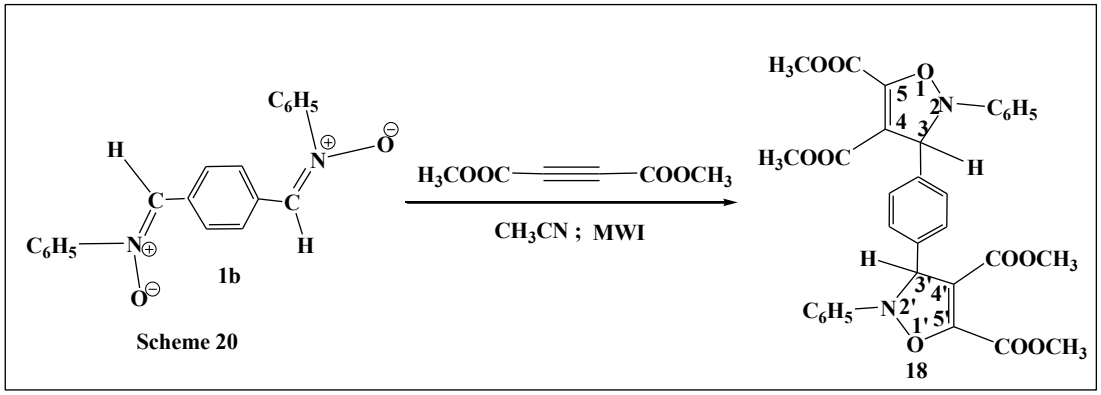
***Spectroscopic data for bisisoxazoline: 1,4-bis((R)-2-benzyl-4,5-bis(trimethylsilyl)-2,3-dihydroisoxazol-3-yl)benzene* 17**

Yellow sticky liquid. Yield 87%; FT-IR (KBr): υ_{max} 3073 (s), 2255 (m), 1665 (s), 1585 (s), 1500 (m), 1470 (m), 1350 (m), 1282 (m), 1025 (m), 860 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.16 (s, 4H, Ar-H), 7.05-6.92 (m, 10H, 2 x Ar-H), 5.02 (s, 2H, 2 x 3-H), 3.43 (s, 4H, 2 x $CH_2C_6H_5$), 0.82 (s, 36H, 4 x $SiMe_3$);

^{13}C NMR ($CDCl_3$): δ 136.66, 134.80 (1,4 Ar-C; phenyl ring carbons linked with isoxazoline rings), 132.54, 131.89 (2,6 & 3,5 Ar-C; phenyl ring carbons linked with isoxazoline rings),129.70, 129.64 (2 x 1,4 Ar-C; phenyl carbons linked with benzyl carbons), 128.75, 128.43 (2 x 2,6 & 3,5 Ar-C; phenyl carbons linked with benzyl carbons), 80.67 (2 x 5-C), 75.90 (2 x 3-C), 56.44 (2 x 4-C), 31.75 (2 x $\underline{CH_2}C_6H_5$), 0.12 (4 x $SiMe_3$ carbons) ; EI - MS (*m/z*): 684 (M^+), 607, 583, 380, 304, 91, 77; Anal. Calcd. for $C_{38}H_{56}Si_4O_2N_2$: C, 66.62; H, 8.23; N, 4.09. Found: C, 66.50; H, 8.12; N, 4.12%.

Cycloaddition reaction of bisnitrone* (1b; R=C_6H_5) *with dimethyl acetylene dicarboxylate

Bisnitrone **1b** (0.40 mmol) and dimethyl acetylene dicarboxylate (0.80 mmole) was dissolved in acetonitrile (10 mL) and was heated in a sealed vessel at 115 ^{0}C for 5 minutes under microwave irradiation (400 W, temperature-controlled mode). The progress of the reaction was monitored by TLC (R_f = 0.54).The resulting reaction mixture was concentrated under vacuum and the crude material was directly purified by column chromatography on silica gel (ethyl acetate:n-hexane =1:6) to afford pure bisisoxazoline **18** (86%) as pale yellow liquid.



Scheme 20

***Spectroscopic data for bisisoxazoline: (3R,3'R)-tetramethyl 3,3'-(1,4-phenylene)bis(2-phenyl-2,3-dihydroisoxazole-4,5-dicarboxylate* 18**

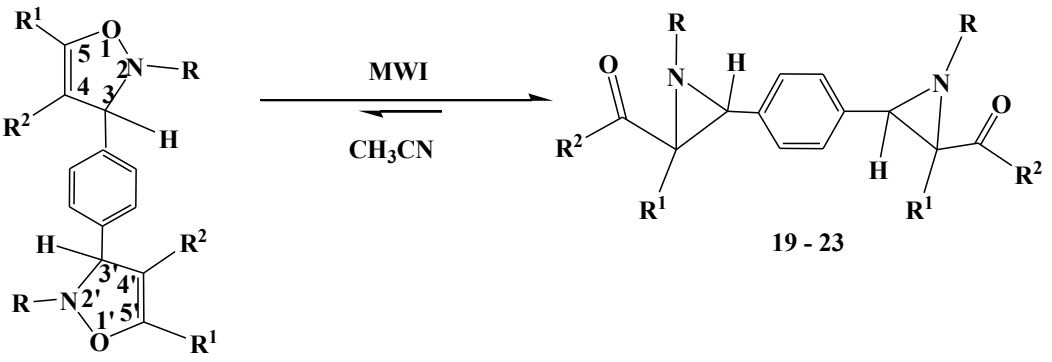
Pale yellow liquid. Yield 86%; FT-IR (KBr): υ_{max} 3018 (s), 2246 (m), 1763 (s), 1712 (s), 1605 (s), 1532 (s), 1436 (s), 1320 (m), 1254 (m), 1184 (s), 776 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.85 (m, 2 x 5H), 6.94 (s, 4H, Ar-H), 5.68 (s, 2H, 2 x 3-H), 3.37 (s, 12H, 4 x -$COOCH_3$); ^{13}C NMR ($CDCl_3$): δ 171.86 (2 x $\underline{CO}OCH_3$), 169.35 (2 x $\underline{CO}OCH_3$),137.54, 137.59 (1,4 Ar-C; phenyl ring carbons linked with isoxazoline rings), 135.62, 135.71 (2,6 & 3,5 Ar-C; phenyl ring carbons linked with isoxazoline rings),

132.60, 129.86 (2 x 1,4 Ar-C; N-phenyl carbons), 127.64, 127.42 (2 x 2,6 & 3,5 Ar-C; N-phenyl carbons), 86.12 (2 x 5-C), 75.48 (2 x 3-C), 61.23 (2 x 4-C), 39.52 (2 x -COO$\underline{CH_3}$), 37.80 (2 x -COO$\underline{CH_3}$); EI - MS (*m/z*): 600 (M^+), 523, 482, 446, 338, 262 (B.P), 77, 59; Anal. Calcd. for $C_{32}H_{28}O_{10}N_2$: C, 63.98; H, 4.69; N, 4.66. Found: C, 63.90; H, 4.57; N, 4.60%.

Reaction type IV (*Synthesis of bisaziridine derivatives*)[15]

*Synthesis of new bisaziridine derivatives (**19-23**) have been studied using terepthalaldehyde derived bisisoxazoline derivatives under microwave irradiation (MWI) The details of these experimental procedures are described as under:*

18. *General experimental procedure for the synthesis of bisaziridine derivatives (19-23) under microwave irradiation* *:*



General scheme of synthesis of bisaziridine derivatives

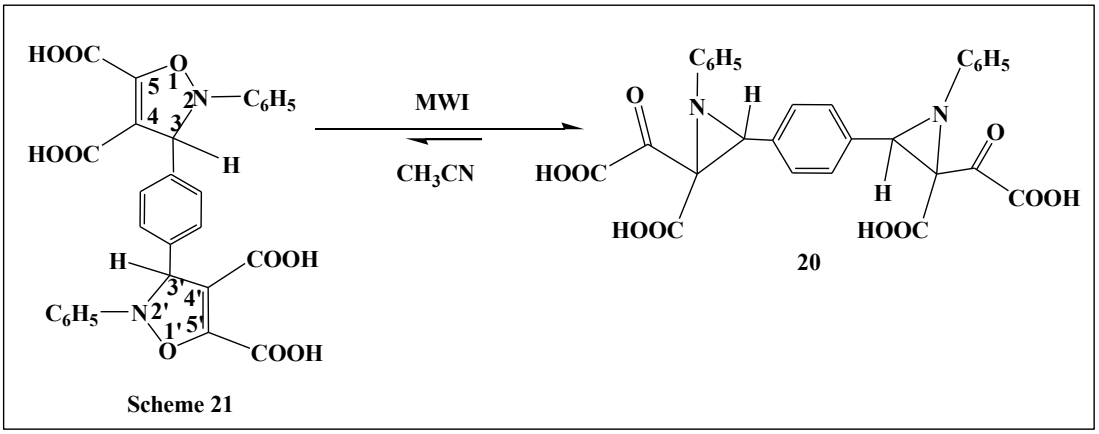
R = CH_3 ; C_6H_5 ; $CH_2C_6H_5$
R^1, R^2 = -COOMe
R^1, R^2 = -COOH
R^1, R^2 = -TMS
R^1 = C_6H_5 ; R^2 = -CO_2CH_3

Bisisoxazoline **14** (0.25 mmol, 120 mg; R=CH_3, R^1, R2 =$COOCH_3$) was dissolved in acetonitrile (10 mL) and was heated in a sealed vessel at 130 ^{0}C for 5 minutes under microwave irradiation (400 W, temperature-controlled mode). The progress of the reaction was monitored by TLC (R_f = 0.52). The resulting reaction mixture was concentrated under vacuum and the crude material was directly purified by column chromatography on silica gel (ethyl acetate:n-hexane =1:6) to afford pure bisaziridine **19** (R=CH_3, R^1, R2 =$COOCH_3$; 78%) as pale yellow gummy mass. Same methodology was adopted for the synthesis of other bisaziridine derivatives **20-23**.

***Spectroscopic data for bisaziridine**: dimethyl 3,3'-(1,4-phenylene)bis(2-(2-methoxy-2-oxoacetyl)-1-methylaziridine-2-carboxylate* **19 (R=CH_3, R^1, R^2 =$COOCH_3$)**

FT-IR (KBr): υ_{max} 3028 (s), 2985 (m), 1766 (s), 1721 (s), 1661 (s), 1592 (m), 1518 (s), 786 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.52 (s, 4H, Ar-H), 4.86 (s, 2H, 2 x aziridine protons), 3.92 (s, 6H, 2 x -$COOCH_3$, linked with aziridine rings), 3.70 (s, 6H, 2 x -$COOCH_3$, linked with keto group), 2.68 (s, 6H, 2 x N-CH_3); ^{13}C NMR ($CDCl_3$): δ 174.10 (2 x C=O), 170.74 (2 x -$\underline{CO}OCH_3$, linked with aziridine rings), 169.20 (2 x -$\underline{CO}OCH_3$, linked with keto group), 130.80, 130.23 (1,4 Ar-C; phenyl ring carbons linked with aziridine rings), 128.15, 127.30 (2,6 & 3,5 Ar-C; phenyl ring carbons linked with aziridine rings), 60.24 (2 x aziridine ring carbons), 54.24 (2 x aziridine ring carbons), 48.60 (2 x CH_3), 35.06 (2 x -$COO\underline{CH_3}$, linked with aziridine rings), 33.18 (2 x -$COO\underline{CH_3}$, linked with keto group); EI - MS (*m/z*): 476 (M^+), 461, 417, 400, 386, 276, 200, 76, 75, 59; Anal. Calcd. for $C_{22}H_{24}O_{10}N_2$: C, 55.44; H, 5.07; N, 5.88. Found: C, 55.26; H, 4.92; N, 5.61%.

Synthesis of bisaziridine **20 (R=C_6H_5 ; R^1=R^2=COOH)**



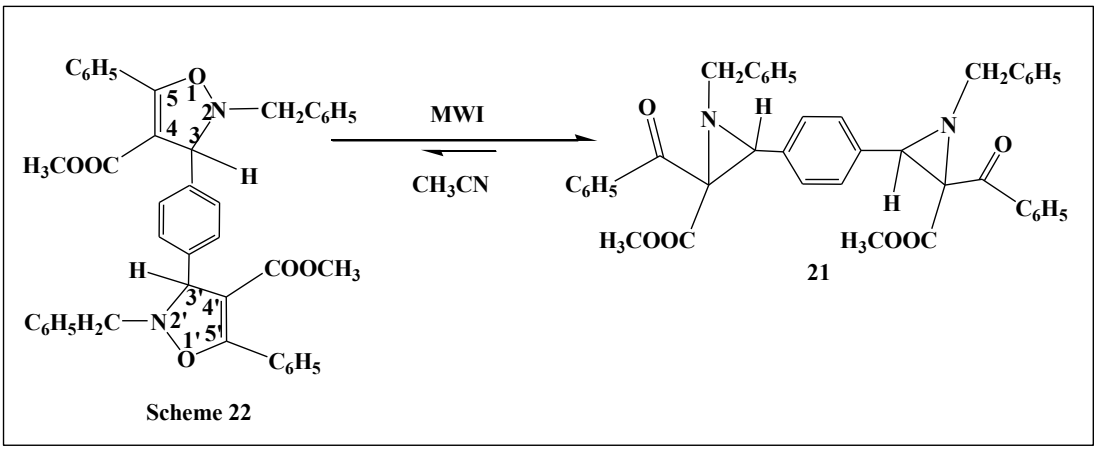
Scheme 21

Bisisoxazoline **15** (0.25 mmol; R=C_6H_5 ; R^1=R^2=COOH) was dissolved in acetonitrile (10 mL) and was heated in a sealed vessel at 130 ^{0}C for 5 minutes under microwave irradiation (400 W, temperature-controlled mode). The progress of the reaction was monitored by TLC (R_f = 0.56). The resulting reaction mixture was concentrated under vacuum and the crude material was directly purified by column chromatography on silica gel (ethyl acetate:n-hexane =1:6) to afford pure bisaziridine **20** (75%) as dark gray gummy mass.

***Spectroscopic data for bisaziridine**: (3R,3'R)-3,3'-(1,4-phenylene)bis(2-phenyl-2,3-phenylaziridine -4,5-dicarboxylic acid* **20**

Dark gray gummy mass (75%), FT-IR (KBr): υ_{max} 3280 (s), 3076 (s), 2250 (m), 1765 (s), 1754 (s), 1682 (s), 1660 (s), 1585 (s), 1540 (s), 1364 (m), 1282 (m), 1016 (m), 870 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 10.20 (s, 2H, 2 x -COOH), 10.05 (s, 2H, 2 x -COOH), 7.14 (s, 4H, Ar-H), 6.77-6.62 (m, 10H, 2 x Ar-H), 4.90 (s, 2H, 2 x aziridine protons); ^{13}C NMR ($CDCl_3$): δ 175.50 (2 x C=O), 174.27 (2 x COOH), 173.45 (2 x COOH), 135.80, 135.26 (1,4 Ar-C; phenyl ring carbons linked with aziridine rings), 132.88, 132.51 (2,6 & 3,5 Ar-C; phenyl ring carbons linked with aziridine rings), 130.12, 129.42 (2 x 1,4 Ar-C; N-phenyl carbons), 128.30, 127.67 (2 x 2,6 & 3,5 Ar-C; N-phenyl carbons), 67.20 (2 x aziridine ring carbons), 60.43 (2 x aziridine ring carbons); EI - MS (*m/z*): 544 (M^+), 499, 466, 394, 310, 234, 77, 45; Anal. Calcd. for $C_{28}H_{20}O_{10}N_2$: C, 61.75; H, 3.70; N, 5.14. Found: C, 61.54; H, 3.74; N, 5.10%.

***Synthesis of bisaziridine* 21 (R=$CH_2C_6H_5$; R^1=C_6H_5, R^2=$COOCH_3$)**



Scheme 22

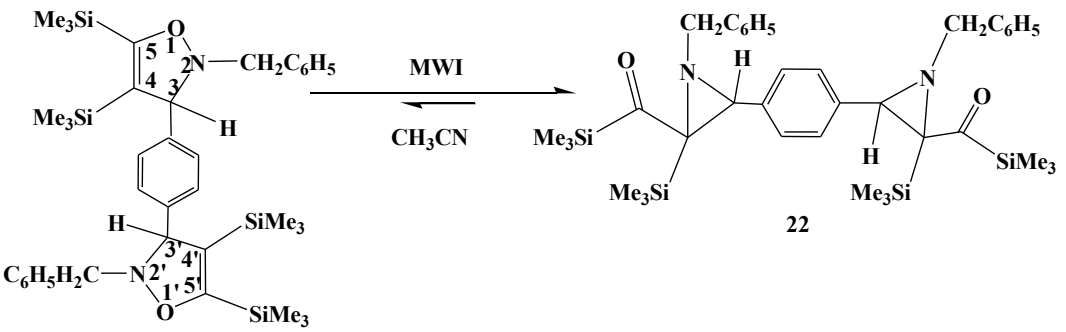
Bisisoxazoline **16** (0.25 mmol; R=$CH_2C_6H_5$; R^1=C_6H_5 , R^2=$COOCH_3$) was dissolved in acetonitrile (10 mL) and was heated in a sealed vessel at 130 ^0C for 6 minutes under microwave irradiation (400 W, temperature-controlled mode). The progress of the reaction was monitored by TLC (R_f = 0.54). The resulting reaction mixture was concentrated under vacuum and the crude material was directly purified by column chromatography on silica gel (ethyl acetate:n-hexane =1:6) to afford pure bisaziridine **21** (74%) as dark gray gummy mass.

***Spectroscopic data for bisaziridine: dimethyl 3,3'-(1,4-phenylene)bis(2-benzoyl-1-benzylaziridine-2-carboxylate* 21**

Gray gummy liquid. Yield 74%; FT-IR (KBr): υ_{max} 3070 (s), 1744 (s), 1714 (s), 1622 (s), 1590 (s), 1484 (m), 1475 (m), 1358 (m), 1282 (m), 1016(m), 850 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.23 (s, 4H, Ar-H), 7.06-6.90 (m, 20H, 4 x Ar-H), 4.82 (s, 2H, 2 x aziridine protons),

3.82 (s, 4H, 2 x $CH_2C_6H_5$), 3.34 (s, 6H, 2 x –$COOCH_3$); ^{13}C NMR ($CDCl_3$): δ 174.68 (2 x C=O), 172.80 (2 x $\underline{CO}OCH_3$), 133.00, 132.74 (1,4 Ar-C; phenyl ring carbons linked with aziridine rings), 132.06, 131.90 (2,6 & 3,5 Ar-C; phenyl ring carbons linked with aziridine rings), 130.68, 130.52 (2 x 1,4 Ar-C; phenyl carbons linked with C_5 & $C_{5'}$ carbons), 129.24, 129.10 (2 x 2,6 & 3,5 Ar-C; phenyl carbons linked with C_5 & $C_{5'}$ carbons), 128.61, 128.30 (2 x 1,4 Ar-C; phenyl carbons linked with benzyl carbons), 127.83, 127.29 (2 x 2,6 & 3,5 Ar-C; phenyl carbons linked with benzyl carbons), 60.46 (2 x aziridine ring carbons), 57.54 (2 x aziridine ring carbons); 37.70 (2 x $\underline{CH_2}C_6H_5$), 27.94 (2 x -COO$\underline{CH_3}$); EI - MS (*m/z*): 664 (M^+), 559, 514, 468, 370, 294, 105, 91, 77; Anal. Calcd. for $C_{42}H_{36}O_6N_2$: C, 75.87; H, 5.45; N, 4.21. Found: C, 75.60; H, 5.27; N, 4.17%.

***Synthesis of bisaziridine* 22 (R=$CH_2C_6H_5$; R^1=R^2=$SiMe_3$)**



Scheme 23

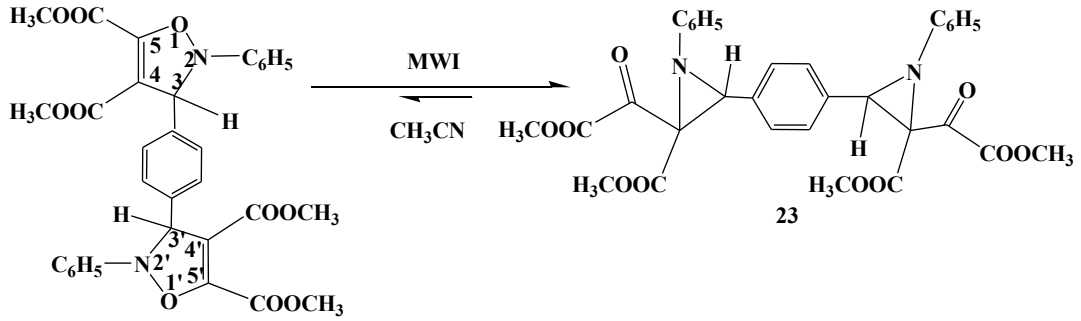
Bisisoxazoline **17** (0.25 mmol; R=$CH_2C_6H_5$; R^1=R^2=$SiMe_3$) was dissolved in acetonitrile (10 mL) and was heated in a sealed vessel at 130 ^{0}C for 7 minutes under microwave irradiation (400 W, temperature-controlled mode). The progress of the reaction was monitored by TLC (R_f = 0.60). The resulting reaction mixture was concentrated under vacuum and the crude material was directly purified by column chromatography on silica gel (ethyl acetate:n-hexane =1:6) to afford pure bisaziridine **22** (73%) as gray gummy liquid.

***Spectroscopic data for bisaziridine: (3,3'-(1,4-phenylene)bis(1-benzyl-2-(trimethylsilyl)aziridine-3,2-diyl))bis((trimethylsilyl)methanone* 22**

Gray gummy liquid. Yield 73%; FT-IR (KBr): υ_{max} 3085 (s), 1762 (s), 1712 (s), 1665 (s), 1584 (s), 1500 (m), 1475 (m), 1356 (m), 1285 (m), 1014 (m), 865 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.03 (s, 4H, Ar-H), 6.87-6.74 (m, 10H, 2 x Ar-H), 4.54 (s, 2H, 2 x aziridine protons), 2.65 (s, 4H, 2 x $CH_2C_6H_5$), 0.80 (s, 36H, 4 x $SiMe_3$); ^{13}C NMR ($CDCl_3$): δ 173.48 (2 x C=O), 135.90, 135.34 (1,4 Ar-C; phenyl ring carbons linked with aziridine rings), 133.68, 132.72

(2,6 & 3,5 Ar-C; phenyl ring carbons linked with aziridine rings),130.54, 130.23 (2 x 1,4 Ar-C; phenyl carbons linked with benzyl carbons), 128.78, 128.16 (2 x 2,6 & 3,5 Ar-C; phenyl carbons linked with benzyl carbons), 57.54 (2 x aziridine ring carbons), 55.75 (2 x aziridine ring carbons), 34.42 (2 x $\underline{CH_2}C_6H_5$), 0.15 (4 x $SiMe_3$ carbons) ; EI - MS (*m/z*): 684 (M^+), 611, 607, 583, 520, 492, 380, 304, 101, 91, 77; Anal. Calcd. for $C_{38}H_{56}Si_4O_2N_2$: C, 66.62; H, 8.23; N, 4.09. Found: C, 66.43; H, 8.14; N, 4.10%.

***Synthesis of bisaziridine* 23 (R=C_6H_5 ; R^1=R^2=$COOCH_3$)**



Scheme 24

Bisisoxazoline **18** (0.25 mmol; R=C_6H_5 ; R^1=R^2=$COOCH_3$) was dissolved in acetonitrile (10 mL) and was heated in a sealed vessel at 130 ^{0}C for 9 minutes under microwave irradiation (400 W, temperature-controlled mode). The progress of the reaction was monitored by TLC (R_f = 0.60). The resulting reaction mixture was concentrated under vacuum and the crude material was directly purified by column chromatography on silica gel (ethyl acetate:n-hexane =1:6) to afford pure bisaziridine **23** (71%) as gray gummy liquid

***Spectroscopic data for bisaziridine: diphenyl 3,3'-(1,4-phenylene)bis(2-(2-methoxy-2-oxoacetyl)-1-phenylaziridine-2-carboxylate* 23**

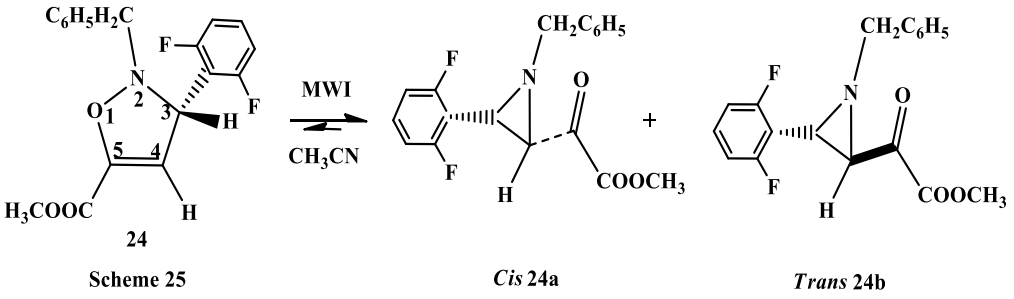
Yellow liquid. Yield 71%; FT-IR (KBr): υ_{max} 3035 (s), 2980 (m), 1763 (s), 1726 (s), 1660 (s), 1585 (m), 1535 (s), 780 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.42 (m, 2 x 5H), 6.50 (s, 4H, Ar-H), 4.74 (s, 2H, 2 x aziridine protons), 3.80 (s, 6H, 2 x -$COOCH_3$, linked with aziridine rings), 3.53 (s, 6H, 2 x -$COOCH_3$, linked with keto group); ^{13}C NMR ($CDCl_3$): δ 173.11 (2 x C=O), 172.06 (2 x -$\underline{CO}OCH_3$, linked with aziridine rings), 170.15 (2 x -$\underline{CO}OCH_3$, linked with keto group), 130.80, 130.23 (1,4 Ar-C; phenyl ring carbons linked with aziridine rings), 129.80, 129.56 (2,6 & 3,5 Ar-C; phenyl ring carbons linked with aziridine rings), 128.06, 127.90 (2 x 1,4 Ar-C; N-phenyl carbons), 127.24, 127.03 (2 x 2,6 & 3,5 Ar-C; N-phenyl carbons), 62.62

(2 x aziridine ring carbons), 59.46 (2 x aziridine ring carbons), 37.12 (2 x -COO$\underline{CH_3}$, linked with aziridine rings), 35.47 (2 x -COO$\underline{CH_3}$, linked with keto group); EI - MS (*m/z*): 600 (M^+), 523, 513, 436, 338, 262 (B.P), 87, 77, 59; Anal. Calcd. for $C_{32}H_{28}O_{10}N_2$: C, 63.98; H, 4.69; N, 4.66. Found: C, 63.81; H, 4.54; N, 4.52%.

***Synthesis aziridine derivatives from N-Benzyl fluoro nitrone*[17]**

*Synthesis of new aziridine derivatives (**25-26**) have been also studied using fluoro isoxazoline derivatives under microwave irradiation (MWI). The details of these experimental procedures are described as under:*

General experimental procedure for the synthesis of new aziridine derivatives (24a, 24b &26) under microwave irradiation:



24

Scheme 25 ***Cis* 24a** ***Trans* 24b**

Isoxazoline **24** (1.5 mmol) was dissolved in acetonitrile (12 mL) and was heated in a sealed vessel at 110 ^{0}C for 5 minutes under microwave irradiation (400 W, temperature-controlled mode). The resulting reaction mixture was concentrated under vacuum and the crude material was directly purified by column chromatography (separation of diastereomers) on silica gel (ethyl acetate:n-hexane =1:10) to give the *N*-substituted aziridines **24a & 24b** (*cis isomer*; 359.7 mg, 76%; *trans isomer*, 12%) as a yellow gummy mass. Same methodology was adopted for the synthesis of other aziridine derivatives **26a & 26b**.

Aziridine 24a (cis isomer): methyl 2-((2R,3R)-1-benzyl-3-(2,6-difluorophenyl)aziridin-2-yl)-2-oxoacetate

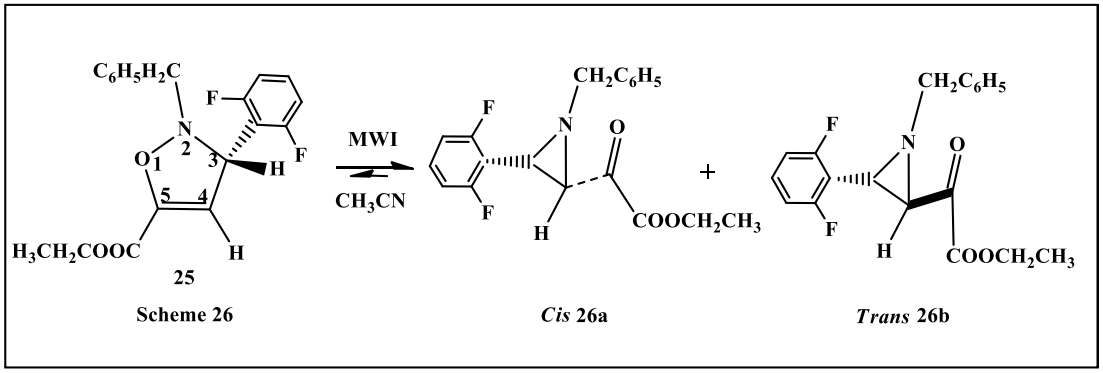
Yellow gummy mass. Yield 76%; R_f = 0.66; IR (KBr): υ_{max} 3010 (m), 2970 (m), 2246 (m), 1740 (s), 1710 (s), 1690 (s), 1474 (s), 1440 (m), 1324 (m), 1176 (s), 782 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.87 – 7.80 (m, 3H, $C_6H_3F_2$), 7.68-7.31 (m, 5H, C_6H_5), 4.24 (d, *J* = 7.90 Hz, 1H), 4.12 (d, *J* = 7.90 Hz, 1H), 3.38 (s, 3H, -$COOCH_3$), 2.68 (s,2H, $C_6H_5CH_2$); ^{13}C NMR ($CDCl_3$): δ 173.52 (-C=O), 168.52 (-$COOCH_3$), 137.20, 137.04, 136.87, 136.66 (aromatic carbons),

132.77, 132.35, 132.08, 131.78, 130.80, 129.90 (2,6 difluoro phenyl carbons), 36.80 (benzylic carbon), 31.54, 30.44 (aziridine ring carbons), 18.42 (-$COOCH_3$); EI - MS (m/z): 331 (M^+), 330, 272, 244 (B.P), 218, 113, 87, 59. Anal. Calcd. for $C_{18}H_{15}O_3F_2N$: C, 65.26; H, 4.56; N, 4.22. Found: C, 65.13; H, 4.41; N, 4.15%.

Aziridine 24b (trans isomer): methyl 2-((2R,3S)-1-benzyl-3-(2,6-difluorophenyl)aziridin-2-yl)-2-oxoacetate

Yellow oil. Yield 12%; R_f = 0.60; IR (KBr): υ_{max} 3014 (m), 2976 (m), 2240 (m), 1744 (s), 1710 (s), 1685 (s), 1470 (s), 1440 (m), 1320 (m), 1172 (s), 780 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.80 – 7.72 (m, 3H, $C_6H_3F_2$), 7.60-7.43 (m, 5H, C_6H_5), 4.15 (d, *J* = 4.20 Hz, 1H), 4.06 (d, *J* = 4.20 Hz, 1H), 3.30 (s, 3H, -$COOCH_3$), 2.70 (s,2H, $C_6H_5CH_2$); ^{13}C NMR ($CDCl_3$): δ 174.28 (-C=O), 170.40 (-$COOCH_3$), 135.73, 135.60, 135.46, 135.54 (aromatic carbons), 133.69, 133.26, 132.78, 132.45, 132.23, 131.93 (2,6 difluoro phenyl carbons), 34.55 (benzylic carbon), 32.27, 31.17 (aziridine ring carbons), 18.24 (-$COOCH_3$); EI - MS (*m/z*): 331 (M^+), 330, 272, 244 (B.P), 218, 217, 113, 87, 59. Anal.Calcd. for $C_{18}H_{15}O_3F_2N$: C, 65.26; H, 4.56; N, 4.22. Found: C, 65.07; H, 4.36; N, 4.08%.

***Synthesis of fluoro aziridine 26 from fluoro ethyl propiolate isoxazoline cycloadduct* (25)**



Scheme 26 ***Cis* 26a** ***Trans* 26b**

Isoxazoline **25** (1.5 mmol) was dissolved in acetonitrile (12 mL) and was heated in a sealed vessel at 110 ^{0}C for 5 minutes under microwave irradiation (400 W, temperature-controlled mode). The resulting reaction mixture was concentrated under vacuum and the crude material was directly purified by column chromatography (separation of diastereomers) on silica gel (ethyl acetate:n-hexane =1:10) to give the *N*-substituted aziridines **26a & 26b** (*cis* isomer, 71%; *trans* isomer, 14%) as a colourless gummy mass.

Aziridine 26a (cis isomer): ethyl 2-((2R,3R)-1-benzyl-3-(2,6-difluorophenyl)aziridin-2-yl)-2-oxoacetate

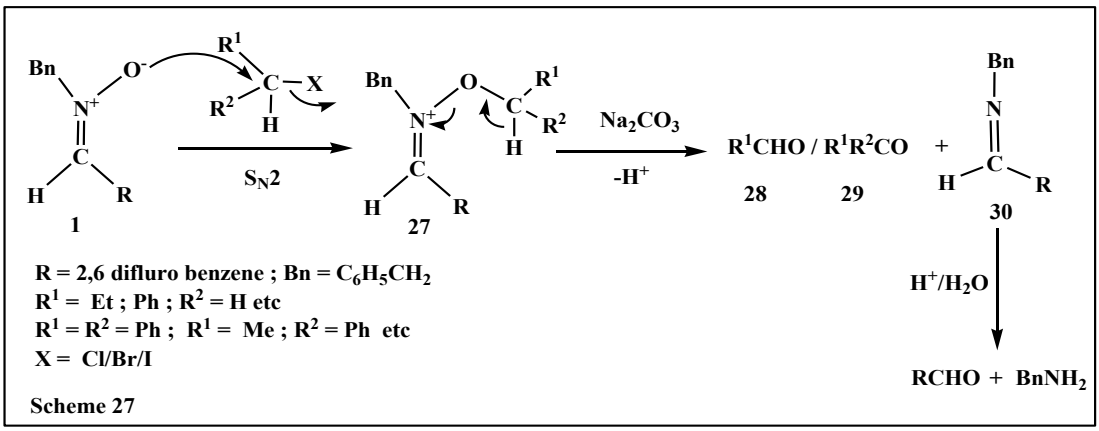
Colourless gummy mass. Yield 71%; R_f = 0.74; IR (KBr): υ_{max} 3016 (m), 2978 (m), 2350 (m), 1744 (s), 1712 (s), 1684 (s), 1474 (s), 1440 (m), 1334 (m), 1176 (s), 782 (s) cm^{-1}; 1H NMR (CDCl3): δ 7.54 – 7.42 (m, 3H, $C_6H_3F_2$), 7.22-7.08 (m, 5H, C_6H_5), 4.52 (d, *J* = 6.96 Hz, 1H), 4.46 (d, *J* = 6.96 Hz, 1H), 2.68 (s,2H, $C_6H_5CH_2$), 2.20 (dd, 2H, *J* = 4.22 Hz, *J* = 4.26 Hz, -$COOCH_2CH_3$), 1.84 (t, 3H, *J* = 3.80 Hz, -$COOCH_2CH_3$); ^{13}C NMR ($CDCl_3$): δ 172.28 (-C=O), 169.80 (-$COOCH_2CH_3$), 135.60, 135.44, 135.25, 135.06 (aromatic carbons), 129.46, 129.37, 129.22, 129.07, 128.85, 128.60 (2,6 difluoro phenyl carbons), 35.20 (benzylic carbon), 32.76, 31.90 (aziridine ring carbons), 19.56, 18.74 (-$COOCH_2CH_3$); EI - MS (*m/z*): 345 (M^+), 300, 272, 244, 232 (B.P), 113, 101, 73, 45. Anal. Calcd. for $C_{19}H_{17}O_3F_2N$: C, 66.08; H, 4.95; N, 4.05. Found: C, 66.02; H, 4.83; N, 3.95%.

Aziridine 26b (trans isomer): ethyl 2-((2R,3S)-1-benzyl-3-(2,6-difluorophenyl)aziridin-2-yl)-2-oxoacetate

Colourless liquid. Yield 14%; R_f = 0.70; IR (KBr): υ_{max} 3026 (m), 2986 (m), 2280 (m), 1748 (s), 1712 (s), 1682 (s), 1480 (s), 1442 (m), 1336 (m), 1235 (s), 788 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.50 – 7.37 (m, 3H, $C_6H_3F_2$), 7.16-7.03 (m, 5H, C_6H_5), 4.46 (d, *J* = 4.16 Hz, 1H), 4.35 (d, *J* = 4.16 Hz, 1H), 2.54 (s, 2H, $C_6H_5CH_2$), 2.34 (dd, 2H, *J* = 3.90 Hz, *J* = 3.96 Hz, -$COOCH_2CH_3$), 1.70 (t, 3H, *J* = 3.28 Hz, -$COOCH_2CH_3$); ^{13}C NMR ($CDCl_3$): δ 170.80 (-C=O), 168.14 (-$COOCH_2CH_3$), 134.46, 134.28, 134.20, 134.12 (aromatic carbons), 130.42, 130.26, 130.12, 130.04, 129.55, 129.47 (2,6 difluoro phenyl carbons), 33.66 (benzylic carbon), 30.40, 29.63 (aziridine ring carbons), 19.52, 18.90 (-$COOCH_2CH_3$); EI - MS (*m/z*): 345 (M^+), 300, 272, 244, 232 (B.P), 231, 113, 101, 73, 45. Anal.Calcd. for $C_{19}H_{17}O_3F_2N$: C, 66.08; H, 4.95; N, 4.05. Found: C, 65.93; H, 4.78; N, 3.88%.

Reaction type V (*Synthesis of aldehyde & ketone using N-Benzyl fluoro nitrone*)[11]

General scheme of synthesis of aldehydes and ketones using N-benzyl fluoro nitrone



Scheme 27

General procedure for synthesis of aldehydes and ketones

To a stirred solution of 2,6-Difluoro benzaldehyde (1 mmol) and *N*-Benzylhydroxylamine (1 mmol; 1 equivalent) in dry ether (25 ml), benzyl chloride (1 equivalent) was added at the time of development of fluoro nitrone **1** (monitored by TLC) and was stirred at RT with a magnetic stirrer under N_2 atmosphere for 1 hour. During this process nitrone **1** underwent S_N2 reaction very quickly with benzyl chloride and developed an intermediate compound (**27; Scheme 27**) which was not isolated**.** The progress of the reaction was monitored by TLC (R_f = 0.38). 2 gms of solid Na_2CO_3 was added at this stage and the reaction mixture was stirred for further 3 hrs and monitored by TLC. The N-O bond was easily cleaved[13] under basic medium in a Kornblum type mechanism and developed benzaldehyde **28** (R^1=Ph, R^2=H ; R_f = 0.43) and imine derivative **30** (R_f = 0.54) respectively (**Scheme 27**). The reaction mixture was filtered and concentrated on a rotary evaporator. Basic work-up followed by silica gel column chromatography using ethyl acetate – hexane results benzaldehyde (**28**) as colourless liquid (706 mg, 88 %) and imine derivative (**30)** as pale yellow gummy liquid (84 mg, 11 %, **Scheme 27**). This general procedure was followed for all the substrates listed in **Scheme 27** & **Table 1** for the synthesis of other aldehydes and ketones.

Table 1: ***Synthesis of aldehydes and ketones using N-benzyl-fluoro nitrone***

Entry	Nitrone	Alkyl halide[a]	Product[b]	Time (hr)	Yield[c] (%)
1	*N*-benzyl fluoro nitrone	Benzyl chloride	Benzaldehyde	4	88
2	*N*-benzyl fluoro nitrone	1-chloro propane	Propionaldehyde	6	78
3	*N*-benzyl fluoro nitrone	Bromo diphenyl methane	Benzophenone	6	77
4	*N*-benzyl fluoro nitrone	1-bromo ethyl benzene	Acetophenone	5	75

[a] Reaction condition : α-chloro nitrone (3.0198 mmol), isopropyl halide (1 equivalent), dry ether, N_2 atmosphere, RT

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

[c] Isolated yield after purification.

***Spectroscopic data for benzaldehyde* (*entry* 1)**

Yield: 712 mg (88%); colourless liquid; R_f = 0.43; IR (KBr): 1695(s), 1320(m), 770(s) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 9.80 (s, 1H, CHO), 7.30 – 7.16 (m, 5H, C_6H_5); ^{13}CNMR ($CDCl_3$): δ 198.00 (CHO), 136.20, 134.55, 132.60, 131.00 (aromatic carbons); EI - MS (*m/z*): 106 (M^+), 105 (B.P), 77, 51, 28; HRMS-EI: Calcd. for C_6H_5CHO (M), 106.0417, Found; M^+, 106.0408.

***Spectroscopic data for propionaldehyde* (*entry* 2)**

Yield: 592mg (87%); colourless liquid; R_f = 0.5; IR (KBr): 2920 (m), 2720 (m), 1720 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.70 (t, 1H, *J* = 6.6 Hz, -CHO), 2.30 (ddd, 2H, *J* = 6.0, 6.0 Hz, -CH_2), 1.00 (t, 3H, *J* = 6.3 Hz, CH_3); ^{13}CNMR ($CDCl_3$): δ 202.4 (CHO), 44.2 (CH_2 carbon), 35.5 (CH_3 carbon); EI – MS: *m/z* 58 (M^+), 57, 29 (B.P); HRMS-EI: Calcd. for C_3H_6O (M), 58.0417, Found: M^+, 58.0403.

Spectroscopic data for benzophenone (entry 3)

White flacks (78%); m.p: 47^{0}C (uncorrected); R_f = 0.4; IR (KBr): 3030 (m), 1685 (s), 776 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.63-7.38 (m, 5H, C_6H_5) ; ^{13}CNMR ($CDCl_3$): δ 195.7 (C=O), 138.2, 137.5, 137.0, 135.9, 133.7, 132.1, 130.8, 129.1; EI – MS: *m/z* 182 (M^+), 105 (B.P), 77, 51; HRMS-EI: Calcd. for $C_{13}H_{10}O$ (M), 182.0720, Found: M^+, 182.0706.

Spectroscopic data for acetophenone (entry 4)

Colourless liquid (81%); R_f = 0.7; IR (KBr): 3035 (m), 1682 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.16-7.04 (m, 5H, C_6H_5), 2.38 (s, 3H, CH_3) ; ^{13}CNMR ($CDCl_3$): δ 200.5 (C=O), 134.8, 132.9, 131.3, 129.5 (aromatic carbons), 28.3 (methyl carbon); EI – MS: *m/z* 120 (M^+), 105, 77 (B.P), 51; HRMS-EI: Calcd. for C_8H_8O (M), 120.0550, Found: M^+, 120.0537.

***Spectroscopic data for imine derivative* 30**

84 mg, 11 %; HRMS-EI: Calcd. for $C_{14}H_{11}F_2N$ (M), 231.103, Found; M^+, 230.846; IR(KBr): 3050 (m), 1682 (s), 780 (s) ; ^1H NMR ($CDCl_3$): δ 7.32 – 7.22 (m, 5H, C_6H_5), 6.76 – 6.63 (m, 3H, $C_6H_3F_2$), 3.75 (s, 1H, -N=C-H), 2.56 (s, 2H, $CH_2C_6H_5$); ^{13}CNMR ($CDCl_3$): δ 136.84, 135.24, 134.50, 132.80, 131.25, 130.00, 128.50, 127.45 (phenyl carbons), 87.00 (C=N); EI – MS: *m/z* 231 (M^+), 113, 91.

Spectroscopic data for benzyl amine

24 mg, 34%; HRMS-EI: Calcd. for C_7H_9N (M), 107.080, Found; M^+, 107.023; IR(KBr): 3440(m), 3205(s), 1635 (s), 1280 (m), 910(m), 774 (s); ^1H NMR ($CDCl_3$): δ 6.88 – 6.72 (m, 5H, C_6H_5), 3.82 – 3.66 (br, 2H, NH_2), 2.78 (s, 2H, benzyl protons); ^{13}CNMR ($CDCl_3$): δ 134.00, 132.50, 129.42, 128.00 (phenyl carbons); EI – MS: *m/z* 107 (M^+).

Biological activity of the new fluoro isoxazolidine and fluoroisoxazoline derivatives

Antimicrobial screening test

Few newly synthesized fluoro isoxazolidine, and isoxazoline derivatives (**2a, 3a, 3b, 5, 6, 7, 8)** obtained from *N*-benzyl-fluoro nitrone were screened for antimicrobial activity. These derivatives were found soluble in dimethyl sulphoxide (DMSO) upto 4%, which was found to be completely free from any type of antimicrobial activity. A stock solution of concentration 1mg/mL was prepared which was further diluted as per requirement. All the cycloadducts (**2a, 3a, 3b, 5, 6, 7, 8)** were subjected to *in vitro* screening against the **14** bacterial strains. Sensitivity test was performed by Agar dilution method and then minimum inhibitory concentration (**MIC**) of the drugs was determined by Disc Diffusion Method and Broth Dilution Method[18]. Previously prepared drug dilutions (4µg/mL, 8µg/mL, 16µg/mL, 32µg/mL, 64µg/mL, 128µg/mL, 256µg/mL and 512µg/mL) of the fluoro isoxazolidine and isoxazoline derivatives with appropriate antibiotic control (Amoxycillin and Gentamycin) were prepared with Mueller Hinton Agar[19]. For agar dilution assay those cycloadduct plates were spot inoculated (2×10^6 cfu per spot). A plate without fluoro isoxazolidines or isoxazolines was taken as control (blank) in order to compare the results. The results were then recorded after incubation for 72 hrs at 37ºC[20]. The minimum drug concentration for which no visible growth was observed was considered as the MIC. MIC was determined by Kirby-Bauer disc diffusion method[21] and Broth Dilution Method[18]. The antifungal activity of the fluoro isoxazolidine and isoxazoline derivatives (**2a, 3a, 3b, 5, 6, 7, 8)** have been assayed *in vitro* at a concentration of 100µg/mL, 200µg/mL, 400µg/mL, 600µg/mL, 800µg/mL and 1000µg/mL by Agar dilution and Broth dilution method against *Aspergillus niger, Candida albicans, Candida tropicalis, Cryptpcoccus neoformans*, which were maintained on sabouraud dextrose agar slants stored at 4°C. Test drugs (**2a, 3a, 3b, 5, 6, 7, 8)** exhibited considerable antibacterial and antifungal activity. They were diluted double fold with Mueller Hinton broth for bacterial strains and sabouraud dextrose broth for fungi in a series of test tubes. An aliquot of 1mL of the bacterial suspension (2×10^6 cfu/mL) and fungal spores (2×10^5 spores/mL) were inoculated into each tube. The control tubes were inoculated with same quantity of broth culture only. All tubes were incubated at 37ºC for 24h and 28°C for 96 h with shaking on a platform shaker at 200 rpm. The test drugs were added to the mid-logarithmic phase of growth and aliquots of 1.0 mL were withdrawn for determination of colony count[22] while the growth of the fungi was determined by dry weight of the sample at 60^0c for 20 h for 3 days[23].

Table 2. *Determination of Minimum Inhibitory Concentration (MIC)*

Name of Organism	MIC values in µg/mL	Name of Organism	MIC values in µg/mL	Name of Organism	MIC values in µg/mL	Name of Organism	MIC values in µg/mL	Name of Organism	MIC values in µg/mL
	2a 4% DMSO	3a 0.17% DMSO	3b 0.17% DMSO	5 0.17% DMSO	6 0.17% DMSO	7 4% DMSO	8 4% DMSO	Amoxy cillin	Genta-mycin
Escherichia coli ATCC 5938	32	128	512	>512	>512	128	16	2	0.25
Klebsiella pneumonia J/	64	64	>512	>512	>512	128	32	4	2
Staphylococcus aureus	32	64	>512	>512	>512	128	64	2	1
Pseudomonas aeruginosa ATCC 27853	64	256	>512	>512	512	64	8	64	2
Vibrio cholerae 14035	32	64	>512	>512	256	128	64	64	0.5
Bacillus subtilis UC 564	64	64	>512	>512	64	32	8	8	4
Shigella dysenteriae 3	64	64	>512	>512	>512	128	16	64	1
Streptococcus faecalis 292	64	128	>512	>512	>512	128	64	64	0.50
Shigella flexneri DN 13	8	16	16	16	32	64	32	32	1
Salmonella typhi DIRW	8	64	16	16	64	256	128	4	1
Vibrio parahaemolyticus 72016	256	256	>512	>512	>512	256	128	16	1
Micrococcus luteus AGD	128	64	>512	>512	>512	512	128	4	8
Salmonella typhimurium	32	64	>512	>512	>512	128	32	8	1
Enterococcus faecalis	64	256	>512	>512	>512	128	32	4	2

Table 3. *Determination of Minimum Inhibitory Concentration (MIC)*

Names of fungal strains	MIC values in µg/mL							
	2a	3a	3b	5	6	7	8	Fluconazole
Aspergillus niger	100	200	600	800	400	100	200	10
Candida albicans	200	100	>1000	600	600	200	200	4
Candida tropicalis	400	200	800	>1000	400	400	200	8
Cryptococcus neoformans	400	400	>1000	>1000	1000	400	100	8
Saccharomyces cerevisiae	200	100	600	800	800	200	100	16

Determination of Minimal Bacteriocidal Concentration ***(MBC)***

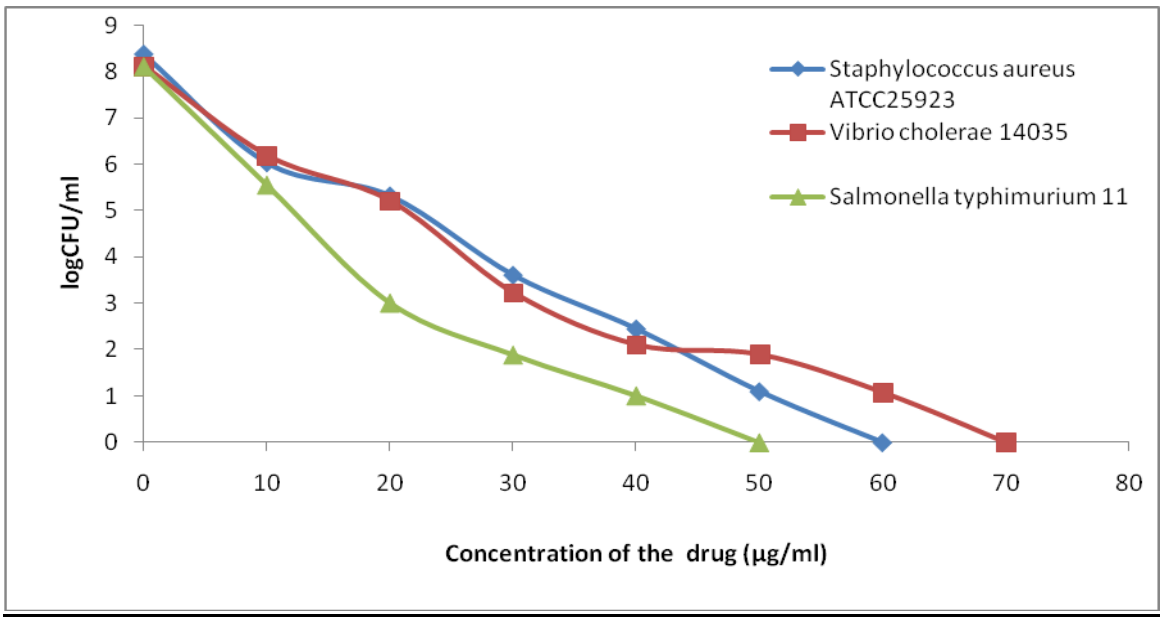


Fig.1. *Effect of drug* ***2a*** *on three bacteria at different concentrations*

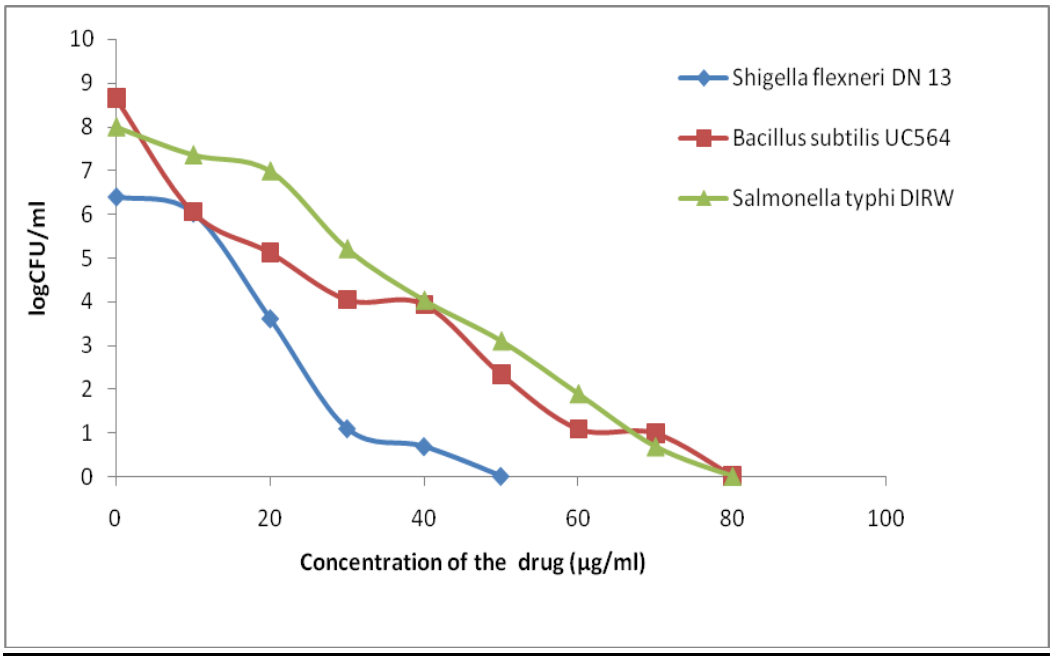


Fig.2. *Effect of drug **3a** on three bacteria at different concentrations*

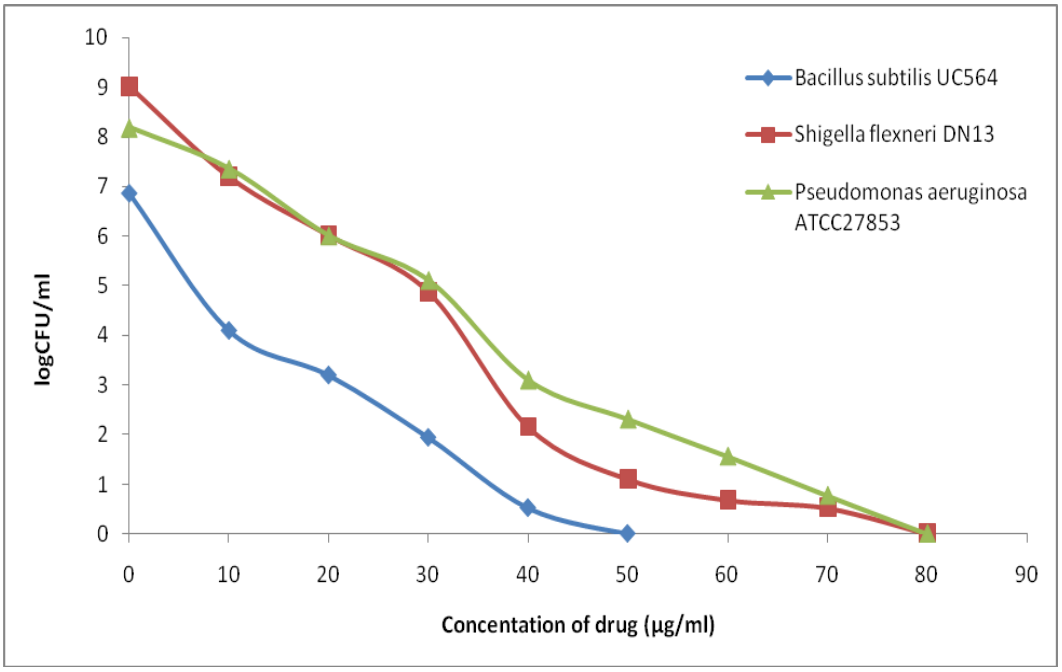


Fig.3. *Effect of drug **3b** on three bacteria at different concentrations*

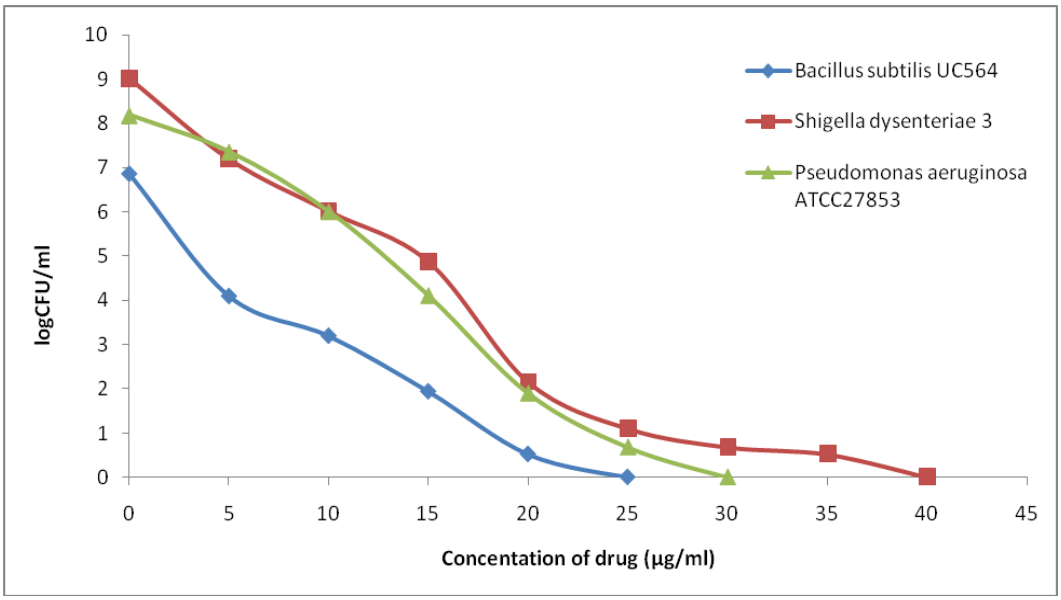


Fig.4. *Effect of drug* ***5*** *on three bacteria at different concentrations*

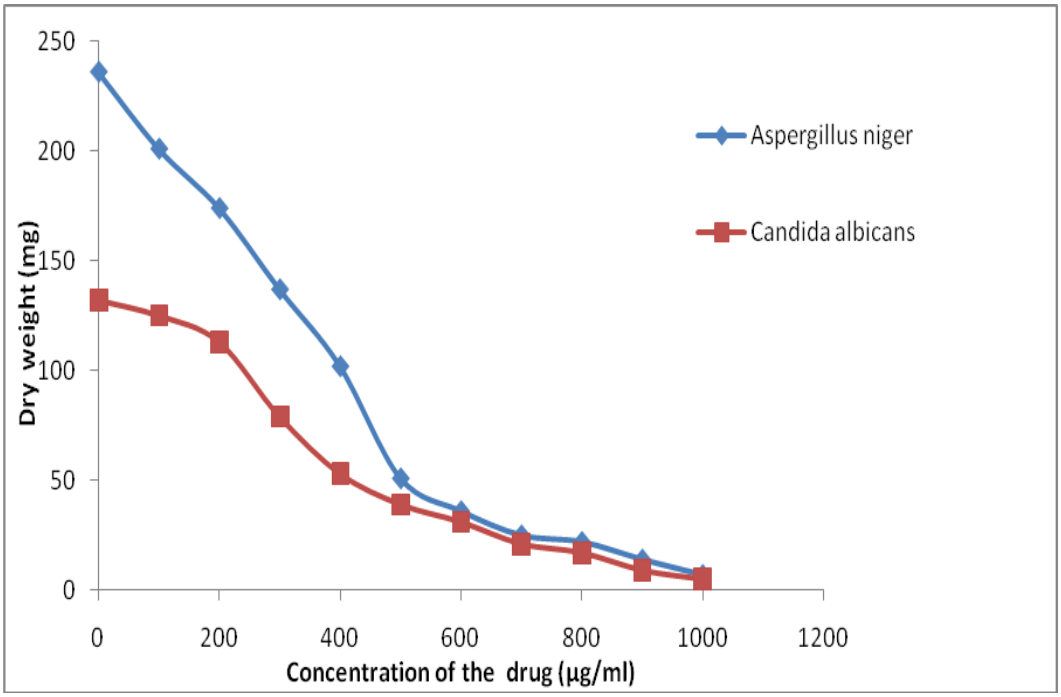


Fig.5. *Effect of drug* ***6*** *on invitro growth of two fungi at different concentrations*

Biological activity of the new bisisoxazoline and bisaziridine derivatives

Significant information is obtained in the studies on antibacterial activities of the new bisisoxazoline and bisaziridine derivatives using viable cell count experiments[24]. Selected newly synthesized bisisoxazoline and bisaziridine derivatives were employed for the biological study and were treated as drugs. For example, bisisoxazoline derivatives **14-18** in Table **4** as drug **1-5** and bisaziridine derivatives **20, 21** in Table **4** as drug **6,7**. Scanning Electron Microscopy (SEM) has been performed to study the mode of action of newly synthesized bisaziridine and bisisoxazolines as test drugs related to morphological studies on the newly synthesized bisaziridine and bisisoxazoline derivatives. The new drugs have shown potential biological activities and detail studies are in progress using TEM. Altogether **15** bacterial strains of both gram positive & gram negative varieties were used using method recommended by National Committee for Clinical Laboratory Standards (NCCLS). These include, *Escherichia coli* 25938, *Salmonella typhi* 62, *Vibrio cholerae* 20, *Klebsiella pneumoniae* 10031, *Shigella dysenteriae* 1, *Pseudomonas* AMRI 100, *Salmonella typhimurium* NTCC 74, *Staphylococcus aureus* 29737, *Bacillus cereus* 11778, *Bacillus subtilis* 6633, *Streptococcus epidermidis* 12228, *Micrococcus luteus* 10240, *Pseudomonas aeruginosa* 25619, *Bacillus pumilus* 14884, *Bordetella bronchiseptica* 4617 respectively. Amoxicillin was used as standard drug. MIC of test drugs was determined by agar dilution method. Two sets of tubes were prepared (control and test) and $2x10^6$cfu/ml of bacterial suspension was added to these tubes. After 24 hrs of incubation cells were harvested, washed with nutrient broth and fixed with 4% glutaraldehyde in phosphate buffer. Obtained cells were dehydrated in series of alcohol mounted on slide. The gold coated samples were examined in JEOL-JSM 6360 Scanning Electron Microscope.

From the experiment it is clear that the tested drugs did not kill the microorganisms completely but significantly reduce the bacterial growth i.e., these drugs have potential bacteriostatic effect. SEM micrographs of few bisaziridines (**6** & **7**, Table **4**) have been found to have potential antimicrobial effects on *B. cereus* 11778 and *M. luteus* 10240 respectively. It was clear that both the bisaziridine derivatives cleaved the cell surface leading to lyses of cell components into several fragments and thus facilitates rapid killing of cells[25,26].

From SEM microscopy it is expected that these drugs may act as potential antimicrobial agents. Drug **1** (Table **4**) kills bacteria by cleaving cell membrane at different junction and leads to cell death. Drug **2** (Table **4**) changes the cell permeability of bacteria. Due to this change fluids are accumulated within cells and eventually lead to death.

Table 4: *Minimum Inhibitory Concentration (MIC) of synthetic compounds against different bacteria*

Organism	Control	Bisisoxazoline & bisaziridines (Drugs in µg/ml)							
		1	**2**	**3**	**4**	**5**	**6**	**7**	Amoxicillin
Escherichia coli 25938	+	600	600	400	600	+	+	+	25
Salmonella typhi 62	+	600	400	+	400	+	+	600	15
Vibrio cholerae 20	+	600	600	200	600	1000	+	600	25
Klebsiella pneumoniae 1003	+	600	600	+	600	+	+	+	25
Shigella dysenteriae 1	+	800	600	400	600	1000	+	+	1
Pseudomonas AMRI 108	+	600	600	+	600	+	+	+	50
Salmonella typhimurium NTCC 74	+	600	600	600	400	+	+	+	25
Staphylococcus aureus 29737	+	600	600	400	+	1000	+	+	5
Bacillus cereus 11778	+	600	400	600	600	1000	+	+	25
Bacillus subtilis 6633	+	600	600	+	600	1000	+	+	50
Streptococcus epidermidis 12228	+	600	400	600	600	1000	+	+	5
Micrococcus luteus 10240	+	600	600	600	600	600	+	+	1
Pseudomonas aeruginosa 25619	+	600	600	600	400	+	+	+	100
Bacillus pumilus 14884	+	600	600	600	600	1000	+	+	50
Bordetella bronchiseptica 4617	+	600	600	600	600	+	+	+	50

"+" represents growth of organism.

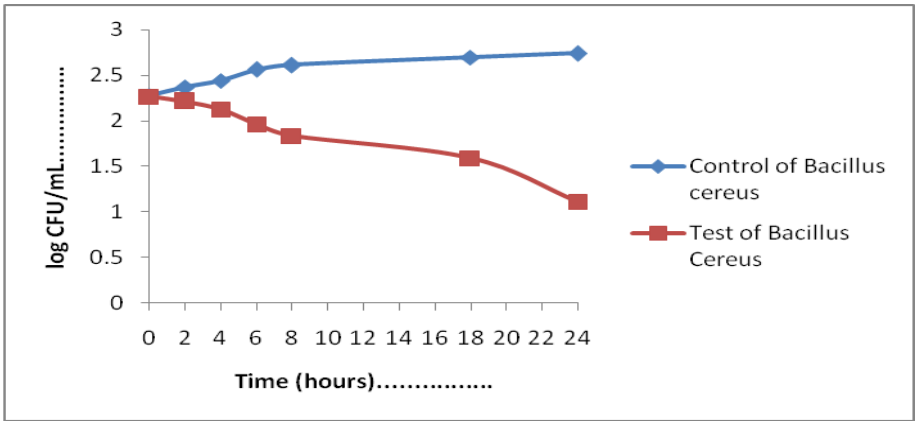
Table 5: *Diameter of Zone of Inhibition at MIC*

Organism	Diameter of Zone of Inhibition(mm) at MIC					
	Drug-**1**	Drug-**2**	Drug-**3**	Drug-**4**	Drug-**5**	Drug-**7**
Escherichia coli 25938	14±0.2	24±0.2	20±0.1	14±0.2	_	_
Salmonella typhi 62	15±0.2	20±0.1	19±0.2	13±0.2	_	30±0.1
Vibrio cholerae 20	14±0.2	27±0.2	18±0.1	33±0.1	18±0.3	26±0.3
Klebsiella pneumoniae 1003	14±0.3	13±0.2	17±0.2	27±0.1	_	_
Shigella dysenteriae 1	20±0.1	25±0.3	23±0.3	17±0.1	26±0.1	_
Pseudomonas AMRI 108	17±0.2	14±0.2	13±0.2	42±0.3	_	_
Salmonella typhimurium NTCC 74	19±0.1	28±0.2	20±0.3	44±0.2	_	_
Staphylococcus aureus 29737	15±0.2	18±0.1	29±0.3	22±0.3	25±0.1	_
Bacillus cereus 11778	16±0.3	26±0.3	28±0.1	35±0.2	25±0.1	_
Bacillus subtilis 6633	14±0.2	33±0.2	26±0.3	37±0.2	25±0.3	_
Streptococcus epidermidis 12228	16±0.1	15±0.1	23±0.1	20±0.3	14±0.2	_
Micrococcus luteus 10240	25±0.2	15±0.1	17±0.2	37±0.2	26±0.2	_
Pseudomonas aeruginosa 25618	21±0.1	12±0.2	12±0.2	_	_	_
Bacillus pumilus 14884	38±0.3	22±0.2	25±0.2	42±0.3	11±0.2	_
Bordetella bronchiseptica 4617	36±0.5	27±0.2	26±0.6	36±0.2	_	_

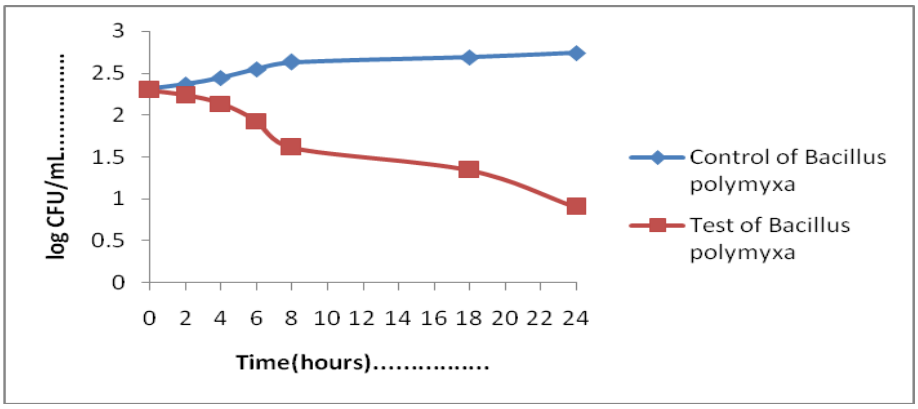
"_" shows no measurable zone of inhibition.

It is clear from the table that the synthetic drugs have an average zone of diameter of 20±0.2mm. Drug **4** has highest zone diameter of 44±0.2 mm on *Salmonella typhimurium* NTCC 74 at MIC. Drug **5** has the lowest zone of inhibition of 11±0.2mm on *Bacillus pumilus* 14884.

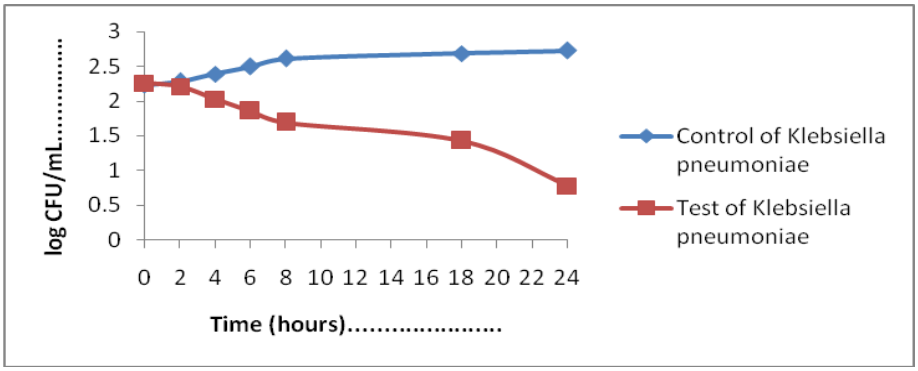
Effect of Drug (bisisoxazoline & bisaziridines) on bacterial growth rate



Time dependent *in vitro* growth curve of *B.cereus* 11778 at their MIC values against bisisoxazoline **3**

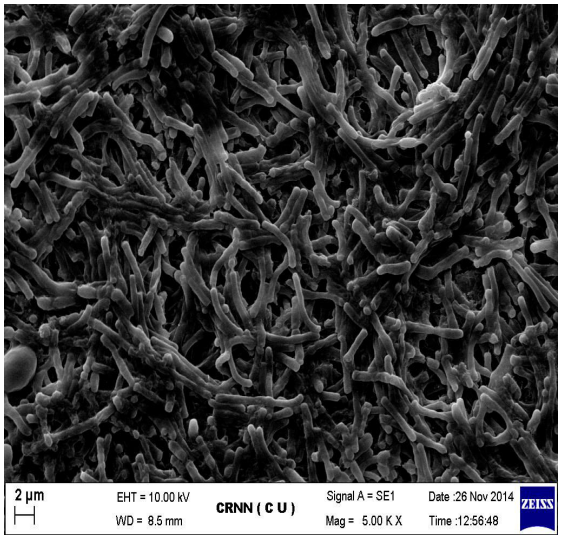


Time dependent *in vitro* growth curve of *Bacillus polymyxa* 4747 at their MIC values against bisisoxazoline **5**

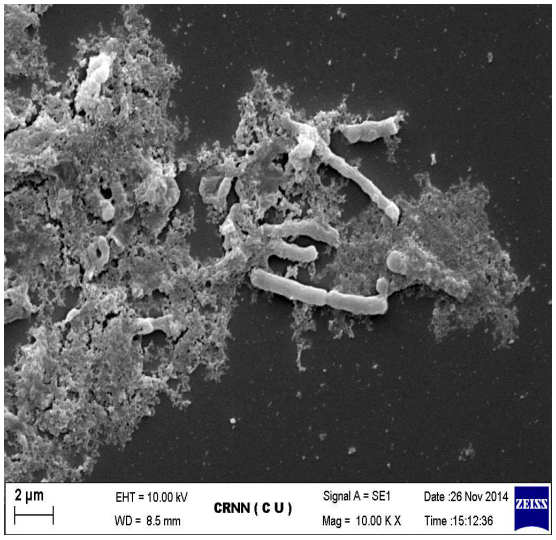


Time dependent in vitro growth curve of *Klebsiella pneumoniae* ATCC 10031 at their MIC values against bisaziridine **5**

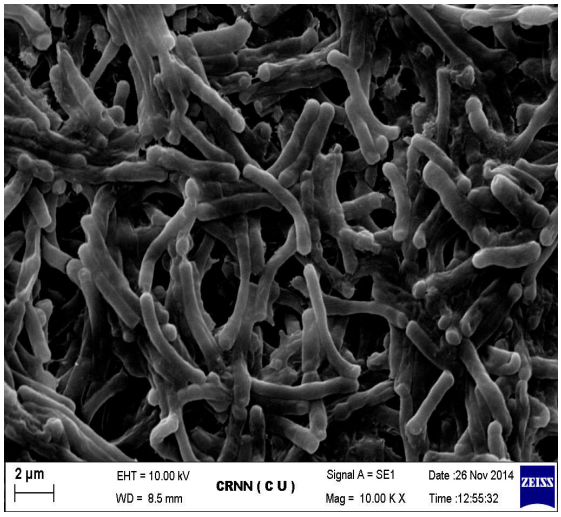
SEM micrographs of bisaziridines as test drugs 6 (20) & 7 (21)



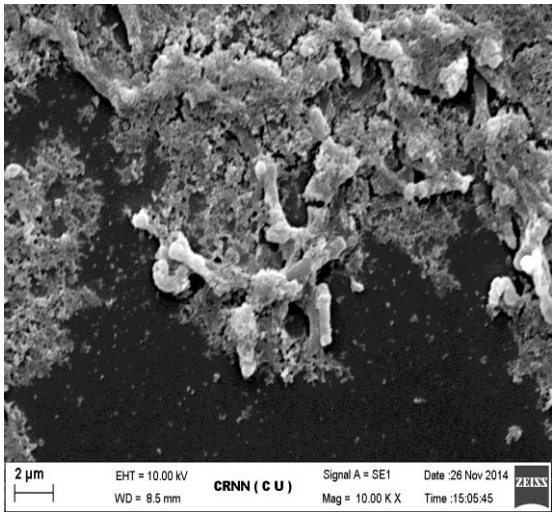
Before treatment with bisaziridine **6 (20)**



After treatment with bisaziridine **6 (20)**



Before treatment with bisaziridine **7 (21)**



After treatment with bisaziridine **7 (21)**

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IR, ^{1}H NMR, ^{13}C NMR, Mass spectra of few newly synthesized fluoro isoxazolidine, isoxazoline, bisisoxazolidine and bisisoxazoline derivatives are enclosed as "Annexure".

"Annexure"

Fig 6: *IR spectram of N-phenylmaleimide bisisoxazolidine (glyoxal derived bisnitrone)*

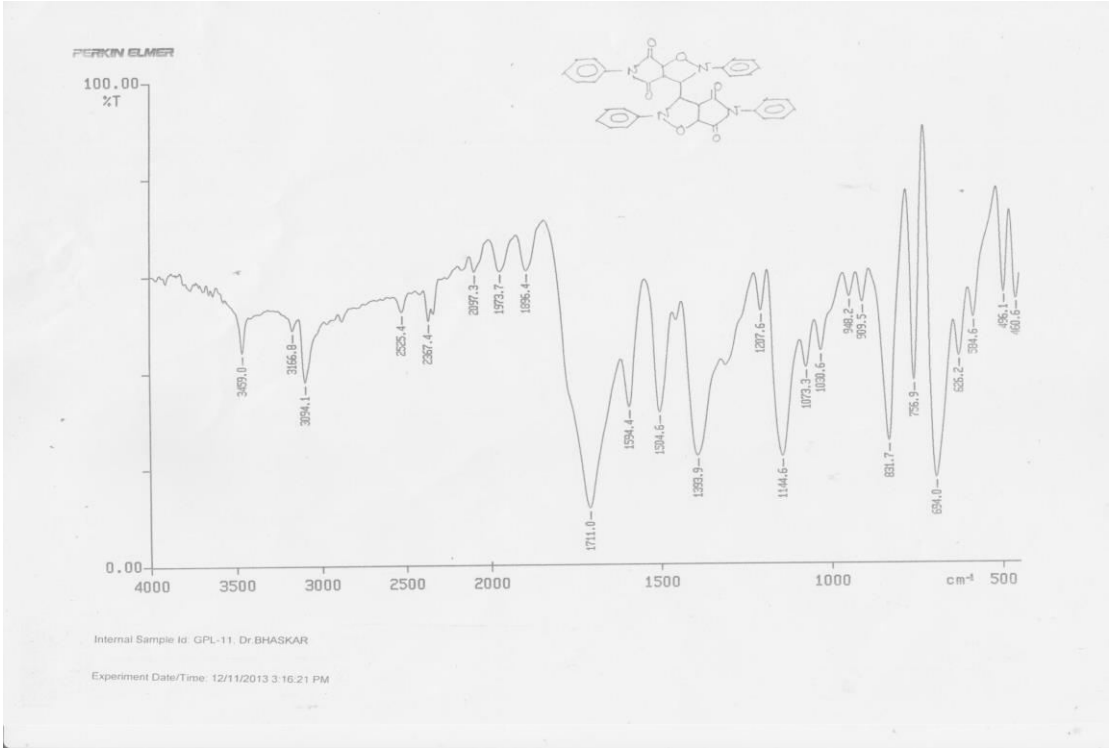


Fig 7: *IR spectram of methyl acrylate bisisoxazolidine (glyoxal derived bisnitrone)*

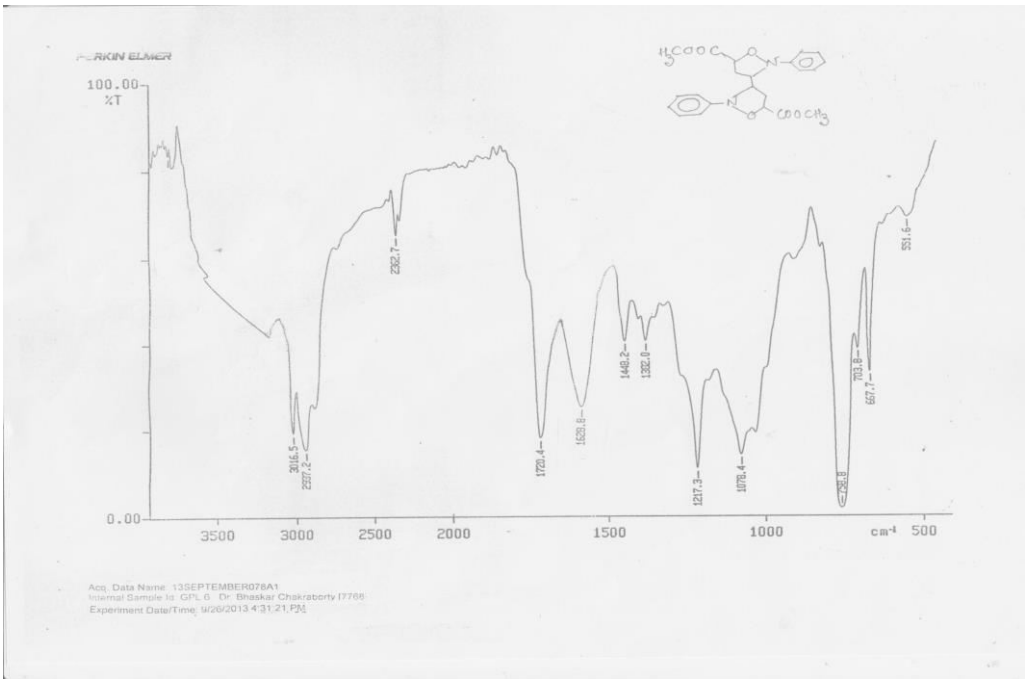


Fig 8: *IR spectram of N-methyl maleimideisoxazolidine (N-benzyl fluoronitrone)*

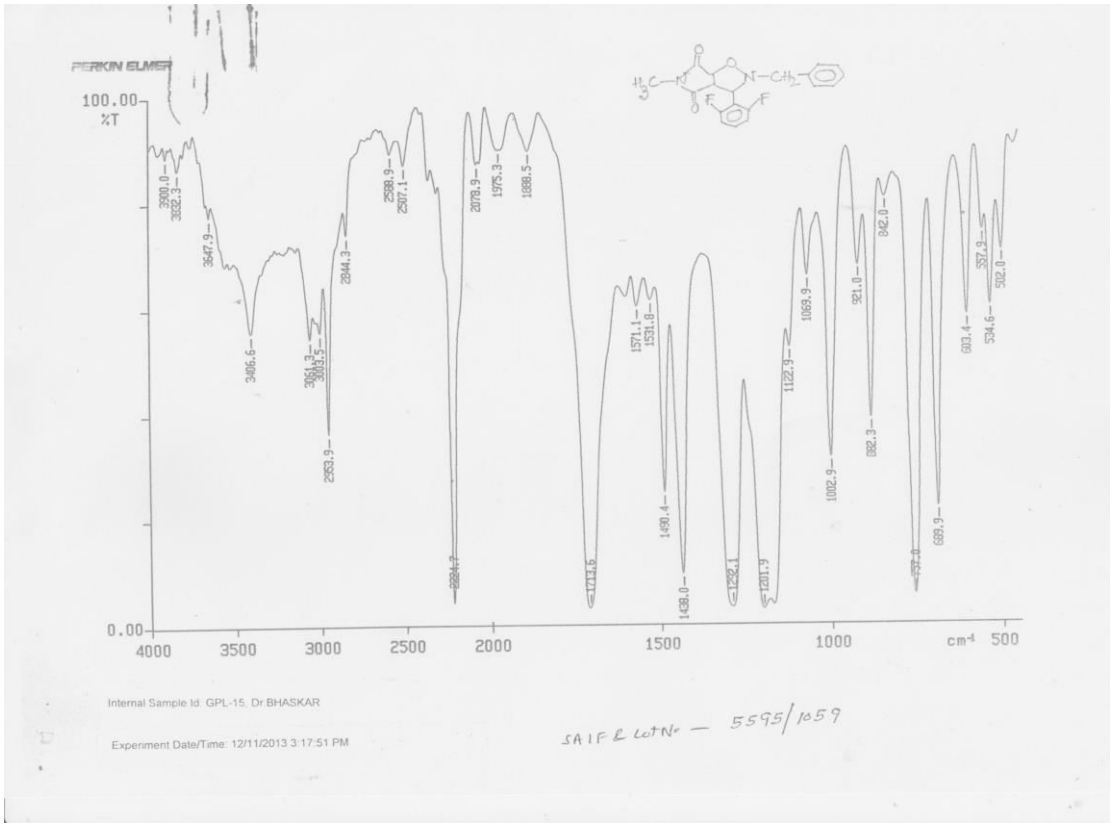


Fig 9: *IR spectram of phenyl methyl propiolate isoxazoline (N-benzyl fluoronitrone)*

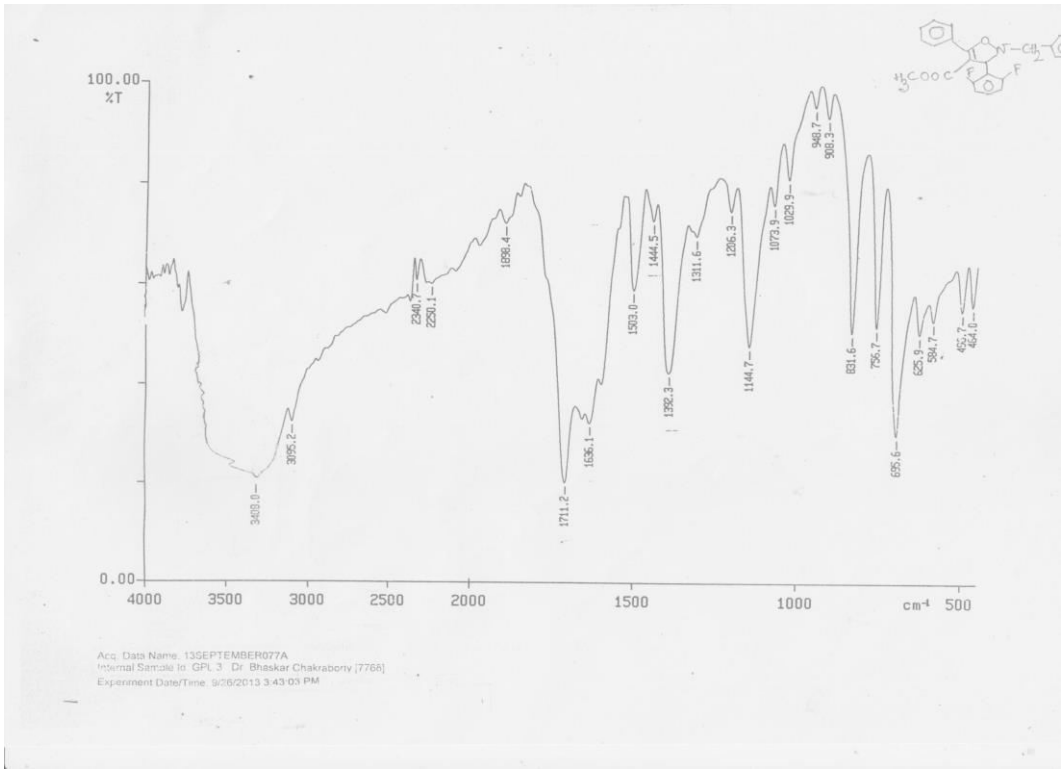


Fig 10: *IR spectram of dimethyl acetylene dicarboxylate isoxazoline (terepthalaldehyde derived bisnitrone)*

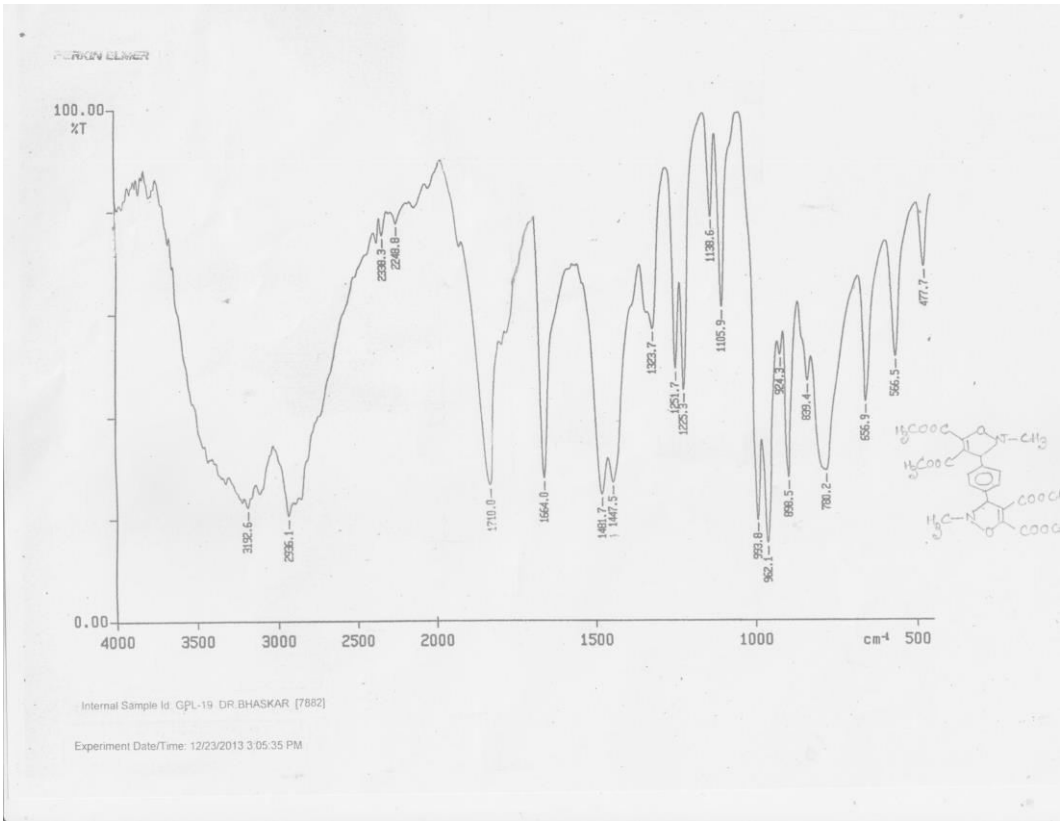


Fig 11: *IR spectram of bisaziridine (terepthalaldehyde derived bisnitrone)*

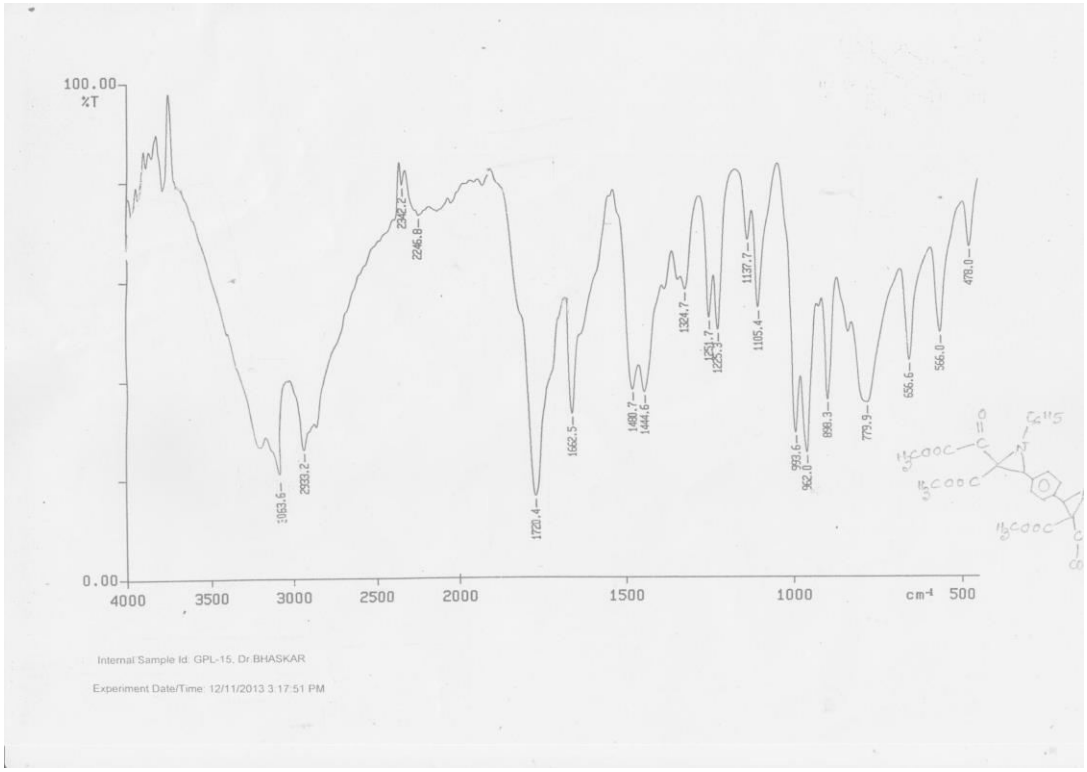


Fig 12: *[1]H NMR spectram of methacrolein cycloadduct (N-benzyl fluoronitrone)*

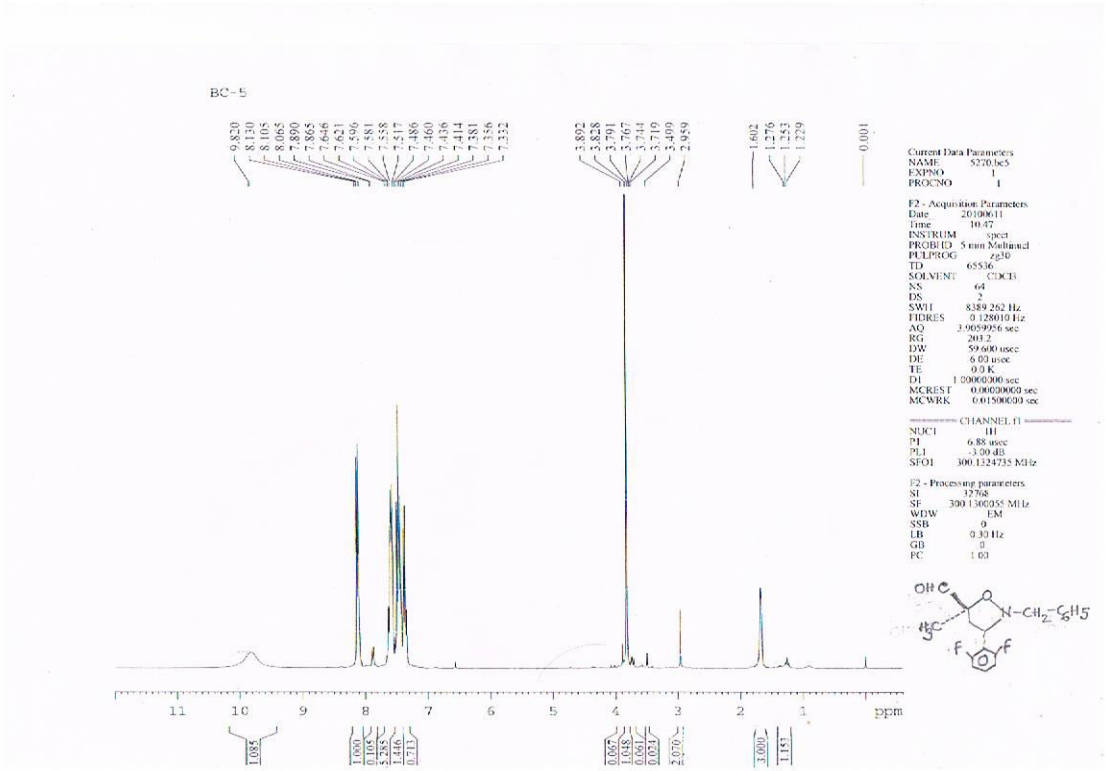


Fig 13: *[1]H NMR spectram of N-phenyl-bisnitrone (glyoxal derived)*

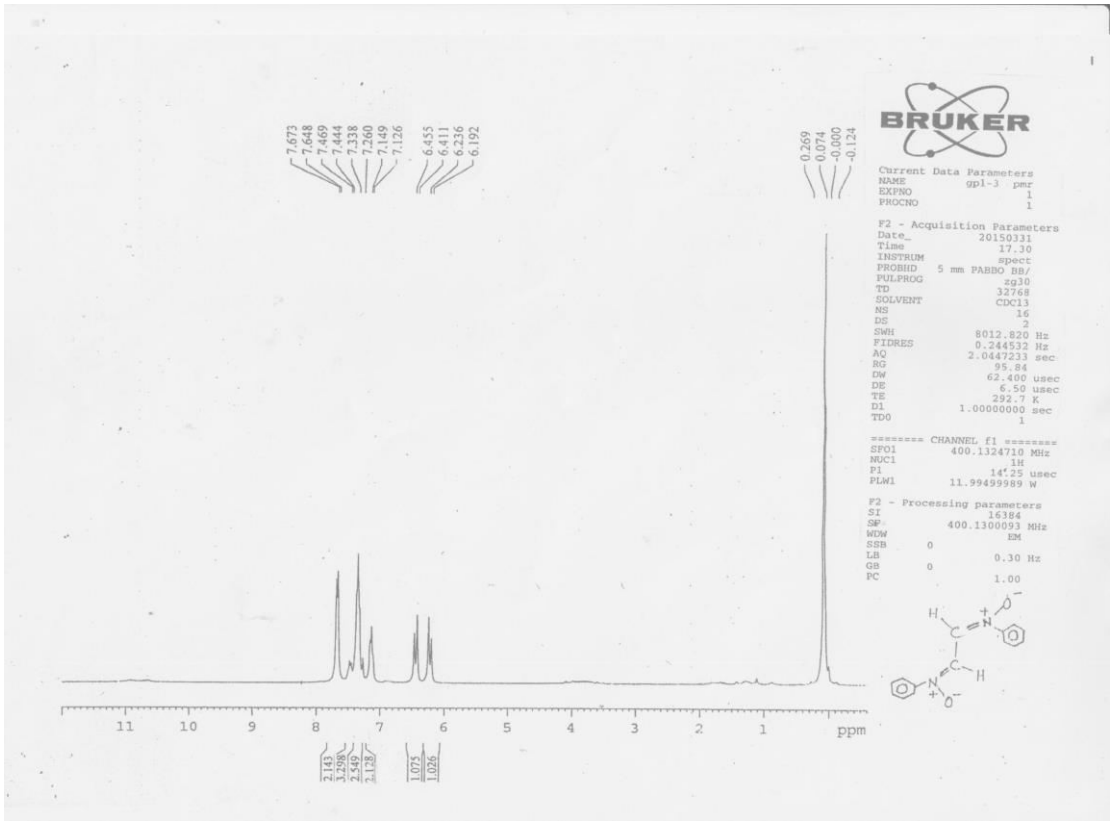


Fig 14: *^{1}H NMR spectram of phenyl methyl propiolate cycloadduct (terepthalal derived bisnitrone)*

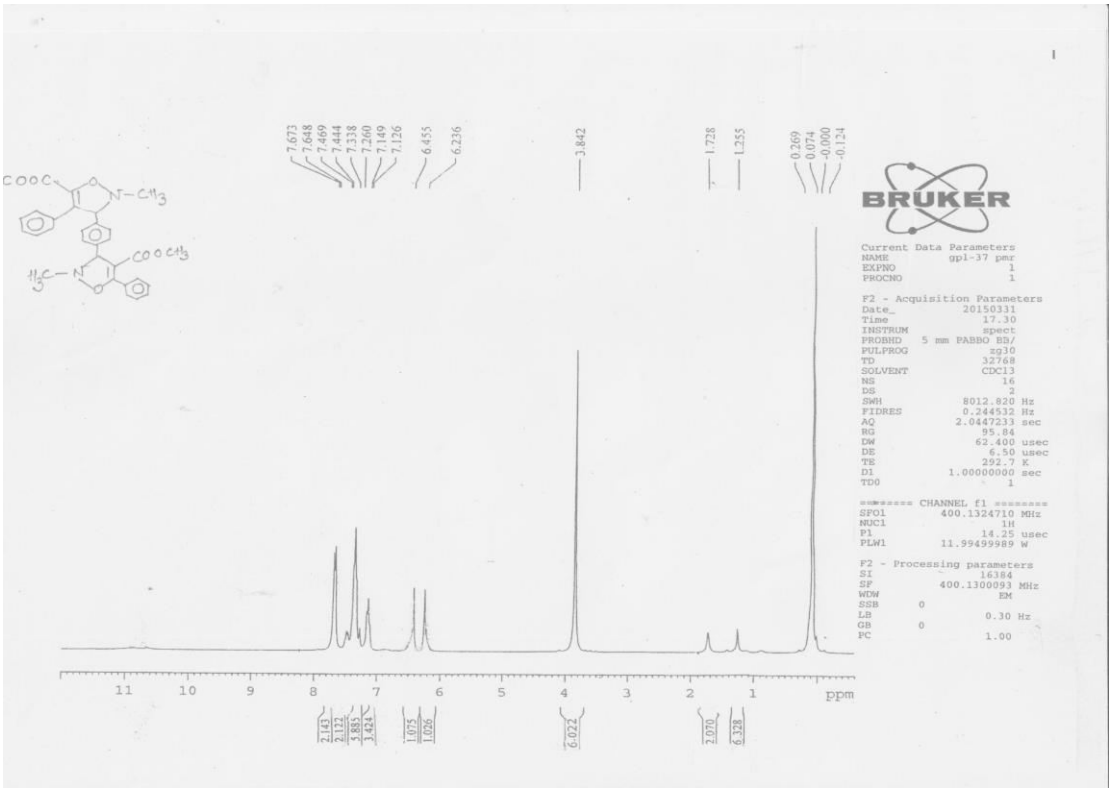


Fig 15:*^{1}H NMR spectram of N-methyl bisnitrone (glyoxal derived)*

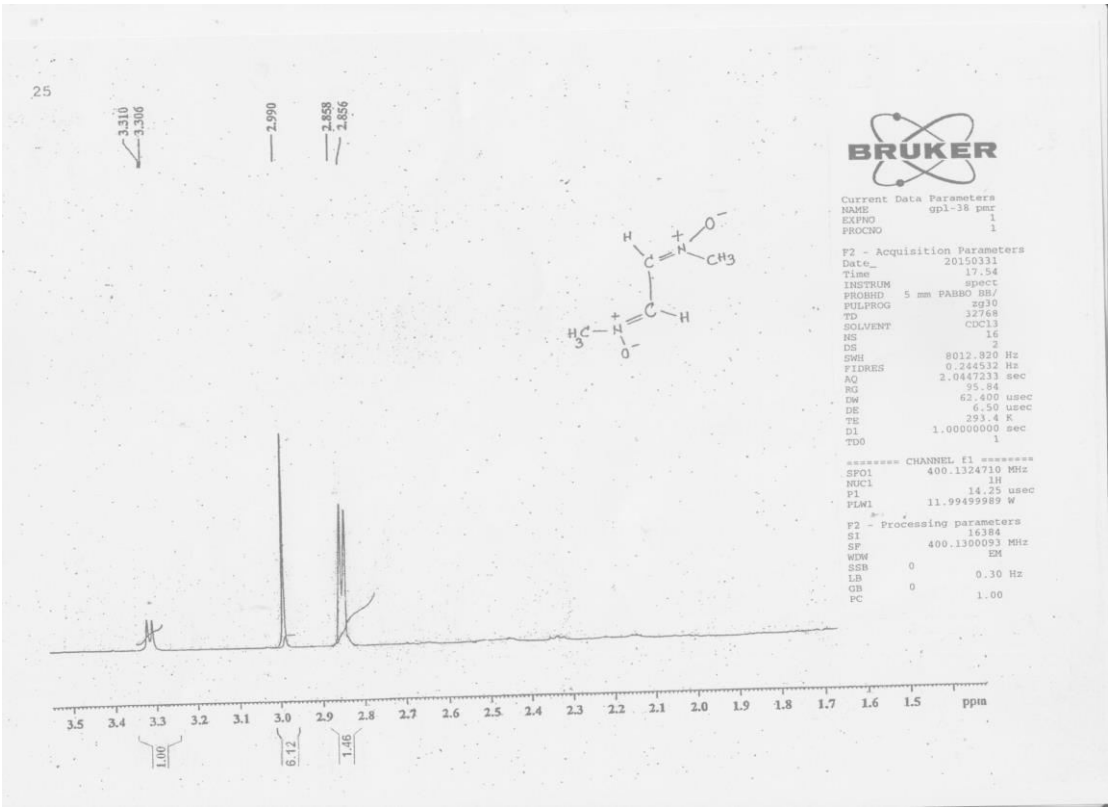


Fig 16: *^{1}H NMR spectram of N-phenyl maleimide bisisoxazolidine (glyoxal derived nitrone)*

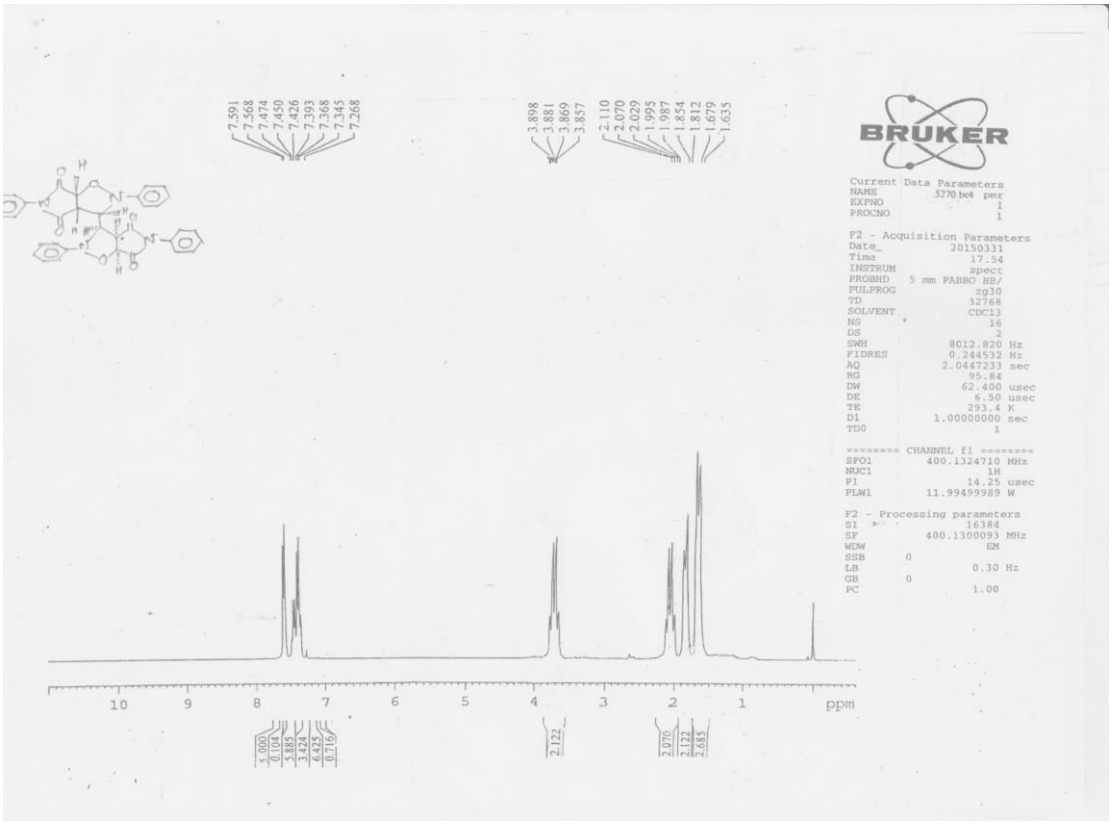


Fig 17: *^{1}H NMR spectram of acetylene dicarboxylic acid isoxazoline (glyoxal derived nitrone)*

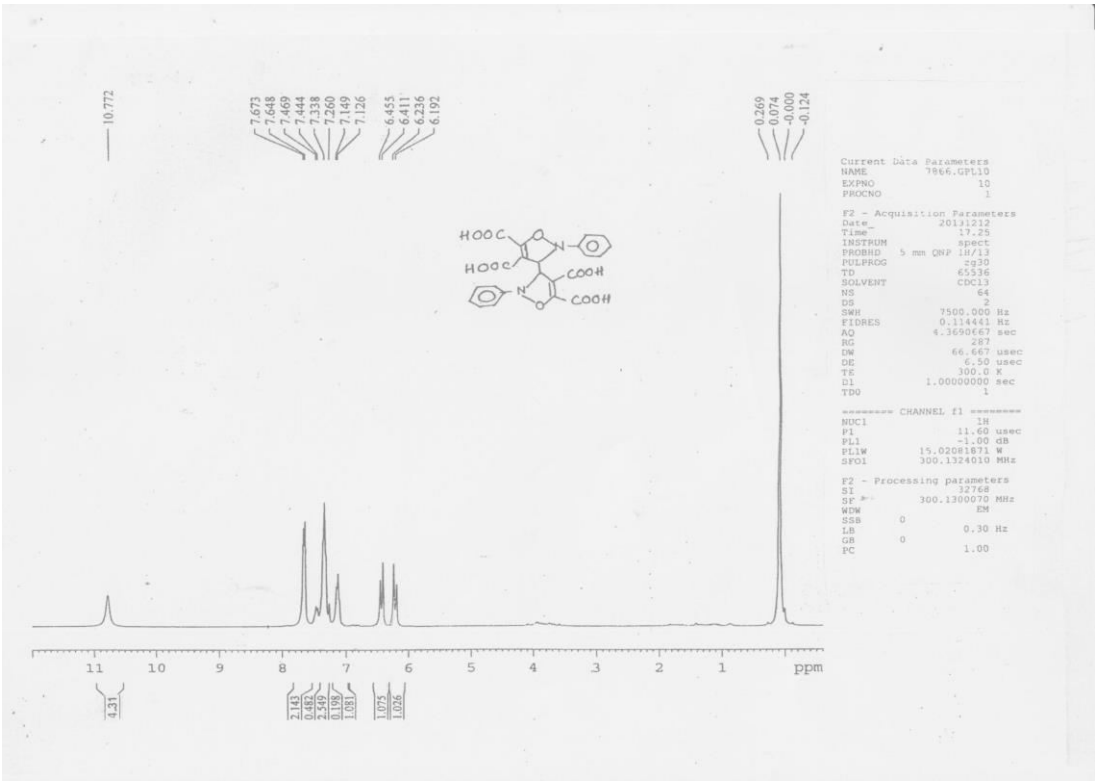


Fig 18: *[1]H NMR spectram of N-benzyl fluoro nitrone*

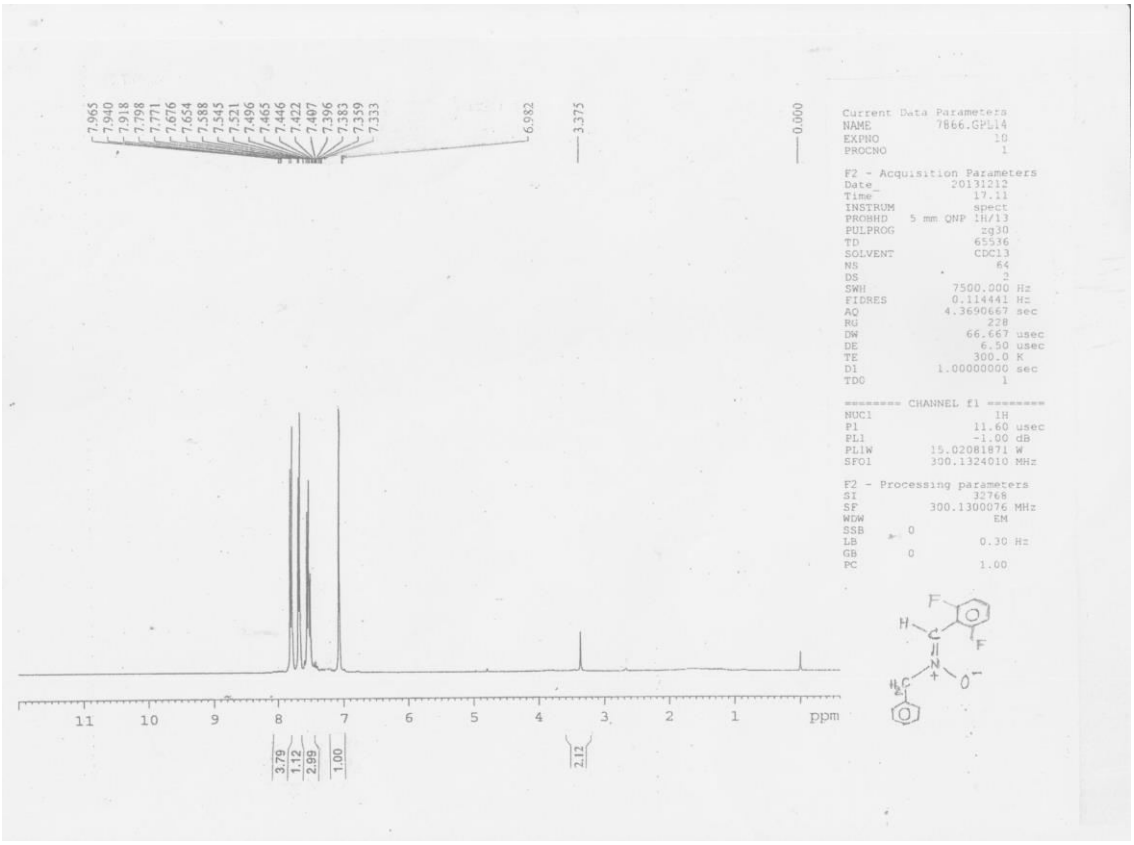


Fig 19: *[1]H NMR spectram N-methyl maleimide fluoro isoxazolidine (N-benzyl fluoro nitrone)*

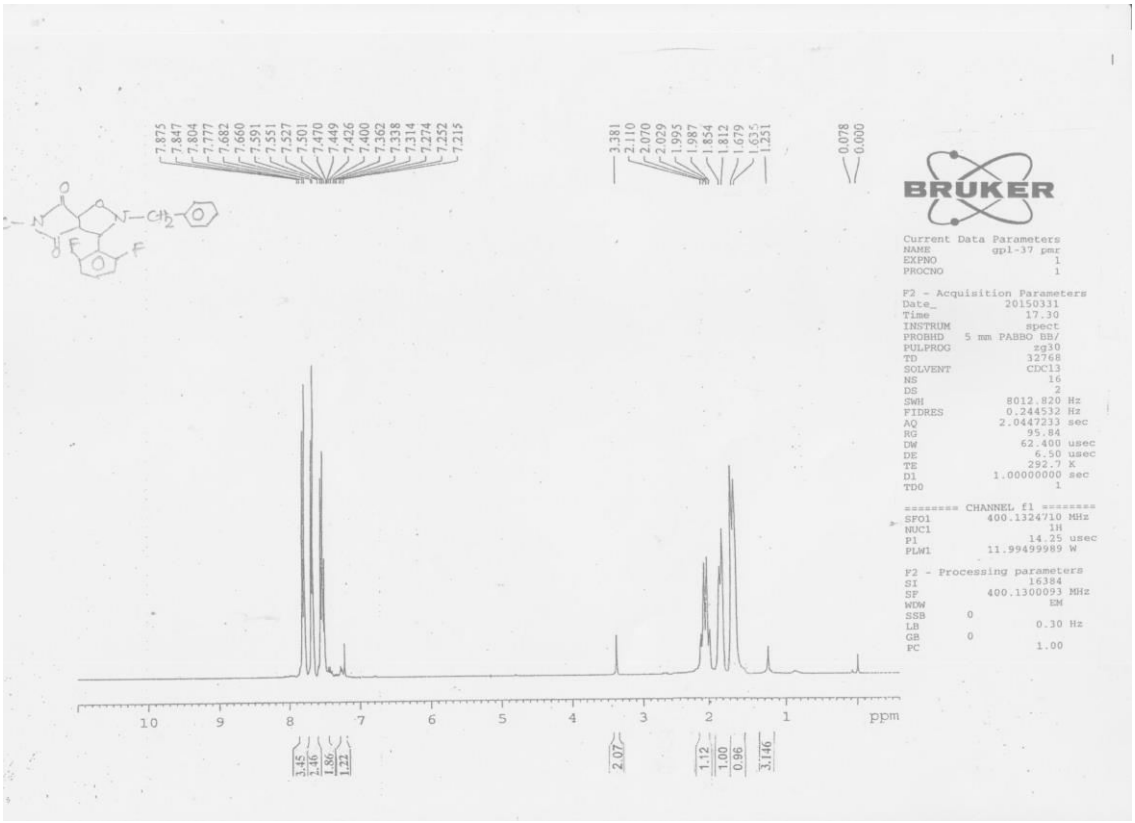


Fig 20: *[1]H NMR spectram of phenyl methyl propiolate fluoro isoxazoline (N-benzyl fluoro nitrone)*

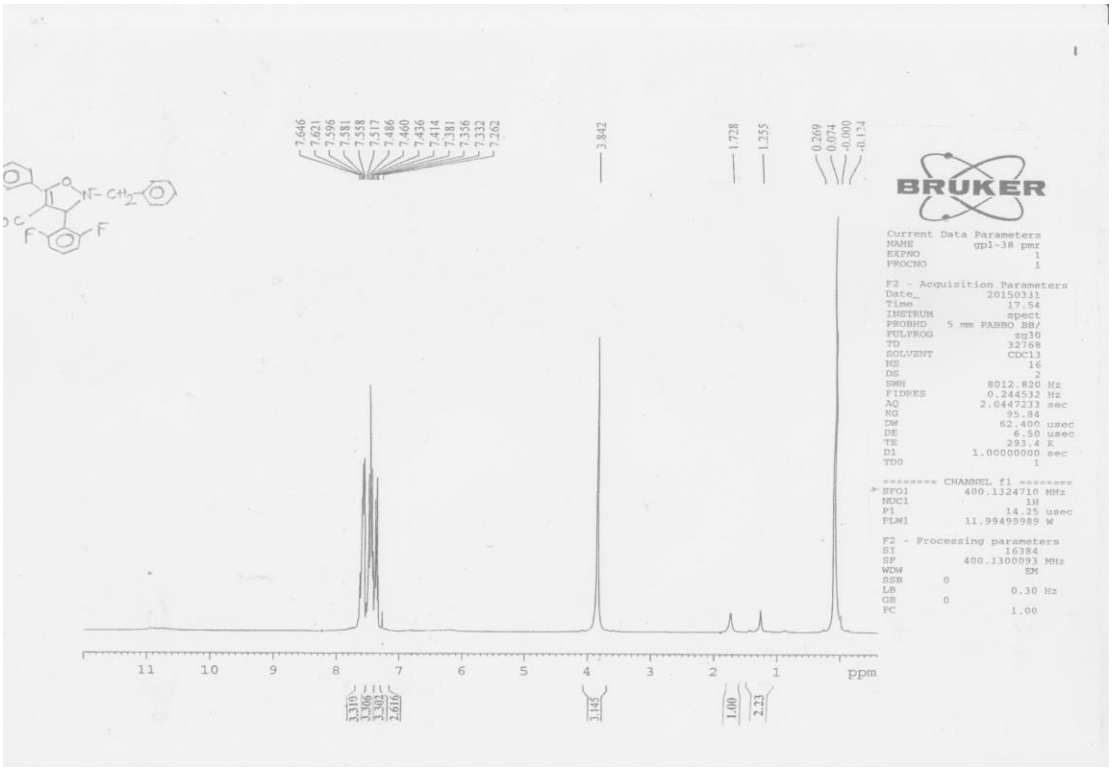


Fig 21: *[1]H NMR spectram of acetylene dicarboxylic acid fluoro isoxazoline (N-benzyl fluoro nitrone)*

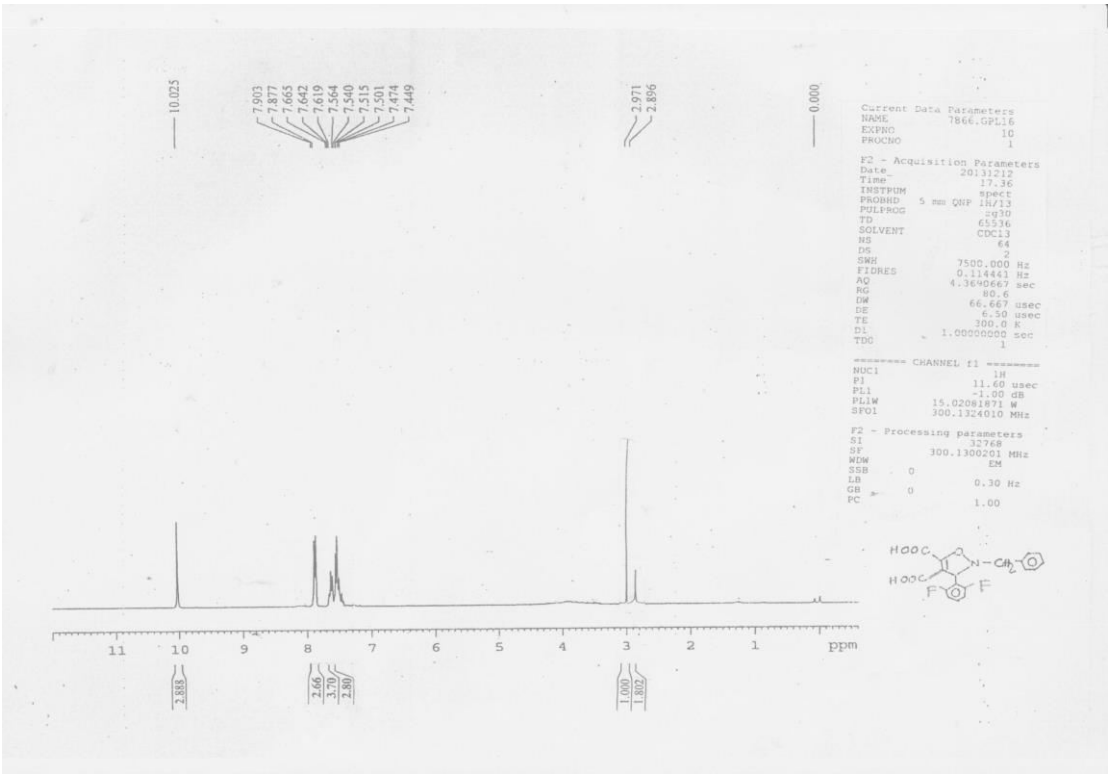


Fig 22: *[1]H NMR spectram of dimethyl acetylene dicarboxylate fluoro isoxazoline (N-methyl nitrone)*

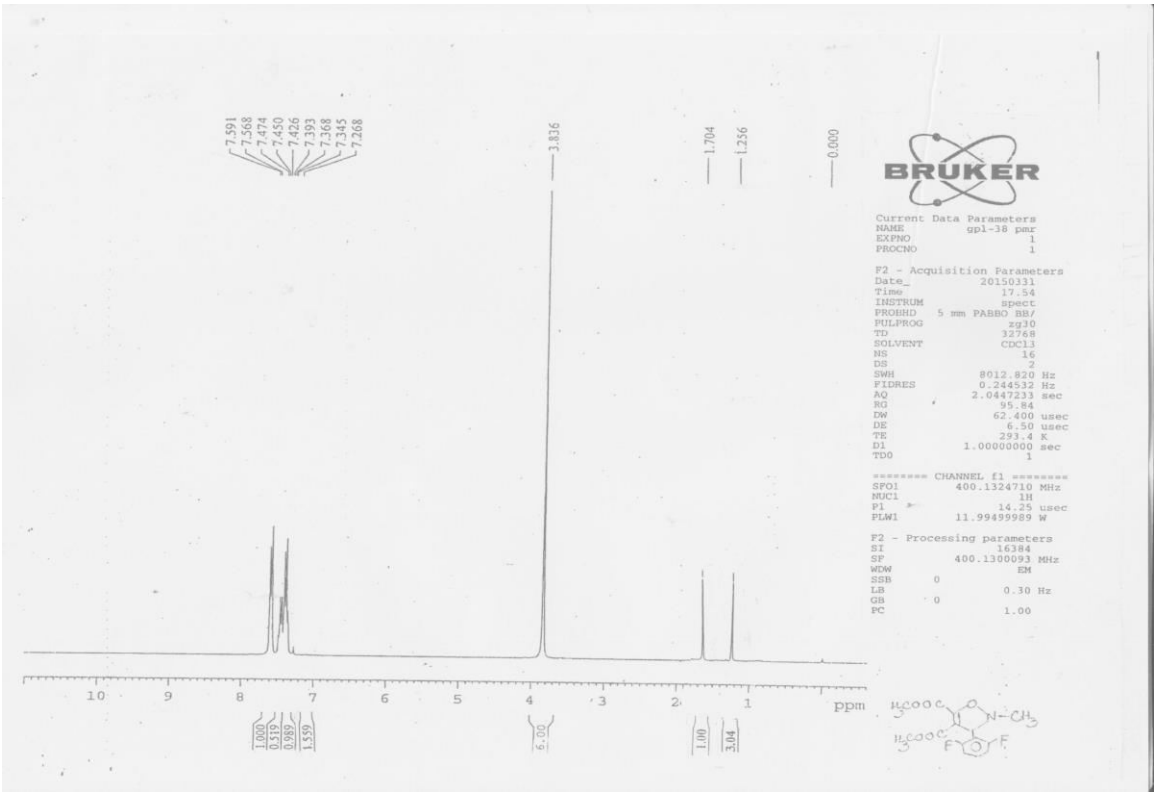


Fig 23: *[1]H NMR spectra of phenyl methyl propiolate fluoro isoxazoline (N-methyl nitrone)*

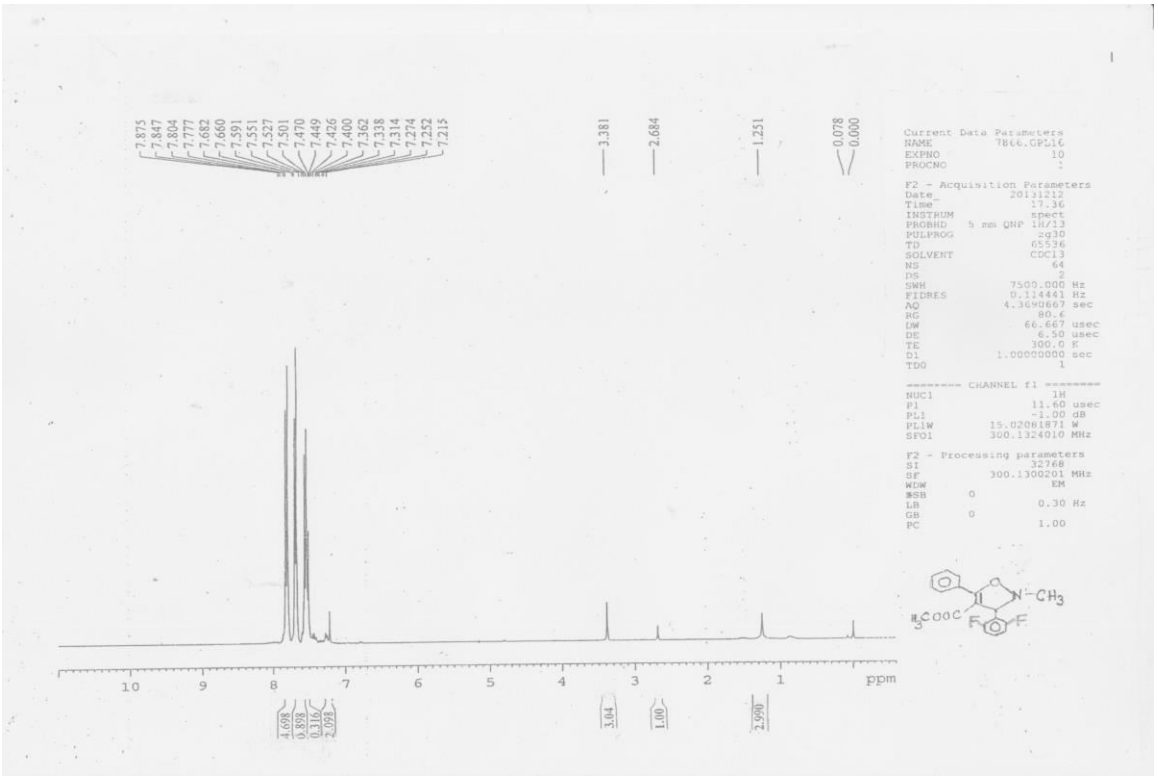


Fig 24: *[1]H NMR spectram of benzaldehyde synthesized using N-benzyl fluoro nitrone*

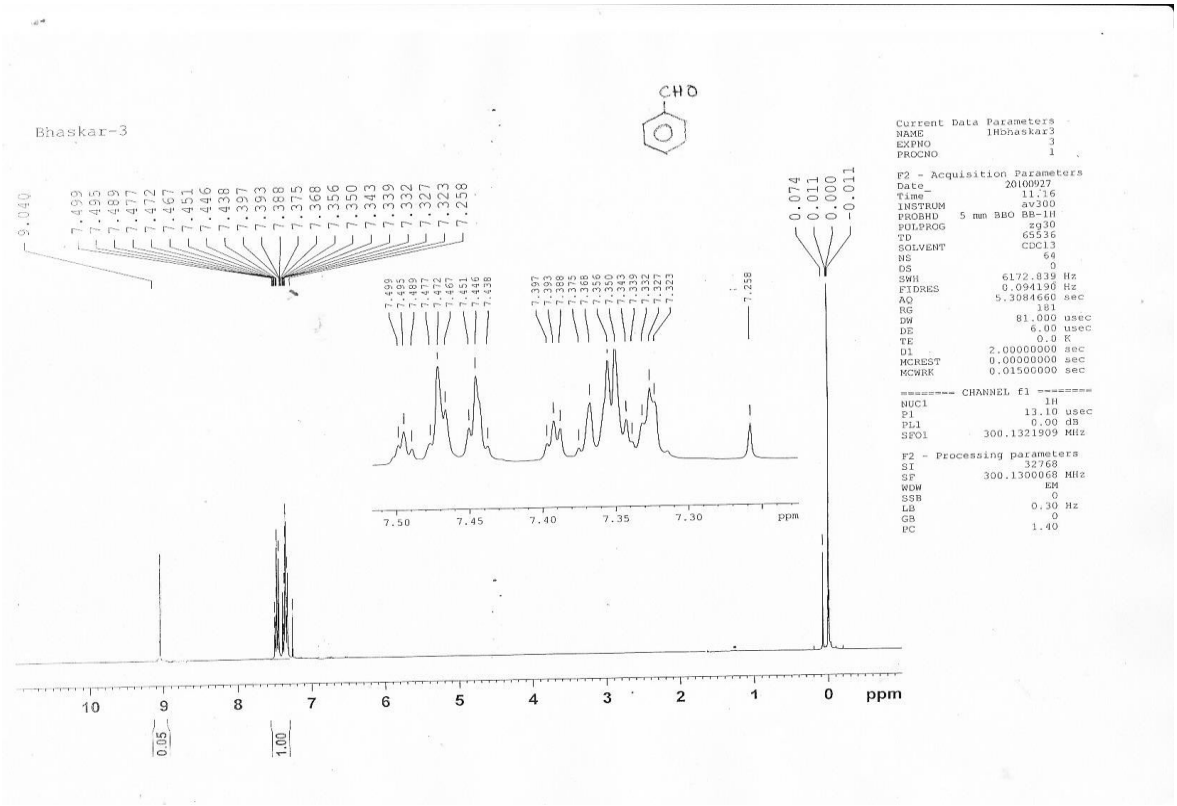


Fig 25: *[13]C NMR spectram of N-methyl maleimide fluoro isoxazolidine (N-benzyl fluoro nitrone)*

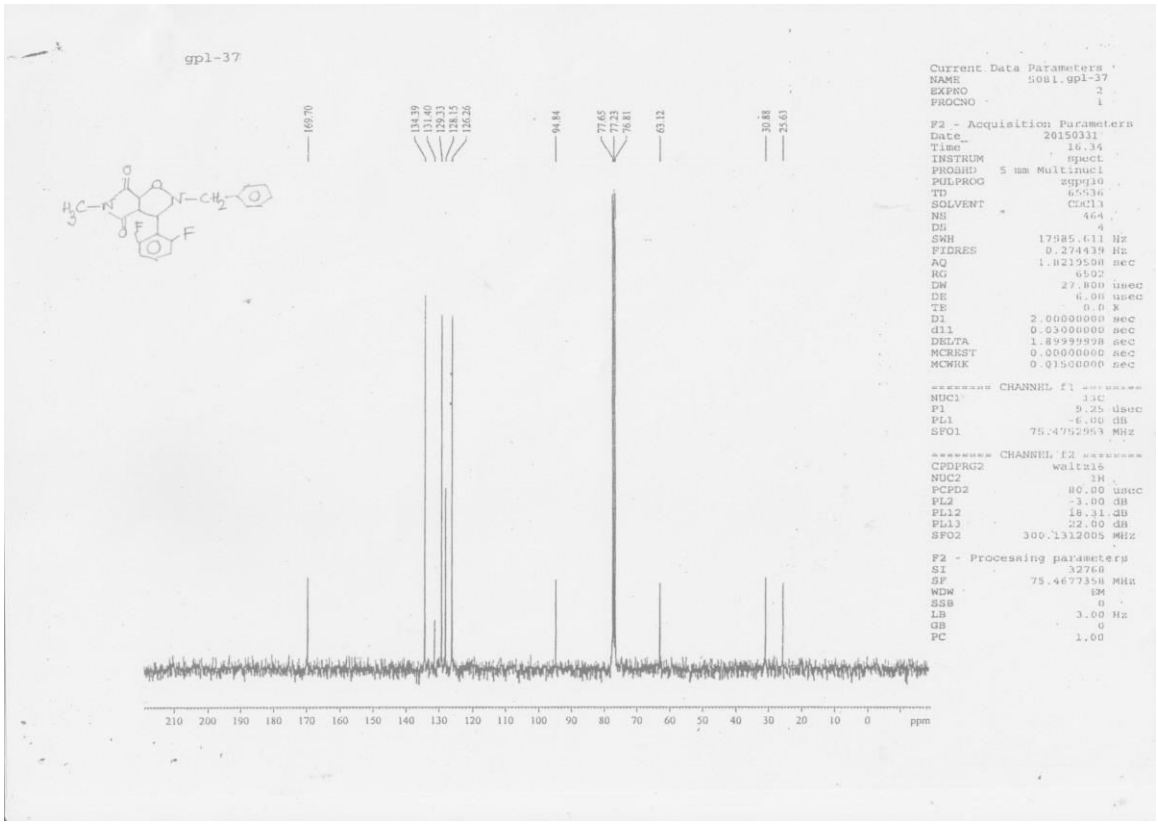


Fig 26: *^{13}C NMR spectram of dimethyl acetylene dicarboxylate bisisoxazoline (terepthalaldehyde derived bisnitrone)*

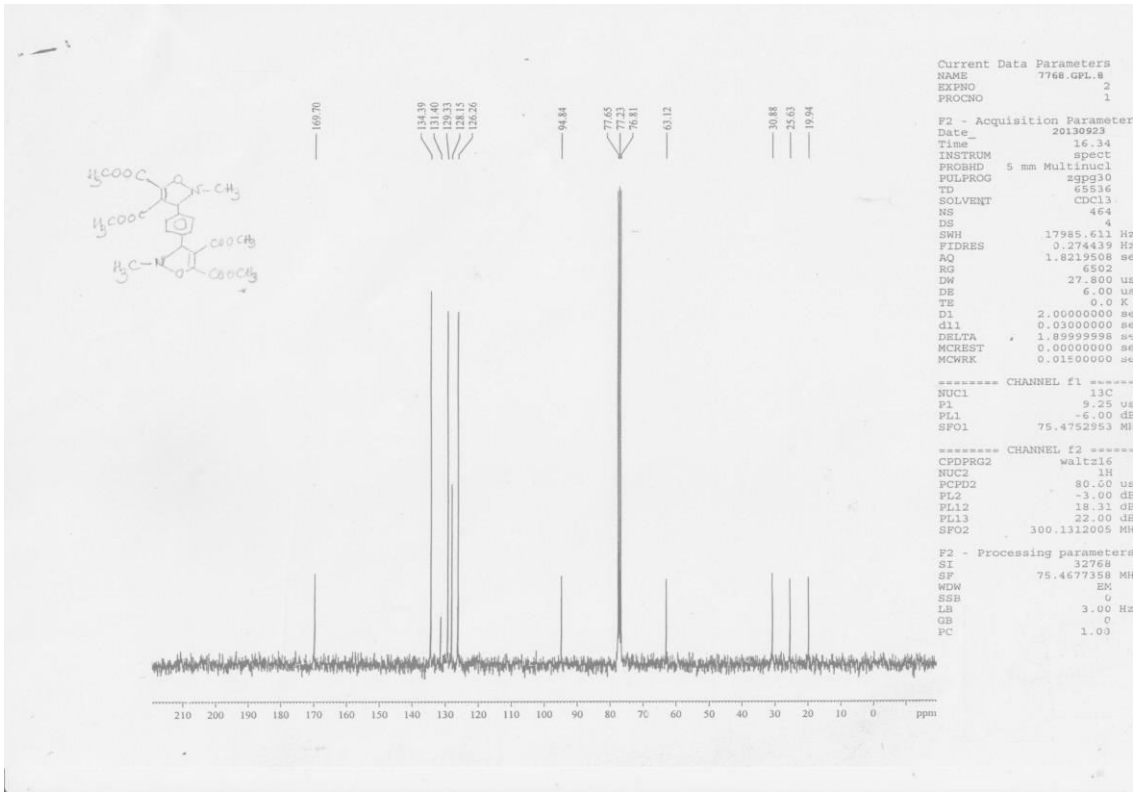


Fig 27: *^{13}C NMR spectram of dimethyl acetylene dicarboxylate bisisoxazoline (terepthalaldehyde derived phenyl bisnitrone)*

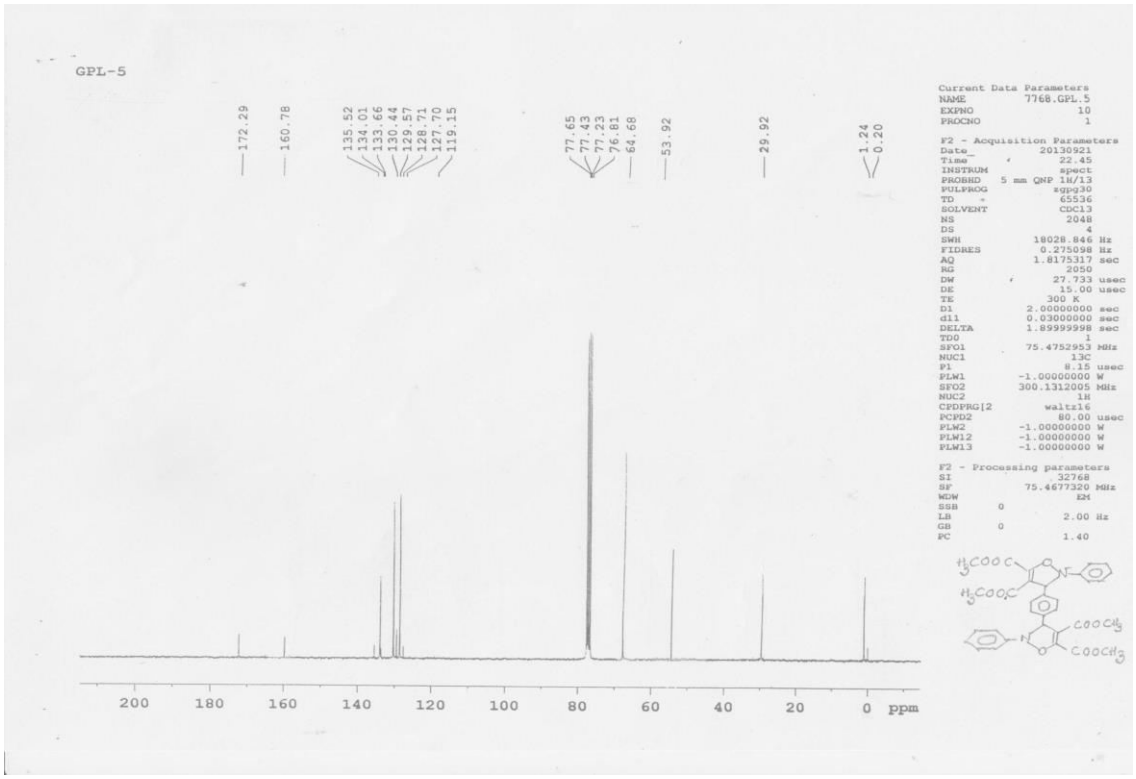


Fig 28: *^{13}C NMR spectram of terepthalaldehyde derived N-methylbisnitrone*

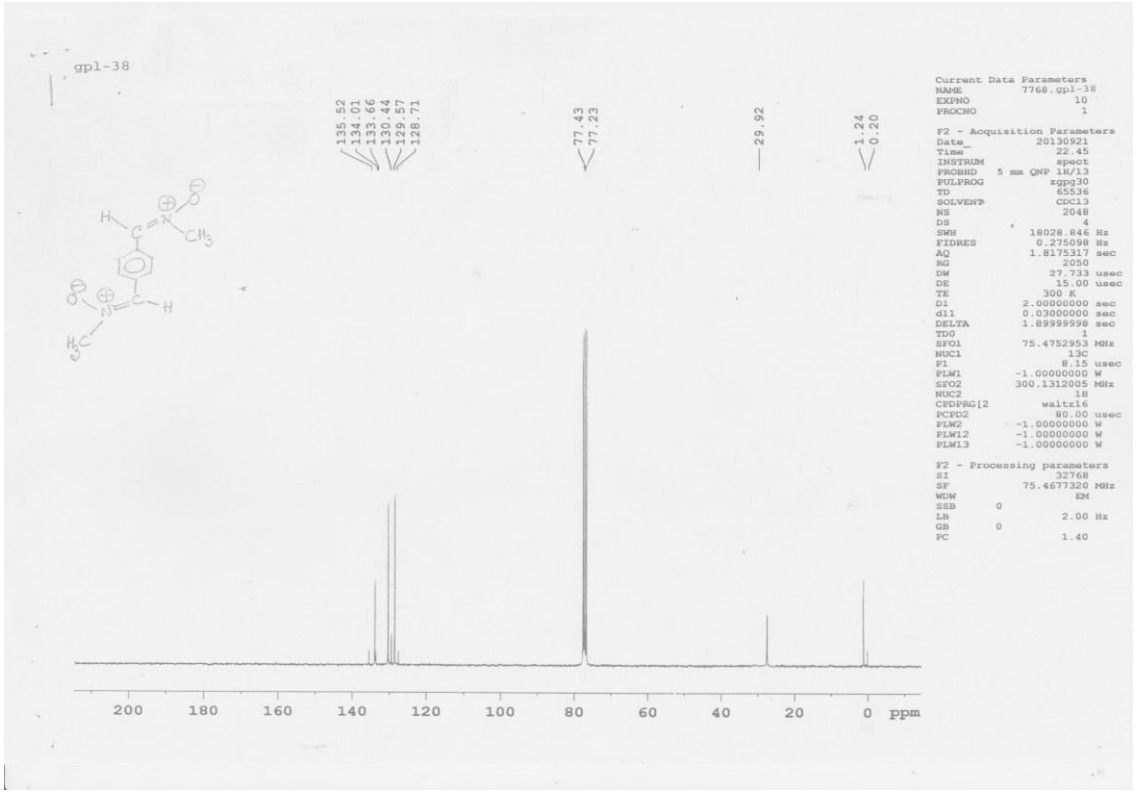


Fig 29: *^{13}C NMR spectram of N-methyl maleimide bisisoxazolidine (glyoxal derived bis nitrone),*

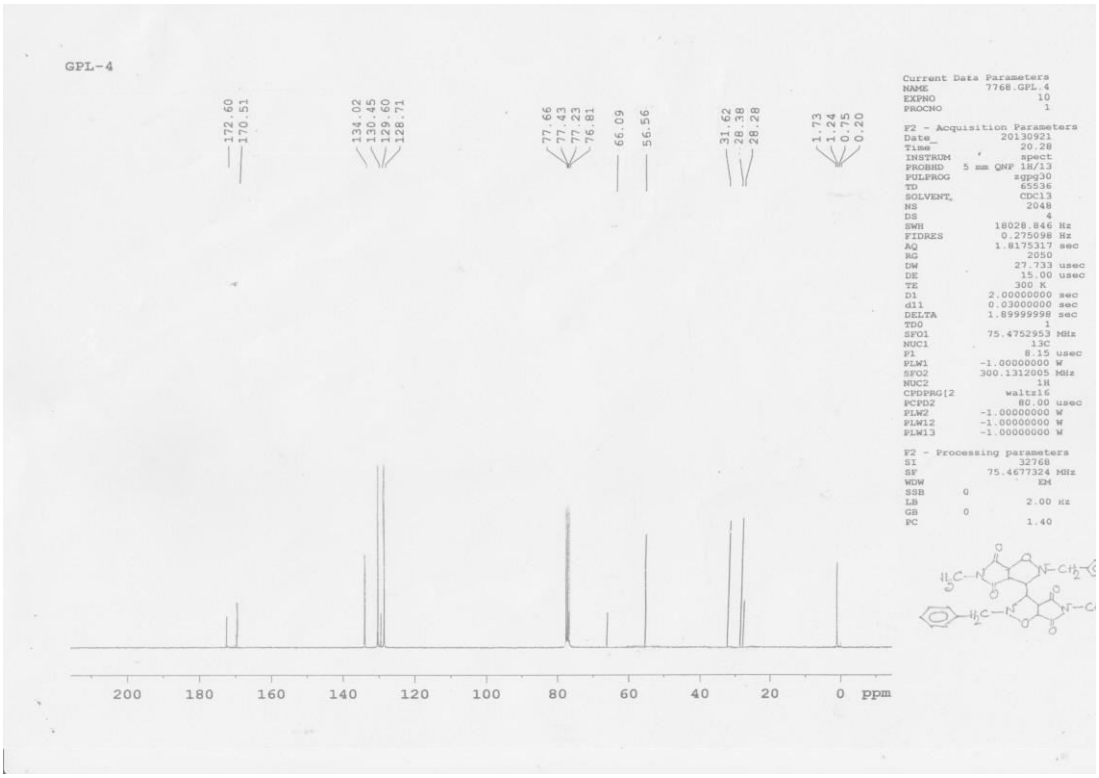


Fig 30: *Mass spectram of terepthalaldehyde derived N-phenylbisnitrone*

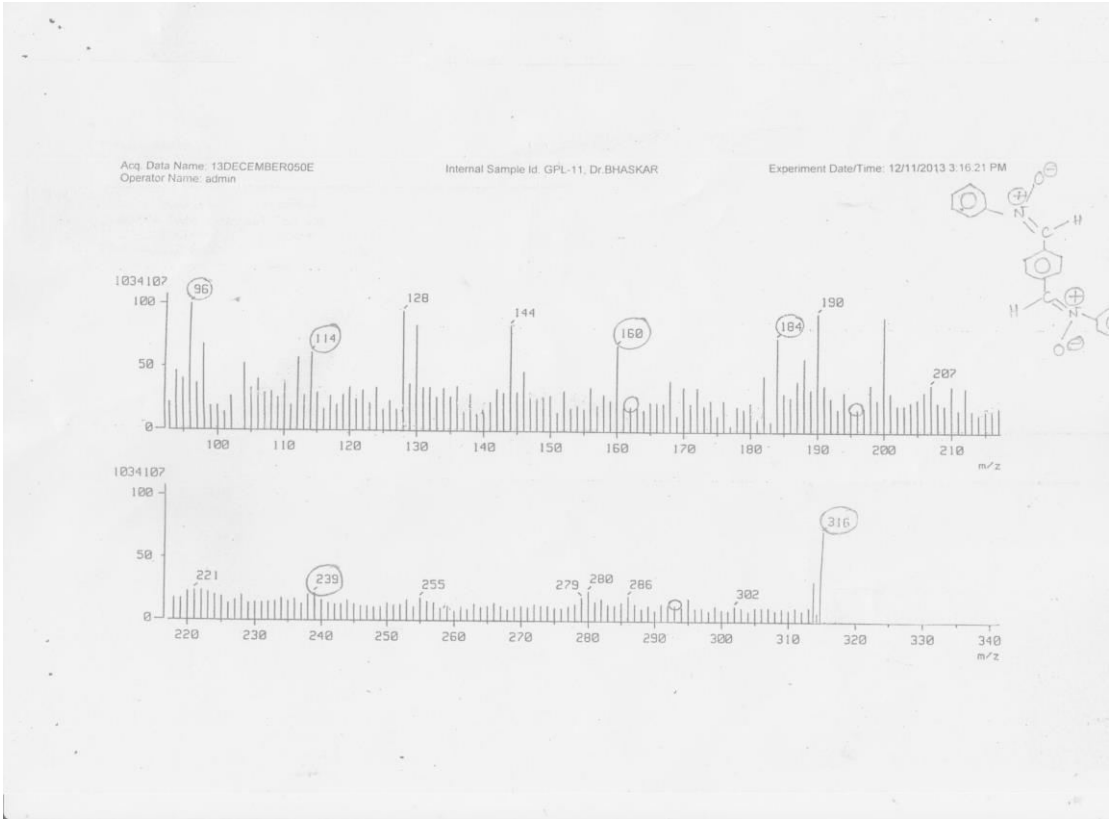


Fig 31: *Mass spectram of terepthalaldehyde derived N-methyl bisnitrone*

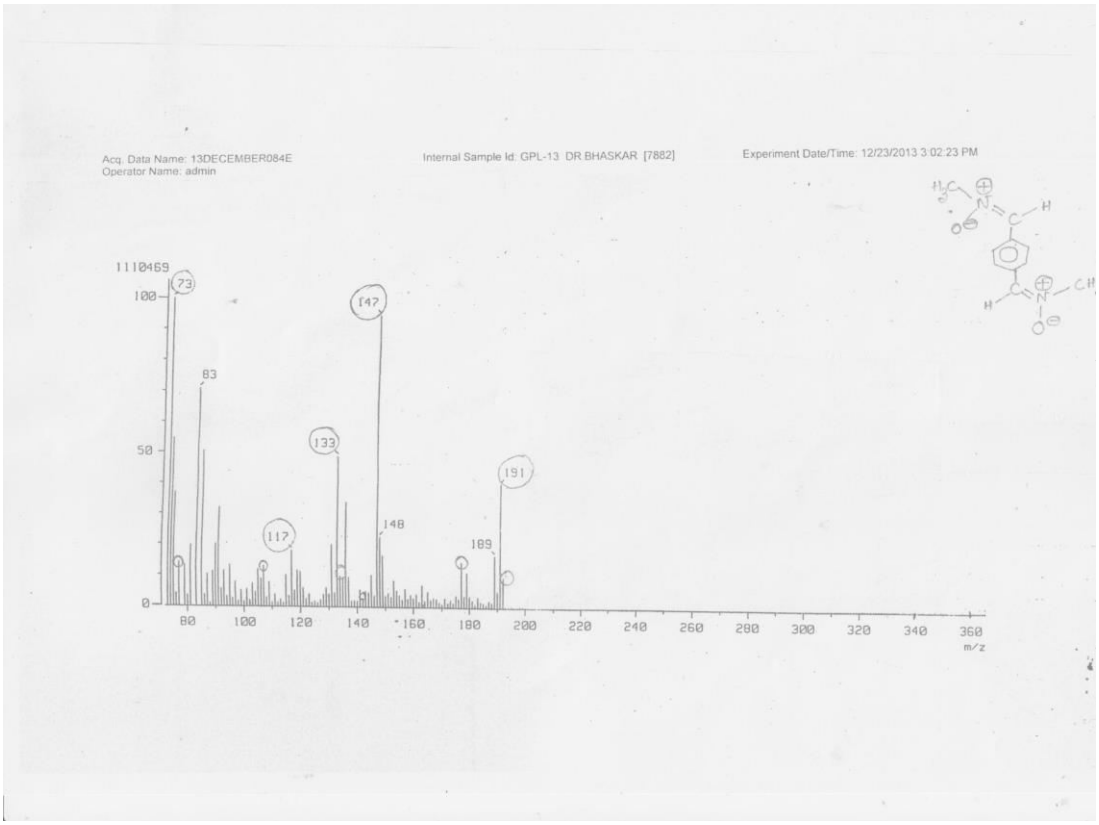


Fig 32: *Mass spectram of styrene bisisoxazolidine (glyoxal derived N-methyl bisnitrone)*

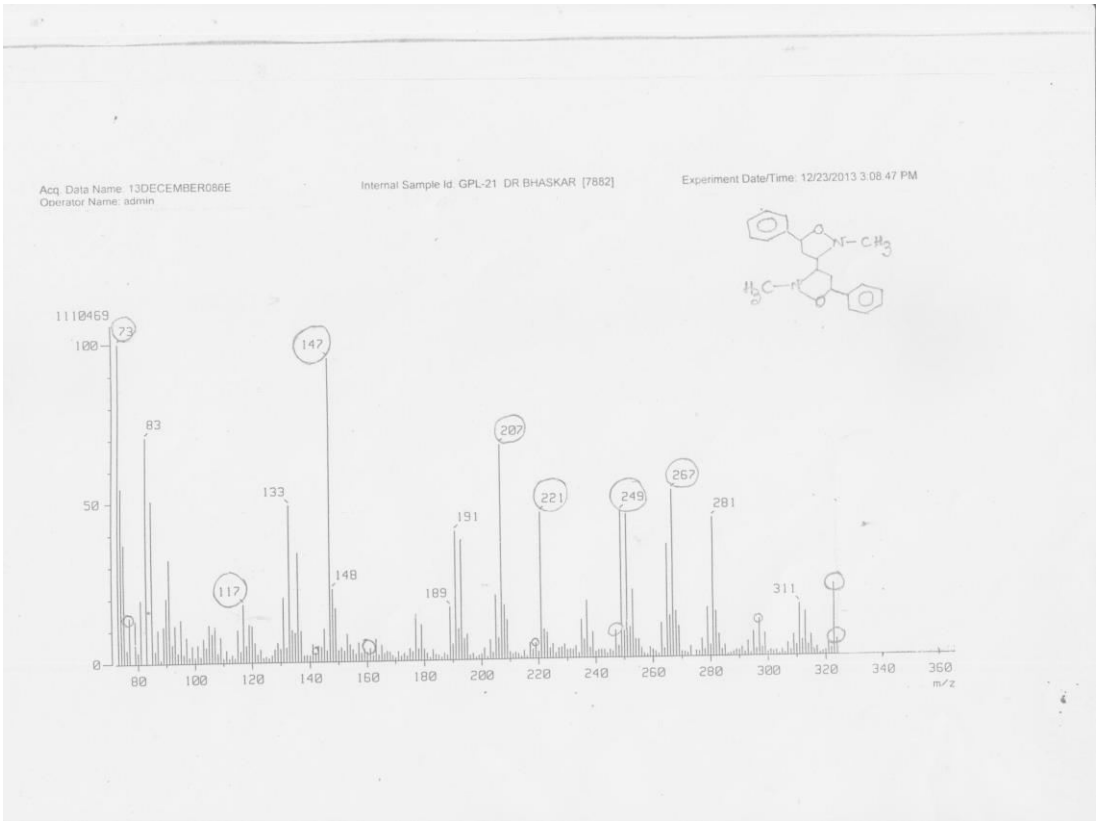


Fig 33: *Mass spectrum of N-methyl maleimide bisisoxazolidine (glyoxal derived N-methyl bisnitrone)*

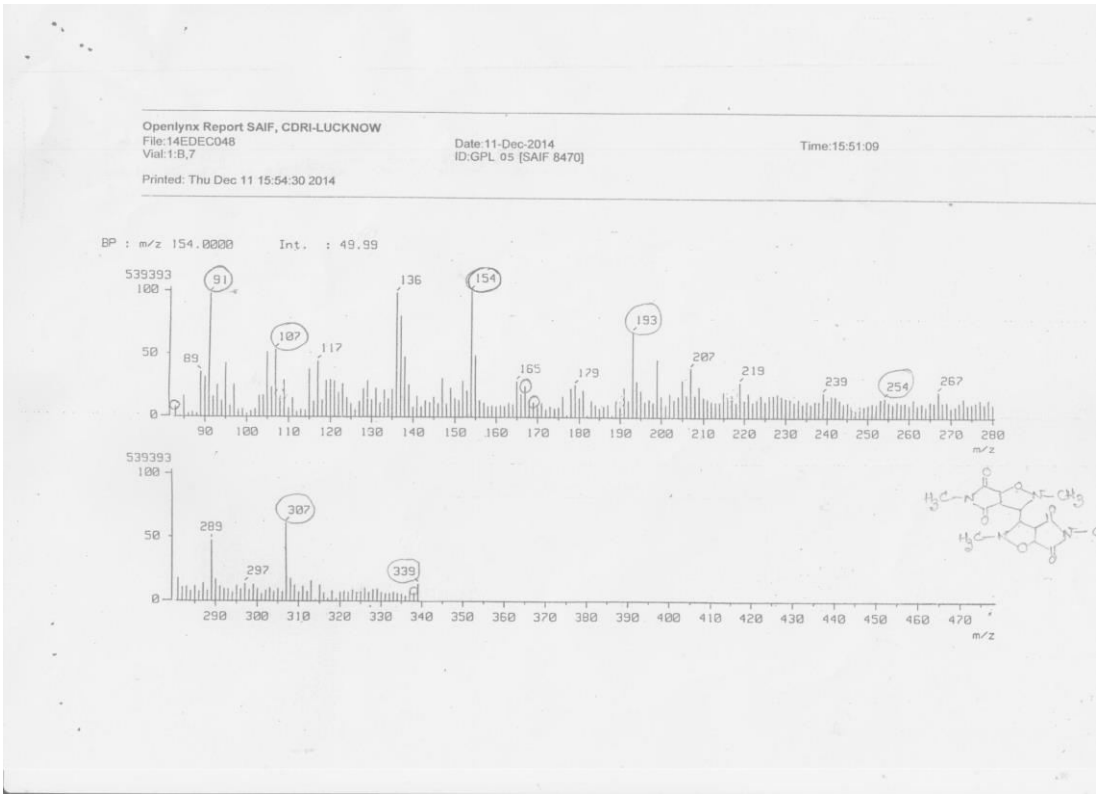


Fig 34: *Mass spectrum of acetylene dicarboxylic acid bisisoxazoline (terepthalaldehyde derived N-methyl bisnitrone)*

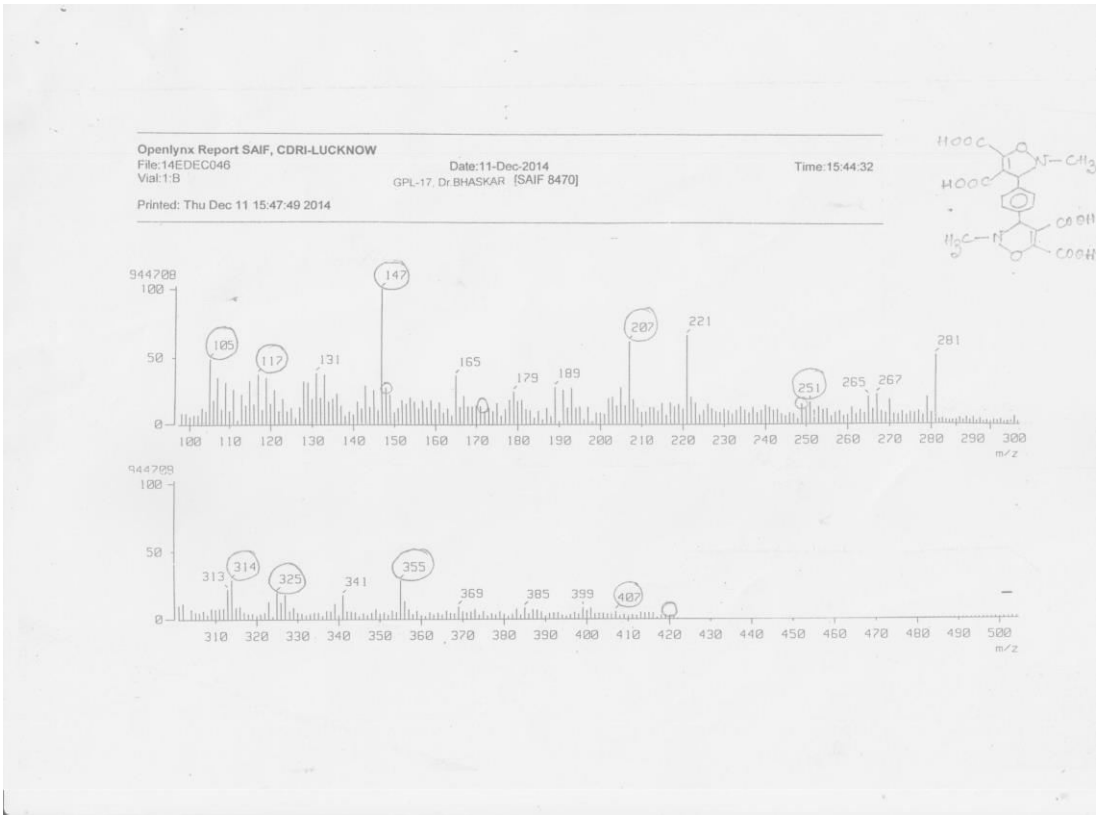


Fig 35: *Mass spectrum of phenyl methyl propiolate fluoro isoxazoline (N-benzyl fluoro nitrone)*

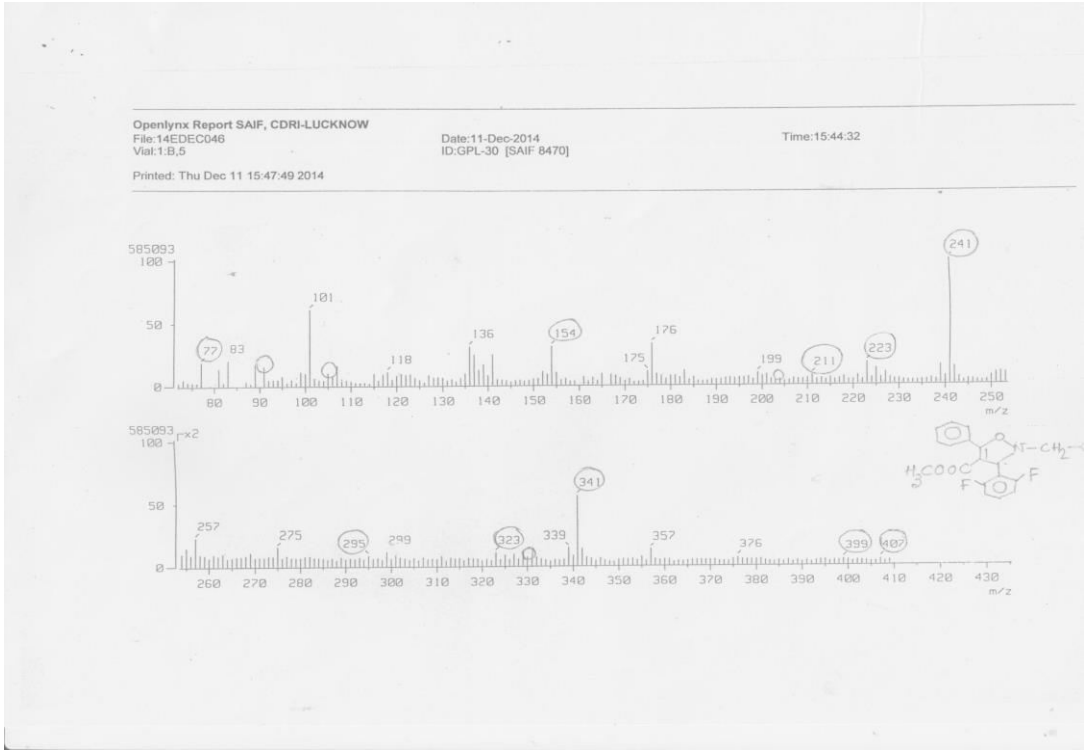


Fig 36: *Mass spectrum of N-methyl maleimide fluoro isoxazolidine (derived from N-benzyl-fluoronitrone*

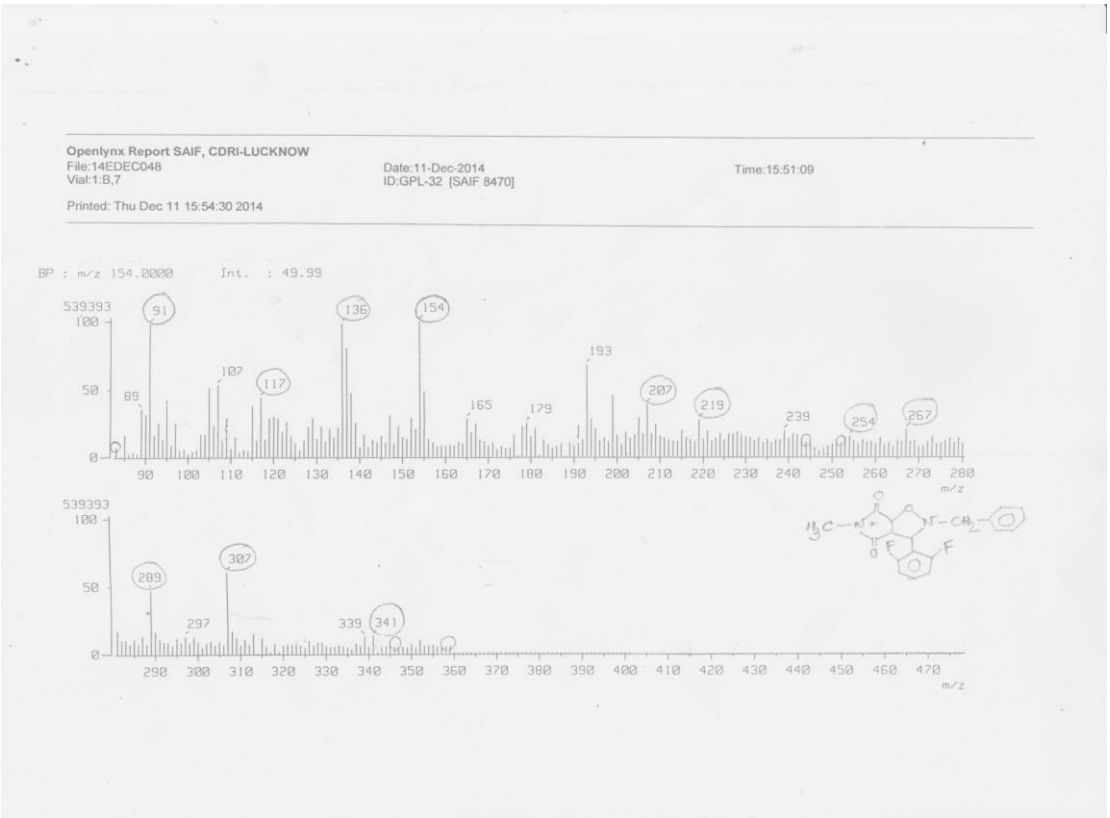
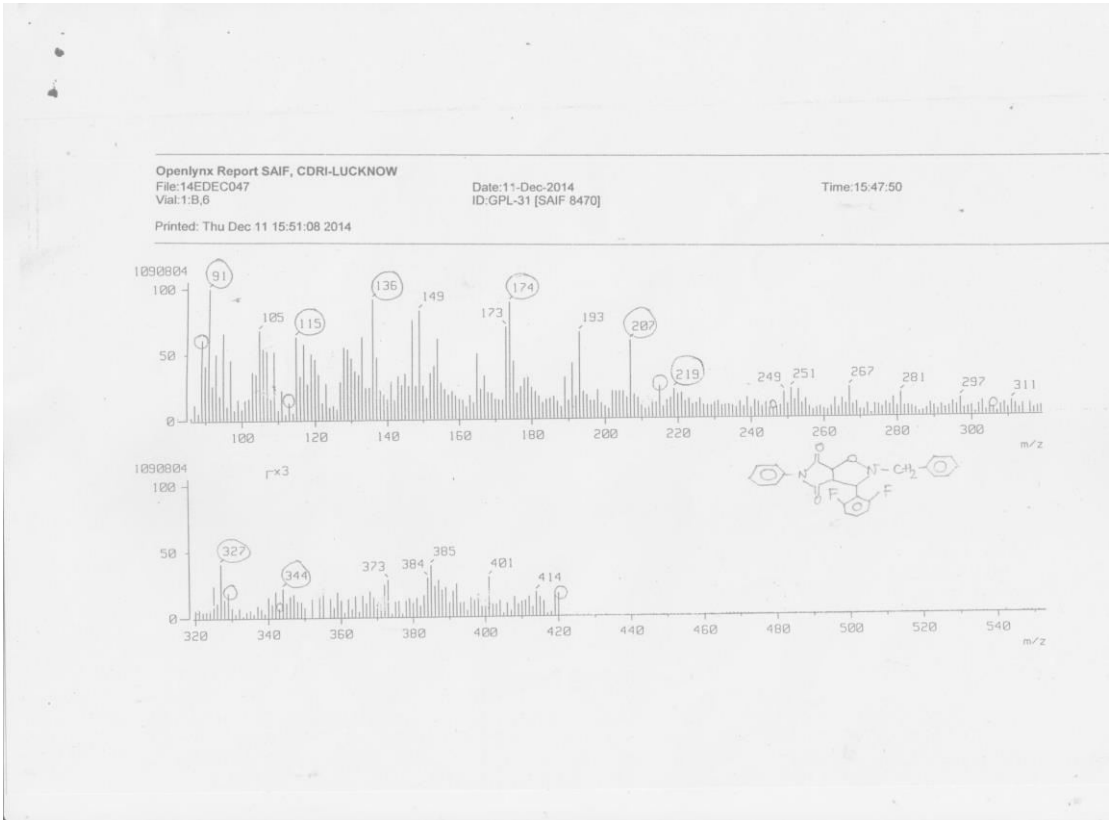


Fig 37: *Mass spectram of N-phenyl maleimide fluoro isoxazolidine (N-benzyl-fluoro nitrone)*



CHAPTER III

Results and Discussion

The present study reports about the synthesis, 1,3-dipolar cycloaddition reaction and applications of *N*-benzyl-fluoro nitrone (**1**)[1,2] and bisnitrones viz, glyoxal derived bisnitrone (**1a**)[3,4] and terepthalaldehyde derived bisnitrone (**1b**)[5,6] following green chemistry methodologies. In the first segment of this chapter of the dissertation, we have reported high yield diastereoselective synthesis of some new fluoro isoxazolidine and fluoro isoxazoline derivatives in ionic liquid. In the second segment, we have reported aqueous phase synthesis and cycloaddition reactions of glyoxal derived bisnitrone in water while in the third segment we have reported synthesis and cycloaddition reactions of terepthalaldehyde derived bisnitrone and their further applications in the synthesis of bisaziridine derivatives[7] under microwave irradiation.

The most important synthetic route for the construction of five-membered heterocycles is 1,3-dipolar cycloaddition reaction. These heterocycles (isoxazolidine & isoxazoline derivatives) are the important frameworks of various natural products[8]. Both the isoxazolidine and isoxazoline derivatives may serve as important intermediates for their conversion into various *β*-amino alcohols and alkaloids[9,10]. Excellent medicinal activities like *antibacterial, antifungal, anticonvulsant, antibiotic and antituberculer activities*[11,12,13] are generally observed in majority of the isoxazolidine and isoxazoline derivatives. Inspite of their potential utility, most of the procedures of their synthesis need drastic reaction conditions like, high temperature and lengthy reaction times and also experiences poor regioselectivity. In some cases, the yields and stereoselectivities are not satisfactory due to the occurrence of several side reactions[14]. It has been observed that, *ionic liquids* are nowadays used widely as green solvents with excellent properties like good solvating ability, wide liquidious range, tunable polarity, high thermal stability, negligible vapour pressure and for its capability of recyclability[15]. Hence majority of classical organic reactions may be performed in ionic liquid with great advantages especially in yield and selectivity compared with conventional conditions. Ionic liquids are also referred as '*designer solvents*' due to their properties like hydrophilicity, hydrophobicity and Lewis acidity. The viscosity and density of IL's can be change by the fine-tuning of certain parameters like the choice of organic cation, inorganic anion and also the length of alkyl chain attached to an organic cation (**Figure 38**).

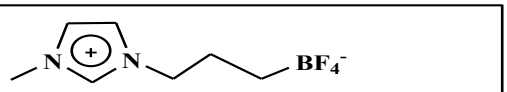


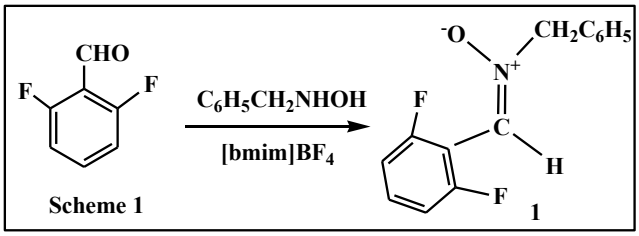
Figure 38- ***Chemical structure of ionic liquid***

Due to the wide scope of structural variations in IL's, a synthetic chemist gets an opportunity to plan for most suitable solvent for a particular reaction. As the ionic liquids are mainly composed of non-coordinating ions, therefore, they can provide a suitable reaction medium for reactions which involve reactive ionic intermediates. The ionic liquids can promote unprecedented stereoselectivities and also increase reaction rates due to the stabilization of charged intermediates. The ionic liquids may be used as recyclable solvents for the immobilization of transition metal based catalysts, Lewis acids and enzymes[16]. Because of their green credentials and potential to increase reaction rates and selectivities, ionic liquids are finding lot of applications in organic synthesis[17] with an ever-increasing interest for exploration of newer synthesis in ionic liquids[18].

It has been observed that when fluorine atom is introduced into a specific position of an organic molecule, it is capable to bring significant changes in molecule towards its stability, lipophilicity and biological activities[19]. It can be explained due to the high electro negativity of the fluorine atom, the strong C-F bond and also the similar size of the fluorine and hydrogen atoms. Based on these observations great efforts are nowadays placed on the development and evaluation of biologically active fluorinated organic molecules[20]. The biological screening of fluorinated organic molecules have been recently investigated. Fluorinated organic molecules are having unique properties, like high thermal stability and lipophilicity and therefore these compounds have been frequently used as biorelated materials, drugs and agrochemicals[21]. Due to a low polarizability and high lipophilicity of the fluoro group it induces a relative stability and improves the bioavailability of the synthesized fluoro heterocycles compared with its hydrocarbon analogues[22,23].

Like other dissertations from our laboratory and published works based upon green methodologies in nitrone cycloaddition reactions[24-29], in this dissertation also we have reported the use of ionic liquid as recyclable solvent in 1,3-dipolar cycloaddition reactions of *N*-benzyl fluronitrone having vast synthetic potentials with active olefines and electron deficient alkynes to synthesize fluoro isoxazolidine and isoxazoline derivatives with potential biological activity in an one-pot reaction (**Scheme 28 ; Table 6**). Compared with conventional methodologies the cycloaddition reactions performed in ionic liquids are are found to be much faster and selective.

Synthesis of N-Benzyl fluoro nitrone (1) in ionic liquid



Scheme 1 **1**

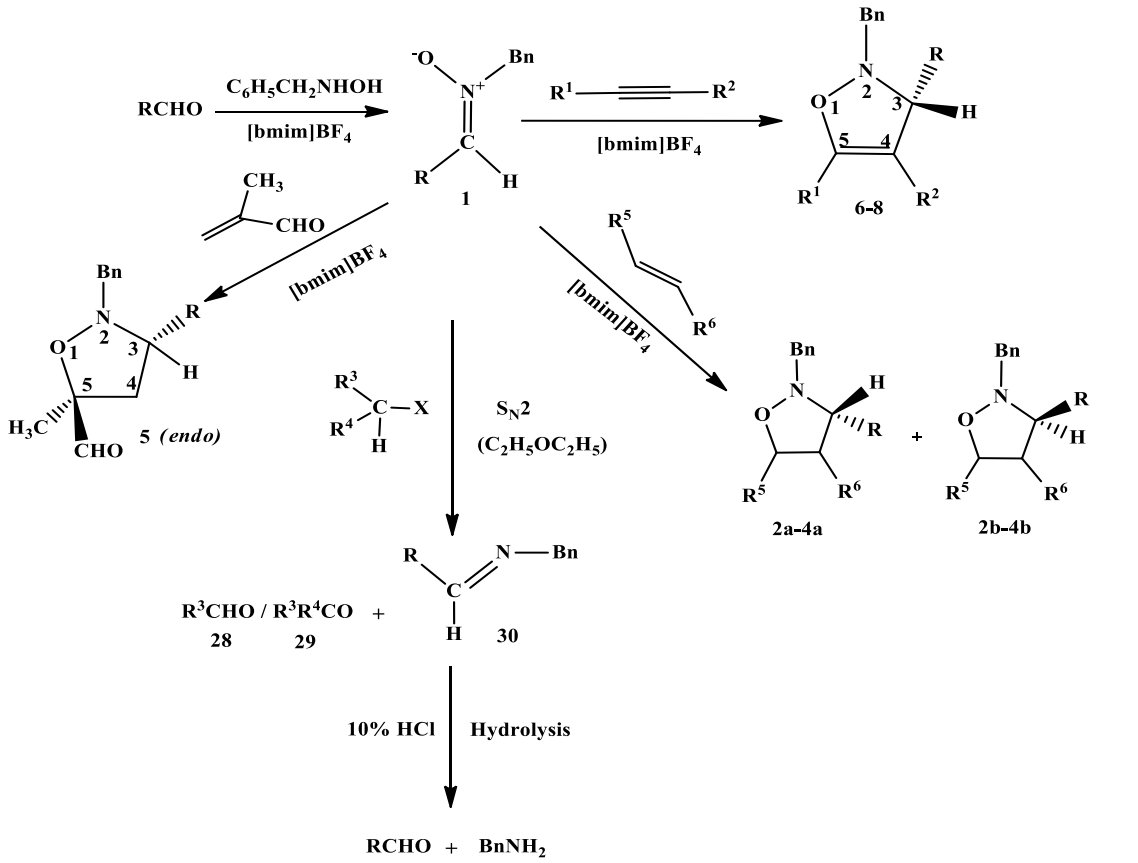
To a stirred solution of 2,6-difluoro benzaldehyde (1 mmol) and [bmim]BF_4 (2 mL) in a 10 mL conical flask, *N*-benzylhydroxylamine (1 mmol;1 equivalent) was added at RT. It was mixed thoroughly and stirred at RT (20^0C) for 1 hr. The development of nitrone was monitored by TLC (ethyl acetate: hexane =1:10; R_f=0.45). Following usual workup, the reaction mixture was washed with diethyl ether (3x10mL) and the combined ether layer was concentrated *in vacuo* to furnish fluoro nitrone **1** as white crystalline solid (m.p 42^0C, uncorrected). It was observed that the fluoro nitrone **1** decomposes if kept at room temperature for few hours. Therefore, *in situ* reactions were performed with various alkene and alkynes.

Spectroscopic data for fluro nitrone **1** UV λ_{max} 238 nm; IR (KBr): υ_{max} 3025 (m), 2235 (m), 1680 (m), 1610 (s), 1440 (m), 1154 (m), 784 (s) cm^{-1}. ^{1}H NMR ($CDCl_3$): 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}CNMR ($CDCl_3$): δ 142.04 (CH=N^+), 134.80, 134.34, 134.12, 133.93 (phenyl carbons), 131.60, 130.00, 129.55, 129.46, 128.67, 128.22 (2,6 difluoro phenyl carbons).

The salient features observed in these cycloaddtion reactions may be explained as follows. The reaction between nitrone **1** and methyl phenyl propiolate develops isoxazoline **6** when the reaction was conducted in CH_2Cl_2 at RT for 17 hrs with 65% yield while 87% yield was recorded in [bmim]BF_4 at RT after 27 minutes for the same reaction (**entry 5; Table 6, Scheme 28**). In this methodology, 1 equivalents of alkyne in [bmim]BF_4 (2 mL) was added *in situ* at the time of development of nitrone **1** under stirring, at RT and the procedings of the reaction was monitored by TLC. The reaction mixture was washed with diethyl ether (3x10mL). The ether extract was concentrated *in vacuo* and the resulting product was directly charged on a silica gel column. The column was eluted with a mixture of ethyl acetate and *n*-hexane (1:8) to afford pure isoxazoline. The remaining ionic liquid was washed with diethyl ether and dried at 80^0C under reduced pressure in order to keep its activity for further reactions. The ionic liquid was reused up to four to five times without loss of its activity or selectivity. Although we stopped recyclying the ionic liquid after the fifth run, but we were convinced that the process may be performed for many more times.

It is noteworthy when the reaction of nitrone **1** with activated alkenes (maleimides) is carried out in RTIL's excellent diastereofacial selectivity and faster reaction reaction rates have been observed. For instance, the reaction between nitrone **1** and *N*-phenyl maleimide when conducted in CH_2Cl_2 at RT afforded cycloaddition derivatives **2a & 2b** in 12 hrs stirring with 68% yield while 88% yield was recorded in [bmim]BF_4 at RT after 30 minutes stirring for the same reaction respectively (**entry 1, Table 6, Scheme 28**). A mixture of diastereomer **2a–4a** and **2b–4b** was obtained when nitrone **1** was added to the maleimides (almost 65: 25 ratios in all cases) and three chiral centres were developed in a single step.

It has been also observed that when these cycloaddition reactions are performed in ionic liquids there is a higher probability of the formation of mixture of diastereomers compared with conventional organic solvents.

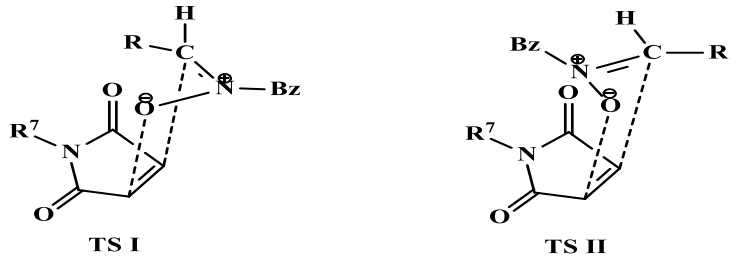


R = 2,6 difluro benzene ; Bn = $C_6H_5CH_2$
R^1 = Ph ; R^2 = $COOCH_3$
R^1 = R^2 = $COOCH_3$
R^1 = R^2 = COOH
R^3 = Et ; Ph ; R^4 = H etc
R^3 = R^4 = Ph ; R^3 = Me ; R^4 = Ph
R^5,R^6 = -COPhCO- ; -COMeCO- ; -COCyCO-

Scheme 28 - ***Synthesis of fluoro isoxazoline & isoxazolidine derivatives using fluoro nitrone and application of the nitrone in atom efficient aldehyde & ketone synthesis***

The results obtained from these cycloaddition reactions can be rationalized by an *exo* approach of nitrone **1** having *Z* configuration for the development of major cycloadducts **2a–4a** (transition state **I, Figure 39**). Similarly, the minor cycloadducts **2b–4b** is formed by the *endo* approach of *Z* nitrone (transition state **II, Figure 39**). The mixture of diastereomers are identified by the consideration of the multiplicity of the proton signals at C3-H and C4-H and also from their coupling constant values[30,31]. The most significant observation noticed in the ^{1}H NMR spectrum for the diastereomers are the position and multiplicity of the C3-H signal.

The coupling constant between C3-H & C4-H has been measured as $J_{3,4}$ ~ 6.26 Hz in the major cycloadducts **2a-4a** indicating a *cis* relationship between C3-H and C4-H, while in case of minor cycloadducts **2b–4b**, the coupling constant has been measured as $J_{3,4}$ ~ 2.26 Hz indicating a *trans* relationship between C3-H and C4-H[30,31].



$R^7 = CH_3/C_6H_5$; $Bz = -CH_2C_6H_5$

Figure 39 - ***Exo/endo approach of the nitrone to the maleimides in cycloaddition reactions***

The reaction of *N*-benzyl fluoro nitrone **1** with methacrolein affords 5-substituted *endo* isoxazolidine in [bmim]BF_4 when stirred for 32 minutes with 90% yield and excellent regioselectivity (**entry 4, product 5; Table 6**). But surprizingly, in the absence of ionic liquids, the reaction did not yield any product even after a long reaction time (30 hrs). Under conventional conditions (CH_2Cl_2 as solvent, RT, 42 hrs), the products were obtained as a mixture of *endo* and *exo*-isomers (80:20) favouring the *endo*-diastereomer. ^{1}H NMR analysis differentiates the signals for the *endo* and *exo* diastereomers [31]. If benzyl groups are present on the nitrogen atom of nitrones they become extremely valuable for the applications in synthesis as these moieties act as versatile protecting groups. We have observed that *N*-benzyl fluoro nitrone **1** afforded the expected *endo* substituted isoxazolidine (**5**) with high yield. The 1,3-dipoles exhibit enhanced reactivity in *ionic liquid* and thereby reducing the reaction times and improving the yields significantly. Moreover, the *ionic liquids* were found to generate better regioselectivity than organic solvents. In addition, these molten salts can be easily recovered on work-up. Since the cycloadducts are fairly soluble in *ionic liquid* therefore, they can be easily extracted with ether. The remaining part of the *ionic liquid* may be recycled in three to four subsequent runs without loss of activity. Incresed reaction rates, good to excellent yields and high *cis*-selectivity are the main features observed in these *ionic solvents*.

We have tested several butylmethylimidazolium based ILs, [bmim]X, with the variation of anions (X=PF_6^-, Br^-, BF_4^-) for the present study. Finally, [bmim]BF_4 was found to be superior as far as the yield (88%) and reaction time (30 minutes) is concerned compared with [bmim]PF_6 (84%; 43 min; entry **1; Table 6**). To study our reactions in optimized conditions, we used the substrates in different ratios and it was observed that best results were obtained using 1:1 reactant ratio.

We have also studied cycloaddition reactions in [bmim]BF_4 conducted at elevated temperatures but no significant improvements were noticed in terms of yields and reaction times. Finally, we examined the reactions under neat condition also, without using IL's, to examine catalytic ability of [bmim]BF_4. The results clearly indicated that [bmim]BF_4 had notable catalytic role in this reaction (**Table 6**).

Table 6 — *Physicochemical data of synthesized compounds* **2a-4a ; 2b-4b; 5 & 6-8**

Entry	Nitrone	Dipolarophile[a]	Time (min)	Cycloadduct, m.p.(°C), **2a-4a: *cis*** ; **2b–4b: *trans***	*Cis/trans ratio (%)*	Yield[b] (%)
1	*N*-benzyl fluoro nitrone	*N*-phenyl Maleimide	30 (12h)	**2a**: White crystals, 128 **2b**: White crystals, 102	**2a**: 66 **2b**: 22	88 (65)
2	*N*-benzyl fluoro nitrone	*N*-methyl Maleimide	35 (13h)	**3a**: White solid, 135 **3b**: White solid, 120	**3a**: 68 **3b**: 20	88 (66)
3	*N*-benzyl fluoro nitrone	*N*-cyclohexyl Maleimide	40 (13h)	**4a**: Yellow crystals, 142 **4b**: Yellow crystals, 113	**4a**: 64 **4b**: 21	85 (66)
4	*N*-benzyl fluoro nitrone	Methacrolein	32 (42h)	**5**: Colourless thick liquid	**5:** (80:20) *Endo/exo*	90 (62)
5	*N*-benzyl fluoro nitrone	Methyl phenyl propiolate	27 (17h)	**6**: Red viscous liquid		87 (65)
6	*N*-benzyl fluoro nitrone	Dimethyl acetylene dicarboxylate	35 (19h)	**7**: Colourless thick liquid		87 (66)
7	*N*-benzyl fluoro nitrone	Acetylene dicarboxylic acid	35 (18h)	**8**: Colourless thick liquid		82 (66)

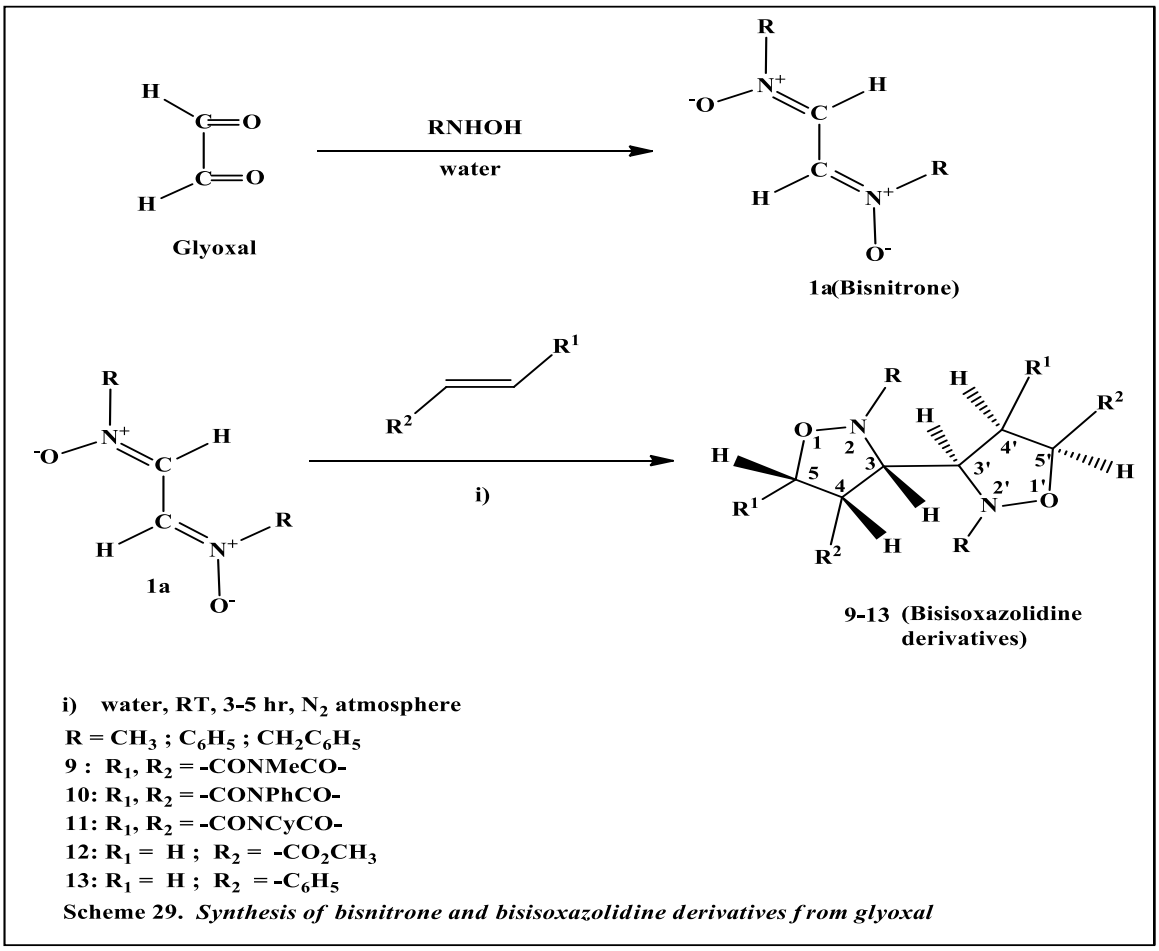
[a] Reaction conditions: nitrone (1 mmol), dipolarophile (1 equivalent), [bmim]BF_4 (2 mL), N_2 atmosphere, RT
[b] All products were characterized by IR, ^{1}H NMR, ^{13}C NMR and MS spectral data.
[c] Isolated yield after purification. Figures in parentheses indicate reactions performed in conventional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

The newly synthesized fluoro cycloadducts are found to be stable. Studies of mass spectrum of the fluoro cycloadducts showed prominent molecular ion peak and base peaks. In case of maleimide cycloadducts a common mass fragmentation pattern was observed. Base peak (B.P) was obtained due to the fragmentation of benzyl and 2,6 difluro phenyl ring from these maleimide cycloadducts. These fragmentation pattern also shows a correlation in their structures.

We have observed a common range of IR absorptions for fluoro maleimide cycloadducts especially for the carbonyl groups aromatic C-H absorptions. This is also in good agreement in support of the structural correlations of the fluoro cycloadducts. Significant mass fragmentation peaks for fluoro isoxazoline derivatives are also obtained due to the development of aziridine derivatives (**6-8**). Loss of PhCO from phenyl methyl propiolate, $COOCH_3$ from dimethyl acetylene dicarboxylate and COOH from acetylene dicarboxylic acid in the fragmentation generates base peaks. Therefore, we may conclude that during mass fragmentation, the fluoro isoxazoline cycloadducts underwent rearrangement to fluoro aziridine derivatives. Based upon the signals obtained in ^{1}H NMR, ^{13}C NMR, MS and FT-IR spectrum the structures of all the fluoro isoxazolidine and fluoro isoxazoline derivatives (**2-8**) have been confirmed. Elemental analysis values were also found to be in good agreement for majority of the new fluoro cycloadducts.

1,3-dipolar cycloaddition reactions are an integral and weighty part of organic chemistry in pedagogy and research as well. The wealthy literature on cycloaddition reactions from their birth up to now, unequivocally witnesses to their leading chemistry. Although *''conventional solvents''* have undoubtedly promoted their success but the toxicity aspect of these solvents impedes their use freely and with no fear. Not only the operating chemist is uncomfortable while experimenting, but also the environment is equally threatened. Working out the cycloaddition reactions and other organic ones in aqueous system would certainly bring some relief to the chemist and to the environment as well. Unusual outcomes in terms of yield, reactivity and selectivity compared to those performed in organic solvents were commonly observed, and have overwhelmed the chemists with surprise indeed[32,33]. The 1,3-dipolar cycloaddition methodology applied to aqueous media has brought forth a number of heterocyclic compounds, usually with a regio and stereoselectivity pecularity. These heterocycles include isoxazoles, isoxazolidines and pyrrolidines. This rate of acceleration of organic reactions in aqueous media was ascribed to one or a combination of the following factors and phenomena[34], the high cohesive energy density of water, the high internal pressure within the medium, the hydrogen-bonding ability, the hydrophobic packing of diene and dienophile in cycloaddition reactions, the hydrophobic vs. antihydrophobic effects, the micellar catalysis, the solvophobicity, and the solvent polarity. Today's status, the insolubility of organic reactants in water, once considered a drawback, turns out to be advantageously a leading factor for the success of organic reactions in pure water. In 2005, Sharpless coined these heterogeneous reactions as *''on-water''* reactions[35,36]. The *''on water''* method consists simply of stirring the reactant(s) with water to generate an aqueous suspension and it has been observed that both kinetics and yields are extremely enhanced in most cases, compared with those in organic solvents.

In continuation of our efforts to establish greener methodologies in nitrone cycloaddition reactions[24-29], in the second part of this dissertation we have reported a new route to the synthesis and 1,3-dipolar cycloaddition reaction of glyoxal derived bisnitrones **1a** (having vast synthetic potentials) with a variety of alkenes to afford novel bisisoxazolidine derivatives (**9-13**) in water (**Scheme 29**) . This is quite a new approach of the synthesis of nitrone from glyoxal. The present study on 1,3-dipolar cycloaddition reaction with bisnitrone **1a** has been carried out with three different maleimides (*N*-methyl/phenyl/benzyl) and methyl acrylate, styrene respectively in water. Simultaneously the reactions have been also studied in organic solvent (CH_2Cl_2) as well.



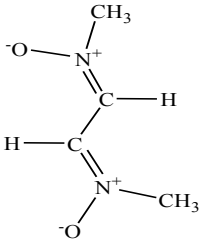
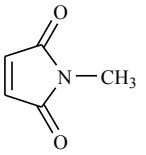
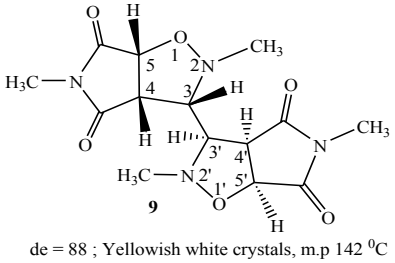
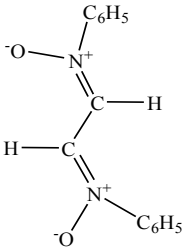
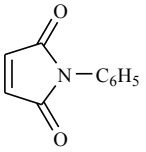
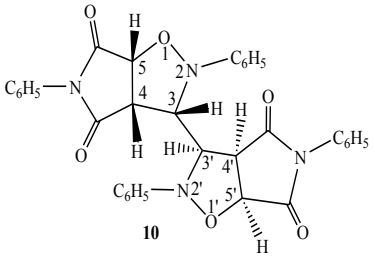
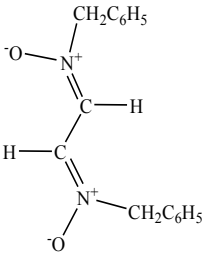
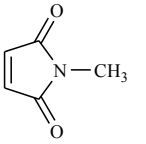
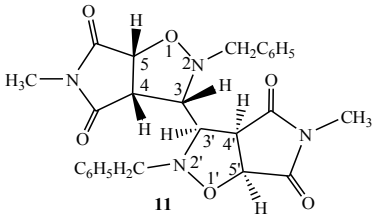
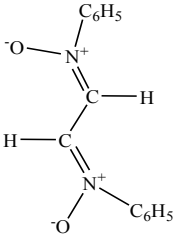
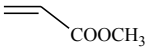
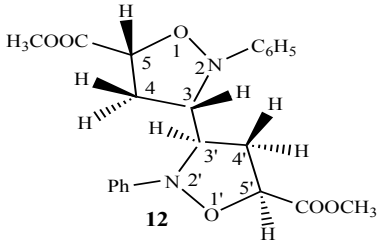
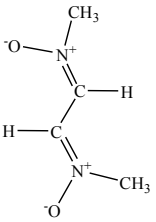
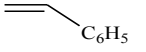
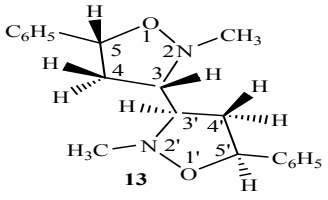
i) water, RT, 3-5 hr, N_2 atmosphere
R = CH_3 ; C_6H_5 ; $CH_2C_6H_5$
9 : R_1, R_2 = -CONMeCO-
10: R_1, R_2 = -CONPhCO-
11: R_1, R_2 = -CONCyCO-
12: R_1 = H ; R_2 = $-CO_2CH_3$
13: R_1 = H ; R_2 = $-C_6H_5$

Scheme 29. ***Synthesis of bisnitrone and bisisoxazolidine derivatives from glyoxal***

We have classified the dipolarophiles into water-super and water-normal on the basis of the magnitude of their rate response to water. A ketone (C=O) conjugated to an alkene or alkyne is a water-super dipolarophile. Similarly, esters, ethers and aryl rings conjugated to an alkene are water-normal dipolarophiles. All the reactions conducted in water are found to be very fast (3-4 hrs in case of maleimides, ethyl acrylate and 5 hrs for styrene) compared with the normal cycloaddition reactions in organic solvents which are reported to take lengthy periods (26 - 48 hrs)[37,10].

It is possible that water promotes the reaction through hydrogen bond formation with the carbonyl oxygen atom of the α,β-unsaturated carbonyl compounds and thereby increasing the eletrophilic character at the β-carbon which is attacked by nucleophilic oxygen atom of the nitrone. Therefore, water activates maleimide, methyl acrylate and thereby greatly facilitates the reaction. The reaction rate is comparatively slower in case of styrene because of very lesser possibility of the formation of hydrogen bonding between water and alkene but still the rate of the reaction and the yield is higher than the cycloaddition reactions performed in solvents like THF, CH_2Cl_2 (**Table 7**). We have suggested an explanation for these results in terms of the frontier molecular orbital (FMO) theory which has been used extensively to explain regioselectivity and to predict the yield, rate in 1,3-dipolar cycloadditions[38,39]. This theory states that the Gibbs energy of activation is related to the energy gap between the interacting HOMO and LUMO. The dipolarophiles like styrene is weak hydrogen bond acceptor, so their FMO's are only slightly affected by hydrogen bond interactions and leads to a reduction of the energy gap between the interacting FMO's (in this case, the HOMO of the dipolarophile and LUMO of the 1,3 dipole). Consequently, the Gibbs energy of activation of the reaction is reduced and the reaction is accelerated in water with good yield. Bisnitrones (**1a**) reacted with *N*-substituted maleimides giving bisisoxazolidines. Diastereoselective reactions of the nitrone **1a** furnished diastereoselective cycloadducts (**9-11**) and are classified as *trans trans* biscycloadducts. The C*3-H* and C*4-H* protons on each isoxazolidine ring are *trans* orientated as evidenced from ^{1}H NMR spectroscopy[30,40]. On the other hand, bisnitrones **1a** reacted with ethyl acrylate and styrene giving exclusively regioselective bisisoxazolidines (**12-13**). All the novel biscycloadducts (**9-13**) are obtained as diastereoselective and regioselective isomeric forms and stereochemical informations dipicted in the drawing implies relative and not absolute relations[41]. The structures of the diastereoselective and regioselective (*5-substituted*) novel bisisoxazolidine derivatives are confirmed on the basis of ^{1}H NMR spectroscopy[30,40]. It is also evident from the ^{1}H NMR spectrum of the diastereoselective bisisoxazolidines (**9-13**) that the structures are expected to be symmetrical in nature and that C3-H, C4-H are *cis* orientated on both rings and vicinal coupling constant has been found to be $J_{3,4} \sim$ 6.80 Hz[42]. Compared with conventional conditions, the cycloaddition reactions performed in water are much faster and selective[43]. As an example, the reaction between nitrone **1a** and *N*-methyl maleimide, afforded bisisoxazolidine (**9**) at room temperature after 26 hrs with 62% yield in CH_2Cl_2 and after 3 hrs in 94% yield in water (**entry 1, Table 7**) respectively. The reaction of nitrone **1a** with various alkenes follow the general mechanistic pattern of 1,3-dipolar cycloaddition reactions as found in literature[10,37]. Initial study reports on the biological screening of the bisisoxazolidine derivatives are also very encouraging.

Table 7. ***1,3-dipolar cycloaddition reaction of glyoxal derived bisnitrones with alkenes in water***

Entry	Bisnitrone[a] (**1a**)	Alkene	Bisisoxazolidine[b] (**9-13**)	Time (hr)	Yield[c] (%)
1			 **9** de = 88 ; Yellowish white crystals, m.p 142 ^{0}C	3 (26)	94 (62)
2			 **10** de = 96, Yellow solid, m.p 116^0 C	3 (27)	91 (59)
3			 **11** de = 92 ; White crystals, m.p 135^0 C	4 (28)	91 (60)
4			 **12** Colourless liquid	4 (30)	88 (60)
5			 **13** Greenish sticky liquid	5 (35)	83 (57)

[a] Reaction conditions: bisnitrone (1 mmol), alkenes (2 equivalent), water (15 mL), N_2 atmosphere
[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 solvents (CH_2Cl_2)

***General procedure for the synthesis of nitrone* 1a**

To a stirred solution of glyoxal (309mg, 5.31 mmole) in diethyl ether (20 mL), *N*-methylhydroxylamine (500mg, 2 equivalent) and anhydrous $MgSO_4$ (2 gms) was added. The reaction mixture was kept at RT with constant stirring with a magnetic stirrer under N_2 atmosphere for 8 hr. The development of bisnitrone was monitored by TLC (R_f = 0.36). Usual workup followed by concentrated *in vacuo* furnished *N*-methyl bisnitrone as white crystals (86%; m.p: 78 ^{0}C). Same methodology was followed for the synthesis of other bisnitrones (R = C_6H_5 ; $CH_2C_6H_5$). All the bisnitrones were found to be stable and were reacted with various activated alkenes in 1,3-dipolar cycloaddition reaction in water at room temperature.

Spectroscopic data for **bis nitrone 1a** (R = CH_3): UV λmax 233 nm. IR (KBr): υ_{max} 1635 (m), 1610 (s) cm^{-1}. 1H NMR (300 MHz, $CDCl_3$): δ 6.45 (d, 1H, *J* = 3.22 Hz, -CH=N$^+$), 6.23 (d, *J* = 3.22 Hz, -CH=N$^+$), 3.84 (s, 6H, 2xCH_3, N$^+$-CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.60 (CH=N$^+$), 140.94 (CH=N$^+$), 24.74, 24.70 (N$^+$-CH_3).

All the novel bisisoxazolidine derivatives (**9-13**) have been found to be very effective against both gram positive and gram negative organisms which give an opportunity to develop new broad spectrum antimicrobial agents. Screening study (SEM and TEM) on these novel bisisoxazolidines are going on at present. The new biscycloadducts are found to be stable and have shown prominent molecular ion peak and base peaks in the mass spectrum. It has been also observed that the *N*-methyl dipole reacts less selectively but furnishes higher yields than its electron poor *N*-phenyl analogue. A plausible stereochemistry of the bisisoxazolidines obtained from maleimides (**9-11**) has been assigned on the basis of C*3-H* and C*4-H* proton signals of both the isoxazolidine rings and are appeared as double doublet and doublets respectively[44,8]. In addition, these bisisoxazolidine derivatives could be easily recovered on work-up. All the products are fairly soluble in water and they could be easily extracted with ether. Important signals of C_3H, C_4H and C_5H protons of both the isoxazolidine rings (*cis, cis*) of the novel bisisoxazolidine derivatives have been found to be merged and obtained as a single signal. Double doublet signal of C_4H protons appeared as broad signal in majority of the novel biscycloadducts and coupling constant values could not be calculated. High selectivity is observed in these simultaneous double cycloaddition reactions and best selectivity (diastereomeric excess) was observed in the cycloaddition reactions of *N*-phenylbisnitrone with *N*-phenyl maleimide (de% 96, **entry 2, Table 7**).

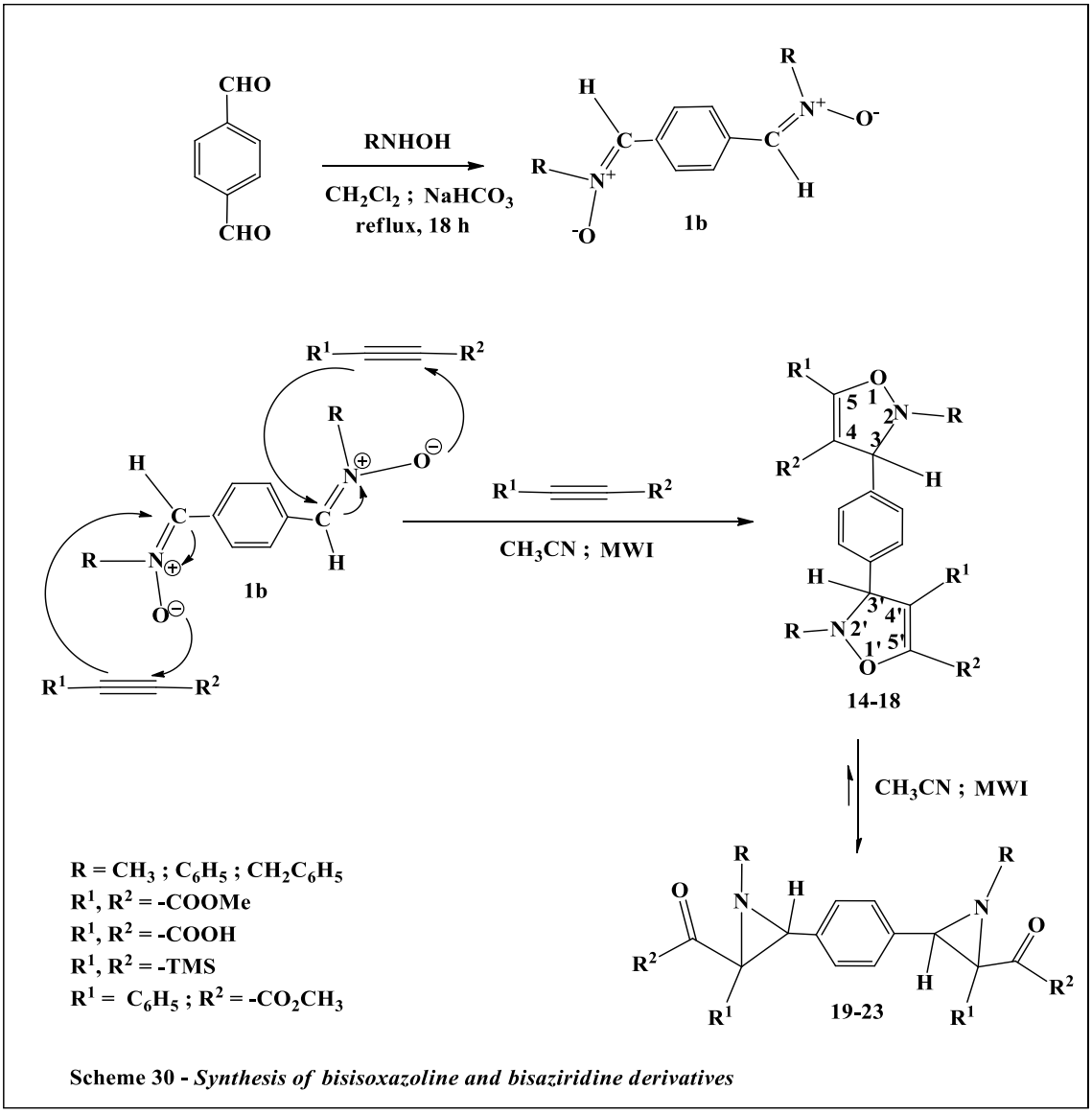
Incresed reaction rates, excellent yields and high selectivity are the notable features observed in these double cycloaddition reactions. All the biscycloadducts are characterized by ^{1}H NMR, ^{13}C NMR, IR and MS spectroscopic data.

The chemistry of aziridines, a three-membered ring heterocycles has attracted the attention of synthetic organic chemists for more than a century because of its ability of acting as versatile species in organic synthesis[45-49]. Baldwin et al have established that 1,3-dipolar cycloaddition reactions of nitrones to alkynes lead to 4-isoxazoline derivatives which rearrange easily under thermal conditions to acylaziridines[50-52].

Continuing our stetegies of establishing new methodologies in organic synthesis[24-29], in the third part of this dissertation we have reported synthesis of some new bisisoxazoline derivatives (**14-18**) from terepthaldehyde in good to excellent yields under microwave irradiation (**Scheme 30, Table 8**). Moreover, these bisisoxazoline derivatives are found to have vast synthetic potential as they could be converted into synthetically more important new bisaziridine derivatives (**19-23**)[53-57,46]. The newly reported bisisoxazoline derivatives are obtained as single pure compound when a mixture of bisnitrone **1b** (1 equivalent) and an alkyne (2 equivalents) are exposed to microwave irradiation for 5-10 minutes at 115 – 130 ^{0}C.

In this present study, terepthalaldehyde and various *N*-substituted hydroxylamines (*N-Methyl/Phenyl/Benzyl*) were employed for the synthesis of bisnitrones **1b** following the reported methodology[5,40,58,59,60]. In the next phase,1,3-dipolar cycloaddition reactions of bisnitrone **1b** with different alkynes (electron deficient and electron rich) were conducted for the synthesis of a variety of bisisoxazoline derivatives (**14-18**) under microwave irradiation applying reported protocol[5,58,60]. The electron deficient alkynes used in the present study were acetylene dicarboxylic acid, methyl phenylpropiolate and dimethyl acetylene dicarboxylate respectively while electron rich alkyne was bis-(trimethylsilyl) acetylene (BTMSA). All the bisisoxazoline derivatives thus obtained were exposed to microwave irradiation (maintaining certain time period and temperature) and thereby a variety of new *N*-substituted bisaziridines were obtained (**Scheme 30, Table 8**).

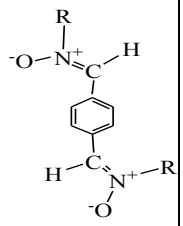
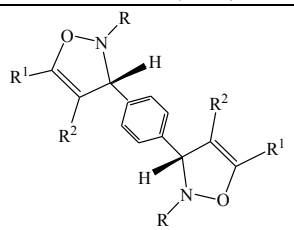
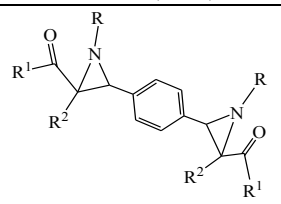
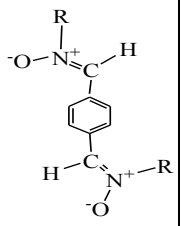
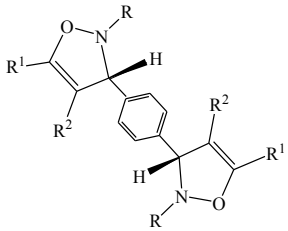
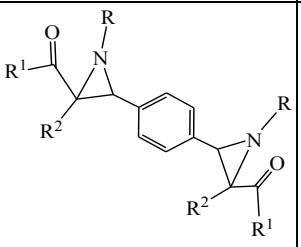
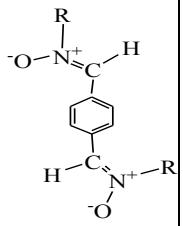
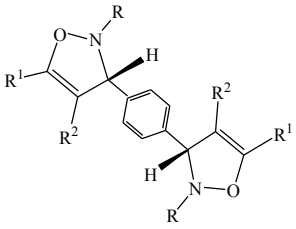
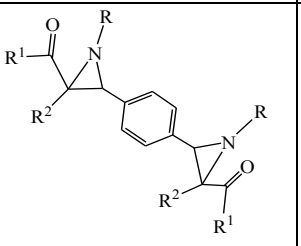
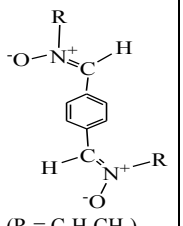
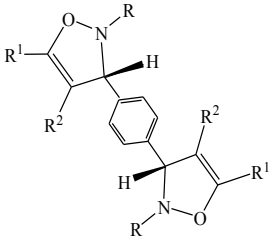
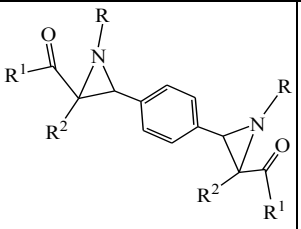
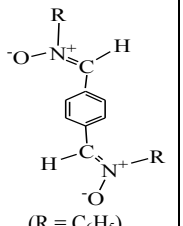
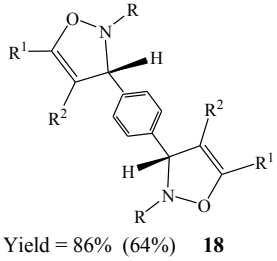
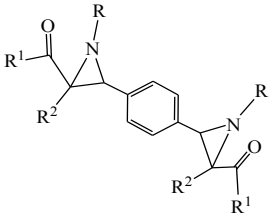
High reaction temperature and long reaction time is generally required to obtain good conversions and yields in these cycloaddition reactions if conducted following conventional methodology. But it has been observed that there is a drastic drop of the yield of cycloadducts due to decomposition if the reactions were conducted under prolonged heating conditions. Because of these disadvantages, microwave irradiation technique was thus undertaken. This methodology is generally faster, cleaner and greener[28,61-63]. The results are summarized in **Table 8**.



Scheme 30 - ***Synthesis of bisisoxazoline and bisaziridine derivatives***

We have also studied the effect of solvent for the rearrangement of fluoro isoxazolines to fluoro aziridines (**24** to ***cis*** **24a &** ***trans*** **24b ; Scheme 25**). Among the various polar solvents used, water and DMSO showed a good level of conversion (90 and 68% respectively) but, unfortunately, also induce the development of extensive amounts of degradation products (63 and 49% transformation respectively). Compared with other solvents used, CH_3CN finally offers better results in terms of efficiency (conversion, transformation and yield) and for practical convenience. At the end of the reaction, the solvent is removed *in vacuo* and the residue is directly loaded on silica gel column for purification which also avoids an aqueous workup (**Table 9 & 10**).

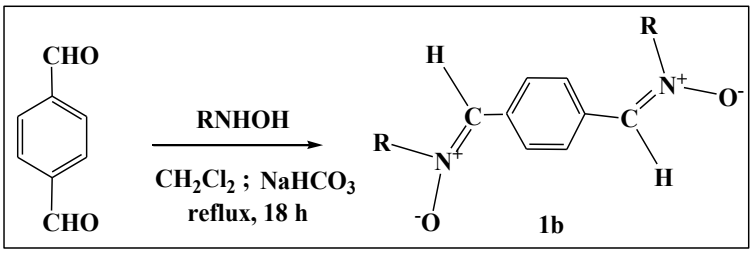
Table 8. ***Synthesis of bisisoxazoline and bisaziridine derivatives***

Entry	Bisnitrone (**1b**)	Bisisoxazoline[a,c] (**14-18**)	Time (min)	Bisaziridine[b,c] (**19-23**)	Time (min)
1	 (R = CH_3)	 Yield = 92% (69%) **14** R^1= $COOCH_3$; R^2 = $COOCH_3$	5	 Yield = 78% **19** R^1= $COOCH_3$; R^2 = $COOCH_3$	5
2	 (R = C_6H_5)	 Yield = 88% (67%) **15** R^1= COOH; R^2 = COOH	5	 Yield = 75% **20** R^1= COOH; R^2 = COOH	5
3	 (R = $C_6H_5CH_2$)	 Yield = 88% (67%) **16** R^1 = Ph ; R^2 = $COOCH_3$	6	 Yield = 74% **21** R^1 = Ph ; R^2 = $COOCH_3$	6
4	 (R = $C_6H_5CH_2$)	 Yield = 87% (65%) **17** R^1 = TMS ; R^2 = TMS	5	 Yield = 73% **22** R^1 = TMS ; R^2 = TMS	6
5	 (R = C_6H_5)	 Yield = 86% (64%) **18** R^1= $COOCH_3$; R^2 = $COOCH_3$	5	 Yield = 71% **23** R^1= $COOCH_3$; R^2 = $COOCH_3$	9

[a] Reaction conditions: Bisnitrone (1 mmol), alkyne (2 equivalent), MWI, MeCN, 5-10 min, 115 – 130 ^{0}C
[b] Isoxazoline (1 mmol), MWI, MeCN, 5-10 min, 130 ^{0}C
[c] Isolated yield after purification.
Figures in the parentheses of yield indicate products obtained in conventional methodology

We have noticed that rearrangement of fluoro isoxazoline derivatives to fluoro aziridines conducted in absence of solvent resulted in complete degradation of the starting material. We therefore, next evaluated the influence of solvent (H_2O and DMSO) for this conversion. But due to the formation of large amounts of degradation products (nearly 55-60%), this methodology was not followed. The best results were obtained for the rearrangement of fluoro isoxazolines to fluoro aziridines when the reaction was conducted in acetonitrile (**Table 9 & 10**).

***General procedure for the synthesis of nitrone* 1b (R = CH_3)**



To a stirred solution of *N*-methylhydroxylamine hydrochloride (2.09 g, 25 mmol) in CH_2Cl_2 (20 ml) in a 50 ml R.B flask terephthalaldehyde (1.34 g, 10 mmol) was added followed by $NaHCO_3$ (2.52 g, 30 mmol). The reaction mixture was heated at reflux for 18 hrs. The reaction was monitored by TLC (R_f = 0.42). After the completion of reaction, the solution was filtered in hot condition and the inorganic solid washed with warm $CHCl_3$. The bisnitrone crystallized from the filtrate as a white solid and was collected at the vacuum pump (1.42 g, 74%, m.p > 250 ^{0}C).

Spectroscopic data for bisnitrone 1b: *N*-Methyl(4-{[methyl(oxido)iminio]methyl{phenyl)methylideneamine *N*-oxide

R_f = 0.50; FT-IR (KBr): υ_{max} 3130 (s), 3010 (m), 2970 (m), 2246 (m), 1690 (s), 1630 (s), 1610 (s), 1515 (s), 1310 (m), 1176 (s), 1150 (s), 782 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): 8.24 (s, 4H, Ar-H), 7.40 (s, 2H, 2 x CH=N$^+$), 3.89 (s, 6H, 2 x CH_3); ^{13}C NMR ($CDCl_3$): δ 134.66 (2 x CH=N$^+$), 131.81, 130.54 (1,4 Ar-C), 128.29, 127.52 (2,6 & 3,5 Ar-C), 54.58 (2 x CH_3); EI-MS (*m/z*): 192 (M$^+$), 176 (M-O), 134 (M-CHNOCH$_3$); Anal. Calcd. for $C_{10}H_{12}O_2N_2$: C, 62.47; H, 6.30; N, 14.58. Found: C, 62.33; H, 6.24; N, 14.35%.

Important fragmentation peaks in the mass spectral studies are obtained in favour of the biscycloadducts and are due to the development of aziridine derivatives. The Base peaks were obtained due to loss of $COOCH_3$ for dimethyl acetylene dicarboxylate and methyl phenyl propiolate while COOH and TMS for acetylene dicarboxylic acid and BTMSA respectively.

For all the cases, development of bisnitrone, bisisoxazolines, fluoro isoxazolines and conversions to bisaziridine, fluoro aziridine derivatives were monitored by TLC (R_f values of bisaziridine derivatives were found to have lower than bisisoxazoline derivatives). Important signals of R, R^1 and R^2 of the bisisoxazoline and bisaziridine derivatives were obtained in the ^{1}H NMR spectrum[30,31] while prominent carbonyl absorptions were observed in IR spectrum as well. ^{1}H NMR spectrum of all the synthesized bisisoxazoline and aziridine derivatives showed that the four (4) hydrogen atoms of the phenyl ring (1,4 & 3,5 protons) linked with isoxazoline and aziridine rings are merged and obtained as single singlet signal. ^{13}C NMR spectrum of the phenyl ring carbons at ortho, meta and para positions have been found to be merged and obtained as single signal. Exact stereochemistry of the bisisoxazoline and bisaziridine derivatives could not be assigned. This is due to the absence of adjacent proton with respect to isoxazoline and aziridine ring protons.

We have also represented our results on the basis of Baldwin rearrangement of fluoro isoxazolines (**24**) considering the influence of three parameters (solvent, temperature and time ; **Table 9 & 10).** The rearrangement furnished predominantly one diastereomer in 83/17 to >95/5 diastereomeric ratio (dr). The *cis* strereochemistry of the major compound has been determined from the comparison of the coupling constant (*J*) values (7.9 Hz)[30,31]. The coupling constant (*J)* value of 4.2 Hz of the minor compound indicates a *trans* relationship between the C substituents. The reaction has been found to be slow and the diastereomeric ratio increases with time. The polarity of the solvent has a minimum influence on the conversion (compare entries **1** and **6**; **Table 9**) but has a significant effect on the diastereomeric ratio. In a more polar solvent, higher selectivities are observed (compare entries **1** and **6**; **Table 9**). High reaction temperatures are generally needed to get good conversions (entry **3**, **4** and **5**; **Table 10**) but prolonged heating time leads to drastic drop of the yield due to decomposition. These results are not that surprising as far as previously reported examples are concerned where strong donating nitrogen substituents help to favour the rearrangement[50]. We have studied the effect of solvent on the rearrangement of **24** considering the following conditions: 0.125 M, 5 min reaction, 110 °C (**Table 9**). We have noticed that in thermal reactions apolar solvents result lower *cis*/*trans* selectivities (see entries **2** and **6**; **Table 9**). When the reaction was conducted in absence of solvent complete degradation of the starting material was noticed. We therefore, next evaluated the influence of reaction conditions (time and temperature) using CH_3CN as solvent (**Table 10**). The reaction was found to be highly sensitive to temperature. For the rearrangement of **24** the best results were obtained when the reaction was carried out above the solvent boiling point, at 110°C (entry **3, Table 10**). Under this condition *cis*-**24a** was isolated as a single diastereoisomer in 76% yield.

Table 9. ***Microwave Assisted Rearrangement of fluoro isoxazolines to aziridines: Solvent study (24 to cis24a/trans 24b)***

Entry[a]	Solvent	*Cis***24a**/*Trans***24b**[b]	Conversion[c] (%)	Transformation[d] (%)
1	CH_3CN	97/3	50	34
2	toluene	85/15	22	20
3	water	77/23	60	53
4	DMF	90/10	38	36
5	DMSO	87/13	68	49
6	EtOH	80/20	39	30
7	Neat		degradation	

[a]Reaction conditions: 1 mmole, 5 min
[b, c]Determined by ^{1}H NMR of crude product.
[d]Isolated yield (degradation product)

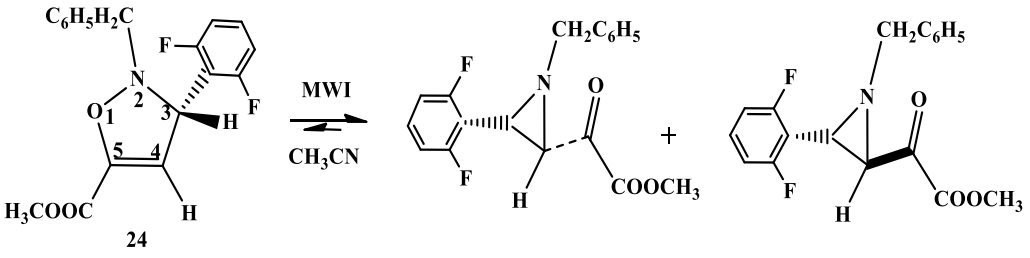
At 90 °C a slow conversion was observed (entry **1**, **Table 10**), while from 120 ^{0}C to 130 °C, product decomposition is detrimental to the transformation (entries **4** and **5**).

Table 10. ***Microwave Assisted Rearrangement of 24 to Cis/trans 24a/24b in CH_3CN: Time and temperature study***

Entry	Time (min)	T (^{0}C)	*Cis***24a**/*Trans***24b**[a]	Conversion[b] (%)	Transformation[c] (%)
1	5	90	97/3	8	16
2	5	100	95/5	18	14
3	5	110	97/3	40	15
4	5	120	94/6	75	61
5	5	130	97/3	97	68
6	10	90	97/3		60
7	15	110			73

[a,b]Determined by ^{1}H NMR of crude product.
[c]Product percentage determined by ^{1}H NMR of crude product

General experimental procedure for the synthesis of new fluoro aziridine derivatives (cis24a & trans 24b) under microwave irradiation:



Scheme 25 ***Cis* 24a** ***Trans* 24b**

Isoxazoline **24** (1.5 mmol, 535 mg) was dissolved in acetonitrile (12 mL) and was heated in a sealed tube at 110 ^{0}C for 5 minutes under microwave irradiation (400 W, temperature-controlled mode). The resulting reaction mixture was concentrated under vacuum and the crude product was directly purified by column chromatography (separation of diastereomers) on silica gel (ethyl acetate/hexane) to afford *N*-substituted aziridines **24a** (*cis isomer*; 359.7 mg, 76%) and **24b** (*trans isomer* 12%) as yellow gummy mass.

Fluoro aziridine 24a (cis isomer): methyl 2-((2R,3R)-1-benzyl-3-(2,6-difluorophenyl)aziridin-2-yl)-2-oxoacetate

Yellow gummy mass. Yield 76%; R_f = 0.66; IR (KBr): υ_{max} 3010 (m), 2970 (m), 2246 (m), 1740 (s), 1710 (s), 1690 (s), 1474 (s), 1440 (m), 1324 (m), 1176 (s), 782 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.87 – 7.80 (m, 3H, $C_6H_3F_2$), 7.68-7.31 (m, 5H, C_6H_5), 4.24 (d, *J* = 7.90 Hz, 1H), 4.12 (d, *J* = 7.90 Hz, 1H), 3.38 (s, 3H, -$COOCH_3$), 2.68 (s,2H, $C_6H_5CH_2$); ^{13}C NMR ($CDCl_3$): δ 173.52 (-C=O), 168.52 (-$COOCH_3$), 137.20, 137.04, 136.87, 136.66 (aromatic carbons), 132.77, 132.35, 132.08, 131.78, 130.80, 129.90 (2,6 difluoro phenyl carbons), 36.80 (benzylic carbon), 31.54, 30.44 (aziridine ring carbons), 18.42 (-$COOCH_3$); EI - MS (*m/z*): 331 (M^+), 330, 272, 244 (B.P), 218, 113, 87, 59. Anal. Calcd. for $C_{18}H_{15}O_3F_2N$: C, 65.26; H, 4.56; N, 4.22. Found: C, 65.13; H, 4.41; N, 4.15%.

Fluoro aziridine 24b (trans isomer): methyl 2-((2R,3S)-1-benzyl-3-(2,6-difluorophenyl)aziridin-2-yl)-2-oxoacetate

Yellow oil. Yield 12%; R_f = 0.60; IR (KBr): υ_{max} 3014 (m), 2976 (m), 2240 (m), 1744 (s), 1710 (s), 1685 (s), 1470 (s), 1440 (m), 1320 (m), 1172 (s), 780 (s) cm^{-1};

^{1}H NMR ($CDCl_3$): δ 7.80 – 7.72 (m, 3H, $C_6H_3F_2$), 7.60-7.43 (m, 5H, C_6H_5), 4.15 (d, *J* = 4.20 Hz, 1H), 4.06 (d, *J* = 4.20 Hz, 1H), 3.30 (s, 3H, -$COOCH_3$), 2.70 (s,2H, $C_6H_5CH_2$); ^{13}C NMR ($CDCl_3$): δ 174.28 (-C=O), 170.40 (-$COOCH_3$), 135.73, 135.60, 135.46, 135.54 (aromatic carbons), 133.69, 133.26, 132.78, 132.45, 132.23, 131.93 (2,6 difluoro phenyl carbons), 34.55 (benzylic carbon), 32.27, 31.17 (aziridine ring carbons), 18.24 (-$COOCH_3$); EI - MS (*m/z*): 331 (M^+), 330, 272, 244 (B.P), 218, 217, 113, 87, 59. Anal.Calcd. for $C_{18}H_{15}O_3F_2N$: C, 65.26; H, 4.56; N, 4.22. Found: C, 65.07; H, 4.36; N, 4.08%.

Expected mass fragmentation peaks were obtained in the mass spectral studies. These peaks are due to the development of aziridine derivatives. Prominent base peaks were obtained due to loss of $COOCH_3$ for methyl propiolate, $COOCH_2CH_3$ for ethyl propiolate and COOH for propiolic acid respectively. In all the cases, the initial progress of the conversions to aziridine derivatives were monitored by TLC (R_f values were found to have lower values than isoxazoline derivatives). In the ^{1}H NMR spectrum, prominent signals of R, R^1, R^2 and R^3 groups of the aziridine derivatives were obtained while excellent carbonyl absorptions were noted in IR spectrum as well.

Interpretation of mass spectra

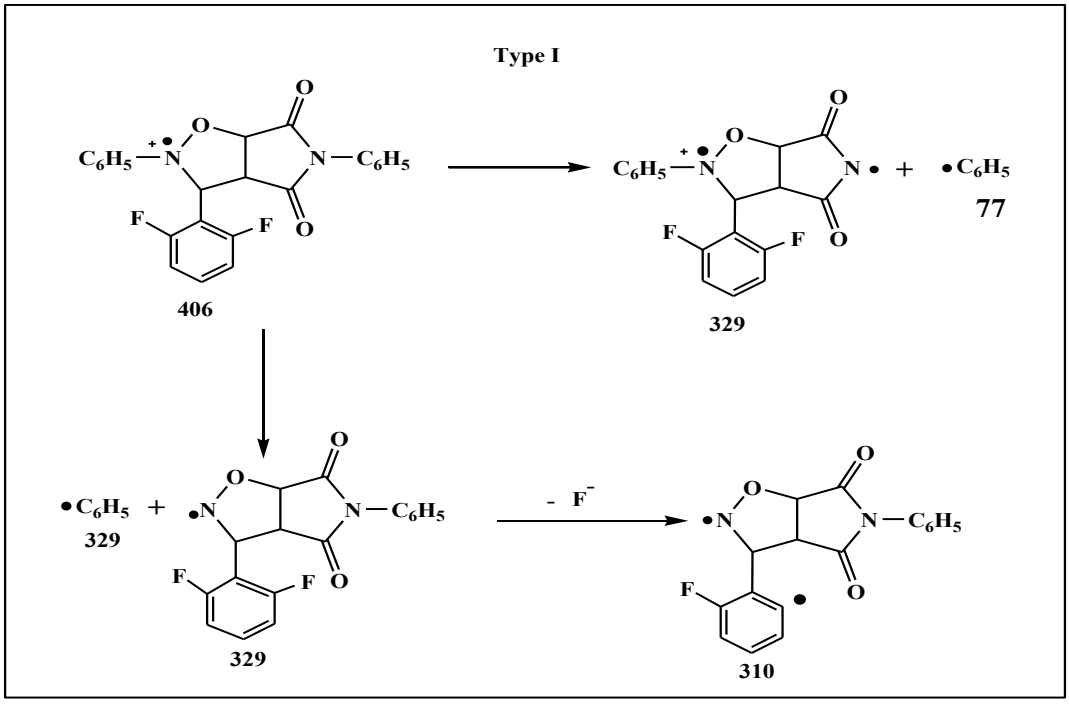
In the case of *N*-benzyl-fluoro nitrone, all the cycloadducts formed possess 2-benzyl-3-(2,6-difluoro)-phenyl-1,2-isoxazolidine moiety in common. On electron impact, mass fragmentation of a molecule would generate generally a radical ion and expectedly one of the non bonding electrons of the nitrogen atom of 1,2-isoxazolidine ring would be removed as the nitrogen atom is tertiary in nature.

Taking *N-phenyl maleimide* cycloadduct as an example in 1,3-dipolar cycloaddition reaction, a general scheme was formulated (**Type I**). The fragmentation pattern of all the maleimide cycloadducts were discussed in the light of this fission pattern.

Mass fragmentation pattern of fluoro cycloadducts derived from N-benzyl-fluoro nitrone

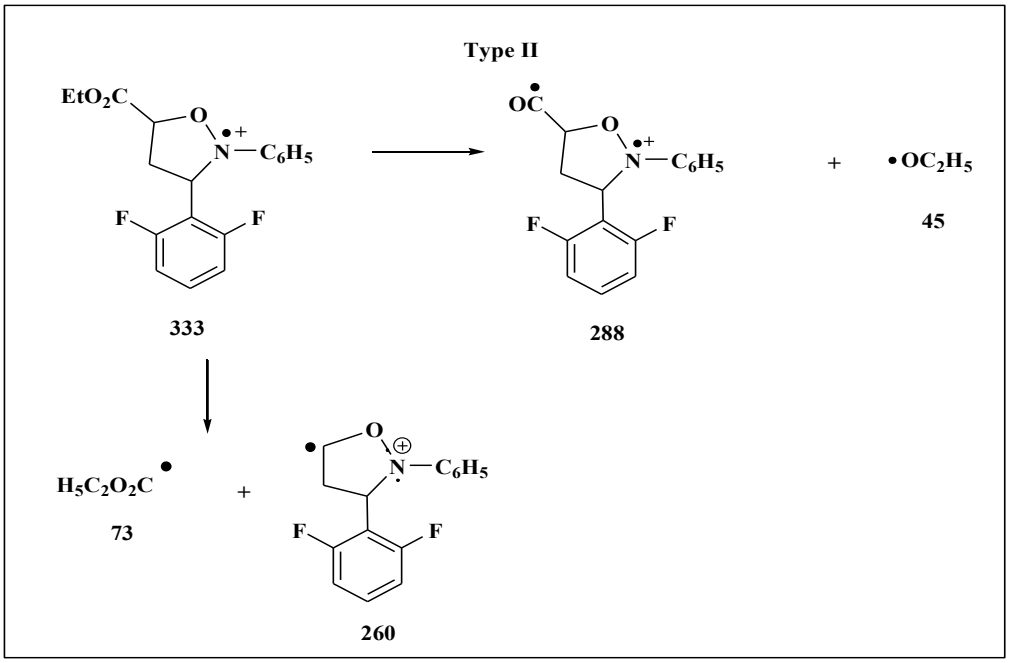
Type I: ***Fluoro-maleimide isoxazolidines***

In the mass fragmentation pattern of maleimides (*N*-phenyl, *N*-ethyl, *N*-methyl etc.) in addition to the common expected fragments, other prominent peaks at *m/e* = 77, 15 for phenyl, methyl were also obtained.



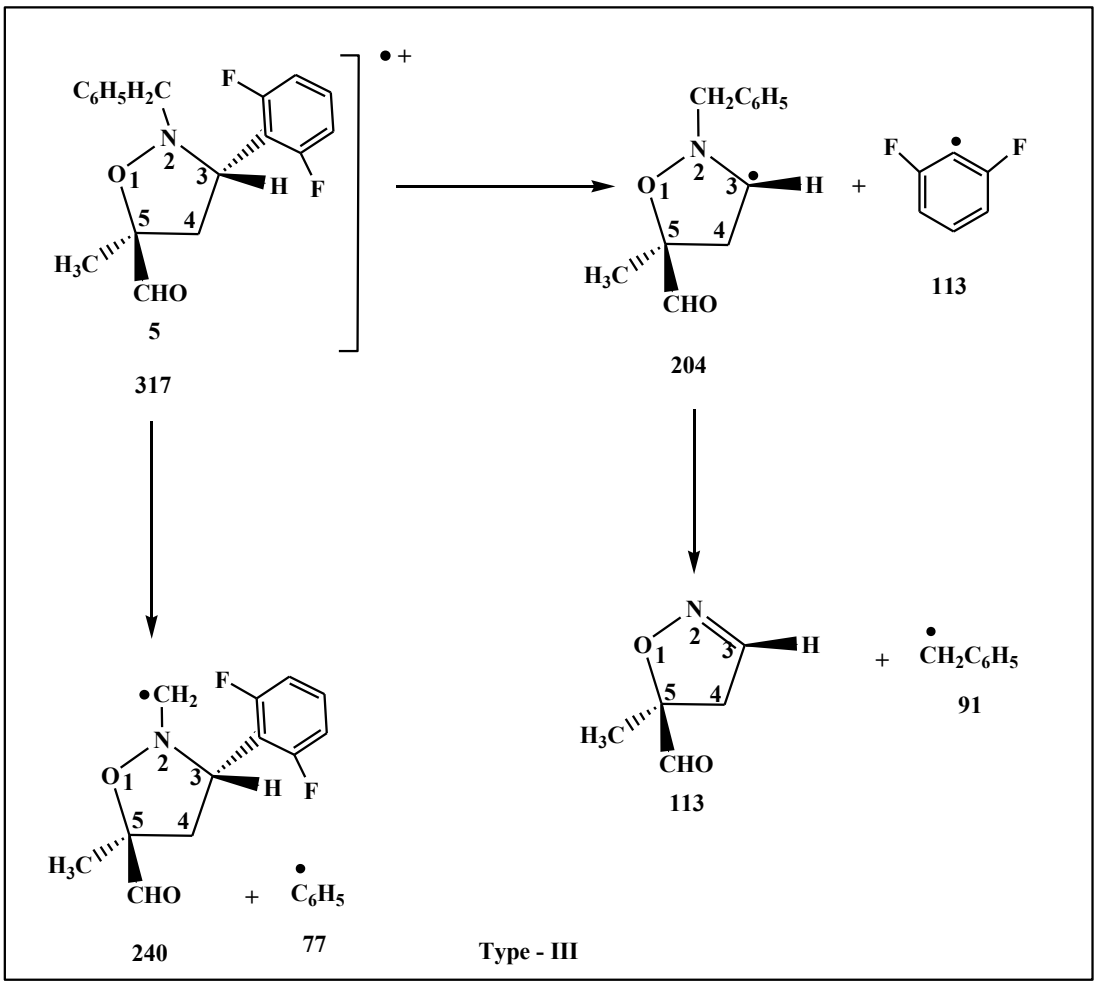
Type II: ***Fluoro-acrylate isoxazolidines***

The fragmentation pattern of ethyl acrylate cycloadduct followed the general pattern with some typical peaks *i.e.* CH_3-CH_2-O (45), CH_3-CH_2-COO (73) shown in **Type II**.



Type III: ***Fluoro-methacrolein isoxazolidines***

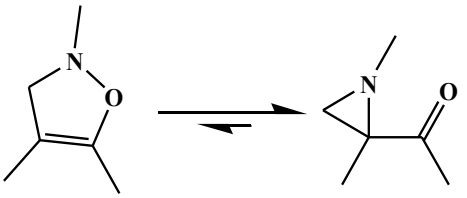
The fragmentation pattern of methacrolein cycloadducts have been explained in **Type III.**



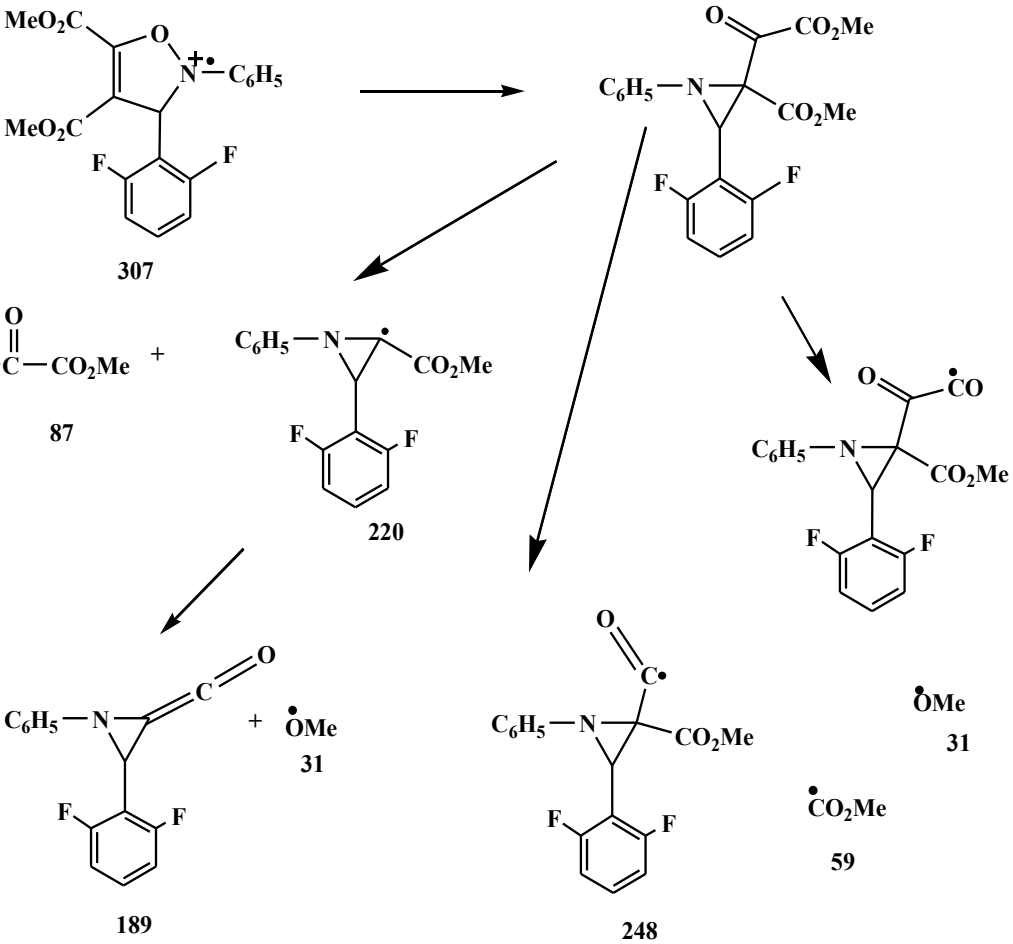
Type IV: Fluoro isoxazoline derivatives

The mass fragmentation pattern of acetylinic cycloadducts is completely different and they are explained in **Type IV.** Expected fragmentation peaks in the mass spectrum are obtained which are due to the development of *aziridine derivatives*. Prominent base peaks are noted and are due to the loss of $COOCH_3$ for dimethyl acetylene dicarboxylate, methyl phenyl propiolate, COOH for acetylene dicarboxylic acid and $COOCH_2CH_3$ for ethyl propiolate respectively.

Type IV

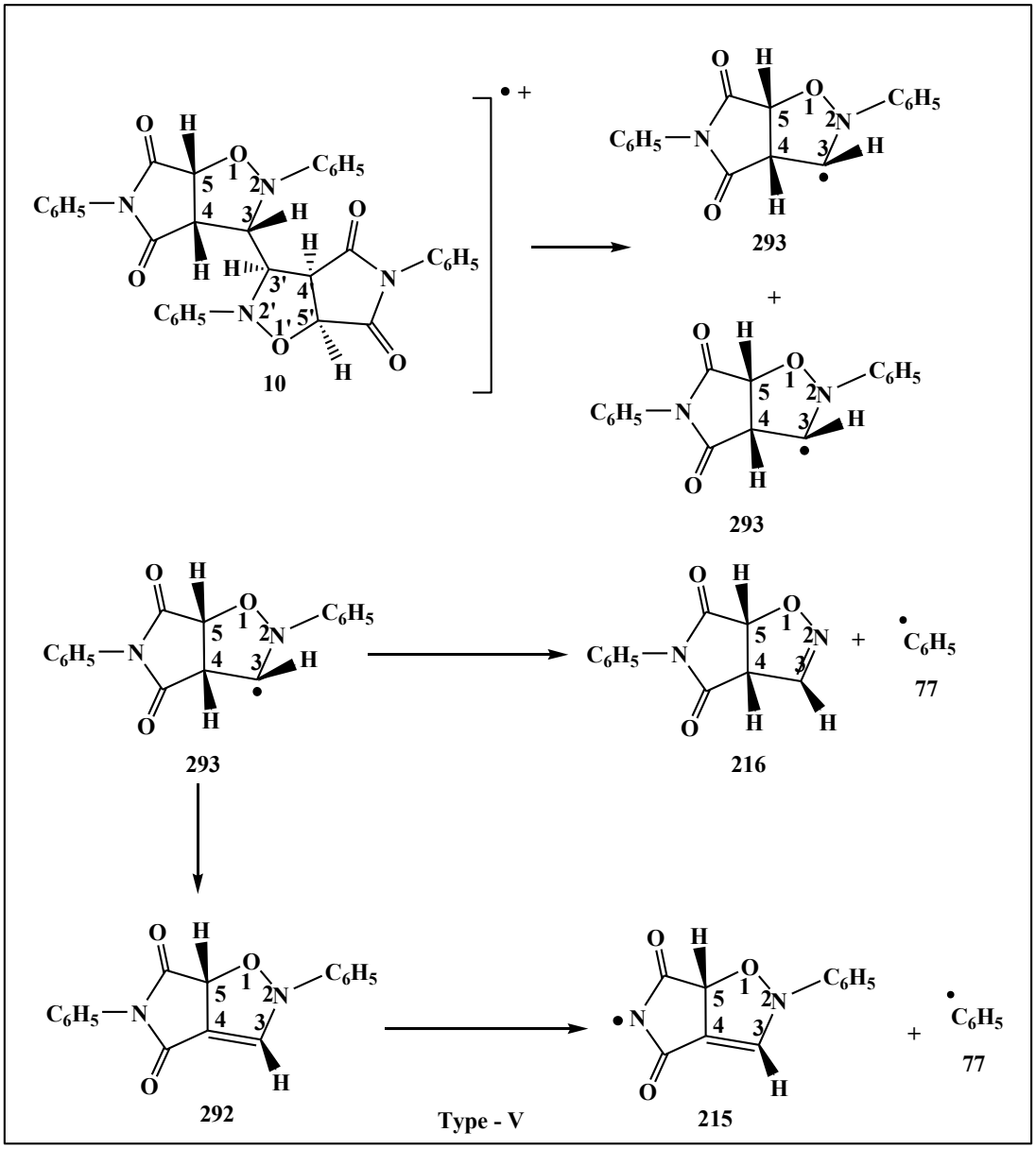


Example with $H_3COOC-C\equiv C-COOCH_3$ **adduct**



Mass fragmentation pattern of bisisoxazolidine derivatives derived from glyoxal derived bisnitrone (maleimide bisisoxazolidines)

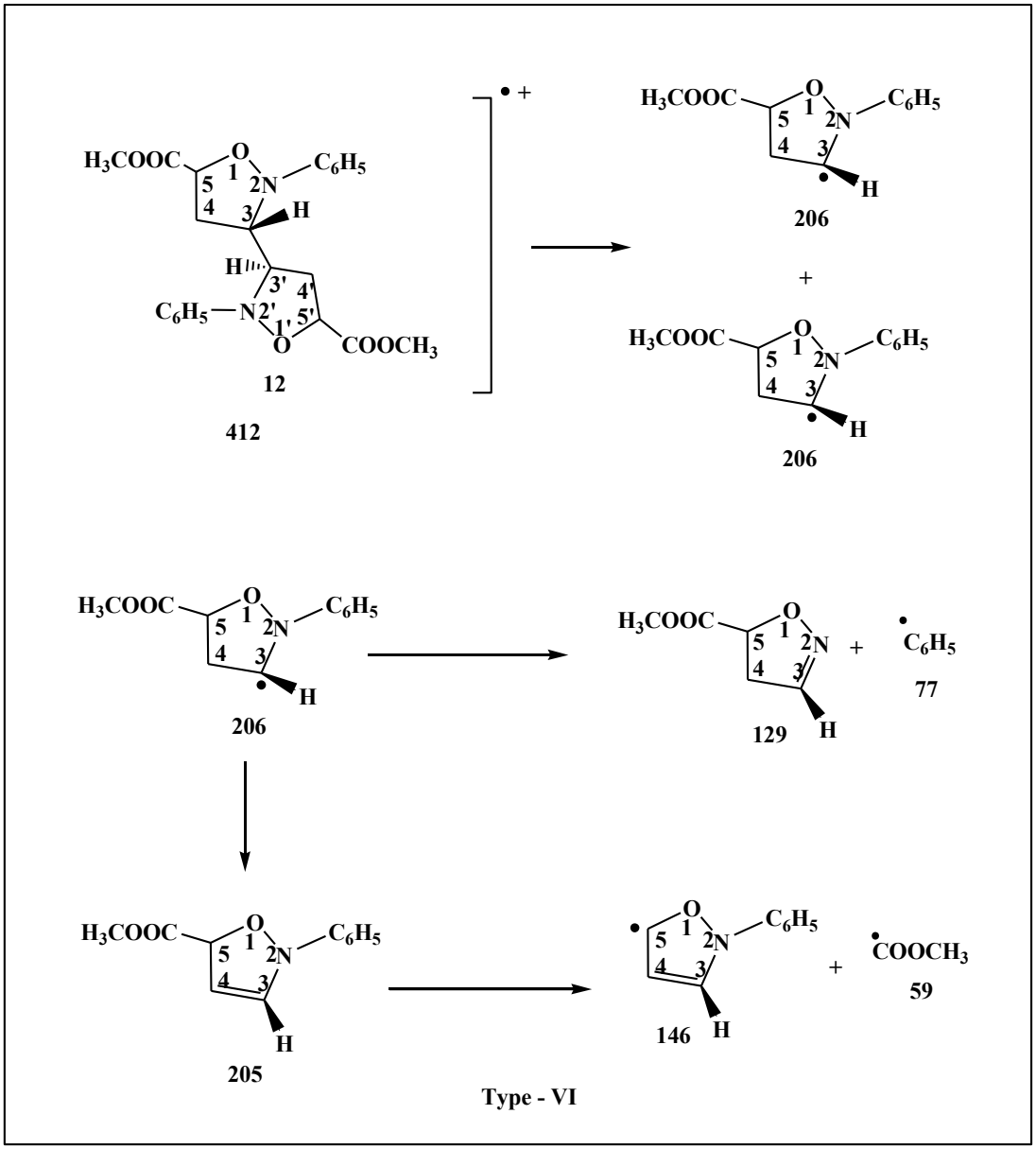
Type V



On electron impact mass fragmentation, the *maleimide bisisoxazolidines* initially develop radical cation which subsequently undergoes cleavage between the C-3 & C-3' carbon atoms. Elimination of phenyl radical and hydride ion are the following significant steps in this fragmentation pattern.

Mass fragmentation pattern of bisisoxazolidine derivatives derived from glyoxal derived bisnitrone (methyl acrylate bisisoxazolidine)

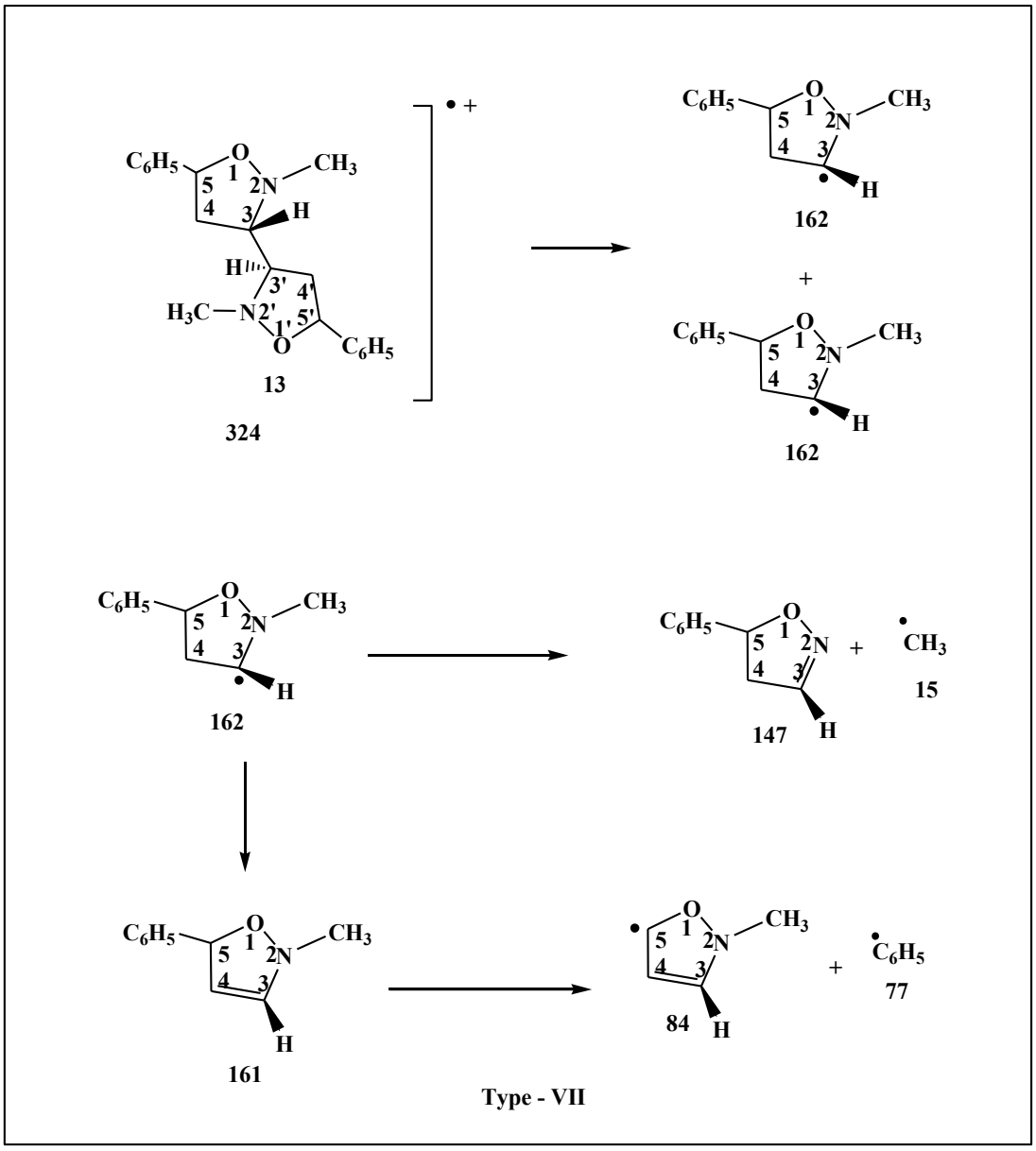
Type VI



On electron impact mass fragmentation, the *methyl acrylate bisisoxazolidine* initially develop radical cation which subsequently undergoes cleavage between the C-3 & C-3' carbon atoms. Elimination of phenyl radical and hydride ion are the following significant steps in this fragmentation pattern. In addition .$COOCH_3$ radical is also expected as fragmentation part.

Mass fragmentation pattern of bisisoxazolidine derivatives derived from glyoxal derived bisnitrone (styrene bisisoxazolidine)

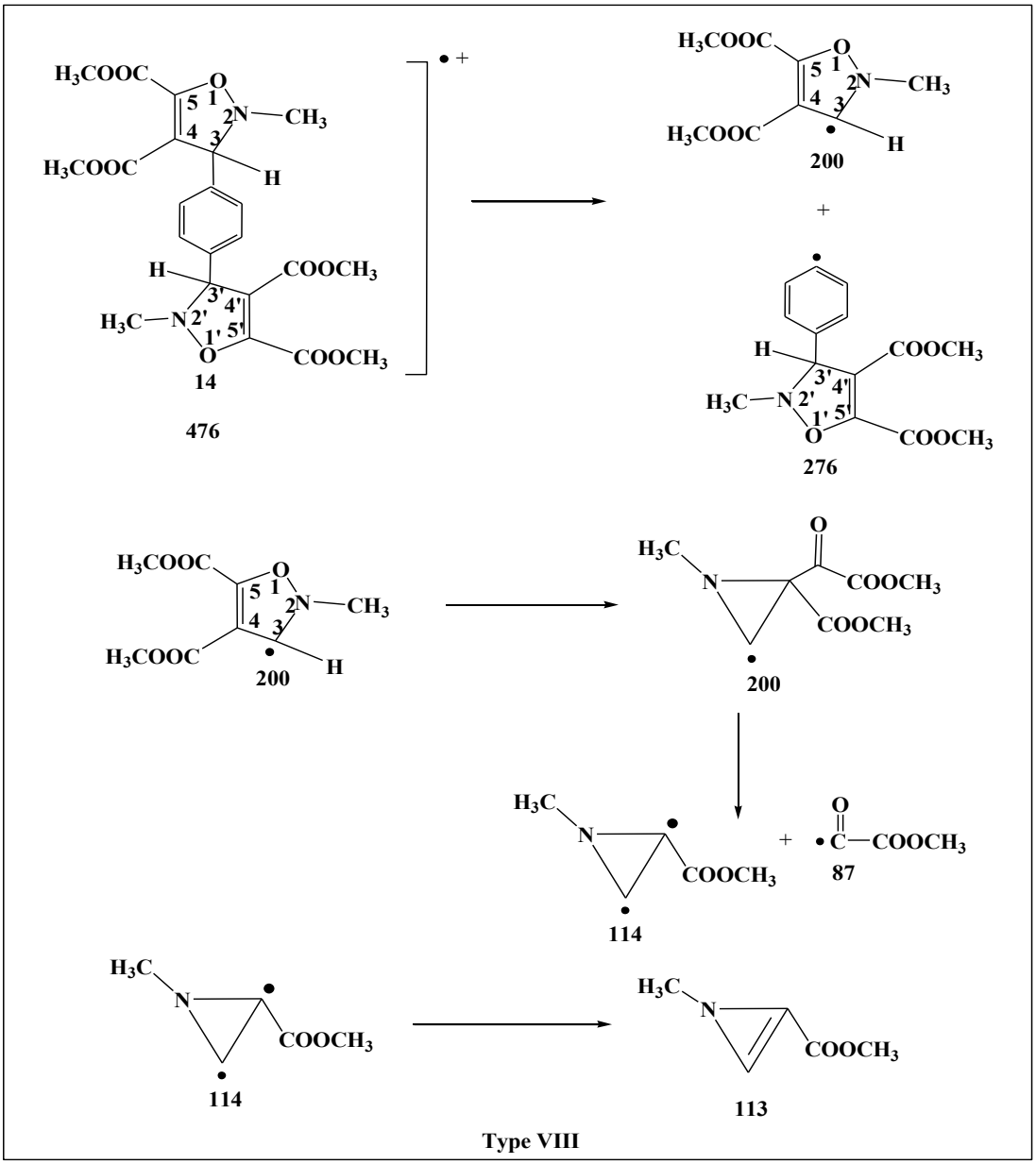
Type VII



On electron impact mass fragmentation, the *styrene bisisoxazolidine* initially develop radical cation which subsequently undergoes cleavage between the C-3 & C-3' carbon atoms. Elimination of phenyl radical and hydride ion are the following significant steps in this fragmentation pattern. In addition, phenyl radical is also expected as fragmentation part.

Mass fragmentation pattern of methyl bisisoxazoline derivatives derived from terepthalaldehyde derived bisnitrone (dimethyl acetylene dicarboxylate bisisoxazoline)

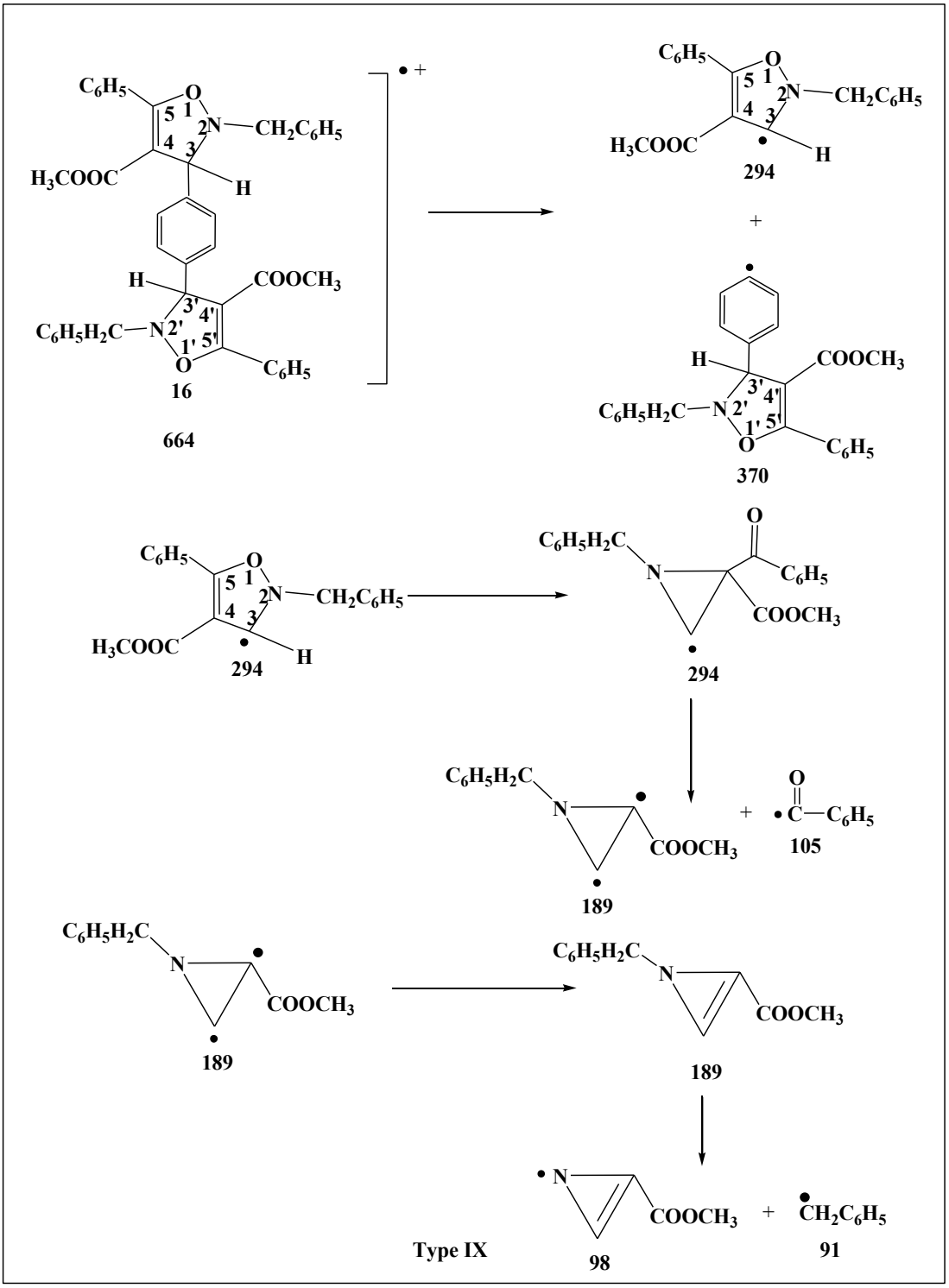
Type VIII



On electron impact mass fragmentation, the *dimethyl acetylene dicarboxylate bisisoxazoline* initially develop radical cation which subsequently undergoes cleavage between the C-3 & phenyl ring linked with second isoxazoline moiety. The isoxazoline moiety without phenyl ring undergoes rearrangement via aziridine ring during fragmentation and the fragmentation pattern is shown in **Type VIII**. The second isoxazoline moiety with phenyl ring follows fragmentation pattern of **Type IV** as shown earlier.

Mass fragmentation pattern of benzyl bisisoxazoline derivatives derived from terepthalaldehyde derived bisnitrone (phenyl methyl propiolate bisisoxazoline)

Type IX



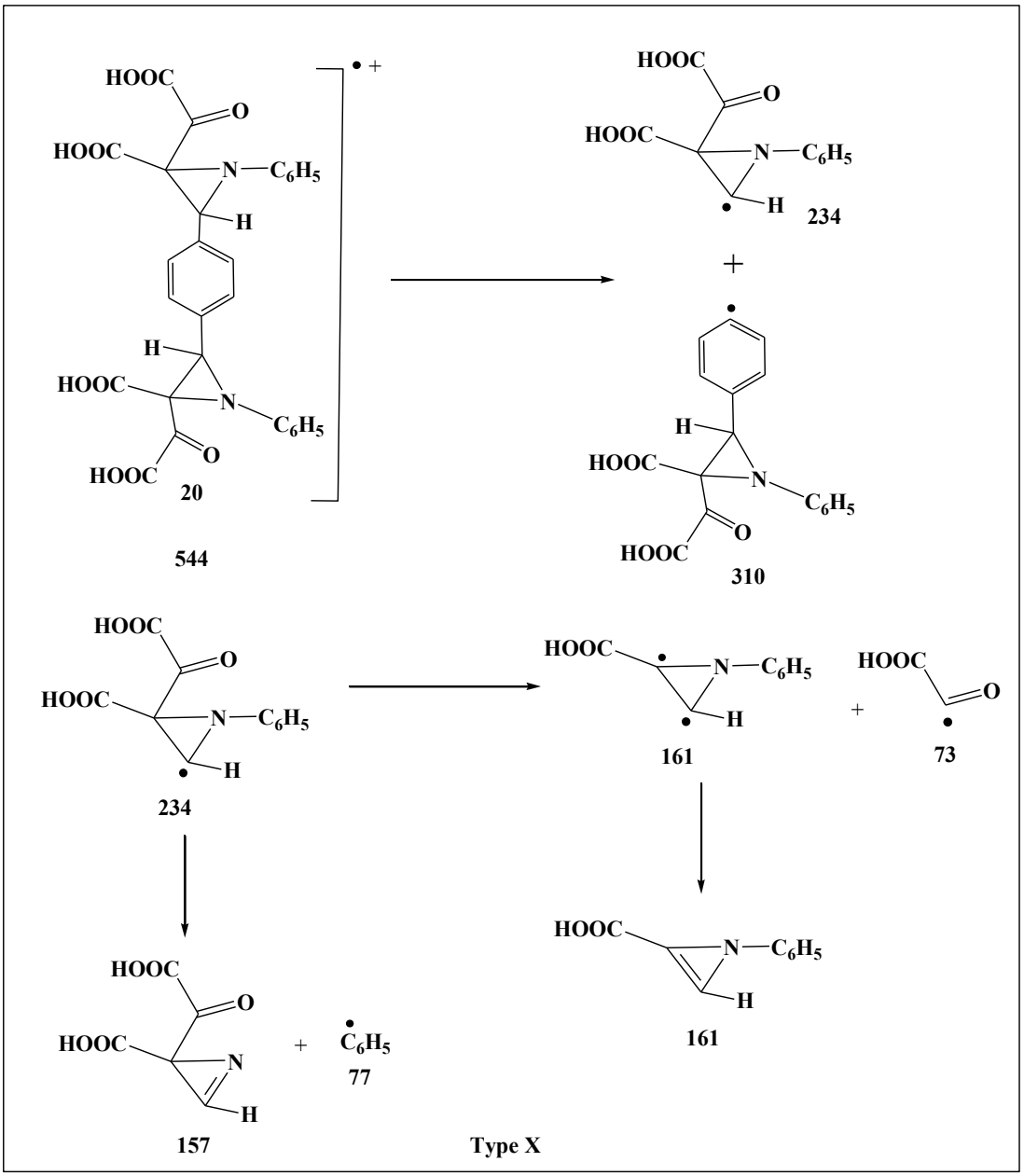
On electron impact mass fragmentation, the *phenyl methyl propiolate benzyl bisisoxazoline* initially develop radical cation which subsequently undergoes cleavage between the C-3 & phenyl ring linked with second isoxazoline moiety. The isoxazoline moiety without phenyl ring undergoes rearrangement via aziridine ring during fragmentation and the fragmentation pattern is shown in **Type IX**. The second isoxazoline moiety with phenyl ring follows fragmentation pattern of **Type IV** as shown earlier. In addition, benzyl radicals are also expected to be obtained during fragmentation.

The mass fragmentation pattern of the remaining bisisoxazoline derivatives (**15, 17 & 18)** derived from terepthalaldehyde derived nitrone follows the same pathway as described in **Type VIII & IX**.

Mass fragmentation pattern of phenyl bisaziridine derivative derived from phenyl bisisoxazoline (terepthalaldehyde derived bisisoxazoline)

Type X

Mass fragmentation pattern of bisaziridines (**19-23**) follows the general mass fragmentation patterns of bisisoxazolines. Taking bisaziridine **20**, the general scheme may be described as follows.



All other bisaziridine derivatives (**19, 21, 22 & 23**) are found to have followed the same fragmentation pattern as evident from their fragmentation peaks obtained.

Interpretation of ^{1}H NMR spectra

On interpretation of ^{1}H NMR spectra of the fluoro cycloadducts (fluoro isoxazolidines), the chemical shifts and the coupling constants for C_5, C_4, C_3 were considered. The *J* value i.e. coupling constant determines the stereochemistry at these positions. In most often cases C_5, C_4, C_3 are asymmetric in nature. In case of diastereomers the products were identified considering the multiplicity of the proton signals at C3-*H* and C4-*H* along with coupling constant values. During the course of the study regarding the *J* values of the fluoro cycloadducts the following representation gives us an idea regarding the stereochemistry of the cycloadducts. Exact stereochemistry of the bisisoxazoline and bisaziridine derivatives could not be assigned due to the absence of adjacent proton with respect to isoxazoline (C_5 & C_4 protons) and aziridine ring protons.

Table 11 (^{1}H NMR values of some C_5H & C_4H protons and coupling constant values in δ ppm): *Fluoro cycloadducts derived from nitrone **1 (N-benzyl fluoro nitrone)** in ionic liquid.*

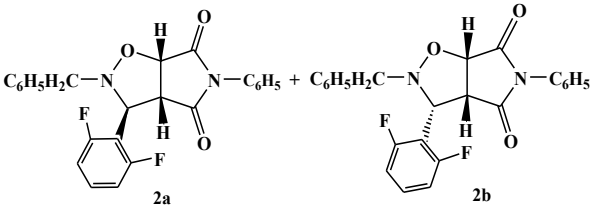
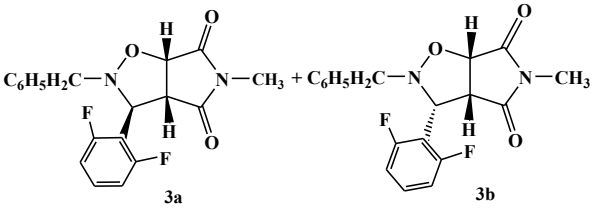
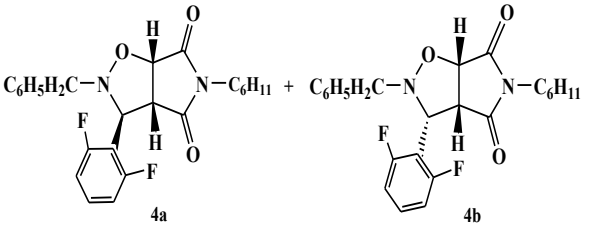
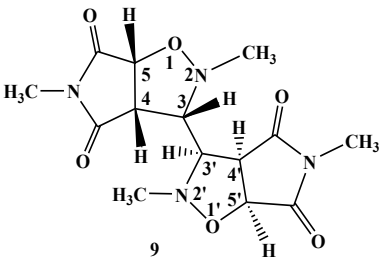
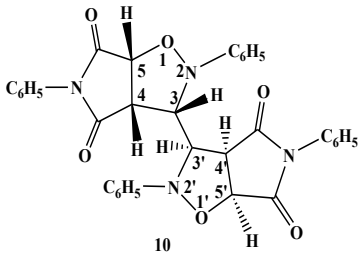
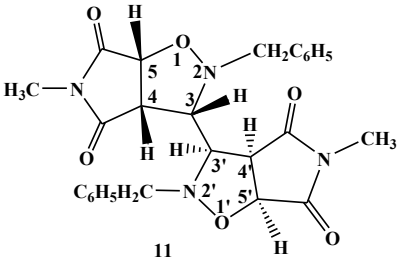
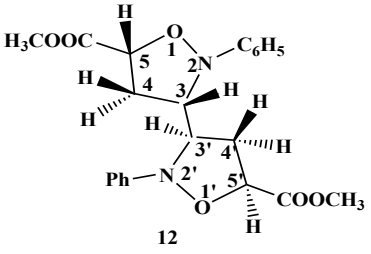
Fluoro isoxazolidines	C_5H [coupling constant values (Hz) in parentheses]	C_4H [coupling constant values (Hz) in parentheses]
 2a + 2b	5.84 (6.70) 5.76 (2.24)	3.40 (6.06, 6.16) 3.63 (2.26, 2.14)
 3a + 3b	6.56 (6.10) 6.52 (3.22)	3.79 (6.00, 5.90) 3.76 (1.96, 2.12)
 4a + 4b	6.30 (6.74) 6.14 (1.88)	3.42 (6.20, 6.10) 3.38 (2.08, 2.04)

Table 12 (^{1}H NMR values of some C_5H & C_4H protons and coupling constant values in δ ppm): *Bis cycloadducts derived from nitrone* ***1a (glyoxal derived)*** *in water.*

Bisisoxazolidines	C_5H coupling constant values (Hz) in parentheses	C_4H coupling constant values (Hz) in parentheses	C_3H coupling constant values (Hz) in parentheses
 9	3.31 (4.06)	2.50 (broad signal, *J* value could not be calculated)	2.85 (4.22)
 10	1.85 (6.0)	2.11 (broad signal, *J* value could not be calculated)	1.67 (6.10)
 11	4.37 (7.16)	2.89 (broad signal, *J* value could not be calculated)	3.24 (7.14)
 12	2.96 (6.32)	3.72 (5.44)	2.59 (6.30)

In our present study nitrone **1** and **1a** exists exclusively in *Z* configuration and *syn* cycloadducts are formed from *Z* nitrone through an *exo* transition state geometry. The relative configurations of C_3, C_4, C_5 protons of the cycloadducts are *syn*, as evidenced by their coupling constant (J ~ 6.06-8.18Hz, for C_4-C_5 & J ~ 6.02-7.50 Hz, for C_3-C_4) values[30,31]. It may be concluded from these J values that the dipolarophiles with *cis* configuration about the double bond gave rise to *cis* adducts and therefore the nitrone additions were stereospecifically *syn* in nature. Considering the multiplicity of the proton signals at C3-H and C4-H and also from their coupling constant values[30,31], the mixture of diastereomers are identified. In the ^{1}H NMR spectrum, the notable differences for the diastereomers are observed especially at the position and multiplicity of the C3-H signal. For the major cycloadducts **2a**–**4a**, coupling constant values between C3-H & C4-H has been calculated as $J_{3,4}$ ~ 6.26 Hz indicating a *cis* relationship between C3-H and C4-H while for the minor cyclo adducts **2b**–**4b**, coupling constant has been measured as $J_{3,4}$ ~ 2.26 Hz indicating a *trans* relationship between C3-H and C4-H[30,31].

From the coupling constant values for *C*-5 proton of the fluoro cycloadducts, we have calculated the dihedral angles between *C*-5 and *C*-4 protons of *N-methyl maleimide, N-phenyl maleimide and methyl acrylate fluoro isoxazolidines* from the standard graph[10,37] (**Figure 40**). From these calculated values and with the assumption that 2-benzyl-1,2-fluoro isoxazolidines will prefer the envelope configuration *N*-benzyl group at equatorial position and 2,6-difluoro phenyl group will also be at equatorial position at *C*-3 (**Figure 41**).

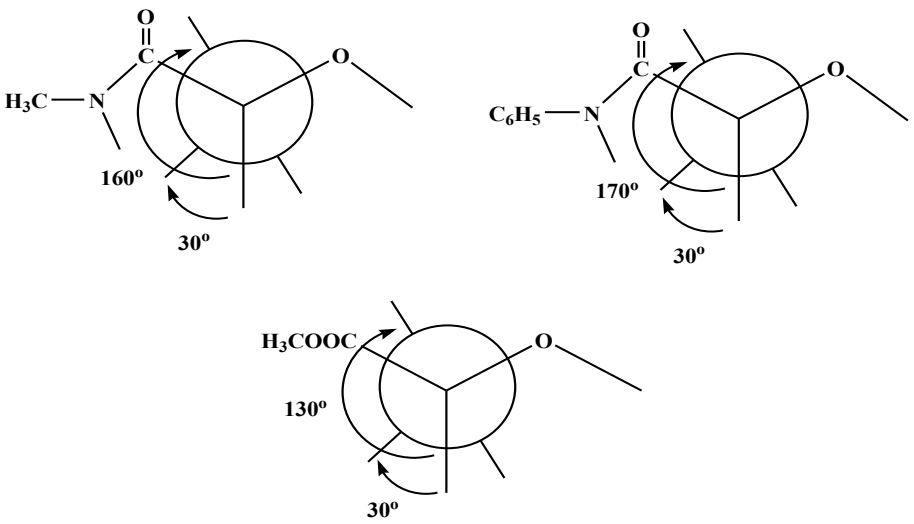


Figure 40 : ***Calculation of the values of dihedral angles between C_5 & C_4 protons in fluoro isoxazolidine derivatives***

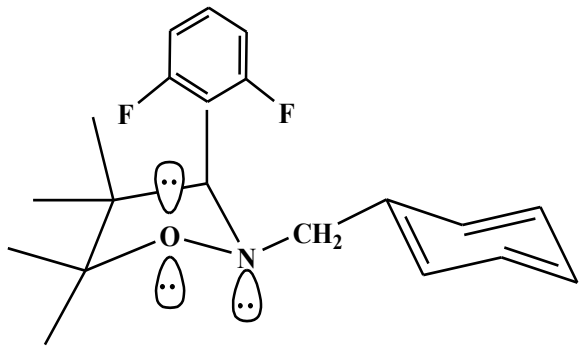


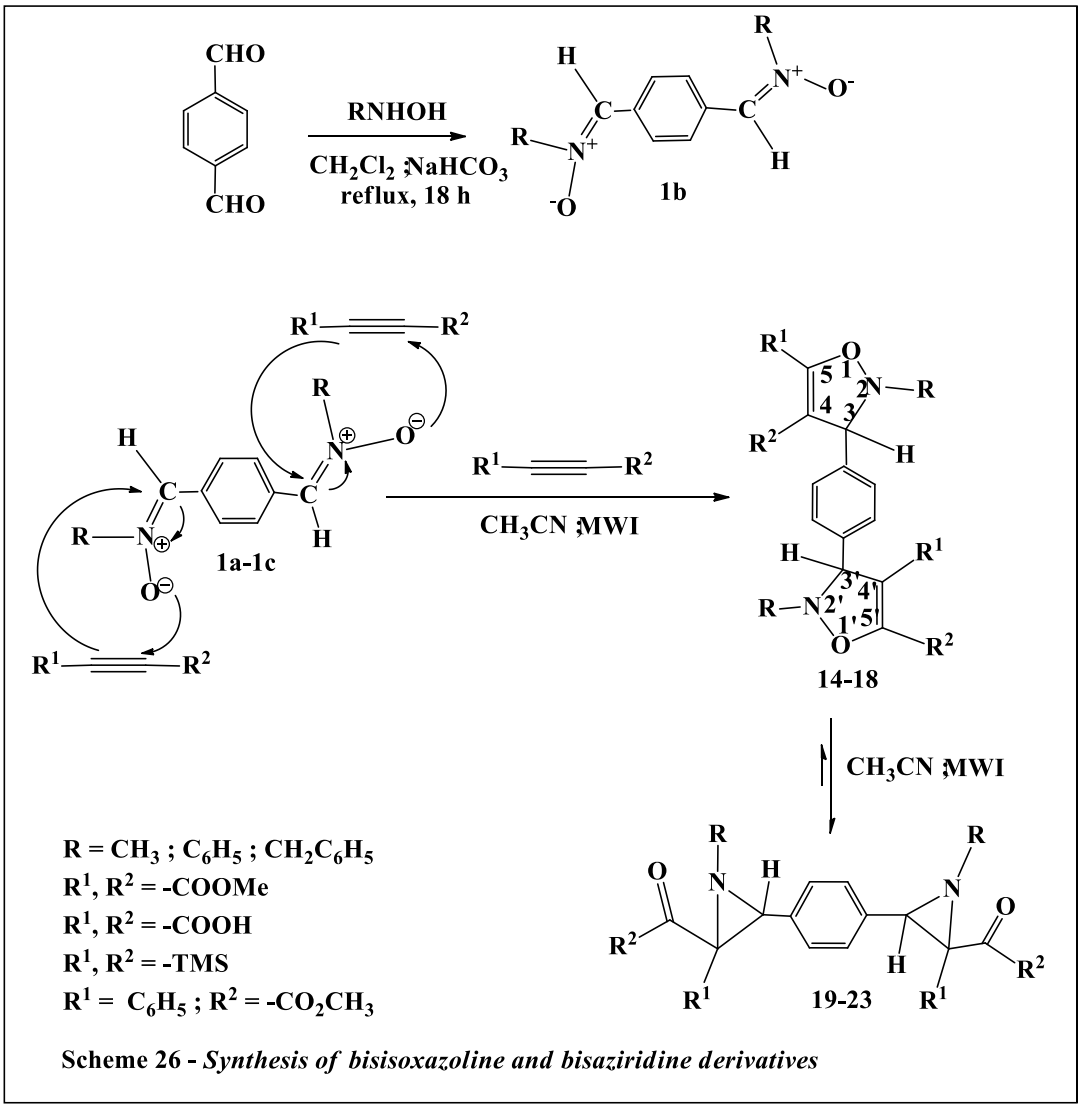
Figure 41: ***Probable conformational structure of fluoro isoxazolidines***

From these figures it is clear that the substituent at the *C*-3 position tries to have an equatorial position as well as the substituent at the *C*-5 position from the quasi equatorial position of the envelope form. As a result the 1,2-isoxazolidine conformation shifts from envelope to half chair form depending upon the bulkiness of the *C*-5 substituent (**Figure 41**).

This indicates that in the reported fluoro cycloadducts, the *C*-5 and *C*-4 protons couple in the same way and comparison with the corresponding dihedral angles suggests that the angles of the protons are nearly 30°. The normal dihedral angle has been found to be 40-30° as found from dihedral angles reported for the cycloadducts in the literature[10,37].

Diastereoselective reactions of the nitrone **1a** (glyoxal derived bisnitrone) furnished diastereoselective cycloadducts (**9-11**) and are classified as *trans trans* biscycloadducts as the 3-H and 4-H protons on each isoxazolidine ring are *trans* orientated as evidenced from ^{1}H NMR spectroscopy[30,40]. On the other hand, bisnitrones **1a** reacted with methyl acrylate and styrene giving exclusively regioselective bisisoxazolidines (**12-13**). All the novel biscycloadducts (**9-13**) are obtained as diastereoselective and regioselective isomeric forms and stereochemical informations portrayed in the drawing implies relative and not absolute relations[41]. The structures of the diastereoselective and regioselective (*5-substituted*) novel bisisoxazolidine derivatives are confirmed on the basis of ^{1}H NMR spectroscopy[30,40]. It is also evident from the ^{1}H NMR spectrum of the diastereoselective bisisoxazolidines (**9-11**) that the structures are expected to be symmetrical in nature and that C3-H, C4-H are *cis* orientated on both the rings while vicinal coupling constant has been calculated as $J_{3,4} \sim 6.80$ Hz[42].

Important signals of R, R^1 and R^2 of the bisisoxazoline and bisaziridine derivatives were obtained in the ^1H NMR spectrum[30]. ^1H NMR spectrum of the all the synthesized bisisoxazoline and aziridine derivatives showed that the four (4) hydrogen atoms of the phenyl ring (1,4 & 3,5 protons) linked with isoxazoline and aziridine rings are merged and obtained as single singlet signal. Exact stereochemistry of the bisisoxazoline and bisaziridine derivatives could not be assigned due to the absence of adjacent proton with respect to isoxazoline and aziridine ring protons (**Scheme 26**).



Scheme 26 - ***Synthesis of bisisoxazoline and bisaziridine derivatives***

In the cycloaddition reaction of fluoro nitrone **1** with methacrolein, 5-substituted fluoro isoxazolidine is formed. It has been observed that C_3 proton couples with adjacent C_4 protons and exhibits triplet signal. This has been confirmed by considering the signals in the proton NMR spectrum of the cycloadducts. In case of maleimides, it has been observed that double doublet signal for *C*-4 proton was obtained due to further coupling from vicinal protons and doublet signals for *C*-5, *C*-3 protons were obtained due to coupling with adjacent protons. In case of the triple bonded dipolarophiles (acetylene compounds) the explanation is quite simple because C_4 protons and C_5 protons are absent and only C_3 proton cannot determine the stereochemistry. Three (3) new chiral centers are developed in the newly formed cycloadducts (fluoro isoxazolidines) at C_3, C_4, C_5 positions. The relative configurations of C_3, C_4, C_5 protons of the cycloadducts are *syn* and is evidenced by their coupling constant (J ~ 6.06 -8.18Hz, for C_4-C_5 & J ~ 6.02 - 7.50 Hz, for C_3-C_4) values[30].

Important signals of C_3H, C_4H and C_5H protons of both the isoxazolidine rings (*cis, cis*) of the novel bisisoxazolidine derivatives (glyoxal derived) have been found to be merged and obtained as a single signal. Double doublet signal of C_4H protons appeared as broad signal in majority of the novel biscycloadducts and coupling constant values could not be calculated.

Nitrone cycloadditions are believed to be a process with similarity of LUMO and HOMO energies in dipole and dipolarophile. As such both HOMO (dipole) - LUMO (dipolarophile) and LUMO (dipole) - HOMO dipolarophile) interactions are important in determining reactivity and regiochemistry. In these cycloaddition reactions, the *C-C* & *C-O* bond formation in the transition state may not happen in a synchronous manner. The *C-C* bond of isoxazolidine ring is more developed in the transition state than *C-O* bond. This process helps to afford products having *syn* configuration at C_3 & C_4 respectively. In addition to the above explanations, all expected signals are obtained and the values are in good agreement with the reported values found in literature[9,10,37]. Signals of three aromatic protons of the 2,6-difluoro benzene and phenyl protons of the benzyl ring found to appear in aromatic region separately. The four aromatic protons of the terepthalaldehyde phenyl ring are found to be merged and appear separately in the aromatic region of the NMR spectrum.

In the present text, following abbreviations are used for identifying NMR signal.

s = singlet, d = doublet, dd = double doublet, ddd = doublet of double doublet. dt = doublet of triplet, q = quartet, m = multiplet, br = broad

We have maintained the style of representing dinitrone as *bisnitrone* in this dissertation following the first pioneering work on dinitrone by Heaney et al (Ref 40) although researchers have also represented dinitrone as *bis(nitrone)* found in literature from 2010 onwards (Ref 58,59,60 & 5).

Interpretation of ^{13}C NMR Spectra

On exhaustive study regarding ^{13}C NMR spectra of reported fluoro nitrones, bisnitrones and cycloadducts, we have found that in almost all the cycloadducts the expected signals for the carbon atom bonded with nitrone ($CH=N^{+}$) are obtained in the range between δ 140 -142 in ppm while expected signals for *C*-5, *C*-4, *C*-3 carbon atoms of the fluoro isoxazolidine, bisisoxazolidine, bisaziridine derivatives, phenyl and carbonyl carbons are obtained. All the signals are in good agreement with the published research articles found in literature. Remarkably the deviated values for the carbonyl groups are obtained when the carbonyl group is either methyl ester or ethyl ester. The signals obtained for the phenyl carbons of the cycloadducts in most often cases are found to be four (4) ranging between δ 138-120 ppm.

These four signals are due to the fact that 2,6 and 3,5 positions of the phenyl ring are identical positions and give rise to only one signal. When the carbonyl carbon is methyl or ethyl ester absorptions at δ 178-180 ppm are obtained while δ 168-170 ppm are obtained for normal C=O bond absorptions. *C*-5, *C*-4, *C*-3 carbons of the cycloadducts absorb in the range of δ 85-88, δ 50-60 and δ 70-75 ppm respectively with some deviations for some certain biscycloadducts. Although ^{13}C NMR spectra cannot predict the stereochemistry of the cycloadducts but plays an important role for the identification of a particular functional group, specific carbon atoms of the cycloadducts.

Interpretation of other spectra

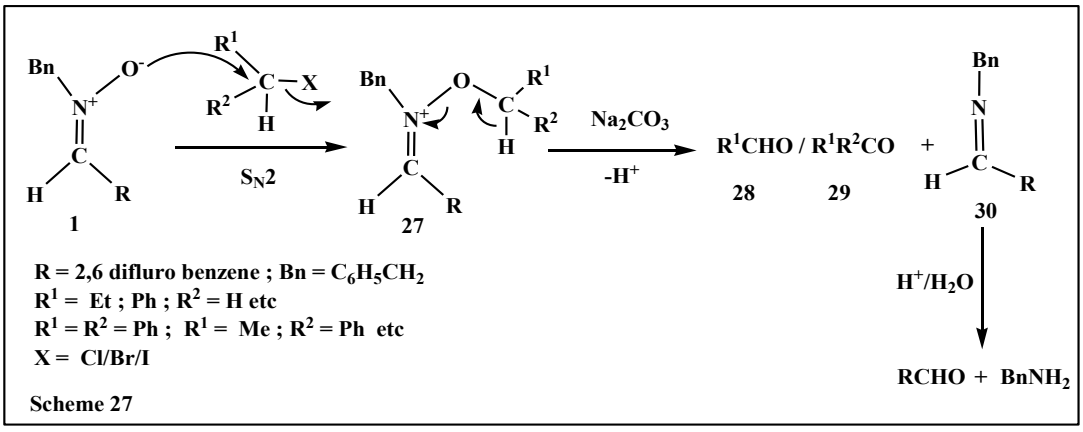
In addition to ^{1}H NMR, MS and ^{13}C NMR spectral study, IR spectral study also have been found to be an important tool for the confirmation of the various functional groups, C-C, C=C, C-N & C-H bonds of the fluoro cycloadducts and biscycloadducts reported in this dissertation. The carbonyl stretching absorption is one of the strongest IR absorptions, and is very useful in structure determination as one can determine both the number of carbonyl groups (assuming peaks do not overlap) but also an estimation of which types. The carbonyl absorptions were obtained around 1680-1740 cm^{-1} depending upon the carbonyl functionality. For example,the IR absorptions of keto group (C=O) of fluoro maleimide cycloadducts and aldehyde group of methacrolein fluoro cycloadducts have been found in the range of 1680-1740 cm^{-1} while IR absorptions of ester carbonyl (COOR) and carboxylic carbons (COOH) are found in the range of 1710-1750 cm^{-1}. The IR absorption bands of C-N-H stretching have been generally obtained around 1240-1320 cm^{-1}.

Sharp singlet absorptions around 750-780 cm^{-1} have been obtained due to phenyl *C-H* bending while aromatic C-H stretching absorptions are found in the range of 3010-3030 cm^{-1}. C-F stretching absorptions have been found in the range of 1000-1350 cm^{-1}. The most important IR absorption band of the fluoro nitrone and bisnitrones ($C=N^{+}$) have been obtained around 1610 cm^{-1}. All the reported IR absorption values in this dissertation are in good agreement with the values reported in literature.

In case of fluoro isoxazoline and bisisoxazoline derivatives, which are comparatively stable than fluoro isoxazolidine and bisisoxazolidine derivatives, study of mass spectrum reveals that prominent molecular ion peak and the base peaks are obtained as expected. The molecular ion clearly indicates the stability of isoxazoline cycloadducts. Base peaks are obtained due to loss of PhCO for phenyl methyl propiolate and $-COOCH_3$ for dimethyl acetylene dicarboxylate cycloadducts for both *N*-benzyl fluoro nitrone and terepthalaldehyde derived bisnitrones respectively.

For few molecules, HRMS spectral analyses were conducted and the results were in good agreement with molecular ion values. Elemental analysis was carried out for almost all the cycloadducts and minimum variation was noticed in the calculated and the analyzed values which also confirms in favour of isolated cycloadducts.

Finally, we have reported an atom efficient *aldehyde and ketone synthesis*[1,2] (**Scheme 27)** using the synthetic potentiality of *N*-benzyl-fluoro nitrone as a potential oxidizing reagent. The side products obtained during the synthesis of the aldehyde & ketones (imines **30)** have been hydrolysed successfully and primary amines are obtained in good yield.



Scheme 27

Biological study of the newly synthesized cycloadducts (fluoro isoxazolidine, isoxazoline derivatives and bisisoxazoline derivatives)

Biological study (*antibacterial, antimicrobial*) on some the newly synthesized fluoro isoxazolidine & isoxazoline derivatives and bisisoxazoline derivatives have been successfully conducted and are found to be active. The *antifungal activity* of the fluoro isoxazolidine and isoxazoline derivatives (**2a, 3a, 3b, 5, 6, 7, 8**) have been assayed *in vitro* at a concentration of 100µg/mL, 200µg/mL, 400µg/mL, 600µg/mL, 800µg/mL and 1000µg/mL by Agar dilution and Broth dilution method against Aspergillus niger, Candida albicans, Candida tropicalis, Cryptpcoccus neoformans, which were maintained on sabouraud dextrose agar slants stored at 4°C. Test drugs (**2a, 3a, 3b, 5, 6, 7, 8**) exhibited considerable *antibacterial and antifungal activity*. Detail studies (using *SEM & TEM*) are now in progress.

Determination of Minimum Inhibitory Concentration (MIC)

All the cycloadducts (**2a, 3a, 3b, 5, 6, 7, 8**) were subjected to in vitro screening against the 14 bacterial strains. Sensitivity test was performed by Agar dilution method and then minimum inhibitory concentration (MIC) of the drugs was determined by Disc Diffusion Method and Broth Dilution Method[64]. Previously prepared drug dilutions (4µg/mL, 8µg/mL, 16µg/mL, 32µg/mL, 64µg/mL, 128µg/mL, 256µg/mL and 512µg/mL) of the fluoro isoxazolidine and isoxazoline derivatives with appropriate antibiotic control (Amoxycillin and Gentamycin) were prepared with Mueller Hinton Agar[65]. For agar dilution assay those cycloadduct plates were spot inoculated (2×106 cfu per spot). A plate without fluoro isoxazolidines or isoxazolines was taken as control (blank) in order to compare the results. The results were then recorded after incubation for 72 hrs at 37ºC. The minimum drug concentration for which no visible growth was observed was considered as the MIC. MIC was determined by Kirby-Bauer disc diffusion method[25] and Broth Dilution Method[64].

Evaluation of Zone of inhibition

Zone of inhibition of test drugs were evaluated by well diffusion methods as per NCCLS protocol (NCCLS, 1993)[65]. 0.1 ml of bacterial suspension was spread on agar plates with sterile spreader to achieve uniform growth. Wells were dug by sterile borer and appropriate concentration of drugs was loaded to the wells. The plates were incubated at 37°C for 24 hrs and clear zone of inhibition around the wells were recorded**.**

Table 2. ***Determination of Minimum Inhibitory Concentration (MIC)***

Name of Organism	MIC values in µg/mL	Name of Organism	MIC values in µg/mL	Name of Organism	MIC values in µg/mL	Name of Organism	MIC values in µg/mL	Name of Organism	MIC values in µg/mL
	2a 4% DMSO	3a 0.17% DMSO	3b 0.17% DMSO	5 0.17% DMSO	6 0.17% DMSO	7 4% DMSO	8 4% DMSO	Amoxy cillin	Genta-mycin
Escherichia coli ATCC 5938	32	128	512	>512	>512	128	16	2	0.25
Klebsiella pneumonia J/	64	64	>512	>512	>512	128	32	4	2
Staphylococcus aureus	32	64	>512	>512	>512	128	64	2	1
Pseudomonas aeruginosa ATCC 27853	64	256	>512	>512	512	64	8	64	2
Vibrio cholerae 14035	32	64	>512	>512	256	128	64	64	0.5
Bacillus subtilis UC 564	64	64	>512	>512	64	32	8	8	4
Shigella dysenteriae 3	64	64	>512	>512	>512	128	16	64	1
Streptococcus faecalis 292	64	128	>512	>512	>512	128	64	64	0.50
Shigella flexneri DN 13	8	16	16	16	32	64	32	32	1
Salmonella typhi DIRW	8	64	16	16	64	256	128	4	1
Vibrio parahaemolyticus 72016	256	256	>512	>512	>512	256	128	16	1
Micrococcus luteus AGD	128	64	>512	>512	>512	512	128	4	8
Salmonella typhimurium	32	64	>512	>512	>512	128	32	8	1
Enterococcus faecalis	64	256	>512	>512	>512	128	32	4	2

Table 4: *Minimum Inhibitory Concentration (MIC) of synthetic compounds against different bacteria*

Organism	Control	Bisisoxazoline & bisaziridines (Drugs in µg/ml)							
		1 (14)	**2 (15)**	**3 (16)**	**4 (17)**	**5 (18)**	**6 (20)**	**7 (21)**	Amoxicillin
Escherichia coli 25938	+	600	600	400	600	+	+	+	25
Salmonella typhi 62	+	600	400	+	400	+	+	600	15
Vibrio cholerae 20	+	600	600	200	600	1000	+	600	25
Klebsiella pneumoniae 1003	+	600	600	+	600	+	+	+	25
Shigella dysenteriae 1	+	800	600	400	600	1000	+	+	1
Pseudomonas AMRI 108	+	600	600	+	600	+	+	+	50
Salmonella typhimurium NTCC 74	+	600	600	600	400	+	+	+	25
Staphylococcus aureus 29737	+	600	600	400	+	1000	+	+	5
Bacillus cereus 11778	+	600	400	600	600	1000	+	+	25
Bacillus subtilis 6633	+	600	600	+	600	1000	+	+	50
Streptococcus epidermidis 12228	+	600	400	600	600	1000	+	+	5
Micrococcus luteus 10240	+	600	600	600	600	600	+	+	1
Pseudomonas aeruginosa 25619	+	600	600	600	400	+	+	+	100
Bacillus pumilus 14884	+	600	600	600	600	1000	+	+	50
Bordetella bronchiseptica 4617	+	600	600	600	600	+	+	+	50

"+" represents growth of organism. Figures in the parenthesis indicate original number of the molecules used in this dissertation.

Determination of killing rate

Antibacterial efficacy of tested compounds were determined by using viable cell count experiments (Rhim et al., 2009)[65]. From the experiment it is clear that the test drugs did not kill the microorganisms completely but significantly reduce the bacterial growth i.e., these drugs have potential bacteriostatic effect. SEM micrographs of few bisaziridines **20 & 21** (**6 & 7, Table 4**) have been found to have potential antimicrobial effects on *B. cereus 11778* and *M. luteus 10240* respectively. It was clear that both the bisaziridine derivatives cleaved the cell surface leading to lyses of cell components into several fragments and thus facilitates rapid killing of cells[66].

From SEM microscopy it is expected that these drugs may act as potential antimicrobial agents. Drug **1** (**Table 4**) kills bacteria by cleaving cell membrane at different junction and leads to cell death. Drug **2** (**Table 4**) changes the cell permeability of bacteria. Due to this change fluids are accumulated within cells and eventually lead to death.

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CHAPTER IV

Scope and objectives

1,3-dipolar cycloaddition reactions are an integral and important part of organic chemistry in pedagogy and research as well. The well described literature on cycloaddition reactions of nitrone and for the synthesis of new isoxazolidine, isoxazoline derivatives and their further functionalizations has been widely illustrated[1,2]. Both the isoxazolidines and isoxazolines may also serve as interesting intermediates for their tranmsformation into *β*-amino alcohols and alkaloids[2,3]. Excellent medicinal activities like antibacterial, antifungal, anticonvulsant, antibiotic and antituberculer activities[4,5] are usually found in both isoxazolidine and isoxazoline derivatives. These wealthy informations were made possible due to the brilliant efforts of some of the eminent scientists in this field *viz* A Padwa[1], S Kobayashi[2], R. Huisgen[3], W.Oppolzer[6], J J Tufariello[7], R Grigg[8], P Deshong[9], S Ali[10], L Fisera[11], V Aggarwal[12] and many more. This chemistry has been also enriched by the contributions of some eminent scientists from our country as well[13,14,15,16]

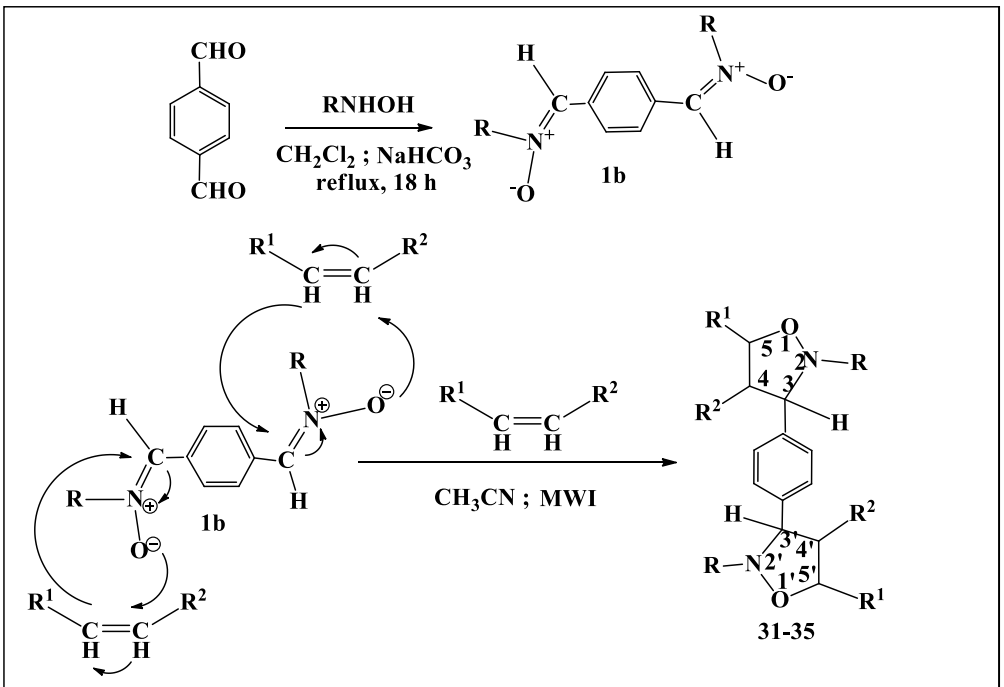
K.N Houk and his co-workers[17] are responsible for the pioneering investigations of regio and stereoselectivity associated with the 1,3-dipolar cycloaddition reactions of nitrone. The discovery of fluoro[18] and chloro nitrone[19] and their cycloaddition reactions paved a new avenue in the nitrone chemistry. The chemistry of α-chloro nitrone was originated and developed by Prof. A. Eschenmoser and his school[19] in the early 70's and developed further by other eminent scientists. Another new vista of the nitrone chemistry is the intramolecular cycloaddition reactions. Such types of reactions have been reviewed by A. Padwa[1] and W. Oppolzer[6]. Due to the vast synthetic potentiality of fluoro and chloro nitrones, a large number of natural products and biologically active products (fluoro isoxazolidine and isoxazoline derivatives) have been synthesized via nitrone routes. A new dimension in nitrone chemistry was invented in early 2000 when Frances Heaney et al reported simaltenous double cycloaddition reactions using novel bisnitrones[20]. The synthesis of bisisoxazolidine and bisisoxazoline derivatives are challenging and needs to explore[21-23] especially because conversions of these derivatives to aziridines via Baldwin rearrangement are found to have vast synthetic potential in this chemistry[24-26]. Therefore the scope of the nitrone chemistry is abundant.

In this dissertation, we have tried to contribute some new features to the synthetic organic chemistry fraternity. This includes synthesis and cycloaddition reactions of new *N-benzyl-fluoro nitrone* and its application in atom efficient synthesis of *aldehydes and ketones*. Therefore, this reaction may be generalized and nitrones may be employed as potential oxidizing reagents in the synthesis of a variety of aldehydes and ketones.

In addition, we have added some new flavours in the synthesis of nitrone cycloaddition reactions. These include simultenous double cycloaddition reactions of bisnitrones (glyoxal derived bisnitrone & terepthalaldehyde bisnitrone respectively) in aqueous phase and under the application of microwave irradiation (MWI). These reactions found to have vast synthetic potential as the bisisoxazoline derivatives could be converted into synthetically more important bisaziridine derivatives and thereby showing a new pathway for the future chemists interested in this chemistry.

Future Scopes

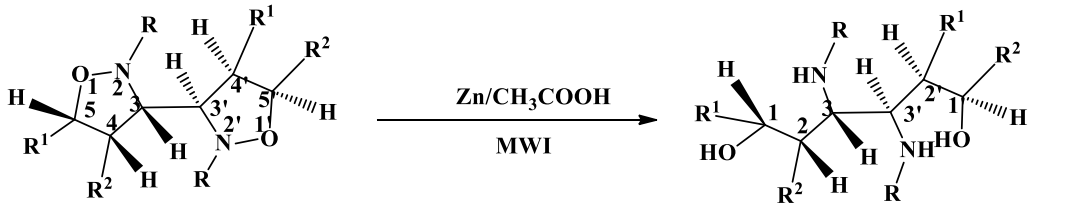
In addition to the reported works presented in this dissertation, we have also started synthesis of bisisoxazolidine derivatives using *terepthalaldehyde derived bisnitrone* (**1b**). The scheme of this synthesis is represented as under:



R = CH_3 ; C_6H_5 ; $CH_2C_6H_5$
R^1, R^2 = -CONMeCO-
R^1, R^2 = -CONPhCO-
R^1, R^2 = -CONCyCO-
R^1 = $COOCH_3$; R^2 = -H

Scheme 28 - Synthesis of bisisoxazolidine derivatives

We have also started the study of synthetic potentiality of glyoxal derived bisisoxazolidine derivatives. Initial study reports suggests that these bisisoxazolidine derivatives (**9-13**) could be converted into *1,3- difunctional amino alcohols* by the reductive cleavage of N-O bond of the isoxazolidine ring (**Scheme 29**). At present studies in this chemistry are in progress.

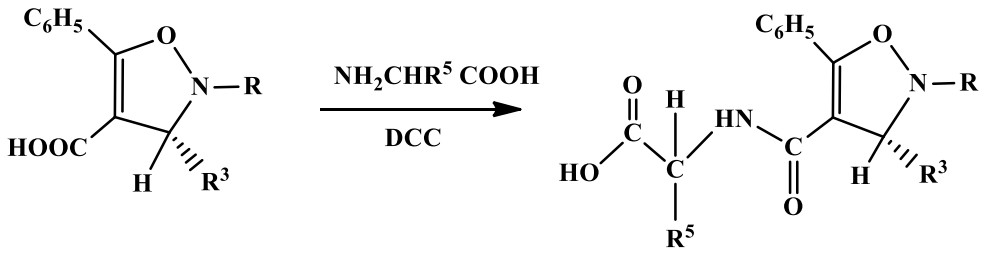


9-13 (Bisisoxazolidine derivatives) **9a-13a(Bis 1,3-amino alcohols)**

Scheme 29. Synthesis of bis 1,3-amino alcohols

Synthesis of Peptides from isoxazoline derivatives

We have also studied synthesis of *peptides* using various isoxazoline derivatives synthesized from the nitrones reported already from our laboratory[27]. We have a plan to synthesize many more *new peptides* using *N-benzyl-fluoro nitrone and bisnitrones* as well (**Scheme 30**).

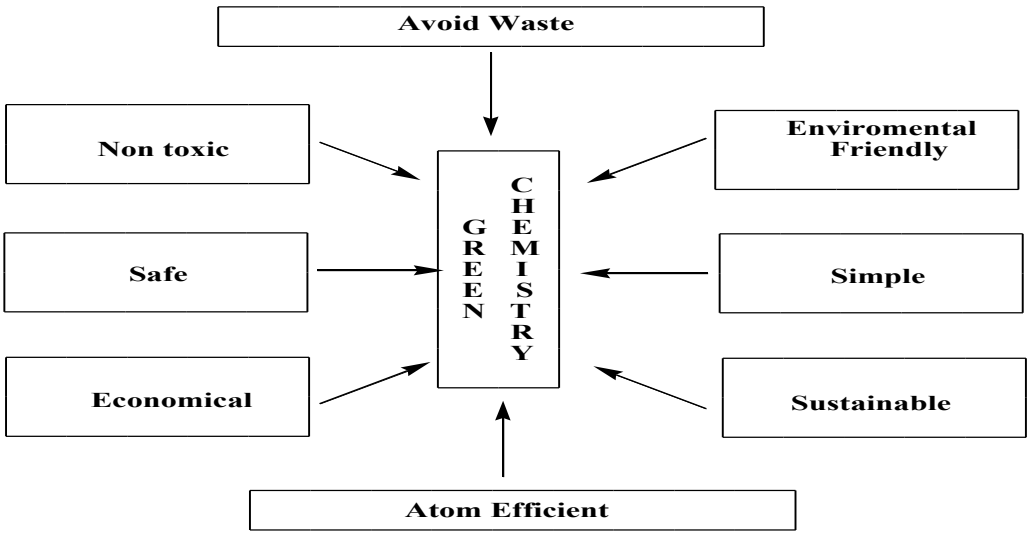


R = $C_6H_5CH_2$
R^3 = 2,6-difluorobenzene

Scheme 30 - Synthesis of peptides using fluoro isoxazoline derivatives

The most important feature of this dissertation is the application of *greener techniques and methodologies* for the synthesis of new fluoro isoxazolidine, isoxazoline derivatives and bisisoxazolidine, bisisoxazoline derivatives via 1,3-dipolar cycloaddition reactions. These include *ionic liquid* mediated cycloaddition reactions, *aqueous phase* synthesis and *microwave irradiated* synthesis. These techniques not only helped us to avoid hazardous solvents (benzene) but also provided us good to excellent yield of the products in a short reaction time.

These methodologies were found completely environment friendly for us and for our society as well. The side product (generally treated as waste) during aldehyde and ketone synthesis (imine derivatives) has been also successfully reused for the synthesis of primary amines and thereby showing another important feature of *green chemistry techniques (atom efficient reactions)*.



In a nutshell, the *salient features* of this dissertation may be summarized as follows:

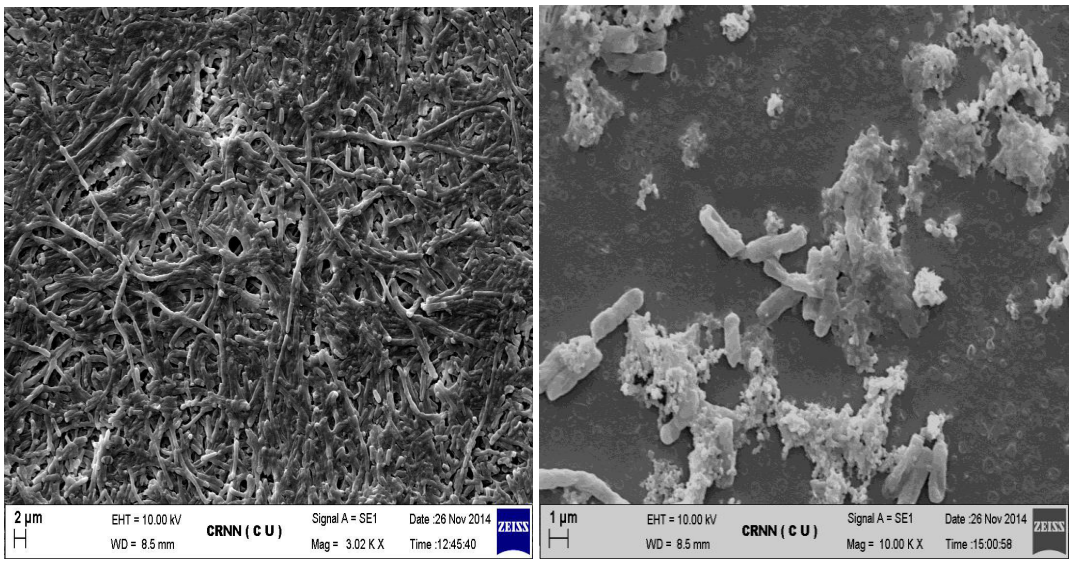
- *Green synthesis of some new class of fluoro isoxazolidine and isoxazoline derivatives via 1,3-dipolar cycloaddition reactions of N-benzyl-fluoro nitrone*
- *Green synthesis of some new class of bisisoxazolidine and isoxazoline derivatives synthesized from glyoxal and terepthalaldehyde derived bisnitrones via 1,3-dipolar cycloaddition reactions*
- *Synthesis of aldehydes and ketones using N-benzyl-fluoro nitrone as potential oxidizing reagent*
- *Successful employment of the side products (obtained during aldehyde and ketone synthesis-imines) in the synthesis of primary amines.*
- *Future scopes for the synthesis of 1,3 amino alcohols from bisisoxazolidine derivatives by the reductive cleavage of N-O bond of isoxazolidines.*
- *Majority of the newly synthesized cycloadducts (mainly fluoroisoxazolidine and isoxazoline derivatives) are found to be biologically active (antibacterial and antimicrobial activities)*

Future perspectives of biological activity of new fluoro isoxazolidine and isoxazoline derivatives

It has been observed that the majority of the new fluoro isoxazolidine and isoxazoline derivatives have *antibacterial activity* against both *gram positive* (*S. Aureus, B. Subtilis*) and *gram negative* (*E. Coli, S. Flexneri*) bacteria, hence it can be concluded that the derivatives used (**2-6**) may be treated as *Broad Spectrum Antibiotics*[28]. The MIC value obtained for fluoro isoxazolidine derivatives (**2-4**) ranges from 10 µg/ml - 50 µg/ml are very close to the MIC values of most commonly used antibiotics like *Penicillin* (10 units), *Sulphonamide* (300 µg/mL), *Nalidixic Acid* etc and hence they are equally effective and can be prescribed after testing of LD_{50}[29]. Moreover, these fluoro isoxazolidine derivatives may be recommended along with other antibiotics in a very low concentration to get more effective result due to the *synergism* and this may avoid drug resistance. Since all the fluoro isoxazolidine derivatives were soluble in DMSO (percentage varying from 1-4%) we can predict that the derivatives were *hydrophobic* in nature and it may cross the cell wall and cell membrane lipid bilayer.

Morphological studies using scanning electron microscope (*SEM*) and transmission electron microscope (*TEM*) of few fluoro isoxazolidine and isoxazoline derivatives are now going on. Initial results are very encouraging.

Initial study report on the mode of action of synthetic drug (2a) by Scanning Electron microscopy (SEM)



Before treatment with fluo isoxazolidine **2a** After treatment with fluoro isoxazolidine **2a**

All the nitrone cycloaddition reactions reported in this dissertation indicate that the synthesis is *asymmetric* in nature (C-3, C-4, C-5 asymmetric centres in case of isoxazolidines and C-3 in of case isoxazoline derivatives). Finally, these nitrone cycloaddition reactions are not only synthetically highly important but also opens a new path for the microbiologists as far as their biological activities are concerned to act as *antifungal, antibacterial* and as a whole a broad spectrum antibiotics. Works are in progress to study in the synthesis of functionalized isoxazolidine and isoxazoline derivatives and also the *gastrointestinal tract infection studies* using *N-benzyl-fluoro nitrone*. Synthesis of *new peptides*, *1,3-amino alcohols*, *aziridines* would be of much interest for the future researchers in this field of study in the coming days.

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Synthesis of some novel fluoro isoxazolidine and isoxazoline derivatives using *N*-benzyl fluoro nitrone via cycloaddition reaction in ionic liquid

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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 nitrone derived *in situ* from 2,6-difluoro benzaldehyde and *N*-benzylhydroxylamine, with activated alkenes and electron deficient alkynes to afford enhanced rates and improved yields of novel isoxazolidines and isoxazolines.

Keywords. *N*-Benzyl fluoro nitrone; cycloaddition reaction; fluoro isoxazolidine and isoxazolines; ionic liquid; 1,3-amino alcohol; aldehyde/ketone synthesis.

1. Introduction

The 1,3-dipolar cycloaddition reactions represent a favourite method for the construction of five-membered heterocycles, important frameworks of various natural products.[1] In particular, the 1,3-dipolar cycloaddition reaction of nitrones with alkenes and alkynes afford isoxazolidines and isoxazolines which are interesting intermediates for the synthesis of β-amino alcohols and alkaloids.[2,3] Isoxazolines possess medicinal activities such as antibacterial, anticonvulsant, antibiotic, antitubercular and antifungal activities.[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 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 (figure 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 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 high electronegativity of the halogen, strong C–F bond and similar size of halogen and hydrogen atoms. The presence of a fluoro group due to a low polarizability and high lipophilicity induces a relative metabolic stability and improves the bioavailability of the modified heterocycles compared to its hydrocarbon analogues.[12,13]

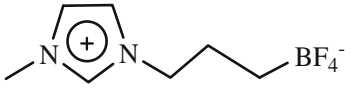
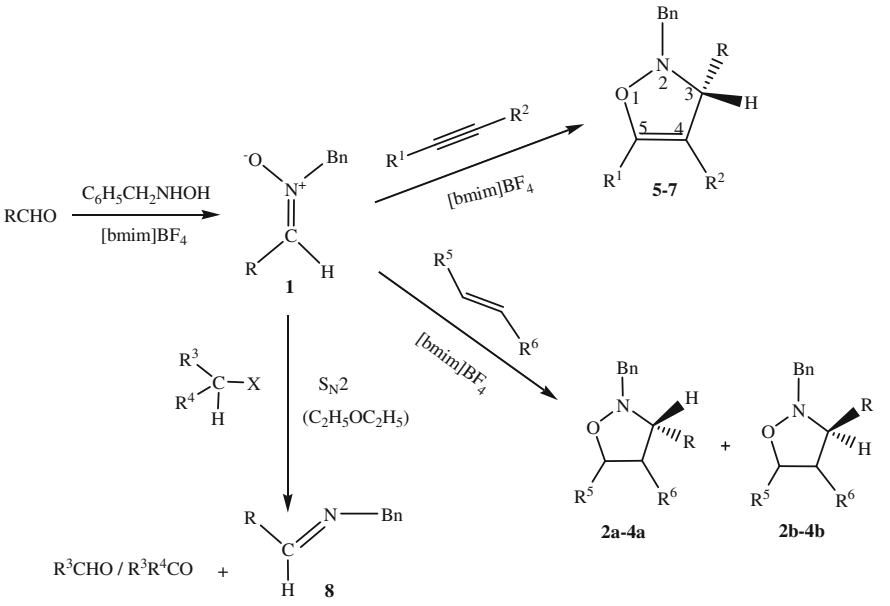


Figure 1. Chemical structure of ionic liquid used in this study.

*For correspondence



R = 2,6 difluro benzene; Bn = $C_6H_5CH_2$
R^1 = Ph; R^2 = $COOCH_3$
R^1 = R^2 = $COOCH_3$
R^1 = R^2 = COOH
R^3 = Et; Ph; R^4 = H etc
R^3 = R^4 = Ph; R^3 = Me; R^4 = Ph
R^5, R^6 = -CONPhCO-; -CONMeCO-; -CONCyCO-

Scheme 1. Synthesis of fluoro isoxazoline and isoxazolidine derivatives using fluoro nitrone and application of the nitrone in atom-efficient aldehyde and ketone synthesis.

In continuation of our effort to establish green methodologies in nitrone cycloaddition reactions,[14–18] herein, we wish to report the use of ionic liquid as recyclable solvent for 1,3-dipolar cycloaddition reactions of *N*-benzyl fluro nitrone (having vast synthetic potentials) with active alkenes and electron deficient alkynes to produce fluoro isoxazolidine and isoxazoline derivatives with vast biological activity in a one-pot operation (scheme 1, table 1). Compared to conventional conditions, cycloaddition reactions performed in ionic liquids are much faster and selective.

Table 1. Physicochemical data of synthesized compounds **2a**–**4a**; **2b**–**4b** and **5**–**7**.

Entry	Nitrone	Dipolarophile[a]	Time (min)	Cycloadduct[b], m.p.(°C), **2a**–**4a**: *cis*; **2b**–**4b**: *trans*	*Cis*/*trans* ratio (%)	Yield[c] (%)
1	*N*-benzyl fluoro nitrone	*N*-phenyl maleimide	26 (12 h)	**2a**: White crystals, 128 **2b**: White crystals, 102	**2a**: 66 **2b**: 22	88 (68)
2	*N*-benzyl fluoro nitrone	*N*-methyl maleimide	30 (13 h)	**3a**: White solid, 135 **3b**: White solid, 120	**3a**: 65 **3b**: 21	86 (66)
3	*N*-benzyl fluoro nitrone	*N*-cyclohexyl maleimide	36 (13 h)	**4a**: Yellow crystals, 142 **4b**: Yellow crystals, 113	**4a**: 63 **4b**: 22	85 (66)
4	*N*-benzyl fluoro nitrone	Methyl phenyl propiolate	26 (17 h)	**5**: Dark red thick liquid		88 (67)
5	*N*-benzyl fluoro nitrone	Dimethyl acetylene dicarboxylate	30 (19 h)	**6**: Red viscous liquid		86 (65)
6	*N*-benzyl fluoro nitrone	Acetylene dicarboxylic acid	32 (18 h)	**7**: Colourless thick liquid		86 (66)

[a]Reaction conditions: nitrone (1 mmol), dipolarophile (1 equivalent), [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 by conventional methods

2. Experimental

2.1 *General procedures*

^{1}H nuclear magnetic resonance (NMR) spectra were recorded with a Bruker DRX 300 spectrometer (300 MHz, FT NMR) using tetra methyl silane (TMS) as internal standard. ^{13}C NMR spectra were recorded on the same instrument at 75 MHz. The coupling constants (J) are given in Hz. IR spectra were obtained with a Perkin-Elmer RX 1-881 machine as film or as KBr pellets for all the products. Mass spectroscopy (MS) spectra were recorded with a Jeol SX-102 (FAB) instrument. Elemental analyses (C,H,N) were performed with a Perkin-Elmer 2400 series CHN analyser. All the reactions were monitored by thin-layer chromatography (TLC) using 0.25 mm silica gel plates (Merck 60F_{254} UV indicator), while column chromatography was performed with silica gel (E Merck India) 60–200 mesh. Starting materials and reagents used in the reactions (*N*-benzylhydroxylamine, 2,6 difluoro benzaldehyde) were obtained commercially from Aldrich, Lancaster, and were used without purification, unless otherwise indicated. All other reagents and solvents were purified after receiving from commercial suppliers.

2.1a *General procedure of synthesis of N-benzyl fluoro nitrone (1) in ionic liquid*: 2,6-Difluoro benzaldehyde (1 mmol) and *N*-benzylhydroxylamine (1 equivalent) was added to [bmim]BF_4 (2 mL) in a 10 mL conical flask, mixed thoroughly and stirred at room temperature for 60 min. The formation of nitrone was monitored by TLC (R_f = 0.40). After completion of reaction, the reaction mixture was washed with diethyl ether (3 × 10 mL) and the combined ether extract was concentrated *in vacuo* to obtain nitrone (**1**) as white crystalline solid (m.p 42°C, uncorrected). As the nitrone decomposes at room temperature, *in situ* reactions were performed with alkene and alkynes.

2.1b *Spectroscopic data of nitrone **1***: UV λ_{max} 238 nm; IR (KBr): υ_{max} 3025 (m), 2235 (m), 1680 (m), 1610 (s), 1440 (m), 1154 (m), 784 (s) cm^{-1}. ^{1}H NMR ($CDCl_3$): 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}CNMR ($CDCl_3$): δ 142.04 (CH=N^+), 134.80, 134.34, 134.12, 133.93 (phenyl carbons), 131.60, 130.00, 129.55, 129.46, 128.67, 128.22 (2,6 difluoro phenyl carbons).

2.1c *General procedure of synthesis of novel diastereomeric fluoro isoxazolidine derivatives (**2–4**) in ionic liquid*: *N*-phenyl maleimide (1 equivalent) was added *in situ* at the time of development of nitrone **1** 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, 0.64), the reaction mixture was washed with diethyl ether (3 × 10 mL). The combined ether extracts were concentrated *in vacuo* and the resulting product mixture was directly charged on silica gel column and eluted with a mixture of ethyl acetate:n-hexane (1:8) to afford pure fluoro isoxazolidines **2a** and **2b** (88%, entry 1, table 1, scheme 1). 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. Same methodology was adopted for the synthesis of other novel fluoro isoxazolidine derivatives (entries 2 and 3).

2.1d *2-Benzyl-3-(2,6-difluorophenyl)-dihydro-5-phenyl-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6 a-H)-dione (**2a**)*: White crystals. Yield 66%; R_f = 0.58; IR (KBr): υ_{max} 3020 (m), 2920 (m), 2835 (m), 1758 (s), 1690 (s), 1480 (m), 1346 (m), 805 (s), 770 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.74–7.68 (m, 3H, $C_6H_3F_2$), 7.12–6.83 (m, 2 × 5H, C_6H_5 protons), 5.84 (d, 1H, J = 6.70 Hz, C_5H), 3.40 (dd, 1H, J = 6.06, 6.18 Hz, C_4H), 3.54 (s, 2H, $C_6H_5CH_2$), 2.95 (d, 1H, J = 6.32 Hz, C_3H); ^{13}C NMR ($CDCl_3$): δ 173.42, 173.10 (carbonyl carbons), 138.10, 138.06, 138.02, 137.97, 136.86, 136.81, 136.78, 136.75 (phenyl carbons), 134.34, 134.14, 134.06, 133.76, 133.65 (2,6 difluoro phenyl carbons), 85.22 (C_5), 77.20 (C_3), 58.46 (C_4), 39.55 ($\underline{CH_2}C_6H_5$); FAB-MS: m/z 420 (M^+, 100%), 343, 329, 306, 252, 216 (B.P.), 113, 91, 77; Anal. Calcd. for $C_{24}H_{18}O_3N_2F_2$: C, 68.57; H, 4.28; N, 6.66 %. Found: C, 68.44; H, 4.19; N, 6.52.

2.1e *2-Benzyl-3-(2,6-difluorophenyl)-dihydro-5-phenyl-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6 a-H)-dione (**2b**)*: White crystals. Yield 22 %; R_f = 0.64; IR (KBr): υ_{max} 3010 (m), 2915 (m), 2830 (m), 1764 (s), 1685 (s), 1486 (m), 1340 (m), 864 (s), 783 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.70–7.66 (m, 3H, $C_6H_3F_2$), 7.30–7.12 (m, 2 × 5H, C_6H_5 protons), 5.76 (d, 1H, J = 2.24 Hz, C_5H), 3.63 (dd, 1H, J = 2.26, 2.08 Hz, C_4H), 3.28 (s, 2H, $C_6H_5CH_2$), 3.06 (d, 1H, J = 3.04 Hz, C_3H); ^{13}C NMR ($CDCl_3$): δ 172.40, 172.24 (carbonyl carbons), 137.80, 137.74, 137.72, 137.57, 137.36, 136.34, 136.26, 136.18 (phenyl carbons), 134.80, 134.60, 134.44, 134.22, 134.13 (2,6 difluoro phenyl carbons), 80.65 (C_5), 76.52 (C_3), 57.90 (C_4),

41.24 ($\underline{CH_2}C_6H_5$); FAB-MS: m/z 420 (M^+, 100%), 343, 329, 306, 216 (B.P.), 113, 91, 77; Anal. Calcd. for $C_{24}H_{18}O_3N_2F_2$: C, 68.57; H, 4.28; N, 6.66%. Found: C, 68.49; H, 4.17; N, 6.50.

2.1f *2-Benzyl-3-(2,6-difluorophenyl)-dihydro-5-methyl-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6 a-H)-dione (**3a**)*: White solid. Yield 65%; $R_f = 0.54$; IR (KBr): υ_{max} 3005 (m), 2935 (m), 2820 (m), 1760 (s), 1675 (s), 1465 (s), 1340 (m), 814 (s), 778 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.89–7.86 (m, 3H, $C_6H_3F_2$), 7.64–7.46 (m, 5H, C_6H_5 protons), 6.56 (d, 1H, $J = 6.10$ Hz, C_5H), 3.89 (s, 2H, $C_6H_5CH_2$), 3.79 (dd, 1H, $J = 6.00$, 5.90 Hz, C_4H), 3.49 (s, 3H, N–CH_3), 2.95 (d, 1H, $J = 6.76$ Hz, C_3H); ^{13}C NMR ($CDCl_3$): δ 170.58, 170.50 (carbonyl carbons), 136.44, 136.40, 136.32, 136.25 (phenyl carbons), 132.70, 132.64, 132.51, 132.43, 132.18 (2,6 difluoro phenyl carbons), 82.98 (C_5), 76.66 (C_3), 59.70 (C_4), 39.60 ($\underline{CH_2}C_6H_5$), 37.54 (N–CH_3); FAB-MS: m/z 358 (M^+, 100%), 345, 267, 252, 244, 154 (B.P.), 113, 91; Anal. Calcd. for $C_{19}H_{16}O_3N_2F_2$: C, 63.68; H, 4.46; N, 7.82 %. Found: C, 63.49; H, 4.36; N, 7.57.

2.1g *2-Benzyl-3-(2,6-difluorophenyl)-dihydro-5-methyl-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6 a-H)-dione (**3b**)*: White solid. Yield 21 %; $R_f = 0.60$; IR (KBr): υ_{max} 3015 (m), 2905 (m), 2828 (s), 1760 (s), 1680 (s), 1460 (s), 1355 (m), 820 (s), 783 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.88–7.84 (m, 3H, $C_6H_3F_2$), 7.60–7.49 (m, 5H, C_6H_5 protons), 6.52 (d, 1H, $J = 3.22$ Hz, C_5H), 3.84 (s, 2H, $C_6H_5CH_2$), 3.76 (dd, 1H, $J = 1.96$, 2.12 Hz, C_4H), 3.47 (s, 3H, N-CH_3), 2.96 (d, 1H, $J = 1.96$ Hz, C_3H); ^{13}C NMR ($CDCl_3$): δ 171.34, 171.27 (carbonyl carbons), 135.98, 135.94, 135.82, 135.75 (phenyl carbons), 133.12, 133.04, 132.91, 132.83, 132.77 (2,6 difluoro phenyl carbons), 84.08 (C_5), 73.80 (C_3), 54.95 (C_4), 41.42 ($\underline{CH_2}C_6H_5$), 39.05 (N–CH_3); FAB-MS: m/z 358 (M^+, 100%), 345, 267, 252, 154 (B.P.), 113, 91, 77; Anal. Calcd. for $C_{19}H_{16}O_3N_2F_2$: C, 63.68; H, 4.46; N, 7.82%. Found: C, 63.42; H, 4.32; N, 7.62.

2.1h *2-Benzyl-5-cyclohexyl-3-(2,6-difluorophenyl)-dihydro-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6 a-H)-dione (**4a**)*: Yellow crystals. Yield 63%, $R_f = 0.50$; IR (KBr): υ_{max} 3015 (m), 2900 (s), 2840 (m), 1760 (s), 1674 (br, s), 1470 (s), 1330 (m), 805 (s), 786 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.60–7.56 (m, 3H, $C_6H_3F_2$), 7.17–7.06 (m, 5H, C_6H_5 protons), 6.30 (d, 1H, $J = 6.74$ Hz, C_5H), 3.60 (s, 2H, $C_6H_5CH_2$), 3.42 (dd, 1H, $J = 6.20$, 6.10 Hz, C_4H), 2.83 (d, 1H, $J = 6.76$ Hz, C_3H), 1.95–1.52 (m, 11H, cyclohexyl protons); ^{13}C NMR ($CDCl_3$): δ 168.54, 168.50 (carbonyl carbons), 131.66, 131.60, 131.55, 131.50 (phenyl carbons), 129.15, 129.06, 128.80, 128.73, 128.68 (2,6 difluoro phenyl carbons), 83.60 (C_5), 74.55 (C_3), 58.24 (C_4), 38.78 ($\underline{CH_2}C_6H_5$), 27.40, 27.29, 26.87, 26.70, 26.58, 26.46 (cyclohexyl carbons); FAB-MS: m/z 426 (M^+, 100 %), 343, 335, 312, 252, 222 (B.P.), 113, 91, 83; Anal. Calcd. for $C_{24}H_{24}O_3N_2F_2$: C, 67.60; H, 5.63; N, 6.57 %. Found: C, 67.46; H, 5.35; N, 6.37.

2.1i *2-Benzyl-5-cyclohexyl-3-(2,6-difluorophenyl)-dihydro-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6 a-H)-dione (**4b**)*: Yellow crystals. Yield 22 %, $R_f = 0.62$; IR (KBr): υ_{max} 3010 (m), 2905 (s), 2835 (m), 1764 (s), 1675 (s), 1466 (s), 1336 (m), 815 (s), 783 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.52–7.85 (m, 3H, $C_6H_3F_2$), 7.25–7.14 (m, 5H, C_6H_5 protons), 6.14 (d, 1H, $J = 1.88$ Hz, C_5H), 3.55 (s, 2H, $C_6H_5CH_2$), 3.38 (dd, 1H, $J = 2.08$, 2.04 Hz, C_4H), 2.80 (d, 1H, $J = 1.80$ Hz, C_3H), 1.90–1.38 (m, 11H, cyclohexyl protons); ^{13}C NMR ($CDCl_3$): δ 169.88, 169.83 (carbonyl carbons), 130.54, 130.49, 130.45, 130.32 (phenyl carbons), 128.77, 128.68, 128.56, 128.53, 128.48 (2,6 difluoro phenyl carbons), 80.44 (C_5), 77.50 (C_3), 58.97 (C_4), 37.05 ($\underline{CH_2}C_6H_5$), 25.30, 25.22, 25.17, 25.06, 24.88, 24.76 (cyclohexyl carbons); FAB-MS: m/z 426 (M^+, 100 %), 343, 312, 252, 222 (B.P.), 113, 91, 83, 77; Anal. Calcd. for $C_{24}H_{24}O_3N_2F_2$: C, 67.60; H, 5.63; N, 6.57%. Found: C, 67.37; H, 5.40; N, 6.33.

2.1j *General procedure of synthesis of novel fluoro isoxazoline derivatives (**5–7**) in ionic liquid*: Methyl phenyl propiolate (1 equivalent) was added *in situ* at the time of development of nitrone **1** and the reaction mixture was further stirred at room temperature for an appropriate time (table 1). After completion of reaction, as indicated by TLC ($R_f = 0.66$), the reaction mixture was washed with diethyl ether (3 × 10 mL). The combined ether extract was concentrated *in vacuo* and the resulting crude product was directly charged on silica gel column and eluted with a mixture of ethyl acetate:*n*-hexane (1:8) to afford pure fluoro isoxazoline **5** (88%, entry 4, table 1, scheme 1). 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. Same methodology was adopted for the synthesis of other novel fluoro isoxazoline derivatives (entries 5 and 6).

2.2 *Methyl-2-benzyl-3-(2,6-difluorophenyl-2,3-dihydro-5-phenylisoxazole-4-carboxylate (**5**)*

Dark red thick liquid. Yield 88%; $R_f = 0.66$; IR (KBr): υ_{max} 3010 (m), 2246 (m), 1740 (s), 1710 (s), 1690 (s), 1610 (s), 1480 (s), 1324 (s), 1215 (s), 810 (m), 782 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.87–7.80 (m, 3H, $C_6H_3F_2$), 7.68–7.31 (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 (–$\underline{CO}OCH_3$), 137.20, 137.04, 136.87, 136.66, 135.65, 135.48, 135.20, 134.93 (aromatic carbons), 132.77, 132.35, 132.08, 131.78, 130.80, 129.90 (2,6 difluoro phenyl carbons), 88.16 (C_5), 73.60 (C_3), 58.45 (C_4), 45.17 (–$COO\underline{CH_3}$), 36.80 (benzylic carbon); FAB-MS (*m*/*z*): 407 ($\overline{M^+}$), 330, 294, 211 (B.P.), 203, 113, 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%.

2.2a *Dimethyl-2-benzyl-3-(2,6-difluorophenyl)-2,3-dihydroisoxazole-4,5-dicarboxylate (**6**)*: Red viscous liquid. Yield 86%; $R_f = 0.60$; IR (KBr): υ_{max} 3015 (m), 2250 (m), 1725 (s), 1685 (s), 1610 (s), 1440 (s), 1260 (s), 1225 (s), 805 (m), 780 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.44–7.36 (m, 3H, $C_6H_3F_2$), 7.10–6.98 (m, 5H, C_6H_5), 3.30 (s, 3H, –$COOCH_3$), 3.24 (s, 3H, –$COOCH_3$), 2.55 (s, 2H, $C_6H_5CH_2$), 1.72 (s, 1H, C_3H); ^{13}C NMR ($CDCl_3$): δ 169.74, 169.58 (–$\underline{CO}OCH_3$, carbonyl carbons of the ester group), 135.80, 135.73, 135.54, 135.47 (aromatic carbons), 133.30, 133.28, 133.24, 133.15, 133.12, 133.05 (2,6 difluoro phenyl carbons), 85.25 (C_5), 77.80 (C_3), 56.90 (C_4), 45.74, 44.82 (–$COO\underline{CH_3}$, methyl carbons of the ester methyl group), 39.23 (benzylic carbon); FAB-MS (*m*/*z*): 389 (M^+), 358, 330, 302, 276, 271 (B.P.), 185, 113, 91, 77; Anal. Calcd. for $C_{20}H_{17}O_5F_2N$: C, 61.69; H, 4.37; N, 3.59. Found: C, 61.58; H, 4.26; N, 3.35%.

2.2b *2-Benzyl-3-(2,6-difluorophenyl)-2,3-dihydroisoxazole-4,5-dicarboxylic acid (**7**)*: Colourless thick liquid. Yield 66%; $R_f = 0.66$; IR (KBr): υ_{max} 3010 (m), 2995 (br), 2246 (m), 1760 (s), 1610 (s), 1480 (s), 1324 (s), 1215 (s), 1105 (s), 800 (m), 782 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 10.02 (s, 2H, 2XCOOH), 7.90–7.87 (m, 3H, $C_6H_3F_2$), 7.66–7.44 (m, 5H, C_6H_5), 2.91 (s, 2H, $C_6H_5CH_2$), 2.88 (s, 1H, C_3H); ^{13}C NMR ($CDCl_3$): δ 173.69, 172.04 (carboxyl carbons), 138.50, 138.44, 138.37, 138.26 (aromatic carbons), 135.44, 135.40, 135.28, 134.93, 134.87, 134.75 (2,6 difluoro phenyl carbons), 88.20 (C_5), 74.43 (C_3), 58.60 (C_4), 37.87 (benzylic carbon); FAB-MS (*m*/*z*): 361 (M^+), 344, 316, 288, 271 (B.P.), 248, 157, 113, 91, 77. Anal. Calcd. for $C_{18}H_{13}O_5F_2N$: C, 59.83; H, 3.60; N, 3.87. Found: C, 59.75; H, 3.40; N, 3.58%.

3. Results and discussion

As an example, the reaction between **1** and alkynes, afforded cycloaddition derivative **5** after 17 h in CH_2Cl_2 in 67% yield and 88% yield (entry **4**) in [bmim]BF_4 at room temperature after 26 min, respectively. In a typical procedure, 1 mmol of nitrone was mixed with 1 equivalent of alkynes/alkenes 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 *in situ* and 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 nor selectivity after five cycles. We have intentionally stopped the recycle at the fifth cycle, however we are convinced that this process may be carried out many more times. Excellent diastereofacial selectivity and faster reaction reaction rates have been observed when the reaction of nitrone **1** with activated alkenes (maleimides) are carried out in room temperature ionic liquids (RTILs). For example, the reaction between **1** with *N*-phenyl maleimide, afforded cycloaddition derivatives **2a** and **2b** after 12 h in CH_2Cl_2 in 68% yield and 88% yield (entry 1) in [bmim]BF_4 at room temperature after 26 min, respectively. The addition of nitrone **1** to maleimides results in a mixture of diastereomer **2a**–**4a** and **2b**–**4b** (almost 65:25 ratio in all cases) and generation of as many as three chiral centres in a single step. Studies of organic reactions in ionic liquid show

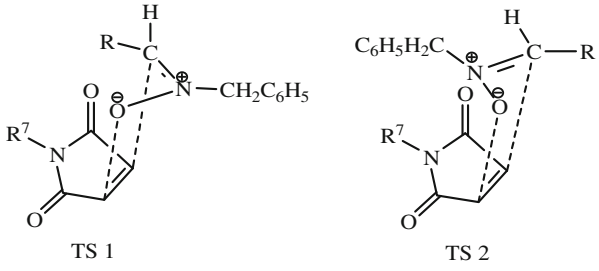
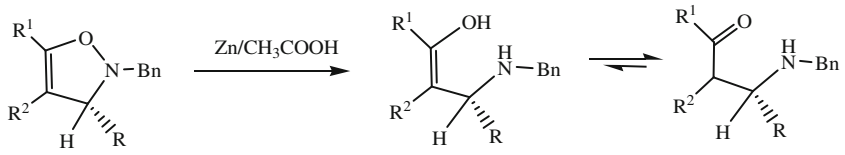


Figure 2. *Exo/endo* approach of nitrone to maleimides in cycloaddition reactions.



Scheme 2. Synthesis of 1,3 amino alcohol from isoxazoline derivatives.

that there is a higher probability of the formation of mixture of diastereomers when ionic liquid is used as solvent rather than conventional organic solvents. These results can be rationalized by an *exo* approach of nitrone **1**, which has *Z*configuration for the formation of major cycloadducts **2a**–**4a** (transition state 1, figure 2).[19] Minor cycloadducts **2b**–**4b** are formed by the *endo* approach of *Z* nitrone (transition state 2, figure 2).[19] The mixture of diastereomers is identified by considering the multiplicity of the proton signals at 3-H and 4-H along with their coupling constant values.[20,21] The most significant differences in the ^{1}H NMR data for the diastereomers is the position and multiplicity of the 3-H signal. In the major adducts **2a**–**4a**, coupling constant between 3-H and 4-H has been measured as $J_{3,4} \sim 6.26$ Hz implying a *cis* relationship between H-3 and H-4, while for minor adducts **2b**–**4b**, $J_{3,4}$ is ~2.26 Hz implies a *trans* relationship between H-3 and H-4.[20,21]

Several butylmethylimidazolium based ionic liquids (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 (88%) and reaction time (26 min) as compared with [bmim]PF_6 (84%; 43 min; entry 4). For optimizing 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 catalytic ability of [bmim]BF_4. This result clearly indicates that [bmim]BF_4 has significant catalytic role in this reaction (table 1).

All the novel fluoro cycloadducts are stable and prominent molecular ion peak, base peaks are obtained in the mass spectrum as expected. In case of fluoro isoxazoline derivatives (**5**–**7**), we have also obtained expected fragmentation peaks due to the development of different aziridine derivatives. Base peaks are obtained due to loss of PhCO for phenyl methyl propiolate, $COOCH_3$ for dimethyl acetylene dicarboxylate and COOH for acetylene dicarboxylic acid cycloadducts, respectively. Hence, it is confirmed that during mass fragmentation, the isoxazoline cycloadducts underwent rearrangement to aziridine derivatives. Expected signals in ^{1}H NMR, ^{13}C NMR, Fourier transformer infrared spectroscopy (FT-IR) were obtained for all the isoxazolidine and isoxazoline derivatives (**2**–**7**). Satisfactory elemental analysis values were also obtained for all the novel cycloadducts.

Furthermore, synthetic potential of the novel fluoro isoxazoline derivatives (**5**–**7**) are tremendous as they could be converted into 1,3 difunctional amino alcohols (scheme 2). Studies are in progress.

Synthetic potentiality of nitrone **1** has been tested successfully as an oxidizing reagent in the conversion of alkyl halides to aldehydes and ketones (scheme 1) following a pattern of atom efficient reactions reported by our group.[14] Studies are in progress at present in our laboratory. We have already reported synthesis of various aldehydes and ketones from alkyl halides using α-chloro nitrones in atom-efficient reactions.[14,22]

4. Conclusion

In conclusion, we have shown that 1,3-dipolar cycloadditions of fluoro nitrones with activated alkenes and electron deficient alkynes may be conveniently carried out in RTIL's by obtaining corresponding novel fluoro isoxazolidines and isoxazolines in good conversions and yields with tremendous synthetic potentiality. The ionic liquid may be recycled several times without loss of activity or selectivity.

Supporting Information

The electronic supporting information can be seen in www.ias.ac.in/chemsci.

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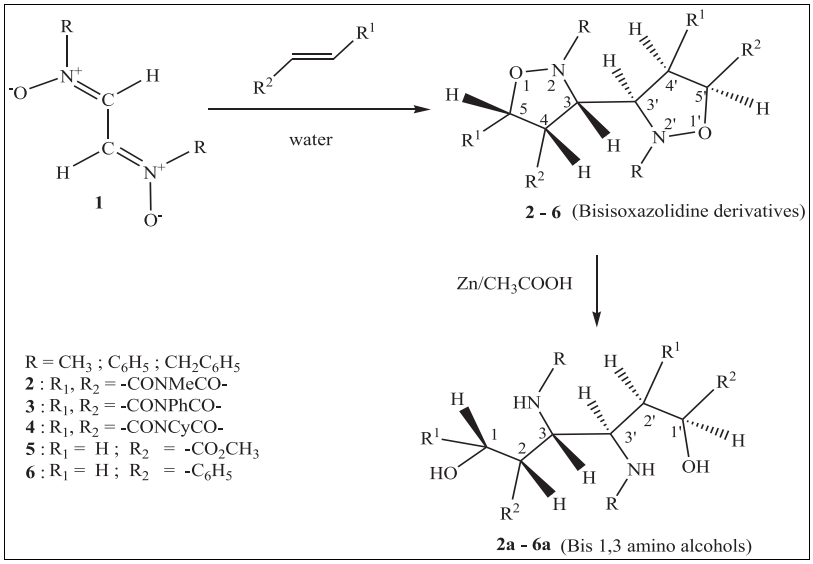

Simultaneous double 1,3-dipolar cycloaddition reactions of glyoxal-derived bisnitrones have been described in water. Significant rate acceleration and improved yields of exclusively diastereoselective and regioselective bisisoxazolidines in water have been observed at room temperature in a short reaction time compared with conventional solvents.

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INTRODUCTION

1,3-Dipolar cycloaddition reactions are an integral and weighty part of organic chemistry in pedagogy and research as well. The wealthy literature on cycloaddition reactions from their birth up to now, unequivocally witnesses to their leading chemistry. The so-called "conventional solvents" are organic solvents that have undoubtedly promoted their success. Yet, the toxicity aspect of these solvents impedes their use freely and with no fear. Not only is the operating chemist uncomfortable while experimenting, but also the environment is equally threatened. Working out the cycloaddition reactions and other organic ones in aqueous system would certainly bring some relief to the chemist and to the environment as well. Unusual outcomes in terms of yield, reactivity, and selectivity compared with those performed in organic solvents were commonly observed and have overwhelmed the chemists with surprise indeed [1,2]. The 1,3-dipolar cycloaddition methodology applied to aqueous media has brought forth a number of heterocyclic compounds, usually with a regio and stereoselectivity pecularity. These heterocycles include isoxazoles, isoxazolidines, and pyrrolidines. This rate of acceleration of organic reactions in aqueous media was ascribed to one or a combination of the following factors and phenomena [3], the high cohesive energy density of water, the high internal pressure within the medium, the hydrogen-bonding ability, the hydrophobic packing of diene and dienophile in cycloaddition reactions, the hydrophobic versus antihydrophobic effects, the micellar catalysis, the solvophobicity, and the solvent polarity. Today's status, the insolubility of organic reactants in water, once considered a drawback, turns out to be advantageously a leading factor for the success of organic reactions in pure water. In 2005, Sharpless coined these heterogeneous reactions as "on-water" reactions [4,5]. The "on water" method consists simply of stirring the reactant(s) with water to generate an aqueous suspension, and it has been observed that both kinetics and yields are extremely enhanced in most cases, compared with those in organic solvents.

In continuation of our efforts to establish green methodologies in nitrone cycloaddition reactions [6–9], herein, we wish to report a new route to the synthesis and 1,3-dipolar cycloaddition reaction of glyoxal-derived bisnitrones (having vast synthetic potentials) with a variety of alkenes to produce

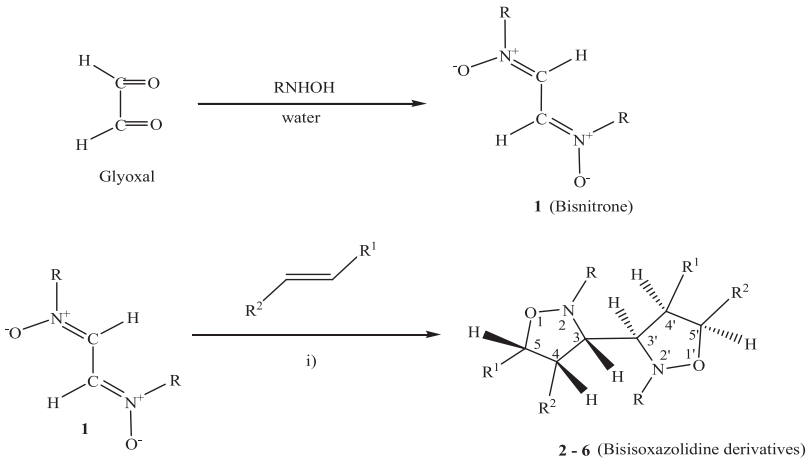
novel bisisoxazolidine derivatives (**2–6**) in water (Scheme 1) . This is quite a new approach of the synthesis of nitrone from glyoxal. The present study has been carried out with three different maleimides (*N*-methyl/phenyl/cyclohexyl) and ethyl acrylate, styrene respectively in water. Simultaneously, the reactions have been also studied in organic solvent (CH_2Cl_2) as well.

RESULTS AND DISCUSSION

We classified dipolarophiles into water-super and water-normal on the basis of the magnitude of their rate response to water. A ketone (C═O) conjugated to an alkene or alkyne is a water-super dipolarophile. Esters, ethers, and aryl rings conjugated to an alkene are water-normal dipolarophiles. Almost all the reactions in water are very fast (3–4 h in case of maleimides, ethyl acrylate and 5 h for styrene) compared with the normal cycloaddition reactions in organic solvents, which are reported to take longer periods (26–48 h) [10,11].

It is possible that water promotes the reaction through hydrogen bond formation with the carbonyl oxygen atom of the α,β-unsaturated carbonyl compounds and thereby increasing the eletrophilic character at the β-carbon, which is attacked by nucleophilic oxygen atom of the nitrone. Thus, water activates maleimide and ethyl acrylate and thereby greatly facilitates the reaction. The reaction rate is comparatively slower in styrene because of very lesser possibility of the formation of hydrogen bonding between water and alkenes but still the rate of the reaction and the yield is higher than the cycloaddition reactions performed in solvents like THF, CH_2Cl_2 (Table 1). We suggest an explanation for these results in terms of the frontier molecular orbital (FMO) theory, which has been used extensively to explain regioselectivity and to predict the yield, rate in 1,3-dipolar cycloadditions [12,13]. This theory states that the Gibbs energy of activation is related to the energy gap between the interacting highest occupied molecular orbital and lowest unoccupied molecular orbital. The dipolarophiles such as styrene are weak hydrogen bond acceptor, which means that their FMO's are only slightly affected by hydrogen bond interactions and leads to a reduction of the energy gap between the interacting FMO's (in this case, the highest occupied molecular orbital of the dipolarophile and lowest unoccupied molecular orbital of the 1,3-dipole). Consequently, the Gibbs energy of activation of the reaction is reduced, and the reaction is accelerated in water with good yield. Bisnitrones (**1**) reacted with *N*-substituted maleimides giving bisisoxazolidines. Diastereoselective reactions of the dipole **1** furnished diastereoselective cycloadducts (**2–4**) and are classified as *trans* biscycloadducts as the 3-H and 4-H protons on each isoxazolidine ring are *trans* orientated as evidenced from ^{1}H-NMR spectroscopy [14,15]. On the other hand, bisnitrones **1** reacted with ethyl acrylate and styrene giving exclusively regioselective bisisoxazolidines (**5–6**). All the novel biscycloadducts (**2–6**) are obtained as diastereoselective and regioselective isomeric forms and stereochemical information portrayed in the drawing implies relative and not absolute relations [16]. The structures of the diastereoselective and regioselective

Scheme 1. Synthesis of bisnitrone and bisisoxazolidine derivatives from glyoxal.

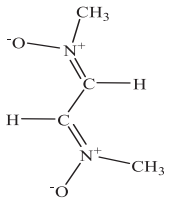
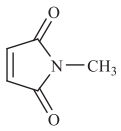
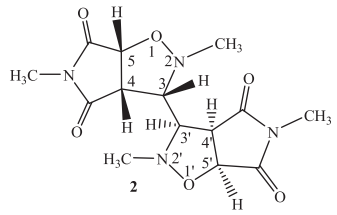
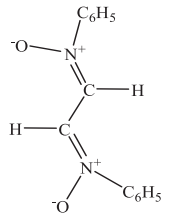
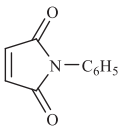
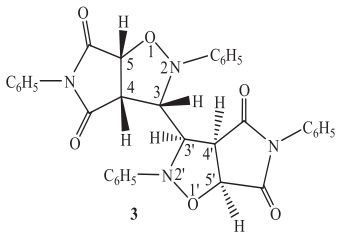
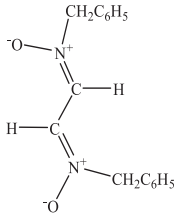
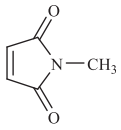
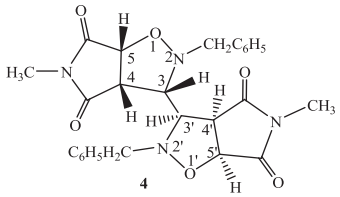
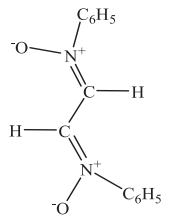
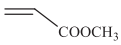
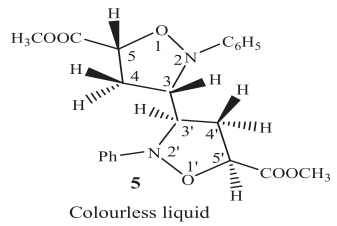
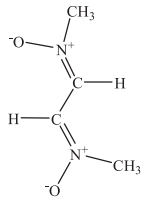
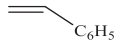
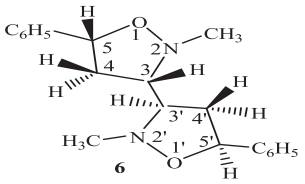


i) water, RT, 3-5 hr, N_2 atmosphere

R = CH_3 ; C_6H_5 ; $CH_2C_6H_5$
2 : R_1, R_2 = -CONMeCO-
3 : R_1, R_2 = -CONPhCO-
4 : R_1, R_2 = -CONCyCO-
5 : R_1 = H ; R_2 = $-CO_2CH_3$
6 : R_1 = H ; R_2 = $-C_6H_5$

Table 1

1,3-Dipolar cycloaddition reaction of glyoxal-derived bisnitrones with alkenes in water.

Entry	Bisnitrone[a] (**1**)	Alkene	Bisisoxazolidine[b] (**2–6**)	Time (h)	Yield[c] (%)
1			 **2** de = 88 ; Yellowish white crystals, m.p 142 ^{0}C	3 (26)	94 (62)
2			 **3** de = 96, Yellow solid, m.p 116^0 C	3 (27)	91 (59)
3			 **4** de = 92 ; White crystals, m.p 135^0 C	4 (28)	91 (60)
4			 **5** Colourless liquid	4 (30)	88 (60)
5			 **6** Greenish sticky liquid	5 (35)	83 (57)

[a]Reaction conditions: bisnitrone (1 mmol), alkenes (2 equivalent), water (15 mL), and N_2 atmosphere.
[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 solvents (CH_2Cl_2).

(5-substituted) novel bisisoxazolidine derivatives are confirmed on the basis of ^{1}H-NMR spectroscopy [14,15]. It is also evident from the ^{1}H-NMR spectrum of the diastereoselective bisisoxazolidines (**2–4**) that the structures are expected to be symmetrical in nature and that 3-H and 4-H are *cis* orientated on both rings while vicinal coupling constant has been found to be $J_{3,4} \sim 6.80$ Hz [17]. Compared with conventional conditions, the cycloaddition reactions

performed in water are much faster and selective [18]. As an example, the reaction between nitrone **1** and alkenes, afforded bisisoxazolidine (**2**) at room temperature (RT) after 34 h in 57% yield in CH_2Cl_2 and after 3 h in 93% yield in water (entry 1), respectively. The reaction of nitrone **1** with various alkenes follow the general mechanistic pattern of 1,3-dipolar cycloaddition reactions as found in literature [10,11]. Initial study reports on the biological activity of the synthesized bisisoxazolidine derivatives are also very encouraging. All the novel bisisoxazolidine derivatives (**2–6**) have been found to be very effective against both gram-positive and gram-negative organisms, which gives an opportunity to develop new broad spectrum antimicrobial agents. Screening study (SEM and TEM) on these novel bisisoxazolidines are going on at present.

Furthermore, these novel biscycloadducts (**2–6**) are found to have vast synthetic potential as they could be converted into 1,3 difunctional amino alcohols (Scheme 2). Studies are in progress.

To explore the potentiality of this procedure, we are now extending the protocol, to *N*-substituted bisnitrones (with hydroxyl derivatives in phenyl ring also) for the synthesis of novel bisisoxazolidine derivatives. Synthesis of various bisisoxazolidine derivatives from terepthaldehyde-derived bisnitrones are also in progress at present. All the biscycloadducts are found to be stable and have prominent molecular ion peak and base peaks in the mass spectrum as expected. It has been observed that the *N*-methyl dipole reacts less selectively but furnishes higher yields than its electron poor *N*-phenyl analog. A plausible stereochemistry of the bisisoxazolidines obtained from maleimides (**2–4**) has been assigned on the basis of 3-H and 4-H proton signals of both the isoxazolidine rings appeared as double doublet and doublets, respectively [19,20].

In addition, these bisisoxazolidine derivatives could be easily recovered on work-up. Because the products are fairly soluble in water, they could be easily extracted with ether. Important signals of C_3H, C_4H, and C_5H protons of both the isoxazolidine rings (*cis*, *cis*) of the novel bisisoxazolidine derivatives have been found to be merged and obtained as a single signal. Double doublet signal of C_4H protons appeared as broad signal in majority of the novel biscycloadducts and coupling constant values could not be calculated. High selectivity is observed in these simultaneous double cycloaddition reactions and best selectivity (diastereomeric excess) was observed in the cycloaddition reactions of *N*-phenylbisnitrone with *N*-phenyl maleimide (de% 96, entry **2**, Table 1). Enhanced reaction rates, excellent yields, and high selectivity are the features observed in these double cycloaddition reactions. All the products are characterized by ^{1}H-NMR, ^{13}C-NMR, IR and mass spectrometry (MS) spectroscopic data.

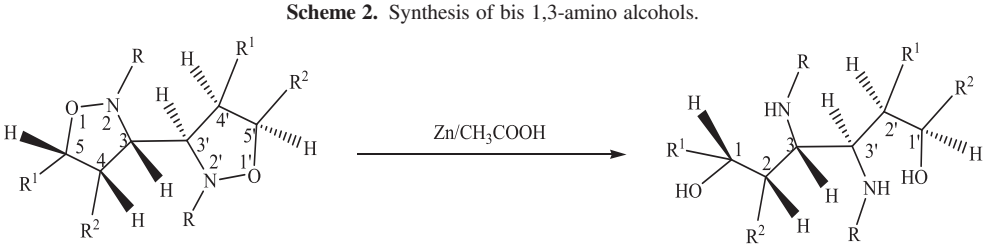
CONCLUSION

In conclusion, we have reported a new methodology of the synthesis of bisisoxazolidines from one pot double cycloaddition reactions on bifunctional nitrones with maleimides and other activated alkenes. *N*-methyl dipoles are more reactive, but less selective than their *N*-phenyl analogs. Biscycloadducts with *N*-methyl/*N*-phenyl substituents on the isoxazolidine ring are *cis* disposed with respect to 3-H and 4-H protons. Finally, we have also shown that these cycloaddition reactions may be conveniently carried out in water with the obtainment of corresponding novel bisisoxazolidines in good conversions and yields with high synthetic potentials, selectivities.

EXPERIMENTAL

^{1}H-NMR spectra were recorded with a Bruker DRX 300 (SAIF-CDRI, Lucknow, Uttar Pradesh, India) spectrometer (300 MHz, FT-NMR) using tetramethylslane as internal standard. ^{13}C-NMR spectra were recorded on the same instrument at 75 MHz. The coupling constants (*J*) are given in hertz. IR spectra were obtained with a Perkin-Elmer RX 1-881 (SAIF-CDRI, Lucknow, Uttar Pradesh, India) machine as film or as KBr pellets for all the products. MS spectra were recorded with a Jeol SX-102 (FAB) (SAIF-CDRI, Lucknow, Uttar Pradesh, India) instrument. All the reactions were monitored by TLC using 0.25 mm silica gel plates (Merck 60 F_{254} UV indicator) while column chromatography was performed with silica gel (E. Merck India) 60–200 mesh. All other reagents and solvents were purified after receiving from commercial suppliers. *N*-Benzylhydroxylamine, *N*-Phenyl maleimide, *N*-Methyl maleimide, starting materials, and reagents used in the reactions were obtained commercially from Aldrich, Lancaster, Fluka and were used without purification, unless otherwise indicated. Characterization of the novel biscycloadducts has been confirmed on the basis of spectral data.

Scheme 2. Synthesis of bis 1,3-amino alcohols.



2 (Bisisoxazolidine derivatives) **2a** (Bis 1,3-amino alcohols)

General procedure for the synthesis of nitrone 1. To a solution of glyoxal (309 mg, 5.3127 m*M*) in diethyl ether (20 mL), *N*-methylhydroxylamine (500 mg, 2 equivalent), and anhydrous $MgSO_4$ (2 g) was added. The reaction mixture was kept at RT with constant stirring with a magnetic stirrer under N_2 atmosphere for 8 h. The formation of bisnitrone was monitored by TLC (R_f = 0.36). Usual workup followed by concentrated *in vacuo* furnished *N*-methyl bisnitrone as white crystals (86%; mp: 78°C). Same methodology was followed for the synthesis of other bisnitrones (R = C_6H_5; $CH_2C_6H_5$). All the bisnitrones were found to be stable and were reacted with various activated alkenes in 1,3-dipolar cycloaddition reaction in water at RT.

Spectroscopic data for nitrone **1** (R = CH_3): UV λ_{max} 233 nm. IR (KBr): υ_{max} 1635 (m), 1610 (s) cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.45 (d, 1H, *J* = 3.22 Hz, –CH = N^+), 6.23 (d, *J* = 3.22 Hz, –CH=N^+), 3.84 (s, 6H, 2×CH_3, N^+–CH_3). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 141.60 (CH=N^+), 140.94 (CH=N^+), 24.74, 24.70 (N^+–CH_3).

General procedure of synthesis of diastereoselective bisisoxazolidine derivatives in water (Table 1; entry 1). *N*-methylmaleimide (2 equivalent) was added to a solution of bisnitrone (1 equivalent; R = CH_3) in water (15 mL), and the reaction mixture was stirred at RT for an appropriate time (Table 1). After completion of reaction, as indicated by TLC (R_f = 0.68, 0.62), the reaction mixture was extracted with diethyl ether (3 × 10 mL), the organic layer was washed with saturated brine (2 × 15 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The resulting crude products were directly charged on silica gel column and eluted with a mixture of ethyl acetate:*n*-hexane (1:6) to afford pure bisisoxazolidines **2** (Table 1, entry **1**, 94% and 6%, respectively) as yellowish white crystals. Same methodology was followed for other substrates depicted in Table 1.

Both the major and minor bis diastereomers gave satisfactory ^{1}H-NMR, ^{13}C-NMR, MS, IR, and elemental analyses data. Spectral data of the major bis diastereomers are represented as follows.

Spectral data of diastereomeric bisisoxazolidine derivatives (2–4)

(3R, 3aR, 6aS)-Dihydro-3-((3′S, 3′aS, 6aR)-hexahydro-2,5-dimethyl-4,6-dioxo-2H-pyrrolo[3,4-d]isoxazol-3-yl)-2′, 5′-dimethyl-2H-pyrrolo[3,4-d]isoxazole-4,6(5H, 6aH) dione 2. **2** (entry 1, Table 1): Yellowish white crystals, Yield 94%; R_f = 0.68; FTIR (KBr): υ_{max} 2820 (m), 1760 (s), 1675 (s), 1465 (m), 1230 (m), 1125 (s) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 3.31 (d, 2H, *J* = 4.06 Hz, 2×C_5H), 3.10 (s, 6H, 2×ONCH_3), 2.99 (s, 6H, 2×(O=C)NCH_3), 2.85 (d, 2H, *J* = 4.22 Hz, 2×C_3H), 2.50 (dd, br, 2H, 2×C_4H). ^{13}C-NMR ($CDCl_3$): δ 174.78, 173.12 (carbonyl carbons), 75.80 (C_5, $C_{5'}$), 69.94 (C_3, $C_{3'}$), 56.77 (C_4, $C_{4'}$), 26.63, 26.58 (methyl carbons). FAB-MS (*m/z*): 338 (M^+), 169, 168, 154. Calcd for $C_{14}H_{18}O_6N_4$: C, 49.68; H, 5.36; N, 16.56%. Found: C, 49.53; H, 5.25; N, 16.44%.

(3R, 3aR, 6aS)-Dihydro-3-((3′S, 3′aS, 6aR)-hexahydro-4,6-dioxo-2,5-diphenyl-2H-pyrrolo[3,4-d]isoxazol-3-yl)-2′, 5′-diphenyl-2H-pyrrolo[3,4-d]isoxazole-4,6(5H, 6aH)dione 3. **3** (entry 2, Table 1): White crystals, Yield 91%; R_f = 0.66; FTIR (KBr): υ_{max} 3025 (m), 2830 (m), 1764 (s), 1660 (s), 1485 (m), 1345 (m), 784 (s) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 7.36–7.26 (m, 10H, 2×(O=C)NC_6H_5), 6.62–6.50 (m, 10H, 2×ONC_6H_5), 2.11 (dd, br, 2H, 2×C_4H), 1.85 (d, 2H, *J* = 6.00 Hz, 2×C_5H), 1.67 (d, 2H, *J* = 6.10 Hz, 2×C_3H). ^{13}C-NMR ($CDCl_3$): δ 172.40, 172.26 (carbonyl carbons), 138.83, 138.12, 137.94, 137.71, 129.74, 129.70, 129.33, 129.04 (aromatic carbons), 76.15 (C_5, $C_{5'}$), 66.47 (C_3, $C_{3'}$), 55.80 (C_4, $C_{4'}$). FAB-MS (*m/z*): 586 (M^+), 293, 292, 216, 77. Calcd for $C_{34}H_{26}O_6N_4$: C, 69.60; H, 4.46; N, 9.55%. Found: C, 69.50; H, 4.38; N, 9.49%.

(3R, 3aR, 6aS)-2-Benzyl-3-((3′S, 3′aS, 6aR)-2′-benzyl-hexahydro-5-methyl-4,6-dioxo-2H-pyrrolo[3,4-d]isoxazol-3-yl)-dihydro-5-methyl-2H-pyrrolo[3,4-d]isoxazole-4,6(5H, 6aH)dione 4. **4** (entry 3, Table 1): White crystals, Yield 91%; R_f = 0.62; FTIR (KBr): υ_{max} 3010 (m), 2900 (m), 1760 (s), 1660 (s), 1482 (m), 1340 (m), 780 (s) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 7.46–7.26 (m, 10H, 2×$CH_2\underline{C_6H_5}$), 4.37 (d, 2H, *J* = 7.16 Hz, 2×C_5H), 3.24 (d, 2H, *J* = 7.14 Hz, 2×C_3H), 2.89 (dd, br, 2H, 2×C_4H), 2.60 (s, 6H, 2×N–CH_3 protons), 2.15 (s, 4H, 2×$\underline{CH_2}C_6H_5$). ^{13}C-NMR ($CDCl_3$): δ 177.18, 177.04 (carbonyl carbons), 133.22, 133.12, 132.90, 132.70 (aromatic carbons), 73.67 (C_5, $C_{5'}$), 64.80 (C_3, $C_{3'}$), 53.77 (C_4, $C_{4'}$), 32.05, 31.94 (benzyl carbons), 28.70, 28.58 (N–Me carbons). FAB-MS (*m/z*): 490 (M^+), 245, 244, 154, 77. Calcd for $C_{26}H_{26}O_6N_4$: C, 63.64; H, 5.34; N, 11.42%. Found: C, 63.57; H, 5.26; N, 11.35%.

General procedure of synthesis of regioselective bisisoxazolidine derivatives in water (Table 1; entry 4). Methyl acrylate (2 equivalent) was added to a solution of bisnitrone (1 equivalent; R = C_6H_5) in water (15 mL), and the reaction mixture was stirred at RT for an appropriate time (Table 1). After completion of reaction, as indicated by TLC (R_f = 0.76), the reaction mixture was extracted with diethyl ether (3 × 10 mL), the organic layer was washed with saturated brine (2 × 15 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The resulting crude product was directly charged on silica gel column and eluted with a mixture of ethyl acetate:*n*-hexane (1:6) to afford pure bisisoxazolidine **5** (Table 1, entry **4**, 88%) as colorless liquid. Same methodology was followed for other substrate depicted in Table 1.

Spectral data of regioselective bisisoxazolidine derivatives (5–6)

(3S,5S)-Methyl-3-(((5′R)-5-(methoxycarbonyl)-2-phenylisoxazolidine-3-yl)methyl)-2′-phenyl isoxazolidine-5′-carboxylate 5. **5** (entry 4, Table 1): Colorless gummy liquid, Yield 88%; R_f = 0.58; FTIR (KBr): υ_{max} 3026 (m), 2890 (m), 1760 (s), 1664 (s), 1485 (m), 783 (s) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 8.07–8.02 (m, 5H, C_6H_5), 7.52–7.45 (m, 5H, C_6H_5), 3.72 (dd, 2×1H, *J* = 5.44, 5.40 Hz, C_4H, *endo*), 3.43 (s, 2×3H, –$COOCH_3$), 2.96 (d, 2H, *J* = 6.32 Hz, 2×C_5H), 2.59 (d, 2H, *J* = 6.30 Hz, 2×C_3H), 1.24 (dd, 2×1H, *J* = 2.80, 2.82 Hz, C_4H). ^{13}C-NMR ($CDCl_3$): δ 170.24, 170.15 (carbonyl carbons), 129.47, 129.38, 129.25, 129.17 (aromatic carbons), 70.46(C_5, $C_{5'}$), 60.54 (C_3, $C_{3'}$), 52.49 (C_4, $C_{4'}$), 17.22, 17.07 (ester methyl carbons). FAB-MS (*m/z*): 412 (M^+), 206, 205, 147, 129, 77, 59. Calcd for $C_{22}H_{24}O_6N_2$: C, 64.05; H, 5.86; N, 6.79%. Found: C, 63.97; H, 5.74; N, 6.70%.

(3S, 5S)-2-Methyl-3-(((5′R)-2′-methyl-5-phenylisoxazolidin-3-yl)methyl)-5′-phenylisoxazolidine 6. **6** (entry 5, Table 1): Greenish thick liquid, Yield 83%; R_f = 0.52; FTIR (KBr): υ_{max} 3215 (m), 2905 (m), 2245 (s), 1484 (m), 780 (s) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 7.88–7.73 (m, 5H, C_6H_5), 7.50–7.44 (m, 5H, C_6H_5), 3.60 (dd, 2×1H, *J* = 6.24, 6.22 Hz, C_4H, *endo*), 2.76 (d, 2H, *J* = 6.06 Hz, 2×C_5H), 2.62 (d, 2H, *J* = 6.28 Hz, 2×C_3H), 2.30 (s, 2×3H, N–Me protons), 1.70 (dd, 2×1H, *J* = 3.66, 3.62 Hz, C_4H). ^{13}C-NMR ($CDCl_3$): δ 136.67, 136.58, 136.52, 136.38, 131.80, 131.72, 131.55, 131.23 (aromatic carbons), 73.60 (C_5, $C_{5'}$), 58.45 (C_3, $C_{3'}$), 55.37 (C_4, $C_{4'}$), 36.64, 35.21 (N–Me carbons). FAB-MS (*m/z*): 324 (M^+), 246, 161, 147, 77. Calcd for $C_{20}H_{24}O_2N_2$: C, 74.03; H, 7.45; N, 8.64%. Found: C, 73.95; H, 7.33; N, 8.59%.

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Synthesis of Some Novel Class of Bis(isoxazoline) and Bis(aziridine) Derivatives

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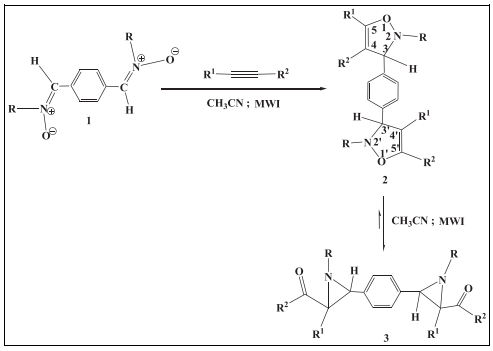

Synthesis of some new bis(isoxazoline) derivatives has been described from terepthaldehyde derived bis (nitrones) using microwave irradiation via 1,3-dipolar cycloaddition reaction. Bis(isoxazoline) derivatives in turn successfully converted into new bis(aziridine) derivatives via Baldwin rearrangement. Simple reaction methodology, non involvement of catalysts, and good to excellent yields are the important features noticed in this synthesis.

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INTRODUCTION

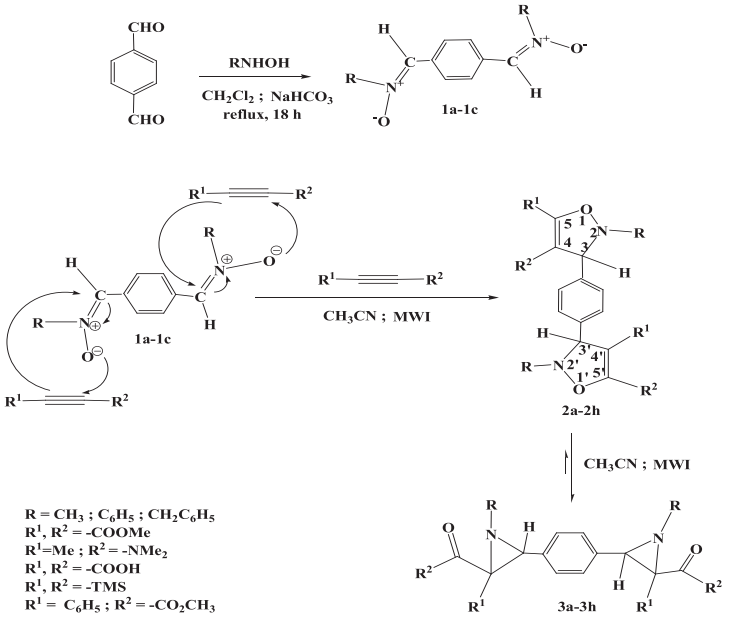
1,3-Dipolar cycloaddition reactions are an integral and weighty part of organic chemistry in pedagogy and research as well. The wealthy literature on cycloaddition reactions of nitrones for the synthesis of isoxazolidine and isoxazoline derivatives and their further applications have been widely illustrated [1–3] while synthesis of bis (isoxazolidine) and bis(isoxazoline) derivatives is challenging and needs to be explored [4–7] especially because conversions of these derivatives to aziridines via Baldwin rearrangement are found to have vast synthetic potential in this chemistry [8–10]. The chemistry of three-membered ring heterocycles, especially aziridines, has attracted the attention of synthetic chemists for more than a century because of its ability of acting as versatile species in organic synthesis [11–15]. Baldwin et al. have shown that 1,3-dipolar cycloaddition reactions of nitrones to alkynes lead to 4-isoxazolines which rearrange easily under thermal conditions to acylaziridine[16–18]. As a part of our ongoing research programme to develop new methodologies in organic synthesis [19–22], herein, we report synthesis of some new bis(isoxazoline) derivatives (2) from terepthaldehyde in good to excellent yields under microwave irradiation (Scheme 1, Table 1). Furthermore, these bis(isoxazoline) derivatives are found to have vast synthetic potential as they could be converted into synthetically more important new bis(aziridines) (3) [23–28]. The newly reported bis(isoxazoline) derivatives are obtained as single pure compound when a mixture of bis(nitrone) 1 (1 equivalent) and alkynes (2 equivalents) is exposed to microwave irradiation for 5–10 min at 115 – 130°C.

RESULTS AND DISCUSSION

To execute proposed study, terepthalaldehyde and various *N*-substituted hydroxylamines (*N-Methyl/Phenyl/Benzyl*) were employed for the synthesis of bis(nitrones) (1) following conventional methodology. This was followed by 1,3-dipolar cycloaddition reactions of bis(nitrone) 1 with different alkynes (electron deficient and electron rich) for the synthesis of a variety of bis(isoxazoline) derivatives (2) under microwave irradiation by employing reported protocol [19,29,30]. The electron deficient alkynes used in this study were acetylene dicarboxylic acid, methyl phenylpropiolate, and dimethyl acetylene dicarboxylate while electron rich alkynes were bis-(trimethylsilyl) acetylene (BTMSA) and *N,N*-dimethylaminoprop-1-yne respectively. Bis(isoxazoline) derivatives thus obtained were exposed to microwave irradiation (maintaining certain time period and temperature) to obtain a variety of new *N*-substituted bis(aziridines) (Scheme 1, Table 1).

In conventional methodology, high reaction temperature and long reaction time are generally required to obtain good conversions and yields in these cycloaddition

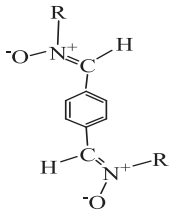
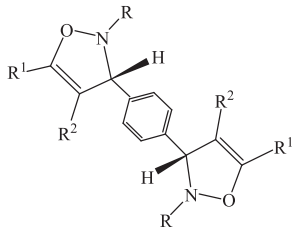
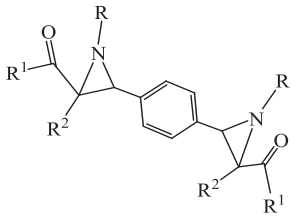
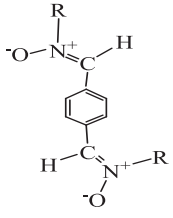
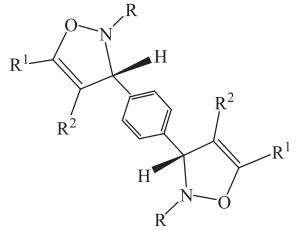
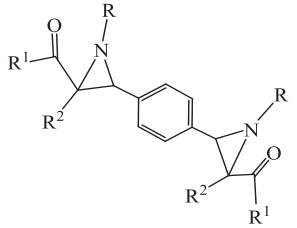
Scheme 1. Synthesis of bis(isoxazoline) and bis(aziridine) derivatives.



reactions but prolonged heating time results in a drastic drop of the yield of cycloadducts because of decomposition. A study of the reaction conditions under microwave irradiation was thus undertaken as this condition is generally faster, cleaner, and greener [20,31–33]. The results are summarized in Table 1. We also examined the effect of solvent on these reactions and also in the rearrangement 2 to **3**. Among the various polar solvents tested, water and DMSO showed a good level of conversion (90 and 68%, respectively) but, unfortunately, also induce the formation of extensive amounts of degradation products (63 and 49% transformation, respectively). As compared to the other solvents used, CH_3CN finally offers the better compromise in terms of efficiency (conversion, transformation,

Table 1

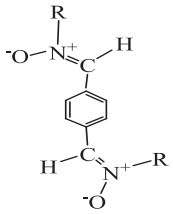
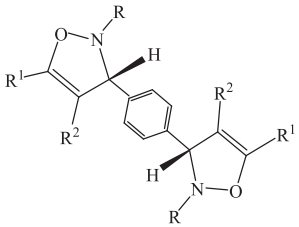
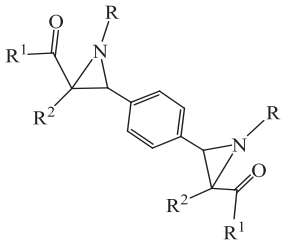
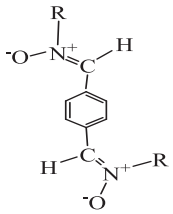
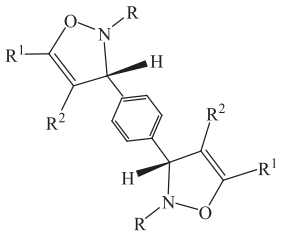
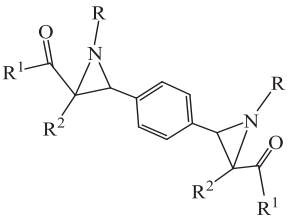
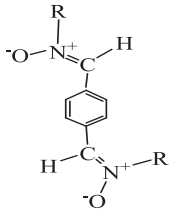
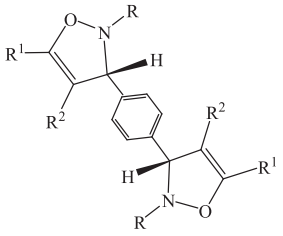
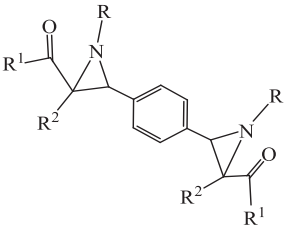
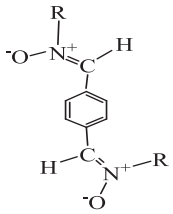
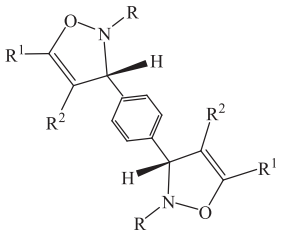
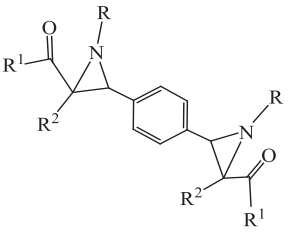
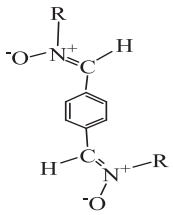
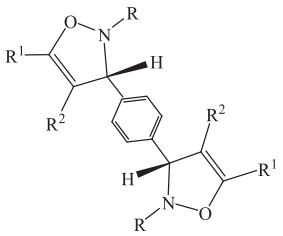
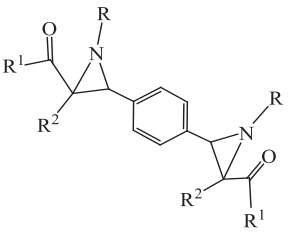
Synthesis of bis(isoxazoline) and bis(aziridine) derivatives.

Entry	Bis(nitrone)(1a–1c)	Bis(isoxazoline)[a,c] (2a–2h)	Time (min)	Bis(aziridine)[b,c] (3a–3h)	Time (min)
1	 1a (R = CH_3)	 Yield = 92% (69%) 2a R^1 = $COOCH_3$; R^2 = $COOCH_3$	5	 Yield = 78% 3a R^1 = $COOCH_3$; R^2 = $COOCH_3$	5
2	 1b (R = C_6H_5)	 Yield = 88% (67%) 2b R^1 = COOH; R^2 = COOH	6	 Yield = 75% 3b R^1 = COOH; R^2 = COOH	6

(*Continued*)

Table 1

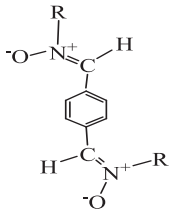
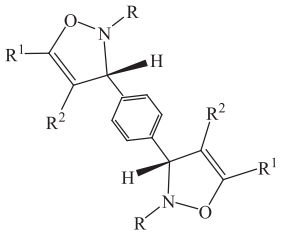
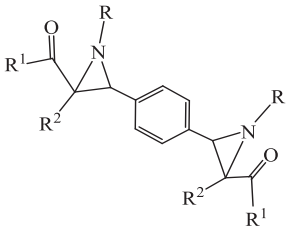
(*Continued*)

Entry	Bis(nitrone)(1a–1c)	Bis(isoxazoline)[a,c] (2a–2h)	Time (min)	Bis(aziridine)[b,c] (3a–3h)	Time (min)
3	 1c (R = $C_6H_5CH_2$)	 Yield = 88% (67%) 2c R^1 = Ph; R^2 = $COOCH_3$	6	 Yield = 74% 3c R^1 = Ph; R^2 = $COOCH_3$	6
4	 1c (R = $C_6H_5CH_2$)	 Yield = 87% (65%) 2d R^1 = TMS; R^2 = TMS	7	 Yield = 73% 3d R^1 = TMS; R^2 = TMS	7
5	 1a (R = CH_3)	 Yield = 86% (66%) 2e R^1 = Me; R^2 = NMe_2	7	 Yield = 70% 3e R^1 = Me; R^2 = NMe_2	7
6	 1b (R = C_6H_5)	 Yield = 86% (64%) 2f R^1 = $COOCH_3$; R^2 = $COOCH_3$	9	 Yield = 71% 3f R^1 = $COOCH_3$; R^2 = $COOCH_3$	9
7	 1a (R = CH_3)	 Yield = 85% (60%) 2 g R^1 = COOH; R^2 = COOH	10	 Yield = 72% 3 g R^1 = COOH; R^2 = COOH	10

(*Continued*)

Table 1

(*Continued*)

Entry	Bis(nitrone)(1a–1c)	Bis(isoxazoline)[a,c] (2a–2h)	Time (min)	Bis(aziridine)[b,c] (3a–3h)	Time (min)
8	 1b (R = C_6H_5)	 Yield = 84% (56%) 2 h R^1 = TMS; R^2 = TMS	10	 Yield = 71% 3 h R^1 = TMS; R^2 = TMS	10

[a]Reaction conditions: Bisnitrone (1 mmol), alkyne (2 equivalent), MWI, MeCN, 5–10 min, 115 – 130°C
[b]Isoxazoline (1 mmol), MWI, MeCN, 5–10 min, 130°C
[c]Isolated yield after purification.
Figures in the parentheses of yield indicate products obtained in conventional methodology.

and yield) and of practical convenience. Indeed, at the end of the reaction, the solvent is removed *in vacuo* and the residue is directly loaded on silica gel for purification, which avoids an aqueous workup. We have also observed that rearrangement of bis(isoxazoline) derivatives to bis (aziridines) conducted in the absence of solvent resulted in the complete degradation of the starting material. We thus next evaluated the influence of solvent (H_2O and DMSO) for this conversion but because of the formation of extensive amounts of degradation products (nearly 55–60%), this methodology was discarded. For the rearrangement of 2 to 3, the best results were obtained when the reaction was carried out in acetonitrile.

We have obtained expected fragmentation peaks in the mass spectral studies and majority of these peaks are due to the development of aziridine derivatives. Base peaks were obtained because of loss of $COOCH_3$ for dimethyl acetylene dicarboxylate, methyl phenyl propiolate while COOH, TMS, and N,N-dimethylaminoprop-1-yne (NMe_2) for acetylene dicarboxylic acid, bis-(trimethylsilyl)acetylene (BTMSA), and *N,N*-dimethylaminoprop-1-yne respectively. For all the cases, development of bis(nitrone), bis (isoxazolines) and conversions to bis(aziridine) derivatives were monitored by TLC (R_f values of bis(aziridine) derivatives were found to have lower than bis (isoxazoline) derivatives). Important signals of R, R^1, and R^2 of the bis(isoxazoline) and bis(aziridine) derivatives were obtained in the ^{1}H NMR spectrum [34] while prominent carbonyl absorptions were found in IR spectrum as well. ^{1}H NMR spectrum of the all the synthesized bis(isoxazoline) and aziridine derivatives showed that the four (4) hydrogen atoms of the phenyl ring (1,4 and 3,5 protons) linked with isoxazoline and aziridine rings are merged and obtained as single singlet signal. ^{13}C NMR spectrum of the phenyl ring carbons at ortho, meta, and para positions have been found to be merged and obtained as single signal. Exact stereochemistry of the bis(isoxazoline) and bis(aziridine) derivatives could not be assigned because of the absence of adjacent proton with respect to isoxazoline and aziridine ring proton.

CONCLUSION

In conclusion, we have reported a green chemistry protocol of the synthesis of bis(isoxazoline) derivatives and also Baldwin rearrangement of these derivatives to various new bis(aziridine) derivatives using microwave irradiation at selected temperature without involvement of any catalysts. The salient feature and the point of attraction in the present methodology are the entire syntheses that involve atom efficient green chemistry methodology which should attract synthetic chemists.

EXPERIMENTAL

^{1}H NMR spectra were recorded with a Bruker DRX 300 spectrometer (300 MHz, FT NMR) using TMS as internal standard. ^{13}C NMR spectra were recorded on the same instrument at 75 MHz. The coupling constants (*J*) are given in Hz. IR spectra were obtained with a Shimadzu FT-IR 8400 machine using KBr pellets for all the products. MS spectra were recorded with a Jeol SX-102/DA-600 (FAB) instrument, and elemental analysis was carried out using Heraus C,H and N rapid analyzer. All the reactions were monitored by TLC using 0.25-mm silica gel plates (Merck $60F_{254}$ UV indicator) while column chromatography was performed with silica gel (E. Merck India) 60–200 mesh. *N*-Methylhydroxylamine, *N*-benzylhydroxylamine, dimethyl acetylenedicarboxylate, methyl phenylpropiolate,

acetylenedicarboxylic acid, bis-(trimethylsilyl) acetylene (BTMSA), and *N,N*-dimethylaminoprop-1-yne etc were obtained commercially from Aldrich, Lancaster, Fluka and from Sigma-Aldrich, Switzerland and were used as received. *N*-Phenylhydroxylamine and *N*-cyclohexylhydroxylamine were prepared following standard methods available in the literature. Microwave studies were carried out in Discover Bench Mate system (Make: CEM-USA) producing continuous irradiation at 2445 MHz and infrared control system. Microwave experiments were carried out in sealed vessels with an effective magnetic stirring and reflux (which avoids all problems of non homogeneity in temperature).

Representative experimental procedure for the synthesis of bis (nitrone) 1a (entry 1,Table 1; R = CH_3). Terephthalaldehyde (1.34 g, 10 mmol) was added to a solution of *N*-methylhydroxylamine hydrochloride (2.09 g, 25 mmol) in CH_2Cl_2 (20 mL) in a 50-mL R.B flask. $NaHCO_3$ (2.52 g, 30 mmol) was added and the mixture heated at reflux for 18 h. The solution was filtered in hot condition and the inorganic solid washed with warm $CHCl_3$. The bis(nitrone) crystallized from the filtrate as a white solid and was collected at the vacuum pump (1.42 g, 74%, m.p > 250°C).

Spectroscopic data for bis(nitrone) 1a: N-methyl(4-{[methyl (oxido)iminio]methyl{phenyl)methylideneamine N-oxide. R_f = 0.50; FT-IR (KBr): υ_{max} 3130 (s), 3010 (m), 2970 (m), 2246 (m), 1690 (s), 1630 (s), 1610 (s), 1515 (s), 1310 (m), 1176 (s), 1150 (s), 782 (s) cm^{-1}; ^1H NMR ($CDCl_3$): 8.24 (s, 4H, Ar—H), 7.40 (s, 2H, 2 × CH=N^+), 3.89 (s, 6H, 2 × CH_3); ^{13}C NMR ($CDCl_3$): δ 134.66 (2 × CH=N^+), 131.81, 130.54 (1,4 Ar—C), 128.29, 127.52 (2,6 and 3,5 Ar—C), 54.58 (2 × CH_3); FAB-MS (*m/z*): 192 (M^+), 176 (M-O), 134 (M-$CHNOCH_3$); *Anal*. Calcd. for $C_{10}H_{12}O_2N_2$: C, 62.47; H, 6.30; N, 14.58. Found: C, 62.33; H, 6.24; N, 14.35%.

General experimental procedure for the synthesis of bis (isoxazoline) derivatives (2a–2h) under microwave irradiation (entry 1, Table 1; R = CH_3). Bis(nitrone) 1a (0.41 mmol, 80 mg) and dimethyl acetylene dicarboxylate (0.82 mmole, 116 mg) were dissolved in acetonitrile (10 mL) and were heated in a sealed vessel at 115°C during 5 min under microwave irradiation (400 W, temperature-controlled mode). The progress of the reaction was monitored by TLC (R_f = 0.58).The resulting reaction mixture was concentrated under vacuum, and the crude material was directly purified by column chromatography on silica gel (ethyl acetate/hexane) to afford pure bis(isoxazoline) 2a (Table 1, entry 1, 92%) as a colourless gummy mass. Same methodology was adopted for the synthesis of other bis (isoxazoline) derivatives 2b–2h (Scheme 1, Table 1, entry 2–8).

Spectroscopic data for bis(isoxazoline) 2a (Table 1, entry 1): (3R,3'R)-tetramethyl 3,3'-(1,4-phenylene)bis(2-methyl-2,3-dihydroisoxazole-4,5-dicarboxylate. FT-IR (KBr): υ_{max} 3036 (s), 2255 (m), 1760 (s), 1710 (s), 1600 (s), 1520 (s), 1440 (s), 1324 (m), 1314 (s), 1260 (m), 1170 (s), 780 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.60 (s, 4H, Ar—H), 5.20 (s, 2H, 2 × 3-H), 3.80 (s, 12H, 4 × —$COOCH_3$), 2.52 (s, 6H, 2 × N—CH_3); ^{13}C NMR ($CDCl_3$): δ 172.54 (2 × $\underline{C}OOCH_3$), 171.13 (2 × $\underline{C}OOCH_3$), 134.28, 133.87 (1,4 Ar—C; phenyl ring carbons linked with isoxazoline rings), 131.13, 130.45 (2,6 and 3,5 Ar—C; phenyl ring carbons linked with isoxazoline rings), 88.62 (2 × 5-C), 77.43 (2 × 3-C), 59.79 (2 × 4-C), 52.20 (2 × CH_3), 38.58 (2 × —$COO\underline{CH_3}$), 36.62 (2 × —$COO\underline{CH_3}$); FAB–MS (*m/z*): 476 (M^+), 460, 400, 386, 276, 185 (B.P), 75, 59; *Anal.* Calcd. for $C_{22}H_{24}O_{10}N_2$: C, 55.44; H, 5.07; N, 5.88. Found: C, 55.39; H, 5.02; N, 5.74%.

General experimental procedure for the synthesis of bis (aziridine) derivatives (3a–3h) under microwave irradiation (entry 1, Table 1). Bis(isoxazoline) 2a (0.25 mmol, 120 mg) was dissolved in acetonitrile (10 mL) and was heated in a sealed vessel at 130°C during 5 min under microwave irradiation (400 W, temperature-controlled mode). The progress of the reaction was monitored by TLC (R_f = 0.52). The resulting reaction mixture was concentrated under vacuum, and the crude material was directly purified by column chromatography on silica gel (ethyl acetate/hexane) to afford pure bis(aziridine) 3a (Table 1, entry 1, 78%) as a pale yellow gummy mass. Same methodology was adopted for the synthesis of other bis(aziridine) derivatives 3b–3h (Scheme 1, Table 1, entry 2–8).

Spectroscopic data for bis(aziridine) 3a (Table 1, entry 1): dimethyl 3,3'-(1,4-phenylene)bis(2-(2-methoxy-2-oxoacetyl)-1-methylaziridine-2-carboxylate. FT-IR (KBr): υ_{max} 3028 (s), 2985 (m), 1766 (s), 1720 (s), 1660 (s), 1590 (m), 1520 (s), 786 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.53 (s, 4H, Ar—H), 4.86 (s, 2H, 2 × aziridine protons), 3.92 (s, 6H, 2 × —$COOCH_3$, linked with aziridine rings), 3.70 (s, 6H, 2 × —$COOCH_3$, linked with keto group), 2.68 (s, 6H, 2 × N—CH_3); ^{13}C NMR ($CDCl_3$): δ 174.10 (2 × C=O), 170.74 (2 × —$C\underline{O}OCH_3$, linked with aziridine rings), 169.20 (2 × —$C\underline{O}OCH_3$, linked with keto group), 130.80, 130.23 (1,4 Ar—C; phenyl ring carbons linked with aziridine rings), 128.15, 127.30 (2,6 and 3,5 Ar—C; phenyl ring carbons linked with aziridine rings), 60.24 (2 × aziridine ring carbons), 54.24 (2 × aziridine ring carbons), 48.60 (2 × CH_3), 35.06 (2 × —$COO\underline{CH_3}$, linked with aziridine rings), 33.18 (2 × —$COO\underline{CH_3}$, linked with keto group); FAB–MS (*m/z*): 476 (M^+), 461, 417, 400, 386, 276, 200, 76, 75, 59; *Anal*. Calcd. for $C_{22}H_{24}O_{10}N_2$: C, 55.44; H, 5.07; N, 5.88. Found: C, 55.26; H, 4.92; N, 5.61%.

Spectroscopic data of bis(isoxazoline) and bis(aziridine) derivatives. Spectroscopic data for bis(isoxazoline) 2b (Table 1, entry 2): (3R,3'R)-3,3'-(1,4-phenylene)bis(2-phenyl-2,3-dihydroisoxazole-4,5-dicarboxylic acid. Gray gummy liquid (88%), FT-IR (KBr): υ_{max} 3285 (s), 3080 (s), 2250 (m), 1760 (s), 1685 (s), 1585 (s), 1545 (s), 1360 (m), 1285 (m), 1015 (m), 880 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 10.13 (s, 2H, 2 × —COOH), 10.06 (s, 2H, 2 × —COOH), 7.05 (s, 4H,

Ar—H), 6.84–6.68 (m, 10H, 2×Ar—H), 5.42 (s, 2H, 2×3-H); ^{13}C NMR ($CDCl_3$): δ 174.27 (2×COOH), 173.45 (2×COOH), 136.54, 135.42 (1,4 Ar—C; phenyl ring carbons linked with isoxazoline rings), 133.25, 132.72 (2,6 and 3,5 Ar—C; phenyl ring carbons linked with isoxazoline rings), 129.44, 128.70 (2×1,4 Ar—C; N-phenyl carbons), 128.12, 127.83 (2×2,6 and 3,5 Ar—C; N-phenyl carbons), 85.71 (2×5-C), 78.32 (2×3-C), 57.14 (2×4-C); FAB–MS (*m/z*): 544 (M^+), 467, 466, 310, 234, 77; *Anal*. Calcd. for $C_{28}H_{20}O_{10}N_2$: C, 61.75; H, 3.70; N, 5.14. Found: C, 61.63; H, 3.57; N, 5.03%.

Spectroscopic data for bis(aziridine) 3b (Table 1, entry 2): dimethyl 3,3'-(1,4-phenylene)bis(2-(2-methoxy-2-oxoacetyl)-1-methylaziridine-2-carboxylate. Dark gray gummy mass (75%), FT-IR (KBr): υ_{max} 3280 (s), 3076 (s), 2250 (m), 1765 (s), 1754 (s), 1682 (s), 1660 (s), 1585 (s), 1540 (s), 1364 (m), 1282 (m), 1016 (m), 870 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 10.20 (s, 2H, 2×—COOH), 10.05 (s, 2H, 2×—COOH), 7.14 (s, 4H, Ar—H), 6.77–6.62 (m, 10H, 2×Ar—H), 4.90 (s, 2H, 2×aziridine protons); ^{13}C NMR ($CDCl_3$): δ 175.50 (2×C=O), 174.27 (2×COOH), 173.45 (2×COOH), 135.80, 135.26 (1,4 Ar—C; phenyl ring carbons linked with aziridine rings), 132.88, 132.51 (2,6 and 3,5 Ar—C; phenyl ring carbons linked with aziridine rings), 130.12, 129.42 (2×1,4 Ar—C; N-phenyl carbons), 128.30, 127.67 (2×2,6 and 3,5 Ar—C; N-phenyl carbons), 67.20 (2×aziridine ring carbons), 60.43 (2×aziridine ring carbons); FAB–MS (*m/z*): 544 (M^+), 499, 466, 394, 310, 234, 77, 45; *Anal*. Calcd. for $C_{28}H_{20}O_{10}N_2$: C, 61.75; H, 3.70; N, 5.14. Found: C, 61.54; H, 3.74; N, 5.10%.

Spectroscopic data for bis(isoxazoline) 2c (Table 1, entry 3): (3R,3'R)-dimethyl 3,3'-(1,4-phenylene)bis(2-benzyl-5-phenyl-2,3-dihydroisoxazole-4-carboxylate. Colourless liquid. Yield 88%; FT-IR (KBr): υ_{max} 3065 (s), 1740 (s), 1660 (s), 1590 (s), 1490 (m), 1480 (m), 1355 (m), 1290 (m), 1020 (m), 830 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.80 (s, 4H, Ar—H), 7.54–7.35 (m, 10H, 2×Ar—H, phenyl protons linked with C_5 and $C_{5'}$ carbons), 7.12–6.94 (m, 10H, 2×$CH_2C_6H_5$), 5.13 (s, 2H, 2×3-H), 3.74 (s, 4H, 2×$CH_2C_6H_5$), 3.30 (s, 6H, 2×–$COOCH_3$); ^{13}C NMR ($CDCl_3$): δ 174.54 (2×$COOCH_3$), 134.07, 133.85 (1,4 Ar—C; phenyl ring carbons linked with isoxazoline rings), 133.14, 133.03 (2,6 and 3,5 Ar—C; phenyl ring carbons linked with isoxazoline rings), 130.92, 130.64 (2×1,4 Ar—C; phenyl carbons linked with C_5 and $C_{5'}$ carbons), 129.75, 129.57 (2×2,6 and 3,5 Ar—C; phenyl carbons linked with C_5 and $C_{5'}$ carbons), 128.77, 128.64 (2×1,4 Ar—C; phenyl carbons linked with benzyl carbons), 128.15, 127.97 (2×2,6 and 3,5 Ar—C; phenyl carbons linked with benzyl carbons), 83.80 (2×5-C), 74.46 (2×3-C), 59.32 (2×4-C), 32.16 (2×$CH_2C_6H_5$), 28.12 (2×—$COOCH_3$); FAB–MS (*m/z*): 664 (M^+), 587, 559, 370, 294, 91, 77; *Anal.* Calcd. for $C_{42}H_{36}O_6N_2$: C, 75.87; H, 5.45; N, 4.21. Found: C, 75.79; H, 5.38; N, 4.23%.

Spectroscopic data for bis(aziridine) 3c (Table 1, entry 3): dimethyl 3,3'-(1,4-phenylene)bis(2-benzoyl-1-benzylaziridine-2-carboxylate. Gray gummy liquid. Yield 74%; FT-IR (KBr): υ_{max} 3070 (s), 1744 (s), 1714 (s), 1622 (s), 1590 (s), 1484 (m), 1475 (m), 1358 (m), 1282 (m), 1016(m), 850 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.23 (s, 4H, Ar—H), 7.06–6.90 (m, 20H, 4×Ar—H), 4.82 (s, 2H, 2×aziridine protons), 3.82 (s, 4H, 2×$CH_2C_6H_5$), 3.34 (s, 6H, 2×–$COOCH_3$); ^{13}C NMR ($CDCl_3$): δ 174.68 (2×C=O), 172.80 (2×$COOCH_3$), 133.00, 132.74 (1,4 Ar—C; phenyl ring carbons linked with aziridine rings), 132.06, 131.90 (2,6 and 3,5 Ar—C; phenyl ring carbons linked with aziridine rings), 130.68, 130.52 (2×1,4 Ar—C; phenyl carbons linked with C_5 and $C_{5'}$ carbons), 129.24, 129.10 (2×2,6 and 3,5 Ar—C; phenyl carbons linked with C_5 and $C_{5'}$ carbons), 128.61, 128.30 (2×1,4 Ar—C; phenyl carbons linked with benzyl carbons), 127.83, 127.29 (2×2,6 and 3,5 Ar—C; phenyl carbons linked with benzyl carbons), 60.46 (2×aziridine ring carbons), 57.54 (2×aziridine ring carbons); 37.70 (2×$CH_2C_6H_5$), 27.94 (2×—$COOCH_3$); FAB–MS (*m/z*): 664 (M^+), 559, 514, 468, 370, 294, 105, 91, 77; *Anal*. Calcd. for $C_{42}H_{36}O_6N_2$: C, 75.87; H, 5.45; N, 4.21. Found: C, 75.60; H, 5.27; N, 4.17%.

Spectroscopic data for bis(isoxazoline) 2d (Table 1, entry 4): 1,4-bis((R)-2-benzyl-4,5-bis(trimethylsilyl)-2,3-dihydroisoxazol-3-yl)benzene. Yellow sticky liquid. Yield 87%; FT-IR (KBr): υ_{max} 3073 (s), 2255 (m), 1665 (s), 1585 (s), 1500 (m), 1470 (m), 1350 (m), 1282 (m), 1025 (m), 860 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.16 (s, 4H, Ar—H), 7.05–6.92 (m, 10H, 2×Ar—H), 5.02 (s, 2H, 2×3-H), 3.43 (s, 4H, 2×$CH_2C_6H_5$), 0.82 (s, 36H, 4×$SiMe_3$); ^{13}C NMR ($CDCl_3$): δ 136.66, 134.80 (1,4 Ar—C; phenyl ring carbons linked with isoxazoline rings), 132.54, 131.89 (2,6 and 3,5 Ar—C; phenyl ring carbons linked with isoxazoline rings),129.70, 129.64 (2×1,4 Ar—C; phenyl carbons linked with benzyl carbons), 128.75, 128.43 (2×2,6 and 3,5 Ar—C; phenyl carbons linked with benzyl carbons), 80.67 (2×5-C), 75.90 (2×3-C), 56.44 (2×4-C), 31.75 (2×$CH_2C_6H_5$), 0.12 (4×$SiMe_3$ carbons); FAB–MS (*m/z*): 684 (M^+), 607, 583, 380, 304, 91, 77; *Anal*. Calcd. for $C_{38}H_{56}Si_4O_2N_2$: C, 66.62; H, 8.23; N, 4.09. Found: C, 66.50; H, 8.12; N, 4.12%.

Spectroscopic data for bis(aziridine) 3d (Table 1, entry 4): (3,3'-(1,4-phenylene)bis(1-benzyl-2-(trimethylsilyl)aziridine-3,2-diyl))bis((trimethylsilyl)methanone. Gray gummy liquid. Yield 73%; FT-IR (KBr): υ_{max} 3085 (s), 1760 (s), 1710 (s), 1665 (s), 1584 (s), 1500 (m), 1475 (m), 1356 (m), 1285 (m), 1014 (m), 865 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.03 (s, 4H, Ar—H), 6.87–6.74 (m, 10H, 2×Ar—H), 4.54 (s, 2H, 2×aziridine protons), 2.65 (s, 4H, 2×$CH_2C_6H_5$), 0.80 (s, 36H, 4×$SiMe_3$); ^{13}C NMR ($CDCl_3$): δ 173.48 (2×C=O), 135.90, 135.34 (1,4 Ar—C; phenyl ring carbons linked with aziridine rings), 133.68, 132.72 (2,6 and 3,5 Ar—C; phenyl ring carbons linked with aziridine rings),130.54, 130.23 (2×1,4 Ar—C; phenyl carbons

linked with benzyl carbons), 128.78, 128.16 (2×2,6 and 3,5 Ar—C; phenyl carbons linked with benzyl carbons), 57.54 (2×aziridine ring carbons), 55.75 (2×aziridine ring carbons), 34.42 (2×$\underline{CH_2}C_6H_5$), 0.15 (4×$SiMe_3$ carbons); FAB–MS (*m/z*): 684 (M^+), 611, 607, 583, 520, 492, 380, 304, 101, 91, 77; *Anal*. Calcd. for $C_{38}H_{56}Si_4O_2N_2$: C, 66.62; H, 8.23; N, 4.09. Found: C, 66.43; H, 8.14; N, 4.10%.

Spectroscopic data for bis(isoxazoline) 2e (Table 1, entry 5): (3R,3'R)-3,3'-(1,4-phenylene)bis(N,N,2,5-tetramethyl-2,3-dihydroisoxazol-4-amine. Deep yellow liquid. Yield 86%; FT-IR (KBr): υ_{max} 3035 (s), 2250 (m), 1680 (s), 1580 (s), 1510 (m), 1465 (m), 1315 (m), 1245 (s), 1005 (m), 858 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.48 (s, 4H, Ar—H), 4.93 (s, 2H, 2×3-H), 2.80 (s, 12H, 2×NMe_2), 2.12 (s, 6H, 2×N—CH_3), 1.63 (s, 6H, 2×CH_3); ^{13}C NMR ($CDCl_3$): δ 134.76, 134.37 (1,4 Ar—C; phenyl ring carbons linked with isoxazoline rings), 133.50, 133.13 (2,6 and 3,5 Ar—C; phenyl ring carbons linked with isoxazoline rings), 83.70 (2×5-C), 73.47 (2×3-C), 55.60 (2×4-C), 39.52 (2×NMe_2), 30.21 (2×N—CH_3), 20.43 (2×CH_3); FAB–MS (*m/z*): 358 (M^+), 343, 342, 242, 217, 141, 126; *Anal*. Calcd. for $C_{20}H_{30}O_2N_4$: C, 66.99; H, 8.43; N, 15.63. Found: C, 66.84; H, 8.32; N, 15.53%.

Spectroscopic data for bis(aziridine) 3e (Table 1, entry 5): 1,1'-(3,3'-(1,4-phenylene)bis(2-(dimethylamino)-1-methylaziridine-3,2-diyl))diethanone. Brown sticky liquid. Yield 70%; FT-IR (KBr): υ_{max} 3042 (s), 2244 (m), 1755 (s), 1715 (s), 1660 (s), 1575 (s), 1510 (m), 1460 (m), 1315 (m), 1250 (s), 1008 (m), 846 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.40 (s, 4H, Ar—H), 4.76 (s, 2H, 2×aziridine protons), 2.74 (s, 12H, 2×NMe_2), 2.10 (s, 6H, 2×N—CH_3), 1.57 (s, 6H, 2×$COCH_3$); ^{13}C NMR ($CDCl_3$): δ 174.06 (2×C=O), 132.96, 132.57 (1,4 Ar—C; phenyl ring carbons linked with aziridine rings), 131.34, 131.10 (2,6 and 3,5 Ar—C; phenyl ring carbons linked with aziridine rings), 54.95 (2×aziridine carbons), 52.64 (2×aziridine carbons), 37.78 (2×NMe_2), 31.60 (2×N—CH_3), 22.43 (2×CO$\underline{CH_3}$); FAB–MS (*m/z*): 358 (M^+), 343, 342, 300, 289, 272, 242, 217, 141, 126, 43; *Anal*. Calcd. for $C_{20}H_{30}O_2N_4$: C, 66.99; H, 8.43; N, 15.63. Found: C, 66.90; H, 8.36; N, 15.44%.

Spectroscopic data for bis(isoxazoline) 2f (Table 1, entry 6): (3R,3'R)-tetramethyl 3,3'-(1,4-phenylene)bis(2-phenyl-2,3-dihydroisoxazole-4,5-dicarboxylate. Pale yellow liquid. Yield 86%; FT-IR (KBr): υ_{max} 3018 (s), 2246 (m), 1763 (s), 1710 (s), 1605 (s), 1532 (s), 1436 (s), 1320 (m), 1254 (m), 1184 (s), 776 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.85 (m, 2×5H), 6.94 (s, 4H, Ar—H), 5.68 (s, 2H, 2×3-H), 3.37 (s, 12H, 4×—$COOCH_3$); ^{13}C NMR ($CDCl_3$): δ 171.86 (2×$\underline{CO}OCH_3$), 169.35 (2×$\underline{CO}OCH_3$),137.53, 137.59 (1,4 Ar—C; phenyl ring carbons linked with isoxazoline rings), 135.62, 135.71 (2,6 and 3,5 Ar—C; phenyl ring carbons linked with isoxazoline rings), 132.60, 129.86 (2×1,4 Ar—C; N-phenyl carbons), 127.64, 127.42 (2×2,6 and 3,5 Ar—C; N-phenyl carbons), 86.12 (2×5-C), 75.48 (2×3-C), 61.23 (2×4-C), 39.52 (2×—COO$\underline{CH_3}$), 37.80 (2×—COO$\underline{CH_3}$); FAB–MS (*m/z*): 600 (M^+), 523, 482, 446, 338, 262 (B.P), 77, 59; *Anal*. Calcd. for $C_{32}H_{28}O_{10}N_2$: C, 63.98; H, 4.69; N, 4.66. Found: C, 63.90; H, 4.57; N, 4.60%.

Spectroscopic data for bis(aziridine) 3f (Table 1, entry 6): diphenyl 3,3'-(1,4-phenylene)bis(2-(2-methoxy-2-oxoacetyl)-1-phenylaziridine-2-carboxylate. Yellow liquid. Yield 71%; FT-IR (KBr): υ_{max} 3035 (s), 2980 (m), 1763 (s), 1726 (s), 1660 (s), 1585 (m), 1535 (s), 780 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.42 (m, 2×5H), 6.50 (s, 4H, Ar—H), 4.74 (s, 2H, 2×aziridine protons), 3.80 (s, 6H, 2×—$COOCH_3$, linked with aziridine rings), 3.53 (s, 6H, 2×—$COOCH_3$, linked with keto group); ^{13}C NMR ($CDCl_3$): δ 173.11 (2×C=O), 172.06 (2×—C$\underline{O}OCH_3$, linked with aziridine rings), 170.15 (2×—C$\underline{O}OCH_3$, linked with keto group), 130.80, 130.23 (1,4 Ar—C; phenyl ring carbons linked with aziridine rings), 129.80, 129.56 (2,6 and 3,5 Ar—C; phenyl ring carbons linked with aziridine rings), 128.06, 127.90 (2×1,4 Ar—C; N-phenyl carbons), 127.24, 127.03 (2×2,6 and 3,5 Ar—C; N-phenyl carbons), 62.62 (2×aziridine ring carbons), 59.46 (2×aziridine ring carbons), 37.12 (2×—COO$\underline{CH_3}$, linked with aziridine rings), 35.47 (2×—COO$\underline{CH_3}$, linked with keto group); FAB–MS (*m/z*): 600 (M^+), 523, 513, 436, 338, 262 (B.P), 87, 77, 59; *Anal*. Calcd. for $C_{32}H_{28}O_{10}N_2$: C, 63.98; H, 4.69; N, 4.66. Found: C, 63.81; H, 4.54; N, 4.52%.

Spectroscopic data for bis(isoxazoline) 2g (Table 1, entry 7): (3R,3'R)-3,3'-(1,4-phenylene)bis(2-methyl-2,3-dihydroisoxazole-4,5-dicarboxylic acid. White liquid. Yield 85%; FT-IR (KBr): υ_{max} 3280 (s), 3073 (s), 2235 (m), 1755 (s), 1684 (s), 1590 (s), 1540 (s), 1358 (m), 1280 (m), 1018 (m), 805 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 10.05 (s, 2H, 2×—COOH), 9.96 (s, 2H, 2×—COOH), 6.80 (s, 4H, Ar—H), 5.42 (s, 2H, 2×C_3H), 2.08 (s, 6H, 2×N—CH_3); ^{13}C NMR ($CDCl_3$): δ 173.78 (2×$\underline{CO}OH$), 173.20 (2×$\underline{CO}OH$), 134.69, 133.80 (1,4 Ar—C; phenyl ring carbons linked with isoxazoline rings), 131.78, 130.80 (2,6 and 3,5 Ar—C; phenyl ring carbons linked with isoxazoline rings), 80.64 (2×5-C), 77.30 (2×3-C), 55.85 (2×4-C), 51.30 (2×N—CH_3); FAB–MS (*m/z*): 420 (M^+), 405, 330, 248, 172, 76; *Anal*. Calcd. for $C_{18}H_{16}O_{10}N_2$: C, 51.41; H, 3.83; N, 6.66. Found: C, 51.33; H, 3.60; N, 6.47%.

Spectroscopic data for bis(aziridine) 3g (Table 1, entry 7): dimethyl 3,3'-(1,4-phenylene)bis(2-(2-methoxy-2-oxoacetyl)-1-methylaziridine-2-carboxylate. Gray liquid. Yield 72%; FT-IR (KBr): υ_{max} 3282 (s), 3070 (s), 2255 (m), 1762 (s), 1756 (s), 1680 (s), 1660 (s), 1580 (s), 1540 (s), 1360 (m), 865 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 10.12 (s, 2H, 2×—COOH), 10.00 (s, 2H, 2×—COOH), 6.90 (s, 4H, Ar—H), 5.10 (s, 2H, 2×aziridine protons), 2.08 (s, 6H, 2×N—CH_3); ^{13}C NMR ($CDCl_3$): δ 173.38 (2×C=O), 172.20 (2×$\underline{CO}OH$), 171.70 (2×$\underline{CO}OH$),134.62, 134.13 (1,4 Ar—C; phenyl ring carbons linked with aziridine

rings), 132.21, 132.10 (2,6 and 3,5 Ar—C; phenyl ring carbons linked with aziridine rings), 65.75 (2×aziridine ring carbons), 61.54 (2×aziridine ring carbons), 50.23 (2×N—CH_3); FAB–MS (*m/z*): 420 (M^+), 405, 360, 347, 332, 73, 45; *Anal*. Calcd. for $C_{18}H_{16}O_{10}N_2$: C, 51.41; H, 3.83; N, 6.66. Found: C, 51.30; H, 3.63; N, 6.44%.

Spectroscopic data for bis(isoxazoline) 2h (Table 1, entry 8): 1,4-bis((R)-2-benzyl-4,5-bis(trimethylsilyl)-2,3-dihydroisoxazol-3-yl)benzene. Yellow gummy liquid. Yield 84%; FT-IR (KBr): υ_{max} 3078 (s), 2256 (m), 1660 (s), 1583 (s), 1500 (m), 1480 (m), 1354 (m), 1280 (m), 1020 (m), 850 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.06 (s, 4H, Ar—H), 6.80–6.62 (m, 10H, 2×Ar—H), 4.86 (s, 2H, 2×3-H), 1.13 (s, 36H, 4×$SiMe_3$); ^{13}C NMR ($CDCl_3$): δ 135.34, 135.18 (1,4 Ar—C; phenyl ring carbons linked with isoxazoline rings), 133.62, 133.40 (2,6 and 3,5 Ar—C; phenyl ring carbons linked with isoxazoline rings),130.68,130.52 (2×1,4 Ar—C; phenyl carbons), 128.48, 127.90 (2×2,6 and 3,5 Ar—C; phenyl carbons), 83.55 (2×5-C), 76.43 (2×3-C), 55.60 (2×4-C), 1.05 (4×$SiMe_3$ carbons); FAB–MS (*m/z*): 656 (M^+), 583, 579, 510, 367, 289, 77; *Anal*. Calcd. for $C_{36}H_{52}Si_4O_2N_2$: C, 65.85; H, 7.92; N, 4.56. Found: C, 65.74; H, 7.82; N, 4.47%.

Spectroscopic data for bis(aziridine) 3h (Table 1, entry 8): (3,3'-(1,4-phenylene)bis(1-phenyl-2-(trimethylsilyl)aziridine-3,2-diyl))bis((trimethylsilyl)methanone. Gray liquid. Yield 71%; FT-IR (KBr): υ_{max} 3080 (s), 1766 (s), 1710 (s), 1664 (s), 1580 (s), 1475 (m), 1355 (m), 1280 (m), 1010 (m), 860 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.95 (s, 4H, Ar—H), 6.80–6.63 (m, 10H, 2×Ar—H), 4.65 (s, 2H, 2×aziridine protons), 0.96 (s, 36H, 4×$SiMe_3$); ^{13}C NMR ($CDCl_3$): δ 174.35 (2×C=O), 136.23, 136.12 (1,4 Ar—C; phenyl ring carbons linked with aziridine rings), 133.47, 133.14 (2,6 and 3,5 Ar—C; phenyl ring carbons linked with aziridine rings),128.80,128.68 (2×1,4 Ar—C; phenyl carbons), 127.66, 127.53 (2×2,6 and 3,5 Ar—C; phenyl carbons), 55.79 (2×aziridine ring carbons), 53.65 (2×aziridine ring carbons), 0.84 (4×$SiMe_3$ carbons); FAB–MS (*m/z*): 656 (M^+), 579, 506, 478, 101,77, 73; *Anal*. Calcd. for $C_{36}H_{52}Si_4O_2N_2$: C, 65.85; H, 7.92; N, 4.56. Found: C, 65.74; H, 7.69; N, 4.42%.

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