Chapter – 3

Synthesis and study of anti-inflammatory activity of

3-Aryl-5-(2-aryl-1,3-oxazol-4-yl)-4,5-dihydro-1,2-oxazoles.

3.1 Introduction

The presence of heteroatoms in a molecule opens up the possibility of their being biologically active compound and depending on its interactions, it may find its application as a therapeutic agents. Due to the same reason heterocyclic compounds have been studied extensively for a wide variety of their biological activities.

The compounds made of combination of two or more heterocycles in their structure are also termed as hybrid heterocyclic compounds. These compounds having at least two heterocyclic entities present in them are expected to have diverse biological activities and have probability to show enhanced or diminished biological activities as per their molecular and bulk properties and possibility of their interaction with the involved biomolecules.

Existence of the α-β unsaturated keto functionality in chalcones makes them prone to undergo reactions with bidentate nucleophiles to give various biologically potent heterocyclic compounds. This property of chalcones is explored in the present work to generate isoxazolines incorporated derivatives of biological interest.

In this chapter five membered heterocycle, isoxazoline is built up on the molecules already possessing 1,3-oxazole in the form of aryl-heteroaryl chalcones as described in the preceding chapter.

Heterocyclic moiety present in a compound could play an important role in influencing their pharmacokinetic properties in biological study by changing their lipophilicity, polarity or other physicochemical properties.[1,2] Heterocyclic rings with nitrogen and oxygen atoms are considered as one of the useful combinations in probing biological activities of new compounds.[3]

Isoxazole is a member of the azole family with oxygen atom next to nitrogen in the five membered heterocycle. It is 1,2-azoles forming a five membered ring. The structural features in isoxazole make it possible for multiple non-covalent interactions, especially hydrogen bonding with the hydrogen bond acceptors N and O, π-π stacking and hydrophobic interactions.

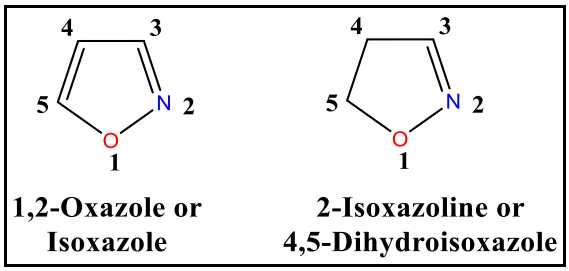


Figure 3.1

Isoxazole can interact with a wide range of protein targets and possesses a broad spectrum of biological activities including anticancer,[4,5] antibacterial,[6–8] antifungal,[9,10] antiviral,[11] anti-tubercular[12,13] and anti-inflammatory activities.[14,15]

Isoxazoline is a 4,5-dihydro isoxazole. Isoxazolines or 4,5-dihydro-1,2-oxazoles have marked their individual existence because of the diverse biological activities. Isoxazolines show a broad range of biological activities including antifungal,[16] anti-inflammatory,[17–19] antibacterial,[20] antioxidant,[21] anticonvulsant,[22] anti-HIV,[23] antidiabetic,[24] anticancer,[25–28] anti-tubercular activity.[29,30]

Furthermore, the isoxazolines represent a unique class of pharmacophore present in many therapeutic agents. For example, acivicin (**1**) (**Figure 3.2**) is an isoxazoline analogue of glutamine. It is an inhibitor of gamma-glutamyl transferase. It is a fermentation product of *S. sviceus*.[31] It interferes with glutamate metabolism and inhibits glutamate dependent synthesis of enzymes, and is thereby potentially helpful in treatment of solid tumours.[32,33]

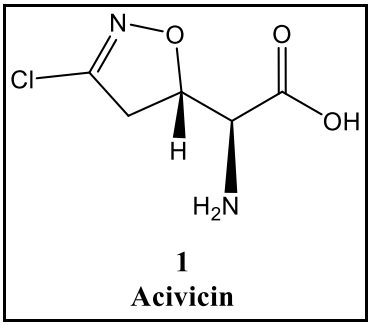


Figure 3.2

Some of the important examples of synthetic biologically active isoxazoline scaffolds (**Figure 3.3**) which were prepared and studied for their anticancer activity include 3,5-diaryl-isoxazoline linked 2,3-dihydroquinazolinone hybrids (**2**),[34] aryl-isoxazoline containing anthranilic diamides (**3**),[27] 3,5- diaryl-isoxazoline linked pyrrolo[2,1-c][1,4] benzo- diazepine (PBD) conjugates (**4**)[28] and novel dibenzo[b,f]azepine tethered isoxazoline derivatives (**5**)[35] (**Figure 3.3**).

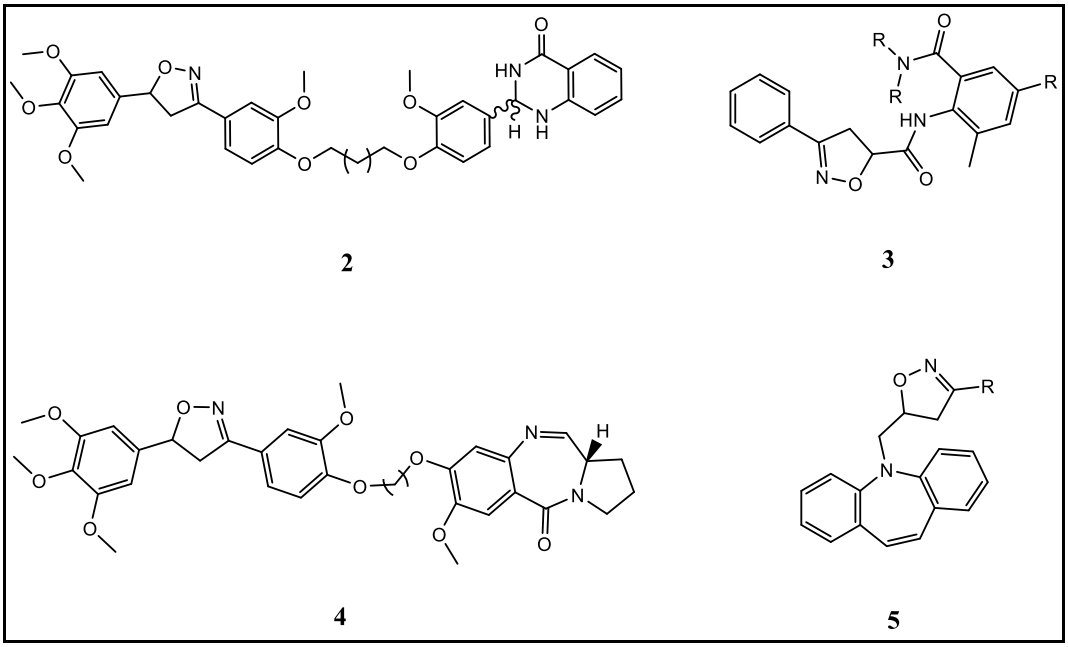


Figure 3.3 ***Isoxazoline derivatives possessing anticancer activity.***

A series of new amidobenzimidazole attached pharmacologically important isoxazolines (**6**) (**Figure 3.4**) were prepared and studied for their IKK (inhibitory kappa B kinase is an enzyme complex that is involved in propagating the cellular response to inflammation) inhibitory activity[36]. Some new anti-inflammatory steroidal drugs with C-16,17 isoxazoline ring system (**7**) (**Figure 3.4**) were prepared and evaluated for their anti-inflammatory activities[37].

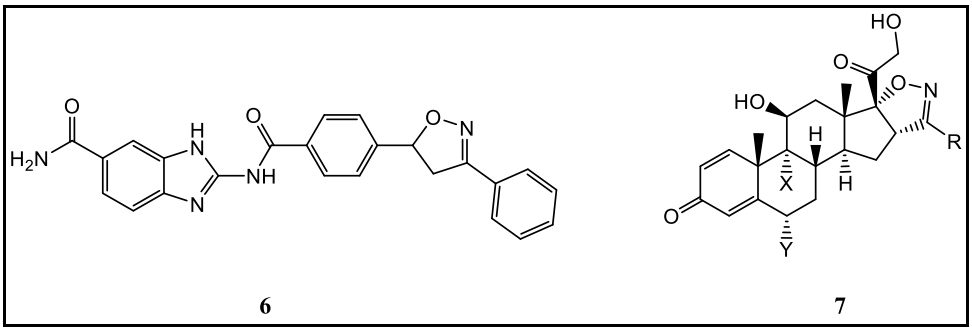


Figure 3.4 ***Biologically active isoxazoline derivatives.***

A novel class of compounds 3-(2-benzyloxyphenyl)-isoxazolines (**8**-**10**) (**Figure 3.5**) were synthesized and studied as cystic fibrosis transmembrane conductance regulator (CFTR) activators.[38]

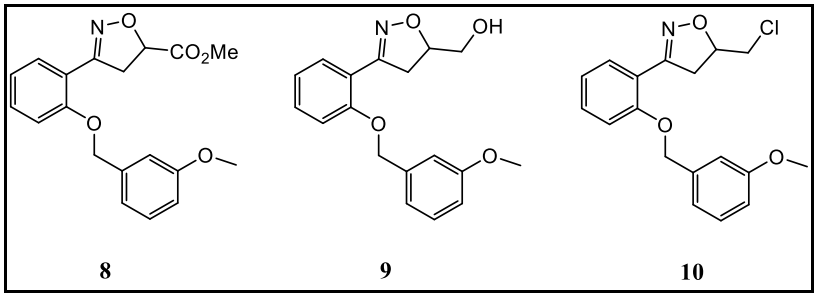


Figure 3.5

A series of novel isoxazolines linked via piperazine to 2- benzoisothiazoles (**11**) (**Figure 3.6**) have been prepared and studied as potent apoptotic agents.[39] Some new harmine derivatives (**12**) were prepared by cycloaddition reaction using various arylnitrile oxides and were evaluated as anti-inflammatory agents.[40] A series of isoxazoline-containing derivatives (**13**) were prepared and studied for their insecticidal activity.[41] Some new disubstituted isoxazolines (**14**) (**Figure 3.6**) were prepared as potent $CRTh_2$ (Chemoattractant Receptor-homologous molecule expressed on T-Helper type 2 cells) antagonists.[42]

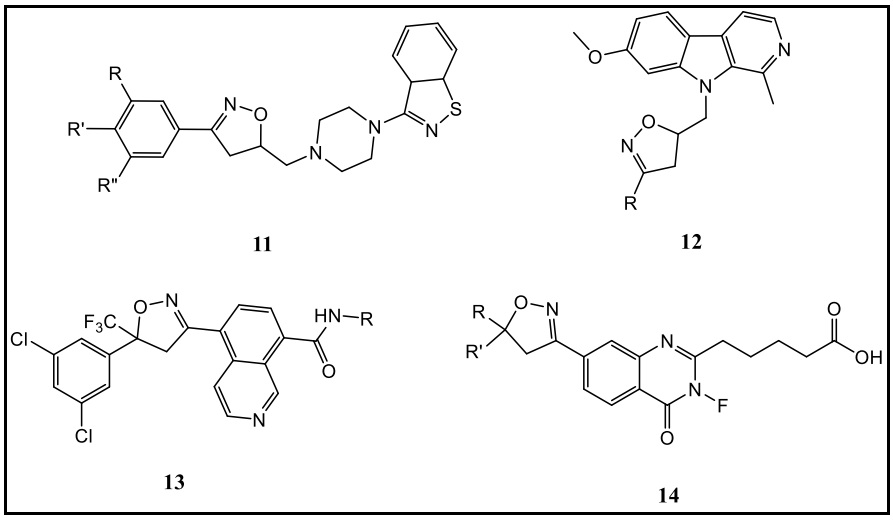
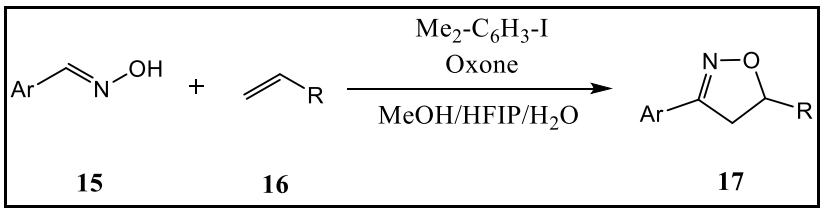


Figure 3.6

Synthesis of isoxazolines

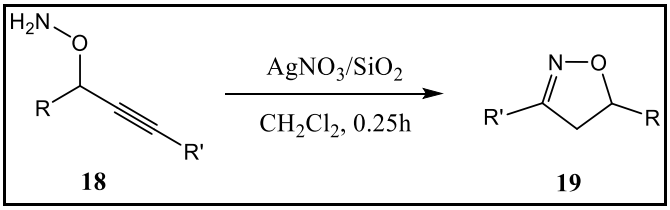
There are a number of methods for the synthesis of isoxazolines and its derivatives. Few of the recently reported methods are as described below.

A hypervalent iodine catalysed oxidation of aldoximes **15** to generate nitrile oxides and subsequent reaction with alkenes **16** gave the corresponding isoxazolines **17** in good yield[43] (**Scheme 3.1**).



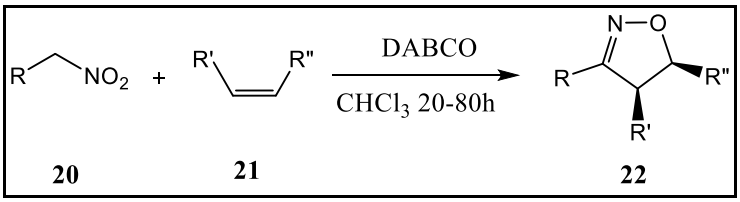
Scheme 3.1

Cyclisation of unprotected O-propargylic hydroxylamines **18** yielded 4,5-dihydro isoxazoles **19** when exposed briefly to silver nitrate adsorbed on to silica gel[44] (**Scheme 3.2**).



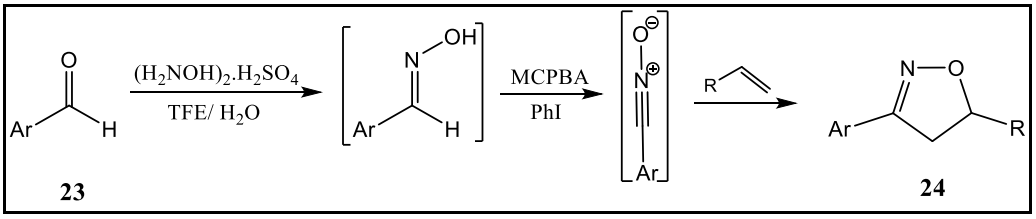
Scheme 3.2

The dehydration of primary nitro compounds **20** by base DABCO (1,4-diazabicyclo[2.2.2]octane) in the presence of dipolarophiles **21** afforded substituted isoxazoline derivatives **22**[45] (**Scheme 3.3**).



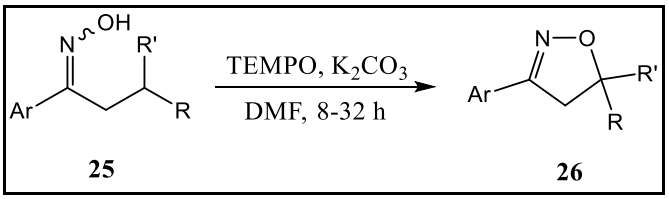
Scheme 3.3

Isoxazolines **24** could also be synthesized by a convenient one-pot, three-step method starting from aldehydes **23**. 1,3-Dipolar cycloaddition between the nitrile oxides and alkenes provide isoxazolines in good yields[46] (**Scheme 3.4**).



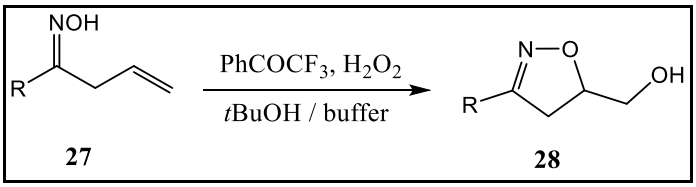
Scheme 3.4

Substituted isoxazoline **26** were prepared by a method involving aliphatic C-H bond oxidation of oximes and hydrazones **25** mediated by (2,2,6,6-tetramethylpiperidin-1-yl) oxydanyl (TEMPO)[47] (**Scheme 3.5**).



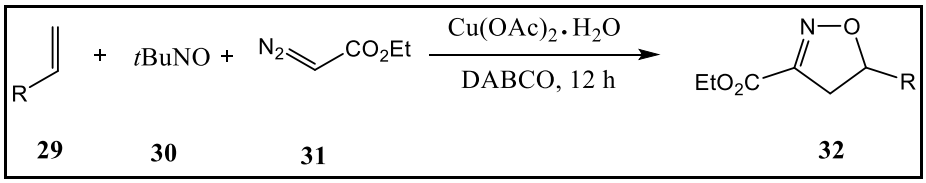
Scheme 3.5

A variety of substituted isoxazolines **28** were prepared by a green and efficient methodology involving 2,2,2-trifluoroacetophenone-catalyzed oxidation of allyloximes **27**[48] (**Scheme 3.6**).



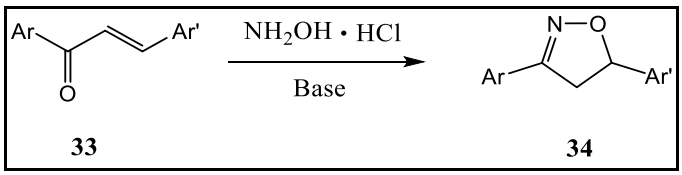
Scheme 3.6

Various substituted isoxazolines **32** were synthesized by an exceptional cross-coupling reaction between olefins **29**, nitroso radicals **30** and copper carbenes from **31** via construction of C-C, C-O, and C=N bonds in a one-pot process[49] (**Scheme 3.7**).



Scheme 3.7

The reaction between α,β-unsaturated carbonyl compounds **33** with hydroxyl amines resulted in various substituted isoxazolines derivatives **34**[50–52] (**Scheme 3.8**).

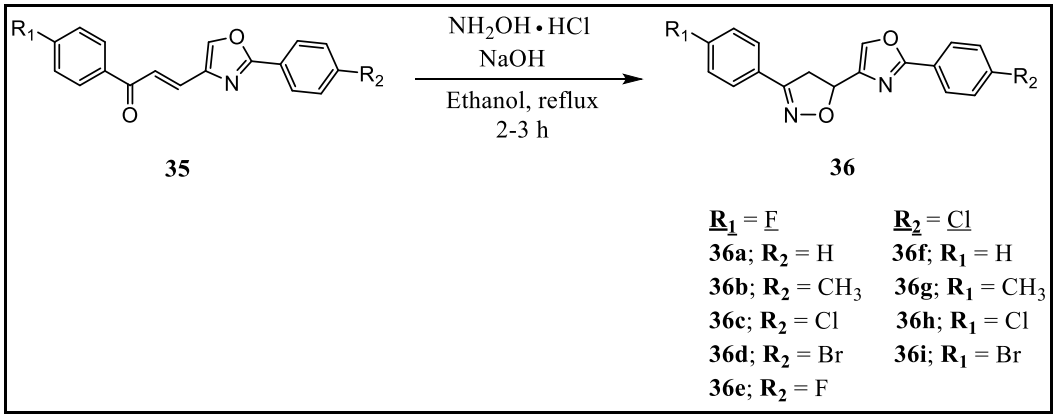


Scheme 3.8

3.2 Results and Discussion

The α,β–unsaturated carbonyl compounds having heterocyclic and aryl substitutions have been widely employed for the synthesis of isoxazolines.[50–54] These compounds undergo a facile reaction at 1 and 3 positions when reacted with dinucleophiles such as hydroxyl amine or its derivatives to give the corresponding isoxazolines derivatives.

In this chapter nine new isoxazolines **36a-i** have been prepared by the reaction of 1-aryl-3-(2-phenyl-oxazol-4-yl)-propenones (chalcones) **35a-i** (reported in chapter-2) and hydroxylamine hydrochloride in alkaline medium (using NaOH solution, pH 8-9, pH paper). The pure products were obtained on column chromatography purification as white solid crystalline stable compounds[55] (**Scheme 3.9**).



35 **36**

R1 = F **R2** = Cl
36a; **R2** = H **36f**; **R1** = H
36b; **R2** = CH_3 **36g**; **R1** = CH_3
36c; **R2** = Cl **36h**; **R1** = Cl
36d; **R2** = Br **36i**; **R1** = Br
36e; **R2** = F

Scheme 3.9

3.2.1 Spectral Characterization

All the newly synthesized aryl-oxazolyl-4,5-dihydroisoxazoles **36a-i** were characterized by various spectro-analytical techniques.

The IR spectra of aryl-oxazolyl-4,5-dihydroisoxazole **36** show aromatic C-H stretching observed between 3030-3160 cm^{-1}. The -C-O stretching bands are observed at ~1240 cm^{-1} and at 1156-1012 cm^{-1}. Stretching bands at ~1500 cm^{-1} and ~1600 cm^{-1} are observed for aromatic C=C stretching.

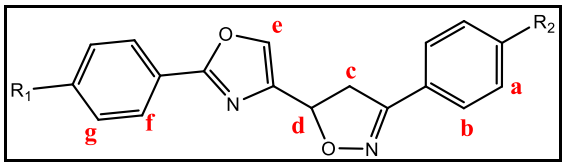


Figure 3.6 ***Proton labels on compounds 36.***

In ^{1}H NMR of aryl-oxazolyl-4,5-dihydroisoxazoles **36** (**Figure 3.6**) the two protons on the methylene carbon **c** of the ring show a doublet at δ 3.7 ppm with vicinal coupling constant ^{2}J = 9.2 Hz. The proton **d** attached to the methine carbon substituted with oxazole ring show a multiplet at δ 5.8 ppm and the proton **e** on the oxazole ring is observed around δ 7.7 ppm as a doublet due to a long range coupling with coupling constant ^{4}J = 0.8 Hz. All the other aromatic protons are observed in between δ 7.2-7.9 ppm. Proton decoupled ^{19}F NMR spectra for fluorine containing compounds **36a-d (**R_2 = F**)** show ^{19}F signal at δ = -105. The compounds **36e (**R_1 and R_2 = F) having fluorine substitution present on both the phenyl ring, ^{19}F NMR spectra show one more signal at δ = -111.

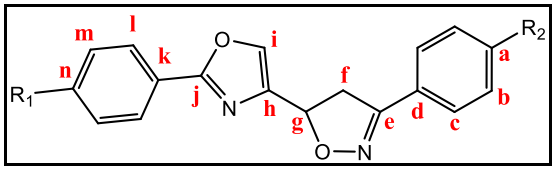


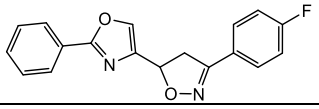
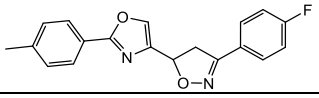
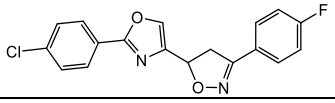
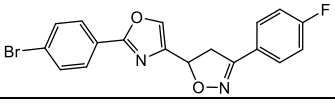
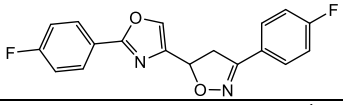
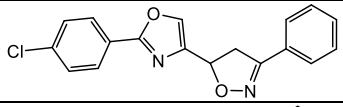
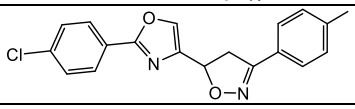
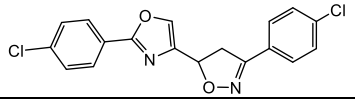
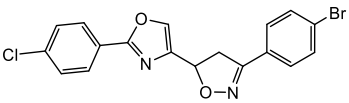
Figure 3.7 ***Carbon labels on compound 36.***

Carbon 13 NMR experiments were carried out for characterization of the newly synthesized compounds. ^{13}C NMR of aryl-oxazolyl-4,5-dihydroisoxazoles **36** show all the expected carbon signals resolved. The methine carbon (-CH) **g** of isoxazolines ring is observed at δ 40. The methylene carbon **f** of isoxazoline ring is observed at δ 75. The sp2 carbon **e** on isoxazole ring is observed most down field at δ 162. For the compounds **36a-d** (R_2 = F) the chemical shift value ~115 is assigned to carbon **b** based on doublets for its ^{13}C-^{19}F coupling with ^{2}J = 22 Hz. Carbon **c** are observed at ~128 with ^{3}J = 9 Hz.

All the aryl-oxazolyl-4,5-dihydroisoxazoles **36a-i** compounds were analysed to confirm their mass with the help of mass spectrometer. The molecular ion peaks of all the compounds were observed as either $(M)^+$ or $(M+H)^+$ and are in accordance with their proposed structures.

The structures, molecular formula, yields, melting points of all the newly synthesized compounds **36a-i** are as summarized in **Table 3.1**.

Table 3.1 ***Physical data (Yield, mp) of newly synthesized compounds.***

ID	Structure	Molecular formula	Yield	mp
36a		$C_{18}H_{13}FN_2O_2$	71%	194 °C
36b		$C_{19}H_{15}FN_2O_2$	70%	212 °C
36c		$C_{18}H_{12}ClFN_2O_2$	73%	176 °C
36d		$C_{18}H_{12}BrFN_2O_2$	72%	202 °C
36e		$C_{18}H_{12}F_2N_2O_2$	74%	178 °C
36f		$C_{18}H_{13}ClN_2O_2$	71%	174 °C
36g		$C_{19}H_{15}ClN_2O_2$	72%	172 °C
36h		$C_{18}H_{12}Cl_2N_2O$	70%	176 °C
36i		$C_{18}H_{12}BrClN_2O_2$	75%	168 °C

3.2.2 Single Crystal X-ray Diffraction Study

One of the isoxazolines derivatives **36c** was crystallized from ethanol and studied for single crystal X–ray diffraction characteristics. The orthorhombic (space group Pnaa) crystals of the isoxazoline is having structure whose ORTEP diagram is shown in (**Figure 3.8**). The study of molecular packing showed the intermolecular CH---π interactions observed between electron π-cloud of C14---H1 (2.832 Å). The intermolecular interactions observed between F---H3 (2.643Å) and between O11---H7 (2.515 Å) are also observed and form 1D linear chain as shown (**Figure 3.9**). This 1D

chain is further linked to form 2D framework through the intermolecular F---H3 interactions. These intermolecular interactions result in 2D as an attractive molecular design (**Figure 3.10**).

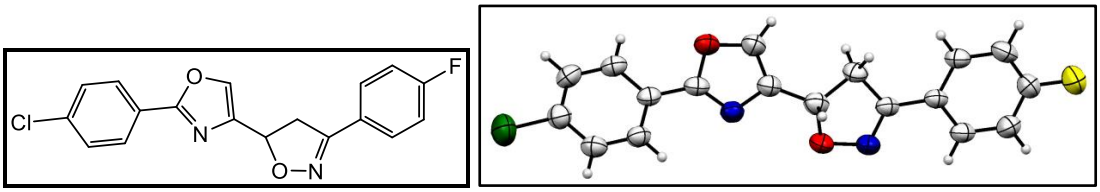


Figure 3.8 ***Structure and ORTEP diagram of compound 36c.***

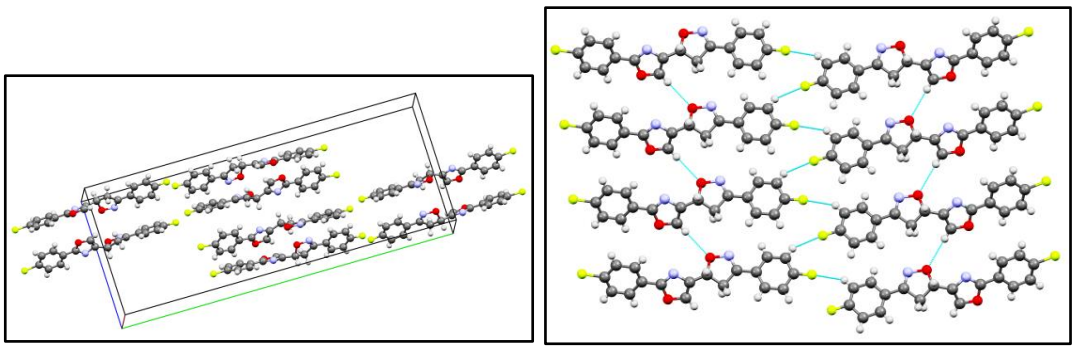


Figure 3.9 ***Unit cell and CH--O and CH--F interactions of 36c.***

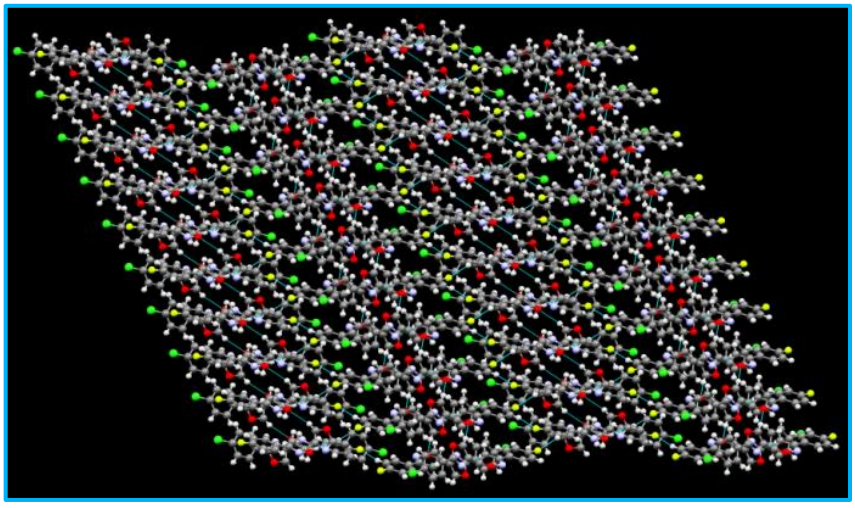


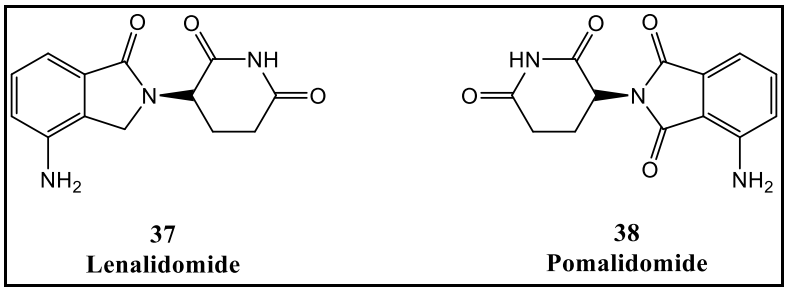
Figure 3.10 ***Molecular packing pattern of 36c.***

3.2.3 Anti-inflammatory Activity Study

Tumour necrosis factor (TNFα) is a cell signalling protein (cytokine) involved in systemic inflammation and is one of the cytokines that make up the acute phase reaction. It is produced chiefly by activated macrophages, although it can be produced by many other cell types such as NK cells, neutrophils, mast cells, eosinophils, and neurons.

The primary role of TNF is in the regulation of immune cells. TNF, being an endogenous pyrogen, is able to induce fever, apoptotic cell death, cachexia, inflammation and to inhibit tumorigenesis and viral replication and respond to sepsis via IL1 & IL6 producing cells. Dysregulation of TNF production has been implicated in a variety of human diseases[56–58] including Alzheimer's disease,[59] cancer,[60] major depression,[61] psoriasis and inflammatory bowel disease(IBD).[62]

A TNF inhibitor is a drug that suppresses the physiologic response to tumor necrosis factor (TNF), which is a part of the inflammatory response. Inhibition of TNF effects can be achieved with a monoclonal antibody such as infliximab,[63] adalimumab,[64] certolizumab pegol,[65] and golimumab[66] or with a circulating receptor fusion protein such as etanercept.[64] Thalidomide and its derivatives lenalidomide[67] (**37**) and pomalidomide[68] (**38**) (**Figure 3.11**) are also active against TNF.



37
Lenalidomide

38
Pomalidomide

Figure 3.11 ***TNF α inhibitors.***

Most of the clinically useful TNF inhibitors are monoclonal antibodies, some are simple molecules such as xanthine derivatives[69] such as pentoxifylline (**39**)[70] and bupropion (**40**)[71] (**Figure 3.12**).

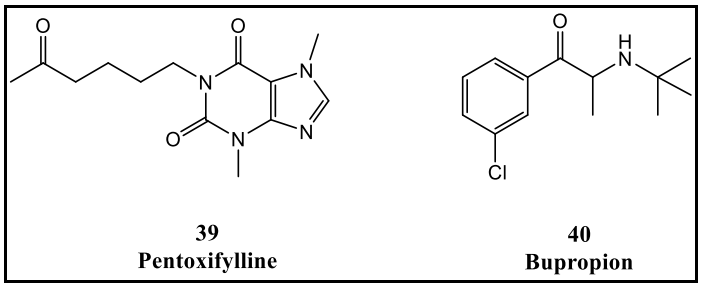


Figure 3.12 ***Clinically useful TNF inhibitors.***

As discussed earlier in this chapter in the introduction part there are many reports on anti-inflammatory activity of isoxazolines. Some imidazolyl substituted isoxazolines (**41**) (**Figure 3.13**) were prepared and screened for their anti-inflammatory activity.[72] New 4,5-diaryl-isoxazolines (**42**) (**Figure 3.13**) as inhibitors of COX-2 were synthesized and studied as anti-inflammatory agents.[19] New benzopyran substituted isoxazolines (**43**) (**Figure 3.13**) were prepared and studied as anti-inflammatory agents.[73]

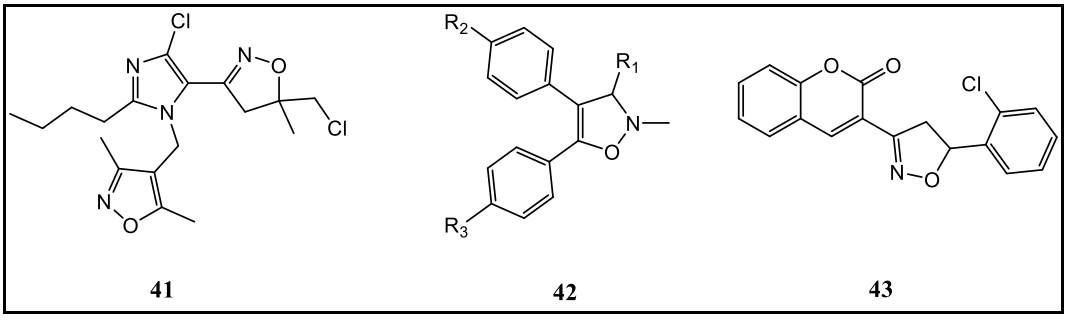


Figure 3.13

Based on the literature with a number of reports on the anti-inflammatory activity of isoxazolines, the newly synthesized aryl-oxazolyl-4,5-dihydroisoxazole analogues were subjected to the study for their preliminary *in vivo* anti-inflammatory (TNFα inhibitory) activity at two different concentrations (10μM and 100μM) in collaboration with the facility at the Zydus Research Centre, Ahemedabad.

The results of the *in vivo* anti-inflammatory activity (TNFα Inhibitory activity) study are summarized in **Table 3.2** and are graphically presented in **Figure 3.15**.

Table 3.2 ***Results of TNF-alpha inhibitory activity in rat whole blood.***

Evaluation of LPS (1µg/mL) induces TNF-alpha inhibitory activity in rat whole blood							
ID	**Conc. (µM)**	**% inhibition**		**ID**	**Conc. (µM)**	**% inhibition**	
		Mean	**S.E.M**			**Mean**	**S.E.M**
36a	10	**29.9**	14.1	**36f**	10	6.5	11.5
	100	**24.0**	4.6		100	12.4	8.7
36b	10	6.8	11.3	**36g**	10	7.1	14.8
	100	**22.2**	4.9		100	**21.4**	15.4
36c	10	7.3	6.8	**36h**	10	9.0	16.3
	100	16.5	7.6		100	13.4	19.0
36d	10	14.5	7.6	**36i**	10	6.5	14.5
	100	**24.9**	0.8		100	20.0	16.5
36e	10	**16.8**	11.8	**Prednis -olone**	10	52.3	9.4
	100	**38.9**	7.3		100	92.8	5.9

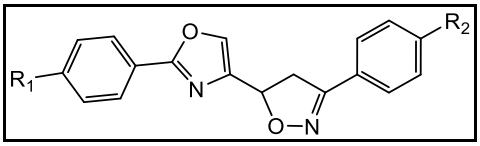


Figure 3.14 ***General structure of isoxazolines 36.***

Results of this study of TNFα inhibitory activity as % inhibition show that some compounds have a weak inhibiting effect even at 100 µM as well as at 10 µM concentrations. Compound **36a** (R_1 = H, R_2 = F) showed 29.9 and 24.0 % inhibition at 10 µm and 100 µm respectively (**Table 3.2** and **Figure 3.15**). Compound **36e** (R_1 and R_2 = F) showed 38.9 % inhibition at 100 µm concentration (**Table 3.2** and **Figure 3.15**). The standard drug prednisolone showed 52.3 % inhibition at 10 µm and 92.8 % inhibition at 100 µm concentration (**Figure 3.15**). A brief experimental procedure adopted TNFα inhibitory activity is included in the experimental section.

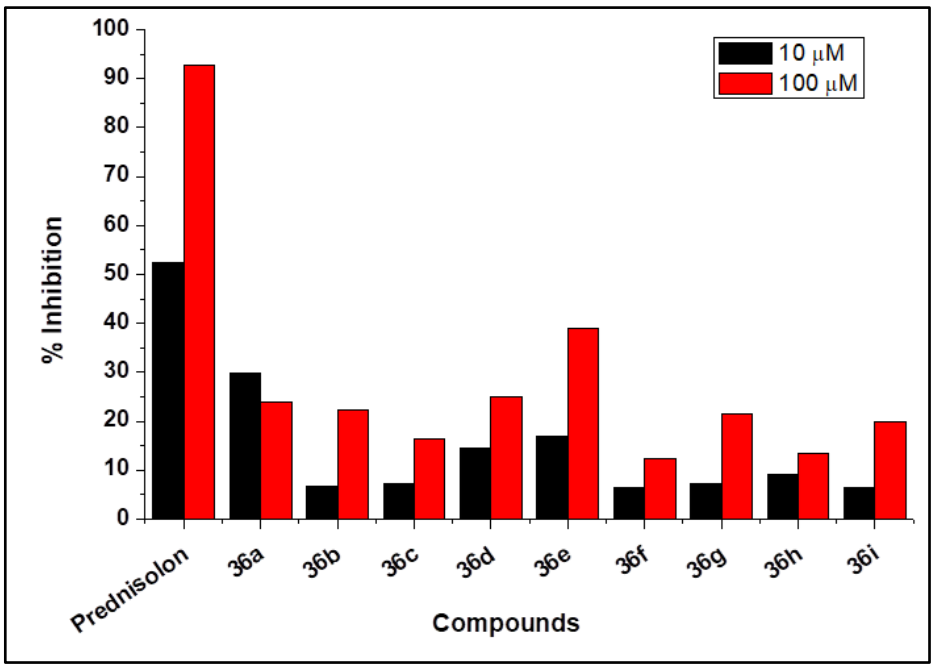


Figure 3.15 ***Results of TNF-α inhibitory activity in rat whole blood.***

3.3 Conclusion

In the present study, nine new aryl-oxazolyl-4,5-dihydroisoxazole derivatives are synthesized by employing the corresponding chalcones. All the new compounds are characterized by various spectroscopic methods and analytical data of all the compounds are in accordance with their proposed structures. Crystal structure of one of the compounds **36c** is studied using single crystal X-ray diffractometer. All the newly synthesized compounds have been screened for their *in vivo* anti-inflammatory activity in terms of measuring TNFα inhibitory activity. The compounds show moderate TNFα inhibitory activity. Noteworthy among them are compound **36a** having 29.9 and 24.0 % inhibition at 10 µM and 100 µM respectively and compound **36e** having 38.9 % inhibition at 100 µM concentration.

3.4 Experimental

General

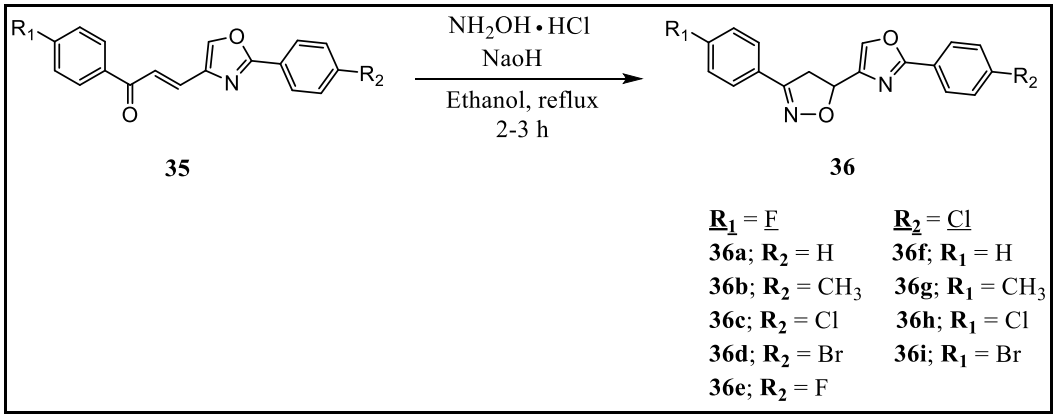
The chemicals were used as received from local companies without further purification. Organic solvents were purified by distillation prior to use.

Column chromatography was carried out using silica gel (60-120 mesh). Thin layer chromatography was performed on the pre-coated silica gel 60 F_{254} aluminium sheets. Melting points are determined in open capillary and are uncorrected.

FT-IR spectra were recorded on Perkin Elmer FT IR spectrometer between 4000-400 cm^{-1} in solid state as KBr discs. The NMR spectra were recorded on 400 MHz Bruker Avance-III instrument and chemical shifts are given in parts per million. In the NMR data for ^{19}F decoupled ^{1}H NMR experiments, the data for the affected signals only are included. ^{19}F chemical shift values are of ^{1}H decoupled ^{19}F signals.

Mass spectra were recorded on Thermo-Fischer DSQ II GC-MS instrument. X-ray diffraction data for the compounds were collected at room temperature using a Bruker Smart Apex CCD diffractometer.

General Procedure for the Synthesis of 3-aryl-5-(2-aryl-1,3-oxazol-4-yl)-4,5-dihydro-1,2-oxazoles 36.[55]

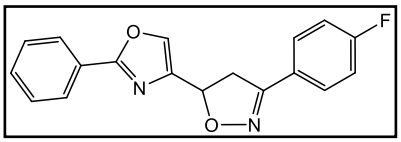


35 **36**

R_1 = F	**R_2** = Cl
36a; **R_2** = H	**36f**; **R_1** = H
36b; **R_2** = CH_3	**36g**; **R_1** = CH_3
36c; **R_2** = Cl	**36h**; **R_1** = Cl
36d; **R_2** = Br	**36i**; **R_1** = Br
36e; **R_2** = F	

To a magnetically stirred mixture of the respective 1-aryl-3-(2-aryloxazole-4-yl)propenone **35a-i** (1 mmole) and hydroxyl amine hydrochloride (1 mmole) in ethanol, NaOH solution (10%) was added drop-wise with stirring to make it basic up to pH 8-9 (pH paper) and the resulting reaction mixture was refluxed for 2-3 hrs. The product is having a greater polarity than that of the starting material as observed on TLC. The reaction mixture was than cooled to room temperature and poured in to ice cold water and was extracted with ethyl acetate. A crude product obtained on evaporation of solvent was subjected to column chromatography to isolate isoxazolines as white solid crystalline stable compounds **36**. Yield = 70-75%.

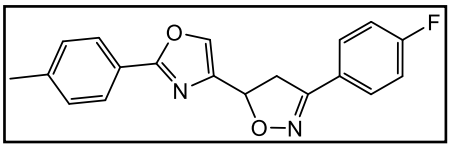
3-(4-Fluorophenyl)-5-(2-phenyl-1,3-oxazol-4-yl)-4,5-dihydro-1,2-oxazole 36a.



Compound **36a** was prepared following the general procedure described above by treating 1-(4 fluorophenyl)-3-(2-phenyloxazol-4-yl)-propenone **35a** (0.29g, 1 mmol) with hydroxylamine hydrochloride (0.068g, 1 mmol) in ethanol as a white crystalline solid. Yield = 0.221g, 71%; M.P. = 194 ^{o}C; **IR (KBr) cm^{-1}**: 3126, 2899, 1670, 1485, 1239, 838; **^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)**: 3.70-3.72 (2H, d, -CH_2 protons, ^{2}J = 9.2 Hz), 5.79-5.84 (1H, m, -CH proton), 7.11-7.16 (2H, m, Ar-H), 7.42-7.46 (2H, m, Ar-H), 7.70-7.77 (2H, m, Ar-H), 7.77-7.78 (1H, d, oxazole-H, ^{4}J = 0.8 Hz), 7.95-7.98 (2H, m, Ar-H); **^{19}F NMR (376 MHz, $CDCl_3$, δ ppm)** : -109.5; **^{13}C**

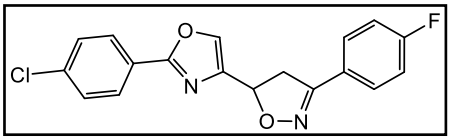
NMR (100 MHz, $CDCl_3$, δ ppm): 40.4 (-**C**H_2), 75.7 (-**C**H), 115.8, 116.0 (d, $^2J_{CF}$ = 22 Hz), 125.5, 125.6, 128.7, 128.1, 128.8, 128.88 (d, $^3J_{CF}$ = 9 Hz), 135.9, 136.7, 141.2, 155.6, 161.6 ; **EI-MS**: (m/z) 309.50 $(M+H)^+$ for $C_{18}H_{13}FN_2O_2$.

3-(4-Fluorophenyl)-5-(2-(4-methylphenyl)-1,3-oxazol-4-yl)-4,5-dihydro-1,2-oxazole 36b.



Compound **36b** was prepared following the general procedure described above by treating 1-(4-fluorophenyl)-3-(2-(4-methylphenyl)oxazol-4 -yl)-propanone **35b** (0.307g, 1 mmol) with hydroxylamine hydrochloride (0.068g, 1 mmol) in ethanol as a white crystalline solid. Yield = 0.225g, 70%; M.P. = 212 °C; **IR (KBr) cm^{-1}**: 3033, 2852, 1693, 1582, 1272, 841; **^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)**: 2.21 (3H, s, -CH_3 protons), 3.70-3.72 (2H, d, -CH_2 protons, ^2J = 9.2 Hz), 5.80-5.84 (1H, m, -CH proton), 7.10-7.14 (2H, m, Ar-H), 7.45-7.48 (3H, m, Ar-H), 7.69-7.74 (2H, m, Ar-H), 7.77 (1H, d, oxazole-H, ^4J = 0.8 Hz), 8.02-8.04 (2H, m, Ar-H); **^{19}F NMR (376 MHz, $CDCl_3$, δ ppm)** : -105.2; **^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)**: 30.9 (-**C**H_3), 40.4 (-**C**H_2), 76.2 (-**C**H), 115.8, 116.0 (d, $^2J_{CF}$ = 22 Hz), 125.5, 126.4, 127.1, 128.8, 128.88 (d, $^3J_{CF}$ = 9 Hz), 135.7, 136.7, 141.0, 155.6, 162.6; **EI-MS**: (m/z) 323.11 $(M+H)^+$ for $C_{19}H_{15}FN_2O_2$.

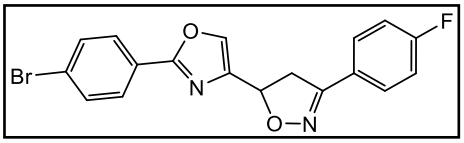
5-(2-(4-Chlorophenyl)-1,3-oxazol-4-yl)-3-(4-fluorophenyl)-4,5-dihydro-1,2-oxazole 36c.



Compound **36c** was prepared following the general procedure described above by treating 3-(2-(4-chlorophenyl)oxazol-4-yl)-1-(4-fluoro phenyl) – propenone **31c** (0.326g, 1 mmol) with hydroxyl amine hydrochloride (0.068g, 1 mmol) in ethanol as a white crystalline solid. Yield = 0.249g, 73%; M.P. = 176 °C; **IR (KBr) cm^{-1}**: 3112, 2848, 1698, 1533, 1263, 866; **^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)**: 3.19-3.50 (2H, dd, -CH_2 protons, ^2J = 8.4 Hz), 4.99-5.03 (1H, m, -CH proton), 7.07-7.11 (2H, m, Ar-H), 7.46-7.48 (2H, m, Ar-H), 7.65 (1H, d, oxazole-H, ^4J = 0.8 Hz), 7.67-7.70 (2H, m, Ar-H), 8.02-8.05 (2H, m, Ar-H); **^{19}F NMR (376 MHz, $CDCl_3$, δ ppm)** : -111.9; **^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)**: 40.3 (-**C**H_2), 75.7 (-**C**H), 115.8, 116.0 (d,

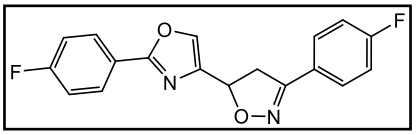
$^{2}J_{CF}$ = 22 Hz), 125.6, 126.8, 127.7, 128.7, 129.1, 129.2 (d, $^{3}J_{CF}$ = 9 Hz), 130.3, 135.9, 136.7, 141.4, 156.5, 161.5; **EI-MS**: (m/z) 381.85 $(M)^{+}$ for $C_{18}H_{12}ClFN_2O_2$.

5-(2-(4-Bromophenyl)-1,3-oxazol-4-yl)-3-(4-fluorophenyl)-4,5-dihydro-1,2-oxazole 36d.



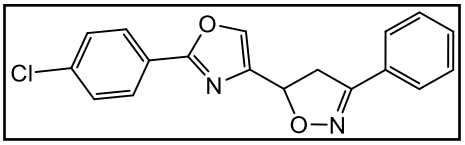
Compound **36d** was prepared following the general procedure described above by treating 3-(2-(4-bromophenyl)oxazol-4-yl)-1-(4-fluoro phenyl) -propenone **35d** (0.372g, 1 mmol) with hydroxyl amine hydrochloride (0.068g, 1 mmol) in ethanol as a white crystalline solid. Yield = 0.277g, 72%; M.P. = 202 °C; **IR (KBr) cm^{-1}**: 3127, 2847, 1651, 1567, 1285, 789; **^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)**: 3.21-3.49 (2H, d, -CH_2 protons, ^{2}J = 9.2 Hz), 4.97-5.02 (1H, m, -CH proton), 7.06-7.12 (2H, m, Ar-H), 7.59-7.62 (2H, m, Ar-H), 7.66 (1H, d, oxazole-H, ^{4}J = 0.8 Hz), 7.67-7.70 (2H, m, Ar-H), 7.88-7.91 (2H, m, Ar-H); **^{19}F NMR (376 MHz, $CDCl_3$, δ ppm)**: -109.6; **^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)**: 40.5 (-**C**H_2), 75.9 (-**C**H), 115.8, 116.0 (d, $^{2}J_{CF}$ = 22 Hz), 125.5, 126.4, 127.1, 128.8, 128.88, (d, $^{3}J_{CF}$ = 9 Hz), 130.6, 135.7, 141.1, 155.6, 162.5; **EI-MS**: (m/z) 386.00 $(M)^{+}$ for $C_{18}H_{12}BrFN_2O_2$.

3-(4-Fluorophenyl)-5-(2-(4-luorophenyl)-1,3-oxazol-4-yl)-4,5-dihydro-1,2-oxazole 36e



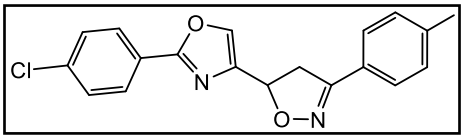
Compound **36e** was prepared following the general procedure described above by treating 3-(2-(4-fluorophenyl)oxazol-4-yl)-1-(4-fluoro phenyl) -propenone **35e** (0.311g, 1 mmol) with hydroxyl amine hydrochloride (0.068g, 1 mmol) in ethanol as a white crystalline solid. Yield = 0.241g, 74%; M.P. = 178 °C; **IR (KBr) cm^{-1}**: 3127, 2847, 1651, 1567, 1285, 789; **^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)**: 3.69-372 (2H, d, -CH_2 protons, ^{2}J = 9.2 Hz), 5.79-5.84 (1H, m, -CH proton), 7.10-7.15 (2H, m, Ar-H), 7.42-7.45 (2H, m, Ar-H), 7.70-7.74 (2H, m, Ar-H), 7.77 (1H, d, oxazole-H, ^{4}J = 0.8 Hz), 795-7.98 (4H, m, Ar-H); **^{19}F NMR (376 MHz, $CDCl_3$, δ ppm)**: -108.5, -111.9; **^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)**: 40.4 (-**C**H_2), 75.7 (-**C**H), 115.8, 116.0 (d, $^{2}J_{CF}$ = 22 Hz), 125.4, 125.5, 125.6, 127.7, 128.0 (d, $^{2}J_{CF}$ = 22 Hz), 128.8, 128.8 (d, $^{3}J_{CF}$ = 8 Hz), 129.1, 135.9, 136.7, 141.2, 155.6, 161.6, 162.6, 165.1 (d, $^{1}J_{CF}$ = 249 Hz); **EI-MS**: (m/z) 326.08 $(M)^{+}$ for $C_{18}H_{12}F_2N_2O_2$.

5-(2-(4-Chlorophenyl)-1,3-oxazol-4-yl)-3-phenyl-4,5-dihydro-1,2-oxazole 36f.



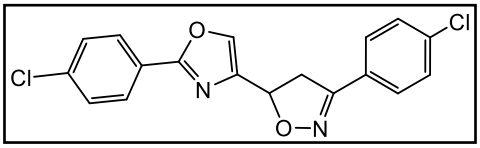
Compound **36f** was prepared following the general procedure described above by treating 3-(2-(4chlorophenyl)oxazol-4-yl)-1-phenyl-prope--none **35f** (0.309g, 1 mmol) with hydroxylamine hydrochloride (0.068g, 1 mmol) in ethanol as a white crystalline solid. Yield = 0.230g, 71%; M.P. = 178 °C; **IR (KBr) cm^{-1}**: 3155, 2927, 1677, 1483, 1292, 796; **^{1}H NMR (400 MHz, CDCl$_3$, δ ppm)**: 3.70-3.74 (2H, q, -CH_2 protons, ^{2}J = 9.2 Hz), 5.80-5.84 (1H, t(b), -CH proton), 7.43-7.47 (5H, m, Ar-H), 7.72-7.74 (2H, m, Ar-H), 7.77-7.78 (1H, d, oxazole-H, ^{4}J = 0.8 Hz), 7.96-7.98 (2H, m, Ar-H); **^{13}C NMR (100 MHz, CDCl$_3$, δ ppm)**: 40.4 (-**C**H_2), 75.7 (-**C**H), 125.6, 126.8, 127.7, 128.7, 128.8, 129.1, 129.2, 130.3, 135.9, 136.7, 141.4, 156.5, 161.5; **EI-MS**: (m/z) 324.06 $(M)^+$ for $C_{18}H_{13}ClN_2O_2$.

5-(2-(4-Chlorophenyl)-1,3-oxazol-4-yl)-3-(4-methylphenyl)-4,5-dihydro-1,2-oxazole 36g.



Compound **36g** was prepared following the general procedure described above by treating 3-(2-(4-chlorophenyl)oxazol-4-yl)-1-(4-methyl-phenyl) -propenone **35g** (0.323g, 1 mmol) with hydroxylamine hydrochloride (0.068g, 1 mmol) in ethanol as a white crystalline solid. Yield = 0.246g, 72%; M.P. = 172 °C; **IR (KBr) cm^{-1}**: 3123, 2920, 1674, 1502, 1285, 823; **^{1}H NMR (400 MHz, CDCl$_3$, δ ppm)**: 2.40 (3H, s, -CH_3), 3.65-3.76 (2H, m, -CH_2 protons, ^{2}J = 8.4 Hz), 5.80-5.84 (1H, m, -CH proton), 7.23-7.25 (2H, d, Ar-H, J = 8.0 Hz), 7.42-7.45 (2H, m, Ar-H), 7.61-7.63 (2H, d, Ar-H, J = 8.4 Hz), 7.77-7.78 (1H, d, oxazole-H, ^{4}J = 0.8 Hz), 7.95-7.98 (2H, m, Ar-H); **^{13}C NMR (100 MHz, CDCl$_3$, δ ppm)**: 21.5 (-**C**H_3), 40.5 (-**C**H_2), 75.5 (-**C**H), 125.6, 126.3, 126.8, 127.7, 129.1, 129.4, 135.9, 136.7, 140.6, 141.5, 156.5, 161.5; **EI-MS**: (m/z) 338.08 $(M)^+$ for $C_{19}H_{15}ClN_2O_2$.

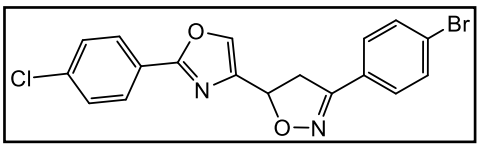
3-(4-Chlorophenyl)-5-(2-(4-chlorophenyl)-1,3-oxazol-4-yl)-4,5-dihydro-1,2-oxazole 36h.



Compound **36h** was prepared following the general procedure described above by treating

1-(4-chlorophenyl)-3-(2-(4-chlorophenyl) oxazol -4-yl)-propenone **35h** (0.343g, 1 mmol) with hydroxylamine hydrochloride (0.068g, 1 mmol) in ethanol as a white crystalline solid. Yield = 0.236g, 70%; M.P. = 176 ^{o}C; **IR (KBr) cm^{-1}**: 3132, 2839, 1611, 1562, 1095, 823; **^{1}H NMR (400 MHz, CDCl$_3$, δ ppm)**: 3.69-3.71 (2H, d, -CH$_2$ protons, ^{2}J = 9.2 Hz), 5.80-5.84 (1H, m, -CH proton), 7.40-7.46 (4H, m, Ar-H), 7.65-7.68 (2H, m, Ar-H), 7.77-7.78 (1H, d, oxazole-H, ^{4}J = 0.8 Hz), 7.95-7.98 (2H, m, Ar-H); **^{13}C NMR (100 MHz, CDCl$_3$, δ ppm)**: 41 (-**C**H$_2$), 75.9 (-**C**H), 125.6, 127.74, 127.78, 128.1, 129.0, 129.1, 136.0, 136.2, 136.8, 141.1, 155.6, 161.6; **EI-MS**: (m/z) 358.02 (M)$^{+}$ for $C_{18}H_{12}Cl_2N_2O_2$.

3-(4-Bromophenyl)-5-(2-(4-chlorophenyl)-1,3-oxazol-4-yl)-4,5-dihydro-1,2-oxazole 36i.



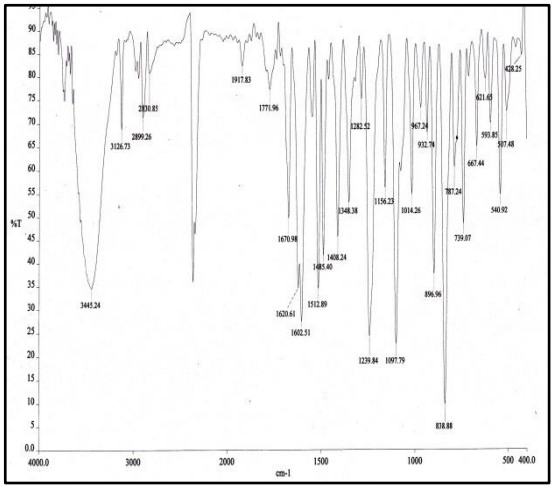
Compound **36i** was prepared following the general procedure described above by treating 1-(4-chlorophenyl)-3-(2-(4-bromophenyl)oxazol -4-yl)-propenone **35i** (0.386g, 1 mmol) with hydroxylamine hydrochloride (0.068g, 1 mmol) in ethanol as a white crystalline solid. Yield = 0.301g, 75%; M.P. = 168 ^{o}C; **IR (KBr) cm^{-1}**: 3136, 2859, 1684, 1502, 1052, 840; **^{1}H NMR (400 MHz, CDCl$_3$, δ ppm)**: 3.69-3.71 (2H, d, -CH$_2$ protons, ^{2}J = 9.2 Hz), 5.80-5.84 (1H, m, -CH proton), 7.42-7.46 (2H, m, Ar-H), 7.55-7.61 (4H, m, Ar-H), 7.77-7.78 (1H, d, oxazole-H, ^{4}J = 0.8 Hz), 7.95-7.98 (2H, m, Ar-H); **^{13}C NMR (100 MHz, CDCl$_3$, δ ppm)**: 41 (-**C**H$_2$), 75.9 (-**C**H), 124.6, 125.6, 127.7, 128.1, 128.3, 129.1, 132.0, 136.0, 136.8, 141.1, 155.7, 161.6; **ESI-MS**: (m/z) 401.97 (M)$^{+}$ for $C_{18}H_{12}BrClN_2O_2$.

Experimental Procedure of Anti-inflammatory Activity.

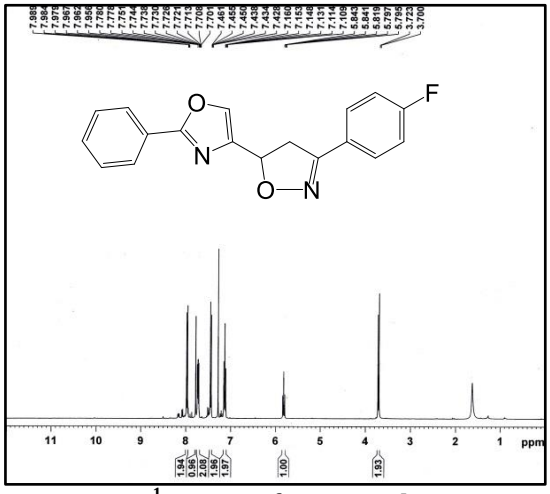
Male SD rats (8-10 weeks) were used in the study. Blood samples were collected from the animals in to heparinized tubes by retro orbital bleeding under isoflurane anaesthesia. Test compounds were dissolved in DMSO to get the desired concentrations. Then the samples were subjected to 1 µg/ml of LPS (E.Coli, Sigma-Aldrich, St. Louis, MO, USA) in PBS and incubated for 5h at 37 ^{o}C. Rat TNF-α was measured in the plasma using ELISA kit (BD biosciences, San Jose, CA, USA).

3.5 Spectral Data

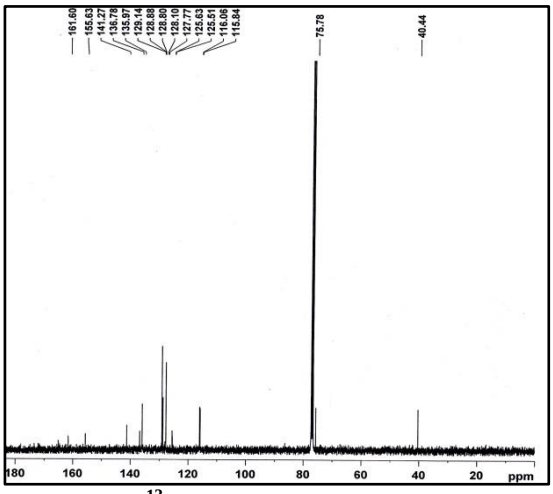
Compound 36a



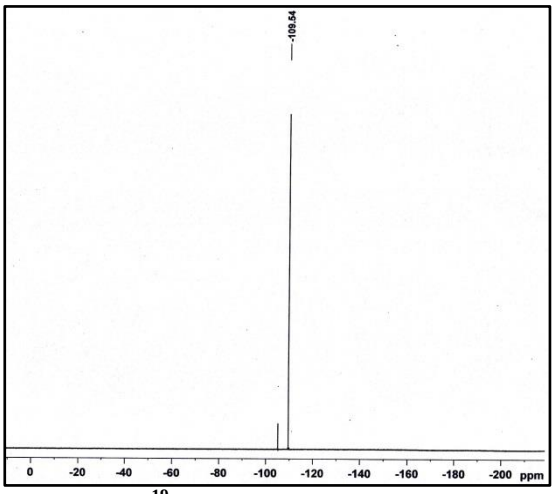
Spectrum 1. IR of compound 36a



Spectrum 2. ^{1}H NMR of compound 36a

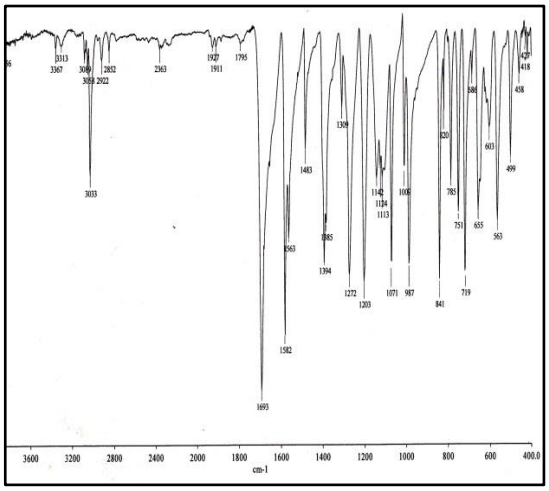


Spectrum 3. ^{13}C NMR of compound 36a

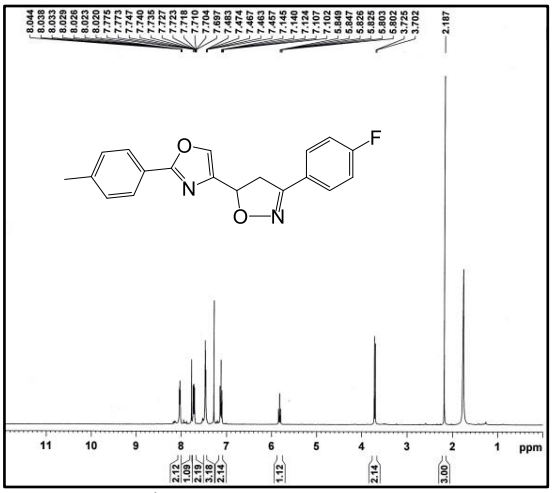


Spectrum 4. ^{19}F NMR of compound 36a

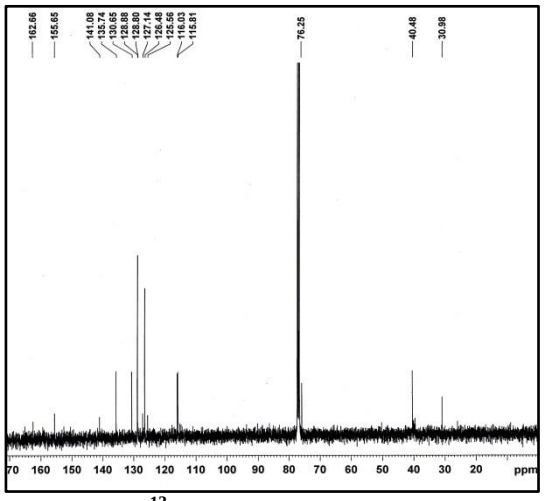
Compound 36b



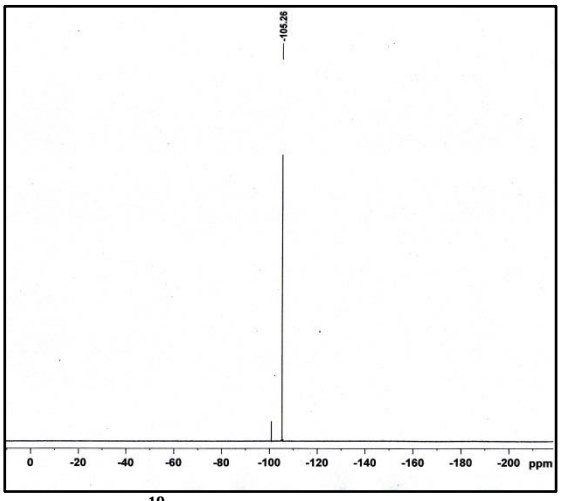
Spectrum 5. IR of compound 36b



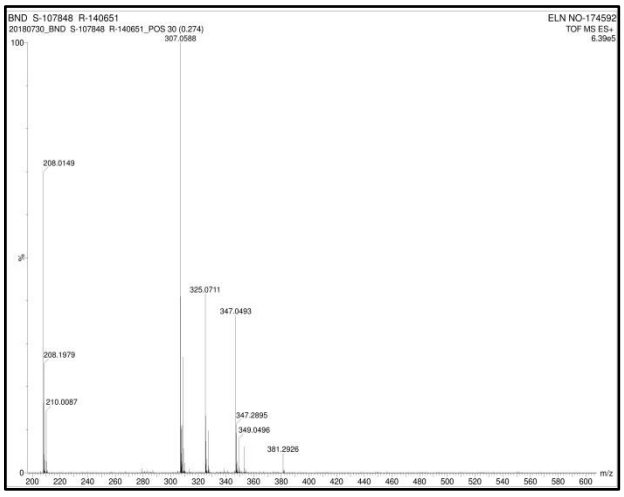
Spectrum 6. ^{1}H NMR of compound 36b



Spectrum 7. ^{13}C NMR of compound 36b

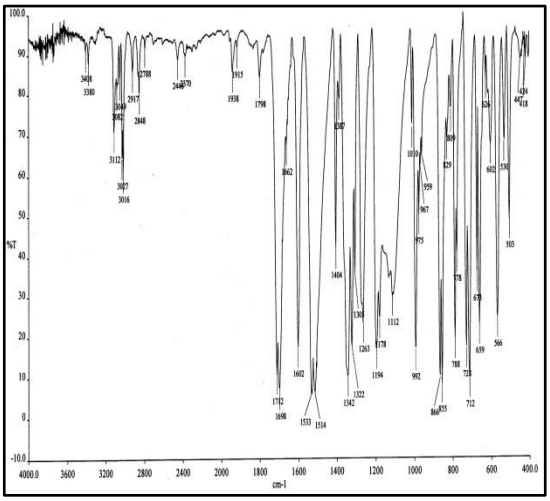


Spectrum 8. ^{19}F NMR of compound 36b

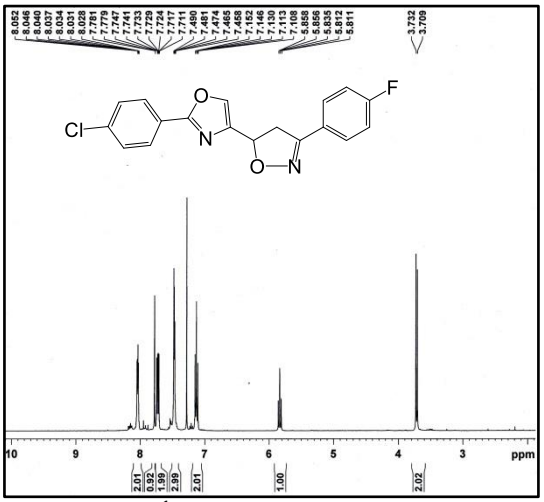


Spectrum 9. MASS of compound 36b

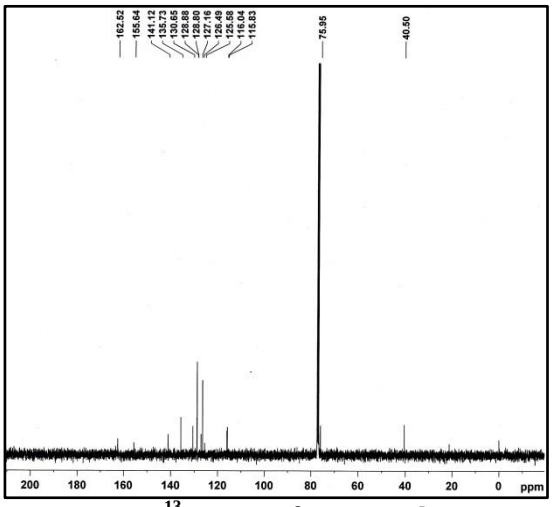
Compound 36c



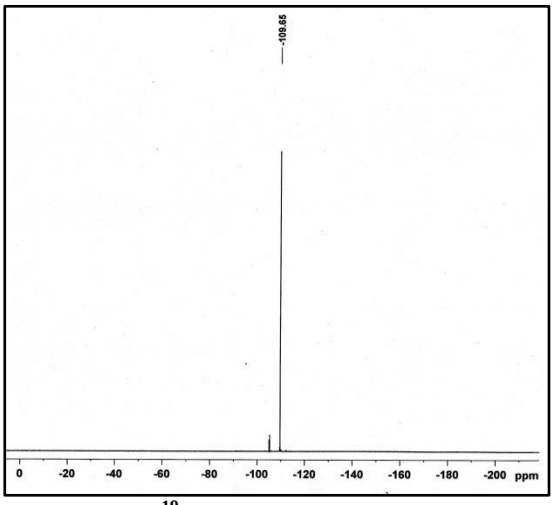
Spectrum 10. IR of compound 36c



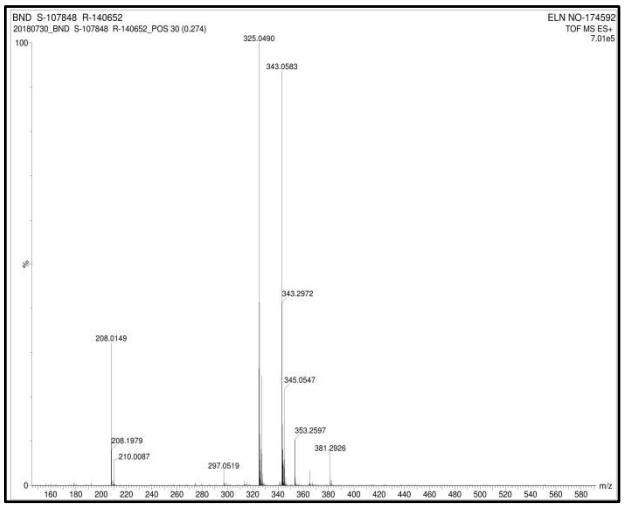
Spectrum 11. ^{1}H NMR of compound 36c



Spectrum 12. ^{13}C NMR of compound 36c

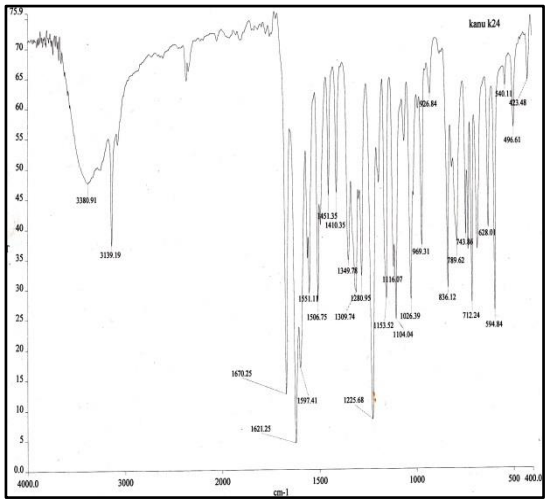


Spectrum 13. ^{19}F NMR of compound 36c

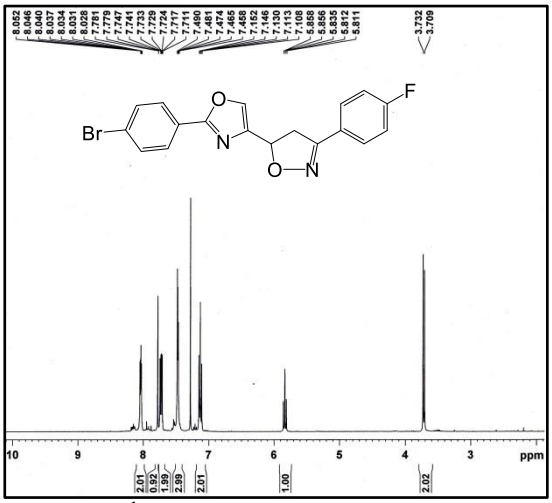


Spectrum 14. MASS of compound 36c

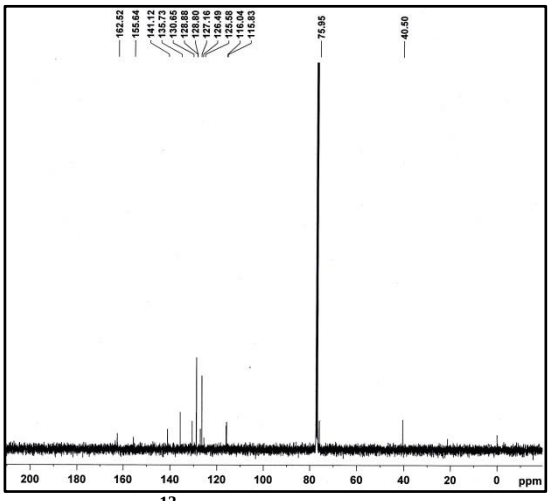
Compound 36d



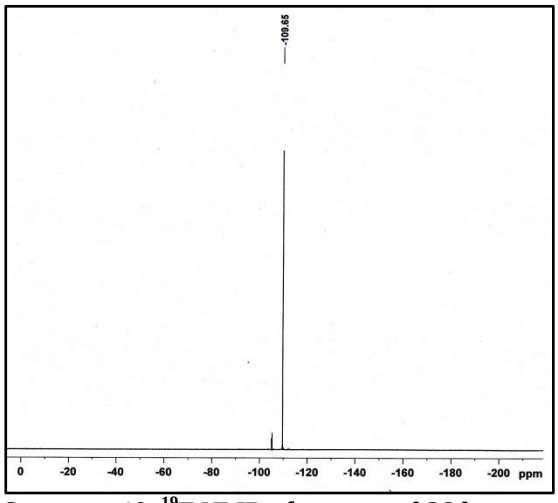
Spectrum 15. IR of compound 36d



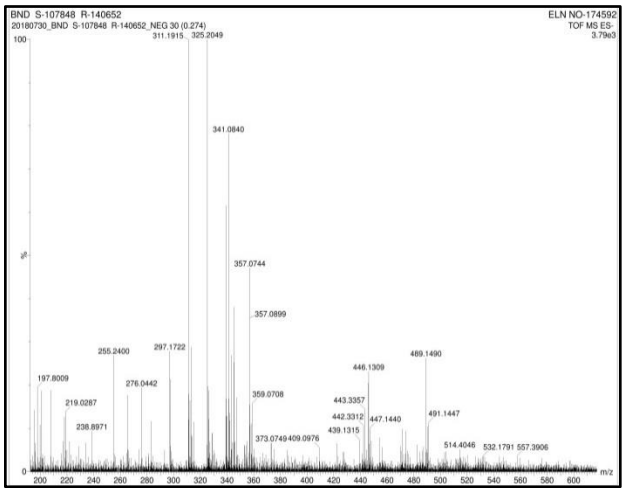
Spectrum 16. ^{1}H NMR of compound 36d



Spectrum 17. ^{13}C NMR of compound 36d

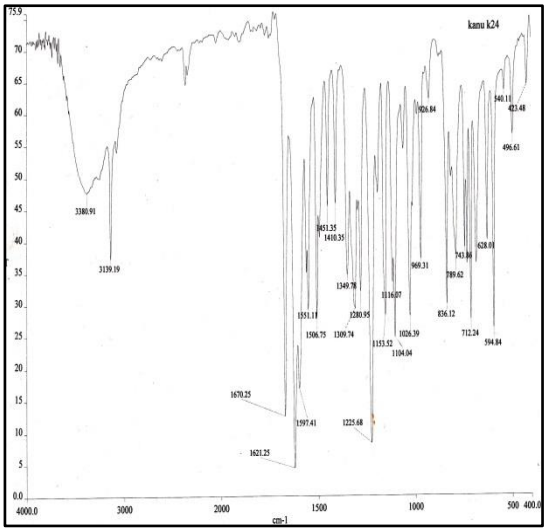


Spectrum 18. ^{19}F NMR of compound 36d

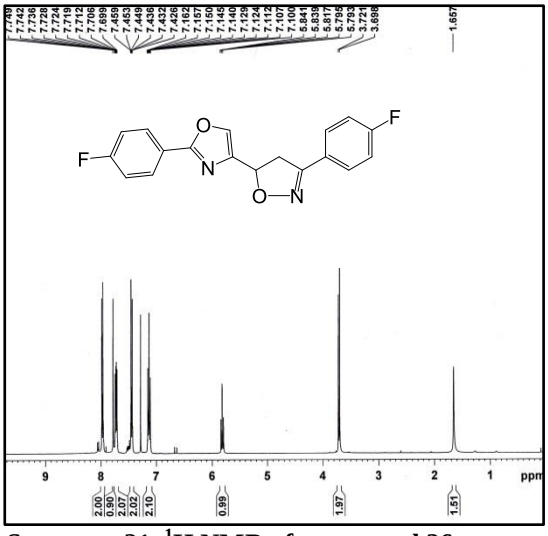


Spectrum 19. MASS of compound 36d

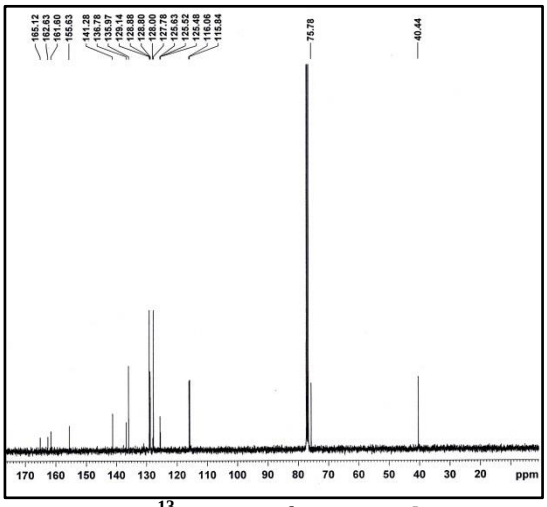
Compound 36e



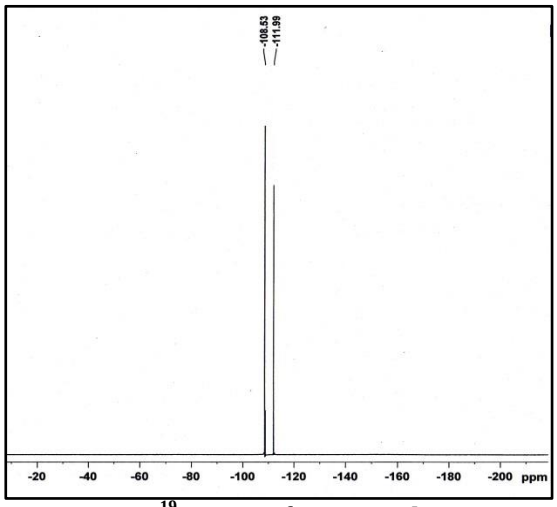
Spectrum 20. IR of compound 36e



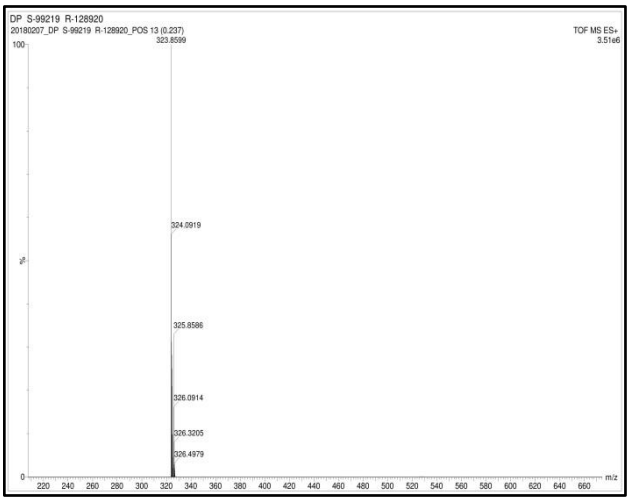
Spectrum 21. ^{1}H NMR of compound 36e



Spectrum 22. ^{13}C NMR of compound 36e

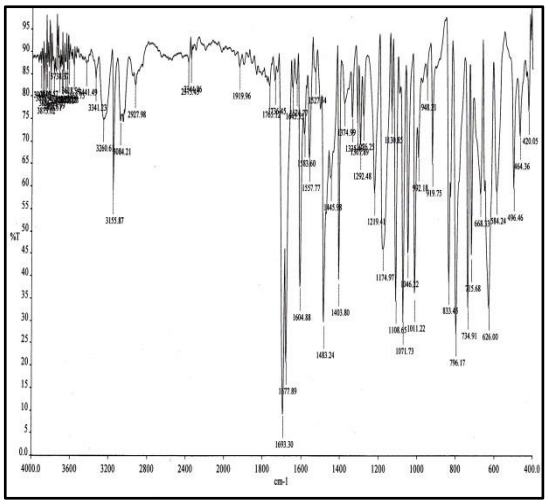


Spectrum 23. ^{19}F NMR of compound 36e

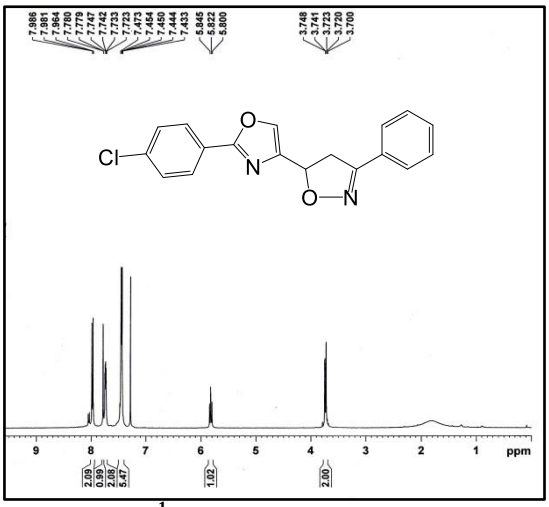


Spectrum 24. MASS of compound 36e

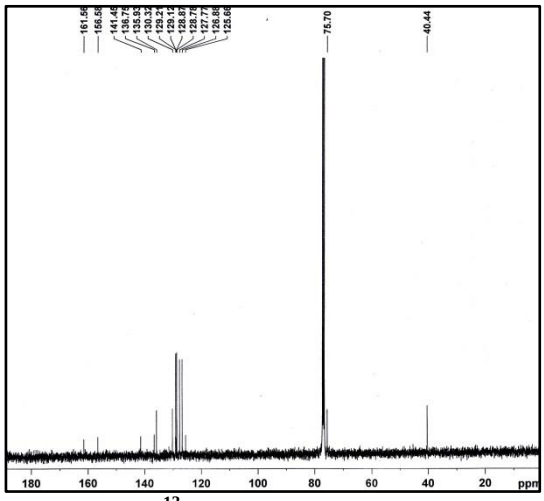
Compound 36f



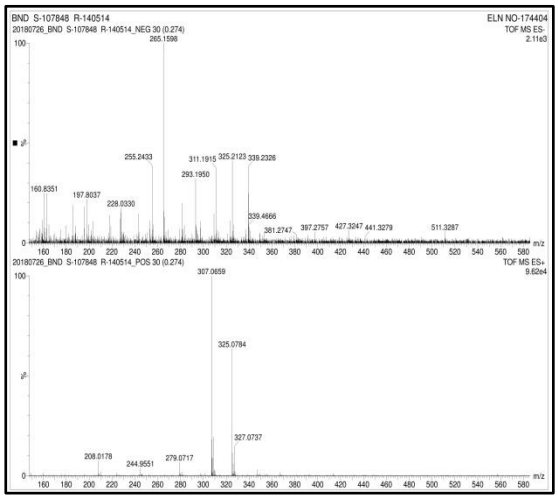
Spectrum 236. IR of compound 36f



Spectrum 26. ^{1}H NMR of compound 36f

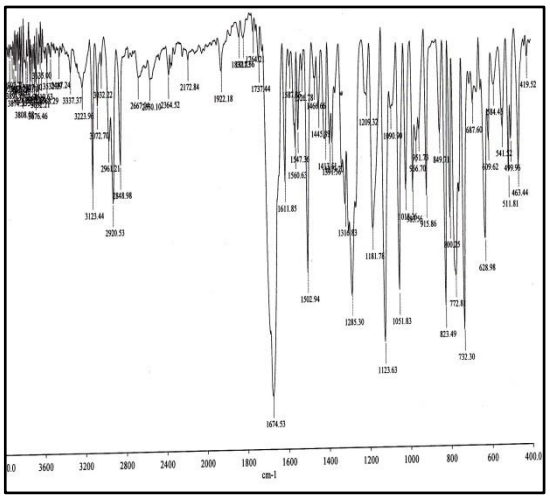


Spectrum 27. ^{13}C NMR of compound 36f

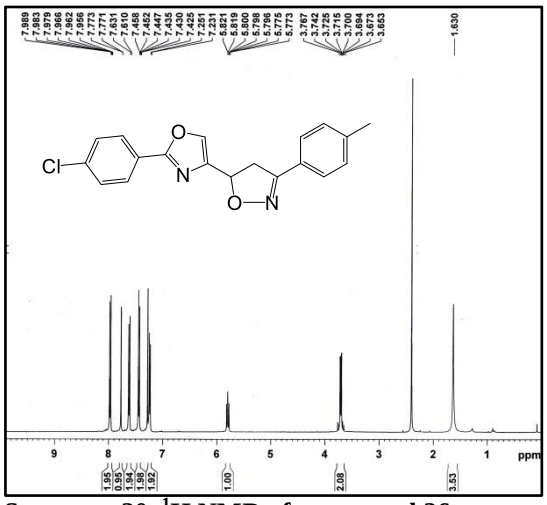


Spectrum 28. MASS of compound 36f

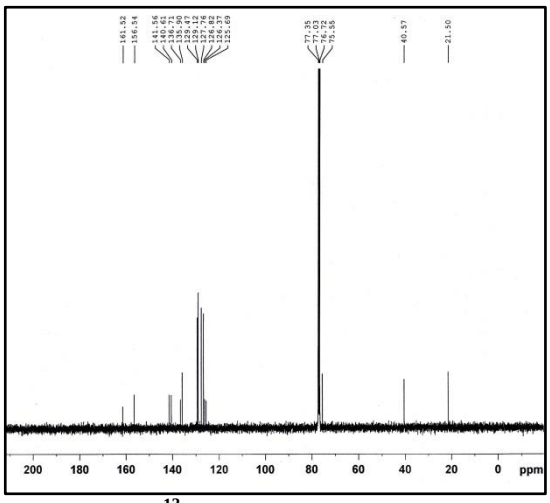
Compound 36g



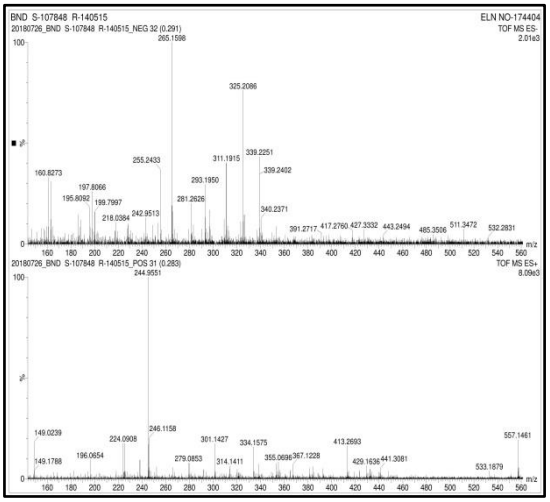
Spectrum 29. IR of compound 36g



Spectrum 30. ^{1}H NMR of compound 36g

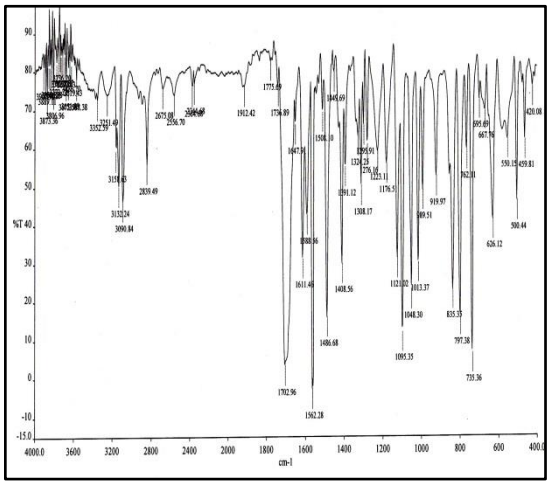


Spectrum 31. ^{13}C NMR of compound 36g

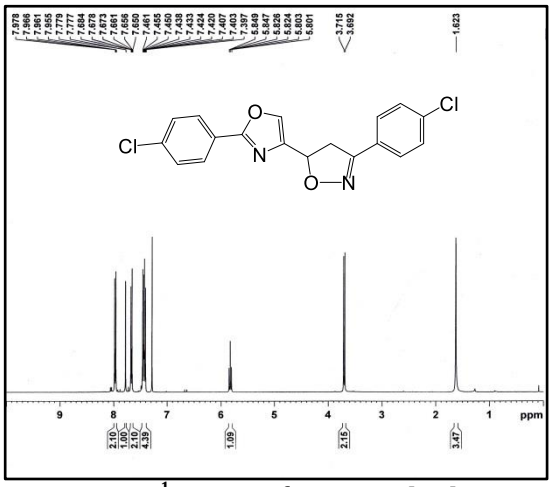


Spectrum 32. MASS of compound 36g

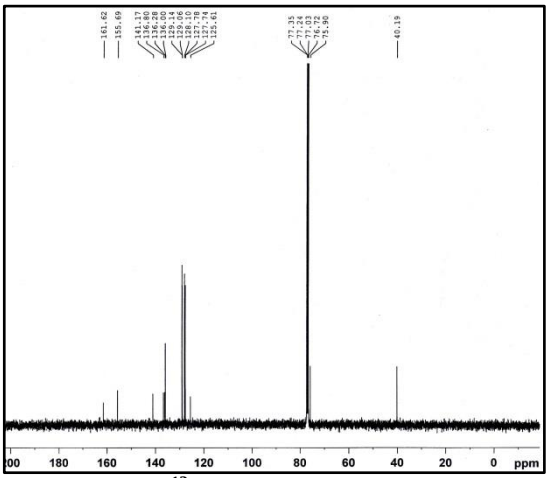
Compound 36h



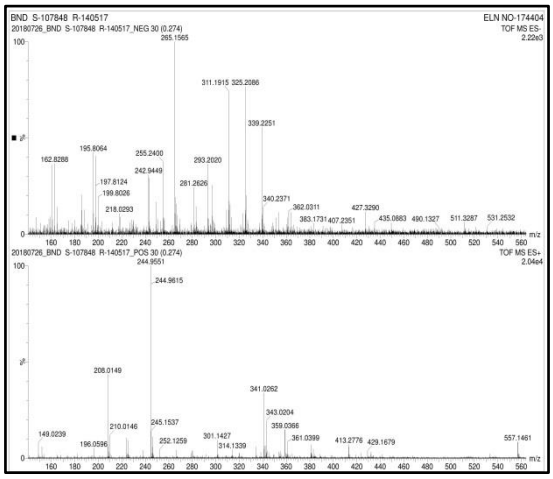
Spectrum 33. IR of compound 36h



Spectrum 34. ^{1}H NMR of compound 36h

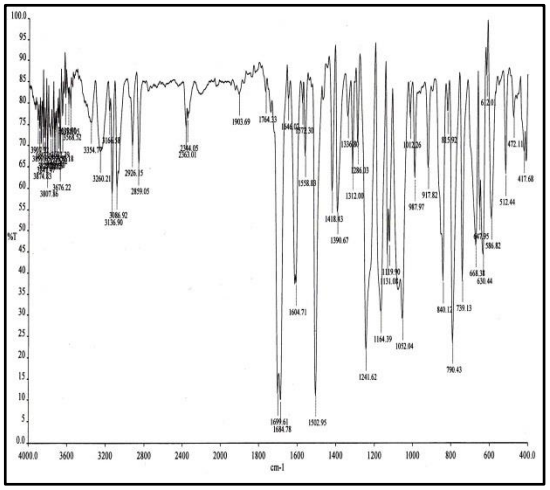


Spectrum 336. ^{13}C NMR of compound 36h

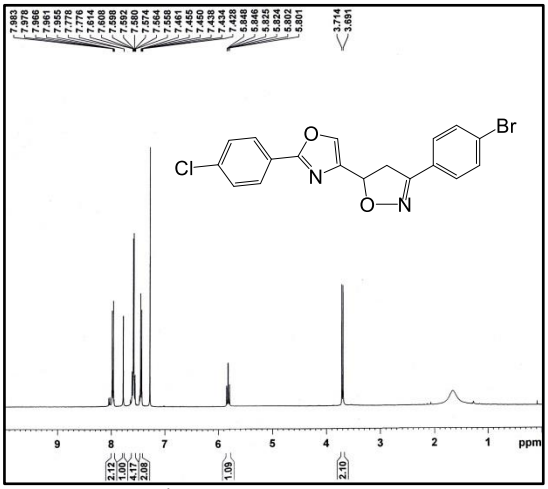


Spectrum 36. MASS of compound 36h

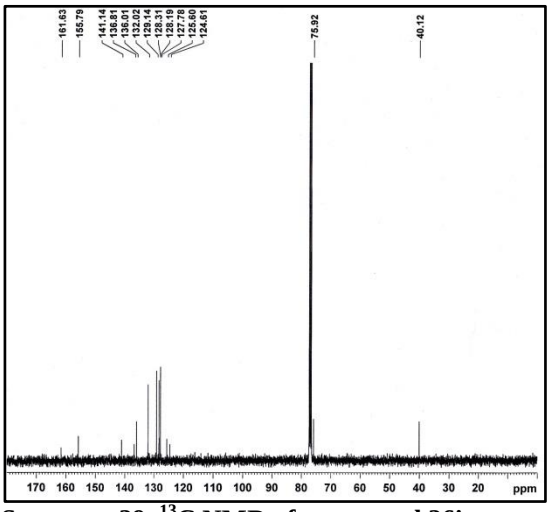
Compound 36i



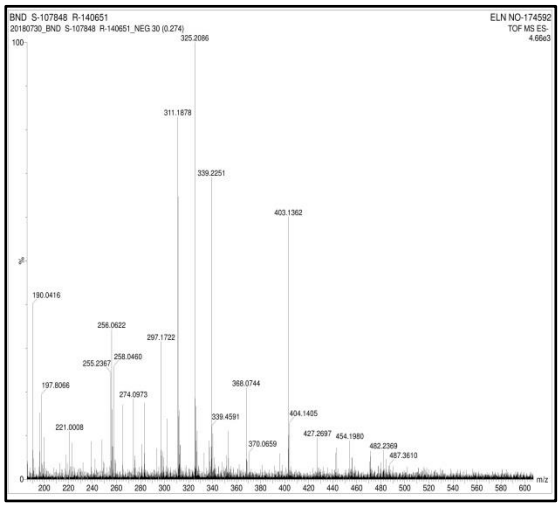
Spectrum 37. IR of compound 36i



Spectrum 38. ^{1}H NMR of compound 36i



Spectrum 39. ^{13}C NMR of compound 36i



Spectrum 40. MASS of compound 36i

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