Chapter – 5

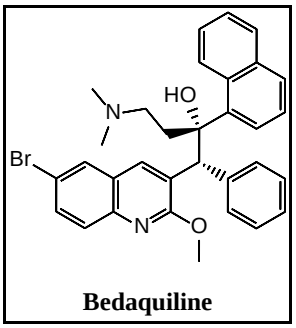
Synthesis and study of anti-tubercular activity of

(E)-N'-((2-Aryl-5-methyl-1,3-oxazol-4-yl) methylene)isonicotino-/nicotino-hydrazides and their docking study.

5.1 Introduction

This chapter deals with the synthesis of some new nicotino/isonicotino hydrazones prepared by the condensation of 1,3-oxazole carbonyl compounds to produce dual heterocyclic entities. The newly synthesized compounds are studied for their anti-tubercular activity and docking studies are carried out to understand the interactions of the active compounds with the enzyme inhA.

Tuberculosis (TB) is one of the deadly diseases and remains a foremost global health problem.[1] Tuberculosis was declared a global health emergency by the World Health Organization (WHO) in 1993.[1] With billions of people being infected, TB is still a leading killer in the world.[1,2] The development of drug-resistant TB (DR-TB), multidrug-resistant TB (MDR-TB) and totally drug resistance (TDR) increase the challenges in elimination of TB globally.[2] According to the recently released statistics, 52 crore (520 million) people in India are suffering from tuberculosis with 20% growth in one decade.[3]



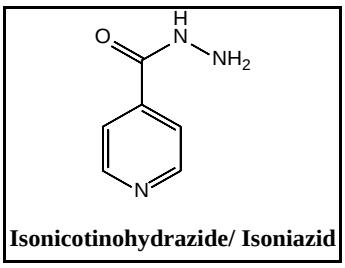
Bedaquiline

Figure 5.1

Bedaquiline (**Figure 5.1**) is the first new medicine for TB in more than 40 years, specifically is useful to treat multidrug-resistant tuberculosis (MDR-TB). It is approved for medical use by U.S. FDA in 2012 for use only in case of multidrug-resistant tuberculosis though is currently in phase-III study.[4] Bedaquiline was discovered by Koen Andries and team at Janssen Pharmaceutica[5] and it was first time described in 2004 at the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC).[6] It is the first member of the new class of drugs called diarylquinolines and acts by blocking the proton pump for ATP synthase of mycobacteria.[7]

Natural products are extremely useful templates for the development of a number of the new drug molecules[8] and they have received a substantial attention as potential anti-TB agents.[9–11] Numerous natural products have been reported to have effective activity against resistant strains of *Mycobacterium tuberculosis.*[12–16] However, no new anti-TB drugs have been developed in the TB therapy in the course of the past few years, creating an urgent need of developing of new drugs and strategies for an effective TB treatment.

Nitrogen containing heterocycles constitute a major part of natural products[9] and possess a wide range of applications as drug molecules.[17–19] Isoniazid (**INH**) (**Figure 5.2**) and its derivatives, the N-containing heterocyclic hydrazide and derivatives, have added importance in medicinal chemistry due to their variety of biological activities such as antimycobacterial,[20–22] antibacterial,[23] antivirus,[24] antifungal,[25] antitumor[26,27] and analgesic[28] activities. Amongst the numerous activities, the anti-TB activity is remarkable and due to that it is currently used in the treatment of tuberculosis.



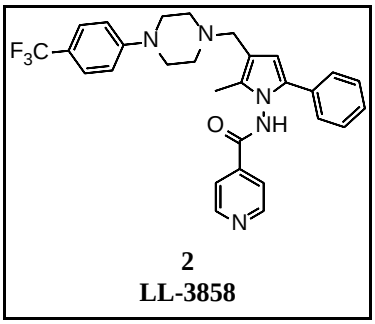
Isonicotinohydrazide/ Isoniazid

Figure 5.2

Isoniazid or **INH** is isonicotinic acid hydrazide, which is a widely employed first-line drug used for the treatment of tuberculosis.[29,30] Within last few years syntheses of a number of derivatives of isoniazid (INH) have been reported and some of them exhibit good *in vitro* antimycobacterial activity.[20–22,31] Isoniazid is a prodrug and gets activated by a catalase-peroxidase enzyme known as KatG in mycobacteria.[32,33] The activated form reacts non-enzymatically with co-enzymes, NAD^+ and $NADP^+$ to form isonicotinoyl-NAD(P) complex, which binds with the enoyl-acyl carrier protein (ACP) reductase InhA. The enzyme, InhA helps in the synthesis of mycolic acid.[34–36] Thus isoniazid inhibits the synthesis of mycolic acid which is essential for the mycobacterial cell wall. Bacterial strains resistant to INH are becoming common and with the

development of multi-drug resistant tuberculosis, especially among persons with HIV infection, even combination therapy is also not useful.

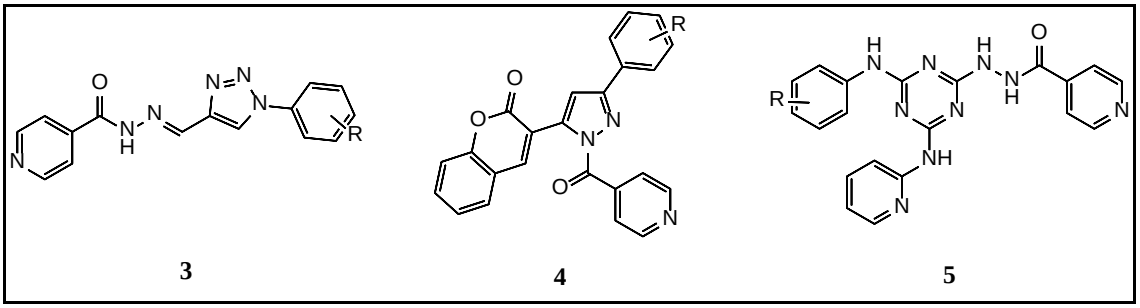
The derivatization of the INH and nicotinic hydrazide is possible as they can easily react with carbonyl compounds via the reactive hydrazide group to form hydrazones or can be cyclo condensed to yield cyclic products. Isoniazid derivative LL-3858 (**2) s**hows activity against both the drug sensitive and multidrug resistant TB and is in the initial stage of phase II clinical trial for the treatment of tuberculosis[20,37,38] (**Figure 5.3**).



2
LL-3858

Figure 5.3

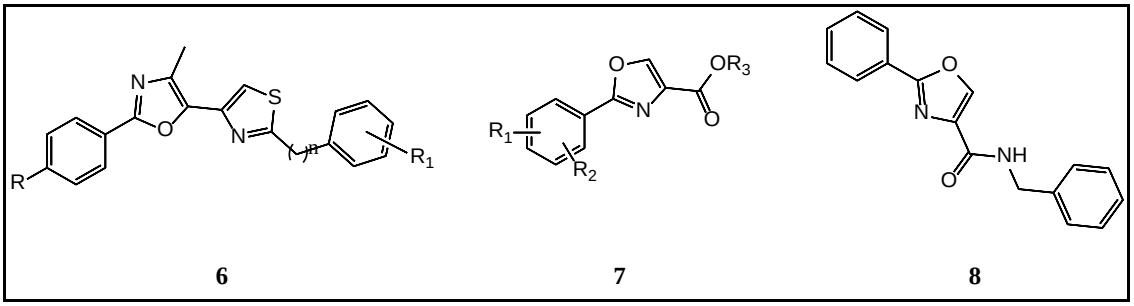
A series of INH-triazole hybrids (**3**) (**Figure 5.4**) were synthesized and evaluated for *in vitro* anti-mycobacterial activity against *tuberculosis* H37Rv.[39] Several INH derived-pyrazole derivatives (**4)** (**Figure 5.4**) along with coumarine moiety were prepared and studied for their *in vitro* anti-mycobacterial activity against *tuberculosis* H37Rv.[40] A variety of INH-triazine hybrids (**5)** (**Figure 5.4**) having pyridine and substituted anilines on 1,3,5-triazine were synthesized and evaluated for their *in vitro* anti-TB activity against *tuberculosis* H37Rv.[41]



3 **4** **5**

Figure 5.4 ***Representative isoniazid containing anti-TB compounds.***

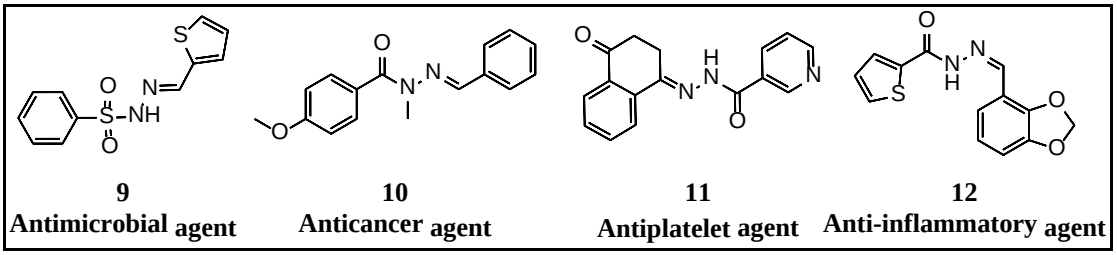
Oxazoles have also shown to possess promising anti-TB activity. A series of thiazolyl-oxazole (**6**) (**Figure 5.5)** have been prepared and evaluated for their preliminary anti-tubercular activity study.[42] Several oxazole esters (**7**) (**Figure 5.5**) have been prepared which have good to excellent anti-tubercular potency.[43] A number of oxazole based, small molecules (**8**) (**Figure 5.5**) were synthesized and were shown to possess an impressive activity against *tuberculosis* with extremely low toxicity.[44]



6 **7** **8**

Figure 5.5 ***Oxazole based anti-tubercular agents.***

On the other hand hydrazones show a diverse biological activities not only because of hydrazone linkage but also due to various heterocyclic moieties brought together either from a hydrazine, hydrazide or from a carbonyl compound. Hydrazones have been studied widely for a numerous bioactivities such as antimycobacterial,[45] antimalarial,[46] antibacterial,[47] antidepressant,[48] anticonvulsant,[49] anti-inflammatory,[50] analgesic[51] and antitumor[52,53] activities. Some of the representative hydrazone molecules with their biological activities are presented in **Figure 5.6**.



9 **Antimicrobial agent** **10** **Anticancer agent** **11** **Antiplatelet agent** **12** **Anti-inflammatory agent**

Figure 5.6 ***Biologically active hydrazones.***

Hydrazones can be prepared by condensation reaction of hydrazine derivatives with aldehydes or ketones (**Figure 5.7**). The chemistry of the formation of this hydrazones involves the nucleophilic addition followed by dehydration. Various derivatives of

hydrazones such as semicarbazones, thiosemicarbazones and guanyl hydrazones are important compounds for the drug design of anti-tubercular agents.

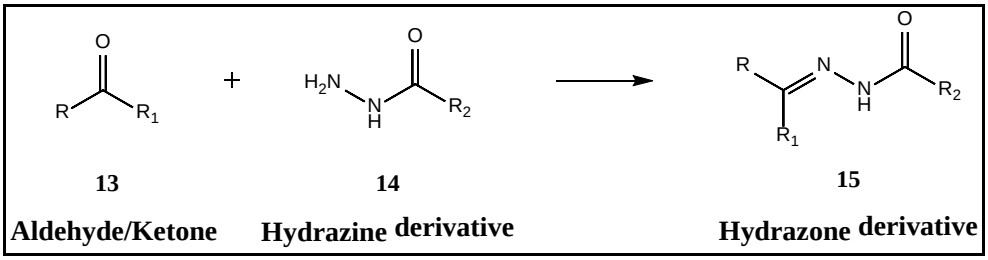


Figure 5.7

Due to a broad biological activities of hydrazones, numerous types of hydrazides and hydrazones have attracted continuous interest in the medicinal field, among them INH hydrazone derivatives exhibit excellent anti-TB activity.[20,47,54–57]

Several new INH hydrazone derivatives **16** (**Figure 5.8**) were studied for their anti-mycobacterial activity against *tuberculosis* H37Rv.[58] A series of INH linked with different anilines via a carbonyl group **17** (**Figure 5.8**) were studied for their *in vitro* antimycobacterial activity against *tuberculosis* H37Rv, *M. avium* 330/88, *M. kansasii* 235/80 and *M. kansasii* 6509/96.[59] A series of INH benzylidene derivatives **18** (**Figure 5.8**) were prepared and evaluated *in vitro* as potential anti-mycobacterial against *M. tuberculosis* H37Rv.[60] A series of hydrazones of INH **19** (**Figure 5.8**) were prepared and evaluated *in vitro* and *in vivo* against *M. tuberculosis* H37Rv and *M. tuberculosis* Erdman.[57]

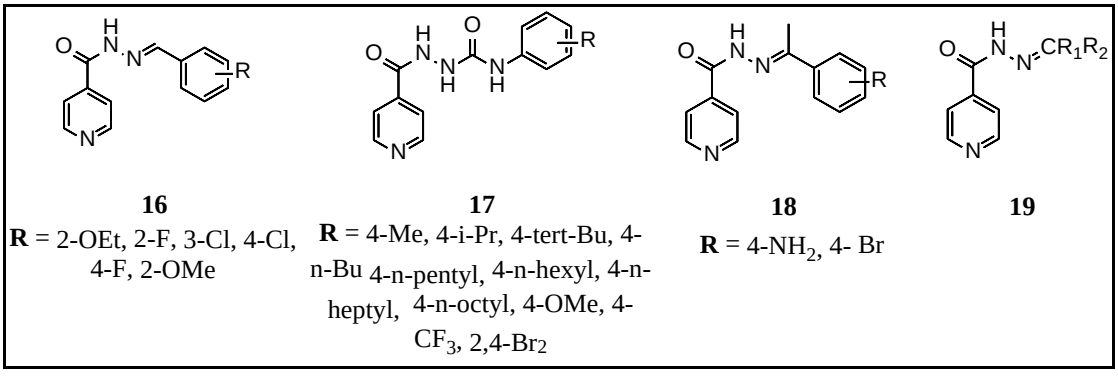
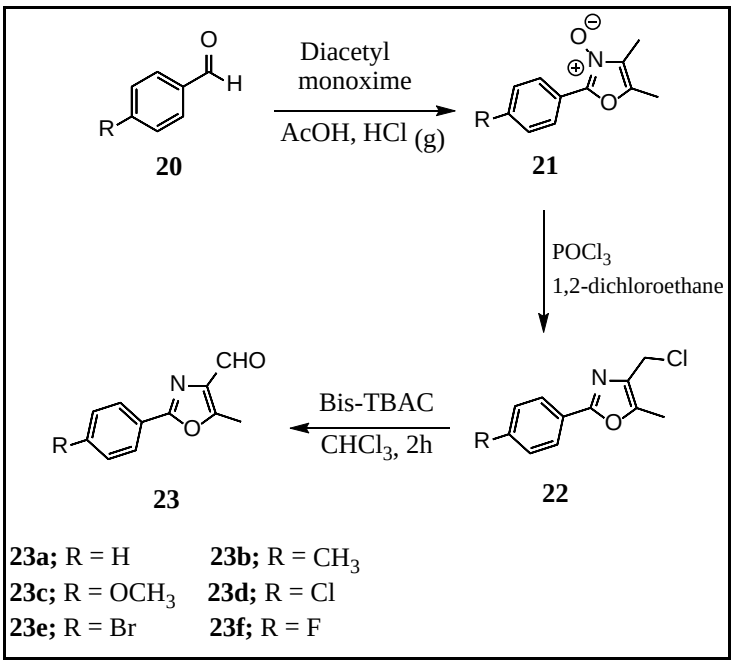


Figure 5.8 ***INH hydrazone derivatives as anti-TB agents.***

5.2 Results and Discussion

In this chapter some new oxazolyl hydrazones have been prepared by employing 2-aryl-5-methyl-1,3-oxazole-4-carbaldehydes and two different isomeric heteroaryl hydrazides namely isonicotinic acid hydrazide and nicotinic acid hydrazide. All the new oxazole containing hydrazones are characterized and evaluated for their *in vitro* anti-tubercular activity.

To start with, the synthesis of six 2-aryl-5-methyl-1,3-oxazole-4-carbaldehydes **23a-e** was undertaken following the procedure discussed in the previous chapter. 4-Substituted aldehydes **20** were reacted with diacetyl monoxime leading to the oxazolyl N-oxides **21** which were treated with $POCl_3$ to give the chloromethyl oxazoles **22.** [61–63] 2-Aryl-5-methyl-1,3-oxazole-4-carbaldehydes **23** were obtained by oxidation of the chlorinated oxazoles **22** with bis-TBAC (bis-tetrabutylammonium dichromate) in chloroform.[64]



Scheme 5.1 ***Synthesis of 2-aryl-5-methyl-1,3-oxazole-4-carbaldehydes 23.***

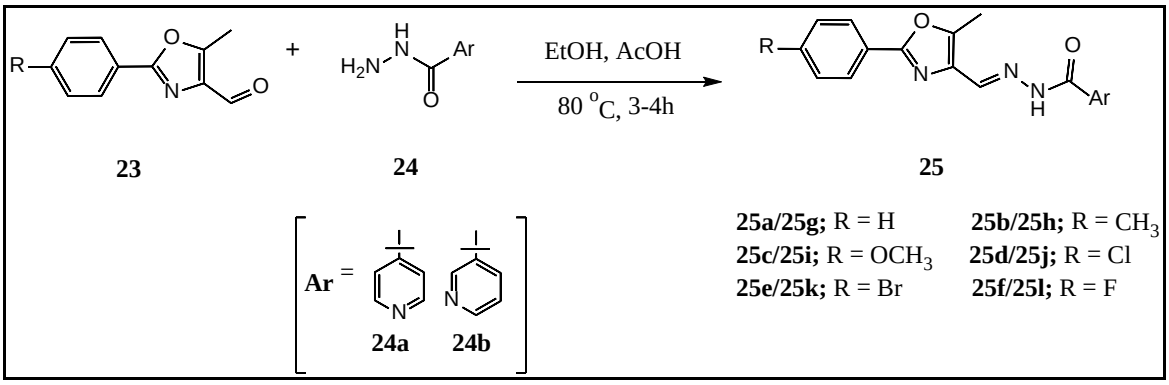
Some 2-aryl-5-methyl-1,3-oxazole-4-carbaldehydes are reported in patents using some other synthetic route with no physical or spectral data available.[65–67]

Physical data (yield, mp) of all the synthesized aryl oxazolyl carbaldehydes are presented in **Table 5.1.**

Table 5.1 ***Physical data (yields, mp) and substitution on 2-aryl-5-methyl-1,3-oxazole-4-carbaldehydes (23a-f).***

	R	Molecular Formula	Yield	mp
23a	-H	$C_{11}H_9NO_2$	49 %	88 ^oC
23b	$-CH_3$	$C_{12}H_{11}NO_2$	48 %	106 ^oC
23c	$-OCH_3$	$C_{12}H_{11}NO_3$	51 %	114 ^oC
23d	Cl	$C_{11}H_8ClNO_2$	59 %	109 ^oC
23e	Br	$C_{11}H_8BrNO_2$	54 %	128 ^oC
23f	F	$C_{11}H_8FNO_2$	50 %	121 ^oC

N'-((2-Aryl-5-methyl-1,3-oxazolyl)methylene)isonicotino/nicotino-hydrazides **25a-l** were synthesized by condensation[68] of 2-aryl-5-methyl-1,3-oxazole-4-carbaldehydes **23a-f** with the corresponding hydrazides **24a/24b** in ethanol using acetic acid as a catalyst to afford the final new nicotinoyl/isonicotinoyl hydrazones **25a-l**.



Scheme 5.1 ***N'-((2-Aryl-5-methyl-1,3-oxazolyl)methylene)isonicotino/nicotino-hydrazides 25a-l.***

5.2.1 Spectral Characterization

All the synthesized aryl oxazolyl carbaldehydes **23(a-f)** and oxazolyl hydrazones **25(a-l)** are characterized by various spectro-analytical techniques.

The IR spectra of aryl oxazolyl carbaldehydes **23(a-f)** show a characteristic aromatic C-H stretching band at ~3080 cm^{-1} and formyl C-H stretching is observed as two bands at ~2742 cm^{-1} and ~2840 cm^{-1} due to the Fermi resonance. A strong C═O stretching band is observed at ~1690 cm^{-1}. The IR spectra of aryl-oxazolyl-isonicotino/nicotino-hydrazides **25(a-l)** show the typical N–H stretching bands in between 3295-3200 cm^{-1}. A strong band of C═O stretching is observed at ~1695 cm^{-1} and C=N stretching band is observed as a strong to medium intensity band between 1554–1560 cm^{-1} flanked by the bands at ~1500 and ~1600 cm^{-1} for aromatic C=C stretching frequency. For all the compounds C-O stretching frequencies are observed at ~1260 cm^{-1} and ~1070 cm^{-1}. C-Cl and C-Br stretching for compound possessing Cl and Br as substituents are observed at ~846 cm^{-1} and ~730 cm^{-1}.

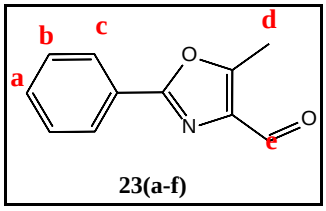


Figure 5.9A ***Proton labels on compounds 23(a-f).***

In the ^{1}H NMR of aryl oxazolyl carbaldehydes **23(a-f)** (**Figure 5.9A**) the methyl group protons **d** is observed at δ 2.7 ppm as a singlet and a the formyl proton **e** is observed at δ 10.02 ppm as a singlet. The other aromatic protons are observed between δ 7.0-8.5 ppm as per the substitution present if any at the position 4 of the aromatic ring.

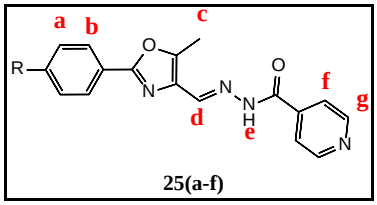


Figure 5.9B ***Proton labels on compounds 25(a-f).***

The (aryl-oxazolyl)-isonicotino-hydrazides **25(a-f)** show characteristic ^{1}H NMR signals with distinct chemical shifts for different kinds of protons (**Figure 5.9B** above). The methyl protons **c** are observed at δ 2.6 ppm for all the twelve compounds. The methylene proton **d** on the imine linkage (-N=CH-) is observed as singlet between δ 7.4-7.5 ppm and N–H proton **e** of the hydrazine group is observed most downfield between δ 12.0-14.0 ppm as a singlet. The aromatic proton **g** of pyridine ring is observed as a doublet at δ 8.8 ppm with coupling constant J = 6.0 Hz and proton **f** of the same pyridine ring is observed as a doublet at δ 7.9 ppm with coupling constant J = 6.0 Hz. While the aromatic protons **a** and **b (**R ≠ H**)** are observed as a doublet at δ 7.5 ppm and δ 8.0 ppm respectively with coupling constant J = 8.0 Hz.

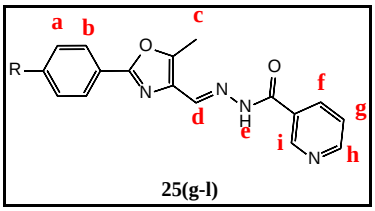


Figure 5.9C ***Proton labels on compounds 25(g-l).***

For compounds **25(f-j)** (**Figure 5.9C** above), the methyl protons appears at δ 2.6 ppm. The aromatic protons **a** and **b** of the substituted phenyl ring are observed as a doublet at δ 7.5 ppm and δ 8.2 ppm respectively with the coupling constant J = 8.4 Hz. The aromatic proton **h** of pyridine ring appears at δ 8.8 ppm (J = 4.4 Hz). while protons **f** and **g** are observed at δ 7.5 ppm and δ 8.4 ppm respectively with the coupling constant J = 8.0 Hz. Proton **i** on the pyridine ring appears quite downfield at δ 9.3 ppm as a doublet with the coupling constant J = 2.0 Hz or just as a singlet.

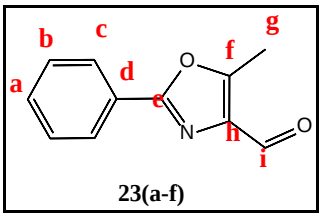


Figure 5.10A ***Carbon labels on compound 23(a-f).***

In the ^{13}C NMR spectra of 2-aryl-5-methyl-oxazole-4-carbaldehydes **23a-f** (**Figure 5.10A** above) the methyl carbon **g** is observed at δ 11.8 ppm and a carbonyl carbon **i** is observed in between δ 183-186 ppm.

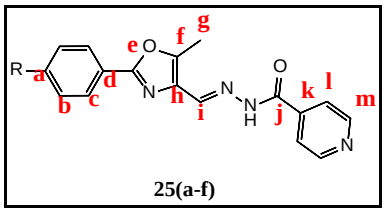


Figure 5.10B ***Carbon labels on isonicotinoyl compounds 25(a-f).***

The ^{13}C NMR spectra of (aryl-oxazolyl)-isonicotino/nicotino-hydrazides **25(a-f)** (**Figure 5.10B** above) show methyl carbon **g** on oxazole ring signal at δ 11.4 ppm and the signal at δ 162 ppm is observed for the carbonyl carbon **j** (-C=O). For compound **25b** aryl methyl carbon appears at δ 21 ppm. The imine carbon **i** (-C=N) is observed at δ 150.7 ppm for all the synthesized compounds.

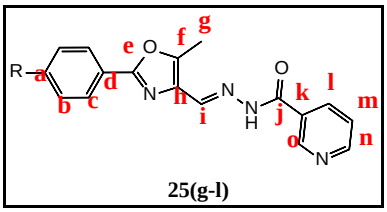


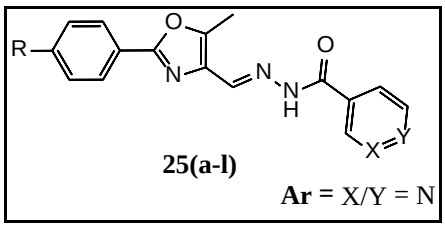
Figure 5.10C ***Carbon labels on nicotinoyl compounds 25(g-l).***

For the compounds **25(g-l**) (**Figure 5.10C**) carbon **o** is observed at δ 148 ppm. The rest of the aromatic carbon signals are similar to the structures of the corresponding INH hydrazone compounds and are found in between δ 124 to 159 ppm.

All the synthesized aryl oxazolyl carbaldehydes **23(a-f)** and oxazolyl hydrazones **25(a-l)** were analysed with the help of Shimadzu, GC-MS QP-2010 Plus mass spectrometer. The molecular ion peaks of all the compounds were observed as $(M+H)^+$ and were found to be in accordance with the expected mass values.

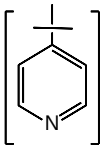
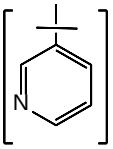
Yield and melting points of the newly synthesized oxazolyl hydrazones are summarized in the following table (**Table 5.2**).

Table 5.2 ***Physical data (yields, mp) of the newly synthesized compounds.***



25(a-l)

Ar = X/Y = N

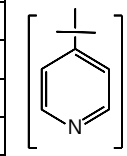
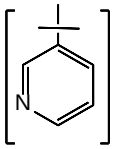
ID	Substitution		Molecular Formula	Yield	mp
	-Ar	-R			
25a		-H	$C_{17}H_{14}N_4O_2$	74 %	174 ^oC
25b		$-CH_3$	$C_{18}H_{16}N_4O_2$	79 %	194 ^oC
25c		$-OCH_3$	$C_{18}H_{16}N_4O_3$	75 %	178 ^oC
25d		-Cl	$C_{17}H_{13}ClN_4O_2$	71 %	192 ^oC
25e		-Br	$C_{17}H_{13}BrN_4O_2$	78 %	184 ^oC
25f		-F	$C_{17}H_{13}FN_4O_2$	74 %	188 ^oC
25g		-H	$C_{17}H_{14}N_4O_2$	76 %	196 ^oC
25h		$-CH_3$	$C_{18}H_{16}N_4O_2$	78 %	178 ^oC
25i		$-OCH_3$	$C_{18}H_{16}N_4O_3$	73 %	182 ^oC
25j		-Cl	$C_{17}H_{13}ClN_4O_2$	70 %	194 ^oC
25k		-Br	$C_{17}H_{13}BrN_4O_2$	76 %	202 ^oC
25l		-F	$C_{17}H_{13}FN_4O_2$	76 %	212 ^oC

5.2.2 Antitubercular Activity Study

As described in the introduction section of this chapter, hydrazone containing oxazole moiety, specially derivatives of INH and its isomer are expected to show antituberculer activity. Keeping this in mind, all the new (aryl-oxazolyl)-isonicotino/nicotino-hydrazide derivatives **25(a–l)** were evaluated for their anti-tubercular activity against *Mycobacterium tuberculosis* H37Rv strain in collaboration with NIRT (National Institute for Research in TB), Chennai. Isoniazid was used as the positive standard. Experimental procedures for anti-tubercular activity are included in the experimental section of this chapter. The activity screening was done at different concentrations ranging from 3.25 μg/mL to 125 μg/mL. MIC is included when it is significant with the compound inhibiting growth of the bacteria >90 % at the given concentration.

The results of the *in vitro* anti-tubercular screening are summarized in **Table 5.3** and are presented in a graphical form in **Figure 5.11**.

Table 5.3 ***Anti-tubercular activity results.***

ID	Substitution		Inhibition (%) (at 250 µg/mL)	MIC (µg/mL)
	-Ar	-R		
25a		-H	**94**	**50**
25b		$-CH_3$	79	---
25c		$-OCH_3$	86	---
25d		-Cl	**96**	**25**
25e		-Br	**97**	**25**
25f		-F	**89**	**100**
25g		-H	70	---
25h		$-CH_3$	**91**	**125**
25i		$-OCH_3$	78	---
25j		-Cl	**93**	**100**
25k		-Br	**95**	**25**
25l		-F	**93**	**50**

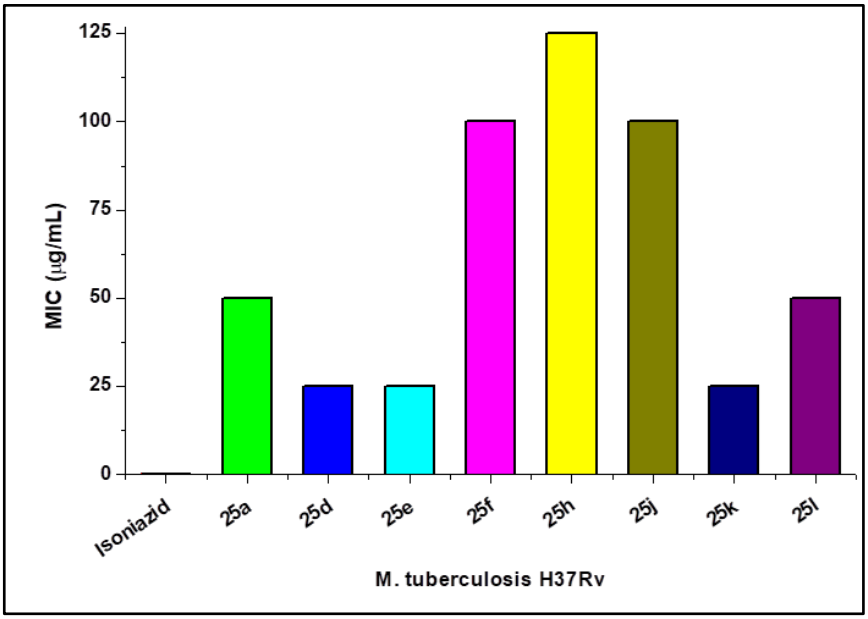


Figure 5.11 ***Anti-tubercular activity results.***

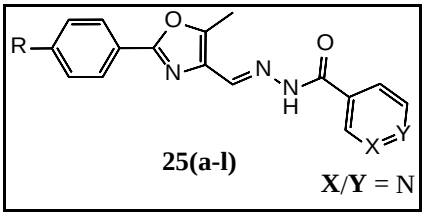


Figure 5.12 ***General structure of 25(a-l).***

Seven of the ten synthesized (aryl-oxazolyl)-isonicotino/nicotino-hydrazide derivatives namely **25a, 25d, 25e, 25f** of the isonicotinyl series and **25j, 25k, 25l** of the nicotinyl derivatives displayed activity with MIC ≤100 μg/mL (**Table 5.3** and **Figure 5.11**). Among these, **25d** (R = Cl, X = H, Y = N), **25e** (R = Br, X = H, Y = N), **25k** (R = Br, X = N, Y = H) are the most active molecules among all which have been studied with a MIC of 25 μg/mL. Compounds **25a** (R = H, X = H, Y = N) and **25l** (R = F, X = N, Y = H) displayed noteworthy inhibition with MIC = 50 μg/mL. While compounds **25f** (R = F, X = H, Y = N) and **25j** (R = Br, X = N, Y = H) showed moderate activity with MIC = 100 μg/mL (**Table 5.3** and **Figure 5.11**).

From the activity results it may be observed that all the compounds show lower inhibition compared to that of the INH. Thus in general, the activity of INH is lowered on condensation with the oxazole derivatives.

It is also observed that there is a little difference between INH derivatives and nicotinyl hydrazide derivatives. The presence of methyl and methoxy substitution dampenes the activity. The highest inhibiting activity is observed with –Br and –Cl substitutions on nicotinyl derivatives. Among the nicotinyl derivatives, bromo derivative shows the highest inhibition. The compound with fluorine substitution has moderate inhibition with MIC of 100 μg/mL and 50 μg/mL in isonicotinyl and nicotinyl derivatives respectively. It is possible that *in vivo* study of the compounds show enhanced activity when administered orally with possibility of metabolic degradation resulting in more active metabolites.

5.2.3 Molecular Docking Study

Molecular docking studies were performed on all new (2-aryl-5-methyloxazolyl)-isonicotino/nicotino-hydrazides **25a-l** of the series with the enzyme, InhA (**PDB code:**

1P44). Docking simulation was done with the aid of Schrödinger Maestro-11.5. The protein structures obtained from the protein data bank (PDB) were initially subjected to various processes such as removal of water molecules and removal of heteroatoms etc. using the Protein Preparation Wizard of Schrödinger 2015. All the compounds (Ligands) were filtered by specifying options for screening like remove molecules that have a molecular weight of greater than 650 remove molecules with too many H-bond acceptor and donor atoms acceptor groups >3, Donor groups >3, Energy minimization was done by choosing a Ligprep (OPLS) module of Schrodinger. The extent of the interactions of the docking study were observed based on the docking score, hydrogen bonding, π–H and π–π interactions of the ligands with the protein. The docking score of the compounds is in the range -7.73 to -9.37 (**Table 5.4**). Along with other types of interactions, one or more hydrogen bonding were observed by the interactions of the compounds with the amino acid residues of InhA.

Table 5.4 ***Docking results of the active anti-TB compounds.***

ID	Docking score	Glide energy	Amino acids interacted with ligands
INH	-13.10	-24.78	Tyr 158, Met 199, Gly 96
22a	-9.37	-49.30	Tyr 158
22d	-8.96	-50.42	Tyr 158
22e	-8.58	-45.88	Tyr 158,Gly 96
22f	-8.27	-50.52	Tyr 158, Met 199
22k	-7.73	-42.27	Tyr 158

The highest docking score was observed for the compound **25a** (-9.37). The docking score of the two active TB compounds of the series namely **25d** and **25e** was found to be -8.96 and -8.57 with H-bond interaction between Tyr 158 and oxygen atom of the carbonyl group (**Figure 5.13**). Compound **25d** (R = Br, X = H, Y = N) also showed π-π interactions with amino acid residue Tyr 158. It is interesting to note that all five (**25a**, **25d**, **25e, 25f, 25k**) and the reference ligand showed interactions with the target enzyme.

The greater inhibitory activity of compound **25d** (R = Cl, X = H, Y = N) and **25e** (R = Br, X = H, Y = N) with –Cl and -Br substitutions respectively when compared with their -F substitution analogue could be justified based on the docking results.

Compounds **25d** (R = Cl, X = H, Y = N) and **25e** (R = Br, X = H, Y = N) showed higher docking score than that of compound **25f** (R = F, X = H, Y = N).

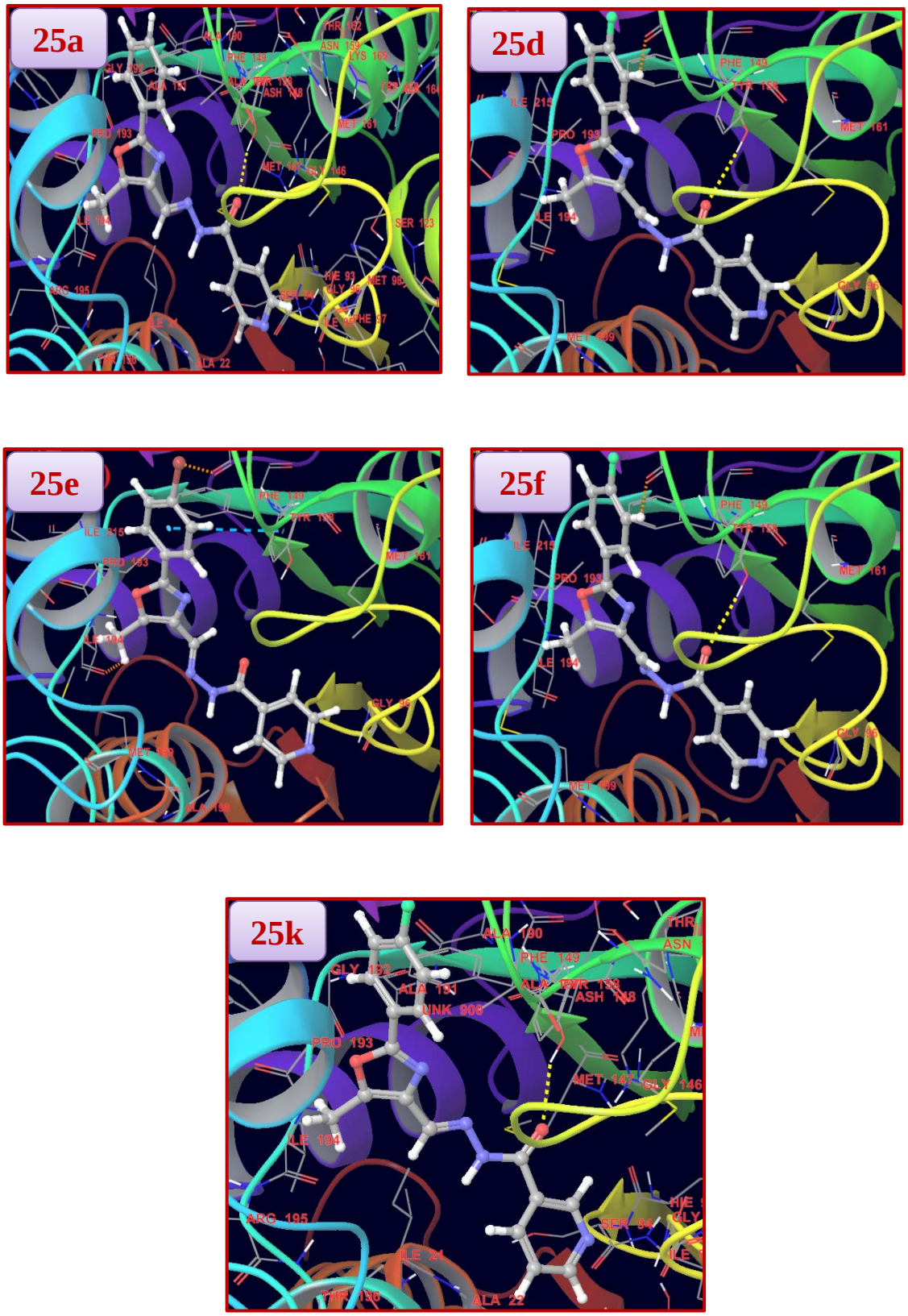


Figure 5.13 ***Docking pose of the compounds in the active pocket of InhA.***

5.3 Conclusion

With the aim to prepare and study some potential new anti-tubercular compounds, some N'-aryl-5-methyloxazolyl)methylene)isonicotino/nicotino-hydrazides (**25a-l**) having 1,3-oxazole and pyridine heterocycles present in them were synthesized from the corresponding acid hydrazides and 2-aryl-5-methyl-1,3-oxazole-4-carbaldehydes. All the newly synthesized compounds are characterized by using various spectro-analytical techniques. Antitubercular activity of all the newly synthesized compounds against *M. tuberculosis* H37Rv is studied. Three of the synthesized compounds namely (**25d**, **25e**, **25k**) displayed good antitubecular activity with MIC 25 μg/mL. Further, the molecular docking study of all the new compounds with InhA enzyme was carried out to understand the favourable interactions of the active molecules with amino acid residues of the enzyme**.** The interactions with the same amino acid residue of the enzyme as shown by the reference ligand signify the inhibitory activity of the synthesized compounds.

5.4 Experimental

General

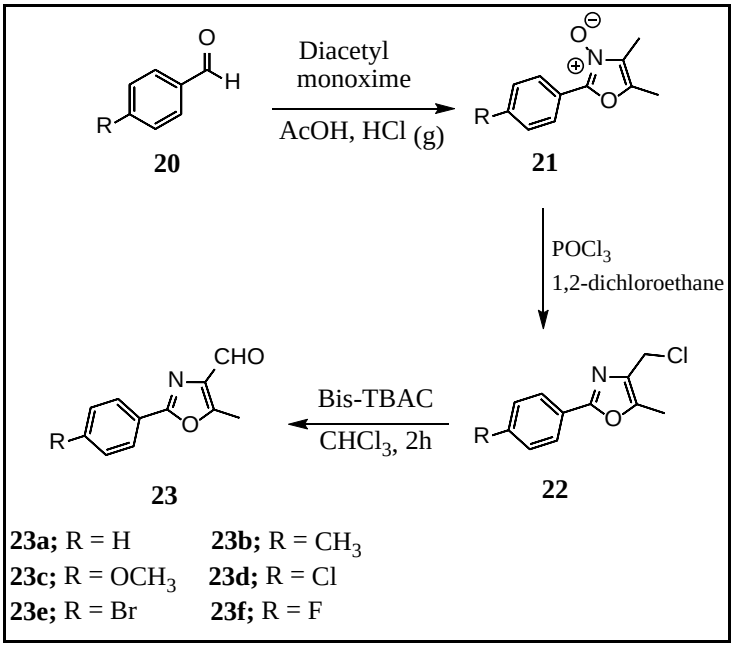
The chemicals were used as received from local companies without further purification. Organic solvents were purified by distillation prior to use.

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 Bruker Alpha FTIR 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 Shimadzu, GC-MS QP-2010 Plus mass spectrometer at Central Salt and Marine Chemicals Research Centre (CSMCRI), Bhavnagar and at Zandu Chemicals Ltd, Ankleshwar.

General Procedure for the Synthesis of 2-aryl-5-methyl-1,3-oxazole-4-carbaldehydes 23.



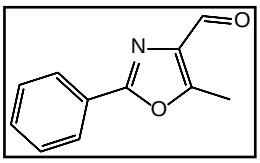
2-Aryl-5-methyl-1,3-oxazole-4-carbaldehydes **23a-f** were prepared from 4-substituted aldehydes and diacetyl monoxime. To an ice-cold mixture of 4-substituted aldehydes **20** (1 eq) and diacetyl monoxime (1 eq) in acetic acid (3 fold), dry HCl gas was passed for 3h at 0 ^{o}C. The reaction mixture was then diluted with diethyl ether (6 fold). Separated solid was filtered, washed with diethyl ether and dried under vacuum to obtain N-oxides **21** as white solids.

To an ice cold suspension of N-oxides **21** (1 eq) in dichloro ethane (DCE) (5 fold) was added $POCl_3$ (1.1 eq) dropwise over a period of 2h at 10 ^{o}C. The reaction mixture was slowly heated to 60 ^{o}C and stirred at that temperature for 3h. The reaction mixture was cooled to room temperature, poured into ice cold water and extracted with DCE. The combined organic extracts were washed with water, dried over $CaCl_2$ and concentrated under vacuum to furnish methyl substituted 1,3-oxazoles **22** in excellent yields.

A homogeneous solution of the chloro methylated 1,3-oxazoles **22** (1eq) and bis-tetrabutyl ammonium dichromate[64] (0.6 eq) in chloroform (7.5 ml) was heated under reflux for 2h. The crude product was filtered through silica gel to eliminate the chromium salt. The silica was than washed with diethyl ether (100 ml). Evaporation of

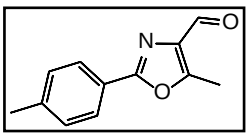
the combined organic layers afforded pure aryl oxazolyl carbaldehydes **23a-f**. Yield: 45-59% (based on compound **22**).

5-Methyl-2-phenyl-1,3-oxazole-4-carbaldehyde 23a.



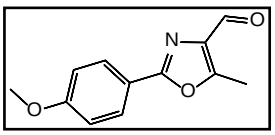
Compound **23a** was prepared following the general procedure described above. Yield = 49%; white Solid; M.P. = 88 °C; **IR (KBr) cm^{-1}**: 3064, 2921, 2840, 2741, 1691, 1597, 1129, 1074, 830; **^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)**: 2.73 (3H, s, -CH_3), 7.49 (3H, m, Ar-H), 8.07 (2H, m, Ar-H), 10.04 (1H, s, -CHO); **^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)**: 11.8 (-**C**H_3), 126.3, 126.5, 128.9, 131.0, 135.9, 156.4, 160.4, 185.5 (-**C**=O). **ESI-MASS**: (m/z) 188.0 $(M+H)^+$ for M = $C_{11}H_9NO_2$.

5-Methyl-2-(4-methylphenyl)-1,3-oxazole-4-carbaldehyde 23b.



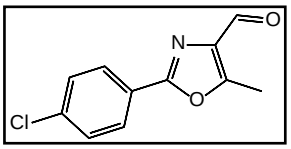
Compound **23b** was prepared following the general procedure described above. Yield = 48%; white Solid; M.P. = 106 °C; **IR (KBr) cm^{-1}**: 2918, 2861, 2740, 1689, 1596, 1112, 1052, 769; **^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)**: 2.41 (3H, s, -CH_3),2.73 (3H, s, -CH_3), 7.28 (2H, d, *J* = 8.0 Hz, Ar-H), 7.94 (2H, d, *J* = 8.0 Hz, Ar-H), 10.01 (1H, s, -CHO); **^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)**: 11.7 (-**C**H_3), 21.5, 123.6, 126.5, 129.6, 135.8, 141.4, 156.3, 160.7, 185.4 (-**C**=O). **ESI-MASS**: (m/z) 202.0 $(M+H)^+$ for M = $C_{12}H_{11}NO_2$.

2-(4-Methoxyphenyl)-5-methyl-1,3-oxazole-4-carbaldehyde 23c.



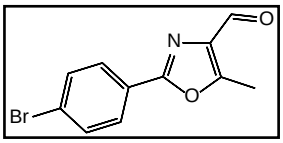
Compound **23c** was prepared following the general procedure described above. Yield = 51%; Light Yellow Solid; M.P. = 114 °C; **IR (KBr) cm^{-1}**: 2920, 2839, 1691, 1597, 1441, 1128, 1046, 829; **^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)**: 2.73 (3H, s, -CH_3), 3.71 (3H, s, -OCH_3), 7.31 (2H, d, *J* = 8.0 Hz, Ar-H), 7.86 (2H, d, *J* = 8.0 Hz, Ar-H), 10.02 (1H, s, -CHO); **^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)**: 11.7 (-**C**H_3), 55.8 (-O**C**H_3), 124.6, 126.5, 128.6, 136.8, 140.4, 155.3, 162.7, 185.6 (-**C**=O). **ESI-MASS**: (m/z) 218.0 $(M+H)^+$ for M = $C_{12}H_{11}NO_3$.

2-(4-Chlorophenyl)-5-methyl-1,3-oxazole-4-carbaldehyde 23d.



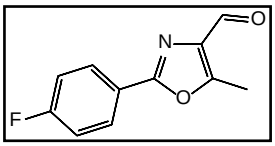
Compound **23d** was prepared following the general procedure described above. Yield = 59%; white Solid; M.P. = 109 °C; **IR (KBr) cm^{-1}**: 3071, 2956, 2853, 2746, 1687, 1596, 1066, 1004, 829; **^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)**: 2.73 (3H, s, -CH_3), 7.46 (2H, d, *J* = 6.8 Hz, Ar-H), 7.90 (2H, d, *J* = 6.8 Hz, Ar-H), 10.02 (1H, s, -CHO); **^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)**: 11.8 (-**C**H_3), 124.8, 127.3, 127.8, 129.0, 129.2, 135.9, 137.4, 156.7, 159.5, 185.3 (-**C**=O). **ESI-MASS**: (m/z) 221.95 $(M+H)^+$ for M = $C_{11}H_8ClNO_2$.

2-(4-Bromophenyl)-5-methyl-1,3-oxazole-4-carbaldehyde 23e.



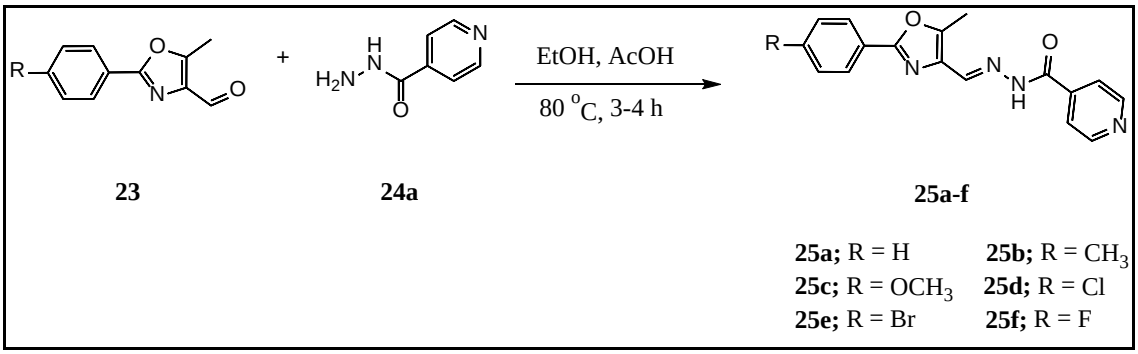
Compound **23e** was prepared following the general procedure described above. Yield = 54%; Light Yellow Solid; M.P. = 128 °C; **IR (KBr) cm^{-1}**: 2956, 2818, 2742, 1687, 1599, 1354, 1064, 1000, 827; **^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)**: 2.73 (3H, s, -CH_3), 7.64 (2H, d, *J* = 8.4 Hz, Ar-H), 7.93 (2H, d, *J* = 8.4 Hz, Ar-H), 10.02 (1H, s, -CHO); **^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)**: 11.8 (-**C**H_3), 125.2, 125.6, 127.7, 127.9, 132.0, 132.2, 136.0, 156.7, 159.6, 185.3 (-**C**=O). **ESI-MASS**: (m/z) 265.90 $(M+H)^+$ for M = $C_{11}H_8BrNO_2$.

2-(4-Fluorophenyl)-5-methyl-1,3-oxazole-4-carbaldehyde 23f.



Compound **23f** was prepared following the general procedure described above. Yield = 50%; Light Yellow Solid; M.P. = 121 °C; **IR (KBr) cm^{-1}**: 3080, 2841, 2740, 1680, 1604, 1506, 1155, 1048, 850; **^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)**: 2.73 (3H, s, -CH_3), 7.18 (2H, m, Ar-H), 8.15 (2H, m, Ar-H), 10.02 (1H, s, -CHO); **^{19}F NMR (376 MHz, $CDCl_3$, δ ppm)**: -107.9; **^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)**: 11.8 (-**C**H_3), 116.2, 116.4, 122.4, 129.20, 129.29, 141.8, 144.4, 162.2, 165.9, 185.9 (-**C**=O). **ESI-MASS**: (m/z) 206.0 $(M+H)^+$ for M = $C_{11}H_8FNO_2$.

General Procedure for the Synthesis of N'-((2-aryl-5-methyl-1,3-oxazol-4-yl)methylene)isonicotinohydrazides 25a-f.[68]

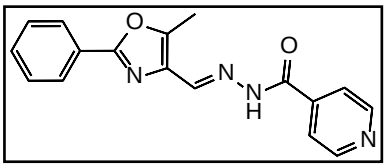


23 **24a** **25a-f**

25a; R = H **25b;** R = CH_3
25c; R = OCH_3 **25d;** R = Cl
25e; R = Br **25f;** R = F

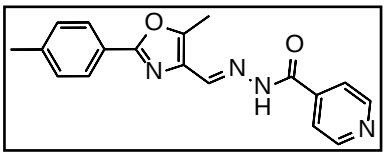
To a magnetically stirred solution of 2-aryl-5-methyl-1,3-oxazole-4-carbaldehydes **23a-f** (0.54 mmol, 1eq.) in ethanol, was added an equimolar amount isoniazid **24a** (0.54 mmol, 1eq.) and a few drops of acetic acid as a catalyst. The reaction mixture was refluxed for 3-4 hour until the completion of the reaction as observed on TLC. After completion of the reaction, the reaction mixture was poured on crushed ice. The solids precipitated were filtered, washed with ethanol and recrystallized from ethanol to afford the desired compounds. Yield: 74-79%.

N'-((5-Methyl-2-phenyl-1,3-oxazol-4-yl)-methylene)-isonicotinohydrazide 25a.



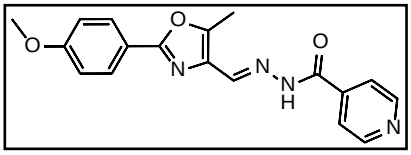
Compound **25a** was prepared following the general procedure described above by treating 5-methyl-2-phenyl-1,3-oxazole-4-carbaldehyde **23a** (0.1g, 0.54 mmol) in ethanol with isoniazid **24a** (0.074g, 0.54 mmol) using acetic acid as a catalyst. Yield = 0.12g, 74%; Light Yellow Solid; M.P. = 174 °C; **IR (KBr) cm^{-1}**: 3248, 1690, 1554, 1287, 1218, 846, 687; **^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)**: 2.65 (3H, s, -CH_3), 7.51 (1H, s, -N=CH-), 7.56 (3H, m, Ar-H), 7.94 (2H, d, *J* = 6.0 Hz, Py-H), 8.02 (2H, d, *J* = 7.6 Hz, Ar-H), 8.87 (2H, d, *J* = 6.0 Hz, Py-H), 13.88 (1H, s, -NH); **^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)**: 10.9 (-**C**H_3), 121.3, 124.5, 126.3, 127.7, 131.3, 132.5, 132.6, 1140.7, 150.7, 152.4, 158.8, 162.0 (**C**=O); **ESI-MASS**: (m/z) 307.11 $(M+H)^+$ for M = $C_{17}H_{14}N_4O_2$.

N'-((5-Methyl-2-(4-methylphenyl)-1,3-oxazol-4-yl)-methylene)isonicotinohydrazide 25b.



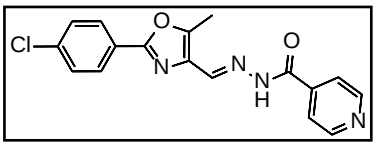
Compound **25b** was prepared following the general procedure described above by treating 5-methyl-2-(4-methylphenyl)-1,3-oxazole-4-carbaldehyde **23b** (0.1g, 0.5 mmol) in ethanol with isoniazid **24a** (0.068g, 0.5 mmol) using acetic acid as a catalyst. Yield = 0.12g, 79%; Light Yellow Solid; M.P. = 194 °C; **IR (KBr) cm^{-1}**: 3246, 1692, 1500, 1288, 122, 839, 731; **^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)**: 2.47 (3H, s, -CH_3), 2.63 (3H, s, -CH_3), 7.35 (2H, d, *J* = 8.0 Hz, Ar-H), 7.49 (1H, s, -N=CH-), 7.90 (2H, d, *J* = 8.4 Hz, Ar-H), 7.94 (2H, d, *J* = 6.0 Hz, Py-H), 8.86 (2H, d, *J* = 6.0 Hz, Py-H), 13.92 (1H, s, -NH); **^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)**: 10.9 (-**C**H_3), 21.6 (-**C**H3), 121.4, 123.0, 126.3, 129.9, 131.1, 133.0, 140.8, 142.2, 150.6, 151.6, 161.9 (**C**=O); **ESI-MASS**: (m/z) 321.14 $(M+H)^+$ for M = $C_{18}H_{16}N_4O_2$.

N'-((2-(4-Methoxyphenyl)-5-methyl-1,3-oxazol-4-yl)methylene)isonicotinohydrazide 25c.



Compound **25c** was prepared following the general procedure described above by treating 5-methyl-2-(4-methoxyphenyl)-1,3-oxazole-4-carbaldehyde **23c** (0.1g, 0.5 mmol) in ethanol with isoniazid **24a** (0.068g, 0.5 mmol) using acetic acid as a catalyst. Yield = 0.12g, 79%; Light Yellow Solid; M.P. = 178 °C; **IR (KBr) cm^{-1}**: 3246, 1690, 1525, 1230, 835, 731; **^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)**: 2.47 (3H, s, -CH_3), 3.71 (3H, s, -OCH_3), 7.34 (2H, d, *J* = 8.0 Hz, Ar-H), 7.51 (1H, s, -N=CH-), 7.92 (2H, d, *J* = 8.0 Hz, Ar-H), 7.92 (2H, d, *J* = 6.0 Hz, Py-H), 8.86 (2H, d, *J* = 6.0 Hz, Py-H), 13.92 (1H, s, -NH); **^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)**: 10.9 (-**C**H_3), 58.1 (-O**C**H_3), 121.5, 124.0, 125.3, 129.7, 130.1, 132.4, 141.7, 141.3, 151.7, 150.8, 161.8 (**C**=O); **ESI-MASS**: (m/z) 336.01 $(M+H)^+$ for M = $C_{18}H_{16}N_4O_3$.

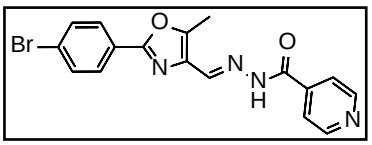
N'-((2-(4-Chlorophenyl)-5-methyl-1,3-oxazol-4-yl)-methylene)-isonicotinohydrazide 25d.



Compound **25d** was prepared following the general procedure described above by treating 2-(4-chlorophenyl)-5-methyl-1,3-oxazole-4-carbaldehyde **23d**

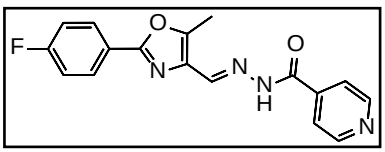
(0.1g, 0.45 mmol) in ethanol with isoniazid **24a** (0.062g, 0.45 mmol) using acetic acid as a catalyst. Yield = 0.10g, 71%; Light Yellow Solid; M.P. = 178 °C; **IR (KBr) cm^{-1}**: 3261, 1695, 1536, 1290, 866, 736; **^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)**: 2.65 (3H, s, -CH_3), 7.49 (1H, s, -N=CH-), 7.53 (3H, d, *J* = 8.8 Hz, Ar-H), 7.91 (2H, d, *J* = 4.4 Hz, Py-H), 7.94 (2H, d, *J* = 8.8 Hz, Ar-H), 7.95 (1H, s, -N=CH-), 8.86 (2H, d, *J* = 4.4 Hz, Py-H), 13.73 (1H, s, -NH); **^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)**: 10.9 (-**C**H_3), 121.3, 124.5, 126.3, 127.7, 131.3, 132.5, 132.6, 1140.7, 150.7, 152.4, 158.8, 162.0 (**C**=O); **ESI-MASS**: (m/z) 341.08 $(M+H)^+$ for M = $C_{17}H_{13}ClN_4O_2$.

N'-((2-(4-Bromophenyl)-5-methyl-1,3-oxazol-4-yl)-methylene)isonicotinohydrazide 25e.



Compound **25e** was prepared following the general procedure described above by treating 2-(4-bromophenyl)-5-methyl-1,3-oxazole-4-carbaldehyde **23e** (0.1g, 0.37 mmol) in ethanol with isoniazid **24a** (0.051g, 0.37 mmol) using acetic acid as a catalyst. Yield = 0.11g, 78%; Light Yellow Solid; M.P. = 184 °C; **IR (KBr) cm^{-1}**: 3264, 1695, 1535, 1283, 866, 731; **^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)**: 2.65 (3H, s, -CH_3), 7.49 (1H, s, -N=CH-), 7.69 (2H, d, *J* = 8.4 Hz, Ar-H), 7.86 (2H, d, *J* = 8.4 Hz, Ar-H), 7.91 (2H, d, *J* = 6.0 Hz, Py-H), 8.86 (2H, d, *J* = 6.0 Hz, Py-H), 13.72 (1H, s, -NH); **^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)**: 10.9 (-**C**H_3), 121.3, 124.5, 126.3, 127.7, 131.3, 132.5, 132.6, 1140.7, 150.7, 152.4, 158.8, 162.0 (**C**=O); **ESI-MASS**: (m/z) 358.03 $(M+H)^+$ for M = $C_{17}H_{13}BrN_4O_2$.

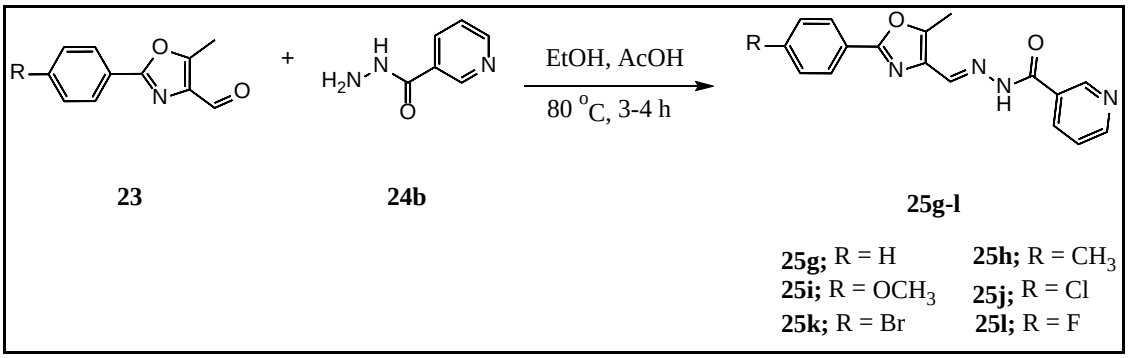
N'-((2-(4-Fluorophenyl)-5-methyl-1,3-oxazol-4-yl)-methylene)isonicotinohydrazide 25f.



Compound **25f** was prepared following the general procedure described above by treating 2-(4-fluorophenyl)-5-methyl-1,3-oxazole -4-carbaldehyde **23f** (0.1g, 0.48 mmol) in ethanol with isoniazid **24a** (0.067g, 0.48 mmol) using acetic acid as a catalyst. Yield = 0.11g, 74%; Light Yellow Solid; M.P. = 188 °C; **IR (KBr) cm^{-1}**: 3255, 1694, 1498, 1290, 871, 739; **^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)**: 2.65 (3H, s, -CH_3), 7.24 (2H, d, *J* = 8.8 Hz, Ar-H), 7.49 (1H, s, -N=CH-), 7.91 (1H, d, *J* = 6.0 Hz, Py-H), 8.02 (2H, m, Ar-H), 8.87 (2H, d, *J* = 6.0 Hz, Py-H), 13.76 (1H, s, -NH);

^{19}F NMR (376 MHz, $CDCl_3$, δ ppm) : -106.6; **^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)**: 10.9 (-**C**H_3), 116.6 ($^2J_{CF}$ = 23 Hz), 121.3, 128.5 ($^2J_{CF}$ = 8 Hz), 131.2 ($^3J_{CF}$ = 3 Hz), 132.8, 140.8, 150.7, 162.0 (-**C**=O) ; **ESI-MASS**: (m/z) 325.11 $(M+H)^+$ for M = $C_{17}H_{13}FN_4O_2$.

General procedure for the synthesis of N'-((2-(4-Aryl)-5-methyl-1,3-oxazol-4-yl)methylene)nicotinohydrazides 25g-l.[68]

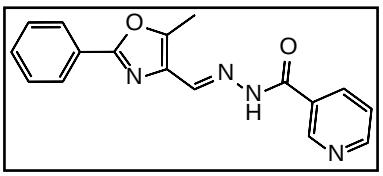


23 **24b** **25g-l**

25g; R = H **25h;** R = CH_3
25i; R = OCH_3 **25j;** R = Cl
25k; R = Br **25l;** R = F

To a magnetically stirred solution of 2-aryl-5-methyl-1,3-oxazole-4-carbaldehydes **23a-f** in ethanol, was added an equimolar (0.54 mmol, 1eq.) amount of nicotino hydrazide **24b** (0.54 mmol, 1eq.) and a few drops of acetic acid as a catalyst. The reaction mixture was refluxed for 3-4 hour until the completion of the reaction observed on TLC. After completion of the reaction, the reaction mixture was poured on crushed ice. The solids precipitated were filtered, washed with ethanol and recrystallized from ethanol to afford compounds **25g-l**. Yield: 70-78%.

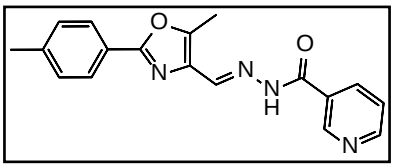
N'-((5-Methyl-2-phenyl-1,3-oxazol-4-yl)methylene)nicotinohydrazide 25g.



Compound **25g** was prepared following the general procedure described above by treating 5-methyl-2-phenyl-1,3-oxazole-4-carbaldehyde **23a** (0.1g, 0.54 mmol) in ethanol with nicotinic hydrazide **24b** (0.074g, 0.54 mmol) using acetic acid as a catalyst. Yield = 0.12g, 76%; Light Yellow Solid; M.P. = 196 °C; **IR (KBr) cm^{-1}**: 3223, 1655, 1561, 1288, 1194, 874; **^{1}H NMR (400 MHz, DMSO-d_6, δ ppm)**: 2.61 (3H, s, -CH_3 protons), 7.54 (1H, s, -N=CH-), 7.58 (4H, m, Ar-H), 7.98 (2H, d, *J* = 4.8 Hz, Py-H), 8.25 (1H, d, *J* = 8.0 Hz, Ar-H), 8.76 (1H, d, *J* = 4.8 Hz, Py-H), 9.04 (1H, d, *J* = 2.0 Hz, Py-H), 12.06 (1H, s, -NH proton); **^{13}C NMR (100 MHz, DMSO-d_6, δ ppm)**: 11.4 (-**C**H_3), 124.2, 126.3, 126.7, 129.4, 129.7, 131.3, 132.1, 135.9, 141.1,

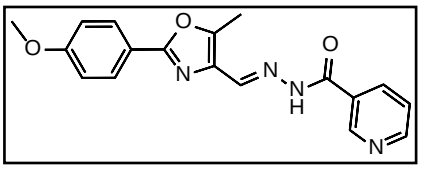
148.8, 151.0, 152.8, 159.8, 162.1 (-**C**=O); **ESI-MASS**: (m/z) 307.12 $(M+H)^+$ for M = $C_{17}H_{14}N_4O_2$.

N'-((5-Methyl-2-(4-methylphenyl)-1,3-oxazol-4-yl)-methylene)-nicotinohydrazide 25h.



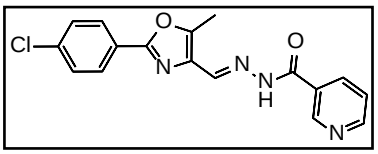
Compound **25h** was prepared following the general procedure described above by treating 5-methyl-2-(4-methylphenyl)-1,3-oxazole-4-carbaldehyde **23b** (0.1g, 0.5 mmol) in ethanol with nicotinic hydrazide **24b** (0.068g, 0.5 mmol) using acetic acid as a catalyst. Yield = 0.12g, 78%; Light Yellow Solid; M.P. = 178 °C; **IR (KBr) cm^{-1}**: 3218, 1560, 1290, 744, 710; **^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)**: 2.47 (3H, s, -CH_3 protons), 2.63 (3H, s, -CH_3 protons), 7.48 (1H, s, -N=CH-), 7.50 (1H, d, *J* = 8.0 Hz, Py-H), 7.53 (1H, s, -CH- proton), 7.70 (2H, d, *J* = 8.4 Hz, Ar-H), 7.89 (2H, d, *J* = 8.4 Hz, Ar-H), 8.41 (1H, d, *J* = 8.0 Hz, Py-H), 8.83 (1H, d, *J* = 4.4 Hz, Py-H), 9.29 (1H, s, Py-H), 13.70 (1H, s, -NH proton); **^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)**: 11.5 (-**C**H_3), 21.5 (-**C**H_3), 124.1, 124.2, 126.3, 129.6, 130.2, 132.0, 135.8, 141.1, 141.3, 148.9, 150.4, 152.8, 159.9, 161.9 (-**C**=O); **ESI-MASS**: (m/z) 321.14 $(M+H)^+$ for M = $C_{18}H_{16}N_4O_2$.

N'-((2-(4-Methoxyphenyl)-5-methyl-1,3-oxazol-4-yl)methylene)nicotinohydrazide 25i.



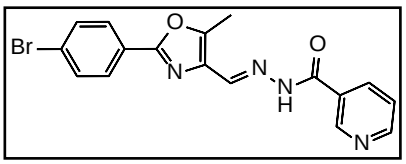
Compound **25i** was prepared following the general procedure described above by treating 5-methyl-2-(4-methoxylphenyl)-1,3-oxazole-4-carbaldehyde **23c** (0.1g, 0.5 mmol) in ethanol with nicotinic hydrazide **24b** (0.068g, 0.5 mmol) using acetic acid as a catalyst. Yield = 0.12g, 78%; Light Yellow Solid; M.P. = 182 °C; **IR (KBr) cm^{-1}**: 3221, 1544, 1275, 836, 721; **^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)**: 2.47 (3H, s, -CH_3 protons), 3.75 (3H, s, -OCH_3 protons), 7.24 (2H, d, *J* = 8.4 Hz, Ar-H), 7.48 (1H, s, -N=CH-), 7.50 (1H, d, *J* = 8.4 Hz, Py-H), 8.04 (2H, d, *J* = 8.4 Hz, Ar-H), 8.42 (1H, d, *J* = 8.0 Hz, Py-H), 8.84 (1H, d, *J* = 3.2 Hz, Py-H), 9.30 (1H, s, Py-H), 13.72 (1H, s, -NH proton); **^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)**: 11.5 (-**C**H_3), 55.8 (-O**C**H_3), 123.1, 124.8, 125.3, 128.7, 131.1, 133.5, 134.8, 140.1, 142.3, 147.5, 151.1, 153.8, 158.6, 161.7 (-**C**=O); **ESI-MASS**: (m/z) 321.14 $(M+H)^+$ for M = $C_{18}H_{16}N_4O_3$.

N'-((2-(4-Chlorophenyl)-5-methyl-1,3-oxazol-4-yl)-methylene)-nicotinohydrazide 25j.



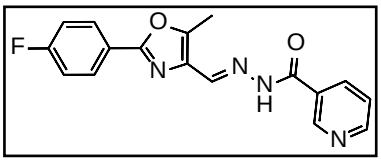
Compound **25j** was prepared following the general procedure described above by treating 2-(4-chlorophenyl)-5-methyl-1,3-oxazole-4-carbaldehyde **23d** (0.1g, 0.45 mmol) in ethanol with nicotinic hydrazide **24b** (0.062g, 0.45 mmol) using acetic acid as a catalyst. Yield = 0.10g 70%; Light Yellow Solid; M.P. = 194 °C; **IR (KBr) cm^{-1}**: 3295, 1690, 1541, 1289, 845, 734; **^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)**: 2.65 (3H, s, -CH_3 protons), 7.52 (1H, s, -N=CH-), 7.52 (3H, m, Ar-H), 7.97 (2H, d, *J* = 8.4 Hz, Ar-H), 8.42 (1H, d, *J* = 4.0 Hz, Py-H), 8.84 (1H, d, *J* = 4.0 Hz, Py-H), 9.30 (1H, s, Py-H), 13.71 (1H, s, -NH proton); **^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)**: 11.6 (-**C**H_3), 124.1, 125.6, 128.1, 129.8, 132.3, 135.9, 141.1, 148.9, 150.9, 15.8, 158.8 (-**C**=O) ; **ESI-MASS**: (m/z) 341.08 $(M+H)^+$ for M = $C_{17}H_{13}ClN_4O_2$.

N'-((2-(4-Bromophenyl)-5-methyl-1,3-oxazol-4-yl)-methylene)-nicotinohydrazide 25k.



Compound **25k** was prepared following the general procedure described above by treating 2-(4-bromophenyl)-5-methyl-1,3-oxazole-4-carbaldehyde **23e** (0.1g, 0.37 mmol) in ethanol with nicotinic hydrazide **24b** (0.051g, 0.37 mmol) using acetic acid as a catalyst. Yield = 0.11g, 76%; Light Yellow Solid; M.P. = 202 °C; **IR (KBr) cm^{-1}**: 3218, 1650, 1561, 1220, 846, 709; **^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)**: 2.64 (3H, s, -CH_3), 7.48 (1H, s, -N=CH-), 7.50 (1H, d, *J* = 8.0 Hz, Py-H), 7.53 (1H, s, -CH- proton), 7.70 (2H, d, *J* = 8.4 Hz, Ar-H), 7.89 (2H, d, *J* = 8.4 Hz, Ar-H), 8.41 (1H, d, *J* = 8.0 Hz, Py-H), 8.83 (1H, d, *J* = 4.4 Hz, Py-H), 9.29 (1H, s, Py-H), 13.70 (1H, s, -NH proton); **^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)**: 10.9 (-**C**H_3), 123.7, 124.5, 126.2, 127.8, 129.4, 131.3, 132.2, 132.6, 135.9, 148.1, 152.0, 158.8, 162.1 (-**C**=O); **ESI-MASS**: (m/z) 385.03 $(M+H)^+$ for M = $C_{17}H_{13}BrN_4O_2$.

N'-((2-(4-Fluorophenyl)-5-methyl-1,3-oxazol-4-yl)-methylene)-nicotinohydrazide 25l.



Compound **25l** was prepared following the general procedure described above by treating 2-(4-fluorophenyl)-5-methyl-1,3-oxazole-4-carbaldehyde **23f** (0.1g, 0.48 mmol) in ethanol with nicotinic hydrazide **24b** (0.067g, 0.48 mmol) using acetic acid as a catalyst. Yield = 0.12g, 76%; Light Yellow Solid; M.P. = 212 ^{o}C; **IR (KBr) cm^{-1}**: 3249, 1692, 1557, 1290, 848, 708; **^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)**: 2.64 (3H, s, -CH_3), 7.24 (2H, d, *J* = 8.4 Hz, Ar-H), 7.48 (1H, s, -N=CH-), 7.50 (1H, d, *J* = 8.4 Hz, Py-H), 8.04 (2H, d, *J* = 8.4 Hz, Ar-H), 8.42 (1H, d, *J* = 8.0 Hz, Py-H), 8.83 (1H, d, *J* = 3.2 Hz, Py-H), 9.30 (1H, s, Py-H),13.72 (1H, s, -NH proton); **^{19}F NMR (376 MHz, $CDCl_3$, δ ppm)**: -106.9; **^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)**: 11.6 (-**C**H_3), 116.8 ($^{2}J_{CF}$ = 22 Hz), 124.1, 128.8,128.9 ($^{2}J_{CF}$ = 9 Hz), 129.5, 132.2, 135.9, 141.2, 148.9, 152.8, 161.9 (-**C**=O) ; **ESI-MASS**: (m/z) 325.12 $(M+H)^+$ for M = $C_{17}H_{13}FN_4O_2$.

Experimental Procedure For Anti-tubercular Activity.

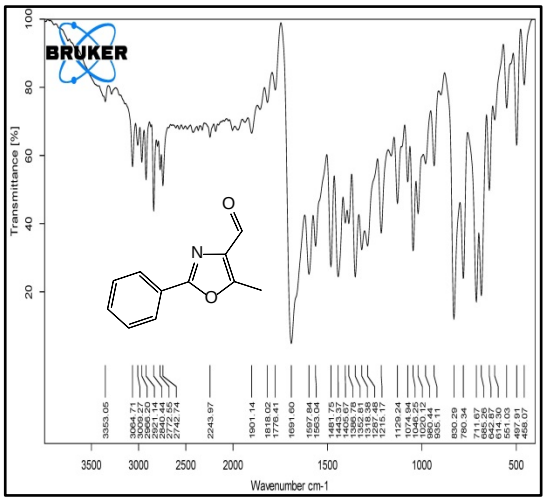
The preliminary antimycobacterial assessment for the final synthesized compounds was carried out using BACTEC MGIT method. The Mycobacterial Growth Indicator Tubes (MGIT) containing 4 ml of modified Middle brook 7H9 Broth Base were numbered as per the title compounds to be tasted for antimycobacterial efficacy at various concentrations prepared. The suspension was allowed to sit for 20 min and the tubes were centrifuged at 3000 rpm for 15 min. After that prepared suspension of 104 to 107 CFU/mL of H37Rv *M.tuberculosis* strain was added in the medium to be incubated and 0.1 mL of egg-based medium (L.J.) was also added. The MGIT tubes were then tightly recapped, mixed well and incubated into BACTEC MGIT instrument at (37 ± 1) °C until positivity is observed. The readings were measured daily starting from the second day of incubation. Positive cultures were usually detected within 10 days. For reading the actual results, the MGIT tubes were removed from incubator and placed on the UV light next to a positive control tube and an inoculated tube (negative control).
Bright fluorescence detected by the corresponding MGIT tube was noticed in the form of bright orange colour in the bottom of the tube and also an orange reflection on the meniscus. The primary screening was conducted at concentration of 6.25 μg/mL against *M. tuberculosis* H37Rv in BACTEC MGIT system. If any compound is demonstrating 99% inhibition in the primary screen is described as the most potent compound. All the other compounds were re-examined for their actual MIC by using Lowenstein-Jensen MIC method. The highest dilution showing at least 99% inhibition is taken as MIC.

The secondary anti-mycobacterial screening for test compounds was obtained for *M. tuberculosis* H37Rv, by using L. J. (Lowenstein and Jensen) MIC method. Stock solutions of primary 1000, 500, 250 μg/mL and secondary 125, 100, 50, 25, 12.5, 6.25, 3.25 μg/mL dilutions of each test compound in DMSO (dimethyl sulfoxide) were added in the liquid L. J. Medium and then media were sterilized by inspissation method. A culture of *M. tuberculosis* H37Rv growing on L. J. medium was harvested in 0.85% saline in bijou bottles. These tubes were then incubated at 37 °C for 24 h followed by streaking of *M. tuberculosis* H37Rv (5 × 104 bacilli per tube). These tubes were then incubated at (37 ± 1) °C. Growth of bacilli was seen after 12 days, 22 days and finally 28 days of incubation. Tubes having the compounds were compared with control tubes

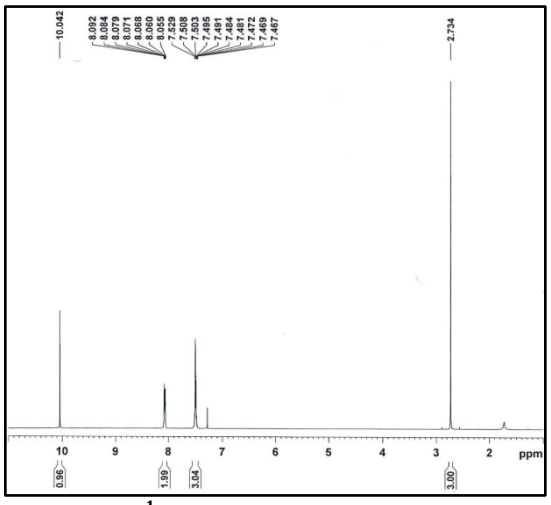
where medium alone was incubated with *M. tuberculosis* H37Rv. The concentration at which no development of colonies occurred or <20 colonies was taken as MIC concentration of test compound. Isoniazid was used as a reference control against *M. tuberculosis* H37Rv being a standard drug in use.

5.5 Spectral Data

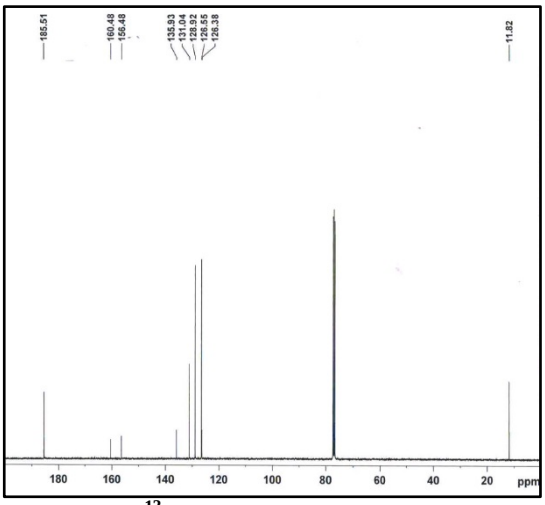
Compound 23a



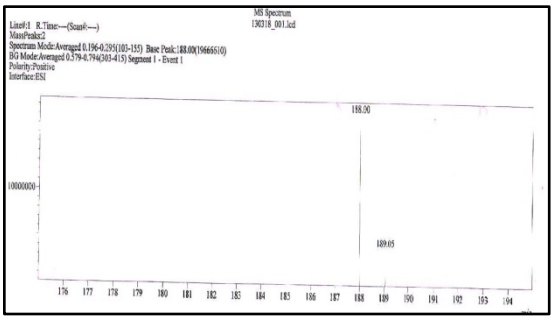
Spectrum 1. IR of compound 23a



Spectrum 2. ^{1}H NMR of compound 23a

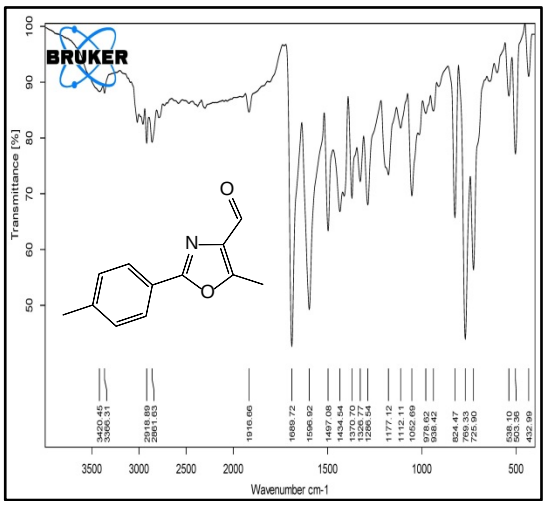


Spectrum 3. ^{13}C NMR of compound 23a

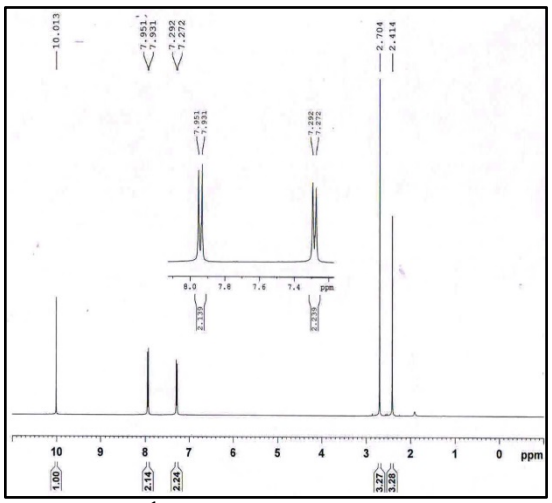


Spectrum 4. MASS of compound 23a

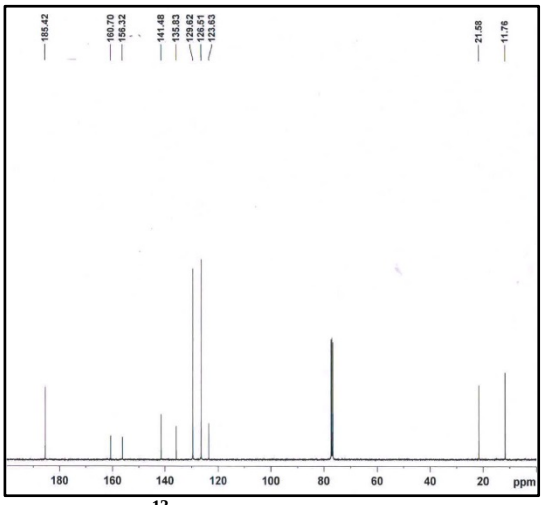
Compound 23b



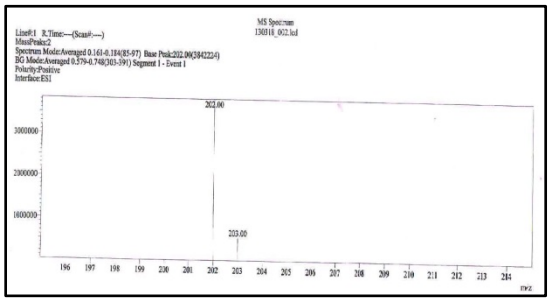
Spectrum 5. IR of compound 23b



Spectrum 6. ^{1}H NMR of compound 23b

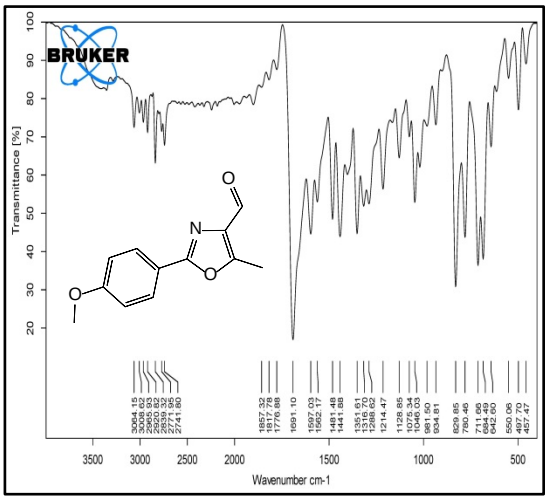


Spectrum 7. ^{13}C NMR of compound 23b

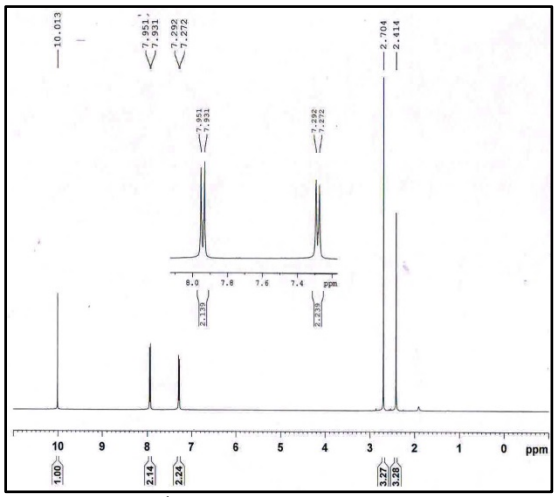


Spectrum 8. MASS of compound 23b

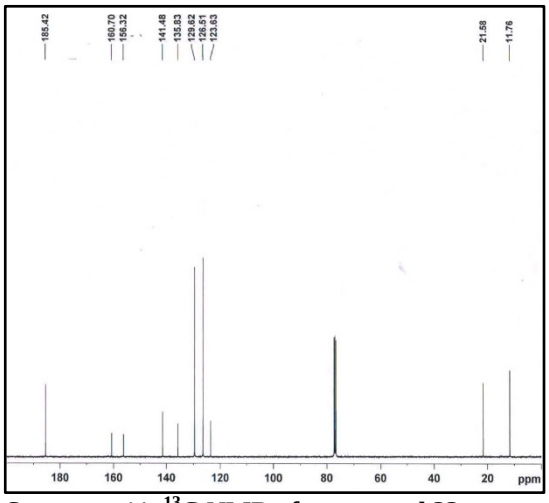
Compound 23c



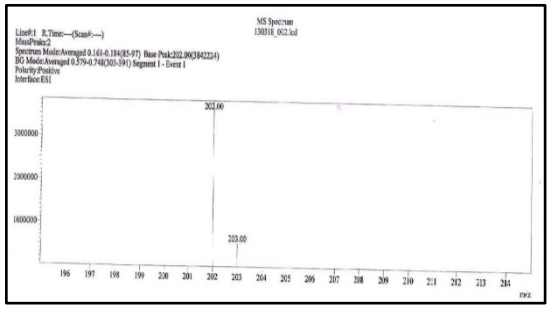
Spectrum 9. IR of compound 23c



Spectrum 10. ^{1}H NMR of compound 23c

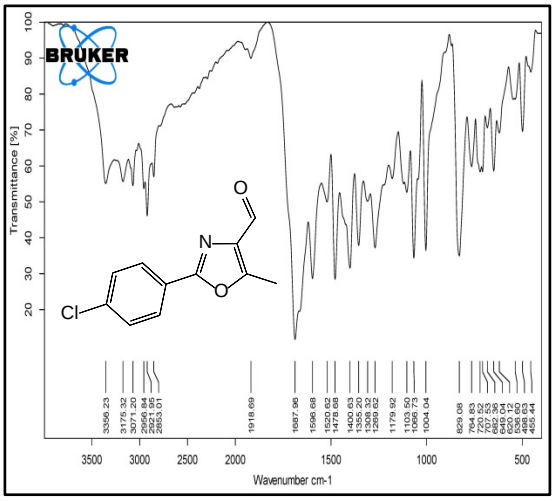


Spectrum 11. ^{13}C NMR of compound 23c

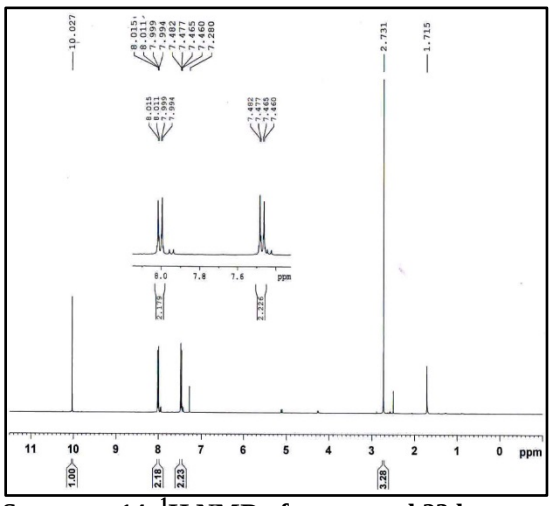


Spectrum 12. MASS of compound 23c

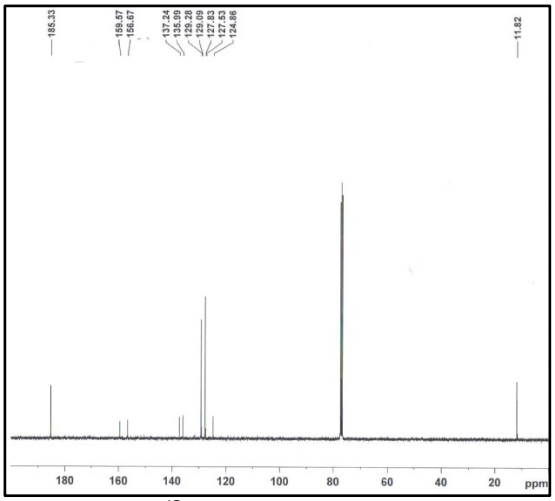
Compound 23d



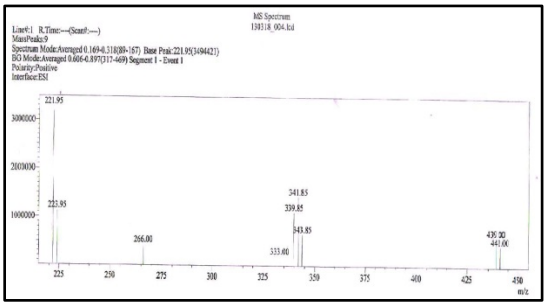
Spectrum 13. IR of compound 23d



Spectrum 14. ^{1}H NMR of compound 23d

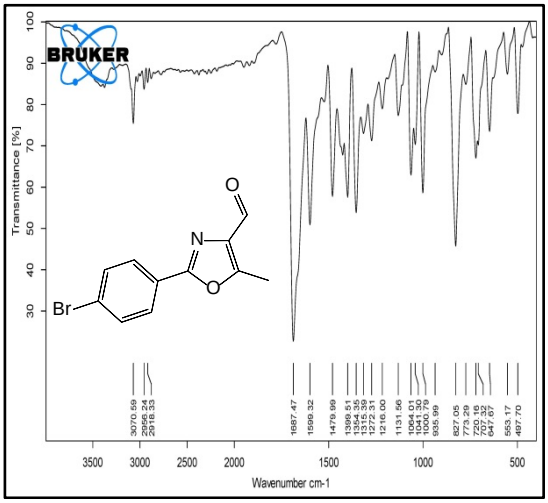


Spectrum 15. ^{13}C NMR of compound 23d

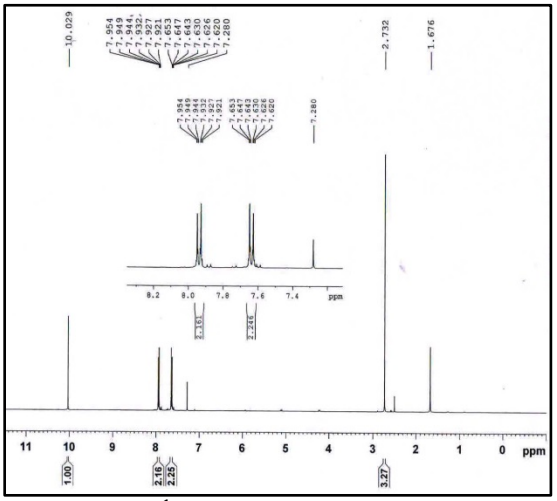


Spectrum 16. MASS of compound 23d

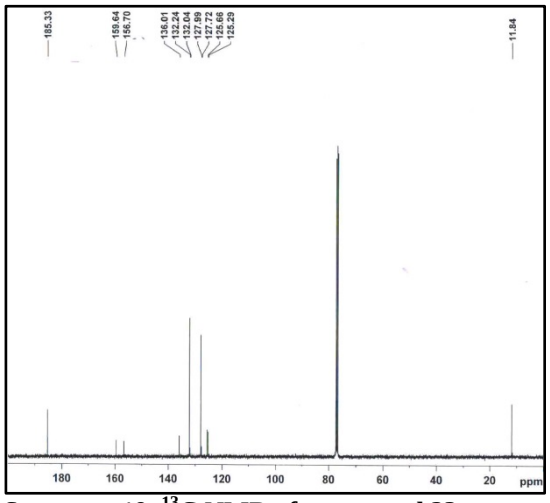
Compound 23e



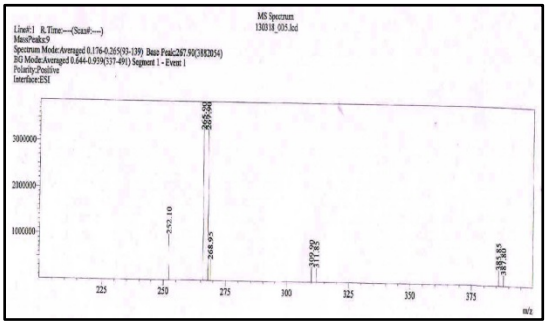
Spectrum 17. IR of compound 23e



Spectrum 18. ^{1}H NMR of compound 23e

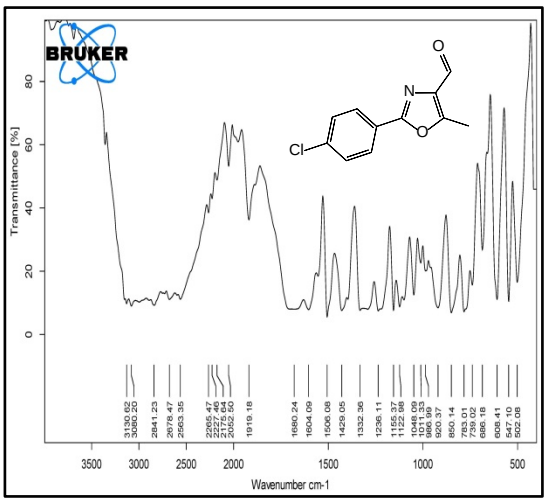


Spectrum 19. ^{13}C NMR of compound 23e

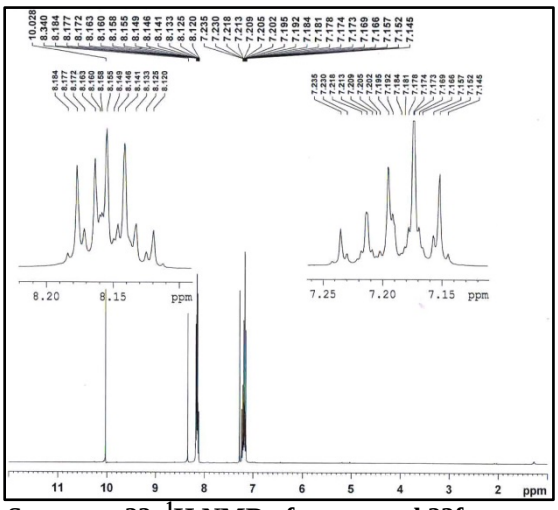


Spectrum 20. MASS of compound 23e

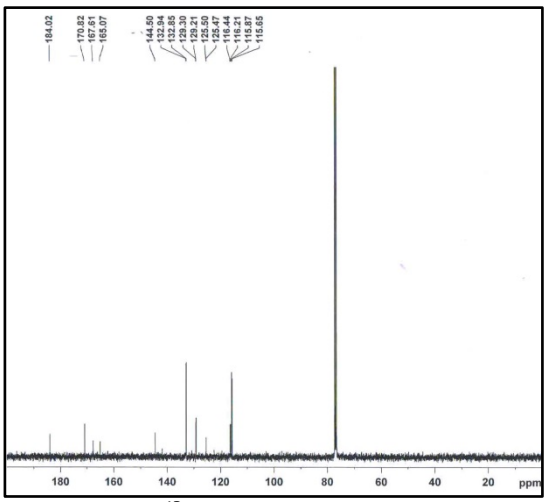
Compound 23f



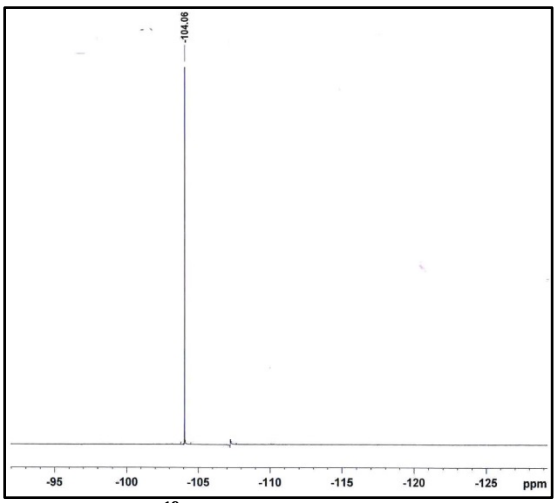
Spectrum 21. IR of compound 23f



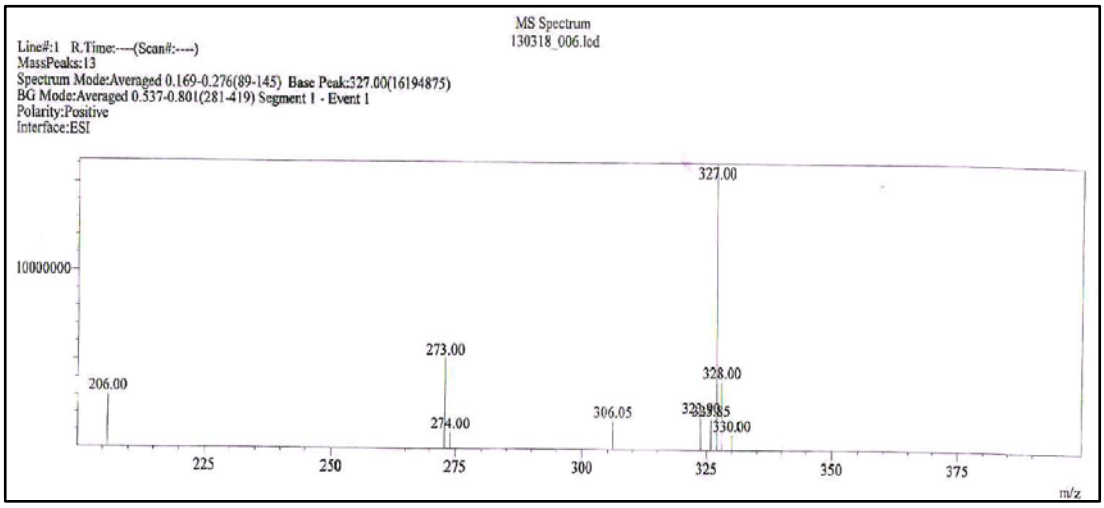
Spectrum 22. ^{1}H NMR of compound 23f



Spectrum 23. ^{13}C NMR of compound 23f

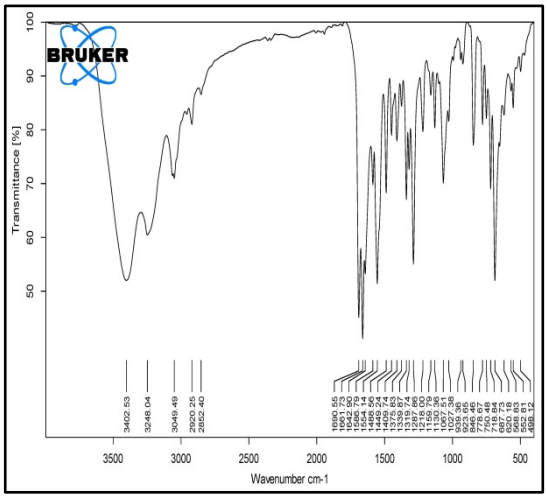


Spectrum 24. ^{19}F NMR of compound 23f

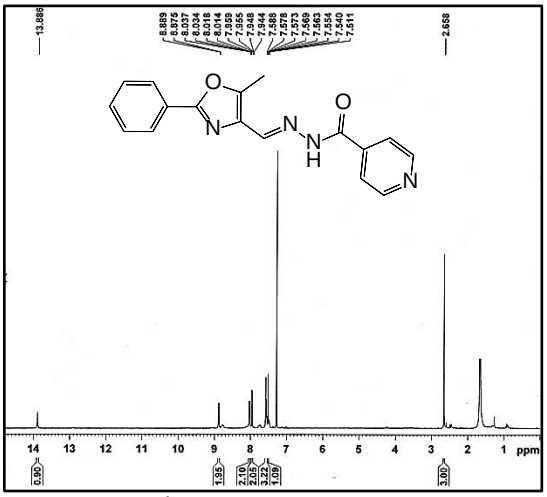


Spectrum 25. MASS of compound 23f

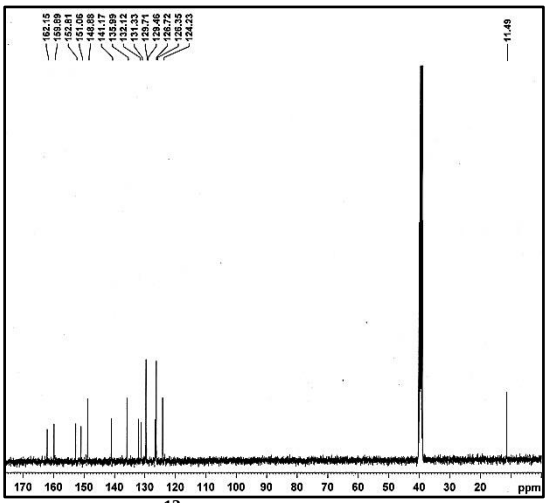
Compound 25a



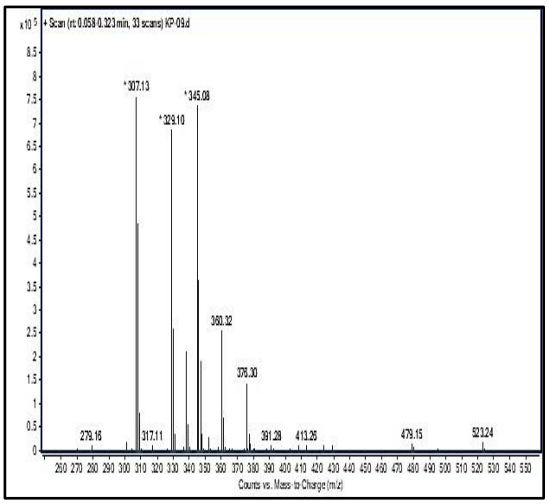
Spectrum 26. IR of compound 25a



Spectrum 27. ^{1}H NMR of compound 25a

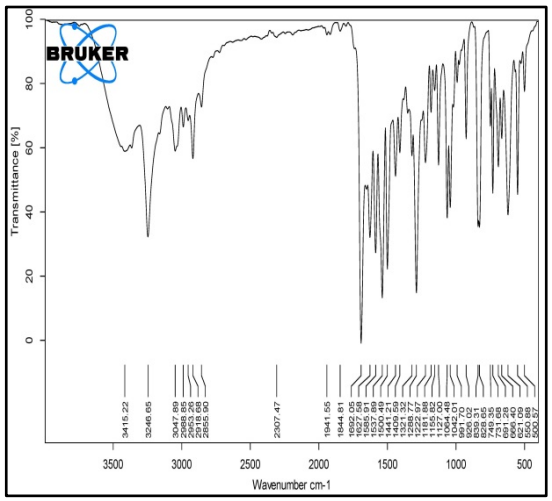


Spectrum 28. ^{13}C NMR of compound 25a

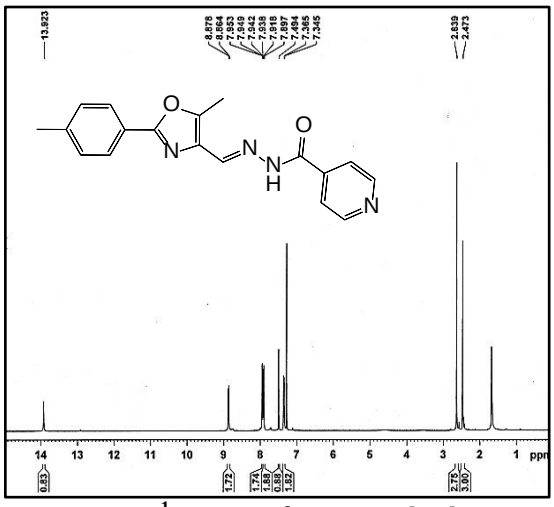


Spectrum 29. MASS of compound 25a

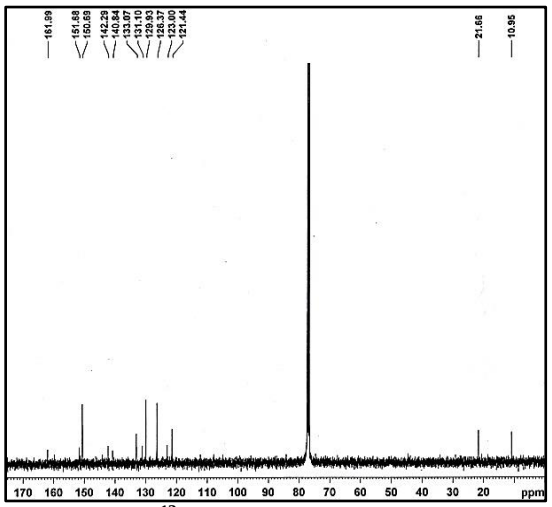
Compound 25b



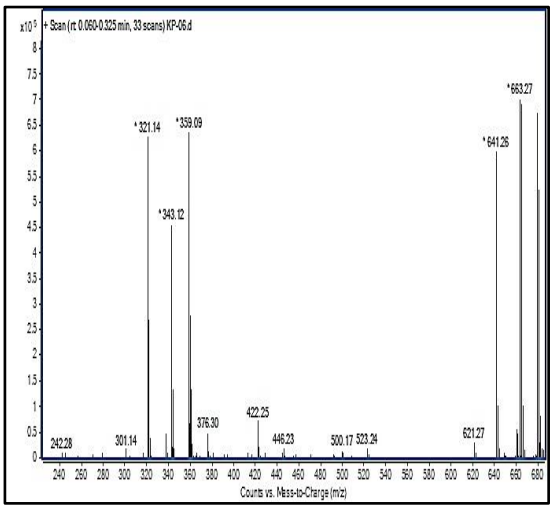
Spectrum 30. IR of compound 25b



Spectrum 31. ^{1}H NMR of compound 25b

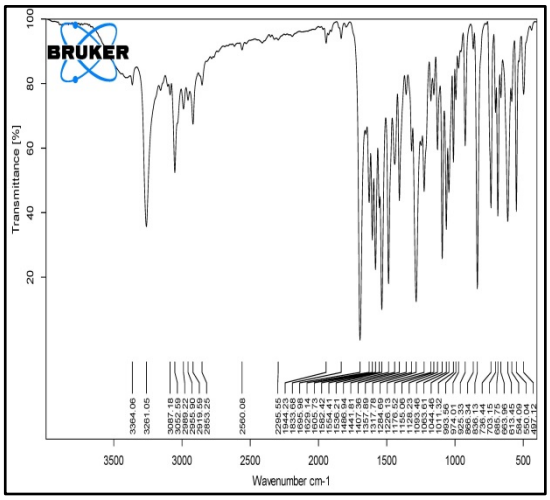


Spectrum 32. ^{13}C NMR of compound of 25b

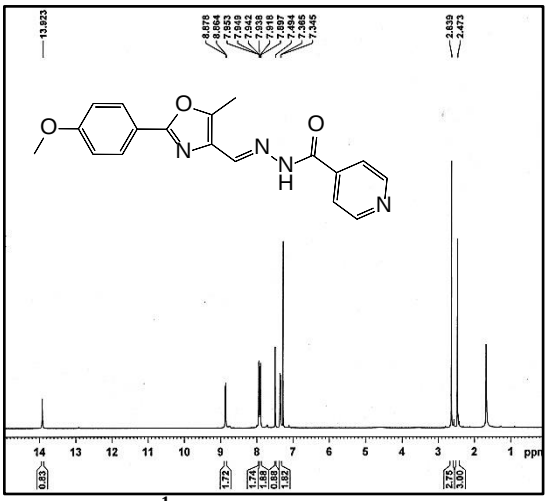


Spectrum 33. MASS of compound 25b

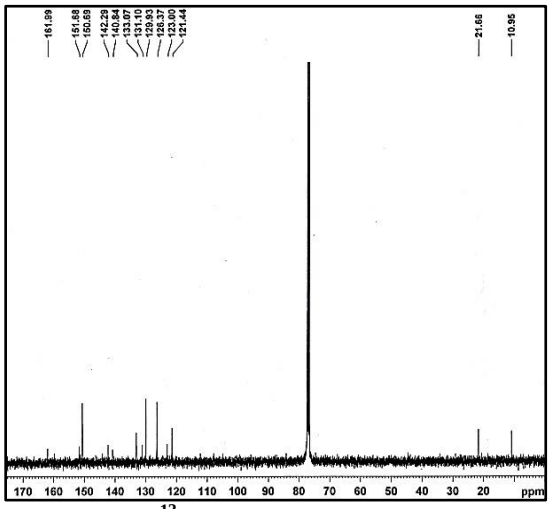
Compound 25c



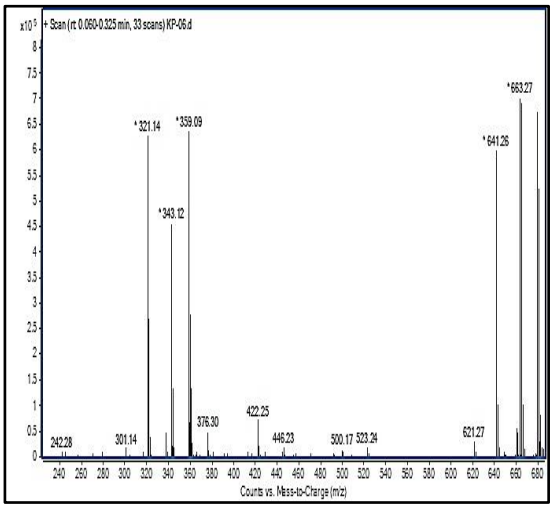
Spectrum 34. IR of compound 25c



Spectrum 35. ^{1}H NMR of compound 25c

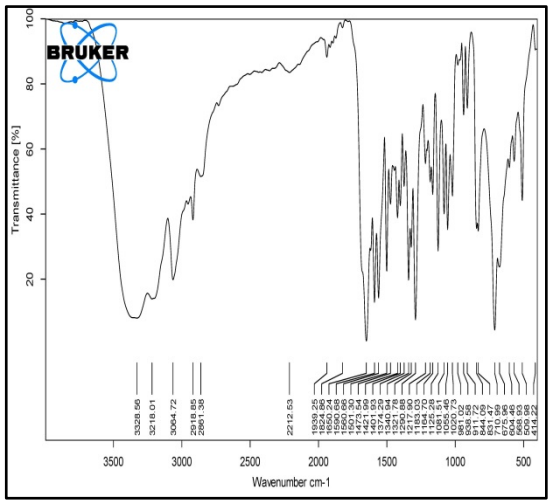


Spectrum 36. ^{13}C NMR of compound of 25c

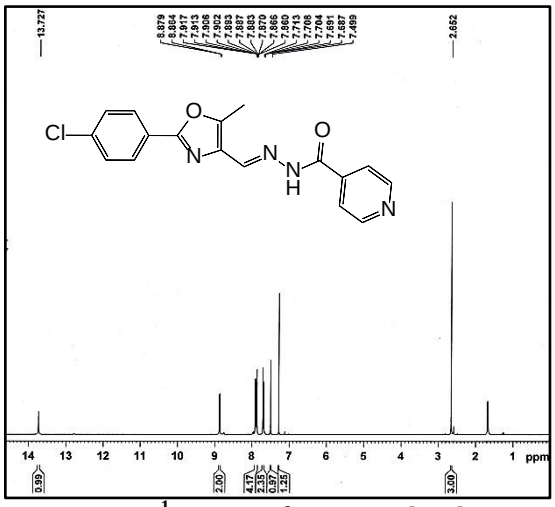


Spectrum 37. MASS of compound 25c

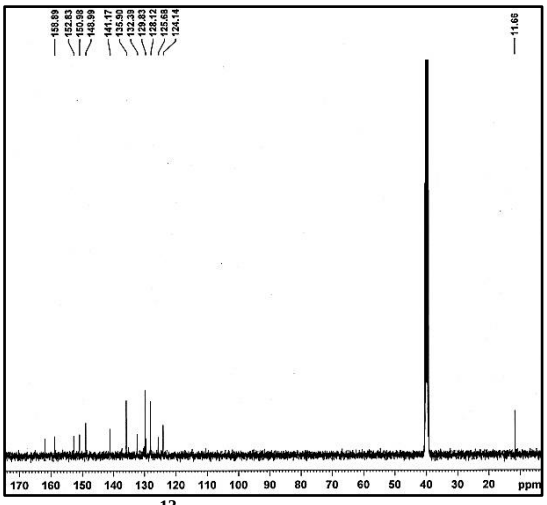
Compound 25d



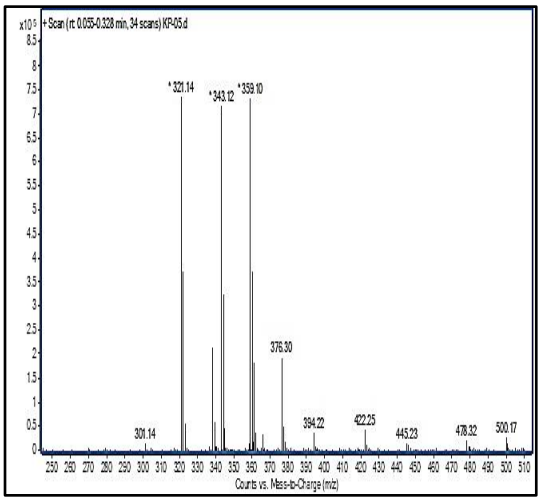
Spectrum 38. IR of compound 25d



Spectrum 39. ^{1}H NMR of compound 25d

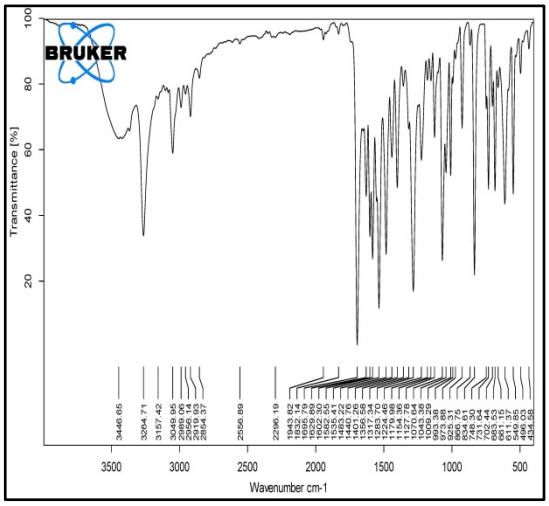


Spectrum 40. ^{13}C NMR of compound 25d

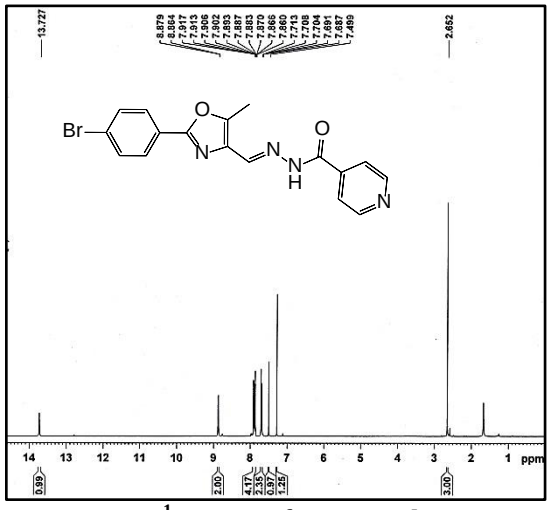


Spectrum 41. MASS of compound 25d

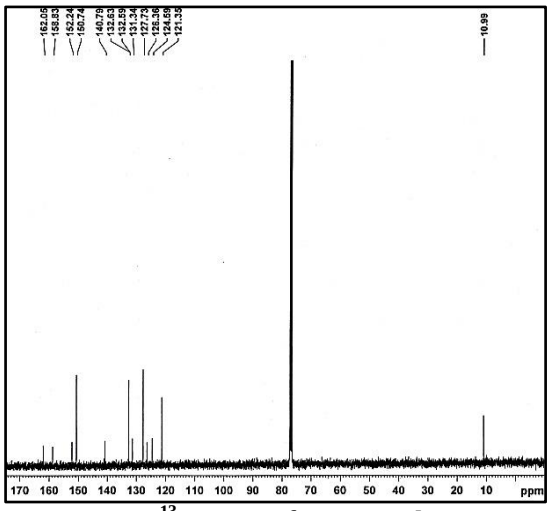
Compound 25e



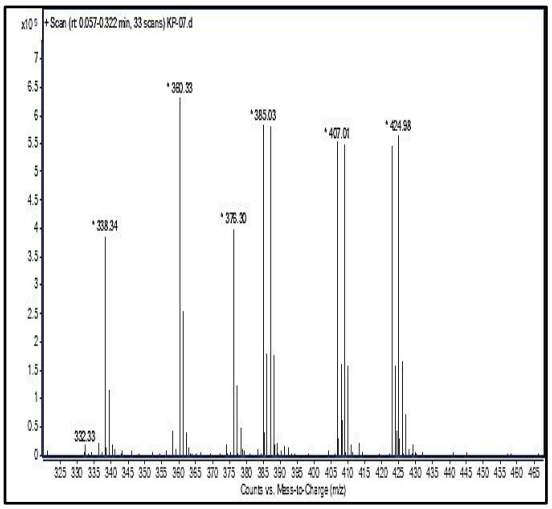
Spectrum 42. IR of compound 25e



Spectrum 43. ^{1}H NMR of compound 25e

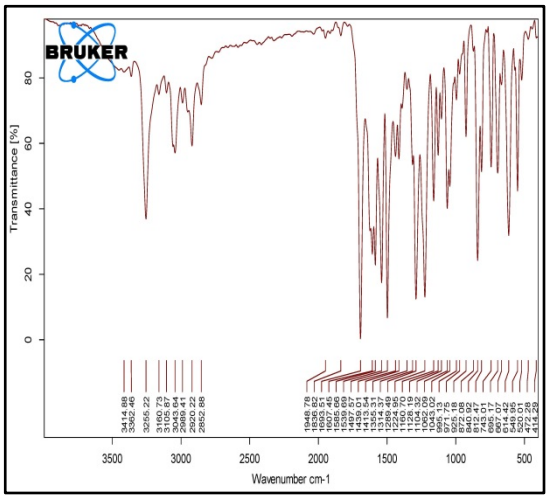


Spectrum 44. ^{13}C NMR of compound 25e

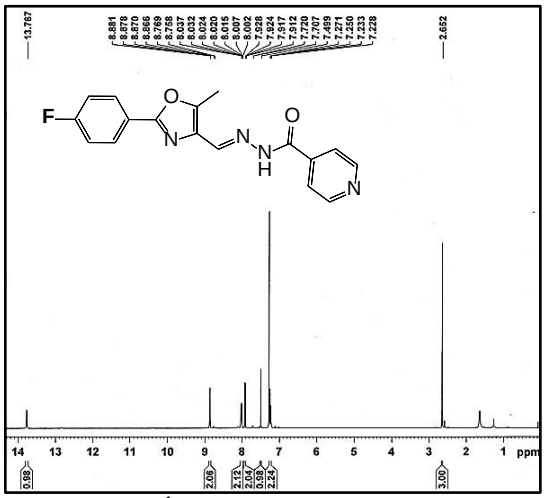


Spectrum 45. MASS of compound 25e

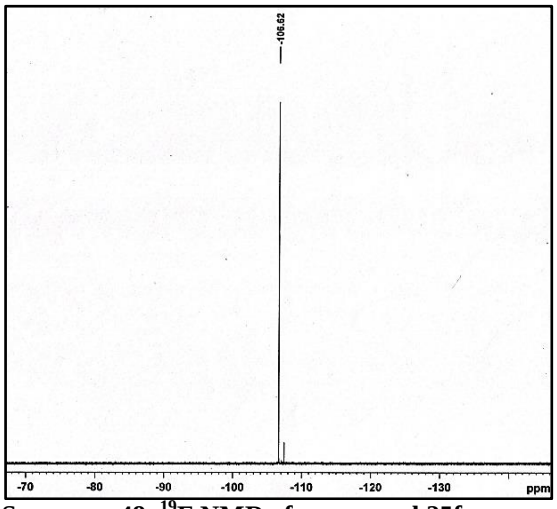
Compound 25f



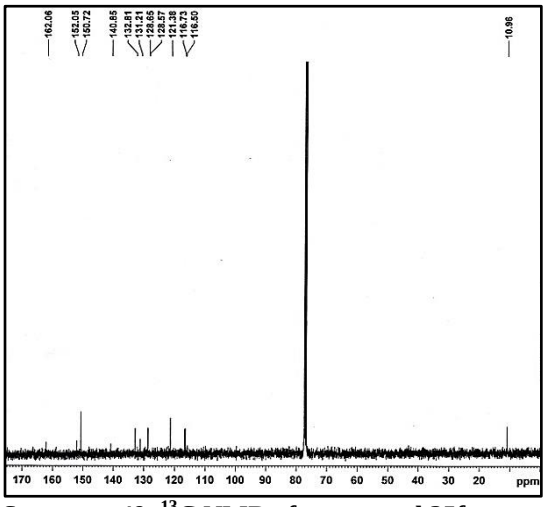
Spectrum 46. IR of compound 25f



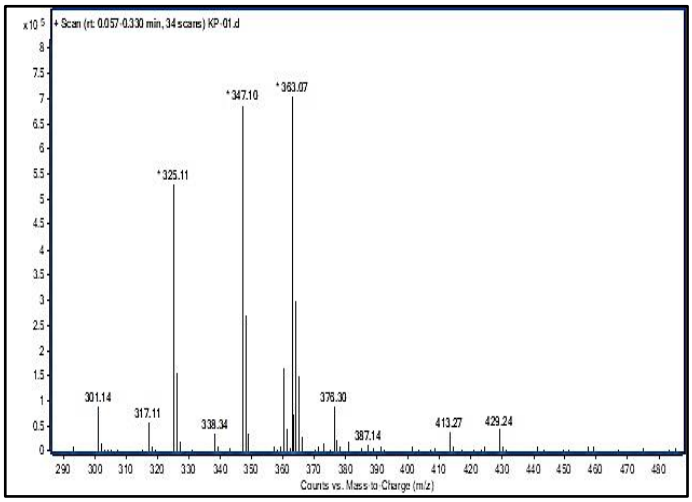
Spectrum 47. ^{1}H NMR of compound 25f



Spectrum 48. ^{19}F NMR of compound 25f

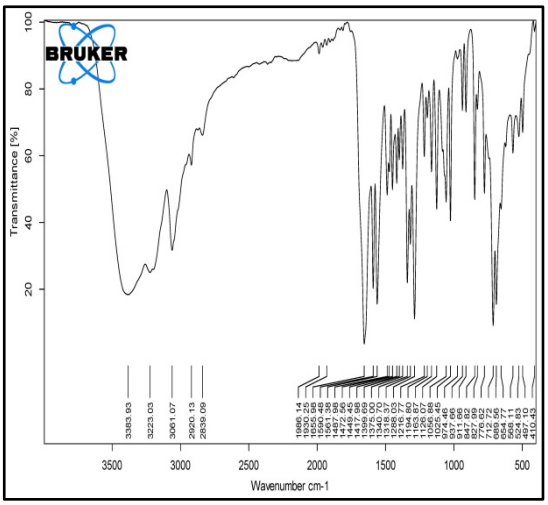


Spectrum 49. ^{13}C NMR of compound 25f

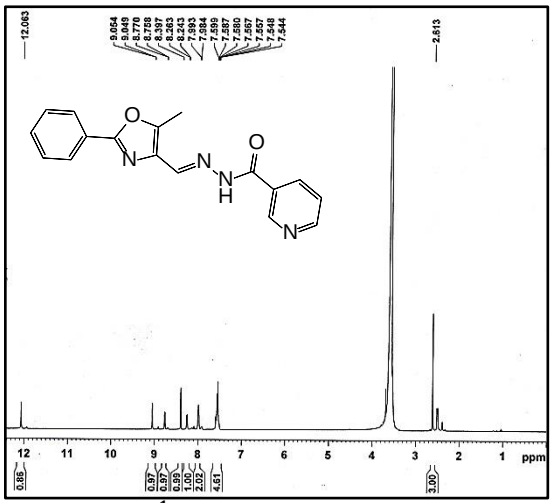


Spectrum 50. MASS of compound 25f

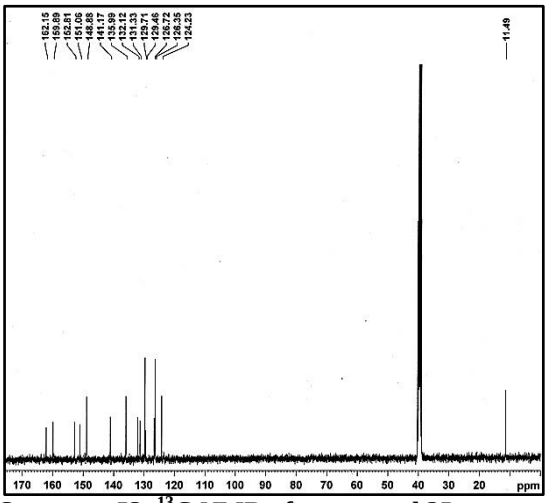
Compound 25g



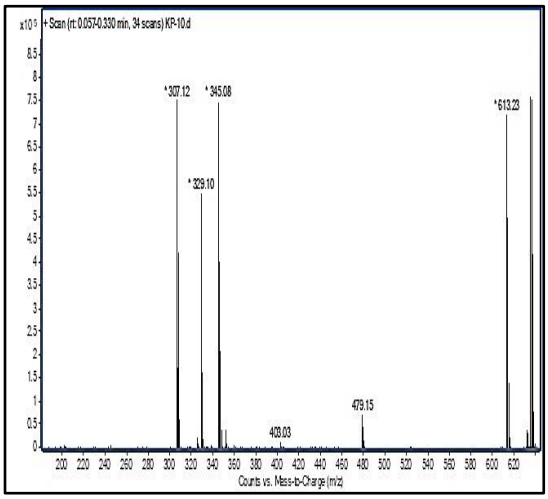
Spectrum 51. IR of compound 25g



Spectrum 52. ^{1}H NMR of compound 25g

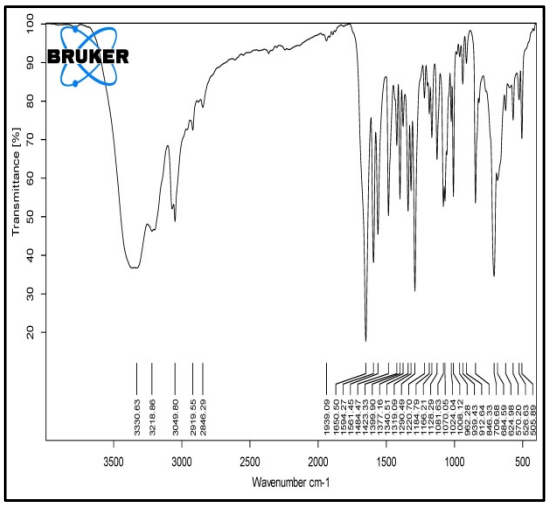


Spectrum 53. ^{13}C NMR of compound 25g

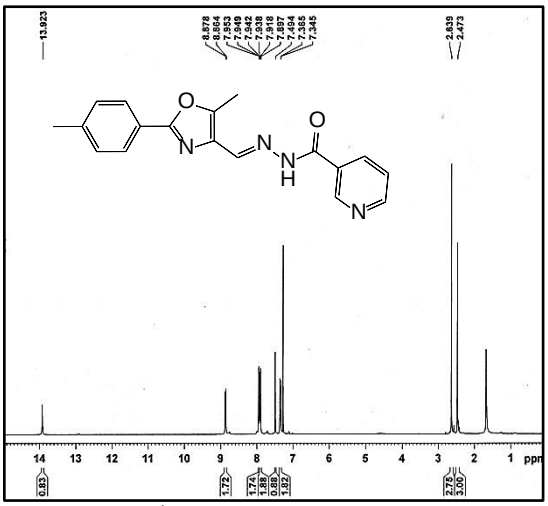


Spectrum 54. MASS of compound 25g

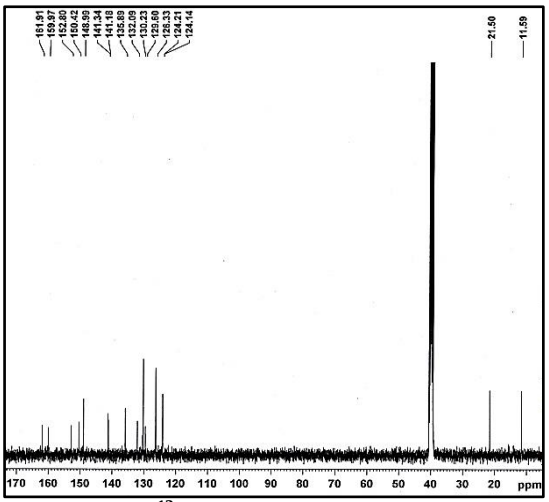
Compound 25h



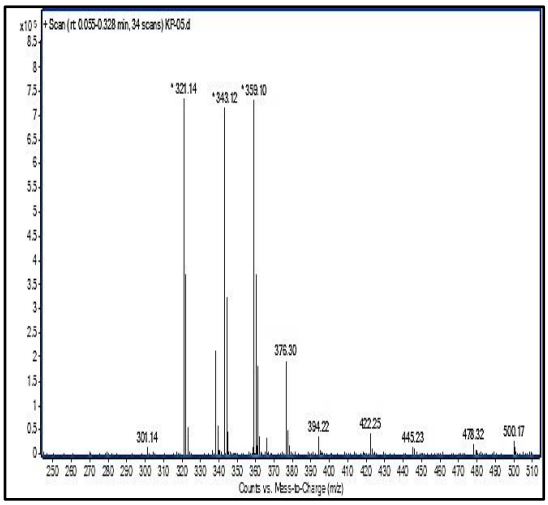
Spectrum 55. IR of compound 25h



Spectrum 56. ^{1}H NMR of compound 25h

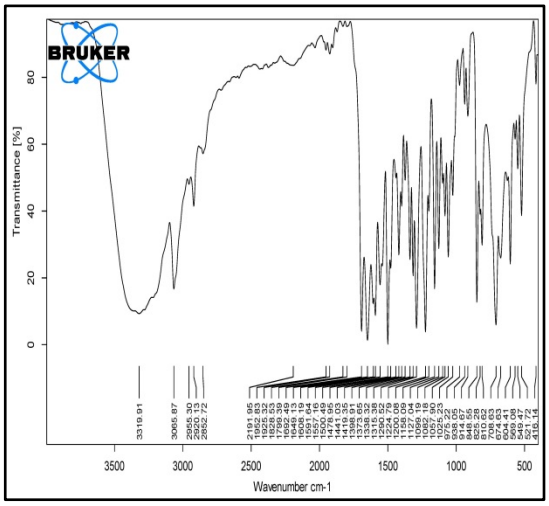


Spectrum 57. ^{13}C NMR of compound 25h

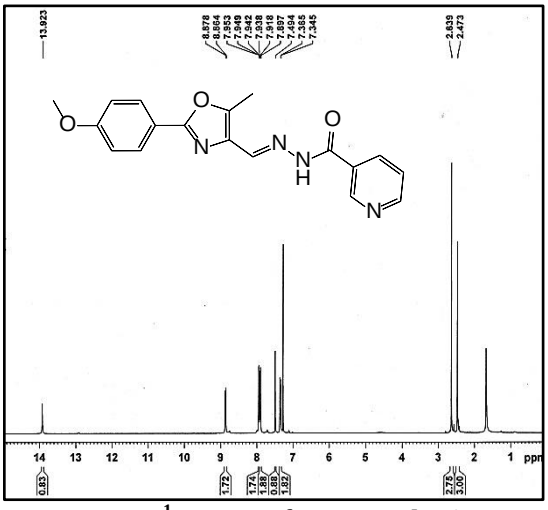


Spectrum 58. MASS of compound 25h

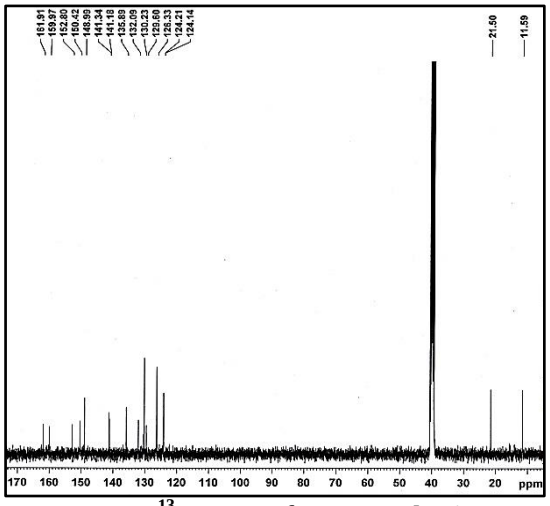
Compound 22i



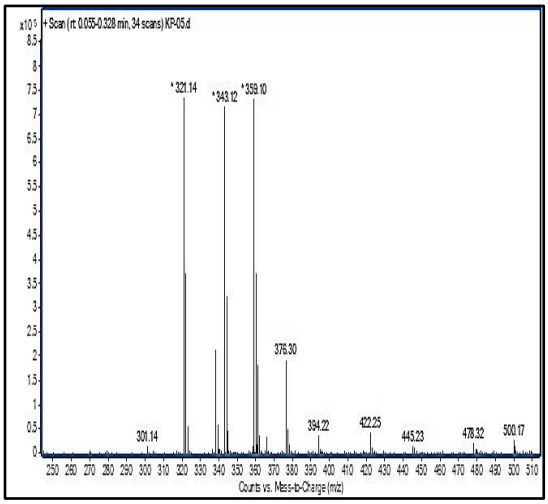
Spectrum 59. IR of compound 25i



Spectrum 60. ^{1}H NMR of compound 25i

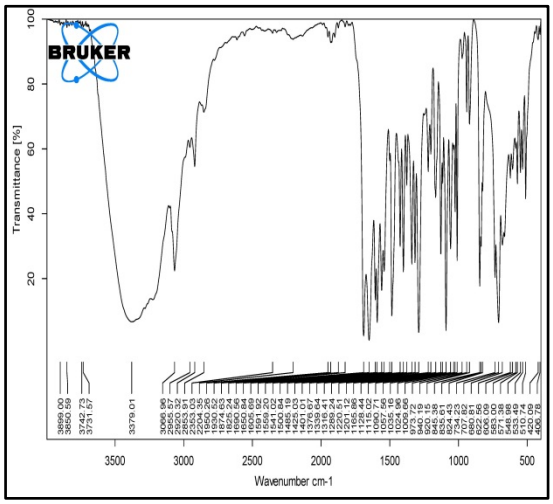


Spectrum 61. ^{13}C NMR of compound 25i

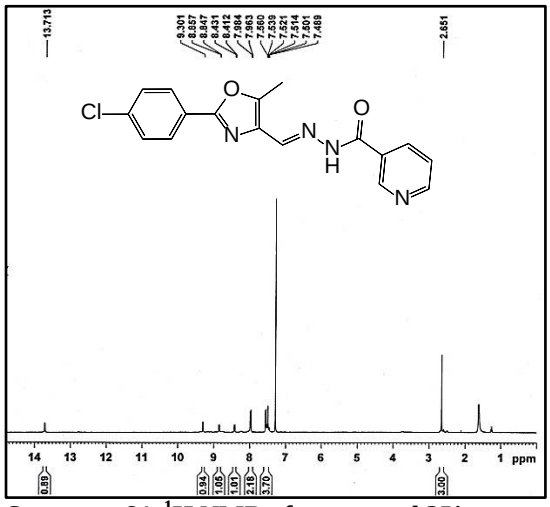


Spectrum 62. MASS of compound 25i

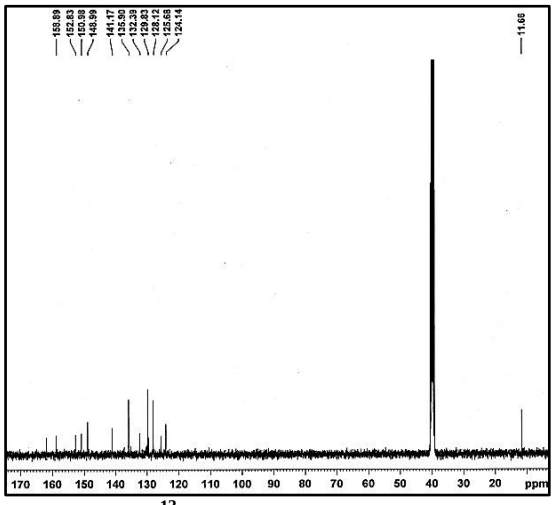
Compound 25j



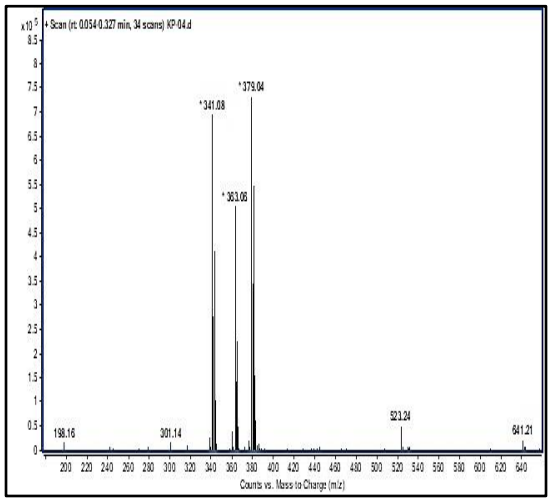
Spectrum 63. IR of compound 25j



Spectrum 64. ^{1}H NMR of compound 25j

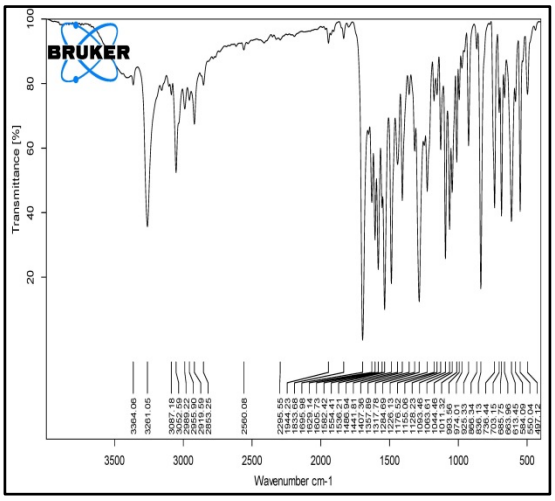


Spectrum 65. ^{13}C NMR of compound 25j

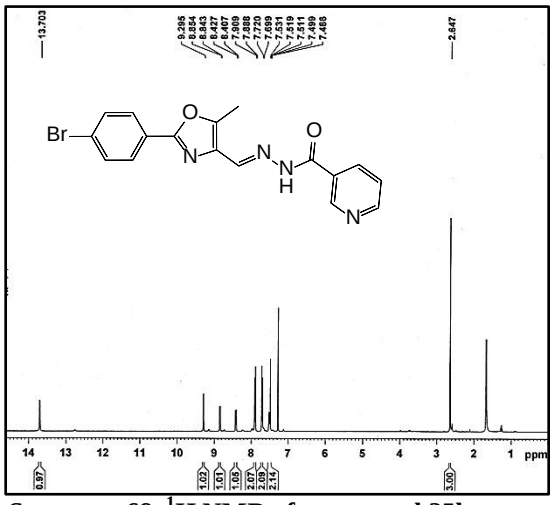


Spectrum 66. MASS of compound 25j

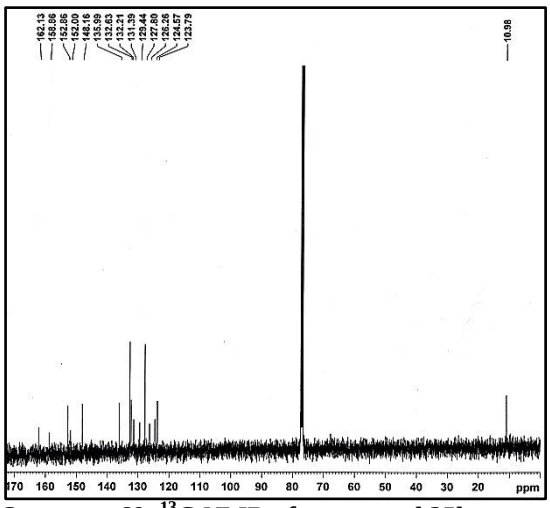
Compound 25k



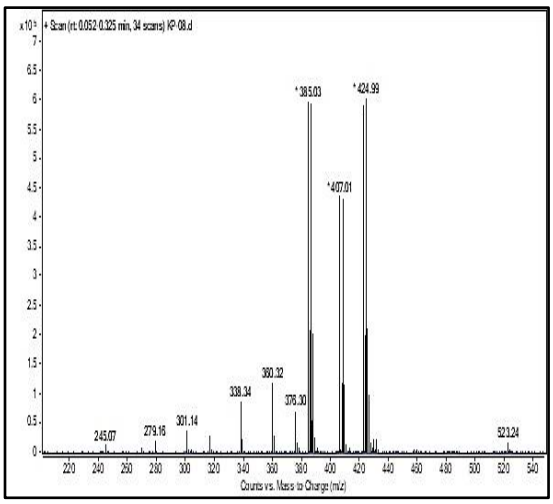
Spectrum 67. IR of compound 25k



Spectrum 68. ^{1}H NMR of compound 25k

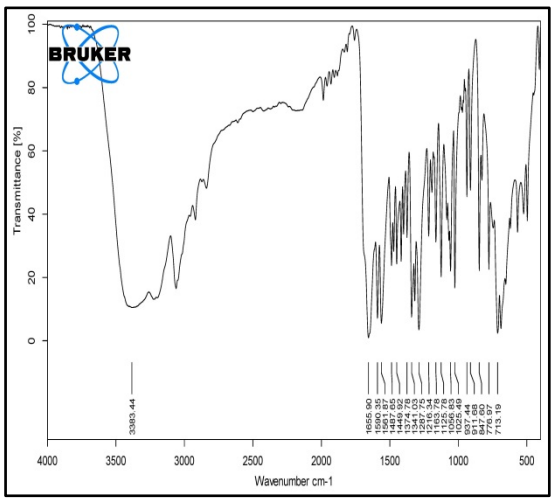


Spectrum 69. ^{13}C NMR of compound 25k

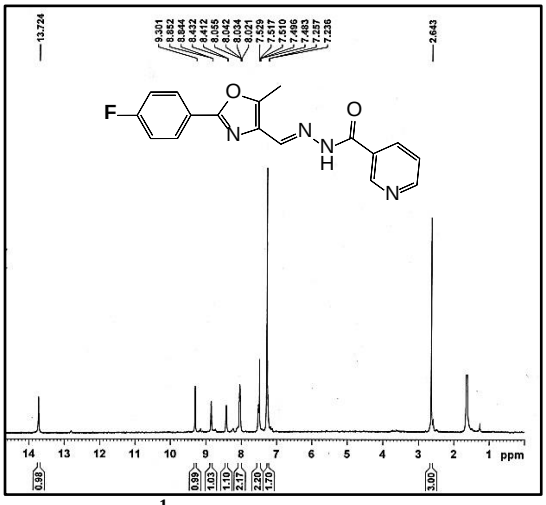


Spectrum 70. MASS of compound 25k

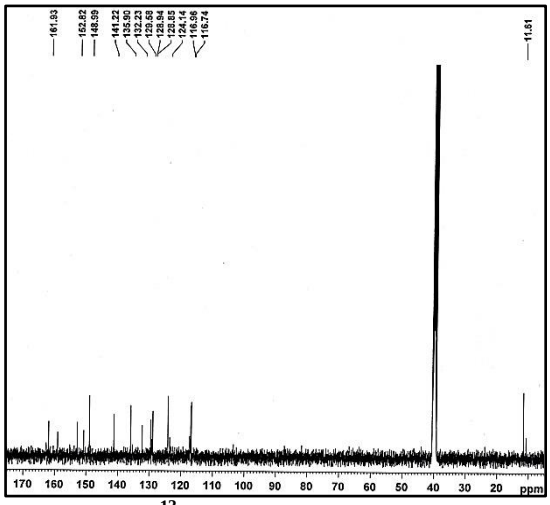
Compound 22l



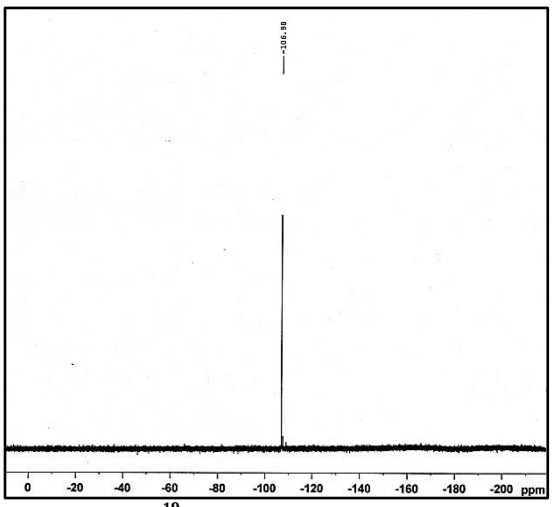
Spectrum 71. IR of compound 25l



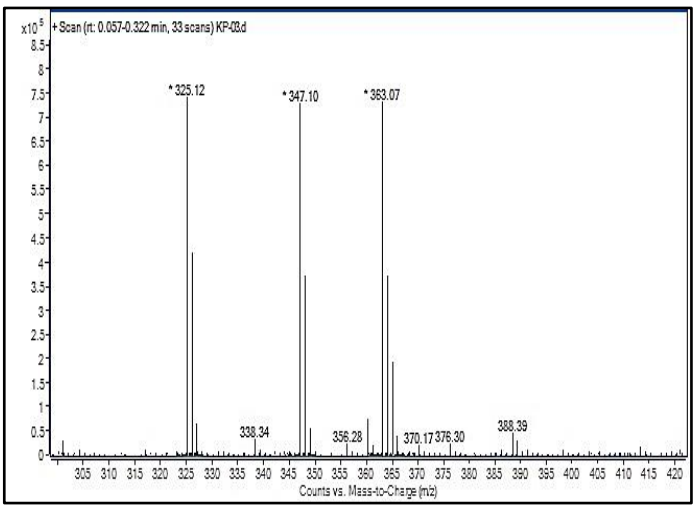
Spectrum 72. ^{1}H NMR of compound 25l



Spectrum 73. ^{13}C NMR of compound 25l



Spectrum 74. ^{19}F NMR of compound 25l



Spectrum 75. MASS of compound 25l

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