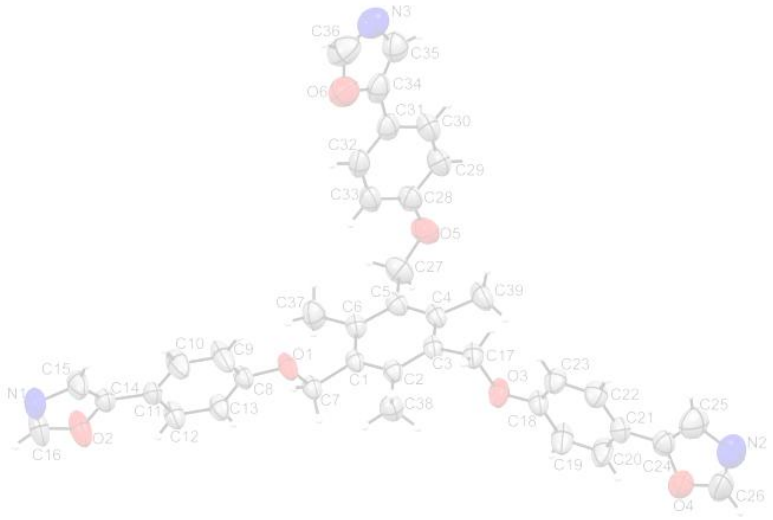
CHAPTER II

Synthesis and characterization of 1,3,5-tris[n-(1,3-oxazol-5-yl)-phenyloxymethyl]-2,4,6-trimethylbenzenes and their biological evaluation



2.1 INTRODUCTION

As was discussed in introduction chapter, C_3 symmetric compounds with tripodal arms having various binding sites embedded, offer supramolecular interactions which can accommodate appropriate guest entity with the help of combinatorial effects of tripods. The binding sites may be present in form of various functional groups or in form of heterocycles. The C_3 symmetric tripodal compounds having heterocyclic moieties have been reported to act as supramolecular hosts, effective catalysts and as materials with a variety of unique properties as detailed in the previous chapter.

With the target to synthesize and study some novel C_3 symmetric tripodal compounds with possibility of supramolecular interactions and other potential applications, a synthesis route was designed starting from a simple readily available starting material- 1,3,5-trimethylbenzene (mesitylene) with an inherent C_3 symmetry element.

With an already developed methodology, 1,3,5-trimethylbenzene can be functionalized on triple bromo-methylation to 1,3,5-trisbromomethyl-2,4,6-trimethylbenzene[1] which was further expanded to tris-aromatic compounds substituted with a useful and reactive formyl functionality[2] (Figure 1).

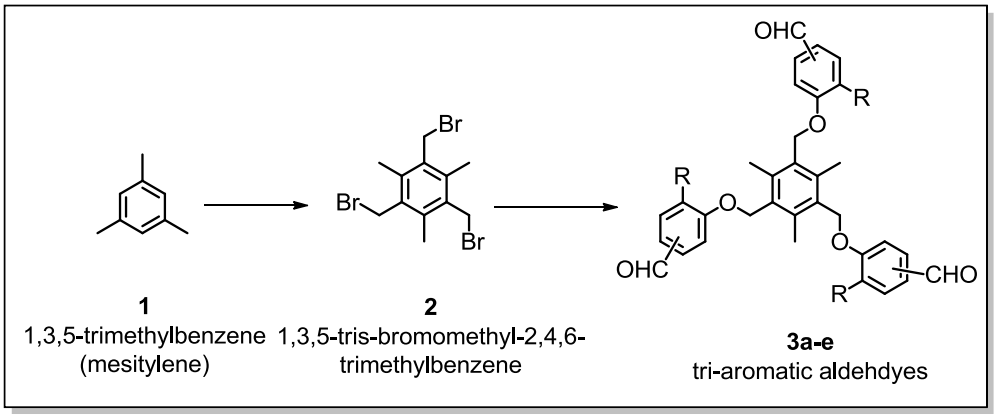


Figure 1 ***Synthesis of C_3 symmetric tris-formyl compounds***

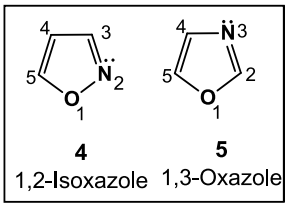
These tripodal tris-aldehydes **3** have unlimited potential for the development of various new C_3 symmetric molecules with tunable properties.

In an improved synthesis method of the coupling of tris-bromomethyl mesitylene with phenolic aldehydes, the coupling reaction was carried out by stirring in presence of K_2CO_3 as a base and acetone as a solvent just at room temperature within 2-3 h of reaction time, and refluxing or heating as reported earlier[2] was found to be unrequired. Thus five tris-aldehydes with varying relative functional group positions were synthesized for their utility for the synthesis of new C_3 symmetric compounds.

Formyl functionality is a versatile functionality which can undergo various nucleophilic addition reactions leading to a variety of new molecules. Using formyl functionalities, it was decided to design and synthesize some novel tris-heterocyclic C_3 symmetric compounds for their study and applications.

A reaction by which a formyl functionality can directly be converted to a heterocyclic moiety was noticed utilizing the van Leusen reagent- *p*-toluenesulfonylmethyl isocyanide which leads to a five member 1,3-azole namely 1,3-oxazole.

There are two isomeric oxazoles; 1,2-oxazole **4** is commonly known as isooxazole and the other is 1,3-oxazole **5** in which oxygen and nitrogen atoms are occupying one and three positions respectively to form the five member heterocycle (Figure 2). The chemistry of oxazole has been well documented and reviewed covering its various aspects.[3]



4 1,2-Isoxazole **5** 1,3-Oxazole

Figure 2 ***Isomeric oxazoles***

It has attracted much attention in recent years following isolation of a number of oxazole containing natural products mainly of marine origin and studied due to their biological activities[4] (Figure 3).

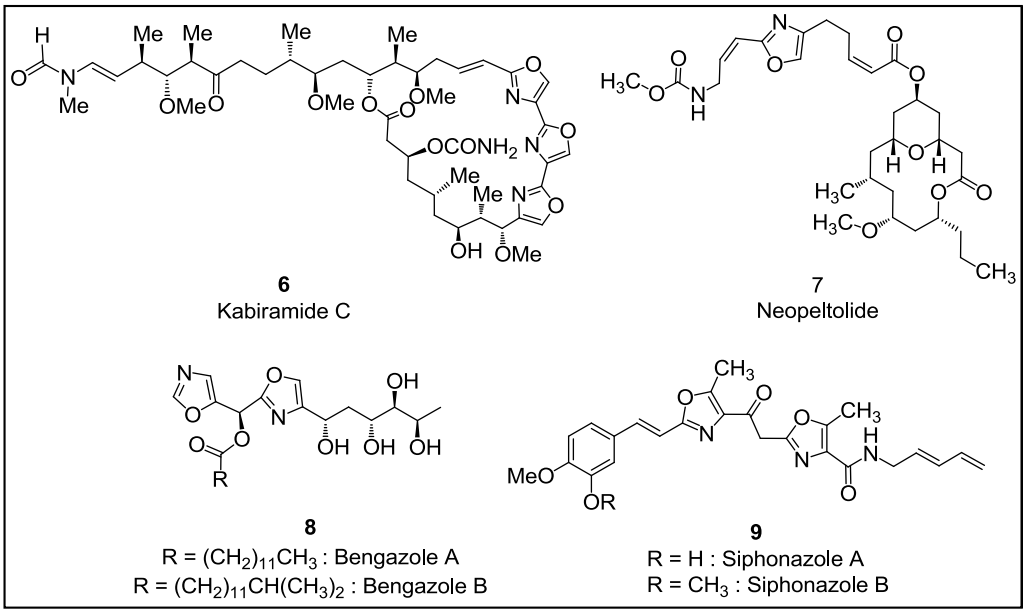


Figure 3 ***Bioactive marine natural products***

Oxazoles are medicinally important compounds and have been studied for various biological activities such as antibiotic,[5] antiproliferative /anticancer,[6] antituberculer/ antimycobacterial,[7] antidiabetic,[8] antiviral,[9] antiinflammatory,[10] antibacterial,[11] antiviral,[11b] as some of the important biological activities (Figure 4).

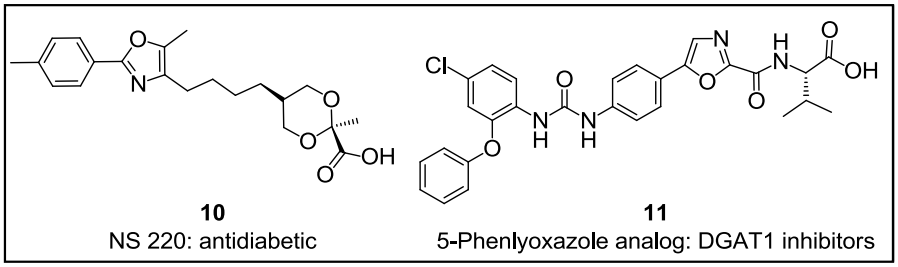
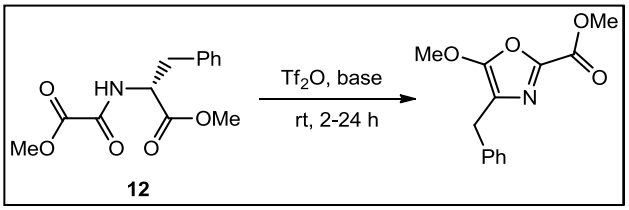


Figure 4 ***Bioactive drug molecules possessing oxazole moiety***

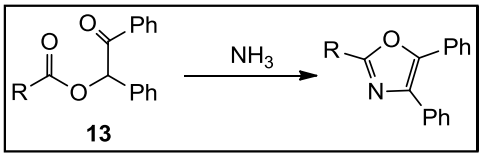
There are a number of methods and substrates which react to give 1,3-oxazoles. A few representative reactions have been mentioned below.

One of the early works involves the cyclization of *N*-acylamino ketones[12] to 1,3-oxazoles under dehydrative condition which is known as the Robinson-Gabriel synthesis. Similarly, *N*-acylamino acid esters **12** were found to cyclize under dehydrative condition giving the 2,4,5-trisubstituted oxazole derivatives[13] (Scheme 2.1).



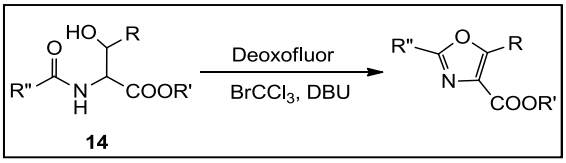
Scheme 2.1

The reaction of esters **13** obtained from benzoin on reaction with ammonia yields aryl substituted oxazoles[14] (Scheme 2.2).

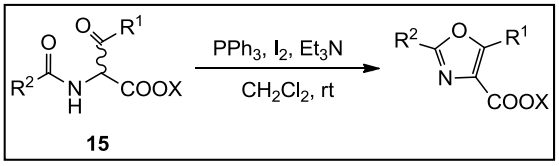


Scheme 2.2

Another approach involved the conversion of β-hydroxyamides **14** [15] (Scheme 2.3) and β-ketoamides or α-amido-β-ketoesters **15** (Scheme 2.4) to oxazoles under mild oxidative reaction conditions.[16]

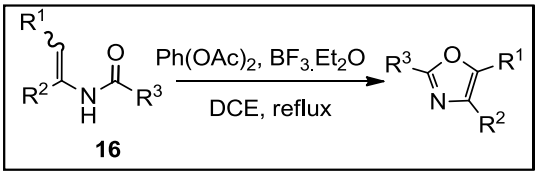


Scheme 2.3

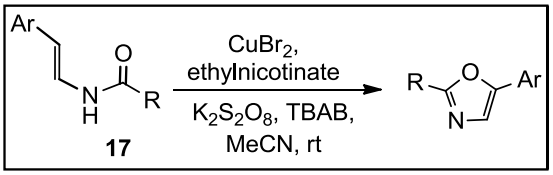


Scheme 2.4

N-Substituted amide derivatives **16** were found to be one of the useful substrates for the synthesis of substituted 1,3-oxazole derivatives following oxidative cyclization reaction condition[17] (Scheme 2.5).



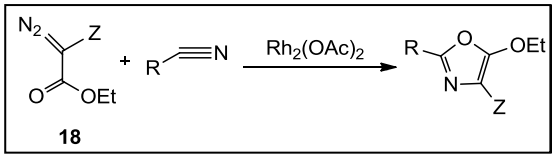
Scheme 2.5



Scheme 2.6

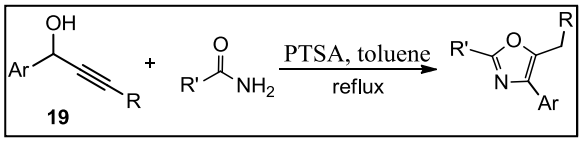
Cu(II) catalyzed oxidative cyclization of *N*-vinyl enamides **17** yielded substituted 1,3-oxazoles[18] (Scheme 2.6).

Diazo-carbonyl compounds **18** react with nitriles in presence of rhodium acetate as a catalyst leading to the functionalized oxazoles[19] (Scheme 2.7).



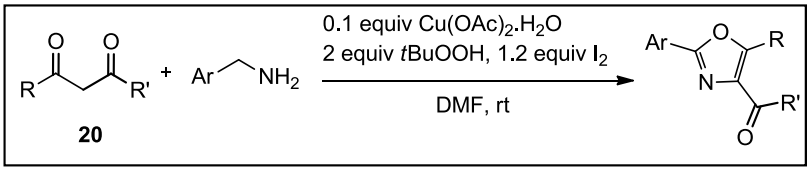
Scheme 2.7

Cyclization of propargyl alcohols **19** with amides provide substituted 1,3-oxazoles using *p*-toluenesulfonic acid monohydrate as a bifunctional catalyst by the cycloisomerization process[20] (Scheme 2.8) and another method reported was using $Zn(OTf)_2$ as a catalyst .[21]



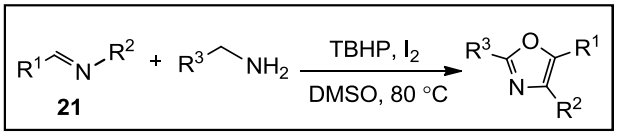
Scheme 2.8

In a Cu(II) catalyzed oxidative cyclization reaction, 1,3-diketones **20** and arylamines react to give substituted oxazoles[22] (Scheme 2.10).

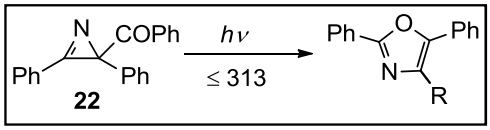


Scheme 2.9

The reaction of aryl alkenes **21** with benzylamine under domoino oxidative cyclization yields a variety of substituted 1,3-oxazole derivatives[23] (Scheme 3.0).



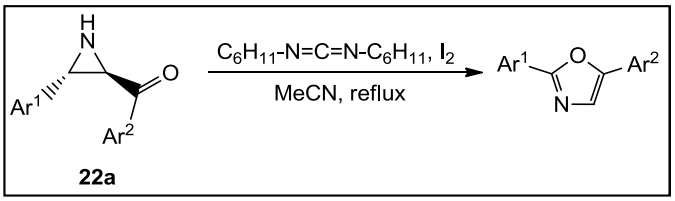
Scheme 2.10



Scheme 2.11

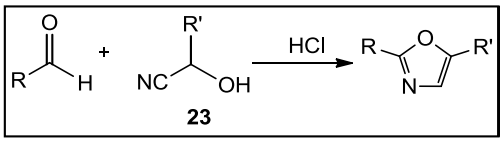
Azirines **22** were converted to oxazoles under photolytic conditions as earlier literature[24] (Scheme 2.11).

Recently, oxazoles were also prepared via ring expansion of keto-aziridines **22a** using DCC and iodine reagent[25] (Scheme 2.12).

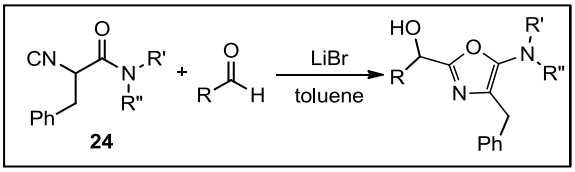


Scheme 2.12

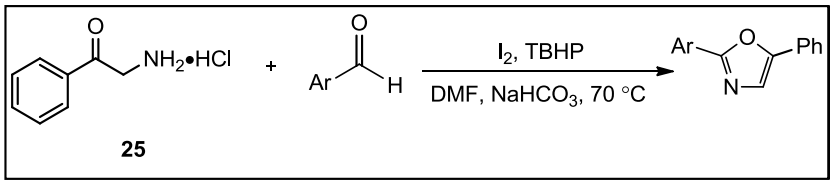
Aldehydes can be transformed into 1,3-oxazoles by reacting with different, substrates such as cyanohydrins **23** under dehydrative reaction conditions,[26] (Scheme 2.13) amides of α-isocyano-β-phenylpropionic acid **24**[27] (Scheme 2.14) and 2-aminoarylketone **25** hydrochlorides[28] (Scheme 2.15).



Scheme 2.13

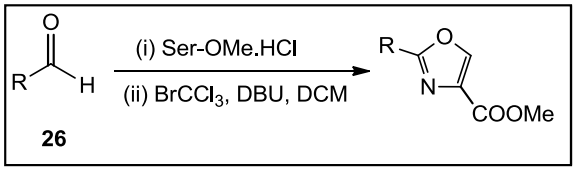


Scheme 2.14



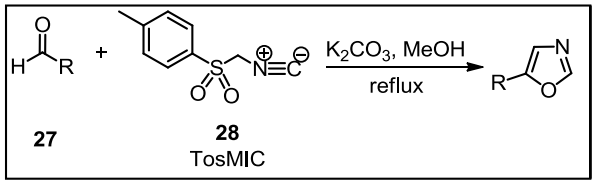
Scheme 2.15

2,4-Disubstituted-1,3-oxazoles were prepared by the condensation of aldehydes **26** with serine followed by oxidation under mild conditions[29] (Scheme 2.16).



Scheme 2.16

One of the convenient methods for the synthesis of 5-substituted-1,3-oxazole involves the reaction of aldehydes **27** with *p*-toluenesulfonylmethyl isocyanide (TosMIC), the van Leusen reagent in the presence of a base as was first reported by van Leusen[30] (Scheme 2.17).



Scheme 2.17

Polymer supported TosMIC reagent was also reported as one of the convenient modification for the synthesis of 5-substituted-1,3-oxazole.[31]

In this chapter, the van Leusen reagent was employed for the synthesis of C_3 symmetric oxazole derivatives from the newly prepared tris-aldehydes as mentioned above.

The oxazoles formed by the van Leusen synthesis have C-2 and C-4 positions unoccupied, the position C-2 being a reactive position may easily be substituted by using various reagents. There are several catalytic methods reported for the direct C-H arylation of the heterocycle.[32] Thus 5-substituted oxazoles can be converted to 2,5-disubstituted-1,3-oxazoles using this methodology.

Oxazoles with conjugated aromatic substitution at position 2- and 5- result in highly fluorescent materials.[33] Such 2,5-disubstituted-1,3-oxazoles have valuable application in the field of fluorescent dyes[34] (Figure 5).

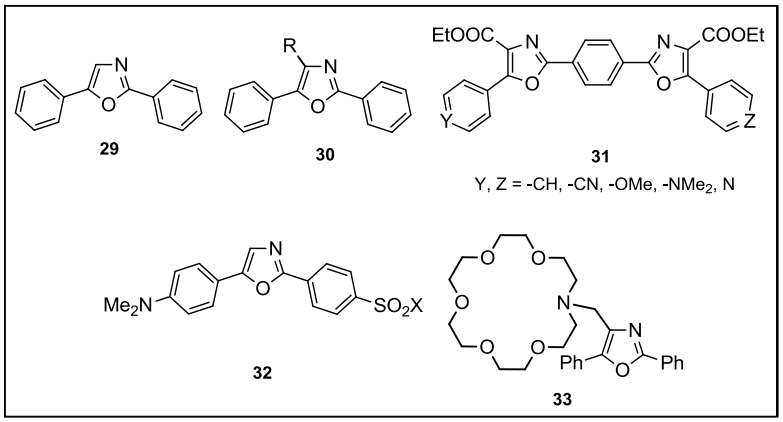
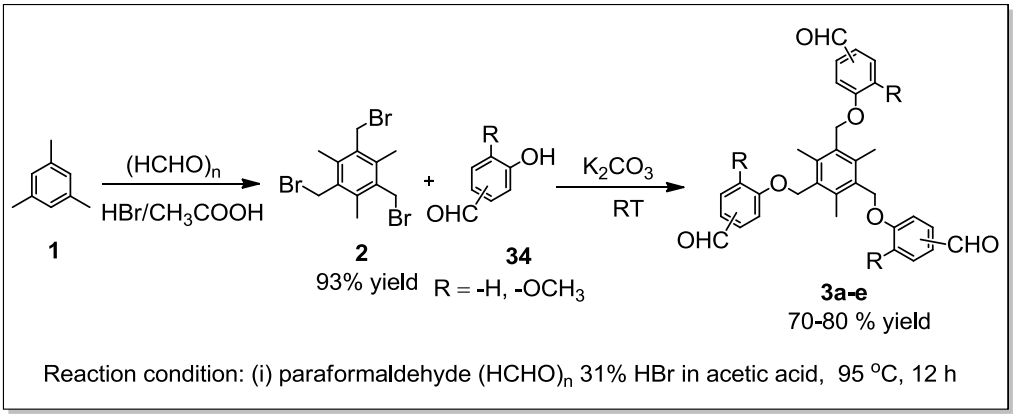


Figure 5 ***2,5-diaryoxazoles***

2.2 RESULTS AND DISCUSSION

2.2.1 *tris-5-substituted-1,3-oxazoles*

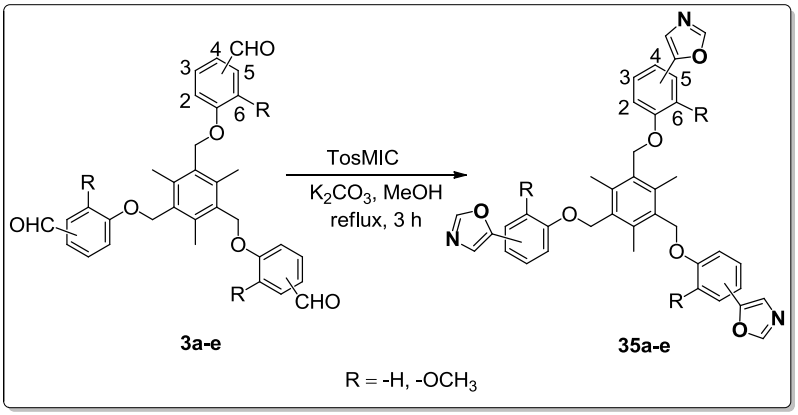
The synthesis of C_3 symmetric compounds started with the functionalization of 1,3,5-trimethylbenzene by reacting it with paraformaldehdye in presence of hydrobromic acid in acetic acid following the reported procedure.[1] The tris-bromomethylmesitylene was further transformed to tris-aldehydes by reacting with phenolic aldehydes in presence of a base by carrying out the reaction at room temperature modifying the reported procedure.[2] (Scheme 2.18)



Scheme 2.18

The structures of tris-aldehydes were confirmed by spectroscopic methods (Section 2.6), and by comparing melting points with the reported ones.[2]

The five aromatic tris-aldehydes **3a-e** thus prepared were subjected to the van Leusen reaction[30] for the synthesis of tris-oxazoles **35a-e** by treating with TosMIC reagent in methanol under reflux condition for about 3 h until the completion of reaction (TLC) (Scheme 2.19).



Scheme 2.19

The tris-1,3-oxazoles thus prepared were characterized using spectroanalytical tools and the results were in full agreement with their proposed structures.

The major change observed in infrared spectra with respect to the starting tris-aldehydes was disappearance of $\nu_{C=O}$. The major bands observed in IR spectra were for the aromatic stretching and ring breathing vibrations along with the bands for Ar-O and $–OCH_2$ ether linkages (see Section 2.6 for spectral data).

In ^{1}H NMR of the synthesized tris-1,3-oxazoles, the methyl group protons ($–CH_3$) on the central aromatic ring were observed as a singlet at δ 2.5 in addition to a singlet for oxygen attached methylene protons ($–OCH_2$) at δ 5.2. The position of oxazole heterocycle on the aromatic ring varies giving different patterns for the aromatic protons depending on 1,4-, 1,3-, 1,2-, 1,2,4- and 1,2,6- substitutions present. A proton at position 2 of the heterocyclic ring is observed as a singlet between δ 7.8 - 8.0 as the most downfield proton signal and the other heterocyclic proton at position 4 is also observed as a singlet at δ 7.2 - 7.3 merging with the aromatic protons.

In ^{13}C-NMR spectra for the tris-5-substituted-1,3-oxazoles, the most downfield carbon signal at about δ 152 to 159 corresponds to the aryloxy-aromatic carbon attached to the electronegative oxygen atom (–OAr). The two quaternary carbon atoms of the oxazole ring are observed nearby each other, next to the most downfield signal, at δ 150 to 145 and 151 to149 depending upon the position of the oxazole ring. The aliphatic region

shows two signals at δ 65 to 70 and 16.0, for methyleneoxy (–OCH_2) and methyl (–CH_3) carbons attached to the central aromatic ring.

All the newly synthesized compounds were characterized by high resolution mass spectral analysis using TOF with electron ionization method. Almost all the compounds showed M^+ molecular ions peak in support to their proposed structures.

One of the tris-oxazoles **35a** was crystallized from ethyl acetate and was studied for single crystal X–ray diffraction characteristics. The triclinic crystals of the tris-oxazole (Figure 5), exhibit the orientation of rings B(C8-C13), C(C18-C23) and D(C28-C33) perpendicular with respect to the central aromatic ring A(C1-C6) having dihedral angels of 99, 95 and 94°. Whereas the terminal oxazole heterocyclic rings E(C14-C16, N1 and O2), F(C24-C66, N2 and O4) and G(C34-C36, N3 and O6) have dihedral angles of 100, 112 and 93° with respect to ring A. The torsion angels between O1-C7 and O3-C17 are anti being -165 and -175° while O5-C27 is gauche 71°, suggesting that one of the arms of tripod is twisted towards the central aromatic ring A. This type of conformation is possible due to flexibility of the tripods intermolecular C-H···π interactions observed between H15 and electron π-cloud of the ring A (Figure 6).

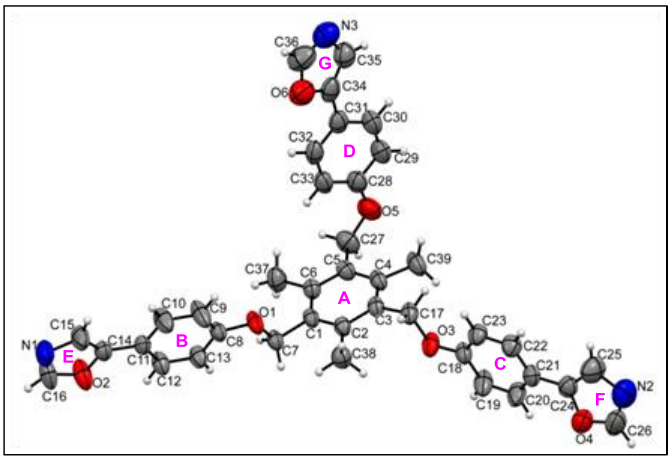


Figure 6 ***ORTEP diagram of 35a***

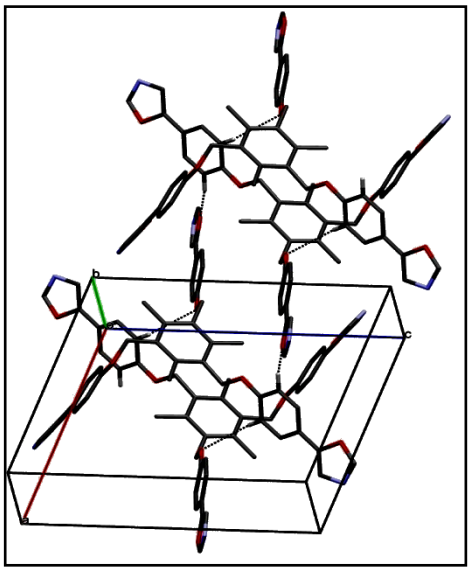


Figure 7 ***Unit cell of 35a***

The crystal is also governed by C-H…O interactions. Two sets of centrosymmetric dimers are formed by intermolecular C-H…O interactions C19-H19…O2 of oxazole ring

E at 2.415 Å [-x, -y+2, -z+1] and between the C23-H23…O1 of methylene oxygen atom at 2.600 Å [-x+1, -y+2, -z+1] (Figure 7).

These intermolecular interactions result in a attractive zig-zag molecular design (Figure 8).

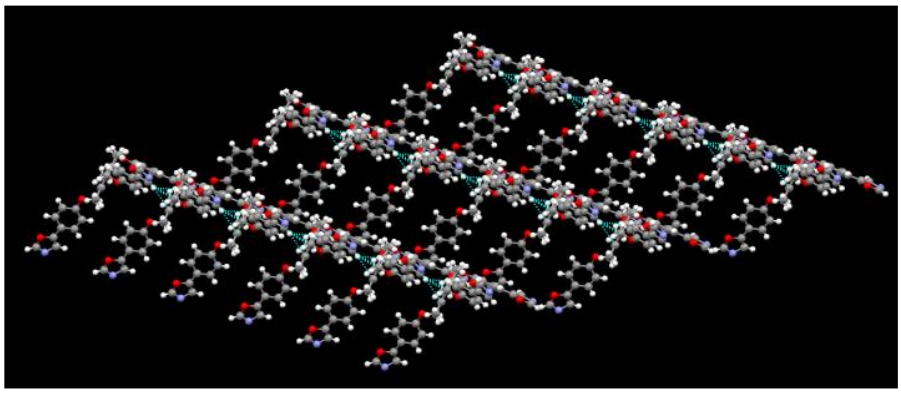


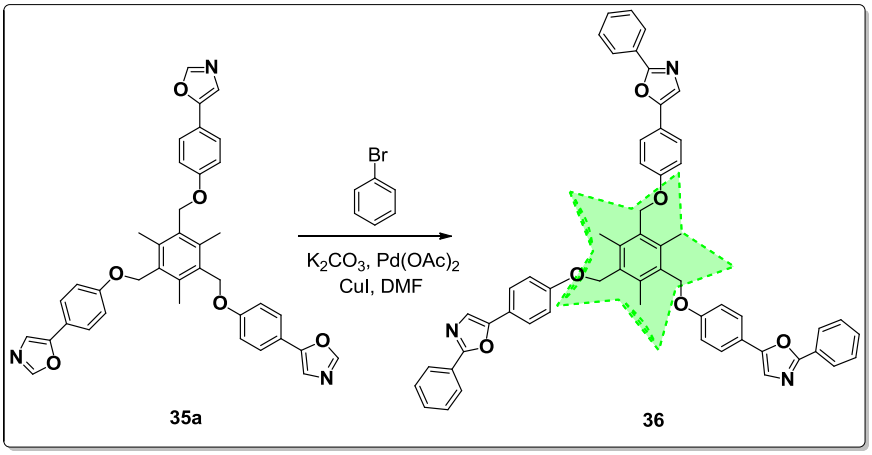
Figure 8 ***Molecular packing pattern of 35a***

Crystal data of **35a**: CCD**C 1403715;** $C_{39}H_{33}N_3O_6$ (*M* =639.68): triclinic, space group P-1 (no. 2), *a* = 11.0751(12) Å, *b* = 11.1638(12) Å, *c* = 13.9139(15) Å, *α* = 100.558(2)°, *β* = 108.883(2)°, *γ* = 98.899(2)°, *V* = 1557.3(3) ^{Å3}, *Z* = 2, *T* = 294.15 K, μ(MoKα) = 0.093 mm^{-1}, *Dcalc* = 1.364 g/m^{m3}, 18425 reflections measured ($3.2 \leq 2\Theta \leq 56.1$), 7290 unique ($R_{int}$ = 0.0235) which were used in all calculations. The final R_1 was 0.0659 (>2σ(I)) and wR_2 was 0.1933 (all data).

2.2.2 *Aryl coupling of a representative tris-1,3-oxazole*

With tris-oxazoles in hand having oxazole heterocycle as the end groups having position 2 and 4 unsubstituted, were subjected to C-H arylation at comparatively more reactive position 2 using Pd(0) catalyzed coupling reaction.

The tris-oxazole 1,3,5–tris[4–(1,3–oxazol–5–yl)–phenyloxy–methyl]–2,4,6–trimethyl-benzene **35a** was subjected to arylation by coupling with bromobenzene in the presence of $Pd(OAc)_2$ in CuI and K_2CO_3 in DMF solvent following a reported procedure[35] using conventional heating in place of microwave radiation in 2 hours of time in moderate yield (Scheme 2.20).



Scheme 2.20

The resulting compound **36** being a tris-2,5-diaryl-oxazole derivative was fluorescent in nature when placed in UV chamber (Figure 9b, inset). The UV-vis absorption of the compound showed a strong absorption band at λ_{max} 316 nm showing a shift towards longer wavelength compared to its parent compound with absorption band at λ_{max} 277 nm. The photoluminescence spectrum for this compound was recorded by exciting at λ 320 nm with emission observed at 430 nm having Stoke's shift as large as 110 nm.

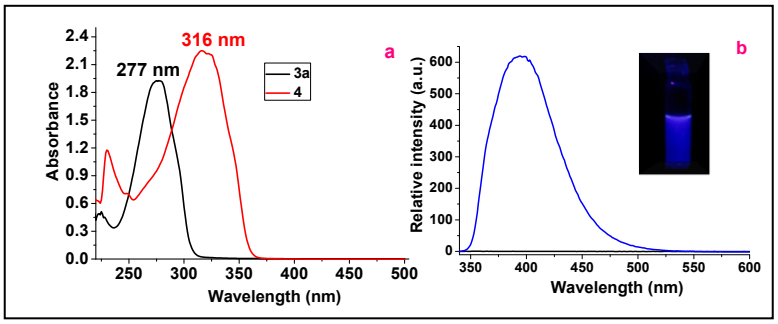


Figure 9 ***(a) UV-vis spectra of compounds 35a and 36; (b) Fluorescence spectra of compound 36 in DCM solution at 10^{-5} M***

Thus the application of the synthesized tris-oxaoles was demonstrated with the help of a representative transformation to a fluorescent dye which could be used as a fluorescent sensor in host guest studies.

The ^{1}H NMR spectrum of the coupled product **36** showed disappearance of C-2 proton of the heterocycle and appearance of mono substituted phenyl ring protons observed at δ 8.12 and 7.50 in 2 : 3 ratio. The sole heterocyclic proton was now well separated from

$CDCl_3$ and observed as a singlet at δ 7.37. In ^{13}C-NMR spectrum, quaternary carbon signals were for heterocyclic carbons and oxygen attached aromatic carbons. The other aromatic carbons are observed between δ 115 to 140. The aliphatic carbon signals are observed at δ 16.0 and 65.1 for $–CH_3$ and $–CH_2$ groups respectively.

2.2.3 *Antibacterial activity study*[36]

MIC values of compounds was determined by microbroth dilution method– *Resazurin microtitre assay method* (REMA) against gram-positive (*S.aureus*) and gram-negative (*E.coli*) bacteria. To study the biological activity following the above technique, the following pre-preparations were required;

i. Preparation of growth medium: Nutrient broth
ii. Preparation of *S.aureus* and *E.coli* broths
iii. Preparation of drug and test compound stock solutions
iv. Dilution of stock solutions
v. Preparation of 0.02% Resazurin solution

Assay Protocol

1. 100 µl of nutrient broth was added into each well of the microtitre plate (leaving the peripheral wells blank).
2. 100 µl test compound was added into the well B2 of a particular concentration and serially diluted (two fold dilution) till B6 well i.e. five dilutions.
3. 100 µl of homogenized bacterial cell culture suspension (10^5 cells per well) was added to all the wells (wells with and without drug).
4. After this, the plate was incubated at 37˚C for 24 h in an incubator.
5. After 24 h, 50 µl of 0.02% Resazurin solution was added; plate was observed after 30 mins and MIC was determined by visual inspection of colour change from blue (inhibition) to pink (growth) (Figure 10).

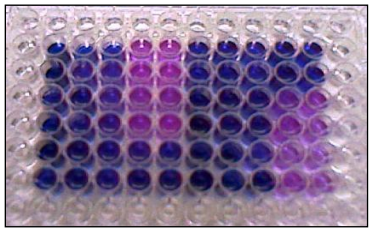
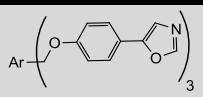
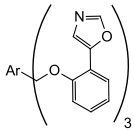
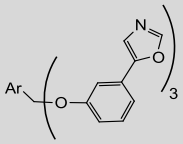
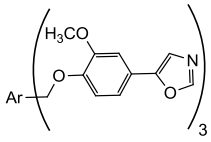
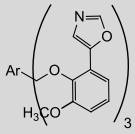


Figure 10 ***96 Well Plate***

Thus, Minimum Inhibition Concentration **MIC** value of compounds was determined in terms of µg/ml.

Table 2.1.0 MIC (µg/ml) values, yields and melting points of 5–subsituted–tris–1,3–oxazoles

Sample ID	Position of A (*wrt –OAr*)	Yield [%]	M.p [°C]	MIC µg/ml *S. aureus*	*E. coli*
35a		75	195	125	inactive
35b		65	205	>125	inactive
35c		68	210	>125	inactive
35d		70	200	>125	inactive
35e		60	210	125	inactive
Standard drug Ciprofloxacin				**0.5**	**0.5**

The antibacterial study results of the tris-5-susbtituted-1,3-oxazoles showed that the compounds are largely inactive against the representative *S. aureus* and *E. coli* bacteria under study. The MIC values of the compounds are listed in the table below (Table 2.1.0).

2.2.4 *Anticancer activity study*

The synthesized compounds bearing the heterocycles were studied for their anticancer bioactivity at NCI. The National Cancer Institute NCI, USA is an institute for cancer

research supported by National Institute for Health (NIH) government of USA. It runs *in vitro* cell line screening project (IVCLP) programme for the new chemical entities, using panel of 60 different human tumour cell lines derived of Leukemia, Non-Small cell lung cancer, Colon cancer, CNS cancer, Melanoma cancer, Ovarian cancer, Renal cancer, Prostate cancer and Breast cancers. Only the selected compounds after first and primary computer aided screening were submitted to NCI. The compounds were screened at a single dose of 10 μM concentration.

The anticancer activity study data of the 5-susbstituted-1,3-oxazoles showed poor to moderate activity for all the compounds except for **35e** which showed better activity against a number of cell lines. The anticancer activity results received from the NCI have been incorporated in the experimental section (Sheet 1, 2, 3, 4, 5).

Compound **35e** was active against many cancer cell lines, with more than 50% of them showed > 50% of growth inhibition. The **35e** showed excellent activity above 90% of growth inhibition for OVCAR-4 and 786-0 cancer cell lines. For SF-539 and SNB-75 cancer cell lines it showed growth inhibition above 80% (Figure 11).

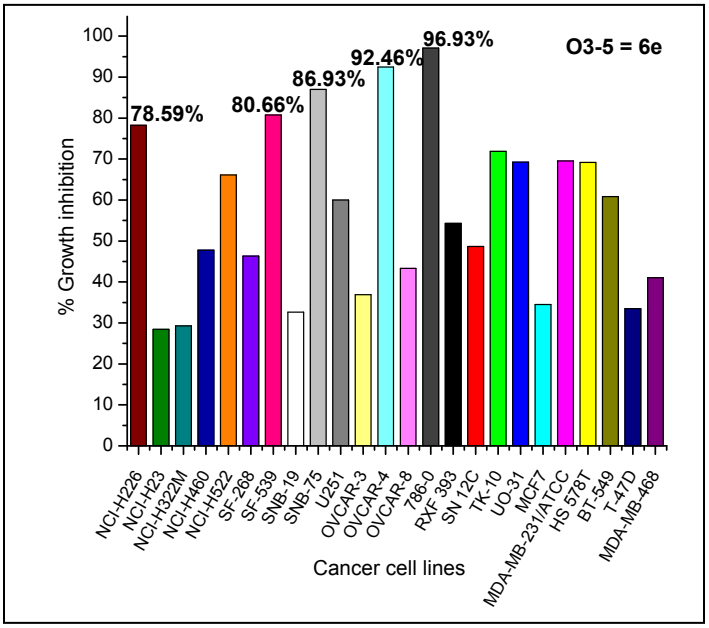


Figure 11 ***Anticancer result of compound 35e***

2.3 CONCLUSION

In conclusion several new, flexible terminal oxazole containing C_3 symmetric compounds have been synthesized from the corresponding tris-aromatic aldehydes and are characterized. The X–ray crystal structure of one of the tris-oxazoles exhibits a unique crystal packing of the molecules in zig-zag fashion. An oxazole scaffold was employed for palladium mediated coupling resulting into conjugated fluorescent materials. Also, the C_3 symmetric tris-5-substituted-1,3-oxazole entities **35a–e** were screened for anticancer activity and among them, tris-2-(5-oxazolyl)-6-methoxy compound **35e** was found to show highest activity against a number of cell lines. Antibacterial study showed that the synthesized compounds were having poor activity against *S. aureus* and were inactive for *E. coli*.

2.4 General

Chemicals were purchased from SRL (India) and used as received without further purification. Solvents were distilled and dried by standard procedures prior to use.

FTIR spectra were recorded on Perkin Elmer FTIR spectrometer between 650-4000 cm^{-1} for all the synthesized compounds in the solid state as KBr discs.

All the NMR spectra (^{1}H, ^{13}CMR, DEPT135, HSQC, HMBC) were recorded on 400 MHz Bruker instrument at respective frequencies and chemical shifts are given in parts per million downfield from TMS.

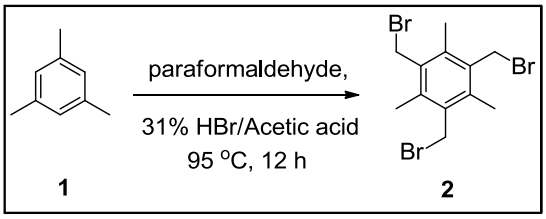
High resolution mass spectra were recorded on either a Q-TOF mass spectrometer or a GC-TOF mass spectrometer.

X-ray data for the compounds were collected at room temperature using a Bruker Smart Apex CCD diffractometer with graphite monochromated MoKα radiation (λ=0.71073Å) with ω-scan method[1] or using a Xcalibur, Eos, Gemini with enhanced Cu X-ray source and data collection was done using CrysAlisPro, Agilent Technologies, Version 1.171.36.28. The structure was solved by direct methods using SHELXS97[37] and refinement was carried out by full-matrix least-squares technique using SHELXL97.[37] Anisotropic displacement parameters were included for all non-hydrogen atoms.

Melting points were determined in open capillaries method and are uncorrected.

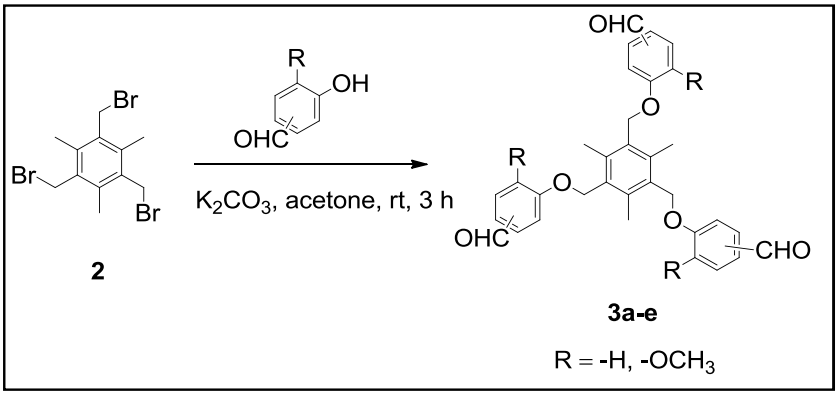
2.5 EXPERIMENTAL

2.5.1 1,3,5-Tris(bromomethyl)-2,4,6-trimethylbenzene 2[1]



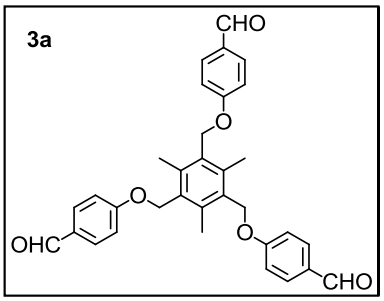
To a stirred mixture of mesitylene **1** (0.1 mol), paraformaldehyde (0.33 mol) and 50.0 mL of glacial acetic acid (50 ml) was added 31% HBr in acetic acid (30 ml) rapidly. The mixture was stirred for 12 hours at 95 °C and the reaction mixture was poured in to 100 mL of water. A white solid product was separated, filtered under vacuum and was dried. The crude product was crystallized from glacial acetic acid to give pure 1,3,5-trisbromomethyl-2,4,6-trimethylbenzene **2**. Yield: 37.1 g (93%); mp.: 185 ˚C.

2.5.2 1,3,5-Tris(n-formyl-phenyloxy)methylene-2,4,6-trimethylbenzene 3[2]



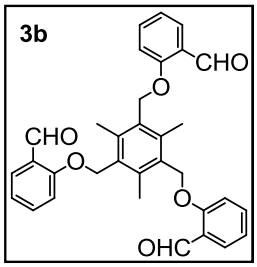
To a stirred solution of a phenolic aldehyde (1.5 mmol) in acetone were added K_2CO_3 (4.5 mmol) and trisbromomethyl mesitylene **2** (0.2 g, 0.5 mmol). The resulting mixture was stirred at room temperature for 3 hours. On completion of the reaction (TLC), acetone was evaporated to a small volume followed by addition of cold water. The solid thus obtained was filtered and crystallized from ethanol to give pure tris-aromatic aldehydes **3a-e**. Yield: 70-80 %.

1,3,5–Tris((4–formylphenyloxy)methylene)–2,4,6–trimethylbenzene 3a



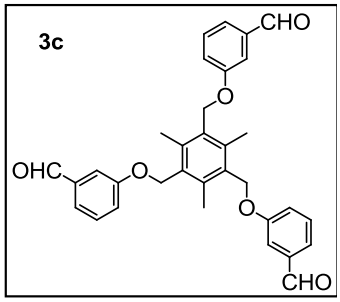
IR (KBr): 2902, 2804, 2736, 1693, 1600, 1575, 1504, 1204 cm^{-1}; **^{1}H NMR ($CDCl_3$): δ** (ppm) 2.46 (9H, s, $–CH_3$), 5.31 (6H, s, $–OCH_2$), 7.15–7.11 (4H, d, *J* = 8.6Hz), 7.90–7.86 (4H, d, *J* = 8.6Hz), 9.97 (s, 3H, –CHO); Yield: 0.22 g, 82%; mp: 194 °C.

1,3,5–Tris((2–formylphenyloxy)methylene)–2,4,6–trimethylbenzene 3b



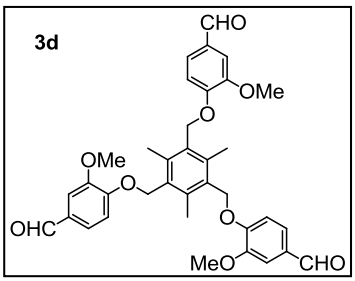
IR (KBr): 2859, 1686, 1596, 1478, 1458, 1258, 1228 cm^{-1}; **^{1}H NMR ($CDCl_3$): δ** (ppm) 2.48 (9H, s, $–CH_3$), 5.25 (6H, s, $–CH_2O$), 7.13-7.05 (2H, t), 7.59-7.26 (2H, dd, J_{ortho} = 8.4, J_2 = 1.68 Hz), 7.67-7.58 (2H, dt, J_{ortho} = 6.9, J_2, J_3= 1.7 Hz), 7.90-7.85 (2H, dd, J_{ortho} = 5.9, J_2 = 1.6 Hz), 10.40 (3H, s, –CHO); Yield: 0.2 g, 75%; mp: 184 °C.

1,3,5–Tris((3–formylphenyloxy)methylene)–2,4,6–trimethylbenzene 3c



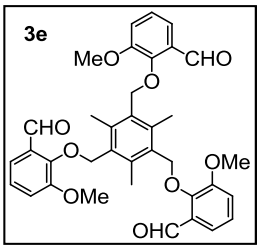
IR (**KBr**): 2910, 2812, 1699, 1587, 1373 cm^{-1}; ^{1}H NMR **($CDCl_3$): δ** (ppm) 2.48 (9H, s, $–CH_3$), 5.20 (6H, s, $–OCH_2$), 7.58-7.29 (12H, m), 10.03 (3H, s, –CHO); **^{13}C -NMR ($CDCl_3$): δ** (ppm) 16.0 ($–CH_3$), 65.2 ($–OCH_2$), 112.2, 122.4, 124.2, 130.2, 131.4, 137.8, 139.6, 159.6, 190.2 (–CHO); **ESI MS+:** calculated for $C_{33}H_{30}O_6$ 522.2042 *m/z*, found 545 *m/z* $(M+Na)^+$; Yield: 0.21 g, 80%; mp: 190 °C.

1,3,5–Tris((4–formyl–6–methoxy)phenyloxy)–2,4,6–trimethylbenzene 3d



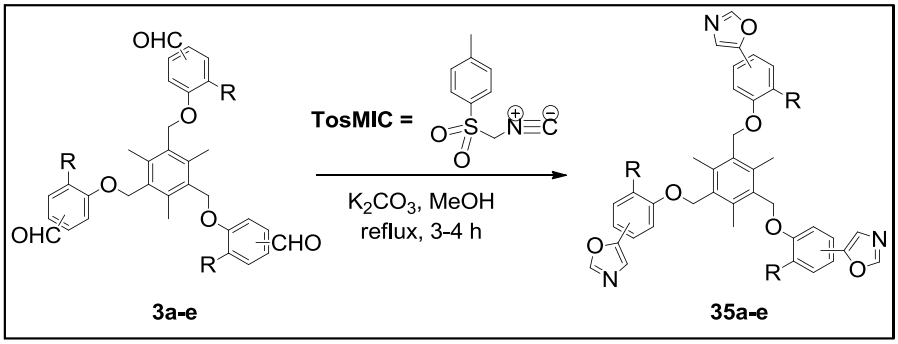
IR (KBr): 2833, 1693, 1681, 1585, 1504, 1265, 1136 cm^{-1}; **^{1}H NMR ($CDCl_3$): δ** (ppm) 2.47 (9H, s, –CH3), 3.9 (9H, s, $–OCH_3$), 5.21 (s, 6H, –OCH2), 7.2, 7.45, 7.52 (9H, Aromatic protons), 9.89 (s, 3H, -CHO); Yield: 0.25 g, 80%; mp: 212 °C.

1,3,5–Tris((2–formyl–6–methoxy)phenyloxy)–2,4,6–trimethylbenzene 4e



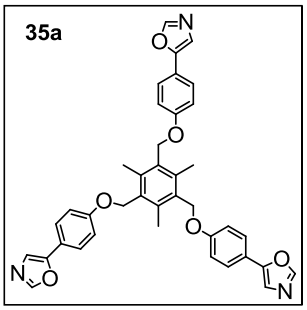
IR (KBr): 2841, 1693, 1583, 1481, 1359, 1265, 1249, 1209 cm^{-1}; **^{1}H NMR ($CDCl_3$): δ** (ppm) 2.48 (9H, s, $–CH_3$), 3.98 (9H, s, $–OCH_3$), 5.37 (6H, s, $–OCH_2$), 7.14 – 7.42 (9H, Aromatic), 10.1 (3H, s, –CHO); Yield: 0.21 g, 70%; mp: 208 °C.

2.5.3 1,3,5-Tris(4-(1,3-oxazol-5-yl)-phenyloxymethyl-2,4,6-trimethylbenzene 35



In a 2-necked round bottom flask (100 ml) was placed a tris-aldehyde **3** (0.1 g), *p*-tolulymethylsulfonylisocyanide (TosMIC) (0.65 mmol) and K_2CO_3 (1.2 mmol) in MeOH as a solvent and the reaction mixture was refluxed for 3-4 hours. On completion of the reaction (TLC), methanol was evaporated under reduced pressure and the residues were purified through column chromatography on silica gel, using EtOAc/hexane = 6:4 to 8:2 giving the corresponding tris-1,3-oxazoles **35** in good yields as white solid. Yield: 60-80%

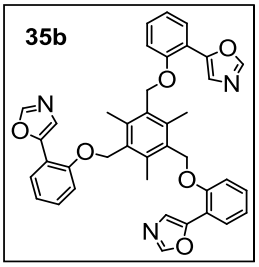
1,3,5-Tris[4-(1,3-oxazol-5-yl)-phenyloxy-methyl]-2,4,6-trimethylbenzene (35a)



35a was prepared from **3a** (0.1 g, 0.19 mmol), TosMIC (0.149 g, 0.65 mmol) and K_2CO_3 (0.2 g, 1.2 mmol) following the general procedure described above as a white solid. Yield: 0.1 g, 75%; mp: 195 °C.

IR (KBr) : 3317, 1615, 1489, 1122 cm^{-1}; **^{1}H NMR (CDCl$_3$) :** δ (ppm) 2.49 (9H, s, $–CH_3$), 5.17 (6H, s, $–OCH_2$), 7.11-7.09 (6H, d, *J* = 8.8 Hz), 7.28 (3H, s oxazole H), 7.66-7.64 (6H, d, *J* = 8.8 Hz), 7.91 (3H, s –N═CH– oxazole); **^{13}C NMR (CDCl$_3$) :** δ (ppm) 16.0, 65.0, 115.0, 120.0, 120.9, 126.0, 131.5, 139.5, 150.0, 151.5, 159.4; **TOF MS ES+:** *m/z* calculated for $C_{39}H_{33}N_3O_6$: 639.2369, found: (*m/z*) 662.2335 $(M+Na)^+$.

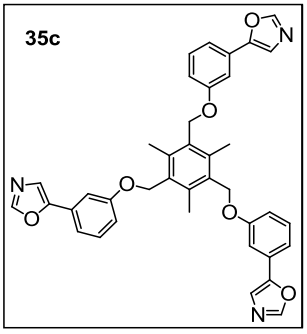
1,3,5-Tris[2-(1,3-oxazol-5-yl)-phenyloxy-methyl]-2,4,6-trimethylbenzene (35b)



35b was prepared from **3b** (0.1 g, 0.19 mmol), TosMIC (0.15 g, 0.65 mmol) and K_2CO_3 (0.2 g, 1.2 mmol) following the general procedure as a white solid. Yield: 0.85 g, 65%; mp: 205 °C

IR (KBr) : 2961, 2849, 1603, 1568, 1487, 1369, 1236, 1117 cm^{-1}; **^{1}H NMR (CDCl$_3$) :** δ (ppm) 2.48 (9H, s, $–CH_3$), 5.30 (6H, s, $–OCH_2$), 7.13-7.11 (3H, dt, J_1 = 15 Hz, J_2 = 7.4 Hz), 7.24-7.22 (3H d, *J* = 8.0 Hz), 7.28 (3H, s, oxazole H), 7.42-7.38 (3H, dt, J_1 = 15.6 Hz, J_2 = 7.6 Hz), 7.85-7.83 (3H, dd, *J* = 8.0 Hz), 7.88 (3H, s, –N═CH– oxazole); **^{13}C NMR (CDCl$_3$) :** δ (ppm) 15.9, 65.4, 111.7, 117.2, 121.1, 125.4, 126.0, 129.3, 131.4, 139.4, 147.8, 149.4, 154.9; **HRMS (TOF MS EI+)** *m/z* calculated for $C_{39}H_{33}N_3O_6$: 639.2369, found: (*m/z*) 639.2369 (M^+) .

1,3,5-Tris–[3-(1,3-oxazol-5-yl)-phenyloxy-methyl]-2,4,6-trimethylbenzene (35c)

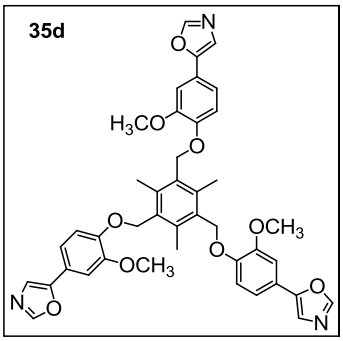


35c was prepared from **3c** (0.1 g, 0.19 mmol), TosMIC (0.149 g, 0.65 mmol) and K_2CO_3 (0.2 g, 1.2 mmol) following the general procedure as a white solid. Yield: 0.89 g, 68%; mp: 210 °C.

IR (KBr) : 3105, 1731, 1573, 1487, 1289, 1202, 1105 cm^{-1} ; **^{1}H NMR (CDCl$_3$) :** δ (ppm) 2.51(9H, s, $–CH_3$), 5.19 (6H, s, $–OCH_2$), 6.95-6.93 (3H, d, *J* = 8.0 Hz), 7.23-7.18 (6H, m), 7.33-7.29 (2H, m), 7.95 (3H, s, –N═CH– oxazole); **^{13}C NMR (CDCl$_3$) :** δ (ppm) 16.0, 65.0, 110.4, 114.9, 117.2, 121.8, 129.0, 130.2, 131.6, 139.4, 150.5, 151.3,

159.4; **HRMS (TOF MS EI+):** *m/z* calculated for $C_{39}H_{33}N_3O_6$: 639.2369, found: (*m/z*) 639.2375 (M^+).

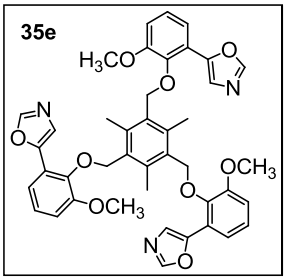
1,3,5-Tris[2-methoxy-4-(1,3-oxazol-5-yl)-phenyloxy-methyl]-2,4,6-trimethylbenzene (35d)



35d was prepared from **3d** (0.1 g, 0.16 mmol), TosMIC (0.138 g, 0.57 mmol) and K_2CO_3 (0.2 g, 1.06 mmol) following the general procedure as a white solid. Yield: 0.09 g, 70%; mp: 200 °C.

IR (KBr) : 2907, 1683, 1585, 1514, 1497, 1243, 1139, 973 cm^{-1}; **^{1}H NMR ($CDCl_3$) :** δ (ppm) 2.51(9H, s $–CH_3$), 3.90 (9H, s, $–OCH_3$), 5.17 (6H, s, $–OCH_2$), 7.13-7.11 (3H, d, J = 8.4 Hz), 7.19-7.18 (3H, d, J = 1.6 Hz), 7.26-7.25 (3H, d, J = 2 Hz), 7.28 (3H, s, oxazole H), 7.90 (3H, s, –N=CH– oxazole); **^{13}C NMR ($CDCl_3$) :** δ (ppm) 16.0 ($–CH_3$), 56.0 ($–OCH_3$), 66.6 ($–OCH_2$), 108.3, 114.5, 117.3, 120.4, 121.5, 131.4, 139.8, 149.2, 149.9, 150.4, 151.5; **HRMS (TOF MS EI+):** *m/z* calculated for $C_{42}H_{39}N_3O_9$: 729.2686, found: (*m/z*) 729.2692 (M^+).

1,3,5-Tris[2-methoxy-6-(1,3-oxazol-5-yl)-phenyloxy-methyl]-2,4,6-trimethylbenzene (35e)

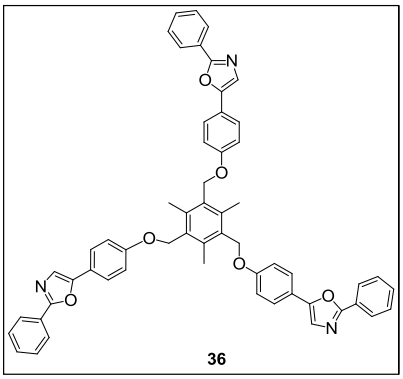


35e was prepared from **3e** (0.1 g, 0.16 mmol), TosMIC (0.138 g, 0.57 mmol) and K_2CO_3 (0.2 g, 1.06 mmol) following the general procedure above as a white solid. Yield: 0.078 g, 60%; mp: 210 °C.

IR (KBr) : 2939, 2834, 1589, 1560, 1503, 1471, 1265 cm^{-1}; **^{1}H NMR ($CDCl_3$) :** δ (ppm) 2.45 (9H, s $–CH_3$), 3.94 (9H, s, $–OCH_3$), 5.31 (6H, s, $–OCH_2$), 6.97-6.95 (3H, dd, J_1 = 8.2 Hz, J_2 = 1.2 Hz), 7.15-7.11 (3H, t), 7.30 (3H, s oxazole H), 7.36-7.34 (3H, dd, J_1 = 8.2 Hz, J_2 = 1.2 Hz), 7.87 (3H, s, –N=CH– oxazole); **^{13}C NMR ($CDCl_3$) :** δ (ppm) 16.1 ($–CH_3$), 55.9 ($–OCH_3$), 70.0 ($–OCH_2$), 112.4, 118.2, 122.1, 123.9, 125.7, 132.5,

139.5, 145.1, 149.7, 153.1; **HRMS (TOF MS EI+):** *m/z* calculated for $C_{42}H_{39}N_3O_9$: 729.2686, found: (*m/z*) 729.2677 (M^+).

2.5.4 1,3,5-Tris(4-(1,3-oxazol-2-phenyl-5-yl)-phenyloxymethyl-2,4,6-trimethyl-benzene 36



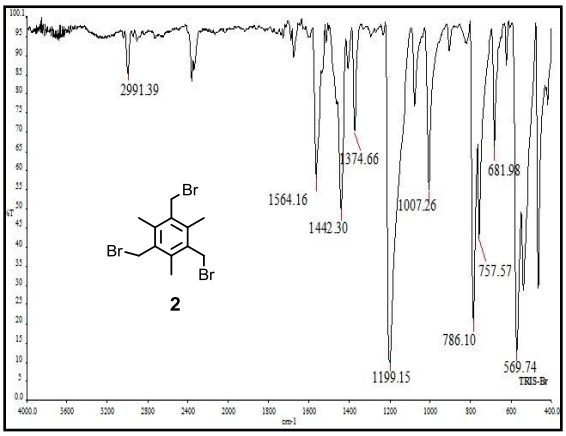
36

In a 2-necked round bottom flask (25 ml) were placed compound **3a** (0.1 g, 0.19 mmol), bromobenzene (0.14 g, 0.86 mmol), K_2CO_3 (1.6 g, 1.15 mmol), $Pd(OAc)_2$ (6 mg, 15 mol%) and CuI (0.10 g, 0.57 mmol) in 4.0 ml DMF as a solvent and the mixture was degassed. The reaction mixture was heated to 150 °C under nitrogen atmosphere. On completion of the reaction (TLC), the solids were removed by filtering through celite and washed with dichloromethane. The filtrate and washings were evaporated under vacuum and residue was purified on silica column using EtOAc-hexane = 3:7 to obtain tris–(2–phenyl–1,3–oxazol–5–yl) **36** as a white solid. Yield: 0.05 g, 35%; mp: 187 °C.

IR (KBr) : 2923, 1612, 1499, 1242, 1176 cm^{-1}; **^{1}H NMR ($CDCl_3$) :** δ (ppm) 2.52 (9H, s, $–CH_3$), 5.20 (6H, s, $–OCH_2$), 7.12–7.14 (6H, d, J = 8.8 Hz), 7.37 (3H, s oxazole H) 7.49-7.50 (9H, d, J = 7.6 Hz), 7.71-7.73 (6H, d, J = 9.2 Hz, J_2 = 1.2 Hz), 8.11–8.13 (6H, dd, J = 7.8 Hz); **^{13}C NMR ($CDCl_3$) :** δ (ppm) 16.0, 65.1, 115.1, 121.2, 122.1, 125.8, 126.1, 127.5, 128.8, 130.1, 131.6, 139.5, 151.2, 159.3, 160.6; **HRMS (TOF MS ES+):** (*m/z*) calculated for $C_{57}H_{45}N_3O_6$: 867.3308, found: (*m/z*) 868.2813 $(M+H)^+$, 890.2594 $(M+Na)^+$.

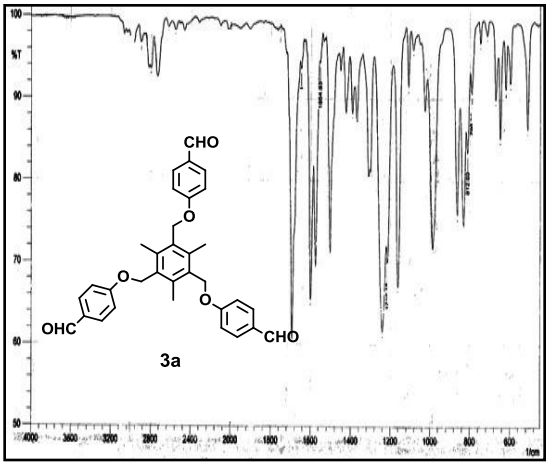
2.6 SPECTRAL DATA

Compound 2

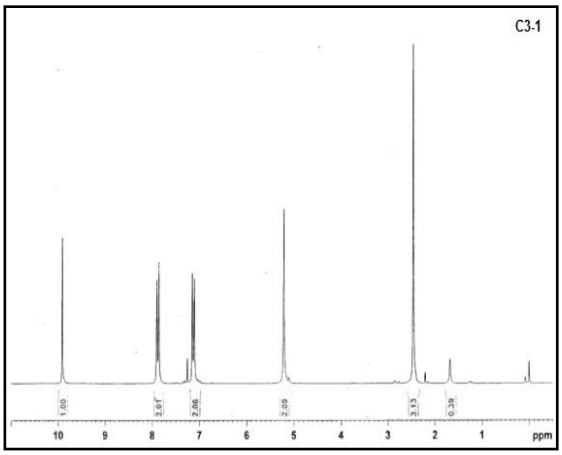


Spectrum 1. IR of 2

Compound 3a

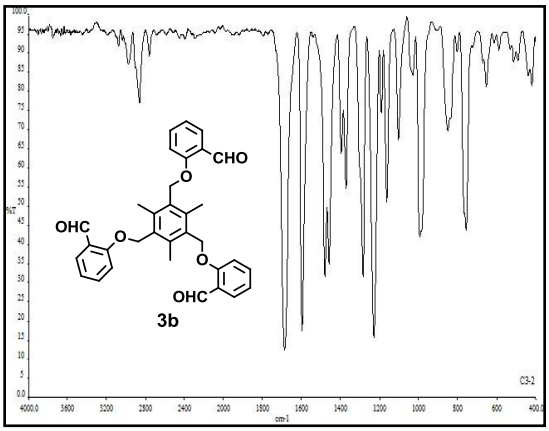


Spectrum 2. IR of 3a

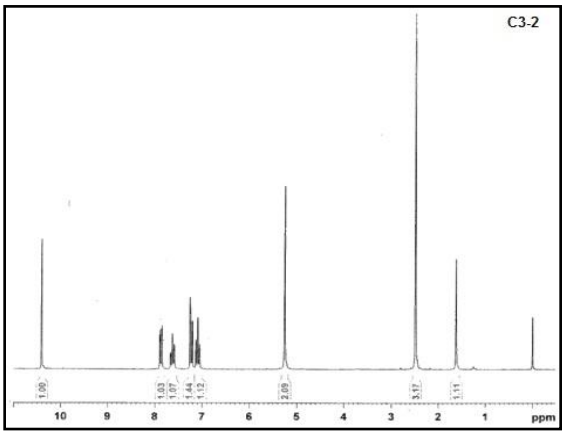


Spectrum 3. ^{1}H NMR of 3a

Compound 3b

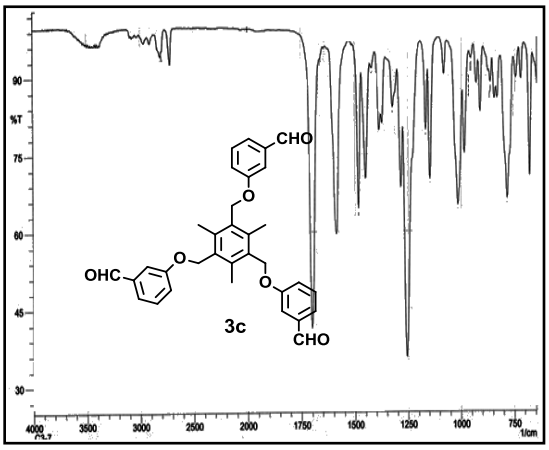


Spectrum 4. IR of 3b

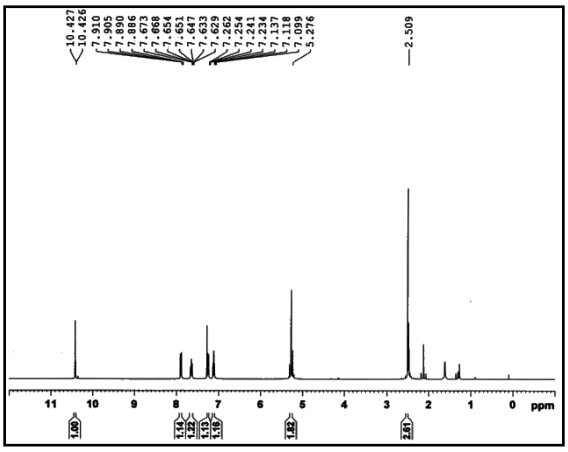


Spectrum 5. ^{1}H NMR of 3b

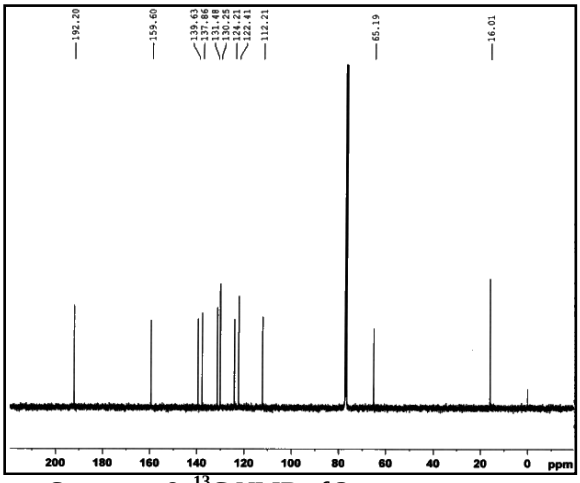
Compound 3c



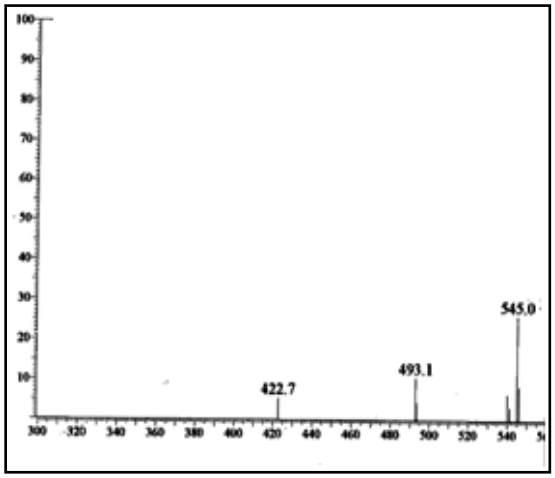
Spectrum 6. IR of 3c



Spectrum 7. ^{1}H NMR of 3c

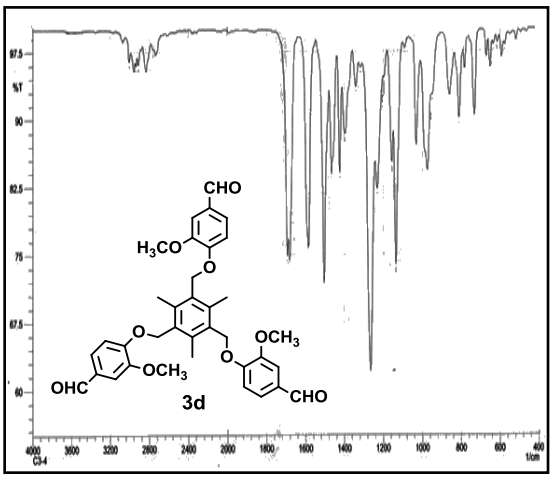


Spectrum 8. ^{13}C NMR of 3c

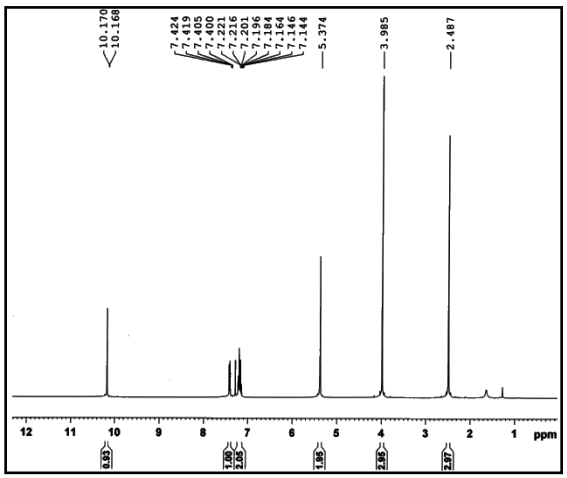


Spectrum 9. Mass of 3c

Compound 3d

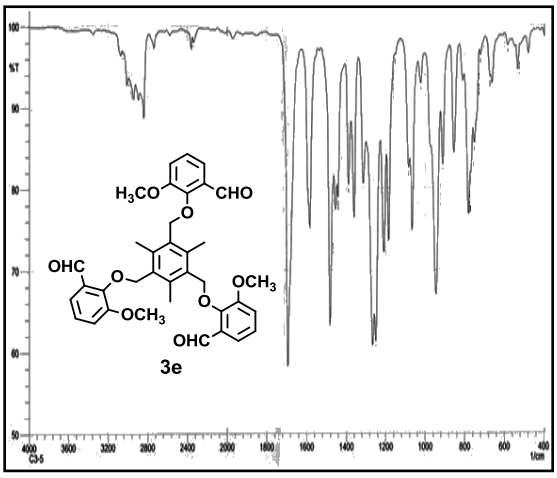


Spectrum 10. IR of 3d

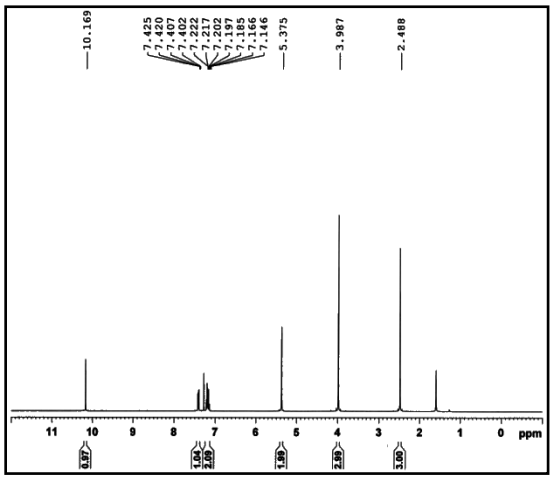


Spectrum 11. ^{1}H NMR of 3d

Compound 3e

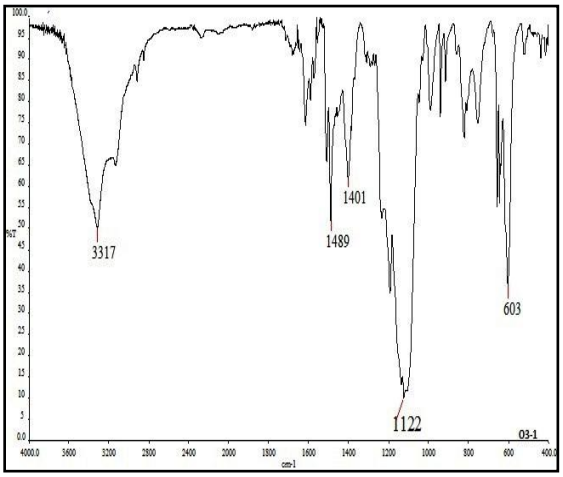


Spectrum 12. IR of 3e

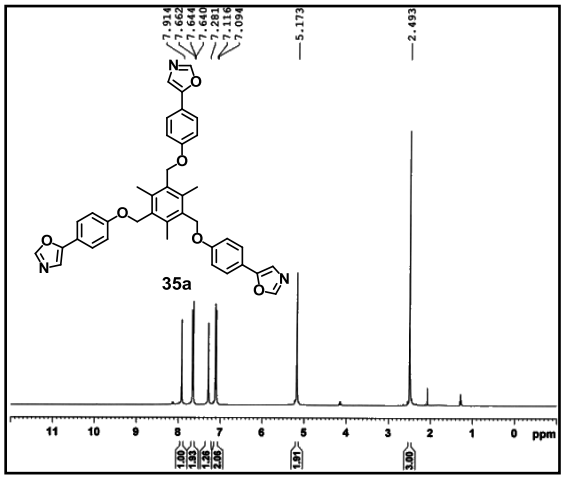


Spectrum 13. ^{1}H NMR of 4e

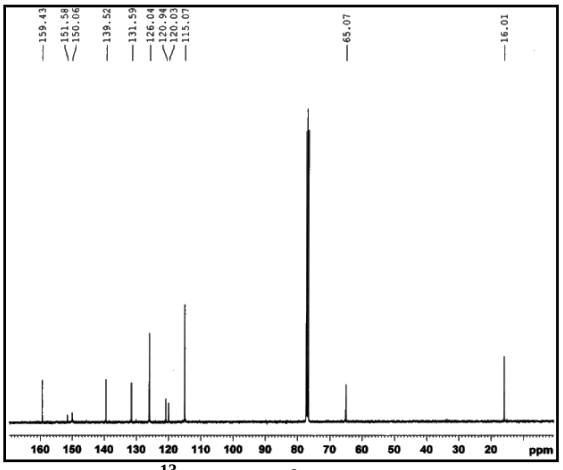
Compound 35a



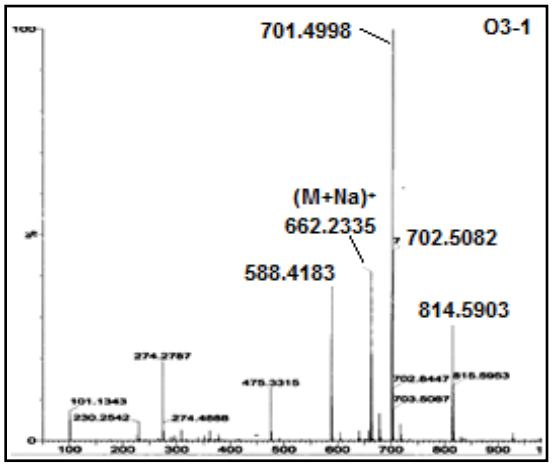
Spectrum 14. IR of 35a



Spectrum 15. ^{1}H NMR of 35a

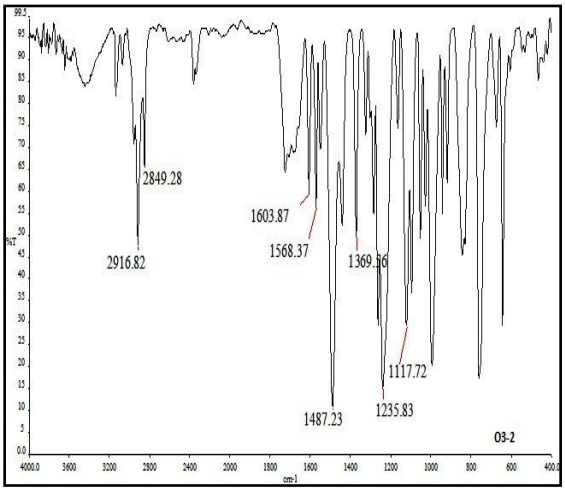


Spectrum 16. ^{13}C NMR of 35a

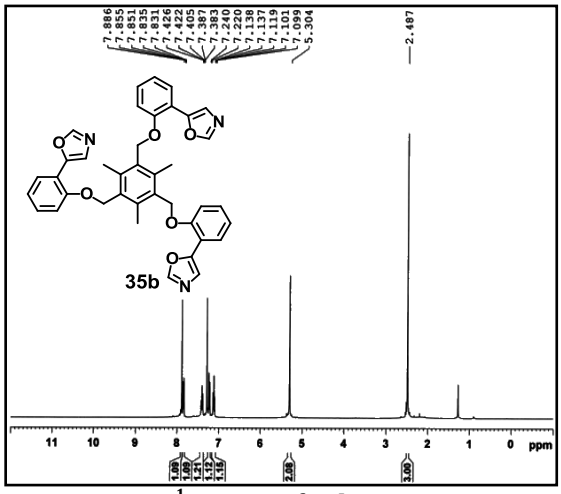


Spectrum 17. Mass of 35a

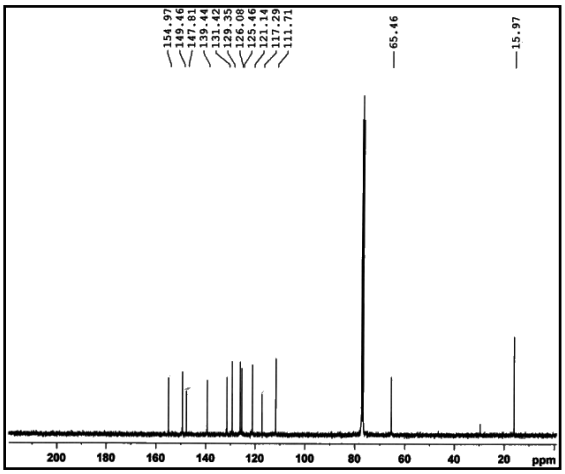
Compound 35b



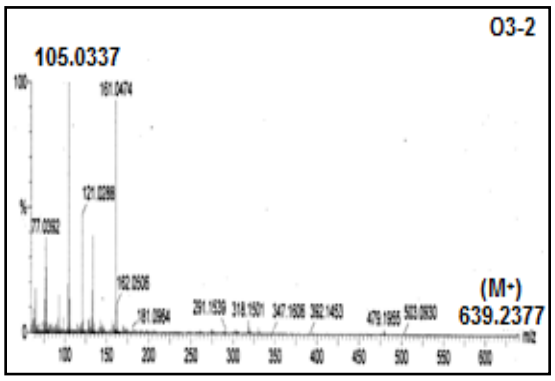
Spectrum 18. IR of 35b



Spectrum 19. ^{1}H NMR of 35b

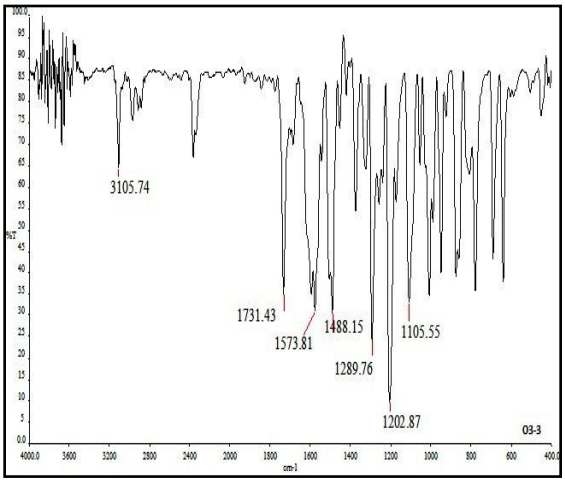


Spectrum 20. ^{13}C NMR of 35b

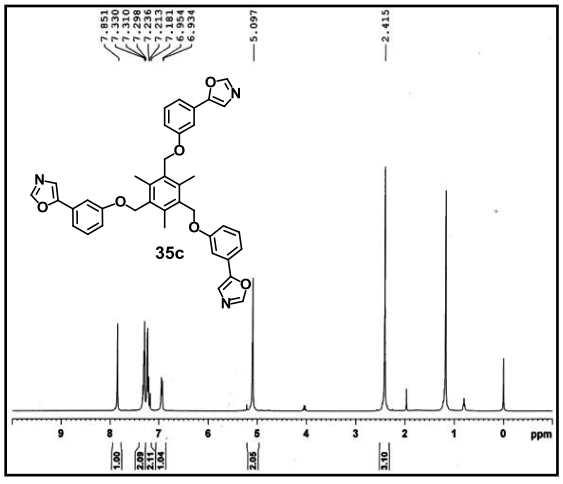


Spectrum 21. Mass of 35b

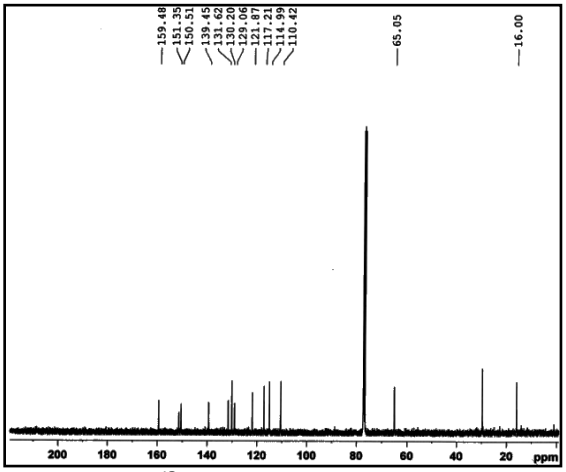
Compound 35c



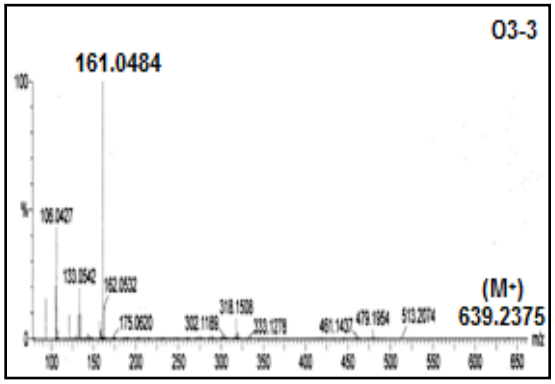
Spectrum 22. IR of 35c



Spectrum 23. ^{1}H NMR of 35c

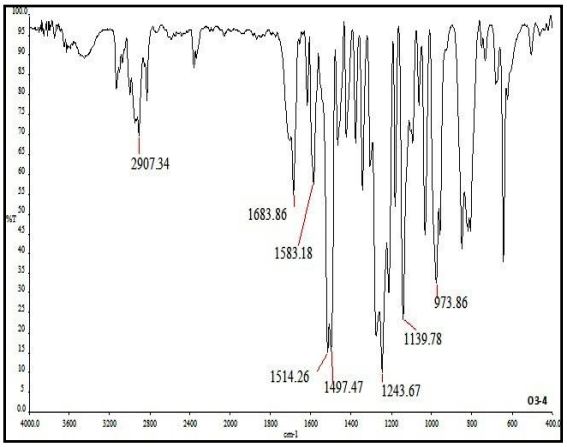


Spectrum 24. ^{13}C NMR of 35c

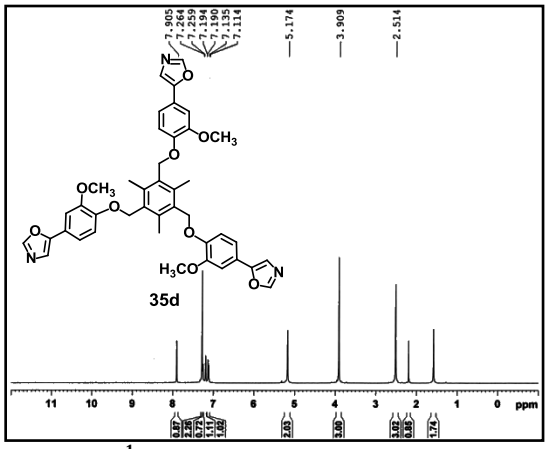


Spectrum 25. Mass of 35c

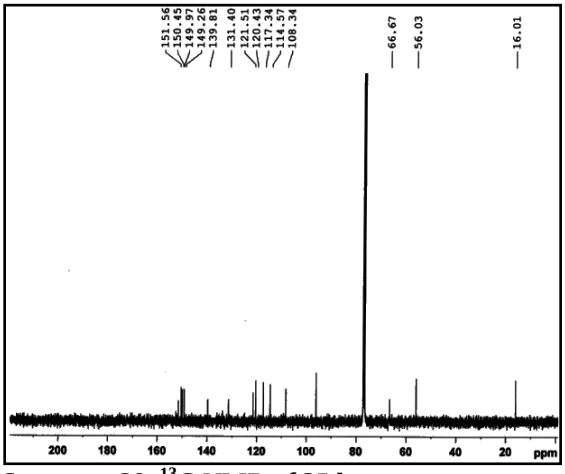
Compound 35d



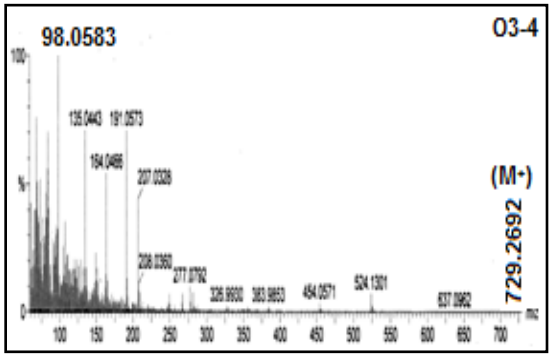
Spectrum 26. IR of 35d



Spectrum 27. ^{1}H NMR of 35d

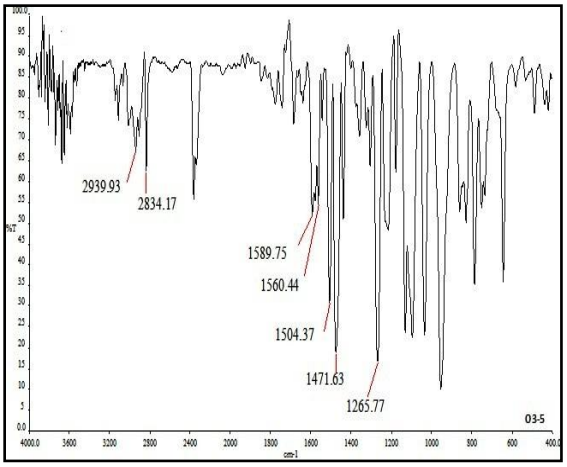


Spectrum 28. ^{13}C NMR of 35d

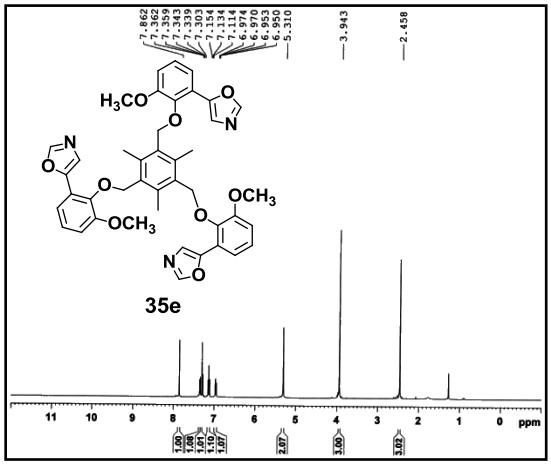


Spectrum 29. Mass of 35d

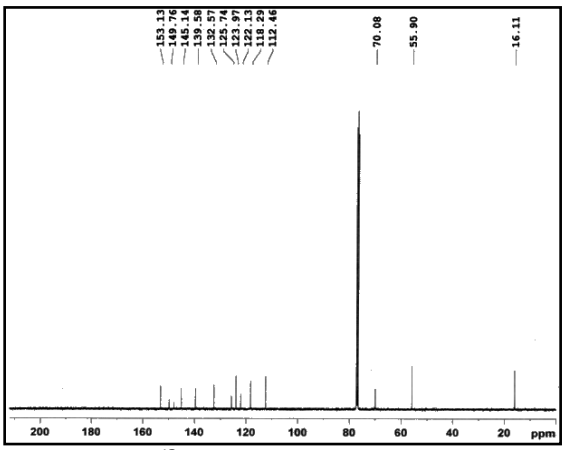
Compound 35e



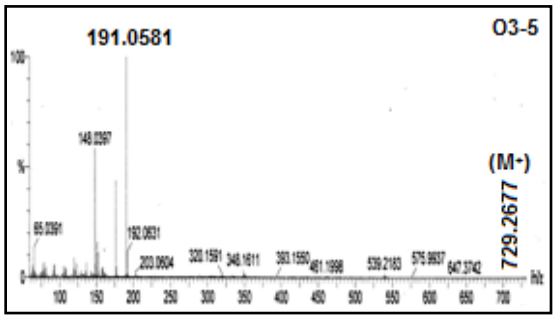
Spectrum 30. IR of 35e



Spectrum 31. ^{1}H NMR of 35e

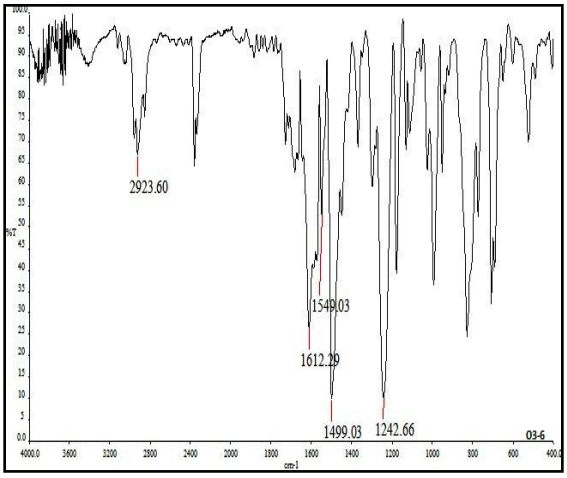


Spectrum 32. ^{13}C NMR of 35e

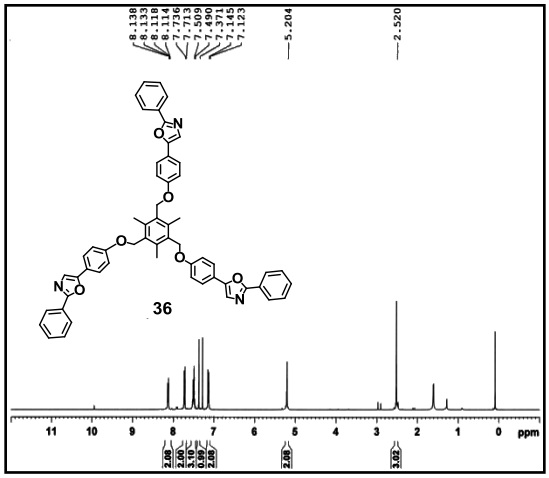


Spectrum 33. Mass of 35e

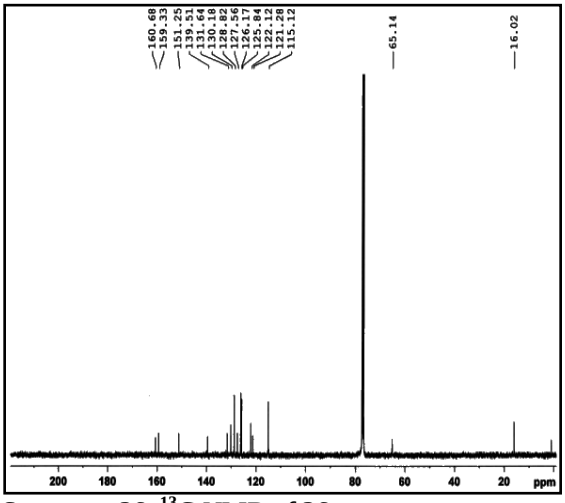
Compound 36



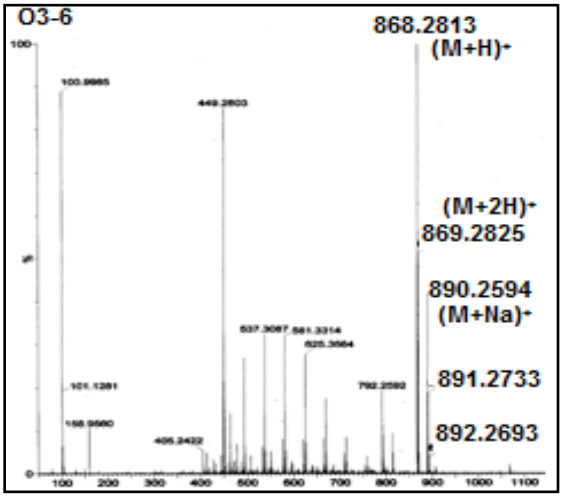
Spectrum 34. IR of 36



Spectrum 35. ^{1}H NMR of 36



Spectrum 36. ^{13}C NMR of 36



Spectrum 37. Mass of 36

2.7 *Anticancer activity results*

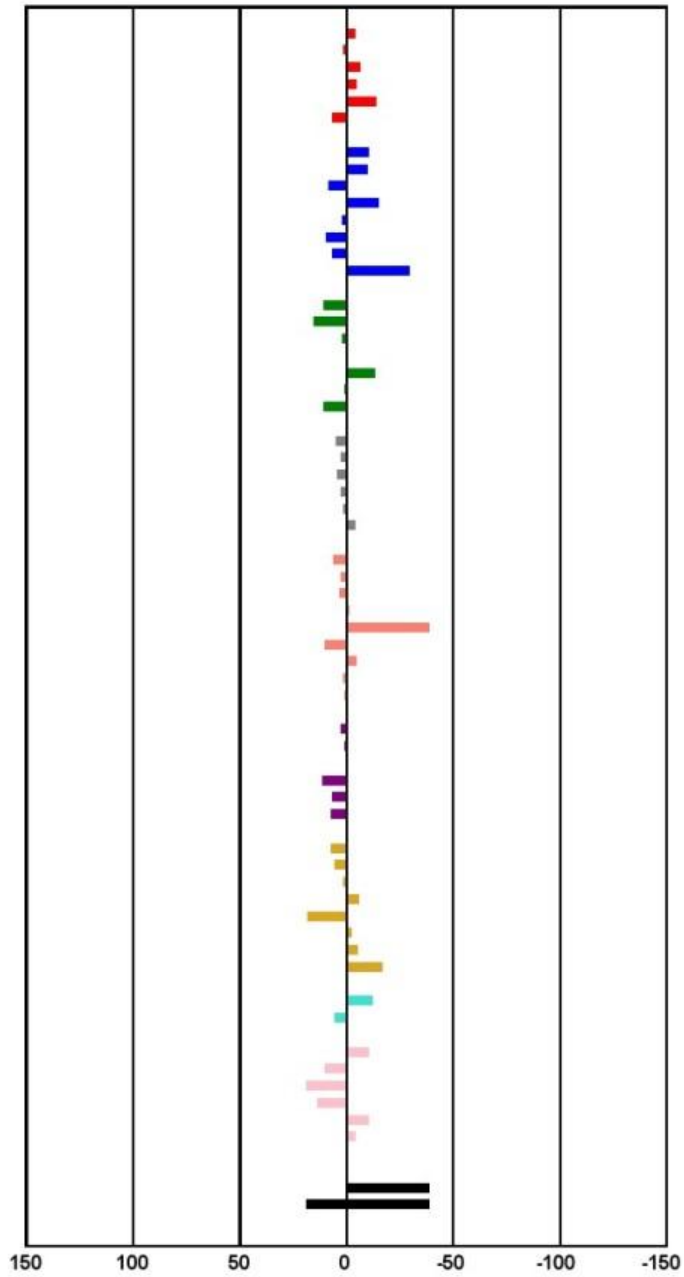
Developmental Therapeutics Program

One Dose Mean Graph

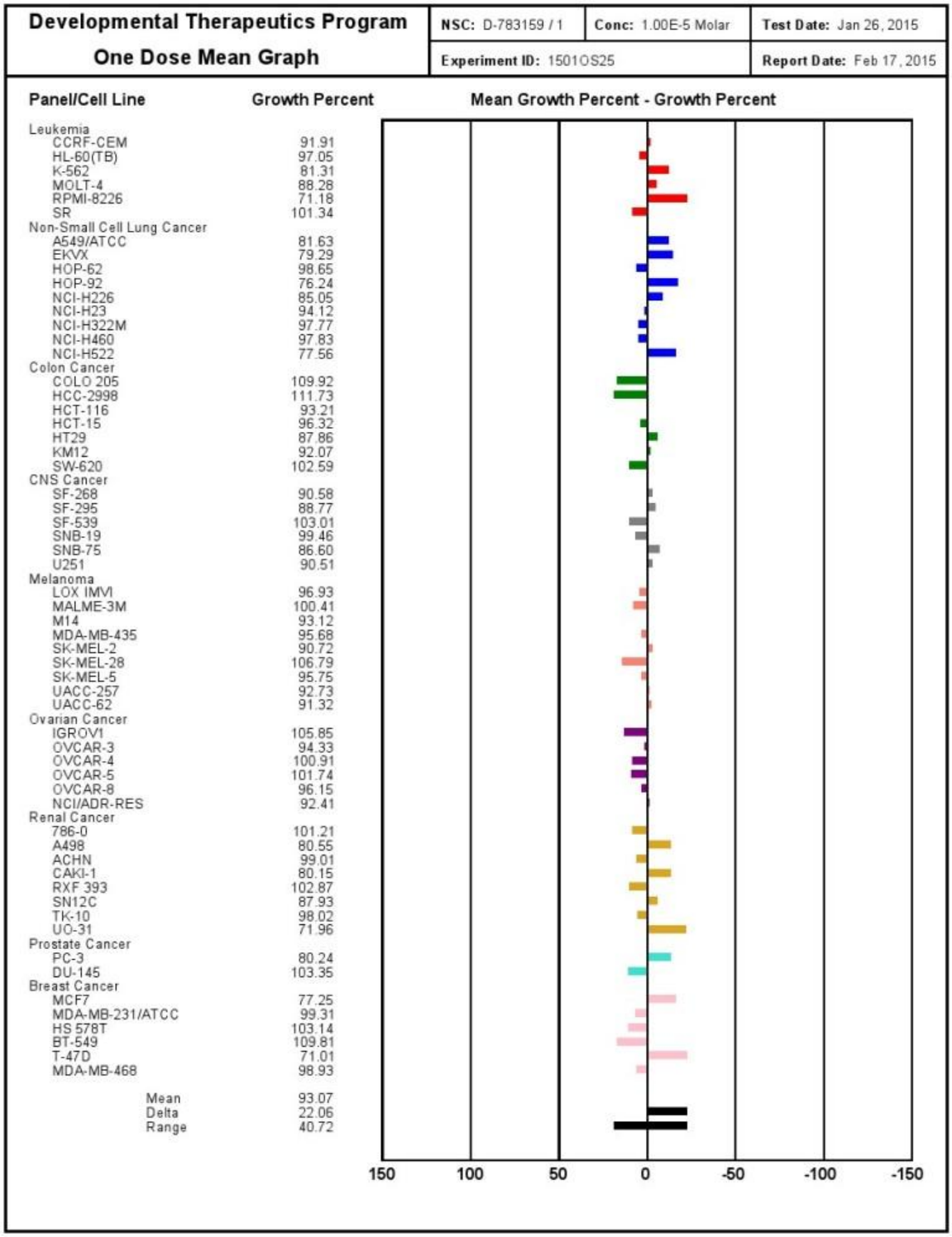
NSC: D-783158 / 1	Conc: 1.00E-5 Molar	Test Date: Jan 26, 2015
Experiment ID: 1501OS25		Report Date: Feb 17, 2015

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	93.75
HL-60(TB)	97.94
K-562	91.21
MOLT-4	92.88
RPMI-8226	83.54
SR	103.46
Non-Small Cell Lung Cancer	
A549/ATCC	87.34
EKVX	87.67
HOP-62	105.25
NCI-H226	82.47
NCI-H23	98.68
NCI-H322M	106.20
NCI-H460	103.22
NCI-H522	67.97
Colon Cancer	
COLO 205	107.32
HCC-2998	111.76
HCT-116	98.68
HCT-15	96.95
HT29	84.56
KM12	97.70
SW-620	107.19
CNS Cancer	
SF-268	101.56
SF-295	99.08
SF-539	100.93
SNB-19	99.14
SNB-75	98.13
U251	93.77
Melanoma	
LOX IMVI	102.44
MALME-3M	99.01
M14	99.95
MDA-MB-435	96.27
SK-MEL-2	58.67
SK-MEL-28	106.76
SK-MEL-5	93.25
UACC-257	98.28
UACC-62	97.74
Ovarian Cancer	
IGROV1	99.37
OVCAR-3	97.40
OVCAR-4	97.08
OVCAR-5	107.70
OVCAR-8	103.27
NCI/ADR-RES	103.81
Renal Cancer	
786-0	103.65
A498	102.07
ACHN	98.17
CAKI-1	91.98
RXF 393	114.99
SN12C	95.42
TK-10	92.63
UO-31	80.80
Prostate Cancer	
PC-3	85.52
DU-145	102.07
Breast Cancer	
MCF7	87.32
MDA-MB-231/ATCC	106.73
HS 578T	115.16
BT-549	110.01
T-47D	87.18
MDA-MB-468	93.44
Mean	97.01
Delta	38.34
Range	56.49

Mean Growth Percent - Growth Percent



Sheet 1. Compound 35a



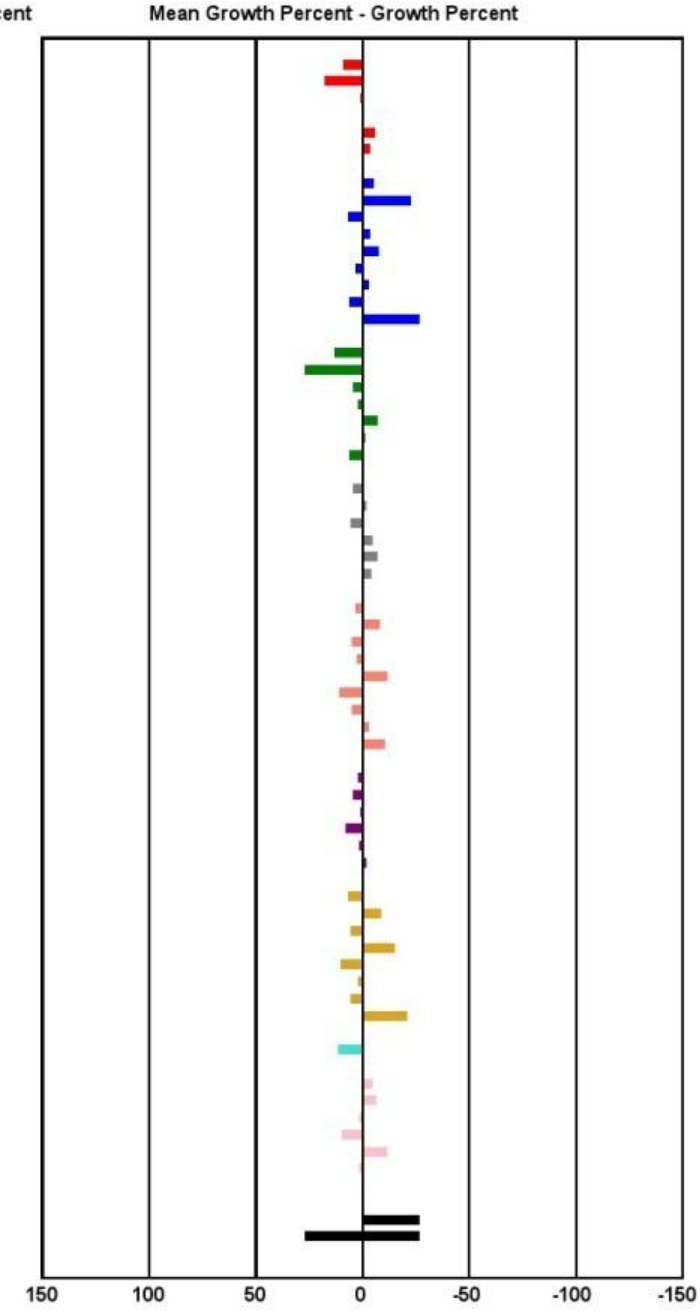
Sheet 2. Compound 35b

Developmental Therapeutics Program

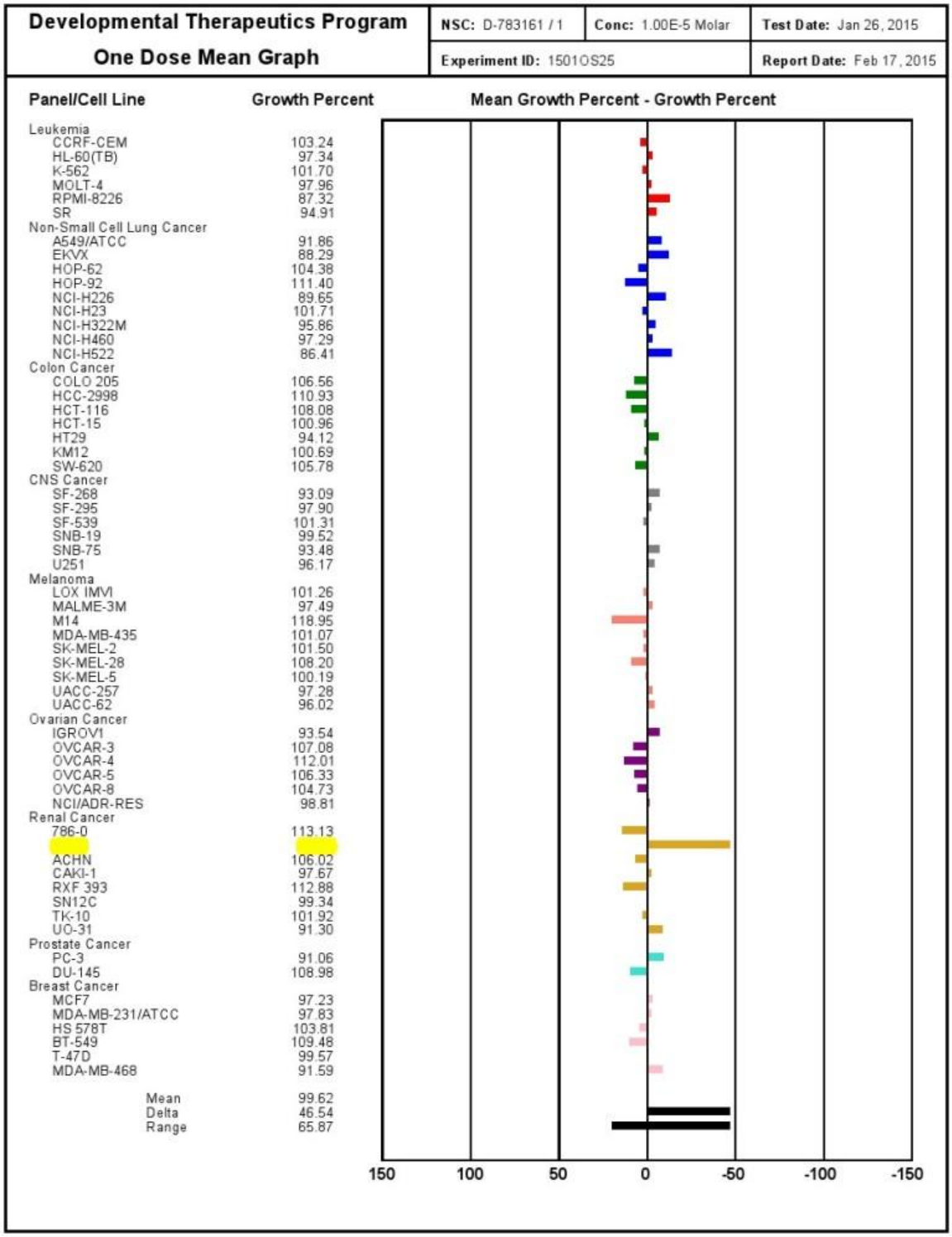
One Dose Mean Graph

NSC: D-783160 / 1	Conc: 1.00E-5 Molar	Test Date: Jan 26, 2015
Experiment ID: 1501OS25		Report Date: Feb 17, 2015

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	101.80
HL-60(TB)	110.53
K-562	93.60
MOLT-4	93.02
RPMI-8226	87.76
SR	90.07
Non-Small Cell Lung Cancer	
A549/ATCC	88.22
EKVX	71.10
HOP-62	99.53
HOP-92	90.29
NCI-H226	86.01
NCI-H23	96.04
NCI-H322M	90.92
NCI-H460	99.02
NCI-H522	67.05
Colon Cancer	
COLO 205	106.02
HCC-2998	119.54
HCT-116	96.94
HCT-15	94.61
HT29	86.59
KM12	92.52
SW-620	98.85
CNS Cancer	
SF-268	97.21
SF-295	92.07
SF-539	98.36
SNB-19	88.83
SNB-75	86.57
U251	89.92
Melanoma	
LOX IMVI	95.71
MALME-3M	85.83
M14	97.72
MDA-MB-435	95.62
SK-MEL-2	81.97
SK-MEL-28	103.45
SK-MEL-5	97.76
UACC-257	90.75
UACC-62	83.09
Ovarian Cancer	
IGROV1	95.04
OVCAR-3	96.81
OVCAR-4	93.59
OVCAR-5	100.41
OVCAR-8	94.00
NCI/ADR-RES	92.07
Renal Cancer	
786-0	99.62
A498	85.16
ACHN	98.26
CAKI-1	78.49
RXF 393	103.01
SN12C	94.81
TK-10	98.40
UO-31	72.99
Prostate Cancer	
DU-145	103.80
Breast Cancer	
MCF7	88.98
MDA-MB-231/ATCC	87.27
HS 578T	94.30
BT-549	102.54
T-47D	82.08
MDA-MB-468	94.06
Mean	93.11
Delta	26.06
Range	52.49



Sheet 3. Compound 35c



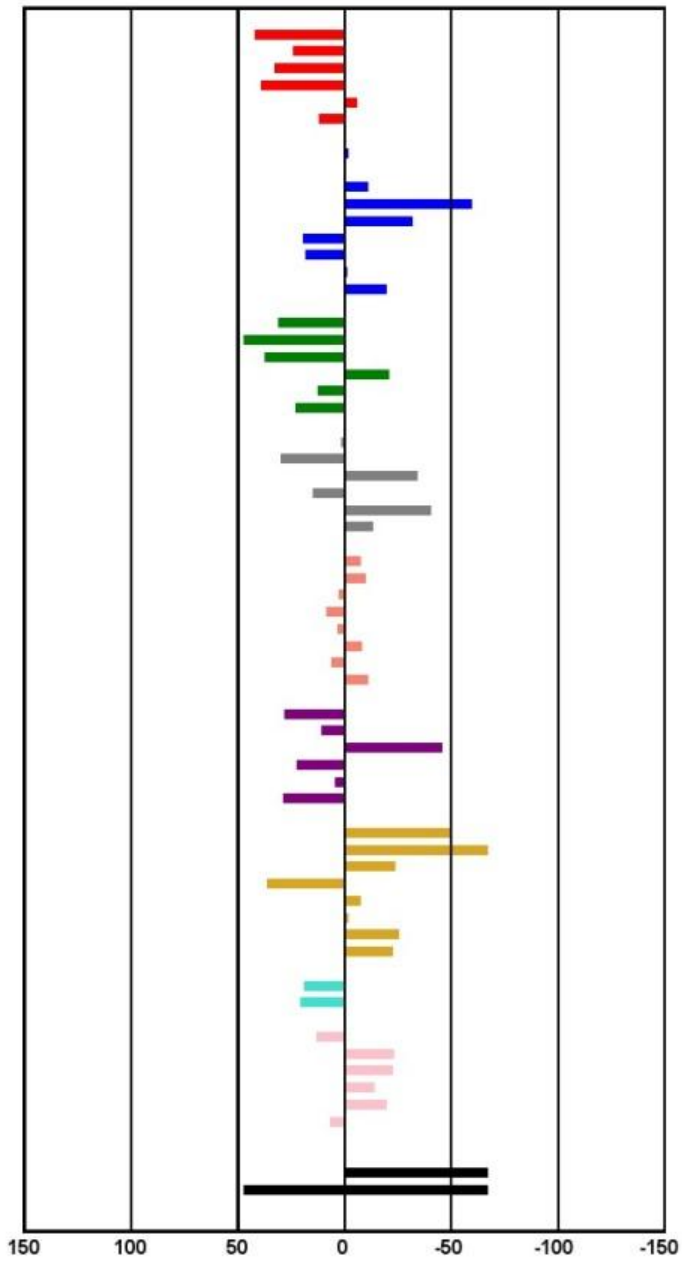
Sheet 4. Compound 35d

Developmental Therapeutics Program

One Dose Mean Graph

NSC: D-783162 / 1	Conc: 1.00E-5 Molar	Test Date: Jan 26, 2015
Experiment ID: 1501OS25		Report Date: Feb 17, 2015

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	94.52
HL-60(TB)	76.42
K-562	84.99
MOLT-4	91.16
RPMI-8226	47.43
SR	64.20
Non-Small Cell Lung Cancer	
A549/ATCC	51.84
EKVX	52.82
HOP-62	42.12
HOP-92	-6.35
NCI-H226	21.77
NCI-H23	71.54
NCI-H322M	70.74
NCI-H460	52.23
NCI-H522	33.90
Colon Cancer	
COLO 205	83.44
HCC-2998	99.26
HCT-15	89.59
HT29	32.74
KM12	64.87
SW-620	74.95
CNS Cancer	
SF-268	53.68
SF-295	82.08
SF-539	19.25
SNB-19	67.35
SNB-75	13.00
U251	39.98
Melanoma	
LOX IMVI	45.59
MALME-3M	43.48
MDA-MB-435	54.90
SK-MEL-2	60.88
SK-MEL-28	55.72
SK-MEL-5	45.25
UACC-257	58.37
UACC-62	42.19
Ovarian Cancer	
IGROV1	80.19
OVCAR-3	63.09
OVCAR-4	7.51
OVCAR-5	74.85
OVCAR-8	56.66
NCI/ADR-RES	81.21
Renal Cancer	
786-0	2.94
A498	-13.62
ACHN	29.59
CAKI-1	88.66
RXF 393	45.68
SN12C	51.35
TK-10	28.13
UO-31	30.77
Prostate Cancer	
PC-3	71.31
DU-145	73.15
Breast Cancer	
MCF7	65.49
MDA-MB-231/ATCC	30.47
HS 578T	30.83
BT-549	39.15
T-47D	33.47
MDA-MB-468	58.97
Mean	52.73
Delta	66.35
Range	112.88



Sheet 5. Compound 35e

2.8 REFERENCES

1. van der Made, A. W.; van der Made, R. H. *J. Org. Chem.* **1993**, *58*, 1262–1263.
2. Vyas, T. A. *Ph. D. Dissertation*, The M. S. University of Baroda, (1998-) **2004**.
3. (a) Palmar, D. C. (Ed.) *The chemistry of heterocyclic compounds 60, Oxazoles*: *Synthesis, reactions and spectroscopy, Part B*, **2004**, John Wiley & Sons; (b) Palmar, D. C. (Ed.) *The chemistry of heterocyclic compounds 60, Oxazoles*: *Synthesis, reactions and spectroscopy, Part A*, **2003**, John Wiley & Sons; (c) Hassner, A.; Fischer, B. *Heterocycles* **1993**, *35*, 1441–1465; (d) Turchi, I. J. (Ed.) *The Chemistry of heterocyclic compounds*, *45*¸ *Oxazoles*, **1986**, John Wiley & Sons; (e) Turchi, I. J.; Dewar, M. J. S. *Chem. Rev.* **1975**, *75*, 389–437; (f) Wiley, R. H. *Chem. Rev.* **1945**, *37*, 401–442.
4. (a) Jin, Z. *Nat. Prod. Rep.* **2013**, *30, 869*–915; **2011**, *28, 1143*–1191; **2009**, *29, 382*–445; **2006**, *23, 464*–496; (b) Blunt, J. W.; Coop, B. R. Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rep.* **2011**, *28, 196*–268; (c) Davyt, D.; Serra, G. *Mar. Drugs* **2010**, *8*, 2755–2780; (f) Wright, A. E.; Botelho, J. C.; Guzma´n, E.; Harmody, D.; Linley, P.; McCarthy, P. J.; Pitts, T. P. *Nat. Prod. Rep.* **2007**, *70, 412*–416; (d) Yeh, V. S. C. *Tetraherdron* **2004**, *60*, 11995–12042; (e) Roy, R. S.; Gehring, A. M.; Milne, J. C.; Belshaw, P. J. Walsh, C. T. *Nat. Prod. Rep.* **1999**, *16*, 249–263; (f) Lewis, J. R. *Nat. Prod. Rep.* **1999**, *16, 389*–416.
5. Broom, N. J. P.; Elder, J. S.; Hannan, P. C. T.; Pons, J. E.; O'Hanlon, P. J.; Walker, J.; Wilson, J.; Woodall, P. *The Journal of Antibiotics* **1995**, *48*, 1336–1344.
6. (a) Scherlach, K.; Brendel, N.; Ishida, K.; Dahsea, H. M.; Hertweck, C. *Org. Biomol. Chem.* **2012**, *10*, 5756–5759; (b) Stefely, J. A.; Palchaudhuri, R.; Miller, P. A.; Peterson, R. J.; Moraski, G. C.; Hergenrother, P. J.; Miller, M. J. *J. Med. Chem.* **2010**, *53*, 3389–3395.
7. Herna´ndez, D.; Altuna, M.; Cuevas, C.; Aligue´, R.; Albericio, F.; A´ lvarez, M. *J. Med. Chem.* **2008**, *51*, 5722–5730; (b) Giddens, A. C.; Boshoff, H. I. M.; Franzblau, S. G.; Barry, C. E.; Copp, B. R. *Tetrahedron Lett.* **2005**, *46*, 7355–7357.
8. (a) Makadia, P.; Shah, S. R.; Pingali, H.; Zaware, P.; Patel, D.; Pola, S.; Thube, B.; Priyadarshini, P.; Suthar, D.; Shah, M.; Giri, S.; Trivedi, C.; Jain, M.; Patel, P.; Bahekar, R. *Bioorg. Med. Chem.* **2011**, *19*, 771–782; (b) Asaki, T.; Aoki, T.;

Hamamoto, T.; Sugiyama, Y.; Ohmachi, S.; Kuwabara, K.; Murakami, K.; Todo, M. *Bioorg. Med. Chem. Lett*. **2008**, *16*, 981–994; (c) Sznaidman, M. L.; Haffner, C. D.; Maloney, P. R.; Fivush, A.; Chao, E.; Goreham, D.; Sierra, M. L.; Le Grumelec, C.; Xu, H. E.; Montana, V. G.; Lambert, M. H.; Willson, T. M.; Jr. Oliver, W. R.; Sternbach, D. D. *Bioorg. Med. Chem*. **2003**, *13*, 1517–1521.

9. Diana, G. D.; Ogelsby, R. C.; Akullian, V.; Carabateas, P. M.; Cutliffe, D.; Mallamo, J. P.; Otto, M. J.; Mckinley, P. J.; Maliski, E. G.; Michalek, S. J. *J. Med. Chem.* **1987**, 383–398.
10. (a) Self, C. R. Barber, W. E.; Machin, P. J.; Osbond, J. M.; Smithen, C. E.; Tong, B. P.; Wicke-Ns, J. C.; Bloxham, D. P.; Bradshaw, D.; Cashin, C. H.; Dodge, B. B.; Ford, H.; Le-Wis, E. S.; Westmacott, D. *J. Med. Chem.* **1991,** 772; (b) Brown, K. *U. S. Patent*, **1971**, 3578671, *Chem. Abstr*. **1972**, 36005; (c) Crank, G.; Foulis, M. J. *J. Med. Chem.* **1971**, *14*, 1075–1077.
11. (a) Stokes, N. R.; Baker, N.; Bennett, J. M.; Chauhan, P. K.; Collins, I.; Davies, D. T.; Gavade, M.; Kumar, D.; Lancett, P.; Macdonald, R.; MacLeod, L.; Mahajan, A.; Mitchell, J. P.; Nayal, N.; Nayal, Y. N.; Pitt, G. R. W.; Singh, M.; Yadav, A.; Srivastava, A.; Czaplewski, L. G.; Haydon, D. J. *Biorg. Med. Chem. Lett.* **2014**, *24*, 53–359; (b) Crank, G.; Neville, M.; Rayden, R. *J. Med. Chem.* **1973**, *16*, 1402–1405.
12. Robinson, R. J. *J. Chem. Soc.* **1990**, *95*, 2167–2174.
13. Thalhammer, A.; Mecinovic, J.; Schofield, C. J. *Tetrahedron Lett.* **2009**, *50*, 1045–1047.
14. Davidson, D.; Weiss, M. Jelling, M. *J. Org. Chem.* **1937**, *2*, 319–327.
15. Phillips, A. J. Uto, Y.; Wipf, P.; Reno, M. J.; Williams, D. R. *Org. Lett.* **2000**, *2*, 1165–1168.
16. Sanz-Cervera, J. F.; Blasco, R.; Piera, J.; Cynamon, M.; Ibanez, I. Murguia, M.; Fustero, S. *J. Org. Chem.* **2009**, *74*, 8988–8996.
17. Zheng, Y.; Li, X.; Ren, C.; Zhang-Negrerie, D.; Du, Y.; Zhao, K. *J. Org. Chem.* **2012**, *77*, 103535–10361.
18. (a) Cheung, C. W.; Buchwald, S. L. *J. Org. Chem.*, **2012**, *77*, 7526–7537; (b) Martín, R.; Cuenca, A.; Buchwald, S. L. *Org. Lett.* **2007**, *9*, 5521–5524.

19. Bagley, M. C.; Buck, R. T.; Hind, S. L.; Moody, C. J. *J. Chem. Soc. Perkin Trans.* **1998**, *1*, 591–600; (b) Tullis, J. S.; Helquist, P. *Organic Synthesis* **1997**, 3761.
20. Pan, Y. M.; Zheng, F. J.; Lin, H. X.; Zhan, Z. P. *J. Org. Chem.* **2009**, *74*, 3148–3151.
21. Kumar, M. P.; Liu, R. S. *J. Org. Chem.* **2006**, *71*, 4951–4955.
22. Wan, C.; Zhang, J. Wang, S.; Fan, J.; Wang, Z. *Org. Lett.* **2010**, *12*, 2338–2341.
23. Jiang, H.; Huang, H.; Cao, H.; Qi, C. *Org. Lett.* **2010**, *12*, 5561–5563.
24. Singh, B.; Zweig, A.; Gallivan, J. B. *J. Am. Chem. Soc.* **1972**, *94*, 1199–1206.
25. (a) Samimim, H. A.; Mohammadi, S. *Synlett* **2013,** *24*, 223–225; (b) Shah, S. R.; Navathe, S. S.; Dikundwar, A. G.; Guru Row, T. N.; Vasella, A. T. *Eur. J. Org. Chem.* **2013,** 264–267.
26. (a) Fischer, E. *Ber.* **1896**, *29*, 205; (b) Conforth, J. W.; Conforth, R. H. *J. Chem. Soc.* **1949**, 1028–1030.
27. Cuny, G.; GamezMontano, R.; Zhu, J. *Tetrahedron*, **2004**, *60*, 4879–4885.
28. Wan, C.; Gao, L.; Wang, Q.; Zhang, J.; Wang, Z. *Org. Lett.* **2010**, *12*, 3902–3905.
29. Graham, T. *Org. Lett.* **2010**, *12*, 3614–3617.
30. van Leusen, A. M.; Hoogenboom, B. E.; Siderius, H. *Tetrahedron Lett*. **1972**, 2369–2372.
31. Barrett, A. G. M.; Cramp, S. M.; Hennessy, A. J.; Procopiou, P. A.; Roberts, R. S. *Org. Lett.* **2001**, *3*, 271–273.
32. Verrier, C.; Lassalas, P.; Théveau, L.; Quéguiner, G.; Trécourt, F.; Marsais, F.; Hoarau, C. *Beilstein J. Org. Chem.* **2011**, *7*, 1584–1601.
33. Shah, S. R.; Thakore, R. R.; Vyas, T. A.; Sridhar, B. *Synlett Conformationally Flexible C_3 Symmetric 1,3-Oxazoles as Molecular Scaffolds* **2015.**
34. (a) Mahuteau-Betzer, F.; Piguel, S. *Tetrahedron Lett*. **2013**, *54*, 3188–3193; (b) Silva, D. L.; De Boni, L.; Correa, D. S.; Costa, S. C. S.; Hidalgo, A. A.; Zilio, S. C.; Canuto, S.; Mendonca, C. R. *Opt. Mater*. **2012,** *34*, 1013–1018; (c) Park, H. J.; Lim, C. S.; Kim, E. S.; Han, J. H.; Lee, T. H.; Chun, H. J.; Cho, B. R. *Angew. Chem. Int. Ed.* **2012,** *51*, 2673–2676; (d) Braem, O.; Penfold, T. J.; Cannizzoad, A.; Chergui, M. *Phys. Chem. Chem. Phys*. **2012**, *14*, 3513–3519; (e) Verrier, C.; Fiol-Petit, C.; Hoarau, C.; Marsais, F. *Org. Biomol. Chem.* **2011**, *9*, 6215–6218; (f) KrishnaMurthy, N. V.; Reddy, A. R.; Bhudevi, B. *J. Fluoresc.* **2008,** *18*, 29–34; (g) Clapham, B.;

Sutherland, A. J. *Chem. Commun.* **2003**, 84–85; (h) Clapham, B.; Richards, A. J.; Wood, M. L.; Sutherland, A. J. *Tetrahedron Lett.* **1997**, *38*, 9061–9064; (i) Diwu, Z.; Lu, Y.; Zhang, C.; Klaubert, D. H.; Haugland, R. P. *Photochemistry and Photobiology* **1997**, *66*, 424–431; (j) Barnett, M. D.; Daub, G.; Hayes, F. N.; Ott, D. G. *J. Am. Chem. Soc.* **1960**, 2282–2285.

35. For similar coupling under microwave condition see Besselievre, F.; Mahuteau-Betzer, F.; Grierson, D. S.; Piguel, S. *J. Org. Chem.* **2008**, *73*, 3278–3280.
36. Martin, A.; Camacho, M.; Portaels, F.; Palomino, J. C. *Antimicrob. Agents And Chemother.* **2003**, *47* (11), 3616–3619.
37. Sheldrick, G. M. **2015**, *Acta Cryst. C71*, 3–8.