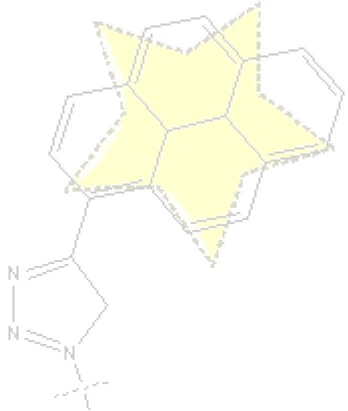
CHAPTER IV

Synthesis and characterization of 1,3,5-tris[{4-(phenyloxymethyl)-1,2,3-triazol-1-yl}-methyl]-2,4,6-trimethylbenzenes via *threefold* click reaction



4.1 INTRODUCTION

This chapter deals with the synthesis of C_3 symmetric tripodal compounds in which 1,2,3–triazole heterocycle has been included providing nitrogen binding sites and functioning as a linker offering aromatic end groups separated by a two or three atom spacer placed at its 4th position.

Triazoles are five member nitrogen heterocycles with either three consecutive nitrogens, known as 1,2,3-triazoles or one nitrogen separated from the other two by a carbon atom known as 1,2,4-triazoles. 1,2,3-Triazoles are most commonly prepared by the addition of azides to alkynes in one of the 1,3-dipolar cycloaddition reactions studied in detail by Huisgen and co workers and is a thermally allowed reaction.[1] The reaction was first reported by Arthur Michael in 1893 for the synthesis of 1,2,3–triazoles **1**[2] (Figure 1).

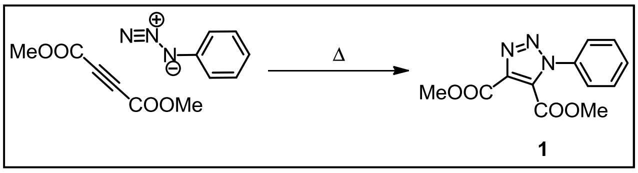


Figure 1 First report of 1,3–dipolar route to triazoles

1,2,3–Triazole itself was prepared from acetylenedicarboxylic acid and benzyl azide by decarboxylation followed by debenzylation by Wiley et al.[3]

The regioselectivity with respect to substitution (1,4- or 1,5- disubstitution), of the reaction depends upon the electronic and steric factors and is somewhat predictable. But many a times this reaction results in a mixture of regioisomers when unsymmetric alkynes are used. The reaction was modified by Sharpless and Fokin using Cu(I) catalyst which was termed as a '*click*' reaction.[4] Click reactions are those reactions that are high yielding, wide in scope, stereospecific and simple to perform.[5] Copper catalyzed synthesis of 1,2,3–triazoles is quite efficient and is having high regioselectivity for 1,4–regioisomer.[6]

Following the simplicity, regioselectivity and high yields in copper catalyzed addition of azides to alkynes, a wide spread interest erupted in all fields of chemistry and it triggered a kind of explosion in number of research papers published on 1,2,3–triazoles. A number of reviews, monographs and books have been published since then on the topic and on the heterocycle. Even a theme issue in Chemical

Society Reviews has been published on application of click chemistry (*of azides*) in 2010.[7] Recent books on click chemistry of 1,2,3–triazoles include a volume in the series *Advances in Heterocyclic Chemistry* edited by Alan R. Katritzky,[8] a volume named *Clicked Triazoles in the series of Topics In Heterocyclic Chemistry*[9] and a recent volume in the same series titled *Chemistry of 1,2,3–triazoles*.[10] Recently a Chemical Society Review highlights the chemistry of supramolecular interactions of 1,2,3–triazoles.[11]

After the click chemistry became a kind of synonym with the azide-alkyne addition leading to 1,2,3-triazoles, the triazoles have been studied extensively and explored for various applications.

A number of molecules possessing 1,2,3-triazole have been explored as pharmacophores and for their medicinal value. The use of combinatorial chemistry in the preparation of a series of compounds with 1,2,3-triazoles has made it possible to prepare and screen a number of triazole derivatives for various bioactivities. They have been studied for anticancer, antituberculosis, antiinflammatory, antifungal and antibacterial, antiviral and other bioactivities. The aspect of bioactivity has been well covered in two recent reviews.[12] Antiproliferative activity against select cancer cell lines has been studied recently for *N*-(1-benzyltriazole) derivatives **2**[13] (Figure 2).

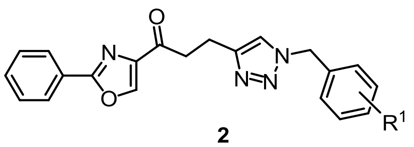


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Figure 2 ***Triazole with anticancer activity***

A series of triazole containing substituted aminopropane diols **3** have been found to possess a potent and selective $S1P_1$ (Sphingosine-1-phoshpate) agonist property[14] (Figure 3).

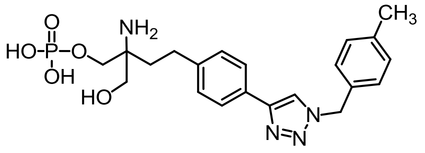

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Figure 3 ***$S1P_1$ agonist triazole***

C_3-Symmetric triazole containing prolinamides **4** have been used as catalyst for asymmetric aldol condensation reactions in water[15] (Figure 4).

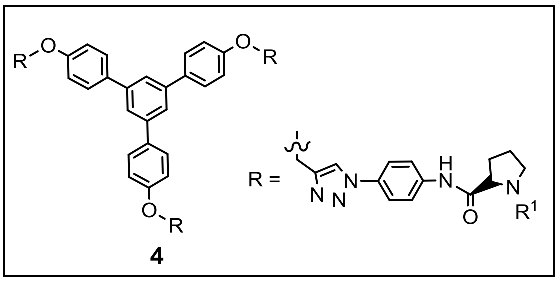

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Figure 4 ***C_3* symmetric triazole as organocatalyst**

Tris-(triazolemethyl)amine copper complexes **5** were employed for an intramolecular click triazole formation[16] (Figure 5).

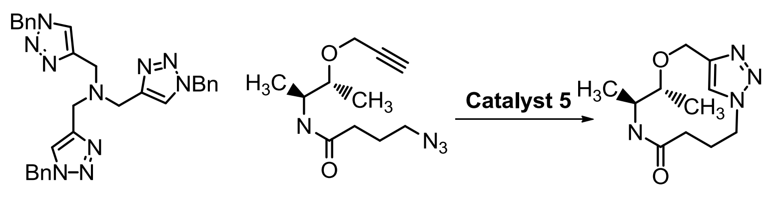

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Figure 5 ***Tris-triazole ligand in the click reaction***

C_3-Symmetric molecules **6** with 1,2,3-triazole attached to the central aromatic ring showing discotic columnar liquid crystalline property have been reported[17] (Figure 6).

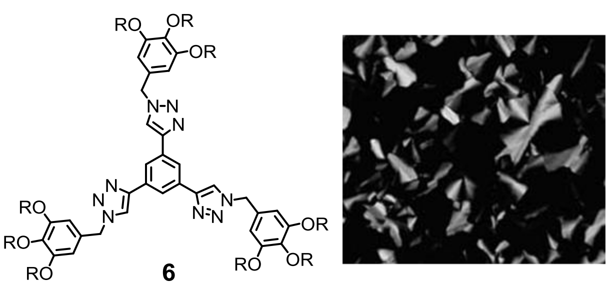

Figure 6 ***C_3* symmetric liquid crystals with triazoles**

1,2,3-Triazole heterocycle can offer various supramolecular interactions as per the structure and conditions as shown in figure **7** and bind with different anions and metal ions[11] (Figure 7).

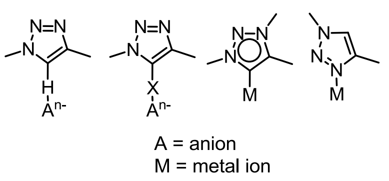

Figure 7 ***Ion binding modes of triazoles***

When these triazoles are part of a macrocycle or a bound to crown structures or a part of calixzarenes they can bind with different metal ions and act as metal ion sensors.[18]

C_3-Symmetric compound **7** containing triazoles substituted with long alkyl chains and linked to a triphenelyene moiety was prepared from alkyl azide and hexapropargenyloxy triphenylene. The resulting hexatriazole derivative showed a sponge like morphology and was studied as chemosensor for detection of nitroaromatics by fluorescence studies[19] (Figure 8).

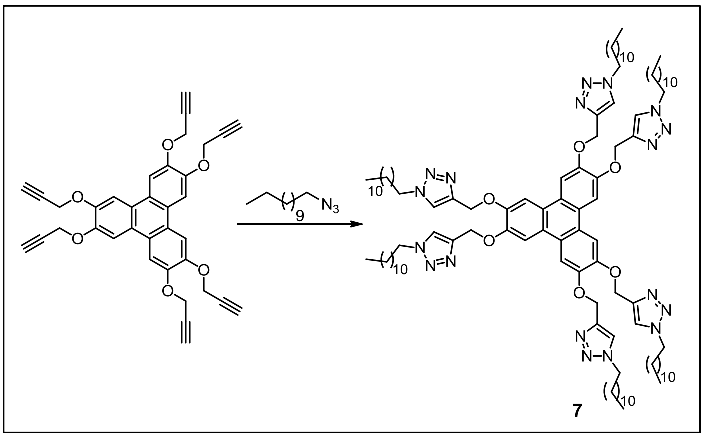

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Figure 8 ***C_3 symmetric hexatriazole chemosensor***

Homo-oxacalix[3]arene functionalized with three triazolyl arene arms **8** was studied for heavy metal ion sensing ability and found to undergo strong binding with Pb^{2+} [20] (Figure 9).

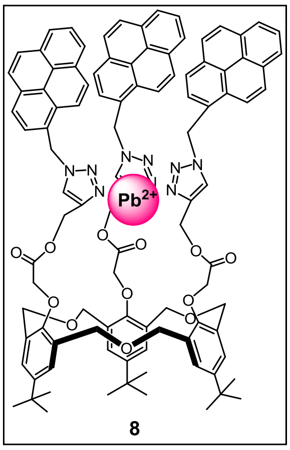

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Figure 9 ***Ion recognition by flexible tripodal triazole***

A cholic acid substituted tripodal triazole **9** was developed and found to bind with metal ions through coordination with three triazole rings. It was also able to enclose pyrene in a polar medium[21] (Figure 10).

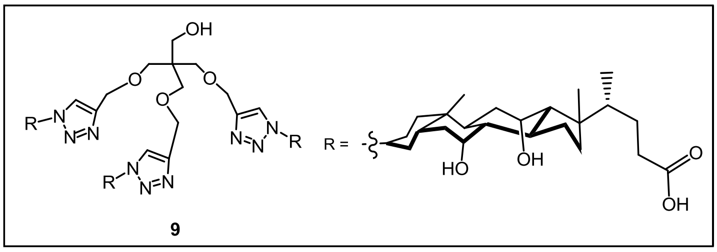


Figure 10 ***Cholic acid substituted tripodal triazole as a host***

A tripodal receptor **10** having triazoles (substituted with 7-azaindole or its pyridine analogue) attached to central aromatic ring, selectively recognizes Cl^- and $H_2PO_4^-$ ions over a series of other anions studied[22] (Figure 11).

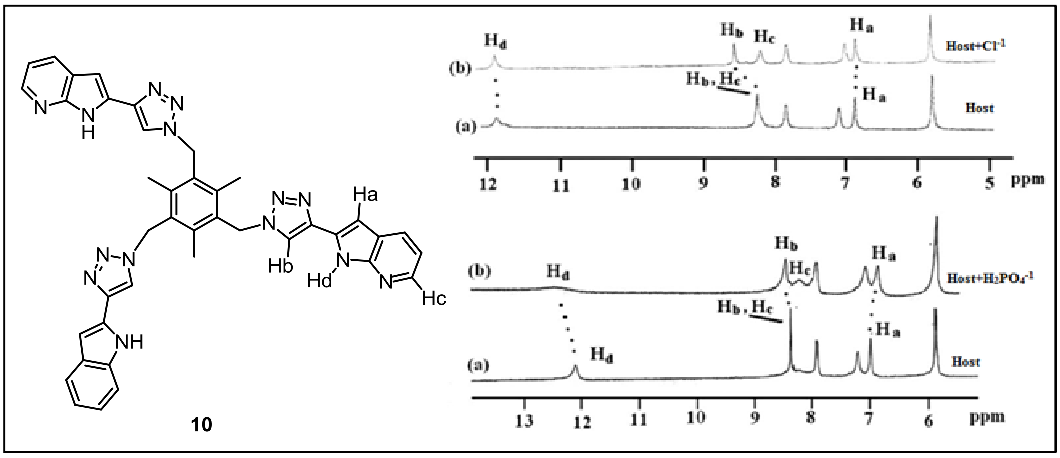


Figure 11 Heteroaromatic triazole as hosts

Tripodal triazole based ligands **11** synthesized by a one-pot triple click reaction of azides generated from anilines, with tripropargylamine formed blue emitting Ce^{3+} complexes[23] (Figure 12).

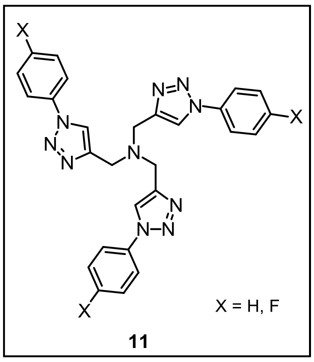


Figure 12 ***Ligand for Ce^{3+} complexation***

The three armed pyrenyl-triazole receptors **12,** a highly fluorescent sensor for citrate anions as well as Cu^{2+} cations, have been recently reported.[24] The related three armed ferrocenyl-triazole receptor **13** behaved as a highly selective chemosensor for Pb^{2+} cations (Figure 13).

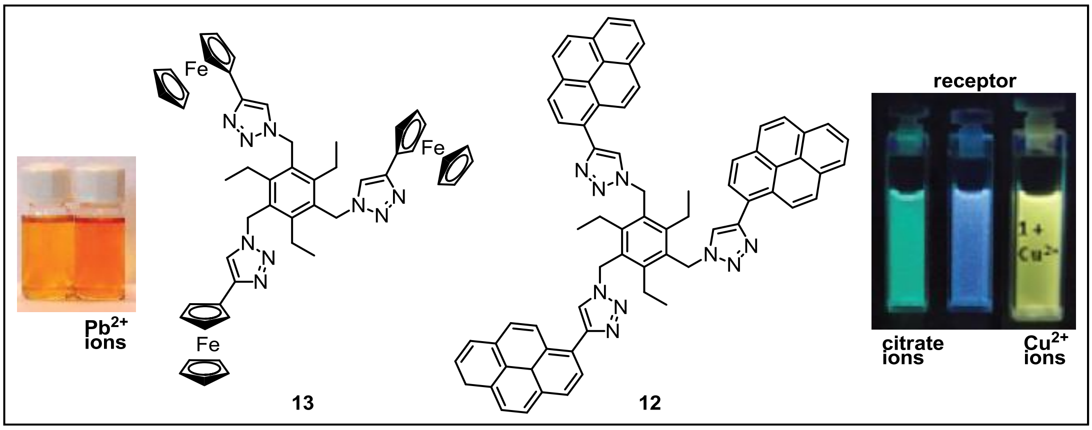


Figure 13 ***Tris-triazoles with different sensing abilities***

A pyrene linked tris-triazole amine fluorescent chemosensor **14** was found to be highly selective for Zn^{2+} switching off the fluorescence[25] (Figure 14).

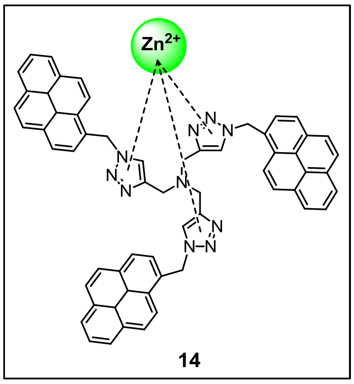
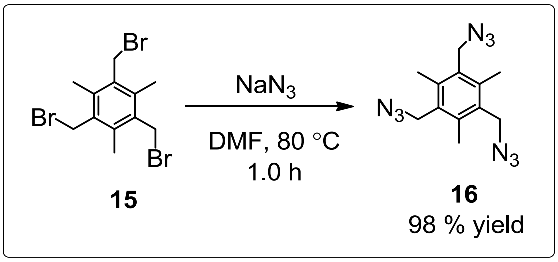


Figure 14 ***Triazole fluorescent chemosensor***

4.2 RESULTS AND DISCUSSION

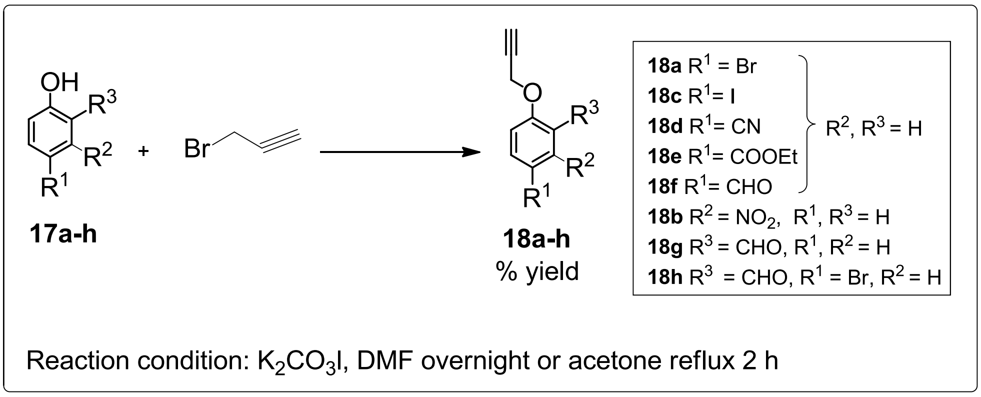
Looking at the importance of the triazole containing tripodal C_3 symmetric compounds because of their ability to undergo supramolecular interactions, some new tripodal triazoles were designed.

For this purpose a tris-azide **16** was prepared from 1,2,3–tribromomethyl mesitylene **15** by reacting with an excess of sodium azide (6.0 equiv.) in DMF (Scheme 4.1). The reported procedure[26] was slightly modified in the following manner. In the reported procedure reaction was carried out for 24 h at 80 °C while it was found that at the same temperature the reaction is completed within 1 h time as observed on TLC.



Scheme 4.1 ***Synthesis of 1,3,5–tris(azidomethyl)–2,4,6–trimethylbenzene***[26]

As a stage was set for the triple click reaction with the triazide **16** in hand, various aromatic alkyne containing aromatic counter parts were prepared by the reaction of substituted aromatic phenols **17** and propargyl bromide giving the corresponding propargyl aromatic ethers **18** (Scheme 4.2). The reaction involved a nucleophilic substitution reaction on propargyl bromide by phenoxide ions generated from phenols by treating them with K_2CO_3 in DMF at room temperature or in acetone under reflux.[27]

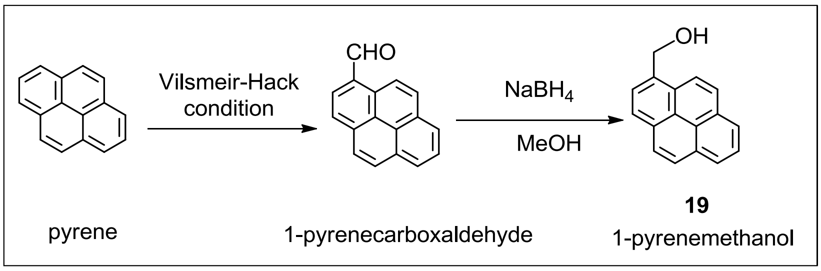


18a R^1 = Br
18c R^1= I
18d R^1= CN
18e R^1= COOEt
18f R^1= CHO
R^2, R^3 = H
18b R^2 = NO_2, R^1, R^3 = H
18g R^3 = CHO, R^1, R^2 = H
18h R^3 = CHO, R^1 = Br, R^2 = H

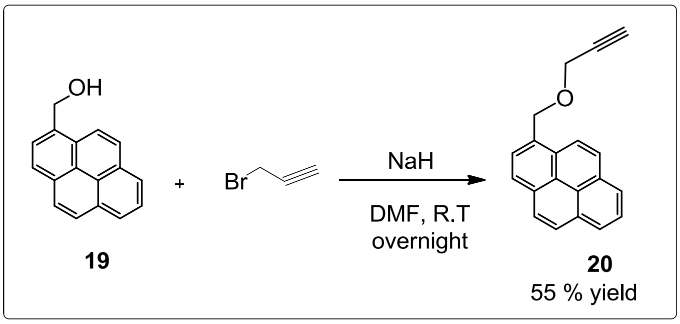
Reaction condition: K_2CO_3l, DMF overnight or acetone reflux 2 h

Scheme 4.2 ***Synthesis of propargyl aryl ethers***[27]

To incorporate the pyrene fluorophore in tripodal triazoles, 1–pyrene methanol **19** was converted to the corresponding propargyl ether **20** (Scheme 4.4).[28] Being weakly acidic, the alcohol required a stronger base, sodium hydride (NaH) to generate pyrene methoxide nucleophile to react with propargyl bromide in DMF (Scheme 4.4). 1–Pyrenemethanol **19** was prepared from 1–pyrenecarboxaldehyde in quantitative yield by reduction with sodium borohydride ($NaBH_4$) in methanol. The 1–pyrenecarboxaldehyde in turn was prepared by introducing a formyl group in pyrene under the Vilsmeir-Hack reaction conditions (DMF–$POCl_3$, 90 °C) (Scheme 4.3).

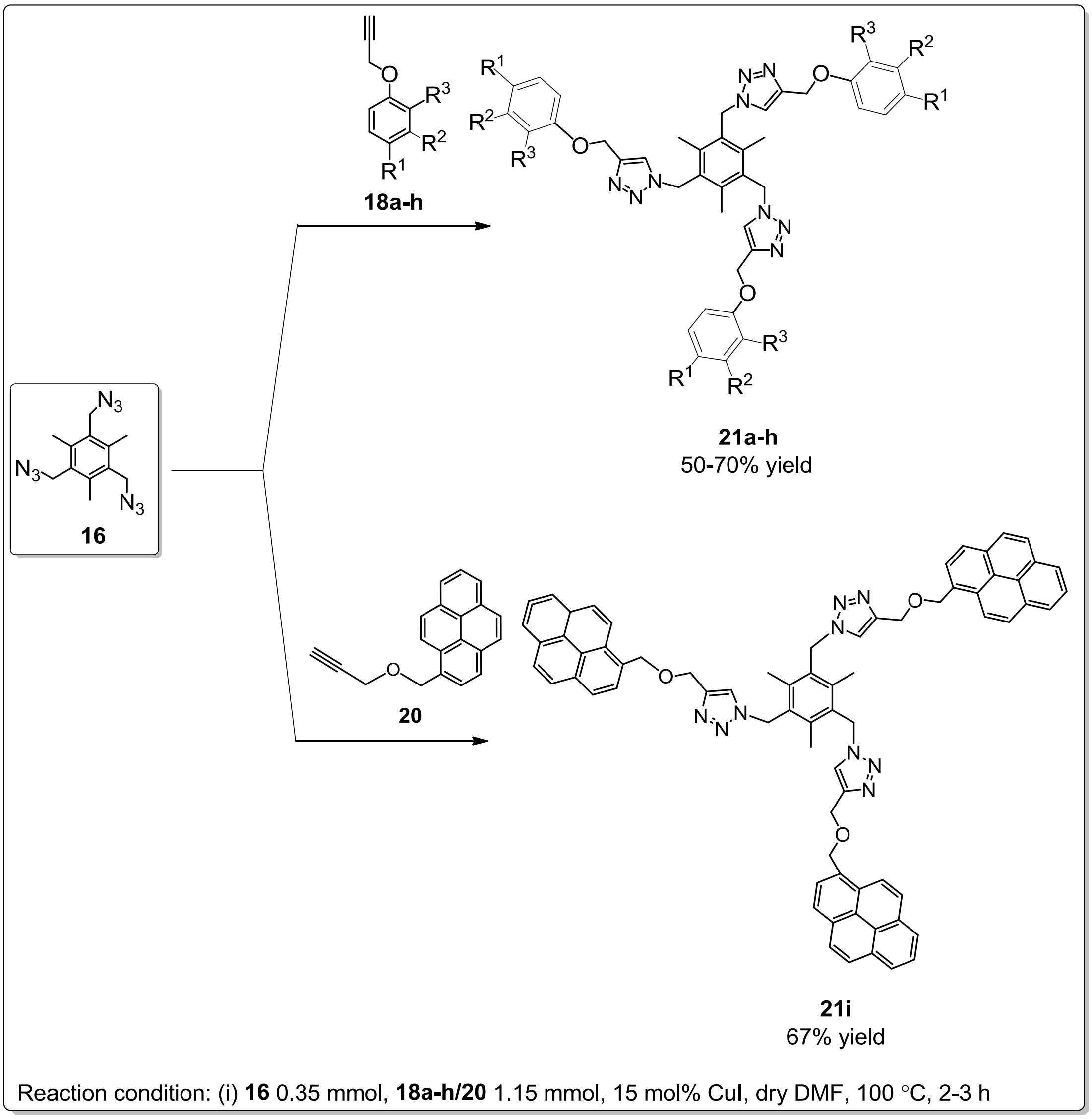


Scheme 4.3 ***Synthesis of 1-pyrenemethanol***



Scheme 4.4 ***Synthesis of 1–pyrenemethyl propargyl ether 20***[28]

The triple triazole forming click reaction was carried out by reacting the triazide **16** with the terminal alkynes in form of aryl propargyl ethers **18a-g** or pyrenemethyl propargyl ether **20** using cuprous iodide (CuI) in DMF as a solvent and heating at 100 °C for 2–3 hours when a major spot was observed on TLC (Scheme 4.5). The products were isolated after normal work up followed by silicagel purification in good yields as mentioned in table (Table 4.1.0).



Reaction condition: (i) **16** 0.35 mmol, **18a-h/20** 1.15 mmol, 15 mol% CuI, dry DMF, 100 °C, 2-3 h

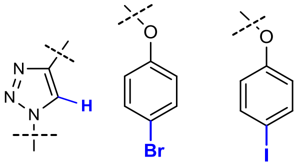
Scheme 4.5 ***Triple click reaction***

Table 4.1.0 ***Yields and Melting points of newly synthesized tris-triazoles***

ID	Substituent			Yield [%]	M.p [°C]
	R^1	R^2	R^3		
21a	-Br	-H	-H	74	195
21b	-H	-H	$-NO_2$	65	200
21c	-I	-H	-H	70	180
21d	-CN	-H	-H	65	210
21e	-COOEt	-H	-H	78	210
21f	-CHO	-H	-H	81	225
21g	-H	-CHO	-H	77	194
21h	-CHO	-Br	-H	78	205
21i	--	--	--	67	137

The resulting tris-triazole derivatives carry substitution on the end group aromatic rings ranging from halides to nitriles and aldehydes or nitro groups. All the eight newly synthesized C_3 symmetric 1,2,3–triazole compounds were characterized by various spectroscopic techniques.

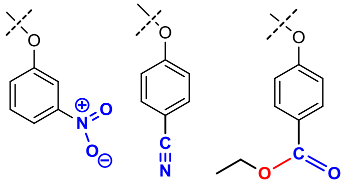
In IR spectra the 5th position $\nu_{C\text{–}H}$ of 1,2,3–triazole was observed at higher values between 3128 to 3152 cm^{-1} (Figure 16). The IR of tripodal triazoles had a characteristic band around 3066-3076 cm^{-1} for aromatic $\nu_{C\text{–}H}$. Another IR band of triazole heterocycle was observed around 1480 –1510 cm^{-1} with variable intensity. As the aromatic rings present in the tripodal compounds have different substituent functional groups attached to them and described below their characteristic IR bands were observed as expected (See spectral data). Aromatic $\upsilon_{C\text{–}Br}$ and $\upsilon_{C\text{–}I}$ for compounds **21a** (Spectrum 8) and **21c** (Spectrum 16) were observed at 506 cm^{-1} in addition to many other bands in the fingerprint region (Figure 15).



21a **21c**

Figure 15 ***Partial structures of tripodal triazoles***

The presence of –NO_2 group in compound **21b** was observed with the typical IR bands at 1527 (s) and 1352 (s) cm^{-1} due to asymmetric and symmetric stretching vibrations (Spectrum 12, Figure 16). Similarly the presence of –C≡N group in compound **21d** (Figure 16) showed a strong $\upsilon_{C\equiv N}$ at 2222 cm^{-1} (Spectrum 20). Ethylester substituent present in compound **21e** (Figure 16) showed $\nu_{C=O}$ at 1707 cm^{-1} and $\nu_{C\text{–}O}$ was observed 1170 cm^{-1} (Spectrum 28).



21b **21d** **21e**

Figure 16 ***Partial structures of tripodal triazoles***

The 4-formyl and 2-formyl substituted compounds **21f** and **21g** (Figure 17) had $\nu_{C=O}$ at 1693 (s) and 1674 (m) cm^{-1} respectively. The $\nu_{C\text{–}H}$ for formyl group showed doublets at 2823 and 2740 cm^{-1} for para substituted compound **21f** (Spectrum 28) and 2851 and 2765 cm^{-1} for ortho formyl compound **21g** due to the Fermi resonance (Spectrum 32). The pyrene containing compound **21i** showed some important bands at 3036, 2856 cm^{-1} for methylene ν_{C-H}, 1697 , 1560 (s) cm^{-1} for aromatic $\nu_{C=C}$ and 845 (s) cm^{-1} for aromatic ν_{C-H} out of plane vibrations (Spectrum 42, Figure 17). All the major values observed in IR are presented in the experimental section and spectral data section respectively.

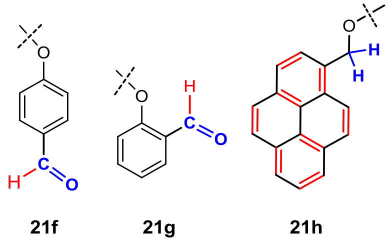


Figure 17 ***Partial structures of tripodal triazoles***

All the tripodal compounds showed typical signals in ^{1}H NMR with $-CH_3$ group on the central ring observed at δ 2.4, $-CH_2$ attached to oxygen is observed at δ 5.1 and $-CH_2$ between aromatic and triazole ring is observed downfield nearly at δ 5.7 (Figure 18).

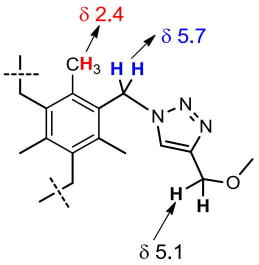
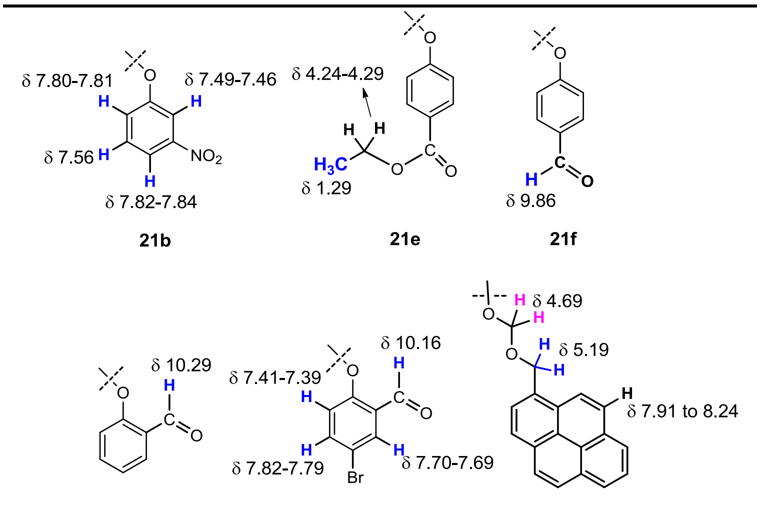


Figure 18 ***General structure of tripodal triazole with aliphatic ^{1}H shifts***

Two doublets observed in aromatic region are due to protons present in para substituted aromatic rings. The most downfield singlet observed at δ 8 to 9 is due to the lone aromatic proton present in the triazole rings.

The aromatic ring protons with $-NO_2$ group situated at position 3 in compound **21b** shows three different signals in aromatic region as expected for meta substitution (Spectrum 13). The triazole **21h** having bromo and formyl substitution clearly shows three different aromatic protons in accordance to its structure (Spectrum 37). Aldehyde protons for 4-formyl and 2-formyl substituted triazole compounds are observed at δ 9.87, 10.29 and 10.16 respectively (Spectra- 29, 33, 37). Ethyl ester in compound **21e** shows the triplet quartet pattern with signals at δ 1.29 and 4.26 for $-CH_3$ and $-CH_2$ protons (Spectrum 25). In pyrene containing tripodal compound **22i**, pyrene ring protons are observed between δ 7.91 to 8.24. A singlet for the triazole proton is observed at δ 7.09 due to shielding effect of pyrene. The aliphatic protons of $-CH_3$ and $-CH_2$ are also shifted to upfield due to pyrene shielding effect. The $-OCH_2$ protons are found at δ 5.20 and 4.69 while methylene between aromatic and triazole is observed at δ 5.34. The methyl group protons attached to the central ring is observed between δ 2.40 to 2.14 (Spectrum 43, Figure 19).



21b **21e** **21f**

21g **21h** **21i**

Figure 19 ***Partial structures of tripodal triazoles indicating ^1H***

^{13}C NMR of the tripodal triazoles had the most downfield carbon signal for oxygen attached aromatic carbon in all the compounds having aryl ether linkage. The next most downfield carbon signal was for the quaternary carbon present in the triazole heterocyclic ring. The other carbon in the same ring is observed at δ 124 in all the compounds except for the pyrene containing product in which it is found along with the aromatic carbons of the pyrene ring (Spectrum 44, Figure 20). The aliphatic region includes three carbons signals in ^{13}C NMR, out of which most downfield is the oxygen attached methylene carbon while the methyl carbon is most upfield at around δ 16.3 to 16.8 (Figure 20).

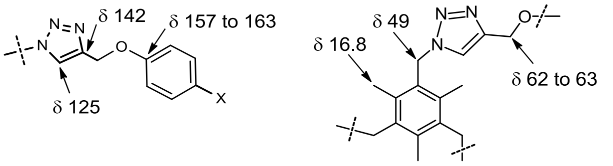


Figure 20 ***Partial structures of tripodal triazoles indicating ^{13}C***

In the iodo compound **21c,** the iodine attached aromatic carbon signal is shifted to upfield and is observed at δ 84.0 (Spectrum 18). For the compound **21d** containing nitrile group in its structure, nitrile carbon signal is observed at δ 103.6 (Spectrum 22). In the compound **21e** containing ethyl ester group, the carbonyl carbon is observed as the most downfield signal at δ 165.8. The ethyl group carbons are observed at δ 60.8 for $–CH_2$ and 14.7 for $–CH_3$ slightly upfield than the analogous carbons present elsewhere in the same compound (Spectrum 26). In the tripodal compounds **21f** and **21g** carrying formyl groups in their structure, carbonyl carbon signals are observed at δ 199.8 and 189.6 (Spectrum 30, 34; Figure 21). In the triazole **21h** possessing pyrene moiety a bunch of aromatic carbons is observed for eighteen carbons from δ 121 to 132 (Spectrum 44).

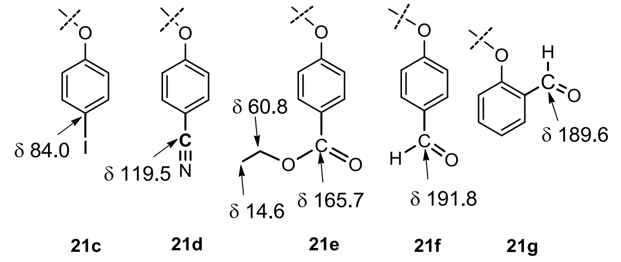


Figure 21 ***Partial structures of tripodal triazoles indicating ^{13}C chemical shifts***

All the final tripodal triazole products were characterized with the help of mass spectrometer having Q-TOF analyzer by using ESI technique. The molecular ion peaks were observed as $(M+Na)^+$ accompanied with $(M+H)^+$ in almost all cases.

The 2D-NMR, HSQC and HMBC spectra were recorded for the compounds **21h** and **21i**. HSQC spectra of **21h** (Spectrum 40) and **21i** (Spectrum 46) showed correlation between the carbons and respective hydrogen atoms attached directly to it, but the bunch of aromatic –CH of pyrene ring were unable to assign individually. HMBC spectra helped in assigning –NH and $–OCH_2$ protons for both the compounds and various other quaternary carbon atoms from the cross peaks observed.

4.2.1 Host-guest binding study of C_3 symmetric tripodal 1,2,3-triazole possessing pyrene fluorophore

The pyrene moiety was introduced as a fluorophore in the C_3 symmetric 1,2,3–triazole containing compounds which may be studied as fluorescent probes to investigate the host–guest interactions with ionic or non-ionic guests.

The UV-Vis spectrum of pyrene containing tripodal compound **21i** was recorded in DMSO as a medium. Five major absorption bands were observed at λ 267, 278, 315, 329 and 346 nm at the concentration of 10^{-5} M (Figure 22).

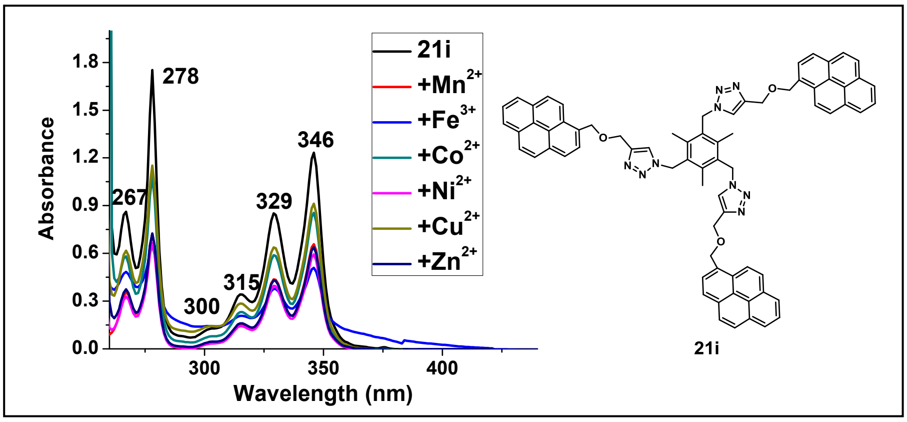


Figure 22 ***UV-Vis spectra of tris-triazoles with pyrene fluorophore***

For fluorescence study, the emission results were observed by exciting the pyrene attached tripodal triazole successively at all the five major wavelengths observed in UV-Vis spectrum. A prominent emission was found to take place when it was excited at 315 nm. So the remaining fluorescence study was carried out by excitation at the same wavelength (Figure 23).

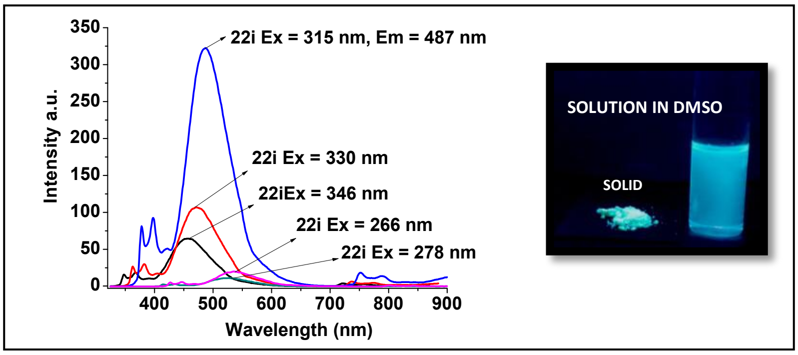


Figure 23 ***Emission spectra of pyrene triazole upon excitation at different λ_{max}***

The pyrene triazole tripodal compound was observed having fluorescence even in solid state and as dilute solution when placed in a UV chamber (Figure 23, inset).

Various first row transition metal ions were studied for their role as guest ions in the presence of tripodal triazole carrying the fluorescent probe. For the study, the potential organic host **21i** was dissolved in DMSO to the concentration of 10^{-6} M and mixed with equal volume of corresponding metal perchlorates having the concentration of 10^{-5} M in DMSO. The emission spectrum was compared with that of the host's. From the present study it was observed that the host molecule binds strongly with Fe^{3+} and Cu^{2+} ions successively. In the presence of Fe^{3+} fluorescence was almost quenched and in the presence of Cu^{2+} only slight difference is observed compared to Fe^{3+} with very low emission intensity, thus showing the extent of binding with the respective ions. When the respective solutions were placed in a UV chamber the mixture with Fe^{3+} had no fluorescence thus confirming that the Fe^{3+} was the best match guest ion with the strongest binding among the first row transition metal ions (Figure 24).

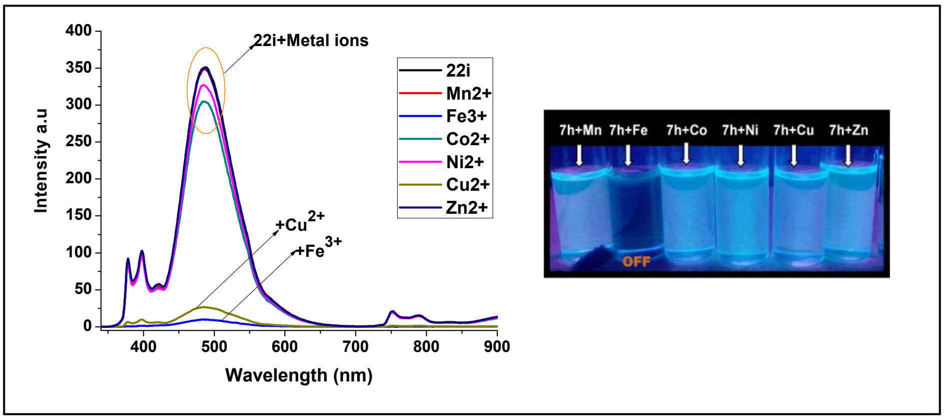


Figure 24 ***Pyrene triazole fluorescence sensor for Fe^{3+} and Cu^{2+} ions***

The selectivity study was carried out by using the mixture of the other metal ion salts with that of Fe^{3+} salt. The host was found to be selective for Fe^{3+} in the presence of the other metal ions except for Cu^{2+}. The mixture of Fe^{3+} and Cu^{2+} was lowering the fluorescence further even compared to the individual metal ions (Figure 25).

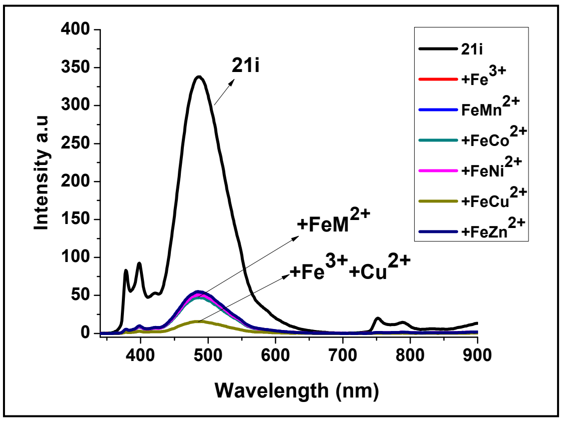


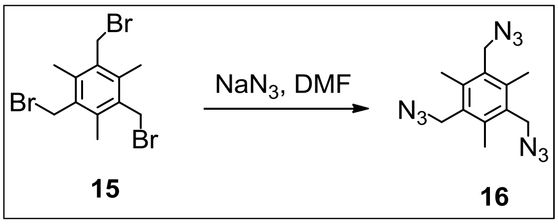
Figure 25 ***Fe^{3+} selectivity studies of the fluorescent tripodal triazole***

4.3 CONCLUSION

Thus in the present study, the new triazole containing C_3 symmetric compounds were synthesized from 1,3,5–trisazidomethyl–2,4,6–trimethylbenzene by triple click coupling reaction with some phenyl propargyl aryl ethers, and a pyrene fluorophore was introduced by coupling with pyrlymethyl propargyl ether. The addition reaction was found to be going well with CuI as a catalyst. All the new products were well characterized by various spectroscopic methods and analytical data of all the compounds are well in accordance with their proposed structures. By using pyrene as the fluorescent probe the binding study shows that the present tripodal triazole is well accommodating Fe^{3+} and Cu^{2+}, the biologically important transition metal ions and thus can be employed for the detection of Fe^{3+} and Cu^{2+} metal ions.

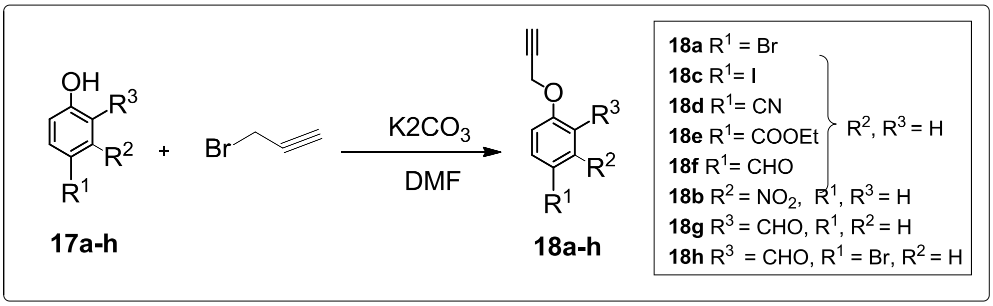
4.4 EXPERIMENTAL

4.4.1 1,3,5–Tris(azidomethyl)–2,4,6–trimethylbenzene[26] 16



1,3,5–Trisbromomehtyl–2,4,6–trimethyl benzene **15** (5.0 g, 12.5 mmol), sodium azide (NaN_3) (5.0 g, 75.24 mmol) and dry DMF (80 ml) were placed in a round bottom flask (100 ml) and the reaction mixture was heated with stirring at 80 °C for 1 hour when the reaction was completed. The reaction mixture was cooled to room temperature and poured into cold water (200 ml). White crystalline solid separated out was filtered and dried under vacuum giving compound **16** in pure form. Yield: 3.5 g (98%); mp. 64-65 °C.[26]

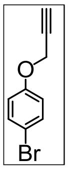
4.4.2 3-Aryloxy propynes 18a–h[27]



To a solution of a phenol **17a–e** (30.0 mmol) and potassium carbonate (K_2CO_3) (90.0 mmol) in dry DMF (10 ml) propargyl bromide (36.0 mmol) was added using a syringe. The reaction mixture was stirred at room temperature for 12 hours or until the completion of the reaction (TLC). Reaction mixture was poured in cold water and extracted with ethylacetate. For the formyl substituted phenols (**17f, 17g** and **17h**) reaction was carried out under reflux condition in acetone following the reported procedure[27]. The solvent was evaporated under vacuum giving the crude product which was purified on silica column using petroleum ether or 1 – 5 % EtOAc in hexane as required. As the propargyl ethers **18a-h** are reported[27] spectral data for some selected compounds are included as follows.

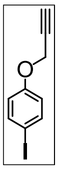
***Spectral data of some propargyloxy derivatives*:**[27,28]

4-Bromo propargyloxybenzene 18a:[27a]



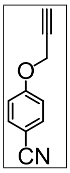
^{1}H NMR (CDCl$_3$): δ (ppm) 2.54 (1H, t, J = 2.4 Hz), 4.68 (2H, d, J = 2.4 Hz), 6.86-6.89 (2H, d, J = 8.8 Hz), 7.40-7.42 (2H, d, J = 8.8 Hz); mp. 144 °C.

1-Iodo-4-(prop-2-yn-1-yloxy)benzene[27a] 18c:[27a]



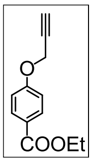
^{1}H NMR (CDCl$_3$): δ (ppm) 2.55 (1H, t, J = 2.4 Hz), 4.68 (2H, d, J = 2.4 Hz), 6.76-6.79 (2H, dd, J_{ortho} = 8.8 Hz), 7.58-7.61 (2H, dd, J_{ortho} = 7.6 Hz); mp. 45-47 °C.

4-Propargyloxy benzonitrile 18d:[27a]



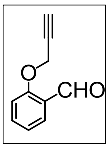
^{1}H NMR (CDCl$_3$): δ (ppm) 2.59 (1H, t, J = 2.4 Hz), 4.77 (2H, d, J = 2.4 Hz), 7.05-7.07 (2H, dd, J_{ortho} = 7.0 Hz), 7.62-7.65 (2H, dd, J_{ortho} = 9.3 Hz); mp. 140-141 °C.

Ethyl-4-(propargyloxy)benzoate 18e:[27a]



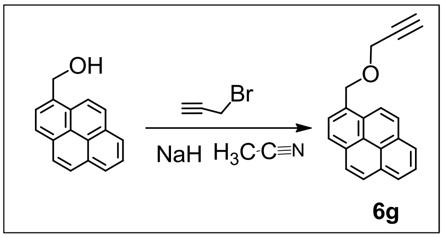
^{1}H NMR (CDCl$_3$): δ (ppm) 1.39 (3H, t, J = 7.2 Hz), 2.57 (1H, t, J = 2.4 Hz), 4.35 (2H, q, J = 7.2 Hz), 4.76 (2H, d, J = 2.4 Hz), 6.99-7.01 (2H, dd, J_{ortho} = 6.8 Hz), 8.01-8.04 (2H, dd, J_{ortho} = 7.0 Hz); mp. 42-44 °C.

2-(Propargyloxy)benzaldehyde 18g:[27b]



^{1}H NMR (CDCl$_3$) : δ (ppm) 2.59, (1H, q, J = 2.4 Hz), 4.85-4.86 (2H, d, J = 2.4 Hz), 7.09-7.15 (2H, m), 7.57-7.61 (1H, m), 7.87-7.89 (1H, m), 10.5 (1H, d); mp. 69-72 °C.

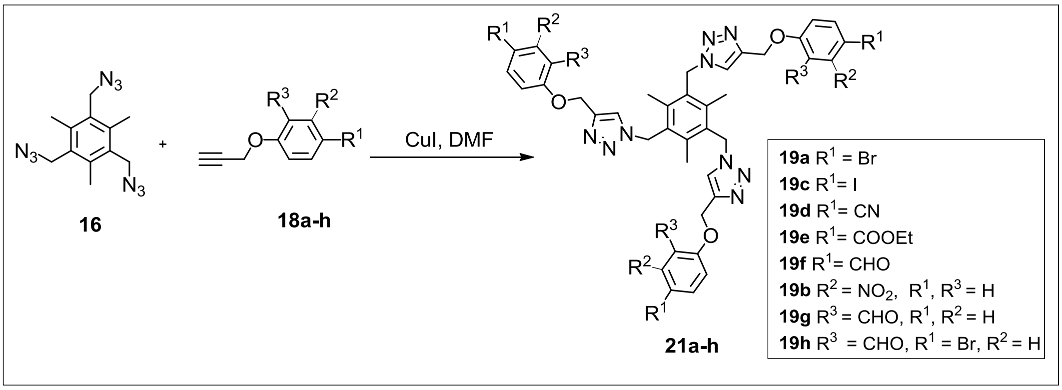
1–((Prop–2–yn–1–yloxy)methyl)pyrene 20:[28]



6g

To a solution of sodium azide (NaH) (0.18 g, 7.5 mmol) in acetonitrile (35 ml) was added pyren-1-methanol (1.4 g, 6.03 mmol). The mixture was stirred at room temperature for 30 min followed by addition of propargyl bromide (0.86 g, 7.28 mmol). The reaction mixture was heated at 70 °C and stirred at that temperature for 17 h. After completion of the reaction (TLC), cold water was added followed by extraction with chloroform. Solvent was evaporated under reduced pressure and the residue was purified on silica gel column using 20% EtOAc in petroleum ether to yield the the desired product as a pale yellow solid. Yield 0.896 g (55%). **^{1}H NMR ($CDCl_3$):** δ (ppm) 2.59 (1H, t, *J* = 2.4 Hz), 4.29-4.30 (2H, d, *J* = 2.4 Hz), 5.36 (1H, s), 8.02-8.09 (4H, m), 8.17-8.24 (4H, m), 8.43-8.45 (1H, d, *J* = 9.6 Hz).

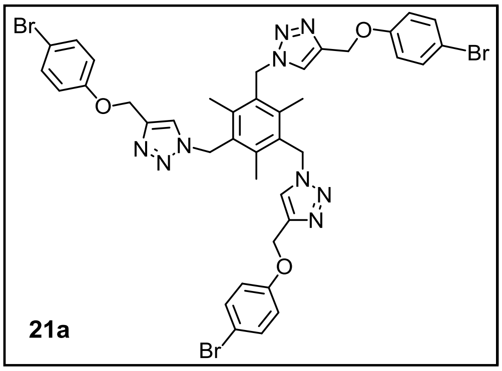
4.4.3 1,3,5-Tris[{4-(4-phenyloxymethyl)-1,2,3-triazol-1-yl}-methyl]-2,4,6-trimethylbenzenes 21



General procedure

To a solution of 1,3,5-trisazidomethyl-2,4,6-trimethylbenzene **16** (0.35 mmol) and the corresponding propargyl ethers **18a-h** (1.15 mmol) in DMF cuprous iodide (CuI) (15 mol%) was added with stirring and the resulting mixture was heated at 100 °C for 2-3 hours (TLC). After cooling to room temperature, the reaction mixture was poured in ice–water. The crude product was separated, filtered, dried and purified on silica gel column using 6:4 to 9:1 EtOAc/petroleum ether giving the corresponding tris-triazole compounds **21a–h** in good yields.

1,3,5–Tris[{4–(4–bromophenyloxymethyl)–1,2,3–triazol–1–yl}–methyl]–2,4,6–trimethylbenzene (21a)

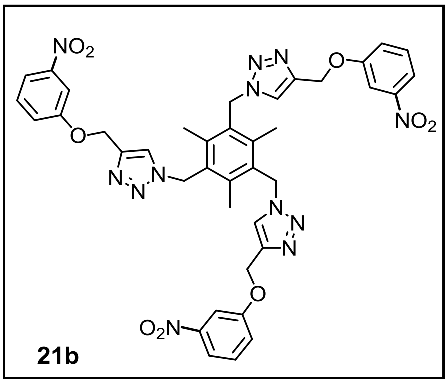


21a was prepared from **16** (0.1 g, 0.35 mmol) and **18a** (0.25 g, 1.15 mmol) in the presence of CuI (0.031 g) following the procedure described above as a white solid. Yield: 0.3 g, 74%; mp: 195 °C.

IR (KBr) : 3066, 1578, 1488, 1243, 1046, 821, 631, 506 cm^{-1}; **^{1}H NMR (DMSO-*d6*) :** δ (ppm) 2.40 (9H, s, $–CH_3$), 5.08 (6H, s, $–OCH_2–$), 5.70 (6H, s, $–NCH_2$), 7.06-

6.96 (6H, ddd, J_{ortho} = 8.8 Hz), 7.41-7.45 (6H, ddd, J_{ortho} = 8.8 Hz), 8.07 (3H, s, –N–CH═C); **^{13}C NMR (DMSO-*d6*) :** δ (ppm) 16.8 (–CH_3), 48.9 (–NCH_2–), 61.6 (–OCH_2–), 112.7, 117.4, 124.9 (triazole C–H), 131.3, 132.5, 139.8, 142.6 (triazole), 157.7 (Ar-O); **Mass (TOF MS ES+):** *m/z* calculated for $C_{39}H_{36}Br_3N_9O_3$: 915.0491, found: (*m/z*) 917.9508 ($(M+3H)^+$, 80%), 939.9312 ($(M+Na+H)^+$, 100%).

1,3,5–Tris[{4–(3–nitrophenyloxymethyl)–1,2,3–triazol–1–yl}–methyl]–2,4,6–trimethylbenzene (21b)

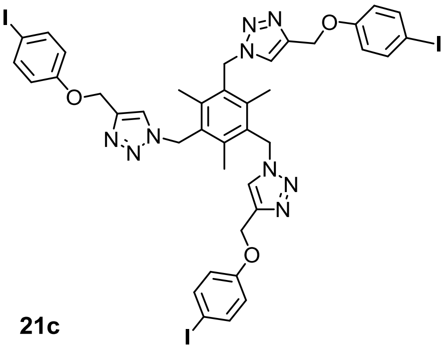


21b

21b was prepared from **16** (0.1 g, 0.35 mmol) and **18b** (0.2 g, 1.15 mmol) in the presence of CuI (0.035 g) following the general procedure described as a white solid. Yield: 0.19 g, 65%; mp: 200 °C.

IR (KBr) : 1690, 1615, 1526, 1352, 1239, 1043, 736 cm^{-1}; **^{1}H NMR (DMSO-*d6*) :** δ (ppm) 2.41 (9H, s, –CH_3), 5.25 (6H, s, –OCH_2–), 5.71 (6H, s, –NCH_2–), 7.46-7.49 (3H, ddd, J_{ortho} = 8.4 Hz), 7.56 (3H, t, *J* = 8.0 Hz), 7.80-7.84 (6H, m), 8.12 (3H, s, –N–CH═C); **^{13}C NMR (DMSO-*d6*) :** δ (ppm) 16.8 (–CH_3), 48.9 (–NCH_2), 61.6 (–OCH_2), 112.7, 117.4, 124.9 (triazole C–H), 131.3, 132.5, 139.8 (triazole), 142.6 (Ar-NO_2), 157.7 (Ar-O); **Mass (TOF MS ES+):** *m/z* calculated for $C_{39}H_{36}N_{12}O_9$: 816.2728, found: (*m/z*) 817.1716 ($(M+H)^+$, 30%), 839.1621 ($(M+Na)^+$, 100%).

1,3,5–Tris[{4–(4–iodophenyloxymethyl)–1,2,3–triazol–1–yl}–methyl]–2,4,6–trimethylbenzene (21c)



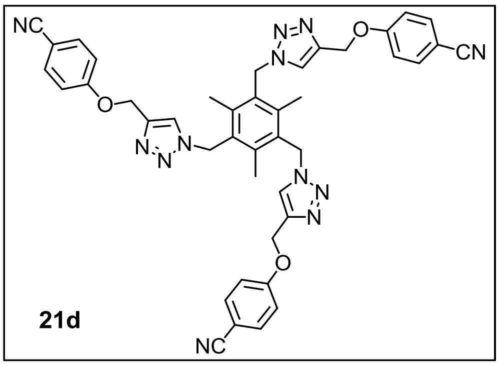
21c

21c was prepared from **16** (0.1 g, 0.35 mmol) and **18c** (0.6 g, 1.15 mmol) in the presence of CuI (0.033 g) following the general procedure described above as a white solid. Yield: 0.63 g, 70%; mp: 180 °C.

IR (KBr) : 3066, 1675, 1583, 1485, 1241, 819 cm^{-1}; **^{1}H NMR (DMSO-*d6*) :** δ (ppm) 2.40 (9H, s, –CH_3), 5.07 (6H, s, –OCH_2–), 5.70 (6H, s, –NCH_2–), 6.85-6.87 (6H, d, *J* ═ 8.8 Hz), 7.57-7.59 (6H, d, *J* ═ 8.8 Hz), 8.08 (3H, s, –N–CH═C); **^{13}C**

NMR (DMSO-*d6*) : (ppm) 16.8 (–CH_3), 48.9 (–NCH_2), 61.5 (–OCH_2), 84.0 (C–I), 118.0, 124.8 (triazole C–H), 131.3, 138.4, 139.8, 142.6 (triazole), 158.3 (Ar-O); **Mass (TOF MS ES+):** *m/z* calculated for $C_{39}H_{36}I_3N_9O_3$: 1059.0075, found: (*m/z*) 1059.8849 ($(M+H)^+$, 45%), 1081.8879 ($(M+Na)^+$, 100%).

1,3,5–Tris[{4–(4–cyanophenyloxymethyl)–1,2,3–triazol–1–yl}–methyl]–2,4,6–trimethylbenzene (21d)

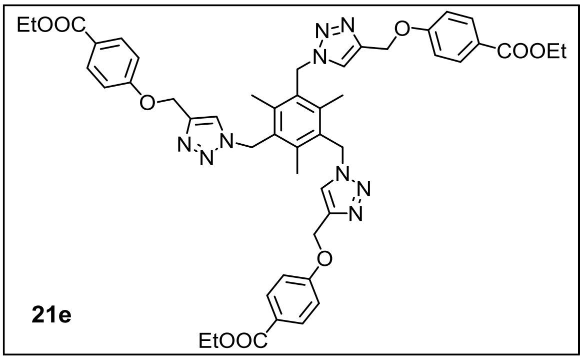


21d

21d was prepared from **16** (0.1 g, 0.35 mmol), **18d** (0.18 g, 1.15 mmol) and CuI (0.033 g) following the procedure described above as a white solid. Yield: 0.35 g, 65%; mp: 210 °C.

IR (KBr) : 3076, 2222, 1604, 1507, 1302, 1259, 1173, 834 cm^{-1}; **^{1}H NMR (DMSO-*d6*) :** δ (ppm) 2.41 (9H, s, –CH_3), 5.20 (6H, s, –OCH_2–), 5.71 (6H, s, –NCH_2–), 7.18-7.20 (6H, d, $J = 7.8$ Hz), 7.76-7.78 (6H, d, $J = 8.8$ Hz), 8.14 (3H, s, –N–CH=C); **^{13}C NMR (DMSO-*d6*) :** δ (ppm) 16.8 (–CH_3), 48.9 (–NCH_2), 61.8 (–OCH_2), 103.5, 116.2, 119.5 (–C≡N), 125.2 (triazole C–H), 131.3, 134.6, 139.8, 142.1 (triazole), 161.8 (Ar-O); **Mass (TOF MS ES+):** *m/z* calculated for $C_{42}H_{36}N_{12}O_3$ 756.3033, found 757.2146 ($(M+H)^+$, 20%), 779.1880 ($(M+Na)^+$, 100%).

1,3,5–Tris[{4–(4–ethoxycarbonyl–phenyloxymethyl)-1,2,3–triazol–1–yl}–methyl]-2,4,6–trimethylbenzene (21e)

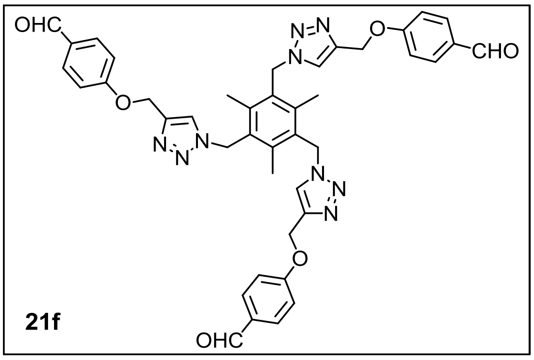


21e

21e was prepared from **16** (0.1 g, 0.35 mmol) and **18e** (0.24 g, 1.15 mmol) in the presence of CuI (0.033 g) following the general procedure described as a white solid. Yield: 0.49 g, 78%; mp: 210 °C.

IR (KBr) : 1707, 1606, 1509, 1281, 1170, 1104 cm^{-1}; **^{1}H NMR (DMSO-*d6*) :** δ (ppm) 1.29 (9H, t), 2.41 (9H, s, –CH_3), 4.25 (6H, q), 5.18 (6H, s, –OCH_2–), 5.71 (6H, s, –NCH_2–), 7.10-7.13 (6H, d, $J_{ortho} = 8.2$ Hz), 7.88-7.90 (6H, d, $J_{ortho} = 8.2$ Hz), 8.11 (3H, s –N–CH=C); **^{13}C NMR (DMSO-*d6*) :** δ (ppm) 14.6 (–CH_3), 16.8 (Ar–CH_3), 60.8 (–NCH_2), 61.6 (–OCH_2), 115.1, 122.8, 125.0 (triazole C–H), 131.3, 131.6, 142.45 (triazole), 162.2 (Ar-O), 165.7 (–C=O); **Mass (TOF MS ES+):** *m/z* calculated for $C_{48}H_{51}N_9O_9$: 897.3810, found: (*m/z*) 898.27280 ((M+H)$^+$, 20%), 920.5888 ((M+Na)$^+$, 100%).

1,3,5–Tris[{4–(4–formylphenyloxymethyl)–1,2,3–triazol–1–yl}–methyl]–2,4,6–trimethylbenzene (21f)

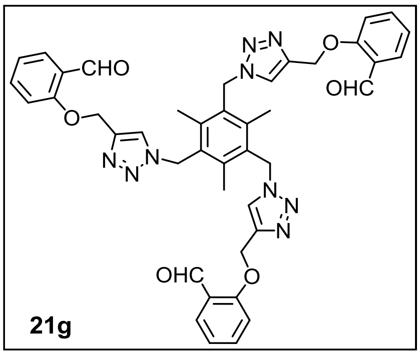


21f

21f was prepared from **16** (0.1 g, 0.35 mmol) and **18f** (0.19 g, 1.15 mmol) in the presence of CuI (0.033 g) following the procedure as described as a white solid. Yield: 0.120 g, 81%; mp: 225 °C .

IR (KBr) : 1693, 1603, 1560, 1508, 1308, 1258, 1163 cm^{-1}; **^{1}H NMR (DMSO-*d6*) :** δ (ppm) 2.42 (9H, s, –CH_3), 5.23 (6H, s, –OCH_2–), 5.72 (6H, s, –NCH_2–), 7.20-7.22 (6H, d, J_{ortho} = 8.8 Hz), 7.84-7.87 (6H, d, J_{ortho} = 8.8 Hz), 8.14 (3H, s, –N–CH=C), 9.86 (3H, s, –CHO); **^{13}C NMR (DMSO-*d6*) :** δ (ppm) 16.8 (–CH_3), 48.9 (–NCH_2), 61.8 (–OCH_2), 115.6, 125.1 (triazole C–H), 130.3, 131.3, 132.2, 139.8, 142.3 (triazole), 163.3 (Ar-O), 191.8 (–C=O); **Mass (TOF MS ES+):** *m/z* calculated for $C_{42}H_{39}N_9O_6$: 765.3023, found: (*m/z*) 766.2064 ((M+H)$^+$, 10%), 788.1940 ((M+Na)$^+$, 100%).

1,3,5–Tris[{4–(2–formylphenyloxymethyl)–1,2,3–triazol–1–yl}–methyl]–2,4,6–trimethylbenzene (21g)

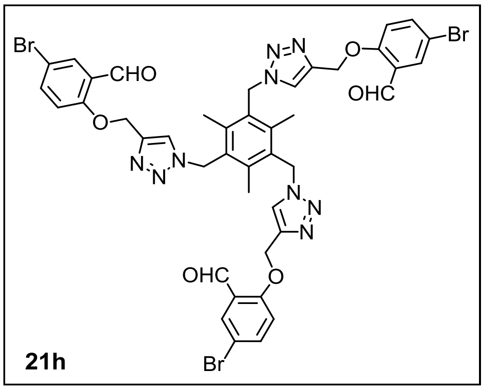


21g

21g was prepared from **16** (0.1 g, 0.35 mmol) and **18g** (0.31 g, 1.15 mmol) in the presence of CuI (0.033 g) following the general procedure described as a white solid. Yield: 1.15 g, 77%; mp: 194 °C.

IR (KBr) : 1674, 1597, 1483, 1291, 1046 cm^{-1}; **^{1}H NMR (DMSO-*d6*) :** δ (ppm) 2.41 (9H, s, –CH_3), 5.30 (6H, s, –OCH_2–), 5.71 (6H, s, –NCH_2–), 7.08 (3H, t), 7.42-7.40 (3H, d, *J* = 8.4 Hz), 7.68-7.63 (6H, m), 8.18 (3H, s, –N–CH=C), 10.29 (3H, s, –CHO); **^{13}C NMR (DMSO-*d6*) :** δ (ppm) 16.8 (–CH_3), 48.9 (–NCH_2), 62.6 (–OCH_2), 114.8, 121.6, 124.9, 125.0 (triazole C–H), 128.1, 131.3, 136.7, 139.8, 142.3 (triazole), 160.8 (Ar-O), 189.6 (–C=O); **Mass (TOF MS ES+):** *m/z* calculated for $C_{42}H_{39}N_9O_6$: 765.3023, found: (*m/z*) 766.1951 ($(M+H)^+$, 10%), 788.1640 ($(M+Na)^+$, 100%).

1,3,5–Tris[{4–(5–bromo–2–formylphenyloxymethyl)-1,2,3–triazol–1–yl}-methyl]-2,4,6–trimethylbenzene (21g)

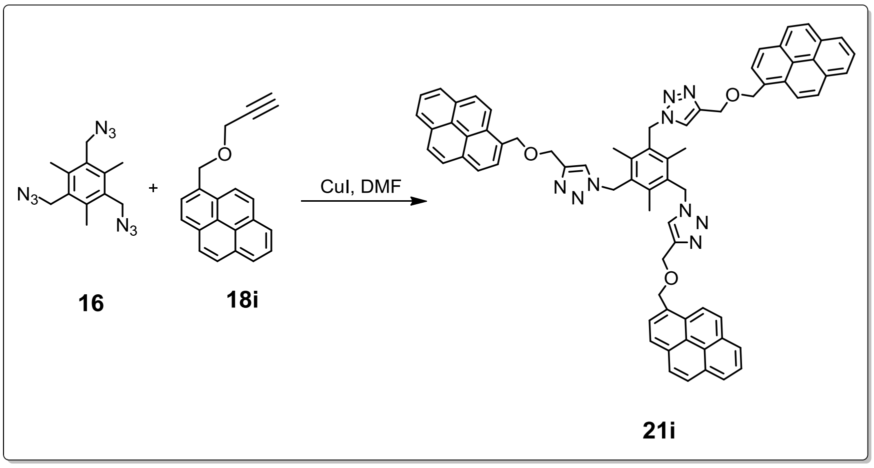

21h

21h was prepared from **16** (0.100 g, 0.35 mmol) and **18h** (0.26 g, 1.15 mmol) in the presence of CuI (0.030 g) following the general procedure described as a white solid. Yield: 0.27 g, 78%; mp: 205 °C.

IR (KBr) : 2921, 2852, 1681, 1589, 1478, 1390, 1271, 1233, 1124, 1044, 624 cm^{-1}; **^{1}H NMR (DMSO-*d6*) :** δ (ppm) 2.39 (9H, s, $-CH_3$), 5.29 (6H, s, $-OCH_2-$), 5.70 (6H, s, $-NCH_2-$), 7.41-7.39 (3H, d, $J = 9.2$ Hz), 7.70-7.69 (3H, d, $J = 2.8$ Hz), 7.82-7.79 (3H, dd, $J_{ortho} = 9.0$ Hz), 8.15 (3H, s, –N–CH=C), 10.16 (3H, s, –CHO); **^{13}C NMR (DMSO-*d6*) :** δ (ppm) 16.8 ($-CH_3$), 48.9 ($-NCH_2$), 62.9 ($-OCH_2$), 113.4, 117.5, 125.0, 126.4, 130.3, 131.2, 138.8, 139.8, 142.2, 159.7, 188.5; **Mass (TOF MS ES+):** *m/z* calculated for $C_{42}H_{36}Br_3N_9O_6$: 999.0339, found: (*m/z*) 1000.0662 ($(M+H)^+$, 20%), 1002.0539 ($(M+2H)^+$, 98%), 1004.0501 ($(M+4H)^+$, 100%), 1006.0547 ($(M+6H)^+$, 30%).

4.4.4 1,3,5-Tris[{4-(pyren-1-ylmethoxy-methyl)-1,2,3-triazol-1-yl}-methyl]–2,4,6–trimethylbenzene *21i*

To a solution of 1,3,5-trisazidomethyl-2,4,6-trimethylbenzene **16** (0.1 g, 0.38 mmol) and the corresponding pyrene based propargyl ethers **20i** (0.32 g, 1.15 mmol) in DMF cuprous iodide (CuI) (15 mol%, 0.031 g) was added with stirring and the resulting mixture was heated at 100 °C for 2-3 hours (TLC). After cooling to room temperature, the reaction mixture was poured in ice–water. The crude product was separated, filtered, dried and purified on silica gel column using 8:2 EtOAc/petroleum ether giving the corresponding tris-triazole compounds **21i** as pale yellow solid. Yield: 0.49 g, 67%; mp: 137 °C.

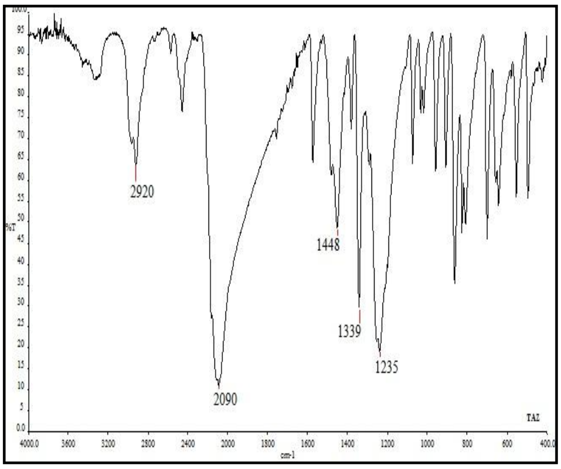


IR (KBr) : 3036, 2856, 1695, 1674, 1560, 1223, 1118, 1044, 845 cm^{-1}; **^{1}H NMR (DMSO-*d6*) :** δ (ppm) 2.19 (9H, s, $-CH_3$), 4.71 (6H, s, $-C\underline{H}_2OCH_2$), 5.22 (6H, s, $-CH_2OC\underline{H}_2$), 5.41 (6H, s, $-NCH_2$), 7.10 (3H, s, $-N-CH{=}C$), 7.93-8.08 (18H, m), 8.13-8.16 (6H, t), 8.24-8.26 (3H, d); **^{13}C NMR (DMSO-*d6*) :** δ (ppm) 16.3 ($-CH_3$), 48.7 ($-NCH_2$), 63.8 ($-OCH_2$), 71.2 (Pyrene $-OCH_2$), 96.1, 121.6, 123.2, 124.4, 124.6, 124.8, 125.2, 125.2, 125.9, 127.1, 127.3, 127.4, 127.6, 129.3, 130.4, 130.7, 130.8, 131.1, 131.3, 139.5, 145.4; **Mass (TOF MS ES+):** *m/z* calculated for $C_{42}H_{39}N_9O_6$: 1095.4584, found: (*m/z*) 1096.3478 ($(M+H)^+$, 50%), 1118.3513 ($(M+Na)^+$, 100%).

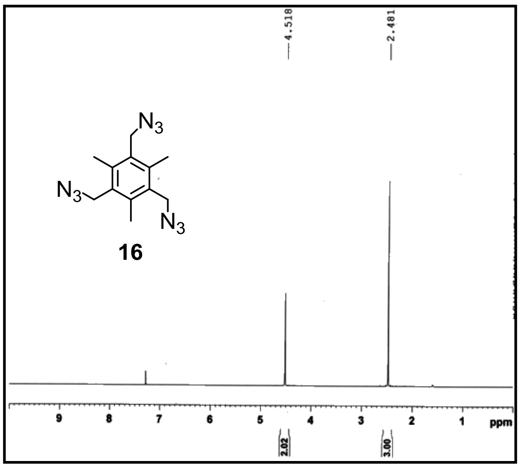
4.5 SPECTRAL DATA

Compound 16

4.5.1 Propargyl derivatives

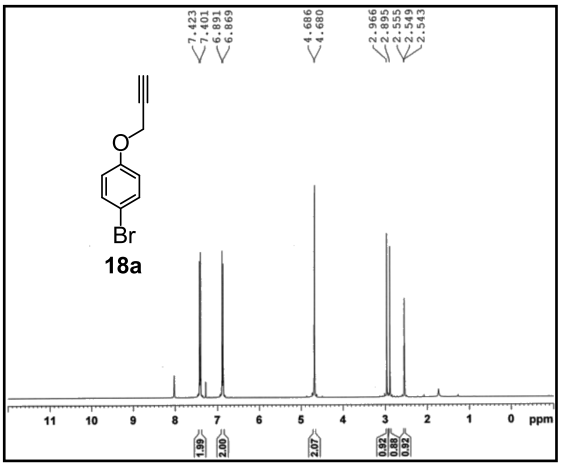


Spectrum 1. IR of 16



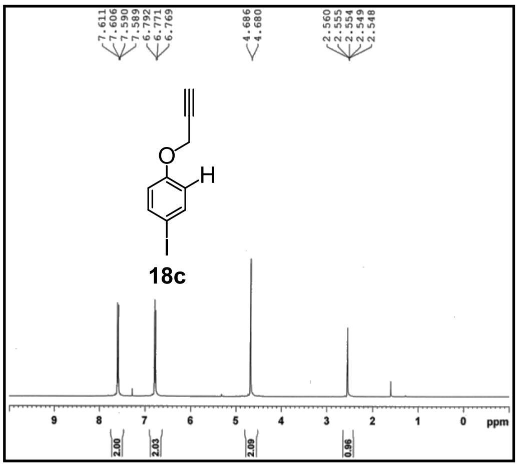
Spectrum 2. ^{1}H NMR of 16

Compound 18a



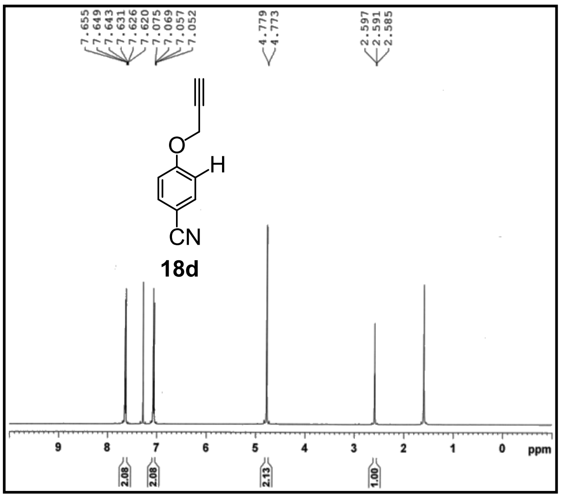
Spectrum 2. ^{1}H NMR of 18a

Compound 18c



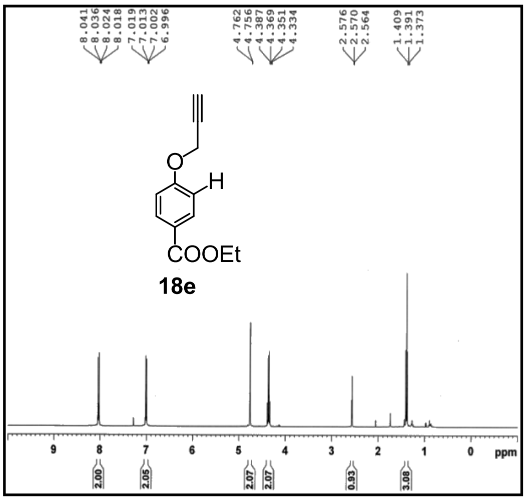
Spectrum 3. ^{1}H NMR of 18c

Compound 18d



Spectrum 4. ^{1}H NMR of 18d

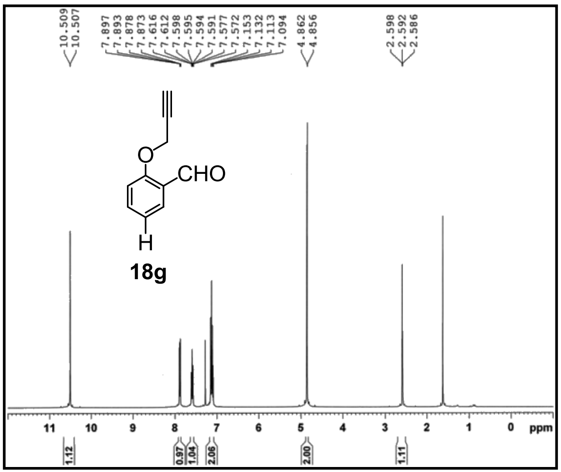
Compound 18e



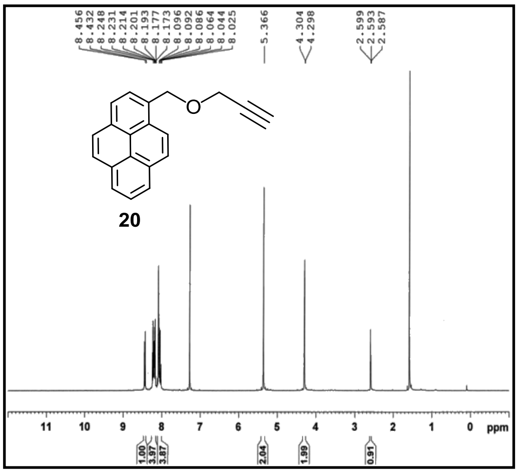
Spectrum 5. ^{1}H NMR of 18e

Compound 18g

Compound 20



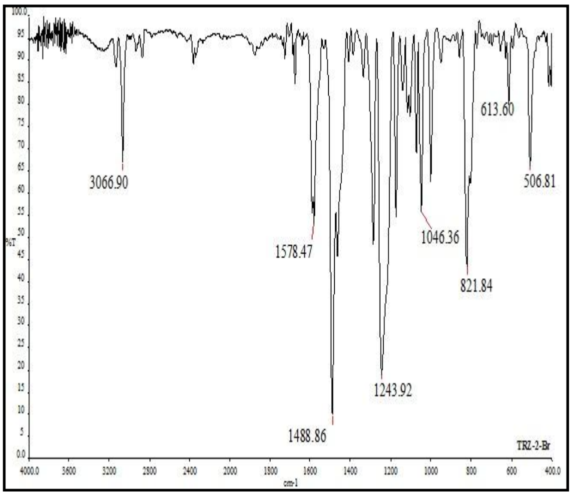
Spectrum 6. ^{1}H NMR of 18g



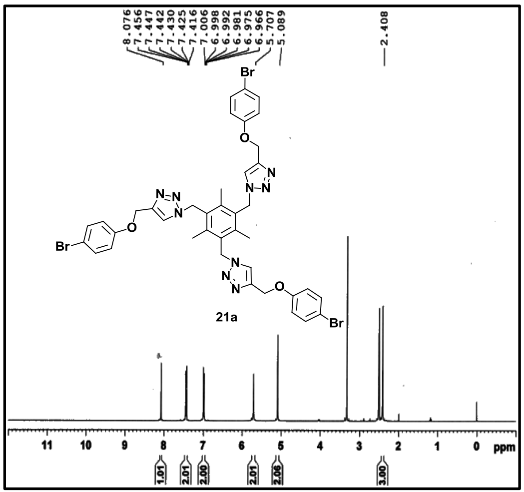
Spectrum 7. ^{1}H NMR of 20

4.5.2 Tris-1,2,3-triazole derivatives

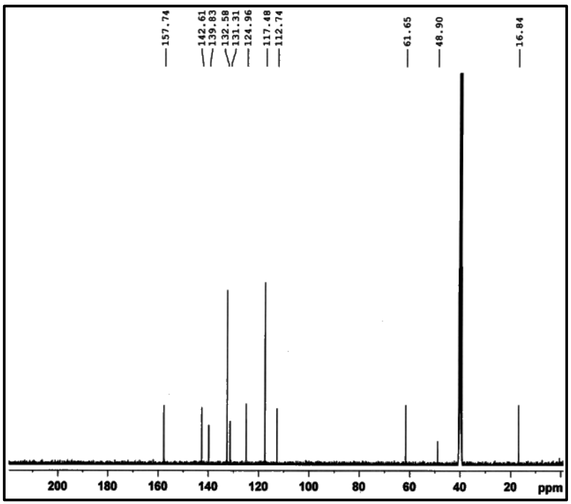
Compound 21a



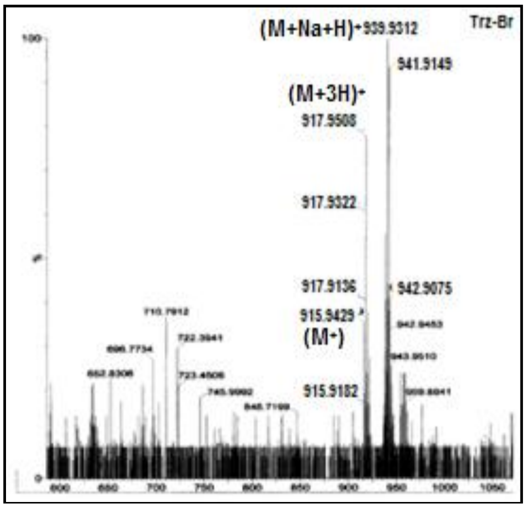
Spectrum 8. IR of 21a



Spectrum 9. ^{1}H NMR of 21a

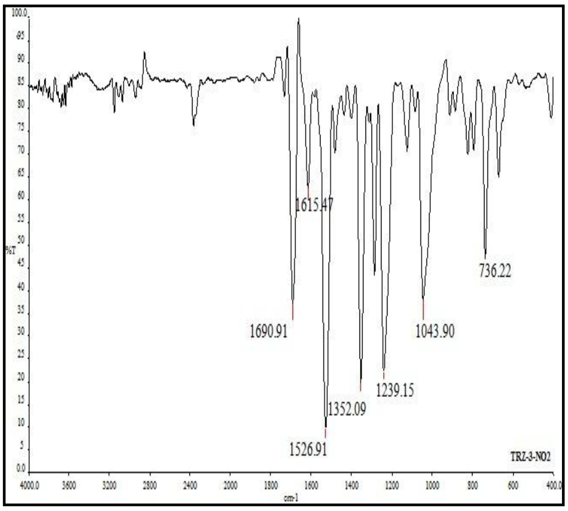


Spectrum 10. ^{13}C NMR of 21a

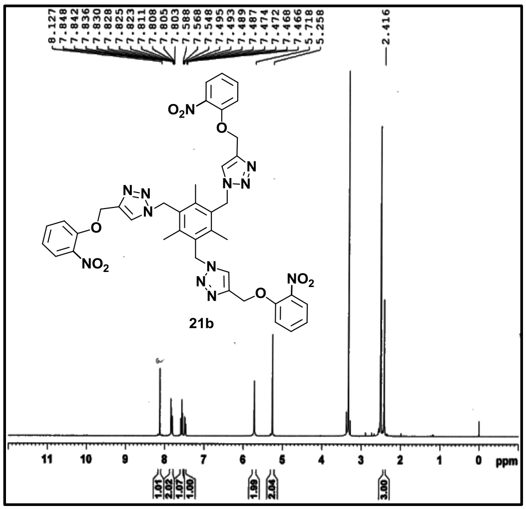


Spectrum 11. Mass of 21a

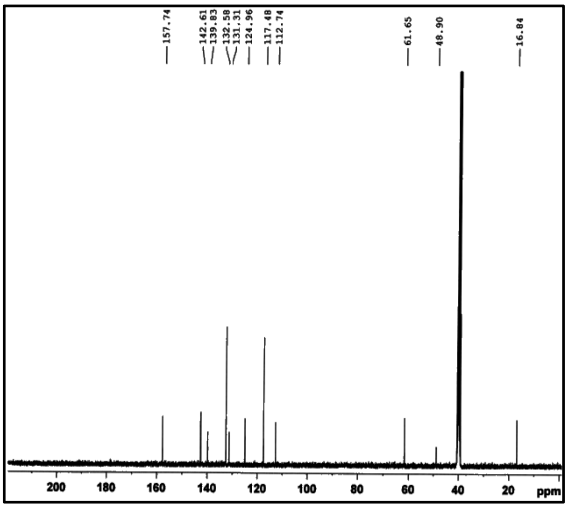
Compound 21b



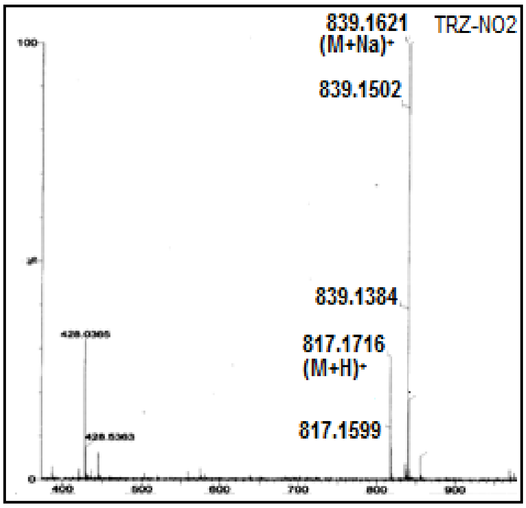
Spectrum 12. IR of 21b



Spectrum 13. ^{1}H NMR of 21b

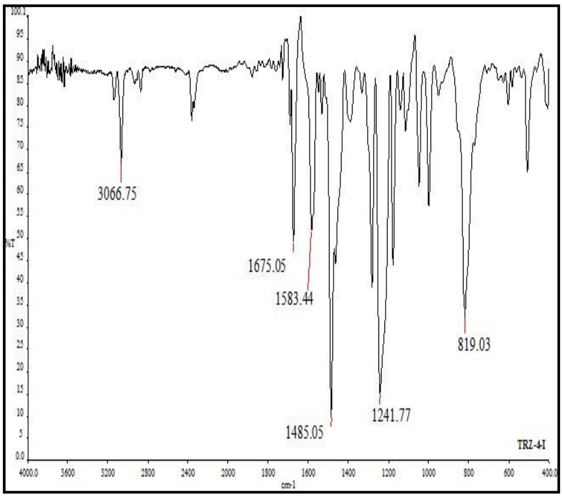


Spectrum 14. ^{13}C NMR of 21b

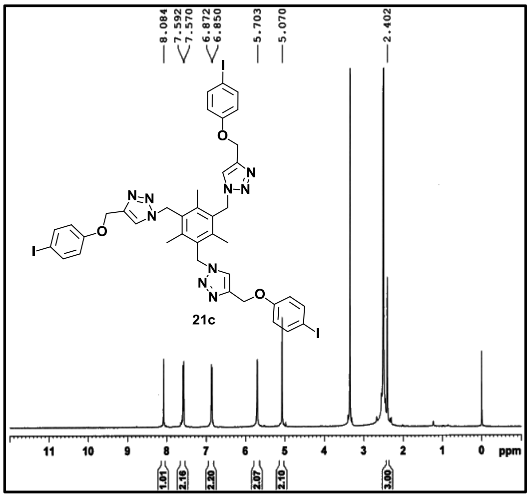


Spectrum 15. Mass of 21b

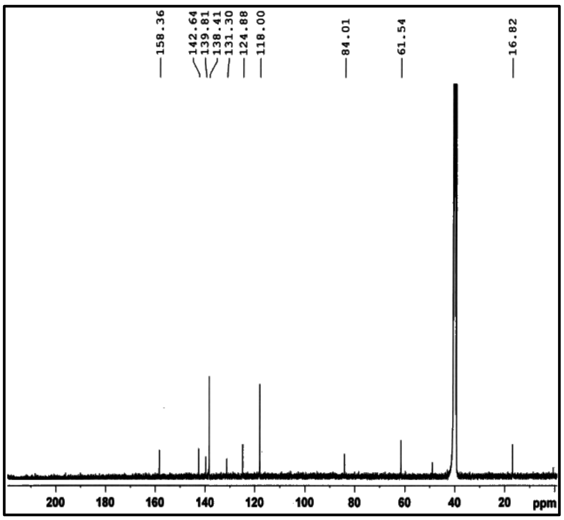
Compound 21c



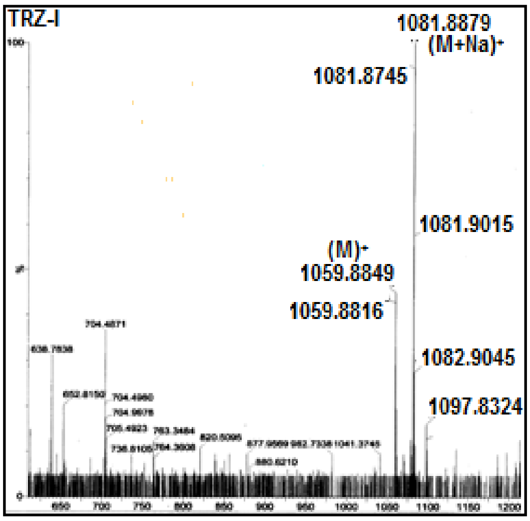
Spectrum 16. IR of 21c



Spectrum 17. ^{1}H NMR of 21c

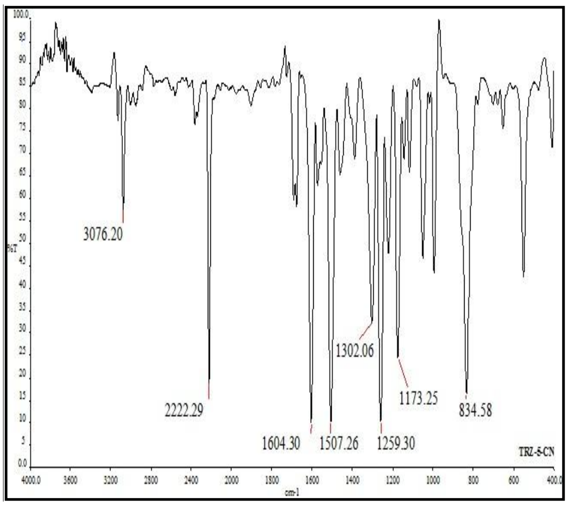


Spectrum 18. ^{13}C NMR of 21c

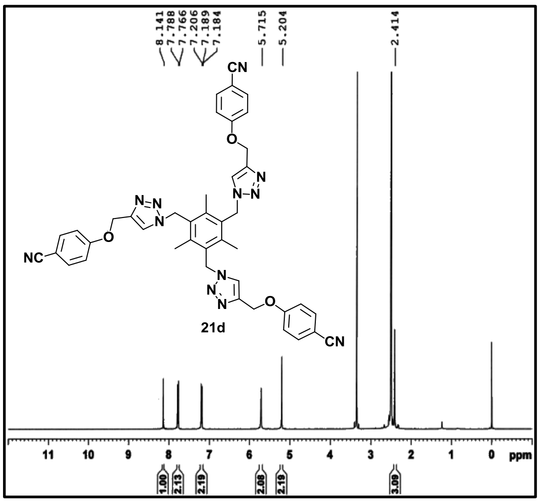


Spectrum 19. Mass of 21c

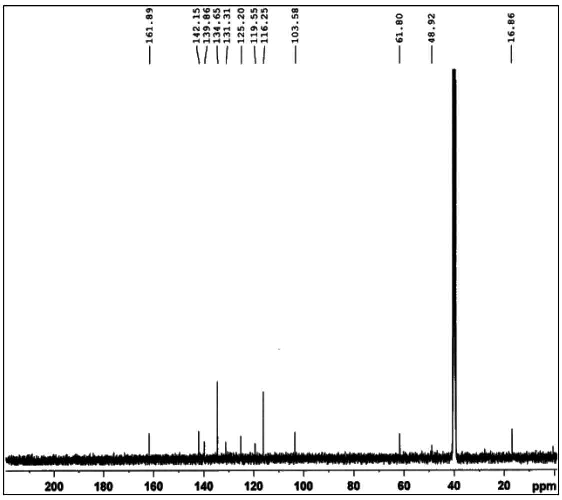
Compound 21d



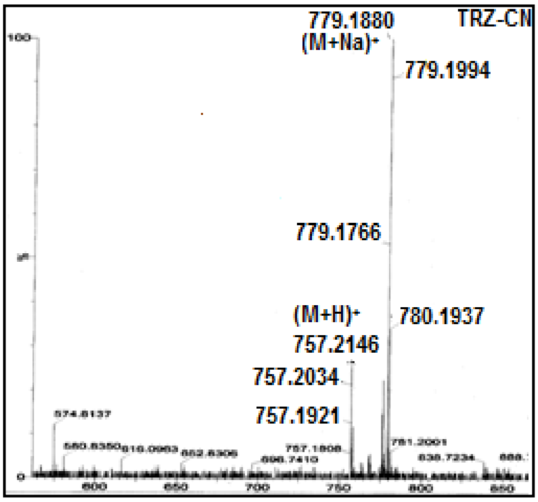
Spectrum 20. IR of 21d



Spectrum 21. ^{1}H NMR of 21d

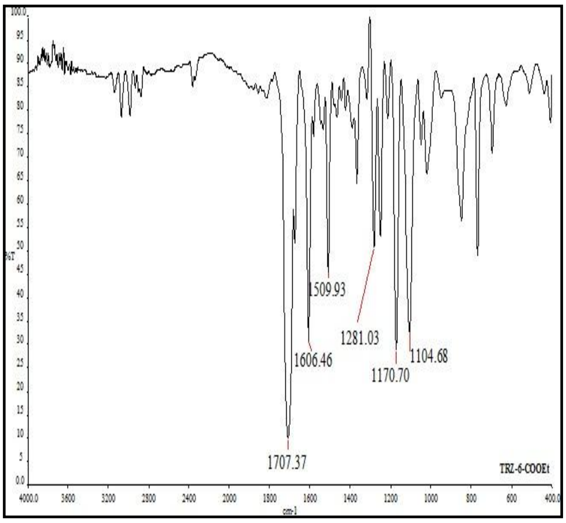


Spectrum 22. ^{13}C NMR of 21d

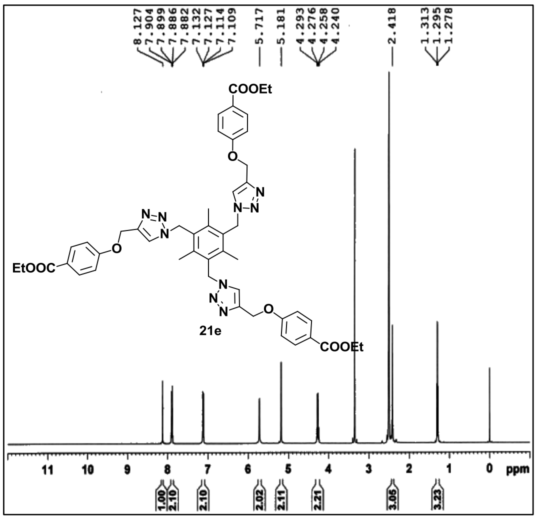


Spectrum 23. Mass of 21d

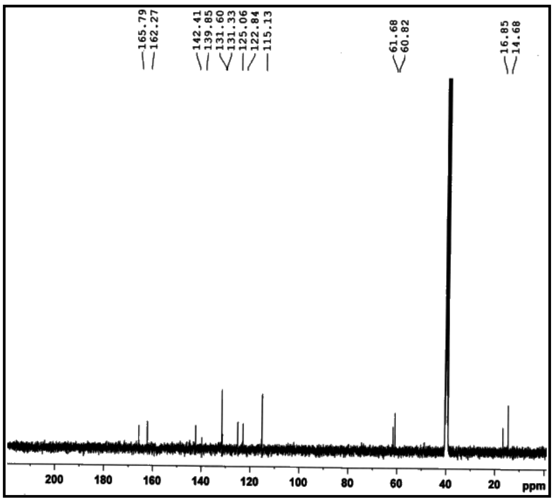
Compound 21e



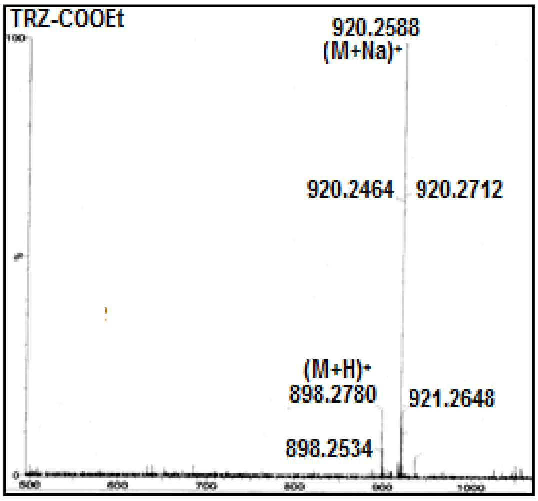
Spectrum 24. IR of 21e



Spectrum 25. ^{1}H NMR of 21e

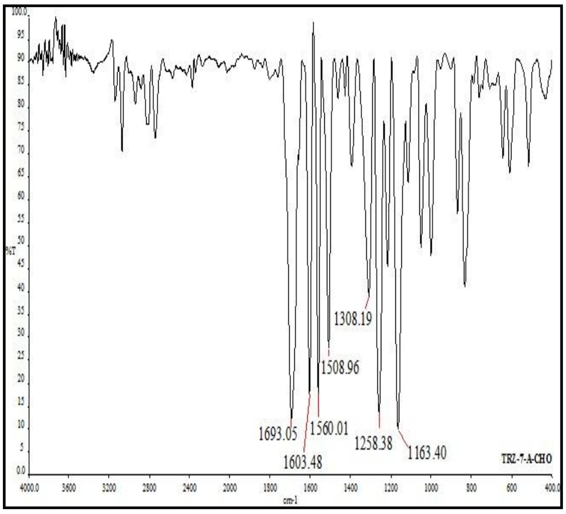


Spectrum 26. ^{13}C NMR of 21e

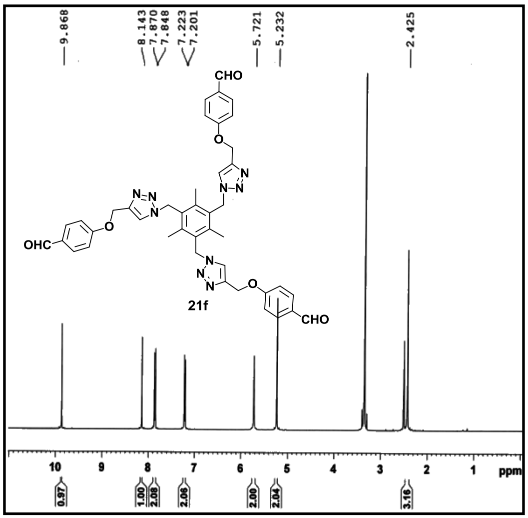


Spectrum 27. Mass of 21e

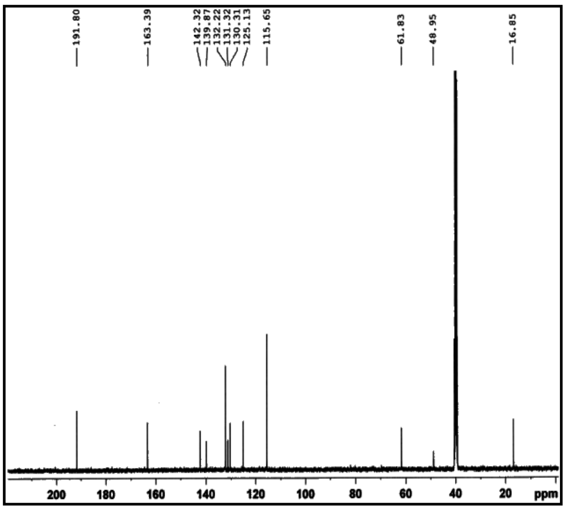
Compound 21f



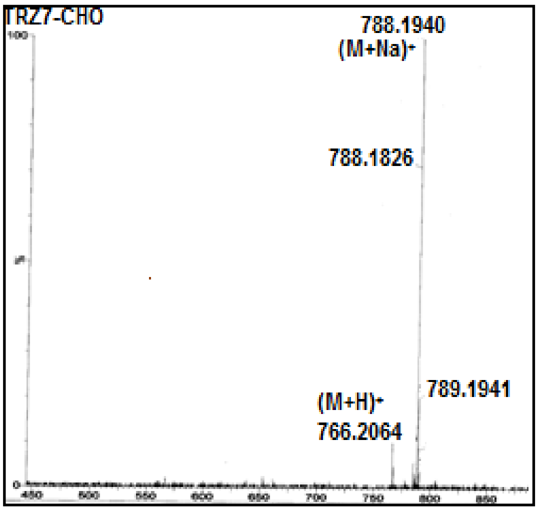
Spectrum 28. IR of 21f



Spectrum 29. ^{1}H NMR of 21f

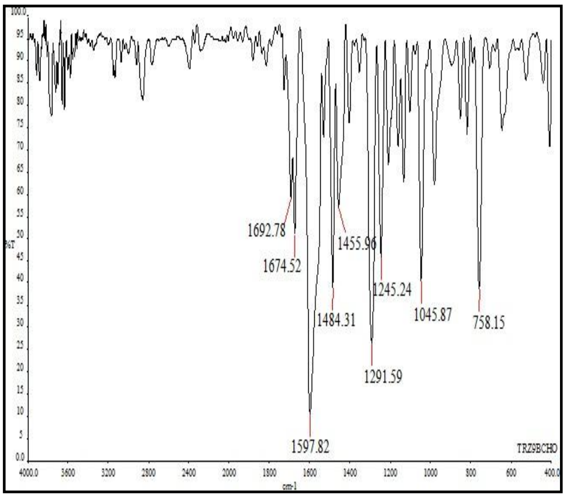


Spectrum 30. ^{13}C NMR of 21f

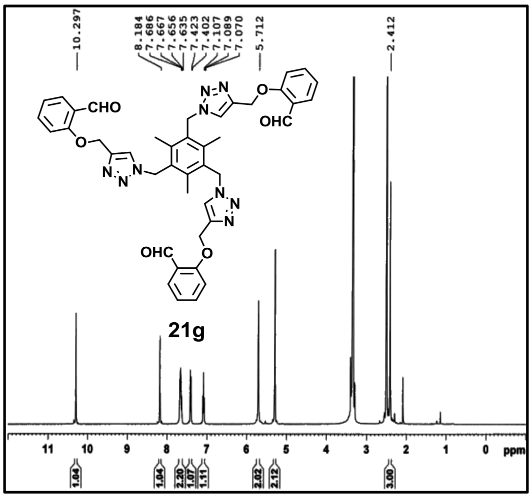


Spectrum 31. Mass of 21f

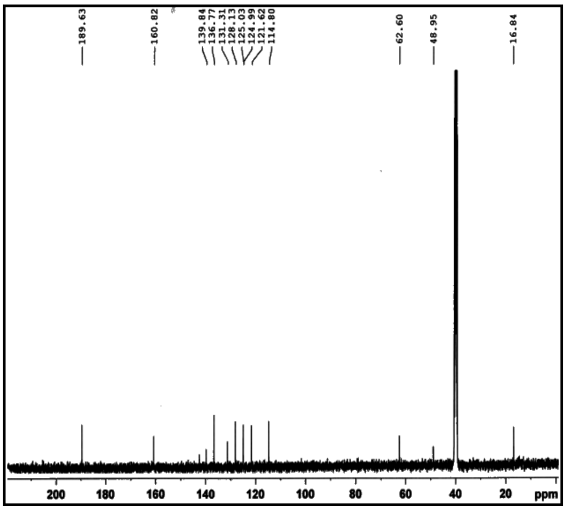
Compound 21g



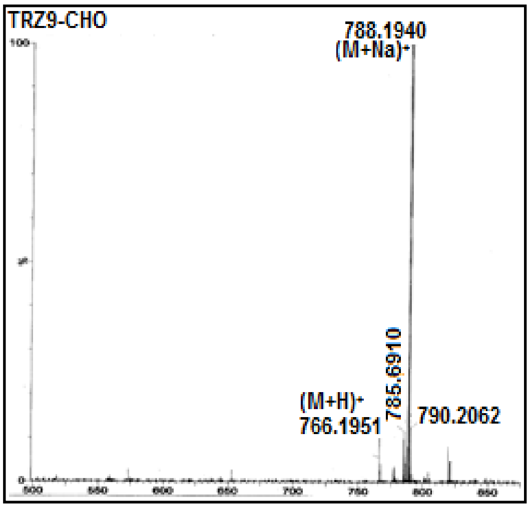
Spectrum 32. IR of 21g



Spectrum 33. ^{1}H NMR of 21g

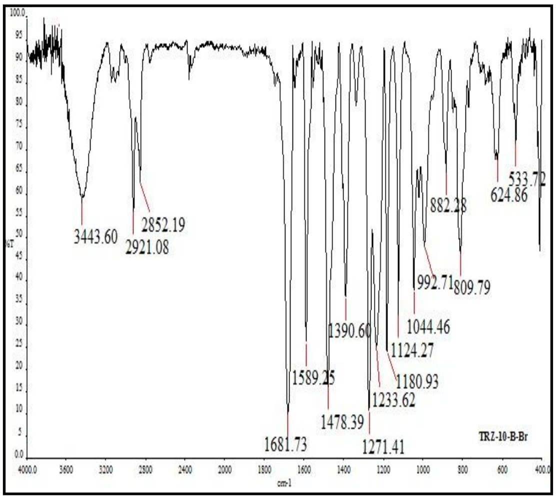


Spectrum 34. ^{13}C NMR of 21g

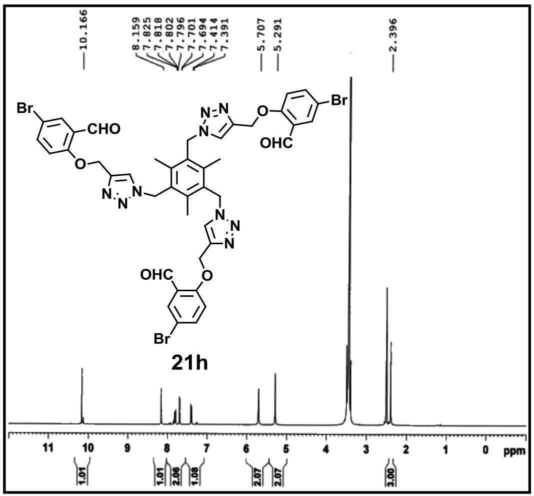


Spectrum 35. Mass of 21g

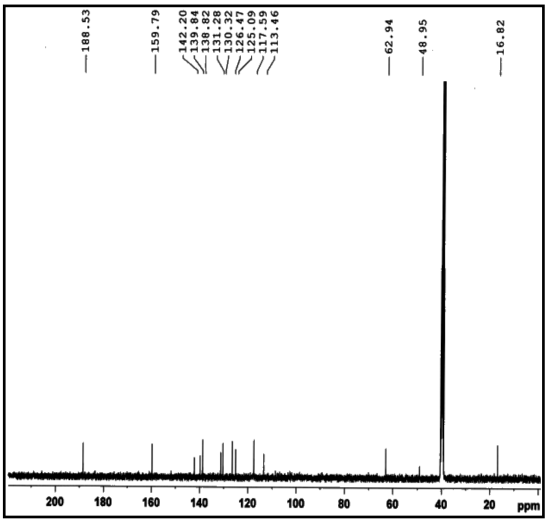
Compound 21h



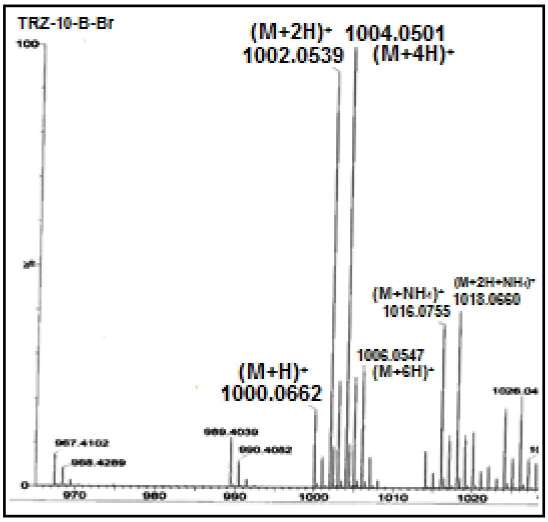
Spectrum 36. IR of 21h



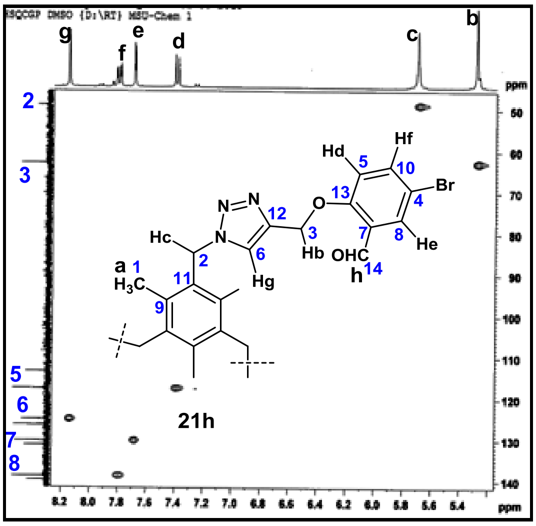
Spectrum 37. ^{1}H NMR of 21h



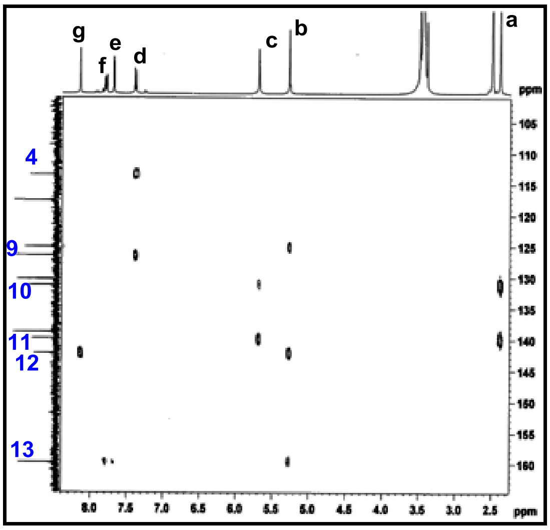
Spectrum 38. ^{13}C NMR of 21h



Spectrum 39. Mass of 21h

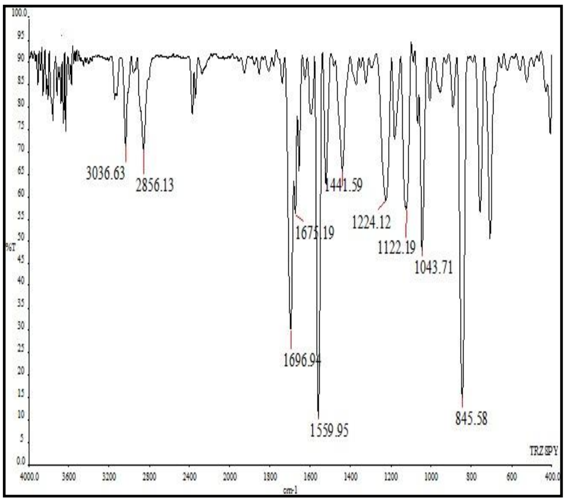


Spectrum 40. HSQC of 21h

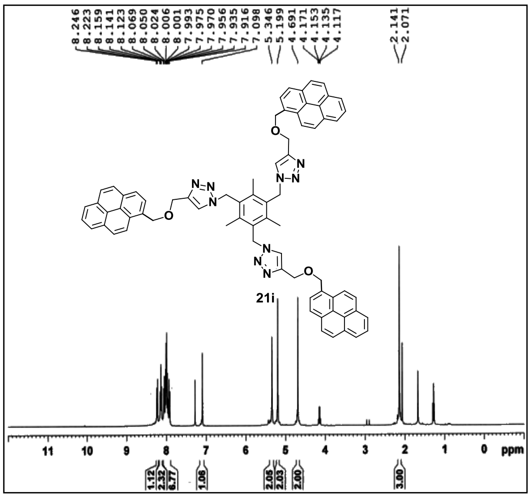


Spectrum 41. HMBC of 21h

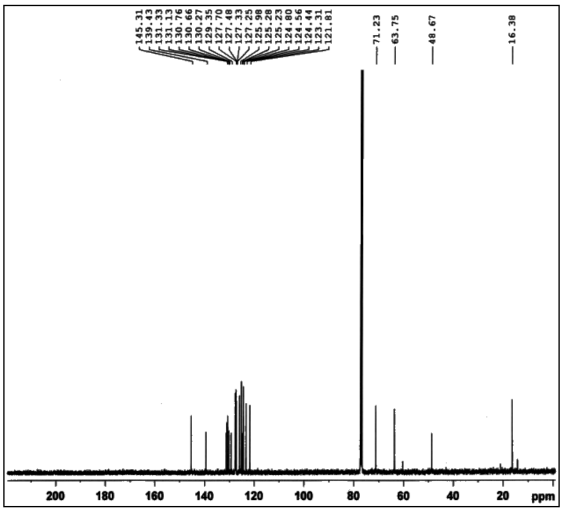
Compound 21i



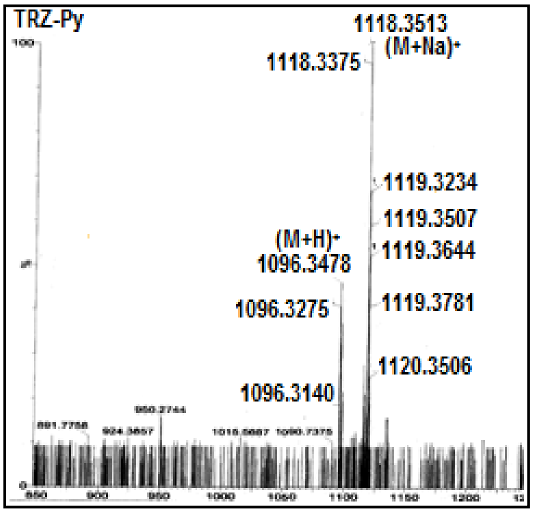
Spectrum 42. IR of 21i



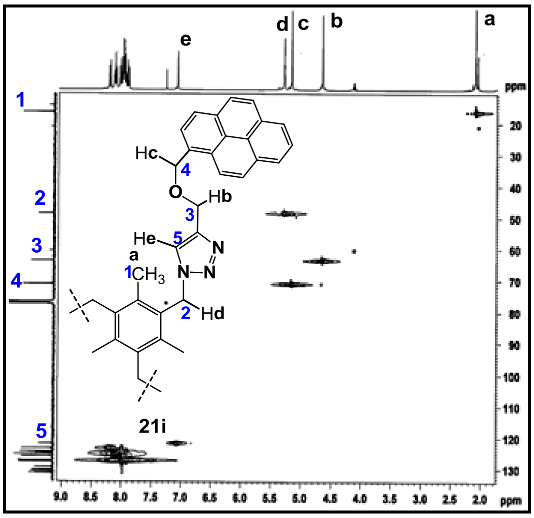
Spectrum 43. ^{1}H NMR of 21i



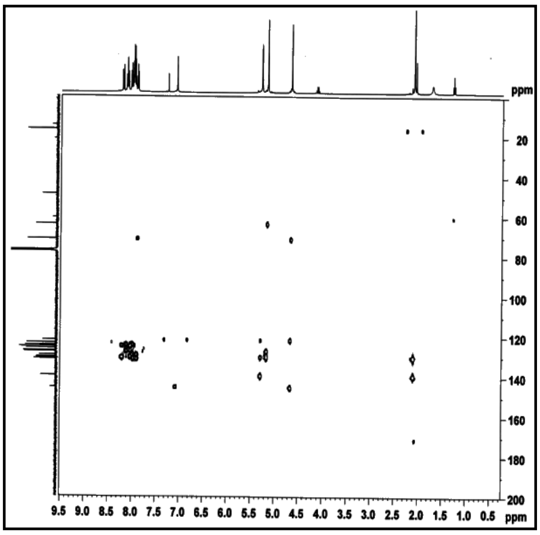
Spectrum 44. ^{13}C NMR of 21i



Spectrum 45. Mass of 21i



Spectrum 46. HSQC of 21i



Spectrum 47. HMBC of 21i

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